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Clinically Relevant Biomarkers in Connective Tissue Disease-Associated Interstitial Lung Disease

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INTRODUCTION

Interstitial lung disease (ILD) is a common manifestation of connective tissue disease (CTD), most often affecting patients with rheumatoid arthritis (RA), systemic sclerosis (SSc), idiopathic inflammatory myopathy (IIM), and mixed CTD.[1–5] ILD can also develop in patients with Sjögren syndrome (SS) and systemic lupus erythematosus, but is less common with these disorders.[6,7] Among patients who do develop CTD-ILD, a subset will develop a progressive phenotype, leading to parenchymal destruction, lung function decline, and early mortality.[8–21] Early and accurate diagnosis is essential for effectively managing patients with CTD-ILD, particularly because effective treatments exist to stabilize disease and sometimes improve lung function. [13–15,22–24] Diagnosing ILD is often nuanced and difficult, as many patients with CTD-ILD have no respiratory symptoms, and symptoms are nonspecific when they do develop.[25,26] Pulmonary function testing (PFT) can help raise suspicion for ILD in patients with CTD, but test performance characteristics are modest.[25,27] Once ILD is diagnosed, the inability to discriminate patients likely to progress remains elusive. Clinical prediction models have been developed to predict ILD progression in patients with CTD, but many are CTD specific, reducing generalizability to the larger CTD-ILD population. The ability to predict CTD-ILD progression would empower patients and clinicians to make better informed decisions about treatment, lung transplantation, and goals of care.

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Biomarkers, defined as indicators of normal biological processes and pathogenic processes, hold promise for improving our ability to accurately diagnose ILD and predict disease trajectory.[28] The ideal biomarker should be noninvasive or minimally invasive, with high accuracy for predicting the end point of interest. Biomarkers most likely to inform clinical decision making in patients with CTD are those that predict early disease before the development of respiratory symptoms and a progressive phenotype. In the past decade, numerous studies have identified candidate blood-based and high-resolution computed tomography (HRCT) biomarkers, and recent -omics investigations have added composite biomarkers to the list of potentially clinically relevant biomarkers in the CTD-ILD population. However, barriers to clinical implementation remain. This review provides an overview of recent advances in CTD-ILD biomarker investigation, focusing on blood-based and HRCT biomarkers, and highlights strategies to advance these biomarkers toward clinical implementation in patients with CTD-ILD.

BLOOD-BASED DIAGNOSTIC BIOMARKERS

Blood-based biomarkers carry high promise for diagnosing ILD in patients with CTD and providing prognostic information for these patients, because many reflect molecular pathways involved in fibrogenesis and can signal early disease before the development of overt fibrosis and respiratory symptoms. Furthermore, the minimally invasive nature of peripheral blood acquisition better positions this class of biomarkers for clinical implementation when compared with more invasive procedures such as bronchoalveolar lavage and surgical lung biopsy. Blood-based biomarkers include clinically approved autoantibodies and inflammatory markers, and research biomarkers identified through targeted and unbiased analysis. The major challenge remaining with blood-based biomarkers, however, is achieving adequate test performance to justify clinical implementation; this is particularly difficult in patients with CTD, because many blood-based biomarkers may reflect systemic and extrapulmonary processes.

The detection of autoantibodies serves a critical role in the diagnosis of CTD-ILD, and autoantibodies are the only blood biomarkers available for clinical use. There are a number of autoantibodies found in patients with CTD that are associated with higher risk of ILD. In patients with SSc, antitopoisomerase I antibody (anti-Scl70) has repeatedly been associated with ILD across cohorts.[29–33] Anti-Th/To ribonucleoprotein antibodies and anti-PM/Scl have also been shown to be associated with ILD, although they are more rarely detected in patients with SSc.[34,35] In addition, in 2 large SSc cohorts, the presence of anti-SSA/Ro was found to be associated with at least a 2-fold increased odds of SSc-ILD.[36,37] Conversely, the absence of anticentromere antibodies is associated with decreased likelihood of ILD.[30,38] In patients with RA, anti-citrullinated cyclic peptide (CCP) antibodies and high-titer rheumatoid factor predict ILD, with some studies demonstrating a correlation between anti-CCP titers and HRCT severity.[39–42] In patients with IIM, anti-tRNA synthetase antibodies are commonly detected, most frequently anti-Jo-1, anti-PL-7, and PL-12 antibodies. These antisynthetase antibodies are the hallmark of antisynthetase syndrome, which carries high risk of developing ILD, with reports of ILD in more than 90% of antisynthetase antibody-positive patients.[43,44] Another antibody found in patients with IIM is the (anti-MDA5/CADM-140), which characterizes a subset with clinically amyopathic myositis and high risk

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of ILD.[45–50] Unfortunately, many of these antibodies tend to signal overall disease extent and risk of ILD, rather than the presence of ILD.

Beyond clinically approved autoantibodies, multiple investigations have focused on molecular markers of lung epithelial cell dysfunction, aberrant immunity (cytokines and chemokines), and abnormal lung remodeling (collagen peptides/extracellular matrix biomarkers) in patients with CTD-ILD. Among those with the best described test performance characteristics is Krebs von den Lungen 6 (KL-6), which is strongly expressed on regenerating type II pneumocytes and thought to be a marker of epithelial injury.[51] At various cutoff points, the sensitivity of KL-6 ranges from 73% to 87% and specificity ranges from 70% to 100% for discriminating CTD-ILD among patients with CTD.[52–60] The area under the curve (AUC), which describes global discrimination without a cutoff threshold, ranges from 0.86 to 0.90, depending on the cohort in which the test is applied. Another well-studied marker of lung epithelial damage and turnover is surfactant protein D (SP-D). As a biomarker of ILD in patients with CTD, sensitivity ranges from 68% to 89.4% and specificity ranges from 70% to 83% depending on the dichotomization threshold used, with an AUC of 0.72 to 0.983.[41,52,53,61] In studies comparing KL-6 and SP-D in the same cohort, the specificity of SP-D is generally lower than that of KL-6.[52,53,62]

Other well-studied blood-based biomarkers are described in Table 1 and include SP-A[62,63]; club cell secreted protein 16[54]; pulmonary and activation-regulated chemokine (PARC)[41]; interleukin (IL)-6, 8, and 10[64]; tumor necrosis factor-α[64]; metalloproteinase (MMP)-7[41]; and Wnt Family member 5a (Wnt5a).[65] Although test performance characteristics are not reported for all biomarkers listed, studies have shown that circulating concentration of these biomarkers are higher in patients with CTD-ILD compared with those with CTD without ILD. Despite the advances made studying these blood-based biomarkers, none have been implemented clinically. Given the complexity of ILD pathogenesis, it is likely that biomarkers from multiple pathways are needed to achieve sufficient test performance to justify clinical implementation. Doyle and colleagues[41] demonstrated the promise of this approach in detecting RA-ILD. A model composed of clinical factors including demographics and autoantibodies, combined with a biomarker signature composed of MMP-7, PARC, and SP-D, outperformed the clinical signature alone or any of the standalone biomarkers.

The emergence of machine learning has further improved risk prediction and is likely to become an important tool in the diagnosis of CTD-ILD. Machine learning comprises mathematical algorithms that build, train, and self-evaluate iterative models to self-improve predictive power.[66] Kass and colleagues[67] demonstrated the promise of machine-learning in patients with RA, showing that biomarker signatures derived using this method could effectively discriminate ILD in these patients with higher sensitivity and specificity than stand-alone proteins. Although this approach can result in a highly in-sample predictive classifier, overfitting remains an issue and out-of-sample validation is required. Kass and colleagues[67] demonstrated this challenge, showing that the highly predictive diagnostic signatures developed in independent RA cohorts differed greatly, with little overlap in covariates. Qin and colleagues[57] pursued a similar approach in patients with RA, showing

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that 3 machine learning algorithms discriminated ILD with AUC of at least 0.95. These results have yet to be externally validated, however.

BLOOD-BASED PROGNOSTIC BIOMARKERS

As with diagnosis, the use of peripheral blood-based biomarkers holds promise as a prognostic tool in CTD-ILD. The outcomes of progression in CTD-ILD studies have generally been survival, lung function decline including forced vital capacity (FVC) and diffusing capacity of carbon monoxide (DLCO), or a composite end point of these measures (Table 2). With the recent publication of consensus definitions to define progressive pulmonary fibrosis,[68] substantial research is expected in the coming years to optimally define progression in this population.

Clinically approved autoantibodies have been studied in the prognosis of patients with CTD. In a large SSc outcome study, the presence of anti-Scl-70 antibody in patients predicted a faster rate of FVC decline.[31] Conversely, presence of anti-PM/Scl antibodies has been associated with less FVC decline and better survival compared with patients with anti-Scl-70.[69] In patients with anti-Jo or anti-MDA-5 antibody, the concurrent positivity with anti-SSA/Ro portends worse ILD and mortality compared with patients without dual antibodies.[70,71] Patients with IIM with anti-MDA-5 positivity have been well described to have rapidly progressive and fatal ILD among Japanese cohorts, with 33% to 66% experiencing 6-month and antibody positivity portending a 6-fold risk of death.[45–48] However, in predominantly Caucasian cohorts in the United States, patients with ILD with anti-MDA5 did not have the rapidly progressive ILD described in Japanese cohorts.[50]

Several studies of novel biomarkers have also evaluated prognosis in CTD-ILD. KL-6 again is among the best studied across common CTD-ILD subtypes.[59,72–74] Among 82 patients with SSc-ILD in the Genetics versus Environment Scleroderma Outcome Study (GENISOS), higher baseline KL-6 levels were predictive of faster progression, with patients averaging 7% more decline in annualized percent change of FVC when baseline KL-6 was greater than the cutoff value.[75] Chitinase-3-like-1 (YKL-40), C-C motif chemokine ligand 18 (CCL18), and IL-6, along with several other biomarkers previously linked to progression in idiopathic pulmonary fibrosis (IPF), have also been shown to predict worse outcome among patients with CTD-ILD (see Table 2). Like diagnostic biomarker studies, investigators have just begun to harness the power of composite biomarkers in risk prediction. In a multicenter retrospective cohort of Japanese patients with IIM-ILD, Gono and colleagues[76] showed that a prediction model based on anti-MDA-5 status, C-reactive protein level, and KL-6 level differentiated survival more effectively than anti-MDA-5 antibody testing alone. In the tocilizumab phase 3 trial, elevated acute phase reactants, as an entry criterion, were associated with marked decline in FVC during 1 year in the placebo group in those with ILD (257 mL in placebo group vs 6.5 mL in active group).[22]

Our group recently completed the first proteomic analysis of patients with non-IPF ILD, which included 245 patients with CTD-ILD across 3 centers.[77] Relative plasma concentration of 368 biomarkers was determined using a medium-throughput proteomic platform, 31 of which were found to be associated with near-term ILD progression, defined

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as death, lung transplant, or 10% or greater relative FVC decline within 1 year of blood draw. Of these 31 proteins identified in the derivation cohort, 17 maintained association in an independent validation cohort, with consistent outcome association in each of the ILD subgroups assessed. Using machine learning, we then derived a 12-analyte proteomic signature, which discriminated 1-year ILD progression with good sensitivity and negative predictive value across cohorts, suggesting this tool could effectively identify patients at low risk of ILD progression, justifying a conservative strategy in this population. Notably, those with a low-risk proteomic signature experienced an increase in FVC over 1 year, whereas those with a high-risk signature experienced an FVC loss of 227 mL, which mirrored that of placebo-treated patients from IPF clinical trials[78,79] (Fig. 1). Prospective validation of these findings could result in a clinically actionable biomarker to inform clinical decision making in patients with CTD-ILD and other fibrosing ILDs.

HIGH-RESOLUTION COMPUTED TOMOGRAPHY: CONNECTIVE TISSUE DISEASE-INTERSTITIAL LUNG DISEASE DIAGNOSIS AND PROGNOSIS

HRCT is a crucial component of the diagnostic evaluation of CTD-ILD, with thin slices and reconstruction algorithms tailored to the detection of patterns and distributions of interstitial, parenchymal, and airway abnormalities.[80,81] With the poor sensitivity of chest radiography [82,83] and PFT,[25,27] reliance on these measures to diagnose or rule out ILD in a patient with CTD is inadequate. An interdisciplinary expert consensus panel recently recommended that all patients with SSc be screened with HRCT at baseline, and the authors recommend a similar approach for all CTDs in which ILD commonly manifests. Major educational efforts have been undertaken to promote HRCT screening,[84,85] which will be critical to reduce the well-described diagnostic delays that occur in patients with ILD.[86,87]

With HRCT as our best tool for diagnosing ILD in patients with CTD, several groups have also investigated the role of HRCT as a predictor of CTD-ILD outcome. Extent of fibrotic disease on baseline HRCT, including the extent of reticulation, traction bronchiectasis, and honeycombing, is consistently associated with worse survival across CTD-ILD subtypes.[40,88–93] Walsh and colleagues[94] evaluated HRCTs and pulmonary function variables in 168 patients with CTD-ILD, and identified severity of traction bronchiectasis and extent of honeycombing as indices independently predictive of mortality. In patients with SSc-ILD, a higher extent of fibrosis on baseline HRCT was associated with subsequent lung function decline in the placebo group of the Scleroderma Lung Study.[95] A cutoff of 20% fibrotic extent has been proposed as an optimal predictor of mortality in patients with SSc-ILD, forming the basis of the Goh simple staging system for mortality risk.[96,97] It should be noted that by combining HRCT and PFTs in this staging system by using an FVC threshold when HRCT fibrotic extent was indeterminate, the risk prediction considerably improved beyond either HRCT or PFTs alone.

An additional question has been the role of the HRCT pattern of abnormality. There are many patterns described in CTD-ILD, with the 2 important patterns being that of nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP).[98] The radiologic pattern of NSIP, characterized by bibasilar ground-glass opacities, is well recognized

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in patients with CTD-ILD, and is the most common pattern in patients with SSc-ILD and IIM-ILD.[99,100] In contrast, the radiologic pattern of UIP, with bibasilar reticulation and fibrotic architectural distortion, is most commonly observed among patients with RA-ILD.[40,101,102] The radiologic pattern of UIP is classically associated with IPF, the prototypic ILD characterized by poor prognosis, so naturally the question of whether UIP portends worse prognosis in the setting of non-IPF ILD arises. Several groups have found that a UIP pattern is associated with worse survival in patients with CTD-ILD.[40,88,94,103–106] In a cohort of patients with RA-ILD evaluated at National Jewish Health, Solomon and colleagues[107] also found that patients with UIP pattern had a shorter survival time than those with radiologic NSIP. However, in all multivariate Cox models that included key clinical variables or pulmonary physiology, baseline HRCT pattern was no longer a predictor of survival.[107] Rather, baseline FVC and evidence of FVC decline were independent predictors of worse survival. It remains unclear what additional information UIP pattern on HRCT provides, other than being a by-product of pulmonary fibrosis.

Although HRCT in cross-section may predict outcome, serial acquisition of HRCT may provide more clues about disease trajectory. Patients with SSc who had an increase in fibrotic extent on serial HRCT were more likely to experience further fibrotic progression and lung function decline[92]; this is congruent with our findings that worsening fibrosis extent on HRCT is a poor prognostic sign, with patients experiencing near-term FVC decline and a 2-fold increased risk of mortality after showing radiologic progression.[108,109] However, the radiation exposure of serial HRCT remains a consideration, especially among younger individuals with CTD-ILD, and in particular women due to radiation exposure to the breast tissue.

RADIOMICS AND QUANTITATIVE HIGH-RESOLUTION COMPUTED TOMOGRAPHY

The widespread use of visual HRCT assessment as biomarker in patients with CTD-ILD is currently limited due to low interobserver agreement.[110,111] Although semiquantitative scoring classifications have been proposed to judge the extent of fibrosis, discrepancy has been observed between radiologists' scoring, even after training.[97] Furthermore, the best studied candidate predictors of progression on HRCT—fibrotic extent and the UIP pattern—are both by-products of progressive pulmonary fibrosis. Tools that more effectively predict CTD-ILD progression before progression has occurred are more likely to be of clinical value.

One possible strategy to obviate interobserver variation is computer-based radiomic analysis. Radiomics is an emerging field that converts medical images into high-dimensional quantitative data and has high potential to serve as a novel avenue for ILD subphenotyping and outcome prediction. Quantification of HRCT features, density, and texture, along with algorithms developed by machine learning, has the potential to not only standardize the role of HRCT interpretation but also detect diagnostic and prognostic data not visually detectable by humans. Deep learning, which is a unique machine learning algorithm that incorporates

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multiple layers of learning architecture to create increasingly complex schema to improve autonomously, has emerged as a useful approach to modeling radiomic data.

In 2016, Anthimopoulos and colleagues[112] trained and tested a deep learning algorithm using HRCT examinations in 120 patients to detect ground-glass opacity, reticulation, consolidation, micronodules, and honeycombing, which had been manually labeled by 2 thoracic radiologists. This deep learning algorithm had an accuracy of 85% in classifying these imaging features. Using a similar approach, Kim and colleagues[113] employed a deep learning algorithm that achieved 95% accuracy for classifying these features of interest on HRCT images of patients with ILD. Advancing beyond individual HRCT features and toward HRCT pattern recognition, Walsh and colleagues[114] used a deep learning algorithm to detect classification of UIP based on the 2011 consensus guidelines. Their algorithm showed an accuracy of 76.4% for the classification of UIP in the derivation cohort, and an accuracy of 73.3% in an external validation cohort. Although promising, these investigations continue to rely on visual assessment as the gold standard, limiting their use to what can be detected by the human eye.

Evaluation of HRCT using density histogram analysis evaluates the lung according to simple density characteristics, deriving metrics of histogram skewness and kurtosis. Although Ash and colleagues[115] demonstrated a 3-fold increased risk of death or transplant in patients with IPF with higher mean lung density, the addition of quantitative HRCT density did not significantly augment prognostication beyond visual assessment of baseline lung fibrosis.[116] A more complex approach is texture-based analysis, which incorporates morphologic features. A quantitative lung fibrosis score can be generated using automated computer-aided diagnosis systems developed for assessing ILD using texture features. In patients with IPF, this texture-based score correlated with longitudinal FVC change, whereas HRCT density alone did not.[117] Kim and colleagues[118] applied this score to the HRCT examinations of 129 patients with SSc-ILD and showed good accuracy for detecting fibrosis when compared with visual assessment. Oh and colleagues[119] applied the quantitative lung fibrosis score to HRCT images of 144 patients with RA-ILD, and found that it predicted 5-year mortality. At a cutoff of 12% of total lung volume, higher quantitative lung fibrosis scores predicted survival similar to patients with IPF.[119] In addition, use of texture-based radiomic features in cluster analysis can predict different disease stages with moderate sensitivity and excellent specificity in patients with SSc-ILD.[120] In a recent study of 90 patients with SSc, texture-based radiomic features were extracted and cluster analysis performed to reveal 2 distinct patient clusters. Despite similar scores on the Goh simple staging system between clusters (based on visual assessment of HRCT and FVC), one texture-based radiomic cluster had significantly more impaired lung function. A radiomic risk score predicted faster disease progression and worse survival.[121]

For well over a decade, advances in CT scanner acquisition speed have led to the increase of volumetric HRCT scans, which can be acquired in a single breath-hold of 5 to 10 seconds, which bypasses the traditional issue of interspaced HRCT images with gaps of 1 cm or more between images, and allows for more precise evaluation of patterns such as honeycombing. Computer Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER) is a tool that employs volumetric structural and textural analysis of the lung,

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trained to label and measure volumetric HRCT data as normal, ground glass, reticulation, low-attenuation, honeycombing, and vessel-related structures.[122] Jacob and colleagues[119] applied this tool in a study of 203 patients with CTD-ILD, with the CALIPER variable of vessel-related structure volume being the one most strongly associated with mortality (Fig. 2).[123] This same CALIPER variable has been shown to best predict mortality in patients with IPF.[122,124,125] Given that IPF mortality is worse than CTD-ILD mortality, Chung and colleagues[126] postulated that CALIPER may be able to differentiate CTD-ILD from IPF in the setting of a UIP pattern, finding that the vessel-related structure volume was greater in patients with IPF than patients with CTD-ILD, potentially showing its promise as a marker to differentiate CTD-ILD from IPF.[126]

CALIPER variables can be integrated into current classification schemes for prognosis in CTD-ILD. The CALIPER algorithm allows unbiased identification of CTD-ILD patient phenotypes using automated stratification. The substitution of this automated CALIPER model in place of pulmonary function variables in the ILD-GAP score, a validated staging score in ILD, resulted in a more sensitive predictor of 1- and 2-year mortality.[123] In addition, Jacob and colleagues[127] conducted a study of 157 patients with RA-ILD to compare 3 prediction models based on HRCT: the Goh scleroderma simple staging system, the Fleischner Society IPF diagnostic guidelines, and CALIPER scores of vessel-related structures. Although all 3 models strongly predicted outcome, combining the CALIPER vessel-related structures threshold with the visual scoring from the Goh and Fleischner systems improved outcome modeling, predicting 4-year survival indistinguishable from a comparator group of patients with IPF.[127]

Although early, these studies are promising and suggest that radiomics has high potential to inform clinical decision making once widespread automation of one or more of these algorithms becomes possible. With machine learning, data extracted from quantitative HRCT carries the potential to develop new imaging biomarkers not discernible by humans and bypass the inherent problems of visual assessment. Radiomics is likely to provide complementary diagnostic and prognostic information with exciting potential for outcome prediction.

UNMET RESEARCH NEEDS AND STRATEGIES FOR BIOMARKER OPTIMIZATION

Although there has been impressive progress in biomarker discovery, unmet needs remain. At present, there are few biomarkers reliably predicting the presence of ILD in patients with CTD, and even fewer have been validated to predict CTD-ILD progression before it occurs. Although we reviewed emerging blood-based and HRCT biomarkers, none have been incorporated into clinical practice, reflecting modest test performance characteristics for most; this stems in large part from a paucity of validation testing for most biomarkers, because most candidate studies have been performed in retrospective single-center studies. Validation of these promising biomarkers in external cohorts will be key in biomarker investigation going forward. Equally important will be the assessment of test performance characteristics, which will allow clinicians to weigh the clinical utility of any biomarker

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advanced for clinical implementation. Furthermore, before clinical application, it will be essential that well-designed, prospective, multicenter studies be conducted.

As multicohort investigations become standard in biomarker investigation, it will be essential to ensure that the outcomes chosen in future studies are uniform and well-defined, particularly in studies of prognostic biomarkers. Understandably, survival should remain to be an important outcome. However, near-term progression should also be prioritized in future biomarker investigation. Near-term lung function decline has clinical implications, because patients may necessitate earlier intervention, as well as implications for drug development in clinical trials. At present, large sample sizes are required to ensure adequate power to detect differences in lung function decline, so the ability to predict near-term progression would allow clinical trial enrichment and more efficient recruitment.

Last, there is increased potential when modeling biomarkers in aggregate. The combination of multiple biomarkers across multiple modalities, perhaps combining clinical, blood-based, and radiomic biomarkers, holds high potential in CTD-ILD risk prediction. Machine learning can seamlessly tackle increasingly large datasets and the rapidly growing number of candidate biomarkers. After deriving and validating candidate signatures retrospectively, it will be necessary to quantify identified biomarkers and to prospectively validate specific thresholds that define individual risk most precisely.

SUMMARY

A number of biomarkers have been proved to be informative in patients with CTD-ILD, derived from blood-based and HRCT data. The development of large blood-based platforms, the refinement of radiomic algorithms, and the use of machine learning have shown early promise in the diagnosis and prognosis of CTD-ILD. A rapid expansion of investigation with aggregate biomarkers is expected in the coming years, making precision medicine closer to reality and improving outcomes in patients with CTD-ILD.

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KEY POINTS

- Blood-based biomarkers that reflect lung epithelial cell dysfunction, aberrant immunity, and abnormal lung remodeling may discriminate the presence of interstitial lung disease in patients with connective tissue diseases.
- High-resolution computed tomography (HRCT) is the current best diagnostic tool for ILD and may have prognostic value in CTD-ILD.
- Texture-based and volumetric HRCT analysis show promise as prognostic biomarkers in CTD-ILD.
- Composite biomarkers improve risk prediction compared with stand-alone biomarkers, showing high promise in the diagnosis and prognosis of patients with connective tissue-associated interstitial lung disease.
- The combination of large blood-based platforms, radiomic algorithms, and use of machine learning is expected to advance the study of CTD-ILD in coming years.

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CLINICS CARE POINTS

- HRCT is the screening and diagnostic tool of choice for patients with CTDs. When screening for ILD, PFT and chest radiography are insufficient and an HRCT should be ordered.
- There are no single blood-based biomarkers validated for the diagnosis or prognosis of CTD-associated ILD. When caring for patients with CTD-ILD, making clinical decisions based on single laboratory tests should be avoided.
- The best prognostic radiographic markers are extent of fibrosis and evidence of progression on serial HRCT. When a patient has a large extent of fibrosis or shows worsening fibrosis on HRCT, the likelihood of future ILD progression is high.

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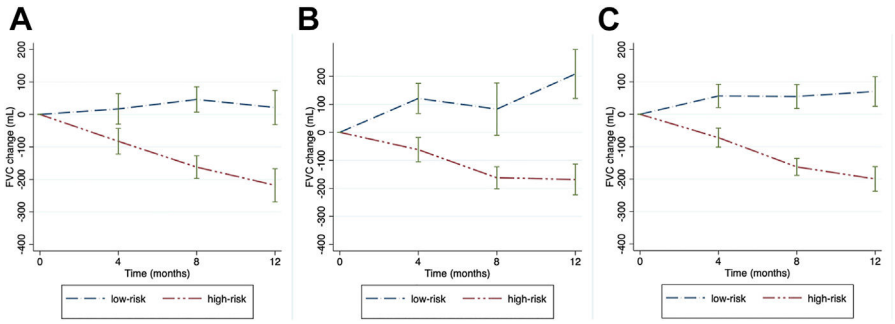

Fig. 1.

Longitudinal plots comparing 1-year change in forced vital capacity between patients with high-risk and low-risk proteomic signature in the derivation (*A*), validation (*B*), and combined cohorts (*C*). (*Reprinted with permission from* Elsevier. The Lancet Respiratory Medicine, June 2022, 10 (6), 593–602.)

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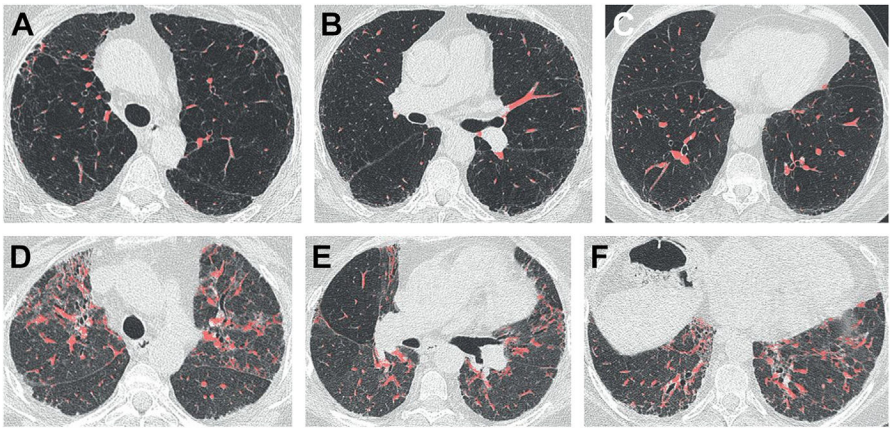

Fig. 2.

Axial HRCT image color maps demonstrating CALIPER-derived vessel-related structures (VRS; red). VRS represent pulmonary arteries and veins (excluding hilar vessels) and connected tubular structures, the latter primarily reflecting adjoining regions of fibrosis. (*A–C*) Axial sections in a 71-year-old female 30-pack-year exsmoker with upper lobe emphysema and fibrosis visible in the lower lobes (VRS 2.1%); (*D–F*) axial sections in a 62-year-old female never smoker with upper lobe-predominant fibrosis (VRS 7.0%). Nonvascular region captures in the VRS signal are visible in the upper lobes (*D*) and adjacent to the right hemidiaphragm (*F*). (Reproduced with permission of the © ERS 2022: European Respiratory Journal 53 (1) 1800869; https://doi.org/10.1183/13993003.00869-2018 Published 3 January 2019.)

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Table 1

Novel blood-based diagnostic CTD-ILD biomarkers

Biomarker	Reference(s)	Diagnostic Test Performance (CTD-ILD from CTD Without ILD)
Lung epithelial cell dysfunction		
CA 125	RA[128]	RA[128]: cutoff 35 U/mL, sens 60.71%, spec 79.52%, AUC 0.78
CC16	SSc[54]	SSc[54]: cutoff 46.0 ng/mL, sens 51.8%, spec 88.8%, AUC 0.76
CCL18	SSc[129]	
E-Selectin	SSc[130,131] RA[132] IIM & SSc[133]	
ET-1	SSc[130]	
ICAM-1	SSc[134]	
KL-6	SSc[52–54,135,136] RA[55,56,137,57] IIM[62,58,138,139,60,140] SS[141] CTD[59]	SSc[52]: cutoff 602 U/mL, sens 73%, spec 70% SSc[53]: cutoff 500 U/mL, sens 78.8%, spec 90.0%, AUC 0.90 SSc[54]: cutoff 302 U/mL, sens 85.5%, spec 85.3%, AUC 0.89 RA[55]: cutoff 277.5 U/mL, sens 86.7%, spec 88%, AUC 0.88 RA[56]: cutoff 399 U/mL, sens 85.71%, spec 90.91%, AUC 0.92 RA[57]: AUC 0.81 IIM[58]: cutoff 437 U/mL, sens 87%, spec 96%, AUC 0.97 CTD[59]: cutoff 275.1 U/mL, sens 79.4%, spec 79.9%, AUC 0.86 IIM[60]: cutoff 549 U/mL, sens 83%, spec 100%
SP-A	SSc[63] IIM[62]	SSc[63]: Cutoff 43.8 ng/mL, sens 33%, spec 100% IIM[62]: Cutoff 39.5 ng/mL, PPV = 70%
SP-D	SSc[52–54] RA[41,137] IIM[62]	SSc[52]: cutoff 62.2 ng/mL, sens 68%, spec 70% SSc[53]: cutoff 90 ng/mL, sens 89.4%, spec 80.0%, AUC 0.983 Ssc[54]: cutoff 91.0 ng/mL, sens 71.4%, spec 77.2%, AUC 0.72 SSc: cutoff 110 ng/mL, sens 77%, spec 83% RA[41]: AUC 0.75 RA[41]: AUC 0.91
VEGF	SSc[130]	
Aberrant immunity		
CCL2	IIM[62,142] SSc[61]	
CX3CL1	SSc[143]	
CXCL10/IP-10	SSc[144,145] RA[146] IIM[147,142] CTD[148]	
CXCL11	CTD[148] IIM[142]	
CXCL12		
CXCL13	SS[149]	
CXCL16	SSc[150]	
CXCL4	SSc[151]	
CXCL9/MIG	SSc[67] CTD[148]	
IL-04	SSc[152]	

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Biomarker	Reference(s)	Diagnostic Test Performance (CTD-ILD from CTD Without ILD)
IL-06	SS[64] IIM[147]	SS[64]: cutoff 7.109 pg/mL, sens 90.88%, spec 62.75%, AUC 0.67
IL-08	SS[64,153] IIM[147]	SS[64]: cutoff 20.094 pg/mL, sens 90.9%, spec 62.8%, AUC 0.71
IL-10	SS[64]	SS[64]: cutoff 5.162 pg/mL, sens 87.54%, spec 78.63%, AUC 0.89
IL-15		
IL-23	SSc[154]	
IL-33	SSc[155]	
IL-35	SSc[156]	
PARC	SSc[135] RA[41]	RA[41]: AUC 0.80 RA[41]: AUC 0.70
TNF-α	SS[64] IIM[147]	SS[64]: cutoff 9.116 pg/mL, sens 80.6%, spec 73.2%, AUC 0.73
Wnt5a	RA[65]	RA[65]: cutoff 4.49, sens 55.6%, spec 4.9%, AUC 0.75
Abnormal lung remodeling		
MMP-7	SSc[157,158] RA[41,146,137] IIM[159]	RA[41]: AUC 0.86, RA[41]: AUC 0.83
MMP-12	SSc[160]	
TIMP-1	SSc[161]	
CCN2/CTGF	RA[162] SSc[163]	
GDF-15	SSc[164–166]	
YKL-40	SSc[167]	

Abbreviations: CC16, club cell secreted protein 16; CCL18, C-C motif chemokine ligand 18; IL, interleukin; MMP, metalloproteinase; PARC, pulmonary and activation-regulated chemokine; sens, sensitivity; spec, specificity; TNF, tumor necrosis factor; YKL-40, chitinase-3-like-1.

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Table 2

Novel blood-based prognostic CTD-ILD biomarkers

Biomarker	Prognostic
	CTD-ILD subtype (reference): outcome of progression
Lung epithelial cell dysfunction	
CA 125	CTD[168]: composite FVC and survival
CC16	SSc[169]: composite FVC and survival
CCL18	SSc[170]: FVC, DLCO, and survival SSc[136]: FVC and radiologic progression
ICAM-1	SSc[134]: FVC
IGFBP-2	SSc[171]: DLCO
KL-6	SSc[75]: FVC SSc[172]: composite FVC, oxygen supplementation, survival IIM[72]: survival SS[73]: survival CTD[74]: survival CTD[59]: HRCT progression
SP-D	CTD[168]: composite (lung function and survival) SSc[173]: FVC
Aberrant immunity	
CCL2	SSc[174]: FVC, survival IIM[142]: survival
CX3CL1	SSc[143]: composite survival, FVC, and HRCT
CXCL10/IP-10	IIM[142]: survival
CXCL11	IIM[142]: survival
CXCL12	CTD[168]: composite FVC and survival
CXCL13	CTD[168]: composite FVC and survival
CXCL4	SSc[175]: FVC SSc[151]: DLCO
IL-06	SSc[176]: FVC, DLCO, survival IIM[177]: survival CTD[178]: survival
IL-08	IIM[147]: survival
IL-10	SSc[174]: FVC IIM[179]: survival
IL-15	IIM[179]: survival IIM[180]: exacerbation, survival
Neopterin	IIM[181]: survival
Abnormal lung remodeling	
MMP-7	SSc[158]: survival IIM[159]: survival
YKL-40	CTD[168]: composite FVC and survival IIM[182]: survival IIM[183]: survival