Quantitative Computed Tomography in Idiopathic Pulmonary Fibrosis: Is It Time to Act?

Quantification of lung abnormalities on high-resolution computed tomography (HRCT) images in patients with idiopathic pulmonary fibrosis (IPF) has been a focus of research for more than 20 years (1). During this time, we have moved from visual scoring to computerized tools of increasing complexity (also known as quantitative CT [qCT]), with the most recent studies using deep learning technology. The progress made has improved the prognostic value of the HRCT features quantified, while at the same time overcoming the well-documented limits of visual scoring, such as interobserver variability and low reproducibility (2). These features also correlate with pulmonary function tests both at a single time point and during follow-up. Another advantage of these computerized tools is their theoretical ability to identify and quantify prognostic imaging biomarkers, which are inaccessible to human eyes (3). Recent publications also show that these technologies generalize well across different HRCT acquisition parameters, in contrast to early qCT, which often required specific and strict protocols to produce robust results (4).

The paper by Thillai and colleagues (pp. 465–472) in this issue of the *Journal* represents a significant step forward (5). Two key strengths of the study deserve emphasis. First, the deep learning models proposed were tested on the Prospective Observation of Fibrosis in the Lung Clinical Endpoints (PROFILE) dataset, a large prospective registry of well-characterized patients with IPF. Second, PROFILE included follow-up imaging, which allowed a prognostic assessment of changes in HRCT features over time. Large, well-curated longitudinal imaging datasets in fibrotic lung disease are relatively uncommon and are therefore valuable test beds for qCT. Four key HRCT features were quantified, namely, pulmonary vessel volume, airway volume, fibrosis extent, and lung volume. Lung volume was the only metric showing a strong correlation with FVC. Each baseline feature showed a significant association with reduced 5-year survival, even when adjusted for baseline disease severity. All the features, except airway volume, correlated with progression-free survival, and the correlation was maintained when the model was adjusted for baseline GAP (gender, age, physiology) index. In a subgroup of patients with follow-up HRCT, an increased risk of death correlated with changes in lung volume and fibrosis extent.

The models developed by Thillai and colleagues have several advantages, including the ability to provide rapid quantitative data and accurate results regardless of the technical acquisition parameters of the HRCT, with high segmentation success rate. Notably, in this paper, lung volume was the only variable associated with FVC, despite the other features showing prognostic value, indicating that these variables represent important, yet distinct, surrogate measures of mortality.

Interestingly the pulmonary vessel volume captured prognostic signal at baseline but not in the longitudinal analysis. This is in contrast to the results of studies performed with Computer-aided Lung Informatics for Pathology Evaluation Ratings (CALIPER) that demonstrated that longitudinal changes in vessel volume are highly prognostic (6). The reason for this may be related to the different technical approach used by this model. Vascular-related structure (VRS), a feature calculated by CALIPER and likely to represent vessel volume, predominantly quantifies pulmonary arteries and veins but also captures connected tubular structures, mainly representing adjoining regions of fibrosis, which are misclassified by the software. Changes over time of these misclassified areas of fibrosis could explain the collinearity between CALIPER-derived VRS and total extent of lung fibrosis and in principle contribute to the prognostic signal captured by VRS in longitudinal follow-up (6).

The model proposed by Thillai and colleagues may be more accurate for extracting pulmonary vessels while avoiding adjacent fibrotic tissue, which could explain the different behavior of the vascular and fibrosis extent measures, both capturing prognostic signal at baseline but only fibrosis significantly changing at follow-up. Several mechanisms have been proposed to explain the association between an increasing vessel volume and a worse prognosis in patients with IPF, independently from the extent of fibrosis (7). Further studies are needed to better understand how vascular structure change over time in patients with IPF.

In the paper by Thillai and colleagues, no comparison was made between computerized quantification and visual scoring. Although no real visual scoring is possible for airways and vascular quantification, lung volume can be compared with manually derived surrogate measurements, such as lung height, aortosternal distance, and oblique fissure retraction distance, all of which have provided independent information about lung volume loss in IPF (8). There are strands of evidence that suggest that visual scoring of fibrosis may still have some prognostic utility despite the overwhelming evidence that qCT is superior in this role. In a recent study, both visual and automated quantification of fibrosis were independently associated with mortality, suggesting that we are not ready to completely dispense with human input; each approach may capture areas of fibrosis that are overlooked or misclassified by the other (9, 10). Performing a visual quantification of fibrosis in the current study may have provided additional prognostic information (10).

Historically, visual scoring of HRCT features has been overlooked as a direct substitute for lung function in clinical trials and in routine clinical practice. However, more than two decades of qCT research has consistently shown how computerized HRCT analysis provides reliable, sensitive, and objective measures of disease severity in fibrotic lung disease. The current study by Thillai and colleagues, reported in a well-characterized prospective IPF registry, represents a major step forward in the development of deep learning–based qCT. ■

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Bystander No More: Small Airway Involvement in Idiopathic Pulmonary Fibrosis

In the current paradigm of idiopathic pulmonary fibrosis (IPF) pathogenesis, repetitive injury to alveolar epithelial cells underlies disease development (1). Structural airway abnormalities, such as traction bronchiectasis, have traditionally been viewed as a consequence of fibrosis rather than its primary driver. Accordingly, the usual interstitial pneumonia (UIP) pattern that defines IPF in the appropriate clinical setting is characterized by interstitial fibrosis in a subpleural/paraseptal distribution, whereas substantial airway involvement typically suggests alternative diagnoses (2, 3).

However, recent studies have challenged this paradigm. A gain-of-function variant in the promoter region of *MUC5B*, which increases mucin production of the bronchial epithelium, has been recognized as one of the strongest risk factors for IPF (4). Single-cell transcriptomics have demonstrated dramatic changes in the expression profile of epithelial cell populations in the distal human lung, including identification of an increased proportion of airway epithelial cells, a decline in alveolar epithelial cells, and the presence of aberrant basaloid cells (5). Micro–computed tomography (micro-CT) has revealed a reduction in terminal bronchioles and alterations in airway stereology in explanted IPF lungs, even in regions of minimal fibrosis (6, 7). These intriguing studies implicate structural and functional abnormalities of the small airways in the development of IPF. However, understanding the exact contribution of small airway disease to IPF has been challenging because of the lack of disease models that recapitulate human pathobiology and the need for more sensitive tools for studying early-stage human disease.

In this issue of the *Journal*, two studies leverage modern imaging and genomic techniques to put small airways front and center and advance our understanding of IPF. Berigei and colleagues (pp. 473–483) use endobronchial optical coherence tomography (EB-OCT) to characterize and quantify small airways in adults with early IPF undergoing diagnostic surgical lung biopsy (8). EB-OCT is an emerging *in vivo* method of microscopic imaging demonstrated to have high correlation with histopathology in ILD (9–11). By sampling multiple sites within each subject without the need for biopsy, the authors take advantage of the heterogeneous nature of fibrosis in IPF to evaluate airways at varying stages of disease progression, despite a relatively small number of participants. Imaging sites are classified as more or less affected on the basis of how many criteria were met for microscopic UIP (9, 10, 12). The authors find that there is significant loss of small airways in both IPF-affected (i.e., those meeting all criteria for microscopic UIP) and less affected areas of the lung. This is consistent with prior findings from the micro-CT studies, confirming them *in vivo* and extending them to patients with early disease.

The authors also find that in sites affected by IPF, small airways are larger and more distorted. Interestingly, in less affected sites, these stereology metrics are indistinguishable from controls, suggesting that changes in airway shape and size may be a consequence of fibrosis,

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