Archivos de Bronconeumología xxx (xxxx) xxx–xxx

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Sociedad Española de Neumología y Cirugía Torácica

ARCHIVOS DE
Bronconeumología

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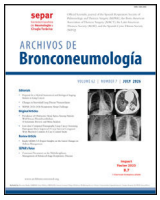

Scientific Letter

Predictive CT Biomarkers for Pulmonary Fibrosis: New Model and Case Example of Pathologic Score

To the Director,

Idiopathic pulmonary fibrosis (IPF) and other forms of progressive pulmonary fibrosis (PPF) are characterized by relentless fibrotic remodeling of the lung parenchyma and increased mortality [1]. Despite the availability of antifibrotic therapies, disease trajectories remain highly variable and difficult to predict at an individual level. Recent advances in machine learning and quantitative imaging offer promise in objective and reproducible metrics of disease presence and quantification in addition to predicting progression on serial high-resolution computed tomography (HRCT) scans [2,3]. However, quantitative biomarkers that predict parenchymal regions of progression or assess the overall risk of future fibrosis progression from a single baseline scan are lacking. The objective of this letter is to summarize the design of an AI model for HRCT-derived prediction in interstitial lung diseases (ILD) and to present a pilot study of two patients with ILD that underwent lung transplantation to which we retrospectively applied our Single Time Point (STP) model. We hypothesized that regions of lung to demonstrate future progressive fibrosis on HRCT by the model would align with fibrosis severity seen on subsequent pathologic specimens.

The STP model was previously developed using HRCT images from a training cohort of 71 IPF patients [434 regions of interest (ROIs)] and tested on 122 IPF patients (549 ROIs) [4,5]. The ROIs of reference truth were segmented by an expert thoracic radiologist based on changes observed between baseline and 6–12-month follow-up HRCT scans (Fig. 1A). The key aspect of the study design was segmenting ROIs at baseline HRCT scan to train prediction of future disease stability or progression (IRB#18-001080). ROIs were labeled as expected to be stable (STP-) or expected to worsen in the next 6–12 months (STP+). Quantum particle swarm optimization (QPSO) and random-forest were used to select important radiomic features and to fit a global-best classifier using 5-fold cross-validation within the training data (Fig. 1A). Model performance in the test set was 70% sensitivity, 70% specificity, and 70% accuracy [4]. The STP model was designed to be integrated with a quantitative ILD system that includes six steps: (a) lung and lobe segmentation, (b) adaptive denoising, (c) grid-sampling, (d) calculation of important radiomic features from denoised CT images, (e) model classification, and (f) calculation of the proportion of classified voxels relative to the total voxel count. The STP score is the proportion of STP-positive (STP+) regions [5]. The output of scores from the ILD system are: QLF (Quantitative Lung Fibrosis): fibrotic reticulation, QGG (Quantitative Ground-Glass): ground-glass patterns as indicator of inflammatory or early fibrotic features, QNL (Quantitative Normal Lung Patterns): normal lung patterns (Fig. 1B) [6]. Fig. 1 illustrates the development of the STP model.

Of the four patients enrolled in a fibroblast activation protein immunohistochemistry (FAPI PET) exploratory trial (IRB#21-000678, NCT05365802) and who underwent lung transplant with available preoperative imaging at least 6 months apart, two (diagnosed with IPF and fibrotic NSIP) subjects had available gross pathology maps that we used for spatial matching of the regions between HRCT and tissue samples [7]. Formalin-fixed, paraffin-embedded lung sections were stained with hematoxylin and eosin and FAPI and scanned to generate digital slides. On these digitally scanned slides, percentages of FAP-positive areas, which represent regions of fibrosis including fibroblastic foci; and honeycomb changes were measured using QuPath (open-source software, https://qupath.github.io) [8]. Pathological extent of fibrosis was expressed in a proportion of fibrotic area to parenchyma tissue ranging 0–100%. Nineteen CT-matched slide pairs were suitable for analysis. ROIs identified on pathology specimens were matched to pre-transplant HRCT images and segmented on the sagittal HRCT slices to maintain consistent orientation, corresponding to the parasagittal plane along which the explanted lung was sectioned from the hilum. Quantitative HRCT scores of 19 radiologic-pathologic matched locations were extracted. Associations between quantitative HRCT scores and pathologic scores were tested using mixed-effects models where the pathologic fibrosis extent was the independent outcome, the quantitative HRCT score was entered as a fixed effect, and subjects included as random effects to encounter for subject variability.

Fig. 2 demonstrates the extent to which severity of fibrosis identified by quantitative imaging from HRCT images acquired 7 months prior to lung transplant, STP positivity, and FAPI-PET avidity correlate with pathologic extent of fibrosis score. STP scores were close to the extent of fibrosis on histopathology, compared with QLF scores from HRCT (Fig. 2G).

We correlated quantitative radiologic scores from HRCT images with the scores from pathologic specimens in ILD patients. Mean extent of fibrosis on histopathology was 71.1% (SD 21.7%; range: 41.5–99.5%) from 19 regions. The corresponding HRCT ROIs acquired 7–14 months pre-transplant showed mean QLF of 37.9% (SD 40.4%) and STP score of 56.8% (SD 18.1%). Differences in means were −29.8% for QLF and −11.1% for STP compared with the extent of fibrosis on histopathology, indicating that STP scores were numerically close to the extent of fibrosis. Statistical modeling demonstrated that the extent of fibrosis on histopathology was significantly associated with STP HRCT scores ($p = 0.012$; slope = 0.64) and with QLF alone ($p < 0.001$; slope = 0.36), suggesting that radio-

https://doi.org/10.1016/j.arbres.2026.08.010
0300-2896/© 2026 Published by Elsevier España, S.L.U. on behalf of SEPAR.

Please cite this article as: G.H.J. Kim, J.W. Song, S.S. Weigt et al., Predictive CT Biomarkers for Pulmonary Fibrosis: New Model and Case Example of Pathologic Score, Archivos de Bronconeumología, https://doi.org/10.1016/j.arbres.2026.08.010

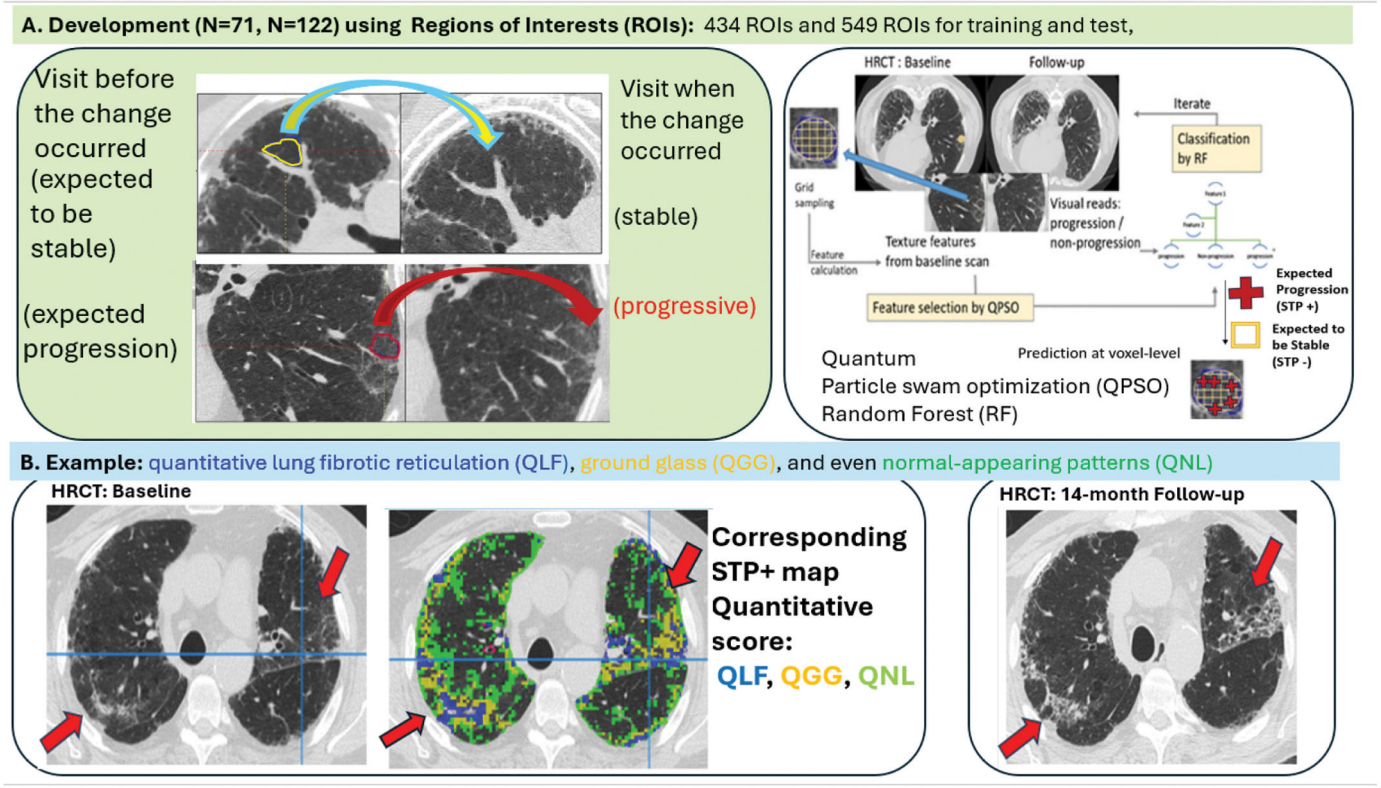

Fig. 1. Schema of single time point prediction (STP) algorithm and pipeline. (A) Development: study design of flow chart and graphical illustration of the small patches of ROI. ROIs were labeled as expected to be stable (STP−) or progressive (STP+). For expected to be progressive ROI area (STP+), ground glass pattern at baseline evolved to a fibrotic reticular pattern in the 1-year follow-up scan (left). The model of STP classier consists of quantum particle swarm optimization (QPSO) and random-forest (RF) were used to select important radiomic features and to classify STP+ area within ROI (right). (B) STP map at baseline predicting disease progression in patient with IPF: Three axial HRCT images of a patient with IPF are shown to illustrate voxel-level prediction of disease progression using STP. Baseline HRCT image demonstrates reticulation and early fibrosis in bilateral lower lobes. Corresponding STP map at baseline: voxels predicted to progress (STP+) are color-coded—blue indicating fibrotic areas, yellow for ground-glass opacities, and green for normal lung patterns. Follow-up HRCT after 14 months shows radiological progression consistent with baseline STP predictions. Red arrows highlight areas of interest where baseline STP-positive regions correspond to subsequent fibrotic progression (right). *Abbreviations*: HRCT: high-resolution computed tomography; ROI: region of interest; PSO: particle swarm optimization; QLF: quantitative lung fibrosis; QGG: quantitative groundglass; QHC: quantitative honeycomb; QNL: quantitative normal pattern; STP: single time point prediction (+).

graphic fibrosis closely reflects underlying tissue remodeling. QGG trended negatively with fibrosis extent ($p = 0.11$; slope = −0.24), aligning with its characterization as an inflammatory, potentially reversible component of ILD.

Monitoring ILD subjects using quantitative scores can be beneficial [9]. In this radiologic-pathologic correlation, regions with high QLF scores corresponded to high pathological fibrosis extent, particularly in the middle and lower lobes. Interestingly, regions in the upper lungs that showed relatively low fibrotic patterns on HRCT—especially in peripheral areas— had high STP imaging score with ground glass or normal appearing patterns. These regions matched pathological fibrosis scores of the corresponding regions (Fig. 2).

While this pilot study provides some evidence that further study of the STP model is merited with the recruitment of large cohorts of patients to which the model can be applied, firm conclusions from the current study cannot be drawn. Another limitation is that while the ROIs on the pathological specimens were matched with the available sagittal HRCT section, they may not perfectly match anatomically in terms of the slice thickness or the sizes of analyzed areas. A validated single time point model would help identify patients who may benefit from early intervention and enrich clinical trial populations with patients more likely to progress, to increase the likelihood of detecting therapeutic benefit. Another limitation is that the ROIs on the pathological specimens were matched with the available sagittal location. The ROIs from pathologic specimens and HRCT images may not be perfectly matched anatomically in terms of the slice thickness or the sizes of analyzed areas.

In conclusion, this pilot analysis provides preliminary evidence supporting the biological relevance of CT-based fibrosis and progression scores; Both STP and QLF scores—derived from machine learning analysis of a single HRCT scan—correlated positively with histologic fibrosis. These findings should be interpreted cautiously given the study's limitations and require confirmation in a larger population of patients with fibrotic.

Final declaration

Grace Hyun Kim: Received consulting fees from Voiant.

Grace Hyun Kim, Johathan Goldin have issued patents of quantitative ILD score (US-9582880-B2, EP 2916739 B1) and Single timepoint Prediction (US-20220327693-A1).

Grace Hyun Kim participated a Data Safety Monitoring Board of CuroCell.

Grace Hyun Kim, Johathan Goldin, and S Sameul Weigt received grants or contracts from Boehringer Ingelheim and Genentech.

Artificial intelligence involvement

The algorithms of quantitative interstitial lung diseases (QILD) and single timepoint prediction (STP) were developed in part through the support of NIH and Department of Radiology research initiatives at UCLA.

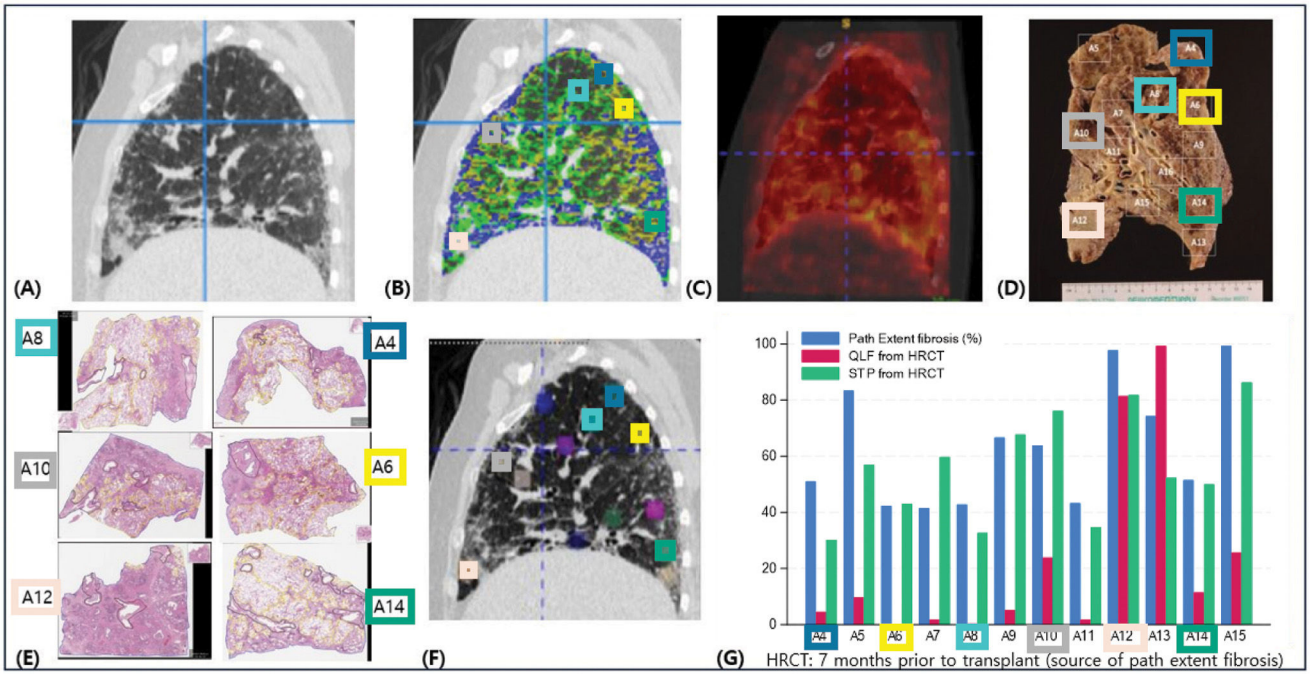

Fig. 2. Association with Rad Path: 68-y-old woman with IPF. (A) Sagittal HRCT 7 months prior to the lung transplant. (B) Visualization of classified areas in a sagittal HRCT image: whole-lung STP score was 57.40%, with QLF and QILD at 21.79% and 48.65%, respectively. Blue, yellow, and green dots indicate STP+ (positive) regions of quantitative lung fibrosis, quantitative ground-glass, and normal lung regions, respectively. (C) Corresponding sagittal fibroblast activation protein inhibitor positron emission tomography (FATPI-PET) image. (D) Ex-transplanted lung – location of parasagittal section 7 mm from hilum with 13 pathologic sample from the regions of FAPI PET activity [7]. Among 13, 12 pathologic samples were usable for QuPath analyses (A16, unusable in path sample). (E) The bright pink areas are collagen fibers. The small white spaces on the hematoxylin and eosin stain correlate with the interstitial fluid-filled spaces. Yellow: non-fibrotic lung, Black: non-parenchymal tissues (large blood vessel, bronchus, lymph node. etc.), Parenchymal tissue = region – nonparenchymal tissue, Fibrotic area = parenchymal tissue – nonfibrotic lung; A4 and A6 are samples from peripheral upper lung with pathologic extent scores of 51% and 42%, respectively. A8, A10, A12, and A14 are from middle and lower lungs with scores of 43%, 64%, 98%, and 51%, respectively. (F) Mapping ROIs: ROI matching of sagittal HRCT plane with path specimens. (G) Bar plots: pathologic extents of fibrosis scores from transplanted lung, and the STP and QLF scores from HRCT 7 months prior to the transplantation were displayed by specimens. *Abbreviations*: STP: single time point prediction; ROI: region of interest; QLF: quantitative lung fibrosis; QILD: quantitative interstitial lung disease.

Funding

Jin Woo Song was supported by grants from the Bio and Medical Technology Development Program (NRF-2022M3A9E4082647) of the National Research Foundation of Korea (NRF), funded by the Ministry of Science and ICT, South Korea. This study was also supported by the National Institute of Health research project (2024ER090500) and the Korea Environment Industry and Technology Institute through Core Technology Development Project for Environmental Diseases Prevention and Management Program funded by the Korea Ministry of Environment (RS-2022-KE002197), South Korea.

S. Sameul Weigt has U.S. Provisional Patent Application No. 63/862,482 entitled BIOMARKER FOR ALLOGRAFT INJURY OR REJECTION. S. Sameul Weigt received honoraria for lectures from Boehringer Ingelheim Pharmaceuticals, Inc. and CareDx. S. Sameul Weigt received grants or contracts Boehringer Ingelheim Pharmaceuticals, CareDx, and Zambon.

Jonathan Goldin is a founder of MedQIA LLC.

Augustine Chung has other-financial or non-financial interest in FDA Orphan Drug Program.

Jeremie Calais received grants or contracts and received payment or Honoria from Novartis, POINT biopharma, Fusion Pharmaceuticals, and Telix Pharmaceuticals. Jeremie Calais received consulting fees from Advancell, Arsenal Bio, Astellas, Bayer, GE Healthcare, Keosys, Mariana Oncology, Nucleus Raiopharma, Pfizer, Radiopharm Theranostics, SOPIE, Blue Earth Diagnostics, Curium Pharma, Coretag, Fibrogen, Janssen Pharmaceuticals, Lantheus, Novartis, Perceptive – Invicro, POINT biopharma, Siemens, Telix. Jeremie Calais participated on a Data Safety Board or Advisory Board of Curium and Novartis.

Elizabeth Volkmann received consulting fees from Boehringer Ingelheim, GSK, AbbVie, and BMS. Elizabeth Volkmann had grants or contracts from Boehringer Ingelheim, Kadmon, Horizon, GSK, Prometheus, Atyr Pharma, and AstraZeneca.

Conflicts of interest

The rest of authors (JK, MH, GAF, VR, PT, JHO, and OA) declare there are no relevant financial conflicts.

Acknowledgments

We thank the UCLA Translational Pathology Core Laboratory for its assistance with whole-slide imaging and Center for Computer Vision and Imaging Biomarkers, Radiological Science with medical imaging analyses.

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