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Research letter

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CT assessment of peripheral traction bronchiolectasis: impact of minimal intensity projection

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To the editor

The Fleischner Society White Paper and the ATS/ERS/JRS/ALAT guidelines recently redefined the computed tomography (CT) scanning patterns of usual interstitial pneumonia (UIP)[1, 2]. Both publications confirmed honeycombing as the cornerstone of UIP pattern diagnosis, and introduced peripheral traction bronchiolectasis (PTB) as a key feature of the new "probable UIP" category. Therefore, improving the distinction between these two features may be critical, especially when the clinical likelihood of IPF is uncertain: a lung biopsy should be discussed for patients with PTB without honeycombing, but is not recommended for patients presenting with clear honeycombing and typical UIP pattern [2].

The Fleischner Society White Paper and the ATS/ERS/JRS/ALAT guidelines both stress the importance of the CT technical parameters for the image acquisition, but only the first publication provides indications for the reading step. It proposes the use of cine mode and multiplanar (MPR) reformations, as well as post-processing with minimum intensity projection (MinIP) to help differentiating honeycombing from peripheral bronchiectasis [1].

We thus evaluated whether the use of MinIP improves inter-reader agreement for the identification of PTB and honeycombing. As a secondary objective, we also tested whether the use of MinIP improves inter-reader agreement for the assessment of CT scanning patterns of UIP, according to the 2018 ATS/ERS/JRS/ALAT guidelines [2].

This prospective study was conducted in 4 reference hospitals for interstitial lung disease in the Paris area, France. Approval was obtained from the Institutional Ethics Committee (CPP Ile-de-France-X, November 2011); all included patients signed an informed consent.

All patients presenting with suspected idiopathic interstitial pneumonia whose cases were discussed for the first time during local multidisciplinary discussions (MDD) from January 2014 to December 2015 were screened for the study. Patients were included if no specific pulmonary diagnosis had been made before the MDD and if a recent (≤3 months) chest CT with contiguous thin sections (≤1.25mm) showing fibrotic features (architectural distortion, traction bronchiectasis/bronchiolectasis, honeycombing) was available. 168 patients were eligible and all agreed to participate in the study. One year after the initial MDD, 16 patients were lost to follow-up; moreover, CT images were missing for 11 patients. These 27 patients were excluded and 141 patients were finally included. The clinical diagnosis established by the second MDD after one year was recorded.

Four thoracic radiologists (including 2 with a specialization in interstitial lung diseases) and 2 pulmonologists (with a specialization in interstitial lung diseases) reviewed the chest CTs. Honeycombing was defined according to the Fleischner Society Glossary [3], and PTB as peripheral bronchiectasis abutting the pleura. The readers participated in a training session before starting their readings. Readers reviewed each case twice on a Picture Archiving and Communication System workstation, using cine mode and MPR only (method 1), and then using additional 3 to 5 mm MinIP post-processing (method 2) during a second session, after a minimal 2-week interval to avoid recall bias. For each session, readers were asked to assess: 1. the presence/absence of PTB and honeycombing in 3 areas (Table 1) and 2. the CT pattern of UIP according to the ATS/ERS/JRS/ALAT guidelines [2].

For the inter-reader analysis, we calculated the Fleiss's Kappa coefficient [4] to estimate agreement between more than two readers and its bootstrapped confidence interval. Agreement were calculated per area and per patient, considering that a patient presented the trait "presence of honeycombing" or "presence of PTB" when at least one area presented the trait. To compare kappa coefficients, we calculated the bootstrapped confidence interval of the difference of kappa between groups and the corresponding p-value. We used the following R packages: the "rel" package (version 1.3-1) and the "boot" package (version 1.3-18). A p-value < 0.05 was taken to represent statistical significance. Statistical analysis was performed with R Version 3.3.2.

Among the 141 included patients, 109 (77%) were male. Median age (range) was 68 (24-91) years old. After a one-year follow-up, 28 patients (20%) had undergone a lung biopsy. The 1-year clinical diagnoses were idiopathic pulmonary fibrosis (IPF) in 66 patients (47%), including 12 patients (9%) who had undergone a lung biopsy, non-specific interstitial pneumonia (NSIP) in 19 (13%) and other specific pneumonia in 4 (3%). Finally, 52 patients (37%) remained unclassified.

Kappa coefficients (95% CI) for inter-reader agreement over the 6 readers for the identification of PTB, for the identification honeycombing, and for the CT patterns of UIP with methods 1 and 2 are presented in Table 1. Inter-reader agreement ranged from 0.44 to 0.65, and was not significantly different between method 1 and method 2 for all 3 parameters (P = 0.397 to 0.945).

With both methods, readers identified PTB in 76 to 100% of IPF patients diagnosed on a lung biopsy, and in 73 to 96% of other IPF patients. Similarly, honeycombing was identified in 17 to 50% of patients when IPF diagnosis relied on a lung biopsy, and in 59 to 91% of patients when the IPF diagnosis was made without histological evidence. Regarding patients with NSIP, PTB was identified in 37 to 84% of patients and honeycombing in 16 to 47%.

PTB is an early hallmark of pulmonary fibrosis; however, honeycombing and PTB commonly coexist and can be confused. Post-processing with MinIP allows detection of low-density structures in a given volume, by projecting the voxel with the lowest attenuation value on every view throughout the volume onto a 2D image. Theoretically, it is an optimal tool to visualize the subtle differences between endobronchial air and lung parenchyma [5]. Therefore, we hypothesized that inter-reader agreement for the identification of PTB and honeycombing would be increased using MiniP post-processing, by improving the distinction between the 2 CT features.

However, based on 141 CT examinations and 6 readers, our study was unable to demonstrate the superiority of MinIP post-processing over conventional reading methods to reliably identify these signs. Inter-reader agreement for PTB was only moderate, and tended to be lower than the inter-reader agreement for honeycombing, which was moderate to substantial, whatever the reading method.

These results may be explained by the difficulty in differentiating PTB from honeycombing on its

peripheral location. These two features, indeed, seem closely intertwined. It has been shown that

honeycombing on CT correspond, at least partly, to traction bronchiolectasis on pathology [6-8]. In

line with Piciucchi et al, we think that PTB and honeycombing are different faces of the same

continuous spectrum of lung remodeling [9], and that, therefore, they are intrinsically

indistinguishable in many cases.

PTB and honeycombing are key components of the CT patterns of UIP according to the 2018

guidelines [2]. As a consequence, it was expected that the inter-reader agreement for the CT patterns

of UIP would be also moderate, and not improved by the use of MiniP reformations either. The recent

guidelines were developed to overcome some limitations of the previous recommendations, and the

category "Probable UIP" was created. PTB is one of its important features. However, PTB was also

identified in up to 84% of our NSIP cases. This finding highlights the importance of analyzing CT

features in the light of the clinical context, especially age and gender, during MDDs.

To conclude, there was no improvement of the inter-reader agreement with MinIP for the

identification of PTB and honeycombing in our study. There was no improvement either of the inter-

reader agreement for the assessment of CT patterns of UIP.. We believe that radiologists should

choose whether to use MiniP reformations for the assessment of fibrotic lung diseases according to

their habits and personal preferences

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References

- 1. Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JR, Goldin JG, Hansell DM, Inoue Y, Johkoh T, Nicholson AG, Knight SL, Raoof S, Richeldi L, Ryerson CJ, Ryu JH, Wells AU. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. Lancet Respir Med 2018; 6: 138-153.
- 2. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F, Flaherty KR, Wells A, Martinez FJ, Azuma A, Bice TJ, Bouros D, Brown KK, Collard HR, Duggal A, Galvin L, Inoue Y, Jenkins RG, Johkoh T, Kazerooni EA, Kitaichi M, Knight SL, Mansour G, Nicholson AG, Pipavath SNJ, Buendía-Roldán I, Selman M, Travis WD, Walsh S, Wilson KC. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018; 198: e44-e68.
- 3. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008; 246: 697-722.
- 4. Conger AJ. Integration and generalization of kappas for multiple raters. Psychol Bull 1980; 88: 322-328.
- 5. Beigelman-Aubry C, Hill C, Guibal A, Savatovsky J, Grenier PA. Multi-detector row CT and postprocessing techniques in the assessment of diffuse lung disease. Radiographics 2005; 5: 1639-1652.
- 6. Johkoh T, Sumikawa H, Fukuoka J, Tanaka T, Fujimoto K, Takahashi M, Tomiyama N, Kondo Y, Taniguchi H. Do you really know precise radiologic-pathologic correlation of usual interstitial pneumonia? Eur J Radiol 2014; 83: 20-26.
- 7. Staats P, Kligerman S, Todd N, Tavora F, Xu L, Burke A. A comparative study of honeycombing on high resolution computed tomography with histologic lung remodeling in explants with usual interstitial pneumonia. Pathol Res Pract 2015; 211: 55-61.
- 8. Seibold MA, Smith RW, Urbanek C, Groshong SD, Cosgrove GP, Brown KK, Schwarz MI, Schwartz DA, Reynolds SD. The Idiopathic Pulmonary Fibrosis Honeycomb Cyst Contains A Mucocilary Pseudostratified Epithelium. PloS One 2013; 8: 9.

9. Piciucchi S, Tomassetti S, Ravaglia C, Gurioli C, Gurioli C, Dubini A, Carloni A, Chilosi M, Colby TV, Poletti V. From "traction bronchiectasis" to honeycombing in idiopathic pulmonary fibrosis: A spectrum of bronchiolar remodeling also in radiology? BMC Pulm Med 2016; 16: 87.

<u>Table 1</u>

Kappa coefficients [95% confidence interval] for each reading method.

	Method 1	Method 2	<i>P</i> -value
Peripheral traction bronchiolectasis			
Superior zone	0.52 [0.43; 0.59]	0.53 [0.44; 0.61]	0.840
Middle zone	0.54 [0.46; 0.61]	0.50 [0.43; 0.57]	0.684
Inferior zone	0.44 [0.36; 0.53]	0.45 [0.36; 0.54]	0.945
Per patient	0.49 [0.39; 0.58]	0.48 [0.38; 0.57]	0.830
Honeycombing			
Superior zone	0.62 [0.53; 0.70]	0.64 [0.55; 0.72]	0.812
Middle zone	0.65 [0.57; 0.72]	0.61 [0.52; 0.69]	0.462
Inferior zone	0.63 [0.55; 0.70]	0.60 [0.51; 0.67]	0.539
Per patient	0.60 [0.53; 0.68]	0.57 [0.49; 0.64]	0.455
CT patterns of UIP			
Per patient	0.55 [0.49; 0.60]	0.52 (0.46; 0.57]	0.397

Method 1: reading using cine mode and multiplanar reformations only

Method 2: reading using cine mode, multiplanar reformations and minimal intensity projection postprocessing

Superior zone: above carina, inferior zone: under inferior pulmonary veins, middle zone: in between CT patterns of UIP (usual interstitial pneumonia): UIP, probable UIP, indeterminate for UIP, alternative diagnosis