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Comparison of quantitative lung computed tomographic findings between idiopathic pulmonary fibrosis patients diagnosed by biopsy and by multidisciplinary discussion without biopsy

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ABSTRACT

Objectives: We aimed to investigate the objective quantitative differences between the parenchymal computed tomography (CT) findings of idiopathic pulmonary fibrosis (IPF) patients diagnosed by surgical lung biopsy and by multidisciplinary discussion without biopsy.

Methods: We performed parenchymal texture analyses in lung CT images of 116 IPF patients, 42 diagnosed by surgical lung biopsy, and 74 by multidisciplinary discussion without biopsy. The relative volumes of the ground-glass, reticular, honeycomb, hyperlucent, and normal parenchymal patterns were measured in six predefined sections of each lung by an automatic texture analysis software (CALIPER: Computer-Aided Lung Informatics for Pathology Evaluation and Rating). The results were compared between the two patient groups.

Results: When the relative volumes of the parenchymal patterns were compared between the biopsied and non-biopsied groups in a total lung-based manner, the mean percentage of only the ground-glass pattern was significantly higher in the biopsied group. When compared between the corresponding lung sections, the percentages of the ground-glass pattern were higher in the biopsied group than those in the non-biopsied group at the bilateral central sections of the upper, middle, and lower lung zones. At the bilateral peripheral sections of the middle and lower lung zones, the sectional reticular pattern percentages were lower in the biopsied group than those in the non-biopsied group.

Conclusions: CALIPER's quantitative CT measurements revealed that the sectional relative volumes of the ground-glass and reticular patterns, but not of the honeycomb, normal, and hyperlucent parenchyma, were significantly different between some of the corresponding lung sections of the biopsied and non-biopsied IPF patients. This information may help a better understanding of the role of the CT findings in biopsy decisions and avoiding some of the unnecessary biopsies in suspected IPF patients.

Keywords: idiopathic pulmonary fibrosis, quantitative computed tomography, texture analysis, surgical lung biopsy, usual interstitial pneumonia

Idiopathic pulmonary fibrosis (IPF) is the most common and most fatal pulmonary fibrotic disease. The American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) guideline recommends a multidisciplinary discussion when IPF is suspected [1]. Surgical lung biopsy is suggested to make a definitive diagnosis in patients without the

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usual interstitial pneumonia (UIP) pattern on high resolution computed tomography (HRCT). It was reported that biopsy may be needed in up to one-third of patients for an accurate diagnosis, and the morbidity and mortality associated with biopsies are as high as 3-4% [2].

HRCT is essential in diagnosis and in biopsy decision. Unfortunately, there is interobserver variability in the identification and interpretation of HRCT features of UIP. Besides, conditions that mimic honeycombing, such as bronchiectasis and emphysema, can cause interobserver disagreement about the presence of honeycombing [3]. Furthermore, some commonly used adjectives in guidelines such as 'mild' and 'predominant' (e.g. 'mild ground-glass opacity (GGO)' and 'predominant GGO') are prone to subjectivity and may increase interobserver variability. Quantification of CT findings decreases interobserver variations.

ATS/ERS/JRS/ALAT guideline has pointed out some research questions and future directions about the potential value of the quantification of parenchymal patterns in IPF diagnosis [1].

Quantitative CT (qCT) has been increasingly used for lung diseases due to its objective and reproducible results. Thanks to advances in hardware and software technologies, computers gained the ability to 'recognize' and quantify parenchymal patterns. CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) is a software algorithm created at the Biomedical Imaging Resource of the Mayo Clinic and has the ability to detect and quantify parenchymal patterns [4, 5].

In this study, we aimed to determine the differences that can be 'seen by the objective eye of the CALIPER', between the CT findings of biopsied and non-biopsied IPF patients.

METHODS

We performed a retrospective qCT analysis of lung parenchyma in 116 IPF patients, 42 diagnosed by surgical lung biopsies (biopsied group) and 74 by multidisciplinary discussion without biopsy (non-biopsied group), in our hospital between 2013-2020. Biopsy decisions and non-biopsy IPF diagnoses were made by our hospital's Institutional Council of Interstitial Lung Diseases (consisted of a radiologist, a pathologist, and at least three respiratory clinicians).

We included only those patients who had volumetric, non-contrast CT scans, performed in our own institution within the 3-month period before the time of diagnosis by using the same acquisition technique (by

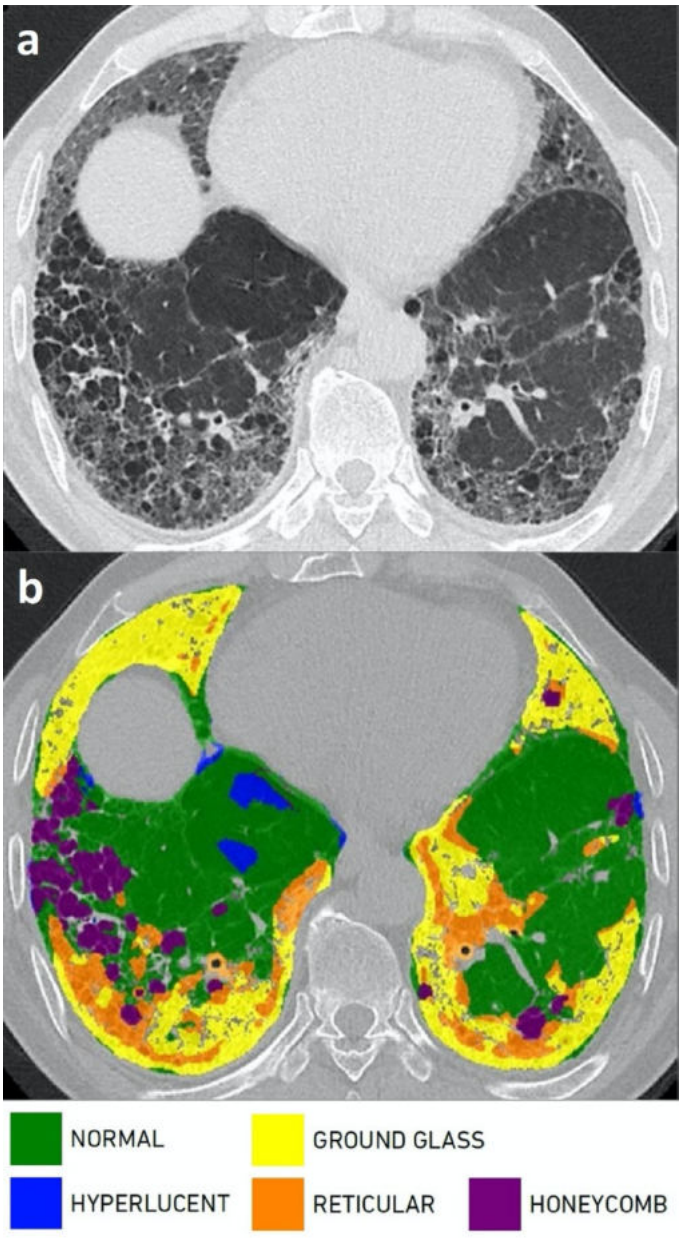

Fig. 1. Axial CT slice (a) and its color overlay (b) representing the mapping of lung texture detection. Five different parenchymal patterns (normal parenchyma, ground glass pattern, hyperlucent parenchyma, reticular pattern, and honeycombing) were automatically detected by the computer. The computer assigned five different colors for these five different parenchymal patterns, as listed below the image (b). The lung parenchyma was then colored regionally by the computer in accordance to the dominant parenchymal pattern in that region.

using Philips Ingenuity 128 slice CT scanner, with a tube voltage of 120 kV, a pitch of 1, a rotation time of 0.4 second, and a reconstruction thickness of 1 mm with filter B).

For quantification, we used Lung Texture Analysis software (Imbio, Minneapolis, Minnesota, USA) based on CALIPER technology developed by the Mayo Clinic (Rochester, Minnesota, USA) (This is an 'investigational use only' software in the USA). This software associated a certain group of neighboring voxels to one of the five basic parenchymal patterns (normal, hyperlucent, ground-glass, reticular, and honeycombing) (Fig. 1), and measured the absolute and relative volumes of each pattern in six predefined lung sections (obtained by dividing each lung's upper, middle, and lower thirds into central 'core' and peripheral 'rind' areas that comprise about half of the lung parenchyma) [5]. The relative volume of a parenchymal pattern was calculated as the percentage of the volume of that pattern in the concerned parenchymal volume. We obtained the sectional relative volumes of five different parenchymal patterns as a tabular data of percentages, in addition to a graphical report illustrating these percentages for each patient (Fig. 2).

This study was approved by our Institutional Review Board and written informed consent was waived because of its retrospective nature.

Statistical Analysis

SPSS Statistics software (version 26) was used to perform two-tailed Student's t-tests.

RESULTS

There were 42 patients in the biopsied and 74 in the non-biopsied group. The mean age was 60.9 ± 8.9 years (55.3 ± 7.3 years in the biopsied group and 64.0 ± 8.9 years in the non-biopsied group). There were 92 male and 24 female patients (in the biopsied group 28 male and 14 females, in the non-biopsied group 64 male and 10 females).

The mean volume percentages of the parenchymal patterns measured by CALIPER in the biopsied and in the non-biopsied patient groups and the results of the comparisons between these two groups are listed in Table 1.

When we compared the volume percentages of the

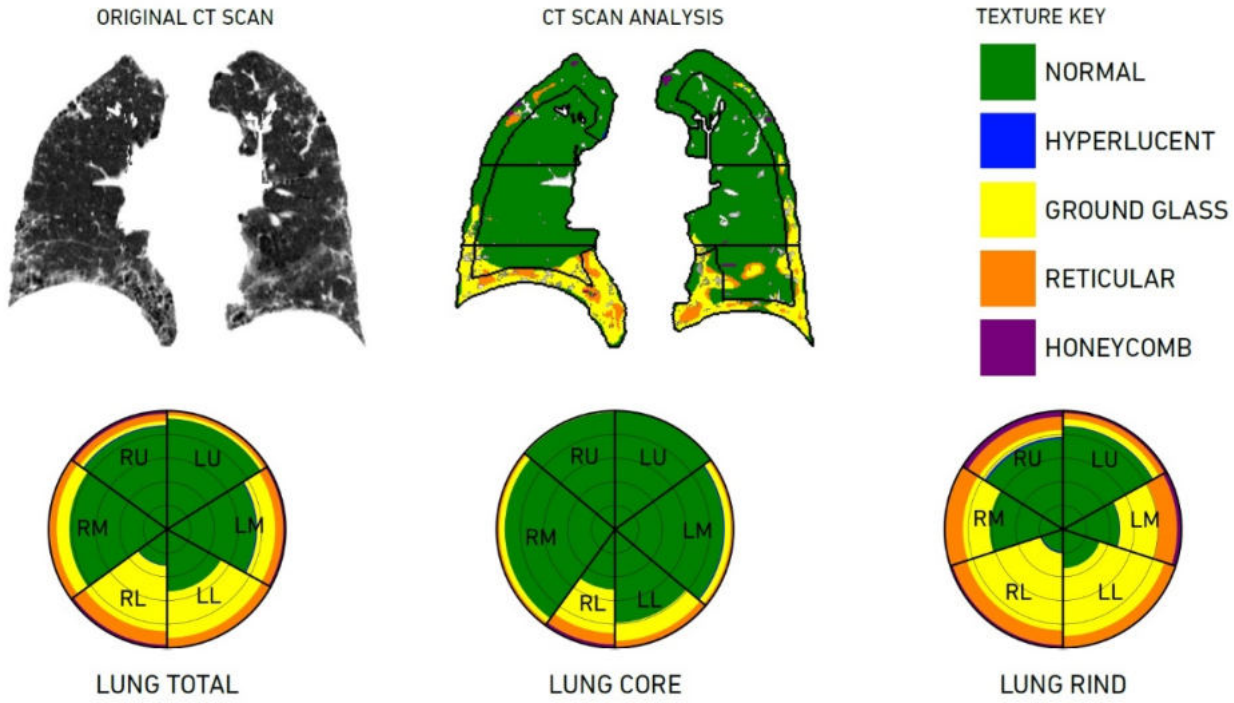

Fig. 2. An example of the graphical report of the quantitative CT analysis of IPF patients. Five different parenchymal patterns were masked by different colors on a mid-coronal CT slice, and the relative volume of each pattern was represented with the same color on circular glyphs. (RU = Right Upper, RM = Right Middle, RL = Right Lower, LU = Left Upper, LM = Left Middle, LL = Left Lower). The 'lung core' and the 'lung rind' glyphs represent the central and peripheral half volumes of the lungs, respectively.

Table 1. **Mean relative volumes (%) of parenchymal patterns in biopsied and non-biopsied groups**

	Normal parenchyma		Hyperlucent		Ground glass			Reticular			Honeycomb	
Lung Section	Biopsied	Non-biopsied	Biopsied	Non-biopsied	Biopsied		Non-biopsied	Biopsied		Non-biopsied	Biopsied	Non-biopsied
RL upper-central	77.0 ± 29.7	84.8 ± 20.0	0.4 ± 1.0	0.8 ± 2.7	15.7 ± 26.9	>	6.2 ± 13.1	5.2 ± 9.8		6.4 ± 11.8	1.7 ± 2.9	1.8 ± 4.1
LL upper-central	81.1 ± 26.9	87.7 ± 18.6	0.5 ± 1.3	1.6 ± 8.0	14.1 ± 26.5	>	4.4 ± 11.9	2.6 ± 4.5		4.6 ± 9.7	1.7 ± 3.0	1.6 ± 5.4
RL middle-central	73.8 ± 27.6	80.0±19.2	0.5 ± 1.3	0.7 ± 1.6	19.1 ± 28.2	>	9.0 ± 12.8	5.2 ± 7.6		8.8 ± 11.9	1.4 ± 2.5	1.5 ± 3.0
LL middle-central	69.5 ± 28.2	79.8 ± 21.1	0.35 ± 0.6	0.6 ± 2.8	24.3 ± 28.7	>	11.5 ± 16.6	4.6 ± 6.6		6.9 ± 9.6	1.2 ± 2.6	1.2 ± 3.0
RL lower-central	47.9 ± 28.3	55.9 ± 30.4	1.25 ± 7.2	0.9 ± 5.7	30.4 ± 29.6	>	14.6 ± 18.5	17.8 ± 20.3		25.6 ± 24.7	2.7 ± 4.7	3.0 ± 5.5
LL lower-central	48.7 ± 35.0	57.8 ± 31.2	0.35 ± 1.4	0.9 ± 3.6	32.0 ± 34.6	>	16.3 ± 20.1	16.9 ± 21.3		22.1 ± 23.3	2.1 ± 4.0	2.8 ± 5.4
RL upper-peripheral	66.9 ± 29.3	70.3 ± 25.4	2.55 ± 3.8	2.9 ± 4.4	17.4 ± 24.5		10.8 ± 15.1	11.6 ± 16.1		14.0 ± 16.2	1.6 ± 2.1	2.1 ± 3.3
LL upper-peripheral	71.5 ± 26.5	76.8 ± 21.4	3.15 ± 5.5	3.5 ± 5.5	15.8 ± 24.5		7.7 ± 13.0	8.1 ± 11.2		10.2 ± 13.6	1.4 ± 1.9	1.7 ± 3.0
RL middle-peripheral	57.3 ± 26.8	57.0 ± 23.5	2.15 ± 2.9	1.8 ± 2.5	26.0 ± 26.7		16.8 ± 16.2	13.2±14.1	<	22.5 ± 16.7	1.4 ± 2.3	2.0 ± 4.0
LL middle-peripheral	51.4 ± 29.0	56.5 ± 28.9	1.3 ± 2.0	1.2 ± 2.1	32.0 ± 29.1	>	19.2 ± 19.4	14.0 ± 15.6	<	21.5 ± 19.4	1.3 ± 2.1	1.7 ± 2.8
RL lower-peripheral	41.0 ± 23.2	41.0 ± 22.6	2.5 ± 5.4	1.7 ± 4.0	34.6 ± 26.0		26.5 ± 19.6	20.4 ± 17.5	<	28.8 ± 18.8	1.5 ± 2.4	2.0 ± 4.0
LL lower-peripheral	41.0 ± 27.9	40.9 ± 25.7	1.8 ± 3.1	1.8 ± 4.9	37.0 ± 29.3		28.5 ± 21.7	18.9 ± 19.0	<	26.8 ± 19.7	1.2 ± 2.0	2.0 ± 3.7
RL total	63.3 ± 25.5	68.1 ± 20.2	1.6 ± 3.1	1.5 ± 2.8	22.8 ± 25.3	>	13.1 ± 12.9	10.7 ±10.8		15.4 ± 13.8	1.6 ± 2.3	1.9 ± 3.2
LL total	63.1 ± 25.3	69.7 ± 20.0	1.4 ± 2.1	1.8 ± 3.3	24.4 ± 25.4	>	13.4 ± 13.2	9.7 ± 10.7		13.3 ± 12.8	1.4 ± 2.0	1.8 ± 2.9
Total lung	64.0 ± 24.3	69.9 ± 19.0	1.4 ± 2.4	1.7 ± 2.9	23.3 ± 24.2	>	13.3 ± 12.8	9.8 ± 10.5		13.2 ± 12.6	1.5 ± 2.1	1.8 ± 2.8

RL = right lung, LL = left lung. The mean relative volumes are given as the means of the relative volume percentages ± standard deviations.

The boxed values with blue backgrounds, with a greater (>) or lesser (<) sign in between, are those that are significantly different in the biopsied and non-biopsied groups with a $p < 0.05$. Note that the ground glass pattern percentages were significantly higher in the biopsied patients than in the non-biopsied ones mainly in the central lung sections. The reticular pattern percentages were significantly lower in the biopsied patients than in the non-biopsied ones only in the peripheral sections of the middle and lower lung zones

parenchymal patterns in the biopsied group with those in the non-biopsied group, in a total lung-based manner, only the ground-glass pattern showed a significant difference (it was higher in the biopsied [23.3%] than in the non-biopsied group [13.3%]) ($p < 0.01$).

When we compared the sectional volume percentages of the parenchymal patterns between the corresponding lung sections of the biopsied and non-biopsied groups for each of the twelve lung sections (six in each lung), we found that the mean percentages of the ground-glass pattern were significantly higher in seven of the lung sections of the biopsied group than those in the corresponding sections of the non-biopsied one (six of these sections were symmetric including the bilateral central sections of the upper, middle, and lower lung zones, and an additional one was asymmetric, the middle-peripheral section of the left lung) (Table 2).

On the other hand, the reticular pattern percentages were significantly lower in the middle and lower peripheral sections of both lungs of the biopsied group than those in the corresponding sections of the non-biopsied group (Table 3).

The relative volumes of the honeycomb, hyperlucent, and normal lung patterns showed no significant difference between the corresponding lung sections of the two patient groups.

DISCUSSION

In our study, CALIPER has detected that, compared to the non-biopsied patients the biopsied patients have significantly higher percentages of the ground-glass volume in the central sections, and lower percentages of the reticular pattern in the peripheral sections of the lungs.

IPF is the most common fibrotic disease of the lung. It is more common in older ages and in males [6, 7]. There was an elder-male dominance in our patient population and this was compatible with the literature.

According to the ATS/ERS/JRS/ALAT guideline, in patients with a definite UIP pattern on lung CT, in the absence of a detectable etiology, surgical lung biopsy is not necessary for an IPF diagnosis. However, biopsy should be considered in patients with CT findings of 'probable UIP' or 'indeterminate for UIP', especially when an alternative diagnosis is not achievable [1, 8, 9]. Radiologically, the main difference between 'definite UIP' and 'probable UIP' is the presence or absence of honeycombing, respectively, and this difference may change a decision from 'no need to biopsy' into 'biopsy'. However, visual evaluation of CT images is subjective and prone to interobserver discrepancies. Sometimes it may be difficult to differentiate honeycombing from bronchiectasis and

Table 2. Comparison of relative volumes of ground-glass pattern (%) in corresponding lung sections of biopsied and non-biopsied IPF groups

	Right Lung		Left Lung	
	Peripheral	**Central**	**Central**	**Peripheral**
Upper	B: 17.4 ± 24.5	B: 15.7 ± 26.9	B: 14.1 ± 26.5	B: 15.8 ± 24.5
	NB: 10.8 ± 15.1	NB: 6.2 ± 13.1	NB: 4.4 ± 11.9	NB: 7.7 ± 13.0
	$p = 0.13$	**$p = 0.04$**	**$p = 0.03$**	$p = 0.60$
Middle	B: 26.0 ± 26.7	B: 19.1 ± 28.2	B: 24.3 ± 28.7	B: 32.0 ± 29.1
	NB: 16.8 ± 16.2	NB: 9.0 ± 12.8	NB: 11.5 ± 16.6	NB: 19.2 ± 19.4
	$p = 0.50$	**$p = 0.04$**	**$p = 0.01$**	**$p = 0.02$**
Lower	B: 34.6 ± 26.0	B: 30.4 ± 29.6	B: 32.0 ± 34.6	B: 37.0 ± 29.3
	NB: 26.5 ± 19.6	NB: 14.6 ± 18.5	NB: 16.3 ± 20.1	NB: 28.5 ± 21.7
	$p = 0.07$	**$p = 0.004$**	**$p = 0.01$**	$p = 0.12$

B = Biopsied IPF group, NB = Non-biopsied IPF group. Values are means ± standard deviations.

Each table cell represents one of the twelve lung sections and positioned on this table in accordance to the position of the corresponding lung section on a postero-anterior chest x-ray. The table cells with blue background represent those lung sections in which a significantly higher percentage of the ground-glass pattern were measured in the biopsied group than in the non-biopsied group with a $p < 0.05$.

Table 3. Comparison of Relative Volumes of Reticular Pattern (%) in Corresponding Lung Sections of Biopsied and Non-Biopsied IPF Groups

	Right Lung		Left Lung	
	Peripheral	**Central**	**Central**	**Peripheral**
Upper	B: 11.6 ± 16.1	B: 5.2 ± 9.8	B: 2.6 ± 4.5	B: 8.1 ± 11.2
	NB: 14.0 ± 16.2	NB: 6.4 ± 11.8	NB: 4.6 ± 9.7	NB: 10.2 ± 13.6
	$p = 0.47$	$p = 0.60$	$p = 0.17$	$p = 0.42$
Middle	B: 13.2 ± 14.1	B: 5.2 ± 7.6	B: 4.6 ± 6.6	B: 14.0 ± 15.6
	NB: 22.5 ± 16.7	NB: 8.8 ± 11.9	NB: 6.9 ± 9.6	NB: 21.5 ± 19.4
	$p = 0.004$	$p = 0.06$	$p = 0.14$	**$p = 0.04$**
Lower	B: 20.4 ± 17.5	B: 17.8 ± 20.3	B: 16.9 ± 21.3	B: 18.9 ± 19.0
	NB: 28.8 ± 18.8	NB: 25.6 ± 24.7	NB: 22.1 ± 23.3	NB: 26.8 ± 19.7
	$p = 0.02$	$p = 0.09$	$p = 0.26$	**$p = 0.04$**

B = Biopsied IPF group, NB = Non-biopsied IPF group. Values are means ± standard deviations.

Each table cell represents one of the twelve lung sections and positioned on this table in accordance to the position of the corresponding lung section on a postero-anterior chest x-ray. The table cells with blue background represent those lung sections in which a significantly lower percentage of the reticular pattern were measured in the biopsied group than in the non-biopsied group with a $p < 0.05$.

emphysema and this may cause interobserver disagreement about the presence of honeycombing [3].

In the ATS/ERS/JRS/ALAT guideline, it is emphasized that 'mild' ground-glass opacities can be seen in 'probable UIP' and, if ground-glass is a 'prominent' feature on CT, then this is suggestive of an alternative diagnosis other than UIP [1]. These 'mild' and 'prominent' adjectives seem to be a little subjective and may cause interobserver discrepancies, especially when there is a lack of experience. Guideline authors pointed out the potential role of quantification of parenchymal patterns and directed future researchers to conduct quantitative studies with automated methods.

Quantitative CT techniques can help us to decrease subjectivity. CALIPER, a computer technology pioneered at the Mayo Clinic, has the ability to detect five parenchymal patterns (normal, ground-glass, reticular, honeycomb, and emphysema). It was reported that interstitial findings measured by CALIPER were predictive of survival, helpful in evaluating the response to pirfenidone, and correlated with the findings of pulmonary function tests in IPF patients [10-12]. CALIPER was shown to produce classification results comparable to expert radiologic judgment [4].

Jacob *et al*. [13] reported that a large proportion of the areas visually labeled as reticular pattern were characterized as ground-glass opacities by CALIPER]. Therefore, in their study, the ground-glass pattern was reported to be the abnormal parenchymal pattern with the highest volume percentage measured by CALIPER in 283 IPF patients, whereas the reticular pattern had the highest percentage measured by visual scoring. In our study, CALIPER's findings were similar and the percentages of ground-glass were higher than those of the reticular pattern in both biopsied and non-biopsied IPF groups.

We used CALIPER's measurements to compare the relative volumes of parenchymal patterns between the biopsied and non-biopsied IPF groups, in a total lung-based manner and then in a section-based manner. To our knowledge, this is the first study doing such a comparison.

When compared in a total lung-based manner, we found that only the ground-glass pattern percentages were significantly different between the two patient groups and it was higher in the biopsied group ($p < 0.01$).

Section-based comparisons revealed that the ground-glass volume percentages were higher in the central sections of the lungs in the biopsied patients than those in the corresponding central sections of the non-biopsied ones (Table 2). Since the ground-glass pattern seen in IPF usually happens in areas of periph-

eral reticulation or honeycombing, it may be thought that the presence of ground-glass in the central lung sections possibly acted in favor of the biopsy decisions in our biopsied patient group.

Reticular pattern percentages were not significantly different in the two groups when compared cumulatively. However, section-based comparisons revealed significantly lower reticular pattern percentages in bilateral middle and lower peripheral lung sections of the biopsied group than those in the corresponding sections of the non-biopsied group (Table 3). In IPF patients, the reticular parenchymal pattern is expected to be observed prominently in bilateral lower peripheral areas of the lungs, and therefore, the relatively lower reticular pattern percentages at the bilateral middle and lower peripheral regions in our biopsied patient group, compared to those in the non-biopsied, may be interpreted as a factor that possibly acted in favor of the biopsy decisions in our biopsied patients.

Interestingly, the relative volumes of the honeycomb pattern were not significantly different in the two groups, neither in total lung-based nor in section-based comparisons, contrary to what might be expected. Since the presence of honeycombing, especially when it is in a bilateral and bibasilar distribution, is in favor of a 'no need to biopsy' decision, we expected that the honeycomb pattern might have a higher percentage in the non-biopsied group. However, CALIPER found similar percentages in the two groups. Jacob *et al*. reported that a substantial proportion of the areas visually labeled as honeycombing were characterized as reticular and/or ground-glass patterns by CALIPER [13]. This was the same in our study and in both of our patient groups CALIPER 'recognized' only some portions of the honeycomb pattern and the percentages of these portions happened to be similar in our two patient groups.

The percentages of normal and hyperlucent parenchyma were not significantly different in the two patient groups, neither cumulatively nor sectionally.

Limitations

Our study has limitations: i) We think that other texture analysis algorithms may have different measurement results from those of CALIPER's. Hence, our findings cannot be generalized to all qCT methods. ii) CALIPER characterizes some portions of the parenchymal patterns different from those of visual labeling. For this reason, our measurement findings cannot be directly translated into routine radiological practice that is mainly dependent on visual labeling. iii) We focused only on the qCT findings of our patients and did not collect and compare the detailed clinical and laboratory findings of the two groups. Therefore, we cannot claim about the independent role of the qCT findings on biopsy decisions.

We think that qCT is a promising tool in the diagnosis and follow-up of interstitial lung diseases, and we hope to inspire future studies that analyze qCT findings in large series to develop quantitative methods that can help to avoid at least some of the unnecessary surgical lung biopsies.

CONCLUSION

Comparison of the CALIPER's measurements between the corresponding lung sections of the biopsied and the non-biopsied IPF patients revealed that the biopsied patients have significantly higher percentages of the ground-glass volume in the central sections of the upper, middle, and lower lung zones, and lower percentages of the reticular pattern in the peripheral sections of the middle and lower lung zones, compared to the non-biopsied patients. Regarding the relative volumes of the honeycomb, hyperlucent and normal parenchyma patterns, CALIPER detected no significant difference between the biopsied and non-biopsied patients. We think that quantification may facilitate a better understanding of the role of CT findings in biopsy decisions and may help to avoid from at least some of the unnecessary biopsies in suspected IPF patients.

Authors' Contribution

Study Conception: AG; Study Design: AG; Supervision: AG; Funding: AG; Materials: AG; Data Collection and/or Processing: AG; Statistical Analysis and/or Data Interpretation: AG; Literature Review: AG; Manuscript Preparation: AG and Critical Review: AG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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