

# Lung MRI to predict lack of response to treatment in interstitial lung disease: initial observations on SSFSE/PROPELLER T2 mismatch

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## Research

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# Abstract

## Background

High-resolution chest computed tomography (HRCT) signs of interstitial lung disease (ILD) are varied, some corresponding to irreparable parenchymal destruction and fibrosis, others representing potentially reversible changes, such as fine reticulation and ground-glass opacities (GGO). GGO frequently correspond to sites of active inflammation that may be responsive to steroids or immunosuppressive agents, but they might also represent intralobular interstitial fibrosis not resolved by current HRCT technique. Our aim was to investigate the ability of lung MRI to predict treatment response in individuals with ILD presenting with predominant GGO.

## Methods

In this prospective cohort, 15 participants (4 male and 11 female) aged 38–84 years, presenting with ILD manifested as predominant GGO and referred for a new treatment regimen with a systemic glucocorticoid and/or an immunosuppressive agent, underwent 1.5 T lung MRI with breath-hold (SSFSE) and respiratory-gated (PROPELLER) T2-weighted pulse sequences, and with dynamic contrast-enhanced fat-suppressed T1-weighted pulse sequence (LAVA). Relative signal intensity on T2-weighted images and relative enhancement of lung lesions were compared to functional response in a dichotomous fashion (response versus non-response) with *t* test for independent samples. SSFSE/PROPELLER T2 mismatch was compared to response with Fisher's exact test. Inter-rater agreement was evaluated with Cohen's kappa coefficient. The primary endpoint for response was a greater than 10% increase in forced vital capacity in 10 weeks.

## Results

Responders (4/15, 27%) and non-responders (11/15, 73%) showed similar relative signal intensity on T2-weighted images and relative enhancement measurements. SSFSE/PROPELLER T2 mismatch was able to discriminate responders from non-responders in 12 of 15 participants (80% accuracy,  $p = 0.026$ ) for readers 1 and 2, and in 13 of 15 participants (87% accuracy,  $p = 0.011$ ) for reader 3, with inter-rater agreement of 87% between readers 1 and 2 (Cohen's kappa coefficient of 0.732) and 93% between readers 1/2 and 3 (Cohen's kappa coefficient of 0.865).

## Conclusions

SSFSE-PROPELLER T2 mismatch was predictive of lack of response to treatment in this small group of ILD patients presenting with predominant GGO at HRCT.

## Key Point

SSFSE/PROPELLER T2 mismatch may help predict lack of response to anti-inflammatory/immunosuppressive treatment in interstitial lung disease, with high accuracy and high

inter-rater agreement.

## Background

Interstitial lung diseases (ILD) encompass a variety of heterogeneous disorders, with diverse and overlapping clinical and pathological features that hinder their diagnosis and management [1, 2]. Medical imaging plays a pivotal role in the non-invasive assessment of ILD patients, with HRCT currently standing as the foremost imaging modality in the depiction of ILD [3, 4]. HRCT signs of ILD are varied, some corresponding to irreparable parenchymal destruction and fibrosis (e.g., honeycombing cysts and traction bronchiolectasis), others representing potentially reversible changes, such as fine reticulation and ground-glass opacities (GGO) [5–7]. GGO frequently correspond to sites of active inflammation that may be responsive to steroids or immunosuppressive agents, but in some cases, they represent intralobular interstitial fibrosis not resolved by current HRCT technique [5].

Since therapy with steroids or immunosuppressive agents is not devoid of risks, a non-invasive marker that could predict the pathological nature of GGO is highly desirable, in order to prevent the futile or detrimental use of the aforementioned drugs, particularly in patients who decline or are unable to undergo surgical lung biopsy.

In this regard, MRI has only scarcely been investigated as a means to detect and characterize ILD. In a recent systematic review [8], the authors found only 24 studies reported in English, from 1996 to 2017, comparing image quality between HRCT and different MRI techniques for parenchymal abnormalities. In one study, T2-weighted MRI was able to detect distinct diffuse lung diseases with a sensitivity of 93%, using HRCT as the reference standard [9]. In a prospective study, a significant correlation between imaging findings at 3.0 T MRI and the predominant underlying pathological pattern (inflammation or fibrosis) was observed in 26 patients with either usual or nonspecific interstitial pneumonia, on a per-biopsy site basis [10].

However, to the best of our knowledge, no study has specifically addressed the ability of MRI findings to predict treatment outcome on a per-patient basis. The aim of our study was to investigate the ability of MRI findings, on conventional body imaging pulse sequences in a clinical 1.5 T scanner, to predict objective functional response to treatment in individuals with ILD presenting with predominant GGO.

## Methods

### Study cohort

This prospective study was approved by our institutional review board and informed consent was obtained from all participants. From September 2015 to December 2018, we enrolled 18 consecutive participants with clinical ILD and predominant GGO at HRCT affecting more than 5% of the lung parenchyma [11], irrespective of the presence of reticular abnormalities or traction bronchiectasis, without honeycombing, without contraindications to MRI, referred for new treatment regimen with a systemic

glucocorticoid, an immunosuppressive agent, or both. Presence of reticular abnormalities and presence of traction bronchiectasis were recorded. Final ILD diagnosis was established on multidisciplinary discussion [3]. One participant was excluded due to biopsy-proven hematological malignancy with lung involvement, and another two were excluded due to premature treatment discontinuation.

## **Functional characterization**

All participants underwent thorough clinical assessment at two time points: baseline (t0), and at 10 weeks of treatment (t1). At each time point, the mMRC Dyspnea Scale [12] score was recorded, and the participants were subjected to the six-minute walk test and pulmonary function tests comprising spirometry and diffusing capacity for carbon monoxide. The six-minute walk test was undertaken according to current guidelines [13]. Pulmonary function tests were obtained with the Vmax® Encore PFT System (CareFusion, Palms Springs CA, USA), according to ATS/ERS standardization [14].

## **Treatment endpoint**

Forced vital capacity (FVC) was chosen as the objective outcome measure. Response evaluation was based on relative change from baseline in the percentage predicted value (e.g., an increase from 70% predicted to 77% predicted corresponds to 10% relative increase). We used the conventional cut-off value of  $\geq 10\%$  relative increase in FVC as the primary endpoint for response.

## **MR Imaging**

MR imaging was performed on a 1.5 T scanner with 33 mT/m gradient and 120 T/m/s slew rate (Signa HDxt, GE Healthcare), within two weeks of the HRCT, before treatment initiation. T2-weighted images were obtained in the transverse plane with fast (breath-hold) and respiratory-gated techniques: single-shot fast spin echo (SSFSE) [15], and periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER) [16], respectively. Dynamic contrast-enhanced MRI was performed in the transverse plane with a 3D fat-suppressed T1-weighted pulse sequence (Liver Acquisition with Volume Acceleration - LAVA) before and 1, 3, 5, and 10 minutes after a macrocyclic gadolinium-based contrast agent injection (gadoteric acid 0.5 mmol/mL, at a dosage of 0.1 mmol/kg and injection rate of 2 mL/s) [10]. Typical values for field of view, frequency/phase encoding matrix size, slice thickness, and repetition/echo times were 380 mm, 256/192, 8 mm, and 800/50 ms for SSFSE; 380 mm, 256/256, 6 mm, and 4000/80 ms for PROPELLER; and 380 mm, 320/160, 4 mm, and 4.2/2.0 ms for LAVA. Regions of interest outlining representative areas of abnormal lung parenchyma and the normal-appearing adjacent lung were manually drawn by a radiologist with 14 years of experience in MRI interpretation to obtain the average SI on a per-lung per-slice basis, avoiding large vessels and airways and artifacts (Fig. 1). Relative extent of the abnormalities was expressed as percentage of lung area on a per-lung per-slice basis, rounded to the nearest multiple of five. Relative SI of lung abnormalities on T2-weighted images was computed as the ratio between average SI in abnormal lung and average SI in adjacent normal-appearing lung. Degree of enhancement of representative area of abnormal lung at a given time point was calculated as percent increase in SI over baseline. Peak enhancement was defined as the largest percentual increase on a per-

patient basis. Time to peak was recorded in minutes at each time point after contrast agent injection. Slope of enhancement was obtained by dividing peak enhancement by time to peak in minutes.

To evaluate the dissimilar visual appearance of interstitial lung abnormalities on SSFSE and PROPELLER T2-weighted images, Two radiologists with distinct levels of expertise in MRI interpretation (reader 1, 10 years; reader 2, in-training), blinded to all clinical and pathological information, independently reviewed each SSFSE/PROPELLER set in a single-monitor, side-by-side comparison mode, using the following criteria: when visual contrast of the lung abnormalities (relative to surrounding soft-tissue structures, mainly fat and muscle) were considered similar in both pulse sequences, on a per-patient basis, they were interpreted as a match; when conflicting, as a mismatch (Fig. 2). A third blinded interpretation (reader 3, 14 years of expertise) was rendered for pseudoarbitration in cases of disagreement [17].

## Statistics

Treatment response was used as dichotomous grouping variable. Relative change in percentage predicted FVC showed non-normal distribution, hence being evaluated with nonparametric tests (independent-samples Mann-Whitney U test, Spearman's rho coefficient for rank correlation). The remaining functional variables and all MRI-derived interval and ratio variables passed Shapiro-Wilk normality test and were statistically evaluated with parametric tests (*t* tests for independent and paired samples, Pearson's product moment for correlation). Two-tailed *p* values were attributed in accordance with Levene's test for equality of variances where appropriate. T2 match/mismatch and the remaining categorical variables were evaluated with Fisher's exact test. Statistical significance was established at  $P < .05$ . Inter-rater agreement for T2 match/mismatch was evaluated with Cohen's kappa coefficient. All statistical analyses were performed with SPSS Statistics (IBM), and image analysis was performed with OsiriX MD (Pixmeo).

## Results

Demographics and baseline functional parameters are shown in Table 1. Fifteen participants completed the study protocol, including four men and 11 women (mean age  $\pm$  standard deviation, 59 years  $\pm$  13; age range, 38–84 years), and had the following diagnoses on multidisciplinary discussion: collagen vascular disease-associated ILD in eight participants; interstitial pneumonia with autoimmune features in one participant; chronic hypersensitivity pneumonitis in three participants; cryptogenic organizing pneumonia in one participant; idiopathic desquamative interstitial pneumonia in one participant; and unclassifiable pulmonary fibrosis in one participant. Collagen vascular disease specific diagnoses comprised dermatomyositis in three participants, Sjögren syndrome in two participants, rheumatoid arthritis in two participants, and systemic sclerosis in one participant. Eight (53%) participants had surgical lung biopsy to corroborate the diagnosis. Seven (47%) participants were non-smokers and eight (53%) were former smokers. Smoking load was 20 pack years  $\pm$  21 (range 1–63 pack years), ceased for 20 years  $\pm$  12 (range 2–40 years). Smoking status did not differ between responders and non-responders ( $p = 0.077$ ). All participants had reduced FVC ( $< 80\%$  of the predicted), none exhibited airflow limitation, and

only two had normal total lung capacity. Baseline FVC showed significant inverse correlation with relative GGO extent ( $r = -0.681$ ;  $P = .005$ ) and with change in % predicted FVC ( $\rho = -0.586$ ;  $p = 0.022$ ). Change in % predicted FVC, however, did not correlate with relative GGO extent ( $\rho = 0.309$ ;  $p = 0.262$ ). Individual FVC measurements at  $t_0$  and  $t_1$  are shown in Table 2. Four participants reached the treatment endpoint, with FVC measurements shown in Table 3. There was no statistically significant difference in the frequency of reticulation ( $p = 1.000$ ), traction bronchiectasis ( $p = 1.000$ ), or extent of GGO ( $p = 0.471$ ) between responders and non-responders.

No difference in anatomical extent of the abnormalities was observed between SSFSE and PROPELLER T2-weighted paired image sets. T2 SI ratios and enhancement parameters did not discriminate responders from non-responders (Table 4).

All four responders showed SSFSE/PROPELLER T2 match for all three readers. T2 mismatch was observed in 8/11 (73%) non-responders for readers 1 and 2, and in 9/11 (82%) non-responders for reader 3. Pseudoarbitration was applied to the two cases of disagreement, rendering the same results given by reader 3. No participants with SSFSE/PROPELLER T2 mismatch responded to treatment (Table 4). SSFSE/PROPELLER T2 match/mismatch correctly identified the response status in 13 of 15 participants (87% accuracy [ $p = 0.011$ ]). Sensitivity, specificity, positive and negative predictive values of SSFSE/PROPELLER T2 mismatch for lack of treatment response were 82%, 100%, 100%, and 67%, respectively. Point-biserial correlation between SSFSE/PROPELLER T2 match/mismatch and baseline FVC was not statistically significant ( $r_{pb} = -0.413$  [ $p = 0.126$ ]). Inter-rater agreement for SSFSE/PROPELLER T2 match/mismatch was 87% (13/15) between readers 1 and 2 (Cohen's kappa coefficient of 0.732), and 93% (14/15) between readers 1/2 and 3 (Cohen's kappa coefficient of 0.865).

## Discussion

Predicting response to treatment with anti-inflammatory drugs is of great importance in ILD patients with equivocal clinical diagnosis and indeterminate HRCT findings, especially when histopathological information is lacking. In our current work, SSFSE/PROPELLER T2 match/mismatch was accurate in predicting treatment response, with excellent interobserver agreement that was independent of reader experience. Importantly, no participants with SSFSE/PROPELLER T2 mismatch responded to treatment in 10 weeks. Of note was the absence of objective functional response in 11/15 (73%) participants in our cohort with predominant GGO, a finding usually associated with reversible change. In addition, reticular abnormalities and particularly traction bronchiectasis, deemed to indicate irreversible parenchymal changes and hence absence of response, were seen with similar frequency in both responders and non-responders. Disease heterogeneity with coexistence of fibrosis and inflammation could at least partially explain this finding.

Previous work [10] has suggested a role for MRI in distinguishing inflammation-predominant from fibrosis-predominant interstitial lung lesions on a per-biopsy site basis, in patients with histological UIP or NSIP and HRCT findings not typical for UIP. According to the authors, an early enhancement pattern and

higher signal intensity on T2-weighted images appeared to be useful to predict disease activity (in effect, inflammation-predominant histology). In this study, we prospectively sought MRI features that could help predict objective clinical response to treatment in patients with predominant ground-glass opacities at HRCT, instead of attempting to identify histological correlates of imaging findings. In this setting, neither enhancement patterns nor signal intensity at T2-weighted images were able to discriminate responders from non-responders. The basis for the SSFSE/PROPELLER T2 match/mismatch is tentative and deserves further investigation. The SSFSE pulse sequence is standard in body imaging due to short acquisition times and hence being less prone to motion artifacts [16, 18], but it suffers from signal loss due to T2 decay [19] and has relatively poor T2 discrimination [20], showing good sensitivity for tissues with long T2 times and suboptimal sensitivity for short T2 lesions in other anatomical regions [21, 22]. PROPELLER is an acquisition technique with intrinsically higher signal-to-noise ratio due to central k space oversampling [16], being less sensitive to field inhomogeneities and motion artefacts, and providing superior image quality relative to conventional pulse sequences [23]. Although it has recently been shown that areas of pulmonary fibrosis have intermediate T2 times [24], we observed that the predominant pattern on SSFSE T2-weighted images of non-responders (presumably due to predominant fibrosis) showed variable signal intensity, despite the relatively short echo time we routinely employ. The increase in apparent signal intensity and contrast of these abnormalities on PROPELLER T2-weighted images, leading to SSFSE/PROPELLER T2 mismatch, may be related to the proton density of fibrotic regions [25], and could not be explained by echo time differences, since one would expect lower signal intensities with longer echo times in fibrotic lesions. Areas of inflammatory changes, with higher T2 times and thus comparably hyperintense on SSFSE, would show SSFSE-PROPELLER T2 match. For those patients with matching hypointense lesions on SSFSE and PROPELLER, one possible explanation would be the presence of sparse abnormalities, with partial volume averaging effect leading to low proton density and, consequently, decreased signal intensity on both pulse sequences.

Although our findings are interesting and, to the best of our knowledge, described for the first time, there are several limitations in this study. First, the small sample size restricts the statistical power, and this could account for the lack of statistical significance in some of the analyses we performed. However, despite being harder to successfully reject a false null hypothesis in an underpowered study, we were yet able to demonstrate a significant association between SSFSE/PROPELLER T2 mismatch and lack of objective response to treatment. Second, using the normal-appearing lung parenchyma as internal reference for baseline signal intensity may be prone to inaccuracy due to incipient compromise of these areas. Nonetheless, in a clinical setting such comparison is more practical and is the actual basis for visual characterization of spatial heterogeneity on cross-sectional imaging. Third, evaluating diffuse lung morphological abnormalities on a per-patient basis has the potential drawbacks of not accounting for disease heterogeneity and of biased selection of representative lung regions for analysis. Still, it can more accurately reflect disease status and better correlate with functional parameters also measured on a per-patient basis.

## Conclusions

In summary, we found a MR imaging sign that may serve as a simple non-invasive predictor of lack of response to anti-inflammatory/immunosuppressive treatment in indeterminate interstitial lung diseases. SSFSE-PROPELLER T2 mismatch does not require unique hardware, software or post-processing techniques, and may be of value in individuals that either cannot or otherwise do not usually undergo surgical lung biopsy, such as ILD associated to collagen tissue disease patients, but its usefulness should be validated in larger populations.

## Abbreviations And Acronyms

- FVC = forced vital capacity
- GGO = ground-glass opacities
- HRCT = High-Resolution Computed Tomography
- ILD = interstitial lung disease
- LAVA = Liver Acquisition with Volume Acceleration
- mMRC = modified Medical Research Council dyspnea score
- MRI = Magnetic Resonance Image
- PROPELLER = Periodically-Rotated Overlapping Parallel Lines with Enhanced Reconstruction
- SI = signal intensity
- SSFSE = Single-Shot Fast Spin Echo

## Declarations

### Ethics approval and consent to participate

This prospective study was approved by our institutional review board and informed consent was obtained from all participants

Institution: University of Brasilia School of Medicine

Number: 701.077 (approved on June 6<sup>th</sup>, 2014)

### Consent for publication

Not applicable

### Availability of data and material

The datasets used and/or analyzed during this current study are available from the corresponding author on reasonable request

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## Competing interests

The authors declare that they have no competing interests in relation to this work

## Author's contribution

Each author has made substantial contribution to this paper and has approved the submitted version

- Wagner Diniz de Paula wrote most part of the paper, discussed the conception and design, acquired radiological data and took part in analyses and interpretation.
- Marcelo Palmeira Rodrigues discussed the conception and design, acquired clinical data and took part in analyses and interpretation, and revised extensively the text
- Nathali Mireise Costa Ferreira discussed the conception and design, acquired clinical data and took part in analyses and interpretation
- Viviane Vieira Passini discussed the conception and design, acquired clinical data and took part in analyses and interpretation
- César Augusto Melo e Silva discussed the conception and design, took part in analyses and interpretation, and revised extensively the text

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## Tables

**Table 1** Demographics and baseline functional parameters stratified by treatment response status for primary endpoint

	All patients (n=15)	Responders (n=4)	Non-responders (n=11)	p value
Age (years)	59 (13)	66 (12)	56 (12)	0.175
Male sex, n (%)	4 (27)	1 (25)	3 (27)	1.000
mMRC	1.6 (1.1)	2.0 (1.1)	1.5 (1.1)	0.571
TLC % predicted	65 (17)	65 (9)	65 (19)	0.956
FVC % predicted	61 (13)	51 (11)	64 (12)	0.082
FEV <sub>1</sub> % predicted	64 (14)	56 (14)	67 (13)	0.175
FEV <sub>1</sub> /FVC ratio	83.7 (4.3)	83.0 (4.0)	84.0 (4.5)	0.705
DL <sub>CO</sub> % predicted	52 (22)	36 (8)	58 (22)	0.070
6MWT (m)	388 (114)	341 (116)	406 (114)	0.355

Data are mean ± SD, unless otherwise specified

*mMRC* modified medical research council dyspnea score, *TLC* total lung capacity, *FVC* forced vital capacity, *FEV<sub>1</sub>* forced expiratory in 1 second, *DL<sub>CO</sub>* carbon monoxide diffusion capacity of the lung, *6MWT* six-minute walk test (distance)

**Table 2** Individual FVC measurements at baseline ( $t_0$ ) and after 10-week treatment ( $t_1$ ), in decreasing order of relative percent interval change from baseline ( $\Delta\%$ )

Patient number (diagnosis)	t <sub>0</sub>		t <sub>1</sub>	Δ%
	FVC, L	FVC, % predicted	FVC, % predicted	
4 (DIP)	1.12	43	71	65 <sup>a</sup>
3 (COP)	1.83	48	76	58 <sup>a</sup>
5 (SjS)	1.24	46	57	24 <sup>a</sup>
8 (RA)	1.60	67	75	11 <sup>a</sup>
15 (IPAF)	1.71	56	60	7
11 (UPF)	2.24	75	79	5
10 (RA)	3.28	71	74	5
14 (CHP)	1.99	45	47	4
2 (SjS)	1.31	79	81	2
7 (DPM)	2.00	46	47	2
9 (SS)	1.94	56	56	1
1 (DPM)	2.43	77	76	-2
13 (CHP)	1.65	60	59	-2
12 (CHP)	2.33	73	70	-3
6 (DPM)	2.55	67	51	-24

<sup>a</sup>: response for primary endpoint (Δ% FVC > 10%)

*DIP* desquamative interstitial pneumonia, *COP* cryptogenic organizing pneumonia, *SjS* Sjögren syndrome, *RA* rheumatoid arthritis, *IPAF* interstitial pneumonia with autoimmune features, *UPF* unclassifiable pulmonary fibrosis, *CHP* chronic hypersensitivity pneumonitis, *DPM* dermatopolymyositis, *SS* systemic sclerosis

**Table 3** FVC measurements at baseline (t<sub>0</sub>) and after 10-week treatment (t<sub>1</sub>), stratified by treatment response status for primary endpoint

	t <sub>0</sub>	t <sub>1</sub>	Δ%	p value (paired)
	% predicted	% predicted	mean (range)	
Responders (n=4)	51.0 ± 10.9	69.8 ± 8.8	39.8	0.040
Non-responders (n=11)	64.1 ± 12.2	63.6 ± 12.8	(11.3-65.2) -0.4 (-23.5-7.0)	0.794

Data are mean ± SD, unless otherwise specified

**Table 4** HRCT findings and MRI results stratified by response status for primary endpoint

	Responders (n=4)	Non-responders (n=11)	<i>p</i> value
Reticulation, n (%)	2 (50)	6 (55)	1.000
Traction bronchiectasis, n (%)	3 (75)	7 (64)	1.000
%GGO	48.5 ± 5.7	41.9 ± 27.8	0.471
SSFSE T2 SI ratio (average)	4.3 ± 2.3	3.5 ± 1.4	0.433
SSFSE T2 SI ratio (maximal)	9.9 ± 8.1	7.3 ± 3.9	0.408
PROPELLER T2 SI ratio (average)	7.5 ± 2.9	7,7 ± 2.6	0.924
Relative enhancement			
At 1 minute	2.2 ± 0.6	2.2 ± 0.4	0.942
Peak	2.4 ± 0.4	2.5 ± 0.5	0.587
Time to peak	2.0 ± 1.2	4.0 ± 2.3	0.129
Slope	1.65 ± 1.11	0.85 ± 0.51	0.247
SSFSE-PROPELLER T2 match, n (%)	4 (100)	2 (18)	0.011
SSFSE-PROPELLER T2 mismatch, n (%)	0 (0)	9 (82)	0.011

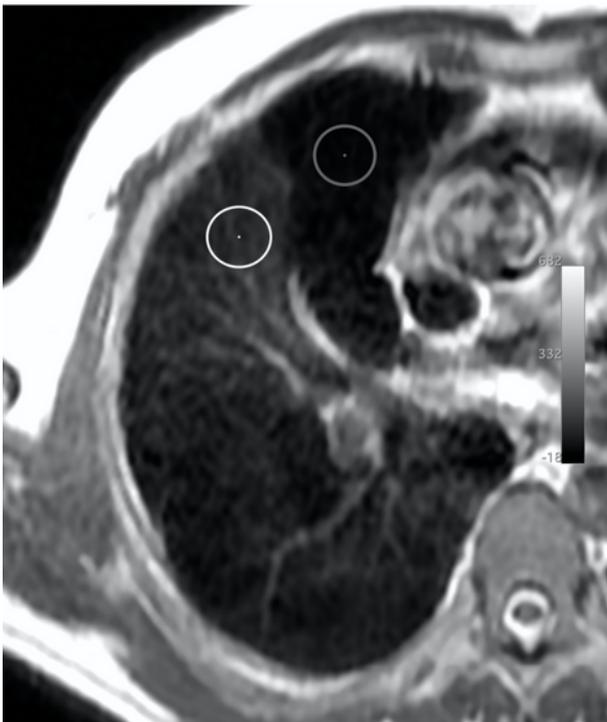
Data are mean ± SD, unless otherwise specified

%GGO percent area of ground-glass opacity (extent of abnormalities), SI/signal intensity

## Figures



A



B

**Figure 1**

ROI selection on T2-weighted MR image. a HRCT image, showing ground-glass opacity sharply demarcated from normal-appearing lung parenchyma. b T2-weighted SSFSE in the transverse plane with ROI inside representative area of lung abnormality (white circle) and in the normal-appearing adjacent lung parenchyma (grey circle). ROI, region of interest.



## Figure 2

a Representative case of SSFSE/PROPELLER T2 match in a 58-year-old female participant with idiopathic DIP that responded to treatment with prednisone (SSFSE T2, PROPELLER T2, HRCT: left to right). b Representative case of SSFSE/PROPELLER T2 mismatch in a 62-year-old female participant with CHP that did not respond to treatment with prednisone and azathioprine (SSFSE T2, PROPELLER T2, HRCT: left to right). DIP, desquamative interstitial pneumonia; CHP, chronic hypersensitivity pneumonitis.