Tracking interstitial lung disease in systemic sclerosis: integrating lung magnetic resonance imaging into a clinically oriented multimodal follow-up strategy

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Abstract

Objective

To assess the utility of lung magnetic resonance imaging (MRI) for monitoring interstitial lung disease (ILD) in patients with systemic sclerosis (SSc), using high-resolution CT (HRCT) as the reference. Additionally, we explored associations between MRI sequences and common imaging and functional parameters in SSc-ILD evaluation.

Methods

SSc patients with ILD requiring treatment initiation or change underwent lung assessment at baseline and after 6 months, including MRI (T2-weighted, T1 post-contrast, and T2 star sequences), HRCT, lung ultrasound, and pulmonary function tests. Six-month MRI and HRCT were qualitatively evaluated for improvement, stability, or progression. A follow-up HRCT was performed 2 years after enrolment.

Results

Fourteen SSc-ILD patients (64.3% female, mean age 48.3 years) were enrolled. MRI showed improvement in 1 patient, stability in 9, and progression in 4; in 2 progressed cases, inflammation decreased while fibrotic features increased. T1 contrast sequence significantly correlated with pleural irregularities on ultrasound (ϱ=0.55; p=0.04) and DLCO (ϱ=-0.65; p=0.01). MRI and HRCT findings at 6 months were concordant in 64.3% of cases, with fair agreement (weighted $\varkappa$=0.25). MRI outcomes at 6 months matched HRCT findings at 2 years in 92.8% of patients (13/14).

Conclusion

Lung MRI is a promising adjunctive tool for monitoring SSc-ILD and may provide complementary information to HRCT on early imaging changes, particularly the transition from inflammation to fibrosis. Among MRI sequences, T1 post-contrast best correlated with functional and ultrasound findings, supporting its role in fibrosis assessment.

Key words

systemic sclerosis, lung magnetic resonance imaging, high resolution computed tomography, lung ultrasound, interstitial lung disease

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Received on March 23, 2026; accepted in revised form on April 20, 2026.

Funding. This work received financial support by GILS ODV ETS Gruppo Italiano per la Lotta alla Sclerodermia.

Competing interests: E. Neri has received consultancies and/or honoraria from Bracco. All other authors report no competing interests.

Introduction

Despite progresses in diagnosis and treatment, interstitial lung disease (ILD) remains the leading cause of mortality in patients with systemic sclerosis (SSc). Consequently, recent literature consistently emphasises the need to identify diagnostic methods that can support and complement the current gold standard, the high-resolution chest CT (HRCT) (1, 2). In this context, magnetic resonance imaging (MRI) emerges as a radiation-free technique with several promising advantages. In fact, MRI is generally recognised for superior tissue characterisation compared with CT, by combining functional and structural information in a single examination. However, its application to lung imaging, and particularly to ILD, is still emerging and under active investigation. On the other hand, long acquisition time, poor spatial resolution, low proton density of lung tissue and respiratory motion artifacts are all acknowledged limitations (3, 4). Several MRI sequences have been designed to overcome those issues and to further improve discrimination between the different ILD components (5, 6).

In addition to its diagnostic role, few studies investigated the prognostic value of lung MRI in SSc-ILD (7, 8). On the contrary, prospective data on the role of lung MRI in follow-up and monitoring the response to treatment are still lacking. The aim of this proof-of-concept study was to evaluate the performance of lung MRI in the monitoring of SSc-ILD patients, using HRCT as a reference. Furthermore, we sought to investigate the relationships between different MRI sequences and various imaging and functional tests commonly used to assess SSc-ILD.

Methods

Study population

This study enrolled adult patients who met the 2013 EULAR/ACR criteria for SSc (9) and had newly diagnosed or worsening ILD requiring initiation or change in treatment. ILD was defined by the presence on HRCT of parenchymal abnormalities consistent with SSc-ILD, as judged by an experienced thoracic radiologist, in line with current consensus statements (10). ILD progression was assessed based on predefined thresholds of radiological worsening on HRCT, relative decline in pulmonary function tests (PFTs), or clinical deterioration, according to ERICE criteria (11). The study was approved by the local ethical committee (Comitato Etico Area Vasta Nord-Ovest, approval n. 15914) and conducted in accordance with the Helsinki Declaration; each patient voluntarily agreed to participate and gave written informed consent for the publication.

Lung parenchyma was imaged by MRI, HRCT (performed within ±7 days from MRI) and LUS (performed on the same day of MRI). PFTs were collected within ±2 weeks from MRI to evaluate the percentage of forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO). Patients underwent all the aforementioned investigations at baseline and after 6 months from the initiation or change in treatment for ILD, in order to detect short-term changes following therapeutic intervention and to mirror real-world clinical decision-making. In particular, 6-months lung MRI and HRCT were assessed to indicate whether the imaging picture presented improvement, stabilization or progression compared to baseline. Another HRCT was performed 2 years after the enrolment for the same classification purposes.

Lung magnetic resonance imaging

The MRI protocol applied was based on the approach previously proposed in the systematic review by Romei *et al.* (3). All patients were examined in the supine position with their arms placed above the head. MRI sequences were acquired either during end-expiratory breath-hold with a duration not exceeding 16 seconds, tailored to the individual patient's respiratory capacity and divided into multiple acquisition blocks when necessary, or using respiratory-triggered acquisitions in patients unable to sustain adequate breath-holds. MRI studies were performed using a 1.5T Magnetom Symphony Tim whole-body system (Siemens, Erlan-

gen, Germany). The imaging protocol included an axial T2-weighted multi-breath-hold multi-shot Turbo Spin Echo sequence (BLADE, Siemens), acquired at the end of both the inspiratory and expiratory phases. For quantitative measurements, regions of interest (ROIs) of at least 100 mm^2 were placed over areas of normal lung parenchyma, pathological lung tissue, and paravertebral muscles. Subsequently, signal intensity ratios were calculated, including the pathological lung-to-muscle (PL-M) ratio and the normal lung-to-muscle ratio. T2 star sagittal maps were acquired using a multi-breath-hold, multi-echo two-dimensional Fast Low Angle Shot (FLASH, Siemens) sequence at the end of expiration. Measurements were obtained by placing ROIs of at least 100 mm^2 on areas of normal lung, pathological lung, and paravertebral muscles within the same patient. ROI placement was guided by visual assessment of the corresponding morphological images. ROIs were placed in lung regions representative of the predominant ILD involvement, without attempting a pattern-based lesion classification. A pre-contrast Volumetric Interpolated Breath-hold Examination (VIBE, Siemens) sequence was acquired in both axial and coronal planes. This acquisition was repeated at 5, 10, and 20 minutes following intravenous administration of the contrast agent gadobutrol. To quantify post-contrast enhancement, three ROIs of at least 100 mm^2 were placed over areas of normal lung, pathological lung, and paravertebral muscles. ROIs were positioned in the same locations as those used for the T2-weighted quantitative measurements. All ROIs were carefully placed to avoid large vessels and major airways. The enhancement curve was analysed to assess the presence of residual signal on T1-weighted images at 20 minutes post-contrast compared to the 5-minute acquisition.

T2-weighted sequences are sensitive to increased lung water content and are typically elevated in areas of active inflammation or oedema. T1-weighted sequences with delayed post-contrast imaging can highlight fibrotic regions due to the prolonged retention of contrast agents in fibrotic tissue. T2 star sequences may provide insights into lung parenchymal changes, with lower values possibly reflecting inflammatory changes and higher values potentially associated with fibrotic features; however, these interpretations remain exploratory and require further validation. Moreover, various histopathological factors can independently influence these MRI parameters, necessitating cautious interpretation. Based on the aforementioned quantitative parameters, including the PL-M ratio, the mean T2 signal of pathological lung regions, and the morphology of the enhancement curve – a comprehensive qualitative global radiological evaluation was performed. Final classification of lung MRI findings as improved, stable, or progressed was reached by jointly integrating these quantitative metrics, all considered with equal weight, along with visual assessment of T2-weighted, T1 post-contrast, and T2 star sequences, and was based on the direction and consistency of changes over time rather than on predefined numerical thresholds. In cases where a reduction in inflammatory signal and a concurrent increase in fibrotic features were observed in the same patient, the MRI was considered as progressing. MRI evaluations were performed by a single experienced radiologist with access to HRCT results, in keeping with the exploratory nature of this proof-of-concept study.

High-resolution chest CT

All CT examinations were performed using a 64-detector system (Somatom Sensation, Siemens Medical Systems, Erlangen, Germany), with images acquired from the entire lung parenchyma at baseline, after 6 months, and again after two years. The imaging protocol consisted of a non-contrast-enhanced scan in the supine position, with a field of view of 290–340 mm, tube voltage of 100-120 kVp, tube current of 250 mA, and a 512 × 512 matrix. Images were reconstructed using a high-spatial-resolution kernel for lung parenchyma (B60f), with a slice thickness of 1.5 mm and an increment of 1 mm. All scans were performed during full inspiration with breath-holding. Images were reviewed by a radiologist experienced in thoracic imaging to assess disease progression. Patients were categorised as improved, stable, or progressed. Improvement was defined as a noticeable reduction in parenchymal abnormalities, while progression was identified by a clear increase in the global extent of interstitial lung abnormalities and/or by longitudinal evolution toward more overt fibrotic features on serial examinations. Stable disease was defined as the absence of significant changes on follow-up imaging.

Lung ultrasound

LUS was performed by two experienced operators who had previously undergone a reliability test using video clips, achieving an intraclass correlation coefficient of 0.80. A 4-13MHz linear probe (MyLab Class C, Esaote, Genoa, Italy) was used to assess 55 intercostal spaces on each patient as previously described (12). LUS images were scored during live scanning for the presence of B-lines (BL, a vertical hyperechoic reverberation artifact that arises from the pleural line, extends to the bottom of the screen without fading, and moves synchronously with lung sliding) and pleural irregularities (PLI, a loss of regularity that may be associated with an increase in thickness, which may be focal, diffuse, linear or nodular) (13, 14). A quantitative score was used for BL, and a semi-quantitative 0-1-2 score for PLI. They were then added to obtain a total BL score and a total PLI score.

Statistical analysis

Continuous data were described by mean and standard deviation, categorical data by absolute and relative frequency. The normality of distribution of continuous variables was assessed by inspection of quantile-quantile plots. Pearson's correlation coefficient was computed to assess relationship between the values of MRI sequences and other continuous variables both at baseline and at 6-months. The agreement between the final qualitative evaluation of MRI and HRCT was measured by weighted Cohen's kappa with

Table I. Epidemiological and SSc-specific characteristics of the cohort.

Patient	Gender	Age	Smoke	Skin	Autoantibody	Baseline IS	New IS
1	F	27	no	dcSSc	Scl70	-	MMF 2g
2	F	28	no	lcSSc	Scl70	MMF 1g	MMF 2g
3	F	54	no	dcSSc	Scl70	-	CYC
4	M	71	no	dcSSc	RNAP	CYC	RTX
5	M	47	no	dcSSc	Scl70	-	CYC
6	F	50	former	lcSSc	Scl70	-	MMF 2g
7	M	56	no	dcSSc	RNAP	-	MMF 2.5g
8	F	50	no	dcSSc	Scl70	MMF 2g	CYC
9	F	49	no	dcSSc	RNAP	MMF 2g	CYC
10	M	61	no	dcSSc	Scl70	-	CYC
11	F	52	former	dcSSc	PM-Scl	-	MMF 2g
12	M	60	former	dcSSc	Scl70	-	CYC
13	F	36	no	dcSSc	fibrillarin	MMF 1g	MMF 2g
14	F	35	no	lcSSc	Scl70	-	MMF 2g

dcSSc: diffuse cutaneous; lcSSc: limited cutaneous; Scl70: anti-topoisomerase I; RNAP: anti-RNA polymerase III; IS: immunosuppressant; MMF: mycophenolate mofetil; CYC: cyclophosphamide; RTX: rituximab.

linear weights. Significance was set at 0.05 and all analyses were carried out with R software (R Core Team 2023, R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

Fourteen SSc patients (64.3% female, mean age 48.3±12.8 years) starting (n=9) or changing (n=5) treatment for a newly diagnosed or worsening ILD were enrolled. Of note, 78.5% had a diffuse skin involvement and anti-topoisomerase I was the most frequent autoantibody (64.3%). All the patients had a non-specific interstitial pneumonia (NSIP) HRCT pattern; 3 of them were former smokers. A complete summary of baseline characteristics and SSc-specific features can be found in Table I.

Lung MRI

Figure 1 represents the trend of the different MRI sequences for each patient from baseline to 6 months. T2 sequences of 2 subjects were discarded because of technical problems. After a comprehensive qualitative assessment of T2, T1 contrast and T2 star results, one patient was considered as improved at lung MRI, whereas stabilization was reached in 9 of them and 4 SSc-ILD cases were evaluated as progressors. Of note, the qualitative MRI assessment showed in 2 patients a reduction of the inflammatory part together with an increase in the fibrotic component; in those cases, lung MRI was considered as progressed.

Correlations between T2, T1 contrast and T2 star values and the outcomes of PFTs and LUS were then analysed. DLCO showed a strong negative correlation at baseline with T1 contrast (ϱ=-0.65; p=0.01), but this finding was not confirmed at 6 months. A moderate direct correlation emerged between PLI and T1 contrast both at baseline and at 6 months (ϱ=0.55 and p=0.04 for both). No correlations were found between RMI sequences and FVC or BL.

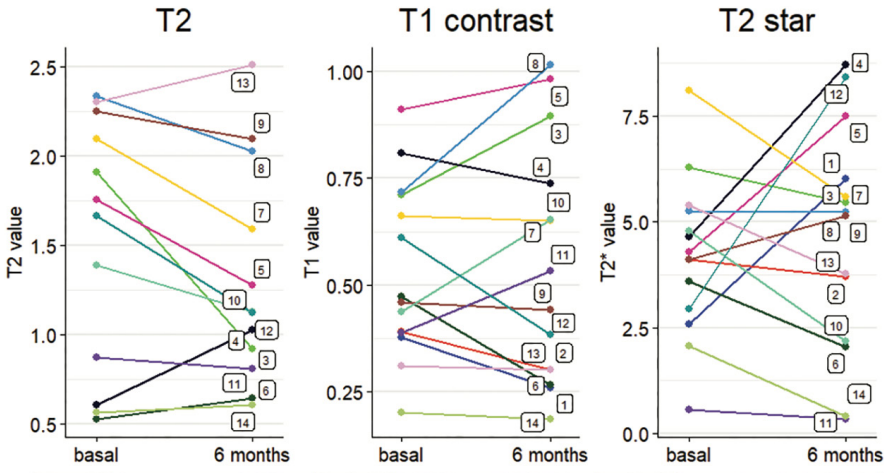
HRCT agreement

The comparison between baseline and 6-months HRCT revealed improvement in 2 patients, stabilisation in 9 and progression in 3. HRCT and qualitative MRI gave the same result in 64.3% of the cases. There was only one patient with a progression for MRI and an improvement for HRCT, in all other 4 cases the discordance between HRCT and MRI concerned only the stabilisation-improvement and stabilisation-progression classifications (Fig. 2). A fair agreement was calculated between the two imaging techniques (weighted k=0.25; standard error 0.21; 95% confidence interval -0.17/0.67) (Supplementary Table S1).

HRCT was then repeated two years after the enrolment. As shown in Figure 2, when comparing the two HRCTs, ten SSc-ILD patients remained in the same classification subgroup, whereas 4 of them had an HRCT change over time. It is worth to note that the outcome observed at 6 months with MRI presented a very high concordance (13 cases out of 14; 92.8%) with HRCT outcome at 2 years.

Discussion

Identifying SSc-ILD patients with a progressing phenotype is an issue of paramount importance. In this regard, the accurate distinction between inflammatory and fibrotic parenchymal areas has a crucial role in the choice of proper therapeutic strategies. HRCT is considered the gold standard for imaging, but still has a limitation in distinguishing the "true" nature of ground glass opacities (GGO), which is the main HRCT feature in NSIP, the most common radiological pattern in SSc-ILD (15). GGO can in fact histopathologically derive either from partial filling of the alveolar spaces or from thickening of the alveolar walls and septal interstitium, and this is consistent with the radiological finding that areas of inflammation and fibrosis may have the same GGO appearance on HRCT (16, 17). When monitoring a SSc-ILD patient suspected of pulmonary progression, the two main radiological issues both involve GGO: spotting areas of inflammation in the setting of fibrosis (usual interstitial pneumonia pattern or fibrotic NSIP) and early identifying the onset of a fibrotic component after an inflammatory phase. In this context, lung MRI could therefore represent a complementary imaging tool that may



1	stabilization	6	stabilization	11	stabilization
2	stabilization	7	improvement	12	progression
3	progression	8	stabilization	13	stabilization
4	stabilization	9	stabilization	14	stabilization
5	progression	10	progression		

Fig. 1. Trend of lung MRI sequences for each patient, with final qualitative classification.
Each line represents a single patient across baseline and 6-month follow-up.

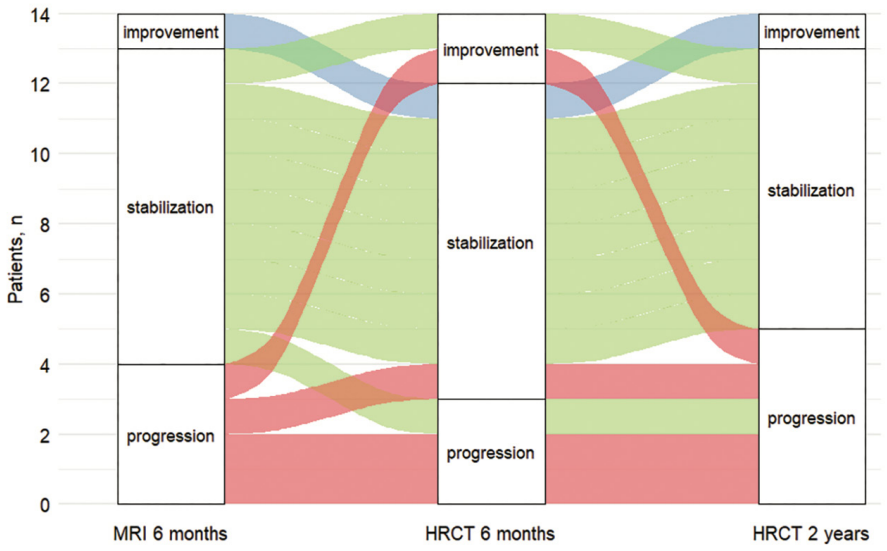


Fig. 2. Alluvial plot depicting the flow of patient classifications from MRI at 6 months to HRCT at 2 years.
Colours are based on MRI qualitative outcomes.

help address some limitations of HRCT, potentially offering comparable accuracy in characterising ILD extent and severity (18). In fact, the use of multiple MRI sequences, each with its own specificity toward different pathological parenchymal features, may allow an overall qualitative evaluation that could suggest whether lung involvement is predominantly inflammatory or fibrotic, or whether these components coexist in different proportions, as observed in the present study.

To the best of our knowledge, this is the first study to longitudinally repeat lung MRI during prospective follow-up of SSc patients undergoing treatment for ILD, in order to evaluate MRI changes over time and relate them to HRCT outcomes. This is part of the recent trend aimed at identifying emerging imaging techniques that may contribute to the assessment and monitoring of SSc-ILD patients during therapy, such as quantitative HRCT and LUS (12). So far, other studies suggested how lung MRI could predict ILD progression or response to treatment (7, 8, 19), but none of them repeated MRI longitudinally to assess temporal changes during therapy. In this context, an interesting subgroup is represented by patients with a discrepancy between a progressed MRI and a stable or improved HRCT. In these cases, discordance was mainly driven by MRI findings suggestive of early fibrotic changes developing within areas of pre-existing inflammatory involvement, in the absence of overt morphologic progression detectable on HRCT. This pattern may explain the direction of disagreement observed in the agreement analysis, with MRI more frequently classifying progression when HRCT remained stable. In fact, although in the improvement/stabilisation/progression classification we found a fair agreement between the two imaging methods, the HRCT repeated after two years suggested a potentially high predictive value of lung MRI, although this finding requires confirmation in larger cohorts. These data suggest that MRI may be sensitive to early imaging changes associated with lung progression, particularly the appearance of fibrotic features following an inflammatory phase. Nevertheless, this observation should be interpreted cautiously, and larger longitudinal studies are needed to determine whether MRI can reliably anticipate changes detectable by HRCT.

Finally, we identified T1 contrast as the MRI sequence more significantly correlating with PFTs and LUS. In particular, the direct correlation with PLI observed both at baseline and follow-up strengthens the value of the T1 contrast sequence in identifying the fibrotic involvement, given that PLI tend to be more specifically influenced by the extent of fibrosis than BL (20).

Our study is burdened by some limitations, in addition to those intrinsic to MRI itself. The fairly small cohort and the fact that the final MRI judgment by the radiologist is qualitative and not based on predefined quantitative thresholds limit both the reproducibility and the generalisability of our results. In addition, the use of a single reader for both HRCT and MRI, with

access to HRCT findings during MRI interpretation, may have introduced observer bias. Accordingly, the present study should be regarded as a proof-of-concept and hypothesis-generating analysis, aimed at exploring the potential of MRI assessment in comparison with HRCT and at providing preliminary evidence to inform the design of future adequately powered studies. Furthermore, histological evidence could have confirmed the speculations about the different extents of inflammatory and fibrotic components as indicated by the MRI sequences. Finally, the inclusion of patients receiving different therapeutic regimens may represent a confounding factor, although it reflects real-world practice and aligns with the exploratory aim of assessing whether MRI can detect changes in inflammatory and fibrotic components independently of the specific treatment used. Overall, the findings of this study represent a preliminary step toward exploring the potential role of lung MRI in clinical practice as a complementary tool in the monitoring of SSc-ILD patients.

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