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Nicholas Landini, Martina Orlandi, Linda Calistri, Cosimo Nardi, Pierluigi Ciet, Silvia Bellando-Randone, Serena Guiducci, Thomas Benkert, Valeria Panebianco, Giovanni Morana, Marco Matucci-Cerinic, Stefano Colagrande

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TITLE

Advanced and traditional chest MRI sequences for the clinical assessment of Systemic Sclerosis related Interstitial Lung Disease, compared to CT:

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AUTHORS

Nicholas Landini[1^], Martina Orlandi[2^], Linda Calistri[3], Cosimo Nardi[3], Pierluigi Ciet[4,5], Silvia Bellando-Randone[2], Serena Guiducci[2], Thomas Benkert[6], Valeria Panebianco[1], Giovanni Morana*[7], Marco Matucci-Cerinic [2,8^^] and Stefano Colagrande[3^^]

^Nicholas Landini and Martina Orlandi are co-first authors for the present paper

^^ Marco Matucci Cerinic and Stefano Colagrande are co-last authors for the present paper

*corresponding author

AFFILIATIONS

[1] Department of Radiological, Oncological and Pathological Sciences, Policlinico Umberto I Hospital, "Sapienza" Rome University, Rome, Italy.

[2] Department of Experimental and Clinical Medicine, Division of Rheumatology AOUC Careggi, University of Florence, 50134 Florence, Italy.

[3] Department of Experimental and Clinical Biomedical Sciences, University of Florence & Radiodiagnostic Unit n. 2 AOUC.

[4]Department of Radiology and Nuclear Medicine, Erasmus MC – Sophia, Rotterdam, Netherlands

[5]Department of Radiology, Policlinico Universitario, Cagliari, Italy.

[6] MR Applications Predevelopment, Siemens Healthcare GmbH, Erlangen, Germany.
[7] Department of Radiology, S. Maria Ca' Foncello Regional Hospital, Treviso, Italy.

[8] Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS San Raffaele Hospital, 20132 Milan, Italy.

Address correspondence to:

Giovanni Morana

Department of Radiology, S. Maria Ca' Foncello Regional Hospital, Treviso, Italy.

E-mail: gmorana61@gmail.com

AUTHORS' FULL ADDRESSES

- Nicholas Landini, MD, PhD

  Department of Radiological, Oncological and Pathological Sciences, Policlinico Umberto I Hospital, "Sapienza" Rome University, Rome, Italy.

  E-mail: nicholas.landini@uniroma1.it

  ORCID ID: 0000-0002-2928-3003

- Martina Orlandi, MD, PhD

  Department of Experimental and Clinical Medicine, University of Florence, Division of Rheumatology AOUC, Florence, Italy.

  E-mail: martina.orlandi@unifi.it

  ORCID ID: 0000-0001-6784-2235

- Linda Calistri, MD, PhD
  Department of Experimental and Clinical Biomedical Sciences, University of Florence-Azienda Ospedaliero-Universitaria Careggi, Florence, Italy.
  E-mail: linda.calistri@unifi.it
  ORCID ID: 0000-0002-3589-4820

- Cosimo Nardi, MD, PhD

  Department of Experimental and Clinical Biomedical Sciences, University of Florence-Azienda Ospedaliero-Universitaria Careggi, Florence, Italy.

  E-mail: cosimo.nardi@unifi.it

  ORCID ID: 0000-0002-5489-7824

- Pierluigi Ciet, MD, PhD

  Department of Radiology, Erasmus University Medical Centre, Rotterdam, the Netherlands

Department of Radiology, Policlinico Universitario, Cagliari, Italy
E-mail: p.ciet@erasmusmc.nl
ORCID ID: 0000-0003-4017-8957

- Silvia Bellando-Randone, MD, PhD
Department of Experimental and Clinical Medicine, University of Florence and Division of Rheumatology AOUC & Scleroderma Unit, Florence, Italy.
ORCID ID: 0000-0002-5926-6263
E-mail: silvia.bellandorandone@unifi.it

- Serena Guiducci, MD, PhD
Department of Experimental and Clinical Medicine, University of Florence and Division of Rheumatology AOUC & Scleroderma Unit, Florence, Italy.
E-mail: serena.guiducci@unifi.it

- Thomas Benkert, PhD

MR Applications Predevelopment, Siemens Healthcare GmbH, Erlangen, Germany

E-mail: benkert.thomas@siemens-healthineers.com
ORCID ID: 0000-0002-3794-5580

- Valeria Panebianco, MD, PhD

Department of Radiological, Oncological and Pathological Sciences, Policlinico Umberto I Hospital, “Sapienza” Rome University, Rome, Italy.

E-mail: valeria.panebianco@uniroma1.it

- Giovanni Morana, MD
Department of Radiology, Ca' Foncello Hospital, Piazzale Ospedale, 1, Treviso, Italy.
E-mail: gmorana61@gmail.com
ORCID ID: 0000-0003-3144-2963

- Marco Matucci-Cerinic, MD, PhD
Department of Clinical and Experimental Medicine, University of Florence, & Department of Geriatric Medicine, Division of Rheumatology AOUC, Florence, Italy.
E-mail: marco.matuccicerinic@unifi.it

ORCID ID: 0000-0002-9324-3161

- Stefano Colagrande, MD

Department of Experimental and Clinical Biomedical Sciences, University of Florence-Azienda Ospedaliero-Universitaria Careggi, Florence, Italy.

E-mail: stefano.colagrande@unifi.it

ORCID ID: 0000-0003-0137-8606

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ABSTRACT

Background

MRI is a radiation-free emerging alternative to CT in systemic sclerosis related interstitial lung disease (SSc-ILD) assessment. We aimed to compare T2 radial TSE and PD UTE MRI sequences with CT in SSc-ILD extent analysis and correlations with pulmonary function tests (PFT).

Material and Methods

29 SSc-ILD patients underwent CT, MRI and PFT. ILD extent was visually assessed. Lin's concordance correlation coefficients (CCC) and Kruskal Wallis test (p-value<0.05) were computed for inter-method comparison. Patients were divided in limited and extended disease, defining extended ILD with two methods: A) ILD>30% or 10%<ILD≤30% with FVC%<70%; B) ILD>20% or 20% with FVC<70%. MRI Sensitivity, specificity, Positive predictive value (PPV), Negative Predictive Value (NPV) and accuracy were assessed. Pearson correlation coefficients r (p-value<0.025) were computed between ILD extents and PFT (FVC% and DLCO%).

Results

Median ILD extents were 11%, 11%, 10% on CT, radial TSE and UTE sequences, respectively. CCC between CT and MRI was 0.95 for both sequences (Kruskal-Wallis p-value=0.64). Sensitivity, specificity, PPV, NPV and accuracy in identifying extended disease were: A) 87.5%, 100%, 100%, 95.5 and 96.6% with radial TSE and 87.5%, 95.2%, 87.5%, 95.2 and 93.1% with UTE; B) 86.7%, 86.4%, 66.7%, 95.0% and 86.2% for both sequences. Pearson r of CT, radial TSE and UTE ILD extents with FVC were -0.66 -0.60 and -0.68 with FVC, -0.59, -0.56 and -0.57 with DLCO, respectively (p<0.002).

Conclusions

MRI sequences may have similar accuracy to CT to determine SSc-ILD extent and severity, with analogous correlations with PFT.

KEY WORDS

Magnetic Resonance Imaging; Computed Tomography; Interstitial Lung Disease; Systemic Sclerosis;

ABBREVIATIONS

Computed Tomography: CT

Diffusion Capacity of the Lungs for Carbon Monoxide: DLCO

Forced Vital Capacity: FVC

Turbo Spin Echo (TSE)

Interstitial Lung Disease: ILD

Lyn's concordance coefficient: CCC

Magnetic Resonance Imaging: MRI

Negative Predictive Value: NPV

Proton Density: PD

Positive Predictive Value: PPV

Pulmonary Function Tests: PFT

Systemic Sclerosis: SSc

Ultrashort Echo Time: UTE

INTRODUCTION

Systemic Sclerosis (SSc) is an autoimmune rheumatic disease with multiorgan involvement[1,2], where interstitial lung disease (ILD) is the major cause of death[3]. Computed Tomography (CT) is the gold standard imaging technique in ILD evaluation[4]. Goh et al.[5] have shown that an extended disease on CT was a significant predictor of mortality, providing two possible methods to identify extended and limited disease, on the background of the ILD extent on CT alone or together with pulmonary function tests (PFT).

Moreover, as known, CT extents of ILD parenchymal alterations correlate with pulmonary function tests (PFT)[6], helping clinicians in understanding the reasons that lies behind functional worsening and addressing their management[4].

Despite the use of low-dose CT protocols in SSC, radiation exposure limits its use in young patients and raising concern for significant cumulative dose related to long-life follow-up[7].

For this reason, the use of chest Magnetic Resonance Imaging (MRI) has been proposed[8]. Chest MRI is limited by respiratory motion artifacts, low proton density of lung parenchyma and magnetic susceptibility of sharp air/parenchyma interfaces, that leads to a fast signal decay. However, lung dedicated MRI protocols have been implemented over years and prototype sequences, e.g. ultrashort echo time (UTE), have developed to partially overcome these limitations and provide diagnostic image quality, as shown in other pulmonary disease, such as cystic fibrosis [9, 10] and, experimentally, also in patients with SSc-ILD[11-18].

Hence, the aim of our work was to prospectively evaluate the reliability of a conventional MRI sequence implemented for lung parenchyma, namely a T2 radial Turbo Spin Echo (TSE) sequence and a Proton Density (PD) UTE sequence for the quantification and stratification of pulmonary abnormalities in SSc-ILD patients with the Goh system[5], compared to CT. We also correlated ILD extents determined with both CT and MRI to Functional Vital Capacity, % predicted (FVC%) Diffusion capacity of the Lungs for Carbon Monoxide, % predicted (DLCO%).

MATERIALS AND METHODS

Study design

This was a prospective observational multicentric study conducted by the Rheumatology Unit in collaboration with the Radiology Unit of the Careggi University Hospital in Florence and the Radiology Department of Ca' Foncello General Hospital in Treviso. The research project was approved by the local Institutional Ethics Committees (Careggi, Florence, 27299/2019, code 15220/oss and CESC Treviso-Belluno, 641/CECEAV). All patients gave their informed consent. From January 2022 to June 2022, the first 60 consecutive SSc patients were evaluated by rheumatologists (MO, MMC) and classified according to the 2013 ACR/EULAR criteria[19]. All patients were ≥ 18 years of age. Patients with a suspicion of ILD underwent CT. When ILD was confirmed at CT, a chest MRI was performed on the same day. Pulmonary function tests (PFT) were performed within one week. The exclusion criteria were: patient's refusal, heart failure, pulmonary disease other than ILD, Raynaud phenomenon, contraindication to MRI (claustrophobia, impossibility to lay supine for the scan time and/or to follow breathing instructions). Patients with low image quality on CT and/or MRI scans were excluded. All data were anonymized and an alpha numeric code was assigned to each patient. Demographic (age, gender) and clinical data (antibody subset, including anti-centromere and Scl-70 antibodies; previous and ongoing therapy; PFT; presence of pulmonary arterial hypertension) of each patient were collected in a password-protected electronic database.

CT, MRI scans and pulmonary function tests

The CT images were acquired with two Siemens scanners (Erlangen, Germany), a Sensation 64 and a SOMATOM Definition Flash, at full inspiration, with the following shared protocol: tube voltage 120 kV, tube current 200 mAs, slice thickness 1 mm, high resolution kernel reconstruction, matrix 512x512. MRI acquisitions were performed with two Siemens 1.5 T scanners (Erlangen, Germany): An Avanto Fit Treviso and an Aera. The MRI protocol was identical and consisted of two sequences:

1) a conventional axial breath-hold end-expiratory 2D T2 radial TSE sequence (repetition time /echo time 2200/89 ms, matrix 256×256, slice thickness 5 mm, distance factor 20%, 4-5 concatenations of 18 s each);

2) a free breathing PD UTE sequence (repetition time/echo time 3.73/0.05 ms, Flip Angle 5°, matrix 320×320, voxel size 1.5x1.5x1.5 mm), scanned in coronal sections to reduce the acquisition time (7-9 minutes), and reformatted in axial plane with 1.5 mm slice thickness (Figure 1).

Contrast agent was not administered, and patients were instructed on how to perform the breathing maneuvers. The PFT were performed with the mass flow sensor and multi-gas analyser V6200 Autobox Body Plethysmograph (Sensor Medics, Yorba Linda, California, USA). Static and Dynamic lung volumes and DLCO were measured according to the American Thoracic Society/European Respiratory Society guidelines[20-22].

ILD extent analysis and stratification

Two radiologists with 10 years of experience in lung MR (GM) discarded low-quality scans, in presence of significant blurring of airways and/or of peripheral lung parenchyma, based on his experience. Then, all acquisitions, were randomized and scored by a radiologist with 10 years of experience in chest imaging (NL), blinded to demographic, clinical and functional data. CT images were analyzed with a standard lung window, while the window of the MR images was adjusted freely to obtain the best contrast-to-noise ratio, as previously performed[18].

The ILD extent was visually computed adopting the Goh et al. system[5]: the percentage of lung involvement was assessed at five levels to the nearest 5% (1-aortic arch at the origin of great vessels, 2-carina, 3-pulmonary veins confluence, 5-diaphragmatic dome, 4-the midway between 3 and 5) and the total extent was determined as average extent among the levels, both on CT and MRI scans.

After a month, all scans were scored again by the same observer to assess intra-reader agreement and by a general radiologist with 15 years of experience (CN), for the inter-reader agreement. Then, based on ILD extent, patients were stratified in limited and extended disease, defined as suggested by Goh et al.[5], as follows:

Method A:

Limited if ILD extent<10% lung parenchyma or 10%<ILD≤30% (indeterminate extents) with FVC%≥70%;

Extended if ILD extent>30% lung parenchyma or 10%<ILD≤30% (indeterminate extents) with FVC%<70%.

Method B:

Limited if ILD extent<20% lung parenchyma or 20% (indeterminate extent) with FVC≥70%;

Extended if ILD extent>20% lung parenchyma or 20% (indeterminate extent) with FVC<70%.

Statistical analysis

Using descriptive statistics, we reported absolute count and percentage and mean with standard deviation or median with interquartile range. The Lin's concordance coefficient (CCC) was adopted to estimate intra- and inter-reader agreements as well as the agreement of ILD extents between CT and MRI. The Kruskal-Wallis test was adopted to compare ILD extents between CT and MRI, with a significant p-value set at <0.05.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were computed for the detection of extended disease with method A and method B, on both MRI sequences, against the gold standard CT. Pearson correlation coefficients (r) were computed to explore the correlations of FVC% and DLCO% with Ct and MRI. A significant p-value was set at <0.05. Bonferroni correction for multiple tests was performed, with a resulting adjusted p-value <0.025. Collected data were analyzed using the SPSS® v. 26.0 statistical analysis software (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL).

RESULTS

Patients

ILD was diagnosed on CT in 29 out of 60 patients; these patients underwent MRI. No scans were excluded for low image quality and all 29 scans were included in the study. The mean age was 40 (±5), 24/29 were female, 11/29 were smokers, mean FVC% was 81% and mean DLCO% was 54%. All demographical and clinical data are shown in Table 1.

ILD assessment, Readers' and CT/MRI agreements

The median of ILD extent at CT was 11%, while with MRI was 11% on T2 radial TSE and 10% on PD-w UTE. (Table 2). The intra-reader CCC was 0.98, 0.97 and 0.95 for CT images, radial TSE and UTE, respectively, while the inter-reader CCC was 0.91, 0.86 and 0.82 for CT images, radial TSE and UTE, respectively. CCC (95% confidence interval) between CT and MRI was 0.95 (0.91-0.98) for radial TSE and 0.95 (0.91-0.97) for UTE (scatterplots in Figure 2). CT and MRI extents were not significantly different (Kruskal-Wallis p-value=0.64).

Disease stratification and correlations with pulmonary function tests

At CT evaluation, the patients with extended disease were 8 and 9 out 29 by the method A and B, respectively. At MRI the results were as follows:

by Method A: 7/29 with radial TSE (24%) and 8/29 with UTE (28%);

by Method B: 7/29 with radial TSE (24%) and 7/29 with UTE (24%).

With method A, 7 out of the 8 patients with extended disease on CT where identified by MRI, with both sequences. With method B, 6 out the 9 patients with extended disease where identified by MRI, with both sequences.

All agreements and disagreements are shown in Table 3.

In the identification of extended ILD with method A, MRI sensitivity, specificity, PPV, NPV and diagnostic accuracy were (Table 4):

87.5%, 100%, 100%, 95.5%, and 96.6% on radial TSE, respectively;

87.5%, 95.2%, 87.5%, 95.2%, and 93.1% on UTE, respectively;

while, with method B, for both sequences, were:

66.6%, 95.0%, 85.7%, 86.4%, and 86.6%, respectively.

Regarding correlations with PFT, CT, radial TSE and UTE correlation coefficients with FVC were:

-0.66 (p-value<0.0001), -0.68 (p-value<0.0001) -0.60 (p-value<0.0006), respectively;

while, with DLCO resulted:

-0.59 (p-value<0.0008), -0.57 (p-value<0.002) and -0.56 (p-value<0.002), respectively.

DISCUSSION

In this study we compared T2 radial TSE and PD UTE sequences with CT in parenchymal abnormalities evaluation and correlations with PFT in SSc-ILD subjects.

Our data showed a good performance of MRI for clinical assessment of SSc-ILD, allowing similar results with CT in extent stratification, especially with the method A, suggested in clinical practice[5], and in terms of correlation with functional deterioration.

MRI T2 sequences for ILD evaluation were firstly adopted by Pinal Fernandez et al.[15], who found a significant correlation of ILD extent with PFT, similarly to CT, as we did. Traditionally, the severity of SSc-ILD is defined by the degree of ventilatory restriction at PFT together with the extension of ILD at CT. Indeed, pulmonary volumes and DLCO are indirect measures and highly variable surrogates for the extent of structural disease abnormality defined at CT[23]. On the other hand PFT parameters may reflect abnormalities other than IDL extent alone (e.g. pulmonary hypertension)[24]. Hence, PFT and CT are both fundamental for clinicians to understand the status of the patient and decide the adequate management, as demonstrated, for example, by the Goh stratification system itself[5]. However, in the cohort of Pinal Fernandez et al.[15], MRI underestimated ILD extents, while in the present study MRI ILD extent was comparable with that detected on CT (Figure 3). This discrepancy could be explained by technical differences between the two acquisition protocols. We adopted a T2 radial TSE sequence that, in order to reduce acquisition times and increase image quality, exploited a different K-space acquisition strategy compared to the Half Fourier T2 sequence utilized by Pinal Fernandez et al.[14]. In fact, our T2 sequence performs a radial sampling of the k-space, which promotes contrast resolution and is more robust against movement artefacts[11]. A T2 radial sequence has been recently tested also in SSc-ILD patients by Hochhegger et al.[25], proving that a MRI score based both on extent and signal intensity analysis could retrospectively predict functional disease progression similarly to CT. In this study, the T2 radial TSE sequences allowed an analogous stratification of SSc-ILD compared to CT, in particular with the method A (i.e. indeterminate extent if 10<ILD≤30%) of the Goh et al. method[5], that is suggested in clinical practice. The Goh et al. ILD severity stratification[3] is widely accepted in clinical practice as prognostic determinant: in fact, extended disease, excluding patients in the early phase of SSc[26], is a well-recognized risk mortality factor[3].

In the current study, we applied a breath hold T2 radial sequence composed of 5 apneas of 18 seconds each, instead of a free breathing sequence as performed by Hochhegger et al.[25]. This choice was made to reduce the total scan time, which also included a free breathing UTE. In fact, based on our previous experience, acquiring T2 radial TSE usually allows 2-3 minutes reduction of total scan time. Nevertheless, some possible drawbacks related to this acquisition strategy need to be mentioned. Specifically, apnea may be not easily held by SSc-ILD patients, while free breathing scans may provide high quality images in a more comfortable breathing condition[27]. However, all our patients were able to perform MRI examination and no images was discarded because of low quality.

Recently, it has been proved that **UTE sequences** provide comparable results to CT in the evaluation of ILD in SSc patients[18]. In SSc-ILD, our data show that UTE sequence performs similarly to T2 radial TSE

sequence (Figure 3), in terms of disease extent assessment and stratification, as well as with regards to PFT correlations. UTE sequences exploit a spiral sampling of the k-space with ultrafast echo times (less than 1 millisecond), that reduce the effects of the fast signal decay in lungs, allowing low slice thickness with high spatial resolution[11, 27]. Moreover, with isotropic acquisitions, images may be reformatted in other spatial planes, similarly to CT, that may be very useful in pulmonary and chest disease evaluation[11, 28]. However, UTE sequences are still provided as research prototype, and not validated for clinical use, contrarily to radial TSE. Moreover, the inter-reader agreement was higher with T2 radial TSE. Being the second reader a general radiologist, the result could be explained by a major confidence with this traditional sequence. Hence, our results suggest the need for an appropriate MRI training to radiologists, who are not familiar with lung MRI.

This study represents a further step in the understanding the potential **utility of MRI** in the evaluation of SSc-ILD, although multicenter studies will have to confirm our findings. Moreover, a longitudinal imaging follow up will be needed to understand the accuracy of MRI in the assessment if ILD extent changes in time. However, since MRI could identify different ILD extents, we expect that it may be able to identify changes over time. On the other hand, our results highlight the need to develop new MRI acquisition strategies for the diagnosis and evaluation of ILD at lower extents. In fact, although MRI ILD extent and severity stratification may result similar to CT, the scatterplots of MRI-CT ILD extents showed a wider dispersion at lower ILD extents (figure 2). We hypothesized that this issue might occur when subtle ILD (e.g. tiny reticulations) could be present in non-dependent parts of the lung, that are more inflated, with a subsequent loss of signal (Figure 4).

For this reason, chest MRI is usually performed at end-expiration, to obtain more signal from the lung parenchyma. However, this strategy may lead to a partial collapse of the pulmonary dependent lung parts, appearing as ground glass opacities, which could be misinterpreted as mild ILD, as already observed on UTE[18] and as it can be also supposed by. Fast breath hold inspiratory UTE sequences have been implemented and tested, for example in follow up of Covid patients[30], where ground glass opacities may represent the main sequela[31-33]. Moreover, low-field MRI, which increases image quality of T2 sequences showed good results to evaluate ground glass opacities[34], and it could be tested with inspiratory breath holds for ILD.

Current clinical implementation of lung MRI could be that of a mid-term follow up tool, to be performed after ILD is confirmed by CT, especially in stable patients, as already done for Cystic Fibrosis[9].

This approach could reduce the cumulative radiation dose, in particular in young SSc-patients[35]. Moreover, a T2 radial TSE sequence in free breathing could be scanned in supine position, repeating just one breath hold scan in prone position, similarly to CT. This approach could avoid misinterpretation of GGO, but he feasibility and reliability of this technique needs to be tested. In order to reduce cumulative radiation dose in SSc patients that may be monitored for an early diagnosis of ILD, lung ultrasound is also one more emerging radiation-free technique for ILD that seems promising in interstitial abnormalities detection, but few data are available[36]. Moreover, the recently developed photon counting detector CT might challenge the use of lung MRI, allowing a significant dose reduction at no expenses of image quality, but their availability is still limited[37].

This study has some **limitations**. Firstly, MRI was performed on a small cohort, with few patients with extended disease. This could have partially affected the results, that need to be confirmed in a larger group of subjects. Secondly, inspiratory CT and free breathing MRI acquisitions could have slightly different respiratory levels, which could affect ILD extent score. However, the scoring system we adopted performs a sampling of a diffuse lung disease, that should counteract small differences deriving from different inspiratory levels, as previously suggested[18]. Moreover, the adopted score was created on sequential CT scans[5], while on volumetric acquisition a whole lung ILD analysis, that could be more accurate, is possible[38]. However, we decided to use the Goh analysis since it was used to create the derived stratification of ILD extent[5], and we believe that represents a simple imaging analysis, easily performable

in the daily practice. Thirdly, the stratification provided by limited and extended ILD with both CT and MRI has not being verified for long term follow up, which crucial evidence to define prognostic value of lung MRI.

In conclusion, CT examination continues to be the gold standard imaging technique for assessing ILD due to its high spatial resolution, feasibility, cost-effectiveness, time efficiency, and widespread availability

In SSc-ILD, our data provide good evidence that MRI is comparable to CT in assessing disease extent and, considering the method suggested in clinical practice, in ILD severity stratification. MRI showed also a similar performance in explaining functional changes. Moreover, the T2 radial TSE sequence, readily accessible in standard MRI scanners and applicable in daily clinical practice, demonstrates reliability even when compared to a more advanced UTE sequence. Given these findings, it is crucial to prioritize efforts aimed at minimizing patient radiation exposure in the future, and further studies investigating the comparison between CT and MRI in SSc-ILD are strongly encouraged for follow-up analysis.

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Figures' captions

Figure 1.

PD UTE images were scanned in coronal (a) and reconstructed in axial for the image analysis (b, level 2)

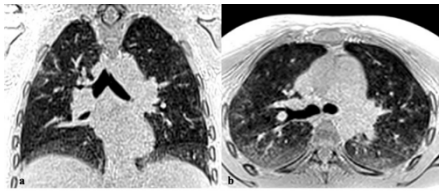
Figure 2. Scatterplots of T2 radial TSE (a) and PD UTE ILD extent analysis against CT

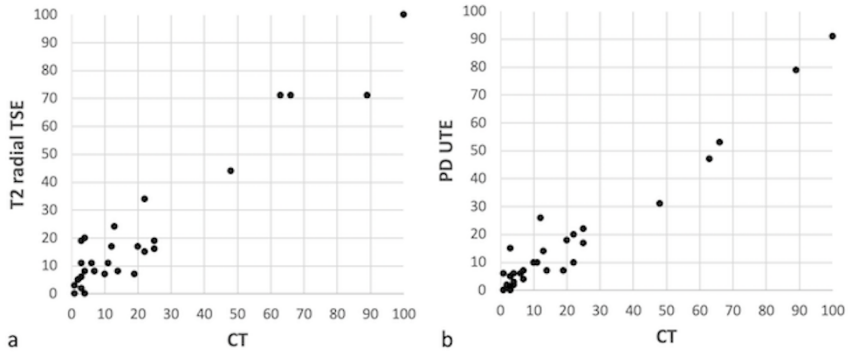
Figure 3.

CT (a), T2 radial TSE (b) and PD UTE (c) images at level 5, extended disease with both evaluation method: ILD extent is similarly quantifiable on CT (a) and MRI sequences (b, c)

Figure 4.

Example of disagreement between CT (a) and MRI (T2 radial TSE, b; PD UTE, c) with method B in identifying extended disease. Tiny antidependant reticulation (arrow) may be overlooked with MRI, leading to an underestimation of ILD extent (level 2).





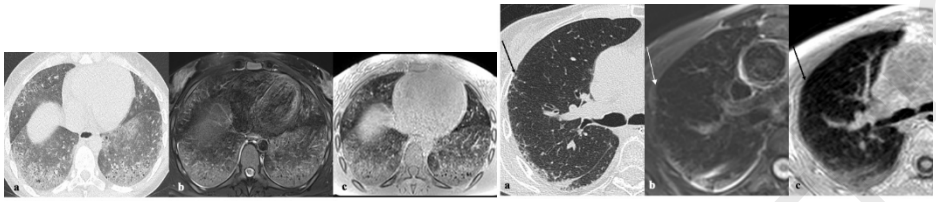


Table 1. Demographic and clinical characteristics of the 29 SSc-ILD patients

Characteristics	n (%) or mean (SD)
Age	40 (5)
Female	24 (83)
ACA	6 (20.7)
Scl70	19 (65.5)
FVC%	81 (23)
FEV1%	83 (20)
DLCO%	54 (17)
Smokers	11 (38)
PAH	5 (17)

Legend: ACA, anti-centromere antibodies; DLCO: Diffusing Capacity of Lung for Carbon Monoxide, % predicted; FVC: Forced Vital Capacity, % predicted; FEV1%: forced expiratory volume in 1 second, % predicted; n: number of patients; PAH: Pulmonary arterial hypertension; Scl70: Anti-Scl-70 antibodies

Table 2. ILD extents as percentage of lung parenchyma and patients with extended disease (indeterminate extents in brackets) assessed on CT, T2 radial TSE and PD UTE.

	CT	T2 radial TSE	PD UTE

ILD extent, median (IQR)	11% (20%)	11% (15%)	10% (16.5%)
Extended disease			
Method A	8 (10)	8 (10)	7 (7)
Method B	9 (1)	7 (1)	7 (1)

Legend: CT, computed tomography; IQR, interquartile range; Method A, extended disease if ILD extent>30% or >10 and ≤30 with FVC%<70%; Method B, extended disease if ILD extent>20% or 20% with FVC%<70%; PD: proton density; TSE: turbo spin echo; UTE, ultra-short echo time

Table 3. Concordance of CT and MRI in identifying extended and limited disease.

		T2 radial TSE		**PD UTE**	
	Method A	Limited	Extended	Limited	Extended
	Limited	21	0	20	1
CT	Extended	1	7	1	7
	Method B	Limited	Extended	Limited	Extended
	Limited	19	1	19	1
	Extended	3	6	3	6

Legend: CT, computed tomography; Method A, extended disease ILD>30% or >10 and ≤30 with FVC%<70%; Method B, extended disease ILD>20% or 20% with FVC%<70%; UTE, ultra-short echo time

Table 4. Sensitivity, specificity PPV, NPV and accuracy (95% confidence interval) of MRI in identifying extended disease, compared to CT.

		T2 radial TSE	PD UTE
Method A	Sensitivity	87.5% (47.4%-99.7%)	87.5% (47.4%-99.7%)
	Specificity	100% (83.9%-100%)	95.2% (76.2%-99.9%)
	PPV	100%	87.5% (50.4%-98.0%)
	NPP	95.5 (77.1%-99.2%)	95.2 (76.1%-99.2%)
	Accuracy	96.6% (82.2%-99.9%)	93.1% (77.2%-99.2%)
Method B	Sensitivity	66.6% (29.9%-92.5%)	
	Specificity	95% (75.1%-95.9%)	
	PPV	85.7 (45.7%-97.7%)	
	NPP	86.4 (74.1%-94.1%)	
	Accuracy	86.6% (69.3%-96.1%)	

Legend: Method A, extended disease ILD>30% or >10 and ≤30 with FVC%<70%; Method B, extended disease ILD>20% or 20% with FVC%<70%; UTE, ultra-short echo time

CONFLICT OF INTEREST

As senior Authos, I state that all the authos (Nicholas Landini, Martina Orlandi, Linda Calistri, Cosimo Nardi, Pierluigi Ciet, Silvia Bellando-Randone, Serena Guiducci, Thomas Benkert, Valeria Panebianco, Giovanni Morana, Marco Matucci-Cerinic and Stefano Colagrande) have no conflict of interest in connection with the submitted manuscript.

Florence, 2023, July 2 nd

Stefano Colagrande