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The evolving role of MRI in pulmonary sarcoidosis: Comparative analysis with PFTs and progression markers

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Abstract. *Background:* Sarcoidosis is a systemic illness with unclear etiology that commonly affects the lungs and intrathoracic lymph nodes. Chest radiography, CT, and, more recently, MRI can be used for assessment, with bilateral hilar lymph node enlargement and interstitial lung disease being common observations. *Objectives:* In adults diagnosed with pulmonary sarcoidosis, how do chest radiography, CT, and MRI compare in the assessment of disease progression? *Study Design and Methods:* This is a prospective study of 77 adults diagnosed with pulmonary sarcoidosis. Each patient underwent pulmonary function testing, chest radiography, HRCT and MRI within a span of 90 days. Chest radiographs were scored using the Scadding stage classification system. HRCT and MRI were both scored using the Scleroderma Lung Study I system. Pulmonary function was re-assessed after 12 months, with progression of disease defined as worsening symptoms AND ≥5% reduction of forced vital capacity (FVC). Disease progression was used as the gold standard to calculate area under the curve (AUC) of the receiver operating characteristic plot for radiography, HRCT, and MRI. *Results:* There is strong correlation between chest radiography and MRI (r=0.649, P < 0.001), and CT and MRI scores (r=0.851, P < 0.05). CT and MRI scores correlated with forced vital capacity (MRI: r =-0.584, P < 0.001; CT: r =-0.308, P = 0.049) and diffusing capacity of the lung for carbon monoxide (MRI: r =-0.564, P =0.004; CT r =-0.216, P = 0.017). AUCs for chest radiography, MRI and CT scores were 0.70 (0.49-0.85), 0.71 (0.42–0.85), and 0.68 (0.26–0.90), respectively. Multivariate regression analysis of CT and MRI scores demonstrated statistically significant prediction of progressive disease by both modalities. *Conclusion:* MRI may be a viable alternative to HRCT in the assessment of lung parenchyma and disease progression in patients with pulmonary sarcoidosis.

Key words: MRI, pulmonary sarcoidosis, PFTS, imaging biomarkers, chest x-ray, CT, disease progression, lung imaging, sarcoidosis biomarkers

Introduction

There are many different clinical and radiological signs and symptoms of sarcoidosis, a systemic illness with unclear etiology. The condition is characterized pathologically by the presence of noncaseating granuloma (1). Approximately 60-70% of patients experience spontaneous remission within three years of diagnosis, but the remaining third develop a chronic

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illness, and some 5% of patients die from sarcoidosis, most from pulmonary complications (1-3). Imaging biomarkers useful in the prognosis of these patients are critical to adequate management (3). Sarcoidosis occurs most often in patients between 20 and 40 years of age (4). Radiation exposure due to medical imaging carries particular implications for young adults, as their longer life expectancy increases the risk of radiation-induced carcinogenesis (2,3,5). Immunosuppressive therapy is also indicated in the treatment of sarcoidosis, further elevating the risk for malignancy (6). It is therefore important to minimize radiation dose while maintaining diagnostic efficacy and consider alternative imaging modalities that do not use ionizing radiation where appropriate. There are several radiologic methods that can be used in pulmonary sarcoidosis, including Chest X-ray, computed tomography (CT), PET/CT and magnetic resonance (1-3,7). The most frequent observation is bilateral hilar lymph node enlargement, which is followed by parenchymal lung disease (5,8). In the diagnosis and management of cardiac sarcoidosis, magnetic resonance imaging (MRI) has been indicated as first line study to both diagnostic and prognostic information (1). MRI has traditionally had limited utility in the evaluation of lung parenchyma. Low proton density of air-filled lungs, artifacts from cardiac and pulmonary motion, and susceptibility effects resulting from differences in magnetism between parenchyma and air are technical challenges that contribute to a weak signal-to-noise ratio and diminished image quality of thoracic MRI (8). Modern MRI techniques (parallel imaging, stronger gradients, 3D imaging, volume interpolation) have improved image quality to the point that the lungs may now be assessed with conventional proton MRI (10,11,12). The major clinical indications for MRI come from three main areas: enhancing other imaging modalities in disease assessment, routine imaging in patients with radiation sensitivity, and imaging in patients with contraindications to CT (11). Accumulated technological advances such as ultrashort echo time and zero echo time pulse sequences, multicoil parallel imaging, acceleration techniques, and post-processing software have improved the speed and quality of MRI to the point that it is comparable to CT in the setting of some parenchymal lung diseases (11, 13). MRI may thus be a viable alternative to CT in the imaging of pulmonary sarcoidosis given the correlation and substantial agreement between MRI and CT scoring (10). Despite a lower sensitivity of MRI compared to CT in the detection of subtle disease, pulmonary MRI may serve well in the setting of long-term imaging follow-up when a baseline study with CT correlation has been obtained. Monitoring of pulmonary sarcoidosis often involves frequent pulmonary function tests with or without imaging. Typically, chest x-rays or CT chest are preferred imaging modalities (5). CT is the most valuable for evaluation of pulmonary sarcoidosis as it is considered diagnostically superior to chest radiography due to a higher sensitivity for parenchymal disease, hilar lymphadenopathy, and pulmonary fibrosis (1,14,15). The relationship between clinical findings, functional lung impairment, and manifestations of sarcoidosis on thoracic CT and chest radiography has been previously examined. However, the literature is unclear whether changes in these imaging modalities correlate with changes in lung function and prognosis. Muller et al. (15) noted that overall extent of disease on CT and chest radiograph findings both correlated significantly with severity of dyspnea and functional lung impairment, however neither modality was shown to be superior in predicting development of functional impairment in patients with sarcoidosis. Chest MRI has also been compared to HRCT in the setting of pulmonary sarcoidosis. Chung et al. (10) reported that total extent scores for MRI and HRCT of patients with known pulmonary sarcoidosis showed significant correlation and agreement, with agreement being greatest in the upper lobes and for scoring parenchymal opacification. The same study described MRI as slightly less sensitive than HRCT for detection of the disease (10). The aim of this study is to demonstrate the accuracy of chest radiography, CT and MRI in assessment of disease progression in sarcoidosis. Also, we will describe the correlation of pulmonary function tests with CT and MRI of the lung in patients with sarcoidosis.

Study design and methods

This is a prospective, descriptive study which was conducted at a tertiary hospital university by enrolling 77 consecutive pulmonary sarcoidosis patients aged ≥18 years, who were diagnosed based on the ATS Statement on Sarcoidosis, with all cases discussed in multidisciplinary discussion with histopathological correlation (Table 1) between July of 2012 and June

Table 1. Baseline patient characteristics

Measure	
Age (years), mean ± SD	45.3± 5.9
Male, n (%)	10 (12.8)
Pulmonary function (baseline), mean ± SD	
FVC (/L)	2.81 ± 0.74
FVC % predicted	78.5 ± 17.05
FEV 1 (/L)	2.09 ± 0.59
FEV 1 % predicted	73.75 ± 18.17
FEV1/ FVC	74.48 ± 10.53
FEV1/ FVC % predicted	93.05 ± 12.12
DLCO % predicted	65.02 ± 20.47
Chest X-ray, n (%)	
No lung involvement	15 (19.4)
Hilar enlargement alone	31 (40.2)
Hilar enlargement plus interstitial lung disease	16 (20.7)
Parenchymal lung disease alone	7 (9.0)
Lung fibrosis	8 (10.3)
Thoracic CT total score, n (%)	
Parenchymal opacification	16 (20.7)
Reticulation	37 (48.0)
Nodules	40 (51.9)
Thoracic MRI total score, n (%)	
Parenchymal opacification	12 (15.8)
Reticulation	30 (38.9)
Nodules	31 (40.2)

Abbreviations: SD = standard deviation; n = sample size; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; DLCO = diffusing capacity of the lung for carbon monoxide; CT = computed tomography, MRI = magnetic resonance imaging.

of 2021. For each patient, chest radiography, chest CT, MRI (containing HASTE sequence), baseline pulmonary function tests, and clinical evaluation were obtained within 90 days of one another. Pulmonary function was re-assessed by PFT and clinical re-evaluation for disease progression after a minimum of 12 months. Two readers (B.H. and M.C.B.; both thoracic radiologists with practice experience of 11 and 28 years, respectively) assessed chest X-ray, MRI, and HRCT images. Readers were blinded to patients across modalities and assessment was randomized and performed first for all MRIs, followed by X-ray and HRCT. Pulmonary function tests were performed based on standards of the American Thoracic Society (17). Patients with claustrophobia were excluded. This study was part of a broad study to assess Biomarkers of Cardiac Sarcoidosis performed in accordance with ethical guidelines and received local IRB approval (IRB201801863). Informed consent was obtained from the participants after describing the benefits of the study, as well as the risks and all the researchers' responsibilities.

Imaging techniques

MRI was performed with a Magnetom Aera 1.5 Tesla device (Siemens Healthcare, Siemens Erlangen, Germany) with an 18-channel anterior body coil and a 32-channel posterior spine coil. The patients were supine with their arms extended along the body and were moved into the device headfirst. The applied sequence was a T2-weighted half-Fourier single-shot turbo spin-echo (HASTE) sequence, performed using an electrocardiograph-gating to reduce cardiac motion artifacts, and respiratory-gating by a navigator signal that monitored the diaphragm position for end expiration. The field of view was patient-adapted. Sequence parameters were repetition time/echo time/flip angle, infinite/92 milliseconds/150 degrees; 25 to 30 slices; slice thickness, 4 mm; distance factor, 20%; transversal orientation (matrix, 380 256); acquisition time, approximately 90 seconds. MRI slice imaging plane was axial and coronal with in-plane resolution of 256.

High resolution chest tomography was performed as part of diagnostic assessment using a 64-section scanner (Light Speed; GE Medical Systems, Milwaukee, WI, USA) during a single breath-hold with standard acquisition parameters: 200 mA with automated dose reduction, 120 kV, pitch = 1, 0.5 s rotation time, 0.625 mm collimation, 400 × 400 mm field of view and 512 × 512 acquisition matrix. Pulmonary CT images were reconstructed using a soft filter to yield contiguous 0.625 mm axial sections from the apex of the lung to the diaphragm. Thin-section (1.25 mm) CT images were reconstructed every 1 mm using a high-spatial-resolution filter. The Scadding stage classification system was used to classify all chest x-rays (18).

Scoring of CT findings

The severity of Sarcoidosis was assessed visually and graded using the semi-quantitative Scleroderma Lung Study (SLS) I system (19). According to this system, three zones of each lung were delineated

using the aortic arch and pulmonary vein (upper, apex to the aortic arch; middle, aortic arch to the inferior pulmonary vein; lower, inferior pulmonary vein to diaphragm). For each zone, the severity of parenchymal opacification, reticulation, and nodules (Figures 1 and 2). were graded on a scale ranging from 0 to 4 (0 = absent, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, 4 = >75%). The two readers (B.H. and M.C.B.) performed this assessment for all HRCT slices, scoring each of the three thoracic zones (range, 0–12). Total CT scores ranged from 0 to 36.

Scoring of MRI findings

MR images were assessed by the same two readers (B.H. and M.C.B) visually with a pulmonary-like window using the SLS I system (19). The extent of pulmonary T2 signal hyperintensity in the three lung zones was scored on a scale ranging from 0 to 4(0 = absent, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, 4 = >75%), in parenchymal opacification, reticulation and nodules like in the CT assessment (20). Final MRI scores ranged from 0–36 (Figure 1).

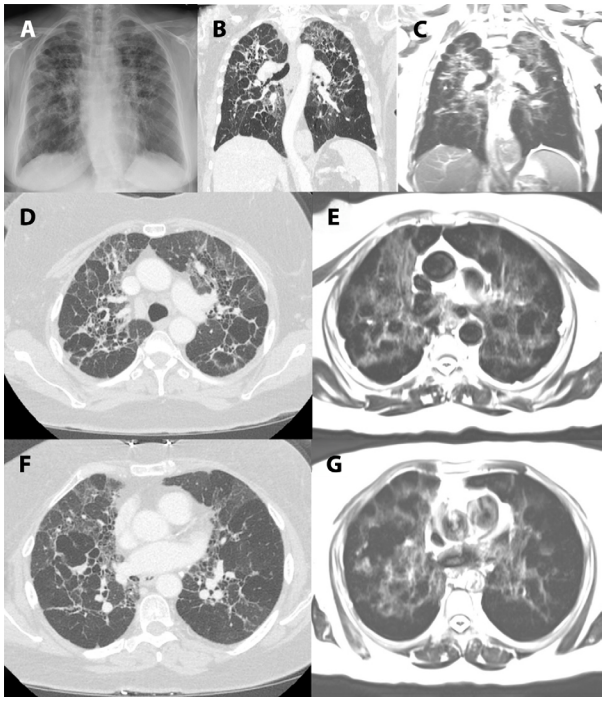

Figure 1. 57-year-old woman with Stage IV pulmonary sarcoidosis and stage IV chest x ray (A). Axial (D and F) and coronal (B) chest CT images with corresponding axial (E and G) and coronal (C) T2 HASTE images show upper lobe predominant reticulation and traction bronchiectasis consistent with fibrosing interstitial lung disease.

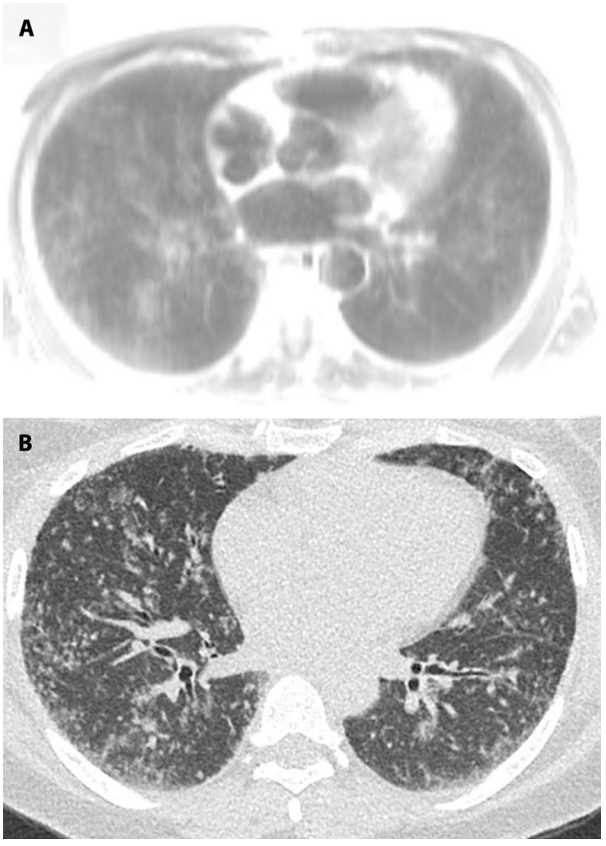

Figure 2. 45-year-old woman with Stage II pulmonary sarcoidosis. Axial MR HASTE images (A) with corresponding chest CT image (B) show upper lobes perilymphatic micronodules consistent with pulmonary sarcoidosis.

Definition of disease progression

A pulmonologist specializing in sarcoidosis followed all patients via regular outpatient clinic appointments. Baseline spirometry and clinic evaluation were compared to follow-up values at minimum 12 months later. The progression of disease was defined as worsening clinical symptoms AND ≥5% decline in forced vital capacity (FVC) on at least 2 consecutive examinations with less than 12 months. This definition of disease progression comes directly from the definition of progressive pulmonary fibrosis in the 2022 American Thoracic Society IPF Guidelines (21).

Statistical analysis

The statistical analyses were performed using SPSS software (v. 18; SPSS Inc., Chicago, IL, USA). The techniques employed in this study closely align

with those used in the authors' prior work (22). The Kolmogorov–Smirnov test was used to determine whether variables were distributed normally. Continuous variables are expressed as means (S.D.) or medians with interquartile range. Discrete variables are expressed as frequencies with percentages. Differences in the median scores were assessed with Student's t-test and the Wilcoxon rank-sum test with Bonferroni correction. The differences of averages were assessed with the paired t-test with Bonferroni correction. Pearson's and Spearman's rank correlation coefficients were calculated to investigate correlations between the imaging scores and PFT results. We utilized multiple regression analysis to determine the relationship between dependent and independent variables. Furthermore, we performed Chi-square tests for categorical variables, and ANOVA for continuous variables to determine statistical significance, adjusting for multiple comparisons using the Bonferroni correction. Using disease progression as the gold standard, we calculated the area under the curve (AUC) of the CT and MRI scores with Harrel's c-index. The best thresholds for the prediction of disease progression using the CT and MRI scores were determined by receiver operating characteristic curve analysis with maximum Youden's Index. The results are expressed in terms of AUCs. AUCs were compared using the method of DeLong (23). We used the intra-class correlation coefficient (ICC). The ICC can take a value from 0 to 1, with 0 indicating no agreement and 1 almost perfect agreement. P-values < 0.05 were considered significant.

Results

The patient demographic characteristics are summarized in Table 1. The study sample comprised 77 patients, whose demographics, PFT results, and imaging findings are detailed in Table 1. From 77 patients, 46 patients (41 due to pulmonary disease; 4 cardiac disease and 1 skin lesions) received anti-inflammatory/immunosuppressive treatment following ERS guideline to dose and drug indication (24). We diagnosis 5 patients (6.4%) with progressive disease in last 12 months based on PFT decline and worsened symptoms (Mean FVC% predicted decrease was 8.3% (+/-1.2). The mean follow-up time was 3.2 years (range 1.1-8.3years). Inter-reader agreement for CT and MRI scores were 0.66 (95% CI: 0.50-0.82) and 0.65 (95% CI: 0.49-0.73), respectively. We found a strong correlation between chest x-ray, CT, and MR scores (Table 2).

Table 2. Correlation between X-ray, CT, and MRI scores

Modality Comparison	Spearman correlation	p-value
CT and MRI		
Parenchymal opacification	0.820	0.044
Reticulation	0.693	0.021
Pulmonary nodules	0.710	0.035
Total score	0.851	0.045
Chest X-ray and CT	0.449	0.270
Chest X-ray and MRI	0.649	<0.001

Chest x-ray, CT, and MRI scores correlated significantly with FVC, FEV-1, and DLCO (Table 3). For multivariate regression analysis, including age, sex and pulmonary function tests, CT score and MRI score demonstrated statistically significant prediction of progressive disease. This is expressed in Table 4 as hazard ratios for progressive fibrosis (as defined earlier by progression of symptoms and decline in FVC) when MRI and CT scores were above the thresholds for optimal accuracy (5 and 8, respectively). The Nodule CT score was statistically significantly higher than MR Nodule score ($p<0.001$) and there are non-statistically significant differences between reticular and opacity CT and MR scores.

The AUCs for MRI and CT scores were 0.71 (0.42–0.85), and 0.68 (0.26–0.90), respectively. There was not a statistical difference between CT score and MRI score AUCs ($p=0.45$). The sensitivity and specificity were 100% and 60%, for the MRI score, and 100%, 20%, respectively, for the CT score – indicating that, while both modalities were sensitive to PFT decline, MRI was more specific.

Discussion

The present study is, to our knowledge, the first to directly compare the efficacy of MRI, HRCT, and chest radiography in assessment of pulmonary sarcoidosis. As a prospective study of 77 consecutive patients, it is also the largest to correlate imaging scores with pulmonary function tests and to use said tests as a benchmark to examine the predictive capacity of each modality. Strong inter-modality correlation and strong inter-reader agreement supports the position that the techniques and scoring methods used in

Table 3. Correlation between lung function and imaging modality

Measure	FVC % predicted	P-value	FEV1% predicted	P-value	DLCO	P-value
Chest X-ray	-0.485	<0.001	-0.469	<0.001	-0.346	0.010
Chest MRI						
Parenchyma opacification	-0.404	0.002	-0.426	0.001	-0.396	0.030
Reticulation	-0.516	<0.0001	-0.469	<0.001	-0.514	<0.0001
Pulmonary nodules	-0.069	0.209	-0.262	0.049	-0.041	0.766
Total score	-0.584	<0.0001	-0.506	<0.001	-0.564	<0.004
Chest CT						
Parenchyma opacification	-0.317	0.04	-0.224	0.861	-0.194	0.497
Reticulation	-0.401	0.03	-0.345	0.046	-0.318	0.019
Pulmonary nodules	0.020	0.880	0.105	0.435	0.040	0.775
Total score	-0.308	<0.0049	-0.279	0.182	-0.216	<0.117

Abbreviations: FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; DLCO = diffusing capacity of the lung for carbon monoxide; MRI = magnetic resonance imaging; CT = computed tomography.

this study are reliable methods to assess parenchymal changes associated with sarcoidosis. CT and MRI scores correlated with declines in %FVC and DLCO at 12 months and shared similar sensitivities for disease progression. The intriguing observation on multivariate analysis that CT and MRI scores using the SLS I system can predict disease progression after 12 months highlights the potential of radiological alterations as a biomarker for impending functional decline and implies that the appreciation of parenchymal changes alone may justify early intervention in the absence of PFT abnormalities. Our data demonstrate a similar decrease in accuracy of MR in detection of pulmonary nodules to that of Chung et al. (10) This reduced accuracy could explain the better correlation with PFTs, because small sarcoid pulmonary nodules do not have PFT influence. MRI may therefore be useful to surveil for disease progression after initial diagnosis of pulmonary sarcoidosis is made by CT. Neither of the AUCs for CT or MRI were significantly different from random for disease progression. There are several possible explanations for this, including skewed class distribution favoring absence of progression (n=5 progressed), and the choice to use established imaging severity scoring methods that considered changes in the lungs which do not directly affect pulmonary function, namely micronodules (25). Low specificity of CT for progression (20%) is likely a result of the latter, as its superior detection of micronodules yielded a much greater proportion of false positives for disease progression. A limitation of this study is its single center design, as is the use of only 2 experienced radiologists for scoring. Collaboration between multiple centers and more radiologists may add generalizability to the inter-observer and inter-modality agreement findings. The subjects in the present study were part of a broader study to assess biomarkers of cardiac sarcoidosis. The prevalence of pulmonary sarcoidosis in these patients with cardiac sarcoidosis was such that this limited the sample size to 77 patients. In an effort to maintain this sample size for analysis, we included patients who did not follow up promptly. Hence, the large range for follow-up time, which certainly limits the power of our claim that chest MRI of sarcoidosis patients scored by SLS I system may predict declining lung function, especially considering the variability in sarcoidosis severity over time, even within the same patient. Minimum timing of the follow-up PFTs and clinical assessment may also be questioned. While it may be argued that extended follow-up time might diminish the relevance of patients' baseline status to the outcome, the minimum follow-up time being set at just 1 year, in conjunction with an already low sample size, very likely contributed to the main limitation of this study: that only 5 patients demonstrated progression of disease. This low proportion of disease progression is not uncommon in the setting of pulmonary sarcoidosis as the

Table 4. Performance of study measures in the prediction of Progression (multivariate regression analyses)

Score	Multivariate Relative risk (95% CI)	p-value
Δ FVC % predicted		
Parenchyma opacification		
CT score	0.984 (0.687 – 1.409)	0.929
MRI score	1.277 (1.002 – 1.627)	0.048
Reticulation		
CT score	1.362 (1.101 – 1.519)	0.052
MRI score	1.646 (1.266 – 1.900)	0.012
Pulmonary nodules		
CT score	1.092 (0.802 – 1.486)	0.578
MRI score	1.139 (0.905 – 1.434)	0.267
Score total		
CT score	1.236 (1.016 – 1.146)	0.044
MRI score	1.594 (1.086 – 1.763)	0.021
Chest X-ray score	1.314 (0.535 – 4.882)	0.395
Δ DLCO % predicted		
Parenchymal opacification		
CT score	1.176 (0.708 – 1.956)	0.053
MRI score	1.210 (0.791 – 1.291)	0.084
Reticulation		
CT score	1.390 (1.002 – 1.244)	0.032
MRI score	1.492 (1.014 – 1.646)	0.029
Pulmonary nodules		
CT score	0.988 (0.723 – 1.350)	0.937
MRI score	1.115 (0.870 – 1.428)	0.390
Score total		
CT score	1.101 (1.001 – 1.314)	0.051
MRI score	1.352 (1.015 – 1.580)	0.027

Abbreviations: FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; DLCO = diffusing capacity of the lung for carbon monoxide; CT = computed tomography; MRI = magnetic resonance imaging.

yearly index of progression of this disease is quite low and spontaneous remission remains a possibility (26). Regardless, 5/77 patients demonstrating progression certainly harms our analysis. Increased sample size and longer time between initial and final lung function evaluation in future studies may yield a higher volume of patients with progression, and thus more robust data to analyze the predictive nature of imaging. In conclusion, the MRI scoring method used in this study was shown to agree with HRCT and chest radiography in the assessment of lung parenchymal changes associated with pulmonary sarcoidosis. The scores of CT and MRI correlated with PFTs. MRI may predict progression of pulmonary sarcoidosis without requiring ionizing radiation, which is of clinical relevance for young, immunosuppressed patients requiring serial imaging.

Abbreviations: AUC = area under the curve; CT = computed tomography; DLCO = diffusion capacity of the lung for carbon monoxide; FEV1 = forced expiratory volume at 1 second; FVC = forced vital capacity; HASTE = T2-weighted half-Fourier single-shot turbo spin-echo; HRCT = high resolution computed tomography; ICC = intra-class correlation coefficient; MRI = magnetic resonance imaging; PFT = pulmonary function test; ROI = region of interest; RV = residual volume; SD = Standard deviation; SLS I= Scleroderma Lung Study I system; TLC = Total lung capacity.

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