

Lung scintigraphy with nonspecific human immunoglobulin G (^{99m}Tc -HIG) in the evaluation of pulmonary involvement in connective tissue diseases: correlation with pulmonary function tests (PFTs) and high-resolution computed tomography (HRCT)

Ch. Kostopoulos · J. Koutsikos · C. Toubanakis ·
L. A. Mouloupoulos · Ch. Mamoulakis · E. Gialafos ·
P. P. Sfikakis · Ch. Zerva · M. Mavrikakis · A. Leondi

Received: 7 May 2007 / Accepted: 15 September 2007
© Springer-Verlag 2007

Abstract

Purpose In patients with connective tissue diseases (CTD), the early detection and evaluation of the severity of the pulmonary involvement is mandatory. High-resolution computed tomography (HRCT) and pulmonary function tests (PFTs) are considered to be valuable noninvasive diagnostic modalities. Radiopharmaceuticals have also been used for this purpose. Our aim was the evaluation of technetium-labeled human polyclonal immunoglobulin G (HIG) lung scintigraphy in the early detection and assessment of the severity of the pulmonary involvement in CTD patients.

Methods Fifty-two nonsmoking CTD patients were studied by PFTs, HRCT, and HIG. According to PFTs, patients were

divided in group A (impaired PFTs—abnormal pulmonary function) and group B (normal pulmonary function). Semi-quantitative analysis was done on HIG and HRCT and corresponding scores were obtained.

Results Significant difference was found between HIG scores in the two groups (0.6 ± 0.07 vs 0.51 ± 0.08 , $P < 0.001$). There was a statistically significant negative correlation between HIG scores and PFTs results and a positive correlation between HIG and HRCT scores. HIG demonstrated similar clinical performance to HRCT. At the best cut-off levels of their score (0.56 and 7, respectively), HIG had a superior sensitivity (77.5 vs 57.5%) with lower specificity (75 vs 91.7%). The combination of the two methods increased the sensitivity of abnormal findings at the expense of specificity. **Conclusions** HIG scintigraphy can be used in the early detection and evaluation of the severity of the pulmonary involvement in CTD, whereas, when used in combination with HRCT, the detection of affected patients can be further improved.

Ch. Kostopoulos · C. Toubanakis · Ch. Mamoulakis · E. Gialafos ·
M. Mavrikakis
Department of Clinical Therapeutics,
Alexandra University Hospital,
Athens, Greece

J. Koutsikos (✉) · Ch. Zerva · A. Leondi
Department of Nuclear Medicine,
Alexandra University Hospital,
Athens, Greece
e-mail: jtkoutsik@yahoo.gr

L. A. Mouloupoulos
Department of Radiology,
Areteion University Hospital,
Athens, Greece

P. P. Sfikakis
Department of Propaedeutic Medicine,
Laikon University Hospital,
Athens, Greece

Keywords Connective tissue diseases (CTD) ·
Interstitial lung disease ·
Human polyclonal immunoglobulin G (HIG) scintigraphy ·
Pulmonary functional tests (PFTs) ·
High-resolution computed tomography (HRCT)

Introduction

Pulmonary involvement in patients with connective tissue diseases (CTD) is very common and is the cause of

severe morbidity and mortality [1]. More than 70% of patients suffering from systemic sclerosis (SSc) develop pulmonary disease, which is considered to be the primary cause of death, while in rheumatoid arthritis (RA), abnormal autopsy findings in the lungs is found in as many as 80% of cases [2, 3].

Early detection and evaluation of the extent and severity of pulmonary involvement is quite critical for disease prognosis and patient management [4, 5]. The most characteristic feature of pulmonary involvement is interstitial lung disease [3, 6, 7] that is definitively established by lung biopsy. The latter is an invasive modality that is not always easy to perform and is difficult to repeat during disease follow-up. Moreover, histological findings are not always concordant with the clinical severity of the lung disease [8].

High-resolution computed tomography (HRCT) and pulmonary function tests (PFTs) are the most commonly used noninvasive methods for the study of interstitial lung disease [4]. HRCT is considered to be the “gold standard,” as its findings are closely related to histological findings [9]. Nevertheless, its clinical significance is not clear, taking into account the qualitative interpretation of HRCT. Additionally, PFTs, which are also related to biopsy and HRCT findings, are the most useful and easy to perform technique for follow up of the disease and the evaluation of the results of therapy [5, 10, 11]. However, if the findings of PFTs and HRCT are equivocal or conflicting, their clinical value is questionable [12]. So, the optimal approach to study pulmonary involvement in patients with CTD is still uncertain.

Nuclear medicine imaging has also been used for the study of interstitial lung disease. Increased uptake of ^{67}Ga -citrate and ^{111}In -octreotide in the lungs and decreased clearance time of $^{99\text{m}}\text{Tc}$ -DTPA aerosol in patients with CTD have been found [13–16]. However, the findings are not precisely concordant with the overall degree of lung involvement or with HRCT and PFTs results.

The technetium ($^{99\text{m}}\text{Tc}$)-labeled nonspecific human polyclonal immunoglobulin G (HIG) is a radiopharmaceutical that has been used successfully for the detection of focal and diffuse infection and inflammation, as well as for the study of immunologic reaction and inflammation in patients with RA [17–19]. We defined that $^{99\text{m}}\text{Tc}$ -HIG uptake should be increased in the lung parenchyma of affected CTD patients, as chronic immunological inflammation, which results in fibrosis, is the major mechanism of pulmonary involvement in these patients [20, 21].

The aim of this study was the evaluation of $^{99\text{m}}\text{Tc}$ -labeled HIG lung scintigraphy in the early detection and evaluation of the severity of the pulmonary involvement in patients with CTD.

Materials and methods

Patients

Fifty two consecutive nonsmoking patients suffering from SSc, RA, or systemic lupus erythematosus and referred to our institution for detection of possible pulmonary involvement were included in this study. All patients fulfilled the criteria of the American Rheumatism Association [22–24]. All of them were informed about the protocol that was in compliance with the European legislation and gave their written consent.

Exclusion criteria included history of chronic respiratory disease, chronic cardiac failure, lung cancer, recent history or signs of respiratory infection at the time of the study, severe pulmonary arterial hypertension (PAH), Ig-A deficiency, and history of immune-mediated reaction to blood transfusion, as well as other exclusion criteria that are used in isotopic studies. Patients were submitted to PFTs, HRCT, and HIG scintigraphy within a week.

Pulmonary function tests

Pulmonary function tests that were performed (Master-Screen Diffusion, Jaeger, Wuerzburg, Germany) included spirometry, lung volume determination by the helium dilution technique, and CO diffusion lung capacity measurement by the single-breath method, according to the American Thoracic Society [25] and the European Respiratory Society [26] guidelines. The obtained values were expressed as percentages of normal predicted values.

Pulmonary function was considered abnormal when total lung capacity (TLC) and/or forced vital capacity (FVC) and/or carbon monoxide lung diffusion (DLCO) were less than 80% of predicted values [20]. Based on these results, patients were divided into two groups; group A ($n=40$) and group B ($n=12$), consisting of those with and without pulmonary disease, respectively.

High-resolution computed tomography

All patients underwent a HRCT of the chest (PHILIPS Tomoscan SR 7.000). Scans were performed at the end of inspiration, in the supine position, at 175 mAs, 120–140 KV, with a slice thickness of 1.5 mm and a slice spacing of 10 mm. The scanning time was 1 s for each slice. Images were reconstructed with a high-resolution algorithm selecting only high frequencies (bone algorithm).

HRCT findings are shown in Table 1. The parenchymal abnormalities identified on HRCT were coded, and a score was defined according to Warrick et al. [27]. For the

Table 1 Parenchymal abnormalities identified on HRCT

	Group A	Group B	Total population
Ground-glass appearance	10	0	10
Irregular pleural margins	6	1	7
Septal/subpleural lines	26	4	30
Honeycombing	3	0	3
Subpleural cysts	5	0	5

estimation of the severity of disease, a point value was assigned to each abnormality as follows: ground-glass appearance, 1; irregular pleural margins, 2; septal/subpleural lines, 3; honeycombing, 4; and subpleural cysts, 5. For each patient, the severity of disease score was obtained by adding these point values with a possible range of 0 to 15. An “extent of disease” score was obtained by counting the number of bronchopulmonary segments involved for each abnormality: one to three segments scored 1, four to nine segments scored 2, and more than nine segments scored 3. Finally, severity of disease and extent of disease scores were added to form a total HRCT score, with a possible range of 0 to 30. For example, a patient with a ground-glass appearance (severity of disease score 1) in five segments (extent of disease score 2) and subpleural lines (severity of disease score 3) also in five segments (extent of disease score 2) would have a total HRCT score of 8.

HIG scintigraphy

^{99m}Tc -HIG was prepared by addition of 740 MBq sodium ^{99m}Tc -pertechnetate in 2 ml saline to a lyophilized kit (TechneScan[®]HIG, Mallinckrodt Medical B.V., Petten, Holland). The pertechnetate was used within 4 h of elution from a generator that had been eluted within the previous 24 h.

All scans were carried out on a single-head γ camera (Sophycamera DS7; Sopha Medical Vision International, Buc Cedex, France) equipped with a high-resolution parallel hole collimator connected to a dedicated computer (Sophy NxT; Sopha Medical Vision International). The matrix was 256×256 pixels and the photo-peak was focused at 140 KeV with a symmetric 20% window. Anterior and posterior views of the thorax were obtained 4 h after the i.v. injection of 1 mg HIG labeled with 20 mCi ^{99m}Tc -pertechnetate. For semiquantitative interpretation, a region-of-interest (ROI) analysis was performed on the posterior view. ROIs of the same size were drawn over the upper, middle, and lower regions of each lung. The ratio of the mean counts of these ROIs and the counts of a ROI over the left ventricle divided by 2 gave a value for each

patient who represented the disease severity using ^{99m}Tc -HIG scintigraphy (HIG score).

Statistical analysis

Statistical analysis was based on the application of parametric (Student’s *t* test) and nonparametric (Mann–Whitney U test) methods, as appropriate, after testing the distribution of all continuous variables for normality and equality of variances with the use of Shapiro–Wilk W test and Levene’s F test, respectively. Kendall’s rank correlation coefficient τ_b and Pearson’s correlation coefficient *r* were calculated in the two groups for testing the null hypothesis of no relationship between (a) HRCT scores and each of the FVC, DLCO, and TLC variables and (b) HIG scores and each of the above PFTs variables, respectively.

Nonparametric and parametric receiver operating characteristic (ROC) analysis was performed, and the respective

Table 2 CTD patients characteristics and comparison between groups with (A) and without (B) pulmonary involvement

	Group A (n=40)	Group B (n=12)
Gender	<i>P</i> =0.663	
Male	7	1
Female	33	11
Type of CTD		
SSc	30	10
RA	9	1
SLE	1	1
Age (years)	<i>P</i> =0.808	
	53.9±11.8 (33–80)	54.9±10.1 (43–73)
Duration of CTD (years)	<i>P</i> =0.481	
	8.2±8.1 (0–40)	9.4±7.2 (0–22)
PFTs (%)		
FVC	<i>P</i> =0.004	
	85.13±15.43 (53–114)	100.00±13.05 (80–120)
DLCO	<i>P</i> <0.001	
	60.83±13.57 (24–80)	86.42±7.23 (80–104)
TLC	<i>P</i> =0.022	
	81.40±12.25 (54–106)	90.17±6.81 (80–104)
HRCT score	<i>P</i> =0.001	
	8.6±6.2 (0–30)	2.9±3.3 (0–9)
HIG scintigraphy score	<i>P</i> <0.001	
	0.60±0.07 (0.45–0.76)	0.51±0.08 (0.42–0.66)

Results are presented as mean±1 SD and range (parenthesis)
SLE systemic lupus erythematosus

Table 3 Correlations between diagnostic scores and PFTs variables in CTD patients

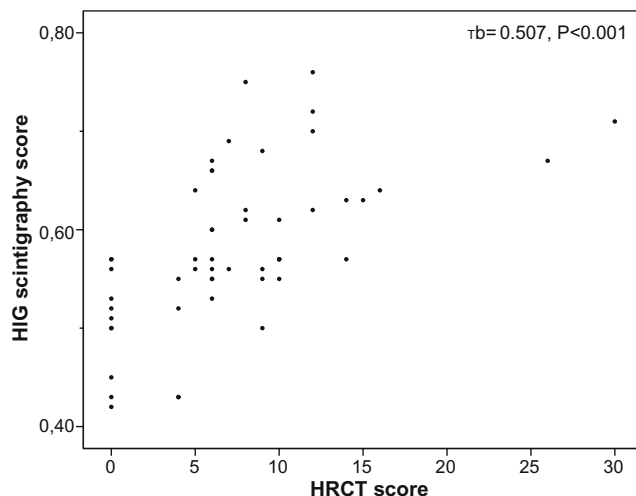
Diagnostic score	Correlation coefficient	PFTs		
		FVC	DLCO	TLC
HIG	Pearson's r	-0.42	-0.46	-0.43
	P	0.002	<0.001	0.002
HRCT	Kendall's τ_b	-0.34	-0.30	-0.32
	P	<0.001	0.003	0.001

areas under the curves (AUCs) of HRCT and HIG were calculated. The AUCs of the two tests were first evaluated separately under the null hypothesis that true area is equal to 0.500 and, finally, they were compared with each other. "Best" cutoff levels for each test were derived from the respective ROC curves. With the use of these limits, sensitivity, specificity, efficiency, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each test, as well as the combination of the tests.

A probability $P < 0.050$ (two-tailed) was considered to indicate statistical significance. Analysis was performed using STATA/SE 8.0 and SPSS 10.0 for Windows statistical packages.

Results

There was no difference in the following variables between groups A and B: gender, age, and disease duration. However, there were significant differences in PFTs (FVC, DLCO, and TLC) and HIG and HRCT scores between these groups. A statistically significant negative correlation was detected between HIG scores and each one of the PFTs in the total population and a positive correlation between

**Fig. 1** Correlation between HIG scintigraphy and HRCT scores in the total population

HIG and HRCT. A negative correlation was also found between the scores of HRCT and PFT results. Patient characteristics and the above results are summarized in Tables 2 and 3 and in Fig. 1. HIG and HRCT scans of each group are shown in Figs. 2 and 3. The distribution of HIG and HRCT scores in both groups are illustrated in Figs. 4 and 5, respectively.

The ROC curves of HIG and HRCT are presented in Figs. 6 and 7, respectively. AUCs with their standard error and 95% confidence intervals, as well as the asymptotic significance of the comparison to the null hypothesis, are shown in Table 4. Both tests demonstrated good clinical

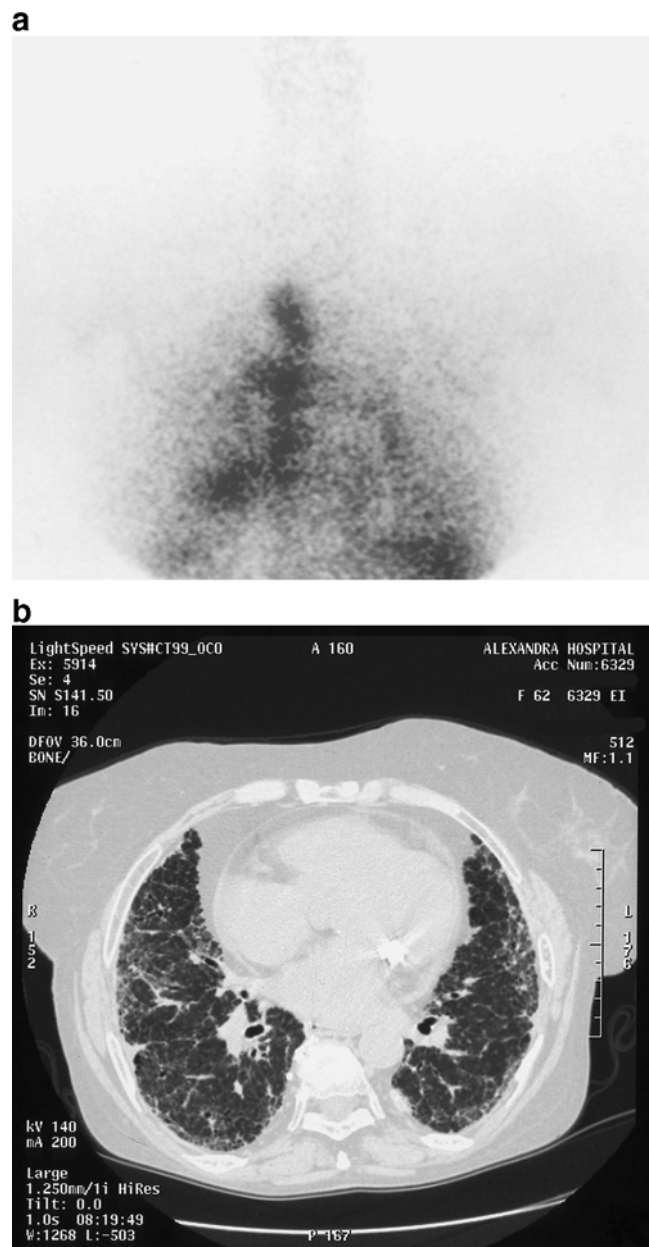
**Fig. 2** a HIG scintigraphy of a patient of group A (score 0.65). b HRCT scan of the same patient (score 15)



Fig. 3 a HIG scintigraphy of a patient of group B (score 0.45). b HRCT scan of the same patient (score 0)

performance because both ROC curves differed significantly from the nondiscrimination line. The tests showed similar performance because their AUCs did not differ significantly ($P=0.826$). The ROC curve derived from the combination of HIG and HRCT scores as possible independent predictors of the pulmonary implication in a logistic regression model is presented in Fig. 8. The combination of the tests showed good performance ($AUC=0.843$; $P=0.001$).

“Best” diagnostic cutoff levels for each test were derived from the respective ROC curves. These “optimum” limits were used to calculate sensitivity, specificity, efficiency,

PPV, and NPV for each test separately, as well as for the combination of the two tests (Table 5). Sensitivity and specificity of the combination of the tests did not differ significantly compared with the sensitivity-specificity of each test separately (combination vs HIG: $P = n.s.$, combination vs HRCT: $P = n.s.$).

Discussion

PFTs and HRCT are the most commonly used noninvasive diagnostic methods for the evaluation of interstitial lung disease in patients with CTD [4, 5, 28]. We used for the first time, to our best knowledge, the nonspecific HIG labeled with ^{99m}Tc (^{99m}Tc -HIG) to study the pulmonary involvement in such patients. The main findings, after semiquantitative analysis of HIG scans, are increased pulmonary uptake of the radiopharmaceutical in patients with, compared to patients without, pulmonary involvement according to PFT findings and that this uptake is related to the severity of the lung disease. Moreover, HIG scan correlated to HRCT findings.

In previous studies, several radiopharmaceuticals have been used for the detection of interstitial pulmonary lesions. ^{67}Ga -citrate is used in the study of sarcoidosis and lung infections. However, its usefulness in CTD is uncertain. In patients with severe pulmonary fibrosis and dyspnoea, although a high uptake of ^{67}Ga -citrate in the lung scan was found, this finding was not related to laboratory indices of the disease [13]. Scintigraphy with ^{99m}Tc -DTPA aerosol is also a useful modality in the study of the pulmonary epithelial permeability in patients with CTD. In a recent study in patients with mixed CTD, ^{99m}Tc -DTPA was found to have decreased clearance time, compared to patients with

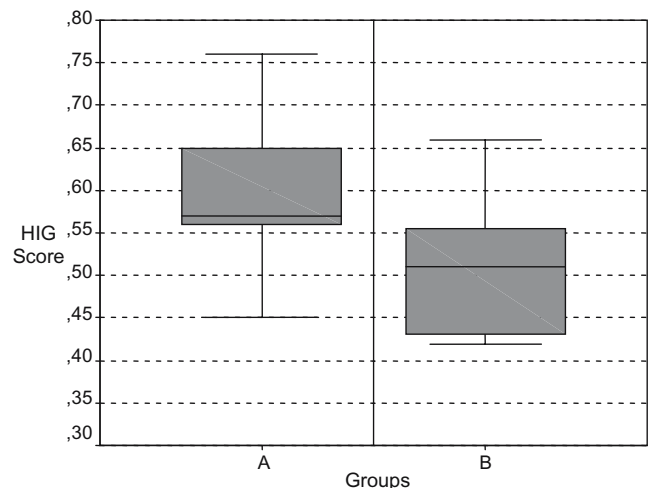


Fig. 4 Box-and-whisker plot of HIG scintigraphy score in CTD patients with (A) and without (B) pulmonary disease. Medians differ significantly ($P < 0.001$)

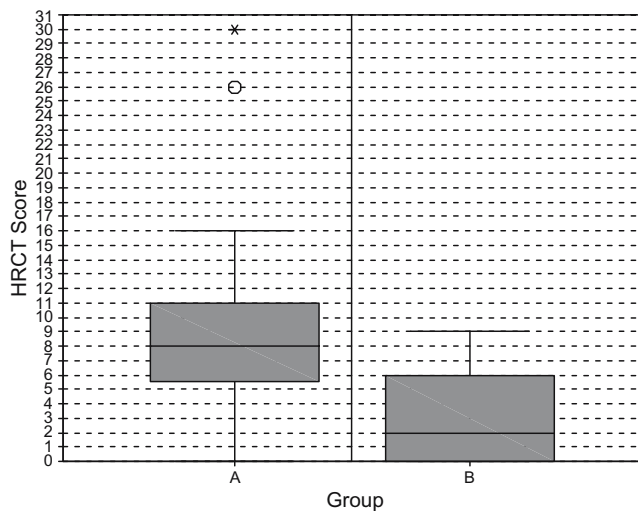


Fig. 5 Box-and-whisker plot of HRCT score in CTD patients with (A) and without (B) pulmonary disease. Extremes (asterisk) and outliers (circle) are marked. Medians differ significantly ($P=0.001$)

and without pulmonary disease, and after treatment, it was normalized, suggesting that, although HRCT is still the gold standard for the diagnosis of interstitial lung disease, ^{99m}Tc -DTPA scintigraphy may also give some information on lung function [29]. On the other hand, Antoniou et al. [30] reported that, in patients with idiopathic pulmonary fibrosis, ^{99m}Tc -DTPA scintigraphy findings are not related to HRCT and PFTs. ^{111}In -octreotide has also been recently used in the study of idiopathic pulmonary fibrosis [16]. An increased uptake was found in lung scans that related to the alterations in the patient's pulmonary function. Nevertheless, the usefulness of radiopharmaceuticals in the detection and evaluation of the severity of the pulmonary involvement in CTD is not established.

^{99m}Tc -HIG is a radiopharmaceutical that has been used in studies of focal infection and inflammation in immune

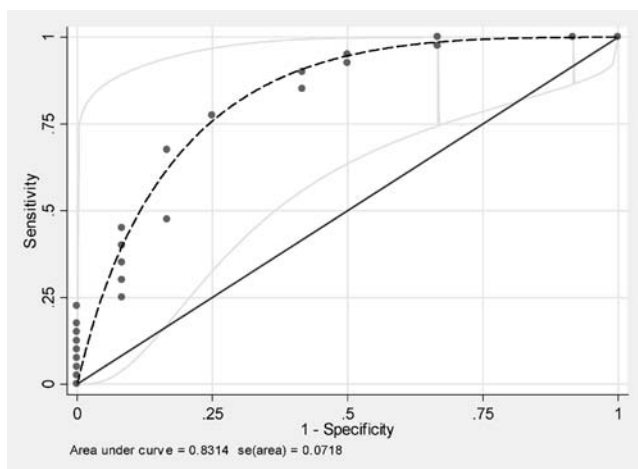


Fig. 6 ROC curve of HIG scintigraphy after fitting a maximum-likelihood ROC model assuming a binormal distribution. Ninety-five percent confidence interval bands are also plotted around the curve

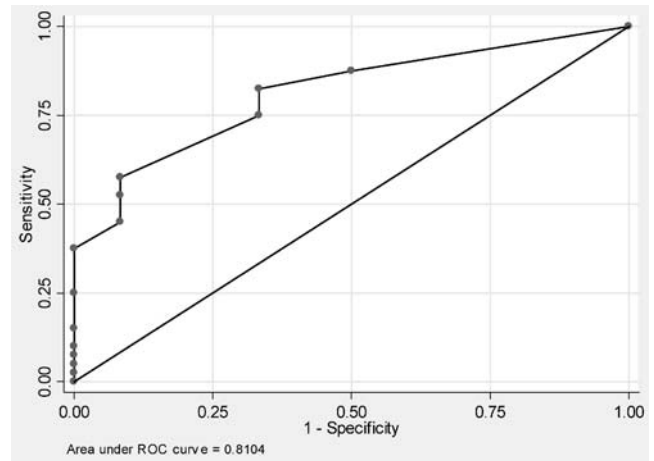


Fig. 7 ROC curve of HRCT

disease, such as RA, Sjogren syndrome, and inflammatory bowel disease [18, 19, 31–33]. Several uptake mechanisms are considered to contribute to its accumulation [34–36]. Primarily, it is thought to be due to increased vascularity and vascular permeability at the site of inflammation. Binding of the Fc component of the IgG molecule with Fc receptors on macrophages and leukocytes that accumulate in the above regions is also involved. The Fab portion of the molecule may also be recognized as a specific protein and result in its binding through oxidative processes to leukocytes and even to the fibrotic tissue at the site of the inflammation. The more important of these mechanisms, however, would seem to be related to the physico-chemical characteristics of the Fc component and its binding to the cellular inflammatory elements and other products of the inflammatory process. The particular environmental conditions associated with this process permit the uptake of such large molecules as HIG. In patients with RA, it is reported that ^{99m}Tc -HIG accumulation is due to the binding of the Fc component of IgG to rheumatoid factor [18]. Similar uptake mechanisms could explain the increased ^{99m}Tc -HIG uptake in the lungs of patients with CTD and pulmonary involvement, which is characterized by the presence of chronic inflammation accompanied by endothelial and epithelial cell damage, interstitial cell infiltration, and fibrosis [21].

Interstitial pulmonary disease that is the most common component of the pulmonary involvement in SSc and RA patients is characterized by a restrictive pattern of ventila-

Table 4 Clinical performance of HIG scintigraphy/HRCT based on ROC curves

ROC curve	AUC \pm SE	95% CI	P value
HIG scintigraphy	0.831 \pm 0.072	0.691–0.972	0.001
HRCT	0.810 \pm 0.064	0.685–0.936	0.001

SE standard error, CI confidence intervals

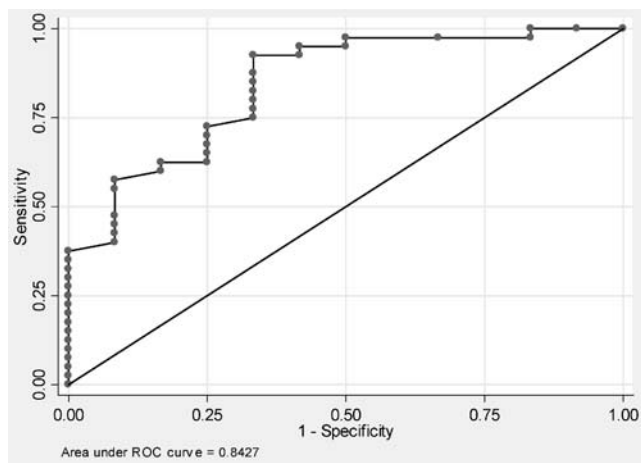


Fig. 8 ROC curve of the combination of HRCT and HIG scintigraphy derived from logistic regression analysis

tory abnormality that is expressed by decreased TLC and FVC and/or DLCO reduction [20, 37, 38]. According to these criteria 40/52 (77%) of our patients had pulmonary involvement of the disease. In these patients (group A) ^{99m}Tc -HIG uptake was greater than in patients who had no pulmonary involvement (group B) (HIG score 0.60 vs 0.51, respectively, $P < 0.001$). A significant negative correlation was also found between the HIG score and TLC ($P = 0.002$), FVC ($P = 0.002$), and DLCO ($P < 0.001$) values.

DLCO reduction that is consistent with pulmonary fibrosis and microvascular damage [5, 39, 40] is widely considered to be the earliest and most sensitive index for the evaluation of the severity of pulmonary involvement and disease prognosis [41, 42]. In patients with SSc, DLCO reduction is related to increased mortality, while in RA, a DLCO value less than 54% is a strong index of disease progression [1, 43, 44]. DLCO reduction was the commonest pulmonary function abnormality in our patients. Among group A patients, 14 (35%) had isolated DLCO reduction (normal FVC and TLC). This reduction is considered as a predictor index of PAH [45, 46].

Because none of our patients had severe PAH, this isolated DLCO reduction might be attributed to pulmonary microvascular damage, and increased membrane permeability constitutes one of the possible ^{99m}Tc -HIG uptake mechanisms. This could be associated with the early detection of pulmonary involvement by HIG scintigraphy. The strong negative correlation between ^{99m}Tc -HIG and

DLCO ($P < 0.001$) justifies the above hypothesis. Furthermore, the correlation of the ^{99m}Tc -HIG scan with TLC and FVC, which are specific and necessary indices of restrictive abnormality in severe fibrosis [20], shows the importance of ^{99m}Tc -HIG in the evaluation of the severity of pulmonary involvement.

The value of the ^{99m}Tc -HIG scan is also underlined by its strong positive correlation with HRCT ($r = 0.507$, $P < 0.001$). HRCT is considered to be the most appropriate modality for the detection of the interstitial parenchymal disease in patients with CTD [47], and it is compatible either with nonspecific interstitial pneumonia (NSIP) or with usual interstitial pneumonia (UIP). NSIP that is characterized by a ground glass pattern suggests early and mild involvement, while UIP, which presents mainly with reticular or honeycombing pattern, indicates a more chronic and more severe involvement [8].

Among our patients with positive HRCT, 24% had a ground glass pattern as the main finding, while the other 76% had findings similar to UIP. These findings do not agree with the dominant concept that the ground glass pattern is the main finding in SSc and RA patients with pulmonary involvement [8, 48]. It seems that many patients in our study had severe pulmonary disease, and this is supported by the strong negative correlation between HRCT score and TLC ($P = 0.001$) and FVC ($P < 0.001$) values, and also as DLCO values ($P = 0.003$).

ROC analysis was used to determine the ideal HRCT and ^{99m}Tc -HIG scores concerning the best compromise between sensitivity and specificity to predict PFT abnormalities. A HRCT score of 7 corresponded to a specificity of 91.67% and a sensitivity of 57.5%, and a ^{99m}Tc -HIG score of 0.56 corresponded to a specificity of 75% and a sensitivity of 77.5%.

The HRCT specificity and sensitivity values were similar to those reported in the study of Diot et al. [10], who correlated HRCT findings with PFTs in patients with SSc. It is interesting that, in this study, the score 7 gives the optimum balance between specificity and sensitivity, as in our study. Additionally, our results suggest that the combination of the two imaging modalities gives a higher sensitivity (82.5%) at the expense, however, of specificity (66.67%).

The conclusion of our study is that the ^{99m}Tc -HIG lung scintigraphy can be used in the early detection and

Table 5 Diagnostic performance of HRCT/HIG scintigraphy at optimum cutoff levels

Test	Cutoff	Sensitivity (%)	Specificity (%)	Efficiency (%)	PPV (%)	NPV (%)
HIG scintigraphy	0.56	77.5	75	76.9	91.2	50
HRCT	7	57.5	91.7	65.4	95.8	60.7
HIG scintigraphy and HRCT	0.56; 7	82.5	66.7	78.8	89.2	46.7

evaluation of the severity of the pulmonary involvement in CTD, whereas, when used in combination with HRCT, the detection of affected patients can be further improved. Further prospective studies performing serial HIG scintigraphies are needed to confirm the method's prognostic value in these patients.

References

- Ferri C, Valentini G, Cozzi F, Sebastiani M, Michelassi C, La Montagna G, et al. Systemic sclerosis: demographic, clinical and serological features and survival in 1.012 Italian patients. *Medicine (Baltimore)* 2002;81:139–53.
- Owens GR, Follansbee WP. Cardiopulmonary manifestations of systemic sclerosis. *Chest* 1987;91:118–27.
- Cervantes-Perez P, Toro-Perez AH, Rodriquez Jurado P. Pulmonary involvement in rheumatoid arthritis. *JAMA* 1980;243:1715–9.
- Grutters JC, Wells AU, Wuyts W, Schenk P, Leroy S, Dawson JK, et al. Evaluation and treatment of interstitial lung involvement in connective tissue diseases: a clinical update. *Eur Respir Mon* 2005;10:27–49.
- Latsi P, Wells A. Evaluation and management of alveolitis and interstitial lung disease in scleroderma. *Curr Opin Rheumatol* 2003;15:748–55.
- Arroliga AC, Podell DN, Matthay RA. Pulmonary manifestations of scleroderma. *J Thorac Imaging* 1992;7:30–45.
- Kostopoulos C, Rassidakis A, Sfikakis PP, Antoniadis L, Mavrikakis M. Small airways dysfunction in systemic sclerosis. A controlled study. *Chest* 1992;102:875–81.
- Bouros D, Wells A, Nicholson A, Colby T, Polychronopoulos V, Pantelidis P, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. *Am J Respir Crit Care Med* 2002;165:1581–86.
- Wells AU, Hansell DM, Corrin B, Harrison NK, Goldstraw P, Black CM, et al. High resolution computed tomography as a predictor of lung histology in systemic sclerosis. *Thorax* 1992; 47:738–42.
- Diot E, Boissinot E, Asquier E, Guilmet JL, Lemarie E, Valat C, et al. Relationship between abnormalities on high-resolution CT and pulmonary function in systemic sclerosis. *Chest* 1998;114: 1623–9.
- Ooi GC, Mok MY, Tsang KW, Wong Y, Khong PL, Fung PC, et al. Interstitial lung disease in systemic sclerosis. *Acta Radiol* 2003;44:258–64.
- Afeltra A, Zennaro D, Garzia P, Gigante A, Vadacca M, Ruggiero A, et al. Prevalence of interstitial lung involvement in patients with connective tissue diseases assessed with high-resolution computed tomography. *Scand J Rheumatol* 2006;35:388–94.
- Greene N, Solinger A, Baughman. Patients with collagen vascular disease and dyspnea: The value of Gallium scanning and bronchoalveolar lavage in predicting response to steroid therapy and clinical outcome. *Chest* 1987;91:698–703.
- Mogulkoc N, Brutsche MH, Bishop PW, Murby B, Greaves MS, Horrocks AW, et al. Pulmonary (99m) Tc-DTPA aerosol clearance and survival in usual interstitial pneumonia (UIP). *Thorax* 2001;56:916–23.
- Wells AU, Hansell DM, Harrison NK, Lawrence R, Black CM, du Bois RM. Clearance of inhaled 99m Tc-DTPA predicts the clinical course of fibrosing alveolitis. *Eur Respir J* 1993;6:797–802.
- Lebtahi R, Moreau S, Marchand-Adam S, Debray MP, Brauner M, Soler P, et al. Increased uptake of ¹¹¹In-Octreotide in idiopathic pulmonary fibrosis. *J Nucl Med* 2006;47:1281–7.
- Rubin R, Fischman A, Gallahan R, Khaw B, Keech F, Ahmad M, et al. ¹¹¹In-labeled nonspecific immunoglobulin scanning in the detection of focal infection. *N Engl J Med* 1989;321:935–40.
- de Bois MH, Arndt JW, van der Velde EA, van der Lubbe PA, Westedt ML, Pauwels EK, et al. ^{99m}Tc human immunoglobulin scintigraphy: A reliable method to detect joint activity in rheumatoid arthritis. *J Rheumatol* 1992;19:1371–6.
- Buscombe JR, Lui D, Ensing G, de Jong R, Ell PJ. ^{99m}Tc-human immunoglobulin (HIG)—first results of a new agent for the localization of infection and inflammation. *Eur J Nucl Med* 1990;16 8–10:649–55.
- Matucci-Gerinic M, D'Angelo S, Deuton C, Vlacoyiannopoulos P, Silver R. Assessment of lung involvement. *Clin Exp Rheumatol* 2003;21 Suppl 29:S19–23.
- Rossi GA, Bitterman PB, Rennard SI, Ferrans VJ, Crystal RG. Evidence for chronic inflammation as a component of the interstitial lung disease associated with progressive systemic sclerosis. *Am Rev Respir Dis* 1985;131:612–7.
- Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980;23:581–90.
- Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
- Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–7.
- American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152:1107–36.
- Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Pelsin R, Yernault JG. Lung volumes and forced ventilatory flows: report working party standardization of lung function tests. European Community for steel and coal: official statement of the European Respiratory Society. *Eur Respir J* 1993;6:5–40.
- Warrick JH, Bhalla M, Schabel SI, Silver RM. High-resolution computed tomography in early scleroderma lung disease. *J Rheumatol* 1991;18:1520–8.
- Remy-Jardin M, Remy J, Wallaert B, Bataille D, Hatron PY. Pulmonary involvement in progressive systemic sclerosis: sequential evaluation with CT, pulmonary function tests and bronchoalveolar lavage. *Radiology* 1993;188:499–506.
- Bodolay E, Szekanecz Z, Devenyi K, Galuska L, Csipo I, Vegh J. Evaluation of interstitial lung disease in mixed connective tissue disease (MCTD). *Rheumatology* 2005;44:656–61.
- Antonioniou KM, Malagari K, Tzanakis N, Perisinakis K, Symvoulakis EK, Karkavitsas N, et al. Clearance of technetium-99m-DTPA and HRCT findings in the evaluation of patients with Idiopathic Pulmonary Fibrosis. *BMC Pulm Med* 2006;6:4.
- de Bois MH, Arndt JW, Tak PP, Kluin PM, van der Velde EA, Pauwels EK, et al. ^{99m}Tc-labelled polyclonal human immunoglobulin G scintigraphy before and after intra-articular knee injection of triamcinolone hexacetonide in patients with rheumatoid arthritis. *Nucl Med Commun* 1993;14:883–7.
- Rubin RH, Fischman AJ. Radionuclide imaging of infection in the immunocompromised host. *Clin Infect Dis* 1996;22:414–23.
- Karanikas G, Babacz K, Becherer A, Wiesner K, Dudczak R, Machold K, et al. Tc-99m-labeled human polyclonal immunoglobulin G (HIG) scintigraphy in Sjögren's syndrome. *Scand J Rheumatol* 2002;31:80–4.
- Chouchakova N, Skokowa J, Baumann U, Tschernig T, Philippens KM, Nieswandt B, et al. FcRIII-mediated production of TNF-alpha induces immune complex alveolitis independently of CXC chemokine generation. *J Immunol* 2001;166:5193–200.

35. Morrel E, Tompkins R, Fischman A. Autoradiographic method for quantitation of radiolabelled proteins in tissues using indium-111. *J Nucl Med* 1989;30:1538–45.
36. Fischman AJ, Rubin RH, White A, Locke E, Wilkinson R, Nedelman M, et al. Localization of Fc and Fab fragments of nonspecific polyclonal IgG at focal sites of inflammatory. *J Nucl Med* 1990;31:1199–205.
37. Lamblin C, Bergoin C, Saelems T, Wallaert B. Interstitial lung diseases in collagen vascular diseases. *Eur Respir J* 2001;32:695–805.
38. Crestani B. The respiratory system in connective tissue disorders. *Allergy* 2005;60:715–34.
39. Steen VD, Graham G, Conte C, Owens G, Medsger TA. Isolated diffusing capacity reduction in systemic sclerosis. *Arthritis Rheum* 1992;35:765–70.
40. Kono H, Inokuma S. Visualization and functional consequence of pulmonary vascular impairment in patients with rheumatic diseases. *Chest* 2003;124:255–61.
41. Morgan C, Knight C, Lunt M, Black CM, Silman AJ. Predictors of end-stage lung disease in a cohort of patients with scleroderma. *Ann Rheum Dis* 2003;62:146–50.
42. De Santis M, Bosello S, La Torre G, Capuano A, Tolusso B, Pagliari G, et al. Functional, radiological and biological markers of alveolitis and infections of the lower respiratory tract in patients with systemic sclerosis. *Respir Res* 2005;6:96.
43. Simeon CP, Armadans L, Fonollosa V, Solans R, Selva A, Villar M, et al. Mortality and prognostic factors in Spanish patients with systemic sclerosis. *Rheumatology* 2003;42:71–5.
44. Dawson JK, Fewins HE, Desmond J, Lynch MP, Graham DR. Predictors of progression of HRCT diagnosed fibrosing alveolitis in patients with rheumatoid arthritis. *Ann Rheum Dis* 2002;6:517–21.
45. Steen V, Medsger TA Jr. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. *Arthritis Rheum* 2003;48:516–22.
46. Sfikakis PP, Kyriakidis MK, Vergos CG, Vyssoulis GP, Psarros TK, Kyriakidis CA, et al. Cardiopulmonary hemodynamics in systemic sclerosis and response to nifedipine and captopril. *Am J Med* 1991;90:541–6.
47. Kim EA, Lee KS, Johkoh T, Kim TS, Suh GY, Kwon OJ, et al. Interstitial lung diseases associated with collagen vascular diseases: radiologic and histopathologic findings. *Radiographics* 2002;22:S151–65.
48. Tanaka N, Kim JS, Newell JD, Brown KK, Cool CD, Meehan R, et al. Rheumatoid arthritis-related lung diseases: CT findings. *Radiology* 2004;232:81–91.