USEFULNESS OF HRCT IN DIAGNOSIS AND FOLLOW UP OF PULMONARY INVOLVEMENT IN SYSTEMIC SCLEROSIS

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ABSTRACT

PURPOSE To assess the usefulness of HRCT in diagnosis and follow up of pulmonary involvement in systemic sclerosis.

MATERIALS and METHODS A total of 159 patients with systemic sclerosis, without overlap features, were studied. Sequential HRCT evaluation was realized in 138 patients. Semiquantification of HRCT findings was based on the grading systems introduced by Wells et al and Warrick et al. Follow up studies included semiquantitative evaluation of change in the extent and coarseness of disease at anatomically comparable sections. The database also included the results of pulmonary function tests and clinical information acquired during follow up of patients.

RESULTS An HRCT score of 7 would be required to consider HRCT abnormalities in systemic sclerosis as predictive of functional impairment. The rates of progression in HRCT findings in diffuse scleroderma patients were higher than in acroscleroderma patients. A statistically significant inverse correlation was found between the score of change in the extent and coarseness of disease and the percentage of changes in DLCO (r_s=-0,33,p=0,01), FVC (r_s=-0,28, p=0,03) and TLC (r_s=-0,34, p=0,02) values, after the first sequential imaging evaluation. Mixed effects models revealed a significant inverse correlation during the entire follow up period between the indices of change in imaging findings and the percentages of change in DLCO (B=-2,35, p=0,005) and TLC values (B=-2,29, p=0,01). Careful HRCT quantification of imaging progression during short term follow up could have prognostic significance regarding changes in functional parameters, with diagnostic accuracy that exceeds 70%.

CONLUSIONS During follow up the change in the extent and coarseness of disease on HRCT is correlated with the correspondent changes in functional indices and could also have prognostic significance regarding functional impairment.

INTRODUCTION

Pulmonary manifestations are the common causes of death in patients with systemic sclerosis. The two major features of lung involvement are interstitial lung disease and pulmonary hypertension. These two types of lung disease are different in their pathogenesis, clinical associations, predictive factors and treatment. HRCT has proved to be of considerable value in the assessment of interstitial lung disease. It is a sensitive tool in detecting early ILD, as well as in assessing progression. Parameters of diagnostic value of HRCT regarding assessment of pulmonary involvement at an isolated point of time and comparison with Pulmonary function Testing results have been under investigation in recent medical reports.

Nevertheless, the natural history of systemic sclerosis interstitial lung disease and the interaction of the interstitial and vascular component are incompletely understood. For that reason, well-designed longitudinal studies are needed to define the long term clinical course of these patients, the accuracy of HRCT findings for studying treatment effects and outcomes and the appropriate imaging and functional algorithm for patient monitoring (of alveolitis and interstitial pulmonary fibrosis). Parameters of diagnostic value of HRCT regarding assessment of pulmonary involvement at an isolated point of time and comparison with Pulmonary function Testing results have been under investigation in recent medical reports.

The purpose of this prospective study was to compare initial findings and longitudinal changes in HRCT semiquantitative evaluation of extent and coarseness of disease with correspondent PFT measurements and investigate the prognostic significance of HRCT findings in assessing progression of SSC-ILD.

MATERIALS and METHODS

The study group comprised 159 patients referred to our institution between January 1997 and November 2004. The patients were diagnosed with SSc by the American Rheumatism Association criteria, excluding cases with overlap features such as SSc associated with rheumatoid arthritis, systemic lupus erythematosus or polyomyosistis and/or dermatomyositis. A detailed clinical examination of Scleroderma activity was performed before every imaging and functional study, *according to European Scleroderma Study Group criteria.* Respiratory system history included questions about previous chest disease, existence of respiratory symptoms and risk factors of respiratory disease. Cigarette consumption was evaluated in pack-years (1 packyear=20/day for 1 year).

Patient demographic and clinical data are shown in table 1. As shown in table 1 88,1% of patients were female, 16,5% were smokers and 56% had limited disease. Demographic and clinical data (sex, smoking history, age at disease onset and disease duration) did not differ between limited and diffuse type.

All patients underwent HRCT and full pulmonary function testing at least once. 138 out of 159 realized follow-up HRCT and PFT assessments. Patients (n=15) with suboptimal quality of CT images were excluded from the study group. Furthermore, 19 patients had no evidence of lung disease at initial HRCT and PFTs, and only 7 of them were included in the study after follow-up (imaging and functional) assessment findings.

HRCT

HRCT scans were interpreted independently by 2 radiologists, who were unaware of the clinical details. A consensus opinion was taken in the event of disagreement. (**Table 1**)

Semiquantification of HRCT findings was based on the grading systems introduced by Wells et al and Warrick et al. Follow up studies included semiquantitative evaluation of change in the extent and coarseness of disease, on previous and subsequent HRCT scans, at anatomically comparable sections (5 slices).

TABLE 1: Baseline imaging findings

	Classification according to ggo-rp proportion and bronchiectasis (B).					
Baseline **HRCT** EXTENSION	**0:** ggo/total=100%, B=0	**1: ggo/total>= 95%,**	**2:** ggo/total= 55-94%	**3:** ggo/total= 45-54%	**4:** ggo/total= 0-45%	TOTAL
0: 0-5%	23	0	0	1	1	25
1: 6-15%	18	2	16	0	0	36
2: 16-30%	3	7	43	5	4	62
3: 31-45%	0	1	18	0	8	27
4: >45%	0	0	4	0	1	5
TOTAL	44	10	81	6	14	155

Pulmonary Function Tests

Pulmonary function testing was performed using a standard protocol according to ATS and ERS criteria and included spirometry, lung volumes and transfer factor measured by single breath diffusing capacity. FVC, TLC ,FEV1, FEV1/FVC,DLCO, DLCO/VA measurements were expressed as percentages of predicted values for age, height and sex according to standardized tables.

Follow-up

The patients were assessed clinically every three months. Chest HRCT was realized at baseline and subsequently every year. (**FIG 1-3**) PFTs were performed in all patients within 2 weeks of the HRCT scan. A semiquantitative scale (range 5 to 25), applied at 5 anatomically comparable slices (range 1 to 5 for every slice: 1=severe improvement, 2=moderate improvement, 3= no detectable change, 4= moderate deterioration, 5=severe deterioration), was used to evaluate change in HRCT findings. A total score more than 15 (or 16) was defined as imaging deterioration. According to ATS and ERS criteria significant changes in PFTs included a rise or a decline of more than 15 % from the baseline value of DLCO and 10% FVC.

Fig. 1

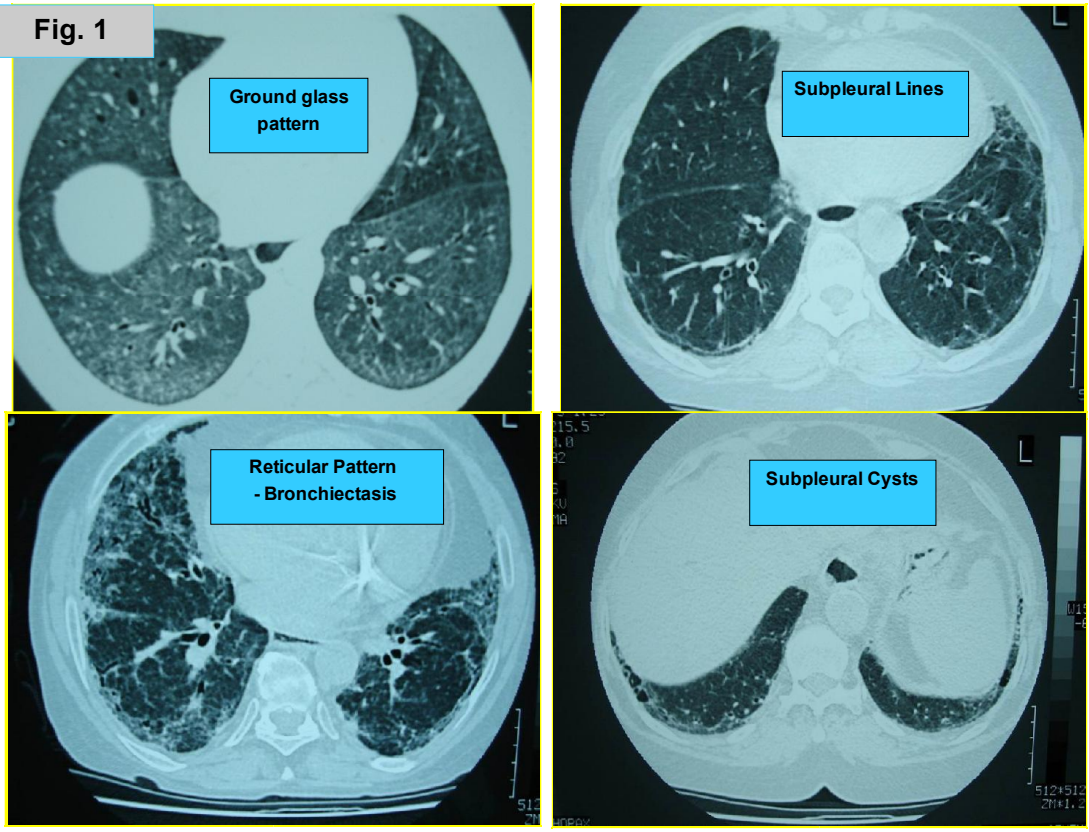

Ground glass pattern
Subpleural Lines
Reticular Pattern - Bronchiectasis
Subpleural Cysts

Fig. 2

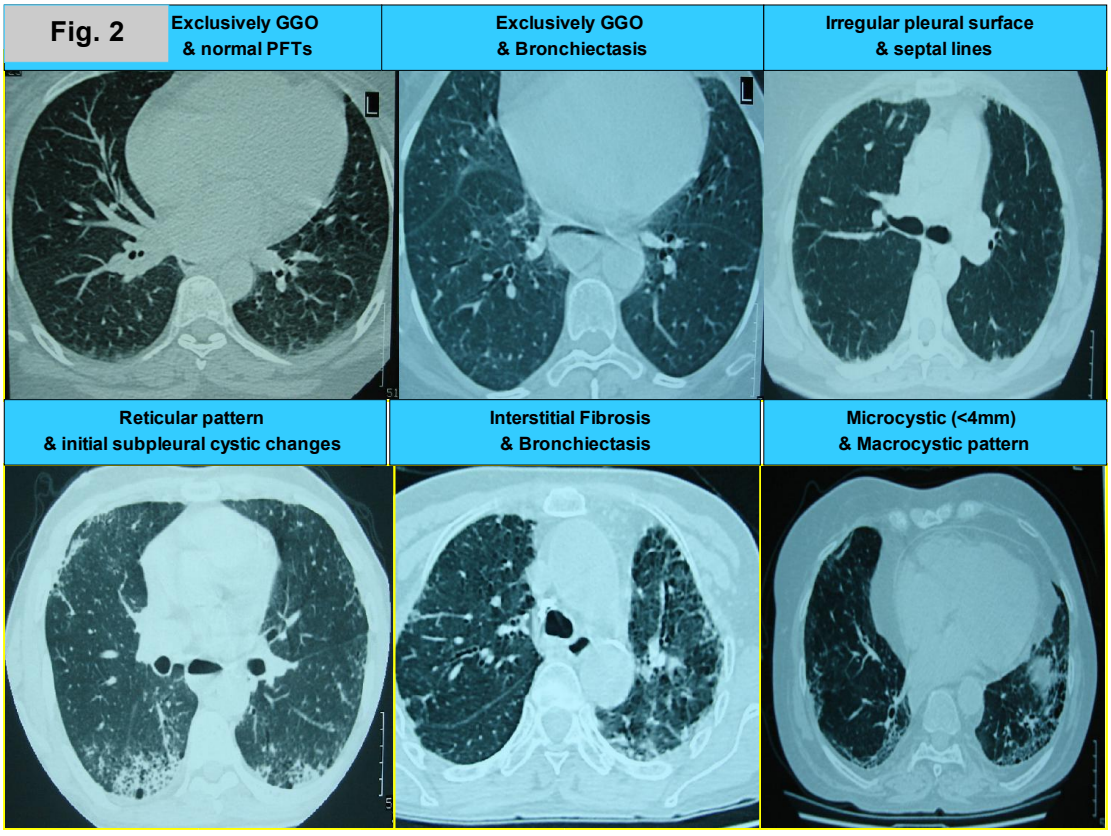
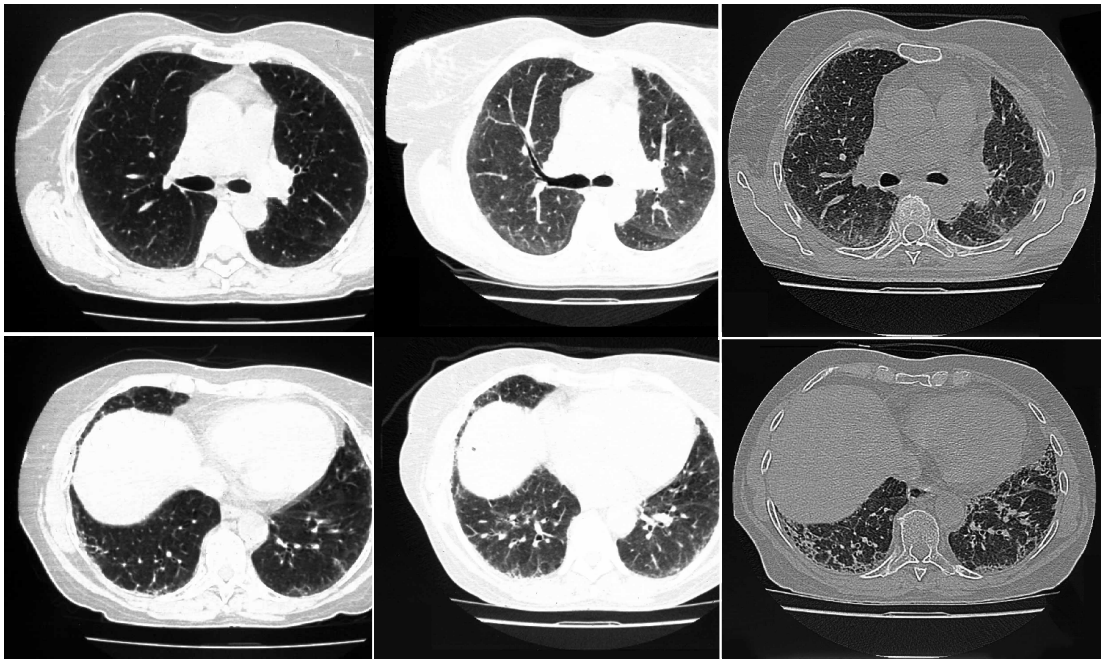

Exclusively GGO & normal PFTs
Exclusively GGO & Bronchiectasis
Irregular pleural surface & septal lines
Reticular pattern & initial subpleural cystic changes
Interstitial Fibrosis & Bronchiectasis
Microcystic (<4mm) & Macrocystic pattern

Fig. 3 **Case with 3 HRCTs: imaging progression**

Baseline HRCT | 1st Follow-up | 2nd Follow-up



Statistical Analysis

Data are expressed as means (SD), or medians (ranges), depending on distribution. A p value < 0.05 was considered significant. A weighted kappa}coefficient of agreement was used for ranked categorical data to quantify observer variation. Group comparisons were made using Student's t test, the Mann-Whitney U test or, when appropriate, chi-squared statistics. Analysis of correlation, multiple linear and logistic regression analysis, ROC analysis and mixed effects models were used.

RESULTS

Initial Evaluation

During initial evaluation, 12 patients with pulmonary involvement in HRCT had normal PFTs, while only 2 patients with abnormal PFTs had normal HRCT. The initial values of extension, coarseness and bronchiectasis score were higher were higher and the proportion GGO/RP was lower in patients with diffuse type of disease ($p<0,05$). Comparisons of FVC, TLC, FEV1 between patients with diffuse cutaneous SScl and patients with limited cutaneous SScl showed statistically significant differences ($p<0,01$), while DLCO values were not significantly different. Coefficients of correlation between extension, coarseness, proportion of GGO/RP, bronciectasis vs DLCO, FVC, LC, FEV1 range from 0,35 to -0,55

(p<0,05). (**FIG 4**). According to multiple linear regression analyses extension and coarseness score are explanatory variables "responsible" for about 30% of the range of PFT values. (**FIG 5**). A total HRCT score of 7 (extension + coarseness score) would be required to consider HRCT abnormalities in SSc as predictive of FVC impairment (diagnostic value paramenters: sensitivity 71,4%, specificity 60%, accuracy 69,5%), and a cut off value of 5 (with parameters of diagnostic value 70,5%, 65% and 74,4% respectively) would be predictive of DLCO impairment. (**FIG 6**).

Fig. 4: Results – Scatter Charts & Box plots

Initial Imaging and Functional Findings

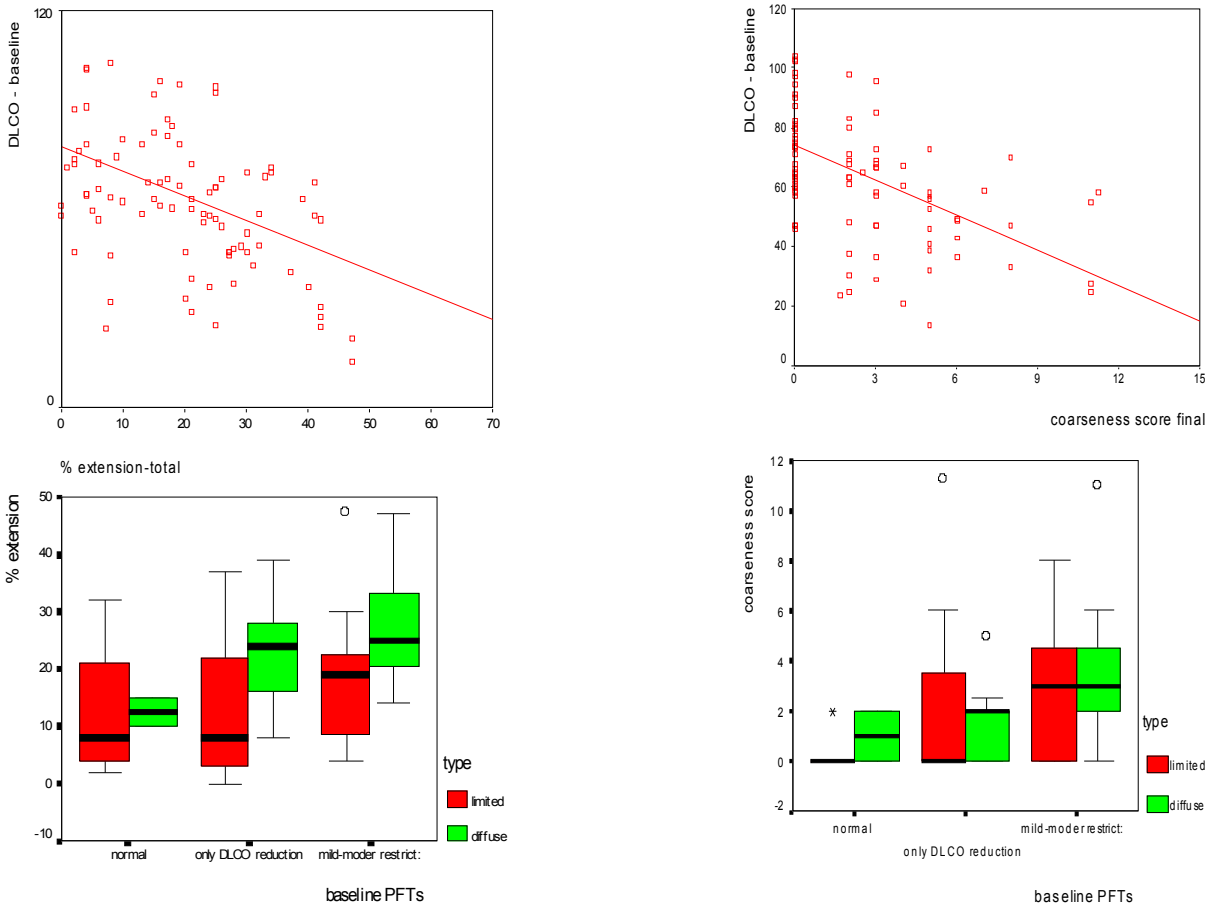


Fig.5: Initial Imaging and Functional Findings

Regression Lines: relationship between PFTs & Exte-Coars Index (lim vs diff type)

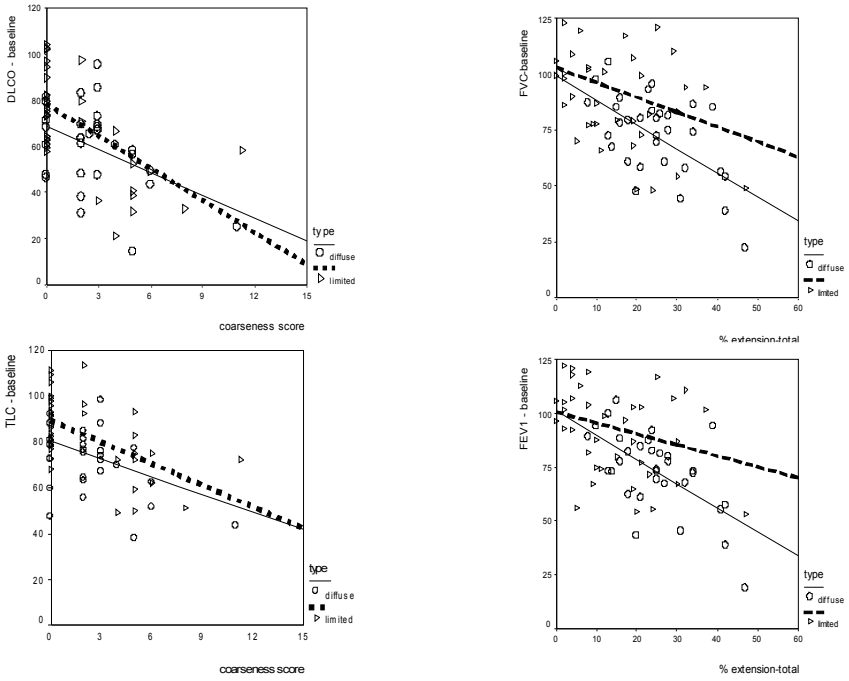
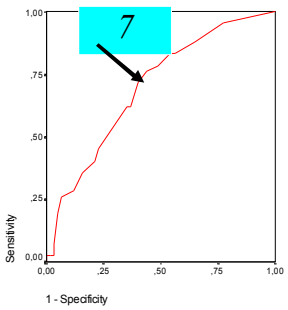
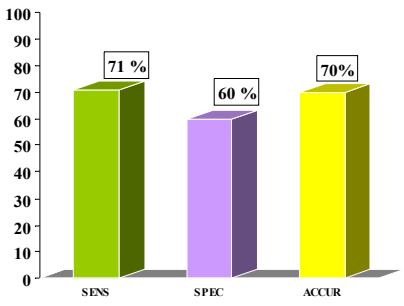


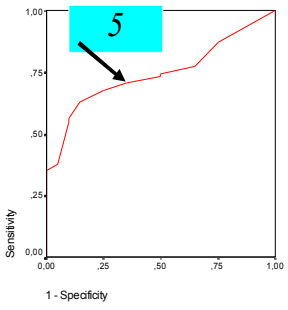
Fig.6: ROC Curves - Baseline evaluation

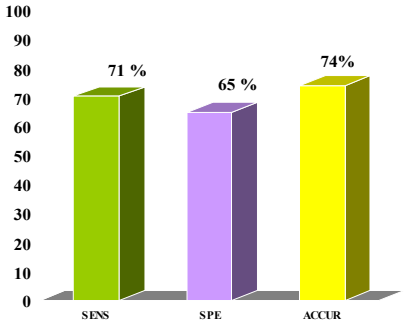
Composite Index (Exte & Coars) vs FVC





Composite Index (Exte & Coars) vs DLCO





HRCT sequential evaluation

There was a positive correlation between the extension on initial HRCT and the indices of imaging findings progression (extension, coarseness, bronchiectasis) during follow up (r_s=+0,41,p<0,001-r_s=+0,28,p<0,001-r_s=+0,24,p<0,001). Multiple linear and logistic regression analysis, using as response variable the correspondent variable of imaging progression, included initial disease extension as a statistically significant independent-explanatory variable. The presence of a proportional (positive) relationship between initial imaging findings and imaging progression indices, according to correlation analyses, does not seem to have a permanent character over time (p>0,05), according to mixed effects models. According to the same statistical method, a significant correlation during the entire follow-up period was found between the type of disease and imaging progression indices. The rates of progression in HRCT findings in diffuse scleroderma patients were higher than in acroscleroderma patients (B=+1,7, p=0,03). The same difference was found in comparisons: a)of HRCT short-term progression rates (Score1-p=0,02) and b) mean values of sequential imaging progression rates (p=0,03). These findings are compatible with the absence of statistically significant difference between patients with diffuse and limited type of disease, who have imaging regression versus imaging findings progression. The cut-off value of initial HRCT extension >15% gives the best compromise between sensitivity and specificity (78,4% and 68% respectively) in prediction of imaging regression (defined as HRCT progression score >15) with diagnostic accuracy of about 75%.

Functional follow-up

Correlation analysis indicates the presence of inversely proportional relationship between initial DLCO, TLC, FVC values and percentages of change after first follow-up study. A proportional relationship of low to moderate strength was found between baseline coarseness score and initial percentages of change from baseline values of DLCO, FVC, TLC. According to mixed effects models initial values of imaging and clinical indices do not correlate significantly during the entire follow-up period with the percentage of change in functional parameters (p>0,05).

Relationship between changes of imaging and functional findings

A statistically significant inverse correlation was found between the score of change in the extent and coarseness of disease and the percentage of changes in DLCO (r_s=-0,33, p=0,01), FVC (r_s=-0,28, p=0,03) and TLC (r_s=-0,34, p=0,02) values, after the first sequential imaging evaluation. Mixed effects models revealed a significant inverse correlation during the entire follow up period between the indices of change in imaging findings (explanatory variable) and change in DLCO (B=-2,35, p=0,005) and TLC values (B=-2,29, p=0,01) (**FIG**.**7**). Using as dependent variable FVC, we found a relationship that nearly exceeds limits of statistical significance (B=-1,62, p=0,06). A value of the index of progression in imaging findings equal to 17,5 (>=18) was identified as the best cut-off in predicting significant change in DLCO (>15% from baseline value) after first follow-up study (**FIG 8**).The mean index of imaging progression gave an area under ROC curve of 70% and a best cut-off value of 16,4 in predicting decline in DLCO during the entire follow-up period (sensitivity 74%, specificity 64%).

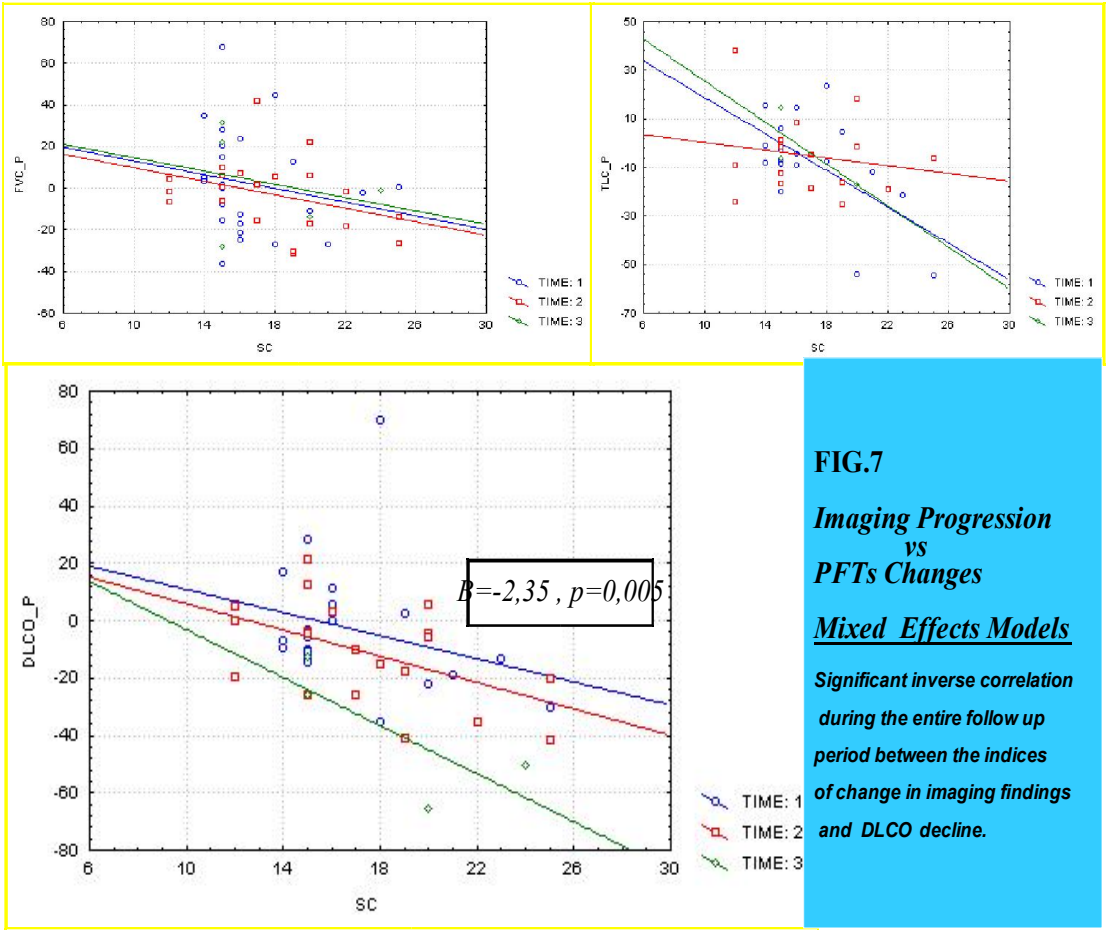


FIG.7

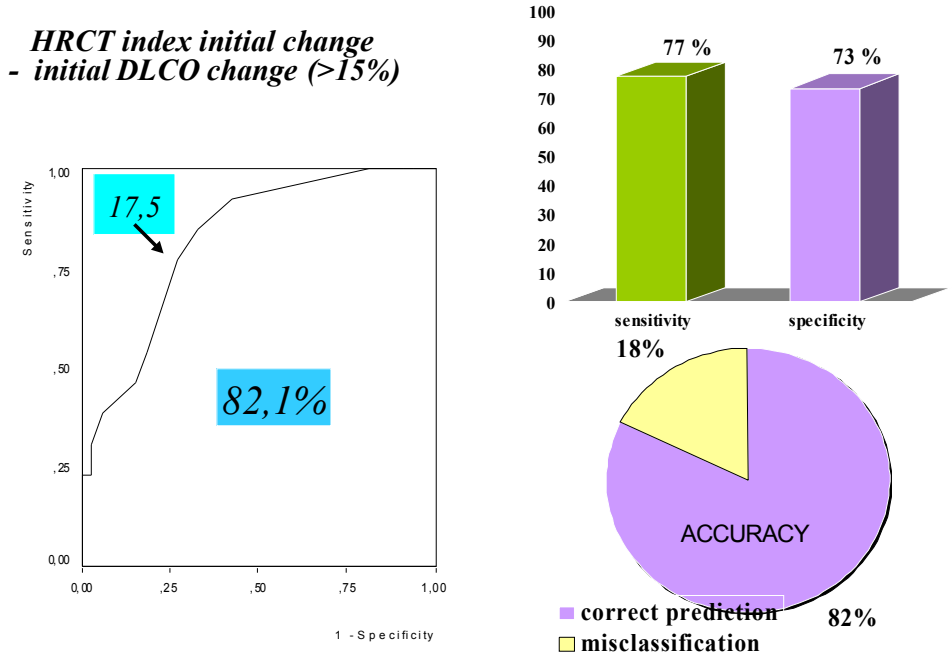
Imaging Progression vs PFTs Changes

Mixed Effects Models

Significant inverse correlation during the entire follow up period between the indices of change in imaging findings and DLCO decline.

Fig.8: ***Imaging Progression vs PFTs Changes***

ROC Analysis



CONLUSIONS

HRCT is a sensitve tool for the identification of pulmonary fibrosis in systemic sclerosis. Initial HRCT findings are corellated with pulmonary function test results and have a potential predictive role regarding functional impairment. Moreover, disease extent on HRCT correlates with progression of imaging findings during follow up. Patients with diffuse scleroderma have worse initial imaging and functional findings and increased rates of progression in HRCT findings.

During follow up of pulmonary involvement the change in the extent and coarseness of disease on HRCT is correlated with the correspondent changes in functional indices. This correlation is significant both in short-term follow-up and during entire follow-up period assessment. Careful quantification of imaging progression during short term follow up could have prognostic significance regarding changes in functional parameters, with diagnostic accuracy that exceeds 70%.

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