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Scoring of Interstitial Lung Disease by High-Resolution Computed Tomography (HCRT) and its Correlation with Functional Parameters

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ABSTRACT

Background: Interstitial lung disease [ILD] is a group of diffuse parenchymal pulmonary disorders which are marked by a high incidence of respiratory failure and mortality when the severity and extent of the condition were unexplored earlier. HRCT, a non-invasive method to comment on the histopathology of the underlying disease has promising diagnostic abilities in staging and assessing the prognosis of the diseases.

The Aim of the work: To determine the relationship between the HRCT assessed extent and severity scores of interstitial lung disease with functional assessment parameters by standard pulmonary function tests [PFT].

Patients and methods: A hospital-based, cross-sectional study was conducted on 30 patients with clinical suspicion of interstitial lung disease referred from various clinical departments, after excluding those ineligible subjects as per exclusion criteria. ILD scoring was done based on a pre-tested and validated scoring system. The correlation between the morphological HRCT scoring and the functional PFT parameters was evaluated, and the reliability of HRCT scoring was assessed statistically.

Results: Males and females were equally represented in the sample. The mean ILD score was 15.8±5.4 and it did not significantly differ among the males [15.8±5.9] and females [15.7±5.1]. There was a significant negative correlation of total HRCT-ILD scores with Forced vital capacity [FVC] [r=-0.48, p=0.007], Forced expiratory volume in the first second [FeV1] [r=-0.41, p=0.003], Diffusing capacity of the lungs for carbon monoxide [DLCO] [r=-0.59, p<0.001] and 6-minute walk test [r=-0.38, p=0.004] showing deterioration in functional parameters as the severity score increases.

Conclusion: The study documented the total ILD scores, including the severity and extent of the underlying pathology in HRCT, and established a significant correlation with the functional lung parameters as assessed by PFT.

Keywords: Pulmonary function test; Interstitial lung disease; Tomography

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INTRODUCTION

The interstitial lung diseases [ILDs] are a group of diseases that cause structural and functional lung damage and eventually result in fibrosis with loss of the elasticity of the lungs. The characteristic feature of interstitial lung disease [ILD] is marked by the thickening of the supporting tissues between the air sacs of the lungs [1]. The pathophysiology, clinical features, and prognosis of ILDs correspondingly vary with the underlying disease. Some patients with ILD need hospitalization in the due course of this illness. The treating clinicians face different challenges during the treatment of ILD patients who are hospitalized. There exist different types of ILD which can be specifically differentiated from each other when clinical data, radiologic imaging, and pathologic findings are linked to derive a confident diagnosis [2].

ILD is considered to be a multidisciplinary disease that requires the diagnostic aid of clinical, radiological, physiological, and histopathological findings [3]. ILD was originally believed to be a rare disease in India. There are challenges in diagnosing ILDs in India. The diagnosis of ILD is influenced by both environmental and cultural factors among those with lung infections caused by Mycobacterium tuberculosis. Due to insufficient resources and the absence of a standardized health care system in India, there is a deficiency in the existence of a standardized systematic approach for the differential diagnosis of ILD. Also, the patients in India, who are phobics of any form of surgical intervention, possess unwillingness and hesitation when confronted with the need for surgical lung biopsy [SLB], which contributes to the current conventional approach to the diagnosis of new onset of ILD in India [4].

The incidence and prevalence of ILD are made available by the prospective disease registries. They also provide a better understanding of the incidence and prevalence rates of ILD, their etiology, associated risks, natural history, and outcomes of disease. In western countries, many randomized controlled clinical trials for ILD have registries for the enrolled patients, whereas databases from India and South East Asian countries regarding the details of the patients with ILD and their demographic details are scarce and differ significantly [4]. The reported incidence of ILDs all over the world varies. Literature evidence shows the incidence of ILDs ranges from 3.62 per 100,000 person-years in southern Spain to 31.5 per 100,000 person-years in males and 26.1 per 100,000 person-years in females in New Mexico, USA, where the data shows a vast eightfold deviation in incidence across the globe. In a developing country like India, many ILDs are often initially misdiagnosed as tuberculosis [TB] because of the higher prevalence of TB [5].

A patient diagnosed with ILD must go through a complete assessment for the detection of ILD. A precise diagnostic approach for ILD needs information about the history of the patient, which includes a thorough examination of medical, social, family, and occupational histories. The important feature in interstitial lung diseases is fibrosis in the interstitium. This leads to the derangement of alveolar architecture and failure in the functioning of alveolar-capillary units. Thus, the appropriate diagnosis of ILD requires a proper discussion between the clinician, radiologist, and pathologist [6].

Chest radiograph findings remain the most significant and convenient first step for the detection, verification, and classification of ILD. The clinician should therefore first look into the previous chest radiograph for review. This helps in ascertaining the onset, chronicity, and rate of development of the disease. The use of high-resolution computed tomography [HRCT] over the past 10 years has revolutionized the approach to ILD [7].

The high-resolution computed tomography [HRCT] images of the chest are therefore considered the main platform for the diagnostic approach [4]. Though there are many studies on ILD from India, they have yet to be CT evaluated. Hence, this study was undertaken to show the correlation between morphological HRCT-determined severity parameters and functional parameters assessed by pulmonary function tests. To determine the relationship between the HRCT assessed extent and severity scores of interstitial lung disease with functional assessment parameters by standard pulmonary function tests.

PATIENTS AND METHODS

This cross-sectional study was conducted in the Department of Radiology, Pondicherry Institute of Medical Sciences and Research

Center [PIMS], Puducherry between October 2015 and July 2017 on 30 patients with clinical suspicion of interstitial lung disease referred from various clinical departments, after excluding those ineligible subjects as per exclusion criteria.

Initially, permission was obtained from the Institutional Ethics Committee for the conduct of the study in the hospital. All the patients were referred to the department of radiodiagnosis, PIMS, with clinical suspicion of interstitial lung disease during the period of study.

Only individuals who had the intention of getting evaluated with HRCT and PFT or referred for relevant clinical pulmonary evaluation were included in the study after they satisfied the inclusion criteria. None of the study subjects were included purely for the purpose of this research.

The individuals selected for the study were explained in their local language about the procedure, its safety and confidentiality. When they were clear about the explanation, informed consent was obtained from the participant.

Demographic details of the patient with a previous history of ILD, clinical examination, HRCT findings, and pulmonary function test parameters were recorded using a structured proforma.

Inclusion Criteria: All patients referred with clinical suspicion of interstitial lung disease among both sexes were included in the study. Patients presenting with collagen vascular diseases like SLE, rheumatoid disease, systemic sclerosis, systemic vasculitides like Wegener‘s granulomatosis, miliary tuberculosis, industrial exposure-related diseases like asbestosis, silicosis, coal worker‘s pneumo-coniosis, infections like Pneumocystis pneumonia, atypical pneumonia , RSV were also included.

Exclusion criteria: Pregnant patients, patients with a history of previous lung resections, and presence of bronchial carcinoma or lobar consolidation were excluded from the study.

Materials used: HRCT was done using Siemens [Model: SOM Sensation64/card 64]. High resonance CT machine [Figure 1] for all patients placed in the supine position.

Images and films were obtained by using standard lung window settings [window level, −700 HU; window width, 1,000–1,500 HU].

Scan time: 0.5-1 sec.

Expiratory scans were obtained for the patients by using similar parameters if necessary.

Figure [1]: Siemens HRCT used during the study

Study tool: A semi-structured proforma containing both open-ended questions was used for obtaining relevant data from the participant records, recording the severity and extent as per HRCT and also the PFT findings. Written informed consent was obtained from each of the participants after explaining the content in their local language. The proforma included the patient's demographic details, brief history, chest examination, chest X-ray findings, HRCT – radiological pattern of ILD, severity and extent scoring, and PFT [Pulmonary function test]-FVC [Forced vital capacity], FeV1 [Forced expiratory volume in the first second], DLCO [Diffusing capacity of the lungs for carbon monoxide], and a 6-minute walk test.

Scoring System: Many different types of scoring systems are available to grade the HRCT abnormalities that have been widely used over a period of time. All the scoring methods have not won the battle of time. But it can be easily discussed under the classification as follows: comparative scoring, semi-quantitative scoring, and quantitative scoring. The comparative scoring method assesses an abnormality [e.g., ground-glass appearance] with another HRCT abnormality [e.g. fibrosis] to determine the severity of the disease. These methods can just give descriptive knowledge about the severity and not about the measurement of the severity.

Semi-quantitative scoring methods estimate the extent of the disease by assigning a grade to each severity, where higher grades correspond to a higher percentage of disease severity. This rates the severity on an ordinal scale. The main advantage of such scoring is that it can be helpful in classifying and designing therapeutic algorithms. This severe staging can be used in triaging the therapy needed and prioritizing the necessary management protocols for the most needed. Quantitative methods estimate the actual proportion or percentage of lung involvement in any particular HRCT. This gives a clear idea of the treatment and planning of surgeries. The functional impairment in the lung can be estimated by this type of scoring [8].

HRCT based ILD scoring was done based on severity and extent as follows:

Table [1]: Severity score

Abnormality	Grading
Ground glass opacities	1
Irregular pleural margins	2
Septal or subpleural lines	3
Honeycombing	4
Subpleural cyst	5
Maximal severity score	

Table [2]: Extent score

Segments involved	Grading
1 to 3 segments involved	1
4-9 segments involved	2
More than 9 segments	3
Maximal extent score	

Statistical Analysis

Descriptive data for frequencies were presented as percentages and proportions. Chi-square [$\chi 2$] test for trends was applied to see significant differences and associations of various parameters like age categories with demographic details, ILD severity scores, and categorical parameters. Pearson Correlation test was applied to check the correlation between two continuous variables like ILD scores and PFT values. For all tests, a p-value of 0.05 or less was considered for statistical significance. Data entry was done in Excel 2010 and analysis was done in SPSS version 20.1.

RESULTS

In the present study, the study participants were mostly higher-aged people [mean age = 56.2±15.8 years], with a majority [43.3%] in the over-60 age group followed by 30% in 46-60 years, 16.6 % in 31-45 years and 10% in 20-30 years. 15 patients [50%] were male and 15 patients [50%] were females [P-value= 0.868, not significant] as shown in table [3].

The mean HRCT Severity score was 8.63± 3.1, and Maximal Severity score= 15 [table 4].

The HRCT score of ILD in our study shows the extent score was 28 patients in septal, 27 patients in irregular pleural margins, 24 patients in honeycombing, 14 in ground glass opacities and 5 in sub pleural cyst. The mean total extent score = 7.2±2.9 and the maximal Extent score = 15 [table 5].

Table [6] shows mean pulmonary function tests values are no significant correlation in FeV1/FVC and DLCO. FVC, FeV1 and 6MWT had significant correlation. [significant - p=<0.05]

Table [7] shows significant correlation between Total ILD vs FVC and FeV1. [Significant - p<0.05]

Our study shows no significant correlation between Total ILD and FeV1, but significant correlation between Total ILD vs DLCO and 6MWT [p<0.05] as shown in table [8].

Table [3]: Age and gender distribution of study participants

Age [in years]	Males [n = 15]	Females [n = 15]
20-30 years	1 [6.7]	2 [13.3]
31-45 years	3 [20]	2 [13.3]
46-60 years	4 [26.7]	5 [33.3]
above 60 years	7 [46.7]	6 [40]
Total	**15 [100]**	**15 [100]**

Table [4]: Severity Score [HRCT Scoring of Interstitial Lung Disease [ILD]]

Abnormality	Grading	Frequency	Percentage
Ground glass opacities	1	14	46.7
Irregular pleural margins	2	27	90.0
Septal or subpleural lines	3	28	93.3
Honeycombing	4	24	80.0
Subpleural cyst	5	5	16.7
Total [N]	**30**	**100**	

Table [5]: Extent score [HRCT Scoring of Interstitial Lung Disease [ILD]]

Radiographic patterns	Extent score		
	1	**2**	**3**
Ground glass opacities [n = 14]	5 [35.7%]	4 [28.6%]	5 [35.7%]
Irregular pleural margins [n = 27]	8 [57.1%]	10 [37.0%]	9 [33.3%]
Septal or sub-pleural lines [n = 28]	0 [0%]	10 [35.7%]	18 [64.3%]
Honeycombing [n = 24]	2 [14.3%]	9 [37.5%]	13 [54.2%]
Sub pleural cyst [n = 5]	5 [35.7%]	0 [0%]	0 [0%]

Table [6]: Mean Pulmonary function tests values among study participants

	Mean±SD	Minimum	Maximum	p-value*
FVC	47.73±16.6	26	89	**0.02**
FeV1	50.77±20.4	30	95	**0.03**
FeV1/ FVC	101.70±17.8	83	150	0.51
DLCO	51.30±17.9	22	80	0.86
6MWT	317.00±37.7	230	370	**0.02**

Table [7]: Correlation between Total ILD score vs FVC and FeV1

		Total ILD score	FVC	FeV1
Total ILD score	**Pearson Correlation**	**1**	**-0.409****	**-0.482****
	Significance. [2-tailed]	**[p-value]**	**0.025**	**0.007**
	Total [N]	**30**	**30**	**30**

Table [8]: Correlation between Total ILD score vs FeV1, DLCO and 6MWT

		Total ILD score	FeV1	DLCO	6MWT
Total ILD score	**Pearson Correlation**	1	-0.006**	-0.598**	-0.382**
	Significance. [2-tailed]	[p-value]	**0.973**	**<0.001**	**0.037**
	Total [N]	30	30	30	30

DISCUSSION

The world of diagnostics has seen more innovations in structural and technical aspects of capturing any disease scenario along with its progress and therapeutic improvements, and the most important of those is the diagnostic ability of high-resolution contrast tomography. The importance that this diagnostic modality has achieved in evaluating patients suspected of interstitial lung disease [ILD] remains un-satisfied [9]. The advantage of this diagnostic tool is that it not merely helps in visualizing the pathology but gives additional information about the probable histological pattern of the disease, the extent of the disease with more precision, the site that would be optimal for biopsy, and the stage of the underlying disease and progression [10].

A total of 30 patients with clinical suspicion/known cases of interstitial lung disease referred to the Department of Radiology, Pondicherry Institute of Medical Sciences and Research Center during the study

period were included in the study as per the inclusion criteria. ILD is most common amongst middle-aged individuals usually uniquely dispersed in the 40 to 70 years age group. The incidence advances with increasing age [11]. 75% of patients turn 60 years of age at the time of diagnosis [12]. In the present study, the study participants were mostly higher-aged people [mean age = 56.2±15.8 years], with a majority [43.3%] in the over-60 age group. Males [50%] and females [50%] contributed equally to the study sample. This could not infer that both genders had an equal incidence of ILD. The sample was selected over some time after much exclusion as per the criteria. This was a bit different from **Maheshwari *et al.*** [13] who reported a slight female predominance [54%] among the population studied in terms of the incidence of ILD. In this study, the gender-wise distribution of age showed that male participants were more in the 30-45 years and above 60 years age groups, whereas female participants were more in the 20-30 years and 40–60 years age groups. This pattern of gender-wise distribution of age was not significantly different. The HRCT patterns to access the severity of the pathology were done and it was detected that irregular pleural margins [n = 27, 90%] and septal and sub-pleural lines [n = 28, 93.3%] were present in a majority of the ILDs. **Nishmura *et al.*** [14] in their radio-diagnostic evaluation reported that most ILDs had reticular shadowing [60-96%] with marked thickening of the interlobular interstitial lining similar to the sub-pleural lines observed in the present study.

Primack and Hartman [15] did an observational study among 61 patients with end-stage lung disease and documented their CT findings. They reported honeycomb cysts in 24% to 90% of the patients, which was a characteristic feature documented in their study. In the present study, honeycombing was found in 24 patients [80%] and was again reported in the elderly with severe cases of ILD.

HRCT plays a decisive role in the diagnosis of severe ILD, a step ahead of the gold standard biopsy. **Wells *et al.*** [16] established their view that the presence and extent of ground-glass opacity along with the evidence of fibrosis is related to the likelihood of prognosis and response to treatment. In the present study, ground-glass attenuation was seen in 46.7% of cases and mostly associated with evidence of fibrosis, representing an inactive process with a relatively poor prognosis. **MacDonald *et al.*** [17] in their study described the HRCT findings, which were predominated by sub-pleural ground-glass attenuation and reticular pattern with or without honeycombing in 24% of patients.

The present study used a quantitative scoring system in estimating the severity of lung cancer involvement as it necessitated the comparison of the scores with functional parameters like the pulmonary function tests. The mean severity score in the present study was 8.63± 3.1. In the study done by **Richardson *et al.*** [18], the total HRCT score was 22.0 and the mean follow-up HRCT score was 23.3 [p = 0.26]. This was quite higher compared to the scores in the present study. The reason for this may be that the previous study included participants who were clinically affected by autoimmune myositis, who had more neuromuscular stiffening compared to the varied array of patients included in our study.

The association of HRCT severity scores with the function parameters is to establish the construct validity, i.e., the ability to predict precisely the accepted measure of an underlying disease. The other parameters that can be used include bronchoalveolar lavage, histopathology, and measures of survival.

In a retrospective study done by **Raj Kumar *et al.*** [19] among 289 patients, radiological characteristics were compared with physiological functional parameters of various subgroups of ILD patients. In the pool of ILDs analyzed, sarcoidosis [37.3%] was found to be the most common subgroup, followed by IPF [27.6%] and NSIP [25.6%]. The most common pattern on chest roentgenogram was the reticular/reticulo-nodular pattern [80.2%] and on HRCT interstitial fibrosis [49.9%]. The mean predicted total lung capacity [TLC] was 64.3%, the lowest being in the IPF group [58.88%]. The mean of predicted DLCO was 50.56%, the lowest being in the IPF group [42.75%]. The overall diagnostic yield of bronchoscopic biopsy was 83.04%, with the highest yield being among sarcoidosis patients [96.29%].

In this present study, the pulmonary function tests analyzed were similar to the previous studies, with a slightly restrictive pattern compared to the former. The parameters were as follows: FVC = 47.73±16.6, FeV1 = 50.77±20.4, FeV1/FVC 101.70±17.8, DLCO = 51.30±17.9 and 6MWT = 317.00±37.7. There

was significant difference between the mean FVC [p=0.02], mean FeV1 [p=0.03] and mean 6-minute walk test [p=0.02] among the males and females. This difference was not observed between the mean Fev1/FVC and mean DLCO values among the males and females. The variations in the pulmonary functional parameters indicate that males and females have different severity and extent of involvement. The severity scores also showed differences in the extent of the lesion among the males and females. Females have more musculature and fibrous tissue compared to the males and a faster progression rate than males in terms of complications of ILD.

ILD is associated with a higher incidence of lung cancer when studied by neutralizing the confounding effects of sex, age, and smoking with matched controls. It was also important that more men with IPF had a higher risk of developing lung cancer compared to their counterparts [20].

In the present study, there was a significant correlation between the HRCT severity scores and the PFT values. The functional parameters showed significant correlations with the morphological severity indicators. There was observed a significant [p=0.007] negative correlation [r^2 = -0.482] between the total ILD scores and the FVC values. As the FVC values decreased, the ILD scores showed an increase.

Pulmonary function studies in ILDs show evidence of restrictive lung disease with values like vital capacity [VC] often decreased and FEV1/FVC ratios increased due to impaired gas exchange [21]. A retrospective study done on 43 patients by **Abo-elhamd *et al*.** [22] measuring their HRCT scores and PFT showed a significant correlation between the overall extent and severity of the disease as measured by HRCT and both FVC [r = 0.350, p = 0.001] and DLCO [r = 0.296, p = 0.004]. In addition, the extent of honeycombing correlated significantly with FVC [r = 0.648, p < 0.001] and DLCO [r=0.393, p<0.001]. The extent of reticulation was significantly correlated with these two PFT parameters: FVC [r = 0.373, p < 0.001] and DLCO [r = 0.272, p = 0.008].

The present study could not alone document the connection between the pathological findings and PFT, but as evident from the higher incidence of honeycombing and reticular patterns interspersed among the study subjects, there was an overall association of reduced FVC and DLCO values with the above mentioned high proportioned patterns in the study. A study done by **Lettieri *et al*.** [23] has shown that the presence of obstructive co-morbidities of the parenchyma like emphysema can influence both FVC and DLCO values in patients with ILD. The effects of such pulmonary patterns are decided by the extent of predominance of the lesion which decides the functional pattern. In ILDs, the predominant functional pattern is restrictive, which is not masked by the presence of pathologies that can show an obstructive pattern in PFT. The study also clearly defined such discrepancies by doing a comparative study of PFT patterns among those with emphysema and those without emphysema and both, documenting a restrictive pattern.

In the present study, there were also cases with documented evidence of mixed patterned pulmonary pathologies yet showed only a predominance of restrictive pattern in PFT. The 6-minute walk test did not show a significant correlation value [r=-0.382], which indicates a negative correlation. This was a contradictory finding, as those with higher severity score could walk longer. Previous studies [22, 23] showed that the vital capacity of the lung had a significant influence on the aerobic capacity and endurance. But there was a negative correlation, which may be because of the types of involvement of the lobes and duration of progression of the disease, which may be confounders needing further evaluation studies.

The study documented that HRCT scanning would dramatically alter the diagnostic approach for ILD patients. The advancements in the technique allow a detailed evaluation of the lung parenchyma by using narrow section collimation with minimal slice thickness that has been reconstructed with an algorithm that maximizes spatial resolution. Hence, HRCT can be used reliably in measuring the severity of ILD and determining early interventions.

Conclusions: The study established the common radiological patterns like irregular pleural thickening, sub-pleural thickening lines, and ground glass opacities among the patients evaluated by HRCT and documented the total ILD scores, including the severity and extent of the underlying pathology in HRCT. It established significant correlation of the total ILD scores with the functional lung parameters as assessed by pulmonary function tests.

Conflict of interest: None to be declared.

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