Original Article

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Role of Pulmonary Function Tests in the Assessment of Lung Impairment in Patients with Diffuse Parenchymal Lung Diseases: Association with Clinicoradiological-Histopathological Profile

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ABSTRACT

Introduction: Diffuse Parenchymal Lung Disease (DPLD) is known to be a common sequela of various lung insults. DPLD is diagnosed by various modalities such as clinical, radiological, lung function and histopathological techniques. There is a limited understanding on the potential clinical application of the non-invasive lung function tests in the evaluation of DPLD.

Aim: To study the role of Pulmonary Function Tests (PFTs) in the assessment of lung impairment in DPLD patients and its association with clinicoradiological and histopathological profiles.

Materials and Methods: A prospective observational study was conducted with 50 DPLD patients who were selected as per the study criteria over a period of 30 months at our tertiary care respiratory centre. Clinicoradiological evaluation and PFTs were carried out for all of the patients. Histopathological examination was done for patients with inconclusive diagnosis. Lung impairment was assessed and its association with clinicoradiologic and histopathologic profile was analysed.

Results: Of the 50 selected patients, diagnosis of a specific subset of DPLD was possible in 33 through the clinicoradiological findings while in 17 through histopathological findings. Overall, idiopathic interstitial pneumonia was found to be common in 31 (62%) followed by sarcoidosis in 14 (28%). Patients showed restrictive and mixed spirometry pattern in 35 (70%), decreased lung volumes in 30 (60%) and some form of diffusion impairment in 42 (84%) while 17 (34%) patients had showed reduced 6-minute walk distance (6MWD). Significant association was noted between: (i) severe diffusion impairment and crackles ($p=0.011$); (ii) severe diffusion impairment and honeycombing pattern ($p<0.001$); (iii) decreased lung volumes and crackles ($p=0.0009$); and (iv) reduced 6MWD and honeycombing pattern ($p<0.001$).

Conclusion: This study confirms the role of the PFTs in the comprehensive assessment of lung impairment in DPLD patients.

Keywords: Diffusion, Idiopathic interstitial pneumonia, Lung volumes, Spirometry

INTRODUCTION

DPLDs, also known as Interstitial Lung Diseases (ILDs) [1], are a diverse cluster of disorders characterised by different grades of inflammation of the lung parenchyma or interstitium leading to pulmonary fibrosis, which causes lung stiffness and reduced oxygen permeability or disordered gas exchange [2,3]. Various aetiological factors of DPLD are environmental (farming, livestock, diesel exhaust, use of wood fires etc.,) and occupational exposures (dust particles of asbestos, coal, silica, beryllium, wood, nylon flock, textile spray etc.,) [4], Connective Tissue Diseases (CTDs), inherited diseases, drug induced and idiopathic /unkown causes [2,3].

The incidence of DPLD is substantial and is a common consequence for a numerous lung diseases [2]. Diagnosis of DPLD has been carried out by both non-invasive (clinical, radiological and lung function) and invasive (histopathology) techniques [5]. In majority of patients the diagnosis of DPLD is made on the basis of the clinical presentation such as cough, progressive dyspnoea on exertion etc., and radiological features such as diffuse infiltrates on chest radiograph and/or High Resolution Computed Tomography (HRCT) chest [6]. The presenting clinical symptoms of DPLD are non-specific and are often ascribed to other illnesses, thus delaying the diagnosis and leading to healthcare burden due to lack of curative therapy. Although histopathology or lung biopsy has been employed for confirmatory diagnosis of DPLD, its use in every single patient is being doubted in view of the difficulty in assessing transbronchial lung biopsies, due to smaller tissue size and scarcity in the facilities of open lung biopsy [7].

DPLDs are categorised into several subsets based on clinicoradiological and histopathological features [3]. In contrast, a similar pattern of physiologic abnormality, restrictive pattern in ventilation and reduced diffusing capacity of the lung for carbon monoxide (DLCO), was found in most of the DPLDs [8]. Though PFTs are not helpful in diagnosis of a specific DPLD and differentiate active lung inflammation and fibrosis, they are found to play a crucial role in the assessment of respiratory symptomatology, narrowing the differential diagnosis, grading of disease severity and monitoring disease progression. Hence, PFTs such as spirometry, plethysmographic lung volumes, diffusion tests and 6MWD are suggested to be included in the initial diagnostic work-up [8,9].

A mixed pattern of restriction and obstruction (reduced airflows on a flow-volume loop or a significant post-bronchodilator response) without emphysema was noted in sarcoidosis, Respiratory Bronchiolitis-ILD (RB-ILD), hypersensitivity pneumonitis, Lymphangioleiomyomatosis (LAM), pulmonary langerhan cell histiocytosis, chronic eosinophilic pneumonia and Churg-Strauss syndrome. An obstructive defect without restriction was suggested in obliterative and constrictive bronchiolitis. An increase in plethysmographic lung volume was noted in LAM while increase in DLCO was observed in DAH [8,9]. A grossly decreased DLCO was found to be indicative of concomitant

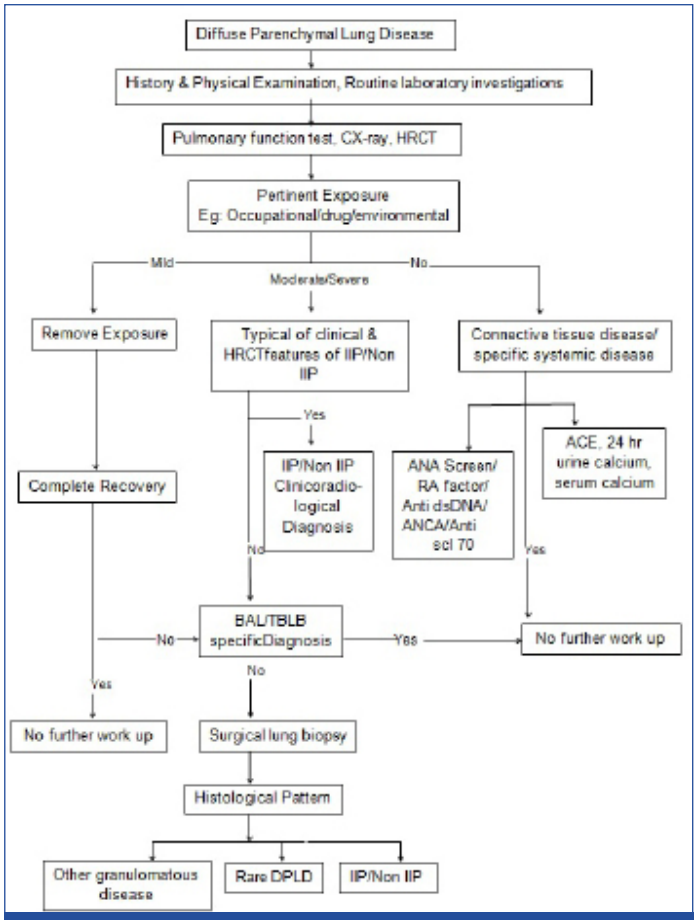
pulmonary vascular diseases such as in scleroderma, pulmonary veno-occlusive disease, chronic pulmonary embolism and also in pulmonary alveolar proteinosis [8,9]. Among PFTs, DLCO was found to relate better with extent of disease on HRCT chest scans than do spirometry or lung volumes [10,11]. A baseline low DLCO, independent of histopathological diagnosis, was found to predict reduced survival [12,13]. Egan JJ et al., have characterized the severity of Idiopathic Pulmonary Fibrosis (IPF) and Non-Specific Interstitial Pneumonia (NSIP) as advanced, if DLCO is less than 39% and limited, if DLCO is greater than 40% [14]. Further, exertional desaturation (trough saturation < 88% for atleast 1 minute) during 6MWD test in IPF patients was found to be associated with poor prognosis [15].

Though majority of DPLDs are known to produce alveolar inflammation and share common physiologic abnormalities, some DPLDs are found to affect the large airways, along with the smaller airways and interstitium and hence presumed to produce distinctive physiologic manifestations [16]. Furthermore, research on the potential clinical application of the non-invasive technique is required, hence this study was focused to understand the role of PFTs in the assessment of lung impairment in patients with DPLD and relate the physiologic findings with their clinicoradiological and histopathological profiles.

MATERIALS AND METHODS

This prospective observational study was conducted at a tertiary care Military Hospital, Cardio Thoracic Centre of Armed Forces Medical College, Pune, India, during May 2008 to October 2010. The study cases comprised of patients with features suspected of DPLD who were referred over a period of 30 months to the respiratory centre for further evaluation. Out of 138 suspected DPLD patients that were referred, 73 patients with no radiological evidence of DPLD, five patients who were unable to perform PFTs and 10 patients those detected with smear positive pulmonary tuberculosis were excluded from the study, while the remaining 50 patients who had suggestive history, clinicoradiologic features of DPLD were included in the study (the sample size calculation is described in supplementary material). The study was approved by the institutional ethical committee and the informed consent was obtained as per the committee guidelines from all the selected patients.

Detailed clinical history of all of these patients was taken, about the occupational exposure, CTDs, drugs, asthma, altered bowel habits, familial background for similar illness, etc. The patients were also subjected to radiological examination (chest radiograph and HRCT chest scan) and routine laboratory studies. Specific investigations for markers of CTDs, serum Angiotensin Converting Enzyme (ACE), 24 hour urinary calcium and serum calcium were carried out wherever indicated. PFTs such as spirometry, 6-minute walk distance (6MWD) test, lung volumes and diffusion tests were carried out by Body box plethysmography (make: JAEGER), SpiroDoc (make: MIR) and portable pulse oximetry for all of the patients. Further, Bronchoalveolar lavage (BAL) along with transbronchial lung biopsy (TBLB) /open lung biopsy (OLB) was done for patients who could not get a conclusive diagnosis. The protocol followed for diagnosis of DPLD cases in this study is as per the guidelines of ATS/ERS/JRS/ALAT [17] and shown in [Table/Fig-1]. The patients were followed-up every six monthly based on clinical symptomatology, spirometry, lung volumes, diffusion tests and 6MWD tests. Statistical analysis was carried out using software packages such as Epi Info 8, version 2.2.1, Minitab 15.0 statistical software and MS-Excel to analyse the lung impairment in DPLD patients and its association with their clinicoradiological and histopathological profiles. The proportions were compared using chi-square test and mid-P exact test. The p-values <0.05 were considered statistically significant.



[Table/Fig-1]: The protocol followed in diagnosis of DPLDs in this study.

RESULTS

1. Analysis of Demographic Data

DPLD was found in both male and female, however, majority of the (n=36, 72%) patients were male. A 78% (n=39) of total patients were of >40 years age and the mean age of patients presented with DPLD in our study was 51.3 years. A 38% (n=19) of the total patients were noted as smokers. Exposure to occupational smoke was noted in 22 (44%) patients in this study, among which largely, 15 (30%) patients were identified as housewives (who had a history of exposure to household smoke and dust).

2. Analysis of Clinicoradiological and Histopathological findings Associated with DPLD

The most commonly identified clinical symptom in this study was cough (n=41, 82%), more so dry cough (n=25, 50%), followed by dyspnoea (n=39, 78%). Most of the patients with dyspnoea had Medical Research Council (MRC) grade 2 or 3. Other symptoms reported were chest pain (n=10, 20%), fever (n=9, 18%), weight loss (n=7, 14%), joint pain (n=5, 10%), ENT symptoms like ear pain, dysphagia, blocked nose and ear discharge (n=4, 8%), wheeze (n=2, 4%), eye symptoms viz., redness and itching in eyes (n=1, 2%) and oral ulcers (n=1, 2%). In majority of patients, crackles (n=32, 64%) sign was elicited followed by clubbing (n=20, 40%), pallor (n=11, 22%), lymphadenopathy (n=6, 12%) and cyanosis (n=5, 10%). A total of 40 patients of this study, each had one or more co-morbidities among which the most common being hypertension (n=32, 62%) followed by coronary artery disease (n=6, 12%) and CTDs (n=3, 6%), were found to be prevalent.

The most common chest radiograph finding that was noted, is reticulonodular opacities (n=18, 36%) which is followed by bilateral hilar lymphadenopathy (n=13, 26%) and reticular opacities (n=12, 24%). Honeycombing was seen in 4 (8%) patients. Many patients had a combination of these findings. Further, chest radiograph showed involvement of the upper zones in 19 (38%) patients, the

lower zones in 17 (34%) and middle zones in 14 (28%). HRCT chest scanning showed mediastinal lymphadenopathy in 19 (38%) patients, followed by interstitial septal thickening in 15 (30%), honeycombing in 14 (28%), nodular pattern in 14 (28%), ground glass opacities in 13 (26%), reticular pattern in 12 (24%), cystic pattern in 4 (8%), linear pattern in 2 (4%), consolidation in 2 (4%) and pleural effusion in 1 (2%). Further, the HRCT scan had revealed involvement of upper/middle lobes in 31 (62%) and lower lobes in 29 (58%).

Diagnosis of 33 (66%) of the total 50 patients was possible with the clinicoradiological findings, as per ATS/ERS/JRS/ALAT diagnostic criteria [17], which include granulomatous DPLD/ sarcoidosis in 11 (22%) patients, Idiopathic Interstitial Pneumonia (IIP) with Usual Interstitial Pneumonia pattern (UIP) in six (12%) patients and IIP with no UIP pattern in 15 (30%) patients and DPLD with known cause in one (2%) patient [Table/Fig-2].

Various diagnoses of DPLD*		No. of cases diagnosed based on clinicoradiological profile (n=33)	No. of cases diagnosed based on pathological profile (n=17)	
			TBLB*	OLB*
Granulomatous DPLD (Sarcoidosis)		11	3	-
IIP* with UIP*		6	2	1
IIP with no UIP	NSIP*	4	3	1
	RBILD*	5	2	-
	Unspecified	6	1	-
DPLD with known cause	Rheumatoid arthritis with DPLD	1	1	-
	Scleroderma with DPLD	-	-	1
	Chronic Hypersensitivity Pneumonitis	-	-	1
Other rare forms of DPLD (Pulmonary Alveolar Proteinosis)		-	-	1

[Table/Fig-2]: Basis of various diagnoses of DPLD.
*DPLD: Diffuse parenchymal lung diseases; IIP: Idiopathic interstitial pneumonia; UIP: Usual interstitial pneumonia; NSIP: Nonspecific interstitial pneumonia; RBILD: Respiratory bronchiolitis interstitial lung disease; TBLB: Trans bronchial lung biopsy; OLB: Open lung biopsy

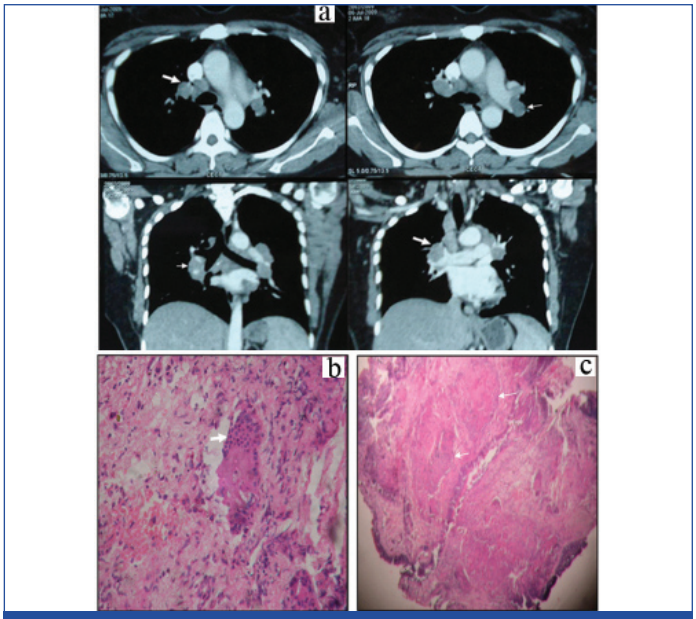
Histopathologic examination was carried out in 17 (34%) patients that were inconclusive with clinicoradiological findings. TBLB was conclusive in 12 (24%) patients while OLB in 5 (10%) patients.

Further, the 17 patients were diagnosed on the basis of histopathological findings as per ATS/ERS/JRS/ALAT diagnostic criteria [17] which include granulomatous DPLD/sarcoidosis (n=3) [Table/Fig-3], IIP with UIP (n=3), IIP with no UIP (n=7), DPLD with known cause (n=3) and other rare forms of DPLD (n=1) [Table/Fig-2].

Overall, IIP was found to be the prevalent (62% of the total patients) type of DPLD in this study. Out of these, 44% were diagnosed as IIP with no UIP (16% as NSIP, 14% as RBILD and 14% had unspecified forms of IIP) and rest 18% had IIP with UIP. Twenty eight percent patients in this study were diagnosed as granulomatous DPLD / sarcoidosis while 8% had DPLD with known cause (DPLD associated with CTDs (rheumatoid arthritis and scleroderma) and chronic hypersensitivity pneumonitis) and 2% were diagnosed with other rare forms of DPLD (pulmonary alveolar proteinosis).

3. Analysis of PFT findings in DPLD Patients

Majority of patients (n=22, 44%) showed mixed (both restrictive and obstructive) pattern of spirometry reading while only restrictive pattern was noted in 13 (26%) patients, obstructive pattern in 5 (10%) and normal in 10 (20%). Most patients (n=30, 60%) presented with decreased lung volumes, while 1 (2%) patient had increased and 19 (38%) had normal lung volumes. Eighty four percent of the



[Table/Fig-3]: Images of a case of sarcoidosis detected in this study (a) CT chest images showing mediastinal (bold arrows) and bilateral hilar lymphadenopathy (arrows); (b) TBLB showing eptheliod multi-nucleated gaint cells within noncaseating granuloma (bold arrow); (c) Lymph node biopsy showing compact non caseating granuloma (arrows).

patients had some form of diffusion impairment. Of these, 17 (34%) had severe impairment while 15 (30%) had mild and 10 (20%) had moderate impairment. Thirty four percent patients had reduced 6MWD while the remaining patients had showed normal 6MWD [Table/Fig-4].

Pulmonary Function Tests	Grade	Percentage of DPLD Cases
Spirometry	Normal	10 (20%)
	Obstructive	5 (10%)
	Restrictive	13 (26%)
	Mixed	22 (44%)
Lung Volumes	Normal	19 (38%)
	Increased	1 (2%)
	Decreased	30 (60%)
Diffusion Studies	Normal	8 (16%)
	Mild	15 (30%)
	Moderate	10 (20%)
	Severe	17 (34%)
6 Minute Walk Distance	Normal	33 (66%)
	Reduced	17 (34%)

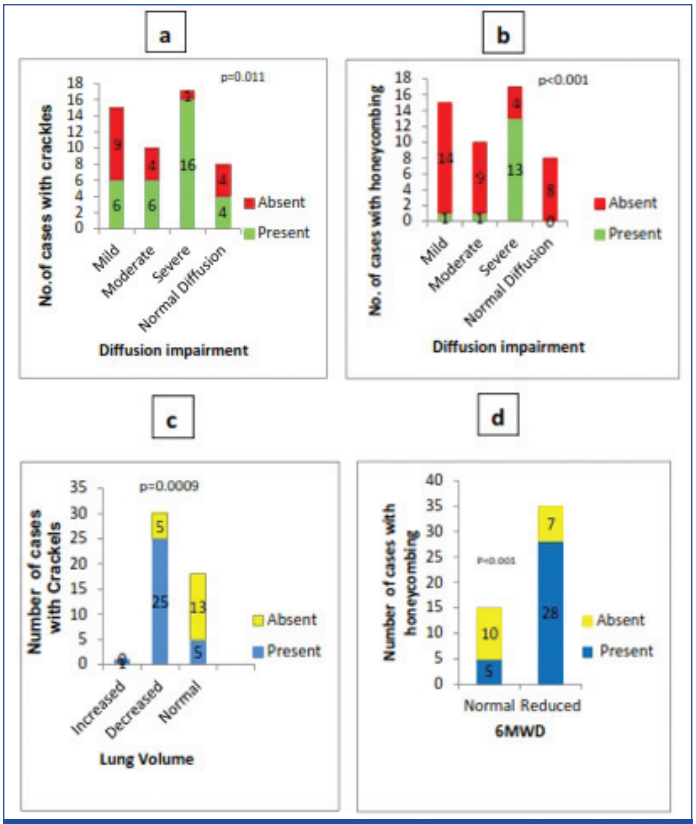
[Table/Fig-4]: Distribution of DPLD cases in this study among different grades of various pulmonary function tests

Association of pulmonary function tests with prevalent clinicoradiological findings was analysed. A significant association was found in between severe diffusion impairment and crackles ($p=0.011$), severe diffusion impairment and honeycombing pattern ($p<0.001$), decreased lung volumes and crackles ($p=0.0009$), reduced 6MWD and honeycombing pattern ($p<0.001$) [Table/Fig-5].

DISCUSSION

Although clinicoradiologic and histopathologic information has been considered as a standard for diagnosis/management of DPLD, inclusion of physiologic studies may also be essential in view of limited accuracy and utility of the standard techniques in every single patient. Henceforth, in this study, physiologic data of suspected DPLD patients were also obtained and analysed along with clinicoradiologic and histopathologic data.

Majority of the patients (n=36, 72%) were males. Though DPLD was noted in all adult age groups (24 to 80 years) in the present study,



[Table/Fig-5]: Analysis of association of PFT findings with prevalent clinicoradoigical findings of DPLD patients in this study (a) Diffusion impairment vs Crackles; (b) Diffusion impairment vs Honeycombing; (c) Lung Volume vs Crackles; (d) 6MWD vs Honeycombing.

it was predominant in patients aged around 50 years (n=39, 78%). Similar age distribution was reported earlier [18]. The bias towards male gender and middle age may be because of the study hospital being a centre primarily for serving personnel and their dependants, secondarily for others.

Notable association with smoking (38%) and occupational smoke exposure (44%) was found in DPLD patients in this study. Ten percent of the patients had an association with both smoking and occupational exposure (farmers (n=2), welder (n=1), painter (n=1) and driver (n=1)). Strikingly, 30% of the study population were housewives who gave a history of exposure to household smoke. This may suggest that smoke/occupational exposure might have a role in DPLD. Similar findings of the history of occupational exposure were noted in 12% ILD patients in a study conducted by Coultas DB et al., [19].

Common clinical symptoms found in patients of this study were cough/dry cough (82%) followed by dyspnoea (78%). Chest pain, fever, weight loss, joint pain, wheezing, oral ulcers, ENT and eye related symptoms were also detected. Predominant clinical sign found in most patients in the present study group was crackles (64%) and other common findings were clubbing, pallor, lymphadenopathy and cyanosis. These findings are consistent with the findings of other workers [20-22].

A total of 40 patients in this study had one or more co-morbidities and the most common was hypertension (62%) followed by coronary artery disease (12%). The prevalence of these co-morbidities may be due to the demographic profile of present study population, which included more of a middle and elderly age group.

Six percent of the study population had CTDs. The prevalence of CTDs was found to be higher in association with DPLD in the present study than that was observed in the general population (0.5 to 3%) [23]. This may suggest that CTDs also have a role in the pathogenesis of DPLD.

Most common finding with chest radiograph was reticulonodular opacities (36%) followed by hilar lymphadenopathy (26%) and reticular pattern (24%). The incidence of reticular and reticulonodular patterns noted (60%) in the present study is comparable to that observed in earlier studies [22,24,25]. On HRCT chest scan, most common finding was mediastinal lymphadenopathy (38%) which is followed by interstitial septal thickening (30%), honeycombing (28%), nodular pattern (28%), ground glass opacities (26%) and reticular pattern (24%). Similar distribution was reported in an earlier study [24]. Predominant zones involved were upper zones in 19 (38%) patients. These were mostly seen in IIP with no UIP and sarcoidosis. Similar findings were reported by Dhagat PK et al., in a study on sarcoidosis [26]. Middle zones were predominantly involved in 14 (28%) patients and was usually seen in IIP with no UIP or unspecified types of IIP. Lower lobes were predominantly involved in 17(34%) patients with most patients having IIP with UIP/IPF, associated with CTDs and chronic hypersensitivity pneumonitis. Peripheral involvement was seen in 8 (16%) patients with most patients being unspecified forms of IIP/IIP with no UIP and sarcoidosis. However, most of the patients of this study had overlapping involvement of different zones [26].

In about two-thirds of patients in this study, the diagnosis of DPLD could be made by clinical and imaging studies including HRCT chest. However, 17 (34%) patients were inconclusive with clinicoradiological findings and underwent lung biopsy. TBLB had given confirmatory diagnosis in 12 patients. In five patients in which TBLB was also inconclusive, OLB was done for confirmation of diagnosis. OLB has been carried out for each one of those conditions indicated [7] such as in younger patients, suspicion of malignancy, patients with atypical presentation, unsatisfactory response to treatment and in patients with diagnostic dilemma. Similar observations were made in two UK based studies [24,27]. In this study OLB has helped to rule out the strong possibility of malignancy in one of the patients while in other patients in confirming the diagnosis.

On the whole, IIP was found to be common in 31 (62%) patients which is followed by sarcoidosis in 14 (28%) [Table/Fig-2], DPLD with known cause in 4 (8%) and other rare forms of DPLD in 1 (2%). The trends of distribution of DPLD types found in this study is similar to that reported in a recent study conducted by Tiwari A et al., however, in contrast with this study [22], IIP with UIP was found to be common in an earlier retrospective study by Sen T et al., [28].

Mixed defect (both restrictive and obstructive) was the most common (44% of the study patients) abnormality detected in the spirometry followed by restrictive defect (26%), normal spirometry (20%) and obstructive (10%) pattern. A large number of patients (44%) in this study showed a mixed pattern on spirometry, of which most of them were diagnosed with sarcoidosis. Similar findings were reported earlier [16,29].

Body box plethysmography showed decreased lung volumes in 60% of the patients who had presented with the clinical features of dyspnoea, clubbing and bibasal crackles (on auscultation of the chest) and honeycombing pattern on HRCT chest.

Through single breath diffusion manoeuvre, 84% of the study patients were found to have diffusion impairment. Among them, 34% had severe diffusion impairment, 30% had mild, whereas 20% had moderate impairment. Ninety-three percent of patients with severe diffusion impairment had shown honeycombing on HRCT chest. On further evaluation 47% of the patients were confirmed to have IIP with UIP. This observation supports the hypothesis made earlier about correlation of the findings of DLCO with HRCT chest scans in relation to extent of the disease [10,11]. Mild to moderate diffusion impairment was seen in 40% sarcoidosis, 40% RBILD and 24% NSIP patients. Of all the study patients who had undergone 6MWD test, 34% of the patients had reduced 6MWD and had presented with honeycombing pattern in the HRCT chest (p<0.001). Further, 28% of the patients had desaturation of more than 4% after walking

for six minutes and all of these patients were stabilised within a few minutes after oxygen inhalation. The significant exertional desaturation noted during 6MWD test in this study patients was found to be associated with severe disease as observed in earlier study by Lama VN et al., [30].

Interestingly, most of the patients presented with severe breathlessness were smokers (84%) detected with decreased lung volumes, severe impairment of diffusion, honeycombing in HRCT chest and UIP pattern in this study. These findings are in agreement with the disease severity characterised by Egan JJ et al., [14]. Dyspnoea was also significantly related to the finding of crackles (p=0.004) and reticulonodular infiltrates on chest radiography (p=0.035). Also, most patients with crackles had honeycombing on HRCT chest (p=0.035), decreased lung volumes (p=0.0009), diffusion impairment (p=0.011), mixed spirometry results and reduced 6MWD. Seventy three percent patients with interstitial septal thickening and decreased lung volumes had some form of diffusion impairment. Sixty-seven percent patients with honeycombing on HRCT had reduced 6MWD, 93% patients with honeycombing on HRCT had decreased lung volumes and 64% patients were later diagnosed as IIP with UIP. Eighty six percent patients with honeycombing on HRCT had severe diffusion impairment (p<0.001). Most patients with mediastinal lymphadenopathy (63%) and/or nodular opacities (42%) on HRCT were later diagnosed as sarcoidosis. Further, these study patients were also found to have mild to moderate impairment of diffusion. Similar observations were made by previous workers [26,31,32].

The findings of clinical, chest radiography and HRCT chest in patients with DPLD were found to be additive and a precise diagnosis was reported to be based on clinical inputs only in 27% of the patients, and was augmented to 53% with the incorporation of chest radiograph findings and a further rise up to 61% was noted with the inclusion of HRCT chest. In the present study, after clinical and radiological assessment, diagnosis was established in 31 (62%) of patients, which is similar to the previous studies [6,33].

LIMITATION

The present study was conducted at only one tertiary care respiratory centre hence had a relatively small study sample.

CONCLUSION

These study findings suggest that PFTs should be carried out in conjunction with clinical, imaging and histopathologic studies in the evaluation of DPLD. The functional abnormalities in DPLDs are typical, and hence, PFTs aid in the diagnosis of DPLDs. Though the identified pattern of defect is not specific or the absolute quantification of histologic fibrosis or inflammation is not possible with PFTs, they provide a rough estimation of histopathological severity. Hence, PFTs play a critical role in the assessment of pulmonary symptoms, help in differential diagnosis and monitoring and grading disease severity.

To date, no previous study was reported which related the clinico-radiogical profile and lung biopsy findings with PFTs. Hence, the present study is useful in making a comprehensive understanding of diagnosis of DPLDs along with functional assessment of the patients. Further, such studies in different patient populations with large sample size would be needed to explore the association between the clinicoradiogical-histopathological profile and PFTs in the evaluation of DPLD.

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