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ANALYSIS OF CLINICAL PROFILE, AETIOLOGY, CLASSIFICATION AND OUTCOME OF INTERSTITIAL LUNG DISEASES AT A SINGLE CENTER OF SRI LANKA- A DESCRIPTIVE STUDY

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ABSTRACT

Background: Interstitial lung diseases (ILD) comprise a diverse group of heterogeneous entities. Epidemiology, clinical profile and prognosis of interstitial lung diseases widely vary globally. Little data are available on ILD in Sri Lanka.

Objective and methodology: A single center descriptive study conducted at Teaching hospital-Kandy, Sri Lanka among diagnosed ILD patients from 2007-2018. Demographic, clinical and radiological data were collected retrospectively to analyse clinical profile, aetiology, classification and outcome of interstitial lung diseases.

Results: 302 subjects were analyzed (mean age 59.5 years, female 61.3%). Idiopathic interstitial pneumonias (IIP) were the commonest (42.3%, N=128) followed by secondary ILD due to known aetiologies(40.7%, N=123), hypersensitivity pneumonitis (14.6%, N=44) and sarcoidosis (2%, N=6). Majority of IIPs were nonspecific interstitial pneumonia (NSIP)(46.8%, N=60), followed by idiopathic pulmonary fibrosis (IPF)(28.1%, N=36). Majority of secondary ILDs were due to connective tissue diseases (87%, N= 107). Shortness of breath and cough were the commonest presenting symptoms, found in 271 (90.3%) and 250 (83.3%) patients respectively. High resolutions computerized tomography (HRCT) was performed in all, but histology was available in 54 (17.8%). Lung functions tests (LFT) were normal in 71 (26.3%), but demonstrated restrictive pattern in 182 (67.4%). Mean percentage predicated forced vital capacity (FVC) was 66.91 ± 18.7% while mean percentage predicted forced expiratory volume at 01 second (FEV1) was 69.92 ± 20.0%. Therewas no significant change in LFT during follow up. Infective exacerbations needing hospitalization was the commonest complication seen in 86 (40.3%). Data on follow up radiological investigations were noted in 143 (47.5%), in which 59 (41.2%) demonstrated radiological improvement, while 34 (23.7%) had progressive changes and 50 (34.9%) had HRCT changes similar to previous images. 184 patients were found surviving, while 43 were dead. Higher mean age, male gender, current or previous smoking, lower distance achieved at 6-minute walking test, or any history of hospitalizations due to infective exacerbations were noted to be associated significantly in patients with mortality.

Conclusion: IIP and secondary ILDs were similar in prevalence in the cohort of diagnosed ILD patients from central Sri Lanka. Idiopathic NSIP outnumbered IPF in the sample.

1. INTRODUCTION

Interstitial lung diseases (ILDs), synonymous with diffuse parenchymal lung diseases are a heterogeneous group of clinical, radiological and pathological entities which primarily affect the pulmonary interstitium. This group of disorders is associated with variable degrees of pulmonary inflammation and fibrosis, leading to common functional outcome such as restricted lung volumes and impaired gas exchange [1].

ILDs as a group consists of more than 200 different clinical entities, many of them are rare or "orphan" diseases [2]. The available data on epidemiology of ILDs varies significantly across the globe. This may represent the real difference attributed to genetic profile, environmental factors, occupational exposure, smoking habits and socio-cultural practices, but may also be due to differences in study designs, disease definition and classification [2]. Though there are several reports from various countries, unfortunately many of them have not used classification proposed by American thoracic society/ European respiratory society (ATS/ERS) in 2002, which is considered as a benchmark in ILD classification now.

The available data on ILDs are sparse in developing countries. Studies have shown that in countries with high prevalence of tuberculosis, ILDs are often misdiagnosed as tuberculosis due to lack of knowledge [3]. This may be applicable to Sri Lanka as well.The epidemiology, aetiology, clinical phenotype and outcome of ILDs may be different in Sri Lanka compared to other countries. But, only a single study has been published in relation to ILDs in Sri Lanka in index journals [4]. However, this too included a small sample of 41 patients. We aimed to analyze demographic data, clinical profile, aetiology, classification and outcome of ILDs in a single tertiary care hospital in central Sri Lanka.

2. METHODOLOGY

This was a single center descriptive cross sectional study. Study population was selected from respiratory treatment unit II, Teaching hospital- Kandy. All patients who provided consent for participation, who were diagnosed as ILD since 1st January 2007 up to 31st December 2018 were enrolled for the study. Data in relation to the time of diagnosis and follow up were obtained by retrospective analysis of their clinical records and by recall through an interview. Relevant details with regard to demographic data, clinical symptoms, aetiological factors and clinical examination were collected. Details of the investigations including chest X ray findings, LFT, 6 minutes walking test (6MWT) were obtained.

The diagnosis was arrived following multidisciplinary discussion among physician, radiologist and pathologist. Histopathological samples included surgical and transbronchial lung biopsies. Hence radiological confirmation was essential for diagnosis of ILDs, all the patients in study group underwent HRCT as par current clinical practice ATS/ERS international multidisciplinary consensus classification of ILDs-2002 [1], supplemented by its update in 2013 [5] and statement on interstitial pneumonias with autoimmune features in 2015 [6] were used in the diagnosis and classification of cases. The diagnosis of cases prior to 2015 was revisited and revised where necessary. The diagnosis of sarcoidosis was based on compatible clinical, radiological, laboratory and/or histopathological features as per the joint statement of the ATS, the ERS and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) following exclusion of other causes of similar features [7].Cases of hypersensitivity pneumonitis (HP) were diagnosed based on history of exposure to organic dust, radiological features combined with histological evidence where available.

ILDs were classified as idiopathic and secondary following a detailed evaluation for the aetiology. This included thorough history, clinical examination and relevant investigations. Evidence of connective tissue disorders (CTD), smoking, occupational and environmental exposures to organic and inorganic toxic substance and drugs were searched by recall and through records. Serological markers of CTDs were performed when necessary. The diagnosis of CTD was made according to American college of rheumatology criteria for individual diseases following an evaluation by a rheumatologist.

Development of complications, progression of LFTs and radiological features and outcome were identified and collected through clinical records.

The data were tabulated and analyzed with Statistical package for social sciences (SPSS) version 16.

Ethical clearance for the study was granted by ethical review committee- Teaching Hospital, Kandy.

3. RESULTS

3.1. DEMOGRAPHIC DATA

Total of 302 subjects were enrolled. The cohort demonstrated a female preponderance, having 185 females (61.3%), compared to 117 (38.7%) males. The mean age± SD was 59.52± 12.84 years, ranging widely from 9 to 87 years. Males were significantly older than females having mean age± SD of 63.5± 10.7 years in contrast to 56.9 ± 13.4 years in females ($p<0.01$).

3.2. DIAGNOSTIC METHODOLOGY

All patients were examined by HRCT. Histological evaluation was attempted in 92 (30.4%), in which 55 (18.2%) and 37 (12.3%) underwent surgical and transbronchial lung biopsies respectively. However, pathological diagnosis was arrived only in 54 (17.8%) patients. Forty-eight (87.2%) of 55 surgical lung biopsies were diagnostic. However, transbronchial lung biopsies were largely unsuccessful, producing positive results only 6 (16.2%) out of 37 procedures.

3.3. PATTERN OF ILDS

IIPs were diagnosed in 128 (42.3%) subjects, being the most prevalent condition. Secondary ILDs followed closely accounting for 123 (40.7%) followed by hypersensitivity pneumonitis HP in 44 (14.6%) and sarcoidosis in 6 (2 %). There was a single case (0.3%) of lymphangioleiomyomatosis.

Thirty-six (28.1%) of all IIP cases were classified as idiopathic pulmonary fibrosis (IPF). Majority of idiopathic interstitial pneumonia other than IPF were non-specific interstitial pneumonias (NSIP), accounted for 60 (46.8%) cases. Occurrence of other types of IIPs is shown in table 01.

Table 1: Prevalence of IIP types

IIP type	Number (%)
Idiopathic pulmonary fibrosis (IPF)	36 (28.1%)
Non-specific interstitial pneumonia (NSIP)	60 (46.8%)
Desquamative interstitial pneumonias (DIP)	9 (7.0%)
Respiratory bronchiolitis-interstitial lung disease	3 (2.3%)
Lymphocytic interstitial pneumonia (LIP)	1 (0.8%)
Acute interstitial pneumonia	1 (0.8%)
Bronchiolitis obliterans organizing pneumonias (BOOP)	16 (12.5%)
Unclassifiable	2 (1.6%)

Connective tissue diseases associated ILDs (CTD-ILD) were responsible for a vast majority of secondary ILDs. There were 107 (87.0%) cases of CTD-ILDs. Drug induced ILD cases were diagnosed in 6 (4.8%). Four (3.2%) patients had occupational ILD, in which 3 had silicosis. Combined pulmonary fibrosis with emphysema, which is considered as a smoking related ILD, was accounted for 6 (4.8%) cases of other secondary ILDs.

Rheumatoid arthritis was the commonest cause for CTD-ILD in the cohort. Other connective tissue diseases associated with ILD are shown in table 02.

Table 2: CTD-ILD types

Connective tissue disease	Number (%)
Rheumatoid arthritis	38 (35.5%)
Systemic sclerosis	26 (24.3%)
Mixed connective tissue diseases	15 (14.0%)
Overlap syndrome	6 (5.6%)
Inflammatory myositis	2 (1.8%)

Systemic lupus erythematosus (SLE)	2 (1.8%)
Sjogren syndrome	0 (0%)
Interstitial pneumonias with autoimmune features (IPAF)	18 (16.8%)

NSIP were recognized in 18 (47.3%) cases as the commonest radiological pattern in rheumatoid arthritis. UIP pattern followed closely and found in 17 (44.7%) patients. NSIP was the most prevalent radiological pattern systemic sclerosis seen in 20 (76.9%) of cases.

The cohort contained 18 cases of IPAF, of which 13 (72.2%) were females. Rheumatoid factor had the highest positive results in this group where 11 (73.3%) out of 15 had elevated titer, in contrast to anti-nuclear antibody where only 4 (25%) out of 16 had significantly positive results. Radiologically 13 (72.2%) were compatible with NSIP pattern; whereas 5 (27.7%) were suggestive of BOOP.

Cases of HP were evaluated for possible underlying aetiology. Known exposures leading to HP was found in 25 (56.8%) cases, in which paddy farming was the commonest, seen in 17 (38.6%), followed by exposure to pigeon in 3 (6.8%), textile industry in 2 (4.5%) and tea dust in 2 (4.5%). However, in 19 (43.1%) patients, a probable aetiology for HP was not recognized.

Mean age ± SD of cases of IIP was 62.9± 11.5 years, which was significantly higher according to T-test ($p<0.001$), compared to 56.9± 13.1 years in other cases. Mean ages ± SD of IPF group and IIP other than IPF group were 66.8 ± 9.3 years and 61.3 ± 12.1 years respectively, which was not significant ($p=0.017$).

IIPs, secondary ILDs and HP had more females. There were 69 (53.9%), 88 (71.5%) and 24 (54.5%) females in these groups respectively. However, males were dominant in IPF group where they constituted for 20 of 36 (55.5%).

3.4. CLINICAL PROFILE

Symptomatology at presentation was assessed. Data were not available in 2 subjects. Shortness of breath and cough were the commonest presenting symptoms, found in 271 (90.3%) and 250 (83.3%) patients respectively. Further details are shown in table 03.

Table 3: Prevalence of symptoms

Symptom	IIP	Secondary ILD	HP	sarcoidosis	Total cohort
Cough	108 (85%)	96 (78%)	41 (93%)	4 (80%)	271 (90.3%)
Shortness of breath	114 (89.7%)	112 (91%)	41 (93.1%)	3 60%)	250 (3.3%)
Fever	14 (11%)	5 (4%)	2 (4.5%)	1 (20%)	22 (7.3%)
Loss of appetite	29 (22.8%)	32 (26%)	18 (40.9%)	1 (20%)	80 (26.6%)
Loss of weight	22 (17.3%)	29 (23.5%)	11 (25%)	1 (20%)	63 (21%)
Haemoptysis	6 (4.7%)	1 (0.8%)	2 (4.5%)	0 (0%)	9 (3%)
Chest pain	6 (4.7%)	8 (6.5%)	3 (6.8%)	0 (0%)	17 (5.6%)

Mean duration of cough at presentation was 14.9 ± 12.0 months for the whole cohort. Shortness of breath was present for mean duration of 15.2 ± 13.5 months. Further analysis revealed mean duration of cough or shortness of breath for cases of IIP; either IPF or other types, secondary ILD and HP was not significantly different.

Details of clinical examination findings were available in 299 patients. Fine crepitations on auscultation of lungs was the most common sign, noted among 251 (83.9%) of cohort. The presence of clinical signs according to ILD categories is tabulated as follows.

Table 4: clinical signs according to ILD categories

	IIP	Secondary ILD	HP	Sarcoidosis	Total cohort
Fine crepitations	107 (85%)	107 (87%)	33 (75%)	2 (40%)	251 (83.9%)
Coarse crepitations	43 (34%)	29 (23%)	15 (34%)	1 (20%)	90 (30.1%)
Clubbing	30 (24%)	10 (8%)	9 (20%)	0 (0%)	51 (17%)
Cyanosis	13 (10%)	8 (6%)	2 (4%)	0 (0 %)	25 (8.3%)
Plethora	16 (12%)	4 (3%)	2 (4%)	0 (0%)	24 (8%)

Loud P2	7 (5%)	11 (9%)	3 (7%)	0 (0%)	23 (7.6%)
Ankle odema	3 (2%)	1 (1%)	2 (4%)	0 (0%)	8 (2.6%)
Elevated JVP	3 (2%)	1 (1%)	1 (2%)	0 (0%)	7 (2.3%)

Further analysis of examination findings according to IPF and other IIPs other than IPF are summarized below. Accordingly, prevalence of clinical signs was similar among two groups (Table 05).

Table 5: of clinical signs according to IIP categories

	IPF	Other IIPs	P value
Fine crepitations	34 (94.4%)	73 (81.1%)	0.059
Coarse crepitations	12 (33.3%)	31 (34.4%)	0.90
Clubbing	11 (30.5%)	19 (21.1%)	0.26
Cyanosis	2 (5.5%)	11 (12.2%)	0.26
Plethora	4 (11.1%)	12 (13.3%)	0.73
Loud P2	2 (5.5%)	5 (5.5%)	1.00
Ankle odema	0 (0%)	3 (3.3%)	0.26
Elevated Jugular venous pulse	0(0%)	3 (3.3%)	0.26

3.5. LUNG FUNCTION TESTS

Records on LFT done at initial presentation were available in 270 (89.4%) patients. Restrictive abnormality, defined by FVC and FEV1 being <80% predicted with FEV1/FVC >70% was detected in 182 (67.4%). LFT was within normal limits in 71 (26.3%) patients. Mean percentage predicated FVC was 66.9 ± 18.7% ranging from 18-118%. Mean value of percentage predicted FEV1 was 69.9 ± 20.0%, with a range of 20-123%.

Distribution of LFT pattern among ILD types was analyzed and shown in following table 06. Accordingly, a similar distribution of LFT pattern was found among major ILD groups.

Table 6: Pattern of LFT among ILD types

	ILD type				
	IIP	Secondary ILD	HP	Sarcoidosis	Total
Normal	31 (27.6%)	29 (26.1%)	10 (24.3%)	1 (20%)	71
Restrictive	74 (66.0%)	77 (69.3%)	27 (65.8%)	3 (60%)	182
Obstructive	0 (0%)	3 (2.7%)	3 (7.3%)	0 (0%)	6
Mixed	7 (6.2%)	2 (1.8%)	1 (2.4%)	1 (20%)	11
Total	112	111	41	5	270

Follow up LFT at 3, 6 and 12 months is shown in figure 01. Though there was an apparent initial decline followed by improvement in FVC and FEV1, paired sample t-test failed to calculate a significant change during the follow up duration.

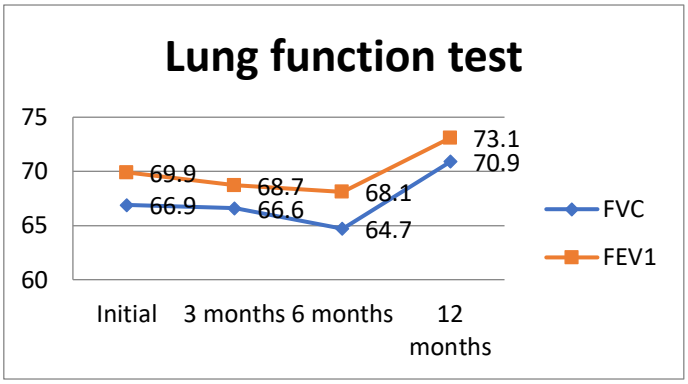

Figure 1: Progression of LFT

Mean of percentage predicted of FEV1 at initial presentation for IIP, secondary ILD and HP were 70.8±20.1, 70.1±19.2 and 67.1±21.7 respectively which were not significantly different.

Details on 6MWT was available in 248 (82.1%) of cohort. The difference of saturation (ΔSpO2) and the distance of walking (6MWD) were assessed. Drop of saturation equal or more than 4% at the end of 6 minute or earlier if walking prematurely terminated was considered as significant desaturation. 115 (46.3%) demonstrated a significant desaturation. Desaturation was significantly higher among IIPs where 54.3% had significant desaturation, while it was 39.4% and 47.5% for secondary ILD and HP respectively (p 0.02).

Bivariate analysis was performed to recognize any correlation among LFT at presentation with distance walked at simultaneously performed 6 MWT. However, no significant correlation among initial FVC and 6MWD was present (Pearson correlation coefficient = 0.17, p= 0.79). Similarly, correlation among initial FEV1 and 6MWD was stastically insignificant (Pearson correlation coefficient =-0.005, p=0.94) as shown in following scatter plot (Figure 02).

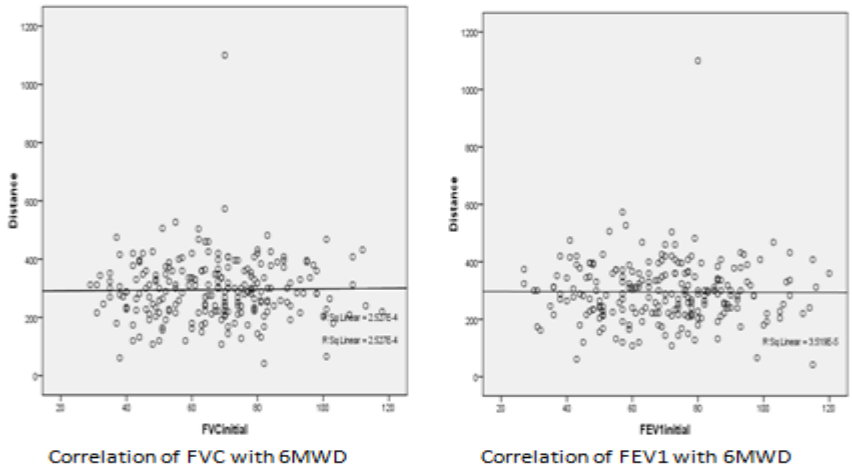

Figure 2: Correlation of LFT with 6MWD

Furthermore, there was no significant correlation among the ΔSpO2 at 6 minute walking test with initial FVC or FEV1 (Figure 03).

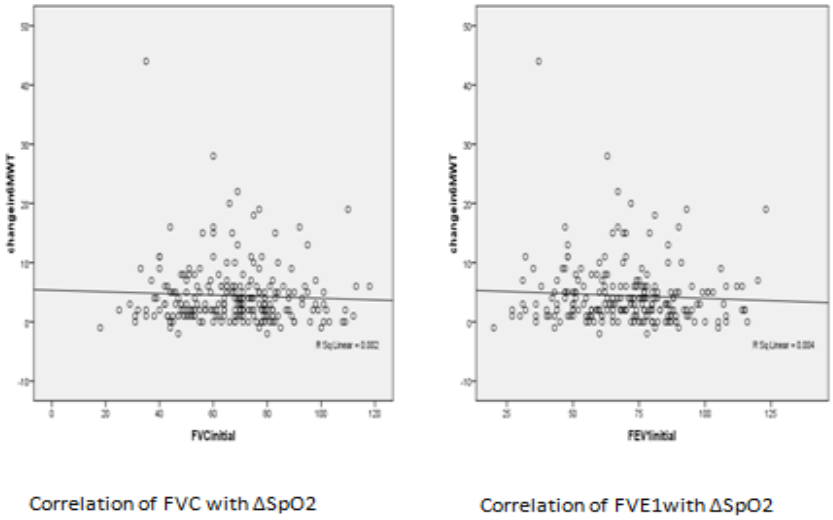

Figure 3: Correlation of LFT and Desaturation at 6MWT

3.6. COMPLICATIONS

Details on development of complications while on follow up were available in 213 (70.5%) subjects, of which infective exacerbations was the commonest. Further details are shown in table 07.

Table 7: Complications

Complication	Number (%)
Infective exacerbations	86 (40.3%)
Type 01 respiratory failure	25 (11.7%)
Type 02 respiratory failure	5 (2.3%)
Polycythemia	20 (9.3%)
Pulmonary hypertension	41 (19.2%)
Bronchiectasis	29 (13.6%)
Malignancy	1 (0.4%)
Tuberculosis	5 (2.0%)
Pneumothorax	4 (1.8%)

3.7. OUTCOME

Data on follow up radiological investigations were noted in 143 (47.5%). Of patients with available data, 59 (41.2%) demonstrated radiological improvement, while 34 (23.7%) had progressive changes compared to previous studies. In remaining 50 (34.9%) HRCT changes were similar to previous images

Subgroup analysis on radiological outcome according to the major ILDs type is shown below (Table 8).

Table 8: radiological outcome

ILD type	Radiological outcome		
	Static (%)	Improved (%)	Progressive (%)
IIP	15 (26.7%)	23 (41.0%)	18 (32.1%)
Secondary ILD	22 (34.9%)	28 (44.4%)	13 (20.6%)
HP	12 (57.1%)	6 (28.5%)	3 (14.2%)

Chi square test was used to assess the relationship of radiological outcome with outcome of lung functions during follow up. No relationship was noted with lung functions at 12 months (p=0.60). The results are tabulated as follows (Table 9).

Table 9: Relationship of radiological outcome and LFT outcome at 12 month

		Radiological outcome			Total
		Static	Static	Progressed	
LFT at 12 month	static	19	21	8	48
	improved	6	15	5	26
	progressive	5	10	2	17
	Total	30	46	15	91

Details on survival outcome were able to be gathered from 227 (75.1%) of the cohort. 184 patients were found surviving, while 43 were dead. According to the results, mortality risk was highest among IPF patients. Prognosis was better in BOOP and DIP compared idiopathic NSIP.

We aimed to study possible predictors of risk of morality. A significantly higher mean age ($p < 0.01$) and lower mean distance achieved at 6 minute walking test ($p < 0.01$) was noted in patients with mortality outcome compared to survivals. Further, mortality figures were significantly higher in male gender ($p<0.01$), current or previous smokers ($p=0.02$) or any history of hospitalizations due to infective exacerbations ($p < 0.001$). However, percentage predicted FVC, FEV1, $\Delta SpO2$ were not significantly different among two groups. Mortality rates were not different

among groups with static, improved or progressive lung functions at 6 or 12 months since presentation. Similarly, no association was detected between mortality risk and trend of 6 minute walking test. Further, there was no significant association of mortality outcome with pulmonary hypertension (p=0.64), type I respiratory failure (p= 0.06), type II respiratory failure (p=0.34) or presence of bronchiectasis (p=0.43).

4. DISCUSSION

4.1. DEMOGRAPHIC DATA

Female preponderance was noted among all major ILD categories except IPF, though most pronounced in secondary ILD. Since CTDs are well known to affect female gender preferably, higher proportion of secondary ILDs was found among females as predicted. IPF group composed of more males. However, comparatively, in Indian ILD registry, 73.6% of IPF were males, opposed to 55.5% in current report [8]. Similar female dominance was demonstrated in studies conducted in India, Saudi Arabia, Greece and Germany [8], [9], [10], [11]. In contrast, a male dominance was noted in studies from Spain, Italy and Denmark, reflecting the geographic variation [12], [13], [14]. However, due to variation of study designs, definitions of diseases and diagnostic methodologies used among different studies, direct comparison between these reports is limited.

The mean age of our sample was similar to many other studies [8], [9], [10], [11], [12], [13]. Another study conducted in Sri Lanka demonstrated that the distribution of age and gender was similar to our study [4]. IPF tends to develop at a later age compared to other IIPs. A similar observation was made in our cohort too, in which themean age of patients with IIPs was 62.9 years compared to 56.9 secondary ($p < 0.01$). This is likely due to occurrence of CTD at a younger age compared to IIPs.

4.2. DIAGNOSTIC INTERVENTIONS

Methodology of diagnosis of ILD has been re-defined in latest clinical practice guidelines. Accordingly, multidisciplinary discussion (MDD) is currently considered as the gold standard protocol to obtain most accurate diagnosis. Therefore, MDD approach has been utilized in several recent studies [8], [14]. However, there are several large studies and registries performed prior to introduction of MDD system [10], [11], [12], [13]. Since our study involved patients diagnosed from 2007, prior to introduction of MDD approach, some of the patients were diagnosed without MDD as in other old registries.

Tools utilized for diagnosis of ILD include HRCT and histopathological sampling. HRCT was performed in all patients in our cohort, similar to reports from India and Saudi Arabia [8], [9]. Though HRCT is a cornerstone tool in ILD evaluation, in certain earlier studies HRCT was performed in some patients only; Eg- Spain (91.9%), Greece (87.4%), Italy (74.4%) and Germany (41%) [10], [11], [12], [13]. Conduction of histological examination varied widely among published reports. Pathological diagnosis was available in 17.8% of our cohort, in which majority obtained by surgical lung biopsies. Comparatively, only 7.5% were subjected for histopathological examination in Indian ILD registry [8]. However, biopsy sampling either by transbronchial or surgical measures were able to provide diagnostic results in 83% in the study by Kumar et al [3]. Similarly, histological evaluation either by surgical or transbronchial biopsies was comparatively higher in some studies; 40.3% in Turkey, 59.5% in Italy and 82.6% in Spain [12], [13], [15]. According to the ATS statement, IPF can be confidently diagnosed without histological examination when HRCT shows typical UIP pattern in appropriate clinical setting where all possible secondary causes excluded [16]. Similarly, the diagnosis of HP can be made using typical history of exposure, radiological appearance and BAL analysis even in the absence of pathological proof [17]. But in other cases histological examination is recommended. However, it is difficult to adhere to this recommendation in real clinical setting, due to lack of facilities coupled with high risk of surgical complications and mortality in ILD patients who are already functionally limited by their disease.

4.3. PATTERN OF ILD

The prevalence of individual types of ILDs varies significantly according to geographical setting. IIP was the most prevalent group in our cohort, which was closely followed by ILDs due to known aetiologies, of which majority were due to CTD. However, IPF werediagnosed only in 11.9% of IIPs. Interestingly, idiopathic NSIP produced the bulk of IIP group, responsible for 46.8%. In contrast to our data, IPF as a single entity was recognized as the commonest type of IIP in many reports globally. IPF was diagnosed as the leading type of ILD in reports from Spain (38.58%), Italy (37.6%), Germany (33%) and Denmark (28%) [11], [12], [13], [14]. Even in countries where IPF was not the most prevalent ILD, it was observed in 23.3% in Saudi Arabia, 19.9%in Turkey and 19.5% in Greece, which was significantly higher than our series [9], [10], [15]. However, some of these series were conducted prior to introduction of joint statement by ATS/ERS on ILD in 2002. Therefore, the disease definition and diagnostic criteria were different among these studies. It can be observed that cases of DIP, NSIP and even LIP have been included in IPF group in some old reports [18]. Hence, comparison of results from these old studies with current study is challenging. The Indian ILD registry by Singhe et al., found IPF only in 13.7%, which was close to the results of our study [8]. Surprisingly, the prevalence of idiopathic NSIP was considerably higher in our cohort (19.8%), compared to other studies where it was ranging from 2.8 to 8.5% [8], [9], [10], [14]. Since our study included real time patients managing according to current clinical practice in local setting, all cases of idiopathic NSIP were not pathologically proven as per recommended international guidelines. Cases of HP could share common radiological appearance as NSIP. In occasions where a history of exposure to culprit antigen was lacking, some cases of HP could have been classified as NSIP. Further, the diagnosis of underling CTD is usual based on clinical features supported by serological investigations. Unavailability of serological evaluation for CTD some cases may have led to under-recognition of CTD with absent or subtle clinical features, thereby misclassifying as idiopathic ILDs.

Even though sarcoidosis was the commonest type of ILD in some reports [10], especially from Europe, it was diagnosed only in 6 (1.98%) cases in our series. This is possibly due to the striking geographical variation of the prevalence of sarcoidosis, being lower in Asia than Europe. Further, it is possible that some proportion of sarcoidosis cases may be misdiagnosed as Tuberculosis in endemic countries like Sri Lanka due to similarities in presentation and behavior. This hypothesis is strengthen by the observation that 22% of cases of sarcoidosis in a study in India had received treatment for tuberculosis providing evidence for diagnostic challenge in real clinical practice, especially in tuberculosis prevalent countries [3].

CTD-ILD was the most common cause of ILDs due to known aetiologies. Similar to IIPs, a wide variation in the prevalence of CTD-ILD was observed worldwide among published data ranging from 2.1- 34.8% [8], [9], [10] [11], [13], [14], [15]. Commonest diagnosis for underlying autoimmune connective tissue disease was rheumatoid arthritis followed by systemic sclerosis in our sample. Similar order of CTD was noted in several other international reports [8], [9].

IPAF was introduced as a new term by ATS/ERS in 2015 to replace several different, but overlapping terms such as “undifferentiated CTD associated ILD”, “lung-dominant CTD” or “autoimmune-featured ILD” [6]. Eighteen cases (16.8% of CTD-ILD) in our cohort were classified as IPAF using ATS/ERS guidelines. Since, this term was introduced in 2015, details on IPAF are available only in recently published literature. Alhamad published a report on ILDs in Saudi Arabia and used the term of lung dominant ILDs and diagnosed 50 cases as the most prevalent (43.47%) type in CTD-ILD category [9]. But, there was an important limitation in Saudi Arabian study, in which the diagnostic criteria used were different from ATS/ERS proposed approach. In the series published by Dhooria et al in India, IPAF was the commonest type accounting for 44.1% (N= 45) all CTD-ILDs [19]. Evaluation of complete autoimmune serological profile is not practiced routinely in Sri Lanka due tofinancial constrain. Hence, some of the cases of IPAF could have been under-recognized in our series leading to comparatively lower prevalence than above studies.

Exposure to certain volatile substances as a result of domestic, occupational and recreational activities is linked to HP. Since such activities are vastly diverse among countries, the occurrence of HP would be expected to range widely. According to published reports from various countries, the prevalence of HP varied from 2.6% in Greece to 47.3% in India [8], [10]. HP was the 3rd commonest category of ILDs in our series, found in 14.5%. HP was the commonest group of ILD in Indian ILD registry, responsible for nearly half of the cases [8]. But some other studies from India demonstrated much lower prevalence similar to results of our study [19]. Although various diagnostic protocols were published, there is no universally accepted diagnostic criterion for HP yet. Therefore, accurate comparison among studies is limited. Along with the prevalence, the implied aetiology also varied significantly between the countries. Paddy farming was the most implicated risk factor in our cohort which is similar to the report

by Dhooria et al., in India [19]. However, pigeon exposure was claimed as the aetiology of HP in all cases in study by Kumar et al [3], whereas, exposure to air cooler was the identified as the commonest in Indian ILD registry [8]. Notably, the cause of HP was not identified in 43.1% of current series, which is considerably higher than other reports globally.

4.4. CLINICAL FEATURES

As expected, shortness of breath and cough were the most reported presenting symptoms. Same symptoms were noted to be the commonest in other reports worldwide with a slight variation in frequency. The frequency and duration of symptoms prior to presentation was not different among IIP, CTD-ILD or HP in our cohort. Fine crepitation on lung auscultation was the predominant clinical sign. Clubbing was recognized in commonly in primary ILDs and HP than in secondary ILDs or sarcoidosis (p=0.01). Though it was noted more frequently in IPF than other primary ILDs it was not statistically significant in our study. It should be highlighted that 25% of idiopathic NSIP had finger clubbing, limiting its value for discrimination of IPF from other IIPs in clinical practice.

4.5. LUNG FUNCTIONS

Lung function test is a fundamental tool in initial evaluations and follow up of ILDs. A restrictive type defect is typically expected with spirometry. More than 2/3 of our cohort comprised restrictive pattern spirometry, while more than a quater having normal lung functions. Approximately half of the cases had FEV1 more than 70% predicted belonging to mild restricted lung functions according to ATS/ERS 2005 classification [20]. The degree of Spirometric abnormality was similar among primary, secondary and HP groups. Also, there was no significant difference of FVC or FEV1 among IPF and non-IPF IIPs. Figures for corresponding parameters in lung functions were markedly different among different series globally. Patients in Indian ILD registry had more severe restriction (FVC= 57.2 ±23.3%) compared to current study [8]. Reports from Europe demonstrated much better results with lung function compared to our and other Asian studies. We analyzed the recorded data of lung functions during the follow up of patients while obtaining the standard treatment. Although there was mild progressive decline of LFT at 3 and 6 months, a trend of improvement was observed at 12 months for the total cohort. Patients in our cohort were managed according to the available standard guidelines. However, since there were patients included from 2007, the treatment regimens were not uniform, because of emergence of new data and alteration of practice guidelines. Moreover, some medications like perfenidione, recommended for treatment of IPF, were available only recently in the state health sector in the country. Similarly, nintedanib, another anti-fibrotic medication, is not yet available in Sri Lanka. Considering the value of real time data, the treatment utilized for management of ILDs in our center in general has been efficacious in prevention of progression of diseases, if not improved. However, we were not able to analyze and compare the efficacy of individual treatment options in details due to complexity and inconsistency of therapeutic regimes and lack of complete data.

4.6. COMPLICATIONS

Disease or treatment related complications are expected during the time line of ILD. Exacerbations due to infections requiring hospitalization was the most frequent complication observed in our cohort, followed by pulmonary hypertension and bronchiectasis. Infective exacerbations were most prevalent among secondary ILDs, followed by HP and IIPs in descending order. This could be related to immunosuppressive therapy received by CTD and HP patients. Immunosuppressive medications used for treatment of ILD clearly predispose patients for infections [21].

Patients with ILD are at higher risk for chronic infections, especially in mycobacterial and fungal origin. A study by Chung et al., demonstrated that the incidence of tuberculosis in ILD patients was five times higher than that of general population [22]. There were five patients of tuberculosis in our cohort. It should be remembered that the presentation may be atypical due to immunosuppression. Hence, a high degree of suspicion is required to diagnose tuberculosis in any ILD patients with unexplained deterioration.

Pulmonary hypertension is a common complication of ILD, often associated with a poor prognosis [23]. Reported prevalence of pulmonary hypertension in IPF varied from 32-85%, depending on patient selection, time of assessment, severity of disease and measuring technique [23]. In our cohort, 19.2% of all ILD were complicated with pulmonary hypertension, observed commonly with secondary ILD, which was predominately composed of CTD-ILD. A positive association among development of pulmonary hypertension and the severity of restriction of lung function is expected. However, we could not recognize a stastically significant difference of percentage predicted FVC or FEV1 with the occurrence of pulmonary hypertension.

4.7. OUTCOME

Radiological outcome greatly depends on ILD type and treatment. Progressive fibrosis is expected in UIP, especially idiopathic form, while largely resolution is expected in DIP and BOOP [24]. In the study by Nishiyama et al., 89% of IPF patients showed progressive radiological changes during 4 years of mean follow up [25]. But, only 53.3% IPF demonstrated progressive worsening of HRCT features in follow up in our study. However, interpretation of radiological changes is subjective. Hence, accurate comparison among different studies is challenging. Akira et al., evaluated radiological outcome of biopsy proven NSIP patients and reported improvement in 38%, worsening in 22% and no significant change in the remaining 40% [26]. Our cohort demonstrated improvement in 45%, deterioration in 30% and unaltered appearance in 25%, which is comparatively similar. Radiological abnormalities are more heterogeneous in hypersensitivity pneumonitis. Generally, inflammatory subtype corresponds to acute and sub-acute HP, whereas fibrotic variety corresponds with chronic HP. Only 28.5% of HP demonstrated radiological improvement with medical treatment and discontinuation of antigen exposure, while majority (57.1%) were static in our report. Therefore, early identification of HP at acute or sub acute stage should be emphasized for optimum outcome.

Prognosis varies according to the ILD type and aetiology. Progressive respiratory failure is the most frequent cause of death, responsible for over 80% of all fatalities in IPF [27]. Heart failure, bronchogenic carcinoma, ischemic heart disease, infection, and pulmonary embolism are also some other cause of mortality in IPF [27]. Mean survival of IPF is only 2-3 years, though some patients live much longer. Evaluation on survival duration and causes of mortality were restricted in our study due to inadequacy of data as a result of retrospective data collection. Though it was thought that the prognosis was better in CTD-ILD compared to IIPs, a study by Kocheril et al., demonstrated rather worse outcome with CTD-ILD than IIPs [28]. However, mortality was similar among CTD-ILD and IIP in our cohort ($p=0.50$).

The survival also depends on the radiological appearance in HRCT. It has been proven that patients with typical UIP pattern in HRCT experience worse outcome when compared to patient with NSIP and those histologically proven UIP that do not have typical UIP feature in HRCT [29]. IPF patients in our cohort had a higher mortality compared to idiopathic NSIP supporting this evidence further.

Predicting accurate prognosis for IPF patients is challenging due to various factors [27]. Du Bois et al., performed a study aiming to identify prognostic indicators and proposed a clinical scoring system. Accordingly, age, respiratory hospitalization, percent predicted FVC, 24-week change in FVC, percent predicted diffusion capacity for carbon monoxide (DLCO), 24-week change in percent predicted DLCO, and 24-week change in health-related quality of life were recognized as independent predictors of mortality [27]. In our sample, advanced age, male gender, lower performance in 6MWD and ever smoking were noted to be significantly associated with mortality. However, the strongest association was detected with any history of infective exacerbations. But no similar association was recognized with presence of pulmonary hypertension, bronchiectasis, type I or type II respiratory failure. Similarly, percentage predicted FVC, FEV1, $\Delta SpO2$ were not significantly different among two groups. The explanation for such lack of association in contrast to expected results was not clear. However, well designed prospective studies with large sample size will be required for precise evaluation of such association.

5. CONCLUSION

The profile of ILDs with their demographic, clinical and outcome data were analyzed and compared with other regional and global studies. The results recognized certain similarities and differences compared to other reports,

formulating a distinctive study among others. Idiopathic interstitial pneumonias were the commonest type of ILD in studied sample, followed closely by secondary ILDs.

6. LIMITATIONS

Since this was a retrospective study, data collected may not be accurate as expected in prospective study. In addition to interviewer-based data collection, some details were collected utilizing existing records, thereby limiting its accuracy and completeness.

The studied cohort included patients over 11-year duration. There have been alteration of internationally followed guidelines on diagnosis and management of ILDs. Though we attempted to re-evaluate all cases and revise its diagnosis, to maintain up to date information, some of the cases may have been misclassified due to lack of relevant information. Though evaluation of efficacy of various therapeutic agents was an initial objective of the study, it was unable to perform due to extreme complexity of treatment regimens.

The current study was based on a cohort of patients presented to a single tertiary care center in the country. Therefore, formulating conclusions regarding general population by direct extrapolation of current data is limited.

List of abbreviations

BOOP- Bronchiolitis obliterans organizing pneumonias
CTD- connective tissue disorders
CTD-ILD- Connective tissue diseases associated ILDs
DIP- Desquamative interstitial pneumonias
DLCO- diffusion capacity for carbon monoxide
FEV1- Forced expiratory volume at 01 second
FVC- Forced vital capacity
HRCT- High resolutions computerized tomography
IIP- Idiopathic interstitial pneumonias
ILD- Interstitial lung diseases
IPAF- Interstitial pneumonias with autoimmune features
IPF- -Idiopathic pulmonary fibrosis
LFT-Lung functions tests
LIP- Lymphocytic interstitial pneumonia
MDD-multidisciplinary discussion
NSIP- Non-specific interstitial pneumonia
ΔSpO2- difference of saturation
6MWD- distance of walking at 6MWT
6MWT- 6 minutes walking test

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CONFLICT OF INTEREST

The author have declared that no competing interests exist.

AUTHORS' CONTRIBUTIONS

AB conducted the research and drafted the manuscript. DM supervised the research and manuscript, SR support data collection and analysis

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