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Original research

Demographic and clinical characteristics of patients with interstitial lung disease admitted to Razi Hospital, the North of Iran

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Abstract

Respiratory disease is the third cause of death, which accounts for one-seventh of all deaths worldwide and millions of people suffer from chronic lung disease in the world. Interstitial lung diseases (ILDs) are one of the most important lung diseases. So, we aimed to evaluate demographic data and clinical characteristics of ILD patients in our region. This cross-sectional descriptive study was conducted on patients diagnosed with ILD who were referred to Razi Hospital, Rasht, Iran during 2013-2018. Out of a total of 300 participants, 160 (53.3%) patients were non-occupational exposed. The most prevalent clinical symptoms and signs were coughs, dyspnea, and abnormal findings in lung auscultation. Totally, 113 (37.7%) of patients mostly consumed methotrexate. Among 158 patients with reported antinuclear antibody (ANA) status, 29 (18.4%) cases were positive. In 186 (71.3%) cases with available pathological findings, alveolar wall thickening, fibroblast deposition, and honeycomb pattern was reported. Also, granulomatous lung tissue and diffuse fibrosis were detected in 58 (22.2%) patients. ILD patients with different clinical conditions may show regional differences in risk factors, patient exposure, access to medical facilities for diagnosis and treatment, and genetic differences, which require careful attention to these factors individually in each region.

Keywords: Demographic data, Clinical characteristics, Radiological findings, Interstitial lung disease

1. Introduction

Respiratory disease is the third leading cause of death, which accounts for one-seventh of all deaths worldwide and millions of people suffer from chronic lung diseases around the world [1]. Interstitial lung diseases (ILDs) or diffuse parenchymal lung diseases (DPLDs) are among the most important lung diseases with a large and heterogeneous set of more than 200 lung diseases characterized by varying degrees of inflammation and fibrosis in the parenchyma, often classified as rare lung disease [2–4]. In ILD, the lung elasticity is reduced due to collagen deposition and interstitial lung fibrosis (ILF), and more pressure difference is required to cause a certain volume change in the lung than the normal state. From the functional and physiological perspective, respiratory function is impaired and its effects are evident in the pulmonary function tests (PFTS). From a pathological point of view, which is examined by a pathologist by evaluating a lung biopsy specimen in the laboratory, the lung

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parenchymal structural change and destruction could be seen. The last viewpoint is the radiological and anatomical aspect of the disease, in which a radiologist determines the ILD patterns by examining the patient's lung images [1]. According to epidemiological studies conducted in different parts of the world, idiopathic pulmonary fibrosis (IPF) and sarcoidosis are the most common forms of ILD, which account for 50% of cases [5]. ILDs represent a large number of conditions that affect the lung parenchyma, including alveolar epithelium, capillary endothelium, and the spaces between these structures, as well as the perivascular and lymphatic tissues. This heterogeneous group of disorders is categorized together because of their similar clinical, radiographic, physiological, or pathological manifestations. Each ILD may have an acute phase but typically they represent a chronic illness. Some ILDs rarely recur and the disease is subclinical at recurrence intervals [6]. Sarcoidosis, IPF, and pulmonary fibrosis with CTDs are the most prevalent ILDs of unknown etiology. The ILDs with known etiologies include contact with occupational and environmental factors, in particular inhalation of inorganic and organic particles, various vapors and gases, infections, drugs, and radiation [5]. Factors affecting ILDs include age, gender [6,7], family history [6], smoking history [2,6], occupational and environmental history [3,6], and so on.

The histopathological findings include varying degrees of inflammation with accumulation and immune cells often associated with abnormal extracellular matrix in the terminal airways, alveolar walls, and interstitium [8]. Dyspnea is a common indicator complaint in patients with ILD [6]. In special cases, serological tests, echocardiography, bronchoscopy, and surgical lung biopsy are also helpful in the specific disease diagnosis [9]. A meta-analysis study was performed to determine specific computed tomography (CT) patterns and clinical features to differentiate between nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP) and showed significantly lower levels of the honeycomb pattern with less peripheral predominance and more subpleural sparing cases. Overall, the honeycomb pattern with peripheral predominance was significantly associated with UIP diagnosis [10].

According to the importance of accurate diagnosis and treatment of ILD, and also due to the few conducted study on this topic in Guilan province, Iran, we aimed to conduct this study to investigate demographic data and clinical characteristics of ILD patients in Razi hospital, Rasht, Iran.

2. Materials and Methods

This cross-sectional descriptive study was conducted on patients diagnosed with ILD who were referred to Razi Hospital, Rasht, Iran during 2013-2018. Inclusion criteria were definitive diagnosis of ILD by a specialist based on history and clinical signs, Chest X-Ray (CXR), lung High resolution computed tomography (HRCT), and pathology. Exclusion criteria were incomplete file information, including age, gender, clinical signs, and results of imaging. This study was approved by the research ethics committee of Guilan University of Medical Sciences, Rasht, Iran with the number code IR.GUMS.REC.1398.078. The informed consent and consent to publication were taken from patients.

Information in files and variables, such as age, gender, heredity, level of education, occupation, and smoking history; laboratory findings including white blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), blood urea nitrogen (BUN), creatinine (Cr), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and calcium (Ca); serological factors such as (anti-nuclear antibody (ANA), rheumatoid factor (RF), cyclic citrullinated peptide antibody (Anti- CCP), autoantibodies against topoisomerase I (Anti-Scl-70), anti–Sjögren's-syndrome-related antigen A autoantibodies (Anti-Ro/SSA), anti-Sjogren's syndrome B autoantibodies to SS-B/LA, Serum (Anti-La/SSB), native double-stranded DNA antibody (Anti-ds DNA), perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA), antineutrophil cytoplasmic autoantibody, cytoplasmic (c-ANCA), Anti-Smith, antinuclear ribonucleoprotein (Anti-RNP), and angiotensin-converting enzyme (ACE); echocardiography, comorbidities, used medications, radiographic patterns [septal thickening, ground-glass attenuation (GGA), honeycomb change, centrilobular nodules, mediastinal lymphadenopathy, emphysema, and reticulation], spirometry parameters, and presence/absence of pathology reporting ILD were recorded in the information form.

Collected data were analyzed by SPSS software (version 18) (IBM, Armonk, NY). Quantitative variables with normal distribution were described

using mean ± standard deviation (95% confidence interval), and median and interquartile ranges were used for quantitative variables with non-normal distribution. Qualitative variables were also described based on the number and percentage. The normal distribution of quantitative variables was verified using the Kolmogorov-Smirnov test.

3. Results

According to our results, 170 (56.7%) patients were male and the rest were female. The mean age of the patients was 56.95 ± 14.78 years with a median of 56.50 years (in the range of 15-93 years). Most of the patients were married and 158 (52.7%) individuals were illiterate or without high school diplomas. All demographical data of participants are illustrated in Table 1.

Table 1. Demographic characteristics of patients diagnosed with ILDs

Variables	Subgroup	Mean ± SD
Age (year)		56.95 ± 14.78
		Number (%)
Sex	Female	130 (43.3)
	Male	170 (56.7)
Marital status	Single	12 (4)
	Married	288 (96)
Level of Education	Illiterate	98 (32.7)
	Without high school diplomas	60 (20)
	Diplomas	99 (33)
	Graduate	43 (14.3)
Occupational status	Housewife	143 (47.7)
	Farmer	59 (19.7)
	Self-employment	30 (10)
	Construction worker	24 (8)
	Staff	19 (6.3)
	Driver	9 (3)
	Unemployed	16 (5.3)

According to the occupational exposure status of patients, smoking was the most frequent one by 160 (53.3%) patients included. Based on the patients' spirometry results, obstructive and restrictive patterns were reported in 103 (34.3%) and 197 (65.7%) patients, respectively. In the studied patients, the most prevalent clinical symptoms were cough (66%), dyspnea (57.7%), and abnormal findings in lung auscultation (25.3%) (Table 2). Also, no cases were reported with symptoms of tachypnea and tachycardia.

The hereditary background was positive in 68 cases of patients based on family history. Furthermore, 110 ILD patients had normal left ventricular ejection fraction (EF) on echocardiography. Medication use was detected in 113 (37.7%) studied patients (Table 3), with methotrexate used most frequently (86.7%). Sarcoidosis, scleroderma, and Churg-Strauss syndrome were the most frequent underlying diseases in ILD patients (Table 3). The laboratory findings are illustrated in Tables 4 and 5. According to the serological results, 29 (18.4%) patients were positive for ANA among 158 reported cases. Also, RF test was positive in 27 (14.8%) cases.

No information was available on the status of anti-Ro/SSA, Anti-La/SSB, Anti-Smith, ACE, and Anti-RNP serological tests.

The radiological findings of patients represented that septal thickening, honeycomb change, mediastinal lymphadenopathy, and GGA were the most frequent in patients. According to histopathological results, alveolar wall thickening (AWT), fibroblast deposition, honeycomb pattern, and interstitial lung fibrosis pattern were reported in 186 (71.3%) patients, and granulomatous lung tissue and diffuse cellular fibrosis were reported in 58 patients (22.2%) (Table 6).

4. Discussion

Due to the result of the current study, middle-aged males were predominant. In a study, it has been reported that the mean age of autoimmune-featured-ILD (AIF-ILD) patients were 66 ± 10 years at the time of referral, which was similar to the IPF group and higher than that of CTD-ILD patients (54 ± 14.6 years) [11]. Alavi Foumani et al., reported that the mean age of evaluated sarcoidosis patients was 42.8 ± 9.8 years with the most frequency in females (63.5%) [12].

Table 2. Occupational exposure status and clinical symptoms of ILD patients

Variable		Subgroup	Number (%)
Non-job exposure		Yes	160 (53.3)
		No	140 (46.7)
Types of Non-job exposure		Smoking	160 (53.3)
		Secondhand Smoke	46 (28.7)
		Opium	32 (20)
		Hookah	3 (1.9)
		Fireplace	10 (6.3)
		Oven old	9 (5.6)
		Rice-crop residue burning smoke	1 (0.6)
		Chemicals	5 (3.1)
		Plaster dust	1 (0.6)
Clinical signs	Shortness of breath	Yes	173 (57.7)
		No	127 (43.3)
	Cough	Yes	198 (66)
		No	102 (34)
	Hemoptysis	Yes	22 (7.3
		No	278 (92.7)
	Fever	Yes	25 (8.3)
		No	275 (91.7)
	Clubbing	Yes	11 (3.7)
		No	289 (96.3)
	Abnormal findings in the lungs	Yes	76 (25.3)
		No	224 (74.7)
	Joint pain	Yes	17 (5.7)
		No	283 (94.3)
	Skin lesions	Yes	6 (2)
		No	294 (98)

*Since some patients were exposed to more than one type of NOE, the total percentage is more than 100

Table 3. Characterization of medications and underlying disease in patients with a diagnosis of ILD

Variables		Subgroup	Number (%)
Taking Medicines		Yes	113 (37.7)
		No	187 (62.3)
Types of drug		Methotrexate	98 (86.7)
		Cyclophosphamide	13 (11.5)
		Amiodarone	2 (1.8)
Sarcoidosis		Yes	94 (31.3)
		No	206 (68.7)
Comorbidity	Scleroderma	Yes	48 (16)
		No	252 (84)
	Churg-Strauss	Yes	18 (6)
		No	282 (94)
	Dermatomycosis	Yes	6 (2)
		No	294 (98)
	Rheumatoid arthritis	Yes	5 (1.7)
		No	295 (98.3)
	Lupus	Yes	3 (1)
		No	297 (99)

Table 3. Characterization of medications and underlying disease in patients with a diagnosis of ILD (**Continued**)

Variables		Subgroup	Number (%)
Comorbidity	Hypersensitivity pneumonitis	Yes	3 (1)
		No	297 (99)
	Sjögren	Yes	3 (1)
		No	297 (99)
	Pneumoconiosis	Yes	3 (1)
		No	297 (99)
	Undetermined lung fibrosis	Yes	3 (1)
		No	297 (99)
	Wegener	Yes	2 (0.7)
		No	298 (99.3)

Table 4. The laboratory data of the studied patients

Variable	Available cases	Mean ±SD
WBC (cumm)	297	8638/2212 ± 77.5
RBC (x10^6mIu/L)	255	3 ± 91.55
Hb (g/dL)	299	11.1 ± 40.33
Platelets (U/L)	294	262955/2212 ± 78.5
BUN (mg/dL)	287	19.9 ± 83.8
Cr (mg/dL)	284	1 ± 11.9
AST (U/L)	103	49.2 ± 75.6
ALT (U/L)	104	45.2 ± 29.2
ALK-P (U/L)	83	393.121 ± 66.3
Ca (mg/dL)	72	10.1 ± 53.3

Abbreviations: WBC (white blood cell), RBC (red blood cell), Hb (hemoglobin), BUN (blood urea nitrogen), Cr (creatinine), AST (aspartate transaminase), ALT (alanine transaminase), ALP (alkaline phosphatase), Ca (calcium)

Table 5. Characterization of serological tests of patients with ILD diagnosis

Variables		Available cases	Number (%)
ANA	Positive	158	29 (18.4)
	Negative		129 (81.6)
RF	Positive	183	27 (14.8)
	Negative		156 (85.2)
Anti-CCP	Positive	1	1 (100)
	Negative		0
Anti-Scl-70	Positive	28	19 (67.9)
	Negative		9 (32.1)
Anti-ds DNA	Positive	18	4 (22.2)
	Negative		14 (77.8)
C-ANCA	Positive	1	1 (100)
	Negative		0
P-ANCA	Positive	17	17 (100)
	Negative		0

Abbreviations: ANA (Anti-nuclear antibody), RF (Rheumatoid factor), CPC (Cyclic Citrullinated Peptide), Scl-70 (Topoisomerase I), ds-DNA **(**Native double-stranded DNA), C-ANCA (Antineutrophil Cytoplasmic Autoantibody, Cytoplasmic), P-ANCA (Perinuclear anti-neutrophil cytoplasmic antibodies)

Table 6. The radiological symptoms and pathological evidence of patients

Variable			Number (%)
Radiological indication	Septal thickening		128 (42.7)
	Honeycomb change		76 (25.3)
	Mediastinal Lymphadenopathy		72 (24)
	Ground glass attenuation		61 (20.3)
	Emphysema		19 (6.3)
	Reticulation		17 (5.7)
	Centrilobular nodules		8 (2.7)
Pathological evidence	Thickening of alveolar septa + fibroblast accumulation + Honeycomb pattern + interstitial lung fibrosis	Yes	186 (71.3)
		No	75 (28.7)
	Granuloma in lung tissue + Diffuse fibrosis	Yes	58 (22.2)
		No	203 (77.8)
	Eosinophilia in lung tissue + Alveolar dense fibrosis	Yes	10 (3.8)
		No	251 (96.2)
	Rheumatoid nodule + Alveolar dense fibrosis	Yes	1 (0.4)
		No	260 (99.6)
	Diffuse histiocytic in lung tissue + Diffuse fibrosis	Yes	6 (2.3)
		No	255 (97.7)
	Lymphocytes in lung tissue	Yes	1 (0.4)
		No	260 (99.6)

*Due to the fact that some patients had more than one finding, the overall percentage has increased to more than 100

In the United States during 2004-2010, a study on people aged 18-64 years indicated that the rise of the age and male gender were two important and influential factors in increasing the incidence of IPF, and individuals under 65 years of age were less likely to develop ILDs in this country [13]. According to another study, smoking, increasing age, and male gender significantly increased the incidence of ILDs, which was 6.9 times higher in patients over 70 years [14]. Alavi Foumani et al., observed that only 3.8% and 1.5% of sarcoidosis patients were active and inactive smokers, respectively [12]. Another study on histological test results of an 81-year-old patient illustrated asbestos accumulation in the lungs due to indirect exposure to domestic asbestos dust by washing asbestos-contaminated industrial clothes of the husband who worked in a textile factory. It can be conducted that exposure to domestic asbestos dust could be considered a risk factor for fatal pulmonary fibrosis [15].

In this present study, occupational history has been identified as an important cause of ILD development. Gysbrechts et al. suggested that exposure to talc in people over 40 years of age is a reason for the development of pulmonary fibrosis [16]. Also, Kim et al. reported ILD development in several construction workers who worked in the outside yard of a company producing hydrofluoric products [17].

According to our results, obstructive and restrictive spirometric patterns were the most reported ones. The most common clinical symptoms and signs were cough, dyspnea. Alavi Foumani et al. also found that the most common signs and symptoms in their sarcoidosis patients were related to the respiratory system, in which 63.3% of patients showed symptoms such as dyspnea and cough, and systemic symptoms (e.g. weight loss and fever) as secondary signs [12]. Dhooria et al. examined the range of ILDs on 803 patients in a specialty center and reported the most common symptoms to be cough (86.1%), dyspnea (76.1%), weight loss (30.9%), anorexia (24.2%), joint pain (23.9%), and fatigue (17.9%), respectively [4].

A review of 4086 studies conducted from 1996 to 2015 demonstrated that the most prevalent symptoms in fibrotic ILD were dyspnea (54-98%) and cough (59-100%), followed by heartburn (25-65%) and depression (49-49%) [18]. Muscle pain, chills, fever, headache, cough, sputum, nausea, vomiting, bloating, arthritis, and decreased total lung capacity have been

reported in patients with ILD [19]. A study by Sheikh et al. on the prevalence of pulmonary disorders in patients with scleroderma represented six (11.5%) patients without dyspnea, 22 (42.3%) without cough complaints, 20 (38.4%) with no crackle in the lungs, and 26 (50%) with no clubbing on examination, but patients represented an abnormal HRCT pattern [20]. In another study, 41 out of 288 patients with proven CTD-ILD initially presented pulmonary symptoms, and the remaining 247 (86%) patients developed extrapulmonary symptoms as the primary manifestation [21].

In our study, sarcoidosis, scleroderma, and Churg-Strauss syndrome were reported in a higher percentage of patients diagnosed with ILD. In a study by Zubairi et al., the most common ILD was IPF in 217 (40.4%) patients, followed by nonspecific interstitial pneumonia, sarcoidosis, and connective tissue disease (CTD)-related ILD in 106 (19.7%), 82 (15.3%), and 56 (10.4%) patients, respectively [22]. Duchman et al. stated that sarcoidosis (42.6%), CTD-ILD (16%), IPF (11.6%), and occupational ILDs (5%) were the most common diagnoses in 848 cases of ILD [23]. The incidence of ILDs in Denmark was reported to be 4.1 cases per 100,000 people per year. IPF was the most common diagnosis with an annual incidence of 1.3 cases per 100,000 patients (28%), followed by CTD-ILD (14%) and HP (7%) [24].

The result of a study showed that out of 2678 patients who were diagnosed with ILD, CTD-ILD and IPF were detected in 1798 (67%) and 299 (11.2%) patients, respectively [21]. Also, in another study, it was reported that out of 381 patients, 325 (85.1%) individuals were classified in the ILD-CTD group (RA 31%, systemic sclerosis 29%, and dermatomyositis 15%), 36 (9.5%) patients in the group of interstitial pneumonia with autoimmune features (IPAF), and 13 (3.5%) patients in the antineutrophil cytoplasmic antibodies (ANCA)-positive ILD group [25]. An investigation demonstrated that HP, CTDILD, and IPF accounted for 47.3%, 13.9%, and 13.7%, respectively, among 1084 patients with ILD [26].

Saghafi et al. performed research on 100 patients with acute sarcoidosis in rheumatology clinics of Mashhad during 2010-13, they found that acute sarcoidosis was more prevalent in females. The average age of patients was 40-50 years and 93% of patients represented the acute phase and 7% of patients were in the chronic phase. Among 91 cases of acute arthritis, 64 were diagnosed with Lofgren's syndrome and out of 93 patients with acute sarcoidosis, the onset of erythema nodosum, uveitis, and general symptoms (fatigue- fever- night sweetly) were reported in 67 (72%), 10 (10.8%), and 41 (44.1%) cases [10].

In this present study, the serological results were incomplete for the majority of patients. Positive ANA result was reported in 18.4% out of 158 patients and positive RF test result was reported in 14.8% of cases. An investigation illustrated that American Indians accounted for 27% of patients with systemic lupus erythematosus (SLE) with a concomitant diagnosis of pulmonary fibrosis, or ILD. African Americans were also divided equally and had high anti-dsDNA (52%) and 23% in controls. An increasing trend was observed in anti-La (43%), anti-Sm (43%), and RNP (53%) compared to the control sample. Among 517 patients, only two cases were anti-Jo1 positive, both of whom were African-American women and lay among significant cases with ILD that also had cytoplasmic ANA patterns and were positive for anti-dsDNA [27].

According to the result of a study in Shanghai Lung Hospital, out of 1044 individuals with interstitial lung disease, 332 (32%) did not receive an accurate diagnosis at early admission, 195 (18.7%) had continuously negative autoantibody tests, and 262 (25.1%) patients initially had negative autoantibodies but became positive in subsequent follow-up courses [21]. It has been reported that the presence of a high ANA titer or RF was attributed to individuals with CT-ILD [28].

Regarding the radiological abnormality results in our study, septal thickening, honeycomb change, mediastinal lymphadenopathy, and GGA were reported in a higher percentage of patients. AWT, fibroblast deposition, honeycomb pattern, and interstitial lung fibrosis were the most frequent reported among patients. In a study by Sheikh et al. the normal HRCT, NSIP, and UIP were reported in 21 (40.4%), 19 (36.5%), and 12 (23.1%) patients, respectively. Normal, mild reticular, clear reticular, and honeycomb CXR were reported in 19 (36.5%), 15 (28.8%), 14 (26.9%), and four (7.7%) patients, respectively (20). In another study, abnormal serology was observed in 114 (82%) out of 139 patients diagnosed with IPF, 53 (38%) cases had greater values of ≥2, 99 (71%) subjects showed an abnormal ANA titer ≥1:80, and the most common ANA positive was 1:

160. Mean values of RF positive, ESR, and CRP were 43 (normal < 14 IU/mL), 48 (normal < 41 mm/h), and 22 (normal < 5 mg/L), respectively. In this study, positive cases were found for RF (18, 13%), anti-SSA (6, 4%), CK (3, 2%), ANCA, anti-dsDNA, anti-smith, and ACCP (1, 0.01 %), and anti SSB (2, 1%), but the results were negative for anti-RNP [11]. In this study, males and older age represented a higher number of ILD that was similar to many other studies. Most of the patients were married which could be due to the high prevalence of diseases in aged people, the high percentage of illiterate or the lower level of high school diploma in the studied patients may indicate various unprotected respiratory exposures in this group that probably referred to their difficult and high-risk jobs.

The results showed that more than 50% of patients were exposed to NOE, among whom smoking, exposure to SHS, and opium were higher than other NOEs. Other studies, however, have shown deleterious effects of chemicals and occupational exposures in lung injury and fibrosis, which may indicate differences in geographic risk factors in each particular area that should be considered in related studies. Based on the spirometric parameters of patients in the patients' data record, the obstructive pattern was detected in 34.3% of patients and the rest of the cases presented restrictive patterns. The significant proportion of obstructive disease among our ILD patients may be due to the presence of smoking and other similar exposure in the significant number of patients. IPF is one of the most common clinical, radiologist, and pathologic diagnoses of ILD. Besides genetic and environmental exposure differences, visiting IPF patients, and disorganized diagnostic approaches to IPF pattern recognition HRCT and pathologic reports may contribute to the small percentage of IPF in this study.

5. Conclusion

In summary, the variety of clinical, radiological, and laboratory findings in ILDs can demonstrate regional differences in risk factors, patients' exposure, access to medical facilities for diagnosis and treatment, genetic differences, and also necessitate careful examination of these factors individually in each region, which therefore explains the epidemiological differences in various parts of Guilan province, Iran.

Authors' contributions

Study design and supervision: HB, BG, AJ. Data collection and analysis: SR, AJ, AA. Interpretation and drafting: HB, BG, SR. final revisions: HB, AA. All authors read and approved the final version of article.

Conflict of interests

None.

Ethical declarations

This study was approved by the research ethics committee of Guilan University of Medical Sciences, Rasht, Iran with the number code IR.GUMS.REC.1398.078. The informed consent and consent to publication were taken from patients.

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