Original Article

Interstitial lung diseases in Saudi Arabia: A single-center study

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Abstract:

BACKGROUND: There are relatively few epidemiological studies on interstitial lung disease (ILD) worldwide.

OBJECTIVE: To report the incident cases of ILD and compare our data with reports from other populations.

METHODS: Newly diagnosed ILDs were prospectively collected at a single tertiary care hospital from January 2008 to December 2011. Detailed demographic and clinical data were collected at the time of diagnosis, along with the results from diagnostic procedures, including high-resolution computed tomography (HRCT), serological tests, bronchoalveolar lavage (BAL), transbronchial lung biopsy, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and surgical lung biopsy.

RESULTS: A total of 330 cases were included. The mean age was 55.4 ± 14.9 years. There was a slight predominance of females (202; 61.2%), and the male-to-female ratio was 1:1.37. The most frequent disease was connective tissue disease (CTD)-associated ILD (34.8%), followed by idiopathic pulmonary fibrosis (IPF) (23.3%), sarcoidosis (20%), and hypersensitivity pneumonitis (6.3%). Non-classifiable ILD was present in 1.8% of the total ILD cases. HRCT was performed in 97.3% of the cases, BAL in 17.5%, transbronchial lung biopsy in 21.8%, EBUS-TBNA in 4.5%, and surgical lung biopsy in 22.7% (38.6% of which were performed among the idiopathic interstitial pneumonia cases).

CONCLUSIONS: CTD-ILD and IPF were the most frequently observed ILDs in this Saudi Arabian population. Similarities and differences were found with respect to the previous reports from other countries.

Key words:

Connective tissue disease, epidemiology, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, interstitial lung disease, lung dominant, sarcoidosis

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Interstitial lung disease (ILD) is a heterogeneous group of disorders that diffusely affects the lung parenchyma while having variable etiologies, clinical presentations, radiographic patterns, and histological appearances. Although significant progress has been made in understanding the various causes of ILD, its diagnosis can be very challenging and requires significant expertise in pulmonary medicine, rheumatology, radiology, and pathology. There are relatively few epidemiological studies on ILD, but the existing studies show that there are wide variations in the incidence and prevalence of the various ILDs between countries.[1-8] It is not yet clear whether this variation reflects true differences in the frequency of ILDs between countries or whether it is related to methodological differences. In 2002, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) provided a consensus classification of the idiopathic interstitial pneumonias (IIPs) in the hope of standardizing the terminology applied to IIPs. They advocated a multidisciplinary approach that includes clinicians, radiologists and pathologists in efforts to improve the accuracy of clinical diagnosis and facilitate targeted therapeutic approaches.[9]

In the present study, we describe a prospectively collected cohort of ILDs newly diagnosed using the ATS/ERS consensus classification of IIPs at a single tertiary care hospital over 4 years, and compare our data with reports from other populations.

Methods

Study population

The present work, which is a descriptive study of consecutive patients newly diagnosed with ILD between January 2008 and December 2011, is part of an ongoing large prospective study of the current diagnostic assessment and outcome of ILDs in our center. This study was approved by the Institutional Review Board/Ethics Committee of the College of Medicine, King Saud University, Riyadh, Saudi Arabia. All patients understood the procedures required to establish the diagnosis and written informed consent was obtained from all participants. A standard form was used to collect clinical information, including symptoms, smoking history, medication use, environmental history, occupational history, family history, and physical findings. High-resolution computed tomography (HRCT), pulmonary function tests, serological tests, bronchoalveolar lavage (BAL), transbronchial lung biopsy, endobronchial ultrasound-guided transbronchial needle

aspiration (EBUS-TBNA) and/or surgical lung biopsy were part of the routine work-up upon first suspicion of ILD. A multidisciplinary approach involving pulmonologists, radiologists and pathologists was implemented on all ILD patients before a final diagnosis was rendered. IIPs were diagnosed according to the ATS/ERS consensus classification.[9] Sarcoidosis was diagnosed based on the criteria published by the ATS, the ERS, and the World Association of Sarcoidosis and Other Granulomatous Disorders.[10] The American College of Rheumatology (ACR) criteria were used to establish the diagnosis of connective tissue disease (CTD).[11-15] Lung-dominant (LD)-CTD was diagnosed based on the criteria proposed by Fischer *et al*.[16] when specific autoantibodies and/or histopathological features were present in the absence of extrathoracic features of a definite CTD [Table 1].

Statistical analysis

The data were entered in MS Excel. Descriptive statistics, i.e., means, standard deviations, frequencies, and percentages, were used to describe the study variables.

Results

The study population included 330 consecutive ILD patients, 302 (91.5%) of whom were native Saudi patients and 28 (8.5%) of whom had other origins (Yemen = 7, Egypt = 5, Pakistan = 5, Sudan = 4, India = 2, Jordan = 2, and 1 each from Syria, Nigeria, and South Africa). The mean age of the participants was 55.4 ± 14.9 years. There was a slight predominance of females (202; 61.2%), and the male-to-female ratio was 1:1.37. The mean age for men was 55.8 ± 15.7 years and that for women was 55.1 ± 14.3 years. The distribution of ILDs among the study cohort is shown in Table 2. CTD (34.8%) and IIPs (32.7%) were the most frequent incident cases, followed by sarcoidosis (20%). The CTD-ILD patients had associated diagnoses of rheumatoid arthritis (n = 22), systemic lupus erythematosus (n = 13), scleroderma (n = 13), mixed CTD (n = 11), and polymyositis/dermatomyositis (n = 6).

Among the LD-CTD patients, 40 had associated diagnoses of usual interstitial pneumonia (UIP) and 10 had associated diagnoses of non-specific interstitial pneumonia (NSIP). The autoantibody profiles among the LD-CTD patients showed that 20 (40%) were positive for one antibody, 20 (40%) were positive for two antibodies, and 10 (20%) had three or more positive serological tests. The anti-nuclear antibody was the most frequently positive autoantibody (n = 47; 94%). The frequencies of the other autoantibodies were, in decreasing order, rheumatoid factor (n = 16; 32%), Anti-Sjogren's Syndrome A (anti-Ro/SSA) (n = 10; 20%), anti-histidyl-trensfere ribonuclic acid (tRNA) synthetase (Jo-1) (n = 6; 12%), anti-double-stranded DNA (n = 5, 10%), anti-cyclic citrullinated peptide (n = 4; 8%), anti-ribonucleoprotein (n = 4; 8%), Anti-Sjogren's Syndrome B (anti-La/SSB) (n = 3; 6%), anti-Sclero 70 (n = 3; 6%), and anti-Smith (n = 2; 4%).

Table 1: Diagnostic criteria for lung-dominant connective tissue disease

NSIP, UIP, LIP, OP, and DAD (or DIP if no smoking history), as determined by surgical lung biopsy specimen or suggested by high-resolution CT and

Insufficient extrathoracic features to allow a specific CTD designation and

No identifiable alternative etiology for interstitial pneumonia and

Any one of the following autoantibodies or at least two of the following histopathological features

Autoantibodies	Histopathological features
High-titer ANA (>1:320) or RF (>60 IU/mL)	Lymphoid aggregates with germinal centers
Nucleolar-ANA	Extensive pleuritis
Anti-CCP	Prominent plasmacytic infiltratiosn
Anti-Scl-70	Dense perivascular collagen
Anti-Ro/SSA	
Anti-La/SSB	
Anti-ds DNA	
Anti-Smith	
Anti-RNP	
Anti–JO-1	
ACA	

These criteria were derived from reference [16]. UIP = Usual interstitial pneumonia, NSIP = Non-specific interstitial pneumonia, LIP = Lymphocytic interstitial pneumonia, OP = Organizing pneumonia, DAD = Diffuse alveolar damage, DIP = Desquamative interstitial pneumonia, CTD = Connective tissue disease, ANA = Anti-nuclear antibody, RF = Rheumatoid factor, CCP = Cyclic citrullinated peptide, Scl-70 = Sclero 70, dsDNA = Double-stranded DNA, RNP = Ribonucleoprotein, JO-1 = Anti-histidyl-tRNA synthetase, and ACA = Anti-centromere antibodies, Ro/SSA = Anti-Sjogren's Syndrome A, La/SSB = Anti-Sjogren's Syndrome B

Table 2: Distribution of interstitial lung diseases

	Incident cases
Total number	330
Idiopathic interstitial pneumonias	108 (32.3)
IPF	77 (23.3)
NSIP	13 (3.9)
COP	5 (1.5)
RB-ILD	6 (1.8)
DIP	3 (0.9)
LIP	3 (0.9)
AIP	1 (0.3)
Connective tissue diseases	115 (34.8)
CTD-UIP	37 (11.2)
Lung-dominant CTD	50 (15.2)
CTD-NSIP	26 (7.9)
CTD-LIP	2 (0.6)
Sarcoidosis	67 (20)
Hypersensitivity pneumonitis	21 (6.4)
Others	
Familial ILD*	3 (0.9)
Drug induced ILD	4 (1.2)
Chronic eosinophilic pneumonia	1 (0.3)
Hemosiderosis	1 (0.3)
Alveolar proteinosis	1 (0.3)
Bronchiolitis obliterans	2 (0.61)
Langerhans cell histiocytosis	1 (0.3)
Non-classifiable	6 (1.8)

Data are presented as number (with percentage). IPF = Idiopathic pulmonary fibrosis, NSIP = Non-specific interstitial pneumonia, COP = Cryptogenic organizing pneumonia, RBILD = Respiratory bronchiolitis associated interstitial lung disease, DIP = Desquamative interstitial pneumonia, LIP = Lymphocytic interstitial pneumonia, AIP = Acute interstitial pneumonia, CTD = Connective tissue disease, UIP = Usual interstitial pneumonia. *Three different families were diagnosed with familial ILDs

The clinical and physiological characteristics of patients with the most frequent types of ILDs are shown in Table 3. The sarcoidosis, CTD and hypersensitivity pneumonitis (HP) patients were younger, more often female, and far more likely to be non-smokers than those in the idiopathic pulmonary fibrosis (IPF) group. As expected, dyspnea and cough were the most common respiratory symptom in all groups. The exposure source for HP was identified in 66.7% of these patients (pigeons and parrots = 7; sheep = 2; insecticides = 3; chemical paint = 1; and humidifiers = 1). Clubbing was less frequently seen in patients with sarcoidosis, CTD, and HP than in the IPF group. In contrast, bibasilar crackles were more commonly noted in patients with IPF, CTD, and HP compared with the sarcoidosis group. A restrictive ventilatory defect with decreased diffusing capacity for carbon monoxide was a common physiological pattern among the four ILD groups. The distribution of sarcoid stages was as follows: Stage I (12%), stage II (31%), stage III (6%), and stage IV (51%).

The procedures performed among ILD patients [Table 4] showed that all patients underwent CT scans of the chest; of them, 321 (97.3%) underwent HRCT and the remaining nine (2.7%) patients had their CTs performed with intravenous contrast material. Surgical lung biopsy was performed in 22.7% of the ILD cases; of them, 38.6% were IIP cases.

Comparison of the ILD distributions in Saudi Arabia with those in other countries showed similarities and differences, as listed in Table 5.

Table 3: Comparison of clinical and physiological characteristics at diagnosis among patients diagnosed with the most frequent types of interstitial lung disease

	CTD *n*=115	IPF *n*=77	Sarcoidosis *n*=67	HP *n*=21
Age at presentation, years	55.3±14.3	63.8±12.2	49.1±12.9	51.1±12.7
Male/Female	30/85	45/32	27/40	1/20
Ever smoker *n* (%)	18 (16)	29 (38)	10 (15)	0
Symptoms				
Dyspnea	99 (86)	69 (90)	37 (55)	17 (81)
Cough	89 (77)	65 (84)	35 (52)	19 (90)
Sputum production	58 (50)	43 (56)	27 (40)	15 (71)
Skin rash	15 (13)	3 (4)	4 (6)	0
Hemoptysis	4 (3)	6 (8)	2 (3)	1 (5)
Fatigue	36 (31)	24 (31)	14 (21)	9 (43)
Weight loss	21 (18)	11 (14)	17 (25)	6 (29)
Chest discomfort	27 (23)	27 (35)	19 (28)	7 (33)
Physical findings				
Clubbing	31 (27)	38 (49)	10 (15)	5 (24)
Crackles	87 (76)	70 (91)	22 (33)	17 (81)
Pulmonary function tests				
FVC, % predicted	62.5±19.9	62.6±20.1	74.9±20.2	64.2±20.8
FEV_1/FVC, ratio	87.9±11.3	91.3±7.1	80.5±5.5	90.2±7.8
TLC, % predicted	60.6±18.1	60.6±16.9	73.8±18.5	67.4±18.1
DL_{CO}, % predicted	40.5±19.4	42.7±19.2	49.8±19.5	44.6±2.8

Data are presented as mean±standard deviation or number (with percentage). CTD = Connective tissue disease, IPF = Idiopathic pulmonary fibrosis, HP = Hypersensitivity pneumonitis, FVC = Forced vital capacity, FEV_1 = Forced expiratory volume in 1 s, TLC = Total lung capacity, DL_{CO} = Diffusion capacity of lungs for carbon monoxide

Discussion

The present study demonstrates that, among newly diagnosed ILD patients enrolled at a single center in Saudi Arabia, CTD and IIPs were the most frequent disease entities.

Epidemiological studies are important tools for measuring the magnitude of health problems, identifying the natural history and etiology of a disease, and facilitating the formation of health care plans for disease prevention and management. Previous study populations for ILDs have provided useful information on the prevalence and incidence of the various types. However, these have been limited by differences in study design and diagnostic methods and criteria.[1-8]

A striking finding of the present study is that CTD-associated ILD was the most frequent disease among the ILDs seen in our center. These data represent the experience of a single center where the other registries[2-8] were multicenter, and there are differences in the study designs, numbers of cases, and study durations. However, some important extrapolations can still be made. IPF and sarcoidosis were the most common diseases in the other registries,[2-8] which differs from our findings. The reason for this difference is not yet clear, but there are several possible explanations. First, we used the term LD-CTD (proposed by Fischer *et al*.[16]) for patients who did not meet the ACR criteria for any of the CTDs, which may have increased the number of CTD-associated ILDs in our cohort. However, even if we removed LD-CTD from this category, the proportion of CTD-associated ILD (19.7%) still exceeds those of the previous reports (2.1-11.6%).[2,4-7] Second, all patients enrolled in our study underwent CT scans of the chest, and 97% had HRCT; this is higher compared with the other reports (91.9% for Spain, 87.4% for Greece, 74.4% for Italy, and 41% for Germany).[4,5,7,8] As such, HRCT may have an increased sensitivity for detecting parenchymal changes among our cohorts compared with plain chest radiographs. Finally, racial differences may be relevant. A future prospective multicenter study will be needed to explore the incidence of CTD-associated ILD among the Saudi population in more detail.

IPF (23.3% incident cases) was the most frequent disease entity among the enrolled IIPs. This is relatively similar to the report from Greece (20.1%), but differs from those of the other registries (18.9-38.6%).[2-8] This discrepancy may reflect that the ATS/ERS consensus classification and diagnostic criteria for IIPs[9] were used in two studies (Greece and Spain)[5,7] but

Table 4: Number of procedures performed among the study cohort

High-resolution computed tomography*	321 (97.3)
Bronchoalveolar lavage	58 (17.5)
Transbronchial lung biopsy	72 (21.8)
Endobronchial biopsy	10 (3)
EBUS-TBNA	15 (4.5)
Surgical lung biopsy, open/VATS	75 (22.7)

Data are presented as number (with percentage).
EBUS-TBNA = Endobronchial ultrasound-guided transbronchial needle aspiration, VATS = Video-assisted thoracic surgery, *The remaining nine patients had computed tomography scans with intravenous contrast material

Table 5: Comparison of interstitial lung disease incident cases in Saudi Arabia and other countries

	Saudi Arabia *n*=330	Greece* *n*=259	Spain* *n*=511	Flanders* *n*=264	Germany* *n*=234	New Mexico* *n*=202
Study duration, months	48	12	12	48	12	48
IPF	77 (23.3)	52 (20.1)	197 (38.6)	50 (18.9)†	76 (32.5)†	63 (31.2)†
CTDs	115 (34.8)	30 (11.6)	51 (9.9)	19 (7.2)	5 (2.1)	18 (8.9)
Sarcoidosis	67 (20)	60 (23.2)	76 (14.9)	69 (26.1)	83 (35.5)	16 (7.9)
Hypersensitivity pneumonitis	21 (6.3)	7 (2.7)	34 (6.7)	32 (12.1)	31 (13.2)	3 (1.5)
Drug-induced ILD	4 (1.2)	4 (1.5)	17 (3.3)	12 (4.5)	6 (2.6)	7 (3.5)
Non-classifiable	6 (1.8)	40 (15.4)	26 (5.1)	27 (10.2)	12 (5.1)	60 (29.7)
Others	40 (12.1)	66 (25.5)	110 (21.5)	55 (20.8)	21 (8.9)	35 (17.3)

Data are presented as number (with percentage). IPF = Idiopathic pulmonary fibrosis, CTD = Connective tissue disease, ILD = Interstitial lung disease. *Number of subjects based on the number of incident cases. See References [2-7]. †The classification of idiopathic interstitial pneumonias (Ref. [9]) was not applied

not in the others.[2-4,6,8] Thus, NSIP, desquamative interstitial pneumonia, and lymphocytic interstitial pneumonia may have been included as IPF cases in the latter studies.[3] Serological profiles were not provided for the IPF patients in the Spanish registry;[5] as such, they may have included patients that fit the proposed criteria for LD-CTD with UIP pattern. Importantly, 80% of our LD-CTD group had an associated UIP pattern based on HRCT and/or surgical lung biopsy. In other centers, these patients might have been considered as having IPF. Vij *et al*.[17] reported that patients who did not fulfill the ACR criteria for any definite CTD should be labeled "autoimmune featured-ILD," and that this was associated with a poor survival similar to that among IPF patients. In another study, Corte *et al*.[18] noted that the presence of undifferentiated CTD (UCTD) in patients diagnosed with IIP was not associated with survival benefits compared with those without UCTD. As such, it is not yet clear whether the presence of positive autoantibodies in the absence of extrathoracic features of definite CTD among IIP patients (i.e., LD-CTD, autoimmune featured-ILD, or UCTD) represents a distinct entity from IIPs (and particularly IPF) with regard to treatment response, disease progression, and survival.

Idiopathic NSIP is distinguished from UIP by its histopathological pattern, favorable response to treatment, and better long-term prognosis. This led the ATS/ERS International Consensus Panel for Classification of ILD in 2002 to include idiopathic NSIP as a provisional form of an IIP.[9] The exact incidence and prevalence is unknown, but retrospective studies reevaluating cases previously diagnosed as IPF identified NSIP in the range of 14-36% of these cases.[19-22] For example, Kinder *et al*.[23] reported that 88% of their patients previously classified as having idiopathic NSIP met the criteria for UCTD. In another study, Corte *et al*.[18] noted that UCTD was present in 31% of their patients with idiopathic NSIP. Collectively, these studies illustrate that previous reports on IIP may have overestimated the true incidence of idiopathic NSIP. In the present study, NSIP represented 3.9% of the total IIP cases seen in our center, which is similar to the proportions in the Greek and Spanish registries (2.6% and 3.3%, respectively).[5,7] Interestingly, 10 NSIP patients in the present study met the proposed criteria for LD-CTD, emphasizing the importance of careful evaluation when identifying a potential cause of NSIP. However, future studies will be needed to determine whether LD-CTD associated with NSIP has prognostic implications compared with idiopathic NSIP.

The incidence and prevalence of sarcoidosis varies worldwide, either because of true ethnic and racial differences or because of differences in the epidemiological studies. Here, sarcoidosis was the third most frequently observed ILD. This stands in contrast to studies from other countries. For instance, sarcoidosis is the most prevalent ILD in Greece, Flanders and Germany, whereas it is the second most common disease after IPF in Spain and Italy.[2-5,7,8] The observed differences may reflect that large proportions of cases go undetected because many individuals with sarcoidosis are asymptomatic, and they are thus identified via incidental findings on chest radiographs.[24,25] Another potential explanation is that tuberculosis is endemic in the Middle East, and many sarcoidosis patients are presumptively treated with anti-tuberculosis drugs and are only referred if they do not respond to treatment. Differences in the sarcoid stage distribution may also explain the observed variations. Our sarcoid data are clearly skewed by the number of stage IV cases (50%), indicating that patients with severe complaints (i.e., in the more advanced stages of sarcoidosis) were more likely to be referred to our center.

In the present study, HP was the fourth most commonly observed ILD. The exact incidence and prevalence of this disease worldwide remains unknown, largely because it varies significantly by region and depends on environmental risk factors, including the antigen type, particle size and solubility, and the frequency and duration of exposure. Although women were predominantly affected in the present study, it is unclear whether this reflects selection bias, host predisposition, or the frequency of exposure to a relevant antigen. Notably, the source of exposure was identified in up to two-thirds of our HP patients, underscoring the importance of taking a meticulous patient history when ILD is encountered. Bird-related exposure was the most common form of HP in the present study, which is consistent with that in the Spanish registry.[5]

Substantial evidence shows that integrating a multidisciplinary approach into clinical practice can produce more precise diagnoses, guide physicians in requesting appropriate investigations, and help modify treatment regimens.[9,26,27] Nonetheless, clinicians may encounter cases of ILD where a firm diagnosis cannot be made despite extensive clinical, radiological, and/or pathological examination; such cases are considered "non-classifiable interstitial pneumonia."[9] In the present study, non-classifiable disease represented 1.8% of the total ILD cases, which is a lower proportion compared with the previous reports of 5.1-29.7% non-classifiable disease.[2-7] This difference may reflect between-country variations in the multidisciplinary approaches, differences in the applied diagnostic procedures, or

the fact that our data represent a single-center study while the other reports involved multiple centers.

The present study does have some limitations. It was based in a single academic center that devotes significant time and resources to the study of diffuse parenchymal lung disorders and, thus, our data may not represent the situation in other hospitals. The majority of the enrolled patients (67.5%) were diagnosed with IIPs and CTD-ILD, which reflects the limited number of transbronchial biopsies and BALs performed in the current study. Furthermore, although surgical lung biopsy was performed in only 22.7% of the patients, at a rate similar to those in the prior reports,[2,3,5,7,8] our data along with others are in keeping with current guidelines that state that when clinicians and radiologists are confident of the diagnosis, surgical lung biopsy can be avoided. Finally, the comprehensive serological profile obtained in our center when ILD was suspected may not represent the situation in other centers.

In conclusion, CTD-ILD was the most frequent type of ILD observed in our center, followed by IPF, sarcoidosis, and HP. The newly described entity, LD-CTD, was quite common among our patients, but future work is needed to determine whether these cases should be viewed differently from IIPs with regard to treatment and prognosis. Comparison of our findings with reports from other countries revealed both similarities and differences. We believe that a future prospective global multicenter epidemiological study is needed to establish the true incidence of various ILDs among different countries. This will improve our understanding of the natural history of the disease and will aid in identifying appropriate targets for therapeutic interventions.

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