Int. j. adv. multidisc. res. stud. 2025; 5(5):1021-1025

Received: 24-08-2025
Accepted: 04-10-2025

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Epidemiology of Interstitial Lung Disease in the Royal Hospital

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Abstract

Introduction: Interstitial lung disease (ILD) is a group of heterogenous disorders that induces inflammation and fibrosis of the lung parenchyma. It is associated with significant morbidity and mortality. The diagnosis is made by histopathology or radiology. There is limited study on the epidemiology of ILD especially in Oman.

Method: This is a clinical observational cross-sectional study conducted at the Royal Hospital. The study included all patients seen in the Medical Out-Patients clinics during the period January 2016 to December who were diagnosed to have interstitial lung disease based on radiological or histopathological findings. We included patients from the age of 13 years and above. We excluded patients without HRCT or biopsy findings. The data was analyzed using the EPI DATA program.

Results: Out of 239 patients included in the study with a mean age of 63.2 years, and 141 were female. Dyspnea and cough were the most predominant symptoms. Arthralgia was more prominent in females and smoking was more prevalent in males. There was no difference between males and females in the lung function test, however, males walked more distance on 6-minute walk test. Also, more males developed pulmonary hypertension and reduced ejection fraction compared to females. The high-resolution computed tomography (HRCT) findings of reticulation, ground glass opacities, and honeycombing were more significant in females. There was no difference between males and females in the treatment, but prednisolone and azathioprine were more used in females. The overall mortality over a mean of 6 years of follow-up was 14.6% among the interstitial lung disease patients.

Conclusion: ILD was more common in females than males. More males developed complications of ILD including pulmonary hypertension and reduced ejection fraction, however no difference in mortality between the two genders. Further prospective studies to examine the effect of management upon the morbidity and mortality of people with ILD are required to further delineate the prognosis of such patients.

Keywords: Epidemiology, Lung Disease, Oman

Introduction

Interstitial lung disease (ILD) is a term used to describe more than 200 different disorders that induce inflammation and fibrosis of the lung parenchyma [1]. It is associated with significant morbidity and mortality, especially among patients with Idiopathic pulmonary fibrosis (IPF) and connective tissue diseases (CTD) [2, 3]. Epidemiological studies on ILD are limited, incidence and prevalence vary worldwide [3, 4], however, recent data suggest increasing incidence likely due to readily available high resolution Computed tomography scans and improved understanding of ILD [5]. The pathophysiological process leading to ILD is not fully understood, however, evidence suggests multiple factors contributing to the disease process including infections, genetics, connective tissue disease, and environmental, and chemical exposure [6, 7]. Clinically patient presents with insidious shortness of breath, dry cough, and a history suggestive of predisposing factors [8]. The typical finding on examination is symmetrical fine crepitation and occasionally clubbing of the fingers. Pulmonary function tests might reveal a reduction in lung volume [9, 10]. In addition, it may lead to a reduction of the lung's diffusion and normal Forced expiratory volume in 1 second to forced expiratory volume [11]. The diagnosis is made based on clinical pictures, radiological findings, or histopathological findings [10, 12]. The treatment goal of ILD is to stop the ongoing inflammation and fibrosis hence corticosteroids, immunosuppressants, and anti-fibrotic agents may play a role in treatment [8, 13]. Long-term oxygen therapy is used as a bridge until the patient gets a lung transplant [14, 15]. There are no studies available to assess the disease prevalence,

burden, characteristics on the Omani population. This study is critical for policy makers to further improve the health system and provision of cost effectiveness management strategies of early detection and treatment of ILD. In addition, this study could be a steppingstone for further research on the disease.

Methodology

This clinical observational cross-sectional study was conducted by the researchers at the Royal Hospital, the largest tertiary center in the country where cases have been referred from all over the country. The data was collected prospectively via the hospital electronic health record system (AL-Shifa 3+). The data was retrieved after obtaining ethical approval from the Royal Hospital Ethical Review Committee. The study included all patients with ILD seen in the Medical Out-Patients clinics during the period 1st January 2016 to 31st December 2022 who were diagnosed to have interstitial lung disease based on radiological or histopathological findings We included patients from the age of 13 years and above. The exclusion criteria were patients who did not have either HRCT or lung biopsy. The data were transcribed initially by the IT department into an Excel spreadsheet and access was restricted only to parties involved in this study. During analysis, researchers used the mean and standard deviation (SD) or continuous data and numbers with percentages were used for dichotomous variable. The data was analyzed by researchers using SPSS program version 26.

Result

The total population of the study was 240, out of these 149 were females and 91 were males, with a mean (SD) of age for the population was 63.2 (14.1), with males being significantly older 65.6 (14.4), P value 0.02. The majority of the patient were Omanis (228) 95.0%, out of these 106 (44.3%) were from the Muscat region, and the rest were from other governates, However, there was no significant difference in the prevalence of ILD cases between the regions, P value 0.2. Males were significantly taller 164.3 (7.4) and heaver 75.4 (17.2), compared to females 152.4 (7.1), 70.6 (17.4), with P Values < 0.01 and 0.02 respectively.

Fig 1 shows the spectrum of interstitial lung disease (ILD) in the study population by gender. Idiopathic pulmonary fibrosis was the most prevalent type of ILD 79 (47.7%), followed by sarcoidosis 61 (25.5%), then nonspecific interstitial pneumonia 60 (24.9%), and the least prevalent was acute interstitial pneumonia and histiocytosis x (0.4%).

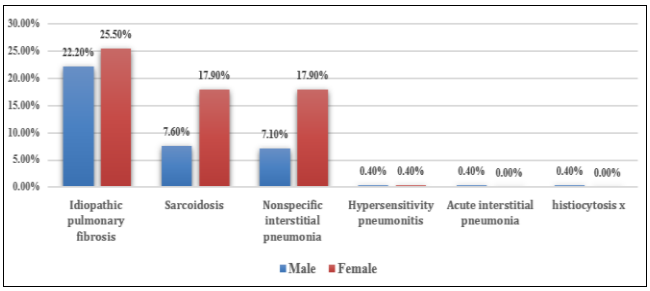

Fig 1: Spectrum of interstitial lung disease (ILD) in the study population by gender

Table 1 shows the clinical manifestations of the study population distributed by gender. Dyspnea and cough were the most common clinical presentation among our patients 65.5% and 54.8% consecutively with no significant difference among males and females, however, arthralgia presence was more significant in females at 15.8% P value < 0.01 and smoking was more prevalent in men at 14.6%, P value of < 0.01.

Table 1: Clinical manifestations, smoking and medication exposure of the study population distributed by gender

	Male, N= 91(%)	Female, N=149 (%)	Overall, N= 240 (%)	P. value
Dyspnea	58 (63.7%)	99 (66.4%)	157 (65.4%)	0.62
Cough	51 (56%)	80 (53.7%)	131 (54.6%)	0.09
Arthralgia	5 (5.6%)	33 (22.1%)	38 (15.8%)	<0.01
Rash	4 (5.4%)	8 (3.0%)	12 (5.0%)	0.7
Crackle	65 (71.4%)	101 (67.7%)	166 (69.2%)	0.6
Clubbing	16 (17.5%)	17 (7.1%)	33 (13.8%)	0.1
Smoking	31 (34.1%)	4 (2.7%)	35 (14.6%)	<0.01
Medication*	4 (4.4%)	13 (8.7%)	17 (7.1%)	0.2

*Medication includes Amiodarone, methotrexate, nitrofurantoin and chemotherapy.

Table 2 shows the comparison of study sample investigations distributed by gender. There was no difference in forced vital capacity (FVC) and diffusion capacity between males and females (P value 0.1 and 0.2 respectively). Males walked longer distances in the 6-minute walk test with an average distance 382.2 (102.7) compared to females 328.0 (106.1), P value <0.01. There was no significant difference in the 6-minute' walk test saturation between gender with the mean (SD) of oxygen saturation (SpO2) being 87.7 (12.0) for men and 90.0 (12.1) for females. Echocardiography showed more men having reduced ejection fraction with a mean (SD) of 49.1 (12.5) and higher pulmonary artery pressure with a mean (SD) of 42.7 (16.6). Erythrocyte sedimentation rate (ESR) was significantly higher among females 53.8 (36.9).

Table 2: Comparison of study sample investigations distributed by gender

	Male	Female	Overall	P-value
FVC	73.9±19.1	78.6±32.8	76.7±28.2	0.1
DLCO	59.0±26.3	60.2±54.6	59.7±24.0	0.4
6 min SpO2	87.7±12.0	90.0±12.1	89.1±12.0	0.8
6 min distance	382.2±102.7	328.0±106.1	347.6±107.7	< 0.01
EF%	49.1±12.5	55.6±7.7	53.0±10.4	<0.01
sPAP	42.7±16.6	38.5±11.5	40.2±13.9	0.04
ESR	53.8±36.9	65.5±35.4	59.7±24.0	0.02

FVC (Forced Vital Capacity), DLCO (diffusing capacity of the lungs for carbon monoxide), 6 min (6 minutes' walk test), EF% (ejection fraction), ESR (Erythrocyte sedimentation rate).

Table 3 shows the distribution of high-resolution CT (HRCT) findings by gender. The high-resolution CT showed reticulation, ground glass opacities, and honeycombing were significantly present in females, while traction bronchiectasis was not significantly different between gender.

Table 3: shows the distribution of high-resolution CT (HRCT) findings by gender

	Male	Female	Overall	P-value
Reticulation	55 (23.3%)	67 (28.3%)	122 (51.6%)	0.02
Honeycombing	55 (23.3%)	64 (27.1%)	119 (50.4%)	0.01
Ground glass	42 (17.8%)	89 (37.7%)	131 (55.5%)	0.03
Bronchiectasis	67 (28.3%)	100 (42.3%)	167 (70.7%)	0.3

Table 4 shows the comparison of treatment among study samples distributed by gender. Females received prednisolone, azathioprine, or a combination more than males and the difference was significant. Prednisolone was prescribed to 51.4% of the study population, 36.4%. Azathioprine was prescribed to 27.1%, out of these 21.7% were female. A 20% received a combination of both azathioprine and prednisolone out of this 15% were female.

Table 4: Comparison of treatment among study samples distributed by gender

Treatment	Male	Female	Overall	P-value
Prednisolone	36 (15.0%)	87 (36.4%)	123 (51.4%)	<0.01
Azathioprine	13 (5.4%)	52 (21.7%)	65 (27.1)	<0.01
Prednisolone+AZA	12(5.0%)	36 (15.0%)	48 (20.0%)	0.03
Pirfenidone	47 (19.6%)	68 (28.4%)	115 (48.2%)	0.3
NAC	32 (13.3%)	56 (23.5%)	88 (36.8%)	0.6
Pred+AZA+NAC	2 (0.9%)	4 (1.6%)	6 (2.5%)	0.8

The outcome of the disease in this population showed overall mortality of 14.6% with higher mortality among the male groups with 68.6% for males compared to 31.4% for females.

Discussion

The present study showed that two thirds of ILD patients were female and were younger in age and lighter in weight than males. Idiopathic pulmonary fibrosis was the most common type of ILD, and cough and dyspnea were the most common manifestations. Males walked longer distances in the 6-minute walk test but there was no difference in PFTs between genders. However, EF was worse for males than females and sPAP was worse for males. Females showed worse HRCT findings regarding reticulation, honeycombing and ground glass appearances. Also, females utilize more prednisolone and azathioprine than males' patients. However, the mortality was worse for males than females.

This study reported the overall prevalence of ILD to be higher in females compared to males, although the difference was insignificant. This finding is inconsistent with multiple studies that revealed ILD to be male predominant disease as evident in Coultas, D.B. *et al* [16] and Joung, K.I. *et al* [17], however, our finding was similar to other studies published in the region such as Saudi Arabia as in Alhamad, E. [18] and Jafri, S. *et al* [19] from Pakistan.

In the present study, patients were older with a mean (SD) of age 63.2 (14.1) compared to previously mentioned studies Alhamad, E. [18] and Jafri, S. *et al* [18]. A German study reported their patients with an almost 65 years old [20]. Previous studies reported that ILD is mainly to occur in those aged over 60 years of age [21, 22].

Among all subtypes of ILD UIP/IPF was the most prevalent, this support previous epidemiological study such Alhamad, E [18], while in other study done in Greece, Karakatsani, A. *et al* [23], and Belgium, Roelandt, M. *et al* [24] reported sarcoidosis to be the most common type of ILD followed by IPF with IPF being more predominance in males. The disparity in this result could be due to genetic, geographical, or environmental factors, further studies are required to establish correlation [25-27].

Dyspnea and cough were the most common clinical presentation of ILD with no difference between males and females, while arthralgia was more common in females, and this was due to more females having connective tissue disease. similar finding reported by Carvajalino, S. *et al* and Albrecht, K. *et al* [28]. Al Ahmed etal. and Araki etal. reported cough and dyspnea as the most common among their patients with ILD [18, 29]. Furthermore, In a systematic review, researchers found that dyspnea and cough were the most common [30].

Lung crepitation was present in 69.4% of the study population while Jafri, S., *et al*. concluded 73% of their population had crepitation. Clubbing in the other hand was only 13.8% among our patients compared to van Manen, M.J.G. *et al* with prevalence range 7-42% [31]. In addition, like our finding van Manen, M.J.G. *et al* reported Smoking to be significantly more common in males than females [31].

Pulmonary function tests including FVC and DLCO are independent markers of disease prognosis [32], In the present study, the overall population means of FVC was 76.7 (28.2) and of DLCO was 59.7 (24.0) that are similar with other studies like Park, J.H. *et al* [33]. *and Martinez, F.J et al. [9].* The difference in the means of FVC and DLCO between males and females wasn't significant. Males walked more distance compared to females in 6 minutes' walk test, however there was no difference in the oxygen saturation test [18, 34].

Echocardiography study showed that males had significantly reduced Ejection fraction than females with the former 49.1 (12.5) and 55.6 (7.7) for the latter, Koteci, A. *et al.* reported similar finding in patient with IPF. A cross section study done in India by Tyagi, R. *et al,* found the overall prevalence of pulmonary hypertension 28.9% and that female had a higher pulmonary artery pressure compared to male, however the difference was insignificant. While among our study population pulmonary artery pressure we found mean (SD) in males 42.7 (16.6) versus females 38.5 (11.5) and the difference was significant, however, this doesn't necessarily reflect that more males developed pulmonary hypertension secondary to ILD due to multiple reasons. Firstly, Echocardiography is not the best modality to assess the pulmonary pressure and secondly the raised pulmonary pressure could be secondary to heart disease.

The erythrocyte sedimentation rate was significantly higher in females 65.5 (35.4) than in males 53.8 (36.9). Similarly, Sun, X. *et al* showed ESR to be elevated more in females, but the difference wasn't significant [35]. This could be the result of underlying connective tissue disease, which is more common in females, rather than ILD [36, 37]. However, further studies are to assess the exact relationship between ESR and disease prognosis.

Bronchiectasis was the most common finding in HRCT followed by ground glass opacities in second reticulation in the third place and honeycombing in last. there is difference in our finding when compared to Sun, X. *et al*, who reported ground glass opacity were the most prevalent in patient with ANCA positive ILD, followed by reticulation, traction bronchiectasis and lastly honeycombing [35]. The reason for difference could be resulted from the overlap ILD with other

disease like bronchiectasis, infection, connective tissue disease pulmonary edema, or malignancy.

Clinicians prescribed Prednisolone for 123 participants of the study, followed by Pirfenidone 115, then N-acetylcysteine. More females were on prednisolone alone, in combination with azathioprine or azathioprine alone. A study in Germany by Marijic, P. *et al.* showed that more patients were on antifibrotic treatment namely pirfenidone/nintedanib, followed by corticosteroid, then N acetylcysteine and lastly immunosuppressant medication including azathioprine [38]. In addition van den Bosch *et al.* found that more patients were on corticosteroid as first line compared to azathioprine which is used as second line in non-IPF ILD [13]. The discrepancy in treatment modality could be result of different disease type among the studies, lack of consensuses on treatment.

Joung *et al.* reported overall mortality 8.7%from ILD in 2018, with mortality higher among males [17]. Similarly Jeganathan & Sathananthan reported mortality rate of 6.6% and that mortality was higher in males than females [39]. Overall mortality was higher among our patients and mortality was higher among males in our study; however, the cause of death was not investigated if it was directly related to ILD or other pathology.

Limitations

This is a retrospective study, as a result there could be a reporting bias. Also, it is a single center study, but although we included patients from the largest center in the country however the result can't be generalized to the whole Omani population.

Conclusion

We reported ILD to be more common in females than males, with males being significantly older than females however mean age of the overall population is within the typical range for patients with ILD. Out of the ILD subtype, UIP/IPF was the most common, followed by sarcoidosis, then NSIP with AIP and histiocytosis x were the least common. Physiological studies though used to predict prognosis; however, they were unreliable and yielded discrepant results when comparing genders. Radiological findings of reticulation, honeycombing, and ground glass opacity were more common in females. The mortality was higher among males compared to females. Studies on ILD are scarce, and more studies are needed on ILD to investigate different aspects of the disease including but not limited to prognosis predictors, characteristic differences between gender and treatment modality, and outcome.

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