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Article

Clinical and Functional Characteristics of Interstitial Lung Disease in Algeria: A Single-Center Prospective Study

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Abstract: Introduction: There are a limited number of epidemiological studies describing the global burden of chronic diffuse interstitial lung diseases (ILD) and their subtypes' heterogeneity worldwide. Our main is to characterize new-onset ILDs in Algeria and compare our results with data from other populations. Materials and Methods: Newly diagnosed ILDs were prospectively collected in a single-center observational cohort study including all patients diagnosed as ILDs in the pulmonology, phthisiology, and allergology departments between 2015 and 2019. Detailed anamnestic and clinical data were collected at the time of diagnosis. The results of high-resolution computed tomography (HRCT), serological tests, biology data, and respiratory functional exploration were systematically performed and collected. Results: A total of 455 cases were included. The mean age was 59.4 ± 13.2 years. There was a slight predominance of females (300; 65.9%). The most common disease was ILD secondary to connective tissue disease (CTD) or ILD-CTD (48.1%), followed by idiopathic interstitial pneumonias (IIPs) (23.5%), sarcoidosis (16.9%), interstitial pneumonia with autoimmune features (IPAF) (12.1%), and hypersensitivity pneumonitis (HP) (2.4%). Idiopathic pulmonary fibrosis (IPF) was present in 8.6% and unclassifiable ILD in 4.6% of the total ILD cases. Conclusions: ILD-CTD, IIP, and sarcoidosis were the most frequently observed ILDs in this Algerian population. Similarities and many differences were found compared to previous data from other countries.

Keywords: epidemiology; interstitial lung disease; connective tissue disease; idiopathic pulmonary fibrosis; sarcoidosis; hypersensitivity pneumonitis

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1. Introduction

Interstitial lung disease (ILD) is a heterogeneous group of rare diseases with different underlying pathophysiology. Most interstitial lung diseases are characterized by inflammation or fibrosis of the interstitial space [1] and damage to the lung parenchyma through different types of inflammation and fibrosis, resulting in a large, heterogeneous group of interstitial lung diseases. The diagnosis of ILD is based on a set of clinical, radiological, and pathological data. ILDs can be caused by connective tissue diseases and exogenous factors such as inhalation of organic or inorganic dust of environmental, domestic, or occupational origin [1–3]. However, a genetic predisposition has been regularly evoked in the genesis of ILD [4], and a large group remains idiopathic. The main consequence of ILD is impaired gas exchange, causing shortness of breath, reduced exercise tolerance, and impaired quality of life, and can be life threatening. Although significant progress has been made in understanding the mechanisms and causes of ILDs, their diagnosis requires expertise in the management of ILDs and multidisciplinary collaboration between a pulmonologist, radiologist, rheumatologist, and pathologist [1]. Few studies focus on the etiologies and risk factors of ILDs, particularly in Africa, and the existing studies show great

disparities in the incidence and prevalence of the different causes of ILD between countries and sometimes within the same country [2,5,6]. It remains difficult to conclude whether this variation reflects a real difference in ILD frequency between geographical areas or whether it is related to different methodological practices, although in 2013 the American Thoracic Society (ATS) and the European Respiratory Society (ERS) provided a consensus [1] on the standardization of terminology applied to idiopathic interstitial pneumonias (IIP), updated in 2022 [5,7]. In the present study, our main goal is to characterize a new-onset ILD cohort, prospectively collected and newly diagnosed in a single pulmonology center over 5 years, and compare our results with data from other populations.

2. Materials and Methods

2.1. Study Design and Patients

This was a single-center, prospective, observational cohort study including all incident patients who were newly diagnosed with ILDs and who paid a first visit to the Department of Pulmonology, Phthisiology, and Allergology (Rouiba Hospital, Algiers, Algeria) between January 2015 and December 2019.

2.2. Inclusion Criteria

Only patients aged 18 years or older with ILD based on High-resolution computed tomography (HRCT) scans were included. They were recruited consecutively among those patients visiting the outpatient specialized lung and autoimmunity consultation of the aforementioned Pulmonology Department.

2.3. Exclusion Criteria

The study did not include patients with underlying malignancies, a history of pulmonary surgery, or pulmonary tuberculosis with destruction/fibrosis of the lung parenchyma.

2.4. Positive Diagnosis of ILD

The diagnosis of ILD was viaHRCT, according to the Fleischner criteria and the latest ATS/ERS/JRS/ALAT guidelines [5,8]. A multidisciplinary approach involving pulmonologists and a radiologist was implemented for all patients with ILD, a rheumatologist was associated in cases of suspicion of autoimmune disease, and this was before a definitive diagnosis was rendered [9]. The etiology of ILD was determined when a diagnosis could be assigned according to the guidelines of the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT) diagnostic criteria for IPF [5,10,11]. The ATS/ERS consensus classification was used to establish diagnosis of IIP [3,12,13] when the diagnosis of sarcoidosis was retained according to the ATS, ERS, and World Association of Sarcoidosis and Other Granulomatosis criteria for the diagnosis of sarcoidosis [14], and all cases of sarcoidosis were histologically proven. The diagnosis of connective tissue disease (CTD) was established according to the criteria of the American College of Rheumatology (ACR) [15–20]. Patients with ILD for whom rheumatologists also confirmed the diagnosis of one type of CTD were considered to have the diagnosis of confirmed ILD-CTD in this study. A diagnosis of interstitial pneumonia with autoimmune features (IPAF) was retained when ILDs were associated with insufficient clinical and/or serological characteristics to meet the classification criteria for a specific autoimmune disease [21].

A guideline panel considered the benefit of MDD to be decisive when the HRCT pattern is probable for UIP, indeterminate for UIP, or an alternative diagnosis, or when there exist discordant clinical, radiologic, and/or histologic data.

2.5. Collected Data

Clinical data were collected using a non-validated standard French medical questionnaire. The latter is used in the daily activity of the outpatient consultation service. Sex and some anthropometric data were determined. The history of the smoker or ex-smoker

was researched and noted as well as the notion of past or current exposure to biomass smoke [22] and patients whose ILD was induced by a drug or occupational exposure. The following characteristics of ILD were noted in the patient's medical record: Frequent comorbidities such as high blood pressure, diabetes mellitus, heart disease, renal failure, respiratory and extra-respiratory symptoms (cough, dyspnea, Raynaud's phenomenon, morning stiffness, etc.). The duration of respiratory and extra-respiratory symptoms (in months) before the diagnosis of ILD was specified.

Biological data were determined all patients underwent serologic tests for autoantibodies for the following conditions at the time of diagnosis rheumatoid factor (RF, IU/mL), anti-nuclear antibody (ANA, titer), including anti-double-stranded DNA, anti-Sm, anti-nRNP, anti-Ro (SSA), anti-La (SSB), anti-M2, anti-PM/Scl, anti-Jo-1, anti-PL7, anti-PL12, anti-Scl-70, antinucleosome, anti-CENP-B, anti-Rib P-protein, anti-histones, and anti-CCP were measured. All the patients underwent aminor salivary gland biopsy (MSGB) [23], and experienced pathologists reviewed the samples to confirm the pSS diagnosis. A positive result of MSGB was defined by $\geq$1 focus of lymphocytes/mm^3. Schirmer's test (ST) was performed by experienced specialists, and the test was considered positive when it was $\leq$5 mm per 5 min [24]. Bronchial endoscopy with spur biopsies and Bronchoalveolar Lavage (BAL) was systematically performed in cases of suspected sarcoidosis, with an extension of the indications to other suspected diagnoses such as PHS, DIP, RB-ILD, etc.

Lung function data (LFD) were measured according to the international recommendations for spirometry and plethysmography [25–28]. LFD were expressed in three ways: (i) absolute values, (ii)percentages of predicted values from the global lung initiative norms for spirometry and static lung volumes [28–30], and (iii) z-scores [28,29,31]. Any LFD z-score below the lower limit of normal (LLN = -1.645) or above the upper limit of normal (ULN = +1.645) was considered abnormal [32].

The following definitions of ventilatory impairments were applied [32–35]:

Obstructive ventilatory impairment (OVI): expiratory volume in one second/forced vital capacity (FEV1/FVC) z-score < -1.645;

Small airways OVI: FEV1/FVC z-score > -1.64, and FVC z-score > -1.64 and MMEF z-score < -1.64;

Restrictive ventilatory impairment (RVI): total lung capacity (TLC)z-score < -1.645;

Mixed ventilatory impairment (MVI): FEV1/FVC z-score < -1.645 and TLC z-score < -1.645;

Non-specific ventilatory impairment (NSVI): FVC z-score < -1.645 and z-score FEV1 < -1.645 and FEV1/FVC z-score $\geq$ 1.645 and TLC z-score $\geq$ 1.645 [9,36];

Lung-hyperinflation: Residual Volume (RV) z-score > 1.645 [9,33];

The following three-level system assessing the severity of lung function impairments (i.e.; OVI and RVI) using FEV1 z-score values was used [34]: (i) mild: z-score between -1.65 and -2.50; (ii) moderate: z-score between -2.50 and -4.00; and (iii) severe: z-score < -4.00.

A previous study detailed the clinical, biological, immunological, radiological, and functional data collection methods [9].

2.6. Statistical Analysis

Descriptive analysis including frequencies and mean, a percentage, and SD for continuous variables were calculated; statistical calculations were performed using statistical software (Statistica, version 10) with a significant threshold of $p < 0.05$.

3. Results

3.1. Registry Population

The study population included 455 consecutive ILD patients. The mean age of the participants was 59.4 $\pm$ 13.2 years. There was a slight female predominance (300; 65.9%).

The mean age for men was 61.8 $\pm$ 14.7 years, and that for women was 58.2 $\pm$ 12.3 years. The distribution of ILD in the cohort of this study is presented in Table 1. All diagnoses were made after a multidisciplinary discussion (MDD). The DDM included a pulmonologist

and a radiologist at all times and a rheumatologist when we found ourselves faced with clinical, immunological, or CT signs suspected of being ILD-CTD. ILD-CTD (48.1%) and IIPs (23.5%) were the most common cases, followed by sarcoidosis (16.9%). The ILD-CTD patients had an underlying diagnosis of rheumatoid arthritis (n = 72), Sjogren syndrome (n = 70), systemic lupus erythematous (n = 26), scleroderma (n = 25), mixed CTD (n = 23), polymyositis/dermatomyositis (n = 35), CTD overlap (n = 40), and CTD-sarcoidosis overlap (n = 17).

Table 1. Distribution of interstitial lung diseases.

	Incident Cases
Total number	455
Idiopathic interstitial pneumonias	107 (23.5)
IPF	39 (8.6)
iNSIP	34 (7.5)
iCOP	4 (0.9)
RB-ILD	7 (1.5)
DIP	2 (0.4)
Histiocytosis	1 (0.2)
Unclassified ILD	20 (4.4)
Connective tissue diseases	219 (48.1)
RA	72 (15.8)
SSp	70 (15.4)
SLE	26 (5.7)
Scl	25 (5.5)
MCTD	23 (5.1)
PM/DPM	**35 (7.7)**
CTD overlap	40 (8.8)
CTD-Sarcoidosis overlap	17 (3.7)
IPAF	55 (12.1)
Sarcoidosis	77 (16.9)
Hypersensitivity pneumonitis	11 (2.4)
Others	
Drug induced ILD	3 (0.7)

ILD = interstitial lung disease, RA = rheumatoid arthritis pSS = primary Sjögren's syndrome, SLE = systemic lupus erythematosus, Scl = scleroderma, CTD: connective tissue disease, PM/DPM = polymyositis/dermatomyositis, MCTD: mixed CTD, IPF = idiopathic pulmonary fibrosis, NSIP = non-specific interstitial pneumonia, COP = cryptogenic organizing pneumonia, HP = hypersensitivity pneumonitis, DIP = desquamative interstitial pneumonia, LIP = lymphocytic interstitial pneumonia, UIP = usual interstitial pneumonia, IPAF = interstitial pneumonia with autoimmune features, i = idiopathic.

3.2. Characteristics of Patients with Most Common Specific ILDs

Among the 219 ILD-CTD patients (48.1%), 48 (10.5%) had HRCT patterns of usual interstitial pneumonia (UIP) and 14 (31.2%) had HRCT patterns of nonspecific interstitial pneumonia (NSIP) (Table 1).

Among all the ILDs, only IPF was distinguished by a male predominance at 56.4%, a higher average age of 66.8 years, and a much more pronounced exposure to tobacco (41.7%) (Table 2).

Table 2. Comparison of clinical and physiological characteristics at diagnosis among patients diagnosed with the most frequent types of ILD.

Characteristic	Sarcoidosis (*n* = 77)	ILD-CTD (*n* = 219)	HP (*n* = 11)	IIP (*n* = 107)		IPAF (*n* = 55)	All Subjects (*n* = 455)
				IIP (*n* = 107)	IPF (*n* = 39)		
Age, y, mean (SD)	49.6 ± 10.7	60.4 ± 12.6	59.8 ± 9.5	61.8 ± 13.5	66.8 ± 11.0	62.0 ± 13.2	59.4 ± 13.2
Male sex, n (%)	20 (26.0)	63 (28.8)	4 (36.4)	47 (43.9)	22 (56.4)	21 (38.2)	155 (34.1)
BMI (kg/m^2) (SD)	27.6 ± 5.4	28.2 ± 6.2	30.2 ± 6.0	28.7 ± 5.7	26.8 ± 4.8	29.0 ± 6.3	28.2 ± 6.0
Smokers, n (%)	12 (15.8)	45 (20.6)	3 (27.2)	29 (28.7)	15 (41.7)	16 (29.6)	104 (23.3)
Biomass smoke exposure	27 (42.9)	96 (62.3)	5 (50.0)	36 (61.0)	17 (70.1)	22 (66.7)	180 (59.2)
Duration of respiratory signs before ILD diagnosis (month)	72.4 ± 102.7	106.3 ± 133.1	67.4 ± 91.6	102.0 ± 133.4	86.8 ± 100.6	94.7 ± 122.2	96.2 ± 126.2
Duration of signs before ILD diagnosis:extra-respiratory signs (month)	54.6 ± 89.4	94.1 ± 119.5	49.4 ± 52.1	57.1 ± 82.1	65.9 ± 82.9	96.5 ± 112.9	78.1 ± 105.7
Diabetes mellitus	10 (13.0)	56 (25.8)	2 (18.2)	22 (20.6)	11 (28.2)	10 (18.2)	99 (21.9)
Arterialhypertension	10 (13.0)	59 (27.1)	5 (45.5)	26 (24.3)	10 (25.6)	22 (40.0)	121 (26.7)
Heart diseases	2 (02.6)	19 (08.7)	3 (27.3)	9 (08.4)	3 (07.7)	9 (16.4)	42 (09.6)
Thyroid pathology	12 (15.6)	33 (15.2)	1 (9.1)	12 (12.1)	4 (10.3)	9 (16.4)	63 (13.9)
Renal failure	4 (05.2)	5 (02.3)	0	4 (03.7)	0	0	12 (02.6)
Prior TB, n (%)	9 (11.7)	14 (06.4)	1 (9.1)	7 (06.5)	1 (02.6)	4 (07.3)	33 (07.3)
Symptoms and physical findings							
Dyspnea	62 (80.5)	193 (88.1)	11 (100)	90 (83.2)	33 (89.2)	49 (89.1)	391 (85.9)
Cough	58 (75.3)	193 (88.1)	9 (81.8)	94 (88.7)	30 (83.3)	46 (83.6)	387 (85.2)
Fatigue	53 (69.7)	171 (82.2)	7 (70.0)	74 (79.4)	25 (75.8)	39 (76.5)	331 (78.3)
Raynaud's phenomenon	28 (36.8)	74 (35.6)	4 (40.0)	31 (34.1)	9 (28.1)	27 (51.9)	155 (36.6)
Morning stiffness	46 (60.5)	161 (77.8)	6 (60.0)	55 (61.1)	18 (58.1)	41 (78.9)	295 (70.1)
Clubbing	16 (21.1)	53 (25.4)	3 (30.0)	31 (33.3)	18 (54.6)	13 (25.5)	110 (25.9)

IPF = idiopathic pulmonary fibrosis, iNSIP = idiopathic non-specific interstitial pneumonia, COP = cryptogenic organizing pneumonia, HP = hypersensitivity pneumonitis, DIP = desquamative interstitial pneumonia, LIP = lymphocytic interstitial pneumonia, CTD = connective tissue disease, UIP = usual interstitial pneumonia, IPAF = interstitial pneumonia with autoimmune features, TB = tuberculosis, BMI = body mass index (kg/m^2). Quantitative and categorical data were expressed as mean ± standard deviation and number (%), respectively. Note: missing data: Smokers (9), Biomass smoke exposure (151), Duration of Respiratory signs before ILD diagnosis (22), Duration of signs before ILD diagnosis: Extra-respiratory signs (32), Diabetes mellitus (2), Arterial hypertension (1), Heart diseases (1), Thyroid pathology (1). Renal failure (1) Prior TB (1), Cough(1), Fatigue (32) Raynaud's phenomenon (32), Morning stiffness (34), Clubbing (30).

Patients with sarcoidosis, CTD, and hypersensitivity pneumonitis (HP) were younger, more often female, and often non-smokers compared to the group of patients with idiopathic pulmonary fibrosis (IPF) (Tables 2 and 3).

Table 3. PFT Abnormality.

Characteristic	Sarcoidosis (*n* = 77)	ILD-CTD (*n* = 219)	HP (*n* = 11)	IIP (*n* = 107)		IPAF (*n* = 55)	All Subjects (*n* = 455)
				IIP (*n* = 107)	IPF (*n* = 39)		
OVI	11 (14.3)	31 (14.2)	1 (9.1)	19 (17.8)	4 (10.3)	13 (16.4)	68 (15.0)
RVI	32 (41.6)	75 (34.2)	6 (54.5)	49 (45.8)	28 (71.8)	24 (43.6)	177 (38.9)
MVI	5 (6.5)	6 (2.7)	0	3 (2.8)	1 (2.6)	2 (3.6)	14 (3.1)
NSVI	6 (7.8)	22 (10.0)	0	8 (7.5)	0	4 (7.3)	40 (8.8)
Lunghyperinflation	8 (10.4)	44 (20,1)	2 (18.2)	28 (26.2)	3 (7.7)	13 (23.6)	95 (20.9)
Small airway OVI	7 (9.1)	27 (12,3)	0	11 (10.3)	0	5 (9.1)	48 (10.6)
Normal	29 (37.7)	81 (37,0)	3 (27.3)	23 (21.5)	6 (15.4)	13 (23.6)	144 (31.7)

Table 3. *Cont.*

Characteristic		Sarcoidosis (n = 77)	ILD-CTD (n = 219)	HP (n = 11)	IIP (n = 107)		IPAF (n = 55)	All Subjects (n = 455)
					IIP (n = 107)	IPF (n = 39)		
Measurements (n = 455)								
Outcome	Unit/Category							
	L	2.74 ± 1.10 *	2.38 ± 0.88	2.41± 0.89	2.37 ± 0.91	2.11 ± 0.93 *	2.40 ± 1.05	2.45 ± 0.95
	%	76.9 ± 21.6	75.4 ± 21.1	72.0 ± 26.8	72.2 ± 22.5	64.2 ± 23.5 *	73.4 ± 24.2	74.9 ± 21.8
	z-score	−1.748 ± 1.684	−1.719 ± 1.510	−1.994 ± 2.005	−1.842 ± 1.500	−2.185 ± 1.481	−1.799 ± 1.667	−1.744 ± 1.543
FEV1	L	2.13 ± 0.86 *	1.85 ± 0.73	1.90 ± 0.65	70.2 ± 21.4	1.75 ± 0.69	1.81 ± 0.81	1.89 ± 0.75
	%	74.5 ± 22.4	74.2 ± 23.7	72.5 ± 25.4	1.81 ± 0.69	68.8 ± 22.2	71.2 ± 25.2	73.3 ± 23.1
	z-score	−1.821 ± 1.594	−1.691 ± 1.557	−1.805 ± 1.798	−1.914 ± 1.358	−1.898 ± 1.318	−1.812 ± 1.622	−1.753 ± 1.522
MMEF	L	2.80 ± 1.06	2.58 ± 1.12	2.73 ± 1.00	2.53 ± 1.20	3.04 ± 1.29 *	2.50 ± 1.05	2.61 ± 1.13
	%	101.3 ± 36.3 *	115.1 ± 48.4	114.3 ± 38.0	112.9 ± 54.3	142.4 ± 60.3 *	113.7 ± 47.5	113.0 ± 48.2
	z-score	−0.073 ± 1.141	0.200 ± 1.351	0.276 ± 1.041	0.116 ± 1.400	0.902 ± 1.144 *	0.154 ± 1.330	0.153 ± 1.336
FEV1/FVC	AV	78.2 ± 09.5	77.8 ± 11.4	80.3 ± 8.8	76.1 ± 12.9	81.3 ±13.7 *	76.6 ±10.5	77.3 ± 11.4
	%	96.7 ± 11.3	97.7 ± 14.2	101.6 ± 11.0	95.6 ± 18.9	101.4 ± 24.0	97.1 ± 13.5	97.1 ± 15.0
	z-score	−0.319 ± 1.302	−0.148 ± 1.427	0.248 ± 1.174	−0.283 ± 1.635	0.550 ± 1.666 *	−0.266 ± 1.351	−0.201 ± 1.448
TLC	L	4.46 ± 1.38	4.48 ± 1.45	4.35 ± 1.73	4.50 ± 1.38	3.79 ± 0.99 *	4.58 ±1.61	4.52 ± 1.43
	%	84.56 ± 19.36	88.53 ± 23.99	81.6 ± 29.9	85.3 ± 24.8	69.8 ± 19.4 *	87.6 ± 22.6	87.4 ± 23.2
	z-score	−1.294 ± 1.561	−0.961 ± 1.890	−1.720 ± 2.594	−1.275 ± 2.006	−2.527± 1.600 *	−1.113 ± 1.927	−1.088 ± 1.884
FRC	L	2.75 ± 0.79 *	2.95 ± 1.04	3.03± 1.19	3.08 ± 1.18	2.62 ± 1.09 *	3.01 ± 1.10	2.98 ± 1.05
	%	104.8 ± 22.3	113.0 ± 35.7	110.1 ± 40.7	112.9 ± 43.3	91.9 ± 41.9 *	110.6 ± 31.3	111.9 ± 35.4
	z-score	0.230 ± 0.895	0.515 ± 1.434	0.280 ± 1.858	0.396 ± 1.786	−0.621 ± 1.700 *	0.356 ± 1.417	0.435 ± 1.469
RV	L	1.73 ± 0.50 *	2.09 ± 0.94	1.99 ± 1.11	2.16 ± 1.01	1.76 ± 0.74 *	2.19 ± 0.89	2.08 ± 0.91
	%	117.5 ± 29.5	127.0 ± 54.6	113.5 ± 48.4	126.8 ± 60.0	90.8 ± 34.6 *	127.7 ± 49.5	126.0 ± 52.1
	z-score	0.559 ± 0.854	0.756 ± 1.541	0.323 ± 1.672	0.681 ± 1.737	−0.450 ± 1.197 *	0.742 ± 1.495	0.713 ± 1.505
RV/TLC	AV	39.8 ± 8.3 *	46.7 ± 12.1	45.2 ± 11.4	47.6 ± 12.3	46.6 ± 13.3 *	48.1 ± 11.3	46.1 ± 11.9
	%	140.4 ± 32.2	142.2 ± 41.3	141.1 ± 34.8	147.6 ± 40.2	132.9 ± 36.1	146.0 ± 38.0	143.8 ± 38.8
	z-score	1.731 ± 1.099	1.885 ± 1.610	1.853 ± 1.564	2.089 ± 1.703	1.542 ± 1.672	2.023 ± 1.546	1.926 ± 1.554

OVI: Obstructive ventilatory impairment. RVI: restrictive ventilatory impairment. MVI: mixed ventilatory impairment. NSVI: non-specific ventilatory impairment. FEV1: forced expiratory volume in one second. FRC: functional residual capacity. FVC: forced vital capacity. MMEF: maximal-mid expiratory flow. RV: residual volume. TLC: total lung capacity. %: percent of predicted values. Data were mean ± SD. AV: absolute value and quantitative and categorical data were mean ± SD and number (%), respectively. * p-value < 0.05: 2sided Chi-square test (comparison of categorical data between the 2 groups); Student's t test (comparison of quantitative data between the 2 groups).

Respiratory symptoms, in particular, dyspnea and cough, were the most common symptoms in all groups. Clubbing was observed less frequently in patients with sarcoidosis, CTD, IPAF, and HP than in the IPF group.

Among patients with IPAF, 8 (14.6%) had a pattern of usual interstitial pneumonia (UIP) and 35 (63.6%) had a pattern of nonspecific interstitial pneumonia (NSIP). The clinical and physiological characteristics of patients with the most common causes of ILD are shown in Table 2. For all patients, antinuclear antibody was the most common positive autoantibody (n = 20; 36.4%), followed in decreasing order by a rheumatoid factor (n = 10; 18.5%), anti-Sjogren's syndrome A (anti-Ro/SSA) (n = 2; 3.6%), anti-double-stranded DNA (n = 12, 21.8%), anti-ribosome (n = 1; 1.9%), anti-nucleosome (n = 2, 3.6%), anti-PCNA (n = 1; 1.9%), antiMi2 (n = 2; 3.6%),anti-AMA-M2 (n = 2; 3.6%), anti-centromere (n = 1; 1.9%), and anti-histone (n =5; 9.1%). A search for precipitins in the serum was conducted if there was suspicion of HP before the notion of exposure or an evocative HRCT image, and all cases had positive avian precipitins. In the sarcoidosis group, it is interesting to note that 36% of patients presented with Raynauds, 60% with morning stiffness, and 21% with clubbing (Table 2), and 17 patients had CTD-sarcoidosis overlap (Table 1).

All patients underwent plethysmography, and the functional profile of patients with ILD is presented in Table 3. The restrictive ventilatory defect was the common ventilatory disorder in all ILD groups, found in 38.9%, and predominant in the IPF in 71.8%. Obstructive ventilatory disorder was found in 15% of cases in our study. Compared with the ILD-CTD group, the IPF group included higher percentages of patients with RVI (71.8 vs. 34.2 respectively), low value of FVC (2.11; 64.2% vs. 2.38; 75.4%, respectively), low value of TLC (3.79; 69.8% vs. 4.48; 88.5%, respectively), low RV (1.76; 90.8% vs. 2.09; 127% respectively).

4. Discussion

The present study is the largest prospective single-center cohort to describe new-onset ILD with diagnosis (n = 455) validated by pulmonologists, radiologist teams of ILD experts, and rheumatologists if necessary and to describe ILD in Algerian patients. The most common diagnosis was ILD-CTD (48.1%), followed in decreasing order by IIPs (23.5%) and sarcoidosis (16.9%), according to the classification of IIPs [6,7,37,38]. However, IPF (8.6%) is the most frequent among the group of IIPs, (Table 1).

The mean duration of respiratory symptoms is higher than that of extra-respiratory symptoms in the ILD-CTD group 72.4 vs. 54.6 months. Indeed, the appearance of the respiratory expression in the first place for the ILD-CTD is explained by the respiratory character of our series, which moreover was often at the origin of consultation in pulmonology, or by the predominance of respiratory symptoms. These results show that respiratory symptoms may be revealing or predominant in ILD-CTD, and ILD is sometimes the initial clinical manifestation of CTD [39–41]. However, IPF is distinguished by a male predominance at 56.4%, a higher average age of 66.8 years, and a much more pronounced exposure to tobacco (41.7%) (Table 1), In accordance with international data [42–45], our results are compared to some studies that Salisbury, M.L. et al. reported in a retrospective study that among 657 patients with IPF who were identified at three tertiary referral centers, 70% were men, and the mean age was 62.9 years [44].

Epidemiological data regarding ILD are varied, probably due in part to differences in study design and patient selection. Like some studies in other countries [6,37,46], our study concerns patients received and diagnosed in the center for respiratory diseases. Differences in inclusion and exclusion criteria and the manner of their application constitute an obstacle to a direct comparison between countries. Comparisons of the distribution of ILDs in our study and those of other countries have found similarities and differences, as well represented in Table 4. It should be noted that in all registries, the most frequent forms of ILD were IPF and sarcoidosis.

Previous prospective ILD registries have found differences between countries; which may be real or due to a selection bias [47].The relatively low frequency of IPF (8.6%) in our study is close to that of the one conducted in India (13.7%) and France (11.6%) [48,49]. The low relative frequency of IPF in the French study was, according to the authors, explained by the young demographic component of the population of the department of Seine-Saint-Denis [49], and it should be commented that a low percentage of IPF and IIPs could be due to underdiagnosis and under recognition of these diseases in primary care, with patients never being referred to the pulmonology department, while CTDs could be more easily recognized due to extra-respiratory complaints.

In addition, international recommendations on IIP [1,5,10] and recent scientific literature work for the careful search for signs of CTD by pulmonologists and suggest systematically exploring autoimmunity in patients with ILD [50].

These data represent the results of a single center, while certain registers relating to multicenter studies [6,37,45,47,49,51–59] have showed the existence of differences in the plans, number, and duration of studies, however, some extrapolations can still be made. Indeed, IPF and sarcoidosis were the most common diseases in some registries [37,47,49,52–54,60,61], which differs from our results. The reason for this difference raises important questions, which can be supported by the following explanations:

The first IPAF pattern proposed by Fischer et al. [21] was suggested for ILD with an underlying autoimmune process that remains insufficient to meet established criteria. However, if we associate IPAF with ILD-CTD, we obtain a total of 60.2% among ILD, which can be explained by the systematic practice of immunological assessment, minor salivary gland biopsy, and Schirmer's test. Note that performing salivary gland biopsies improved the diagnosis of IPAF [62]. Yang Hu reported similar results in a retrospective study, which found that patients with ILD-CTD represented 67.1% of the total number of patients with ILD, and 32% did not receive an accurate diagnosis at the initial hospital admission [63].

Secondly, HRCT was practiced for all patients included in our study, which was higher compared to the other studies (91.9% in Spain, 87.4% in Greece, 74.4% in Italy, 41% in Germany, and 97% in Saudi Arabia) [6,37,47,49,52,60].

Third, prevalence and incidence rates can be influenced by geographical origin observed in the North African population concerning sarcoidosis and ILDs-CTDs [49], and the authors suggest performing new prospective multi centre studies, necessary to clarify in more detail the epidemiology of ILD-CTD among the North African population.

To the best of our knowledge, a single previous study has characterized ILD in Algeria; it was a prospective monocenter study with 110 patients that found sarcoidosis to be the most common (33.6%) followed by ILD-CTD (25.4%) and IPF (5.4%) [64].

On the other hand, other registries report frequencies that vary from 27 to 39%, probably due to the inclusion of other IIPs [37,53,65–68].However, we recorded the highest rate of ILD-CTD at around 48.1%, much higher than the results found in a study in Saudi Arabia at 34.8% [60]; this can be explained by the purely respiratory nature of our series. However, variability in the global prevalence of ILD has been clearly specified [69]. These disparities may reflect methodological differences and demographic or environmental specificities, although the frequency of the majority of ILDs is influenced by age, sex, ethnicity, and tobacco exposure [70], and ILD-CTD often do not receive an accurate diagnosis on initial exploration due to negative results for autoantibodies and the absence of suggestive extrapulmonary symptoms. Thus, patients with ILD, extrapulmonary symptoms, and autoantibodies should be routinely screened at follow-up [63]. Our findings suggest that in Algeria, sarcoidosis as well as IPF has a relatively low incidence among all ILDs, although, based on the population seen only in a pulmonological environment, however, a selection bias cannot be excluded.

Among the enrolled IIPs, IPF (36.4%) was the most frequent pathological variant. This is relatively similar to the data from some registries (18.9–38.6%) [6,37,47,51–53,55–58]. Importantly, 14.6% of the IPAF entity has a UIP pattern based on HRCT. In a different interpretation, these patients could have been considered to have IPF [71].

In our study, the frequency of iNSIP 34 was 7.5% among IIPs, which is close to the data from the Greek (2.6%) and Spanish (3.3%) [6,37] registers. The incidence and prevalence of iNSIP remain difficult to specify, however, retrospective studies estimate this prevalence in the range of 14 to 36% of these cases [72]. For example, Kinder et al. [73] reported that 88% of their patients classified as NSIP idiopathic later developed criteria for undifferentiated connective tissue disease UCTD. In another study, Corte et al. [74] noted that UCTD was reported in 31% of their patients with idiopathic NSIP. Overall, these studies show that previous reports of IIP have likely overestimated the true incidence of idiopathic NSIP. Sarcoidosis is the most common ILD in Greece, but also in Flanders and Germany; however, it is second, after IPF, in Spain and Italy [6,37,51,52]. The differences may correspond to a large proportion of undetected cases mainly in people with asymptomatic sarcoidosis on the one hand or identified and treated in peripheral health centers on the other hand. In our study, we have found the most frequent antecedent of tuberculosis among sarcoidosis patients is 11.7%, but a potential explanation is that TB is endemic in North Africa, and many sarcoidosis patients are diagnosed and treated as suspected TB patients and only reconsidered after treatment failure, similar results are found in an Indian study [48].

In the present study, HP was weakly represented. The incidence and prevalence of this disease throughout the world remains highly variable and differs considerably from one region to another depending on environmental risk factors, in particular the nature of the antigens, the particles, as well as their size and their solubility, in addition to the frequency and duration of exposure. Indeed, bird-related exposure is the most common form of HP in the present study, which is consistent with that of the Spanish registry [37], but largely different from the Indian registry, where HP accounts for up to 47.3% of ILDs [48]; in fact, mold antigen could be a rare occurrence in Algeria (probably related to climate differences).

Table 4. Comparison of Completed, Published Registries Including Patients with All Types of ILD.

N (%)		Source Case Ascertainment	Time Period	IIP	IPF	ILD-CTD	Sarcoidosis	HP	Drug Induced ILD	IPAF	Occupational	Unclassifiable
North America												
New Mexico, USA [65]	258 (prevalent cases)	Chart review Indigenous population	1988–1990	-	58 (22.5)	33 (12.8)	30 (11.6)	-	5 (1.9)	-	36 (14.0)	29 (11.2)
Canada [59]	1.285	Multi center MDD	2016–2017	356 (27.7)	317 (24.7)	428 (33.3)	41 (3.2)	97 (7.5)	-	47 (4)	-	286 (22.3)
Europe												
Flanders(Belgium) [51]	362 Prevalent cases)	Multi survey	1992–1996	-	72 (20.0)	27 (7.5)	112 (30.9)	47 (13.0)	12 (3.3)	-	20 (5.5)	33 (9.1)
Greece [6]	967 (Prevalent cases)	Multi center survey	2004	285 (29.5)	189 (19.5)	120 (12.4)	330 (34.1)	25 (2.6)	17 (1.8)	-	20 (2.0)	82 (8.5)
Denmark [58]	431 (incident cases)	Single center MDD	2003–2009	-	121 (28.1)	54 (12.5)	Excluded	32 (7.4)	20 (4.6)	-	-	62 (14.4)
Spain [37]	511 (incident cases)	Multi center survey	2000–2001	-	197 (38.6)	51 (10.0)	76 (14.9)	34 (6.6)	17 (3.3)	-	-	26 (5.1)
Italy [68]	3.152	Multi center survey	1998–2005	-	864 (27.4)	-	1063 (33.7)	93 (33.7)	39 (1.2)	-	-	-
Paris–France [49]	848 (Prevalent cases)	County MDD	2012	145 (17.1)	98 (11.5)	145 (17.1)	361 (42.6)	28 (3.3)	31 (3.7)	-	42 (5.0)	66 (7.8)
Asia												
Turkey [61]	2245 (incident cases)	Multi center survey	2007–2009	532 (26.0)	408 (18.2)	201 (9.0)	771 (34.3)	82 (3.7)	35 (1.6)	-	241 (10.7)	99 (4.4)
India [48]	1084 (incident cases)	Multi center MDD	2012–2015	-	148 (13.7)	151 (13.9)	85 (7.8)	513 (47.3)	3 (0.3)	-	33 (3.0)	2 (0.2)
Pakistan [55]	744	Multi center MDD	2016–2019	-	256 (34.4%)	121 (16.3%)	68 (9.1%)	132 (17.7%)	6 (0.8%)	5 (0.7%)	2 (0.3%)	1 (0.1%)
China (Guangzhou) [57]	1945 (incident cases)	Single Center MDD	2012–2017	784 (40.3)	395 (20.3)	356 (18.3)	123 (6.3)	59 (3.0)	13 (0.7)	348 (17.9%)	13 (0.7)	285 (14.7)
China (Yang Hu) [63]	2678 (incident cases)	Single Center MDD	1999–2013		299 (11.2)	1798 (67)	-	-	-	-	-	-
Saudi Arabia [60]	330 (incident cases)	Single center MDD	2008–2011	108 (32.3)	77 (23.3)	115 (34.8) include IPAF	67 (20)	21 (6.3)	4 (1.2)	-	-	6 (1.8)
Australia												
Australia [56]	705	Multi center survey	2016–2019	-	240 (34.0)	125 (17.7)	44 (6.2)	66 (9.4)	7 (1.0)	3(0.4)	11 (1.6)	51 (7.2)
North Africa												
Algeria [64]	110 (incident cases)	Single center	**2005–2008**	-	6 (5.4)	28 (25.4)	37 (33.6)	7 (6.3)	3 (2.7)	-	5 (4.5)	-
Our study	455 (incident cases)	Single center MDD	**2015–2019**	107 (23.5)	39 (8.6)	219 (48.1)	77 (16.9)	11 (2.4)	3 (0.7)	55 (12.1)	-	21 (4.6)

IPF = idiopathic pulmonary fibrosis, iNSIP = idiopathic non-specific interstitial pneumonia, COP = cryptogenic organizing pneumonia, RB-ILD = respiratory bronchiolitis-associated interstitial lung disease, HP = hypersensitivity pneumonitis, DIP = desquamative interstitial pneumonia, LIP = lymphocytic interstitial pneumonia, CTD = connective tissue disease, UIP = usual interstitial pneumonia, IPAF= Interstitial pneumonia with autoimmune features.

Concrete evidence shows that the multidisciplinary approach in clinical practice can guide investigations and improve management [17,18,47,59].

In the present study, unclassified ILD represented 4.4% of the total ILD cases, which is close compared with the previous studies between 5.1–29.7% [6,51,52,65] but superior to 1.8% in the Saudi study [60].

Regarding respiratory function, the following abnormalities were observed in the IPF group according to ATS/ERS guidelines for lung function testing [27,34], namely lower FVC, FEV1, RV, functional residual capacity (FRC), and TLC on the one hand and on the other hand, higher FEV1/FVC and maximal-mid expiratory flow (MMEF) ratio and higher ratio RV/TLC similar to other types of ILD (Table 3). The restrictive ventilatory defect was the classique ventilatory disorder in all ILD groups, found in 38.9%, especially in the IPF in 71.8%; however, obstructive ventilatory disorder was found in 15% of cases in our study, the same result was reported by Julien Guiot, who had identified among the ILD about 14.7% of them presented an obstructive ventilatory impairment, the distribution of which was close to our results and displays as follows there are 6.1% of IPF, 14.6% of IIP associated with an increase of RV, FRC, and TLC [75].

Strengths and Limitations

The strength of this work lies in the fact that all patients were recruited, diagnosed, and followed by the same competent multidisciplinary team made up of a pulmonologist, a radiologist, and a rheumatologist in the event of suspicion of CTD, and the application of the latest recommendations.

The second strength of this study is the practice of high-resolution CT scans, immunologic tests, salivary gland biopsies, and Schirmer tests for all patients.

The present study has some limitations. The main limitation of this study is the lack of DLCO measurement. Since it was not available, this study concerned a single center of pulmonology that devotes significant time and resources to the diagnosis of ILD and, thus, our data cannot represent the situation in other hospitals.

The very limited number of lung biopsies in the current study can potentially influence the rate of IIPs (23.5%), because the lung biopsies were performed in only 2 cases. In similar studies, the rate of lung biopsies was performed from 3.4 to 59.9% of cases [47,53]; in fact, the diagnostic problem arises particularly for DIP and RB-ILB as well as iNSIP, which require a more histological diagnosis, whereas IPF can be diagnosed without surgical lung biopsy [76], surgical biopsy should also be avoided in the majority of patients with ILD [77], and our data are consistent with current guidelines which state that when clinicians and radiologists are certain of the diagnosis, surgical lung biopsy should be avoided [78]. Recent ATS/ERS/JRS/LATS guidelines condition surgical lung biopsy when HRCT shows "probable UIP", whereas a recent statement by Fleischer opts against biopsy in this category of ILD [5,8].

5. Conclusions

This is the largest prospective study with more than 450 Algerian patients with newly diagnosed ILD and a high proportion of patients diagnosed in a multidisciplinary collaboration. ILD-CTD constitutes the largest proportion of our cohort, followed by sarcoidosis and IPF. A comparison of our results with data from other countries revealed both similarities and differences, which confirmed the great variability in the causes of ILD. Indeed, future work is much needed to determine the exact proportion of each component of ILD. We propose a multicenter prospective international epidemiological study to establish the real incidence of ILD in different countries and their components to improve our understanding of the disease and its risk factors, allowing better management.

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participated in its design, helped to draft the manuscript. All authors have read and agreed to the published version of the manuscript.

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