Review

Characteristics, management and outcome of hospitalized patients with interstitial lung disease in Greece

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ABBREVIATIONS
AE-IPF: acute exacerbation of idiopathic pulmonary fibrosis
ALI: acute lung injury
ANA: antinuclear antibodies
ARDS: acute respiratory distress syndrome
BAL: bronchoalveolar lavage
COP: cryptogenic organizing pneumonia
CPFE: combined pulmonary fibrosis and emphysema
CTD: connective tissue disease
DLCO: diffusing capacity for carbon monoxide
HP: hypersensitivity pneumonitis
HRCT: high resolution computed tomography
ICU: intensive care unit
IIP: idiopathic interstitial pneumonia
ILD: interstitial lung disease
IPF: idiopathic pulmonary fibrosis
MRC: medical research council
NSIP: non-specific interstitial pneumonia
SD: standard deviation
TLC: total lung capacity
UIP: usual interstitial pneumonia

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ABSTRACT. AIM: To investigate retrospectively patients' characteristics, reason of admission, medical management and outcome of hospitalized patients with interstitial lung disease (ILD) within the years before the establishment of the latest guidelines and subsequently to reassess their diagnosis with respect to the novel international recommendations. METHODS: Medical records of patients who were hospitalized in the 1st and 6th pulmonary department of Sotiria chest hospital and diagnosed with ILD within the years 1992-2008 were retrieved and analysed. RESULTS: Seventy files were found suitable. There were 36 men and 34 women with a mean age of 67.4±13.7 years, most of them being non smokers. An underlying aetiologic condition was identified in 16 patients (22.8%). Only 8 patients (11.4%) had already undergone or were referred for a surgical lung biopsy. For 29 patients (41%) lung function data were found in files. The most common reasons for admission were dyspnea and fever. Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) was the most frequent cause of inhospital mortality. Subacute deterioration of ILD, first investigation and acute exacerbation most often led to hospitalization. Unclassifiable ILD was the diagnosis at discharge in most cases. In almost half of the cases an alternative diagnosis occurred after re-examination of files. CONCLUSION: The implementation of the novel international recommendations regarding ILD in combination with the multidisciplinary approach led to an alternative diagnosis in almost half of the patients with ILD. A new prospective registry concerning ILD epidemiology, diagnosis, management and treatment is necessary in Greece. *Pneumon 2015, 28(2):154-160.*

INTRODUCTION

Diffuse or interstitial lung diseases (ILD) comprise a heterogeneous and multiplex group of disorders characterized by a widespread pulmonary parenchymal pathology. In a great proportion of these disorders the airspaces

and peripheral airways in addition to the interstitium are involved[1]. Idiopathic pulmonary fibrosis (IPF) and sarcoidosis are the two most common ILD[2]. A subset of acute and chronic interstitial lung disorders of unknown etiology are defined as idiopathic interstitial pneumonias (IIP)[3]. Major progress has been made in understanding the clinical, radiological and pathological manifestations of interstitial lung diseases which has led to the establishment of the recent classification of IIP[4]. Guidelines and recommendations based on the literature published over the last decade have altered the clinical management of patients with ILD and especially IPF[5]. Modifications are mainly related to diagnostic pathways and therapeutic strategies[5]. A great issue regarding ILD is the significant financial burden on health-care resources, with respect to the increasing annual number of hospital admissions noticed in other countries which has resulted in escalating costs of inpatient care[6,7]. This is of great importance in our country where patients are often hospitalized in order to get through diagnostic workup or re-evaluation studies, which are difficult to be performed in an outpatient due to impediments of the current health system.

In Greece little information exists about the epidemiology, clinical features and management of patients with ILD. We aimed to investigate retrospectively the patients' characteristics, reason of admission, medical management and outcome of patients with ILD hospitalized in a chest diseases hospital in the capital of Greece within the years before the establishment of the recent guidelines and subsequently to reassess their diagnosis with respect to the novel international recommendations.

METHODS

Medical records of patients who were hospitalized in the 1st and 6th pulmonary department of Sotiria chest hospital and diagnosed with interstitial lung disease within the years 1992-2008 were retrieved. Only files containing a complete medical history, adequate laboratory data and a high resolution CT (HRCT) of the chest were included for analysis. Patients with sarcoidosis were excluded. Records were then carefully reviewed by 3 pulmonologists, 1 radiologist and 1 pathologist when it was considered necessary. Demographics, clinical, radiographic and laboratory data were recorded and analyzed. Medical intervention and treatment were also recorded. Length and outcome of hospitalization were then assessed according to files. Finally, the initial diagnosis of interstitial lung disease was reassessed through clinical data, radiological, laboratory and pathological features when feasible, according to the recent guidelines and literature. When possible, information retrieved after patients' discharge was also used to establish a definite and more confident diagnosis.

RESULTS

The records of 210 patients were initially retrieved, but only 70 were found complete and suitable for further evaluation. Demographic and clinical data are shown in table 1. There were 36 men and 34 women with a mean age of 67.4±13.7 years. Mean age at diagnosis was 65.8±14 years, while most of them were non smokers. An underlying aetiologic condition was identified in 16 patients (22.8%) that was mainly either a connective tissue disease (CTD) or a documented exposure to asbestos. A great proportion of patients suffered from arterial hypertention, while ischemic heart disease and diabetes mellitus were also often recorded. Only 8 patients (11.4%) had already undergone or were referred for a surgical lung biopsy during or soon after hospitalization. Results of

TABLE 1. Demographic and clinical data

Men/Women	36/34
Mean age (years±SD)	67.4±13.7
Mean age at diagnosis (years±SD)	65.8±14
Smoking status	
Smokers	15
Non smokers	35
Ex smokers	20
Known underlying aetiologic condition (%)	16 (22.8%)
Comorbidities	
Arterial hypertention	33 (47%)
Diabetes mellitus	13 (18.5%)
Coronary disease	12 (17%)
Thyroid disease	9 (12.8%)
Surgical biopsy (%)	8 (11.4%)
Cough (%)	49 (70%)
Dyspnea score MRC (n=67)	
1	14 (20%)
2	21 (31.3%)
3	16 (23.8%)
4	11 (16.4%)
5	5 (7.4%)
Corticosteroids	29 (41.4%)

pathological examination showed Langerhans cell histiocytosis in 4 cases, usual interstitial pneumonia (UIP) in one patient and unclassifiable interstitial lung disease in the remaining cases. The most commonly reported symptoms were cough and dyspnea (Table 1). Twenty nine patients (41.4%) were already receiving corticosteroids as outpatients before admission.

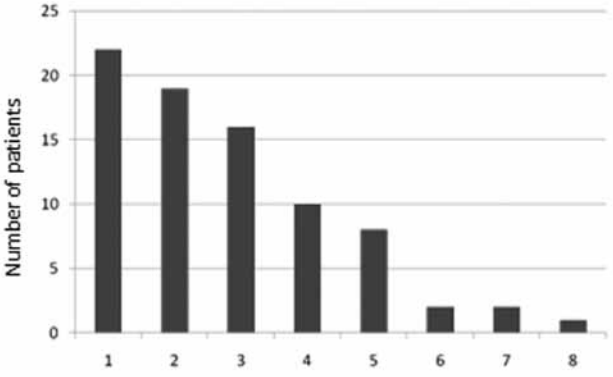
The most common reasons for visiting the emergency department and subsequently being admitted to hospital were dyspnea (56 patients), fever (21 patients), cough (19 patients), production of purulent sputum (7 patients), weakness (4 patients) and blood stained sputum in 4 patients. In addition, 5 patients were admitted for the first evaluation of a newly diagnosed interstitial lung disease without reporting any urgent medical symptom or sign.

Data of hospitalization are shown in table 2. Mean duration of hospital stay was 9 days (SD 6). For 29 patients (41%) lung function data were found in files, but only 19 patients had undergone total lung volumes and diffusing capacity measurements. Pulmonary hypertension was investigated in 24 patients by cardiac ultrasonography which revealed abnormally elevated pulmonary systolic arterial pressure in half of them, without evidence of further investigation with catheterization according to files. In 57 patients tests for the presence of antinuclear antibodies (ANA) were done and positive results were noticed in 26.3% of patients (titer ≥1:160). Forty patients were placed on supplementary oxygen therapy during hospitalization due to respiratory failure. In 20 patients a bronchoalveolar lavage (BAL) examination was obtained by fiberoptic bronchoscopy. Fifty five (78.5%) and 38 (54.2%) patients were treated with antibiotics and corticosteroids respectively during their hospital stay, while 30 patients received both antibiotics and corticosteroids. Seven patients were intubated and 18 patients died during hospitalization. Thirteen patients died due to acute exacerbation of IPF (AE-IPF) (81% mortality), 2 patients due to pneumonia, 2 as a consequence of pulmonary embolism and 1 because of end stage disease. Only 4 patients with AE-IPF were intubated. Among these patients 3 died during hospitalization, while the other was transferred in an intensive care unit (ICU) with unknown outcome. There was no difference concerning the incidence of AE-IPF between the patients already treated with corticosteroids before admission and those without corticosteroid treatment- 8 patients were on treatment with corticosteroids out of 16 with AE-IPF.

Diagnosis that were set at the end of hospitalization with regard to the clinical state that led to admission are shown in figure 1. Subacute deterioration of ILD, investigation/first diagnosis and acute exacerbation were the most common disorders, followed by pneumonia, cardiac failure, pulmonary embolism, pneumothorax and sepsis. Investigation regarding the type of the underlying interstitial lung disease revealed unclassifiable ILD in most cases, followed by end-stage fibrosis, IPF, Langerhans cell histiocytosis and ILD-CTD. Asbestosis, ILD and lung cancer, infiltrating lung disease, hypersensitivity pneumonitis and cryptogenic

TABLE 2. Hospitalization data

Mean duration of hospitalization (days)	9
Lung function tests	
Flow-volume loop	29 (41%)
TLC+DLco	19 (27%)
Pulmonary hypertension	
(Triplex, n=24)	12 (17%)
YES	12 (17%)
NO	
Antinuclear antibodies (ANA) (+) (n=57)	15 (26,3%)
Respiratory failure	40 (57%)
BAL	20 (28,5%)
Antibiotics	55 (78,5%)
Corticosteroids	38 (54,2%)
Intubation	7 (10%)
Non-survivors	18 (25,7%)
Modification of diagnosis	32 (45,7%)



1: Subacute deterioratin. **2:** First diagnosis. **3:** AE-IPF. **4:** Pneumonia. **5:** Cardiac failure. **6:** Pulmonary embolism. **7:** Pneumothorax. **8:** Sepsis.

FIGURE 1. Diagnosis that were set at the end of hospitalization with regard to the clinical state that led to admission.

organizing pneumonia (COP) were diagnosed in a few patients (Figure 2). After re-evaluating patients' files, a new diagnosis occurred in a considerable proportion of patients shown in figure 3. Thirteen patients were characterized as IPF while 16 patients were diagnosed with AE-IPF. In 6 patients a diagnosis of ILD was doubted because of an alternative definite diagnosis which was lymphangitic spread of cancer in 3 patients, miliary tuberculosis in 2 patients and fibrous tissue with bronchiectasis due to past pneumonia in one. Three patients with combined pulmonary fibrosis and emphysema were identified and 1 patient with non-specific interstitial pneumonia (NSIP)

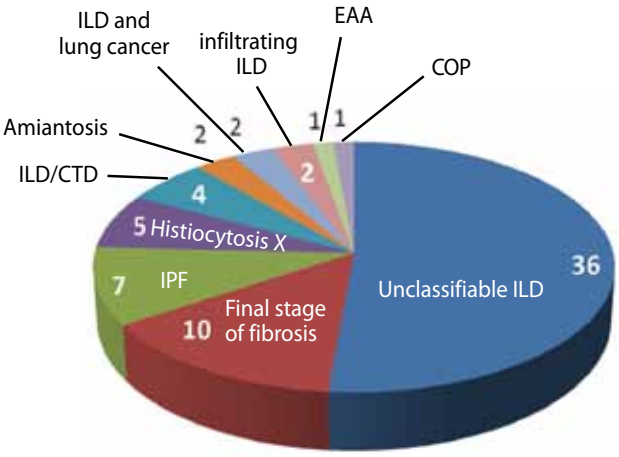


FIGURE 2. Diagnosis that were set at the end of hospitalization with regard to the type of the underlying interstitial lung disease.

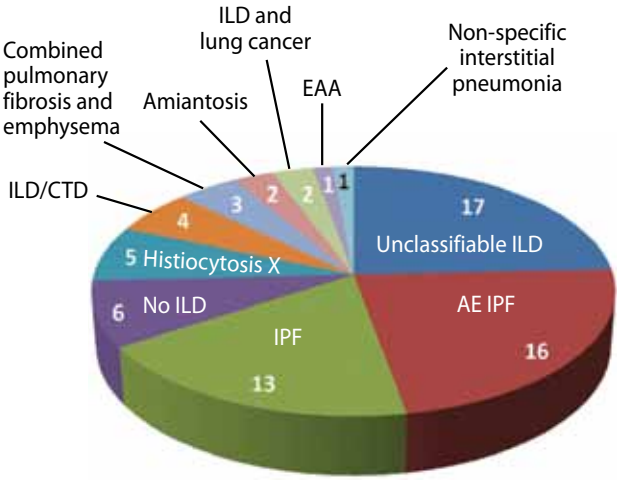


FIGURE 3. Diagnosis of ILD that were set after re-evaluating patients' files are shown. A new diagnosis occurred in a considerable proportion of patients.

after re-examination of histological specimen from lung biopsy. Overall, there were 32 cases of modification of the first diagnosis (45.7%).

DISCUSSION

In this study we aimed to retrospectively examine the records of patients with ILD that were hospitalized in a chest diseases hospital within the years before the establishment of the recent guidelines with regard to patients' demographics, clinical, laboratory and radiological data, hospitalization characteristics, reason of admission, medical management and final diagnosis and then reassess their ILD diagnosis. We found a low frequency of surgical lung biopsy and a very frequent use of corticosteroids in outpatients and inpatients as well. The most common reasons for admission were dyspnea and fever, but noteworthy a substantial proportion of patients were admitted for a first diagnosis and evaluation of ILD. AE of IPF was the most common reason of inhospital mortality. Subacute deterioration of ILD, first investigation and acute exacerbation were the most common underlying disorders that led to hospitalization. Unclassifiable ILD was the diagnosis at discharge in most cases, followed by end-stage fibrosis and IPF. In almost half of cases an alternative diagnosis occurred after re-examining records mostly concerning new IPF and AE-IPF cases.

Among our study population a rather low number of patients that had undergone a surgical lung biopsy was noticed despite the common diagnosis of unclassifiable ILD. According to previous guidelines the diagnosis of IPF remains uncertain in the absence of a surgical lung biopsy[8]. However the establishment of major and minor criteria have obviated the need for surgical biopsy in appropriate cases. In recent guidelines it is recommended that if a surgical biopsy is available, it should be taken in account with the integration of clinical and radiological information as it could become misleading if considered in isolation. This has led to the establishment of the multidisciplinary approach between pulmonologists, radiologists, and pathologists experienced in the diagnosis of ILD that increases the accuracy of the diagnosis of these disorders[5].

Surprisingly, a very low proportion of patients had data of pulmonary function tests and even less had undergone tests of total lung volumes and diffusing capacity of the lung for carbon monoxide (DLCO). This could be partially explained by the retrospective type of the study, as some spirometric tests that could have

been performed might have not been finally included in files. According to guidelines a ≥10% change in FVC and ≥ 15% change in diffusing capacity are described as indices of improvement or worsening of disease[8]. Indeed, patients with ≥10% decline in FVC within 6 or 12 months have a poor prognosis[9,10]. In particular, FVC has been the most commonly employed and widely accepted endpoint in clinical trials of IPF to date[11]. Therefore, the lack of information of lung function profile for ILD patients is disadvantageous not only for the initial estimation but for the follow up as well.

Patients with IPF may have a mildly positive antinuclear antibody titer and/or rheumatoid factor level without any other clinical features of connectine tissue disease[5]. Actually, up to 30-40% of patients with IPF have positive ANA or rheumatoid factor, however, these titers are generally not high[12]. In the present study only 57 patients were tested for the presence of ANA, and 15 of them were positive. Fischer et al reported 34% ANA positivity in a cohort of 285 patients with IPF, defined as ≥1:40[13], but without any survival difference between IPF patients who were ANA positive in comparison with ANA negative. Vij et al studied an IPF cohort of 58 patients and found that 41% had an ANA titer ≥1:160[14]. Differences in the reported studies can be explained by the different titer thresholds that are used to define ANA positivity and the type of ILD population included in every study cohort. In the present study a different result might have been found if serology tests were available for all patients.

Another issue of great importance is the noteworthy proportion of patients taking corticosteroids before admission. One would notice that it was only in 2011 that a clear statement against the use of corticosteroids and other immunosuppressant agents for IPF was declared, based on the disappointing results of recent studies[5,15]. Actually, long-term corticosteroid therapy was correlated with substantial morbidity[15]. Indeed, corticosteroid preoperative use has been recognized as an independent risk factor for the development of an acute exacerbation of interstitial lung disease among patients with lung cancer and ILD undergoing pulmonary resection[16]. No randomized controlled trials have been conducted with corticosteroids for the majority of other than IPF ILDs. In particular, patients with sarcoidosis for whom the beneficial role of corticosteroids when indicated is unquestionable, were excluded from our study. Furthermore, other ILDs that usually have a favourable response to corticosteroid treatment such as COP or acute and subacute hypersentitivity pneumonitis were rarely reported among our study population. Therefore, there is an excess corticosteroid use within our ILD patients. In addition, 30 patients received both antibiotics and corticosteroids, a fact that may be due to the difficulty in setting the differential diagnosis of the underlying condition that led to deterioration and hospitalization, especially in the case of infection, as patients with ILD often present with nonspecific symptoms despite their severe clinical state.

The classical clinical phenotype of IPF, the most common of the IIPs, is one of slowly progressive decline in lung function and worsening of dyspnea leading to death within several years of diagnosis. However, a rapidly progressive disease within 6 months from the first presentation and AE-IPF, the most devastating state of IPF are potential clinical courses of IPF[17]. In the present study dyspnea and fever were the most common reasons for visiting the emergency department, while subacute deterioration, first investigation/diagnosis and acute exacerbation of ILD were the most common diagnosis set at the end of hospitalization. It is the lack of the current medical system of our country that necessitates patients to visit the emergency department and get admitted to hospital in order to have a thorough examination for their health problem even in cases without an urgent medical issue. This is the main reason why a great proportion of patients being on stable clinical state were hospitalized at their first diagnosis. On the other hand IPF exacerbations represent acute and clinically significant deteriorations of unidentifiable cause, transforming the slow, rapid or steady disease decline to the unexpected appearance of acute lung injury/acute respiratory distress syndrome (ALI/ARDS) with mortality approaching 100%[18]. In this study AE-IPF was identified in 16 patients with a mortality rate of 81%, which is in accordance with previous studies[19-21]. Furthermore, the prognosis of ventilated IPF patients is disappointing[22-24]. Mechanical ventilation has been characterized as a second hit for the lung parenchyma, further deteriorating the mechanical properties of the lung and introducing a vicious cycle that ends in death[18]. Nevertheless, there is not enough evidence to support that patients with AE-IPF should be denied intubation. In the present study, 3 out of 4 patients died after intubation in the pulmonary clinic, while the 4th was transported in ICU with unknown outcome.

Different diagnosis that were set after examining patients' files mainly concerned patients with IPF and AE-IPF. It is the establishment of new guidelines that makes the diagnosis of IPF more feasible and accurate by a multidisciplinary team even in the absence of a surgical

lung biopsy[5]. Concerning AE-IPF, it was not until 2007 that criteria for a diagnosis of this devastating clinical entity were published[21].

Thus, it is reasonable that clinicians in previous years could not confidently recognize and diagnose this accelerating form of IPF. Another diagnosis that was set only after re-examination of medical records was pulmonary fibrosis with emphysema. The concept of combined pulmonary fibrosis and emphysema (CPFE) was first introduced as a distinct clinical entity in 2005 to describe the coexistence of any type and grade of radiological pulmonary emphysema and the idiopathic usual interstitial pneumonia CT pattern as well as any pathologically confirmed case[25,26].

A very low frequency of hypersensitivity pneumonitis (HP) was noticed among this group of ILD patients. Data from European registries of interstitial lung disorders indicate that HP represents 4% to 15% of all interstitial diseases[27,28]. In Greece HP has been estimated with a frequency of 2.6% among interstitial lung disease patients[29]. Interestingly, in a recent prospective study almost half of 46 patients being initially diagnosed with IPF on the basis of 2011 criteria, were subsequently diagnosed with chronic hypersensitivity pneumonitis using tests beyond conventionally used such as specific IgG determination, bronchial challenge testing with suspected antigens, and re-review of histopathological features in existing and subsequently obtained surgical lung biopsy samples and from lung explants[30]. In the present study some unrecognized cases of HP might have been included among the unclassifiable ILD cases.

The possible limitations of our study are the small number of patients included, its retrospective design and the small number of lung biopsies in order to secure diagnosis. Nevertheless, no similar report exists in the greek pulmonary domain so far.

In conclusion, in almost half of ILD cases an alternative diagnosis occurred after re-examining records in accordance with the latest guidelines, mostly concerning IPF and AE-IPF cases. The introduction and utilization of the new ILD recommendations is of great importance regarding the establishment of a secure diagnosis in order to proceed to the most appropriate treatment, as it is now widely accepted that corticosteroids and other immunosuppressants have no role in the treatment of IPF/UIP, while they can be helpful in other ILD. In addition, the diagnosis of IPF should be ensured before starting treatment with the new regimens recently approved for IPF. A new prospective registry for ILD that would idealy include several medical centers of the country, is necessary to enable a clear view of the epidemiology, management and outcome of patients with ILD in Greece.

COMPETING INTERESTS

The authors have indicated no financial conflicts of interest.

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