# Interstitial lung diseases: an observational study in patients admitted in "Marius Nasta" Institute of Pulmonology Bucharest, Romania, in 2011

**Irina Strâmbu[1], Ionela Belaconi[1], Ileana Stoicescu[1], Diana Ioniță[2], Felicia Cojocaru[3], Camelia Nița[3], Daniela Dospinoiu[3], Roxana Bumbăcea[2]**

*1. "Marius Nasta" Institute of Pulmonology Bucharest, Romania,*

*2. Elias Emergency Hospital, Bucharest, Romania*

*3. ARENSIA Exploratory Medicine Bucharest, Romania*

***Correspondence:***
***Dr. Irina Strâmbu***
***Institutul de Pneumologie „Marius Nasta"***
***Șos. Viilor 90, sector 5, București***
***e-mail: istrambu@yahoo.com***

**Abstract**

*Interstitial lung diseases (ILD) are a large group of rare diseases, with difficult diagnosis and management. Very little is known about prevalence, diagnosis and management of ILDs in Romania. This study aims to gather information on how ILDs are diagnosed and managed in Romania, focusing on a tertiary hospital with expertise and equipment needed for accurate diagnosis. We analyzed retrospectively the files of patients admitted with ILD in 2011 in "Marius Nasta" Institute of Pulmonology Bucharest. There were 178 eligible patient files with ILDs and 186 sarcoidosis cases. The ILD diagnosis were: 41 cases idiopathic pulmonary fibrosis (IPF), collagen disease associated ILD (29 cases), hypersensitivity pneumonia (19 cases), alveolar proteinosis (9 cases), cryptogenic organizing pneumonia (9 cases), undefined ILD (46 cases), other (25 cases). The investigations used for the diagnosis were: chest X-ray (100%), spirometry (157 pts, 88.21%), diffusion capacity (127 pts, 71.43%, broncho-alveolar lavage (92 pts, 51.69%), CT scan (141 pts, 79.22%), lung biopsy (26 pts, 14.6%), similar to other European centers, but fewer lung biopsies are performed. There is need for a prospective registration of ILD cases in a national registry, for creating local guidelines for diagnosis of ILDs, to improve the suspicion of ILD and referring of patients to specialized centers. Diagnosis can be improved by a multidisciplinary approach of each case, involving the clinician, the radiologist, the pathologist and the thoracic surgeon.*
***Keywords:*** *interstitial lung diseases, diagnosis, idiopathic pulmonary fibrosis, undefined interstitial lung disease*

**Rezumat**

***Pneumopatiile interstițiale difuze: un studiu observațional asupra pacienților internați în Institutul de Pneumologie „Marius Nasta" București, România, în 2011***

*Pneumopatiile interstițiale difuze (PID) reprezintă un grup mare de boli rare, ce ridică dificultăți de diagnostic și îngrijire. Se știe foarte puțin despre epidemiologia, diagnosticul și îngrijirea PID în România. Acest studiu și-a propus să adune informații despre felul în care PID sunt diagnosticate și tratate în România, concentrându-ne asupra unui spital terțiar care deține experiența și echipamentele necesare pentru un diagnostic corect. Am analizat retrospectiv foile de observație ale pacienților internați în 2011 în Institutul de Pneumologie „Marius Nasta" București. Au fost 178 de dosare eligibile cu diagnostic de PID și 186 de sarcoidoze. Diagnosticele de PID au fost: 41 fibroze pulmonare idiopatice (FPI), 29 PID asociate colagenozelor, 19 alveolite alergice extrinseci, 9 proteinoze alveolare, 9 pneumonite criptogenice în organizare, 46 de cazuri de PID neprecizat, 25 de alte diagnostice. Investigațiile folosite pentru diagnostic au fost: radiografie pulmonară (100%), spirometrie (157 bv, 88,21%), măsurarea difuziunii (127 bv, 71,43%), lavaj bronho-alveolar (92 bv, 51,69%), tomografie computerizată (141 bv, 79,22%), biopsie pulmonară (26 bv, 14,6%), similar cu alte centre europene, dar cu un număr mai mic de biopsii pulmonare. Sunt necesare înregistrarea prospectivă a cazurilor de PID într-un registru național, crearea unui ghid local dedicat PID pentru a îmbunătăți suspectarea cazurilor de PID și trimiterea lor către centre specializate de diagnostic. Diagnosticul poate fi îmbunătățit printr-un abord multidisciplinar al fiecărui caz, implicând clinicianul, radiologul, anatomo-patologul și chirurgul toracic.*
***Cuvinte-cheie:*** *pneumopatii interstițiale difuze, diagnostic, fibroză pulmonară idiopatică, pneumopatie interstițială difuză neprecizată*

## Introduction

The term "Interstitial lung diseases" (ILD) represents a large group of rare diseases sharing diffuse involvement of lung parenchima and common clinical, radiological and functional features.

**ILDs were classified as[1]:**

- Of known cause (drug-induced, hypersensitivity pneumonia, associated to collagen-vascular diseases)
- Granulomatosis (sarcoidosis, other)
- Other ILDs (lymphangioleiomiomatosis, X hystiocytosis etc.)
- Idiopathic. The name suggests that cause is unknown. Still, some are associated to smoking (descuamative interstitial pneumonia, bronchiolitis-related ILD). The other "true" idiopathic include cryptogenic organizing pneumonia, acute interstitial pneumonia, non-specific interstitial pneumonia and, the most important, idiopathic pulmonary fibrosis.

Nowadays we find these diseases well defined and pinned in a specific place of the classification. Anyway, many cases fail to be typical, in many patients features of

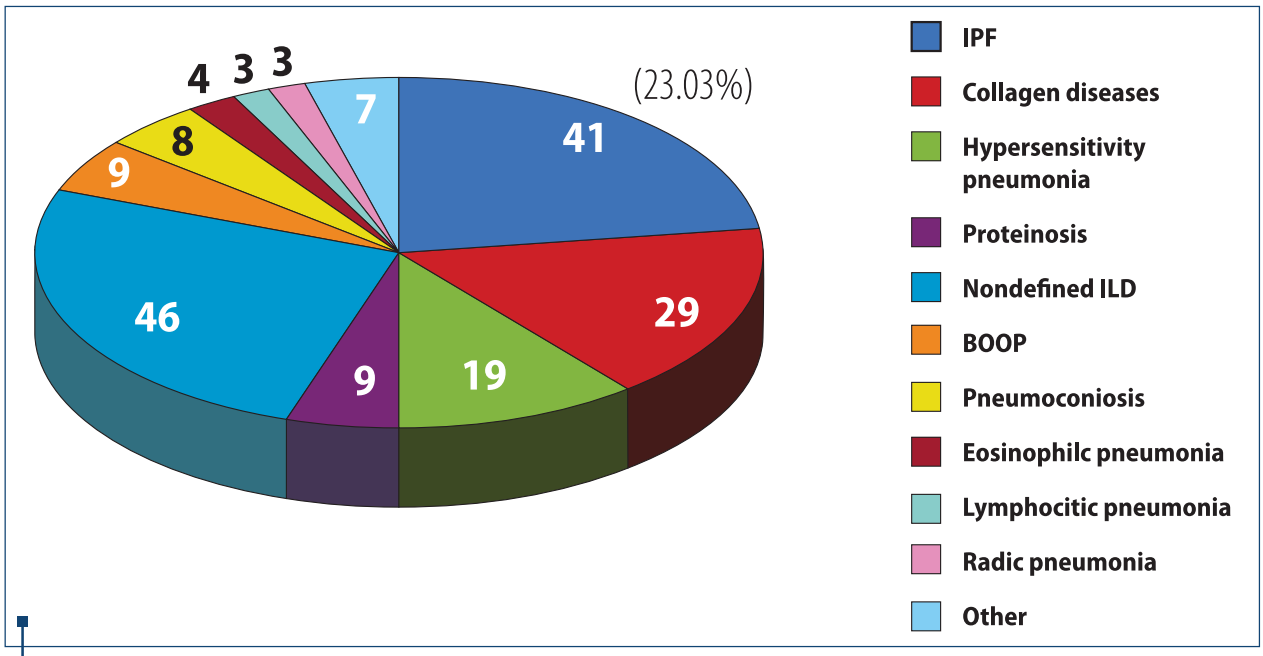


***Figure 1.*** *Distribution of ILD diagnosis (178 cases)*

different diseases seem to overlap. This facts, along with the low prevalence of these diseases and the scattering of the few patients in many centers, makes difficult for the clinician to make a correct diagnosis and to build up a personal clinical experience with ILD patients.

In Romania, based on the lack of data regarding the prevalence, distribution of diagnosis, management and outcome of the patients with ILD, we can assumed there is underdiagnosis of ILD, many patients being probably misdiagnosed as other conditions associating chronic dyspnea or diffuse radiologic changes.

Our group proposed previously to initiate a national registry of patients with ILDs and sarcoidosis (REGIS)[2]. The first step would be to analyze retrospectively the existing information about these patients, as a base for future actions to make a prospective registration and analysis of these data.

In this study we analyzed retrospectively the files of patients admitted during one year (2011) in "Marius Nasta" Institute of Pulmonology Bucharest, a tertiary hospital clustering many patients with ILD all over the country and having the expertise and complete infrastructure for correct diagnosis of these cases.

## Objectives

This study aimed to analyze the distribution of different interstitial lung diseases in our hospital, to analyze what investigations were used for making the diagnosis and what treatments were prescribed. We aimed to compare this data with other data published by other European centers, as retrospective studies or national registries.

## Materials and method

We performed a retrospective analysis of the files of patients admitted in "Marius Nasta" Institute of Pulmonology Bucharest during 2011. The files were selected from the hospital database according to CIM 10 codes of disease, looking for codes of interstitial lung diseases, sarcoidosis, hypersensitivity pneumonia, collagen diseases, alveolar proteinosis and unspecified interstitial lung diseases.

Initial count showed 925 patient files with ILD codes in one year. After excluding files of patients admitted several times during 2011, files containing not enough information, miscoded files (e.g. files of children with acute pneumonias miscoded as interstitial lung disease), the number of eligible files was reduced to 178 files of patients with different interstitial lung diseases and 186 files of patients with sarcoidosis.

In this study we analyzed the 178 files of patients with interstitial lung diseases.

We collected data regarding: age, gender, smoking habit, main symptoms, time since onset of symptoms. We considered the diagnosis of the disease as specified by the physician. We analyzed the investigations performed for making the diagnosis: chest X-ray, spirometry, diffusion capacity, bronchoscopy and broncho-alveolar lavage, high resolution computer tomography, lung biopsy. Data regarding the associated conditions and treatment prescribed were also collected. Considering just one of the admittances of each patient in 2011, we could not collect consistent information regarding the evolution of the disease, except for a few cases.

All the data were checked for consistency with the final diagnosis by a team of pulmonologists, working in this study. The data collected were included in an Excell database.

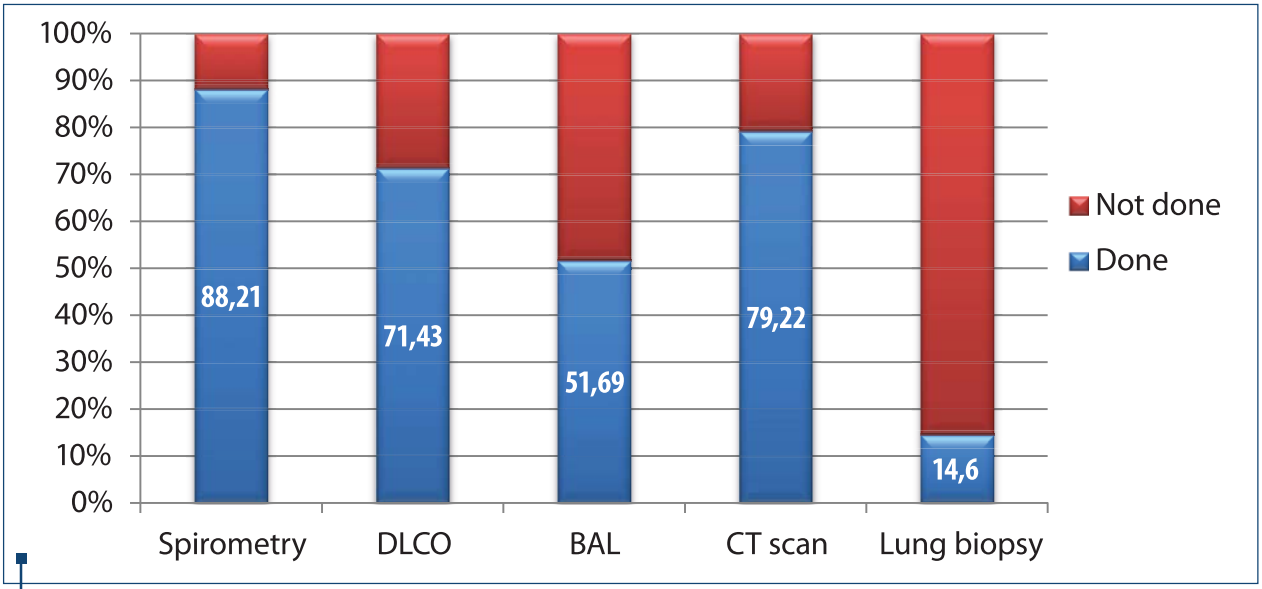


***Figure 2.*** *Investigations performed for the diagnosis (178 patients)*

## RESULTS

Among the 178 patients, there were 87 men and 91 women; mean age was 55.75 years (between 18 and 81). There were 102 never smokers (57.3%), 21 current smokers and 55 ex-smokers.

**The onset of symptoms was mentioned as:**

- less than one month in 20 patients
- 2-4 months: 26 patients
- less than 1 year: 13 patients
- more than 1 year: 7 patients
- unknown: 112 patients.

Patients with onset of symptoms for more than 1 year or unspecified in the patient file were usually patients previously diagnosed with ILD and being admitted in 2011 for evaluation or treatment.

The distribution of the diagnosis, as established by the treating physician, and confirmed by the study team, was as follows **(see also Figure 1)**:

- ✔ idiopathic pulmonary fibrosis: 41 cases (23.03%)
- ✔ collagen diseases with lung involvement: 29 cases (16.29%)
- ✔ hypersensitivity pneumonia: 19 cases (10.67%)
- ✔ alveolar proteinosis: 9 cases (5.05%)
- ✔ cryptogenic organizing pneumonia: 9 cases (5.05%)
- ✔ undefined ILD: 46 cases (25.84%)
- ✔ other: 25 cases (radic pneumonia: 3 cases, pneumoconiosis: 8 cases, eosinophilic pneumonia: 3 cases, lymphangioleiomiomatosis: 2 cases, X hystiocitosis: 1 case, non-specific interstitial pneumonia: 2 cases, alveolar haemorrhage: 1 case, bronchiolitis related-ILD: 1 case).

**Hypoxemia** was found in 45 patients (25.28%).

Associated conditions were found to be:

**Ischaemic heart diseases:** 33 patients
**Arterial hypertension:** 30 patients
**Gastro-esophageal reflux:** 21 patients
**Diabetes:** 20 patients
**Pulmonary hypertension:** 9 patients
**Depression:** 6 patients
**Osteoporosis:** 6 patients

Other (SAS, bronchectasis, emphysema, chronic kidney disease, hypothiroidia, etc.) in 1-2 cases each.

We analyzed the investigations performed for making the diagnosis **(Figure 2)**.

All patients had a standard chest X-ray, which showed unspecific bilateral diffuse interstitial changes in most of the patients (118 cases). Nodular opacities were found in 16 patients, diffuse micronodules in 7, consolidation in 10 patients, 2 patients had a pneumothorax, 1 patient associated diffuse hyperlucency, in 6 patients there was a combination of interstitial changes and consolidation.

Spirometry was documented in the patient file in 157 patients (88.21%), measurement of diffusion capacity in only 127 patients (71.43%). Bronchoscopy with broncho-alveolar lavage was performed in 92 patients (51.69%). CT scan was done in 141 patients (79.22%).

Surgical lung biopsy was performed in 26 patients (14.6%).

We described in more detail the features of the patients with some distinct diagnosis.

So, there were 41 patients with idiopathic pulmonary fibrosis (IPF), with a mean age of 61.41 years (between 37 and 79 years). There were 19 never smokers, 19 ex-smokers and 3 current smokers. In 22 patients the onset of symptoms was not documented in the file; in 5 patients the onset was less than 1 month, 2 to 4 months in 2 patients, less than 1 year in 4 patients, and more than 1 year (up to 13 years) in 10 patients. The radiologic features were non-specific, all patients having a standard chest X-ray with interstitial changes. The CT scan was performed in only 33 patients (80.48%), showing typical UIP pattern in 30 patients and possible UIP

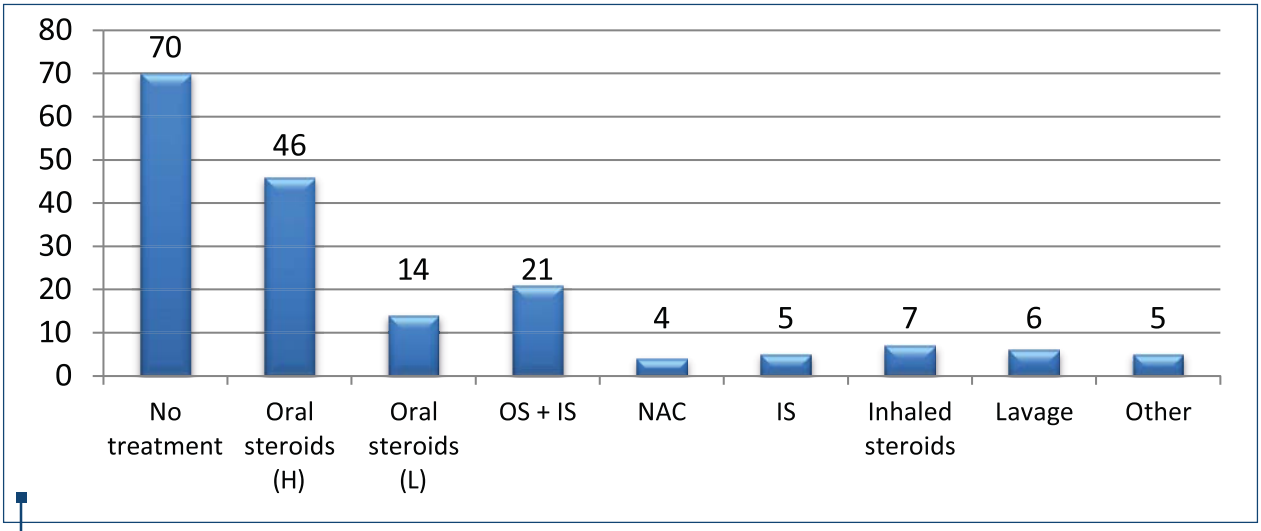


***Figure 3.*** *Treatment recommended in ILD patients (178 cases)*

pattern in 3. Ground glass pattern was described in the CT scans of 4 patients. BAL was performed in less than half of the patients: 18 (43.9%), showing neutrophilic alveolitis in 10 patients, lymphocytic dominance in 2 and being inconclusive in 6 patients.

The spirometry, performed in all patients, showed restriction or normal values, with a forced vital capacity (FVC) between 19.7 and 128% of predicted (11 patients had a FVC > 80% of predicted). Diffusion capacity was measured in 32 patients, with a mean DLCO of 40.72% of predicted (between 15.1% and 88% of predicted value).

Seventeen patients associated hypoxemia (41.46%).

The evolution, as judged by the treating physician in patients who had a previous diagnosis, was worsening in 8 patients, stable in 9 and improved in 3 patients. The evolution was not known in 21 patients.

It was interesting to analyze more in detail the group of patients with so-called "undefined" interstitial lung disease. We considered this diagnosis in the absence of a more specific diagnosis formulated by the treating physicians, and not being able to define a clear diagnosis based on the retrospective check of the patient files by our study team. There were 46 patients in this group, with a mean age of 57.95 years (between 33 and 85 years). There were 21 never-smokers, 17 ex-smokers, and 8 current smokers. Radiologic aspect showed interstitial changes (37 patients), diffuse micronodular (2 patients), or nodules, consolidation or hyperinflation. CT scan was performed in 33 patients (71.7%), showing honeycombing (6 patients), traction bronchectasis (8 cases), reticular pattern (15 cases), micronodular (6 cases) or ground glass opacification (12 patients). Broncho-alveolar lavage was performed in 20 patients (43.47%), showing lymphocytic alveolitis in 4 patients, neutrophilic alveolitis in 8 patients and being inconclusive in the rest.

Spirometry showed normal values or restriction, with FVC values between 32.5 and 126% of predicted (9 patients with FVC higher than 80% of predicted). Diffusion capacity was measured in 29 patients (63.5%), with a mean DLCO of 55.08% of predicted (between 12.1% and 92.7%). Eight patients (17.39%) associated hypoxemia.

Lung biopsy was performed in 9 patients (19.56%), this being unable to further define the actual diagnosis in this patient group.

Evolution could not be assessed in 36 patients, the others showing worsening (1 patient), improvement (5 patients) or stable state (4 patients).

In the group of patients with ILD associated to a systemic collagen disease, the underlying condition was already known in all patients: rheumatoid arthritis in 11 cases, systemic lupus erithematosus in 3 patients, systemic sclerosis in 12 and unspecified collagen disease in 2 patients. The lung biopsy was performed in only one patient. BAL was performed in 13 patients, with no specific findings, and mean DLCO was 46.82% of predicted.

In patients with alveolar proteinosis (9 patients), BAL was performed in all cases, showing the typical milky aspect of the BAL fluid, in 7 patients PAS positive bodies were found in BAL fluid. Six of the patients were treated with total lung lavage.

We noted the **treatment prescribed** for the entire group of patients **(see Figure 3)**. In 70 cases, no treatment recommendation was found in the patient file. Oral corticosteroids were prescribed in 46 patients in high dose (over 40 mg prednisone/day) and in 14 patients in low dose (less than 20 mg prednisone/day). In 21 patients a combination of oral corticosteroids and immunosuppressive drugs was recommended (mostly cyclophosphamide in pulse-therapy, but also azathyoprine). Five patients received immunosuppressive agents alone. Only 4 patients were recommended N-acetylcysteine. Inhaled steroids were recommended in 7 patients, in 6 patients total lung lavage was performed, 5 patients received other prescriptions (erdosteine, monoclonal antibodies, sildenafil, tamoxifen).

Patients with IPF were recommended:
**No treatment:** 12 patients
**Oral corticosteroids in high dose:** 9 patients
**Oral corticosteroids in low dose:** 4 patients
**Combination of oral corticosteroids and immunosuppressive agents:** 7 patients
**Immunosuppressive agents:** 3 patients
**N-acetylcysteine:** 3 patients
**Inhaled steroids:** 2 patients
**Sildenafil:** 1 patient.

In 2011, pirfenidone was not yet an option for IPF treatment in Romania.

## Discussion

"Marius Nasta" Pulmonology Institute in Bucharest is a tertiary hospital, hosting under one roof all the expertise and equipment needed for making a complete ILD diagnosis, thoracic surgery included, and receiving patients with suspected ILD referred from other specialties or from pulmonologists all over the country.

The distribution of the diagnosis of various ILDs is different from other reports with respect to the IPF-sarcoidosis ratio, usually almost equal number of patients with sarcoidosis and IPF being reported[3]. In our series, there were only 41 patients with IPF and 186 patients with sarcoidosis. This difference is probably due on one hand to the clustering of sarcoidosis cases from all the country, referred to the Institute, on the other hand probably due to underdiagnosis of IPF cases, the patients being probably considered as different conditions (TB, asthma, cancer, pulmonary hypertension) and never being referred to our hospital.

It was difficult for the study team to re-check retrospectively the data in the patient files in the absence of the actual patient, so we had no ground to re-allocate a different diagnosis to the cases.

The percentage of about 25% cases with undefined ILD is similar to what was reported in other international centers[4,5]. These patients received the same diagnostic procedures as the other patients, the fact that finally the diagnosis could not be defined more precisely might be due to the great variability and atypical presentation of these cases. Almost one fifth of these patients had a surgical lung biopsy, which could not bring further progress to the diagnosis. The surgical sampling might not be enough, relying only on one or two fragments, or the surgical sampling might be performed in areas with consistent fibrosis, showing no specific pathologic features for one disease or another. Another reason for the undefined diagnosis could be the fact that multidisciplinary discussion of the cases is not routine in our hospital, the diagnosis being the sole responsibility of the clinician. We can assume that some of the undefined ILD are true IPF cases with atypical HRCT, or with no HRCT performed.

The investigations performed for making the diagnosis are similar to other centers in Europe[6,7,8,9]. It is probably needed that all patients should perform high resolution CT scan. Our data are based on the analysis of the patient files, in which the CT scan might have been missing (performed in another center or kept by the patient) or the CT scan was not high resolution. CT scan is nowadays considered the main tool for confirming ILD and for defining the specific diagnosis[1]. In our patients, some of the CT scans were performed in other centers, with no special interest in pulmonary imaging. The correct interpretation of the imaging results needs "more eyes", or at least a recheck of the images by a radiologist with special interest in interstitial diseases. Also, a better communication between the clinician and the radiologist is needed to improve the understanding of the patient's condition.

Broncho-alveolar lavage is easily accessible in our hospital, so the relative low percentage of patients in whom it was performed (less than a half in IPF and non-defined ILD) has no explanation. BAL might contribute to better understanding of the underlying disease, to differential diagnosis, it is a hallmark for the diagnosis of sarcoidosis, hypersensitivity pneumonia and alveolar proteinosis and is relatively non-invasive. The important number of inconclusive BAL fluid results might be due to a low recovery of the BAL fluid during the procedure, which is typically performed under local anesthesia.

Lung biopsies were performed in a relatively small number of subjects, 14.5%, which is lower than most reports in other European centers[8,9,10]. Typically, in our hospital lung biopsies are performed by open lung surgery, so many patients with severe functional impairment are not eligible for this procedure. In our series, we had patients with very low DLCO in whom the lung biopsy was ruled out. For having a good quality pathology result, several lung fragments from different lobes need to be sampled. In this retrospective study we could not assess the operation protocol and check this aspect. A good pathology result needs also a dedicated pathologist, able to differentiate the features of various ILDs. "Marius Nasta" Institute being a hospital entirely dedicated to respiratory diseases, the pathology laboratory has the needed expertise in ILDs.

The current concept for IPF weights less the lung biopsy for the diagnosis and stresses the importance of HRCT. So, in the perspective of improving the imaging technique, as well as the communication between clinician and radiologist, lung biopsy should remain important only for atypical cases, in the effort to define as clearly as possible if the patient has IPF or has a different condition. This difference is most important, as it is demonstrated that, while many ILDs are still suitable for immunosuppressive treatment, IPF seems to have a worse outcome and lower survival if treated with corticosteroids and immunosuppressive agents[11,12].

The treatment regimens for ILDs are difficult to evaluate in a retrospective study, our data are based on the treatment recommendation made at the discharge of the patient, and there is no information if the patient really followed this prescription. The choice of treatment regimen was at the treating physician's decision and not based on specific guidelines. Nonetheless, most

patients received in 2011 a double therapy: oral corticosteroids and immunosuppressive agents, for IPF and also for other conditions.

The evolution could not be evaluated properly in this retrospective study, most patients being admitted just once in the hospital. The information regarding their follow-up visits and clinical and functional evolution is probably stored in the physicians own out-patient databases, with no correspondence with the initial patient file.

## Conclusions

This retrospective study analyzes the current approach of the diagnosis of interstitial lung diseases in a Romanian tertiary hospital.

The diagnosis distribution in a group of 178 patients with ILD shows fewer IPF cases than in other European centers, probably due to under-referral and under-diagnosis of the disease. The percentage of undefined ILDs is similar to reports from other centers. It is possible that some of these cases are actually true IPF cases, needing a more attentive multidisciplinary approach. The number of sarcoidosis patients admitted in one year is bigger than the total number of patients with any other ILD, probably due to clustering of sarcoidosis cases in this center.

The investigations used for building up the diagnosis are similar to other European centers, but probably BAL should be used more.

This data should be a starting point for a prospective registration and analysis of ILD cases in a national registry, and as well for building up local guidelines for the diagnosis of ILDs. Such guidelines should be able to help physicians suspect early an interstitial lung disease, differentiate it from other confounding situations (tuberculosis or other causes of chronic dyspnea, like COPD, pulmonary hypertension or heart failure), and refer the patients to the centers capable of making an accurate diagnosis.

In this tertiary hospital, the quality of diagnosis can be improved by a multidisciplinary approach of the cases, involving together the pulmonologist, the radiologist, the pathologist and also the thoracic surgeon. This might give the opportunity of a coherent diagnosis and therapeutic approach, and will also increase the expertise of each participant in the multidisciplinary team regarding the ILDs. ■

## References

1. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. Raghu G, Collard HR, Egan JJ, et al. on behalf of the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* Vol 183. pp 788–824, 2011.
2. Strâmbu I, Ioniță D, Belaconi I, Stoia I, Tudorache V. Romanian National Registry for Interstitial Lung Diseases and Sarcoidosis (REGIS): rationale and methods. *Pneumologia* 2012, 61:20-24.
3. Thomeer MJ, Costabel U, Rizzato G, Poletti V, Demedts M. Comparison of registries of interstitial lung diseases in three European countries. *Eur Resp J* 2001; 18: Suppl.32, 114s-118s.
4. Ryerson CJ, Urbania TH, Richeldi L, Mooney JJ, Lee JS, Jones KD, Elicker BM, Koth L, King Jr TE, Wolters PJ, Collard HR. Prevalence and prognosis of unclassifiable interstitial lung disease. *Eur Resp J* September 1, 2013 vol. 42 no. 3 750-757.
5. Cottin V, Wells A. Unclassified or unclassifiable interstitial lung disease: confusing or helpful disease category? Eur Respir J. 2013 Sep; 42(3):576-9.
6. Roelandt M, Demedts M, Callebaut W et al. Epidemiology of interstitial lung disease (ILD) in Flanders: registration by pneumologists in 1992-1994. Working Group on ILD, VRGT. Acta Clin Belg. 1995; 50(5):260-8.
7. Schweisfurth H. Report by the Scientific Working Group for Therapy of Lung Diseases: German Fibrosis Register with initial results. *Pneumologie*. 1996 Dec; 50(12):899-901.
8. Schweisfurth H, Kieslich C, Satake N et al. How are interstitial lung diseases diagnosed in Germany? Results of the scientific resgistry for the exploration of interstitial lung diseases ("Fibrosis registry") of the WATL. *Pneumologie*. 2003 Jul; 57(7):373-82.
9. Tinelli C, De Silvestri A, Richeldi L, Oggionni T. The Italian register for diffuse infiltrative lung disorders (RIPID): a four-year report. Sarcoidosis Vasc Diffuse Lung Dis 2005 Dec; 22 Suppl 1:S4-8.
10. Xaubet A, Ancochea J, Morell F et al.; Spanish Group on Interstitial Lung Diseases, SEPAR. Report on the incidence of interstitial lung diseases in Spain. Sarcoidosis Vasc Diffuse Lung Dis 2004 Mar; 21(1):64-70.
11. National Heart, Lung and Blood Institute. Commonly used three-drug regimen for idiopathic pulmonary fibrosis found harmful. http://www.nih.gov/news/health/oct2011/nhlbi-21.htm Date last accessed: November, 7, 2013.
12. Wells AU, Behr J, Costabel U, Cottin V, Poletti V. Triple therapy in idiopathic pulmonary fibrosis: an alarming press release. *Eur Resp J* April 1, 2012 vol. 39 no. 4 805-806