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Functional features in interstitial lung diseases

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Abstract

Background: Interstitial lung diseases (ILD) are a group of disorders that are generally thought to commonly share a restrictive ventilatory defect and reduced diffusing capacity for carbon monoxide (DLCO). The aim was to find distinctive features of the pulmonary function tests (PFT) results in different types of ILD.
Material and methods: We conducted a retrospective study of 40 consecutive patients with ILD admitted to the Institute of Pthisiopneumology, Chisinau, the Republic of Moldova, during January 2019 – February 2020. The cohort included 10 cases of sarcoidosis patients, 8 cases of idiopathic pulmonary fibrosis (IPF) patients, 7 patients with nonspecific idiopathic interstitial pneumonia, 9 cases with hypersensitivity pneumonitis (HP) and 6 histiocytosis cases. All patients have been evaluated by pulmonary function tests (PFT), 6 minutes walk test, Medical Research Council scale for dyspnea, etc.
Results: Overall, we found normal mean spirometry parameters, a slightly increased mean residual volume (127.5±42.1), a mildly decreased mean total lung capacity (88.8±22.3) and moderately reduced DLCO (52.6±21.5). We found a dominant restrictive pattern in 75% of patients, and obstruction only in 7.5% when we used spirometry parameters. When we applied the bodyplethismographic values, we have found that an *air-trapping* pattern was identified in 32.5% cases of patients. This pattern has been identified in 1/3 of HP patients and in 10% of sarcoidosis patients.
Conclusions: PFT can help identifying individual features of different types of ILD being able to show even obstructive changes in a group of diseases thought to be strictly restrictive.
Key words: interstitial lung diseases, pulmonary function tests, obstruction, restriction.

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Introduction

Interstitial lung diseases (ILD) are defined as a variety of heterogeneous and diffuse parenchymal lung disorders associated with significant morbidity and mortality, sharing similar clinical, radiographical, physiological, or pathological manifestations [1]. These diseases are generally thought to share a common pattern of physiologic abnormality, characterized by a restrictive ventilatory defect and reduced diffusing capacity for carbon monoxide (DLCO) [2, 3].

Conflicting reports have been published regarding small airway function using more sophisticated testing [1, 4-6]. Unfortunately, these abnormalities are not specific for any particular ILD and the magnitude of the changes varies widely from patient to patient. DLCO typically is reduced in ILD to a greater extent than the lung volume at which it is measured. This statement is particularly true with IPF more than any other ILDs [7].

Hypersensitivity pneumonitis (HP) and sarcoidosis are two entities which have as a morphological marker the epithelioid granuloma. This seems to have a certain repercussion over the pulmonary function tests. It is not clear whether it is the granulomatous interstitial inflammation that imposes an obstructive defect in these diseases. Pulmonary function tests in HP typically demonstrate as any other ILD a restrictive defect, but some studies suggest obstructive, or mixed abnormality [8].

Pulmonary function tests (PFT) in sarcoidosis commonly reveal a restrictive pattern as well, with a reduction in the DLCO, although some studies suggested that airflow limitation may be the most common abnormality in newly diagnosed patients [4, 5, 9].

Adult Langerhans' cell histiocytosis (Hx) is a smoke related ILD and has different stages, which start with nodular lesions, which in the end transform into cysts [10]. Considering this, the functional abnormalities can vary in correspondence with the stage and also with the morphological changes. Similar to HP and sarcoidosis, in Hx the inflammation and the fibrotic process has a particular predilection for the peribronchiolar region [11], this is why we would expect that restrictive lesions would combine with air-trapping or air-flow obstruction.

Considering all the above mentioned, the exact physiology of pulmonary ventilation in different types of intersti-

tial lung diseases is unclear, this is why the aim of the study was to find distinctive features of the pulmonary function tests results in different types of ILD.

Material and methods

We have performed a retrospective study based on the data collected from 40 consecutive medical records of patients with ILD admitted to the Phthisiopneumology Ward of the *Chiril Draganiuc* Institute of Phthisiopneumology, Chisinau, the Republic of Moldova, during January 2019 – February 2020.

Patients who fulfilled the following criteria were considered eligible for inclusion in the study: age older than 18; diagnosis of a specific type of ILD established after a multidisciplinary ILD specialists discussion based on suitable clinical, imaging and/or morphology criteria; ILDs from the following list of entities: Idiopathic pulmonary fibrosis (IPF), Nonspecific Interstitial Pneumonia (NSIP), Sarcoidosis, Hypersensitivity pneumonitis (HP), and Adult Langherhans' cell Histiocytosis (Hx). Exclusion criteria were the following: patients with ILD and a high suspicion of a concomitant infectious disease (patients with positive sputum cultures and C reactive protein >20mg/dl); patients with ILD and a concomitant malignancy, patients with an ILD secondary to a collagen disease.

We have collected the following data from the medical records: major pulmonary symptoms, comorbidities, oxygen saturation (Sa02), Medical Research Council (MRC) scale for dyspnea, 6 minute walk test (6MWT), and pulmonary function test results (forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), the ratio FEV1/FVC, residual volume (RV), total lung capacity (TLC), and DLCO).

The statistical analysis was performed using the soft IBM SPSS statistics version 25. We have expressed the results in median and quartiles (for non-continuous variables, such as the MRC score) and the continuous variables (FEV1, FVC, FEV1/FVC, TLC, RV, DLCO) were expressed as mean and standard deviation. For multiple group analysis we used ANOVA test in case of normally distributed variables, and for group discrimination the Tuckey post hock analysis was used. For non-parametric variables we applied the Kruskal Wallis test and the post hock analysis. For calculation of correlation between non-parametric variables we used Spearman rank correlation. The level for statistical significance was $p<0.05$.

Results

After processing the data we have obtained 8 cases of IPF patients, 10 sarcoidosis patients, 7 NSIP patients, 9 HP patients and 6 Hx patients. The mean age in our cohort was 58.95±14.1 years, having the oldest patients (mean 69.7±8.3 years) in the IPF subgroup, and the youngest (mean 38.3±15.6 years) in the Hx group (tab. 1), $p<0.001$. In the general cohort 80% of the patients were older than 50 years.

Table 1

Age distribution through subgroups in the study cohort

Groups	Age Mean±SD
General cohort	58.95±14.11
IPF	69.75±8.26
NSIP	64.86±7.11
Sarcoidosis	61.40±8.81
HP	55.79±12.2
Hx*	38.33±15.58

* – Hx patients were significantly younger than the rest of the subgroups, $p<0.001$

IPF – idiopatic pulmonary fibrosis, **NSIP** – nonspecific indiopatic pneumonia, **HP** – hypersensitivity pneumonitis, **Hx** – Adult Langerhans cell histiocytosis.

In the gender distribution, women slightly prevailed over men (55% vs 45%). Although the gender was distributed statistically homogenous within subgroups ($p = 0.059$), fig. 1 shows a predominance of women in the Sarcoidosis subgroup (7 (70%)) and in HP subgroup (8 (89%)) while in IPF and Hx there was a male predominance.

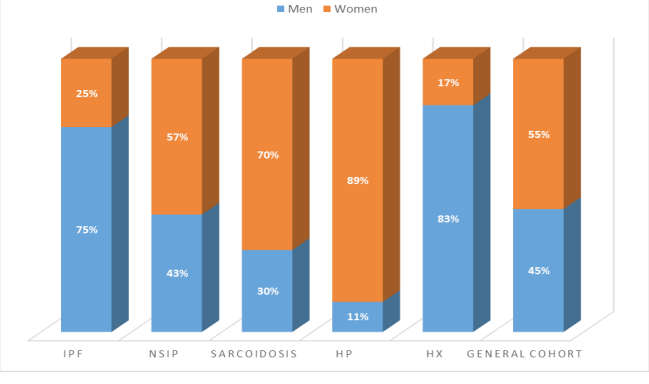

Fig. 1. Gender distribution through groups

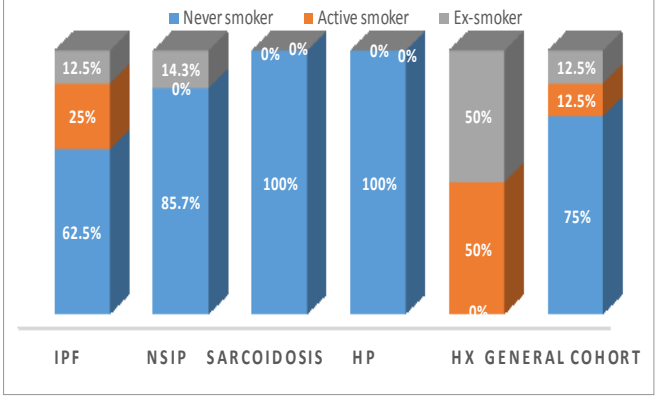

Fig. 2. Smoking status in patients in the general cohort and within subgroups

Since the study analyzes the pulmonary function test, presenting the smoking habits in our cohort is of great interest. As it can be seen from fig. 2, the great majority of our patients were non-smokers (75%). When compared be-

tween groups, there was a statistically significant difference of the prevalence of smokers and ex-smokers from the Hx subgroup (p<0.001) with the rest of them. Other prominent fact is that both sarcoidosis patients and HP patients are 100% never smokers.

Among clinical manifestations of ILD, dry cough is an important symptom, found in 31 (77.5%) cases. Dyspnea is another frequent symptom among patients with ILD. We have checked the impact of dyspnea in different types of ILD using the MRC scale. The median of MRC dyspnea score in the cohort was 3 [2,3]. When compared by subgroups, we found that patients with Hx and patients with sarcoidosis had the same level of dyspnea (p>0.05). Fig. 4 shows that the rank of dyspnea in patients with IPF, HP and NSIP is statistically simmilar and is the most severe. In this way, IPF patients presented significantly more dyspnea when compared to sarcoidosis (p=0.03), or Hx patients (p=0.007). Similarly, HP patients complained of significantly more severe dyspnea when compared to Hx patients (p=0.031) (fig. 3 and 4).

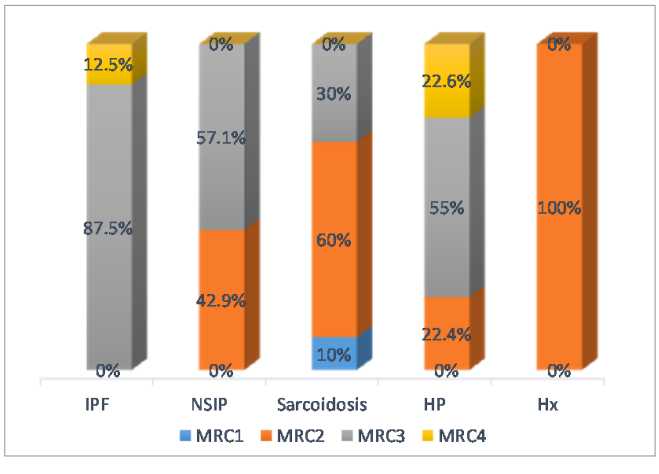

Fig. 3. Dyspnea scores distribution according to MRC scale among groups

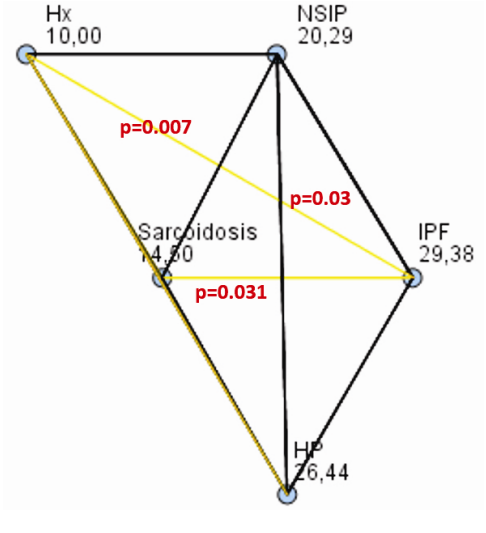

Fig. 4. Pairwise comparison of MRC scale of dyspnea according to groups of ILD

Weight loss of different degree can be also a symptom that may accompany ILD especially in episodes of exacerbation. So, 25 (62.5%) patients didn't experience any modifications in their body weight. Five (12.5%) patients have lost less than 5 kg, 7 (17.5%) patients have lost 5-10 kg, and more than 10kg loss of body weight within a short period of time was documented in 3 cases (7.5%). Both cough and weight loss variables were homogenously distributed among groups (p>0.05).

Analyzing the spectrum of comorbidities (fig. 5), we found that arterial hypertension was the most frequent comorbidity, being registered in almost half of the study cohort (19 (47.5%) patients), diabetes mellitus type II (DM type II) was documented in 10 (25%) cases and ischemic heart disease in 5(12.5%). One of the most severe complications of ILDs that portends a poor prognosis is pulmonary hypertension (PHT), which was found in 7 (17.5%) patients with no predilection for any of the subgroups (p>0.05). Still, PHT was found more frequent in HP patients (33.3%), while in sarcoidosis subgroup we didn't isolate this complication in any of patients. In fig. 5 we can see that arterial hypertension is a frequent comorbidity in the IPF subgroup of patients, probably related to the fact that these are also the oldest patients in our study group. The same age factor (younger age this time) can be attributed to the relative lack of comorbidities in Hx patients. There has been identified a statistically significant difference between the amount of comorbidities in IPF patients vs Hx patients (p = 0.014).

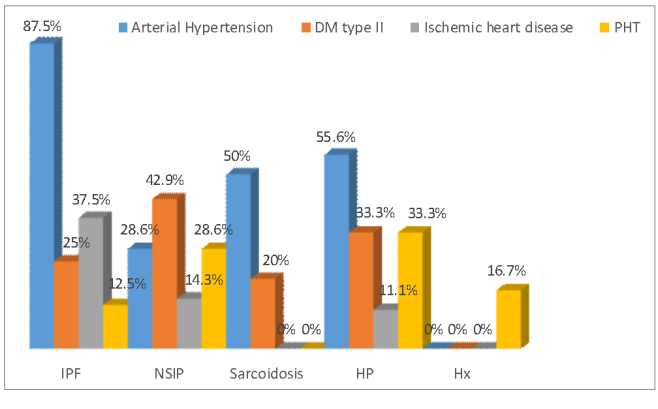

Fig. 5. Comorbidities prevalence within subgroups

In terms of pulmonary function tests we found normal FEV1 (80.8±21.7) and FVC mean values (78.4±21.5), a slightly increased mean RV (127.5±42.1), a mildly decreased mean TLC (88.8±22.3) and a moderately decreased DLCO (52.6±21.5).

According to the ERS/ATS series task force [12], we defined FEV1/FVC below 70% – **as obstructive pattern**, when above 80% – **as restriction**, and between 70% and 80% – **as normal range.** So, based on FEV1/FVC only, we found a predominant restrictive pattern present in 75% of patients from our cohort (fig. 6) with no significant differences among groups (p>0.05).

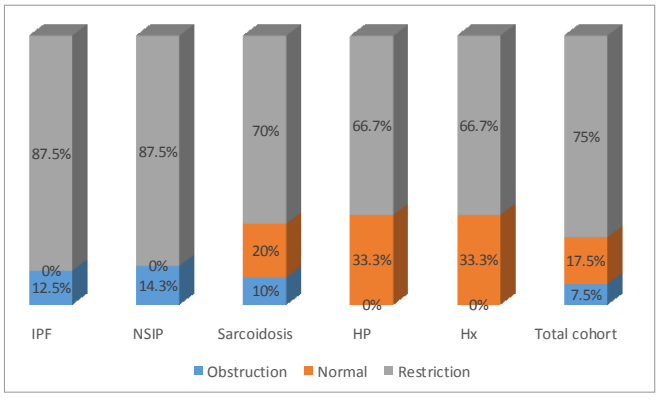

Fig. 6. Distribution of functional patterns based on FEV1/FVC

Similarly, we have analyzed the body-plethysmograph's parameters. We have found the presence of an *air-trapping* pattern, defined as elevated RV [12] (>140% of the predicted) in 13 (32.5%) cases (fig. 7). Hx patients have shown a clear cut statistical difference (p<0.001) in terms of *air-trapping* pattern presence, when compared especially with IPF patients (p<0.001) and with NSIP patients (p<0.002), in which this functional abnormality was absent. The other two diseases have demonstrated a different degree of *air-trapping* pattern, with 10% in the sarcoidosis subgroup and up to 1/3 in HP patients.

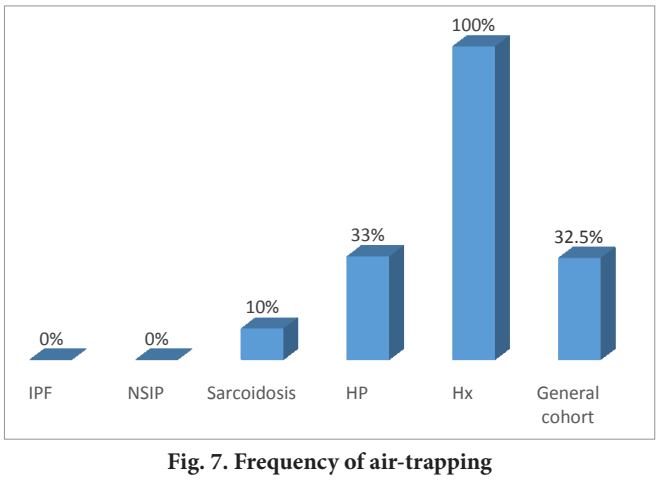

Fig. 7. Frequency of air-trapping

DLCO is one of the most important functional parameters for ILDs. Even though in the general cohort the mean value of DLCO has demonstrated only a mild decrease, we wanted to find out the variation of this parameter within the entities included in the subgroups.

First, we have scaled the severity of DLCO as follows: normal DLCO – values that range between 80 and 140% of the predicted, mild decrease – 80-60%, moderate decrease – 60-40% and severe decrease – less than 40%. In fig. 8 it is shown that we found 2 (5%) patients with normal DLCO in the general cohort, mainly sarcoidosis patients. Within the sarcoidosis subgroup, normal values of DLCO accounted for 20%, while the rest 8 (80%) were patients with mild decrease of DLCO. The highest rate of severely decreased DLCO was registered in the HP subgroup, phenomenon found in 7(78%) patients. We found a statistically significant difference in the distribution of severity of DLCO (p<0.001) between subgroups. The degree of DLCO impairment was significantly different in sarcoidosis patients when compared with IPF subgroup (p=0.042) and HP patients (p<0.001), while IPF patients and NSIP patients had almost identical proportion of categories of DLCO decrease.

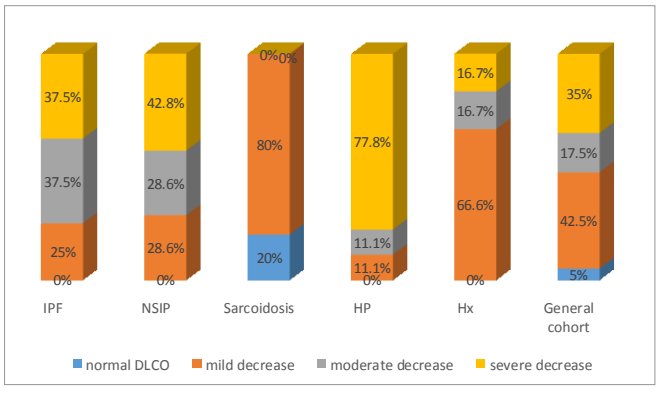

Fig. 8. Distribution of DLCO according to severity

After including the static pulmonary function test, we wanted also to analyze the features of these patients during exercise. So, 6MWT was the easiest test to assess. What we found was a mean of the predicted distance in the general cohort of 67.88±26.7%. So, we have set the cut-off value of 60% of the predicted distance and divided into two categories: under 60% and above 60%. In this way, we have found an acceptable exercise tolerance in 29 (72.5%) cases, while in almost 1/3 the physical tolerance was poor. The biggest proportion of patients with poor exercise tolerance was in the HP subgroup, while the NSIP subgroup had the best results, with statistically significant difference (p=0.041) (fig. 9).

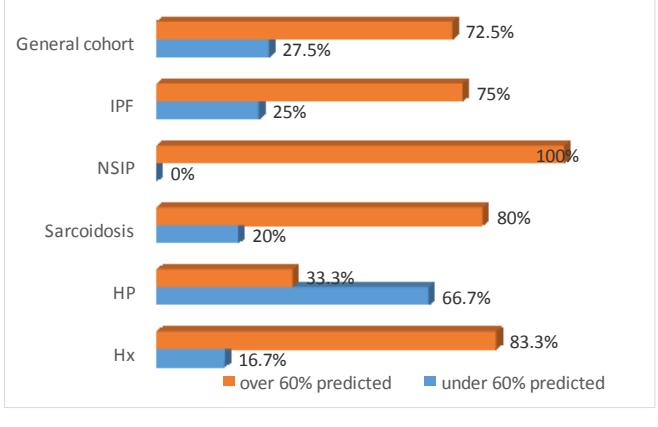

Fig. 9. 6MWT results in the general cohort and within subgroups

Having analyzed all these results, we wanted to find out if any of the clinical features of the ILD patients could reflect the functional abnormalities. Spearman rank correlation analysis (tab. 2) showed that dyspnea score correlates weakly with restriction and inversely with the 6MWT re-

sults, and also a moderate and inverse correlation with DLCO variations. Smoking status as it would be expected correlated weakly with the presence of air trapping changes. Moreover, the correlational analysis established a linear association between PHT and both DLCO and 6MWT.

Table 2

Correlation of clinical parameters with functional abnormalities

	Air-trapping	Restriction	DLCO	6MWT
Dyspnea score	-0.27	0.4*	- 0.57**	-0.43**
Smoking status	0.33*	-0.22	0.03	0.09
Cough	-0.16	0.11	-0.09	0.10
PHT	-0.04	-0.15	-0.43**	-0.45**

– correlation is significant at 0.05 level, ** – correlation is significant at 0.01 level,

PHT – pulmonary hypertension, DLCO – diffusing lung capacity for carbon monoxide, 6MWT – six minute walk test.

Discussion

Interstitial lung diseases commonly share a pattern of physiologic abnormality characterized by a restrictive ventilatory defect and reduced diffusing capacity. Various mechanisms can contribute to these changes, including loss of lung volume, reduced alveolar size, and increased surface tension because of surfactant abnormalities [13]. As a consequence, static lung volumes typically are reduced in ILDs. Our study found that IPF and NSIP in terms of ventilatory changes are very similar, showing a pure restrictive defect. The other 3 entities (sarcoidosis, HP and Hx) besides restriction, showed various degrees and incidence of obstruction. Considering that these 3 diseases share a peribronchiolar predilection of lesions, we supposed that pathological changes in the lung parenchyma and the interstitial space may be reflected in the lung function.

Supporting data also show that airflow limitation can be found in sarcoidosis [4, 9] and in some smoke related interstitial lung diseases, such as histiocytosis [10]. Residual volume is often elevated (likely related to small airways involvement) in sarcoidosis, and hypersensitivity pneumonitis, for example, but is normal or reduced in IPF [14]. In terms of gas exchange, *Boros et al.* stated that DLCO is reduced disproportionately in IPF compared with sarcoidosis, even at comparable lung volumes [15]. We found similar results, having a statistically significant difference between sarcoidosis and both IPF and HP subgroups, while IPF patients and NSIP patients had almost identical proportion of categories of DLCO decrease.

Several authors found that in hypersensitivity pneumonitis the most common finding seems to be reduced DLCO [16, 17]. In our HP patients we found gas exchange impairment in all the cases, with about 3/4 having a severely decreased DLCO. Some publications state that airflow reduction is a common feature for HP, and that it may reflect bronchiolitis, which is a prominent histopathologic feature of acute HP, while emphysema is a common feature among chronic HP patients [2, 18]. Having found the functional *air-trapping* pattern in 1/3 of our HP patients, our results confirm this statement. Moreover, the degree of DLCO reduction could also be explained in our group by the highest prevalence of PHT, an important comorbidity which portends a poor prognosis.

Pulmonary function tests in sarcoidosis typically reveal a restrictive pattern as well, with a reduction in the DLCO, although some studies suggested that airflow limitation may be the most common abnormality in newly diagnosed patients attributed either to narrowing of the bronchial wall because of granulomatous lesions or fibrotic scarring [4, 5, 9], compression by enlarged lymph nodes, airway distortion caused by pulmonary fibrosis, small airway disease, or bronchial hyperreactivity [4, 19, 20].

As we have previously stated in the cases of other entities, in Hx, as well, pulmonary function abnormalities are variable and depend on both the pathological lesions and disease duration [11]. Several studies suggest that, similar to HP and IPF, DLCO reduction in Hx patients is the most common functional abnormality, and can be found in 70–90% of cases [21, 22]. Even though we have registered decreased DLCO in all Hx cases, the degree of severity is significantly different from HP and IPF, having 2/3 of patients with only mildly reduced gas exchange. In fact, in our cohort a common finding was *air-trapping* as well, found in all patients. This could be explained by the fact that Hx is a smoking related disease, and in our subgroup 100% of patients were exposed to smoke, even though studies suggest that the degree of airway obstruction is predominantly related to the bronchiolar location of Hx lesions and not to the amount of total cigarette consumption [21]. In Hx patients, restrictive defect seems to be quite a rare finding [22].

Besides the functional changes, symptoms are a valuable piece in the diagnostic puzzle. We found that IPF, HP and NSIP patients express more symptoms with more severe degree of breathlessness when compared to Hx and sarcoidosis individuals. Our results also showed that the degree of dyspnea is reflected by the gas exchange impairment.

Although we had enough patients to make comparative statistical analysis of the proposed data, our study limitation was the small amount of patients within the subgroups. Due to this fact, we were not able to take into consideration the imaging features, and to identify dominant patterns within the subgroups that would have reflected or possibly predicted the functional disturbances.

Conclusions

Restriction is the dominant functional abnormality of most ILDs, but it coexists in various extents with *air-trapping*, found especially in patients with Hx, HP and sarcoidosis, this finding is related probably to the bronchiolocentric anatomical lesions in these entities. DLCO is almost universally decreased in ILDs, with the lowest levels registered in HP and in IPF patients, while mildly decreased and even normal values can be found in sarcoidosis and in Hx. IPF,

HP and NSIP patients are more dyspneic, while Hx subjects are less symptomatic. Also, IPF patients show more comorbidities, while PHT as a complication is more frequently found in HP. The 6MWT has shown the best results in the NSIP patients and the worst in HP subgroup. Clinical parameters like dyspnea and PHT are directly associated with low DLCO and less walked distance at the 6MWT.

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Authors' contribution
DC acquired, interpreted the data and drafted the first manuscript; DR acquired the data; AD acquired the data; VB designed the trial and revised the manuscript critically. All the authors revised and approved the final version of the manuscript.

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Ethics approval and consent to participate
The research was approved by the Ethic Committee of *Nicolae Testemitanu* State University of Medicine and Pharmacy (protocol No 18 of November 21, 2017).

Conflict of Interests
The authors have no conflict of interests to declare.