Clinico-radiography and pulmonary functional assessment of patients with diffuse parenchymal lung diseases in al-fayoum governorate

Hoda Ali AbouYoussef[a], Youssriah Y.Y. Sabri[c], Assem F. El Essawy[d], Sabah A. Mohamed Hussein[b], Eman K. Ibrahim[b], Mona I. Ahmed[d]

Background Diffuse parenchymal lung diseases (DPLDs) constitute a heterogeneous group of lung diseases characterized by variable degrees of inflammation and fibrosis. In some DPLD, significant morbidity and unfavorable prognosis, comparable to those of neoplastic diseases, are seen. Efficient and safe methods for the diagnosis of DPLD are needed.

Aim of the work To assess the characteristic features of DPLD in Fayoum Governorate based on clinical, radiological, and functional assessment.

Patients and methods This study included 100 patients with undiagnosed DPLD who were selected from the Chest Department, Fayoum University Hospital, during the period from June 2015 to June 2016. All patients were subjected to written informed consent, full medical history, echocardiography, collagen profile, arterial blood gas analysis, spirometry, 6 min walk test, high-resolution computed tomography (HRCT) of the chest and lung biopsy when indicated.

Results Out of the 100 patients included in the study, 72 (72%) were women, 28 (28%) were men, 15 (15%) were smokers, and 73 (73%) had a history of raising birds. The mean age was 45.4 years (range, 8–85 years). HRCT showed different patterns of parenchymal affection. Idiopathic interstitial pneumonia was the predominant diagnosis (51%), followed by DPLD of known cause (33%), then granulomatous DPLD (12%), and lastly other rare forms of DPLD (4%).

Conclusion The historical 'gold standard' of histological DPLD diagnosis is replaced by a 'dynamic integrated approach' using multidisciplinary discussion. The optimal HRCT technique for the evaluation of DPLD is crucial. HRCT of the chest was the diagnostic tool in 75% of the study patients without the need for biopsy.
Egypt J Bronchol 2019 13:125–131
© 2019 Egyptian Journal of Bronchology

Introduction

Diffuse parenchymal lung diseases (DPLDs) represent a heterogeneous group of pulmonary disorders with multiple etiological factors; however, in many disorders the causative factor could not be identified [1]. The previous term 'interstitial' in description of DPLD was misleading, as the pathological process does not involve the interstitium only but also the the alveolar and airway architecture [2].

The clinical course of patients with DPLD is variable; it has usually a chronic course that ranges from 6 months to 10 years at the time of diagnosis; however, some clinical entities present with acute symptoms such as Hamman–Rich syndrome and acute hypersensitivity pneumonitis. Also the rate of physiological deterioration and prognosis are variable depending on the specific etiological factor and the histological pattern [3].

Radiologic imaging has a central role in the diagnosis and follow up of DPLD. The development of high-resolution computed tomography (HRCT) has resulted in marked improvement in diagnostic accuracy of DPLD [4].

Diagnosis of DPLD is often a difficult challenge for clinicians especially when no diagnostic clues are present after a thorough clinical assessment, laboratory examination including serology for specific connective tissue disease and HRCT. The next step will be open lung biopsy which is considered the gold standard in the diagnosis of these entities [5].

The aim of the present study was to assess the characteristic features of DPLDs in Fayoum Governorate on the bases of clinical, radiological, and functional assessment and also to assess the percent of different subtypes of DPLD.

Patients and methods

This prospective study was performed on 100 patients with DPLD who were admitted to the Chest Department, Fayoum University Hospital, during the period between June 2015 and June 2016. Informed consent was obtained from the patients. The study was approved by the Ethics Committee of Kasr Al Ainy School of Medicine, Cairo University.

All patients were submitted to the following to reach a proper diagnosis:

(1) Full history taking including history of smoking, occupational history, history of raising birds, or exposure to injurious agents, history of systemic disease, that is collagen vascular disease, history of medication usage, and history of any other comorbidities.
(2) Full clinical examination.
(3) Routine investigation in the form of complete blood count, aspartate transaminase, alanine transaminase, urea, creatinine, serum glucose, electrolyte profile, coagulation profile as well as serum albumin, tuberculin skin test, microbiological examination of sputum, erythrocyte sedimentation rate, and collagen profile.
(4) Arterial blood gas analysis.
(5) 6-min walk test: with post-test measurement of SpO_2 and pulse rate by the oximeter.
(6) Spirometry was done using MiniSpir MIP s.r.l. 00155 (Roma, Italy) device.
    The following measurements were obtained:

    (a) Forced expiratory volume in the 1 s (FEV_1).
    (b) Forced vital capacity (FVC).
    (c) FEV_1/FVC ratio.
    (d) Peak expiratory flow.
    (e) Forced expiratory flow (FEF), also known as mid-expiratory flow; the rates at 25, 50, and 75% FVC are given.
    Interpreting spirometry:
    (f) Obstructive disorder FEV_1/FVC ratio less than 0.7.
    (g) Restrictive disorder based on decreased FVC and normal or increased FEV_1/FVC ratio (in case no lung volume study is available): mild restriction: FVC 70–80 (% predicted); moderate restriction: FVC 60–69 (% predicted); moderately severe restriction: FVC 50–59 (% predicted); severe restriction: FVC 35–49 (% predicted); very severe restriction: FVC less than 35 (% predicted). FEF_{25-75}% was used for small airway dysfunction assessment: 65–45% for mild affection, 45–25% for moderate affection, and less than 25% for severe affection [6].

(7) Radiological examinations including plain chest radiography and HRCT of the chest. Interstitial lung disease (ILD) protocol for HRCT scanning of the chest:
    (a) Supine imaging: the device used was Asteion Toshiba 4 slice CT scanner, United States, Arizona.
        (1) 1–1.5 mm collimation at 1 cm intervals in full inspiration.
        (2) Measure field of view.
        (3) High spatial frequency reconstruction algorithm (can use bone algorithm on GE machine).
        (4) Full inspiration.
        (5) Window: mediastinum 440 width, level 40; lung 1000 width, level 700 [7].
(6) ECG and echocardiography with pulmonary arterial systolic pressure estimation and full cardiological assessment. The European Society of Cardiology guidelines for the diagnosis of pulmonary hypertension (PH) suggest to consider (a) PH unlikely for tricuspid regurge velocity (TRV) less than or equal to 2.8 m/s, systolic pulmonary artery pressure (SPAP) less than or equal to 36 mmHg (assuming an RAP of 5 mmHg), and no additional echocardiographic signs of PH; (b) PH possible for TRV less than or equal to 2.8 m/s and SPAP less than or equal to 36 mmHg, but the presence of additional echocardiographic signs of PH or TRV of 2.9–3.4 m/s and SPAP of 37–50 mmHg with or without additional signs of PH; and (c) PH likely for TRV more than 3.4 m/s and SPAP more than 50 mmHg with or without additional signs of PH [8].
(7) Bronchoalveolar lavage and transbronchial lung biopsy were done when indicated. Video-bronchoscopy was performed using a flexible videobronchoscopy system (EVIS EXERA II video system center CLV-180 bronchoscope, CLV-180 Xenon light source, and LMD-2140MD LCD monitor; Olympus, Japan). The transbronchial biopsy specimen consists of four to six samples, with at least one sample containing full-thickness bronchial mucosa and some alveolar parenchyma [9].
(8) Medical thoracoscopy lung biopsy, video assisted thoracoscopic surgery (VATS), and open lung biopsy were done when indicted. Thoracoscopic lung biopsy by medical thoracoscopy under local anesthesia using the deviceVISERA laparothoraco videoscope Olympus LTF type V3, CLV-180

Xenon light source, and LMD-2140MD LCD monitor; Olympus, Japan.

(9) Pathological examination of biopsies were done in 25 patients. All biopsy specimens were fixed in 10% formalin and embedded in paraffin wax, sections 4 μm thick were cut from each block and stained with hematoxylin and eosin and were examined under a light microscope.

Statistical analysis

The collected data was organized, tabulated, and statistically analyzed using the statistical package for the social sciences software statistical computer package, version 18 (SPSS Inc., USA). For quantitative data mean, SD, and range were calculated. One-way analysis of variance test was used to compare between different groups of DPLD regarding arterial blood gases (ABG) and spirometric data. For qualitative data, the number and percent distribution were calculated. χ^2 test was used to determine significant associations between different qualitative variables. The significance level was set at P less than or equal to 0.05.

Results

This study included 100 patients with DPLD. They were 28 men and 72 women. Their ages ranged from 8 to 85 years with mean±SD of 45.4±17.0. The main presenting symptoms were shortness of breath and cough for more than 6 months. Regarding risk factors which was identified in the study participants (Table 1), 15 (15%) patients were smokers, three (3%) were exsmokers only, two (2%) were passive smokers, and 80 (80%) were nonsmokers. Biomass exposure was found in 21 (21%) patients. History of raising birds was positive in 73 (73%) patients. Family history was positive in five (5%) patients for DPLDs, and in one (1%) patient for tuberculosis (TB).

In this study, the most common associated medical condition was gastroesophageal reflux disease (GERD), which was identified in 58% of the patients, followed by collagen vascular diseases in 10%, and chronic hepatitis C virus (HCV) in 4% of our patients.

Regarding functional assessment of the study patients (Table 2), echocardiography showed pulmonary hypertension in 42 (42%) patients and right ventricular dilatation in 16 (16%) patients. Estimated pulmonary artery systolic pressure ranged from 30 to 95 mmHg with a mean±SD of 51.2±14.9. Arterial blood gas analysis showed that the PO_2 range was 31–96 with mean±SD 68.10±14.19. The SO_2 range was 56–99 with mean±SD 90.99±8.10. Regarding spirometric data, the FVC% range was from 19 to 129% with mean±SD 49.21±17.44, the FEV_1% range was from 19 to 114% with mean±SD of 46.76±17.61, and the FEV_1/FVC ratio range was from 32 to 100 with mean±SD 82.84±12.29. $FEF_{25–75}$% range was from 11 to 132% with mean ±SD 48.30±26.03. Six-minute walk distance (6MWD) range was from 40 to 480 m with mean±SD 249.96 ±138.84.

In 75 (75%) patients, the diagnosis was based on clinical characteristics and radiological features, while in 25 (25%) patients, the diagnosis required biopsy. Thirteen (13%) patients underwent transbronchial lung biopsy (TBLB), seven (7%) patients underwent image-guided biopsy, two (2%) patients were diagnosed by medical thoracoscopic lung biopsy, one (1%) patient was diagnosed by VATS, one (1%) patient was diagnosed by open lung biopsy, and one (1%) patient was diagnosed by transbronchial lung cryobiopsy.

Table 1 Risk factors among the study participants

Variables	n (%) (N=100)
Smoking	
Nonsmokers	80 (80.0)
Smokers	15 (15.0)
Exsmokers	3 (3.0)
Passive smokers	2 (2.0)
Raising birds	
Yes	73 (73.0)
No	27 (27.0)
Biomass	
Yes	21 (21.0)
No	79 (79.0)
Family history	
Family history of DPLD	5 (5.0)
Family history of TB	1 (1.0)

DPLD, diffuse parenchymal lung diseases; TB, tuberculosis.

Table 2 Functional assessment of study participants

Variables	Mean±SD (N=100)	Range
Pulmonary artery systolic pressure	51.2±14.9	30–95
PH	7.40±0.05	7.29–7.53
$PaCO_2$ (mmHg)	37.89±7.32	23–69
PaO_2 (mmHg)	68.10±14.19	31–96
HCO_3 (mEq/l)	23.86±4.92	11–48
SO_2 (%)	90.99±8.10	56–99
FVC%	49.21±17.44	19–129
FEV_1%	46.76±17.61	19–114
FEV_1/FVC ratio	82.84±12.29	32–100
$FEF_{25–75}$%	48.30±26.03	11–132
6MWD (m)	249.96±138.84	40–480

Functional assessment included arterial blood gases analysis, spirometry, 6-min walk distance, and pulmonary artery systolic pressure. 6MWD, 6-min walk distance; FEF, Forced expiratory flow; FEV_1, forced expiratory volume in the 1 s; FVC, forced vital capacity; PH, pulmonary hypertension.

Idiopathic interstitial pneumonia was the predominant diagnosis; it was found in 51% of the study patients [idiopathic pulmonary fibrosis (IPF) cases were 18 (18%), the nonspecific interstitial pneumonia cases were 11 (11%), the cryptogenic organizing pneumonia cases were 8 (8%), the respiratory bronchiolitis ILD cases were 5 (5%), and the desquamative interstitial pneumonia was 1 (1%) case. Idiopathic lymphocytic interstitial pneumonia were 2 (2%) cases, idiopathic pleuroparenchymal fibroelastosis cases were 6 (6%)], followed by DPLD of known cause [33 (33%) cases included collagen associated in 10 (10%) cases, chronic hypersensitivity pneumonitis in 14 (14%) cases, malignancy in eight (8%) cases, alveolar proteinosis in 1 (1%) case], then granulomatous DPLD in 12 (12%) cases [included sarcoidosis in 11 (11%) cases and TB in 1 (1%) case], and lastly other rare forms of DPLD in four (4%) cases [included three (3%) cases of lymphangioleomyomatosis, and 1 (1%) case of idiopathic pulmonary hemosiderosis] (Table 3).

HRCT of the chest showed different patterns of parenchymal affection (Fig. 1) in the form of reticular pattern in 54 (54%) patients, ground glass opacity in 39 (39%) patients, honey combing in 23 (23%) patients, nodular in 19 (19%) patients, consolidation in 11 (11%) patients, dense fibrosis in 10 (10%) patients, bronchocentric nodules in nine (9%) patients, subpleural sparing in six (6%) patients, halo sign in three (3%) patients, cysts in five (5%) patients, tree in bud in three (3%) patients, beaded fissure in three (3%) patients; other findings were air trapping in one (1%) patient, crazy paving in 1 (1%) patient, and associated mediastinal lymphadenopathy in 20% of the cases.

Discussion

DPLD represent a wide scale of pulmonary disorders with more than 200 different disease entities. The clinical course of these disorders is usually chronic and associated high mortality. The most common features of DPLD are diffuse pulmonary infiltrates, worsening of pulmonary functions, and impairment of gas exchange [10]. The present research studied clinical, radiological, and functional characteristics of DPLD patients in Fayoum Governorate and assessed the percent of each subtype of DPLD.

The number of patients included in the study was 100 of different ages ranging from 8 to 85 years, mean 45.4±17.0. They were predominantly women, 72 (72.0%) patients and men were 28 (28.0%) patients. These results were matched with another study which was conducted on patients with DPLD selected from the Chest Department inpatients, Kasr Al Ainy Hospital during the period from June 2103 to August 2015. Their ages ranged from 10 to 67 years with a mean±SD value of 39.96±13.31. They included 32 (58.2%) women and 23 (41.8%) men [11].

Also, this was matched with another study performed on 30 nonusual interstitial pneumonia (UIP) patients with diffuse lung infiltrates on HRCT of the chest of unconfirmed diagnosis selected from the Chest Department inpatients, Kasr Al Ainy Hospital (between March 2013 and October 2014). The mean±SD age for the study sample was 36.7±14.1 years with a minimum of 15 years and a maximum of 70 years. They were 18 (60%) female patients and 12 (40%) male patients [12]. However, other authors have found a slight male predominance [13], which may be explained by the disease heterogeneity and different sample ethnicity.

There are many risk factors associated with the injurious effect on DPLD, for example smoking,

Table 3 Spectrum of diffuse parenchymal lung diseases among the study participants

Diagnoses	n (%) (N=100)
Idiopathic interstitial pneumonias [51 (51%)]	
IPF	18 (18.0)
NSIP	11 (11.0)
COP	8 (8.0)
PPFE	6 (6.0)
RBILD	5 (5.0)
LIP	2 (2.0)
DIP	1 (1.0)
Granulomatous DPLD [12 (12%)]	
Sarcoidosis	11 (11.0)
Tuberculosis	1 (1.0)
DPLD of known cause [33 (33%)]	
HP	14 (14.0)
UIP (collagen)	5 (5.0)
NSIP (collagen)	4 (4.0)
Bronchiolitis (collagen)	1 (1.0)
Adenocarcinoma	5 (5.0)
Alveolar carcinoma	1 (1.0)
Metastatic adenocarcinoma	1 (1.0)
Signet ring carcinoma	1 (1.0)
Alveolar proteinosis	1 (1.0)
Other forms of DPLD [4 (4%)]	
Idiopathic pulmonary hemosiderosis	1 (1.0)
LAM	3 (3.0)

COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; DPLD, diffuse parenchymal lung diseases; HP, hypersensitivity pneumonitis; IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleomyomatosis; LIP, lymphocytic interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; PPFE, pleuroparenchymal fibroelastosis; RBILD, respiratory bronchiolitis interstitial lung disease; UIP, usual interstitial pneumonia.

Figure 1
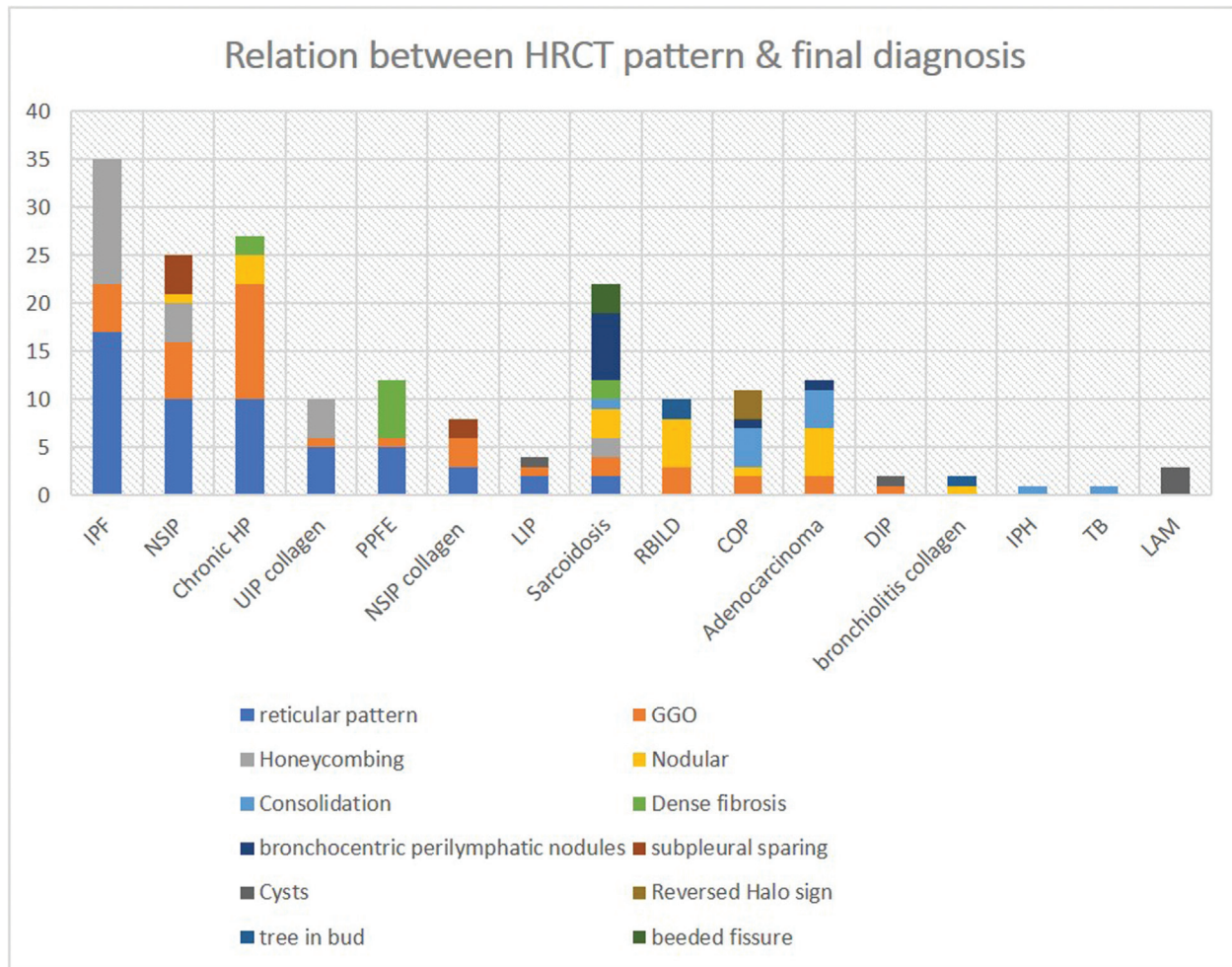
Bar chart showing the relation between HRCT pattern and final diagnosis. COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleomyomatosis; LIP, lymphocytic interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; PPFE, pleuroparenchymal fibroelastosis; RBILD, respiratory bronchiolitis interstitial lung disease; TB, tuberculosis; UIP, usual interstitial pneumonia.

pollution, etc. Table 1 represents the risk factors of the study participants. Positive smoking history was found in 20 (20.0%) patients and this was in agreement with a study performed by Ahmed *et al.* [11], who found a positive smoking history in 25.5%. Also, some authors reported that smoking causes subclinical parenchymal lung affection which could be detected by spirometry and CT imaging, and this supports that smoking is considered as a risk factor for DPLD [14]. Regarding other risk factors in the present study, biomass exposure was positive in 21 (21%) patients, history of raising birds was positive in 73 (73%) patients, family history was positive in five (5%) patients for DPLDs, and in one (1%) patient for TB.

It is well known that avian antigens are extremely potent inducers of immunologic lung disease, and a careful search for their presence must be included in the history taking of patients with suspected hypersensitivity pneumonitis [15].

In this study, the most common associated medical condition was GERD, which was identified in 58% of patients, followed by collagen vascular diseases in 10% (rheumatoid arthritis was found in nine patients and mixed connective tissue in one patient), and chronic HCV in 4% of our patients. It is well known that chronic microaspiration is responsible for the initial insult of the lung parenchyma which in turn results in abnormal wound healing and activation of cascade of pulmonary fibrosis [16].

Some authors have found a strong association between IPF and GERD. They confirmed GERD diagnosis in 68–94% of their studied patients with IPF [17]. This matched with the present study as a history of GERD was found in 58% of the study group. Collagen vascular diseases were identified in 10% of our patients, this was matched with another study,which found positive collagen profile in 21.8% of their patients [11]. Many authors found a relationship between IPF and

liver cirrhosis caused by hepatic C [18]. This may explain HCV-associated DPLD in the present study.

Functional assessment of the study patients included echocardiography, ABGs analysis, spirometry, and 6MWD. Pulmonary hypertension was found in 42 (42%) patients and right ventricular dilatation in 16 (16%) patients. Estimated pulmonary artery systolic pressure ranged from 30 to 95 mmHg with a mean±SD of 51.2±14.9. Arterial blood gas analysis in the study group revealed that the PaO_2 range was 31–96 mmHg with a mean±SD of 68.10±14.19. The SaO_2 range was 56–99% with a mean±SD of 90.99±8.10. Regarding spirometry results, about 89% of the patients showed a restrictive pattern. FVC% range was from 19 to 129% with a mean±SD of 49.21±17.44. The FEV_1% range was from 19 to 114% with a mean±SD of 46.76±17.61. The FEV_1/FVC ratio range was from 32 to 100 with a mean±SD of 82.84±12.29. The FEF_{25-75}% range was from 11 to 132% with a mean±SD of 48.30±26.03. The 6MWD range was from 40 to 480 m with a mean±SD of 249.96±138.84 (Table 2).

In a study done on 79 patients with ILD, they documented the diagnosis of PH in about 32% of their patients [19]. Another study was conducted on 124 patients with advanced IPF who underwent an evaluation for lung transplantation by right heart catheterization, the diagnosis of PH was confirmed in 44% of the patients [20]. These studies showed an overall high rate of PH-ILD especially in patients with advanced disease and this was matched with this study results.

Regarding pulmonary function testing, it is recommended in the management of patients with DPLD because it is important to establish disease severity, define prognosis, and to monitor response to therapy and disease progression [21]. In a study performed on 30 non-UIP patients, it was found that 93% of the patients had restrictive pattern with mean ±SD values of FVC being 54.03±15.82% with a minimum of 12% and maximum of 84% [12], which is matched with our findings. Some authors studied 6MWD in patients with ILD; they found that patients with reduced 6MWD and exertional desaturation had poorer prognosis with worse 4-year survival rate [21].

Tissue biopsy was done in 25% of the study patients and in 75 (75%) patients diagnosis was established based on clinical characteristics and radiological features. Some researchers stated that lung biopsy is required for the diagnosis of DPLD in about one-third of their patients. Transbronchial biopsy is less painful, less invasive, and considerably less costly, compared

with open or thoracoscopic procedure, and entails a lower incidence of mortality and morbidity. However open or thoracoscopic lung biopsy have higher diagnostic yield [22]. Although pathologic diagnosis is a very important way to confirm the diagnosis of DPLD and to classify the disease into a specific category, pathologic results should be interpreted with the clinical information [23]. For example, in our study there were four patients with a radiological pattern of UIP, who were categorized as rheumatoid arthritis related DPLD 'UIP RA.' Thus, confirmation of the diagnosis requires multidisciplinary decision that clinicians, radiologists, and pathologists confer together. Also, rheumatologist and pulmonologist interdisciplinary discussion is recommended.In this study, idiopathic interstitial pneumonia was the predominant diagnosis, It was found in 51 (51%) cases of the study patients [IPF cases in 18 (18%), nonspecific interstitial pneumonia cases in 11 (11%), cryptogenic organizing pneumonia cases in eight (8%), respiratory bronchiolitis ILD cases in five (5%), desquamative interstitial pneumonia in one (1%) case, idiopathic lymphocytic interstitial pneumonia in two (2%) cases, and lastly idiopathic pleuroparenchymal fibroelastosis in six (6%) cases], followed by DPLD of known cause in 33 (33%) cases [included collagen associated in 10 (10%) cases, chronic hypersensitivity pneumonitis in 14 (14%) cases, malignancy in eight (8%) cases, alveolar proteinosis in one (1%) case], then granulomatous DPLD in 12 (12%) cases [included sarcoidosis in 11 (11%) cases and TB in one (1%) case] and lastly other rare forms of DPLD in four (4%) cases [included three (3%) cases of lymphangioleomyomatosis and idiopathic pulmonary hemosiderosis in one (1%) case] (Table 3).

These results matched with those who reported that idiopathic interstitial pneumonia (43.64%) was the predominant diagnosis within 55 DPLD patients involved in their study [11]. Also another author found that 40% of their patients were diagnosed as idiopathic interstitial pneumonias (IIP), 23.3% granulomatous lung disease with higher percentage of malignancy in about 13.3% [12]. In contrast some authors studied DPLD found that the most common diagnoses were neoplasm in 40% of the study group [24]. The difference between their data and this study data may be related to the differences in sample size, ethnicity, and environmental factors.

Regarding HRCT of the chest patterns of parenchymal affection (Fig. 1), it revealed reticular pattern in 54 (54%) patients, ground glass opacity in 39 (39%)

patients, honey combing in 23 (23%) patients, nodular in 19 (19%) patients, consolidation in 11 (11%) patients, cysts in five (5%) patients, crazy paving in one (1%) patient, dense fibrosis in 10 (10%) patients, bronchocentric nodules in nine (9%) patients, subpleural sparing in six (6%) patients, halo sign in three (3%) patients, tree in bud in three (3%) patients, beaded fissure in three (3%) patients, and air trapping in one (1%) patient.

Conclusion

In conclusion, the historical 'gold standard' of histologic DPLD diagnosis is replaced by a 'dynamic integrated approach' using multidisciplinary discussion. The optimal HRCT technique for the evaluation of DPLD is crucial. Also semiquantitative HRCT scoring methods have been developed to give a more exact evaluation of the quantity and type of DPLD abnormalities [25]. HRCT of the chest was the diagnostic tool in 75% of the study patients without the need for biopsy. The meticulous clinical, radiological, and physiologic assessment for DPLD patients allowed accurate diagnosis noninvasively reducing the need for intervention.

Conflicts of interest
There are no conflict of interest.

References

1 Belloli EA, Beckford R, Hadley R, Flaherty KR. Idiopathic non-specific interstitial pneumonia. *Respirology* 2016; **21**:259–268.

2 Talmadge KE Jr. Approach to the adult with interstitial lung disease: clinical evaluation. *UpToDat* 2014; 214.

3 Raghu G, Chen SY, Yeh WS, Maroni B, Li Q, Lee YC, Collard HR. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001–11. *Lancet Respir Med* 2014; **2**:566–572.

4 Desai SR, Wells AU. Imaging. In: Costabel U, Du Bois RM, Egan JJ, (eds). *Diffuse parenchymal lung disease*. Basel: Karger 2007. 36: 29–43.

5 Travis WD, Costabel U, Hansell DM, King TE Jr, David A. An official AmericanThoracic Society/European Respiratory Society Statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care* 2013; **188**:733–748.

6 Perez LL. Office spirometry. *Osteopathic Fam Physician* 2013; **5**:65–69.

7 Webb WR, Muller NL, Naidich DP. *High-resolution CT of the lung* (5th ed.). In: Lawrence R. Goodman (ed). LWW 2014. 752.

8 Bossone E, D'Andrea A, D'Alto M, Citro R, Argiento P, Ferrara F, *et al.* Echocardiography in pulmonary arterial hypertension from diagnosis to prognosis. *J Am Soc Echocardiogr* 2013; **26**:1–14.

9 Sehgal IS, Bal A, Dhooria S, Agrawal P, Gupta N, Ram B, *et al.* A prospective randomized controlled trial comparing the efficacy and safety of cup vs alligator forceps for performing transbronchial lung biopsy in patients with sarcoidosis. *Chest* 2016; **149**:1584–1586.

10 Clement A, Nathan N, Epaud R, Fauroux B, Corvol H. Interstitial lung diseases in children. *Orphanet J Rare Dis* 2010; **5**:22.

11 Ahmed S, El Hindawi A, Mashhour S. Spectrum of diffuse parenchymal lung diseases using medical thoracoscopic lung biopsy: an experience with 55 patients during 2013–2015. *Egypt J Chest Dis Tuberc* 2016; **65**:717–722.

12 Abdel Salam E. *Medical thoracoscopy for diagnosis of DPLD other than UIP [MD thesis]*. Cairo: Faculty of Medicine, Cairo University. 2015.

13 López-Campos J, Rodríguez-Becerra E; Neumosur Task Group; Registry of Interstitial Lung Diseases. Incidence of interstitial lung diseases in the south of Spain 1998-2000: the RENIA study. *Eur J Epidemiol* 2004; **19**:155–161.

14 Lederer DJ, Enright PL, Kawut SM, Hoffman EA, Hunninghake G, van Beek EJR, *et al.* Cigarette smoking is associated with subclinical parenchymal lung disease the multi-ethnic study of atherosclerosis (MESA)-lung study. *Am J Respir Crit Care Med* 2009; **180**: 407–414.

15 McSharry C, Dye GM, Ismail T, Anderson K, Spiers EM, Boyd G. Quantifying serum antibody inbird fanciers' hypersensitivity pneumonitis. *BMC Pulm Med* 2006; **6**:16.

16 Appel JZ, Lee SM, Hartwig MG, Li B, Hsieh CC, Cantu E IIIrd, *et al.* Characterization of the innate immune response to chronic aspiration in a novel rodent model. *Respir Res* 2007; **8**:87.

17 Raghu G, Freudenberger TD, Yang S, Curtis JR, Spada C, Hayes J, *et al.* High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. *Eur Respir J* 2006; **27**:136–142.

18 Manganelli P, Salaffi F, Pesci A. Hepatitis C virus and pulmonary fibrosis. *Recenti Prog Med* 2002; **93**:322–326.

19 Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest* 2006; **129**:746–752.

20 Hamada K, Nagai S, Tanaka S, Handa T, Shigematsu M, Nagao T, *et al.* Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. *Chest* 2007; **131**:650–656.

21 Martinez FJ, Flaherty K. Pulmonary function testing in idiopathic interstitial pneumonias. *Proc Am Thorac Soc* 2006; **3**:315–321.

22 Ishie RT, Cardoso J, Silveira RJ, Stocco L. Video-assisted thoracoscopy for the diagnosis of diffuse parenchymal lung disease. *J Bras Pneumol* 2009; **35**:234–241.

23 Wuyts W. Surgical lung biopsy is not the golden standard in diagnosis of diffuse parenchymal lung diseases. *Eur J Cardiothorac Surg* 2008; **34**:1271–1272.

24 Chang AC, Yee J, Orringer MB, Iannettoni MD. Diagnostic thoracoscopic lung biopsy: an outpatient experience. *Ann Thorac Surg* 2002; **74**:1942–1947.

25 Faraga TS, Adawya ZR, Sakrb LK, Abdellateefa HS. Transthoracic ultrasonographic features of diffuse parenchymal lung diseases. *Egypt J Bronchol* 2017; **11**:179–187.