Clinical Retrospective Analysis of Interstitial Lung Disease Patients Associated with Pulmonary Hypertension

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Background: Pulmonary hypertension is a common complication of interstitial lung disease. This study was conducted to retrospectively analyze the incidence of pulmonary hypertension among interstitial lung disease patients and the correlation between systolic pulmonary artery pressure (PASP) and pulmonary functions. We also intended to investigate whether antinuclear antibody (ANA) could be an effective indicator of pulmonary hypertension.

Material/Methods: There were 182 patients diagnosed with interstitial lung disease through high-resolution computed tomography (HRCT). Pulmonary hypertension was defined as an increase of mean pulmonary arterial pressure (PAPm) ≥25 mmHg (~PASP ≥40 mmHg) at rest. Severe pulmonary hypertension was defined as PAPm ≥35 mmHg. There were 104 cases including in this study. There were 67 cases from the ANA positive (ANA+) group and 37 cases from the ANA negative (ANA–) group. All study patients had pulmonary function tests, which included the measurements of maximal voluntary ventilation (MVV), residual volume (RV), total lung capacity (TLC), forced expiratory volume (FVC), vital capacity (VC), and diffusing capacity of the lungs for carbon monoxide (DLCO).

Results: The pulmonary hypertension incidence in the study cohort was 25%, and the severe pulmonary hypertension incidence was 6.48%. The incidence of pulmonary hypertension in ANA+ cases was 22.22%. The incidence of pulmonary hypertension in the ANA– cases was 32.14%. The lung function test results showed moderate relationships between DLCO, FVC%, VC%, and PASP; no relationship between MVV, FEV1/FVC%, RV/TLC, and PASP; minimum relationship between FVC%, VC%, and PASP in the ANA+ group; and moderate relationship between FVC%, VC%, and PASP in the ANA– group.

Conclusions: Pulmonary hypertension occurred in 25% of the 182 interstitial lung disease patients and was negatively associated with deteriorated lung functions (specifically VC%, FVC%, and DLCO parameters). ANA level was not associated with the prognosis of pulmonary hypertension of patients with interstitial lung disease, and it did not significantly affect the correlation between PASP and pulmonary functions. Thus, ANA level did not seem to be a necessary indicator of pulmonary hypertension, and a more effective treatment method for pulmonary hypertension of patients with interstitial lung disease is urgently needed.

MeSH Keywords: Lung Diseases, Interstitial • Persistent Fetal Circulation Syndrome • Respiratory Function Tests

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Background

The interstitium is a network of connective tissue and localizes between the alveolar and capillary basement membrane (parenchymal) around the bronchi and vasculature, and between the pleura and interlobular septae (sub pleural) [1,2]. Interstitial lung disease (ILD) is a panel of lung conditions that affect the interstitium and result in connective tissue fibrosis [3,4], which therefore leads to thickened interstitial tissue replacing healthy capillaries, alveolar and interstitium [5–8]. Due to similar clinical, radiologic, pathologic, and physiologic presentations, more than 200 connective tissue disorders, such as rheumatoid arthritis (RA), systemic sclerosis, and systemic lupus erythematosus (SLE), are classified together. These disorders occur as either a primary condition involving the lung parenchyma or a substrate of multiorgan involvement [9]. The diagnosis of ILD is commonly performed using high resolution computed tomography (HRCT) scan and biopsy. Lung function tests such as spirometry and diffusion capacity of carbon monoxide (DLCO) are also conducted to assess the severity of ILD [9].

An increase of mean pulmonary arterial pressure (PAPm) of ≥25 mmHg at rest defines pulmonary hypertension (PH). The occurrence of PH to those with ILD can worsen the impaired quality of lung functions especially when the PAPm exceeds 35 mmHg, which defines severe PH [10,11]. PH is a clinical manifestation of many lung diseases, including ILD and pulmonary fibrosis. The presentation of PH is similar; there is reduced exercise capacity and poor survival outcome [12–17]. Right heart catheterization (RHC) is the gold standard for PH diagnosis, while echocardiography is used for screening [18,19]. The most frequent cause of mortality of patients with ILD is due to respiratory failure; a previous study showed that PH is a marker of early mortality of ILD [20].

To date, the research regarding ILD-associated PH has been under slow development. Most published studies have been focused on lung transplant-, idiopathic pulmonary fibrosis (IPF)-, sarcoidosis- and systemic sclerosis-related PH. Different ILD types predict different PH incidence. To have a better view of the prevalence of PH among the patients with ILD, this research used a retrospectively study of the association of PH in patients with various types of ILD. We also grouped our participants into ANA+ and ANA– groups to see whether ANA played an important part in PH prognosis. In this study, we found that PH occurred in 25% of the 182 ILD patients and severe PH occurred in 6.48% of all the ILD patients. PASP was found negatively associated with deteriorated lung functions (specifically VC%, FVC%, and DLCO parameters). ANA level was not associated with the prognosis of PH in patients with ILD, and it did not significantly affect the correlation between PASP and pulmonary functions. Our outcome suggested that ANA level did not seem to be a useful indicator of ILD-related PH. And considering the

high incidence rate of PH among ILD patients, a more effective treatment method for PH of ILD patients is urgently needed.

Material and Methods

Patient inclusion and exclusion criteria

Patients who were diagnosed as ILD through high-resolution computed tomography (HRCT) in Shandong Provincial Hospital and Taishan Medical College affiliated Laigang Hospital Respiratory Medicine Department during October 2012 and December 2016 were enrolled in this study. Patients with congenital heart disease, left heart failure, chronic thromboembolism, lung cancer, chronic lung diseases (e.g., bronchial asthma, chronic obstructive pulmonary disease, and bronchiectasia), pleura disease, as well as other cardiac, pulmonary, liver, and blood vessel diseases were excluded. Also, those with a history of thoracic operation, and human immunodeficiency virus (HIV) infection were excluded from this study. The study was approved by the ethics committee of the hospital (No. A20120919).

PH definition and characteristics of included patients

We used the diagnosis criteria of the 2015 European Society of Cardiology (ESC) and the European Respiratory Society (ESC/ERS) Guidelines for the diagnosis and treatment of PH, which defined PH as an increase of PAPm ≥25 mmHg (~PASP ≥40 mmHg) at rest as diagnosed by right heart catheterization (RHC). In this study, we were particularly interested in patients with PH due to ILD (classified into group 3.2 according to the 2015 ESC/ERS Guidelines). The baseline characteristics of the included patients are shown in Tables 1 and 2.

Echocardiography and RHC

The accuracy of echocardiography in diagnosis of PH is low in patients with advanced lung disease, however, it still is the most widely used tool for PH diagnosis [21,22]. The procedure for Doppler echocardiography of a previous research [11] was employed. Briefly, the maximal tricuspid regurgitation velocity was measured and the tricuspid pressure regurgitation gradient (TR) signal was obtained. TR >40 mmHg was screened out for RHC (a sterile catheter was used for each patient), the gold standard for PH diagnosis. The 182 diagnosed patients were divided into antinuclear antibody (ANA)+ and ANA– groups. There were 126 in the former group, and 56 in the latter group.

Pulmonary function tests

Tested pulmonary function parameters included maximal voluntary ventilation (MVV), residual volume (RV), total lung capacity (TLC), forced expiratory volume in 1 second (FEV1), vital

Table 1. Baseline characteristics of the included patients.

Characteristics	No. (%)
Age, years	60.9±13.7
Gender	
Male	92
Female	90
BMI, kg/m²	27.8±5.4
Systolic pulmonary pressure, mmHg	54.6±7.6
ANA positive (n=126)	
Systemic lupus erythematosus (SLE)	13
Rheumatoid arthritis (RA)	20
Sjogren Syndrome	10
Overlap syndrome	12
Non-identified connective tissue disease	5
Cryptogenic organizing pneumonitis (COP)	5
Idiopathic pulmonary fibrosis (IPF)	3
Others	58
ANA negative (n=56)	
Suspected RA	3
Idiopathic pulmonary fibrosis (IPF)	3
Non-identified ILD	50

Table 2. Baseline characteristics of the patients who had lung function test (n=104).

Characteristics	NO. (%)
Age, years	51±10.5
Gender	
Male	54
Female	50
BMI, kg/m²	27.2±4.8
Systolic pulmonary pressure, mmHg	46.2±5.1
Lung function parameters	
MVV, L/min	77.38±28.3
VC%	70.62±20.74
RV/TLC%	39.40±13.32
FVC%	67.66±19.93
FEV1/FVC	88.35±10.36
DLCO	50.96±23.11
ANA positive (n=67)	
Systemic lupus erythematosus (SLE)	5
Rheumatoid arthritis (RA)	11
Sjogren Syndrome	6
Overlap syndrome	9
Non-identified connective tissue disease	3
Cryptogenic organizing pneumonitis (COP)	5
Idiopathic pulmonary fibrosis (IPF)	2
Others	26
ANA negative (n=37)	
Suspected RA	2
Idiopathic pulmonary fibrosis (IPF)	3
Non-identified ILD	32

MVV – maximal voluntary ventilation; RV – residual volume; TLC – total lung capacity; FVC – forced expiratory volume; VC – vital capacity; DLCO – diffusing capacity of the lungs for carbon monoxide.

capacity (VC)%, forced vital capacity (FVC)%, and diffusing capacity of the lungs for carbon monoxide (DLCO) following the American Thoracic Society guidelines. The pulmonary function parameters were measured using a Zan 100 PC-based diagnostic spirometer (nSpire Health Inc, KY, CO, USA).

Statistical analysis

SPSS 17.0 was used to analyze the correlation between PASP levels and pulmonary function parameters as well as other baseline characteristics. Normally distributed data are expressed as means ± standard deviation, non-parametric data are expressed as mean with range. *P*<0.05 was set as the statistical significance threshold. Chi-square test was used to compare the incidence rate of PH of different groups. Linear regression was performed with variables of interest.

Results

The incidence rate of PH among patients with ILD

Among the 182 patients diagnosed with ILD, 54 had PASP higher than 40 mmHg, suggesting a PH incidence rate of

29.67%. In addition, 14 of the 182 patients had PASP higher than 60 mmHg, indicating a 7.69% incidence rate of severe PH. Antinuclear antibodies (ANA) is one of the markers of autoimmunity commonly used in clinical practice [23]. A higher ANA level has been shown to predict a better prognosis [24]. We calculated the incidence rate of PH among the patients diagnosed with ILD to see whether a higher ANA level was associated with a better prognosis of PH. In our study, the PH incidence rate in the ANA+ group was 22.22% (28 out of 126 patients), whereas in the ANA– group, it was 32.14% (18 out

Table 3. The incidence rate of PH among patients diagnosed with ILD that went through echocardiography in ANA+ and ANA– groups.

	Number	The number of patients with PH	PH incidence rate
ANA+	126	28	22.22%
ANA–	56	18	32.14%
ANA diagnosed cases	182	46	25.30%

PH – pulmonary hypertension; ILD – interstitial lung disease; ANA – antinuclear antibody.

Table 4. The correlation between PASP and pulmonary function indexes.

Group	The correlation coefficient r		
	VC%	FVC%	DLCO
ANA+ (N=67)	−0.482	−0.506	−0.676
ANA– (N=37)	−0.783	−0.725	−0.713
Total	−0.645	−0.614	−0.681

of 56 patients, see Table 3). No significant difference of the PH incidence rate between the ANA+ group and the ANA– group was noted, suggesting that the ANA level was not associated with the prognosis of patients with ILD.

The correlation between PASP and pulmonary function parameters

Among all the 104 patients who underwent pulmonary function tests, it was found that PASP was significantly negatively correlated with VC%, FVC%, and DLCO. PASP was found not significantly correlated with MVV, FEV1/FVC%, and RV/TLC in this case. Additionally, in neither the ANA+ group or the ANA– group was PASP found significantly negatively correlated with VC%, FVC% and DLCO (see Table 4 and Figures 1–3, data regarding MVV, FEV1/FVC% and RV/TLC are not shown).

Discussion

In this research, we studied the prevalence of PH among patients with ILD and the relationship between ILD-associated PH and pulmonary functions. Patients with various types of ILD were included in this research. The prevalence of PH in our study cohort was 25% and severe PH was 6.48%. PASP was demonstrated to have significant correlations with VC%, FVC%, and DLCO in despite of ANA level.

The prevalence of PH has varied in different study cohorts. For instance, 212 patients with mixed types of ILD were included in a study by Anderson et al., and 14% of these patients had PH with 25 mmHg and 35 mmHg defined as the threshold for mild and severe PH, respectively [9]. In the Andersen et al. study 18 patients went through RHC to eliminate false positives and

negatives produced from echocardiography diagnosis for PH. In a study by Nadrous et al. in a tertiary center, 88 patients with IPF, in whom PASP were assessed with transthoracic echocardiography, the mean PASP ranged from 28 mmHg to 116 mmHg [25]. In the Nadrous et al. study, RHC, which is used to confirm the presence and degree of PH, was not conducted. A study by Handa et al. of 246 consecutive Japanese sarcoidosis patients who were evaluated for PH (defined as PASP ≥40 mmHg) by Doppler echocardiography found that 5.7% of the participants had PH [26]. Another retrospective study analyzing a large number of RHC data from patients registered with the ultrasound lung transplant registry showed that 46.1% of patients with IPF waiting for lung transplantation had PH [27]. During 2004 and 2005, David et al. performed a retrospective study on 454 patients with IPF who were registered for lung transplantation with the United Network for Organ Sharing; 376 patients underwent RHC and 36% of them had PH [28]. Our analysis revealed that PH affected ~25% of the included participants, and severe PH was relatively infrequent at 6.48%. The incidence rate of PH in patients with ILD can be very different due to the type of ILD, the severity of ILD, and the diagnostic method of PH. We hypothesized that the most possible reason for the difference between our result and the result of the Anderson et al. study, was because of the different physiological conditions of the study cohorts. Both studies both enrolled mixed types of ILDs, and our cohort included in-patients, suggesting a severe condition of disease in these patients. Compared to other studies, our patient cohort had mixed types of ILD, whereas most of the other studies included cohorts with only one type. Lastly, it is notable that the incidence rate of PH of our cohort was 25%, whereas normally it has been reported that 30% to 40% of patients with ILD have PH. This is primarily because we used the internationally recognized definition whereas PASP ≥30/35 mmHg as this value has been defined as the criteria for PH in China.
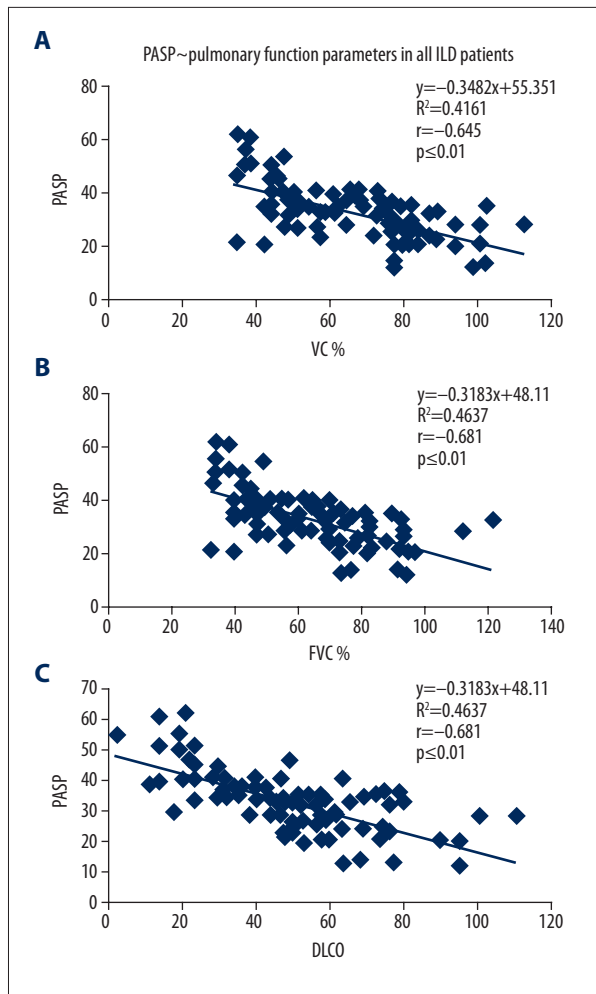
Figure 1. The correlation between the PASP of ILD patients and the pulmonary function parameters. (**A**) The correlation between the PASP (x-axis) of ILD patients and VC% (y-axis). (**B**) The linear correlation between the PASP (x-axis) of ILD patients and FVC% (y-axis). (**C**) The linear regression analysis of the PASP (x-axis) of ILD patients and DLCO (y-axis). PASP – pulmonary artery systolic pressure; ILD – interstitial lung disease; VC – vital capacity; FVC – forced expiratory volume; DLCO – diffusing capacity of the lungs for carbon monoxide.

Figure 2. The correlation between the PASP of ANA negative ILD patients and pulmonary function parameters. (**A**) The correlation between the PASP (x-axis) of ANA– ILD and VC% (y-axis). (**B**) The linear regression analysis between the PASP of ANA– ILD (x-axis) and FVC% (y-axis). (**C**) The correlation between the PASP of ANA– ILD (x-axis) and DLCO (y-axis). PASP – pulmonary artery systolic pressure; ANA – antinuclear antibody; ILD – interstitial lung disease; VC – vital capacity; FVC – forced expiratory volume; DLCO – diffusing capacity of the lungs for carbon monoxide.

The correlation between lung function parameters and PH might not be as clinically meaningful as expected, and appears to be speculative rather than causative, i.e., this correlation might help with the prediction of PH but not with the understanding of the mechanism of PH. Caminati et al. pointed out that pulmonary function parameters, such as FVC, are useless as a routine assessment of ILD severity [10]. No significant positive correlation was noted between FVC and PH in studies by Nadrous et al. [29] and Shorr et al. [30], suggesting that ILD with PH might not be attributable to FVC but other causes. However, in another study, PASP correlated best with
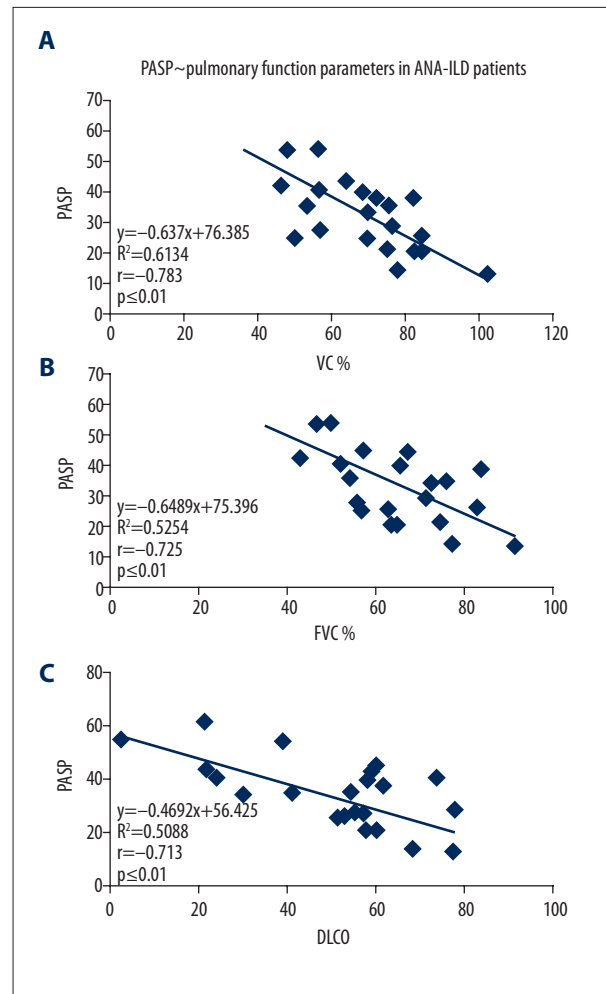
DLCO, to which it was inversely related and had a significant adverse impact on survival. Also, when PASP was >50 mmHg, the patients were more prone to require oxygen supplementation [29]. Similarly, another study concluded that a reduced DLCO should raise the suspicion of undiagnosed PH. The authors pointed out that patients with the need for supplemental oxygen in conjunction with a DLCO of less than 40% were much more likely to have PH than those without either of these 2 features [31]. Nadrous et al. [29] also reported that the prevalence of PH in those with late-stage IPF was significantly correlated with DLCO. In our study, we found that in all patients
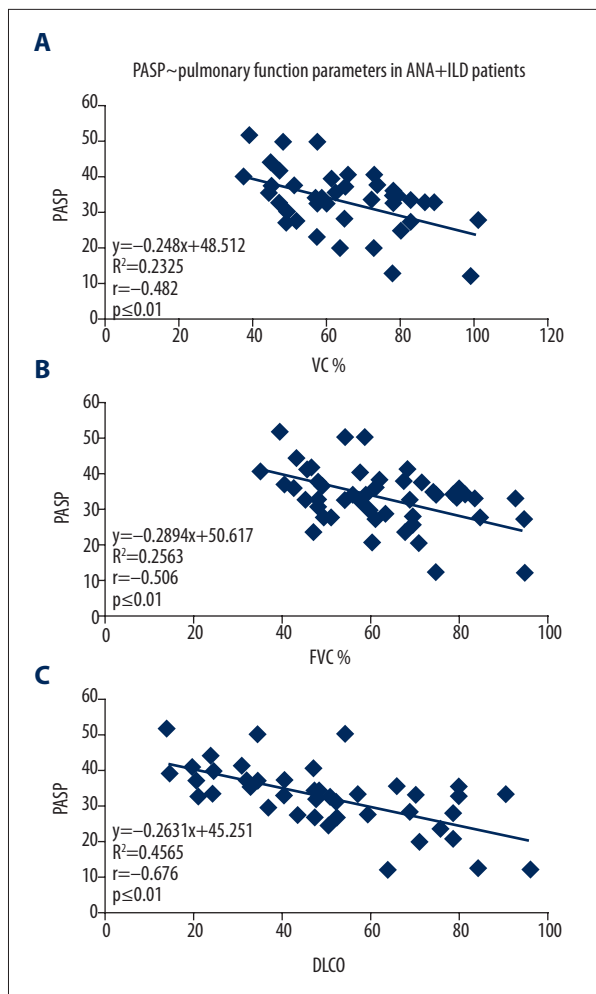
Figure 3. The correlation between the PASP of ANA positive ILD patients and pulmonary function parameters. (**A**) The correlation between the PASP of ANA positive ILD (x-axis) and VC% (y-axis). (**B**) The linear regression analysis between the PASP of ANA positive ILD (x-axis) and FVC% (y-axis). (**C**) The correlation between the PASP of ANA positive ILD (x-axis) and DLCO (y-axis). PASP – pulmonary artery systolic pressure; ANA – antinuclear antibody; ILD – interstitial lung disease; VC – vital capacity; FVC – forced expiratory volume; DLCO – diffusing capacity of the lungs for carbon monoxide.

with ILD, PASP was found significantly correlated with FVC%, VC%, and DLCO despite the ANA grouping. Among all the patients with ILD, PASP was most significantly correlated with DLCO; in the ANA+ group, PASP was found significantly correlated with DLCO; and in the ANA– group, PASP was found significantly correlated with VC%. And no significant difference of the correlation was noted between the ANA+ group and the ANA– group. A reduction of VC% alone is not considered to be

direct evidence of a restrictive ventilation, and reduced FVC% is considered to be an indicative of a restrictive defect in ILD. DLCO, on the other hand, represents the diffusing capacity of the lung [32]. Thus, VC%, FVC%, and DLCO together can reflect a relatively accurate lung functioning state. Our results suggested that PASP had a significant association with lung function parameters, i.e., PH has a significant correlation with ILD. ANA is one of the markers of autoimmunity commonly used in clinical practice [23,33,34]. Those with a higher ANA titer level are reported to have a better prognosis [24]. However, in our study, we found that ANA did not show a significant correlation with PH because no significant difference of PH incidence was noted between the ANA+ group and the ANA– group, suggesting that ANA cannot be a useful biomarker of PH. Also, in neither the ANA+ group or the ANA– group, was PASP found to be significantly correlated with lung functions, and there was no significance between the 2 groups, suggesting that ANA did not directly link to ILD, either.

A major weakness of our study was that it was a retrospective study. A retrospective study is designed to use pre-existing data, making it subjected to numerous biases, such as selection bias, because the control group was recruited by convenience sampling, and thus did not represent the general population. Another limitation of our study was that other risk factors might have been present that were not measured. Only the association but not the causation could be determined. Compared to prospective studies, retrospective studies usually have an inferior level of evidence. The correlation between PASP and pulmonary functions in this study was statistically significant, meaning it was unlikely to have occurred by chance; however, to determine the clinical significance, we believe a clinical practice study is needed.

Conclusions

This was a retrospective study that aimed to analyze the correlation between ILD and PH by analyzing the correlations between lung function parameters and PSAP. ILD was diagnosed by HRCT. PH was diagnosed using echocardiography and RHC. The incidence rate of PH in patients with mixed types of ILD was 25%. We found that significant relationships existed between PASP and DLCO, VC%, FVC% in the patients with ILD, suggesting that PASP was correlated with impaired lung functions, and thus can be used to predict ILD. In addition, no significant difference of PH prevalence was seen between the ANA+ group and the ANA– group. In light of the prevalence of PH in ILD and the correlation between PH and ILD, coupled with a limited therapeutic option for PH in ILD, clinical trials of agents directed at controlling the PASP in ILD seem warranted.

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