Analysis of clinical features and risk factors of pulmonary hypertension associated with interstitial lung disease

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Abstract. Pulmonary hypertension (PH) can significantly impact the prognosis of interstitial lung disease (ILD). There are limited studies on the clinical characteristics and risk factors of PH associated with ILD (PH-ILD). The present study aimed to analyze the clinical characteristics of patients with PH-ILD and explore the correlation and predictive value of the easily obtainable indicators with respect to the severity of PH in patients with ILD. The results indicated that the red blood cell distribution width (RDW) and mean platelet volume (MPV) of patients with ILD with the moderate-to-severe PH (Ms-PH) were significantly higher compared with those of patients with ILD without PH and those with Mild-PH ($P<0.05$). Age, RDW, MPV and immunoglobulin G levels were emerged as independent risk factors for Ms-PH in patients with ILD. Receiver operating characteristic curve analysis demonstrated that the combination of RDW and MPV enhances the diagnostic efficiency for Ms-PH in patients with ILD. Consequently, the present study demonstrated that RDW and MPV are predictive factors for Ms-PH in patients with ILD.

Introduction

Interstitial lung disease (ILD) is a heterogeneous diffuse lung disease characterized by varying degrees of alveolar and interstitial damage. Pulmonary hypertension (PH) is a significant cause of dyspnea, increased oxygen consumption and elevated mortality risk in patients with ILD (1). Previous studies have indicated that 3-86% of patients with ILD suffer from PH, with ~30-50% having moderate-to-severe PH (Ms-PH) (2). The severity of idiopathic pulmonary fibrosis (IPF) influences the prevalence of PH in patients with IPF, with a prevalence rate of 8-15% at diagnosis (3,4), 35-44% prior to lung transplantation evaluation (5,6), and 86% during lung transplantation (7). The early clinical manifestations of PH associated with ILD (PH-ILD) are often non-specific and obvious, while the late stages of the disease manifest significant changes, impacting the quality of life of patients. Therefore, analyzing the clinical characteristics of patients with PH-ILD and identifying risk factors for Ms-PH, as well as searching for simple and low-cost biological markers related to PH-ILD, are particularly important for early diagnosis and treatment.

Currently, PH is defined as having the mPAP ≥25 mmHg, as measured via right heart catheterization (RHC) at sea level and in the resting state (8). RHC demonstrates high accuracy in measuring PH, yet its invasiveness and potential risk of infection have prevented it from being adopted as a routine screening method for PH in clinical practice. Echocardiography is the most commonly used method for screening PH in the clinical practice and can be used to detect suspected or confirmed PH caused by various factors, observe abnormal changes in both the left and right heart, estimate hemodynamic parameters, and provide important reference value for disease assessment. Multiple studies have demonstrated a strong correlation between pulmonary artery systolic pressure (PASP) measured by echocardiography and mean pulmonary artery pressure (mPAP) measured by a RHC (9). It has been reported that a PASP of 35 or 36 mmHg, as measured by echocardiography, can serve as a normal resting value, at which point non-invasive diagnosis of PH exhibits favorable sensitivity and specificity (10). Due to the long duration and insidious onset of ILD, by the time patients exhibit noticeable clinical symptoms, they are often in the advanced stages of the disease, accompanied by Ms-PH, which leads to numerous patients not receiving timely diagnosis and missing the optimal treatment opportunities. Therefore, it is of great significance to analyze the clinical characteristics of patients with PH-ILD and use simple and easy indicators in clinical practice to assess whether patients with ILD have Ms-PH as early as possible.

Patients and methods

Study population. A retrospective analysis was conducted on the clinical characteristics and risk factors of patients with ILD with complete clinical data who sought treatment at the Third Affiliated Hospital of Sun Yat-sen University

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(Guangzhou, China) from January 2017 to December 2021. All data were collected from the medical records of the Third Affiliated Hospital of Sun Yat-sen University. Inclusion criteria were as follows: patients must meet the diagnosis of ILD, be aged ≥18 years, and have complete clinical data. For patients who were hospitalized multiple times during the study period, the first hospitalization was considered. Individuals who met any of the following criteria were excluded: <18 years of age; suffering from congenital heart disease, rheumatic heart disease, left heart failure or chronic thromboembolic disease; having other chronic lung diseases, including chronic obstructive pulmonary disease (COPD), asthma, pulmonary infection; being afflicted with liver cirrhosis, portal hypertension, chronic renal failure; having idiopathic PH. Ultimately, 226 patients were included in the study.

The present research protocol was approved (approval no. SL-II2024-004-01) by the Institutional Review Board of the Third Affiliated Hospital of Sun Yat-sen University (Guangzhou, China). Informed consent was waived because of the retrospective nature of the study. All data are sourced from the Third Affiliated Hospital of Sun Yat-sen University.

Calculation of sample size. Sample size is fundamental to a study, and a sufficient sample size ensures a reliable foundation for research findings. The present study employed a retrospective analysis to investigate the research content, primarily comprising two parts: One involves descriptive analysis of clinical characteristics, while the other explores the risk factors for moderate and severe PH. The sample size was calculated based on an analysis of influencing factors. Specifically, the sample size requirement for multi-factor analysis is at least 5 to 10-fold the number of independent variables (11,12). In the current analysis, it was considered whether moderate or severe PH occurred simultaneously as the dependent variable. Incorporating previous research (13), at least 10-15 independent variables were included. A logistic model was utilized for multivariate analysis. Based on 10-fold the number of independent variables, the sample size for the present study was we determined, resulting in an estimated minimum of 150 cases.

Diagnostic criteria. Based on the diagnostic criteria for idiopathic interstitial pneumonia established by experts from the American Thoracic Society/European Respiratory Society in 2013 (14), the main diagnostic criteria include the presence of the following respiratory symptoms or signs, accompanied by significant interstitial changes in the lungs confirmed by chest computed tomography (CT): Ground-glass opacities, interlobular septal thickening, linear shadows, reticular shadows and tracking bronchiectasis. Two experienced radiologists independently reviewed the CT images to determine the consistency of the observations. If there was a disagreement between the two opinions, a third radiologist was invited to independently review the images and make a diagnosis. The diagnosis of various connective tissue disease (CTD) conforms to the corresponding guidelines (15-19).

The patient was placed in the left decubitus position with calm breathing. Experienced color Doppler ultrasound physicians conducted color Doppler ultrasound examinations on the patient (model E9; Cytiva), utilizing M5S probes to assess the patient's cardiac structure, with probe frequencies ranging from 1.7 to 3.4 MHz. The PASP was determined using the tricuspid regurgitation velocity method, while the maximum tricuspid regurgitation velocity was measured in the apical four-chamber view. Continuous Doppler sampling lines were employed to document the tricuspid regurgitation spectrum, and the maximum regurgitation velocity was subsequently measured. The machine automatically computes the pressure difference between the right ventricle and right atrium. The velocity of the tricuspid regurgitation jet could only be measured when the complete flow pattern of tricuspid regurgitation was present and the peak velocity was clearly visible. During sinus rhythm, each echocardiogram indicator was measured three times and the average value was calculated, though not necessarily continuously. When assessing right atrial systolic pressure, right atrial pressure was estimated based on tricuspid regurgitation velocity. Specifically, when there was mild tricuspid regurgitation and the right atrial diameter was normal or slightly enlarged, the estimated right atrial pressure was set at 5 mmHg. For moderate tricuspid regurgitation and moderate enlargement of the right atrial diameter, the estimated right atrial pressure stands at 10 mmHg. In cases of severe tricuspid regurgitation and extreme enlargement of the right atrial diameter, the estimated right atrial pressure rises to 15 mmHg. The modified Bernoulli equation was used to calculate PASP: PASP (mmHg)=right ventricular systolic pressure=tricuspid valve pressure difference (4v2, v=maximum tricuspid valve reflux velocity) + right atrial pressure (RAP) (20). According to the PASP value, a necessary condition for diagnosing PH is PASP ≥35 mmHg (10). Patients were categorized into three groups based on PASP: Non-PH group (PASP <35 mmHg), Mild-PH group (PASP 35-49 mmHg) and Ms-PH group (PASP ≥50 mmHg) (21).

Clinical data. Baseline data encompassed age, sex, smoking, drinking, diabetes and hypertension. Using a conversion formula, the doses of methylprednisolone (4 mg) and prednisone (5 mg) were uniformly adjusted to match the dose of methylprednisolone. Patients were categorized into three groups based on the hormone dose cited in (22): No hormone group, low-dose group (≤0.5 mg/kg/d) and sufficient dose group (1-2 mg/kg/d). Immunosuppressants included cyclophosphamide, methotrexate, mycophenolate mofetil, leflunomide, hydroxychloroquine, azathioprine, cyclosporine. *Tripterygium wilfordii* and iguratimod were also included. Anti-fibrosis drugs encompassed nintedanib and pirfenidone. Therapies for PH encompassed endothelin receptor antagonists, such as bosentan and axentan.

Fasting venous blood was collected within 24 h after admission and subjected to routine blood testing using a Sysmex XE-5000 fully automatic hematology analyzer. The routine blood parameters encompassed white blood cell count, red blood cell (RBC) count, hemoglobin level, platelet (PLT) count, neutrophil count, lymphocyte count, PLT-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, red blood cell distribution width (RDW) and PLT distribution width (PDW).

The Hitachi 7180 fully automatic biochemical analyzer is utilized to measure the levels of albumin, blood urea nitrogen, uric acid (UA), serum creatinine, lactate dehydrogenase (LDH). The latex agglutination method is employed to detect

C-reactive protein (CRP) levels. Additionally, the erythrocyte sedimentation rate was determined using an Italian ALIfax text1 fully automatic sedimentation instrument.

Using the Roche E601 fully automated electrochemiluminescence immunoassay, serum autoantibodies were detected, including immunoglobulin (Ig) G, IgA, IgM and rheumatic antibodies [antinuclear antibodies (ANAs) and extractable nuclear antigen (ENA)]. These antibodies included anti-double stranded DNA antibody (anti-dsDNA), anti-Sjogren's syndrome antigen A, anti-Sjogren's syndrome antigen B, anti-Smith antibodies, anti-kinetochore antibodies, anti-perinuclear anti-neutrophil cytoplasmic antibodies, anti-cytoplasmic anti-neutrophil cytoplasmic antibody, anti-myeloperoxidase anti-neutrophil cytoplasmic antibody and anti-scleroderma-70 antibody.

Echocardiography. After the patient was positioned in the left lateral position and allowed to breathe calmly, our ultrasound technician used Doppler echocardiography (model E9; Cytiva) to measure the main pulmonary artery width, PAP and cardiac function parameters, mainly including the left ventricular diameter (LVD), left atrial diameter (LAD), right ventricular dimension (RVD), right atrial long diameter, right atrial transverse diameter, main pulmonary artery and left ventricular ejection fraction (LVEF).

Pulmonary function test. The experienced pulmonary function technician from the Third Affiliated Hospital of Sun Yat-sen University utilized the pulmonary function tester to assess pulmonary function. All examinations were conducted by professional technicians in the pulmonary function room, and patients were advised to avoid using bronchodilators for 24 h prior to the examination. Indicators such as forced vital capacity as percentage of predicted value (FEV1/FVC%), forced expiratory volume in 1 sec (FEV1)/forced volume vital capacity (FVC) ratio (FVC% pred), diffusing capacity for carbon monoxide (DLCO), carbon monoxide diffusion capacity as percentage of predicted value (DLCO% pred), diffusing capacity for carbon monoxide to alveolar volume ratio (DLCO/VA% pred), total lung volume (TLC) and residual volume (RV) were collected.

Statistical analysis. Statistical analysis was performed using SPSS version 25 software (IBM Corp.). Continuous data with a normal distribution is expressed as the mean ± standard deviation (SD). The measurement data with skewed distribution are expressed by median and quartile M (P25, P75). Data with a normal distribution should be compared by analysis of variance (ANOVA), all data underwent post hoc analysis using the Least Significant Difference test. Kruskal-Wallis test is reserved for non-parametric distributions. The counting data were expressed as a constituent ratio, and the comparison between groups was performed using the χ^2 test or Fisher's exact probability method. Pearson correlation analysis was used for normal distribution data, and Spearman correlation analysis was used for skewed distribution data and rank data. Logistic regression analysis was employed to perform both univariate and multivariate analyses on the factors influencing Ms-PH in patients with ILD. Receiver operating characteristic (ROC) curve was plotted to evaluate the predictive value of biomarkers for Ms-PH in occurrence of patients with ILD. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Baseline characteristics and treatment. Based on the inclusion and exclusion criteria, a data of 226 patients with ILD confirmed by chest CT or lung biopsy were included, among whom 91 patients had ILD accompanied by PH, constituting 40.27% of the total population. The non-PH group comprised 135 cases, including 35 men and 100 women aged from 27-89 years, with an average age of 51.69±12.77 years. The Mild-PH group had 72 cases, consisting of 17 men and 55 women, aged from 23 to 78 years, with an average age of 53.67±13.16 years. The Ms-PH group included 19 cases, with 7 men and 12 women aged from 40-80 years, averaging 59.21±11.66 years. The age difference among these three groups was statistically significant ($P=0.05$), whereas no significant differences were observed in sex, smoking, drinking, diabetes, hypertension and ILD subtypes ($P>0.05$). A total of 45 patients underwent oxygen therapy, 194 received hormone therapy, and 29 were treated with pH-targeted drugs. Significant differences were noted in the use of oxygen therapy, hormone therapy and pH-targeted drug therapy among these three patient groups ($P<0.05$). A comparison of baseline characteristics and treatments is shown in Table I.

Blood and immunological indicators. Serological comparison revealed that the mean RDW in the non-PH group was 0.135 (0.127, 0.148), in the Mild-PH group it was 0.141 (0.132, 0.150), and in the Ms-PH group, it was 0.152 (0.134, 0.164). Significant differences were observed among these three groups ($P=0.007$). Similarly, the mean PLT volume (MPV) in the non-PH group was 10 (9.4, 10.6), in the mild PH group it was 10.1 (9.6, 10.8), and in the Ms-PH group, it was 10.8 (10.1, 12.6), with statistically significant differences ($P=0.005$). Additionally, significant differences were noted in PDW, UA, CRP and LDH among the three groups ($P<0.05$). No statistically significant differences were observed in the other indicators among the three groups ($P>0.05$). Statistical analysis revealed significant differences existed in the levels of immunological indicators, such as IgG, IgA and C4, among the three groups ($P<0.05$). However, no statistically significant difference was observed in IgM and C3 levels among the three groups ($P>0.05$). A comparison of serological indicators among these three groups is presented in Table II.

Rheumatoid antibodies. All patients with CTD-ILD underwent rheumatic antibody testing. There was no statistically significant difference in the ANA positivity rate or anti-dsDNA antibody level among the three groups ($P>0.05$). In the anti-ENA antibody profile, a statistically significant difference was observed in anti-U1 ribonucleoprotein (U1RNP) antibody among the three groups ($P=0.009$), whereas no statistically significant difference was found in the positivity rates of other rheumatoid antibodies among the three groups ($P>0.05$). The detailed results are included in Table SI.

Table I. Comparison of baseline characteristics and treatment of three groups.

Characteristics	Non-PH (n=135)	Mild-PH (n=72)	Ms-PH (n=19)	P-value
Age	51.69±12.77	53.67±13.16	59.21±11.66	0.05
Sex (male/female)	35/100	17/55	7/12	0.504
Smoking, n (%)	17 (12.6)	8 (11.1)	5 (26.3)	0.207
Drinking, n (%)	3 (2.2)	2 (2.8)	2 (10.5)	0.195
Diabetes, n (%)	10 (7.4)	3 (4.2)	3 (15.8)	0.208
Hypertension, n (%)	15 (11.1)	10 (13.9)	3 (15.8)	0.758
ILD subtypes, n (%)				0.065
Idiopathic pulmonary fibrosis	9 (6.7)	6 (8.3)	5 (26.3)	
Connective tissue disease-related-ILD	123 (91.1)	66 (91.7)	14 (73.7)	
Sarcoidosis	3 (2.2)	0 (0)	0 (0)	
Oxygen, n (%)	24 (17.8)	13 (18.1)	8 (42.1)[a,b]	0.009
Glucocorticoid, n (%)				0.002
≤0.5 mg/kg/d	104 (77.0)	51 (70.8)	8 (42.1)	
1-2 mg/kg/d	15 (11.1)	15 (20.8)	1 (5.3)	
Immunosuppressant, n (%)				0.249
Cyclophosphamide	44 (32.6)	33 (45.8)	9 (47.4)	
Methotrexate	11 (8.1)	5 (6.9)	1 (5.2)	
Mycophenolate mofetil	20 (14.8)	11 (15.3)	2 (10.5)	
Leflunomide	8 (5.9)	4 (5.6)	1 (5.3)	
Hydroxychloroquine	66 (48.9)	33 (45.8)	6 (31.6)	
Azathioprine	7 (5.2)	3 (4.2)	0 (0)	
Cyclosporine	2 (1.5)	0 (0)	0 (0)	
Tripterygium Wilfordii	9 (6.7)	4 (5.6)	2 (10.5)	
Iguratimod	10 (7.4)	2 (2.8)	3 (15.8)	
PH drugs, n (%)				0. 024
Bosentan	12 (8.9)	5 (6.9)	4 (21.1)	
Axentan	14 (10.4)	5 (6.9)	6 (31.6)	
Combined with PH drug therapy, n (%)	5 (3.7)	2 (2.8)	3 (15.8)	0.075
Antifibrotic therapy, n (%)				0.312
Nintedanib	8 (5.9)	3 (4.2)	0 (0)	
Pirfenidone	35 (25.9)	19 (26.4)	9 (47.4)	

Compared with mild PH group, [a]P<0.05; Compared with Ms-PH group, [b]P<0.05. ILD, interstitial lung disease; PH, pulmonary hypertension; Ms, moderate-to severe.

Echocardiographic parameters. Significant differences were observed in RVD, right atrial long diameter, right atrial short diameter and main pulmonary artery width among the three groups (P<0.05). However, no significant differences were found in the LVD, LAD and LVEF% among the three groups (P>0.05). The specific results are shown in Table III.

Pulmonary function tests. Among the three groups, 84 cases completed the pulmonary function examination, with 50 cases in the non-PH group, 25 cases in the Mild-PH group, and 9 cases in the Ms-PH group. Pulmonary function tests revealed restrictive ventilatory dysfunction in 55 patients and normal results in 29 patients. No significant difference was observed in the types of lung function impairment among the three groups (P>0.05). Statistical analysis indicated significant differences in the FVC% pred, DLCO, DLCO% pred, and DLCO/VA% pred values among the three groups (P<0.05). Compared with the non-PH group, both FVC%pred and DLCO% pred values decreased significantly in the mild-PH group (P<0.05). The mean values of DLCO% pred and DLCO/VA% pred in the Ms-PH group were found to be lower compared with the non-PH group, with a statistically significant difference (P<0.05). However, there were no statistically significant differences in FEV1/FVC%, TLC, or RV among the three groups (P>0.05). The comparison of lung function test results among the three groups is presented in Table IV.

Risk factors for ILD associated with Ms-PH

Univariate analysis. To explore the risk factors for patients with ILD with Ms-PH, patients with ILD were divided into two groups based on the value of PASP. The non-PH group and mild-PH group were combined to form the nmPH group, while the remaining patients formed Ms-PH group. Using Ms-PH as the dependent variable and age, sex, smoking, drinking,

Table II. Comparison of blood and immunological indicators of three groups.

Variable	Non-PH (n=135)	Mild-PH (n=72)	Ms-PH (n=19)	P-value
White blood cells (10^9/l)	6.17 (4.88, 8.65)	7.15 (5.55, 9.25)	6.85 (5.78, 10.22)	0.278
Hemoglobin (g/l)	124 (114, 133)	123 (110, 132)	124 (114, 140)	0.619
Red blood cell distribution width	0.135 (0.127, 0.148)	0.141 (0.132, 0.150)	0.152 (0.134, 0.164)[a,b]	0.007
Platelet distribution width	10.8 (9.8, 12.0)	11.3 (10.0, 12.4)	11.9 (10.9, 13.1)	0.033
Mean platelet volume (fl)	10 (9.4, 10.6)	10.1 (9.6, 10.8)	10.8 (10.1, 12.6)	0.005
Neutrophils (10^9/l)	3.95 (3.03, 6.05)	4.40 (3.25, 6.93)	4.52 (3.55, 6.64)	0.238
Lymphocytes (10^9/l)	1.45 (1.05, 1.96)	1.51 (0.98, 1.98)	1.20 (0.94, 1.74)	0.730
Platelets (10^9/l)	237 (203, 298)	257 (213, 314)	246 (185, 328)	0.359
Neutrophil-to-lymphocyte ratio	2.92 (2.00, 4.16)	3.08 (1.84, 5.75)	3.42 (2.44, 6.71)	0.354
Platelet-to-lymphocyte ratio	168.38 (118.89, 230.85)	172.22 (121.42, 280.79)	176.19 (129.07, 333.33)	0.520
Albumin (g/l)	37.14±4.88	36.32±5.34	34.62±4.92	0.101
Erythrocyte sedimentation rate (mm/h)	29 (16, 54)	31 (14, 60)	40 (35, 74)	0.141
C-reactive protein (mg/l)	3.55 (1.10, 14.29)	3.45 (1.80, 21.20)	16.80 (1.90, 31.15)	0.040
Lactate dehydrogenase (U/l)	221 (182, 285)	274 (205, 353)[a]	295 (241, 309)[b]	<0.0001
Uric acid (μmol/l)	321 (255, 372)	321.5 (282, 391)	408 (347, 441)[a,b]	0.002
Serum creatinine (μmol/l)	57 (49, 65)	57 (48, 69)	66 (51, 101)	0.161
Immunoglobulin G (g/l)	14.31 (11.36, 17.39)	16.13 (11.92, 18.20)	21.00 (16.29, 25.66)[a,b]	<0.0001
Immunoglobulin A (g/l)	2.62 (1.87, 3.46)	2.37 (1.96, 2.87)	3.42 (2.85, 4.06)[a,b]	0.010
Immunoglobulin M (g/l)	1.29 (0.95, 1.88)	1.14 (0.83, 1.73)	1.46 (1.09, 1.75)	0.394
Complement 3 (g/l)	1.19±0.21	1.17±0.25	1.17±0.35	0.279
Complement 4 (g/l)	0.24±0.07	0.22±0.08	0.19±0.08[b]	0.027

Compared with non-PH group, [a]P<0.05; Compared with mild PH group, [b]P<0.05. PH, pulmonary hypertension; Ms, moderate-to severe.

diabetes, hypertension, treatment, immunology, rheumatic antibody and serological indicators as independent variables, logistic regression analysis was conducted to analyze risk factors. The results of univariate regression analysis revealed statistically significant differences (P<0.05) in 12 variables were between the nmPH group and Ms-PH group. The results are shown in Table V.

Multivariate analysis. Variables with P<0.05 from Table V were included in the multivariate logistic regression analysis. The results indicated that age, RDW, MPV and IgG levels were independent risk factors for the occurrence of Ms-PH in patients with ILD, with the detailed results presented in Table VI.

Diagnostic efficacy of RDW and MPV for patients with ILD with Ms-PH. As shown in Table VI, RDW and the MPV were found to be independent risk factors for Ms-PH in patients with ILD. To explore the diagnostic value of RDW and MPV in patients with Ms-PH, SPSS software was utilized to analyze the area under the curve (AUC), with the sensitivity as the y-axis and 1-specificity as the x-axis. The optimal cutoff value was determined based on the Youden index (sensitivity + specificity-1). ROC curve analysis revealed that the optimal cutoff value for RDW in predicting Ms-PH in ILD is 0.323, with an AUC of 0.672, a 95% confidence interval (CI) ranging from 0.547 to 0.796, and sensitivity and specificity of 0.579 and 0.744, respectively (P=0.013). For MPV, the optimal cutoff value for predicting Ms-PH in ILD is 0.378, with an AUC of 0.714, a 95% CI ranging from 0.583 to 0.845, and sensitivity and specificity of 0.842 and 0.536, respectively (P=0.002). When RDW and MPV were combined, the AUC increases compared with when they are diagnosed separately (AUC=0.78, P<0.0001), enhancing the diagnostic efficacy in predicting Ms-PH in ILD. Detailed results are presented in Table VII and Fig. 1.

Discussion

The incidence of PH-ILD was ~40.27% in the present study. Most patients with PH-ILD were middle-aged or elderly. Currently, the possible pathogenesis of PH-ILD encompasses the following aspects:

Pulmonary interstitial fibrosis. Progressive pulmonary fibrosis in patients with ILD can lead to a decrease in the surface area and vascular density of pulmonary capillaries, compressing the capillaries and causing vascular occlusion. Simultaneously, persistent chronic inflammation can result in medial vascular hypertrophy, obstructive intimal hyperplasia and fibrosis, further narrowing the pulmonary vascular bed, increasing pulmonary vascular resistance, and continuously elevating PAP (23). Research indicates that IPF is associated with the inflammatory expression of the senescence-associated

Table III. Comparison of echocardiographic parameters of three groups.

Variable	Non-PH (n=135)	Mild-PH (n=72)	Ms-PH (n=19)	P-value
Pulmonary artery systolic pressure (mmHg)	28 (25, 31)	38 (36, 43)	55 (55, 64)	<0.0001
Left ventricular diameter (mm)	44 (42, 46)	44 (41, 46)	44 (40, 48)	0.891
Right ventricular diameter (mm)	20 (19, 22)	21 (19, 23)	24 (22, 26)[a,b]	<0.0001
Left atrial diameter (mm)	30 (27, 32)	30 (28, 33)	32 (29, 33)	0.071
Right atrial long diameter (mm)	40 (38, 43)	41 (39, 43)	45 (43, 55)[a,b]	<0.0001
Right atrial short diameter (mm)	30 (28, 32)	31 (30, 33)	36 (31, 42)[a,b]	<0.0001
Main pulmonary artery width (mm)	21 (20, 23)	23 (21, 24)[a]	25 (24, 27)[a,b]	<0.0001
Left ventricular ejection fraction (%)	68 (64, 70)	69 (64, 73)	67 (62, 73)	0.258

Compared with non-PH group, [a]P<0.05; Compared with mild PH group, [b]P<0.05. PH, pulmonary hypertension; Ms, moderate-to severe.

Table IV. Comparison of pulmonary function test of three groups.

Variable	Non-PH (n=50)	Mild-PH (n=25)	Ms-PH (n=9)	P-value
Types, n (%)				0.143
Normal	21 (42)	7 (28)	1 (11.1)	
Restrictive	29 (58)	18 (72)	8 (88.9)	
Forced vital capacity as percentage of predicted value, %	78.40±19.19	68.23±15.72[a]	66.75±14.73	0.033
Forced expiratory volume in 1 sec/forced volume vital capacity, %	104.43±8.50	103.24±8.29	103.04±6.90	0.797
Diffusing capacity for carbon monoxide (mmol/min/Kpa/l)	5.11 (3.96, 6.05)	4.12 (3.80, 4.80)	3.26 (2.16, 4.44)	0.002
Carbon monoxide diffusion capacity as percentage of predicted value, %	66.62±18.14	54.31±13.42[a]	43.97±12.89[a,b]	0.008
Diffusing capacity for carbon monoxide to Alveolar Volume Ratio, %	83.68±18.14	76.02±15.90	65.41±12.99[a,b]	0.203
Total lung capacity, l	3.92±0.96	3.75±0.93	3.32±0.74	0.438
Residual volume, l	1.72±0.41	1.79±0.44	1.59±0.30	0.143

Compared with non-PH group, [a]P<0.05; Compared with mild PH group, [b]P<0.05. PH, pulmonary hypertension; Ms, moderate-to severe.

secretory phenotype (SASP), encompassing biological factors such as transforming growth factor beta, tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6). SASP promotes the progression of fibrosis, with the TNF-α component of SASP being considered a significant mediator of age-related fibrosis in IPF (24). Additionally, another study revealed that long-term exposure to TNF-α elevates the levels of reactive oxygen species (ROS) within B cells and intensifies the activation of nuclear factor kappa B. This exposure further triggers the aging of lung endothelial cells and fibroblasts, activates the SASP pathway, and ultimately leads to interstitial remodeling and the formation of PH (24,25), suggesting that elderly patients with ILD are more susceptible to developing PH.

Pulmonary vasoconstriction. Hypoxemia in patients with ILD can increase the production of ROS, which can enhance the concentration of calcium ions in pulmonary artery smooth muscle cells and induce vascular constriction. Additionally, pulmonary fibrosis can render alveoli more susceptible to collapse, thereby aggravating alveolar hypoxia and further promoting hypoxic pulmonary vasoconstriction. Persistent pulmonary vasoconstriction can elevate pulmonary vascular resistance and trigger the development of pulmonary arterial hypertension (24).

Abnormal phenotype of vascular endothelial cells. IL-6 stimulation induces and increases p53 protein expression and ROS levels (26,27). P53 is involved in cell cycle arrest and is expressed in both pulmonary artery endothelial cells (PAECs) and pulmonary artery smooth muscle cells (PASMCs). The expression of P53 in PASMCs induced by hypoxia is lower than that in PAECs. Additionally, it stimulates the proliferation of PASMCs, promotes Ca^{2+} entry into PASMCs, and leads to pulmonary vascular remodeling (28,29). P21 and P16 are also involved in the process of cell cycle arrest, and cells expressing P16 and P21 have been detected in plasma lesions

Table V. Univariate analysis of interstitial lung disease complicated with moderate to severe PH.

Variable	Regression coefficient	P-value	Odds ratio	95% confidence interval	
				Lower limit	Upper limit
Age	0.042	0.030	1.043	1.004	1.083
Sex (Female)	0.553	0.270	1.739	0.650	4.650
Smoking	-0.956	0.090	0.385	0.128	1.159
Drinking	1.559	0.074	4.753	0.857	26.355
Diabetes	-1.029	0.137	0.357	0.092	1.385
Hypertension	0.311	0.640	1.365	0.371	5.019
Anti-nuclear antibodies	0.069	0.906	1.071	0.339	3.386
Anti-double stranded DNA antibodies	1.084	0.344	2.956	0.313	27.948
Anti-Ro52	-0.405	0.458	0.667	0.229	1.943
Anti-Ro60	-0.703	0.280	0.495	0.138	1.773
Anti-U1 ribonucleoprotein	1.163	0.061	3.345	1.042	9.827
Anti-scleroderma-70 antibody	-1.477	0.042	3.199	0.030	1.765
Oxygen	-1.344	0.007	0.261	0.097	0.697
Glucocorticoid	-1.713	0.001	0.180	0.066	0.493
Immunosuppressor	-0.911	0.105	0.402	0.134	1.209
PH-targeting drugs	1.275	0.013	3.580	1.302	9,844
Combined with PH targeted drug	1.678	0.023	5.357	1.263	22.728
Antifibrotic drugs	-0.699	0.148	0.497	0.193	1.283
White blood cells (10^9)	0.028	0.734	1.029	0.875	1.210
Red blood cell distribution width	24.264	0.015	$3.451x10^{10}$	117.761	$1.011x10^{19}$
Platelet distribution width	0.190	0.069	1.209	0.986	1.483
Mean platelet volume (fl)	0.740	0.000	2.095	1.434	3.062
Neutrophil-to-lymphocyte ratio	0.024	0.738	1.025	0.889	1.181
Platelet-to-lymphocyte ratio	0.000	0.761	1.000	0.997	1.004
Uric acid (μmol/l)	0.009	0.000	1.009	1.004	1.013
Lactate dehydrogenase (U/l)	0.001	0.126	1.001	1.000	1.003
C-reactive protein (mg/l)	0.009	0.287	1.009	0.992	1.027
Erythrocyte sedimentation rate (mm/h)	0.013	0.084	1.013	0.998	1.027
Serum creatinine (μmol/l)	0.009	0.069	1.009	0.999	1.019
Immunoglobulin G (g/l)	0.116	0.000	1.123	1.061	1.190
Immunoglobulin A (g/l)	0.334	0.019	1.396	1.056	1.845
Immunoglobulin M (g/l)	0.015	0.962	1.015	0.561	1.836
Complement 3 (g/l)	-1.882	0.051	0.152	0.023	1.008
Complement 4 (g/l)	-7.793	0.020	0.000	0.000	0.294

PH, pulmonary hypertension.

and vascular endothelial cells (30,31). These changes reduce the production of nitric oxide and prostaglandins in the microenvironment, which leads to endothelial cell aging. PASMCs and PAECs produce pro-inflammatory and pro-fibrotic fluids, which are involved in pulmonary artery remodeling (32).

The treatment of patients with PH-ILD includes basic and etiological therapies. The primary focus of basic treatment is oxygen therapy, which aids in alleviating hypoxia. The present study revealed that the proportion of patients with Ms-PH requiring oxygen therapy was significantly higher compared with those with non-PH and mild PH, with a statistically significant difference (P<0.05), aligning with findings from foreign studies (33). Conversely, another domestic study indicated no significant difference (P>0.05) between patients with IPF with PH who received hormone therapy and those without, contradicting the results of the present study (34). This discrepancy could be attributed to the larger sample size of patients with CTD-ILD included in the present study.

RDW is one of the commonly used blood analysis indicators in clinical practice to assess changes in RBC volume, evaluate RBC morphology, and diagnose anemia. Due to its advantages such as easy accessibility and straightforward operation, it has been widely used in clinical settings in recent years and can be used as a predictor of poor prognosis for various diseases such as heart failure, COPD (35), and community-acquired pneumonia (36). Foreign studies suggest

Table VI. Multifactor analysis of interstitial lung disease complicated with moderate and severe PH.

Variable	Regression coefficient	P-value	Odds ratio	95% confidence interval	
				Lower limit	Upper limit
Age	0.077	0.034	1.080	1.006	1.159
Oxygen	1.564	0.084	4.779	0.810	28.196
glucocorticoid	-1.828	0.081	0.161	0.021	1.257
PH-targeted drug therapy	1.926	0.116	6.859	0.623	75.556
Combined with PH targeted drug therapy	2.483	0.084	11.980	0.714	201.079
Red blood cell distribution width	39.996	0.022	$2.345x10^{17}$	309.548	$1.777x10^{32}$
Mean platelet volume (fl)	0.830	0.009	2.294	1.232	4.274
Uric acid (μmol/l)	0.006	0.069	1.006	1.000	1.257
Immunoglobulin G (g/l)	0.152	0.008	1.164	1.040	1.303
Immunoglobulin A (g/l)	0.230	0.423	1.259	0.717	2.210
Complement 4 (g/l)	-8.464	0.213	0.000	0.000	128.127
Constant	-20.704	0.001	0.000		

PH, pulmonary hypertension.

Table VII. Diagnostic efficiency of RDW, MPV and their combination in interstitial lung disease complicated with moderate-to-severe pulmonary hypertension.

Variable	Area under the curve	P-value	95% confidence interval	Sensitivity	Specificity	Optimal cutoff value
Single index						
RDW	0.672	0.013	(0.547, 0.796)	0.579	0.744	0.323
MPV (fl)	0.714	0.002	(0.583, 0.845)	0.842	0.536	0.378
Combined index						
RDW + MPV	0.780	<0.0001	(0.671, 0.889)	0.737	0.729	0.466

RDW, red blood cell distribution width; MPV, mean platelet volume.

that RDW is an independent factor affecting COPD-related PH, and RDW levels can be used to assess disease severity and prognosis (37). Numerous studies have shown that RDW is associated with adverse outcomes in idiopathic PH and chronic thromboembolic PH (38,39). Ozgul *et al* (37) discovered that RDW possesses clinical utility in predicting PASP and assessing lung function among patients with COPD-related PH. In the present study, the RDW level among patients with Ms-PH was significantly higher compared with the non-PH group (P<0.05) and mild-PH group (P<0.05). This finding is similar to the study conducted by Yang *et al* (40), which revealed an increase in RDW is associated with the severity of PH and a poor prognosis of the disease. Another study revealed that elevated RDW was an important diagnostic indicator for PH (95% CI: 2.866-13.698, P=0.013), and ROC curve suggested that an RDW ≥13.05% represents the optimal cutoff value, achieving a sensitivity of 82.1% and a specificity of 71.4% (41) which was aligned with the results of the present study. However, the primary distinction between the current study and prior research lies in the research subjects and their grouping. Previous studies investigated whether patients with ILD exhibit clinical characteristics of PH, whereas the present study delves deeper into analyzing the risk factors associated with Ms-PH in patients with ILD. Currently, the mechanism behind RDW and the progression of pulmonary arterial hypertension remain unclear. One potential explanation is that patients with chronic lung disease often experience hypoxia and inflammation in their respiratory system. It has been previously indicated that ineffective erythropoiesis, oxidative stress, thrombosis, inflammation, endothelial dysfunction and other factors can all impact RDW levels (42). The increase in RDW may reflect an increase in immature reticulocytes. A decrease in erythrocyte deformability may stimulate PLT aggregation, leading to vascular damage and decreased blood viscosity. Changes in erythrocyte size, decreased deformability and increased adhesion may contribute to thrombosis (43). Pulmonary ischemia-reperfusion is accompanied by hypoxemia, promoting vascular remodeling, fibroblast proliferation and intraluminal microthrombosis, ultimately leading to increased pulmonary vascular resistance and elevated PAP (44).

MPV is an indicator of the average volume of PT in the body, commonly used to evaluate PLT function. Research on MPV in patients with PH-ILD was limited, whereas there

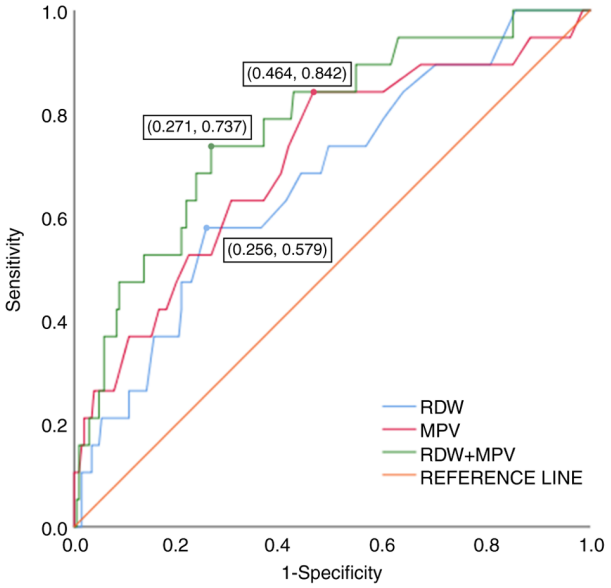

Figure 1. ROC curve analysis of RDW, the MPV alone and RDW combined with the MPV in patients with ILD with Ms-PH. In the ROC curve analysis, the optimal cut-off value for RDW predicting Ms-PH among patients with ILD was determined to be 0.323, with an AUC of 0.672 (95% CI: 0.547 ~ 0.796). For MPV, the AUC stood at 0.714 (95% CI: 0.583~0.845), the optimal cutoff value was 0.378, the sensitivity was 84.2%, and the specificity was 53.6%. When RDW and MPV were combined for diagnostic use, the diagnostic performance surpassed that achieved by using either indicator alone, with an AUC of 0.780. Furthermore, the areas under the RDW, MPV and RDW-MPV combination curves were found to be statistically significant (P<0.05). ROC, receiver operating characteristic; RDW, red blood cell distribution width; MPV, mean platelet volume; ILD, interstitial lung disease; Ms-PH, moderate-to severe pulmonary hypertension; CI, confidence interval.

was a wealth of studies on patients with other chronic lung diseases, such as COPD. According to the multivariate logistic regression analysis conducted by Huang (13), an elevated MPV has predictive value for the severity of PH-ILD, which aligned with our research findings. It is currently considered that MPV contributes to the development of PH-ILD via various mechanisms:

Impaired function and structure of pulmonary vascular endothelium. PLT activation promotes adhesion and aggregation, increasing the likelihood of thrombosis and elevating pulmonary vascular resistance. Furthermore, the increased release of thromboxane A2 and endothelin-1 stimulates bronchial and pulmonary vascular smooth muscle contraction, reduces the production of vasodilator nitric oxide, exacerbates airway stenosis and pulmonary vascular resistance, ultimately leading to the development of PH (45).

Chronic inflammation. inflammation triggers the release of inflammatory cytokines, such as IL-6, which affects the production of megakaryocytes and increases PLT volume and reactivity (46). Additionally, inflammation can induce PLT activation, adhesion and aggregation, thereby increasing pulmonary vascular resistance.

Immunoglobulin is an immunocompetent molecule synthesized and secreted by plasma cells. It is involved in immune regulation. IgG is the most abundant and important immunoglobulin secreted by the body, often indicating that the body is in a state of re-immune response, especially to infectious agents such as bacteria and viruses. The mechanism by which IgG promotes PH formation may be related to its immunomodulatory role in the body. IgG participates in the entire systemic inflammatory response and local inflammation in the pulmonary artery. In a study on chronic thromboembolic PH, it was found that low galactosylation of IgG is positively correlated with circulating inflammatory cytokines, while normal galactosylation of IgG is negatively correlated with these inflammatory cytokines. This finding suggests that the increase in proinflammatory immune response mediated by IgG galactosylation may play a role in the occurrence and progression of PH (47). Complement is a glycoprotein containing enzymatic activity. The levels of IgG and IgA in the Ms-PH group were higher than those in the non-PH group and mild PH group, while the level of C4 was lower, with statistical significance (P<0.05). Multivariate logistic regression analysis suggested that elevated IgG was an independent risk factor for Ms-PH in patients with ILD, which was consistent with the research of Lei *et al* (48). However, the aforementioned research primarily focused on patients with systemic lupus erythematosus complicated by PH, and there was a scarcity of literature on IgG and ILD-PH. The present study targets patients with ILD, including those with CTD-ILD, to explore the impact of IgG on ILD-PH. It addresses the limitation of previous studies that did not consider PH in CTD without ILD.

The positive rate of anti-U1RNP antibody demonstrated significant differences among the three groups (P<0.05), which was similar to the results of a previous study (48). However, the rates of positivity for other antibodies were not significantly different among the three groups, which was similar to the results of the study by Jin *et al* (49).

Chang *et al* (50) observed the differences in RVD, right atrial long diameter and right atrial short between the mild PH group and the non-PH group, which one was consistent with the present results. This may suggest that the disease onset is early, resulting in minimal damage to the lung structure and compensatory changes in lung function and cardiac structure. Conversely, another study revealed early right ventricular diastolic and systolic myocardial dysfunction in patients with IPF-PH, contradicting our results (51). Further prospective studies are warranted to elucidate the relationship between cardiac structure and PH-ILD.

Upon analyzing the differences in FVC% pred, DLCO, DLCO% pred and DLCO/VA% pred among patients who underwent pulmonary function tests, it was observed that the lung function of patients with Ms-PH decreased compared with that of patients with non-PH and mild-PH (P<0.05). The results were similar to the results of the study by Oliveira *et al* (52), suggesting a correlation between the severity of patients' lung function and PASP.

There are certain limitations to the present study. Firstly, this was a single-center study, and variations across different regions and ethnic groups may exert influence on the results. Secondly, due to the retrospective nature of the study, clinicians may introduce certain biases during the information collection process. Thirdly, due to the study being retrospective, it is not known exactly how long numerous patients used the drug before measuring PASP, which is a shortcoming. Therefore, prospective or randomized controlled studies are required to strictly control for confounding factors and further validate

the diagnostic value of RDW, MPV and their combination in the diagnosis of PH-ILD.

In conclusion, middle-aged and elderly patients with ILD should be vigilant about the occurrence of PH. By combining clinical manifestations, rheumatic antibodies, cardiac color ultrasound and pulmonary function tests, early diagnosis and treatment of PH-ILD can be facilitated. Elevated RDW, MPV and IgG levels serve as independent risk factors for patients with Ms-PH among patients with ILD, and these indicators may assist in assessing the severity of PH-ILD. Moreover, the combination of RDW and MPV offers certain predictive value for ILD complicated by Ms-PH.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

BQW designed the experiments and revised the manuscript. YXL collected and analyzed the data, and wrote the manuscript. YXL and BQW confirm the authenticity of all the raw data. Both authors revised the work critically for intellectual content, read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved (approval no. SL-II2024-004-0) by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (Guangzhou, China). Informed consent was waived because of the retrospective nature of the study. The study was performed in accordance with the Declaration of Helsinki. All methods were carried out in accordance with the relevant guidelines and regulations for ethics approval.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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