The chest CT signs for pulmonary veno-occlusive disease correlate with pulmonary haemodynamics in systemic sclerosis

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Short title: Chest CT signs for PVOD in SSc

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Abstract

Objective: Pulmonary arterial hypertension associated with systemic sclerosis (PAH-SSc) sometimes accompanies pulmonary veno-occlusive disease (PVOD). We aimed to reveal the relation between clinical signs of PVOD and severing of pulmonary vasculopathy in SSc.

Methods: This study comprised 52 consecutive SSc patients who had pulmonary haemodynamic abnormalities (mPAP>20 mmHg, PVR>2 W.U. or PAWP>15 mmHg). The chest CT scan was evaluated in all patients. Patients were divided into two groups, the 0-1 group and the 2-3 group, according to the number of chest CT signs for PVOD, including 1) mediastinal lymph node enlargement, 2) thickened interlobular septal wall, and 3) ground glass opacity. Pulmonary haemodynamics, echocardiography and MRI-based cardiac function, pulmonary function, and serum biomarkers were compared between the two groups.

Results: Mediastinal lymph node enlargement, thickened interlobular septal wall, and ground glass opacity were observed in 11 (21%), 32 (62%), and 11 (21%) patients, respectively. The 2-3 group (n=15) had higher mPAP ($p = 0.02$) while lower DLco/VA ($p = 0.02$) compared with the 0-1 group (n=37). Other parameters, including PAWP, cardiac output, left ventricular ejection fraction, left atrial diameter, forced vital capacity, brain natriuretic peptide, and Krebs von den Lunge-6 were not different between the

two groups.

Conclusion: The CT signs for PVOD had positive correlation with mPAP but negative correlation with DLco in SSc patients, indicating that PAH-SSc may reflect a spectrum of pulmonary vascular disease that ranges from the pulmonary artery to the vein.

Key words: pulmonary arterial hypertension, systemic sclerosis, pulmonary veno-occlusive disease, chest CT.

Key messages:

- The significance of the CT signs for PVOD was evaluated exclusively in PAH-SSc.
- The CT signs for PVOD correlated with mPAP and DLco.
- PAH-SSc would have a wide spectrum of vascular disease ranging from the artery to the vein.

Introduction

Pulmonary arterial hypertension (PAH) is a common and fatal complication of systemic sclerosis (SSc), accounting for one-fourth of the deaths in those patients [1]. Pathohistologically, PAH-SSc is a distinctive vasculopathy compared to other PAH. Not only pulmonary arterial/arteriolar remodeling but also fibrosis of pulmonary veins/venules are frequently found in the lung tissue of PAH-SSc patients [2,3,4]. From a clinical point of view, PAH-SSc is also unique, as it is often accompanied by a decreased diffusing capacity of the lungs for carbon monoxide (DLco) [5]. In addition, a triad of chest computed tomography (CT) features for pulmonary veno-occlusive disease (PVOD), including mediastinal lymph node enlargement, thickened interlobular septal wall, and ground glass opacity was documented [6], left heart disease and/or interstitial lung disease also contribute to the pulmonary haemodynamic abnormalities in PAH-SSc, making its pathophysiology quite complex [7]. However, it is still unclear whether the pulmonary haemodynamic abnormalities of SSc derive from two distinct pathological entities, remodeling of the pulmonary arteries/arterioles and that of the pulmonary veins/venules, or a spectrum of pulmonary vascular disease. Moreover, it also remains to be elucidated whether the chest CT triad for PVOD specifically reflects remodeling of the pulmonary veins/venules or is an unspecific feature also related to left heart disease and/or

interstitial lung disease (ILD).

In this study, we aimed to clarify the clinical significance of the chest CT triad for PVOD in SSc by assessing its relationship with pulmonary haemodynamics, cardiac function, and pulmonary function in patients with SSc.

Methods

Study design

This was a single-centre retrospective study performed at Hokkaido University Hospital in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Approval was obtained from the local authority (Hokkaido University Certified Review Board, CRB022-0135; approval number: 022-0279).

Patients and data extraction

This cross-sectional study involved a cohort of consecutive patients who met the 2013 American College of Rheumatology/European League against Rheumatism classification criteria of SSc [8], underwent right heart catheterization (RHC) from January 2007 to January 2022 in Hokkaido University Hospital, had pulmonary haemodynamic abnormalities including mean pulmonary arterial pressure (mPAP)>20 mmHg, pulmonary vascular resistance (PVR)>2 W.U. or pulmonary artery wedge

pressure (PAWP)>15 mmHg [9], and underwent Multi-Detector CT (MDCT) scan of the chest within one year from RHC. Patients who were unwilling to make their clinical data available were excluded. Patients' privacy data were strictly protected. Demographic, laboratory, and radiological findings were extracted from the medical records.

Right heart catheterization (RHC)

RHC was performed using a balloontipped 7.0F thermodilution catheter (Becton-Dickinson, Franklin Lakes, NJ, USA) via the internal jugular vein or the femoral vein. PVR was determined as follows: PVR = (mPAP - PAWP)/CO (cardiac output). CO was measured by the thermodilution technique.

Computed Tomography (CT) scan of the chest

CT scan of the chest images were obtained during inspiration in the supine position using a 256-MSCT scanner (Brilliance iCT Elite scanner, Philips Healthcare, Cleveland, OH, USA) or an 80-MDCT scanner (Aquilion PRIME scanner, Canon Medical Systems Corporation, Tochigi, Japan). All CT scan images were obtained without contrast administration. The interval between MDCT scan and RHC was within 30 days in all patients. The presence or absence of CT features for PVOD, including mediastinal

lymph node enlargement, thickened interlobular septal wall, and ground glass opacity, was evaluated by a certified radiologist (Y.K.) in a blinded manner. Subpleural ground glass opacity was considered to reflect ILD and thus excluded from CT features for PVOD. Centrilobular and central patterns were both included as ground glass opacity. An example of these three findings is shown in Supplementary Figure 1. Based on accounting for the number of findings, we divided the patients into two groups: one group had 0 or 1 finding, and the other group had 2 or 3 findings.

Cardiac magnetic resonance (CMR) imaging

CMR was performed using a 3.0-tesla whole-body scanner (Ingenia Elition X, Philips Medical Systems, Best, the Netherlands) with dS Torso coil, a 3.0-tesla whole-body scanner (Achieva TX, Philips Medical Systems, Best, the Netherlands) with a 32-channel phased-array receiver torso-cardiac coil, or a 1.5-tesla whole-body scanner (Achieva dStream, Philips Medical Systems, Best, the Netherlands) with dS Torso coil. CMR images were analyzed using commercially available analysis software (ISP, Philips Medical Systems, Best, the Netherlands). All sequences were obtained with breath-holding in expiration. Cine CMR images were analyzed using commercially available analysis software (ISP, Philips Medical Systems, Best, the Netherlands).

Statistical analysis

Continuous variables were expressed as median (interquartile range) and compared using the Mann–Whitney U-test. Categorical variables were expressed as number (percentage) and compared using the χ^2 test or Fisher's exact test. Statistical significance was defined as a P-value <0.05. All analyses were performed using the JMP Pro software (ver. 16.0; SAS Institute Inc., Cary, NC, USA).

Results

Patients

A total of 52 patients were enrolled in this study (table1). Of these, 11 (21%), 32 (61%), and 12 (23%) had mediastinal lymph node enlargement, thickened interlobular septal wall, and ground glass opacity, respectively. In terms of the number of three findings applicable, no, 1, 2, and 3 findings were found in 14 (26%), 23 (44%), 13 (25%), and 2 (4%) patients, respectively. Fifteen patients had two or more of these features for PVOD (the 2-3 group) while the other 37 patients had one or none of them (the 0-1 group). Among autoantibodies, anti-centromere antibody was most prevalent (n = 21), followed by anti-topoisomerase antibody (n = 14), anti-U1-RNP antibody (n = 12), and anti-RNA polymerase III antibody (n = 2). ILD was observed in 44 patients (Table 1).

Pulmonary haemodynamics, cardiac function, pulmonary function, and serum biomarkers in the 0-1 group and the 2-3 group

To clarify the clinical significance of the chest CT features for PVOD in SSc, we compared pulmonary haemodynamics, transthoracic echocardiography and MRI-based cardiac function, pulmonary function, and serum biomarkers between the 0-1 group and the 2-3 group (Table 2, Figure 1). mPAP ($p = 0.02$), diastolic PAP ($p = 0.02$) and forced vital capacity (FVC)/ diffusing capacity for carbon monoxide (DLco) ($p = 0.04$) were higher while DLco/VA ($p = 0.02$) was lower in the 2-3 group than in the 0-1 group with statistical significance. Other parameters, including PAWP, cardiac output, left ventricular ejection fraction, left atrial diameter, forced vital capacity, brain natriuretic peptide, and Krebs von den Lunge-6 were not different between the two groups. ILD was observed in 44 patients whereas diffusing capacity for carbon monoxide (DLco) was not statistically different in patients with and without ILD (Supplementary Figure 2)

The impact of each of the chest CT triad for PVOD on pulmonary haemodynamics, cardiac function, pulmonary function, and serum biomarkers

Given the heterogeneity of PAH-SSc pathophysiology, while the specificity of CT features for PVOD remains unknown, we further compared pulmonary

haemodynamics, echocardiography and MRI-based cardiac function, pulmonary function, and serum biomarkers between patients with and without each of the followings; mediastinal lymph node enlargement, thickened interlobular septal wall, and ground glass opacity. PAWP ($p = 0.04$), FEV1/FVC ($p = 0.03$), FVC/DLco ($p = 0.03$), and KL-6 ($p = 0.01$) were higher while DLco ($p = 0.001$) and DLco/VA ($p = 0.01$) were lower in patients with mediastinal lymph node enlargement than those without (Table 3). Right ventricular ejection fraction ($p = 0.047$) was lower in patients with thickened interlobular septal wall than those without (Table 4). VC ($p = 0.01$) and FVC ($p = 0.01$) were higher in patients with ground glass opacity than those without (Table 5).

Discussion

We herein clarified the clinical significance of the chest CT features for PVOD in SSc, by integrating the data of RHC, MDCT, transthoracic echocardiography, CMR, pulmonary function test with DLco, and serum biomarkers.

Consistent with previous studies [10,11,12], the chest CT triad for PVOD, including mediastinal lymph node enlargement, thickened interlobular septal wall, and ground glass opacity, was correlated with a decreased DLco in our study, indicating that it also in SSc reflects remodeling of the pulmonary veins/venules and capillaries. Conversely,

our study has also demonstrated its correlation with an increased PAP, suggesting that severe pulmonary vasculopathy is accompanied by remodeling of the pulmonary veins/venules and capillaries in PAH-SSc. In addition, the chest CT triad for PVOD was suggestive to be correlated with prognosis (Supplementary Figure 3). Therefore, PAH-SSc may reflect a spectrum of pulmonary vascular disease that ranges from the pulmonary artery to the vein rather than either of two distinct pathological entities, remodeling of the pulmonary arteries/arterioles and that of the pulmonary veins/venules. The current data were in line with a previous pathohistological study demonstrating the morphologically indistinguishable pulmonary arterioles and venules in PAH-SSc [3]. Global pulmonary vascular remodeling was also observed in PAH lungs carrying BMPR2 gene mutations and PVOD linked to EIF2AK4 gene mutations [13,14].

The chest CT triad for PVOD was indicated by several studies to be a prognostic factor in PAH-SSc [6,15,16]. As it was associated with pulmonary edema on therapy, these studies discussed the significance of pulmonary venous disease in PAH-SSc. Conversely, given our current findings, another interpretation could be made. The prognosis of PAH-SSc is associated with severe pulmonary vasculopathy that is accompanied by remodeling of the pulmonary veins/venules and capillaries. We treated 14 patients in the 2-3 group using pulmonary vasodilators, with only one

occurrence of pulmonary edema (data not shown). Although further studies are necessary, pulmonary vasodilators may not always be contraindicated for patients with PAH-SSc and PVOD, since their positive effect on a pulmonary arterial disease can be greater than their negative effect on an a pulmonary venous disease.

Among the chest CT triad for PVOD, mediastinal lymph node enlargement was significantly associated with DLco. Mediastinal lymph node enlargement is considered to occur secondary to pulmonary venous congestion, veno-lymphatic shunts, and angiogenetic factors [17]. Since ground glass opacity reflects histopathological changes of the pulmonary capillaries [18], the current data would support pulmonary capillary remodeling in SSc. Given that ground glass opacity (excluding subpleural ground glass opacity) was rather associated with preserved VC and FVC, ILD and a pulmonary vascular disease might occur independently in SSc. This is in line with the epidemiological characteristics of SSc; ILD and anti-topoisomerase antibody are more frequent in diffuse cutaneous SSc whereas PAH and anti-centromere antibody are common in limited cutaneous SSc [19]. In the current study, although not statistically significant, anti-topoisomerase antibody was less prevalent in the 2-3 group than in the 0-1 group (13% v.s. 32%, $p = 0.30$, data not shown in the result section). The correlation between mediastinal lymph node enlargement and PAWP suggests a shared pathophysiology in PVOD and group 2 pulmonary hypertension that has been

indicated in a previous study using quantitative histomorphometry [20].

Our study has several limitations. First, it was conducted at a single centre, thus having a small sample size, with a retrospective cross-sectional design. Moreover, our study included only Japanese population, therefore it remained uncertain if the data in this study are applicable to other populations. Second, the presence or absence of CT features for PVOD was evaluated by single radiologist. Further validation by other specialists would confirm our results.

In conclusion, the chest CT signs for PVOD correlated positively with pulmonary haemodynamics and negatively with DLco in SSc. The current data indicates that PAH-SSc may reflect a spectrum of pulmonary vascular disease that ranges from the pulmonary artery to the vein. It would also be suggestive when considering treatment strategies in patients with SSc and suspicion of PVOD since some of those patients might benefit from pulmonary vasodilation.

Acknowledgements

The authors would like to acknowledge Syuhei Takeyama, Masato Tarumi, Yui Kosumi, Yotaro Oki, Kazuro Kamada, Kenichi Miyamoto, and Yuta Inoue for their clinical supports.

Author Contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Masaru Kato had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Kato, Moriya, Ninagawa, Atsumi.

Patient recruitment. Kato, Moriya, Ninagawa, Hisada, Kono, Fujieda.

Clinical evaluation. Kato, Moriya, Ninagawa, Kikuchi, Tsujino, Sato.

Acquisition of data. Kato, Moriya, Ninagawa.

Analysis and interpretation of data. Kato, Moriya.

Statistical analysis. Kato, Moriya.

Funding

No funding was received for this study.

Competing interest

M Kato has received research grants from AbbVie, Actelion, GlaxoSmithKline, Janssen, Nippon Shinyaku and Novartis and speaking fees from Astellas and Eli Lilly. M Kono has received research grants from GlaxoSmithKline, Mitsubishi Tanabe, Astellas, Sanofi, Taisho, Nippon Shinyaku, Taiju Life Social Welfare Foundation, Kowa,

Terumo, Kyocera, Chugai, Mochida, Lotte, Hitachi, Takeda and Yamazaki Baking. I Tsujino received research support from Nippon Shinyaku Co., Ltd., Mochida Pharmaceutical Co., Ltd., Boehringer Ingelheim Japan, Takeyama Co., Ltd., Kaneka Co., Ltd., and Medical System Network Co., Ltd. T Atsumi has received research grants from Astellas, Takeda, Mitsubishi Tanabe, Chugai, Daiichi-Sankyo, Otsuka, Pfizer, Alexion, Bayer, Otsuka, Chugai, Takeda, Eisai, Bristol-Myers Squibb, Daiichi Sankyo, Mitsubishi Tanabe and Asahi Kasei, consultant fees from Ono, Sanofi, Daiichi Sankyo and Pfizer and speaking fees from Mitsubishi Tanabe, Chugai, Astellas, Takeda, Pfizer, Daiichi Sankyo, Bristol-Myers Squibb and Eli Lilly. Other authors have nothing to declare.

Patient consent for publication

Written informed consent was obtained for participation in the study, as well as consent for the publication of study results.

Ethical approval

This study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Approval was obtained from Hokkaido University Certified Review Board (Approval number: 022-0279).

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data and materials used in this study are available on request.

Supplementary material

This content has been supplied by the authors in another file.

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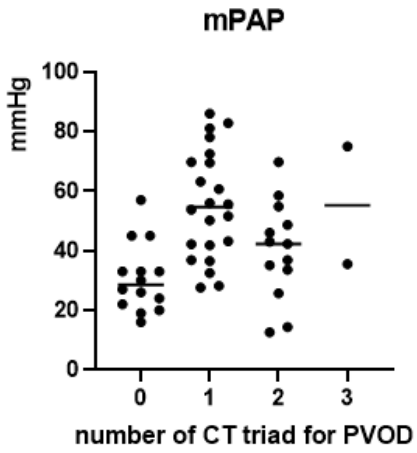
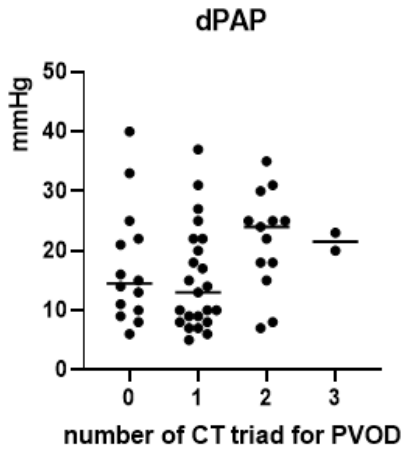
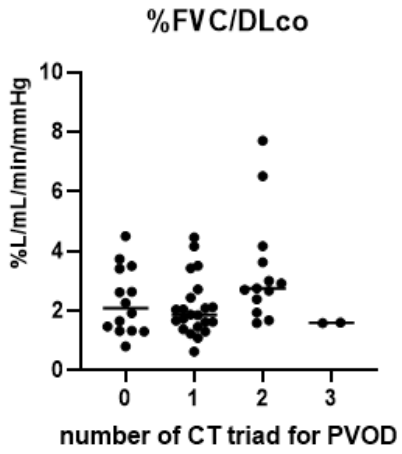
Figure Legend

Figure 1. Pulmonary haemodynamics and pulmonary function, including mean pulmonary arterial pressure (mPAP), diastolic PAP (dPAP), forced vital capacity (FVC)/ diffusing capacity for carbon monoxide (DLco) and DLco/VA, according to the number of CT scan triad for PVOD.


mPAP
mmHg
100
80
60
40
20
0
0
1
2
3
number of CT triad for PVOD


dPAP
mmHg
50
40
30
20
10
0
0
1
2
3
number of CT triad for PVOD


%FVC/DLco
%L/mL/mIn/mmHg
10
8
6
4
2
0
0
1
2
3
number of CT triad for PVOD

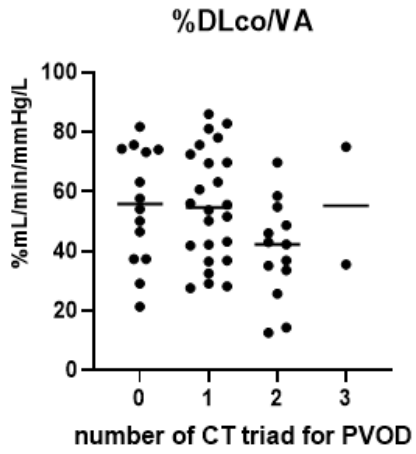

%DLco/VA
%mL/min/mmHg/L
100
80
60
40
20
0
0
1
2
3
number of CT triad for PVOD

Table1. Characteristics of enrolled patients (n=52)

	N=52		
Age, years, medians (IQR)	66		[56:71]
Sex, female, n (%)	45		87
Number of months from onset of present illness to CT scan (IQR)	19		[0.1:50]
Autoantibodies			
Anti-centromere, n (%)	21		(40)
anti-topoisomerase antibody, n (%)	14		(27)
Anti-RNA polymerase III, n (%)	2		(4)
Anti-U1-RNP, n (%)	12		(23)
Organ involvement			
Interstitial lung disease	44		(85)
Renal crisis	4		(8)
Gastroesophageal reflux disease	42		(81)

Values listed as mean (S.D.) unless otherwise stated.

mPAP: mean pulmonary artery pressure; sPAP, dPAP, and mPAP, systolic, diastolic, and mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary arterial wedge pressure; CO: cardiac output; CI: cardiac index; SvO2: mixed venous oxygen saturation; RAP: right atrial pressure; VC: vital capacity; FVC: forced vital capacity; FEV1: forced expiratory volume in 1s; DLco: diffusing lung capacity for carbon monoxide; VA: ventilation alveolar; ePASP: estimated pulmonary artery systolic pressure; TRV: tricuspid regurgitation velocity; FS: fractional shortening; LAD: left atrial dimension; E/A: early diastolic transmitral flow velocity/late diastolic transmitral flow velocity; E/e': early diastolic transmitral flow velocity/early diastolic mitral annular velocity; e'septal: early diastolic mitral annular velocity at septal site; e'lateral: early diastolic mitral annular velocity at lateral site; LVEF: left ventricular ejection fraction; RVEF: right ventricular ejection fraction; BNP: brain natriuretic peptide; KL-6: Krebs von den Lungen-6.

Table2. Pulmonary haemodynamics, cardiac function, pulmonary function, and serum biomarkers in the 0-1 group and the 2-3 group.

	The 0-1 group		The 2-3 group	
Parameter	n=37		n=15	p value
●RHC				
mPAP	24	(17-33)	30	(25-44)	**0.029**
sPAP	38	(31-57)	50	(39-70)	0.127
dPAP	14	(9-22)	23	(18-25)	**0.024**
PVR	3.8	(2.9-5.9)	5.3	(3.2-12.7)	0.137
PAWP	7	(5-8)	9	(5-10)	0.532
CO	3.7	(3.3-4.8)	4	(3.3-4.5)	0.895
CI	2.6	(2.2-3.1)	2.6	(2.3-3.2)	0.723
SvO2	72	(66-75)	70	(68-75)	0.738
RAP	4	(2-5)	4	(2-7)	0.933
●Pulmonary function test				
%VC	74	(55-99)	90	(65-115)	0.093
%FVC	76	(55-102)	96	(66-110)	0.140
FEV1/FVC	81	(77-86)	80	(69-89)	0.701
%DLco	40	(26-57)	32	(20-48)	0.346
% DLco/VA	54	(39-73)	42	(34-55)	**0.028**
%FVC/DLco	1.9	(1.4-2.7)	2.7	(1.7-3.6)	**0.044**
●transthoracic echocardiography				
ePASP	49	(38-60)	53	(34-83)	0.418
TRV	3.3	(2.9-3.7)	3.4	(2.7-4.4)	0.436
%FS	39	(34-42)	36	(33-44)	0.551
LAD	36	(33-42)	34	(29-41)	0.181
E/A	0.8	(0.7-1.2)	0.8	(0.6-0.8)	0.140
E/e'	8.6	(6.9-11.5)	7.8	(5.8-9.0)	0.086
e'septal	7.1	(5.5-10.0)	7	(6.1-9.5)	0.707
e'lateral	10	(7.4-12.1)	9.7	(7.8-11.1)	0.754
●Cardiac magnetic resonance (CMR) imaging				
LVEF	63	(60-71)	58	(53-71)	0.246
RVEF	45	(37-53)	37	(29-46)	0.057
●biomarker				
BNP	91	(25-297)	51	(29-313)	0.862
KL-6	492	(319-1165)	622	(383-1318)	0.824

Table3. The impact of mediastinal lymph node enlargement on pulmonary haemodynamics, cardiac function, pulmonary function, and serum biomarkers.

	mediastinal lymph node enlargement			
Parameter	(-)		(+)	
	n=41		n=11	p value
●RHC				
mPAP	25	(18-35)	29	(21-38)	0.452
sPAP	39	(32-62)	46	(36-66)	0.352
dPAP	15	(9-23)	20	(10-25)	0.357
PVR	4.2	(2.9-7.3)	3.2	(2.7-5.8)	0.364
PAWP	7	(5-8)	9	(6-13)	**0.042**
CO	3.7	(3.1-4.7)	4.4	(3.8-5.0)	0.109
CI	2.6	(2.3-3.1)	2.7	(2.6-3.3)	0.272
SvO2	71	(66-76)	73	(68-75)	0.615
RAP	4	(2-6)	4	(2-7)	0.790
●Pulmonary function test					
%VC	84	(60-103)	65	(53-116)	0.124
%FVC	86	(61-106)	70	(54-77)	0.139
FEV1/FVC	80	(74-83)	87	(81-88)	**0.030**
%DLco	44	(29-60)	23	(16-30)	**0.001**
% DLco/VA	55	(42-72)	36	(26-54)	**0.013**
%FVC/DLco	1.9	(1.5-2.7)	2.8	(1.6-4.1)	**0.030**
●transthoracic echocardiography					
ePASP	50	(39-61)	47	(31-77)	0.848
TRV	3.6	(2.9-3.7)	3.2	(2.5-4.2)	0.831
%FS	39	(35-44)	34	(33-38)	0.088
LAD	35	(31-42)	35	(30-43)	0.813
E/A	0.8	(0.6-1.1)	0.8	(0.8-0.8)	0.599
E/e'	8.6	(6.9-10.6)	7.4	(5.8-11.8)	0.34
e'septal	7.3	(5.6-10.0)	6.4	(5.6-9.2)	0.622
e'lateral	10.2	(7.9-12.1)	7.7	(4.7-10.7)	0.075
●Cardiac magnetic resonance (CMR) imaging					
LVEF	62	(58-70)	63	(58-71)	0.892
RVEF	44	(33-53)	41	(37-49)	0.702
●biomarker					
BNP	78	(28-297)	78	(16-244)	0.716
KL-6	477	(261-1078)	1040	(669-1386)	**0.013**

Table4. The impact of thickened interlobular septal wall on pulmonary hemodynamics, cardiac function, pulmonary function, and serum biomarkers.

	thickened interlobular septal wall			
	(-)	(+)		
Parameter	n=20	n=32		p value
●RHC				
mPAP	25	(20-33)	26	(18-40)	0.631
sPAP	40	(33-60)	42	(32-64)	0.985
dPAP	13	(9-22)	19	(10-25)	0.235
PVR	3.9	(3.1-6.0)	4.3	(2.6-7.4)	0.955
PAWP	7	(5-8)	8	(5-10)	0.393
CO	3.9	(3.4-4.5)	3.9	(3.2-4.9)	0.672
CI	2.7	(2.5-3.2)	2.6	(2.3-3.1)	0.522
SvO2	73	(67-76)	70	(65-74)	0.311
RAP	3	(2-6)	4	(3-7)	0.288
●Pulmonary function test					
%VC	77	(61-101)	80	(55-103)	0.770
%FVC	86	(61-104)	81	(56-105)	0.672
FEV1/FVC	80	(75-83)	81	(75-87)	0.665
%DLco	45	(25-56)	36	(23-57)	0.469
% DLco/VA	55	(39-72)	46	(36-63)	0.279
%FVC/DLco	2.1	(1.5-3.2)	2	(1.6-3.0)	0.802
●transthoracic echocardiography					
ePASP	50	(39-59)	48	(35-77)	0.97
TRV	3.3	(2.9-3.7)	3.3	(2.7-4.2)	0.977
%FS	39	(34-44)	38	(33-42)	0.494
LAD	37	(34-40)	35	(29-42)	0.213
E/A	0.9	(0.7-1.2)	0.7	(0.6-0.9)	0.074
E/e'	8.6	(7.0-12.9)	7.8	(6.3-9.6)	0.247
e'septal	6.9	(5.6-9.1)	7.3	(5.7-10.0)	0.688
e'lateral	10.1	(6.5-12.1)	9.8	(7.8-11.7)	0.814
●Cardiac magnetic resonance (CMR) imaging					
LVEF	63	(60-70)	62	(56-71)	0.305
RVEF	48	(42-53)	42	(30-47)	**0.047**
●biomarker					
BNP	113	(25-389)	56	(28-294)	0.592
KL-6	467	(260-978)	608	(391-1529)	0.210

Table5. The impact of thickened ground glass opacity on pulmonary hemodynamics, cardiac function, pulmonary function, and serum biomarkers.

	ground glass opacity		
	(-)	(+)	
Parameter	n=40	n=12	p value
●RHC			
mPAP	26 (19-35)	27 (17-45)	0.777
sPAP	42 (33-62)	41 (33-70)	0.965
dPAP	15 (9-24)	21 (10-25)	0.433
PVR	4.1 (3.2-6.2)	3.4 (2.1-12.7)	0.728
PAWP	8 (6-9)	6 (4-8)	0.079
CO	3.8 (3.3-4.9)	4 (3.2-4.4)	0.487
CI	2.6 (2.3-3.1)	2.6 (2.2-3.2)	0.802
SvO2	71 (64-76)	72 (69-75)	0.460
RAP	4 (2-5)	3 (2-8)	0.711
●Pulmonary function test			
%VC	71 (55-98)	104 (74-115)	**0.016**
%FVC	72 (56-100)	109 (81-121)	**0.012**
FEV1/FVC	81 (77-87)	78 (70-86)	0.245
%DLco	36 (23-53)	48 (34-64)	0.100
% DLco/VA	50 (37-73)	51 (43-67)	0.739
%FVC/DLco	2.1 (1.5-3.5)	2 (1.6-2.6)	0.739
●transthoracic echocardiography			
ePASP	50 (38-62)	44 (37-73)	0.777
TRV	3.3 (2.9-3.8)	3.2 (2.8-4.1)	0.845
%FS	38 (33-42)	38 (34-44)	0.870
LAD	36 (32-42)	34 (28-40)	0.253
E/A	0.8 (0.7-1.2)	0.7 (0.5-0.9)	0.105
E/e'	8.1 (6.5-11.3)	8.8 (7.9-9.3)	0.635
e'septal	7.1 (5.6-10.0)	7 (6.0-8.9)	0.863
e'lateral	10.5 (7.4-12.1)	9.3 (8.7-11.1)	0.742
●Cardiac magnetic resonance (CMR) imaging			
LVEF	63 (58-71)	59 (55-71)	0.287
RVEF	44 (37-52)	39 (24-53)	0.274
●biomarker			
BNP	91 (22-299)	66 (30-290)	0.734
KL-6	623 (423-1382)	399 (236-1072)	0.072