Assessment of right and left ventricular functions in interstitial lung diseases

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Background: Subclinical or overt cardiovascular affection in patients with interstitial lung diseases (ILD) may expect to have increased mortality and/or reduced exercise capacity.

Objective: Echocardiographic (echo) assessment of right ventricular (RV) and left ventricular (LV) functions in patients with ILD.

Patients and methods: Conventional echo, tissue Doppler imaging (TDI) and two-dimensional speckle tracking echo (2D STE), spirometry [forced vital capacity (FVC%), forced expiratory volume in 1 s% and forced expiratory volume in 1 s/FVC], and functional exercise capacity (6 min walking test) were performed on 60 patients with ILD and 60 age-matched and sex-matched controls. Pulmonary involvement was identified in high-resolution computed tomography (HRCT) and scored according to a semiquantitative Warrick score.

Results: Using conventional echo-Doppler, TDI, and 2D STE, there are statistically significant impairments in both RV systolic and diastolic functions, as well as LV diastolic functions in ILD patients compared with controls ($P<0.05$). LV systolic dysfunction was detected by TDI and STE only; however, ejection fraction was normal by standard echo. In the ILD group, the tricuspid annular plane systolic excursion was positively correlated with PaO_2 and FVC%, while it was negatively correlated with the HRCT score. RV global longitudinal strain% was positively correlated with both 6 min walking distance and FVC%. Moreover, LV global longitudinal strain% was positively correlated with both 6 min walking distance and PaO_2, while it was negatively correlated with HRCT score.

Conclusion: Both RV and LV systolic and diastolic dysfunctions were detected by echo in ILD patients. Ventricular dysfunctions were related to hypoxemia, radiological score, and vital capacity of the lungs. Ventricular dysfunction has a negative impact on function exercise capacity of patients with ILD.

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Introduction

Interstitial lung disease (ILD) represents a group of disorders that include common functional features including a decrease in pulmonary compliance as well as impairment of gas exchange. Cardiovascular impairment may not easily add to the impact of the restrictive ventilatory impairment on exercise capability in ILD; it may be really the primary determinant of exercise restriction in ILD [1–3].

Transthoracic Doppler echocardiography (echo) appears to be an important, easy, and noninvasive method to determine ventricular dysfunction in patients with ILD [4]. Recently an advanced modality as speckle tracking echocardiography (STE) has been used in clinical practice [5]. STE had been used for the assessment of regional myocardial function of both ventricles while not angle dependency, which is the most important demerit of strain-rate imaging, based on the tissue Doppler technique [6].

This study was to assess right ventricular (RV) and left ventricular (LV) functions in patients with ILD using different echo modalities.

Patients and methods

This descriptive case–control study included 120 patients (60 ILD patients and 60 healthy, age-matched and sex-matched control group). They were recruited from Al-Zahraa University Hospital from November 2016 to February 2018. The ethics committee of the university hospital institute approved the study. An informed written consent was obtained from all participants before their enrollment into the study. All patients were diagnosed according to the diagnostic algorithm of ILD [7]. The diagnosis of ILD cases was based mainly on clinical presentation, spirometry, and high-resolution computed tomography (HRCT) pattern and distribution. Serological markers, bronchoscopy with bronchoalveolar lavage, and/or tissue biopsy were done for some patients if diagnostically indicated.

Exclusion criteria

Any patients with cardiovascular comorbidities were excluded from the study, that is systemic arterial hypertension, coronary artery diseases, cardiomyopathy, valvular disease, congenital heart diseases, diabetes mellitus, end-stage renal failure, history of malignancy, and/or under chemotherapy or radiotherapy [8].

Study design

All participants were subjected to the following:

(1) Anthropometric measurements, smoking status, and disease duration.
(2) Resting arterial blood gas analysis via 'rapid lap analyzer 248' apparatus; the following values were recorded: SaO_2%, PaO_2 (mmHg), $PaCO_2$ (mmHg), HCO_3 (mEq/l), pH, and A-a gradient.
(3) Spirometry was carried out for all patients using MEDISOFT-HYPAIR compact +flow meter pulmonary function testing (Belgium). The following indices were recorded forced expiratory volume in 1 s ($FEV_{1\%}$), forced vital capacity (FVC%), and FEV_1/FVC ratio. Spirometric indices were calculated using best out of three technically satisfactory trials in accordance with the guidelines of ATS [9].
(4) The 6 min walking test was performed according to ATS guidelines [10]. The total distance walked and SaO_2 before and after the test were recorded.
(5) HRCT was performed for patients only by standard protocol using a multidetector scanner (160 detectors; Toshiba, Prime Aquilion, Japan). Pulmonary involvement was identified and scored according to a semiquantitative Warrick score [1]. The total Warrick HRCT scores range from 0 (no involvement) to 30 (the worst involvement).
(6) Resting transthoracic Doppler echo was performed using Vivid-E9 GE system with tissue Doppler and speckle tracking imaging capability attached to Echo-Pac work station version (201) following guidelines from the American Society of Echocardiography and the European Association of Cardiovascular Imaging [11]. The LV and RV functions were assessed using various echo-Doppler modes including M-mode, two-dimensional (2D) echo, conventional Doppler flow imaging, tissue Doppler imaging (TDI), and STE. The following parameters were obtained:
    (a) RV parameters included: RV dimensions, tricuspid annular plane systolic excursion (TAPSE), and percentage of fractional area change. Measures of RV diastolic function by pulsed Doppler through tricuspid flow including (tricuspid early and late diastolic filling velocities and tricuspid flow early deceleration time). Right ventricular systolic pressure (RVSP) assessment in case of presence of tricuspid regurgitation using peak systolic gradient across the tricuspid valve and inferior vena cava diameters and collapse. RV Tei index reflects both systolic and diastolic RV functions=(isovolumic relaxation time +isovolumic contraction time)/ejection time. Tissue Doppler velocities of the tricuspid valve annulus at the RV free wall were determined. Measured velocities include peak systolic tricuspid annular velocity, early diastolic tricuspid annular velocity, and late diastolic tricuspid annular velocity and RV global longitudinal strain (GLS) by 2D speckle tracking.
    (b) LV parameters included:

    LV internal dimensions and M-mode/2D echo ejection fraction (EF).Measures of LV diastolic function by pulsed Doppler transmitral flow including (mitral early and late diastolic filling velocities and timely mitral flow early deceleration), Tei index, tissue Doppler velocities averaged from four mitral annular sites for the calculation of peak systolic mitral annular velocity, early diastolic mitral annular velocity, and late diastolic mitral annular velocity and LV-GLS by 2D speckle tracking.

Statistical analysis

Statistical analysis was conducted by IBM SPSS software package version 16 (IBM Corp., Armonk, New York, USA). Data were presented as mean±SD for quantitative variables and as number and frequencies for qualitative variables. Unpaired Student's t test was used to compare quantitative data between two groups and χ^2 test was used to compare qualitative variables between two groups. Linear correlation coefficient test was used to assess the relation between two quantitative variables in the same group. P values less than 0.05 were considered significant.

Results

Table 1 shows that both groups are age matched and sex matched with a female predominance; no significant statistical differences were detected in smoking history and BMI between both groups. Regarding 6 min walking test, the mean of 6 min

Table 1 Comparison between interstitial lung disease group and control group concerning the studied parameters

Parameters	ILD (*N*=60)	Control (*N*=60)	*t* value	*P* value
Sex				
Females	52 (86.7)	50 (83.3)	0.180	0.672
Males	8 (13.3)	10 (16.7)		
Age	49.47±9.07	49.37±7.99	0.051	0.959
	30.00–69.00	36.00–67.00		
BMI	26.53±3.45	25.57±3.09	1.282	0.203
Smoking				
Non	31 (51.7)	40 (66.7)	3.430	0.330
Smoker	4 (6.7)	6 (10.0)		
Passive	23 (38.3)	14 (23.3)		
Ex-smoker	2 (3.3)	0 (0.0)		
6MWT				
SpO_2 before (%)	92.40±3.84	96.83±1.18	–6.170	0.001*
6MWD (m)	287.13±75.11	472.43±26.56	–13.078	0.001*
SpO_2 after (%)	88.40±6.30	96.27±0.98	–6.784	0.001*
ABG				
pH	7.42±6.03	7.38±2.29	2.978	0.004*
$PaCO_2$ (mmHg)	35.78±4.92	39.33±3.00	–3.629	0.001*
PaO_2 (mmHg)	75.44±14.69	95.04±2.85	–9.432	0.001*
SaO_2%	93.50±3.80	96.93±1.23	–6.212	0.001*
A-a gradient	33.68±14.67	8.36±4.22	9.239	0.001*
Spirometry				
FVC%	54.08±12.63	87.00±4.23	–13.852	0.001*
FEV1%	53.10±12.31	87.60±5.07	–14.701	0.001*
FEV1/FVC	87.77±9.21	92.33±5.24	–2.508	0.014*

Data are presented as mean±SD, range, and *n* (%). 6MWD, 6 min walking distance; 6MWT, 6 min walking test; A-a gradient, alveoloarterial gradient; ABG, arterial blood gas; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ILD, interstitial lung disease; SaO_2, oxygen saturation in arterial blood (by ABG sample); SpO_2, peripheral capillary oxygen saturation (by pulse oximetry).
*Significant.

walking distance (6MWD) and SpO_2 before and after performance of the test, as well as all arterial blood gas parameters were significantly lower in ILD patients. Regarding PFTs, there are highly statistically significant decreases in FVC% and FEV_1% and FEV_1/FVC ratio in the ILD group in comparison to the control group.

Table 2 shows that by conventional echo, there are statistically significant increases in RV dimensions (RVOT proximal PLAX, RVOT proximal PSAX, and RV long), with impaired RV systolic and diastolic functions (decrease in TAPSE, RV-fractional area change, RV E wave, RV E/A ratio, and increase in Tei index) in the ILD group compared with the control group. There is a statistically significant increase in RVSP in the ILD group compared with the control group.

Table 3 shows that by advanced echo, there is statistically significant impairment in both RV systolic and diastolic functions in the ILD group than the control group.

Table 4 shows that by conventional echo, there is a statistically significant increase in left atrial, interventricular septum thickness, left ventricular posterior wall thickness, and Tei index between the ILD group and the control group, while there is no statistically significant difference in EF by M-mode or by biplane. As regards the LV diastolic function, there is a statistically significant decrease in the ILD group compared with the control group.

Table 5 shows that by advanced echo, there is a statistically significant impairment in both LV systolic and diastolic functions in ILD group compared with the control group.

Table 6 shows that in the ILD group the TAPSE was positively correlated with PaO_2 and FVC% while it was negatively correlated with HRCT score. RV-GLS % was positively correlated with both 6MWD and FVC%. As regards RVSP, there was a positive correlation with HRCT score and duration of the disease and negative correlation with 6MWD, PaO_2, and FVC%. Moreover, LV-GLS% was positively correlated with both PaO_2 and 6MWD, while it was significant negatively correlated with the HRCT score (P=0.008).

Table 2 Comparison of right ventricular conventional echocardiographic parameters between the interstitial lung disease group and the control group

Conventional echo	ILD (*N*=60)	Control (*N*=60)	*t* value	*P* value
RVOT prox. PLAX (mm)	31.12 ±3.20	28.63±3.56	3.343	0.001*
RVOT prox. PSAX (mm)	31.07 ±3.23	28.57±3.87	3.238	0.002*
RVOT dist. PSAX (mm)	21.57 ±3.05	21.23±3.41	0.470	0.640
RV FAC (%)	44.52 ±9.15	50.90±5.45	–3.517	0.001*
RV basal (mm)	31.93 ±7.27	33.87±4.71	–1.322	0.190
RV mid (mm)	28.05 ±6.56	26.20±5.93	1.300	0.197
RV long (mm)	64.37 ±10.78	58.27±5.46	2.913	0.005*
TAPSE (mm)	18.43 ±3.02	23.53±2.39	–8.074	0.001*
RV-MPI (Tei index)	0.38±0.13	0.27±0.11	4.117	0.000*
RV E. wave (m/s)	50.00 ±12.16	61.03±11.32	–4.150	0.001*
RV A. wave (m/s)	57.75 ±17.05	50.77±10.80	2.044	0.044*
RV E/A ratio	0.85±0.29	1.13±0.34	–4.052	0.001*
RVSP (mmHg)	38.20 ±16.71	24.00±3.85	4.582	0.001*

Data are presented as mean±SD. ILD, interstitial lung disease; RV A. wave, right ventricular peak velocity transtricuspid flow during atrial systole; RV E. wave, right ventricular peak velocity transtricuspid flow in the early phase; RV FAC, right ventricular fractional area change; RV-MPI, right ventricular myocardial performance index; RVOT dist. PSAX, right ventricular outflow distal diameter in parasternal short axis; RVOT prox. PLAX, right ventricular outflow proximal diameter in parasternal long axis; RVOT prox. PSAX, right ventricular outflow proximal diameter in parasternal short axis; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion. *Significant.

Table 3 Comparison of right ventricular parameters using tissue Doppler imaging and speckle tracking echo (advanced echocardiography) between the interstitial lung disease group and the control group

Advanced echo	ILD (*N*=60)	Control (*N*=60)	*t* value	*P* value
RV Sa (cm/s)	9.18±2.41	11.36±1.30	–4.611	0.001*
RV Ea (cm/s)	8.01±2.91	10.75±2.26	–4.516	0.001*
RV Aa (cm/s)	11.39±2.51	9.99±2.47	2.511	0.014*
RV-GLS%	17.49±4.23	23.63±2.14	–7.476	0.001*

Data are presented as mean±SD. ILD, interstitial lung disease; RV Aa, right ventricular late diastolic myocardial velocity at tricuspid annulus; RV Ea, right ventricular early diastolic myocardial velocity at tricuspid annulus; RV Sa, right ventricular systolic myocardial velocity at tricuspid annulus; RV-GLS, right ventricular global longitudinal strain. *Significant.

Table 4 Comparison of echocardiographic parameters of left atrium and left ventricle between interstitial lung disease group and control group by conventional echocardiography

Conventional echo	ILD (*N*=60)	Control (*N*=60)	*t* value	*P* value
LAD (mm)	36.90±4.38	32.20±4.40	4.796	0.001*
LVEDD (mm)	45.61±5.20	45.60±4.61	0.030	0.976
LVESD (mm)	29.73±5.28	29.17±2.91	0.547	0.586
IVS (mm)	9.93±1.84	8.50±1.22	3.856	0.001*
LVPWT (mm)	9.67±1.64	8.03±1.33	4.725	0.001*
FS (%)	37.35±4.89	38.07±3.13	–1.307	0.195
EF by M-mode (%)	65.55±5.24	66.73±3.84	–0.757	0.451
EF by biplane (%)	60.22±6.54	62.73±3.38	–2.683	0.075
LV E. wave (m/s)	67.61 ±21.97	80.27±16.04	–2.802	0.006*
LV A. wave (m/s)	73.38 ±14.94	64.63±10.82	2.853	0.005*
LV E/A ratio	0.98±0.28	1.25±0.27	–4.225	0.001*
LV-MPI(Tei index)	0.49±0.11	0.42±0.14	2.575	0.012*

Data are presented as mean±SD. EF, ejection fraction; ILD, interstitial lung disease; IVS, interventricular septum thickness; LAD, left atrial diameter; LV A. wave, peak velocity transmitral flow during atrial systole; LV E. wave, peak velocity transmitral flow in the early phase; LV-MPI, left ventricular myocardial performance index (Tei index); LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; LVPWT, left ventricular posterior wall thickness. *Significant.

Table 5 Comparison of left ventricular parameters using tissue Doppler imaging and speckle tracking echo (advanced echocardiography) between the interstitial lung disease group and the control group

Advanced echo	ILD (N=60)	Control (N=60)	t value	P value
LV Av.Sa4 (cm/s)	5.84±1.11	7.23±0.90	-5.931	0.001*
LV Av.Ea4 (cm/s)	6.92±2.09	10.15±1.91	–7.096	0.001*
LV Av.Aa4 (cm/s)	7.04±1.20	7.36±1.66	–0.940	0.350
LV E/Av.Ea4	10.64 ±5.08	8.18±2.03	2.546	0.013*
LV-GLS%	17.29 ±2.97	21.73±2.09	–7.343	0.001*

Data are presented as mean±SD. ILD, interstitial lung disease; LV $Av.Aa_4$, averaged left ventricular late diastolic myocardial velocities from 4 mitral annular sites; LV $Av.Ea_4$, averaged left ventricular early diastolic myocardial velocities from 4 mitral annular sites; LV $Av.Sa_4$, averaged left ventricular systolic myocardial velocities from 4 mitral annular sites; LV $E/Av.Ea_4$, peak velocity transmitral flow in the early phase/averaged left ventricular early diastolic myocardial velocities from 4 mitral annular sites; LV-GLS, left ventricular global longitudinal strain. *Significant.

Discussion

Echo is used to evaluate the cardiac involvement in ILD. However, in some cases, there may be clinical evidence of cardiac affection and conventional echo reveals normal study. Echo using different modalities was used for accurate assessment of LV and RV functions [12].

In the present study, ILD patients had significant RV dilatation [increased RVOT proximal in both long-axis and short-axis views and increased RV long (mm)

Table 6 Correlations of right ventricular systolic function (tricuspid annular plane systolic excursion and right ventricular global longitudinal strain%), pulmonary artery pressure (right ventricular systolic pressure) and left ventricular systolic function (left ventricular global longitudinal strain% with duration of the disease, 6 min walking distance (m), PaO_2, forced vital capacity, and high-resolution computed tomography score among the interstitial lung disease group

	TAPSE (mm)		RVSP (mmHg)		RV-GLS%		LV-GLS%	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Duration	–0.013	0.924	0.256	0.048*	0.028	0.832	0.059	0.655
6MWD (m)	0.251	0.053	–0.380	0.003*	0.264	0.042*	0.264	0.042*
PaO_2 (mmHg)	0.333	0.009*	–0.328	0.010*	0.241	0.063	0.382	0.003*
FVC%	0.379	0.003*	–0.306	0.017*	0.257	0.047*	0.248	0.056
HRCT score	–0.560	0.001*	0.372	0.003*	–0.214	0.101	–0.340	0.008*

6MWD, 6 min walking distance; FVC, forced vital capacity; HRCT, high-resolution computed tomography; LV-GLS, left ventricular global longitudinal strain; RV-GLS, right ventricular global longitudinal strain; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion. *Significant.

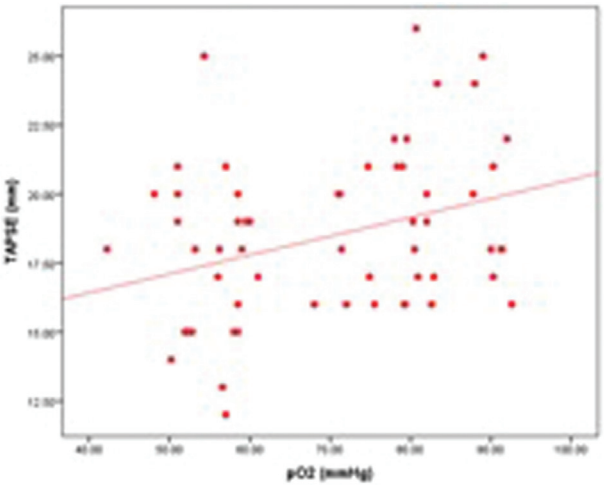
dimension] when compared with the control group (Table 2). Our results were concordant with that obtained by D'Andrea *et al.* [13], who reported that RV basal tract diameter, RV mid-tract diameter, and RV long-axis diameter were significantly higher in interstitial pulmonary fibrosis (IPF) patients with and without pulmonary hypertension (PH) compared with healthy controls.

Another result of our study was RV systolic dysfunction in ILD group compared with the control group that was evident by significant reduction of TAPSE, RV-fractional area change, and RV systolic velocity by TDI and RV-GLS by 2D STE with significant prolongation of RV myocardial performance index. Moreover, our study revealed that ILD patients had also RV diastolic dysfunction detected by reduced RV E/A ratio and RV Ea compared with the control group (Tables 2, 3). This is in agreement with a study carried out by Papadopoulos *et al.* [14]; they documented that IPF patients showed impairment of both systolic and diastolic RV function compared with controls.

PH is one possible cause of dyspnea and exercise limitation in patients with ILDs [15]. Our study describes that RVSP (pulmonary artery pressure) was significantly increased in ILD patients compared with the control group (Table 2); moreover, RVSP (mmHg) was negatively correlated with 6MWD and FVC% and was positively correlated with HRCT score and duration of the disease (Table 6). This elucidated that the more severe the ILD and the longer the duration of the disease, the more the pulmonary artery pressure elevation.

Increased after load caused by hypoxic pulmonary vasoconstriction is one of the important mechanisms for RV remodeling and dysfunction in patients with ILD [16]. There were positive correlations between PaO_2 level and RV function (TAPSE) while RVSP

Figure 1



TAPSE was positively correlated with PaO_2. TAPSE, tricuspid annular plane systolic excursion.

(pulmonary artery pressure) was negatively correlated with PaO_2 (Table 6 and Fig. 1). This means that hypoxemia could play a major role in the cardiovascular sequels of ILD and this is in agreement with Zisman *et al.* [17], who observed a strong association between high mPAP and low SpO_2, suggesting that vasoconstriction in response to hypoxia is an important factor in the development of PH in patients with IPF.

The link between RV and LV function suggests ventricular interdependence and such interaction between both ventricles is additionally supported by the concomitant recovery of each RVEF and LVEF after lung transplantation [18]. LV dysfunction, if present, may be an extra factor that will promote exercise performance impairment and have an early effect on ILD prognosis [14]. In our study there was positive correlation between LV systolic function (LV-GLS%) with 6MWD (Table 6). This was in agreement with Jastrzebsk *et al.* [19], who found positive

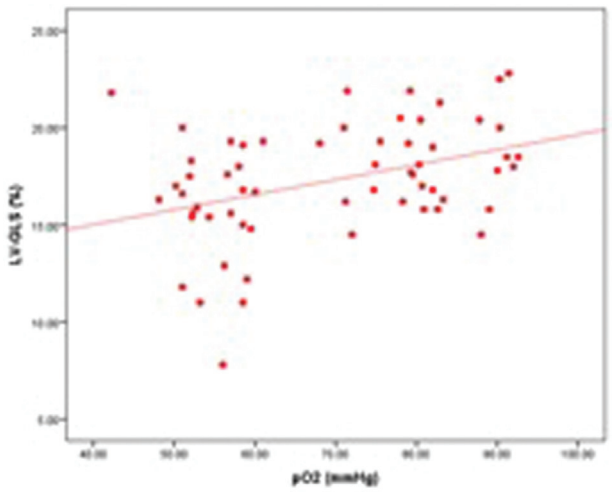
correlations between 6MWD and variables connected with LV morphology detected by echo.

The current study demonstrated that ILD patients had impaired LV diastolic function (detected by reduced E/A ratio by pulsed Doppler and increased E/Av.Ea_4 by TDI) (Tables 4, 5). This is in agreement with Papadopoulos *et al.* [14], who confirmed the presence of LV diastolic dysfunction in IPF patients by mitral annular TDI analysis.

EF, although it is the most commonly used parameter for the assessment of systolic function, may not be true in the case of an abnormally shaped LV as in ILD as it depends on LV geometry [20]. In our study conventional systolic function parameter (EF by M-mode/biplane) was normal in the ILD group and no statistically significant difference was detected when compared with the control group. This is in agreement with Papadopoulos *et al.* [14], who stated that the systolic function of the LV (EF) is preserved in patients with IPF. But when we used advanced methods, our study revealed that ILD patients had subclinical LV systolic dysfunction (detected by impaired LV myocardial velocity by both TDI and LV-GLS) when compared with the control group (Tables 4, 5). D'Andrea *et al.* [13] reported early impairment of LV myocardial contractile function in IPF patients, at a time when other global and regional systolic parameters remain normal.In addition Table 6 and Fig. 2, demonstrated significant positive correlation between LV systolic function (LV-GLS%) with PaO_2 (mmHg). This may suggest that chronic hypoxic pulmonary vasoconstriction might generate increasing pulmonary vascular resistance and a secondary decreased LV filling. On the other hand, hypoxemia may additionally have a direct effect on cellular metabolism that results an impaired cardiac muscle relaxation [21]. Other causes apart from hypoxemia that lead to LV dysfunction may be subclinical sarcoid cardiomyopathy as most of our patients were diagnosed as sarcoidosis (20.0%, *n*=12/60). The same results were obtained by Joyce *et al.* [22], who observed that LV-GLS (17.3±2.5) is impaired in sarcoidosis patients, suggesting subclinical cardiac dysfunction despite the absence of conventional evidence of cardiac disease [23].

The degree of the impairment of both ventricles was related to the severity of ILD and this was illustrated by positive correlation of RV and LV systolic functions (TAPSE and LV-GLS%) with the HRCT score (Table 6).

Figure 2



LV-GLS (%) was positively correlated with PaO_2. LV-GLS, left ventricular global longitudinal strain.

Conclusions and recommendations

Both RV and LV systolic and diastolic dysfunctions were detected in ILD patients. Ventricular dysfunctions were related to hypoxemia, radiological score, and vital capacity of the lungs. Ventricular dysfunction has a negative impact on function exercise capacity of patients with ILD. Echo is useful for the detection of RV and LV dysfunction in ILD patients; advanced echo is needed to detect the subclinical cardiac impairment.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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