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ILD-PH: a real world diagnosis with lung function and treatment approach

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Abstract

Background: PH (pulmonary hypertension) in ILD (interstitial lung disease) affects the functionality, quality of life, and survival adversely. Most often, the patients remain untreated for lack of right heart catheterization and a published recommendation. Hence, an alternate exercise to decide PH-specific therapy in ILD is welcome.

Methods: Stable Symptomatic ILD patients having PH diagnosed on clinico-radio-echocardiographic evaluations were selected. The willing patients having "DLCO-FVC distance≥30" (percentage-predicted values) were given option to receive grading dose of sildenafil or tadalafil in an open, prospective, real-world protocol. We assessed the impact in terms of 2-Chair-Test parameters and CAT score at the first follow up visit.

Results: Sixty-nine patients qualified for treatment, but 32 of them did not opt for it. The qualified-treated group (n=37) differed significantly with lower value of baseline SpO_2 (p=0.01), minimum SpO_2 after exercise (p=0.006), degree of de-saturation (p=0.04), the systolic echocardiography measured PAP (p=0.004), DLCO (p=0.0001), FVC/DLCO (p=0.004) but not in the FVC-DLCO distance from the qualified-untreated group (n=32). Post treatment, (120.7±86.33 vs. 182.5±156.9 days); the treated group showed improvement in all the measurements as baseline heart rate (p=0.08), maximum pulse rate (p=0.27), health status (CAT-score) (p=0.0001), baseline SpO_2 (p=0.21),, minimum SpO_2 (0.001), and desat-max (0.0004). There was general worsening in all these parameters including significant worsening in baseline SpO_2 (p=0.04) in the untreated group. The non-qualified patients (n=32) showed no difference in status on follow up for 130.9±105.8 days.

Conclusion: The FVC-DLCO distance guided strategy to treat ILD-PH appears potentially prospective. Relatively sicker patients tended to opt vasodilator therapy.

Key words: ILD; Pulmonary Hypertension; DLCO; FVC; 2 Chair Test

Abbreviations: ILD: Interstitial Lung Disease; PH: Pulmonary Hypertension; PAH: Pulmonary Arterial Hypertension; CAT: COPD Assessment Test; 2CT: 2 Chair Test; PAP: Pulmonary Artery Pressure; RHC: Right Heart Catheterization; TPG: Transpulmonary Gradient; PVR: Pulmonary Vascular Resistance; PDE5: Phosphodiesterase-5; SpO_2: Arterial Oxygen Saturation; PERR: Post-Exercise Recovery Response

Introduction

Pulmonary hypertension (PH) can develop in ILD (interstitial lung diseases) patients as a complication. The prevalence of such PH referred to as ILD-PH can be frequent depending on the definition, the underlying etiology of PH, the severity of ILD, and the mode of diagnosis of PH [1-3]. PH in ILD imparts an adverse impact on a patient's functional capacity, health related quality of life, supplemental oxygen demand, risk of hospitalization, and the survival prospect [4,5]. The treatment of ILD-PH patients with supplemental oxygen and/or diuretics is accepted. But, the role pulmonary vasodilators for their treatment remains inconclusive and often controversial [6]. Several PH-specific treatment trials with different classes of pulmonary vasodilators are published and reviewed [7]. There were both positive and negative results and sometimes even deleterious outcome as increased hospitalization or clinical worsening. [8-16]. The PDE5 inhibitor, sildenafil showed hope in some trials [8,9,13-15] and, lately, the trial with parenteral treprostinil was encouraging [17]. Finally, the recent publication of the results of INCREASE trial showed both reduction in clinical worsening and disease in progression of ILD with functional improvement (6-minute walk distance) using inhaled treprostinil in ILD-PH compared to placebo [18].

The real world of diagnosis and treatment of ILD is burdened with significant logistic constraints in India [19]. The gold-standard diagnostic evaluation for PH, the right heart catheterization, is often not accessible or feasible. Hence, in the patients of ILD-PH, PH remain mostly unidentified allowing the patients to suffer progressively and relentlessly. Therefore, framing an objective and effective mode of diagnosis of ILD-PH

without subjecting the patients to right heart catheterization is both difficult and daunting. Furthermore, advocating treatment with pulmonary vasodilators demands extra caution and evidence for ethical acceptance. Here, in the manuscript, the authors have presented an observation of diagnosing and treating ILD-PH in real-word on a rational and consensus endorsed approach with PDE5 (phosphodiesterase-5) inhibitor.

Materials and Methods

The real world protocol was approved by the Institutional Ethics Committee of the Institute of Pulmocare and Research, Kolkata and was subsequently enrolled in clinical trial registry of India (CTRI number-CTRI/2015/07/005962). The study was also endorsed by a consensus decision of the PH group, Kolkata been formed of a few physicians from the related fields showing interest in treatment and research of PH. The group engaged and forwarded an approach of identifying and treating ILD-PH in situations of logistic constraints when a right heart catheterization deems impossible or not feasible.

Utilizing the clinico-radio-echocardiographic algorithm of diagnosis of PH by the institute [20], the group evolved an effective strategy to treat ILD-PH with a PDE5 inhibitor (sildenafil or tadalafil) through a consensus decision using information from spirometry and DLCO. The method included:

Diagnosis of ILD and basic physiological evaluations: The diagnosis of ILD was accomplished with joint opinion of at least two experts (a radiologist and a pulmonologist) on high-resolution computerized tomography (HRCT) pictures of thorax in clinic-radiologically (chest-x-ray) suspected patients. Spirometry with estimation of DLCO was done in all observing the standard norm of performance.

Diagnosis of PH: The diagnosis of PH was achieved through exercising the institute's clinico-radio-echocardiographic criteria-based PH identifying algorithm [20].

Determination of post exercise recovery response by 2 chair test: A single expert technician performed all the 2-Chair Tests [2CT]. This test has been developed by the institute to assess the post-exercise recovery response (PERR) uniformly in patients with various respiratory diseases [21]. The test can be performed in patients with chronic lung diseases observing defined inclusion and exclusion criteria and provision of flexibility. This desat-max or the maximum de-saturation in the post exercise period is seen to correlate best with the perceived sickness by the patient (unpublished data). Concomitant recording of the CAT (COPD assessment test) score was a routine practice in all the visits.

Selection of patients for anti-PH treatment: Any patient of having ILD with PH on the clinico-radio-echocardiographic criteria underwent spirometry and the measurement of the diffusion capacity as per standard recommendation of regular evaluation of ILD. We noted the percentage-predicted values of their FVC (forced vital capacity) and the adjusted diffusion capacity (measured in the same sitting). Those who showed a FVC-DLCO distance to be ≥30 were considered eligible by the consensus opinion of the members of the PH group for treatment with a pulmonary vasodilator. Patients unwilling to undergo pulmonary vasodilator therapy for any reason, those having any other concomitant lung disease or any significant systemic problem, and patients with obvious contraindication or known intolerance for PDE5 inhibitors were excluded at this stage.

Specific anti-PH treatment: Only the willing and the qualified (FVC-DLCO distance ≥30) patients for vasodilator therapy were prescribed an oral PDE5-inhibitor as sildenafil (10 mg thrice daily) or tadalafil (10 mg once daily) to start with and on toleration, doubling the dose after 5 to 7 days and subsequently continuing it. The patients were informed about the adverse reaction of the drug before prescription and they were requested to report any obvious or suspected adverse reactions. Stand by provision of oxygen supplementation was a universal pre-requisite to start such treatment. Oxygen supplementation was advised to keep SpO_2>90% in case of any observed desaturation (SpO_2<90%) with any activity or in the 2-chair test.

The follow-up plan: The patients were instructed to follow up at least once every 12 weeks or/and whenever necessary without any prescribed follow-up schedule. At each follow up, the 2CT was repeated along with CAT (COPD assessment test); a repeat echocardiography, though suggested at least after 3 months, was not made mandatory.

The statistical calculations were done after recording the status at the first follow up visit; the statistical exercise included unpaired Student's 't tests' for intergroup comparison between the qualified treated and the qualified but not treated groups and the former with the disqualified group at the beginning. Further paired 't-test' was applied for intra-group comparison separately for all the groups of subjects comparing the initial and the final follow up measurements of the 2-chair test variables (baseline pulse rate, maximum pulse rate, baseline SpO_2, maximum SpO_2, and the desat-max or maximum de-saturation) and CAT score.

Results

Sixty-nine out of 109 subjects qualified but finally 37 out of them agreed for treatment. The comparison between the qualified and treated vs. qualified and untreated patients in terms of demography, lung function (spirometry and DLCO), echocardiography, CAT score, and 2 chair test parameters are shown in (Table 1). The change from the baseline values in the same parameters (2CT-variables and the CAT score) were noted in intra group comparison following treatment (Table 2).

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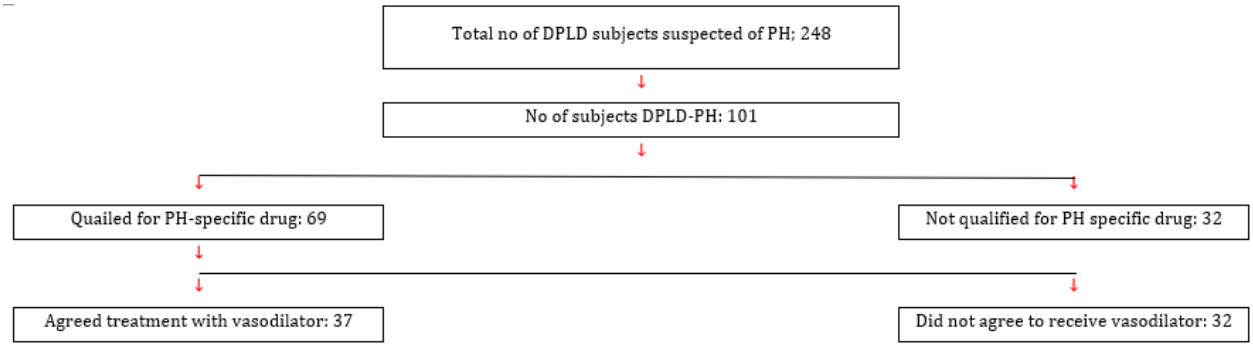
Table 1(a): Elaborates the baseline differences between patients opting and not opting for anti-PH therapy; both the groups being qualified for treatment.



Groups → Characteristics ↓	Qualified with FVC-DLCO difference ≥ 30 (%- Predicted Values)		
Inter – Group Analysis	**Qualified and Treated**	**Qualified but Untreated**	**P-Value**
Number (n)=	37	32	
Male: Female	27:10	23:9	
Age	66.10 ± 7.72	64.71 ± 9.06	0.36
BMI	23.33 ± 4.12	24.73 ± 3.71	0.06
Mean duration of Follow up	120.7 ± 86.33	182.5 ± 156.9	0.01
Base line pulse rate (PR)	85.97 ± 11.56	85.59 ± 14.57	0.92
Maximum PR (MPR) after Exercise	108.7 ± 12.27	107.6 ± 13.79	0.78
Base line SpO_2 at exercise	95.08 ± 3.09	96.56 ± 1.95	0.01
Minimum SpO_2 after exercise	86.7 ± 5.13	90.34 ± 6.68	0.006
Desaturation on exercise	8.37 ± 4.26	6.21 ± 5.47	0.04
PAP (systolic)	49.76 ± 7.7	43.94 ± 6.9	0.004
EF	60.29 ± 4.36	60.25 ± 7.01	0.09
FVC (litre)	1.95 ± 0.46	1.95 ± 0.46	0.99
FVC %	72.51 ± 12.17	78.59 ± 19.34	0.05
DLCO (ad)	25.59 ± 7.74	36.94 ± 13.09	<0.0001
FVC% - DLCO(Distance)	46.92 ± 14.97	41.66 ± 12.18	0.53

Table 1(b): Elaborates the difference between those who qualified and those who did not qualify for consideration of PH specific treatment.

	Qualified for PH-Specific Treatment	Not Qualified for PH-Specific Treatment	
Groups → Characteristics ↓	**[FVC-DLCO Difference ≥ 30 (in % Predicted Values)]**	**FVC-DLCO Difference < 30 (in % Predicted Values)**	**p-value**
Number (n)=	37	32	
M: F	27:10	11:21	
Age	66.11± 7.72	58.81 ± 9.93	0.003
BMI	23.33 ± 4.12	27.26± 4.93	0.001
Mean duration of Follow up	120.7 ± 86.33	130.9 ± 105.8	0.78

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Baseline pulse rate (PR)	85.97 ± 11.56	85.5 ± 15.25	0.95
Maximum PR after exercise	108.7 ± 12.27	111.3 ± 15.62	0.66
Base line SpO_2 at exercise	95.08 ± 3.09	96.41 ± 1.8	0.03
Minimum SpO_2 after exercise	86.7± 5.13	90.34 ± 4.36	0.002
Maximum desaturation on exercise (desat max)	8.37 ± 4.26	6.06 ±3.64	0.01
PAP (systolic)	49.76 ± 7.7	46.25 ± 4.89	0.12
EF	60.29 ± 4.36	63.1 ± 2.57	0.001
FVC (litre)	1.95 ± 0.46	1.56 ± 0.55	0.004
FVC%	72.51 ± 12.17	55.41 ± 14.6	< 0.0001
DLCO (ad)	25.59 ± 7.74	45.47 ± 18.23	< 0.0001
FVC% - DLCO (Distance)	46.92 ± 14.97	17.25 ± 9.93	0.0001

Table 2(a): elaborates the changes in the baseline parameters and follow up of qualified treated vs qualified but not-treated groups of ILD-PH '2(a)' and qualified treated vs unqualified groups of ILD-PH '2(b)'.

Intra Group Comparison Between the Qualified Treated and Qualified but Not-Treated Groups Of ILD-PH						
	Initial Visit	**Follow-Up Visit**	**P-Value**	**Initial Visit**	**Follow-Up Visit**	**P-Value**
n=	37			32		
Base line pulse rate	85.97 ± 11.5	80.68 ± 13.62	0.08↑	85.59 ± 14.5	87.16 ± 15.6	0.58 ↓
Maximum pulse rate	108.7 ± 12.2	106 ± 12.74	0.27 ↑	107.6 ± 13.7	111.7 ± 15.6	0.25 ↓
Health status (CAT)	13.3 ± 4.12	7.75 ± 4.47	<0.0001 ↑	11.16 ± 5.32	12.03 ± 7.79	0.39 ↓
Base line SpO_2	95.08 ± 3.09	95.85 ± 1.94	0.21 ↑	96.56 ± 1.95	95.91 ± 2.02	0.04 ↓
Minimum SpO_2	86.7 ± 5.13	89.85 ± 5.62	0.001↑	90.34 ± 6.68	89.47 ± 7.49	0.41 ↓
Desat max	8.37 ± 4.26	5.51 ± 4.58	0.0004↑	6.21 ± 5.47	6.43 ± 6.05	0.9↓

Table 2(b):

Intra Group Comparison Between Qualified Treated and Unqualified Groups						
	Initial Visit	**Follow-Up Visit**	**P-value**	**Initial Visit**	**Follow-Up Visit**	**P-value**
n=	(Treated group; n=37)			(Not-treated group; n= 32)		
Base line pulse rate	85.97 ± 11.56	80.68 ± 13.62	0.08	85.5 ± 15.25	83.47 ± 11.85	0.47
Maximum pulse rate	108.7 ± 12.27	106 ± 12.74	0.27	111.3 ± 15.62	107.2 ± 10.87	0.26
Health status (CAT)	13.3 ± 4.12	7.75 ± 4.47	<0.0001 ↑	12.25±6.31	10.43±7.09	0.13
Base line SpO_2	95.08 ± 3.09	95.85 ± 1.94	0.21	96.41 ± 1.8	96.53 ± 1.75	0.52
Minimum SpO_2	86.7 ± 5.13	89.85 ±5.62	0.001	90.34 ± 4.36	91 ± 5.06	0.22
Desat max	8.37 ± 4.26	5.51 ± 4.58	0.0004	6.06 ± 3.64	5.53 ± 4.14	0.27

The common adverse effects of the treated patients (compared to the qualified but not treated patients) were pedal swelling (18.92% vs. 6.25%), headache (13.52% vs. 3.12%), reduced appetite (10.81% vs. 6.25%), weight loss (8.11% vs. none), and muscle cramps 5.40 % vs. none). The latter group (qualified, not-treated patients), however, had higher sleeplessness (6.25% vs. 2.70%), itching (9.37% vs. 2.70%) and facial puffiness as (6.25% vs. 2.70 %). Weakness (12.5%), weight loss (12.5%), loss of appetite and constipation (both 9.37%) were the common side effects of those who did not qualify for treatment. The common comorbidities of both the groups were diabetes, hypertension, and hypothyroidism.

Discussion

The results show interesting revelations. The qualified-treated group (n = 37) had significantly lower DLCO [(25.59±7.74 vs 36.94±13.09; p=0.0001)] and lower %-predicted FVC [(72.51±12.17 vs 78.59±19.34; p=0.05)]. This made their FVC-DLCO distance significantly higher [(46.92±14.97 vs. 41.66±12.18; p=0.53)] and the same happened to the FVC/DLCO ratio [(2.81±1.51 vs. 2.27±0.54; p=0.004] compared to the qualified but unwilling for vasodilator treatment group [(FVC-DLCO difference>30%) group; (n=32)] (Table 1). The age and the BMI of the treated patients were similar to those refusing treatment.

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The treated group was worse compared to those not qualifying the treatment (Table 2). They had higher age (p=0.003), lower BMI (P = 0.001), lower base line saturation before exercise (p=0.03), minimum saturation after exercise (p=0.002), lower FVC (p=0.004), lower ejection fraction (p=0.001), and lower DLCO (25.59±7.74 vs. 45.47±18.23; p<0.0001) with higher FVC-DLCO distance (46.92±14.97 vs. 17.25±9.93; p=0.0001) (Table 2).

The intragroup analysis after treatment reveals the global positive changes in the treated group reflected in baseline pulse rate (p=0.08), minimum post-exercise SpO_2 (p=0.001) and degree of de-saturation (desat max) (0.0004) while the qualified but untreated group had global worsening with significant reduction in baseline SpO_2 (p=0.04) (Table 1).

The planning and execution of the study was done much before the publication of the majority of the vasodilator trials in ILD-PH. Hence, we adopted the mean pulmonary artery pressure (mPAP) value >25mm of Hg satisfying old definition of PH. ILD happens to be a common etiology of Group-3 PH and compared to the other members of the group, it shows the worst survival [22]. The development of PH in ILD appears ominous.

Highly predictive radiological features of PH in chest x-ray [23] can support the clinical suspicion of PH. In CT/HRCT chest, the ratio of the diameter of pulmonary trunk to the adjacent aorta may turn ≥1 [24] and the same between pulmonary artery branch diameter and the accompanying bronchus [25] appearing ≥1 (more than one) in three or more lobes strongly indicates presence of PH. Our clinico-radio-echocardiographic mode of diagnosis of PH included these features with supportive evidences by echocardiography to diagnose PH [20]. We could not use the gold-standard hemodynamic criteria for PH from right heart catheterization (RHC) for obvious real world reason. RHC, in our real world, is rarely practiced; hence, to outwit the problem, we evolved a clinico-radio-echocardiographic mode for diagnosis of PH [20] and innovated separate treatment strategies for COPD-PH and ILD-PH. The strategy on COPD-PH was based on maximum de-saturation in 2CT [26] and for ILD-PH, we endorsed an idea of offering PH-specific treatment based on an indirect assessment of the impact of PH. ILD-PH patients are often observed by physicians helplessly deteriorating with development of cor-pulmonale. A treating physician finds himself trapped in the crossfire of conscience and the quest of evidence with having no RHC data to decide treatment of PH.

Both FVC (forced vital capacity) and DLCO are affected in both PH and ILD; however, PH primarily does not influence the FVC. In ILD without PH, the DLCO is expected to correlate and move somewhat parallel to the FVC, a marker of restriction been produced by tissue fibrosis. However, the DLCO is expected to fall 'disproportionately' from a co-presence of PH in ILD.. This is endorsed in IPF with FVC over 70% of predicted where a DLCO<30 % suggests a higher prevalence and greater severity of PH than patients with DLCO>30% [27]. Since DLCO has been found to be the best individual prognostic marker in IPF, the co-presence of PH in ILD is likely to contribute to such poor survival [28].

Significant correlations between FVC/DLCO (in %-predicted values) and the level of systolic and mean PAP (pulmonary artery pressure) have been found (p<0.05) [29]. The FVC/DLCO ratio has been regarded as a marker of presence of pulmonary hypertension by some authorities. In patients with systemic sclerosis associated PH, a ratio >1.91 was found 87.5 % sensitive and 100 % specific for the presence of PH [30]. When calculated, in our patients show a mean FVC/DLCO ratio of 2.81 (far above 1.91) signifying obvious co-presence of PH. Therefore, on consensus, we decided a cut-off mark of FVD-DLCO distance as ≥ 30% as 'disproportionate' reduction of DLCO to qualify for PH-specific treatment. Further, the consensus allowed us to monitor these patients for the effect of treatment with the 2-Chair Test. We have forwarded this novel test of post-exercise recovery response (PERR) as a tool to assess the functional jeopardy of cardiopulmonary reserve [25]. We have noticed that the desat-max in 2CT remained the best parameter to appreciate the degree of sickness (unpublished data). The highly significant improvement observed in the post exercise saturation with treatment even with the relatively small sample size is encouraging despite the lack of RHC data.

The lung disease related PH (PH developing as a complication of a chronic lung disease) is marked by protracted hypoxia from a primary reduction in the respiratory reserve (ventilation and / or diffusion capacity) along with a concomitant and subsequent reduction in circulatory reserve leading to the development of PH as a secondary phenomenon. The cumulative effect of the depletion of both the reserves determines the physiological impact and the symptomatology. Since the pathology in ILD is usually likely to reverse very little in most of the cases and the PH imparts deleterious effects on the right ventricle, the treatment of pulmonary hypertension on objective basis should be explored. We pursued decision policy within initiation of a PDE5 inhibitor (sildenafil/ tadalafil) since they have been tried already [8, 9, 13, 14]. The scaling up of the dose was done to avoid the chance acute pulmonary vasodilatation induced worsening of ventilation-perfusion (V/Q) mismatch leading to clinical worsening. The maintenance of a fixed dose in our experience, though small, is rewarding. The modification of dose with repeat assessment of the FVC-DLCO could have been better.

The treatment efforts of ILD-PH with PH specific drugs especially the PDE5 inhibitors have yielded mixed results with hope [8,9,13,14]. Randomized trial with bosentan was a failure [10]. The ARTEMIS-IPF trial with ambrisentan was terminated early for increased disease progression and hospitalization in the ambrisentan group of the randomized controlled trial compared to placebo [12]. In the STEP-IPF trial, sildenafil was tried in IPF and it showed slower decline in 6MWD and improvement in quality-

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of-life measurements in a subgroup of patients [13,14]. Similarly, a randomized riociguat trial (RISE-IIP) was unsuccessful [15]. Amidst the negative scenario, parenteral treprostinil was found associated with increased 6MWD, RV function, and hemodynamics in ILD-PH (mPAP>35mm) [17]. Recently, inhaled treprostinil has shown a great promise in treating ILD-PH in INCREASE trail [18] that revealed improvement in 6MWD (six minutes and reduction in the clinical worsening with other positive effects including improvement in lung function.

The weaknesses are many folds. They include the relatively small number patients, the lack of hemodynamic data from RHC (right heart catheterization) and the lack of assessing the dynamics of FVC-DLCO following treatment. The echocardiographic information could have been more inclusive especially with right ventricular functional assessments with TAPSE (Tricuspid Annular Plane Systolic Excursion), right ventricular E/e' and the free wall GLS (global longitudinal strain) of right ventricle. A more holistic assessment with inclusion of repeat echocardiography, and change in parameters as quality of life and 6MWD would have been better. The duration of follow up was not uniform for the real world reasons. The dynamics of decline of both the parameters (FVC and DLCO) may be different in different etiologies, nature (predominantly fibrotic or not), and at different stage of ILD. Hence, the FVC-DLCO distance may not be applicable in advanced and predominantly fibrotic ILD where FVC may reduce significantly. Despite the shortcomings, we feel that the novelty of the approach needs attention and criticism. Subject to validation and modification with further research, the philosophy may find place in future in the diagnostic work up and/or treatment decision of the ILD associated PH especially in resource poor situations.

Conclusion

It appears that in selected situations, ILD-PH can be identified with lung function (spirometry and DLCO) alone and such PH may qualify treatment based on relatively disproportionate reduction of DLCO compared to FVC. Further research is warranted with hemodynamic endorsement of the approach.

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