Journal of the Medical Sciences
(Berkala Ilmu Kedokteran)

Volume 55, Number 2, 2023; 151-159
https://doi.org/10.19106/JMedSci005502202307

Reconsidering the limited role of right heart catheterization on severe pulmonary hypertension-due to progressive interstitial lung disease in young male patient: a case report

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Submitted: 2021-08-17
Accepted : 2021-11-08

ABSTRACT

Pulmonary hypertension (PH)-associated with interstitial lung disease (ILD) develops as a consequence of progressive underlying lung disease or disproportionately to the underlying disease. The PH investigation by right heart catheterization (RHC) for defining PH severity is recommended in patients with ILD who show more severe symptoms than expected from lung disease, appearance of right heart failure, and clinical deterioration not matched by the declining lung function. In patient with progressive ILD, RHC is only considered if it affects the future treatment such as lung transplantation or enrollment in clinical trial/registry. The decision to undertake the RHC in progressive ILD was still fraught with doubts. Here we reported a young adult male patient with ILD whom developed progressive signs and symptoms. By RHC, he had severe precapillary PH with hemodynamic parameters indicated the presence of pulmonary vascular disease. A PH-specific treatment, sildenafil citrate, was administered, and patient responded well and was clinically stable during the addition of sildenafil citrate. This case highlights the clinical implication of performing RHC in progressive ILD, which can change the treatment decision by PH-specific drugs. Therefore, the RHC decision making in patient with progressive ILD need reconsideration.

ABSTRAK

Hipertensi pulmonal (PH)-terkait dengan penyakit paru interstitial (ILD) terjadi sebagai konsekuensi dari penyakit paru-paru progresif yang mendasari atau tidak proporsional dengan penyakit paru-paru yang mendasarinya. Penentuan diagnosis PH dengan kateterisasi jantung kanan (RHC) sebagai standar emas untuk menentukan tingkat keparahan PH direkomendasikan pada ILD dengan gejala yang lebih parah dari yang diharapkan berdasarkan fungsi paru, munculnya tanda gagal jantung kanan, dan perburukan klinis yang tidak diimbangi dengan penurunan fungsi paru. Pada pasien dengan ILD progresif, RHC hanya dipertimbangkan jika mempengaruhi pengobatan seperti transplantasi paru atau pendaftaran dalam uji klinis. Keputusan untuk melakukan RHC pada ILD progresif masih kontroversi. Kasus ini melaporkan seorang pasien pria dewasa muda dengan ILD yang mengalami tanda dan gejala progresif. Dengan RHC, didiagnsosi dengan PH prekapiler yang parah dengan parameter hemodinamik yang menunjukkan adanya penyakit pembuluh darah paru. Pengobatan spesifik PH yaitu sildenafil sitrat diberikan dan pasien merespons dengan baik dan stabil secara klinis selama penambahan sildenafil sitrat. Kasus ini menekankan implikasi klinik melakukan RHC pada penyakit ILD progresif, yang dapat mengubah pengobatan dengan obat spesifik PH. Dengan demikian, pengambilan keputusan untuk melakukan RHC perlu dipertimbangkan kembali pada kasus ILD progresif.

Keywords:
interstitial lung disease;
pulmonary hypertension;
heart catheterization;
pulmonary arterial remodeling;
sildenafil citrate

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INTRODUCTION

Pulmonary hypertension (PH) is defined by mean pulmonary arterial pressure (mPAP) >20 mmHg at rest as measured by the right heart catheterization (RHC).[1] The PH is classified into five clinical groups, one of them is PH due to lung disease and/or hypoxia.[2] In addition to chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) is one of the most common lung diseases associated with PH.[2] There is an increasing prevalence of PH among patients with progressive and advanced ILD.[3] Pulmonary hypertension-associated with ILD usually mild to the moderate degree with mean pulmonary artery pressure (mPAP) 20-30 mmHg and does not need PH-specific treatment.[3]

Pulmonary hypertension-associated with ILD may develop as a consequence of progressive lung disease and hypoxia (PH group 3 or PH-due to lung disease/hypoxia) or disproportionately to the underlying disease.[4] Several patients experience an out-of-proportion PH, with mPAP ≥35 mmHg but with mild-to-moderate ILD, a term to indicate a disproportionate increase in mPAP that is not suitable with the severity of fibrotic lung disease due to ILD.[3,4] In these populations, the pulmonary vascular remodeling coexists and may predominate the pathogenesis of PH mimicking those of pulmonary arterial hypertension (PAH) in whom the PH-specific treatment will have a beneficial impact.[5] The RHC is the gold standard examination for determining the severity of PH in ILD. However, the current guideline limits the recommended use of RHC for PH-associated with ILD only for patients with more severe signs and symptoms than expected from lung function, the appearance of right heart failure, clinical deterioration not matched by the declining lung function, and candidate of lung transplantation or candidate for enrollment in clinical trial/registry.[2,3] The RHC is considered in patients with chronic lung disease when severe PH is suspected and the result of RHC will likely affect patient treatment.[6] The patient with progressive or advanced ILD is not recommended to get an RHC examination, since RHC may not give effect to severe PH.[6] Here we report a young male progressive ILD patient with severe PH, determined by RHC, and indicated as severe PH due to lung disease/hypoxia or PH group 3. The patient was successfully treated with the addition of PH-specific treatment. This case report aimed to discuss about reconsidering the decision-making to perform RHC in the progressive ILD case, which may alter the management of patients.

CASE

A male patient aged 39 y.o. came to be hospitalized with complaints of increasing shortness of breath, productive cough, and fatigue. The patient was an active smoker with two packs a day of cigarettes on average. No history of cardiovascular and cerebrovascular disease was reported. From the physical examination patient was tachypneic, with a blood pressure of 108/69 mmHg, pulse 102 times per min, respiratory rate 32 times per min, and temperature of 36.6°C. Peripheral oxygen saturation was 89% on nasal cannula 3 L per min. The increased jugular venous pressure (JVP) at 5+3 cmH_2O was observed. Chest examination showed right heart border was enlarged with increased vesicular lung sound and hoarse rhonchi in both lung fields. No parasternal lifts or prominent heart murmurs were detected. No hepatomegaly and ascites in abdominal examination. The extremities were non oedema. There were clubbing fingers.

The electrocardiogram examination showed sinus rhythm and poor R wave progression (FIGURE 1). There was an elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) 2.045 pg/mL. The chest X-rays showed in both lung field the presence of inhomogeneous

opacity in the suprahiller and perihiller region, bilateral paracardial amorphous boundary forms of air-bronchogram, widening of visible intercostal space, and slippery and horizontal contour of right diaphragm; in the heart there was enlargement of right atrium (FIGURE 2). The thorax CT scan indicated an interstitial lung disease with signs of interstitial pneumonia (FIGURE 3). Patients had previously undergone work-up for tuberculosis, HIV, chronic hepatitis and all shown negative result. The work-up for autoimmune diseases yielded negative results. Lung function test showed FVC was 31% predicted and FEV1 was 33% predicted, indicated severe reduced lung function both obstructive and restrictive.

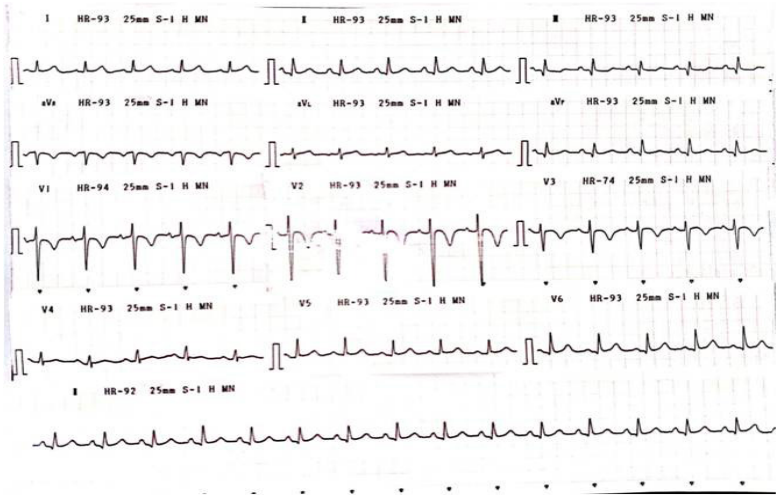

FIGURE 1. An ECG on admission showed sinus rhythm, normoaxis, symmetrical inversion T in the precordial leads, V1 to V3.

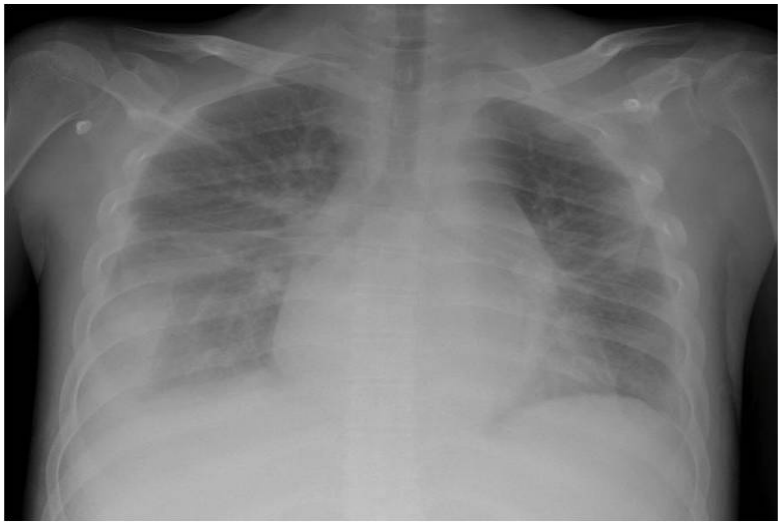

FIGURE 2. A Chest X-ray showed AP projections, supine position, asymmetric, inspirational, and sufficient conditions, the results of the two apex pulmo were calm, visible inhomogeneous opacity in the suprahiller, perihiller, and bilateral paracardial amorphous boundary forms of airbronchogram, cephalization (-), no visible widening of the two pleural spaces, visible SIC was widened and the dextra diaphragm was slippery and horizontal, the heart's waist disappeared and enlarged right atrium with CTR = 0.56

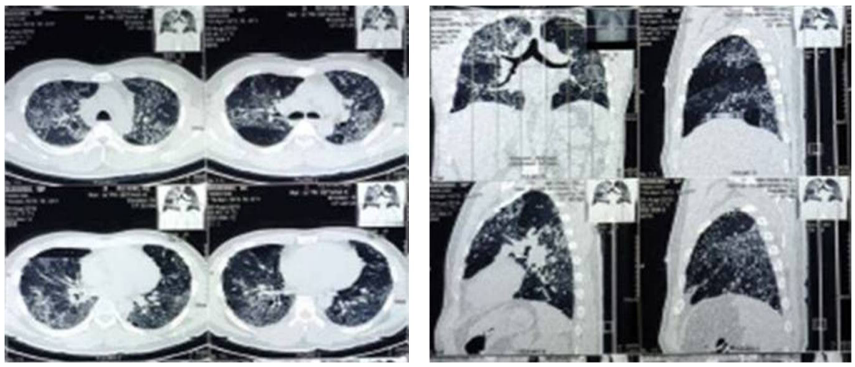

FIGURE 3. A Thorax CT scan showed interstitial pneumonia results in a differential diagnosis of interstitial lung disease with heart size within normal limits.

During the hospitalization, the patient was diagnosed with interstitial pneumonia and progressive hypoxia due to ILD. The internist-pulmonologists took care of the patient in the intensive care unit and internal medicine ward. The patient has undergone antibiotics treatment, antiinflammations (steroids), and continuous oxygen therapy, however during the treatment course little improvement was achieved. The internist-pulmonologists suspected PH as an accompanying disease in the patient and consulted cardiologists for further work-up. The initial work-up of suspicion of PH was performed by transthoracic echocardiography (TTE) and indicated the dilatation of the right atrium and ventricle (diameter of 42 mm and 34 mm, respectively), normal left ventricular (LV) systolic function (with LV ejection fraction of 76%), normal right ventricular systolic function (with tricuspid annular plane systolic excursion (TAPSE) of 23 mm) and tricuspid valve regurgitation (pressure gradient of 48 mmHg and velocity 3.46 cm/s). From the TTE result, the patient was assessed with a high probability of PH (FIGURE 4). Since our center had a long experience with PAH patients,[7] the invasive hemodynamic assessment by RHC was proposed to be completed to determine the severity of PH.

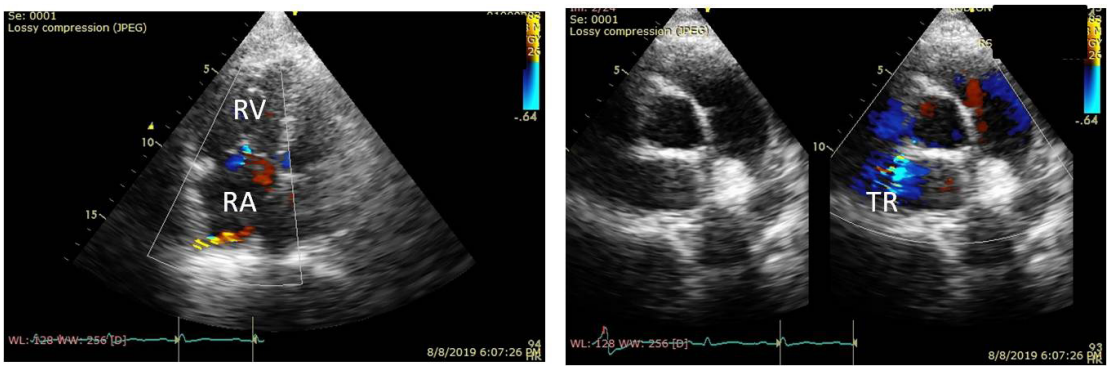

FIGURE 4. A transthoracal echocardiography appeared a jet of tricuspid regurgitation (TR) and right atrial (RA) and ventricular (RV) dilatation, a sign of a high probability of PH.

We proceeded to perform the RHC to measure the hemodynamic and determined severity of PH. The hemodynamics showed the aortic pressure systolic/diastolic (mean): 133/97 (115) mmHg, left ventricle

systolic/diastolic: 143/14 mmHg, right atrium systolic/diastolic: 14/12 mmHg, right ventricle systolic/diastolic: 61/11 mmHg, and pulmonary artery systolic/diastolic (mean): 51/25 (38) mmHg. The oxygen saturation measured in the aorta was 88.4%, the inferior vena cava was 71.5%, the superior vena cava was 60.7%, the right atrium was 68%, the right ventricle was 66%, the pulmonary arteries were 68.1%, and the left ventricle 90.2%. The pulmonary vascular resistance (PVR) index was 8.5 Wood Unit/m^2 and the cardiac index was 1.45 L/min/m^2 (FIGURE 5 and 6). During RHC, pulmonary angiography was also performed to exclude the possibility of chronic thromboembolic pulmonary hypertension or pulmonary artery obstructions. The result indicated there was no stenosis, obstruction, or thrombus in pulmonary artery branches.

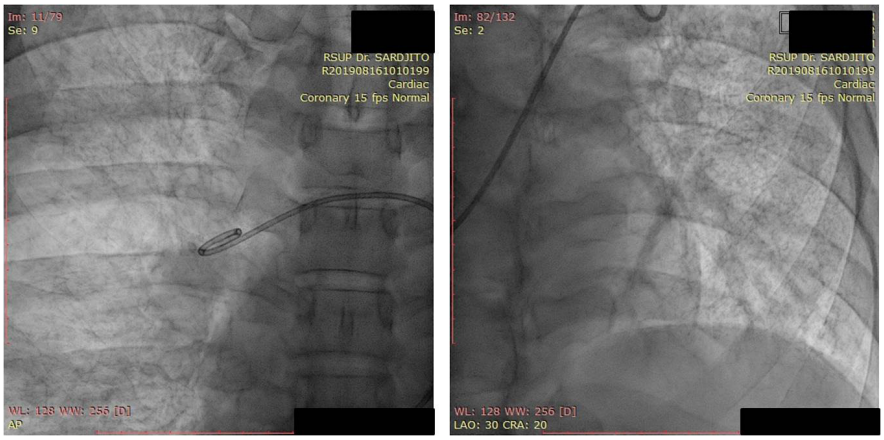

FIGURE 5. A right heart catheterization (RHC) and pulmonary angiography with no visible features of stenosis or thrombus.

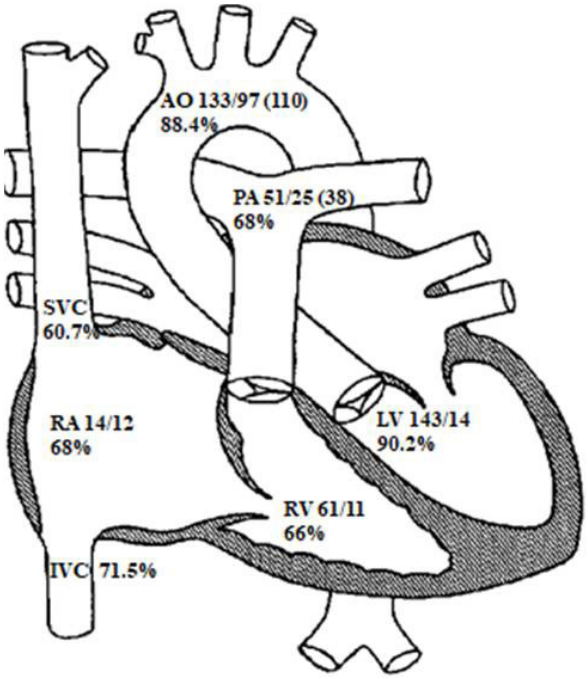

FIGURE 6. A haemodynamic diagram from the RHC indicated the low oxygen saturation and increased mean pulmonary artery pressure.

The patient's mean pulmonary artery pressure (mPAP) was ≥35 mmHg, which indicated a severe form of PH.[5] This was most likely due to the consequence of severe ILD progression or PH group 3 (severe PH-due to lung disease). The patient was decided to be given oral sildenafil citrate starting from 20 mg every 8 hr. We closely monitored him during the first dose of 20 mg oral sildenafil until 4 hr to detect the intolerance or side effects (Emoto, personal communication). The result showed no reduced peripheral oxygen saturation, no increasing dyspnea or tachypnea, and no headache or flushing sensation. We, therefore, continued to give the patients oral sildenafil citrate 20 mg t.i.d. until discharge. During six mo of follow-up, the patients doing well, with no need for continuous oxygen supplementation at home, and still using sildenafil citrate in their daily routine. He recited that daily activity can be performed without significant complaint. Unfortunately, he did not show up for objective evaluation performed routinely in our PH clinic every 6 mo, such as 6 min walking test, TTE evaluation, and NT-proBNP examination.

However, sildenafil citrate was discontinued since March 2020 because the patient did not visit our PH clinic ever since. The patient could not come to our hospital due to the COVID-19 pandemic, therefore he relied on medication from a district hospital that could not provide sildenafil citrate. Since then, the patient had relapsed and was hospitalized for about 3 times in a district hospital due to increased shortness of breath. From the district hospital, he was discharged without sildenafil citrate medication, and at home, the patient still often used supplementary oxygen when the shortness of breath attacked. In August 2020, the patient had a sudden recurrence of shortness of breath while working in the field and was taken to the nearest hospital but experienced respiratory failure and was declared dead.

DISCUSSION

Here we reported a young adult patient with severe PH due to ILD, diagnosed by RHC. The recommendation to perform RHC in chronic lung disease was limited. In general, RHC should be performed when significant PH is suspected and the management will likely be influenced by its results, such as lung transplantation, clinical trials or registry enrollments, or compassionate use of PH-specific therapy.[5,6]

The role of RHC to confirm the diagnosis and determine the severity of PH is recommended especially in ILD patients with (1) more severe symptoms than those expected based on pulmonary function data, (2) appearance of right heart failure signs, and (3) clinical deterioration that is not matched by the decline in lung function test.[3] We decided to perform RHC in this patient because the TTE showed a high probability of PH and the suggestion that we would try to give PH-specific treatment if the patient had severe PH by RHC. The haemodynamic data from RHC of this patient indicated severe PH,[5,6] i.e increased mPAP ≥35 mmHg and PVR index >3 Wood Unit. m^2. Therefore, the use of pulmonary vasodilator such as sildenafil citrate may have a beneficial impact. In this patient, we suspected that the extent of ILD progression was in-line with the increase of mPAP and PVR index, which lead to worsened symptoms. The addition of sildenafil citrate along with optimum therapy for ILD was conducted to keep the patient clinically stable. Therefore, our case indicates that RHC performed in progressive ILD gives a beneficial impact on altering patient management by guiding and administering PH-specific drugs. We suggest that the decision-making on performing RHC needs reconsidering in patients with ILD who

show worsened symptoms even if they are associated with the progressiveness of ILD. The referral to PH-center to perform PH investigation, including RHC, is an important step for specialists or general practitioners while treating progressive ILD patients.

Several studies in patients with chronic lung disease show that up to 90% of patients have mPAP >20 mmHg, with most ranging between 20 and 35 mmHg.[6] Only about 1-5% of patients have higher mPAP >35 mmHg rest, which indicates a loss of flexibility in pulmonary arteries and vascular distensibility.[5,6] This extent of PH impact circulatory impairment that considerably deteriorates exercise capacity already reduced caused by obstructive/restrictive ventilatory impairment.[5] The mPAP cut-off point of 35 mmHg was used to determine the PH severity in ILD, because ILD with mPAP ≥35 mm Hg resulted in significantly reduced lung capacity to diffuse carbon monoxide, lower arterial oxygenation at rest, lower exercise capacity, and decline of arterial oxygenation upon exercise, regardless lung function tests.[5,6] In this case, the mPAP 38 mmHg is parallel with a worsened clinical condition.

The mechanism of the occurrence of PH in patients with ILD is mostly associated with pulmonary fibrosis which involves several types of cells and interactions between various cellular components and mediators that determine the pattern and severity of fibrosis.[8] This mediator induces fibroblast activation by extracellular matrix deposition leading to fibrosis.[9] Pro-apoptotic endothelial cells reduce vasodilators, such as nitric oxide and prostacyclin, and increase vasoconstrictor agents, such as endothelin-1, which lead to an increase in vasoconstriction of smooth muscle cells.[8,9] Apoptotic endothelial cells decrease vascular density, increase the production of vascular growth factors and give rise to the proliferation of resistant endothelial cells so that the lesions become angioproliferative.[9] Therefore, in ILD, the presence of pulmonary vascular remodeling is indicated by the profound increased of mPAP and PVR. In this case, the measured mPAP was 38 mmHg, and calculated PVR index was 8.5 Wood Unit/m^2 which supported the presence of pulmonary vascular disease.

Patients with more severe lung disease (ILD with FVC <70% of predicted or COPD with FEV1 <60% of predicted) and accompanying by less severe PH (mPAP 20–24 mmHg with PVR ≥ 3 WU or mPAP 25–34 mmHg) represent the majority of patients presenting with PH-associated ILD.[6,10] Current data do not support therapy with PH-specific drugs in these patients.[2,6,11] However, patients with more severe lung disease and severe PH as defined earlier (mPAP >35 mmHg and PVR ≥ 3 WU) have a poor prognosis and should be referred to a centre with expertise in both PH and chronic lung disease for individualized patient care.[5,6] The PH-specific drugs in these patients may be beneficial to stabilize and retard the disease progression.[12,13] The decision to use PH-specific treatment shoud be based on hemodynamic parameters by RHC, regardless ILD severity.[14,15] Based on an open-label study, sildenafil citrate improved 6 min walking distance and in a controlled trial among advanced idiopathic pulmonary fibrosis, sildenafil citrate improved arterial oxygenation, lung diffusion capacity of CO, dyspnea score, and quality of life.[5,6] Our patient showed improvement and stabilization of clinical condition during adding sildenafil citrate into his treatment. However, since the advanced ILD is progressive disease, the underlying parenchymal lung disease, along with the unexpected termination of sildenafil citrate, deteriorated patient condition.

CONCLUSION

In conclusion, we reported a young

adult male patient with severe PH-due to ILD (severe PH due to lung disease or PH group 3) diagnosed by RHC. The clinical presentation was consistent with the progressivity of ILD and complicated by severe PH. Based on high-probability PH on TTE examination and clinical decision to guide the PH-specific treatment, we performed RHC in this progressive ILD patient. The adding of PH-specific drug was responded well and clinically stabilized the patient. The reconsideration of performing RHC in advanced or progresive ILD should be suggested since the patient may get a beneficial impact of adding PH-specific treatment. The referral to PH-center to perform PH investigation, including RHC, is an important step to improve the management of ILD-associated PH patients.

ACKNOWLEDGEMENT

We acknowledged the assistance of Internal Medicine Residents in Dr. Sardjito Department Hospital, Yogyakarta, Indonesia, who provided patients data during hospitalisation.

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