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RESEARCH ARTICLE

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The hemodynamic characteristics of severe chronic lung disease referred for lung transplantation

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Abstract

Severe pulmonary hypertension (PH) is not common even in patients with severe chronic lung disease (CLD) but data on hemodynamic characteristics among patients with severe CLD is scarce. All adult patients who had right heart catheterization for lung transplant assessment for severe CLD in the only lung transplant service and for PAH management in the only tertiary pulmonary hypertension service in Hong Kong from 2010 to 2020 were included and classified into CLD group and PAH group. Patient characteristics and hemodynamic parameters were analyzed. There were 153 patients included with 106 patients in the CLD group and 47 in the PAH group. There were only 19.8% of the patients in the CLD group had severe pulmonary hypertension. Patients in the CLD group had significantly lower systolic pulmonary arterial pressure (PAPs), lower mean pulmonary arterial pressure (PAPm), higher cardiac index, and lower PVR when compared with the PAH group ($p < 0.001$). The area under curve (AUC) of PAPs, PAPm, and PVR were excellent, 0.973, 0.970, and 0.938, respectively for discrimination between CLD and PAH on receiver operator characteristics curve analysis. Optimal cutoff values were 55.5 mmHg, 35.5 mmHg, and 6.1 Wood Units for PAPs, PAPm, and PVR with Youden Index 0.85, 0.80, and 0.82, respectively. There were distinct hemodynamic characteristics between the CLD group and the PAH group. Systolic pulmonary arterial pressure, mean pulmonary arterial pressure, and pulmonary vascular resistance are useful to discriminate between the phenotype of severe CLD and PAH.

KEYWORDS

chronic lung disease, lung transplantation, pulmonary hemodynamics, pulmonary hypertension, right heart catheterization

1 | INTRODUCTION

Pulmonary hypertension secondary to chronic lung disease (CLD) is classified into Group 3 pulmonary hypertension (PH) whereas precapillary pulmonary arterial hypertension (PAH) is classified into Group 1 PH in the World Health Organization (WHO) classification. However, stratification between the two groups may not be easy because the severity of CLD and hemodynamic profile represent a continuum with significant overlapping and gray zone.[1] It has been recognized that the degree of PH in CLD was usually modest,[1–4] severe PH in CLD is uncommon, as well as patients with PH in CLD exhibit functional limitation more due to vascular cause rather than parenchymal disease.[3,5–9] Therefore despite pulmonary arterial hypertension targeted therapies are not recommended in patients with WHO Group 3 PH, individualized care for patients with severe PH with CLD is suggested.[1,10] Criteria for severe PH in CLD utilizing mean pulmonary arterial pressure, cardiac index, and pulmonary vascular resistance were used in different observational studies or consensus statements, and cutoff were usually defined arbitrarily in epidemiological studies or derived from studies on functional assessment.[1–5] There is a lack of data to define best hemodynamic variables and thresholds to stratify different patient phenotypes as pointed out in the sixth World Symposium of Pulmonary Hypertension.[1] In this study, the hemodynamic profiles of patients with severe CLD were analyzed and compared with those among patients with PAH in the only tertiary lung transplant service and the only tertiary pulmonary hypertension referral center in an Asian city.

2 | METHODS

2.1 | Patient population

There is only one lung transplantation, heart transplantation, and pulmonary hypertension tertiary referral service in our city serving a population of roughly seven million. Right heart catheterization has been part of the standard assessment and management for patients referred to our center for assessment of transplantation as well as for management of pulmonary hypertension. This is a retrospective cohort study and patients with age more than 18 years old who had right heart catheterization (RHC) performed between the period January 2010–December 2020 in our center were screened. All consecutive patients were identified if they had undergone RHC as part of lung transplant evaluation for severe CLD or if they had undergone RHC for pulmonary arterial hypertension assessment and fulfilled the hemodynamic criteria of pulmonary arterial hypertension defined as mean pulmonary arterial pressure more than or equal to 25 mmHg and mean pulmonary capillary wedge pressure less than or equal to 15 defined in the 2015 European Society of Cardiology and European Respiratory Society guideline for the diagnosis and treatment of pulmonary hypertension.[2] For patients who have RHC for pulmonary arterial hypertension assessment, only patients who met the clinical classification of World Health Organization (WHO) Group 1 pulmonary arterial hypertension, including Group 1′ pulmonary veno-occlusive disease (PVOD), were included while patients confirmed to have WHO Group 4 chronic thrombo-embolic pulmonary hypertension by ventilation-perfusion scan, computed tomography of the pulmonary artery (CT-PA), and/or conventional pulmonary angiogram was excluded.[2] All patients were followed till events including lung transplantation, death, or until June 30, 2021 whichever occurred earlier.

2.2 | Data attributes

Patient characteristics include gender, age, diagnosis, WHO functional class, 6-minute walk distance, long term oxygen therapy requirement, use of noninvasive positive pressure ventilation, as well as a history of smoking, diabetes mellitus, hypertension, hyperlipidemia, overweight defined as body mass index more than 25 kg/m^2,[11] coronary artery disease, atrial arrhythmia, cerebral vascular accident, simple congenital heart disease which includes secundum atrial septal defect, ventricular septal defect, and patent ductus arteriosus, complex congenital heart disease which includes conditions other than simple congenital heart disease, systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, other connective tissue diseases, obstructive sleep apnea, chronic kidney disease with estimated glomerular filtration rate less than 60 ml/min/1.73 m^2, hepatitis, liver cirrhosis, prior malignancy, prior tuberculosis, and a total number of comorbidities were retrieved. Parameters of lung function test include forced expiratory volume in one second (FEV1), percentage predicted FEV1, forced vital capacity (FVC), percentage predicted FVC, ratio of FEV1 and FVC (FEV1/FVC), and percentage predicted of diffusing capacity for carbon monoxide were reviewed. Computed tomography (CT) of thorax findings was reviewed and graded into minimal to mild parenchymal changes, moderate parenchymal changes as well as extensive parenchymal changes.[1] Parameters on echocardiogram including left ventricular ejection fraction (LVEF), ratio of the peak early mitral

inflow velocity over the early diastolic mitral annular velocity (E/e'), tricuspid annular plane systolic excursion (TAPSE), longitudinal systolic excursion velocity of tricuspid annulus by tissue Doppler (RV-S'), right ventricular systolic pressure (RVSP), end-systolic area of the right atrium (RA ESA), and pericardial effusion were retrieved.

Invasive hemodynamics data on right heart catheterization were collected. The height, weight, and body surface area of the patient were retrieved. All patients underwent right heart catheterization via the internal jugular or femoral vein with a Swan-Ganz catheter in a standard manner.[1,2] Resting heart rate was recorded while resting systemic systolic arterial blood pressure (SBP), diastolic arterial blood pressure (DBP), and mean arterial blood pressure (MBP) were recorded by invasive arterial pressure monitoring or by noninvasive blood pressure measurement if no concomitant artery vascular access is required during the procedure. Right atrial, ventricular, pulmonary arterial and pulmonary capillary wedge pressures were registered. Cardiac output was determined by the thermodilution method but in patients with congenital heart disease with the presence of intracardiac shunting, the systemic and pulmonary blood flow were calculated by Fick's method. The cardiac index was calculated by dividing the cardiac output by the body surface area. Stroke volume index was calculated by dividing cardiac index by heart rate. Transpulmonary pressure gradient was obtained by mean pulmonary arterial pressure (PAPm) minus mean pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure (LVEDP) if reliable PCWP was difficult to obtain. Pulmonary vascular resistance (PVR) was calculated from the ratio of transpulmonary pressure gradient and the pulmonary blood flow and was expressed in the Wood unit (mmHg/min/L). Right ventricular stroke work index (RVSWI) was calculated as the product of the difference between PAPm and mean right atrial pressure (RAP) and the stroke volume index. Pulmonary artery pulsatility index (PAPi) was calculated by the difference between systolic pulmonary arterial pressure (PAPs) and diastolic pulmonary arterial pressure (PAPd) divided by RAP.

2.3 | Statistical analysis

Continuous variables were expressed as mean ± standard deviation of the mean (mean ± *SD*). Categorical data were expressed as numbers and percentages. Missing values were tackled by multiple imputations with five imputations used for final pooled analysis. Patients with underlying severe chronic lung disease (CLD) who underwent right heart catheterization for lung transplant assessment were classified as the CLD group while patients with WHO Group 1 pulmonary arterial hypertension (PAH), including Group 1' pulmonary veno-occlusive disease, were classified as the PAH group. Patients in the CLD group were subcategorized into CLD without PH (PAPm < 21 mmHg, or PAPm 21–24 mmHg with pulmonary vascular resistance (PVR) < 3 Wood Units (WU)) (CLD-no PH); CLD with PH (PAPm 21–24 mmHg with PVR ≥ 3 WU, or PAPm 25–34 mmHg) (CLD-PH); as well as CLD with severe PH (PAPm ≥ 35 mmHg, or PAPm ≥ 25 mmHg with low cardiac index (<2.0 $L \cdot min^{-1} \cdot m^{-2}$)) (CLD-severe PH).[1] Continuous variables were compared by student's *t* test or analysis of variance as appropriate. χ^2 test was used to determine the differences between categorical variables. Survival was analyzed by Kaplan–Meier method and compared by the Log-rank test. Receiver-operating characteristic (ROC) curves based on different hemodynamic and nonhemodynamic parameters were used to determine the discriminating power between the CLD and PAH groups. The Youden index was used to determine the optimal cutoff value to discriminate between the CLD and PAH groups based on the ROC curve analysis. All tests were two sided, and a *p*-value < 0.05 was considered statistically significant. Statistical analyses were performed in SPSS for Windows version 28 (SPSS Inc.).

2.4 | Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board (IRB) of The University of Hong Kong and Hospital Authority Hong Kong West Cluster (IRB/REC No. UW 20-346) and individual consent for this retrospective analysis were waived.

3 | RESULTS

There were 153 patients included in the study after screening 2402 RHC procedures and excluding 8 patients with confirmed CTEPH, with 106 patients in the CLD group and 47 in the PAH group (Figure 1). Majority of the RHC procedures were performed for protocol-driven regular reassessment after heart transplantation which accounted for 1136 procedures (47.3%), followed by heart failure-related assessments including advanced heart failure evaluations, regular reassessments for heart transplant candidates active on a waiting list as well as pre- and post-left ventricular assist device assessments,

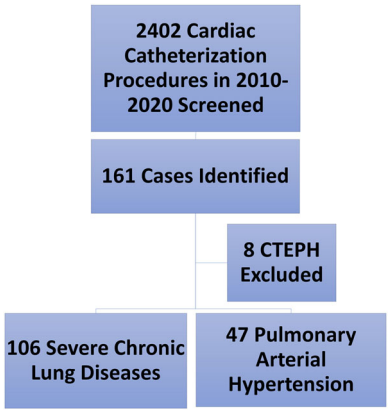

FIGURE 1 Flow diagram for study cohort. Figure 1 showed a flow diagram illustrating the identification of the present cohort of 153 patients after screening of 2402 cardiac catheterization procedures during the study period from January 2010 to December 2020 and after excluding eight cases with chronic thromboembolic pulmonary hypertension (CTEPH). There were 106 patients with severe chronic lung diseases and 47 patients with World Health Organization Group 1 Pulmonary Arterial Hypertension.

which accounted for 812 procedures (33.8%). Preoperative assessments for valvular heart disease and congenital heart disease assessments accounted for 148 (6.1%) and 71 (3.0%) procedures, respectively. The remaining RHC procedures were performed for miscellaneous indications such as evaluation of amyloidosis, cardiomyopathy, pericardial disease, myocarditis, and liver transplant workup. Overall, there were 4.16% missing data. Data of the original cohort and after multiple imputation were presented in Table 1. Among the 106 patients who had CLD, 37 (34.9%) did not have pulmonary hypertension (CLD-no PH), 48 (45.3%) had CLD-PH, and 21 (19.8%) had CLD-severe PH. There were 59 (55.7%) patients in the CLD group who had PAPm ≥ 25 mmHg. Chronic obstructive pulmonary disease (COPD) represented the largest subgroup among patients with CLD, followed by interstitial lung disease (ILD) and bronchiolitis obliterans syndrome (BOS) which accounted for 37.7%, 23.6%, and 16.0% in the CLD group, respectively. (Table 2) Among the 47 patients in the PAH group, 19 (40.4%) patients were associated with congenital heart disease, 12 (25.5%) patients were associated with connective tissue disease, 15 (31.9%) patients were idiopathic PAH (IPAH) and 1 (2.1%) patient had PVOD.

Patients in the CLD group tended to be more male predominant (66.0% vs. 19.1%), older (mean age 53.2 vs. 44.7 years old) and higher smoking history (54.7% vs. 19.1%) when compared to the PAH group. Although patients in the CLD group tended to be taller and thinner, there was no significant difference in body surface area between the CLD and PAH groups (1.5 vs. 1.6, $p = 0.204$). While there was no significant difference in left ventricular ejection fraction on echocardiogram assessment, estimated right ventricular systolic pressures were significantly higher in PAH group (mean 81.3 mmHg vs. 44.3 mmHg, $p < 0.001$). Lung function tests were significantly worse among the CLD group with FEV1% (31.2% vs. 78.8%), FVC% (53.1% vs. 86.7%), as well as percentage predicted diffusing capacity for carbon monoxide (DLCO) (35.1% vs. 55.9%). CT thorax findings were significantly different between the CLD group and PAH group with extensive, moderate, and minimal to mild parenchymal CT changes present in 92.5%, 7.5%, and 0%, respectively in the CLD group when compared with 0%, 8.5%, and 91.5%, respectively in the PAH group ($p < 0.001$). WHO functional status was worse among the CLD group (3.0 vs. 2.6, $p < 0.001$) with lower six-min walk distance (252.3 m vs. 342.1 m, $p < 0.001$) when compared with the PAH group. The amount of long-term oxygen therapy requirement was higher in the CLD group (1.8 L/min vs. 0.8 L/min, $p = 0.001$) with more use of noninvasive positive pressure ventilation (10.4% vs 0%) when compared with the PAH group. Other comparisons of patient characteristics were shown in Table 3.

Among the whole cohort, mean follow-up time was 15.4 and 36.0 months for the CLD group and PAH group, respectively. During the study period, 49 patients (46.2%) in the CLD group and six patients (12.8%) in the PAH group had undergone lung transplantation ($p < 0.001$). There were 38 patients (35.8%) in the CLD group and 13 patients (27.7%) in the PAH group who died during the study period without lung transplantation ($p = 0.322$). The 1-, 3-, and 5- year survival rates were 77.0%, 47.9%, and 16.3% for the CLD group and 86.6%, 73.0%, and 73.0% for the PAH group, respectively ($p = 0.003$) (Figure 2). Among the 55 patients who undergone lung transplantation in the present cohort, patients with PAH had a significant higher occurrence of severe post-op primary graft dysfunction (PGD) in 3 out of 6 patients when compared to both whole CLD group in 6 out of 49 patients (50% vs. 12.2%, $p = 0.18$) and CLD group with PH in 10 out of 30 patients (50% vs. 13.3%, $p = 0.038$). Post-lung transplant survival was similar between the PAH group when compared with the CLD group (5-year survival 80% vs. 73.8%, $p = 0.783$). There was no statistically significant difference in post-lung transplant survival among different diagnosis subgroups with 5-year survival rates of 57.1%, 37.5%, 75.5%, 100%, 100%, 66.7%, 100%, and 100% for BOS, bronchiectasis, COPD, ILD, lymphangioleiomyomatosis, IPAH, PAH associated with congenital heart disease, PAH associated with connective tissue disease, respectively ($p = 0.173$).

Patients in the CLD group have significantly lower RAP, lower systolic pulmonary arterial pressure (PAPs),

TABLE 1 Showed the characteristics of parameters of the original cohort and after multiple imputation.

	Original cohort			After multiple imputation	
Parameters	***N***	**Number/mean**	**Percent/*SD***	**Number/mean**	**Percent/*SD***
Gender (Male)	153	79	51.6%	79	51.6%
Age	153	50.6	10.5	50.6	10.5
Smoking	153	67	43.8%	67	43.8%
Diabetes mellitus	153	16	10.5%	16	10.5%
Hypertension	153	18	11.8%	18	11.8%
Hyperlipidemia	153	12	7.8%	12	7.8%
Overweight	153	4	2.6%	4	2.6%
Coronary artery disease	153	11	7.2%	11	7.2%
Atrial arrhythmia	153	12	7.8%	12	7.8%
Cerebral vascular accident	153	1	0.7%	1	0.7%
Simple congenital heart disease	153	18	11.8%	18	11.8%
Complex congenital heart disease	153	1	0.7%	1	0.7%
Systemic lupus erythematosus	153	10	6.5%	10	6.5%
Systemic sclerosis	153	1	0.7%	1	0.7%
Rheumatoid arthritis	153	5	3.3%	5	3.3%
Other connective tissue disease	153	1	0.7%	1	0.7%
Obstructive sleep apnea	153	5	3.3%	5	3.3%
Chronic renal impairment	153	1	0.7%	1	0.7%
Hepatitis	153	5	3.3%	5	3.3%
Liver cirrhosis	153	2	1.3%	2	1.3%
Prior malignancy	153	4	2.6%	4	2.6%
Prior tuberculosis	153	26	17.0%	26	17.0%
Number of comorbidities	153	2.5	1.7	2.5	1.7
WHO Functional Class	153	2.9	0.5	2.9	0.5
6-minute walk distance (meters)	140	274.6	115.2	279.9	124.8
NIPPV	153	11	7.2%	11	7.2%
Oxygen requirement (L/min)	153	1.5	1.9	1.5	1.9
FEV1 (Litre)	144	1.1	0.7	1.2	0.8
Percentage predicted FEV1 (%)	144	44.4	28.1	45.8	28.4
FVC (Litre)	143	2.0	0.8	2.0	0.9
Percentage predicted FVC (%)	141	62.8	24.7	63.4	25.1
FEV1/FVC (%)	137	64.9	29.0	66.0	29.9
Percentage predicted DLCO (%)	101	41.0	21.1	41.5	31.3
CT thorax extensive parenchymal changes	153	98	64.1%	98	64.1%
LVEF (%)	148	63.5	8.1	63.3	8.4
E/e'	69	10.0	3.3	10.0	2.6
TAPSE (mm)	118	1.9	0.4	1.9	0.5

(Continues)

TABLE 1 (Continued)

	Original cohort			After multiple imputation	
Parameters	***N***	**Number/mean**	**Percent/*SD***	**Number/mean**	**Percent/*SD***
RV-S' (cm/s)	93	10.8	2.1	11.2	4.2
RVSP (mmHg)	122	58.2	25.6	55.7	26.4
RA ESA (cm^2)	116	18.1	10.4	19.4	13.1
Pericardial effusion	138	18	13.0%	25.2	16.5%
Height (cm)	153	161.6	9.0	161.6	9.0
Weight (kg)	153	52.0	12.8	52.0	12.8
BSA (m^2)	153	1.5	0.2	1.5	0.2
Heart Rate (beats per minute)	153	83.1	15.2	83.1	15.2
SBP (mmHg)	153	119.5	18.2	119.5	18.2
DBP (mmHg)	153	73.2	10.3	73.2	10.3
MBP (mmHg)	153	92.8	12.6	92.8	12.6
PAPs (mmHg)	152	55.8	28.4	55.7	28.4
PAPd (mmHg)	152	24.6	13.0	24.5	13.0
PAPm (mmHg)	153	36.8	17.9	36.8	17.9
RAP (mmHg)	152	6.7	5.2	6.7	5.2
PCWP (mmHg)	153	9.6	4.2	9.6	4.2
Cardiac output (L/min)	153	4.3	1.3	4.3	1.3
Cardiac index ($L/min/m^2$)	153	2.9	0.8	2.9	0.8
Mixed venous saturation (%)	146	68.5	9.6	68.6	9.8
SVR ($dynes*sec*cm^{-5}$)	153	1714.5	534.2	1714.5	534.2
PVR (Wood units)	153	7.4	7.2	7.4	7.2
RVSWI ($mmHg*mL*m^{-2}$)	153	1613.8	958.1	1613.8	958.1
PAPi	149	7.2	7.6	7.3	7.7
Listing for lung transplantation	153	107	69.9%	107	69.9%
Lung Transplantation	153	55	35.9%	55	35.9%
Death	153	51	33.3%	51	33.3%
Lung transplantation or death	153	106	69.3%	106	69.3%
Follow-up duration (months)	153	21.8	22.4	21.8	22.4

Note: Overweight: body mass index >25 kg/m^2; Chronic renal impairment, estimated glomerular filtration rate <60 $ml/min/1.73\,m^2$.

Abbreviations: BSA, body surface area; DBP, diastolic systemic blood pressure; DLCO, diffusing capacity for carbon monoxide; E/e', ratio of the peak early mitral inflow velocity over the early diastolic mitral annular velocity; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; MBP, mean systemic blood pressure; NIPPV, noninvasive positive pressure ventilation; PAPs, systolic pulmonary arterial pressure; PAPd, diastolic pulmonary arterial pressure; PAPm, mean pulmonary arterial pressure; PAPi, pulmonary artery pulsatility index; PCWP, mean pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA ESA, end-systolic area of right atrium; RAP, mean right atrial pressure; RV-S', longitudinal systolic excursion velocity of tricuspid annulus by tissue Doppler; RVSP, right ventricular systolic pressure; RVSWI, right ventricular stroke work index; SBP, systolic systemic blood pressure; *SD*, standard deviation; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization.

lower PAPm, higher cardiac output, higher cardiac index, higher mixed venous saturation, and lower PVR when compared to the PAH group (Table 4). On the other hand, while there was no significant difference in the systolic systemic blood pressure and PCWP between the two groups, patients in the CLD group had significantly higher heart rate, higher mean systemic blood pressure, and lower systemic vascular resistance.

TABLE 2 Showed the diagnosis of the cohort and the World Symposium of Pulmonary Hypertension 2018 classification for pulmonary hypertension in chronic lung disease.

			WSPH 2018 CLD-PH Classification					
Diagnosis of the cohort ($N = 153$)	**Number**	**Percentage**	**CLD without PH**		**CLD with PH**		**CLD with severe PH**	
Severe chronic lung disease ($N = 106$)								
Bronchiolitis obliterans syndrome	17	16.0	12	70.6%	4	23.5%	1	5.9%
Bronchiectasis	13	12.3	1	7.7%	7	53.8%	5	38.5%
Chronic obstructive pulmonary disease	40	37.7	16	40%	19	47.5%	5	12.5%
Interstitial lung disease	25	23.6	4	16%	13	52%	8	32%
Lymphangioleiomyomatosis	8	7.5	2	25%	4	50%	2	25%
Others	3	2.8	2	66.7%	1	33.3%	0	0%
			37	34.9%	48	45.3%	21	19.8%
Pulmonary arterial hypertension ($N = 47$)								
Idiopathic pulmonary arterial hypertension	15	31.9	0	0%	0	0%	15	100%
PAH-CHD	19	40.4	0	0%	1	5.3%	18	94.7%
PAH-CTD	12	25.5	0	0%	0	0%	12	100%
Pulmonary veno-occlusive disease	1	2.1	0	0%	0	0%	1	100%
			0	0%	1	2.1%	46	97.9%

Abbreviations: CLD, chronic lung disease; CLD without PH, mean pulmonary arterial hypertension (mPAP) <21 mmHg, or mPAP 21–24 mmHg with pulmonary vascular resistance (PVR) < 3 Wood Units (WU)); CLD with PH, mPAP 21–24 mmHg with PVR ⩾ 3 WU, or mPAP 25–34 mmHg); CLD with severe PH, mPAP ⩾ 35 mmHg, or mPAP ⩾ 25 mmHg with low cardiac index (<2.0 L/min/m^2); PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PAH-CTD, pulmonary arterial hypertension associated with connective tissue disorder; PH, pulmonary hypertension; WSPH, World Symposium of Pulmonary Hypertension.

RVSWI was significantly higher in the PAH group (Table 4). Among patients with CLD, severe PH has the highest occurrence in bronchiectasis (38%) followed by ILD (32%), LAM (25%), COPD (12.5%), BOS (5.9%), and none in others which included cases of sarcoidosis and pleuro-parenchymal fibroelastosis. On the contrary, severe PH using CLD patient definition is present in 100% of patients with IPAH, PAH with connective tissue disease, and PVOD, as well as 94.7% in patients with PAH associated with congenital heart disease (Table 2). There were five patients in the CLD group who received PAH targeted therapy with two of them having subsequently undergone lung transplantation and three of them died before receiving lung transplantation. All of them received sildenafil and no other type of PAH targeted therapy was used. All of them had CLD-severe PH and all of them received sildenafil treatment within the last 1 year before the terminal event of death or lung transplantation.

Both the PAPs and PAPm showed excellent discriminating power between the CLD group and the PAH group (AUC 0.973 and 0.970, respectively) (Figure 3A,B) while PVR also showed incredibly good discrimination power with AUC 0.938. (Figure 3C) AUC of different hemodynamic parameters were shown in Figure 4A. For non-hemodynamic parameters, FEV1%, FEV1, and RVSP all showed excellent discriminating power between the CLD group and the PAH group (AUC 0.954, 0.945, and 0.921, respectively). (Figure 4B) Optimal cut-off values were 55.5 mmHg, 35.5 mmHg, and 6.1 Wood Unit for PAPs, PAPm, and PVR with Youden Index 0.85, 0.80, and 0.82, respectively. Sensitivities at these cut-offs were 97.9%, 95.7%, and 93.6% while specificities were 86.8%, 84.0% and 88.7% for PAPm, sPAP, and PVR, respectively. Optimal cutoff points for nonhemodynamic parameters FEV1%, FEV1, and RVSP were 49.6%, 1.3 L/min, and 52.6 mmHg with Youden index 0.82, 0.87, and 0.67, respectively. Sensitivities at these cutoffs were 97.9%, 97.9%, and 93.6% while specificities were 84.0%, 88.7%, and 73.6% for FEV1%, FEV1, and RVSP, respectively. A second-best cutoff value for FEV1% was 60.5% with excellent specificity 91.5% with slightly lower sensitivity 89.4% (Table 5).

TABLE 3 Showed the differences in characteristics between patients with pulmonary arterial hypertension and patients with severe chronic lung disease.

Characteristics	Pulmonary arterial hypertension ($n = 47$)		Severe chronic lung disease ($n = 106$)		p value
	Number/mean	Percent/*SD*	Number/mean	Percent/*SD*	
Gender (male)	9	19.1%	70	66.0%	**<0.001**
Age	44.7	11.3	53.2	9.0	**<0.001**
Smoking	9	19.1%	58	54.7%	**<0.001**
Diabetes mellitus	5	10.6%	11	10.4%	0.961
Hypertension	6	12.8%	12	11.3%	0.798
Hyperlipidemia	7	14.9%	5	4.7%	**0.031**
Overweight	3	6.4%	1	0.9%	0.052
Coronary artery disease	2	4.3%	9	8.5%	0.349
Atrial arrhythmia	9	19.1%	3	2.8%	**0.001**
Cerebral vascular accident	1	2.1%	0	0.0%	0.132
Simple congenital heart disease	18	38.3%	0	0.0%	**<0.001**
Complex congenital heart disease	1	2.1%	0	0.0%	0.132
Systemic lupus erythematosus	9	19.1%	1	0.9%	**<0.001**
Systemic sclerosis	1	2.1%	0	0.0%	0.132
Rheumatoid arthritis	2	4.3%	3	2.8%	0.647
Other connective tissue disease	1	2.1%	0	0.0%	0.132
Obstructive sleep apnea	2	4.3%	3	2.8%	0.647
Chronic renal impairment	1	2.1%	0	0.0%	0.132
Hepatitis	2	4.3%	3	2.8%	0.647
Liver cirrhosis	1	2.1%	1	0.9%	0.552
Prior malignancy	2	4.3%	2	1.9%	0.397
Prior tuberculosis	1	2.1%	25	23.6%	**0.001**
Number of comorbidities	3.0	2.0	2.3	1.6	**0.011**
WHO Functional Class	2.6	0.7	3.0	0.4	**<0.001**
6-min walk distance (meters)	342.1	143.5	252.3	104.8	**<0.001**
NIPPV	0	0.0%	11	10.4%	**0.022**
Oxygen requirement (L/min)	0.8	1.5	1.8	1.9	**0.001**
FEV1 (L)	2.0	0.6	0.8	0.5	**<0.001**
Percentage predicted FEV1 (%)	78.8	18.3	31.2	17.9	**<0.001**
FVC (L)	2.7	0.8	1.8	0.8	**<0.001**
Percentage predicted FVC (%)	86.7	18.5	53.1	20.3	**<0.001**
FEV1/FVC (%)	82.4	18.9	58.8	31.0	**<0.001**
Percentage predicted DLCO (%)	55.9	33.4	35.1	27.5	0.085
CT thorax parenchymal changes					**<0.001**
Minimal to mild changes	43	91.5%	0	0	
Moderate changes	4	8.5%	8	7.5%	
Extensive changes	0	0%	98	92.5%	

TABLE 3 (Continued)

Characteristics	Pulmonary arterial hypertension ($n = 47$)		Severe chronic lung disease ($n = 106$)		p value
	Number/mean	Percent/*SD*	Number/mean	Percent/*SD*	
LVEF (%)	64.4	8.2	62.9	8.5	0.304
E/e'	10.2	3.2	9.9	2.3	0.538
TAPSE (mm)	1.8	0.5	1.9	0.5	0.118
RV-S' (cm/s)	9.9	3.0	11.8	4.5	0.051
RVSP (mmHg)	81.3	19.4	44.3	20.5	**<0.001**
RA ESA (cm^2)	26.9	14.3	16.1	11.1	**<0.001**
Pericardial effusion	12.4	26.4%	12.8	12.1%	**0.0286**
Listing for lung transplantation	17	36.2%	90	84.9%	**<0.001**
Lung Transplantation	6	12.8%	49	46.2%	**<0.001**
Death	13	27.7%	38	35.8%	0.322
Lung transplantation or death	19	40.4%	87	82.1%	**<0.001**
Follow-up duration (months)	36.0	30.8	15.4	13.5	**<0.001**

Abbreviations: Chronic renal impairment, estimated glomerular filtration rate <60 ml/min/1.73 m^2; DLCO, diffusing capacity for carbon monoxide; E/e', ratio of the peak early mitral inflow velocity over the early diastolic mitral annular velocity; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; NIPPV, noninvasive positive pressure ventilation; Overweight, body mass index >25 kg/m^2; RA ESA, end-systolic area of right atrium; RV-S', longitudinal systolic excursion velocity of tricuspid annulus by tissue Doppler; RVSP, right ventricular systolic pressure; *SD*, standard deviation; TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization.

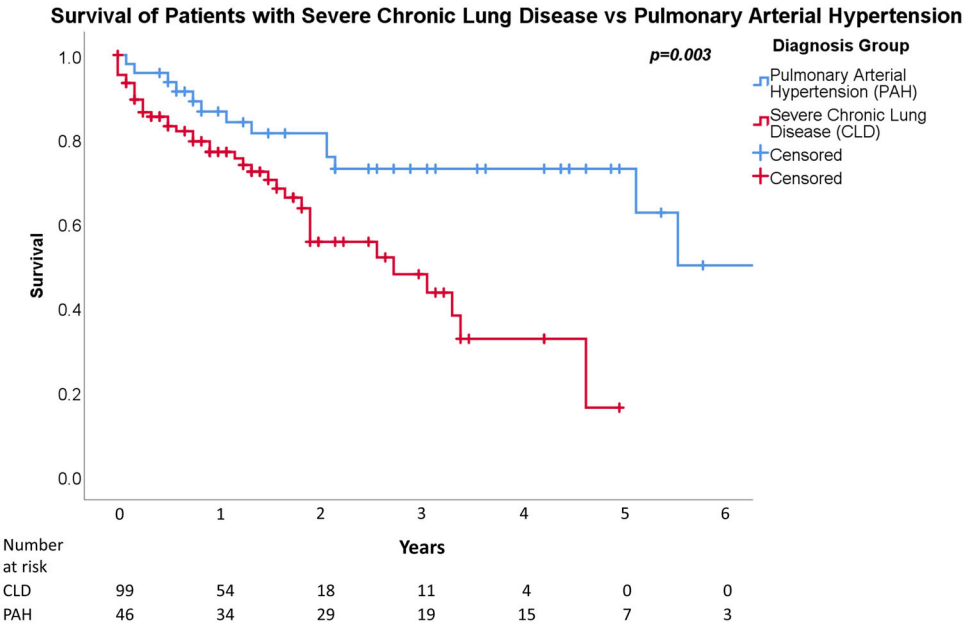

FIGURE 2 Survival of patients with severe chronic lung disease and pulmonary arterial hypertension. Survival of patients who has severe chronic lung disease (CLD) and World Health Organization Group 1 pulmonary arterial hypertension (PAH) after hemodynamic assessment was shown in Figure 2. The 1-, 3-, and 5-year survival rate were 77.0%, 47.9%, and 16.3% for the CLD group and 86.6%, 73.0%, and 73.0% for the PAH group, respectively ($p = 0.003$).

TABLE 4 Showed the differences in hemodynamic parameters between patients with pulmonary arterial hypertension and patients with severe chronic lung disease.

	Pulmonary arterial hypertension ($n = 47$)		Severe chronic lung disease ($n = 106$)		
Hemodynamic parameters	**Mean**	***SD***	**Mean**	***SD***	***p* Value**
Height (cm)	158.7	8.0	162.9	9.1	**0.007**
Weight (kg)	55.5	12.1	50.5	12.9	**0.022**
BSA (m^2)	1.6	0.2	1.5	0.2	0.204
Heart rate (beats per minute)	78.6	16.8	85.1	14.0	**0.012**
SBP (mmHg)	115.9	19.9	121.1	17.2	0.102
DBP (mmHg)	67.9	9.7	75.6	9.6	**<0.001**
MBP (mmHg)	85.7	11.1	95.9	12.0	**<0.001**
PAPs (mmHg)	90.0	22.3	40.4	13.5	**<0.001**
PAPd (mmHg)	38.5	13.1	18.3	6.4	**<0.001**
PAPm (mmHg)	58.1	15.3	27.4	8.3	**<0.001**
RAP (mmHg)	10.0	6.4	5.2	3.7	**<0.001**
PCWP (mmHg)	9.0	3.2	9.9	4.6	0.243
Cardiac output (L/min)	3.4	0.9	4.7	1.2	**<0.001**
Cardiac index (L/min/m^2)	2.2	0.6	3.1	0.8	**<0.001**
Mixed venous saturation (%)	61.3	11.1	71.8	7.1	**<0.001**
SVR (dynes*sec*cm^{-5})	1878.0	549.2	1642.0	513.6	**0.01**
PVR (Wood units)	14.9	8.3	4.1	3.0	**<0.001**
RVSWI (mmHg*mL*m^{-2})	2413.2	1157.6	1259.4	573.5	**<0.001**
PAPi	8.2	7.5	7.0	7.8	0.381

Abbreviations: BSA, body surface area; DBP, diastolic systemic blood pressure; SBP, systolic systemic blood pressure; MBP, mean systemic blood pressure; PAPs, systolic pulmonary arterial pressure; PAPd, diastolic pulmonary arterial pressure; PAPm, mean pulmonary arterial pressure; PAPi, pulmonary artery pulsatility index; PCWP, mean pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, mean right atrial pressure; RVSWI, right ventricular stroke work index; *SD*, standard deviation; SVR, systemic vascular resistance.

4 | DISCUSSIONS

To the best of our knowledge, this is the first cohort study demonstrating the excellent discriminating power of PAPs, PAPm as well as PVR between patients with severe CLD and PAH.

The indications for lung transplant referral for chronic lung disease in this cohort were largely similar to the International Society for Heart and Lung Transplantation (ISHLT) registry with COPD and ILD being the most common reasons for referral and lung transplantation.[12] PH only accounted for 4.4% of lung transplantation in the ISHLT registry[12] while the proportion was slightly higher at about 10.9% in our cohort. Cystic fibrosis and alpha-1 antitrypsin deficiency were not found in our cohort because of the low incidence among patients of Chinese descent. No lung re-transplantation has been performed since the beginning of the lung transplantation program in our city.

The prevalence of PH was difficult to obtain because echocardiogram was not accurate enough for diagnosis and right heart catheterization was not universally performed among patients with CLD.[1,4] The prevalence of PH with PAPm $\geq$ 25 mmHg among patients with severe CLD referred for lung transplantation or surgical lung volume reduction surgery was found to be between 30% and 70%.[4,11,13–17] In this cohort, there were 59 (55.7%) patients in the CLD group had PAPm $\geq$ 25 mmHg which was consistent with previous reports. Although the cutoff of PAPm $\geq$ 25 mmHg was widely adopted in a lot of epidemiological studies, pulmonary hypertension registries, and clinical trials of PAH treatments since its introduction in 1975 during the first WSPH, this definition was consensus-based rather than evidence-based and thus has been recently revisited in

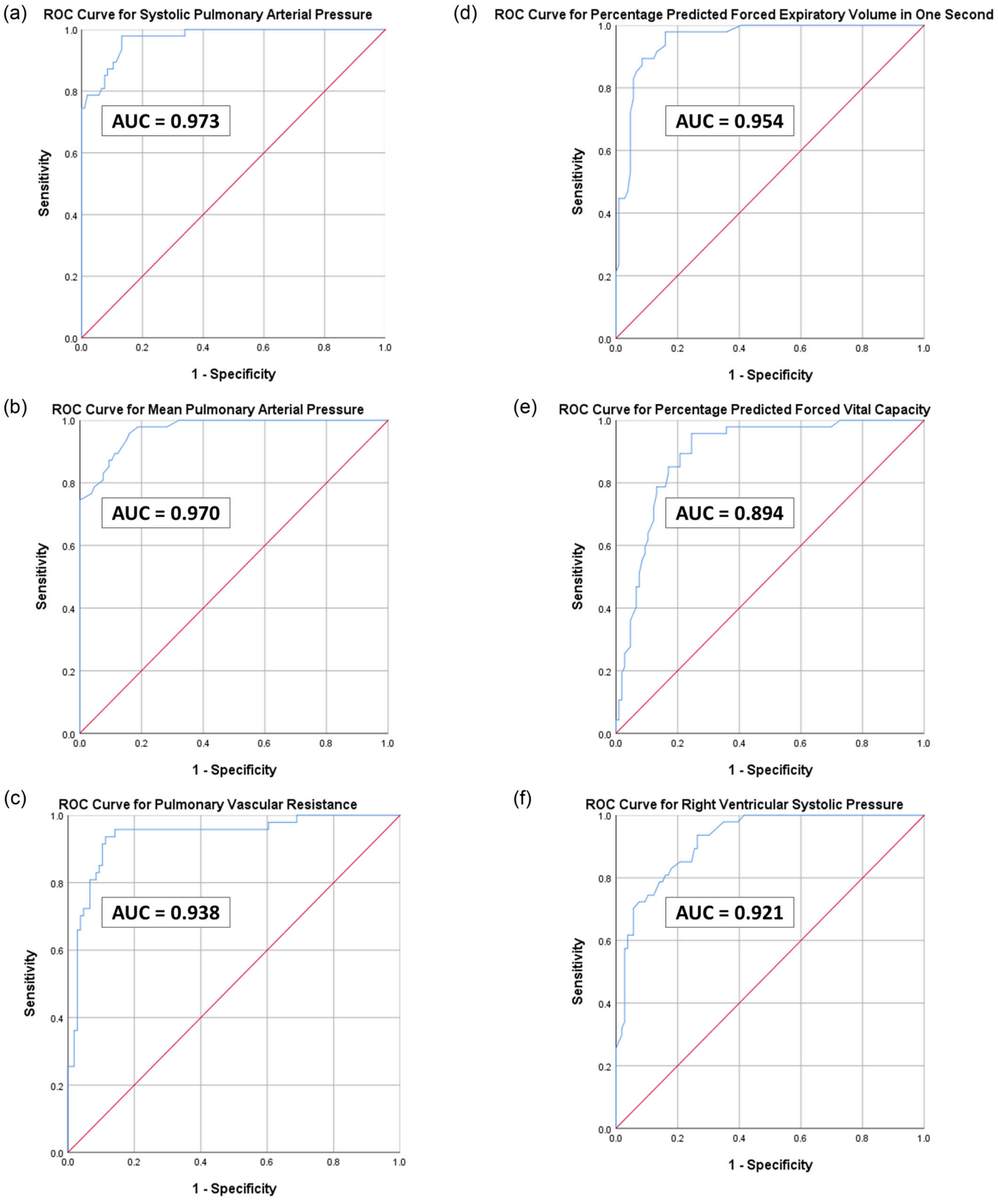

FIGURE 3 Receiver operating characteristics curve of different hemodynamics and non-hemodynamics parameters Figure 3 showed the areas under curve (AUC) of different hemodynamic and non-hemodynamic parameters in differentiating between the two phenotypes of severe chronic lung disease and pulmonary arterial hypertension. Receiver operating characteristics (ROC) curve of (A) systolic pulmonary arterial pressure, (B) mean pulmonary arterial pressure, (C) pulmonary vascular resistance, (D) percentage predicted forced expiratory volume in 1 s, (E) predicted forced vital capacity, and (F) estimated right ventricular systolic pressure by echocardiography were demonstrated.

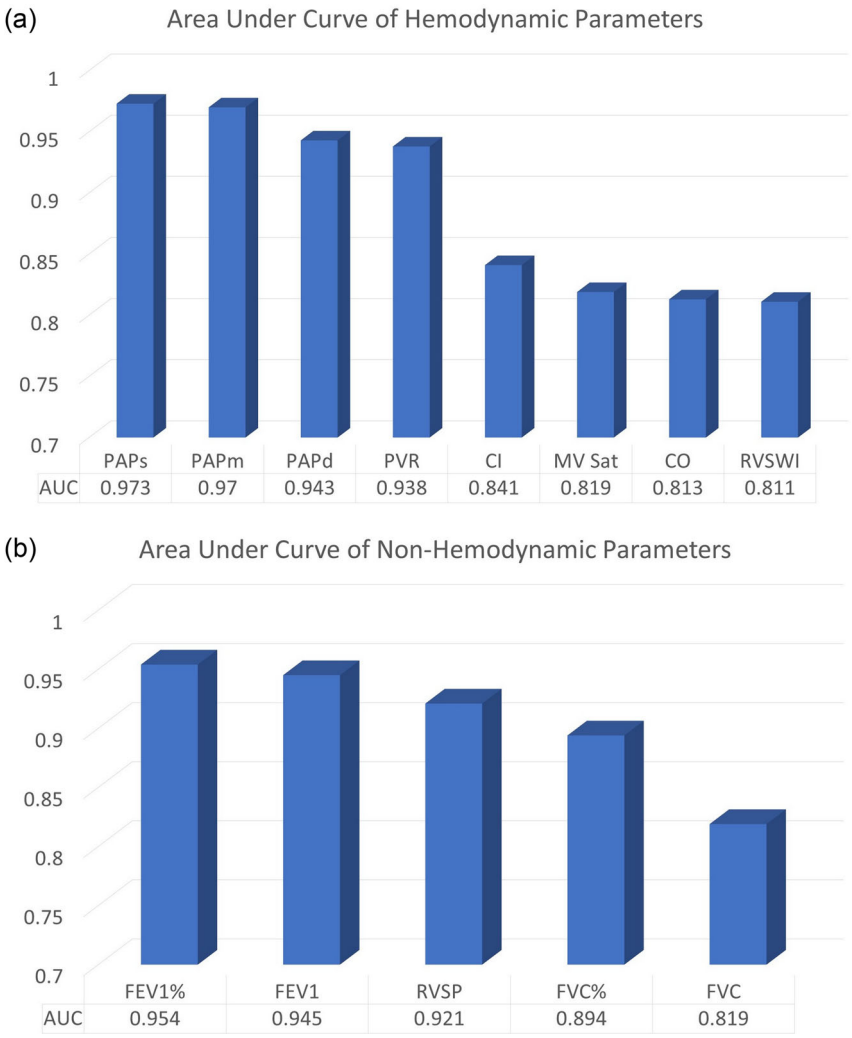

FIGURE 4 Area under curve (AUC) for hemodynamic and non-hemodynamic parameters. (A) Showed AUC of systolic pulmonary arterial pressure (PAPs), mean pulmonary arterial pressure (PAPm), diastolic pulmonary arterial pressure (PAPd), pulmonary vascular resistance (PVR), cardiac index (CI), mixed venous saturation (MV Sat), cardiac output (CO), and right ventricular stroke work index (RVSWI) while (B) showed AUC of percentage predicted forced expiratory volume in one second (FEV1%), forced expiratory volume in one second (FEV1), estimated right ventricular systolic pressure on echocardiogram (RVSP), percentage predicted forced vital capacity (FVC%), and forced vital capacity (FVC) in differentiating between severe chronic lung disease and pulmonary arterial hypertension.

the sixth WSPH in 2018 and a more evidence-based cutoff PAPm > 20 mmHg was proposed given that normal PAPm was 14.0 mmHg with SD 3.3 mmHg among normal subjects.[18,19] Therefore, this latest recommendation of hemodynamic definition of PAPm 21–24 mmHg with PVR ≥ 3 WU, or PAPm 25–34 mmHg was adopted in the present study[1] and the prevalence of pulmonary hypertension was 65.1% among patients with CLD in this cohort with this definition.

The definition for severe pulmonary hypertension in CLD is more elusive. Criteria such as PAPm ≥ 35–40 mmHg, cardiac index <2.0–2.5 L/min/m^2, PVR > 6 Wood's units, alone or in combinations were proposed or used to define severe pulmonary hypertension in CLD in different observational studies or consensus statements.[1–5] The main rationales for using PAPm ≥ 35 mmHg were that this represents a minority of patients with chronic lung disease[1,3–5] and this group of patients exhibit functional limitation more due to vascular cause rather than parenchymal disease.[3,5–9] In addition, a recent randomized controlled multicenter clinical trial has demonstrated the hemodynamic and functional beneficial effect of sildenafil without significant safety concern in a group of patients with severe COPD, defined by PAPm ≥ 35 mmHg if the percentage predicted FEV1 < 30% or PAPm ≥ 30 mmHg for a percentage predicted FEV1 > 30%.[10] Despite these supporting rationales, the choice of the absolute cutoff was still arbitral and mostly consensual. In the recent sixth WSPH, it was commented that the spectrum of severity of both the pulmonary vascular and parenchymal lung disease is likely a continuum, which often makes the distinction between Group 1 and Group 3 PH difficult. As a result, the best hemodynamic variable and threshold to define the patient phenotype was needed to guide future optimal patient phenotype for trials of therapy.[1] Our study provided a clear answer to this gap of knowledge.

Our cohort represented a group of severe CLD referred for lung transplantation consideration. The findings of poor lung function test parameters (FEV1 31.2% predicted, FVC 53.1% predicted, and DLCO 35.1%

TABLE 5 showed the optimal cutoff value, sensitivity, specificity, and Youden index of different hemodynamic and no-hemodynamic parameters to differentiate between pulmonary arterial hypertension and severe chronic lung disease.

Parameters	Cutoff	Sensitivity (%)	Specificity (%)	Youden Index
Hemodynamic parameters				
PAPs (mmHg)	55.5	97.9	86.8	0.85
PAPm (mmHg)	35.5	95.7	84.0	0.80
PAPd (mmHg)	25.5	87.2	84.0	0.71
PVR (Wood Units)	6.1	93.6	88.7	0.82
Cardiac Index (L/min/m^2)	2.7	87.2	76.4	0.64
Mixed Venous Saturation (%)	67.7	76.6	82.1	0.59
Cardiac Output (L/min)	3.9	76.6	75.5	0.52
RVSWI (mmHg*mL*m^{-2})	1995.4	59.6	90.6	0.50
Nonhemodynamic parameters				
Percentage predicted FEV1 (%)	49.6	97.9	84.0	0.82
Percentage predicted FEV1 (%) (Second-best)	60.5	89.4	91.5	0.81
FEV1 (L)	1.3	97.9	88.7	0.87
RVSP (mmHg)	52.6	93.6	73.6	0.67
Percentage predicted FVC (%)	64.3	95.7	75.5	0.71
FVC (L)	2.0	85.1	70.8	0.56

Abbreviations: FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PAPs, systolic pulmonary arterial pressure; PAPd, diastolic pulmonary arterial pressure; PAPm, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; RVSWI, right ventricular stroke work index; RVSP, right ventricular systolic pressure.

predicted), significant functional limitation with mean six-minute walk distance of 245 m, high proportion of severe pulmonary hypertension (~19.8% of the CLD cohort) and poor clinical outcomes (~16.3% 5-year survival in the CLD group) were consistent with features of end-stage CLD. On the other hand, the relatively low percentage of patients required lung transplantation and the relatively favorable clinical outcomes of the PAH subgroup were consistent with a general overall cohort of PAH. Despite the extremely sick profile in this CLD cohort, the hemodynamic profile of the CLD group was still significantly better than that of the PAH group. This founding agreed with the well-known phenomenon that pulmonary hypertension in CLD was mostly modest and highlighted the distinct hemodynamic characteristics of pulmonary hypertension in CLD and in PAH.[2,3,20] Our study confirmed the excellent discriminating power of commonly used hemodynamics parameters such as PAPm and PVR with AUC > 0.9 while cardiac index also demonstrated a good discriminating ability with AUC > 0.8. In addition, our study also demonstrated that PAPs also had excellent discriminating profiles with AUC > 0.9. Not surprisingly, the optimal cut-off values derived with the use of Youden Index for mPAP and PVR were 35.5 mmHg and 6.1 Wood's Unit, respectively which were largely consistent with the previously proposed cutoff of PAPm ≥ 35 mmHg and PVR > 6 Wood's Unit. The sensitivity and specificity were good at >93% and >84%, respectively. This means that on one hand our findings were consistent with the findings of previous epidemiological and functional studies as well as the consensus among experts in this field, on the other hand our findings provide additional evidence-based support to the choice of optimal cutoff for the definition of severe PH in CLD. In addition, both lung function test parameters FEV1% and FVC% also demonstrated excellent discriminative power with AUC 0.954 and 0.894, respectively among different non-hemodynamic parameters, which was also consistent with the recommendation in using these parameters to discriminate the phenotype of WHO Group 3 versus Group 1 pulmonary hypertension.[1] In our cohort, the optimal cutoff value for FVC % was 64.3% which was similar to the suggested cutoff value of 70% in restrictive lung disease.[1] Although the optimal cutoff value for FEV1% was 49.6% in the present cohort, the suggested cutoff value of 60% in obstructive

lung disease[1] was in fact the second-best cutoff value (60.5%) with even higher specificity 91.5% and slightly lower sensitivity 89.4%. Not surprisingly, RVSP on echocardiogram, which is a noninvasive estimation of PAPs, was also carrying excellent discrimination ability with AUC 0.921. Furthermore, the extent of parenchymal changes on CT thorax significantly differs in the present study between CLD and PAH groups which was consistent with the latest recommendation for its use to discriminate between the two phenotypes.[1] Therefore, the non-hemodynamic characteristics of the present cohort are largely consistent with the latest consensus recommendations.[1]

The strength of this study is that there was only one tertiary referral center in the territory and thus our cohort represented real-world homogenous data in a seven million population. Also, our data were largely consistent with previously reported figures and consensus definitions. Missing data in the present cohort was not excessive at 4.16% and were tackled by multiple imputations. However, our study was limited due to the relatively small sample size due to the relatively small service volume of lung transplantation in our city.[21] In addition, being a city with a predominant Asian population, might limit the generalizability of our data to the other part of the world. An additional multicenter study involving different countries may be needed to confirm our findings. Furthermore, PCWP is a surrogate of the gold standard LVEDP and there are important concerns about the accuracy of PCWP in reflecting LVEDP, especially in patients with chronic lung disease because of air trapping or distortion of lung architecture and low correlation between PCWP and LVEDP resulting in misclassification has been demonstrated in a cohort of a veteran with a high proportion of chronic lung disease.[22] Unfortunately, LVEDP was not routinely recorded in the present study and thus accuracy of PCWP in reflecting left ventricular filling pressure was uncertain. A future study utilizing both PCWP and LVEDP would be important to address the correlation between the two parameters in patients with chronic lung disease as well as to differentiate pre-capillary and post-capillary pulmonary hypertension in a more accurate manner in patients with chronic lung disease. Lastly, the hemodynamic assessment was only performed once as a prelung transplant evaluation. Serial hemodynamic data as well as hemodynamic condition immediately before lung transplantation was not available in the present study. As a result, patients with normal pulmonary pressure at the time of lung transplant listing who subsequently developed PH due to hypoxemia or worsening lung parenchymal condition while on the waiting list could not be demonstrated in the present study. Future study with protocol-driven serial hemodynamic reassessment while the patient is on the lung transplant waiting list would be important to demonstrate the trend of hemodynamic change among this group of patients.

5 | CONCLUSION

There were distinct hemodynamic characteristics between the CLD group and the PAH group. Systolic pulmonary arterial pressure, mean pulmonary arterial pressure, and pulmonary vascular resistance can be useful to discriminate between the phenotype of severe chronic lung disease and pulmonary arterial hypertension.

AUTHOR CONTRIBUTIONS

Wood Hay Ian Ling, Chi Fong Wong, See Wan Yan, Yue Yan Katherine Fan, and Ka Lam Wong were involved in the conception and design, administrative support, provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL STATEMENT AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board (IRB) of The University of Hong Kong and Hospital Authority Hong Kong West Cluster (IRB/REC No. UW 20-346) and individual consent for this retrospective analysis were waived.

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