EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Jaafar S, Visovatti S, Young A, *et al*. Impact of the Revised Hemodynamic Definition on the Diagnosis of Pulmonary Hypertension in Patients with Systemic Sclerosis. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.00586-2019).

Impact of the Revised Hemodynamic Definition on the Diagnosis of Pulmonary Hypertension in Patients with Systemic Sclerosis

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Introduction: Pulmonary arterial hypertension (PAH) is one of the leading causes of mortality in scleroderma-spectrum disorders (SSc). We explored the impact of the updated hemodynamic definition of pulmonary hypertension (PH), as proposed by the 6th World Symposium on Pulmonary Hypertension.

Methods: In this single center retrospective analysis, patients with SSc who had right heart catheterizations (RHCs) were included. We compared the prior PH definition, which defined PH as mPAP ≥25 mmHg and further classified into pre-capillary PH [PAH and PH due to lung diseases], post-capillary PH, and combined pre- and post-capillary PH. For the updated definition, we classified PH as mPAP >20 mmHg and further classified them into different groups defined above. We validated our findings in the DETECT cohort.

Results: Between 2005 and March 2019, 268 RHCs were performed in single center cohort. Using the prior definition, 137 (51%) were diagnosed with PH, with 89 classified as pre-capillary PH (56 with PAH; 33 with PH-lung diseases), 29 as post-capillary PH, and 19 as combined PH. When the updated definition was applied to the cohort, 7 of 131 (5%) with no PH were reclassified to pre-capillary PH (PAH [N=1], PH-lung diseases [N=3]) and post-capillary PH (N=3). In those with mPAP of 21-24 mmHg, no left heart or lung disease, 1 of 28 (4%) in our cohort and 4 of 36 (11%) in the DETECT cohort were reclassified as PAH.

Conclusion: The updated PH definition does not appear to have a significant impact on the diagnosis of PH in 2 different screening cohorts.

Introduction

Systemic sclerosis- related pulmonary arterial hypertension (SSc-PAH) is the one of the leading causes of mortality[1, 2] and accounts for up to 26% of deaths[3]. Recent data from clinical trials and observational registries suggest better outcomes, including survival, are

associated with uniform screening and early, aggressive combination therapies[4-6]. Previous World Symposia on Pulmonary Hypertension (WSPH) defined pulmonary hypertension (PH) as the mean pulmonary artery pressure (mPAP) ≥ 25 mmHg and PAH is characterized hemodynamically by the presence of pre-capillary PH, including an end-expiratory pulmonary arterial wedge pressure (PAWP) ≤ 15 mm Hg and a pulmonary vascular resistance (PVR) ≥ 3 Wood units[7-9].

Kovacs et al[10] published a systematic review where they analyzed available data obtained by right heart catheterization (RHC) studies in healthy individuals and revealed that the mean (SD) mPAP is 14.0±3.3 mmHg; 2 standard deviations support that mPAP > 20 mmHg is above the upper limit of normal. In addition, data from various scleroderma cohorts suggest that patients with borderline elevations of mean pulmonary artery pressures (defined as mPAP 21-24 mm Hg) are an intermediate step between normal PAP (≤ 20 mm Hg) and PH (mPAP ≥ 25 mmHg), associated with decreased exercise capacity and greater risk of developing resting PH[11-15]. Based on this and other data, the 2018 WSPH Task Force proposed an updated hemodynamic definition of PAH as mPAP > 20 mmHg, PAWP ≤ 15 mmHg, and PVR ≥ 3 Wood units (Table 1)[16, 17]. The 6th WSPH Task Force recommended to include PVR ≥ 3 Wood units for classification of pre-capillary PH to discriminate the elevation of mPAP due to other causes [driven by contribution of cardiac output (CO) and/or PAWP].

We analyzed the retrospective data in scleroderma-spectrum disorders from a PAH screening database at the University of Michigan (UM) cohort to assess the impact of the updated hemodynamic definition of PH, including reclassification of patients with non-PH to PH and validated our data in the DETECT study cohort[1]. Our objectives were to investigate the impact of the updated clinical PH classification in scleroderma-spectrum disorders and the impact of including the PVR in the updated definition of PH.

Patients and Methods

Patients were included in this retrospective analysis of a prospective cohort (referred as UM cohort from hereon) if they had scleroderma-spectrum disorders (SSc and overlap syndrome with scleroderma spectrum) [18], were evaluated at UM Scleroderma and PH clinics, and had a RHC at UM. This population represents an ongoing cohort to validate the DETECT algorithm [11] and other screening algorithms in scleroderma-spectrum disorders that include transthoracic echocardiogram, pulmonary function tests, and NT-ProBNP [18] and we recently published the details[19]. Diagnosis of SSc was confirmed by a rheumatologist with expertise in scleroderma. Chart review was performed to extract age, race, gender, subtype of SSc, disease duration (defined from initial non-Raynaud's phenomenon sign or symptom), scleroderma-specific autoantibodies, and pulmonary function test results. High-resolution computer tomography (HRCTs) were reviewed by 2 thoracic radiologists who assessed the degree of total lung involvement in increments of 10% to up to 30% or > 30% lung involvement, and if there was concomitant emphysema. If emphysema was present, it was classified as mild, moderate, or severe. RHCs had been performed by a cardiologist due to concern for PH based on a positive screening test[18] or clinical signs/symptoms of PH. The thermodilution method was used to calculate the cardiac output and PVR[7, 20].

We compared the prior PH definition to the updated PH definition. The prior definition classified PH as mPAP $\geq$ 25 mmHg and further divided into Group 1 or PAH, post-capillary PH or Group 2, Group 3 or PH due to chronic lung disease (HRCT showing > 20% total lung involvement due to ILD or if the total lung involvement due to ILD was 10-20% but the patient had concomitant moderate-to-severe emphysema) and if HRCT is not available, then FVC < 70% predicted within a median of 2 months of the RHC) and combined pre-and post-capillary PH (See Table 1 for details)[21]. For the updated classification, we used the published definitions where the mPAP was changed from $\geq$ 25 mmHg to > 20 mmHg and PVR was changed from > 3 WU [21] to $\geq$ 3 WU. They were then further classified into 4 subsets, as defined above[17]. We validated our results in the DETECT study cohort[1, 11]. Briefly, the DETECT study was a multi-center study that systematically evaluated 466 SSc

patients at increased risk for development of SSc-PAH. DETECT was the first SSc- PAH detection study to evaluate all subjects with RHC. Patients (N=244) were included in the current analysis if they had: 1) a PAWP ≤15 mmHg by RHC; 2) no significant ILD; defined as FVC <60% or FVC between 60 and 70% with moderate-to-severe ILD on HRCT; 3) no systemic hypertension (stage-I hypertension defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90); and 4) no left atrial enlargement.

Descriptive statistics for baseline demographics were performed based on PH groups. For continuous variables that followed a normal distribution, means and standard deviations were compared across groups using Student's T test. For continuous variables that did not follow a normal distribution, medians and ranges were compared using the Wilcoxon rank sum test. For categorical variables, counts and proportions were calculated and compared across groups using Chi-Squared tests or Fisher exact test, depending on the proportion of cells with count less than 5. A significance level of 0.05 was used for all statistical tests. Missing data, if any, was not imputed. Analyses were conducted in SAS 9.4 (SAS Institute Inc.).

Results

In the UM cohort of scleroderma-spectrum disorders (11 patients diagnosed with overlap syndrome also met the criteria for SSc according to the 2013 SSc classification criteria[22]). Between 2005-March 2019, 268 RHCs were performed at the UM in patients who were at risk for PH based on PAH screening algorithms and guidelines and are included in this retrospective analysis (Figure 1a and 1b).

The mean (SD) age of the cohort was 60.6 (11.7) years, 85% were female, disease duration was 9.8 (9.1) years, 35% had diffuse cutaneous SSc and 57% had limited cutaneous SSc.

The mean (SD) mPAP on RHC for the overall cohort was 30.6 (11.9) mmHg, mean PAWP was 12.6 (4.7) mmHg, and mean PVR was 3.9 (3.7) WU. In patients with PH based on the updated definition (N=144), the mean age was 61.5 (11.3) years, 85% were female, disease duration was 9.4 (9.5) years, and 53% had limited cutaneous SSc (Table 2). The mean (SD) mPAP on RHC was 37.9 (11.2) mmHg, mean PAWP was 13.9 (5.4) mmHg, and mean PVR was 5.6 (4.3) WU.

Impact of updated classification

Based on the hemodynamics data, 131 patients within this cohort did not have PH based on the prior PH definition (Figure 1a). In the updated definition, seven patients were reclassified from non-PH to pre-capillary PH (PAH (N=1), Group 3 (N=3)), or post-capillary PH (N=3; Figure 1b and Table 3). The one patient, who was reclassified as having PAH according to the updated definition has had stable disease with no signs/symptoms of progression of PAH **(**7 years after the RHC, Table 3). Also, for those subjects who were reclassified as WHO Group II or III according to the new definition, one patient with WHO Group II PH and WHO Group III PH died, primarily due to severe malabsorption due to GI dysmotility.

Of the 124 patients not diagnosed with PH according to the new hemodynamic definition, 76 had mPAP > 20 mmHg, PAWP ≤ 15 mmHg, and PVR < 3 WU (Figure 1b). Of these, 45 had mPAP of 21-24 mmHg, PAWP ≤ 15 mmHg, and PVR < 3 WU. 19 patients out of the 45 had lung disease; 7 with PVR <2 WU and 11 with ≥2 but < 3 WU.

Impact of addition of PVR in the updated definition

Previous publications in SSc have defined pre-capillary PH as mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, and have not uniformly included PVR as part of the definition[11-15]. We explored the impact of excluding PVR on the pre-capillary PH. With updated classification, there were 169 patients who had mPAP > 20 and PAWP ≤ 15 mmHg. Of these patients, 87 had no to minimal lung disease (defined as <20% total lung involvement due to ILD (Figure 2 a). In the updated classification, there were 47 patients who had mPAP between 21-24

mmHg and PAWP ≤ 15 mmHg. Of these patients, 28 had no to minimal lung disease (Figure 2 a) and only 1 patient (3%) had PVR ≥ 3 WU.

Validation in the DETECT Study Cohort

We had previously shown that 36 of 244 (14.75%) patients in the DETECT cohort had mPAP between 21-24 mmHg (patients with PAWP≥15 mmHg, significant ILD, enlarged left atrium and systemic hypertension were excluded[11]). Based on new classification, 4 of 36 (11%) of the patients met the new PAH criteria. Of the remaining 32 patients, 19 (53%) had PVR between ≥2 and <3 WU and 13 (36%) had PVR <2 WU (Figure 2 b).

Discussion

The updated hemodynamic definition of PH has been proposed by the 6th WSPH based on growing evidence in the literature, especially in high-risk groups, such as SSc[11-15]. Our data suggests that the updated definition did not have a significant impact on reclassification, with only 7 patients (5%) being classified as PH in the UM cohort. Of these patients, 4 belong to pre-capillary PH group, with one classified as Group 1 and three as Group 3 PH. In those with mPAP of 21-24 mmHg, no left heat disease or clinically meaningful lung disease, 1 of 28 (4%) in the UM cohort and 4 of 36 (11%) in the DETECT study cohort were reclassified as PAH.

Previous data from different scleroderma cohorts suggest that patients with SSc and borderline mPAP (mPAP 21-24 mmHg) have a decreased exercise capacity and an increased risk of developing resting PH. Using the DETECT study cohort, Visovatti et al[11] showed that borderline mPAP is an intermediate stage and may be a continuum between normal mPAP and PAH. Of 244 patients, 36 (15%) had borderline mPAP. Univariable logistic regression showed the mean tricuspid regurgitation velocity in patients with borderline PAP (mean 2.7 m/sec) to be intermediate between normal mPAP (mean 2.3 m/sec) and PAH mean 3.0 m/sec). When comparing borderline PAP vs. PAH, the statistically significant differences included less likelihood to be in functional class III/IV,

lower percentage with telangiectasia, lower FVC% /DLCO% ratio, lower percentage with anti-centromere antibody, and lower right atrial pressure, all $p < 0.05$. Coglan et al[14] published follow up on cohort from 2 centers in Europe using the DETECT inclusion criteria and showed that a greater proportion of patients converted to PH at median follow up at 3 years in the borderline mPAP (33.3%) compared to 22% in the normal mPAP group. There was no difference in the survival between the 2 groups. Valerio et al[15] reviewed data at a large scleroderma center in the UK and showed a hazard ratio of 3.7 for the diagnosis of PH on subsequent RHC in the group with borderline mean PAP compared with the normal mean PAP (mean PAP $\leq$ 20 mm Hg) was 3.7 ($p<0.001$). Within the borderline mPAP group, 18.5% developed PAH within 3 years, and 27.1% developed PAH within 5 years. There was no difference in survival in those with normal mPAP vs. borderline mPAP. Bae et al[13] reviewed the PHAROS registry and after excluding patients with significant ILD, compared SSc patients with normal mPAP and borderline mPAP and showed the latter group to have significantly higher right ventricular systolic pressures on echocardiogram, higher PVR, and a higher transpulmonary gradient. Follow-up data involving 24 patients who underwent repeat RHC, based on signs and symptoms, at mean follow up of 13.7 months found that 32% of patients with normal mPAP and 55% of patients with borderline mPAP developed resting PH. Finally, Kovacs et al[12] showed that patients with SSc who have borderline mPAP had lower exercise capacity, as measured by six-minute walk test and peak $V(O_2)$ on cardiopulmonary exercise. All of these studies highlight the importance of borderline mPAP in SSc population.

Review of the above published data suggest that definition of PAH was based on mPAP and PAWP without inclusion of PVR cut off. When applied in UM cohort, 28 patients had mPAP $\geq$21-24 mmHg, PAWP $\leq$15 mm Hg, and no significant lung disease. Addition of PVR had a large effect, with only 1 patient (of 28 or 3%) being reclassified as PAH and 11% in the DETECT study cohort (4 of 36) met the new definition. Indeed, the addition of PVR is important as PH in SSc is often multifactorial and PH can be contributed by pulmonary artery

vasculopathy, ILD, left heart disease or combination of these[23, 24]. In addition, combined pulmonary fibrosis and emphysema and pulmonary veno-occlusive disease also play a role in the differential diagnosis of these complex patients[24]. In UM cohort, out of the 7 patients who were reclassified from non-PH to PH, 3 had combined pulmonary fibrosis and emphysema.

One of the hypotheses of the 6th WSPH Task Force was that a lower mPAP threshold will capture patients with early and milder pulmonary vascular disease in hopes of initiating earlier treatment, especially in patients who are at risk of progressive pulmonary vascular disease. Our data suggests that a large proportion of UM and DETECT study cohorts had milder hemodynamic parameters (mPAP of 21-24 mmHg and PVR < 3 WU) at the time of the RHC. The PVR ≥3 WU was consensus based during the 6th WSPH meeting and we believe that it may be too conservative. A systematic review by Kovacs et al [10] supports this assertion—they showed that the mean (SD) resting PVR in healthy subjects is 0.86 (0.35) WU and 1.1 (0.19) WU in 24-50 years and 51-69 years, respectively. In the UM cohort, lowering the PVR to ≥2 WU, which is > 1 SD for healthy adults (based on Kovacs et al), we would have captured 8 of 28 (29%) additional patients and 23 (64%) in the DETECT study cohort. It is currently unknown if mPAP > 20 mmHg and PVR ≥2 WU represents a phenotype with risk of progressive pulmonary vascular disease or reflects an incidental hemodynamic finding where these patients would have done well without developing progressive PH but were diagnosed due to uniform screening algorithm, especially due to high prevalence of pulmonary vascular disease in scleroderma autopsy studies[25, 26]. Long term follow-up is necessary to answer this important question.

Our study has many strengths. First, our patients in the UM cohort had a thorough evaluation and prospective data collection in a well characterized cohort of patients with scleroderma-spectrum and we validated our data in another international screening cohort. Second, all RHC were performed at UM by an experienced cardiology team. Third, in the UM cohort, we had the HRCTs reviewed and scored by thoracic radiologists and classified

PAH vs. WHO Group 3 based on these findings. Finally, all patients underwent standardized screening for PH, including the DETECT and other proposed algorithms after 2012[18].

Although this study has many strengths, it is not without limitations. Both UM cohort and the DETECT study cohort are screening cohorts and the data may not be generalizable if this is not instituted uniformly in other cohorts. In addition, the UM cohort is a retrospective analysis of a prospective cohort and is subject to entry selection. Because UM cohort is a detection cohort, RHC was not performed in a systematic manner, except after a positive screening test or due to signs or symptoms attributable to pulmonary vascular disease. However, the analysis of the DETECT study cohort showed similar findings and provides confidence in our analysis.

Conclusion

In conclusion, the updated hemodynamic definition of PH does not appear to have a significant impact on the diagnosis of PAH in 2 screening cohorts of scleroderma-spectrum disorders. Further analyses are needed to see the impact of the updated definition on long term outcomes, including survival.

Funding

Dinesh Khanna, MD, MSc is supported by NIH/NIAMS K24 AR063120.

Dr Khanna Consultancies: Acceleron, Actelion, Astra Zeneca, Bayer, BMS, Boehringer-Ingelheim, Corbus, Cytori, Galapagos, Genentech/Roche, GSK, Sanofi-Aventis/Genzyme, UCB Pharma. Stock ownership or options: Eicos Sciences, Inc/ CiviBioPharma, Inc. Employment: University of Michigan and CiviBioPharma, Inc.

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Table 1 – Hemodynamic Definitions of Pulmonary Hypertension (PH)

	Prior Definition	New Definition
Group I (PAH)	mPAP ≥ 25 mmHg and PVR > 3 WU	mPAP > 20 mmHg and PVR ≥3 WU
	PAWP ≤ 15 mmHg	PAWP ≤ 15 mmHg
	No/Mild ILD or FVC ≥ 70%	No/Mild ILD or FVC ≥ 70%
Group II (LH Disease)	mPAP ≥ 25 mmHg	mPAP ≥ 20 mmHg
	PAWP > 15 mmHg	PAWP > 15 mmHg
	PVR < 3 WU	PVR < 3 WU
Group III (ILD)	mPAP ≥ 25 mmHg and PVR > 3 WU	mPAP > 20 mmHg and PVR ≥ 3 WU
	PAWP ≤ 15 mmHg	PAWP ≤ 15 mmHg
	Moderate/Severe ILD or FVC <70%	Moderate/Severe ILD or FVC <70%
Group IV (Combined pre- & post-capillary)	mPAP ≥ 25 mmHg	mPAP > 20mmHg
	PAWP > 15 mmHg	PAWP > 15 mmHg
	PVR > 3 WU	PVR ≥ 3 WU

mPAP: mean Pulmonary Artery Pressure; PVR: Peripheral Vascular Resistance; WU: Wood Units; PAWP: Pulmonary Arterial Wedge Pressure; ILD: Interstitial Lung Disease; FVC: Forced Vital Capacity; Group I: PAH; Group II: due to Left Heart Disease; Group III: PH due to Chronic Lung Disease. *HRCT Showing > 20% total lung involvement due to ILD; or if the total lung involvement due to ILD was 10-20% but the patient had concomitant moderate-to-severe emphysema.

Table 2: Baseline Characteristics of the Cohort

	Total (N=268)	No PH (N=124)	PH (N=144)	P value
Age (years), mean (SD), N=268	60.6 (11.7)	59.6 (12.1)	61.5 (11.3)	0.323
Female Sex, N (%), N=268	228 (85.07%)	106 (85.48%)	122 (84.72%)	0.862
Race, N (%), N=268				
Caucasian	212 (79.10%)	98 (79.03%)	114 (79.17%)	0.112
African American	38 (14.18%)	14 (11.29%)	24 (16.67%)	
Other	18 (6.72%)	12 (9.68%)	6 (4.17%)	
Type of Systemic Sclerosis, N (%), N=268				
Limited Cutaneous SSc	154 (57.46%)	77 (62.10%)	77 (53.47%)	0.174
Diffuse Cutaneous SSc	94 (35.07%)	42 (33.87%)	52 (36.11%)	
Sine Scleroderma	9 (3.36%)	3 (2.42%)	6 (4.17%)	
MCTD	11 (4.10%)	2 (1.61%)	9 (6.25%)	
Disease duration* (years), mean (SD), N=268	9.8 (9.1)	10.3 (8.8)	9.4 (9.5)	0.152
Autoantibodies, N (%)				
Anti-Nuclear Antibody (ANA), N=236	213 (90.25%)	99 (89.19%)	114 (91.20%)	0.603
Anti-centromere, N=181	44 (24.31%)	18 (21.43%)	26 (26.80%)	0.401
Anti-RNA polymerase 3, N=84	17 (20.24%)	8 (19.51%)	9 (20.93%)	0.872
Anti-Scl-70, N=225	32 (14.22%)	21 (20.79%)	11 (8.87%)	0.011
Anti-U1 ribonucleoprotein (RNP), N=218	32 (14.68%)	12 (11.65%)	20 (17.39%)	0.232
HRCT showing ILD, N (%), N=226	164 (72.57%)	80 (77.67%)	84 (68.29%)	0.116
PFT				
FVC %, Mean (SD), N=268	76.4 (20.3)	80.2 (18.7)	73.1 (21.0)	0.004
DLCO %, Mean (SD), N=253	50.0 (18.5)	57.1 (17.2)	43.8 (17.4)	<.0001
RHC, N=268				
mPAP, Mean (SD)	30.6 (11.9)	22.0 (5.0)	37.9 (11.2)	<.0001
PAWP, Mean (SD)	12.6 (4.7)	11.1 (3.0)	13.9 (5.4)	<.0001
TPG, Mean (SD)	18.0 (11.5)	10.9 (4.0)	24.0 (12.3)	<.0001
CO (thermodilution), Mean (SD)	5.5 (1.6)	5.9 (1.5)	5.0 (1.5)	<.0001
PVR, Mean (SD)	3.9 (3.7)	1.9 (0.6)	5.6 (4.3)	<.0001

*****Disease duration calculated from date of first non-Raynaud's symptom to date of RHC; SSc: Systemic Sclerosis; MCTD: Mixed Connective Tissue Disease; PH: Pulmonary Hypertension; PFT: Pulmonary Function Test; FVC: Forced Vital Capacity; DLCO: Carbon Monoxide Diffusing Capacity; HRCT: High Resolution Computed Tomography; ILD: Interstitial Lung Disease; RHC: Right Heart Catheterization; mPAP: Mean Pulmonary Artery Pressure (mmHg); PAWP: Pulmonary Arterial Wedge Pressure (mmHg); TPG: Trans-Pulmonary Gradient (mmHg); CO: Cardiac Output (L/min); PVR: Peripheral

Vascular Resistance (TD)

Table 3: Individual data on 7 patients who have been reclassified as PH based on the updated definition by the 6th WSPH

	Age	Updated Classification	Gender	Antibody	Type of SSc	Disease duration (years)*	FVC %	DLCO%	ILD and severity	mPAP	PAWP	CO (TD)	PVR (TD)	Management	Current status
Patient #1	68	PAH	F	Nucleolar pattern on ANA	Limited SSc	16	105	56	Emphysema, No ILD	22	8	4.1	3.41	Sildenafil 20 mg three times a day	Alive
Patient #2	59	Group 2 PH	F	Anti-Centromere+	Limited SSc	18	95	80	HRCT not performed	21	16	5.7	0.87	Diuretics	Alive
Patient #3	51	Group 2 PH	M	Nucleolar pattern on ANA	Limited SSc	1	97	85	No ILD on HRCT	21	16	5.6	0.89	Diuretics	Alive
Patient #4	61	Group 2 PH	F	Anti-SCL 70+	Diffuse SSc	7	73	33	NSIP pattern, <20% ILD	23	17	3.95	1.52	N/A	Died due to recurrent aspiration pneumonia and GI dysmotility
Patient #5	70	Group 3 PH	M	Negative scleroderma Ab	Diffuse SSc	5	63	33	CPFE; NSIP pattern, > 30% ILD & mild emphysema	22	10	3.55	3.38	N/A	Deceased due to failure to thrive (severe pseudo-obstruction)
Patient #6	81	Group 3 PH	F	Anti-Centromere+	Sine SSc	1	108	52	CPFE; UIP pattern, 20-30% ILD	23	6	4.37	3.89	No PAH or scleroderma specific therapy	Alive
Patient #7	61	Group 3 PH	F	Anti-SCL 70+	Diffuse SSc	2	43	19	CPFE; UIP pattern, >30% ILD & severe emphys	23	6	3.43	4.96	Mycophenolate mofetil	Lost to follow up 6 years ago

									ema						

*from onset of symptoms to RHC

PH: Pulmonary Hypertension; PAH: Pulmonary Arterial Hypertension; SSc: Systemic Sclerosis; FVC: Forced Vital Capacity; DLCO: Carbon Monoxide Diffusing Capacity; ILD: Interstitial Lung Disease; HRCT: High-Resolution Computed Tomography; NSIP: Non-Specific Interstitial Pneumonia; UIP: Usual Interstitial Pneumonia; CPFE: Combined pulmonary fibrosis and emphysema; mPAP: Mean Pulmonary Artery Pressure (mmHg); PAWP: Pulmonary Arterial Wedge Pressure (mmHg); CO: Cardiac Output; TD: Thermodilution; PVR: Pulmonary Vascular Resistance.

Figure 1a: Classification according to Prior Hemodynamic Definition of PH in the UM Cohort

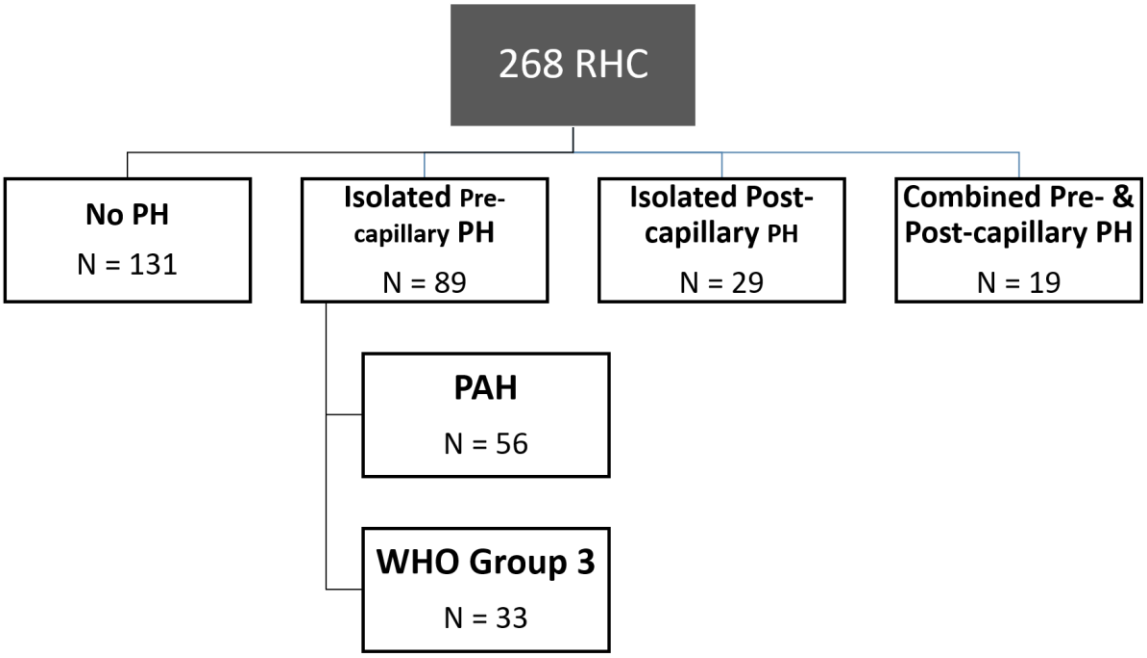

Figure 1b: Classification according to New Hemodynamic Definition of PH in the UM Cohort

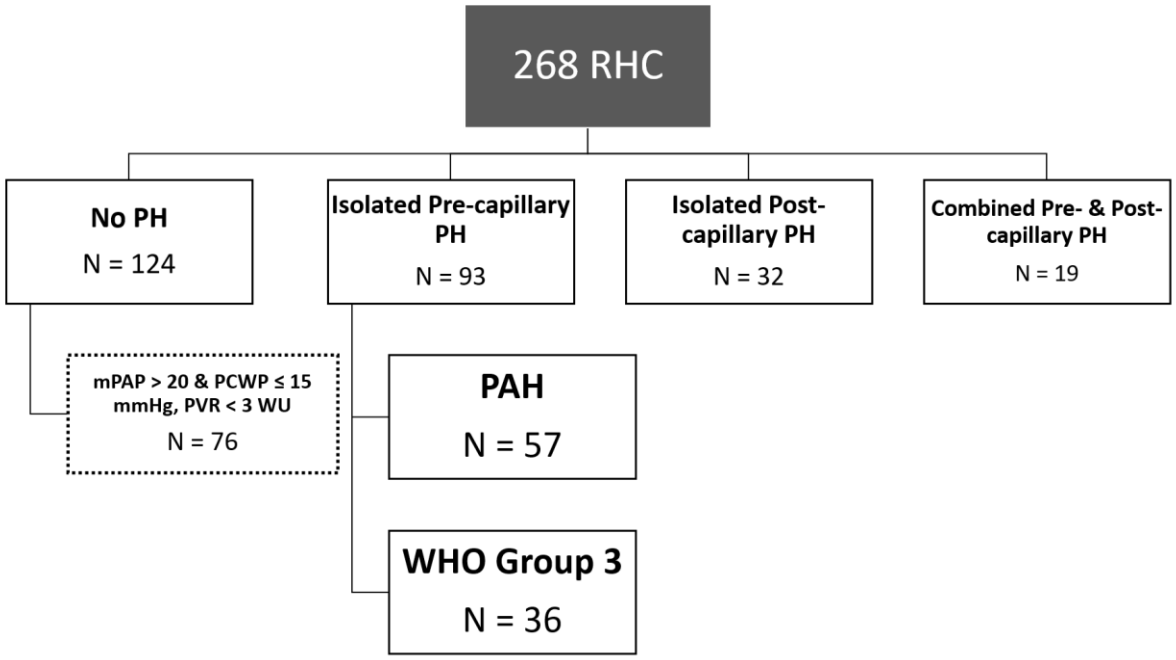

Figure 2a: Distribution of borderline mPAP (>20 mmHg) in the UM cohort, stratified by PVR

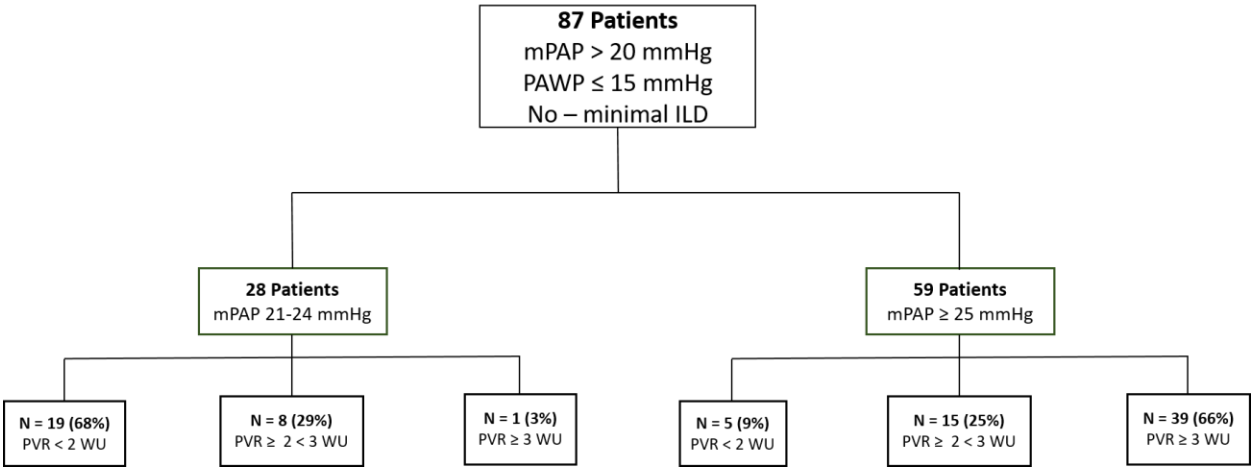

Figure 2 b Distribution of borderline mPAP (21-24 mmHg) in the DETECT study cohort, stratified by PVR