

Hemodynamic Reclassification Under the 2022 Definition in Connective Tissue Disease-Associated Pulmonary Arterial Hypertension: A Single-Center Cohort Study

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Abstract

Introduction: The 2022 pulmonary hypertension guidelines lowered the hemodynamic thresholds for pulmonary hypertension and pulmonary arterial hypertension, potentially expanding the spectrum of connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH). The profile of patients identified only by the updated definition remains incompletely characterized. We aimed to quantify the reclassification impact of the 2022 hemodynamic definition in a catheterization-based cohort of clinically adjudicated CTD-associated Group 1 PAH and to explore whether patients identified only by the updated definition represented an early, low-burden clinical-hemodynamic phenotype. **Methods:** We retrospectively analyzed 27 patients with CTD-associated Group 1 PAH. Within the clinically adjudicated CTD-PAH cohort, patients fulfilling the previous mPAP and PVR threshold set were classified as established CTD-PAH, whereas those fulfilling the 2022 threshold set but not the previous threshold set were classified as having a 2022-only early CTD-PAH phenotype. Clinical, pulmonary function, echocardiographic, and hemodynamic variables were compared. Exploratory high burden was defined as ≥ 4 positive components among PVR ≥ 5 WU, mPAP ≥ 35 mmHg, right atrial mean pressure ≥ 8 mmHg, cardiac index < 2.5 L/min/m², NT-proBNP/ProBNP ≥ 300 , and TAPSE < 18 mm. **Results:** Overall, 22 patients (81.5%) had established CTD-PAH, while 5 patients (18.5%) were classified as having a 2022-only early CTD-PAH phenotype. Compared with established CTD-PAH, the 2022-only group had lower mPAP, sPAP, dPAP, PVR, and TPG, with more preserved FVC. ILD was absent in this group. No patients with the 2022-only early CTD-PAH phenotype had a high-burden phenotype, compared with 45.5% of established CTD-PAH patients. **Conclusion:** In this CTD-associated Group 1 PAH cohort, the 2022 definition reclassified nearly one-fifth of patients as 2022-only early CTD-PAH. These patients demonstrated a milder hemodynamic profile, preserved pulmonary function, absence of ILD, and no high-burden phenotype, suggesting the potential clinical relevance of early hemodynamic recognition in CTD-PAH.

Keywords: Hypertension, Pulmonary; Connective Tissue Diseases; Hemodynamics; Pulmonary Arterial Hypertension; Cardiac Catheterization.

1. Introduction

Connective tissue diseases (CTD), particularly systemic sclerosis, are among the patient groups at high risk for developing pulmonary arterial hypertension (PAH). Since CTD-associated Group 1 PAH (CTD-PAH) is associated with right heart failure and mortality when diagnosed late, early diagnosis and accurate hemodynamic classification are of critical importance in clinical management^{1,2}.

The definition of pulmonary hypertension has been revised in recent years; the 2022 ESC/ERS guidelines established an mPAP threshold of >20 mmHg for PH, and the definition of precapillary PH has been updated to mPAP >20 mmHg, PAWP ≤15 mmHg, and PVR >2 WU³. This change may allow for the identification of patients—particularly in high-risk populations such as those with connective tissue diseases (CTD)—who were not classified as having PAH under the previous definition but may fall at the early end of the pulmonary vascular disease spectrum^{4–6}.

However, it remains unclear how the 2022 hemodynamic definition affects patient classification and clinical-hemodynamic phenotypes in real-world cohorts of CTD-associated Group 1 PAH. Therefore, the primary objective of this study was to quantify the reclassification impact of the 2022 hemodynamic definition in patients with clinically adjudicated CTD-associated Group 1 PAH evaluated by right heart catheterization. We hypothesized that the updated mPAP and PVR thresholds would identify a subset of patients who fulfilled the 2022 classification but not the previous PAH definition. As an exploratory secondary hypothesis, we further assessed whether this 2022-only group represented an early, lower-burden phenotype characterized by less severe pulmonary vascular and right-heart involvement compared with established CTD-PAH.

2. Materials and Methods

2.1. Study design and study population

This study was designed as a single-center, retrospective, observational cohort study. Patients who underwent right heart catheterization between June 2018 and July 2026 were screened for eligibility. The study included adult patients evaluated for suspected CTD-PAH and who underwent right heart catheterization at a tertiary-care rheumatology and cardiology/pulmonary hypertension center. CTD diagnoses were determined based on patient charts, electronic records, and evaluation by a rheumatologist. Systemic sclerosis was classified according to the 2013 ACR/EULAR classification criteria; rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria; and Sjögren's syndrome according to the 2016 ACR/EULAR classification criteria. For undifferentiated connective tissue disease, the diagnosis was based on rheumatologist assessment, compatible clinical and serological features suggestive of systemic autoimmune disease, and the absence of sufficient criteria for a defined CTD^{7–9}. Diagnoses of systemic sclerosis, rheumatoid arthritis, Sjögren's syndrome, and undifferentiated connective tissue disease were recorded separately. The presence of systemic sclerosis was also evaluated as a binary variable in the analyses.

2.2. Inclusion and exclusion criteria

Patients aged 18 years and older with a confirmed diagnosis of CTD, who were classified as having CTD-PAH based on clinical and hemodynamic evaluation, and for whom right heart catheterization data were available, were included in the study. For hemodynamic evaluation, the availability of data on mean pulmonary artery pressure, systolic and diastolic pulmonary artery pressures, pulmonary artery wedge pressure, left ventricular end-diastolic pressure, pulmonary vascular resistance, cardiac output, and/or cardiac index was considered necessary.

Patients whose CTD diagnosis could not be confirmed, whose right heart catheterization data were insufficient for classification, or whose PH was thought to be primarily due to chronic thromboembolic disease, congenital heart disease, significant left heart disease, or another cause unrelated to CTD were excluded from the study. The final analysis population consisted of patients clinically diagnosed with CTD-PAH.

2.3. Data collection

Data were retrospectively obtained from patient charts, electronic hospital records, right heart catheterization reports, transthoracic echocardiography reports, pulmonary function test records, high-resolution computed tomography (HRCT) of the thorax reports, and laboratory results. For each patient, the index evaluation was defined as the right heart catheterization included in the study.

Demographic data included age, sex, height, weight, body mass index, and body surface area. Clinical data included the diagnosis of connective tissue disease, the presence of systemic sclerosis, the subtype of systemic sclerosis, the presence of interstitial lung disease, and the WHO functional class. From the laboratory data, hemoglobin, hematocrit, and NT-proBNP or ProBNP levels were recorded. If multiple results were available, the value closest to the date of right heart catheterization was used.

2.4. Echocardiography and pulmonary function tests

For the echocardiographic evaluation, the transthoracic echocardiography report that most closely resembled right heart catheterization findings was used as the basis. Left ventricular ejection fraction, maximum tricuspid regurgitation velocity, estimated systolic pulmonary artery pressure, TAPSE, right atrial dilation, right ventricular dilation, and the presence of pericardial effusion were recorded.

From the pulmonary function tests, the percentage of FVC and the percentage of DLCO were obtained. The FVC/DLCO ratio was calculated by dividing the percentage of FVC by the percentage of DLCO. The presence of interstitial lung disease was classified as “present” or “absent” based on HRCT reports and clinical records. In this study, the prevalence of ILD or the fibrotic burden was not quantitatively scored.

2.5. Right heart catheterization and hemodynamic definitions

Right heart catheterization data were obtained from the original procedure reports. Hemodynamic values were abstracted as reported in the original catheterization records. When available, the method used for cardiac output measurement, including thermodilution or the Fick method, was reviewed; however, because of the retrospective design, methodological details regarding cardiac output assessment and oximetric sampling were not uniformly documented across all patients and throughout the study period. Therefore, cardiac output, cardiac index, and PVR values were analyzed according to the values reported in the catheterization reports. Systolic, diastolic, and mean pulmonary artery pressures; right atrial pressure; pulmonary artery wedge pressure; left ventricular end-diastolic pressure; cardiac output; cardiac index; pulmonary vascular resistance; and oxygen saturation levels were recorded.

Pulmonary hypertension was defined as mPAP >20 mmHg according to the 2022 ESC/ERS criteria³. For terminology, the overall study population is referred to as the clinically adjudicated CTD-associated Group 1 PAH cohort at first mention and as the CTD-PAH cohort thereafter. Patients who fulfilled the previous mPAP and PVR threshold set were termed established CTD-PAH, whereas patients who fulfilled the 2022 mPAP and PVR threshold set but not the previous threshold set were termed the 2022-only early CTD-PAH phenotype. The term precapillary PH was used only when referring to guideline-based hemodynamic definitions and was not used as a subgroup label in the analyses. Within this clinically adjudicated CTD-PAH cohort, the 2022 hemodynamic threshold set was defined as mPAP >20 mmHg and PVR >2 WU³, whereas the previous threshold set

was defined as mPAP ≥ 25 mmHg and PVR ≥ 3 WU⁴. The transpulmonary gradient was calculated as the difference between mPAP and PAWP; the diastolic pulmonary gradient was calculated as the difference between diastolic pulmonary artery pressure and PAWP.

2.6. Subgroup and phenotype analyses

Three main subgroup analyses were performed in the final CTD-PAH cohort. First, patients with established CTD-PAH were compared with those with 2022-only early-stage CTD-PAH. Second, patients with systemic sclerosis-associated PAH were compared with those with non-systemic sclerosis-associated CTD-PAH. Third, patients were compared based on the presence of interstitial lung disease (ILD), distinguishing between ILD-positive and ILD-negative patients.

An exploratory hemodynamic/right heart load phenotype was created to assess right heart load and hemodynamic severity comprehensively. This phenotype was used for in-cohort phenotyping rather than as a formally validated risk score. The components were defined as: PVR ≥ 5 WU, mPAP ≥ 35 mmHg, mean right atrial pressure ≥ 8 mmHg, cardiac index < 2.5 L/min/m², NT-proBNP/ProBNP ≥ 300 , and TAPSE < 18 mm. The selection of these variables was based on hemodynamic burden, right heart function, and biomarker-based approaches used in the PAH risk assessment literature; however, the resulting score was not evaluated as a prognostic model intended to replace COMPERA or REVEAL^{10,11}.

Patients were classified into low-burden, intermediate-burden, and high-burden phenotypes based on the number of positive components. Low burden was defined as 0–1 positive component, intermediate burden as 2–3 positive components, and high burden as 4–6 positive components. In the main comparison, patients in the high-burden phenotype were compared with the non-high-burden group, which consisted of the combined low- and intermediate-burden groups.

The primary analysis was designed as a descriptive hemodynamic reclassification analysis comparing the previous and 2022 PAH threshold sets. The secondary exploratory analysis evaluated whether patients classified as 2022-only early CTD-PAH showed a lower-burden clinical-hemodynamic profile compared with established CTD-PAH.

2.7. Data validation and management of missing data

Critical variables that could affect hemodynamic classification were cross-checked against the original right heart catheterization reports before analysis. In particular, mPAP, PAWP, LVEDP, PVR, cardiac output, and cardiac index values were reviewed. The primary analysis variables were complete in the final dataset. Missing values were not imputed; the number of available patients for each variable was also recorded.

2.8. Statistical analysis

Analyses were performed using IBM SPSS Statistics version 31.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as the median [interquartile range, IQR], taking into account sample size and distribution characteristics. Categorical variables were reported as counts or percentages. For comparisons between two groups, the Mann–Whitney U test was used for continuous variables and Fisher's exact test for categorical variables. Primary comparisons were made between the established CTD-PAH and 2022-only early CTD-PAH phenotype, the SSc-PAH and non-SSc CTD-PAH groups, ILD-positive and ILD-negative patients, and high-burden and non-high-burden phenotypes. In the ILD subgroup analysis, false discovery rate correction was applied using the Benjamini–Hochberg method to account for the effects of multiple comparisons, and q-values were reported. All tests were evaluated as two-sided, and a p-value of < 0.05 was considered statistically significant. Due to the small sample size, subgroup analyses

and hemodynamic/right heart load phenotype analyses were considered exploratory; therefore, the results were interpreted as hypothesis-generating.

3. Results

A total of 27 patients with CTD-PAH who had undergone right heart catheterization were included in the study. All patients met the 2022 definition of pulmonary hypertension and the 2022 hemodynamic threshold set used in the study. According to the previous threshold set, 22 patients were classified as having established CTD-PAH. In comparison, 5 patients fulfilled the 2022 threshold set but not the previous threshold set and were classified as having the 2022-only early CTD-PAH phenotype. In the cohort, 17 patients had SSc-PAH, and 10 patients had non-SSc CTD-PAH. ILD was present in 10 patients, and 10 patients were classified as having a high-burden hemodynamic/right heart phenotype. The overall cohort classification is presented in Supplementary Table 1.

The median age in the total cohort was 65.0 [50.5–70.0] years, and 23 of the patients were female (85.2%). The most common connective tissue disease was systemic sclerosis (17/27, 63.0%); this was followed by Sjögren's syndrome (5/27, 18.5%), rheumatoid arthritis (4/27, 14.8%), and undifferentiated connective tissue disease (1/27, 3.7%). The prevalence of ILD was 37.0%. The median WHO functional class was 2.0 [2.0–3.0], NT-proBNP/ProBNP was 208.3 [130.3–776.1], FVC was 77.0% [67.5–88.5], DLCO was 70.0% [56.5–74.5], and the FVC/DLCO ratio was 1.19 [0.99–1.36]. In the echocardiographic evaluation, the median TRVmax was 3.50 [3.30–3.70] m/s, the estimated sPAP/PASP was 50.0 [43.5–55.0] mmHg, and TAPSE was 20.0 [16.0–25.5] mm. In right heart catheterization, the median mPAP was 27.0 [25.0–40.0] mmHg, PAWP was 11.0 [8.5–12.0] mmHg, PVR was 3.90 [3.12–6.62] WU, cardiac index was 2.32 [2.00–2.75] L/min/m², TPG was 17.0 [15.0–28.5] mmHg, and DPG was 8.0 [6.0–12.0] mmHg (Table 1).

Table 1. Baseline characteristics of the total CTD-PAH cohort

Variable	Total CTD-associated Group 1 PAH cohort (n=27)
Demographics	
Age, years	65.0 [50.5–70.0]
Female sex	23/27 (85.2%)
BMI, kg/m ²	30.1 [25.7–33.0]
BSA, m ²	1.8 [1.6–1.8]
Clinical characteristics	
CTD diagnosis	SSc: 17 (63.0%); RA: 4 (14.8%); Sjögren: 5 (18.5%); UCTD: 1 (3.7%)
Systemic sclerosis	17/27 (63.0%)
WHO functional class	2.0 [2.0–3.0]
Hemoglobin, g/dL	12.3 [11.2–13.4]
NT-proBNP / ProBNP	208.3 [130.3–776.1]
Pulmonary involvement	
ILD	10/27 (37.0%)
FVC, % predicted	77.0 [67.5–88.5]
DLCO, % predicted	70.0 [56.5–74.5]
FVC/DLCO ratio	1.19 [0.99–1.36]
Echocardiography	
TRVmax, m/s	3.50 [3.30–3.70]

Variable	Total CTD-associated Group 1 PAH cohort (n=27)
Echo-estimated sPAP/PASP, mmHg	50.0 [43.5–55.0]
TAPSE, mm	20.0 [16.0–25.5]
LVEF, %	60.0 [60.0–60.0]
RA dilatation	15/27 (55.6%)
RV dilatation	9/27 (33.3%)
Pericardial effusion	2/27 (7.4%)
Right heart catheterization	
mPAP, mmHg	27.0 [25.0–40.0]
sPAP, mmHg	45.0 [40.0–71.0]
dPAP, mmHg	18.0 [16.0–22.5]
PAWP, mmHg	11.0 [8.5–12.0]
LVEDP, mmHg	12.0 [8.5–12.0]
PVR, WU	3.90 [3.12–6.62]
Cardiac output, L/min	4.10 [3.63–4.80]
Cardiac index, L/min/m ²	2.32 [2.00–2.75]
RA mean pressure, mmHg	8.0 [7.0–10.0]
PA oxygen saturation, %	66.0 [58.4–69.0]
Aortic oxygen saturation, %	95.2 [92.0–96.5]
TPG, mmHg	17.0 [15.0–28.5]
DPG, mmHg	8.0 [6.0–12.0]

Abbreviations: BMI, body mass index; BSA, body surface area; CI, cardiac index; CTD, connective tissue disease; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; DLCO, diffusing capacity of the lung for carbon monoxide; dPAP, diastolic pulmonary artery pressure; DPG, diastolic pulmonary gradient; FVC, forced vital capacity; ILD, interstitial lung disease; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; PAWP, pulmonary arterial wedge pressure; ProBNP, pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; RA, rheumatoid arthritis in CTD diagnosis and right atrial in echocardiographic/hemodynamic variables; RV, right ventricular; sPAP, systolic pulmonary artery pressure; SSc, systemic sclerosis; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary gradient; TRVmax, maximum tricuspid regurgitation velocity; UCTD, undifferentiated connective tissue disease; WHO, World Health Organization; WU, Wood units

The established CTD-PAH and 2022-only early CTD-PAH phenotype were generally similar in terms of demographic and baseline clinical characteristics. Of the 5 patients in the 2022-only early CTD-PAH phenotype, 4 had a diagnosis of systemic sclerosis, and 1 had undifferentiated connective tissue disease; no ILD was detected in this group (Supplementary Table 4). Compared with the established CTD-PAH group, FVC was higher in the 2022-only early CTD-PAH phenotype (89.0 [87.0–93.0] vs. 72.5 [66.2–86.8], $p=0.029$), while DLCO was numerically higher but did not reach statistical significance (73.0 [72.0–103.0] vs 69.0 [53.2–72.5], $p=0.061$). In terms of hemodynamics, the 2022-only early CTD-PAH phenotype had lower mPAP (23.0 [22.0–24.0] vs 28.0 [26.0–44.8], $p=0.001$), sPAP (40.0 [36.0–40.0] vs 47.0 [40.5–74.2], $p=0.031$), dPAP (14.0 [12.0–16.0] vs 18.0 [16.5–26.0], $p=0.011$), PVR (3.00 [2.71–3.60] vs 4.54 [3.33–9.82], $p=0.029$), and TPG (13.0 [12.0–17.0] vs 18.0 [15.2–35.2], $p=0.039$) were significantly lower. No significant differences were observed in cardiac output, cardiac index, PA oxygen saturation, TAPSE, RA/RV dilation, or pericardial effusion (Table 2; Figure 1).

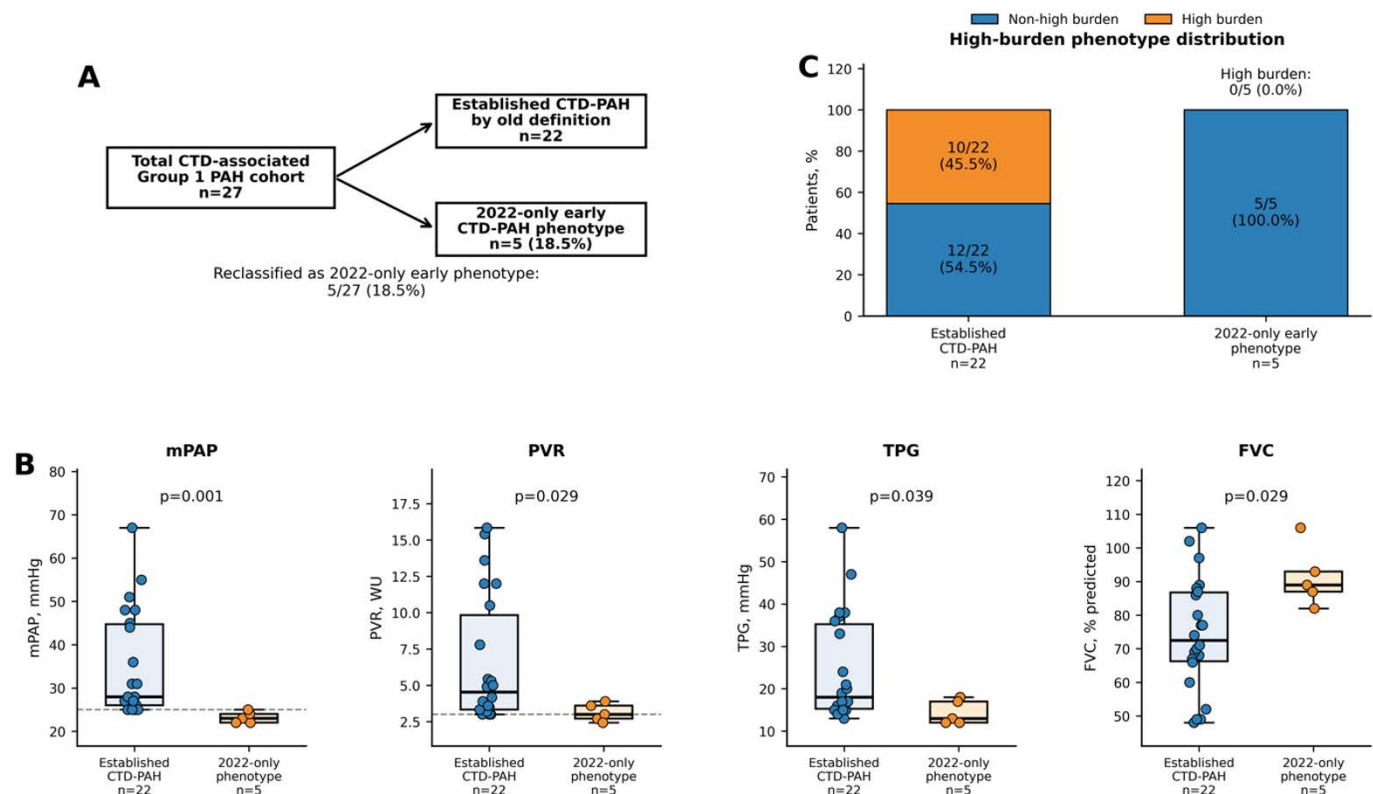


Figure 1. Hemodynamic reclassification identifies a low-burden early CTD-PAH phenotype under the 2022 definition. Panel A shows the reclassification of the clinically adjudicated CTD-associated Group 1 PAH cohort according to the previous and 2022 hemodynamic threshold sets. Patients fulfilling the previous threshold set are shown as established CTD-PAH, whereas those fulfilling the 2022 threshold set but not the previous threshold set are shown as having the 2022-only early CTD-PAH phenotype. Panel B compares mPAP, PVR, TPG, and FVC between established CTD-PAH and the 2022-only early CTD-PAH phenotype. Individual dots represent patients, and boxplots show median and interquartile range. Dashed reference lines indicate the previous mPAP threshold of 25 mmHg and previous PVR threshold of 3 WU. Panel C shows the distribution of high-burden and non-high-burden phenotypes across definition groups. High burden was defined as ≥ 4 positive components among PVR ≥ 5 WU, mPAP ≥ 35 mmHg, RA mean pressure ≥ 8 mmHg, cardiac index < 2.5 L/min/m², NT-proBNP/ProBNP ≥ 300 , and TAPSE < 18 mm.

Table 2. Comparison of established CTD-PAH and the 2022-only early CTD-PAH phenotype

Variable	Established CTD-PAH (n=22)	2022-only early CTD-PAH (n=5)	p value
Demographics and clinical characteristics			
Age, years	65.5 [54.5–70.0]	64.0 [47.0–69.0]	0.755
Female sex	19/22 (86.4%)	4/5 (80.0%)	1.000
BMI, kg/m ²	30.7 [25.3–33.7]	27.5 [27.2–29.7]	0.201
Systemic sclerosis	13/22 (59.1%)	4/5 (80.0%)	0.621
WHO functional class	2.0 [2.0–3.0]	2.0 [1.0–2.0]	0.165
Hemoglobin, g/dL	12.4 [11.3–13.6]	12.3 [11.2–12.6]	0.708
NT-proBNP / ProBNP	188.9 [125.0–868.1]	230.9 [142.5–367.1]	0.512
Pulmonary involvement			
ILD	10/22 (45.5%)	0/5 (0.0%)	0.124
FVC, % predicted	72.5 [66.2–86.8]	89.0 [87.0–93.0]	0.029
DLCO, % predicted	69.0 [53.2–72.5]	73.0 [72.0–103.0]	0.061
FVC/DLCO ratio	1.18 [1.02–1.38]	1.19 [0.90–1.21]	0.553

Variable	Established CTD-PAH (n=22)	2022-only early CTD-PAH (n=5)	p value
Echocardiography			
TRVmax, m/s	3.50 [3.32–3.68]	3.50 [3.30–3.70]	0.925
Echo-estimated sPAP/PASP, mmHg	49.5 [43.2–54.5]	52.0 [49.0–55.0]	0.511
TAPSE, mm	19.5 [16.2–25.8]	23.0 [14.0–25.0]	0.731
RA dilatation	13/22 (59.1%)	2/5 (40.0%)	0.628
RV dilatation	8/22 (36.4%)	1/5 (20.0%)	0.636
Pericardial effusion	2/22 (9.1%)	0/5 (0.0%)	1.000
Right heart catheterization			
mPAP, mmHg	28.0 [26.0–44.8]	23.0 [22.0–24.0]	0.001
sPAP, mmHg	47.0 [40.5–74.2]	40.0 [36.0–40.0]	0.031
dPAP, mmHg	18.0 [16.5–26.0]	14.0 [12.0–16.0]	0.011
PAWP, mmHg	12.0 [9.0–12.0]	10.0 [8.0–10.0]	0.195
PVR, WU	4.54 [3.33–9.82]	3.00 [2.71–3.60]	0.029
Cardiac output, L/min	4.05 [3.62–4.75]	4.60 [4.00–4.80]	0.532
Cardiac index, L/min/m ²	2.20 [1.94–2.70]	2.60 [2.50–2.80]	0.200
RA mean pressure, mmHg	9.0 [7.0–11.5]	7.0 [5.0–8.0]	0.068
PA oxygen saturation, %	65.5 [55.6–69.0]	69.0 [65.1–69.0]	0.223
TPG, mmHg	18.0 [15.2–35.2]	13.0 [12.0–17.0]	0.039
DPG, mmHg	7.5 [6.0–13.0]	8.0 [2.0–8.0]	0.209

Abbreviations: BMI, body mass index; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; DLCO, diffusing capacity of the lung for carbon monoxide; dPAP, diastolic pulmonary artery pressure; DPG, diastolic pulmonary gradient; FVC, forced vital capacity; ILD, interstitial lung disease; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; PAWP, pulmonary arterial wedge pressure; ProBNP, pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary gradient; TRVmax, maximum tricuspid regurgitation velocity; WHO, World Health Organization; WU, Wood units.

No significant differences were observed between the SSc-PAH and non-SSc CTD-PAH groups in terms of age, sex, BMI, WHO functional class, FVC, DLCO, FVC/DLCO ratio, echocardiographic parameters, and invasive hemodynamic variables (Supplementary Table 2). Although NT-proBNP/ProBNP levels were numerically higher and RA dilation was more common in the SSc-PAH group, these differences did not reach statistical significance. This analysis was considered exploratory due to the small subgroup sizes.

In ILD-positive patients, compared with ILD-negative patients, FVC (67.5 [61.5–75.0] vs 87.0 [74.0–89.0], $p=0.021$) and DLCO (57.0 [45.0–69.2] vs 72.0 [69.0–78.0], $p=0.015$) were lower in ILD-positive patients. However, these differences did not remain statistically significant after correction for multiple comparisons. The presence of ILD did not show a significant association with mPAP, PAWP, PVR, cardiac output, cardiac index, TPG, DPG, TRVmax, echocardiographic sPAP/PASP, TAPSE, RA/RV dilation, or pericardial effusion (Supplementary Table 3). All patients in the 2022-only early CTD-PAH phenotype were ILD-negative.

Based on the exploratory hemodynamic/right heart burden score, 10 patients (37.0%) were classified as having a low-burden phenotype, 7 patients (25.9%) as having an intermediate-burden phenotype, and 10 patients (37.0%) as having a high-burden phenotype (Supplementary Table 5). In the high-burden group, FVC was lower (70.5 [66.8–76.2] vs 87.0 [68.0–93.0], $p=0.025$), TAPSE was lower (17.5 [15.2–18.8] vs 25.0 [20.0–26.0], $p=0.025$),

and NT-proBNP/ProBNP was higher (793.6 [205.3–2692.4] vs 167.9 [108.4–367.1], $p=0.027$). The hemodynamically high-burden phenotype was characterized by higher mPAP, PVR, TPG, and DPG; and lower cardiac output, cardiac index, and PA oxygen saturation. Since some of these variables were correlated with score components, these findings were interpreted not as independent prognostic associations but as results supporting the internal consistency of the defined burden phenotype. Most importantly, while the high-burden phenotype was not detected in any of the 2022-only early CTD-PAH patients, the high-burden rate in the established CTD-PAH group was 45.5% (Table 3, Supplementary Table 6).

Table 3. Exploratory hemodynamic/right-heart burden phenotype

Variable	High burden (n=10)	Non-high burden (n=17)	p value
Clinical characteristics			
Age, years	68.5 [40.8–70.0]	64.0 [56.0–69.0]	0.880
Female sex	8/10 (80.0%)	15/17 (88.2%)	0.613
BMI, kg/m ²	26.0 [24.3–29.6]	32.0 [27.5–33.7]	0.047
WHO functional class	3.0 [2.0–3.0]	2.0 [2.0–2.0]	0.081
Systemic sclerosis	6/10 (60.0%)	11/17 (64.7%)	1.000
ILD	4/10 (40.0%)	6/17 (35.3%)	1.000
Established CTD-PAH	10/10 (100.0%)	12/17 (70.6%)	0.124
2022-only early CTD-PAH phenotype	0/10 (0.0%)	5/17 (29.4%)	0.124
Pulmonary and echocardiographic variables			
FVC, % predicted	70.5 [66.8–76.2]	87.0 [68.0–93.0]	0.025
DLCO, % predicted	68.5 [53.2–70.8]	70.0 [61.0–78.0]	0.327
FVC/DLCO ratio	1.09 [0.96–1.26]	1.21 [1.10–1.44]	0.280
TRVmax, m/s	3.45 [3.32–3.58]	3.50 [3.30–3.70]	0.631
Echo-estimated sPAP/PASP, mmHg	48.0 [43.2–53.8]	52.0 [46.0–55.0]	0.615
TAPSE, mm	17.5 [15.2–18.8]	25.0 [20.0–26.0]	0.025
RA dilatation	7/10 (70.0%)	8/17 (47.1%)	0.424
RV dilatation	5/10 (50.0%)	4/17 (23.5%)	0.219
Pericardial effusion	2/10 (20.0%)	0/17 (0.0%)	0.128
Right heart catheterization and biomarkers			
mPAP, mmHg	44.5 [30.0–50.2]	25.0 [25.0–28.0]	0.003
PVR, WU	11.25 [5.33–13.20]	3.33 [3.00–3.60]	<0.001
RA mean pressure, mmHg	8.5 [8.0–9.8]	8.0 [7.0–10.0]	0.543
Cardiac index, L/min/m ²	1.91 [1.85–2.14]	2.70 [2.40–2.84]	<0.001
Cardiac output, L/min	3.60 [3.13–3.85]	4.60 [4.10–5.30]	<0.001
NT-proBNP / ProBNP	793.6 [205.3–2692.4]	167.9 [108.4–367.1]	0.027
PA oxygen saturation, %	54.8 [50.8–62.4]	69.0 [65.1–69.5]	<0.001
TPG, mmHg	35.0 [21.8–38.0]	16.0 [14.0–17.0]	0.001
DPG, mmHg	13.0 [10.2–23.5]	6.0 [6.0–8.0]	0.005

Abbreviations: BMI, body mass index; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; DLCO, diffusing capacity of the lung for carbon monoxide; DPG, diastolic pulmonary gradient; FVC, forced vital capacity; ILD, interstitial lung disease; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; ProBNP, pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary gradient; TRVmax, maximum tricuspid regurgitation velocity; WHO, World Health Organization; WU, Wood units.

4. Discussion

In this right heart catheterization-based cohort of clinically adjudicated CTD-associated Group 1 PAH, we evaluated the impact of the 2022 hemodynamic threshold set on patient classification and early phenotype identification. The main finding was that 22 patients fulfilled the previous mPAP and PVR threshold set and were classified as established CTD-PAH, whereas 5 patients (18.5%) fulfilled the 2022 threshold set but not the previous threshold set and were classified as having a 2022-only early CTD-PAH phenotype. Compared with established CTD-PAH, this phenotype was characterized by lower mPAP, sPAP, dPAP, PVR, and TPG values, better-preserved FVC, absence of ILD, and no high-burden hemodynamic/right heart phenotype.

The shift from the previous PH threshold of mPAP ≥ 25 mmHg to mPAP > 20 mmHg was based on data showing that mild elevations in pulmonary arterial pressure and resistance may carry clinical significance. The 2022 ESC/ERS guidelines define precapillary PH as mPAP > 20 mmHg, PAWP ≤ 15 mmHg, and PVR > 2 WU³, consistent with the emphasis after the 6th World Symposium that mPAP, PAWP, and PVR should be interpreted together⁴. However, these updated thresholds should not be detached from clinical context or directly converted into treatment indications¹². Our findings support this balance. Patients in the 2022-only early CTD-PAH phenotype had a milder hemodynamic profile than established CTD-PAH, but their PVR values above 2 WU indicate that this group is not simply an artifact of lowering the mPAP threshold.

A key nuance is that the 2022-only early CTD-PAH phenotype was not composed exclusively of patients with mPAP between 21 and 24 mmHg. One patient had an mPAP of 25 mmHg but did not fulfill the previous PAH definition because PVR was < 3 WU. Thus, the effect of the 2022 definition is not limited to lowering the mPAP threshold; lowering the PVR threshold from 3 WU to > 2 WU also contributes to reclassification. Accordingly, the 2022-only early phenotype should be interpreted as a clinically meaningful but heterogeneous group that includes both mild mPAP elevation and pulmonary vascular resistance below the previous diagnostic threshold.

The systemic sclerosis literature supports the clinical relevance of this early hemodynamic range. Valerio et al. showed that borderline mPAP in systemic sclerosis is associated with later development of pulmonary hypertension, particularly when TPG is elevated⁵. In the DETECT post-hoc analysis, patients with mPAP 21–24 mmHg appeared to represent an intermediate stage between normal hemodynamics and overt PAH¹³. PHAROS data similarly showed that systemic sclerosis patients with borderline mPAP differ clinically from those with normal hemodynamics¹⁴, while Nagel et al. reported impaired right ventricular-pulmonary vascular reserve during exercise in systemic sclerosis patients with mild pulmonary artery pressure elevation¹⁵. Therefore, the absence of high-burden phenotype in our 2022-only group should not be interpreted as absence of risk, but rather as identification at an earlier resting hemodynamic stage.

Prospective data further support this interpretation. A subset of high-risk systemic sclerosis patients with baseline mPAP < 25 mmHg later developed pulmonary hypertension¹⁶. Puigrenier et al. showed that applying the 2022 definition to systemic sclerosis reclassified patients with mPAP 21–24 mmHg and PVR ≥ 2 WU as precapillary PH; many subsequently progressed to mPAP ≥ 25 mmHg, and PVR was associated with mortality⁶. Although our study did not assess progression or mortality, the similar hemodynamic range of the 2022-only group supports the view that the updated definition may reveal early pulmonary vascular disease in CTD, particularly in systemic sclerosis.

Nevertheless, early recognition should not be equated with automatic early treatment. The EDITA trial of ambrisentan in systemic sclerosis patients with mild mPAP

elevation or exercise-induced PH did not meet its primary endpoint, although some secondary hemodynamic signals improved¹⁷. Larger studies indicate that mild increases in mPAP or PVR are associated with mortality and clinical deterioration^{18–21}. However, these data do not justify immediate PAH-specific therapy for all patients with 2022-only early CTD-PAH. The more appropriate implication is close surveillance with serial echocardiography, pulmonary function tests, biomarker monitoring, and repeat right heart catheterization when clinically indicated.

In our cohort, ILD was absent in the 2022-only early CTD-PAH phenotype and FVC was better preserved than in established CTD-PAH. This suggests that the early phenotype was unlikely to be explained solely by parenchymal lung disease. PAH screening in systemic sclerosis aims to detect disease before symptomatic right heart burden develops. The DETECT algorithm was designed to reduce missed right heart catheterization-confirmed PAH²², and systematic screening has been associated with earlier diagnosis and better long-term outcomes than symptom-based detection^{2,23,24}. In this context, the 2022-only early group may represent the hemodynamic counterpart of screening: identification of pulmonary vascular disease before advanced right heart burden and functional reserve loss become evident.

CTD-PAH is heterogeneous, and systemic sclerosis-associated PAH is recognized as a distinct phenotype. REVEAL data showed that SSc-associated PAH is characterized by lower DLCO, higher BNP levels, and poorer survival compared with other CTD-PAH subgroups¹. Prognostic studies in SSc-PAH have linked mPAP, cardiac index, DLCO, 6-minute walk distance, and right ventricular workload variables with survival^{25–27}. In our cohort, SSc-PAH and non-SSc CTD-PAH did not differ significantly in invasive hemodynamics. This may reflect limited sample size, clinical selection of Group 1 PAH, and small numbers of non-SSc CTD subtypes. The numerically higher NT-proBNP/ProBNP and more frequent RA dilation in SSc-PAH are consistent with the concept of greater right heart vulnerability in systemic sclerosis, but should be interpreted as hypothesis-generating.

ILD is another major determinant of CTD-PH phenotype. PH associated with ILD in systemic sclerosis and scleroderma-spectrum disease has been linked to worse prognosis than isolated PAH^{28,29}, and Young et al. emphasized that RHC-confirmed PH with ILD in systemic sclerosis represents a clinically important phenotype³⁰. In our study, FVC and DLCO were lower in ILD-positive patients, but these differences did not remain significant after multiple comparison adjustment. More importantly, ILD-positive and ILD-negative patients did not differ significantly in mPAP, PAWP, PVR, cardiac output, cardiac index, TPG, or DPG, suggesting that ILD presence alone did not determine hemodynamic burden. However, ILD was assessed only as present or absent; future analyses incorporating HRCT extent, fibrotic pattern, quantitative fibrosis scores, and lung volumes would better distinguish CTD-PAH from CTD-ILD-PH.

In systemic sclerosis, pulmonary hypertension may reflect PAH, left heart disease, ILD-associated PH, combined pre- and post-capillary PH, or pulmonary veno-occlusive disease spectrum^{31,32}. Therefore, CTD hemodynamics must be interpreted beyond numerical thresholds. Our final analysis population consisted of patients clinically classified as CTD-associated Group 1 PAH, reflecting real-world multidisciplinary adjudication. PAWP, LVEDP, ILD, left heart disease, and parenchymal lung burden should be considered together. Thus, the reclassification analysis should be understood not as an automated diagnostic algorithm, but as a demonstration of the phenotypic impact of the 2022 definition within a clinically adjudicated CTD Group 1 PAH cohort.

The exploratory hemodynamic/right heart burden analysis complemented the main finding. Overall, 37.0% of patients were classified as high burden, 25.9% as intermediate burden, and 37.0% as low burden. High-burden patients had higher mPAP, PVR, TPG,

and DPG, lower cardiac output, cardiac index, and PA oxygen saturation, as well as lower TAPSE and higher NT-proBNP/ProBNP. Because several variables were score components, these differences should be interpreted as internal consistency rather than independent prognostic associations. Importantly, no 2022-only early CTD-PAH patient had a high-burden phenotype, whereas 45.5% of established CTD-PAH patients did. This supports the interpretation that the 2022-only group represents an earlier stage in terms of global hemodynamic and right heart burden.

This exploratory burden phenotype was not intended to replace validated risk tools such as COMPERA or REVEAL. COMPERA 2.0, REVEAL 2.0, and REVEAL Lite 2 demonstrate the prognostic relevance of functional class, exercise capacity, BNP/NT-proBNP, right ventricular afterload, and hemodynamic variables in PAH^{10,11,33}. The burden components used here align conceptually with these models, as they reflect pulmonary vascular load, right heart pressure and function, advanced hemodynamic compromise, and biomarker evidence of ventricular strain. However, because prognostic value, mortality prediction, and treatment response were not tested, this score should be viewed only as an in-cohort phenotyping and hypothesis-generating tool.

This study has several limitations. It was retrospective and single-center, with a small sample size and only five patients in the 2022-only early CTD-PAH phenotype. In addition, because the study was conducted at a tertiary rheumatology and pulmonary hypertension referral center, referral and selection bias cannot be excluded; patients evaluated in this setting may represent more complex or clinically severe CTD-PAH phenotypes than those managed in non-tertiary centers. Subgroup analyses are therefore underpowered and exploratory. The absence of systematic follow-up data on progression, mortality, treatment response, or repeat right heart catheterization limits interpretation of the natural history of the 2022-only phenotype. ILD was classified only as present or absent, without quantitative HRCT assessment. In addition, right heart catheterization was performed under treatment in some patients, which may have underestimated hemodynamic severity. Another limitation is that right heart catheterization protocols may not have been fully standardized across the study period, particularly with regard to cardiac output measurement method, such as thermodilution versus Fick, and oximetric sampling procedures. Because these methodological details were not uniformly available in the retrospective records, potential measurement heterogeneity could not be fully assessed. Finally, the burden score is not validated and should not be used as a clinical decision-making tool.

In conclusion, the 2022 ESC/ERS hemodynamic definition reclassified approximately one-fifth of patients in this clinically adjudicated CTD-associated Group 1 PAH cohort as 2022-only early CTD-PAH. This group was characterized by lower pulmonary artery pressures, lower PVR and TPG, better-preserved FVC, absence of ILD, and absence of high-burden hemodynamic/right heart phenotype. These findings do not support automatic PAH-specific treatment, but suggest that the updated definition may identify an early pulmonary vascular phenotype requiring close monitoring and, when appropriate, repeat hemodynamic evaluation. Larger prospective studies with serial right heart catheterization, quantitative HRCT, exercise hemodynamics, and long-term outcomes are needed to clarify the prognosis and management of this early CTD-PAH phenotype.

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Supplementary Material

Supplementary Table 1. Cohort classification

Category	n
Total CTD-associated Group 1 PAH cohort	27
PH according to the 2022 definition	27
PAH according to the 2022 hemodynamic definition	27
Established PAH by old definition	22
2022-only early CTD-PAH	5
SSc-PAH	17
non-SSc CTD-PAH	10
ILD-positive CTD-PAH	10
ILD-negative CTD-PAH	17
High-burden phenotype	10

Abbreviations: CTD, connective tissue disease; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; SSc, systemic sclerosis.

Supplementary Table 2. SSc-PAH versus non-SSc CTD-PAH

Variable	SSc-PAH (n=17)	non-SSc CTD-PAH (n=10)	p value
Age, years	64.0 [47.0–69.0]	68.5 [57.5–73.0]	0.340
Female sex	14/17 (82.4%)	9/10 (90.0%)	1.000
BMI, kg/m ²	29.7 [24.6–32.4]	31.1 [27.4–33.2]	0.514
WHO functional class	2.0 [2.0–3.0]	2.0 [2.0–2.8]	0.683
Hemoglobin, g/dL	12.3 [11.2–12.8]	12.2 [11.3–13.9]	0.563
NT-proBNP / ProBNP	367.1 [167.9–2038.4]	144.1 [110.8–287.6]	0.093
ILD	5/17 (29.4%)	5/10 (50.0%)	0.415
FVC, % predicted	77.0 [69.0–87.0]	78.5 [61.5–95.0]	0.900
DLCO, % predicted	68.0 [54.0–72.0]	71.5 [70.0–80.5]	0.247

Variable	SSc-PAH (n=17)	non-SSc CTD-PAH (n=10)	p value
FVC/DLCO ratio	1.19 [1.04–1.30]	1.23 [0.95–1.44]	0.940
TRVmax, m/s	3.40 [3.20–3.80]	3.50 [3.42–3.60]	0.724
Echo-estimated sPAP/PASP, mmHg	50.0 [44.0–55.0]	49.5 [43.8–52.8]	0.580
TAPSE, mm	19.0 [16.0–24.0]	25.5 [16.2–28.8]	0.182
RA dilatation	12/17 (70.6%)	3/10 (30.0%)	0.057
RV dilatation	7/17 (41.2%)	2/10 (20.0%)	0.406
Pericardial effusion	1/17 (5.9%)	1/10 (10.0%)	1.000
mPAP, mmHg	27.0 [25.0–44.0]	27.5 [25.0–34.0]	0.980
sPAP, mmHg	46.0 [39.0–70.0]	43.0 [40.0–66.0]	1.000
dPAP, mmHg	18.0 [16.0–23.0]	17.0 [15.0–21.0]	0.402
PAWP, mmHg	10.0 [9.0–12.0]	12.0 [8.5–12.0]	0.465
PVR, WU	3.90 [3.00–10.50]	3.75 [3.37–5.32]	0.821
Cardiac output, L/min	4.10 [3.66–4.80]	4.05 [3.62–4.55]	0.841
Cardiac index, L/min/m ²	2.40 [1.92–2.80]	2.26 [2.12–2.68]	0.860
RA mean pressure, mmHg	9.0 [7.0–12.0]	8.0 [6.2–9.0]	0.418
PA oxygen saturation, %	66.0 [55.0–69.2]	65.5 [60.5–68.8]	0.821
TPG, mmHg	18.0 [15.0–33.0]	16.5 [14.2–22.2]	0.481
DPG, mmHg	8.0 [6.0–13.0]	6.0 [3.2–9.5]	0.206

Abbreviations: BMI, body mass index; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; DLCO, diffusing capacity of the lung for carbon monoxide; DPG, diastolic pulmonary gradient; FVC, forced vital capacity; ILD, interstitial lung disease; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; PAWP, pulmonary arterial wedge pressure; ProBNP, pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; sPAP, systolic pulmonary artery pressure; SSc, systemic sclerosis; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary gradient; TRVmax, maximum tricuspid regurgitation velocity; WHO, World Health Organization; WU, Wood units.

Supplementary Table 3. ILD-positive versus ILD-negative CTD-PAH

Variable	ILD-positive (n=10)	ILD-negative (n=17)	p value	q value
Age, years	62.5 [56.2–67.8]	65.0 [47.0–73.0]	0.744	0.913
Female sex	8/10 (80.0%)	15/17 (88.2%)	0.613	0.913
BMI, kg/m ²	30.7 [26.9–33.4]	29.7 [24.2–32.4]	0.422	0.913
WHO functional class	2.0 [2.0–3.0]	2.0 [2.0–3.0]	0.462	0.913
Systemic sclerosis	5/10 (50.0%)	12/17 (70.6%)	0.415	0.913
Established PAH by old definition	10/10 (100.0%)	12/17 (70.6%)	0.124	0.670
2022-only early CTD-PAH	0/10 (0.0%)	5/17 (29.4%)	0.124	0.670
Hemoglobin, g/dL	11.9 [10.7–13.6]	12.6 [11.3–13.3]	0.782	0.918
NT-proBNP / ProBNP	188.9 [105.8–741.4]	230.9 [142.5–710.3]	0.920	0.994
FVC, % predicted	67.5 [61.5–75.0]	87.0 [74.0–89.0]	0.021	0.281
DLCO, % predicted	57.0 [45.0–69.2]	72.0 [69.0–78.0]	0.015	0.281
FVC/DLCO ratio	1.31 [1.14–1.45]	1.10 [0.94–1.27]	0.114	0.670
TRVmax, m/s	3.40 [3.23–3.58]	3.50 [3.40–3.80]	0.235	0.905
Echo-estimated sPAP/PASP, mmHg	47.0 [43.2–52.2]	52.0 [47.0–55.0]	0.268	0.905
TAPSE, mm	23.5 [16.8–25.8]	19.0 [16.0–25.0]	0.615	0.913
mPAP, mmHg	27.5 [25.2–34.0]	27.0 [25.0–44.0]	0.820	0.923
PAWP, mmHg	12.0 [9.2–12.0]	10.0 [8.0–12.0]	0.481	0.913

Variable	ILD-positive (n=10)	ILD-negative (n=17)	p value	q value
PVR, WU	3.62 [3.05–5.40]	3.90 [3.33–10.50]	0.687	0.913
Cardiac output, L/min	4.51 [4.05–5.22]	3.91 [3.60–4.60]	0.183	0.824
Cardiac index, L/min/m ²	2.65 [2.23–2.77]	2.20 [2.00–2.60]	0.407	0.913
RA mean pressure, mmHg	7.5 [6.2–9.8]	9.0 [7.0–10.0]	0.510	0.913
PA oxygen saturation, %	64.5 [57.9–69.0]	66.0 [63.6–69.0]	0.744	0.913
TPG, mmHg	16.5 [15.2–23.2]	17.0 [14.0–37.0]	1.000	1.000
DPG, mmHg	7.5 [6.2–10.8]	8.0 [6.0–13.0]	0.742	0.913
RA dilatation	5/10 (50.0%)	10/17 (58.8%)	0.706	0.913
RV dilatation	4/10 (40.0%)	5/17 (29.4%)	0.683	0.913
Pericardial effusion	1/10 (10.0%)	1/17 (5.9%)	1.000	1.000

Abbreviations: BMI, body mass index; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; DLCO, diffusing capacity of the lung for carbon monoxide; DPG, diastolic pulmonary gradient; FDR, false discovery rate; FVC, forced vital capacity; ILD, interstitial lung disease; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; PAWP, pulmonary arterial wedge pressure; ProBNP, pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary gradient; TRVmax, maximum tricuspid regurgitation velocity; WHO, World Health Organization; WU, Wood units.

Supplementary Table 4. Patient-level characteristics of 2022-only early CTD-PAH

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
CTD diagnosis	SSc	SSc	SSc	SSc	UCTD
SSc	Yes	Yes	Yes	Yes	No
ILD	No	No	No	No	No
mPAP	23	22	24	25	22
sPAP	32	36	40	46	40
dPAP	18	12	14	16	11
PAWP	10	4	12	8	10
PVR	2.71	3.90	3.00	2.43	3.60
FVC %	89	93	82	87	106
DLCO %	109	103	69	72	73
FVC/DLCO	0.82	0.90	1.19	1.21	1.45
TRVmax	3.7	3.8	3.2	3.3	3.5
Echo sPAP/PASP	55	58	42	49	52
TAPSE	23	14	26	14	25
NT-proBNP/ProBNP	23.2	367.1	380.6	230.9	142.5
Burden score	1	2	1	1	2
Burden category	Low burden	Intermediate burden	Low burden	Low burden	Intermediate burden

Table note: This table presents patient-level characteristics of the 2022-only early CTD-PAH group. Burden score was calculated using six components: PVR ≥ 5 WU, mPAP ≥ 35 mmHg, RA mean pressure ≥ 8 mmHg, cardiac index < 2.5 L/min/m², NT-proBNP/ProBNP ≥ 300 , and TAPSE < 18 mm. Low burden was defined as 0–1 positive component, intermediate burden as 2–3 positive components, and high burden as ≥ 4 positive components.

Abbreviations: CTD, connective tissue disease; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; DLCO, diffusing capacity of the lung for carbon monoxide; dPAP, diastolic pulmonary artery pressure; FVC, forced vital capacity; ILD, interstitial lung disease; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; PAWP, pulmonary arterial wedge pressure; ProBNP, pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary gradient; TRVmax, maximum tricuspid regurgitation velocity; WHO, World Health Organization; WU, Wood units.

resistance; sPAP, systolic pulmonary artery pressure; SSc, systemic sclerosis; TAPSE, tricuspid annular plane systolic excursion; TRVmax, maximum tricuspid regurgitation velocity; UCTD, undifferentiated connective tissue disease; WU, Wood units.

Supplementary Table 5. Burden score components and burden category distribution

Component / category	n/N or n (%)
PVR ≥ 5 WU	10/27 (37.0%)
mPAP ≥ 35 mmHg	8/27 (29.6%)
RA mean pressure ≥ 8 mmHg	17/27 (63.0%)
CI < 2.5 L/min/m ²	15/27 (55.6%)
NT-proBNP/ProBNP ≥ 300	12/27 (44.4%)
TAPSE < 18 mm	9/27 (33.3%)
Low burden, 0–1 components	10 (37.0%)
Intermediate burden, 2–3 components	7 (25.9%)
High burden, 4–6 components	10 (37.0%)

Abbreviations: CI, cardiac index; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; ProBNP, pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; RA, right atrial; TAPSE, tricuspid annular plane systolic excursion; WU, Wood units.

Supplementary Table 6. Distribution of high-burden phenotype across key subgroups

Subgroup	Non-high burden	High burden
Definition group		
2022-only early CTD-PAH	5/5 (100.0%)	0/5 (0.0%)
Established PAH old definition	12/22 (54.5%)	10/22 (45.5%)
CTD group		
SSc-PAH	11/17 (64.7%)	6/17 (35.3%)
non-SSc CTD-PAH	6/10 (60.0%)	4/10 (40.0%)
ILD group		
ILD-negative	11/17 (64.7%)	6/17 (35.3%)
ILD-positive	6/10 (60.0%)	4/10 (40.0%)

Abbreviations: CTD, connective tissue disease; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; ILD, interstitial lung disease; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; ProBNP, pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; RA, right atrial; SSc, systemic sclerosis; TAPSE, tricuspid annular plane systolic excursion; WU, Wood units.