# Screening for pulmonary arterial hypertension in patients with systemic sclerosis in the era of new pulmonary arterial hypertension definitions

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## Abstract

### Objective

*This study compares the performance of three composite pulmonary arterial hypertension (PAH) screening tools in a real-life SSc cohort, according to both the previous 2015 ESC/ERS guideline and the recent 2022 ESC/ERS guideline haemodynamic criteria.*

### Methods

*Consecutive SSc patients without a previous diagnosis of pulmonary hypertension (PH) were screened for PAH using the European Society of Cardiology/European Respiratory Society (ESC/ERS), DETECT, and Australian Scleroderma Interest Group (ASIG) algorithms. Right heart catheterisation (RHC) referral performances for PAH were compared according to the 2022 ESC/ERS PAH criteria.*

### Results

*Thirty-five of the 81 patients required RHC; 15 (18.5%) according to ESC/ERS, 27 (33.3%) according to DETECT, and 25 (31%) according to ASIG. The final diagnoses were no-PH in 17 patients, WHO group 1 PH (PAH) in 8 patients, WHO group 2 PH in 8 patients, and WHO group 3 PH in 2 patients. When the hemodynamic criteria of the previous ESC/ERS guideline were applied, only one patient was diagnosed with PAH. The sensitivities of the algorithms for the diagnosis of PAH were 62.5% for ESC/ERS, 75% for DETECT, 87.5% for ASIG according to the 2022 ESC/ERS guideline definition, and 100% for all according to the previous ESC/ERS guideline.*

### Conclusion

*With the recent criteria, PAH diagnosis in patients with SSc increased by 1.8-fold. Current algorithms for screening PAH are less sensitive with these revised criteria. Although the ASIG algorithm seems more sensitive, it can still miss the diagnosis. The multimodal/algorithmic approach seems to be the best option for predicting PAH.*

**Key words**
systemic sclerosis, scleroderma, pulmonary, diagnostic criteria

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## Introduction

Pulmonary arterial hypertension (PAH) is one of the leading causes of morbidity and mortality in patients with systemic sclerosis (SSc) and is seen in 8-19% of these patients (1-3). The 3-year estimated mortality rate among SSc patients with PAH is 56%, and 26% of all deaths were attributed to PAH in patients with SSc (1, 2).

Most patients with PAH are diagnosed late with advanced symptoms (4, 5). Reducing the time to diagnose PAH is essential for better long-term outcomes in patients with SSc (6, 7). Although current recommendations suggest annual screening of these patients, there is no consensus on the optimal screening strategy (6, 8). Right heart catheterisation (RHC) is the gold standard diagnostic tool for diagnosing PH, but due to its invasive nature, it tends to be reserved for patients with a high probability of PH (9-11). Over the past decade, various strategies have been proposed to improve screening and diagnosis. Transthoracic echocardiography (TTE) was recommended for annual screening of patients with SSc by the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines (10, 11). RHC was recommended for patients with intermediate or high-risk for PAH, according to TTE findings(10-12).

Other stratified screening algorithms that use TTE as a second-step investigation are the DETECT and the Australian Scleroderma Interest Group (ASIG) algorithms (13, 14). The DETECT algorithm requires the results of 6 non-echocardiographic variables to determine a referral for echocardiography in step 1. The second step determines the need for RHC by evaluating the TTE features. The ASIG algorithm evaluates serum NT-proBNP levels and FVC/DLCO ratio on pulmonary function tests (PFTs). If either result is positive, the algorithm indicates further evaluation of the presence of PH.

Currently, PAH is hemodynamically defined as an increased mean pulmonary artery pressure (mPAP) >20 mmHg with normal left heart filling pressures (pulmonary arterial wedge pressure (PAWP) ≤15 mmHg or left ventricular end-diastolic pressure ≤15 mmHg) and an increased pulmonary vascular resistance (PVR) >2 WU in the absence of other causes (11, 15-17). These cut-off levels described in the 2022 ESC/ERS guidelines aim to diagnose PH earlier than the 2015 ESC/ERS guidelines, where the cut-off was 25 mmHg for mPAP and >3 WU for PVR. The current guideline recommends using algorithms, especially DETECT, and a multimodal approach (symptoms echocardiography, PFTs, and ProBNP) in the screening of PAH (11). However, studies that were conducted for developing these algorithms used previous diagnostic hemodynamic criteria (mPAP ≥25 mmHg, PAWP ≤15 mmHg) for diagnosing PAH (18, 19).

Thus, we aimed to compare the performance of the ESC/ERS- echo criteria, DETECT, and ASIG algorithms for diagnosing PAH in our SSc cohort according to the most recent (2022) and the former (2015) hemodynamic cut-off levels for diagnosing PAH.

## Materials and methods

### *Study population and design*

Consecutive SSc patients attending our outpatient clinic between July 2018 and March 2020 who fulfilled the 2013 ACR/EULAR SSc Classification Criteria, who were ≥18 years old, and who did not already have a diagnosis of PH were included.

Patients were excluded if they had been diagnosed PH (mean PAP >20 mmHg) by RHC prior to enrollment or had any evidence of clinically relevant left heart disease, FVC of <50% of predicted, obstructive lung disease (FEV1/FVC <70%), chronic thromboembolic disease (CTED), acute or chronic kidney injury, chronic severe liver disease, or were pregnant (for further details supplementary appendix). In patients who were already receiving a phosphodiesterase-5 inhibitor, endothelin receptor antagonist, or prostacyclin analog for severe Raynaud's phenomenon and digital ulcers, these were recorded.

All patients provided written informed consent. The study was conducted in accordance with the standards of the Ethics Committee of Istanbul University Cerrahpasa Medical School (No:

## ESC /ESR

**Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension***

| Peak tricuspid regurgitation velocity (m/s) | Presence of other echo PH signs | Echocardiographic probability of pulmonary hypertension |
|---|---|---|
| ≤2.8 or unmeasurable | No | Low |
| ≤2.8 or not measurable | Yes | Intermediate |
| 2.9–3.4 | No | |
| 2.9–3.4 | Yes | High |
| >3.4 | Not required | |

**Additional echocardiographic signs suggestive of pulmonary hypertension**

| A: The ventricles | B: Pulmonary artery | C: Inferior vena cava and right atrium |
|---|---|---|
| RV/LV basal diameter/area ratio>1.0 | RVOT AT <105 ms and/ormid-systolic notching | Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration) |
| Flattening of the interventricularseptum (LVEI >1.1 in systole and/or diastole) | Early diastolic pulmonary regurgitation velocity >2.2 m/s | Right atrial area (end-systole) >18 cm2 |
| TAPSE/sPAP ratio <0.55 mm/mmHg | PA diameter >AR diameter and/or PA diameter >25 mm | |

**Diagnostic management suggested according to echocardiographic probability of pulmonary hypertension in asymptomatic patients with risk factors for pulmonary arterial hypertension**

| PH probability according to echocardiography | Risk factors or associated conditions for PAH or CTEPH** | Recommendation |
|---|---|---|
| Low | No | Alternative diagnosis |
| | Yes | Echo follow-up |
| Intermediate | No | |
| | Yes | If associated scleroderma, RHC should be considered |
| High | - | Further intervention***/ RHC is recommended if indicated**** |

*AR, aortic root; IVC, inferior vena cava; LV, left ventricle; LVEI, left ventricle eccentricity index; PA, pulmonaryartery; RA, right atrium; RV, right ventricle; RVOT AT, right ventricular outflow tract acceleration time; sPAP, systolicpulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitationvelocity.*
**Signs contributing to assessing the probability of PH in addition to TRV. Signs from at least two categories (A/B/C) must be present to alter the level of echocardiographic probability of PH. ** Systemic sclerosis is a risk factor for PAH ***Further testing may be necessary (e.g.imaging, CPET) ****RHC should beperformed if useful information/a therapeutic consequence is anticipated (e.g.suspected PAH or CTEPH), and may not be indicated in patients without risk factors or associated conditions for PAH or CTEPH (e.g.whenmild PH and predominant LHD or lung disease are present).*

## DETECT

**STEP 1**
**Identify patients who required echocardiography**

| | |
|---|---|
| **Non-echocardiographic variables:**<br>- FVC % predicted / DLCO % predicted ratio<br>- Presence of current / past telengiectasias<br>- Serum anticentromere antibody<br>- Serum NT-ProBNP level<br>- Serum urate level<br>- Presence of right axis deviation | Total risk point of step 1 is calculated by adding individual risk points of non-echocardiographic variables according to the nomogram<br><br>⇨ Refer to echocardiography if total risk point in step 1 is >300 |

**STEP 2**
**Identify patients who required RHC**

| | |
|---|---|
| **Echocardiographic variables:**<br>Right atrium area<br>Tricuspid regurgitant velocity | Total risk point in step 2 is calculated by adding risk point of step 1 (converted point accroding to nomogram) and 2 echocardiographic risk point<br><br>⇨ Refer to RHC if total risk in step 2 is >35 |

## ASIG

| | |
|---|---|
| Perform RHC if;<br><br>- NT-ProBNP >210 pg/ml and/or<br><br>- DLCO <70% with FVC/DLCO ≥1.8 | Exclude other conditionts as indicated such as left hearth disease, ILD, pulmonary artery thromboembolic disease |

**Fig. 1.** Summary of the PAH screening algorithms.

83045809-604.01.02/05.06.2020-68360) and in accordance with the Helsinki Declaration of 1975/83.

*Data collection and analysis*

All patients were examined by the same physician (ME) for the SSc subtype, SSc symptoms and organ involvement, general medical history, and symptoms. Disease duration was calculated from the first Raynaud's symptoms to the screening date. Demographic and clinical parameters were recorded in a standard form. All diagnostic tests were done within three months before RHC (Supplementary File) (20).

Serum test (NT-proBNP, anti-centromere antibody, uric acid) results were recorded from the electronic patient recording system. Transthoracic echocardiography (TTE) was performed and analyzed by a European Association of Cardiovascular Imaging (EACVI) certified cardiologist (BKA) following the American Society of Echocardiography and EACVI guidelines (21). Electrocardiography recordings were interpreted (BKA) for right axis deviation. PFTs were performed. High-resolution computed tomography (HRCT) of the lungs was performed to assess ILD, if not performed during the previous two years or if there was suspicion of progressive disease (decline in FVC >5% compared to the last PFT, new crackles in the examination, new or worsening dyspnea) in patients without known severe ILD disease. ILD was staged radiologically as mild (<10%), moderate (10-30%), or severe (>30%) according to the percentage of involvement (22).

Three different algorithms (ESC/ERS-echo criteria, DETECT, and ASIG) were used for screening PAH in each patient (Fig. 1). RHC was performed if indicated according to at least one of these algorithms. The ability of each algorithm to correctly identify patients who required RHC was determined by using a number of patients with PAH as true positives and a number of patients without PH as true negatives for calculating the sensitivity and specificity of each algorithm.

Patients were classified as either non-PH (mPAP ≤20 mmHg on RHC), WHOgroup 1 - PAH (mPAP >20 mmHg, PAWP or LVEDP ≤ 15 mmHg and PVR >2 WU on RHC and absence of other causes), WHO group 2 PH – left heart disease (mPAP >20 mmHg, PAWP >15 mmHg on RHC), or WHO group 3 PH – lung disease/hypoxia (mPAP >20 mmHg, PAWP or LVEDP ≤15 mmHg and PVR >2 WU on RHC and FVC of <60% or an FVC between 60 and 80% and/or severe involvement on HRCT) according to current definitions (11, 13). WHO group 2 patients were further classified according to PVR as isolated post-capillary PH (IpcPH) [PVR ≤2 WU] and combined post- and pre-capillary PH (CpcPH) [PVR > 2WU].

We also tested the sensitivity of each algorithm according to the former definition of PAH, in which the mPAP threshold was 25 mmHg, and PVR was >3 WU (10).

All patients who required RHC ac-

**Table I.** Demographic and clinical features of patients.

| | All patients, n=81 |
|---|---|
| **Age, median [IQR]** | 51 (44-64) |
| **Disease duration, median years [IQR]** | 13 [5-21] |
| **Male subjects /female subjects** | 7/74 |
| **Type of skin involvement, n/N (%)** | |
| Limited | 62 (77) |
| Diffuse | 19 (23) |
| **SSc specific antibody profile, n/N (%)** | |
| Anti-scl70 (+), n/N (%) | 32/74 (43) |
| Anticentromere (+), n/N (%) | 21/74 (28) |
| **Presence of ILD, n/N (%)** | 45 (56) |
| Mild or moderate | 33/45 (73) |
| Severe | 12/45 (27) |
| **Presence of digital ulcer (ever), n/N (%)** | 40 (49) |
| **Presence of GIS involvement, n/N (%)** | 44 (54) |
| **Presence of telangiectasia, n/N (%)** | 55 (68) |
| **Presence of peripheral oedema n/N (%)** | 16 (20) |
| **Presence of dyspnoea, n/N (%)** | 34 (42) |
| NHYA FC-1 | 47 (58) |
| NHYA FC-2 | 30 (37) |
| NHYA FC-3 | 4 (5) |
| NHYA FC-4 | 0 |
| **Receiving PAH-specific treatment (for digital ulcer) n/N (%)** | **30 (37)** |
| PDE-5 inhibitors | **20 (25)** |
| ERAs | **14 (17)** |
| **NT-proBNP, median (pg/ml) [IQR]** | 120 ( 57-188) |
| **Serum uric acid, median (mg/dl)** | 4 (3-5) |
| **Pulmonary function tests and DLCO results** | |
| FVC, median (% predicted) [IQR] | 90 [75-105] |
| DLCO, median (% predicted) [IQR] | 65 [ 51.25-79.25] |
| FVC/ DLCO ratio, median [IQR] | 1.35 [1.16-1.65] |
| **Measurements on TTE** | |
| sPAP, median (mmHg) [IQR] | 30 [26-36] |
| TRV, mean (m/sec) [SD] | 2.54 [0.33] |
| Patients with a TRV >2.8 m/sec, n/N (%) | 18/81 (22) |
| RAA, $mm^2$, median [IQR] | 14 [11-15] |
| TAPSE, mm, median [IQR] | 23 [21-26] |
| **Haemodynamic parameters acquired by RHC** | |
| mPAP (mmHg), mean (SD) | 21.6 (6.3) |
| PVR (WU), mean (SD) | 11.9 (3.6) |
| PAWP (mmHg), mean (SD) | 2.3 (1) |
| RAP (mmHg), mean (SD) | 7.1 (2.4) |
| CI ($L/min/m^2$) | 2.6 (0.6) |

CI: cardiac index; DLCO: diffusing capacity of the lung for carbon monoxide; ERA: endothelin receptor antagonist; FVC: forced vital capacity; GIS: gastrointestinal system; ILD: interstitial lung disease; IQR: interquartile range; mPAP: mean pulmonary artery pressure; NHYA FC: New York Heart Association functional capacity; PAH: pulmonary hypertension; PAWP: pulmonary artery wedge pressure; PDE-5: phosphodiesterase-5; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SSc: systemic sclerosis; TTE: transthoracic echocardiography.

cording to at least one of the screening algorithms were assessed by V/Q scan to exclude CTED. If the V/Q scan was suggestive of CTED, CT pulmonary angiography was performed to confirm the result.

## Results

A total of 131 consecutive patients with SSc were screened, and 46 did not meet the eligibility criteria (Supplementary Appendix). Among the remaining 85 patients, four more were excluded during the study due to the absence of measurable tricuspid regurgitation velocity (TRV) in echocardiography. The remaining 81 patients (62%) (74 female subjects, median age 51 (IQR:44.5 - 63) years, median disease duration of 13 (IQR: 5 - 20) years) were included in the analyses. The demographic and disease characteristics of the included patients are provided in Table I.

Among the 81 patients, 36 (44%) had dyspnoea, and most of the patients were in WHO functional class (FC) -1 (58%) or FC-2 (37%). The number of patients using ERA and/or PDE5I due to digital ulcers or severe Raynaud's phenomenon was 30 (37%).

On echocardiography, the mean TRV was 2.54±0.33 m/sec, and the number of patients with a TRV >2.8 m/sec was 15 (19%). None of the patients required RHC for PH due to other echocardiographic parameters related to the ventricles, pulmonary artery, right atrium, or inferior vena cava.

### *Patients who required RHC*

Thirty-five (43%) patients required RHC, according to at least one of the algorithms. Among them, nine patients were using ERA and/or PDE5I therapy due to digital ulcers. The number of patients requiring RHC was 15 (18.5%) according to ESC/ERS, 27 (33.3%) according to DETECT, and 25 (31%) according to the ASIG algorithms (Fig. 2). Among these 35 patients, the final diagnoses were no-PH in 15 patients, WHO group 1 PH (PAH) in 8 patients, WHO group 2 PH in 8 patients, and WHO group 3 PH in 2 patients and unclassified PH in 2 patients (Table II). Among the patients with WHO group 2 PH, 3 had IpcPH, and 5 had CpcPH.

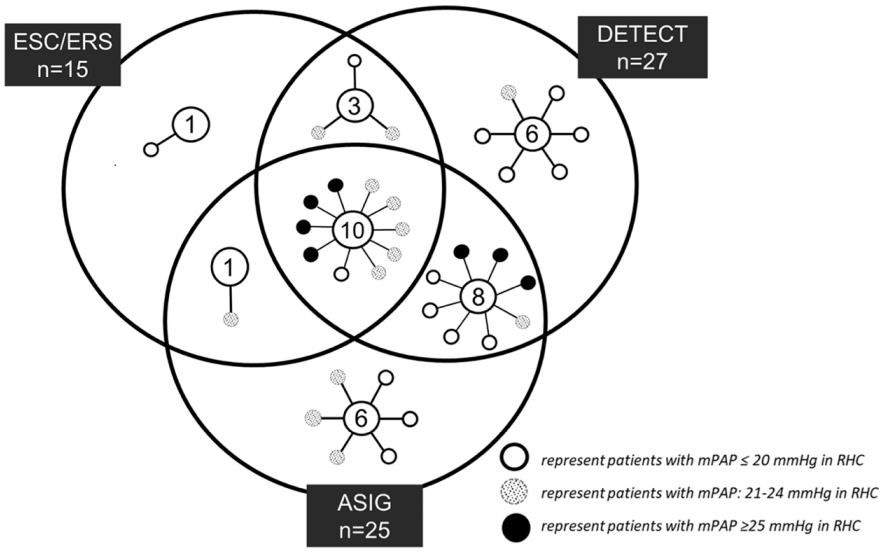


**Fig. 2.** Number of patients required RHC according to the algorithms.

**Table II.** Number of patients with no PH, group 1 and 2 PH according to the current guideline and algorithms (11).

| Guideline/algorithm | RHC referral n (% study population) | No PH (n=15) | Group 1 PH (n=8) | Group 2 PH (n=8) |
|---|---|---|---|---|
| ESC/$ESR_{echo}$ intermediate/high risk | 15 (19)* | 3 | 5 | 5 |
| DETECT positive | 27 (33)** | 11 | 6 | 8 |
| ASIG positive | 25 (31)** | 8 | 7 | 7 |

*Two patients had Group 3 PH.
**One patient had Group 3 PH, and one patient had unclassified PH.
***Two patients had Group 3 PH, and one patient had unclassified PH.

When the 2015 ESC/ERS PAH hemodynamic criteria were used, the final diagnoses were WHO group 1 PH in 1 patient, WHO group 2 PH in 5 patients, and WHO group 3 PH in 1 patient.

The frequency of PH increased significantly from 8.6% to 24.7% (a 2.9-fold /absolute 16% increase in patient numbers) and the frequency of PAH increased from 1.2% to 9.9% (an 8.2-fold increase/additional 8.6% patients) based on the current PH and PAH definitions in the cohort of the incident 81 patients.

When the original inclusion criteria for DETECT (DLCO <60% and disease duration of >3 years) were applied to our cohort, among 31 patients, 15 (48%) patients were referred for RHC. Five patients had no PH, 3 were diagnosed as WHO group 1 PH, 5 were diagnosed as WHO group 2 PH, and 2 were diagnosed as WHO group 3 PH according to current criteria.

### *Comparison of screening algorithms*

In order to compare the performance of the three algorithms for detecting PAH, we excluded patients with WHO group 2 and WHO group 3 PH. We included patients with PAH as true positives and those without PH as true negatives in order to calculate each algorithm's sensitivity and specificity, similar to the methodology used in developing the DETECT algorithm (13).

According to new diagnostic criteria, the sensitivity for PAH was 62.5% for ESC/ERS, 75% for DETECT, 87.5% for ASIG, and the specificity was 95% for ESC/ERS, 82% for DETECT, and 87% for ASIG. When PAH was defined according to the former (2015) criteria, the sensitivity for detecting PAH was 100% for all algorithms, and the specificity was 85% for ESC/ERS, 73% for DETECT, and 76% for ASIG (Table III). The number of patients that the algorithms missed the diagnosis according

to the new PAH criteria were; 3 patients according to ESC/ERS echo criteria, 2 patients according to DETECT algorithm, and one patient according to the ASIG algorithm. (Table II) There was no patient with PAH according to the new and former PAH criteria, which was missed by all of the algorithms or by DETECT and ASIG at the same time. In the subgroup of patients with DLCO<60% and disease duration of >3 years (original inclusion criteria for DETECT), the sensitivities of the algorithms according to the new PAH criteria were 67% for ESC/ERS, 50% for DETECT and, 100% for ASIG algorithm. The specificity of ASIG was also higher (88%); than DETECT (64%) and ESC/ESR (68%). According to the original DETECT inclusion criteria DETECT algorithm missed the PAH diagnosis in 3 patients according to the new PAH criteria due to the exclusion of patients with a DLCO >60.

**Table III.** Performances of the algorithms detecting patients with PAH according to the previous and current criteria.

| | | | Sensitivity, % | Specificity, % | PPV**, % | NPV**, % |
|---|---|---|---|---|---|---|
| Performance for detecting PH | mPAP >20mmHg Cut-off (n=81) | ESC/ERS | 60 | 95 | 80 | 88 |
| | | DETECT | 80 | 82 | 59 | 93 |
| | | ASIG | 85 | 87 | 68 | 95 |
| | mPAP ≥25mmHg Cut-off (n=81) | ESC/ERS | 57 | 85 | 27 | 95 |
| | | DETECT | 100 | 73 | 26 | 100 |
| | | ASIG | 100 | 76 | 28 | 100 |
| Performance for detecting PAH* | PH – mPAP ≥25 mmHg (n= 75) | ESC/ERS | 100 | 85 | 8 | 100 |
| | | DETECT | 100 | 73 | 5 | 100 |
| | | ASIG | 100 | 76 | 5 | 100 |
| | PAH –mPAP > 20 mmHg and PVR > 2 WU (n= 69) | ESC/ERS | 62.5 | 95 | 62.5 | 95 |
| | | DETECT | 75 | 82 | 35 | 96 |
| | | ASIG | 87.5 | 87 | 47 | 98 |

*Performances of the algorithms for detecting PAH were calculated among patients who had Group 1 PH and who do not have PH (Patients with group 2 and 3 and unclassified PH were excluded)
ASIG: Australian Scleroderma Interest Group; DETECT: ESC/ERS: European Society of Cardiology and by the European Respiratory Society; PPV: positive predictive value; NNP: negative predictive value; PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; mPAP: mean pulmonary arterial hypertension; RHC: right heart catheterisation; WU: woods unit.

*Differences in patient characteristics between patients fulfilling each algorithm*

The median disease duration of patients who required RHC according to ESC/ERS was longer (16 years) than the other two algorithms (14 years for DETECT and 11 years for ASIG). Limited SSc pattern was more frequent in the DETECT positive group (90%) than the ESC/ERS (70%) and ASIG (64%) positive groups. The hemodynamic assessments of patients acquired by RHCs were summarized in Table III.

## Discussion

Early diagnosis and treatment of PAH improved the prognosis of patients with SSc, which can only be possible with reliable and feasible screening methods (7). There are more than thirty studies on PH screening (23). Echocardiography, PFTs, 6-minute walking test, ECG, cardiopulmonary exercise test, and clinical signs were used as screening tools as a part of composite algorithms such as ESC/ERS, DETECT, and ASIG (10, 11, 13, 14) or as a sole screening tool with diferent diagnostic performances (23). Higher sensitivity and lower specificity were reported for DETECT and ASIG algorithms compared with the ESC/ERSecho algorithm in the validation studies (13, 22). The current ESC/ERS guideline recommends mainly the DETECT algorithm for screening of PAH in patients with SSc duration > 3 years with FVC >%40 and DLCO <60% with class IB indication level (11). However, both DETECT and ASIG algorithms derived from studies that defined PH as mPAP ≥25 mmHg and PAH as mPAP≥25 mmHg with PCWP ≤15 mmHg, and they were not validated according to the recently proposed PAH criteria (mPAP >20 mmHg, PCWP ≤15 mmHg and PVR >2 WU) (13, 14).

The present study is the first to prospectively evaluate and compare the performance of the ESC/ERSecho, DETECT, and ASIG algorithms according to recent PAH diagnostic criteria. We found the following; 1) with new PAH criteria, all three algorithms have lower sensitivity to predict PAH than former PAH criteria; 2) the ASIG algorithm has better sensitivity among these three algorithms; 3) diagnosis of PH and PAH in patients with SSc were increased by 2.9 and 8.2 fold respectively with the most recent diagnostic criteria. 4) Group 2 and Group 3 PH are diagnosed in a considerable number of patients, even with strict exclusion criteria.

There are some possible explanations for why the diagnostic sensitivity of these algorithms decreases with the new PAH criteria. For temporal reasons, the cut-off values of the items used in these algorithms were not tested for the new mPAP or PVR cut-off values. So, rearranging the cutoff values of the items used in the algorithms, such as TRV, NT-proBNP, and FVC/DLCO ratio, might increase the sensitivities of these algorithms. Another issue is that our SSc patient population is younger, mostly asymptomatic or having mild symptoms, and lower NTproBNP levels than DETECT and ASIG populations.

The original DETECT algorithm was derived from a high PAH risk SSc population (patients with SSc disease duration >3 years and DLCO level <60% were included). It was also tested in unselected SSc populations in comparison with 2015 ESC/ERS echocardiography criteria (24). Vandecasteele *et al*. found a significantly higher rate of RHC referral using the DETECT algorithm (30%) compared to the 2015 ESC/ERS echo criteria (17%), and both algorithms identify the same number of patients who had PAH (3 in 195 patients). The RHC referral rate in our study was quite similar (33.3%

*vs*. %18.5, respectively). While both algorithms identified one patient who had PAH (1 in 81 patients) according to the 2015 ESC/ERS PAH definition, when the 2022 revised definition of PAH is applied, the DETECT algorithm diagnosed 6 and ESC/ERS echo criteria diagnosed 5 out of 8 patients with PAH. In the original DETECT population with DLCO <60%, sensitivity was even lower than in the whole study population (50% vs 75%). This suggests that the DETECT algorithm may miss the mild disease forms. On the other hand, in our study, the ASIG algorithm showed better performance than DETECT, even in patients with DLCO <60%; however, it also missed one subject with PAH.

Although the number of RHC required per PAH diagnosis was lower with ESC/ERSecho criteria (3 patients) than DETECT (4.5 patients) and ASIG (3.6 patients), it missed more PAH patients than the other algorithms. The DETECT and ASIG algorithms both included TTE in their algorithm, but TTE results are not essential to proceed to RHC, and the accumulation of other risk points may indicate the need for RHC. In our study protocol, we excluded patients with unmeasurable TRV. Still, TTE was not sufficient to detect PAH in these patients. Using more than one algorithm/investigation at least until a new/updated algorithm is determined can solve this issue. Additional new TTE modalities may have complementary benefits in the future (25, 26). In line with this, the current guideline recommends assessing multiple parameters such as symptoms, echocardiography, PFTs, and BNP/NT-proBNP to assess the risk of PAH with class IIa B indication level (11).

Furthermore, it is crucial to consider the heterogeneity of PH aetiology in SSc patients, as they can develop various types of PH, including group 1 PAH, group 2 PH, and group 3 PH, often with overlapping causes (26). Notably, a significant proportion of SSc patients exhibit left ventricular dysfunction, even in the absence of apparent signs of cardiac involvement (26). This issue aligns with our results, where we identified several patients with group 2 PH associated with left ventricular diastolic dysfunction without evident left ventricular systolic dysfunction or valvular heart disease on TTE. For PAH detection prevailing guidelines advocate the utilisation of algorithms, notably the DETECT algorithm, however, our findings indicate that these algorithms are not capable of differentiating PH of other etiologies, particularly group 2 patients, predominantly exhibiting Cpc-PH, from PAH. There is no recommendation for these patients with overlapping pulmonary vascular and left heart pathologies.

An essential finding of our study is the substantial impact of the 2022 ESC criteria on the diagnosis of PAH, resulting in an 8.6% increase in the identification of PAH cases. Notably, the 2018 recommendations from the World Pulmonary Hypertension Symposium (WSPH) Task Force, which involved lowering the mPAP criterion from 25 mmHg to 20 mmHg while maintaining the PCWP threshold at ≤15 mmHg and PVR ≥3.0 WU, did not significantly increase the number of diagnosed PAH cases among scleroderma patients (15, 27). In contrast, the recent guideline, recommending lowering the PVR criterion in addition to reducing the mPAP criterion to >20 mmHg, appears to have a substantial impact on the diagnosis of PAH in SSc patients. To support this perspective, Jaafar *et al*. found only one additional PAH patient, out of 268 SSc patients who underwent RHC, with the WSPH Task Force definition, but when extrapolating the results according to current criteria (PVR >2 WU), nine additional patients met the PAH diagnosis as opposed to ESC 2015 criteria (27). The DETECT cohort in that study saw an even more pronounced increase, with four more patients meeting WSPH criteria and 23 additional patients meeting the current criteria compared to ESC 2015 criteria. Since in a recent study it was shown that the survival of patients with connective tissue disorders with an mPAP 21-24 mmHg and PVR 2-3 WU is worse than those with normal haemodynamics, it should be considered that the increase in the number of patients with PAH with the recent criteria will have clinical implications (28). The question of whether these additional patients require PAH-specific therapy is crucial and necessitates further studies with long-term follow-up data to provide answers.

The potential impact of pre-existing pulmonary vasodilator treatment (specifically ERA and/or PDE5I) administered for alternative indications, such as digital ulcers or Raynaud's phenomenon, on both screening algorithms and the subsequent diagnosis of PAH in patients with SSc remains an unresolved question. In the current study, only 30% of patients (9 individuals) using pulmonary vasodilators underwent RHC, while the remaining 70% (21 individuals) did not undergo this procedure, primarily due to the absence of RHC referrals in the screening algorithms. This raises the possibility that pre-existing pulmonary vasodilator therapy might have obscured the diagnosis of PAH, emphasising the potential underdiagnosis of pulmonary vascular involvement. It is noteworthy that, for the benefit of patients, we did not discontinue ERA/PDE5I therapies for indications other than PAH before RHC. Considering that alterations in pulmonary hemodynamics in response to PAH-specific treatment typically manifest after 3 to 6 months of initiation (11), conducting haemodynamic studies under these drugs may impact our results. Currently, there is no consensus or recommendation regarding the timing or necessity of discontinuation of these treatments before RHC in patients with SSc. Nevertheless, a comprehensive exploration of this aspect awaits future studies with a larger cohort to generate more statistically robust conclusions.

Our study is subject to various limitations. Given the invasive nature of RHC and the prevailing guidelines that advocate noninvasive screening tools before considering RHC referral, our study could not conduct RHC on the entire patient cohort. Additionally, the absence of a sample size calculation and the constrained patient admissions resulting from the COVID-19 pandemic constitute additional limitations. It is important to note that we included

all patients prospectively, and despite these limitations, we believe that our results provide valuable insights into the real-life SSc patient population.

In conclusion, the implementation of the recent PAH diagnostic criteria has led to a notable increase in the diagnosis of PH and PAH. Our prospective study, conducted on an unselected real-life SSc population, revealed that existing screening algorithms for PAH exhibit reduced sensitivity with the revised criteria. Among these algorithms, the ASIG algorithm demonstrated the highest sensitivity, although it still carries the potential to overlook diagnoses. Therefore, the combined use of these algorithms is suggested as a pragmatic approach until the development of a validated PAH screening algorithm.

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