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Screening for Pulmonary Hypertension in Connective Tissue Diseases: Literature Review and Multidisciplinary Consensus Statement

ABSTRACT

Patients with connective tissue diseases (CTDs) are at increased risk for the development of pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH), which is a specific subtype of PH characterized by progressive remodeling of precapillary pulmonary arterioles. Evidence suggests that early detection of PH through screening in this patient group may be associated with better outcomes. Various methods, including cardiac and thoracic imaging, blood biomarkers, pulmonary function tests, and composite algorithms, have been employed for screening of PH. Here, a multidisciplinary consensus group composed of 10 rheumatologists, 4 cardiologists, and 3 pulmonologists was formed with the objective of developing recommendations and a screening algorithm for PH in patients with CTD. A systematic literature review in the PubMed database focusing on the studies evaluating the performance of different screening methods on detecting PH in CTDs was conducted. The literature review identified 33 relevant articles after title, abstract, and full-text evaluation. The included studies had considerable heterogeneity regarding hemodynamic definitions of PH and PAH, the diagnostic cutoff values of screening methods utilized, and the symptom status of the patients. With the exception of 2 studies, the populations in included studies consisted of only patients with systemic sclerosis (SSc). Consensus-based recommendations and an algorithm prioritizing echocardiography for screening and early detection of PH in patients with SSc and patients with CTD exhibiting overlap features of SSc were developed based on literature data and incorporating the perspectives of group members. No recommendations could be made for asymptomatic patients with CTDs without overlap features of SSc due to limited data.

Keywords: Connective tissue disease, pulmonary hypertension, screening, systemic sclerosis

INTRODUCTION

Pulmonary hypertension (PH) is a disorder associated with multiple clinical conditions and confers a poor prognosis.[1] Left heart disease and pulmonary disorders are the most common causes of PH all over the world.[2] Patients with connective tissue diseases (CTDs) are at particular risk for the development of PH.[3] Although any type of PH can occur in the course of CTDs, pulmonary arterial hypertension (PAH) is the leading cause of PH in systemic sclerosis (SSc) and is also common in other CTDs such as mixed connective tissue disorder (MCTD) and systemic lupus erythematosus (SLE).[4] The PAH is characterized by increased pulmonary vascular resistance (PVR) due to the remodeling of pulmonary vasculature, which eventually leads to progressive right ventricular failure and death if untreated.[5] The prognosis of PAH has improved significantly after the widespread use of specific treatments.[6] Despite similar responses to treatment, the prognosis of connective tissue disease–associated PAH (CTD-PAH) is significantly worse compared to idiopathic PAH and a 3-year mortality rate is reported about 50% in SSc-associated PAH (SSc-PAH).[7]

Right heart catheterization (RHC) is mandatory for the diagnosis of PH. According to current hemodynamic criteria, PH is defined as an elevated mean pulmonary artery pressure (mPAP >20 mm Hg) at rest.[1] The PAH is hemodynamically characterized by

CONSENSUS REPORT

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increased PVR >2 WU and normal pulmonary capillary wedge pressure (≤15 mm Hg) in the absence of other causes of precapillary PH, such as chronic thromboembolic PH (CTEPH) and PH associated with lung diseases.[1] The symptoms of PAH are non-specific, with progressive dyspnea being the most common.[8] Additional symptoms may include fatigue, palpitations, syncope, chest pain, and hemoptysis.[8] Co-existing conditions such as interstitial lung disease (ILD) and left ventricular diastolic dysfunction (LVDD) may also contribute to these non-specific symptoms in patients with CTD. Thus, the differential diagnosis of PAH is challenging in CTDs, and most of the patients have symptoms and advanced disease at the time of diagnosis.[9] Early detection through screening, ideally before symptom onset, may allow for early intervention and contribute to improved outcomes. The RHC is not considered an appropriate screening test for PH and PAH due to its invasive nature, highlighting the necessity for the development and utilization of noninvasive methods.

Screening is defined as the detection of a disease in an at-risk population before the development of symptoms.[10] To be considered suitable for screening, a disease should be prevalent, have an early pre-symptomatic period and there must be evidence that early intervention improves outcomes. Additionally, the test used in screening should be noninvasive, easily accessible, reproducible and have high sensitivity and specificity.[11] The PAH is rare in the general population (with an estimated prevalence of 48-55 cases per million); therefore, population-wide screening is not feasible and practical.[12] However, the high prevalence of PAH in SSc (7%-19%) may justify systematic screening in this high-risk group.[13] The PAH accounts for 30% of SSc-related deaths indicating that it is a major complication of SSc.[14] Furthermore, evidence suggests that SSc-PAH patients diagnosed via screening have less functional and hemodynamic impairment at diagnosis and better survival rates.[15] Recent SSc-PAH registries employing PAH screening have reported 3-year survival rates of approximately 75%.[16] Although lead-time bias cannot be completely excluded, these findings suggest that early diagnosis may improve prognosis in SSc-PAH. However, the prevalence of PAH in other CTDs is much lower than SSc, and the potential benefit of screening in these populations remains uncertain.

Several methods including cardiac and thoracic imaging, blood biomarkers, pulmonary function tests and composite algorithms have been used for PH screening in patients with CTDs. This study aimed to provide a literature review on the performance of these methods for PH and present multidisciplinary consensus-based recommendations and an algorithm for screening and early detection of PH in patients with CTDs for physicians in Türkiye who are involved in the routine care of this patient group.

METHODS

The consensus group was composed of 10 rheumatologists, 4 cardiologists and 3 pulmonologists. Research questions were formulated by 2 authors (A.S. and A.A.), and the systematic literature review (SLR) team (B.F.Y., M.E.Y., D.T.K., M.E., B.D.D., S.A., Y.Y.) conducted an extensive search in the PubMed database for studies published up to January 1, 2024. The search terms used and the flow diagram

HIGHLIGHTS

- Pulmonary arterial hypertension (PAH) is an important cause of mortality and morbidity in connective tissue diseases (CTDs), particularly systemic sclerosis (SSc).
- Earlier diagnosis of PAH via screening may be associated with better outcomes in this patient group.
- Screening strategies for PH in patients with CTD should be tailored to the specific conditions and resources of each country.
- A PH screening algorithm was developed that prioritizes echocardiography for patients with SSc and other CTDs exhibiting overlap features of SSc.

illustrating the study selection process are provided in the Supplementary Appendix. Only original studies written in English that met the following criteria were included: 1) diagnosis of PH and/or PAH was confirmed by RHC and 2) provided data on the performance of the relevant methods in detecting PH and/or PAH. The patient population of interest consisted of individuals with CTDs, including SSc, SLE, MCTD, and Sjogren's syndrome. The diagnostic and screening methods evaluated included electrocardiography (ECG), transthoracic echocardiography (TTE), cardiac magnetic resonance imaging (MRI), natriuretic peptides (brain natriuretic peptide (BNP) and N terminal pro BNP (NT-proBNP)), chest X-ray, chest computed tomography (CT), pulmonary function tests (spirometry and diffusion capacity for carbon monoxide [DLCO]), 6-minute walk test (6MWT), and composite screening algorithms. The performance of these methods in detecting PH and/or PAH was assessed based on sensitivity, specificity, and positive predictive values (PPVs)/negative predictive values (NPVs). Results of the literature review were summarized by the SLR team in order to inform the consensus group (Supplementary Table 1). The draft recommendations were formulated and sent to the members of the consensus group via email. Group members voted on the draft recommendations by indicating whether they agreed or disagreed with each item. Each final recommendation required ≥70% agreement to be approved. The quality of evidence (high, moderate, low, and very low) and strength of recommendations (strong or conditional) were determined using the GRADE approach.[17,18] In addition, an algorithm for screening and early detection of PH for patients with SSc and other CTDs exhibiting overlap features of SSc tailored to the specific conditions of Türkiye was developed and approved by all members of the consensus group. Artificial intelligence–assisted technologies were not used in the production of this submitted work.

RESULTS

The literature search identified 7864 publications and 33 articles were included after title, abstract, and full-text evaluation. Among the included studies, 31 involved only patients with SSc, whereas 2 studies included a small number of patients with MCTD, SLE, Sjogren's syndrome, rheumatoid arthritis and undifferentiated CTD (UCTD), in addition to SSc patients (Supplementary Table 1; article no 10 and 15). The hemodynamic definitions of PH and PAH, the cutoff values used for diagnostic methods and the symptom status of patients varied across the studies.

Echocardiography

Transthoracic echocardiography is one of the most widely used methods for PH screening in CTDs and is recommended for annual screening in SSc patients by international PH guidelines.[19] Echocardiography can estimate systolic pulmonary artery pressure (sPAP) using tricuspid regurgitation velocity (TRV) and provides information about other signs suggesting PH, such as right ventricular enlargement, increased pulmonary artery diameter, interventricular septal flattening, reduced right ventricular outflow tract acceleration time, and tricuspid annular plane systolic excursion (TAPSE) (Table 1).[1] However, a significant limitation of echocardiography is that TRV is not detectable in all patients due to inadequate Doppler signal.[20] In SSc patients, studies have reported the sensitivity of different cutoff values for tricuspid gradient (TG) and estimated sPAP in detecting PH, precapillary PH, or PAH as 47%-100%, with a specificity of 70%-100%.[21-26] In a study including a heterogeneous group of patients with CTD, Rajaram et al[27] found that TG ≥ 40 mm Hg on echocardiography had a sensitivity of 86%, specificity of 82%, PPV of 91%, and NPV of 72% for detecting PAH.

In early stages of pulmonary vascular disease, patients with SSc with normal hemodynamic findings at rest may display an abnormal hemodynamic response in exercise. However, such a response does not necessarily indicate pulmonary vascular disease and may also occur in the presence of other conditions such as LVDD.[28,29] In SSc patients with reassuring resting echocardiographic findings, TRV measurement during dobutamine and exercise stress echocardiography showed sensitivity of 80% and 90% and specificity of 84% and 80%, respectively, for detecting PAH.[30,31] Suzuki et al[32] also demonstrated that exercise echocardiography had superior sensitivity (93% vs. 79%) and specificity (90% vs. 76%) compared to resting echocardiography for detecting PAH in patients with CTDs.

Natriuretic Peptides

Increased myocardial wall stress in PH results in the release of natriuretic peptides from cardiomyocytes.[33] Several studies have investigated the diagnostic, predictive, and prognostic value of increased natriuretic peptides, particularly in SSc-PAH.[34] However, serum levels of natriuretic peptides may remain normal in the early stages of PAH, which limits their utility for early diagnosis. Additionally, some other factors such as age, gender, body weight, and renal function can affect their serum levels.[33] In the reviewed studies, different cutoff values for BNP had a sensitivity of 60%-85% and a specificity of 35%-87% in detecting PH or PAH in patients with SSc.[35,36] Different cutoff values of serum NT-proBNP levels were reported to have a sensitivity of 45%-92%, a specificity of 90%-100%, and a negative predictive value of 56%-93% for detecting PH or PAH in patients with SSc.[36-38]

Electrocardiography

Common ECG findings associated with PH include right axis deviation, increased P wave amplitude (P pulmonale), and right bundle branch block.[39] Since these changes reflect advanced disease with increased right ventricular wall tension and hypertrophy, ECG is often normal in the early stage of PH. The sensitivity and specificity of different ECG findings for detecting PH or PAH have been reported to be between 44%-73% and 67%-97%, respectively[35,40-42] in patients with SSc.

Chest X-ray

Enlargement of the pulmonary arteries and right heart chambers are chest x-ray findings suggesting PH. Unfortunately, these findings are often absent in early-stage disease, thus a normal chest x-ray does not exclude PH.[43] A study of 49 SSc patients by Ungerer et al[42] reported a sensitivity of 25% for right descending pulmonary artery enlargement, with a specificity and positive predictive value of 100% in detecting PAH.

Table 1. Echocardiographic Probability of Pulmonary Hypertension[1]

Peak Tricuspid Regurgitation Velocity (m/s)	Presence of Other Echocardiographic "Pulmonary Hypertension Signs"*	Echocardiographic Probability of Pulmonary Hypertension
≤2.8 or unmeasurable	No	Low
≤2.8 or unmeasurable	Yes	Intermediate
2.9-3.4	No	
2.9-3.4	Yes	High
>3.4	Yes/No	

*Additional echocardiographic signs suggestive of pulmonary hypertension:
The ventricles: RV/LV ventricle basal diameter/area ratio >1.0, flattening of the interventricular septum, TAPSE/sPAP ratio <0.55 mm/mmHg.
Pulmonary artery: RVOT AT <105 ms and/or mid-systolic notching, early diastolic pulmonary regurgitation velocity >2.2 m/s, PA diameter >AR diameter, PA diameter >25 mm.
Inferior vena cava and RA: IVC diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration), RA area (end-systole) >18 cm^2.

Pulmonary Function Tests

A disproportionate reduction in carbon monoxide diffusing capacity (DLCO) with a relatively preserved forced vital capacity (FVC) can be observed in SSc-PAH.[44] Most SSc patients have DLCO levels below 60% at the diagnosis of PAH; however, decrease in DLCO begins several years prior to diagnosis.[45,46] In addition, other conditions such as ILD may also lead to decrease in DLCO in patients with SSc, which limits its specificity for PAH. Sensitivity and specificity of different cutoff values of DLCO for detecting PH or PAH in SSc patients ranged from 39%-100% and 86%-100%, respectively.[21,26,38,42] A sensitivity of 64%-100% and specificity of 32%-96% was reported for the FVC/DLCO ratio in detecting PH or PAH across the reviewed studies.[26,32,35,38] Sivova et al[47] suggested that the pulmonary capillary blood volume (Vcap) component of DLCO had better diagnostic performance than DLCO and the FVC/DLCO ratio for detecting precapillary PH in SSc patients with ILD; thus, partitioning of DLCO in this patient group may be beneficial. In another study, a formula derived using peripheral oxygen saturation and DLCO showed a sensitivity above 90% in detecting PH in SSc patients with equivocal findings in TTE, which indicates PFTs may be used as a complementary tool to echocardiography.[48]

Chest Computed Tomography

Chest CT findings suggesting the presence of PH include enlargement of pulmonary arteries and right ventricle, increased pulmonary artery-to-aorta diameter ratio and lung perfusion changes.[43] Condliffe et al[24] reported that pulmonary artery-to-aorta diameter ratio (dPa/dAo) >1 and right ventricle to left ventricle diameter ratio (dRV/dLV) >1 both have sensitivities around 80% for detecting PH in SSc patients. They also demonstrated that a composite index incorporating dPa/dAo and dRV/dLV has higher sensitivity (89%) with a specificity of 89%.[24] Another study showed a sensitivity of 65% and specificity of 67% for increased right ventricular wall thickness (>3.5 mm) in detecting PAH in patients with CTDs.[27]

Cardiac Magnetic Resonance Imaging

Cardiac MRI allows both morphological and functional assessments of cardiac structures and pulmonary arteries. It provides valuable information for diagnosing PH, risk stratification, and prognostication.[49] The advantages of cardiac MRI are that it is noninvasive, does not contain ionizing radiation, and is highly reproducible. Its limitations include high cost, limited accessibility, and longer examination time. Pulmonary artery-to-aorta diameter ratio, ventricular mass index (VMI), pulmonary artery velocity, and pulmonary artery distensibility are some parameters used for PAH detection in cardiac MRI.[49] In a study including SSc patients, a VMI >0.56 showed 100% sensitivity and 70% specificity in detecting PH.[25] Rajaram et al[27] reported 85% sensitivity and 82% specificity for VMI >0.45 and 80% sensitivity and 78% specificity for pulmonary artery distensibility <15% for PAH diagnosis in patients with CTDs. In another study, Hsu et al[22] reported a moderate sensitivity (68% and 57%) and specificity (57% for both) for pulmonary artery diameter and maximum pulmonary artery velocity in detecting PH in SSc patients. A case-control study showed that both right ventricular free wall GLS (RVFW GLS) and right ventricular ejection fraction (RVEF) measured by cardiac MRI have high sensitivity (84% and 95%) and specificity (77% and 84%) in detecting SSc-PAH.[50]

6-Minute Walk Test

6-minute walk test (6MWT) is widely used to assess exercise capacity in patients with PH. However, it may be affected by other conditions such as ILD, LVDD, and musculoskeletal involvement in patients with CTDs, limiting its specificity for PH.[51] Gadre et al[52] reported that a DIBOSA (distance walked in 6 minutes, Borg dyspnea index, and saturation of oxygen at 6 minutes) score of 0 or 1 in 6MWT had a sensitivity of 100% and a specificity of 36.3% for detecting PH in patients with SSc.

Composite Screening Algorithms

Since individual use of each method has disadvantages, combinations of different tests such as ECG, echocardiography, CT, and pulmonary function tests have been used in several studies to improve performance in detecting PH. These studies have reported sensitivity of 87%-100%, with specificity between 48% and 92% in detecting SSc-PH or SSc-PAH.[24,35,53-57] Gladue et al[53] demonstrated that combining echocardiographic right ventricular systolic pressure (RVSP) and pulmonary function test parameters (DLCO and FVC/DLCO ratio) has better sensitivity and NPV for detecting PAH compared to individual use of each method.

The prospective, multicenter DETECT study enrolled a SSc population enriched for PAH (DLCO < 60% and disease duration > 3 years), and RHC was systematically performed in all patients.[56] Among participants, 64% were in WHO functional class I or II. The study proposed a 2-step algorithm to identify patients who should undergo RHC. In step 1, the included parameters were FVC/DLCO ratio, presence of telangiectasia, anti-centromere antibody positivity, serum uric acid and NT-proBNP levels, and right axis deviation on ECG. Step 2 consisted of 2 echocardiographic parameters: right atrial area and TRV. The algorithm demonstrated a sensitivity of 96%, specificity of 48%, PPV of 35%, and NPV of 98% for detecting PAH. Subsequent single-center studies confirmed that the DETECT algorithm has higher sensitivity and NPV than echocardiographic evaluation alone, even in patients with DLCO ≥ 60%.[58,59] However, a recent post-hoc analysis of the original DETECT cohort revealed a decrease in sensitivity when the current hemodynamic criteria were applied.[60] The high referral (62%) and false-positive rates of the DETECT algorithm have led to further research to improve its specificity and PPV. Santaniello et al[61] showed that adding cardiopulmonary exercise test (CPET) to the DETECT algorithm improved its specificity (77.8%) and PPV (63%) without affecting the sensitivity. Similarly, Colalillo et al[62] demonstrated that combining TAPSE/sPAP ratio with the DETECT algorithm increased the PPV from 31% to 62%.

In a study of 49 SSc patients who underwent RHC, Thakkar et al[57] proposed the ASIG screening model, which combines NT-proBNP and pulmonary function test results. The algorithm demonstrated a sensitivity of 94.1%, specificity of 54.5%, PPV of 61.5%, and NPV of 92.3%. This "first-tier" algorithm suggests that if either of 2 components is present (DLCO <70% predicted with FVC/DLCO ≥ 1.8 AND/OR NT-proBNP > 210 pg/mL), the patient should undergo further evaluation with TTE, high-resolution CT, ventilation-perfusion (V/Q) scanning, and 6MWT; and RHC should be performed in cases suspected of PAH. Further investigation for PAH is unnecessary in patients where both components are absent.

In a comparison of the DETECT, ASIG, and 2009 ESC/ERS algorithms for PAH screening in SSc patients, Hao et al[63] reported that both DETECT and ASIG algorithms had higher sensitivity (100% for both) than the ESC/ERS (96.3%) algorithm. The ASIG algorithm had higher specificity (54.5% vs. 35.3%) and PPV (60% vs. 55.1%) and a lower referral rate compared to the DETECT algorithm. In another study, Vandecasteele et al[64] compared the DETECT algorithm with the 2009 and 2015 ESC/ERS echocardiographic screening algorithms. All 3 algorithms captured all PAH patients, though DETECT had the highest referral rate (30%) and lowest PPV (6%). Interestingly, the DETECT algorithm more frequently recommended RHC (93%) than the 2009 and 2015 algorithms (29% and 71%, respectively) in patients with mean pulmonary artery pressure (mPAP) between 21 and 24 mm Hg.

Consensus-based recommendations and algorithm for screening and early detection of PH in patients with CTD are illustrated in Table 2 and Figure 1.

DISCUSSION

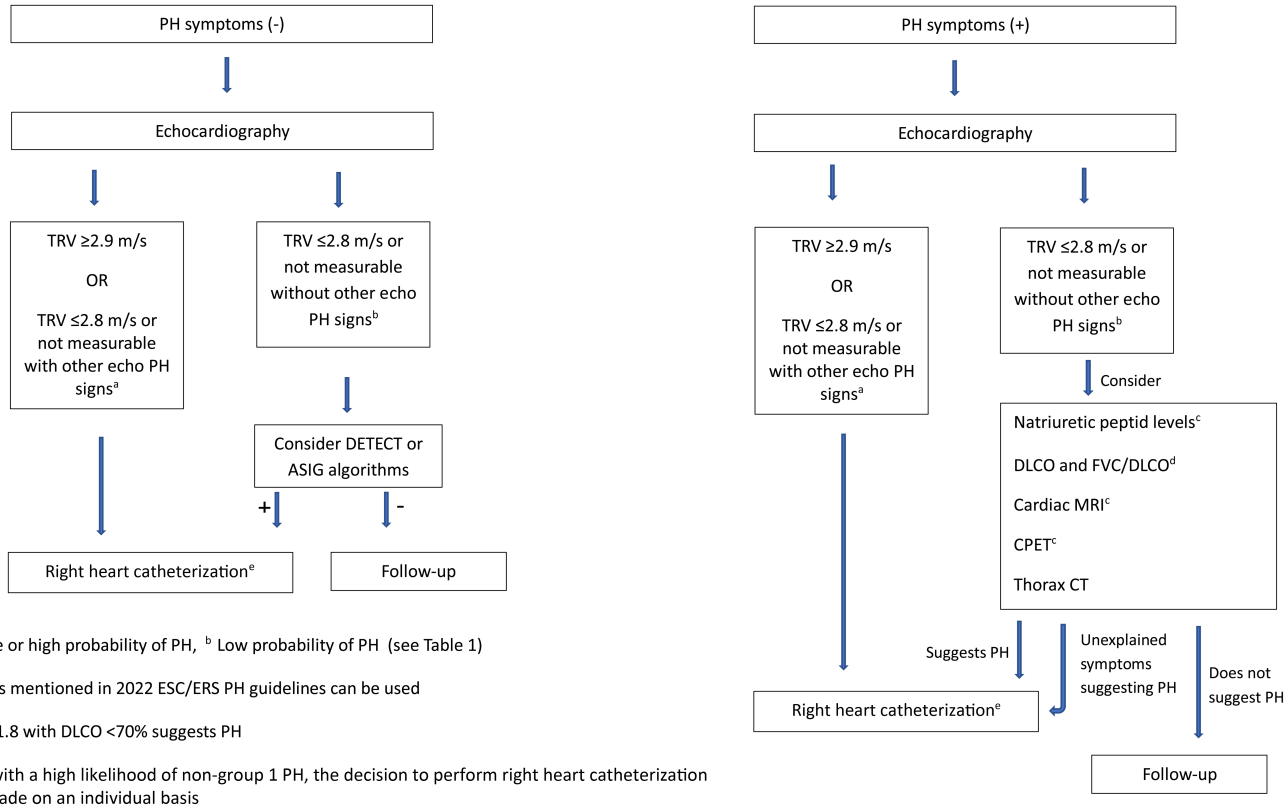
Review of the literature revealed that various noninvasive diagnostic methods have been evaluated for detecting PH or PAH in patients with SSc while data is limited for other CTDs. Most of the conducted studies included symptomatic patients with an increased risk of PH rather than a true screening population (asymptomatic or mildly symptomatic individuals). With the exception of 1 study, most did not systematically perform RHC, and therefore predictive values of relevant methods for PAH may not be accurately determined.

Unfortunately, current methods other than DLCO do not have the capability to identify patients with PAH prior to the

Table 2. Recommendations for Screening and Early Detection of Pulmonary Hypertension in Patients with Connective Tissue Disease

Recommendation	Quality of Evidence	Strength of Recommendation	Agreement (%)
It is recommended that all patients with CTDs be evaluated for symptoms and signs of PH	Low	Strong	94
Annual echocardiography is suggested for PH screening in patients with SSc (and other CTDs with overlap features of SSc)	Low	Conditional	94
Use of the DETECT or ASIG algorithms is suggested for PH screening in asymptomatic patients with SSc (and other CTDs with overlap features of SSc) with low echocardiographic probability of PH	Low	Conditional	94
Use of additional methods, such as natriuretic peptides, pulmonary function tests, cardiac MRI, and CPET is suggested in the evaluation of symptomatic patients with SSc (and other CTDs with overlap features of SSc) with low echocardiographic probability of PH	Low	Conditional	94
RHC is suggested in patients with SSc (and other CTDs with overlap features of SSc) with unexplained sypmtoms suggesting	Very low	Conditional	94
Evaluation for the presence of PH in patients with CTDs without overlap features of SSc is suggested only if symptoms, signs, or imaging or laboratory findings are suggestive of PH	Very low	Conditional	94

CTD, connective tissue disease; MRI, magnetic resonance imagigng; PH, pulmonary hypertension; RHC, right heart catheterisation; SSc, systemic sclerosis.



[a] Intermediate or high probability of PH, [b] Low probability of PH (see Table 1)

[c] Cut off values mentioned in 2022 ESC/ERS PH guidelines can be used

[d] FVC/DLCO ≥1.8 with DLCO <70% suggests PH

[e] In patients with a high likelihood of non-group 1 PH, the decision to perform right heart catheterization should be made on an individual basis

Figure 1. Proposed screening and early detection algorithm for pulmonary hypertension in patients A) with SSc and B) with CTD with overlap features of SSc (see Table 3) PH, pulmonary hypertension; TRV, tricuspid regurgitation velocity; DLCO, carbon monoxide diffusing capacity; FVC, forced vital capacity; MRI, magnetic resonance imaging; CPET, cardiopulmonary exercise testing; ESC, European Society of Cardiology; ERS, European Respiratory Society.

elevation of pulmonary artery pressure. However, as mentioned above, DLCO levels begin to decline years before the diagnosis of PAH, and it is not clear how these patients should be followed. As a result, very early diagnosis of PAH does not seem to be achievable using current methods, underscoring the need for reliable biomarkers. There are several promising circulating biomarkers that have shown acceptable performance in the identification of CTD-PAH such as asymmetric dimethylarginine, growth differentiation factor-15, follistatin-like 3, and midkine; however, they need to be validated in large patient cohorts before being implemented in routine clinical practice.[65]

Echocardiography is the most commonly used method for PH screening in patients with CTD and allows for direct estimation of pulmonary artery pressure. Echocardiography can also identify other conditions such as valvular heart disease and left ventricular dysfunction, which may contribute to the development of PH. Most of the composite algorithms utilize echocardiography to determine patients at high risk for PH or PAH, prior to RHC. In Türkiye, studies investigating PH in CTDs have mostly used echocardiography as the diagnostic tool and reported the frequency of PH as 19%, 1.8%-8.2%, and 23.4% in SSc, SLE, and Sjögren's syndrome, respectively, indicating that these patients are at increased risk for the development of PH.[66-69] In a survey conducted among rheumatologists in Türkiye, echocardiography was reported as the most frequently used method for PH screening in patients with CTDs. Approximately 80% of respondents indicated that echocardiographic evaluation is performed within one month of ordering at their respective centers.[70] The fact that the age

Table 3. Features suggestive of systemic sclerosis

Clinical	Laboratory/Imaging
Raynaud's phenomenon	SSc specific autoantibodies (anti centromere, anti-topoisomerase-1, anti RNA-polimerase-3 etc.)
Puffy hands	"Scleroderma-like" nailfold capillaroscopic pattern
Sclerodactyly	
Esophageal dismotility	
Digital ulcers	
Renal crisis	
Telangiectasia	

at diagnosis of SSc-PAH is lower in Türkiye than previously reported registries suggests that screening methods are easily accessible in the Turkish healthcare system.[71] It is believed that each country needs to define appropriate screening strategies by considering its unique healthcare resources along with accessibility and cost of screening methods. In addition, the preferences of healthcare professionals involved in the routine care of patients are also of importance. Consequently, the consensus group developed an algorithm that prioritizes echocardiography for screening and early detection of PH in patients with SSc and other CTDs exhibiting overlap features of SSc, while also identifying circumstances where alternative screening methods to echocardiography would be appropriate. Although a literature review on CPET was not performed, CPET was incorporated into the proposed algorithm. Despite its complexity and the fact that it can only be performed in a limited number of centers in Türkiye, CPET may provide valuable data in identifying both the presence and underlying etiology of PH in selected patients.[72] The suggested algorithm has been designed for physicians practicing in Türkiye, and its applicability to other countries may vary based on their regulations and healthcare resources.

The optimal frequency of PAH screening in patients with CTDs remains uncertain. Some studies suggest that the identification of SSc patients with very low probability of PAH based on symptoms, DLCO, and NT-proBNP, may eliminate the need for annual echocardiographic screening in this population.[55] Findings from the Australian scleroderma study cohort revealed that the majority of patients were diagnosed with PAH at the initial screening; however, those diagnosed on subsequent annual screenings had more favorable functional capacity and hemodynamic parameters.[73] Considering the high mortality rate of PAH, it is recommended that annual screening for PAH in patients with SSc and other CTDs with overlap SSc features of SSc, though evidence supporting this strategy is limited.

Due to the time frame used in the literature review, the included studies mostly used the previous hemodynamic cutoff values for mPAP and PVR. Recent studies suggest that the sensitivity of the DETECT algorithm may be lower in identifying SSc-PAH according to the new haemodynamic definition.[60,74] A prospective study conducted in Türkiye also demonstrated that the sensitivity of the ESC/ERS, DETECT, and ASIG algorithms for detecting PAH in patients with SSc decreased when revised hemodynamic criteria were applied.[66] This underscores the need for validated diagnostic algorithms tailored to the updated hemodynamic criteria. Feasibility and benefit of screening PH is controversial in CTDs other than SSc. Although these patients are clearly at increased risk of PH development, data about PH screening is quite limited. Thus, evaluation of CTD patients without overlap features of SSc for PH is recommended only if they have symptoms or signs suggesting PH. In patients with CTD exhibiting SSc features, the same algorithm used for SSc patients can be applied for the detection of PH.

In conclusion, an updated literature review was provided along with consensus-based recommendations for screening and early diagnosis of PH in CTDs. An algorithm incorporating patients' symptom status and different diagnostic methods was also proposed for clinical use by physicians in Turkiye. Future validation of this algorithm in large prospective patient cohorts would be valuable for evaluating its applicability and effectiveness.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Informed Consent: This work is a manuscript review and consensus statement; therefore, it does not involve any patient data.

Peer-review: Externally peer-reviewed.

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TERMS USED IN PUBMED SEARCH

1. (pulmonary hypertension OR PH) AND (connective tissue disease OR systemic sclerosis OR scleroderma OR systemic lupus erythematosus OR SLE OR sjogren*) AND (BNP or Nt-proBNP)
2. (pulmonary hypertension OR PH) AND (connective tissue disease OR systemic sclerosis OR scleroderma OR systemic lupus erythematosus OR SLE OR sjogren*) AND (chest computed tomography OR chest CT)
3. (pulmonary hypertension OR PH) AND (connective tissue disease OR systemic sclerosis OR scleroderma OR systemic lupus erythematosus OR SLE OR sjogren*) AND (ECG OR electrocardiogra*)
4. (pulmonary hypertension OR PH) AND (connective tissue disease OR systemic sclerosis OR scleroderma OR systemic lupus erythematosus OR SLE OR sjogren*) AND (chest X-ray OR chest plain radiogra* OR chest plain x-ray)
5. (pulmonary hypertension OR PH) AND (connective tissue disease OR systemic sclerosis OR scleroderma OR systemic lupus erythematosus OR SLE OR sjogren) AND (DLCO OR diffusion capacity)
6. (pulmonary hypertension OR PH) AND (connective tissue disease OR systemic sclerosis OR scleroderma OR systemic lupus erythematosus OR SLE OR sjogren*) AND echo*
7. (pulmonary hypertension OR PH) AND (connective tissue disease OR systemic sclerosis OR scleroderma OR systemic lupus erythematosus OR SLE OR sjogren*) AND cardiac MR imaging
8. (pulmonary hypertension OR PH) AND (connective tissue disease OR systemic sclerosis OR scleroderma OR systemic lupus erythematosus OR SLE OR sjogren*) AND algorithm*
9. (pulmonary hypertension OR PH) AND (connective tissue disease OR systemic sclerosis OR scleroderma OR systemic lupus erythematosus OR SLE OR sjogren*) AND (six minute walk test OR 6MWT OR "6-MWT")

Supplementary Table 1. Summary of included studies

No	Author, year, study type	Population	Assessed method(s)	Definition of PH/PAH	Results
1	Ninagawa, 2019, retrospective[33]	58 SSc patients with dyspnea Exclusion criteria: • ILD with FVC <60% • Renal insufficiency • Pulmonary embolism • Left-sided heart disease • Pulmonary venous stenosis • PCWP > 15 mm Hg • Indication for RHC: unexplained dyspnea	• BNP • ECG • FVC/DLCO ratio • Echocardiography	Elevated PAP: 1) mPAP≥ 25 mm Hg 2) mPAP> 20 mm Hg	**For mPAP ≥ 25 mm Hg** BNP cut off 79 pg/mL: sensitivity 71%, specificity 66% (AUC: 0.70) Right axis deviation in ECG: sensitivity 63%, specificity 94% FVC/DLCO ratio cut off 1.47: sensitivity 100%, specificity 32 % (AUC: 0.71) **For mPAP > 20 mm Hg** BNP cut off 24.8 pg/Ml: sensitivity 85%, specificity 35% (AUC: 0.61) Right axis deviation in ECG: sensitivity 48%, specificity 96% FVC/DLCO ratio cut off 1.78: sensitivity 78%, specificity 72% (AUC: 0.80) Algorithm including autoantibodies, BNP, uric acid, right axis deviation in ECG, FVC/DLCO ratio: sensitivity 92%, specificity 57% Addition of TRV to algorithm: sensitivity 87.5%, spesificity 92% (AUC:0.92)
2	Cavagna, 2010, prospective [34]	135 patients with SSc Exclusion criteria: • Extended ILD • FVC/DLCO >1.4 • Deep venous thrombosis, or pulmonary thromboembolisms • Previous diagnosis of PAH under treatment • Pregnancy • Significant valvular disease; Systolic or diastolic dysfunction • History of atrial fibrillation, myocardial infarction, neoplasia, or severe hepatic diseases • Indications for RHC: sPAP ≥36 mm Hg in echocardiography, DLCO< %50, ≥20% decrease in DLCO in previous yearin the absence of pulmonary fibrosis, unexplained dyspnea	• BNP • NT-proBNP	PAH: mPAP ≥ 25 mmHg	**For PAH** • BNP cut off 64 pg/ml: sensitivity 60%, specificity 87%, NPV 93% olarak (AUC: 0.74) • NT-proBNP cut off 239.4 pg/ml: sensitivity 45%, specificity 90%, NPV 93% (AUC: 0.63)
3	Williams, 2006, prospective case-control[35]	109 patients with SSc (68 with SSc-PAH and 41 SSc without PAH) Exclusion criteria: • Significant renal impairment (creatinine >150 mmol/L]. • Evidence of LV impairment on echocardiography or at cardiac catheterization (pulmonary capillary wedge pressure>15 mmHg). • Indications of RHC: not specificied	NT-proBNP	Not specified	**For PAH** NT-proBNP cut off 395 pg/ml: sensitivity 55.9%, specificity 95.1%, PPV of 95.1%, and NPV 56.5%

(*Continued*)

Supplementary Table 1. Summary of included studies (*Continued*)

No	Author, year, study type	Population	Assessed method(s)	Definition of PH/PAH	Results
4	Couperus, 2016, retrospective[38]	• 273 patients with SSc (196 lcSSc, 77 dcSSc • Indications for RHC: suspicion of group 1 PH with elevated sPAP on echocardiography	• ECG	PAH: mPAP ≥25 mmHg, PAWP ≤15 mmHg ve PVR ≥3 WU	**For PH** • VG-RVPO >-7 mV.ms cut off: sensitivity 62%, specificity 86%, PPV 97% in lcSSc • VG-RVPO >-9 mV.ms cut off: sensitivity 29%, specificity 80%, PPV 13%, NPV 92% in dcSSc
5	Wokhlu,2006, retrospective[39]	23 patients with SSc (12 lcSSc) Exclusion criteria: • PH unrelated to SSc, pulmonary venous hypertension and conditions associated with increased left atrial pressure • Indications for RHC: not specificed	• ECG	Not specificed	**For mPAP >25 mmHg** • P wave amplitude in derivation II cut off 0.12 mV: sensitivity 73% and specificity 67%
6	Ungerer,1983, prospective[40]	49 patients with SSc • Exclusion criteria: not specificied • Indications for RHC: not specificied	• Chest X-ray • ECG • Echocardiography • DLCO	• Definite PAH: mPAP≥22 mmHg and PCWP≤12 mmHg • Borderline PAH: mPAP≥20 mmHg and PCWP≤12 mmHg	**For all PAH (mPAP ≥20 mmHg)** • Enlargement of right pulmonary artery on chest X-ray: sensitivity %25, spesificity %100, PPV %100 • Right bundle branch block or right ventricular hypertrophia, or right atrial enlargement on ECG: sensitivity %44, spesificity %97, PPV % 100 • Right ventricular enlargement or pulmonary valve abnormalities or decreased diastolic E-F slope on echocardiography: sensitivity %38, spesificity %88, PPV % 60 • DLCOc cut off 43% : sensitivity %50, spesificity %88, PPV %67 **For absolute PAH (mPAP ≥22 mmHg)** • Enlargement of right pulmonary artery on chest X-ray: sensitivity %50, • Right bundle branch block or right ventricular hypertrophia, or right atrial enlargement on ECG: sensitivity 73% • Right ventricular enlargement or pulmonary valve abnormalities or decreased diastolic E-F slope on echocardiography: sensitivity 50% • DLCOc cut off 43% : sensitivity 87%

No	Author, year, study type	Population	Assessed method(s)	Definition of PH/PAH	Results
7	Mukerjee,2004, prospective[19]	137 patients with SSc (85 mild or no ILD, 52 stage 3-4 fibrosis) • Indications for RHC: TG>35 mm Hg on echocardiography or pulmonary acceleration time <100ms or DLCO <50% (in the absence of stage 3-4 fibrosis), 20% decrease in DLCO in previous 2 years, unexplained decrease in exercise capacity	• Echocardiography • DLCO	PAH: not specificed for rest Excercise PAH: mPAP >30 mmHg when <25 mmHg at rest	**For PAH** • ≥ 45 mmHg on echocardiography: sensitivity 47%, specificity 97%, PPV 98%, NPV 41% • DLCO ≤50% in patients with no or mild ILD: sensitivity 39%, specificity 90%, PPV 88%, NPV 46%
8	Hsu,2008, prospective[20]	49 patients with SSc Exclusion criteria • LV dysfunction on echocardiography or RHC, airway obstruction, CTEPH, congenital heart disease, portopulmonary PH,HIV • Indications for RHC: progressive dyspnea and/or loud P2, sPAP >40 mm Hg on echocardiography, FVC/DLCO >1.4 with decreased DLCO	• Echocardiography • Cardiac MRI • Pulmonary function tests	PH: mPAP ≥ 25 mmHg and PCWP ≤ 15 mmHg at rest, mPAP ≥ 30 mmHg and PCWP ≤ 15 mmHg on exercise	**For PH** • RVSP >47 mmHg on echocardiography: sensitivity 58%, specificity 96%, PPV 93%, NPV 71% (AUC 0.84) • PA diameter >28 mm on MRI: sensitivity 68%, specificity 71%, PPV 71%, NPV 68% (AUC 0.78) • Maximum pulmonary artery velocity <66 cm/s on MRI: sensitivity 57%, specificity 57%, PPV %57, NPV 57% (AUC 0.70) • FVC/DLCO >2: sensitivity 71%, specificity 72%, PPV 71%, NPV 72% (AUC 0.76)
9	Kooranifar,2021, cross-sectional[21]	15 patients with lcSSc • Indications for RHC: not specificed	• Echocardiography • Chest CT	PAH: mPAP ≥ 25 mmHg	**For PAH** • Pulmonary artery length cut off 29.9 mm on CT: sensitivity and specificity 100% • PAP cut off 22.88 mmHg on echocardiography: sensitivity 72%, specificity 100% (AUC =0.841)
10	Rajaram, 2012, retrospective[25]	81 CTD patients with suspicion of PH (66 SSc, 5 SLE, 4 MCTD, 3 RA, 3 undifferantiated CTD) • Indications for RHC: unexplained dyspnea, TG ≥40 mm Hg on echocardiography, TG 30-40 mm Hg with DLCO < 50%	• Echocardiography • Chest CT angiography • Cardiac MRI	PH: mPAP ≥ 25 mm Hg PAH: mPAP ≥ 25 mm Hg and PCWP ≤ 15 mm Hg	**For PAH** **Cardiac MRI** • Ventricular mass index ≥ 0.45: sensitivity 85%, spesificity 82%, PPV 92%, NPV 69% • Pulmonary artery distensibility ≤ 15: sensitivity 80%, spesificity 78%, PPV 90%, NPV 59% **Chest CT** • RV wall thickness ≥ 3.5 mm: sensitivity 65%, spesificity 67%, PPV 88%, NPV 35% • Hepatic venous reflux: sensitivity 41%, spesificity 85%, PPV 89%, NPV 35% • PA/Ao ≥ 1: sensitivity 54%, spesificity 74%, PPV 87%, NPV 40% **Echocardiography** • TG ≥ 40 mm Hg: sensitivity 86%, spesificity 82%, PPV 91%, NPV 73%

(*Continued*)

Supplementary Table 1. Summary of included studies (*Continued*)

No	Author, year, study type	Population	Assessed method(s)	Definition of PH/PAH	Results
11	Condliffe,2011, retrospective[22]	89 SSc patients with suspected PAH • Indications for RHC: not specificed	• Echocardiography • CT pulmonary angiography (CTPA)	PH: mPAP ≥ 25 mm Hg PAH: mPAP ≥ 25 mm Hg and PCWP ≤ 15 mm Hg	**For PH** **CTPA** • PA/ascending aorta diameter ≥ 1: sensitivity 80%, specificity 89%, PPV 95%, NPV 61% • RV/LV diameter ≥ 1: sensitivity 80%, specificity 35%, PPV 73%, NPV 39% **Echocardiography** • TG ≥40 mm Hg: sensitivity 79%, specificity 80%, PPV 90%, NPV 62% **CT-echocardiography composite index** < 28: sensitivity 89%, specificity 89%, PPV 95%, NPV 77% **CT-echocardiography composite index <28 or tricuspit regurgitation on CT** Sensitivity 100%, specificity 63%, PPV 87%, NPV 100%
12	Hagger, 2009, retrospective[23]	40 patients with SSc • Indications for RHC: abnormalities based on echocardiography, decreased gas transfer, symptoms compatible with PH	• Echocardiography • Cardiac MRI	PH at rest: mPAP ≥ 25 mm Hg PAH: mPAP ≥ 25 mm Hg and PCWP ≤15 mm Hg at rest Exercise PH: mPAP≥ 30 mm Hg on exercise with normal mPAP at rest	**For PH at rest** • Ventricular mass index cut off 0.56: sensitivity 100%, specificity 70%, PPV 88%, NPV 100% • TG cut off 40 mmHg on echocardiography: sensitivity 100%, specificity 70%, PPV 86%, NPV 100%
13	Rallidis, 2021, prospective[28]	36 patients with SSc Inclusion criteria • TRV 2.7-3.2 m/s, LVEF >55%, preserved RV functions, no ischemic or valvular heart disease, no diastolic dysfunction, sinus rythm FEV1 ≥55%, TLC >60%	• Dobutamin stress echo	PAH: mPAP > 20 mm Hg and PCWP ≤15 mm Hg and PVR ≥ 3WU	**For PAH** • Maximal TR velocity > 3.1 m/s: sensitivity 80%, specificity 84%, PPV 79.2%, NPV 84.8%
14	Rallidis , 2021, prospective[29]	46 patients with SSc Inclusion criteria • TRV 2.7-3.2 m/s, LVEF >55%, preserved RV functions, no ischemic or valvular heart disease, no diastolic dysfunction, sinus rythm FEV1 ≥55%, TLC >60%	• Exercise doppler echo	PAH: mPAP > 20 mm Hg and PCWP ≤15 mm Hg and PVR ≥ 3WU	**For PAH** • Post-exercise TRV > 3.4 m/s: sensitivity 90.5%, specificity 80%, PPV 79.1%, NPV 90.9% • Post-exercise- pre-excercise TRV >0.5 m/s: sensitivity 90.5%, specificity 64%, PPV 67.8%, NPV 88.9%

No	Author, year, study type	Population	Assessed method(s)	Definition of PH/PAH	Results
15	Suzuki, 2013, prospective[30]	52 CTD patients (36 SSc, 8 MCTD, 5 SLE, 3 Sjogren) Exclusion criteria • Previous diagnosis of PAH, sPAP ≥50 mm Hg at rest, FVC <80%, LVEF< 60%, LV diastolic dysfunction • Indications for RHC: post exercise sPAP ≥50 mm Hg with 6MWD ≤400 m	• Resting echocardiography • Exercise echocardiography	PAH: mPAP ≥25 mm Hg	**For PAH** • sPAP cut off 38.6 mm Hg on resting echocardiography: sensitivity 79%, specificity 76% (AUC:0.79) • sPAP cut off için 69.6 mm Hg on exercise echocardiography: sensitivity 93%, specificity 90% (AUC:0.91)
16	Lui, 2023, retrospective[52]	130 patients with SSc • Indications for RHC: not specificied	• ECG • Echocardiography • Pulmonary function tests • Chest CT	PH : mPAP >20 mm Hg	**For PH** • Random forest model: sensitivity 95%, specificity 80% (AUC: 0.92)
17	Gladue, 2013, retrospective[51]	347 patients with SSc (69 PAH, 179 non-PH) Exclusion criteria • Group 2 and group 3 PH • Indications for RHC: RVSP > 40 mm Hg on echocardiography, DLCO <50% in the absence of pulmonary fibrosis, unexplained dyspnea	• Echocardiography • Pulmonary function tests	PAH: mPAP≥ 25mmHg and PCWP ≤ 15mmHg with an FVC ≥ 70% predicted and none or-mild ILD on high resolution CT	**For PAH** • RVSP >40 mmHg on echocardiography and DLCO <60%: sensitivity 97%, specificity 62%, PPV 50%, NPV 98% • RVSP >40 mmHg on echocardiography and FVC/DLCO ≥ 2:sensitivity 97%, specificity 79%, PPV 64%, NPV 98%
18	Semalulu, 2020, retrospective[53]	925 patients with SSc (37 PAH) • Indications for RHC: not specificied	• Dyspnea index • NT-proBNP • DLCO	Not specificied	**For PAH** • Composite model including dyspnea index, NT-proBNP, DLCO: sensitivity 87%, specificity 74%
19	Yoneda, 2023, retrospective[24]	44 patients with SSc Exclusion criteria • PCWP >15 mm Hg • Indications for RHC: not specificied	• Echocardiography • Pulmonary function tests	Precapillary PH: mPAP >20 mmHg and PCWP ≤ 15 mmHg	**For precapillary PH** • sPAP cut off 35 mmHg on echocardiography: sensitivity 62.5%, specificity 86.1% • DLCO >%70: sensitivity 62.5%, specificity 86.1% • FVC/DLCO >1.56: sensitivity 71.4%, specificity i 92%
20	Gadre, 2017, retrospective[50]	286 patients with SSc (129 PH) • Indications for RHC: not specificied	• Composite score consisting of 3 parameters in 6MWT (walking distance, BORG dyspnea index, oxygen saturation at the end of the test)-DIBOSA score	PH: mPAP ≥ 25 mm Hg	**For PH** • DIBOSA score 0 or 1: sensitivity 100%, specificity 36.3%, PPV 56.3%, NPV 100% • DIBOSA score 2 or 3: sensitivity 58.1%, specificity 92.4%, PPV 86.2%, NPV 72.9%

(*Continued*)

Supplementary Table 1. Summary of included studies (*Continued*)

No	Author, year, study type	Population	Assessed method(s)	Definition of PH/PAH	Results
21	Distler, 2023, prospective[58]	• DETECT study cohort	• Post-hoc analysis of DETECT study	PH: mPAP >20 mm Hg PAH: mPAB >20 mm Hg, PCWP ≤ 15 mm Hg, PVR >2WU	DETECT algorithm: sensitivity 88.2%, specificity 50.8%, PPV 46.9%, NPV 89.7%
22	Young, 2021, retrospective[56]	68 patients with SSc (mild or no ILD) • Indications for RHC: not specificied (all patients were routinely screened for PAH based on 2013 CTD-PAH recommendations and DETECT algorithm	• DETECT algorithm • 2015 ESC/ERS guidelines	PAH: 1. mPAP >20 mm Hg and PCWP ≤ 15 mm Hg, PVR ≥ 3WU and ILD on HRCT < 20% (2018 definition) 2. mPAP ≥25 mm Hg and PCWP ≤ 15 mm Hg, no or mild ILD (2009 definition)	**For PAH (2018)** **All patients** • DETECT algorithm: sensitivity 100%, specificity 20%, PPV 29%, NPV 100% • 2015 ESC/ERS algorithm: sensitivity 80%, spesificity 57%, PPV 24%, NPV 94% **Patients with DLCO ≥60%** • DETECT algorithm: sensitivity 100%, specificity 29%, PPV 15%, NPV 100% • 2015 ESC/ERS algorithm: sensitivity %67, spesificity %67, PPV %20, NPV %94 **For PAH (2009)** **All patients** • DETECT algorithm: sensitivity 100%, specificity 33%, PPV 36%, NPV 100% • 2015 ESC/ERS algorithm: sensitivity 74%, spesificity 61%, PPV 41%, NPV 86% **Patients with DLCO ≥%60** • DETECT algorithm: sensitivity 100%, specificity 30%, PPV 24%, NPV 100% • -2015 ESC/ERS algorithm: sensitivity 60%, spesificity 70%, PPV 30%, NPV 89%
23	Santaniello, 2020, prospective[59]	96 patients with SSc (disease duration > 3 years, DLCO <60%)- 54 patients DETECT positive • Indications for RHC: DETECT algorithm	• CPET before RHC in patients who are positive for DETECT algorithm	PAH: mPAP ≥25 mm Hg and PCWP ≤ 15 mm Hg, PVR ≥ 3WU Precapillary PH: mPAP >20 mm Hg and PCWP ≤ 15 mm Hg, PVR ≥ 3WU	**For PAH** • VE/VCO2 cut off 39: sensitivity 100%, specificity 77.8%, PPV 63%, NPV 100% **For pre-capillary PH** • VE/VCO2 cut off 36: sensitivity 100%, specificity 71.4%, PPV 71.4%, NPV 100%
24	Colalillo, 2022, prospective[60]	51 patients with SSc Exclusion criteria • Uncontrolled HT, valvular heart disease, heart failure, hepatic or renal failure, diabetes, coagulopathy • Indications for RHC: DETECT algorithm	• TAPSE/sPAP ratio on echocardiography RHC in patients who are positive for DETECT algorithm	Not specificed	**For PAH** • TAPSE/sPAP ratio cut off 0.60 mm/mmHg: PPV 61%

No	Author, year, study type	Population	Assessed method(s)	Definition of PH/PAH	Results
25	Del Castillo, 2017, retrospective[57]	83 patients with SSc Exclusion criteria • FVC <40%, DLCO ≥ 60%, disease duration < 3 years • Indications for RHC: RVSP >36 mm Hg on echocardiography, FVC/DLCO >1.6, unexplained dyspnea	• DETECT algorithm • ESC/ERS 2009 algorithm	PH: mPAP ≥ 25 mm Hg PAH: mPAP ≥ 25 mm Hg, PCWP ≤15 mm Hg, PVR>3WU Borderline mPAP: mPAP 21-24 mm Hg, PCWP ≤15 mm Hg	**For PH** • DETECT algorithm: sensitivity 98%, specificity 45%, PPV 75%, NPV 93% • ESC/ERS 2009 algorithm: sensitivity 81%, specificity 87%, PPV 91%, NPV 73% **For PAH** • DETECT algorithm: sensitivity 100%, specificity 43%, PPV 69%, NPV 100% • ESC/ERS 2009 algorithm: sensitivity 91%, specificity 86%, PPV 89%, NPV 89% **For mPAP ≥ 21 mmHg** • DETECT algorithm: sensitivity 94%, specificity 64%, PPV 90%, NPV 75% • ESC/ERS 2009 algorithm: sensitivity 70%, specificity 86%, PPV 94%, NPV 44%
26	Coghlan, 2014, prospective[54]	466 patients with SSc (disease duration > 3 years, DLCO <60%) Exclusion criteria • FVC< 40%, renal insufficiency, previous PAH diagnosis, pregnancy, left heart disease • 68% symptomatic • All patients systematically underwent RHC	DETECT algorithm 1. step: FVC/DLCO ratio, presence of telengiectasies, anti-sentromer antibody positivity, NT-proBNP, uric acid, right axis deviation on ECG 2. step: right atrial area and TRV on echocardiography	PAH: mPAP ≥ 25 mm Hg and PCWP ≤15 mm Hg	**For PAH** • DETECT algorithm: sensitivity 96%, specificity 48%, PPV 35%, NPV 98% • ESC/ERS algorithm: sensitivity 71%, specificity 69%, PPV 40%, NPV 89%
27	Thakkar, 2012, retrospective[36]	94 patients with SSc • 94% symptomatic • Indications for RHC: sPAP ≥ 40 mmHg on echocardiography, DLCO ≤50%, 20% decrease in DLCO in previous year, unexplained dyspnea	• NT-proBNP • Pulmonary function tests	PAH: mPAP ≥25 mm Hg, PCWP ≤15 mm Hg, no or mild ILD on HRCT	**For PAH** • NT-proBNP cut off 209.8 pg/ml: sensitivity 92.9%, specificity 100% • DLCO cut off 70.3%: sensitivity 100%, specificity 100% • FVC/DLCO ≥1.66: sensitivity 64.3%, specificity 96.7% • FVC/DLCO ≥1.82 and DLCO <70.3%: sensitivity 50%, specificity 100% • FVC/DLCO ≥1.82 and DLCO <70.3% and/or NT-proBNP ≥209.8 pg/ml: sensitivity 100%, specificity 100%

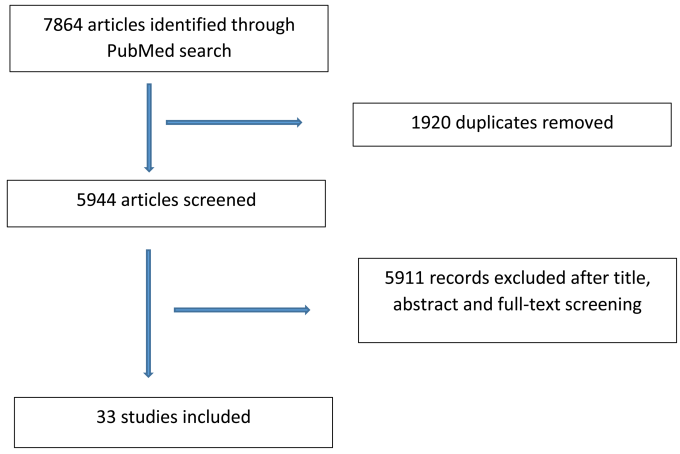
(*Continued*)

Supplementary Table 1. Summary of included studies (*Continued*)

No	Author, year, study type	Population	Assessed method(s)	Definition of PH/PAH	Results
28	Thakkar, 2013, prospective[55]	49 patients with SSc • 94% symptomatic • Indications for RHC: sPAP ≥ 40 mm Hg on echocardiography, DLCO ≤50%, 20% decrease in DLCO in 1 year, unexplained dyspnea	ASIG algorithm: Component A: DLCO ≤70% with FCV/DLCO ≥ 1.8 Component B: NT-proBNP ≥210 pg/ml (No further investigation if both negative, further investigation and RHC if necessary if either positive)	PH: mPAP ≥25 mm Hg PAH: mPAP ≥25 mm Hg, PCWP ≤15 mm Hg, no or mild ILD on HRCT, FVC >70%	**For PH** • Algorithm sensitivity 88.9%, specificity 54.5%, PPV: 70.6%, NPV 80% • ESC/ERS algorithm: sensitivity 92.6%, specificity 31.8%, PPV: 62.5%, NPV 77.8% **For PAH** • Algorithm sensitivity 94.1%, specificity 54.5%, PPV: 61.5%, NPV 92.3% • ESC/ERS algorithm: sensitivity 94.1%, specificity 31.8%, PPV: 51.6%, NPV 87.5%
29	Hao, 2015, prospective[61]	73 patients with SSc Exclusion criteria • Previous diagnosis of PH, FVC <40%, pregnancy, renal insufficiency • Symptom status: not specificied • Indications for RHC: sPAP ≥ 40 mmHg on echocardiography, DLCO ≤50% (with FVC >85%)	• DETECT algorithm • ASIG algorithm • ESC/ERS 2009 algorithm	PH: mPAP ≥25 mm Hg PAH: mPAP ≥25 mm Hg, PCWP ≤15 mm Hg, no or mild ILD on HRCT, FVC >60%	**For PAH (vs. non-PH)** • DETECT algorithm: sensitivity 100%, specificity 35.3%, PPV 55.1%, NPV 100% • ASIG algorithm: sensitivity 100%, specificity 54.5%, PPV 60.0%, NPV 100% • ESC/ERS 2009 algorithm: sensitivity 96.3%, specificity 32.3%, PPV 55.3%, NPV 90.9%
30	Vandecasteele,2017, prospective[62]	195 patients with SSc • 70% symptomatic • Indications for RHC: Positive DETECT or ESC/ERS 2009 algorithm	• DETECT algorithm • ESC/ERS 2009 algorithm • ESC/ERS 2015 echocaridography screening	PH: mPAP ≥25 mm Hg Borderline elevayed mPAP: 21-24 mm Hg PAH: mPAP ≥25 mm Hg and PCWP ≤15 mm Hg in the absence of extensive ILD	**For PAH** • DETECT algorithm: sensitivity 100%, PPV 6% • ESC/ERS 2009 algorithm: sensitivity 100%, PPV 23% • ESC/ERS 2015 echocardiography screening: sensitivity 100%, PPV 11%
31	Lindholm, 2019, case-control[48]	38 patients with SSc, 19 patients with SSc-PAH, 19 healthy controls Exclusion criteria • Postcapillary PH, left-sided heart disease, cardiac shunts, congenital heart disease • Symptom status: not specificed • Indications for RHC: not specificied	• Cardiac MRI	PAH: mPAP ≥25 mm Hg an PCWP ≤15 mm Hg at normal to low cardiac output	**For PAH** • RVFW strain cut off -26.2%: sensitivity 84%, specificity 77% • LV strain cut off -20.0%: sensitivity 84%, specificity 58% • RVEF cut off 52%: sensitivity 95%, specificity 84% • Combination of RVFW and RVEF: sensitivity 90%, specificity 90%

No	Author, year, study type	Population	Assessed method(s)	Definition of PH/PAH	Results
32	Sivova, 2013, retrospective[45]	63 patients with SSc (26 without ILD and PAH, 6 with PAH, 19 ILD without PH, 12 ILD an precapillary PH) Exclusion criteria • Another pulmonary disease than ILD, LVEF <55%, history of pulmonary embolism, no available RHC while having having a TRV > 2.8 m/s or additional echocardiographic variables suggesting the presence of PH • Symptom status: 72% symptomatic • Indications for RHC: not specificied	• Pulmonary function tests • DLCO • FVC/DLCO • Components of DLCO (membran conductance of DLCO [DmCO] and alveolar capillary blood volume [Vcap])	Precapillary PH: mPAP ≥25 mm Hg an PCWP ≤15 mm Hg PAH: not specificed	**For precapillary PH in whole group** • AUC of Vcap, Vcap/alveolar volume (VA), DLCO, FVC/DLCO, DmCO: 0.91,0.89,0.89,0.88,0.87,respectively) • Vcap <19 mL: sensitivity 53%, specificity 100% • DLCO <33%: sensitivity 53%, specificity 100% **For PAH in patients without ILD** • Vcap/VA <8.6 mL/L: sensitivity 100%, specificity 90%, PPV 75%, NPV 100% • DLCO < 57%: sensitivity 100%, specificity 88% • FVC/DLCO >1.6: sensitivity 100%, specificity 77% **For PH in patients with ILD** • Vcap < 19 mL: sensitivity 83%, specificity 100%, PPV100%, NPV 90% • DLCO <34%: sensitivity 72%, specificity 100% • FVC/DLCO >1.6: sensitivity 100%, specificity 50%
33	Schreiber, 2011, retrospective[46]	386 patients with SSc (257 patients in derivation and 129 patients in validation cohort) undergone complete pulmonary function testing within 6 months of the RHC (63% had PH) • Symptom status: not specificed • Indications for RHC: TRV> 3.2 m/s, TRV 2.8–3.2 m/s with clinical suspicion of PH, TRV <2.8 m/s with strong clinical suspicion of PH or unexplained progression of exertional dyspnea	• Calculating mPAP using the formula derived using 02 saturation and DLCO (predicted mPAP =136 - SpO2 - 0.25 x DLCO % predicted)	PH: PAH: mPAP ≥25 mm Hg	**For PH** **In validation cohort:** • Formula-predicted mPAP ≥25 mm Hg: sensitivity 90.1%, specificity 29.2% • Formula-predicted mPAP ≥30 mm Hg: sensitivity 59.3%, specificity 70.8% • Formula-predicted mPAP ≥35 mmHg: sensitivity 25.9%, specificity 97.9% **In whole cohort:** • Formula-predicted mPAP ≥25 mm Hg: sensitivity 90.1%, specificity 35% **In patients with echocardiographic data** • RV ≥3.4 m/s or formula-predicted mPAP ≥25 mm Hg: sensitivty 95%, specificity 41.7%

PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis; ILD, interstitital lung disease; FVC, forced vital capacity; PCWP, pulmonary capillary wedge pressure; RHC, right heart catheterisation; BNP, brain natriuretic peptide; ECG, electrocardiography; DLCO, diffusing capacity of the lung for carbon monoxide; PAP, pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; TRV, tricuspid regurgitation velocity; AUC, area under curve; NT-proBNP, n terminal pro brain natriuretic peptide; sPAP, mean pulmonary arterial pressure; LV, left ventricle; PPV, positive predicitive value; NPV, negative predicitive value; lcSSc, limited cutaneous systemic sclerosis; dcSSc, diffuse cutaneous systemic sclerosis; TG, tricuspide gradient; CTEPH, chronic thromboembolic pulmonary hypertension, HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; RVSP, right ventricular systolic pressure; PA, pulmonary artery; CT, computed tomography; SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; RV, right ventricle; Ao, Aorta; LVEF, left ventricular ejection fraction; FEV, forced expiratory volume in the first second; CTD, connective tissue disease; ESC, European Society of Cardiology; ERS, European Respiratory Society; VE/VCO2, minute ventilation/carbon dioxide production; TAPSE, tricuspid annular plane systolic excursion; HT, hypertension; RVFW, right ventricular free wall global longitudinal strain; RVEF, right ventricular ejection fraction



Supplementary Figure 1. Study flow-diagram.