European Journal of Internal Medicine 78 (2020) 17–25

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Screening for pulmonary arterial hypertension in systemic sclerosis: A systematic literature review.

Cosimo Bruni[a,1,*], Giacomo De Luca[b,c,1], Maria-Grazia Lazzaroni[d,1], Elisabetta Zanatta[e,1], Gemma Lepri[a], Paolo Airò[d], Lorenzo Dagna[b,c], Andrea Doria[e], Marco Matucci-Cerinic[a]

[a] Dept. Experimental and Clinical Medicine, Division of Rheumatology, University of Florence, Viale Pieraccini 18, Florence, 50139, Italy
[b] Unit of Immunology, Rheumatology, Allergy and Rare diseases, IRCCS San Raffaele, Milano, Italy
[c] Vita-Salute San Raffaele University, Milano, Italy
[d] Dept. of Clinical and Experimental Sciences, Rheumatology and Clinical Immunology Unit, ASST Spedali Civili of Brescia, University of Brescia, Brescia, Italy
[e] Rheumatology Unit, Department of Medicine (DIMED), University of Padova, Padova, Italy

ARTICLE INFO

Keywords:
Pulmonary arterial hypertension
Systemic sclerosis
Screening
Algorithms

ABSTRACT

Pulmonary arterial hypertension (PAH) carries a high morbidity and mortality burden in Systemic Sclerosis (SSc). Therefore, PAH screening and early detection are pivotal. A systematic literature review (SLR) to search for all screening tools and modalities for SSc-PAH was performed in reference to right heart catheterization as diagnostic gold standard. Papers from 2 previously published SLRs and derived from a systematic search on Pubmed, EMBASE, Web of Science for papers published from 03/10/2017 to 31/12/2018 were manually included. A total of 199 papers were reviewed and 32 were extracted, with a low bias risk according to QUADAS2. Echocardiography, pulmonary function tests, clinical features and serum biomarkers were the most frequently tools used for screening, with different parameters combined in a variable fashion, as single item or as part of composite algorithms. Among the composite algorithms, the DETECT score, ESC/ERS 2009 or 2015 guidelines, ASIG and ITINER-air algorithms were the most commonly used in a wide range of patients. In different cohorts, DETECT and ASIG showed higher sensitivity and negative predictive value than ESC/ERS 2009. In conclusion, the literature shows echocardiography as the leading screening tool for SSc-PAH. In particular, systolic pulmonary arterial pressure (sPAP) and tricuspid regurgitation velocity (TRV), both as single items or part of composite algorithms, including also serum biomarkers, clinical and functional items, are the most frequent parameters evaluated.

1. Introduction

Pulmonary arterial hypertension (PAH) is a rare and severe disease characterized by proliferative remodeling of the small pulmonary arteries, leading to increased pulmonary vascular resistance (PVR), ultimately resulting in right heart failure and death. In Systemic Sclerosis (SSc), PAH remains one of the main determinants of mortality in about 8–12% of patients [1,2]. Several studies conducted on large cohorts have highlighted that all SSc patients carry a certain risk, although variable, to develop PAH [3]. Moreover, it is well recognized that even with the same hemodynamic conditions, SSc-PAH patients have a worst outcome as compared to those with the idiopathic form (IPAH) [4], possibly related to a more prominent maladaptive remodeling of the right ventricle (RV) [5]. Nevertheless, some recent randomized controlled trials (RCTs) on new drugs (i.e. macitentan [6], selexipag [7]) and combination therapies (i.e. the AMBITION trial [8]) have yielded encouraging results even in SSc-PAH, consistent with those of the entire PAH study population.

Since PAH prognosis and response to specific therapies largely depend on the functional class at the time of diagnosis, early recognition of this complication is essential to significantly reduce SSc-PAH mortality. Therefore, many studies in the last years have focused the attention on the identification of screening tools and the creation of specific screening algorithms for SSc-PAH. To the best of our knowledge, no systematic literature research (SLR), exclusively focused on the screening and diagnostic tools in SSc-PAH, has been conducted so far. Notably, SSc-PAH seems to represent an unique PAH phenotype, distinct from other connective tissue disorders (CTD)-PAH [9],

* Corresponding author.
E-mail address: cosimo.bruni@unifi.it (C. Bruni).
[1] Equal contribution as first author.

https://doi.org/10.1016/j.ejim.2020.05.042
Received 24 March 2020; Received in revised form 4 May 2020; Accepted 27 May 2020
Available online 12 June 2020

Table 1
Stepwise selection of manuscripts.

Step 1: PICO Questions
1. In adult SSc patients, can TTE parameters be used as screening tool for PAH in comparison to RHC?
2. In adult SSc patients, can 6MWT parameters be used as screening tool for PAH in comparison to RHC?
3. In adult SSc patients, can PFTs be used as screening tool for PAH in comparison to RHC?
4. In adult SSc patients, can biomarkers be used as screening tool for PAH in comparison to RHC?
5. In adult SSc patients, can clinical signs be used as screening tool for PAH in comparison to RHC?
6. In adult SSc patients, can other parameters and combined indexes be used as screening tool for PAH in comparison to RHC?
7. In adult SSc patients, can the repeated application of screening algorithms detect new cases of PAH?
STEP 2: Inclusion Criteria
1. Articles on SSc
2. Articles with PAH as main topic
3. Articles published before October 3rd, 2017 and included in two recently published SLRs plus papers published from October 3rd 2017 to December 31st 2018
4. Articles in which SSc patients can be separately identified
5. Articles with full text in English/Italian/French
6. Randomised clinical trials, retrospective or observational studies, registries, case series with and without controls and case reports with ≥ 20 patients.
7. Reviews were examined to search for the references repla that were not otherwise available
STEP 3: Exclusion Criteria
1. Non-human studies
2. Studies without clinical or imaging outcomes (genetic, in vitro data)
3. Pediatric subjects
4. Articles including only patients with overlap syndrome by ACR/EULAR classification criteria
5. Case reports/series of < 20 patients
6. Screening not outcome
7. PAH not diagnosed with RHC
8. Full text not available

PICO = Patients, Interventions, Comparator, Outcome; SSc = systemic sclerosis; TTE = trans-thoracic echocardiographic; RHC = right heart catheterization; PAH = pulmonary arterial hypertension; 6MWT = six minutes walking test; PFTs = pulmonary function tests; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; SLR = systematic literature research.

necessitating specific screening considerations.

2. Materials and methods

Studies were included in the SLR if they were focused on SSc, considering PAH screening as the main topic, including at least 20 SSc patients in randomized clinical trials, retrospective or observational studies, registries or case series (Table 1, Step 2). Articles on non-human non-clinical studies, including pediatric patients, patients with overlap syndromes, with PAH not diagnosed with Right Heart Catheterization (RHC) or non-available full text were excluded (Table 1, Step 3).

PICO questions were formulated on specific Population (adult SSc patients), Intervention (any SSc-PAH screening intervention), Comparator (RHC) and Outcome (diagnosis of PAH) (Table 1, Step 1).

A systematic research was conducted across three databases — the Web of Science Core Collection, Embase via Embase.com, Medline via PubMed – using the following search details: "(systemic sclerosis OR scleroderma OR sclerosis) AND (pulmonary arterial hypertension or pulmonary hypertension) AND (screening OR diagnosis)", for papers published from October 3rd 2017 to December 31st 2018. Articles published before October 3rd 2017 were pre-selected from two recently published SLRs on a similar topic and using a comparable search algorithm [10,11].

All papers were reviewed according to the specified criteria on three different rounds (title, abstract and full text evaluations) by two couples of extractors (CB and EZ, GDL and MGL); in case of disagreement between the two reviewers, a third evaluator (GL) reviewed title, abstract and manuscript. For articles evaluating trans-thoracic echocardiography (TTE), right ventricular systolic pressure (RVSP) was converted to tricuspid regurgitation velocity (TRV), as performed by the two previously cited SLRs [10,11].

Each couple of reviewers independently assessed bias risk and study quality using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) evaluation tool [12], with a third author [GL] resolving any disagreement.

3. Results

The steps of the review (title, abstract and full text evaluations) are

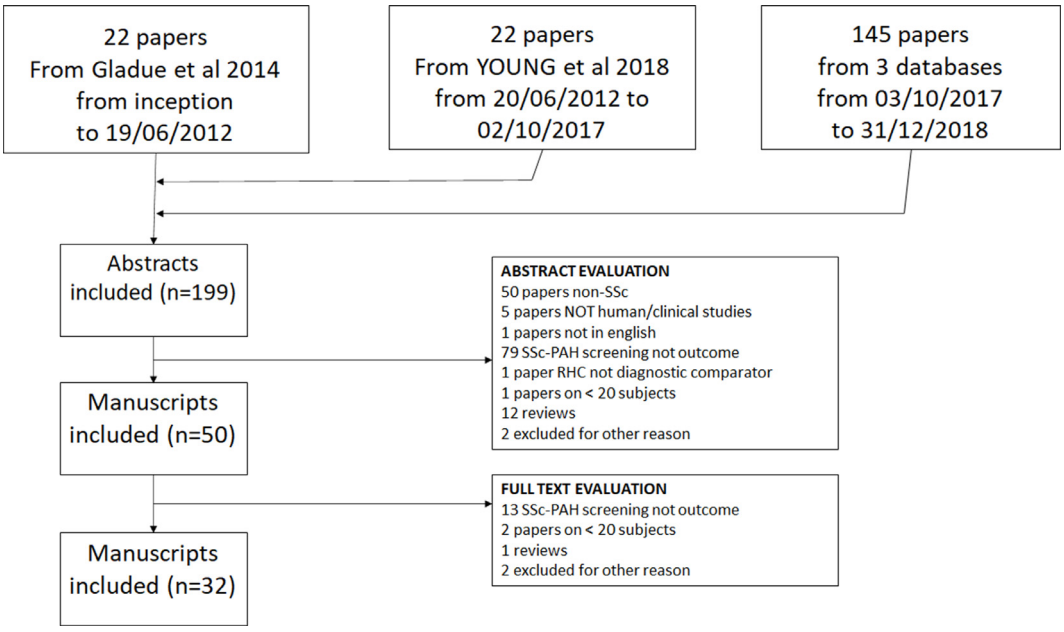

Fig. 1. Systematic review schematic flow diagram. *PAH = pulmonary arterial hypertension; SSc = systemic sclerosis; RHC = right heart catheterization; n = number.*

Table 2
Quality assessment of diagnostic accuracy studies (QUADAS) for articles included in the systematic review.

	bias patient selection	bias index test	bias reference standard	bias flow & timing	applicability patient selection	applicability index test	applicability reference standard
Allanore et al., 2008 [1]	0	0	0	0	0	0	0
Avouac et al., 2015 [54]	0	0	0	0	0	0	0
Avouac et al., 2010 [19]	0	0	0	0	0	0	0
Cavagna et al., 2010 [18]	2	0	0	0	0	0	0
Chung et al., 2017 [55]	0	2	0	0	0	0	0
Coghlan et al., 2014 [28]	0	0	0	0	0	0	0
Dumitrescu et al., 2017 [35]	0	0	0	0	0	0	0
Gladue et al., 2013 [56]	0	0	0	0	0	0	0
Guillen-del-Castillo et al., 2017 [32]	0	0	0	0	0	0	0
Hachulla, 2009 [20]	0	0	0	0	0	0	0
Hachulla et al., 2005 [17]	0	0	0	0	0	0	0
Hao et al., 2015 [34]	0	0	0	0	0	0	0
Hekimsoy et al., 2018 [47]	0	2	0	2	0	0	0
Hoffmann-Vold et al., 2018 [52]	0	0	0	0	0	0	0
Iudici et al., 2013 [53]	0	2	0	0	0	0	0
Jansa et al., 2012 [50]	0	2	0	0	0	2	0
Launay et al., 2007 [46]	2	0	0	0	0	0	0
Meune et al., 2016 [58]	0	0	0	0	0	0	0
Meune et al., 2011 [57]	0	0	0	2	0	0	0
Morrisroe et al., 2016 [41]	0	1	0	0	0	0	0
Morrisroe et al., 2017 [39]	0	0	0	2	0	0	0
Mukerjee et al., 2003 [40]	0	0	0	0	0	0	0
Mukerjee et al., 2004 [36]	0	0	0	0	0	0	0
Niklas et al., 2018 [31]	0	0	0	0	0	0	0
Phung et al., 2009 [48]	0	2	0	2	0	0	0
Soukup et al., 2016 [33]	1	0	0	0	0	0	0
Soumagne et al., 2018 [16]	0	0	0	0	0	0	0
Thakkar et al., 2012 [38]	0	0	0	0	0	0	0
Vandecasteele et al., 2016 [22]	0	0	0	0	0	0	0
Yoo et al., 2016 [49]	0	0	0	0	0	0	0
Zhao et al., 2018 [51]	0	2	0	2	0	0	0

QUADAS-2 comprises 4 domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias; and the patient selection, index test, and reference standard domains are also assessed regarding applicability. O= low risk; 1= high risk; 2= unclear risk.

presented in the schematic flow diagram (Fig. 1).

In the first step, 199 articles were included: 44 from the 2 recent SLRs [10,11] and 145 from our databases search papers published from October 3rd 2017 to December 31st 2018. The first selection excluded 149 articles, based on the abstract evaluation according to exclusion criteria (Table 1).

The two most frequent exclusion reasons for were: PAH screening not representing the outcome of the study (n = 79) and inclusion of patients other than SSc (n = 50). Among the remaining 50 papers evaluated as full text, the 32 finally extracted included 11,179 patients, with 83.4% females (data available for 30 papers). In most cases, the design of the study was prospective (23/32, 72%), while in 5 it was cross-sectional, in 3 retrospective and in 1 in the form of guidelines. Regarding the SSc classification criteria, 8 used the 2013 ACR/EULAR criteria [13], 8 the 1980 ARA criteria [14], 9 other criteria (including Leroy [15] and others) and 7 did not specify this information.

The quality assessment of diagnostic accuracy of the 32 manuscripts eventually included was conducted with the QUADAS-2 tool (Table 2).

Regarding the risk of bias, 20/32 (62.5%) were scored as low risk in all the four domains: 10/32 (31.25%) had an unclear risk in at least one of the domains, and 2/32 (6.25%) had high risk of bias in one of the domains. Regarding the applicability concerns, only one study presented unclear risk in one of the domains.

The results of the research are summarized in the sections below and illustrated in the tables, divided by the type of screening method used (representing the Intervention in our PICO questions). The categories of screening tools identified were echocardiographic parameters, pulmonary function tests and six minutes walking test parameters, biomarkers, clinical signs, other type of parameters and composite measures. Finally, a dedicated section regarding to application of screening methods over time for the detection of PAH incidental cases during the follow-up is reported.

3.1. Echocardiographic parameters

Echocardiographic parameters were used as screening tools for PAH in 31 out of 32 studies (Table 3).

Systolic pulmonary arterial pressure (sPAP) was the most frequently used parameter (22/32 studies, 9111 patients) with different cut-offs, ranging from 30 to 50 mmHg and representing a part of a composite algorithm in 9 of 22 papers. The most frequent cut-off was 40 mmHg, considered in 12 out of 22 papers including altogether 6716 patients. In one article on 572 patients, sPAP was used as a continuous variable [16].

The second most frequently used echocardiographic parameter was Tricuspid Regurgitation Velocity (TRV) in 16/31 papers, including altogether 3804 patients and as part of a composite algorithm in 10 cases. TRV was considered as a continuous variable in 6/16 studies including 1126 patients. In the remaining 10 articles, a pre-established cut-off for TRV was considered, ranging from 2.7 to 3.4 m/s when used alone, or from 2.5 to 2.8 m/s when in combination with symptoms or other echo signs. Sensitivity and specificity were available in only one paper [17].

The third most frequently used echocardiographic parameter was right atrium (RA) area, considered in 9/31 studies (1177 patients), always as part of a composite algorithm. In 5 studies the cut-off area was 18 cm^2, while in 4 it was used as a continuous variable.

Among the other echocardiographic parameters applied in a significant number of patients, right atrial pressure (RAP) as a continuous

Table 3
Echocardiographic parameters as screening tools for PAH.

	N patients (n articles)	Cut-off	Sensitivity	Specificity	PPV	NPV	References
RV/LV basal diameter ratio	385 (5)*	1.0					[22] [26] [31] [32] [33]
Acceleration time	385 (5)*	105 ms					[22] [26] [31] [32] [33]
IVC diameter	385 (5)*	21 mm					[22] [26] [31] [32] [33]
RA area	385 (5)*	18 cm^2					[22] [26] [31] [32] [33]
	792 (4)*	continuous					[22] [28] [34] [33]
Early diastolic PRV	385 (4)*	2.2 m/s					[26] [31] [32] [33]
Flattening of IVS with LV eccentricity index	385 (4)*	1.1					[26] [31] [32] [33]
PA diameter	385 (4)*	25 mm					[26] [31] [32] [33]
TRV	1126 (6)*	continuous					[36] [46] [22] [28] [34] [33]
	80 (1)	>2.8 m/s or <2.8 m/s + symptoms					[47]
	851 (4)*	>2.8 m/s + TTE signs OR >3.4 m/s					[22] [26] [31, 33]
	184 (1)	>2.5 m/s + symptoms OR >2.7 m/s					[48]
	570 (1)*	2.5–3 m/s + dyspnea or >3 m/s	100	97.3	54.5	100	[17]
	384 (1)	>3.0 m/s or >2.8 m/s + symptoms					[20]
	609 (2)	>3.0 m/s					[16] [49]
sPAP	572 (1)	continuous					[16]
	203 (1)	30 mmHg	54.5	94.4	35.3	100	[50]
	343 (3)	36 mmHg					[18] [32] [51]
	6716 (12)*	40 mmHg					[1] [19] [38] [52] [53] [54] [55] [56] [41] [57] [58] [39]
	221 (2)	41 mmHg					[48] [49]
	859 (2)*	45 mmHg					[36] [40]
	1971 (1)	50 mmHg					[46]
RAP	309 (3)*	continuous					[18] [38] [47]
Trans-mitral E/A	212 (1)	continuous					[58]
Ea	212 (1)	10 cm/s	59.2	64.9	19.7	91.6	[58]
Trans-tricuspid E/a	212 (1)	0.8					[58]
Tricuspid systolic anular velocity	212 (1)		22.2	95.1	40	89.3	[58]

TTE = trans-thoracic echocardiography; n = number; PPV = positive predictive value; NPV = negative predictive value; ref = references; RV = right ventricular; LV = left ventricular; IVC = inferior vena cava; RA = right atrium; PRV = peak pulmonary regurgitation velocity; TRV = tricuspid regurgitation peak velocity; sPAP = systolic pulmonary arterial pressure; RAP = right atrial pressure; E/A = ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave); Ea = lateral annulus early diastolic velocity; mmHg = millimetres of mercury; mm = millimetres; cm = centimetres; m = metres; s = seconds.

variable was present in 3 studies including 309 total patients. In 1 of them, RAP was used as part of a composite algorithm together with lateral annulus early diastolic velocity (Ea) in 135 patients [18].

The other echocardiographic parameters were used in smaller cohort of SSc patients (Table 3).

3.2. Pulmonary function tests and six minutes walking test

Pulmonary function tests (PFTs) parameters were used as screening tools for SSc-PAH in 22/32 papers (Table 4), with% predicted Lung Diffusion for Carbon Oxide (DLCO) as the most frequently used in 21 out of 22, including 6529 patients.

The 50% cut-off was applied in 11/21 studies and was included in a composite algorithm in 13/21. Among the other 10 studies, 6 used higher DLCO cut-offs, ranging from 55 to 72%, while 4 used DLCO as a dynamic parameter, considering a decline of >20%. DLCO was also evaluated in the form of% predicted Forced Vital Capacity (FVC)/DLCO ratio in other 12 studies, mainly as part of a composite algorithm (in 8/12). In one study a specificity of 87% and a negative predictive value (NPV) of 98% were reported for an FVC/DLCO ratio >1.5.

Table 4
Pulmonary function tests and 6 min walking distance as screening tools for PAH.

	N patients (N articles)	Cut-off	Sensitivity	Specificity	PPV	NPV	References
6 min walking distance	1087 (3)	continuous					[32] [53] [55]
FVC/DLCO	2794 (11)	continuous					[16] [17] [18] [22] [28] [38] [34] [32] [33] [55] [56]
	135 (1)	1,4					[18]
	572 (1)	1.5	77	87	30	98	[16]
	342 (3)*	1.6					[38] [32] [56]
	230 (2)*	1.8 or 1.82					[34] [55]
DLCO/VA	101 (1)*	<70%	88	80	27	99	[1]
DLCO	6259 (11)	<50%					[18] [19] [36] [38] [54] [55] [41] [57] [58] [39] [40]
	2357 (4)*	>20% decline					[18] [36] [38] [39] [40]
	1024 (2)§	<55%					[53] [55]
	63 (1)*	<60%					[32]
	645 (2)*	<70% or 70.3%					[16] [34]
	197 (1)	<72%					[46]

N = number; min = minutes; PPV = positive predictive value; NPV = negative predictive value; ref = references; FVC = forced vital capacity at pulmonary function tests (expressed as percentage of predicted values); DLCO = diffusing capacity of lung for carbon monoxide at pulmonary function tests (expressed as percentage of predicted values); DLCO/VA = diffusing capacity divided by the alveolar volume (expressed as percentage of predicted values); *as a part of a composite algorithm.
§ *with FVC > 70%.*

Table 5
Serum biomarkers and clinical signs as screening tool for PAH.

	N patients (N articles)	Cut-off	Sensitivity	Specificity	PPV	NPV	Reference
ACA positivity	2434 (6)*	continuous					[22] [28] [32] [33] [34] [41]
Urate	855 (5)*	continuous					[22] [28] [32] [33] [34]
hs Troponin T	161 (1)	14 ng/ml			20	95	[54]
NT-proBNP	1016 (6)*	continuous					[22] [28] [34] [32] [33] [54]
	230 (2)*	210 pg/ml	73	78			[34] [55]
	135 (1)	239.4 pg/ml	45	90		90	[18]
	101 (1)*	97° percentile	75	83	27	97	[1]
BNP	157 (1)	>64 pg/ml	71	69			[55]
	135 (1)	>65 pg/ml	60	87		93	[18]
CCL21	326 (1)	>0.4 g/ml			33		[52]
Red Cells Distribution Width	145 (1)	>14.3%	78.6	69.9			[51]
Telangiectasias**	855 (5)*						[22] [28] [34] [32] [33]
Unexplained dyspnea	4717 (9)*						[3] [19] [36] [38] [54] [56] [57] [39] [40]
Esophageal stricture plus calcinosis plus DUs plus ILD plus sicca syndrome	1579 (1)*						[41]
Worsening of 1 NYHA functional class after first RHC	384 (1)*						[20]

N = number; hs = high sensitive; PPV = positive predictive value; NPV = negative predictive value; ref = references; ACA = anti-centromere antibodies; BNP = brain natriuretic peptide; CCL21 = Chemokine (CC motif) ligand 21; DUs = digital ulcers; ILD = interstitial lung disease; NYHA = New York Heart Association classification; RHC = right heart catheterization; as a part of a composite algorithm.** current or past.

Moreover, walking distance (as continuous variable) at six minutes walking test was a screening parameter in 3 out of 32 papers, including a large number of patients (n = 1087).

3.3. Biomarkers

For SSc-PAH, serum biomarkers were used as screening tools in 12/32 papers (Table 5).

The most frequently tested was N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) in 10/12 papers, including altogether 1482 patients. In 7 studies it was part of a composite algorithm and in 6 manuscripts NT-proBNP was considered as a continuous variable, while in the others fixed cut-offs of 210 pg/ml (2 papers), 239 pg/ml (1 paper) or at the 97th percentile (1 paper) were considered. Other 2 studies considered B-type Natriuretic Peptide (BNP) with a cut-off of 64–65 pg/ml.

The anti-centromere antibodies (ACA) positivity was used as screening tool in 6/12 papers including the largest number of subjects in the category of serum biomarkers (n = 2434), but in all the cases as part of a composite algorithm. Among the other serum biomarkers, urate concentration as a continuous variable was applied in 5 out of 12 papers globally including 855 patients, in all the cases as part of a composite algorithm.

Other serum biomarkers, each one used in only one study, were high sensitivity troponin T, CCL21 e red cells distribution width.

3.4. Clinical signs

This category of screening tools included different clinical parameters and was identified in 15/32 papers (Table 5). Most of these papers used unexplained dyspnea (9/15, 4717 patients) or the current or past presence of telangiectasias (5/19 manuscripts, 855 patients).

3.5. Other tests

In SSc, other tests used as screening tools for PAH were identified in 9/32 studies (Table 6), mainly ECG alterations including right axis deviation (5 papers, 855 patients) and PH signs (1 paper, 867 patients). Other tests considered were parameters from cardio-pulmonary exercise test (CPET) (1 study, 173 patients) or strain echocardiogram (1 study, 80 patients).

3.6. Composite measures

In more than half of the papers, the parameters used as a screening tools for SSc-PAH were part of a composite algorithm (19/32 manuscripts) (Table 6). These composite algorithms were the following: DETECT (5/19), European Society of Cardiology (ESC)/ European Respiratory Society (ERS) guidelines 2009 (4/19) or ESC/ERS 2015 (3/19) guidelines, Australian Scleroderma Interest Group (ASIG, 2/19) and ITINER-air (1/19). In different cohorts, DETECT and ASIG showed higher sensitivity and NPV than ESC/ERS 2009.

3.7. Repetition of screening over time

Ten out of 32 manuscripts reported data regarding the repetition of screening algorithm over time, for a mean follow-up over two years. Patients were evaluated with the screening tools at least once a year on 9/10 papers, according to detailed parameters used to refer the patient to RHC. These studies allowed both the detection of prevalent cases of PAH (meaning those cases detected cross-sectionally at the moment of the first observation) and the incident PAH cases (new cases of PAH detected during the follow-up period). Annual incidence of PAH ranged from 0.61 to 1.50 cases per 100 patients-year (more details are reported in Table 7).

4. Discussion

The present study focuses on screening and diagnostic modalities for SSc patients affected by PAH, considering the existing literature until December 31st 2018. Although this SLR partially updates previous findings by *Gladue* et al. [10] and *Young* et al. [11] on CTD-PAH, it is noteworthy that only studies involving SSc patients, but not other CTDs, were included. This is very relevant considering that SSc-PAH has been identified as an unique phenotype of PAH in the REVEAL register [9]. Specific considerations for screening should be done, like for example, patients with SSc-PAH have a lower DLCO as compared to other CTD-PAH.

In SSc, the PAH prevalence reported in literature ranged from 5% to 17% globally and was 9% among European Caucasians in a large meta-analysis [19]. By contrast, the incidence of PAH in SSc was low, with estimates of 0.61% per year [20] and 1.5% per year in more recent studies [21–23]. Moreover, survival of incident SSc-PAH cases remains poor in the current era [4], despite a recent report from the PHAROS

Table 6
Other parameters and composite indexes as screening tools for PAH.

	N patients (N articles)	Cut-off	Sensitivity	Specificity	PPV	NPV	References
Right axis deviation on ECG	855 (5)*						[22] [28] [34] [32] [33]
ECG with PH signs	867 (1)						[53]
RV apex peak longitudinal systolic strain on strain TTE	80 (1)	> –14–48%	62	100			[47]
Peak VO2 on CPET	173 (1)	18.7 mL/min/kg	30.9				[35]
Nadir VE/VCO2 on CPET	173 (1)	>45.5		31.1			[35]
Tricuspid gradient + DLCO + unexplained dyspnea	2024 (3)				20.4–63.5		[19] [36] [40]
ACA+, esophageal stricture, calcinosis, DUs, ILD, sicca	1579 (1)		100	99.9	100	91.8	[41]
at least one of: sPAP on TTE ≥ 40 mmHg, or DLCO ≤ 50% predicted with FVC > 85%, or fall in DLCO ≥ 20%	94 (1)						[38]
HS-cTnT + NT-proBNP	161 (1)				67	92	[54]
DLCO/VA and NT-proBNP	101 (1)						[1]
FVC/DLCO or DLCO + sPAP	248 (1)						[56]
COCHIN RPS score	443 (1)	2,73	93.8	73.5			[57]
ESC/ERS 2009 guidelines	792 (4)		71–96.3	32.3–69	40–55.3	89–90.9	[22] [28] [34] [33]
ESC/ERS 2015 guidelines	264 (3)				9–11		[22] [26] [31]
DETECT	855 (5)		85–100	35–72	35–69	94–100	[22] [28] [34] [32] [33]
ASIG	1436 (2)		100	54.5	60	100	[34] [39]
ITINER-Air	384 (1)				31		[3]

N = number; PPV = positive predictive value; NPV = negative predictive value; ref = references; ECG = electrocardiography; RV = right ventricle; TTE = transthoracic echocardiography; CPET = cardio-pulmonary exercise testing; VO2 = oxygen uptake; VE/VCO2 = ratio ventilation/carbon dioxide output; DLCO = diffusing capacity for carbon monoxide at pulmonary function tests (expressed as percentage of predicted values); ACA = anti-centromere antibodies; sPAP = systolic pulmonary arterial pressure; FVC = forced vital capacity at pulmonary function tests (expressed as percentage of predicted values); RPS = risk prediction score; ESC = European Society of Cardiology; ERS = European Respiratory Society DETECT = detection of pulmonary arterial hypertension in SSc; ASIG = Australian Scleroderma Interest Group; ITINER-Air = French multicenter transversal observational study; *as a part of a composite algorithm.

study [24] reporting a better outcome than in other SSc-PAH cohorts (e.g. 75% 3-years survival versus 56% in the French cohort described by *Launay* et al. [4]). This discrepancy may at least partially be explained by the higher proportion of patients diagnosed with PAH in NYHA functional class I and II (59%) in the PHAROS study [24]. Overall, these data suggest that screening for PAH in SSc patients is of crucial importance, since an early diagnosis and a prompt therapeutic intervention may translate into better outcomes. Furthermore, the effectiveness of such screening approach was confirmed by *Humbert* et al. [25], that reported a 64% 8-years survival of incident PAH diagnosed through the early detection program versus the 17% in those diagnosed through the usual clinical practice. Therefore, a detailed knowledge of the currently used screening methods is crucial for improving early diagnosis and therapy.

Our SLR highlights that TTE is the most frequently used screening tool for SSc-PAH, either individually or as part of a composite algorithm. The majority of the papers considered the estimated sPAP, mainly with a cut-off >40 mmHg. The second more frequently used measure was TRV, more frequently with a cut-off >2.8 m/s or ≤ 2.8 m/s with the presence of symptoms or other echocardiographic signs of PAH, as suggested by the 2015 ESC/ESR guidelines [26]. Notably, one of the limitations of TTE is that TRV is unattainable in up to 15% of individuals, due to an inadequate tricuspid regurgitation Doppler signal [27]. This was corroborated by the DETECT study, which found that 38.5% RHC-confirmed PAH patients had a TRV ≤2.8 m/s at TTE [28]. TRV also carries an intrinsic inaccuracy in estimating sPAP, with a frequent over- or under-estimation [29]. These limitations may at least partially explain why the latest preliminary recommendations for PAH screening in SSc prefer a multi-parametric approach to the sole TTE screening in patients considered at greater risk of PAH (i.e. patients with DLCO <80%)[30].

In our SLR, they key TTE parameters identified are the area of the right atrium (RA), mostly with a cut-off of 18 mmHg, and a RV/LV basal diameter ratio > 1, both suggestive of an enlargement of the right heart chambers as an adaptive response to increased pressure in the pulmonary artery. In fact, the diameter of the pulmonary artery itself was taken into consideration in some studies [26,31–33].

Although evaluated only in one study [34], the two-dimensional speckle tracking echocardiography appears as a promising tool, given its potentiality to detect RV longitudinal strain and occult intrinsic RV dysfunction or increased RV afterload at early PAH stages.

Another potentially promising tool for early SSc-PAH screening is CEPT, although used only in one study by *Dumitrescu* et al. [35], which found a peak rate of oxygen consumption (peak VO_2) > 18.7 mL/kg/min and nadir minute ventilation to CO_2 production ratio (nadir VE/VCO_2) > 45.5 to be the most accurate parameters to exclude PAH at diagnosis.

Our review also confirmed the importance of PFTs as screening tool for SSc-PAH, either DLCO and FVC/DLCO ratio. Most studies used a DLCO cut-off <50% of the predicted value, which yielded a higher specificity (98%) and positive predictive value (PPV) (88%) versus other cut-offs considered in a study by *Mukerjee* et al. [36]. However, DLCO >60% of the predicted value showed as single parameter a good but imperfect ability to exclude PAH in some studies [36,37] and for this reason the aforementioned outgoing guidelines suggest a multiparametric screening approach in patients with higher DLCO (i.e. 80%) [30]. Moreover, we found 4 studies considering a DLCO decline >20% during the follow-up as a sign of suspected PAH, thus confirming the importance of monitoring this PFT parameter over time [18,36,38–40].

An elevated FVC/DLCO ratio, found in 19 studies, was confirmed as another key PFT parameter able to detect an isolated DLCO reduction, in the absence of significant interstitial lung disease, thus suggesting a pulmonary vascular disease. In particular, this was part of two important composite algorithms, with a cut-off of 1.6 in the DETECT study [28] and of 1.8 in the ASIG study [38].

Concerning serum biomarkers, NT-proBNP alone or combined with other tests (e.g. HS-cTnT or DLCO/Va, [1]) or included in specific composite algorithms (DETECT [33], ASIG [41]) was found in many studies, confirming its role in PAH detection, although it was frequently normal in the early stages [42,43].

Table 7
Papers with repeated applications of screening tools over time for the detection of incidental PAH cases.

Manuscript authors, year of publication	N° patients included	Follow-up duration	Parameters to send for RHC (periodical screening)	Frequency of periodical screening	n° PAH total cases diagnosed over time (baseline prevalent + follow-up incident cases)	N° PAH follow-up incident cases	PAH incidence rate
Hoffmann-Vold et al., 2018 [52]	326	mean 6.5 ± 3.1 years*	Increasing or unexplained dyspnoea AND/OR significant decline in DLCO% AND/OR increasing NT-proBNP levels AND/OR echocardiographic sPAP > 40 mmHg, DETECT algorithm step 2 score > 35.	every 12 months	57	na	na
Iudici et al., 2013 [53]	867	mean 51.7 ± 34.3 months	Electrocardiographic findings suggesting PH AND/OR an estimated echocardiographic sPAP > 40 mmHg AND/OR presence of both DLCO < 55% and FVC > 70%, either associated or not with an impaired six-minute walking test.	every 6–12 months	29	19	1.02 per 100 patients-year
Chung et al., 2017 [55]	157	mean 3.5 ± 1.7 years	As clinically indicated and determined by the treating physician.	every 12 months	na	16	na
Morrisroe et al., 2016 [41]	1579	mean 3.2 ± 2.5 years	Echocardiographic sPAP ≥ 40 mmHg AND/OR DLCO ≤ 50% predicted with FVC ≥ 85% (without adequate explanation on HRCT of the lung or ventilation-perfusion scan of lung or both).	every 12 months	132	na	0.7 per 100 patients-year
Morrisroe et al., 2017 [39]	1363	mean 3.7 ± 2.7 years	Echocardiographic sPAP ≥ 40 mmHg AND/OR DLCOc ≤ 50% predicted with FVC ≥ 85% (without adequate explanation on HRCT of the lung or ventilation-perfusion scan of lung or both).	every 12 months	251	129	1.4 per 100 patients-year
Hachulla et al., 2009 [20]	384	mean 41.0 ± 5.7 months	TRV ≥ 2.8 m/s + nexplained dyspnea OR TVR ≥ 3.0 m/s.	on a regular basis, specific schedule not imposed.	na	8	0.61 per 100 patients-year
Allanore et al., 2008 [1]	101	mean 28 months^	Echocardiographic sPAP ≥ 40 mmHg AND/OR DLCO ≤ 50% in the absence of pulmonary fibrosis AND/OR unexplained dyspnea.	at least every 12 months	na	8	na
Meune et al., 2011 [57]	443	3 years°	Echocardiographic sPAP ≥ 40 mmHg AND/OR DLCO ≤ 50% in the absence of pulmonary fibrosis AND/OR unexplained dyspnea.	every 6 months	na	17	1.5 per 100 patients-years

DLCO = diffusion lung for carbone oxyde; FVC = forced vital capacity; HRCT = high resolution computed tomography; na = not available; NTproBNP = *N*-terminal pro-Brain Natriuretic Peptide; PAH = pulmonary arterial hypertention; PH = pulmonary hypertension; SD = standard deviation; sPAP = systolic pulmonary arterial hypertension; TRV = tricuspid regurgitation velocity.
*datum provided by direct contact with the author; ^ SD not available; ° mean ± SD not available.

One of the current issues in SSc-PAH is the impact that the new proposed hemodynamic definition of PAH will provide on PAH screening [44]. In the definition of pre-capillary PH at RHC, mPAP values will be shifted from ≥25 mmHg to >20 mmHg, with pulmonary vascular resistance (PVR) ≥3 Woods Unit and a wedge pressure ≤15 mmHg [44]. However, it has been recently reported that in two SSc cohorts screened for PAH with DETECT and other screening algorithms, the updated haemodynamic definition of PH did not significantly impact on the PAH diagnosis [45]. In this regard, *Vandecasteele* et al. [22] performed RHC in 93% of patients with a mPAP between 21 and 24 mmHg applying the DETECT algorithm, versus only 71% and 29% with the 2015 and 2009 ESC/ERS guidelines, respectively. This confirms the great sensitivity and NPV of DETECT as a screening tool, also in the context of the new proposed hemodynamic definition of PAH. Similar evidence of high sensitivity and NPV were reported for the ASIG algorithm [34], though it has not been re-evaluated in the light of the new proposed hemodynamic definition.

Finally, we presented data on 10 articles regarding the utility of repeating serial screening programs over time: in particular, the periodical evaluation of SSc patients who turned negative to a first (prevalent) screening assessment, could still detect new (incident) cases of PAH over time, allowing the initiation of a targeted treatment. Despite limited to a minority of the manuscripts included in our SLR, this subgroup of papers shows that TTE and PFT parameters, as well as clinical signs, can change during the patient follow-up and, therefore, multiple assessments over time are necessary to capture more cases.

Unfortunately, we were unable to perform a meta-analysis because most of the studies did not report true and false negatives. In addition to these missing data, the DETECT algorithm and the ESC/ERS 2009 guidelines were the only parameters/algorithms being used on the same population in multiple manuscripts. Despite a meta-analysis of these two could have been attempted, we decided not to perform it as of minimal impact to daily practice: in fact, the new 2015 ESC/ERS guidelines have been available from few years now, replacing the 2009 edition and, therefore, limiting the up-to-date applicability of a meta-analytic evaluation. Nevertheless, we observed that more than half of the studies employed a combination of echocardiographic parameters and PFTs, reinforcing the concept of the added value of a multi-parametric approach for the screening of PAH in SSc.

One of the main difficulties in this field remains the balance between the higher cost of a serial screening program versus the potential of early disease detection and improved outcomes. In SSc, further studies are warranted to improve the screening potential and consequently the outcome of SSc-PAH, particularly considering the new proposed hemodynamic definition.

Funding

This study was supported by an Actelion Pharmaceuticals unrestricted research grant.

Declaration of Competing Interest

CB received honoraria from Actelion and Eli-Lilly; GDL received honoraria from SOBI, Novartis, Pfizer, MSD, Celgene; MGL: none; EZ: received consultancy fee from GlaxoSmithKline; GL: none; PA received consultancy and/or travel expenses from Bristol-Myers-Squibb, CSL Behring, Janssen, Novartis, Pfizer, Roche, SOBI; LD received consultation honoraria from Abbvie, Amgen, Biogen, Bristol-Myers Squibb, Celltrion, Novartis, Pfizer, Roche, Sanofi-Genzyme, and SOBI. AD received honoraria/speaking fees from GSK, Eli-Lilly, Roche, Janssen, Pfizer; MMC reports receipt of grant/research support and/or speaker's bureau attendance from Actelion, Pfizer, GlaxoSmithKline, Bristol-Myers Squibb, Bayer - MSD, Biogen Italia, Eli Lilly.

References

[1] Allanore Y, et al. High N-terminal pro–brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. Arthritis Rheum 2008;58(1):284–91.
[2] Distler O, Pignone A. Pulmonary arterial hypertension and rheumatic diseases—from diagnosis to treatment. Rheumatology 2006;45(suppl_4):iv22–5.
[3] Hachulla E, et al. Is pulmonary arterial hypertension really a late complication of systemic sclerosis? Chest 2009;136(5):1211–9.
[4] Launay D, et al. Survival in systemic sclerosis-associated pulmonary arterial hypertension in the modern management era. Ann Rheum Dis 2013;72(12):1940–6.
[5] Kato M, Atsumi T. Pulmonary arterial hypertension associated with connective tissue diseases: a review focusing on distinctive clinical aspects. Eur J Clin Invest 2018;48(2). e12876.
[6] Pulido T, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013;369:809–18.
[7] Gaine S, et al. Selexipag for the treatment of connective tissue disease-associated pulmonary arterial hypertension. Eur Respir J 2017;50(2). 1602493.
[8] Coghlan JG, et al. Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial. Ann Rheum Dis 2017;76(7):1219–27.
[9] Chung L, et al. Unique predictors of mortality in patients with pulmonary arterial hypertension associated with systemic sclerosis in the REVEAL registry. Chest 2014;146(6):1494–504.
[10] Gladue H, et al. Screening and diagnostic modalities for connective tissue disease-associated pulmonary arterial hypertension: a systematic review. Semin Arthritis Rheum 2014;43(4):536–41.
[11] Young A, et al. Update of screening and diagnostic modalities for connective tissue disease-associated pulmonary arterial hypertension. Semin Arthritis Rheum 2019;48(6):1059–67.
[12] Whiting PF, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Int Med 2011;155(8):529–36.
[13] van den Hoogen F, et al. Classification criteria for systemic sclerosis: an ACR-EULAR collaborative initiative. Arthritis Rheum 2013;65(11):2737.
[14] Masi AT. S.F.S.C.o.t.A.R.A. Diagnostic, and T.C. Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23(5):581–90.
[15] LeROY EC, Medsger Jr TA. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001;28(7):1573–6.
[16] Soumagne T, et al. Global Lung Initiative equations for pulmonary hypertension screening in systemic sclerosis. Eur Respir J 2018;52(3).
[17] Hachulla E, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis Rheum 2005;52(12):3792–800.
[18] Cavagna L, et al. Comparison of brain natriuretic peptide (BNP) and NT-proBNP in screening for pulmonary arterial hypertension in patients with systemic sclerosis. J Rheumatol 2010;37(10):2064–70.
[19] Avouac J, et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J Rheumatol 2010;37(11):2290–8.
[20] Hachulla E, et al. The three-year incidence of pulmonary arterial hypertension associated with systemic sclerosis in a multicenter nationwide longitudinal study in France. Arthritis Rheum 2009;60(6):1831–9.
[21] Morrisroe K, et al. Survival and quality of life in incident systemic sclerosis-related pulmonary arterial hypertension. Arthritis Res Ther 2017;19(1):122.
[22] Vandecasteele E, et al. Screening for pulmonary arterial hypertension in an unselected prospective systemic sclerosis cohort. Eur Respir J 2017;49(5). 1602275.
[23] Nihtyanova SI, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis Rheumatol 2014;66(6):1625–35.
[24] Kolstad KD, et al. Long-term outcomes in systemic sclerosis-associated pulmonary arterial hypertension from the pulmonary hypertension assessment and recognition of outcomes in scleroderma registry (PHAROS). Chest 2018;154(4):862–71.
[25] Humbert M, et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. Arthritis Rheum 2011;63(11):3522–30.
[26] Galiè N, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46(4):903–75.
[27] Gladue H, et al. Screening and diagnostic modalities for connective tissue disease-associated pulmonary arterial hypertension: a systematic review. Seminars in arthritis and rheumatism. 2014. Elsevier.
[28] Coghlan JG, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2014;73(7):1340–9.
[29] D'Alto M, et al. Accuracy and precision of echocardiography versus right heart catheterization for the assessment of pulmonary hypertension. Int J Cardiol 2013;168(4):4058–62.
[30] Frost A, et al. Diagnosis of pulmonary hypertension. Eur Respir J 2019;53(1). 1801904.
[31] Niklas K, et al. Prevalence of pulmonary hypertension in patients with systemic sclerosis and mixed connective tissue disease. Medicine (Baltimore) 2018;97(28).
[32] Guillén-Del Castillo A, et al. High sensitivity and negative predictive value of the

DETECT algorithm for an early diagnosis of pulmonary arterial hypertension in systemic sclerosis: application in a single center. Arthritis Res Ther 2017;19(1):135.
[33] Soukup T, et al. Application of the DETECT algorithm for detection of risk of pulmonary arterial hypertension in systemic sclerosis: data from a Czech tertiary centre. Rheumatology 2016;55(1):109–14.
[34] Hao Y, et al. A comparison of the predictive accuracy of three screening models for pulmonary arterial hypertension in systemic sclerosis. Arthritis Res Ther 2015;17(1):7.
[35] Dumitrescu D, et al. Cardiopulmonary exercise testing for detecting pulmonary arterial hypertension in systemic sclerosis. Heart 2017;103(10):774–82.
[36] Mukerjee D, et al. Echocardiography and pulmonary function as screening tests for pulmonary arterial hypertension in systemic sclerosis. Rheumatology 2004;43(4):461–6.
[37] Degano B, et al. Combined measurement of carbon monoxide and nitric oxide lung transfer does not improve the identification of pulmonary hypertension in systemic sclerosis. Eur Respir J 2017;50(4).
[38] Thakkar V, et al. N-terminal pro-brain natriuretic peptide in a novel screening algorithm for pulmonary arterial hypertension in systemic sclerosis: a case-control study. Arthritis Res Ther 2012;14(3):R143.
[39] Morrisroe K, et al. Epidemiology and disease characteristics of systemic sclerosis-related pulmonary arterial hypertension: results from a real-life screening programme. Arthritis Res Ther 2017;19(1):42.
[40] Mukerjee D, et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum Dis 2003;62(11):1088–93.
[41] Morrisroe K, et al. Risk factors for development of pulmonary arterial hypertension in Australian systemic sclerosis patients: results from a large multicenter cohort study. BMC Pulmonary Med 2016;16(1):134.
[42] Mukerjee D, et al. Significance of plasma N-terminal pro-brain natriuretic peptide in patients with systemic sclerosis-related pulmonary arterial hypertension. Respir Med 2003;97(11):1230–6.
[43] Williams MH, et al. Role of N-terminal brain natriuretic peptide (N-TproBNP) in scleroderma-associated pulmonary arterial hypertension. Eur Heart J 2006;27(12):1485–94.
[44] Simonneau G, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53(1). 1801913.
[45] Jaafar S, et al. Impact of the revised haemodynamic definition on the diagnosis of pulmonary hypertension in patients with systemic sclerosis. Eur Respir J 2019;54(2). 1900586.
[46] Launay D, et al. Prevalence and characteristics of moderate to severe pulmonary hypertension in systemic sclerosis with and without interstitial lung disease. J Rheumatol 2007;34(5):1005–11.
[47] Hekimsoy V, et al. Echocardiographic assessment of regional right ventricular systolic function using two-dimensional strain echocardiography and evaluation of the predictive ability of longitudinal 2D-strain imaging for pulmonary arterial hypertension in systemic sclerosis patients. Int J Cardiovasc Imaging 2018;34(6):883–92.
[48] Phung S, et al. Prevalence of pulmonary arterial hypertension in an Australian scleroderma population: screening allows for earlier diagnosis. Intern Med J 2009;39(10):682–91.
[49] Yoo S-J, et al. Prevalence of pulmonary arterial hypertension in Korean adult patients with systemic sclerosis: result of a pilot echocardiographic screening study. J Cardiovasc Ultrasound 2016;24(4):312–6.
[50] Jansa P, et al. Pulmonary arterial hypertension associated with systemic sclerosis in the Czech Republic. Clin Rheumatol 2012;31(3):557–61.
[51] Zhao J, et al. Red blood cell distribution width as a related factor of pulmonary arterial hypertension in patients with systemic sclerosis. Clin Rheumatol 2018;37(4):979–85.
[52] Hoffmann-Vold AM, et al. CCL21 as a potential serum biomarker for pulmonary arterial hypertension in systemic sclerosis. Arthritis Rheumatol 2018;70(10):1644–53.
[53] Iudici M, et al. Pulmonary hypertension in systemic sclerosis: prevalence, incidence and predictive factors in a large multicentric Italian cohort. Clin Exp Rheumatol 2013;31(2 Suppl 76):31–6.
[54] Avouac J, et al. Cardiac biomarkers in systemic sclerosis: contribution of high--sensitivity cardiac troponin in addition to N-terminal pro-brain natriuretic peptide. Arthritis Care Res 2015;67(7):1022–30.
[55] Chung L, et al. Utility of B-type natriuretic peptides in the assessment of patients with systemic sclerosis-associated pulmonary hypertension in the PHAROS registry. Clin Exp Rheumatol 2017;35(4):106–13.
[56] Gladue H, et al. Combination of echocardiographic and pulmonary function test measures improves sensitivity for diagnosis of systemic sclerosis-associated pulmonary arterial hypertension: analysis of 2 cohorts. J Rheumatol 2013;40(10):1706–11.
[57] Meune C, et al. Prediction of pulmonary hypertension related to systemic sclerosis by an index based on simple clinical observations. Arthritis Rheum 2011;63(9):2790–6.
[58] Meune C, et al. A right ventricular diastolic impairment is common in systemic sclerosis and is associated with other target-organ damage. Seminars in arthritis and rheumatism. 2016. Elsevier.