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Screening for the early detection of pulmonary arterial hypertension in patients with systemic sclerosis: A systematic review and meta-analysis of long-term outcomes

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ABSTRACT

Background: Systemic sclerosis (scleroderma, SSc) is a chronic multisystem autoimmune disease characterised by fibrosis of the skin and internal organs and vasculopathy. One of the major contributors to mortality in patients with SSc is pulmonary arterial hypertension (PAH). International recommendations advise annual screening for the early detection of PAH in asymptomatic patients with SSc.
Objectives: To evaluate by systematic review current measures employed for screening for PAH. To summarise by meta-analysis the current evidence for long-term outcomes of screening for PAH in SSc.
Methods: Manuscripts published until 12th March 2019 were identified through searching Medline, Embase and Cochrane Central Register of Controlled Trials and Database of Systematic Reviews. Eligible studies included abstracts or full reports investigating patients with SSc undergoing screening by any protocol to detect PAH. Risk of bias was assessed with reference to the QUADAS-2 tool.
Results: The review resulted in 580 unique citations with 15 manuscripts included for final systematic review of screening methods, and six for meta-analysis. The systematic review demonstrated that there are varying protocols for screening for PAH. Screened populations were reported to have better risk stratification parameters at PAH diagnosis. Meta-analysis showed improved survival in patients with SSc-PAH diagnosed as a result of screening. There were trends towards having better risk stratification parameters at PAH diagnosis in those screened, although not all of these were statistically significant.
Limitations: There are no randomised controlled trials of screening for PAH in patients with SSc and the evidence presented in this review is derived from publications of registry data, cross-sectional and cohort studies.
Conclusions: This review demonstrates long-term benefit through the systematic screening of patients with SSc of varying disease duration for the early detection of PAH. Screened cohorts had improved survival, and were more likely to have better prognostic factors at the time of diagnosis with PAH.
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Background

Systemic sclerosis (SSc, scleroderma) is a chronic multisystem autoimmune connective tissue disease characterised by fibrosis of skin and internal organs, vasculopathy, inflammation, and the presence of autoantibodies [1]. Amongst the rheumatic diseases, SSc carries the highest burden of mortality, with a standardised mortality ratio of 4.0 and an average of two decades of life lost per patient [2]. Although multiple organs may be affected, and despite the availability of advanced therapies, pulmonary arterial hypertension (PAH) is the major determinant of mortality and hospitalisation in SSc [3].

PAH is a condition of increased resistance in the pulmonary vasculature resulting in dyspnoea, reduced exercise tolerance and right heart failure. It is defined as an elevated mean pulmonary arterial pressure (mPAP) greater than 25 mmHg, a pulmonary artery wedge pressure (PAWP) of less than 15 mmHg with pulmonary vascular resistance (PVR) of more than 3 Woods Units (WU) at rest assessed by right heart catheterisation (RHC). Following the 6th World

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Symposium on Pulmonary Hypertension (WSPH), a proposed definition of pre-capillary pulmonary hypertension with mPAP $>$ 20 mmHg with PAWP of $\leq$ 15 mmHg and PVR $\geq$ 3 WU based on a scientific approach is gaining acceptance [4]. PAH occurs with a prevalence of up to 12% amongst patients with SSc [3,5–7]. Therapies such as the endothelin receptor antagonists (ERA) including bosentan, ambrisentan and macitentan; and phosphodiesterase-5 inhibitors (PDE5i) for example, sildenafil and tadalafil, have had a substantial impact on PAH outcomes increasing median survival from 2 to 4.5 years [3]. Despite this almost half of patients with SSc-PAH die within four years of PAH diagnosis [3,8].

Data from the Australian Scleroderma Cohort Study (ASCS), as well as from cohorts in France and the United States, demonstrate that survival is improved when PAH is diagnosed early through systematic annual screening of SSc patients, allowing institution of therapy early in the disease course, compared to a diagnosis made during usual care, often following the development of symptoms and signs of right heart failure [3,9–11].

The observed improvement in survival may be due to improved therapeutic options available in the modern era and/or lead-time bias; however the results from contemporary cohorts undergoing screening also indicate that early diagnosis detects patients with more favourable prognostic risk factors at baseline that have been shown to correlate with improved outcomes [10].

Current practice for PAH screening in SSc is centred around the 2015 ESC/ERS international guidelines which recommend annual screening incorporating one or more of transthoracic echocardiography (TTE), or respiratory function tests (RFT) with diffusion capacity for carbon monoxide (DLCO), and serum biomarkers to identify patients who require further investigation with RHC for the presence of pulmonary hypertension [12]. Two multidimensional algorithms for screening patients with SSc have also been proposed and evaluated, including the DETECT algorithm and the Australian Scleroderma Interest Group (ASIG) algorithm [13]. In addition to annual TTE, these were included in the new recommendations for screening published in a review following the 6th WSPH [14].

Objectives

We undertook a systematic review of the literature regarding methods of screening for PAH in patients with SSc to summarise and evaluate current practices for screening. We also sought to quantify by meta-analysis the potential long-term benefits of screening for PAH in patients with SSc in terms of survival, and known risk stratification (prognostic) factors at the time of diagnosis.

Methods

Protocol

Inclusion criteria and methods of analysis were specified in advance and the review and meta-analysis were undertaken according to the preferred reporting of items for systematic reviews and meta-analyses (PRISMA) and the Cochrane Handbook for Systematic Reviews of Interventions [15,16].

Eligibility criteria

Studies were considered for inclusion in the systematic review according to pre-defined inclusion and exclusion criteria.

We included retrospective and prospective multicentre or single centre cohort or cross-sectional studies and publications reporting registry data in which patients with SSc were screened for PAH. For inclusion in the meta-analysis eligible publications compared patients undergoing screening for PAH to a group who did not undergo systematic screening. All studies defined as such in any language were eligible for inclusion.

Types of participants

We included any individual with a diagnosis of SSc defined according to accepted classification criteria including American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR), or the Le Roy Medsger criteria, or American Rheumatology Association (ARA) criteria for both the systematic review and meta-analysis [17–19]. We included the old and new definition of a diagnosis of PAH.

Outcome measures

For the systematic review, the primary outcome of interest was a description of the methods used to screen patients for PAH.

For the meta-analysis the primary outcome was mortality (survival) and secondary outcomes included risk stratification factors present at diagnosis with PAH, defined as parameters included in the ESC/ERS 2015 risk assessment table including haemodynamic parameters, 6MWD, functional class using the World Health Organisation (WHO) or New York Heart Association (NYHA) classification, RFT parameters, and serum NT-proBNP) [12]. Reporting one or more of the outcomes listed here was not an inclusion criterion for the review.

Search methods or information sources

We identified publications from searches of the following databases up to 12th March 2019 performed with the assistance of a librarian (JB):

1 Medline 1946 to 12 March 2019.
2 Embase Classic and Embase 1947 to 12 March 2019.
3 Cochrane Central Register of Controlled Trials 1991 to February 2019.
4 Cochrane Database of Systematic Reviews 2005 to 6 March 2019.

We hand-searched conference abstracts and grey literature.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references.

Search strategy

For Medline search strategy:

1 (pulmonary arterial hypertension or Hypertension, Pulmonary or pulmonary hypertension).mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms].
2 (scleroderma or systemic sclerosis).mp.
3 (screen* or detect*).mp.
4 1 , 2 and 3.

For Embase:

1 (pulmonary arterial hypertension or Hypertension, Pulmonary or pulmonary hypertension).mp. [mp = title, abstract,heading word, drug trade name, original title, device manufacturer, drug

manufacturer, device trade name, keyword, floating subheading word, candidate term word].
2 (scleroderma or systemic sclerosis).mp.
3 (screen* or detect*).mp.
4 1 , 2 and 3.
5 Limits "Exclude MEDLINE Journals".

For Cochrane Central Register of Controlled Trials and Database of Systematic Reviews:

1 (pulmonary arterial hypertension or Hypertension, Pulmonary or pulmonary hypertension).mp. [mp = ti, ab, tx, kw, ct].
2 (scleroderma or systemic sclerosis).mp.
3 (screen* or detect*).mp.
4 1 , 2 and 3.

Study selection

One review author (ZB) independently screened abstracts to determine if they met the inclusion criteria for the review. Full-text publications for those papers were sought. Two review authors (ZB and MN) independently reviewed full-text articles to determine eligibility, recording reasons for ineligibility for those that did not using a 'data extraction template'. We resolved any disagreements through discussion. A PRISMA study flow diagram documents the screening process and the characteristics of the included studies are summarised in Appendix A.

Data collection process and items

One review author (ZB) independently extracted data from included studies, and where appropriate, pooled data in the Cochrane statistical software Review Manager 5.3 for further analysis. We used a data extraction template (designed by ZB and MN) after testing this on one study. It included the following data:

1 Methods: study design, duration, setting, date of study.
2 Participants: number, mean age, gender, inclusion and exclusion criteria.
3 Intervention: method of screening.
4 Outcomes: primary and secondary as specified, time points collected.
5 Risk of bias summary based on 'Cochrane risk of bias tool'.
6 Other: funding for study, conflicts of interest.

Obtaining or confirming data from investigators was not required for any included articles.

Risk of bias in individual studies

Two review authors (ZB and MN) assessed the included studies for risks of bias using the revised Quality Assessment of Diagnostic Accuracy (QUADAS-2) tool. QUADAS-2 evaluates publications for bias in terms of risk and applicability in four domains: patient selection, index test, reference standard and flow and timing [20].

Summary measures

Where possible we presented results from continuous variables and calculated the mean difference (MD) with the 95% confidence interval (CI). We combined data only if reported at a defined time point (at the time of diagnosis with PAH). Functional class results were pooled and analysed as a dichotomous outcome comparing patients with a functional class of I to II with III to IV. For meta-analysis of time-to-event data (survival) we used the methods described by Tierney et al. [21].

Synthesis of results

We used a random effects model and performed a sensitivity analysis if significant heterogeneity was present. For pooled analyses we quantified statistical heterogeneity using the I^2 statistic, which is used to determine if observed differences in results are due to chance alone. We considered significant statistical heterogeneity to be present if I^2 was greater than 25% [22]. Where significant heterogeneity was identified we performed a sensitivity analysis by excluding the study assessed at the highest risk of bias using the QUADAS-2 assessment tool.

Results

Study selection

We identified 580 citations in the initial search, and after screening the abstracts, 50 studies were selected for full-text review. After excluding studies that did not meet the inclusion criteria or were duplicates, we included 21 studies in the final review, 15 studies for qualitative synthesis and systematic review and six studies for meta-analysis (see Fig. 1). For multicentre registries where there were

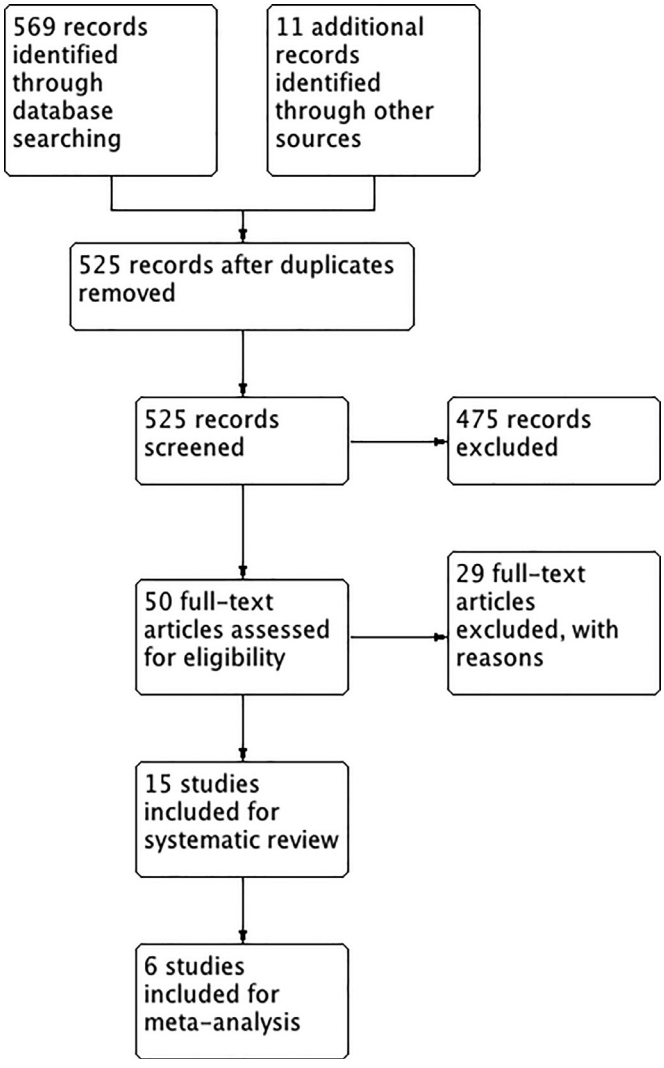


Fig. 1. Flow diagram (blank).

several citations, we included the most recently published or citations specifically regarding screening in the final analysis. We excluded 29 studies for the following reasons: citation using data from a cohort or registry if a more recent publication of the same data exists (14 publications), ineligible study design (14 publications), patients with newly diagnosed PAH though unclear if underwent screening (1 publication). Please see 'Characteristics of included studies' in the appendices.

Included studies

Systematic review

We included 15 studies for analysis in a systematic review, summarised in Tables 1, 2 and 3. Launay et al.reported outcomes from a prospective multicentre registry of patients with newly diagnosed SSc-PAH [9], and Iudici et al.reported a prospective multicentre cohort of patients with SSc [23]. Kolstad et al., Coghlan et al.and Khanna et al.reported prospective multicentre cross-sectional and cohort studies of patients with SSc undergoing screening to detect PAH [24–26]. Ancuta et al., Coirier et al., Koutsianas et al. and Hoffmann-Vold et al. reported prospective monocentric studies applying the DETECT algorithm to patients with SSc undergoing routine screening [27–30]. Hao et al. reported a retrospective comparison of the DETECT algorithm, the ASIG algorithm and the 2009 ESC/ERS guidelines using data from patients enroled in the Australian Scleroderma Cohort Study (ASCS) [6]. Guillen-Del Castillo et al. and Soukup et al. reported retrospective monocentric studies which applied the DETECT algorithm to patients with SSc who had been screened according to the 2009 ESC/ERS guidelines [31,32]. Gladue et al., Thakkar et al. and Young et al. reported systematic reviews of screening for the detection of pulmonary hypertension in patients with connective tissue diseases (CTD) [13,33,34].

Methods of screening for PAH

Launay 2013 reported outcomes for patients with incident SSc-PAH enroled in the French Pulmonary Arterial Hypertension Network (FPHN) between January 2006 and November 2009. However, the authors reported that the results of this study suggested that most of these patients were diagnosed during routine practice rather than through systematic screening.

Iudici et al. was a prospective multicentre inception cohort study of patients with SSc to determine the prevalence and incidence of PAH. Investigators performed at baseline complete clinical history and examination, ECG, HRCT of the lungs, RFT, TTE and RHC, if indicated. Patients were then reviewed every six to 12 months to assess the course of the disease [23].

Kolstad et al. reported outcomes from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) registry in which patients with pre-PAH and incident PAH were assessed at baseline and annually by performing physical examination, brain natriuretic peptide (BNP) or *N*-terminal pro-BNP (NT-proBNP). High resolution thoracic computed tomography (HRCT) scans, RHC, TTE and 6MWD were performed as clinically indicated based on assessment by the clinician investigator [24].

Coghlan et al. reported a prospective multicentre cross-sectional study between 2008 and 2011 in which RHC and TTE were performed systematically according to standardised procedures in order to select predictive variables to develop the DETECT algorithm for screening patients with SSc for PAH. The inclusion criteria specified adult patients with SSc meeting the ACR/EULAR criteria and patients with other connective tissue diseases of more than 3 years duration from the onset of the first non-Raynaud's symptom and with a DLCO predicted of $< 60\%$, thereby enriching the population for those at risk of PAH. The DETECT algorithm is a two-step assessment, where step one of the algorithm evaluates six non-echocardiographic variables and determines the need for referral for step two which is a TTE. Based on echocardiographic variables in step two patients are referred for RHC if indicated [25].

Khanna et al. reported a prospective multicentre observational cohort study in which physicians were provided with an algorithm developed by the steering committee to screen patients with SSc for PAH at baseline, six months and yearly for three years. At baseline all patients underwent RFT, chest *X*-ray and TTE with guidelines for when to refer for additional tests including *V*/*Q* scan or RHC [26].

Ancuta et al. reported a prospective monocentric cross-sectional study which applied the DETECT algorithm to 41 patients with SSc between January 2013 and December 2016. Investigators compared frequency of referral for RHC using the DETECT algorithm with echocardiographic criteria recommended by the 2009 ESC/ERS guidelines [35].

Coirier et al. reported a monocentric non-interventional cohort study in which the DETECT algorithm was applied prospectively to patients with SSc and compared to standard practice whereby patients were assessed with clinical examination, pathology evaluation for auto-antibodies, NT-proBNP and uric acid, electrocardiogram (ECG), RFT and TTE. If indicated, patients were referred for RHC following discussion at a multidisciplinary meeting at the Centre Hospitalier Universitaire de Rennes in France. Two analyses were undertaken, firstly the DETECT algorithm was applied to the entire population and secondly only to patients meeting the inclusion criteria described by Coghlan et al., those with a DLCO $<60\%$ and with SSc symptoms other than Raynaud's phenomenon of more than three years [27].

Koutsianas et al. reported a prospective monocentric cohort of patients with SSc who were screened with the DETECT algorithm and compared to screening with the 2015 ESC/ERS algorithm [30].

Hoffmann-Vold et al. reported outcomes in patients with SSc meeting 2013 ACR/EULAR classification criteria for SSc attending the Oslo University Hospital (OUH) and who were included in an ongoing, prospective observational SSc cohort. Screening at OUH from 2009 to 2013 was performed according to an OUH protocol and included annual clinical examination, TTE, RFT, 6MWT and NT-proBNP. In January 2014 the DETECT algorithm was also added to the OUH protocol. This study included patients who had a primary, diagnostic RHC, divided patients into two cohorts, an 'Early cohort' of 161 patients who had a RHC between 2009 to December 2013, and had therefore been screened according to the OUH protocol, and the 'DETECT cohort' which comprised 84 patients seen from 2014. The reported outcomes included frequency of diagnosis of PAH, functional status and risk assessment at baseline and at diagnosis in patients with PAH or borderline PH [29].

Hao et al. retrospectively compared the DETECT and 2009 ESC/ERS guidelines with the ASIG algorithm in a cohort of patients with SSc who had undergone RHC. The ASIG algorithm evaluates annual serum NT-proBNP level and RFT and recommends referral for further evaluation with TTE and/or RHC if the serum NT-proBNP is $\geq$ 210 pg/mL or the FVC/DLCO ratio is $\geq$ 1.8 with a DLCO% predicted of $<$ 70%. This is in accordance with recommendations for screening published following the 6th WSPH [14].

Methods of screening were assessed retrospectively in monocentric cohorts by Guillen-Del Castillo et al. and Soukup et al., which evaluated the DETECT algorithm compared to the 2009 ESC/ERS guidelines. However, Soukup et al. applied a modified DETECT algorithm, and replaced right atrium area with a modified variable (1.4 x diameter of the right ventricle outflow tract (RVOT))^2 [36].

The methods of screening evaluated in each publication are summarised in Table 2.

Thakkar et al., Gladue et al., and Young et al., published systematic reviews of screening for PAH in patients with connective tissue diseases (CTDs), including SSc. Thakkar et al. identified nine publications evaluating the performance of composite screening algorithms in patients with SSc. Gladue et al. and Young et al. evaluated

Table 1
Summary of studies evaluating survival in patients with SSc who underwent screening for the early diagnosis of PAH

	Study type	Participants	Intervention/ Screening applied	Country	Multicentre	Duration	Number of Participants	Inclusion Criteria	Exclusion Criteria	Age, years (mean & SD)[1]	Subtypes, n (%)	Survival (%)[2]		
												1 year	2 year	3 year
Kolstad 2018	Prospective registry	median 8.6 years (0 – 43.2 years)	(PHAROaS)[3] 97[4]	Adults >18 years, ACR/LeRoy classification criteria for SSc	Baseline screening: serology, BNP/NT-proBNP, SSc-HAQ, SF-36, HRCT, RHC, RFT, TTE, 6MWD as clinically indicated.	Canada, USA	Yes, 19 centres	Median follow-up 7.1 years (2006 to 2016)	160	Incident PAH (enrolled within 6 months of diagnosis of PAH based on Dana Point criteria)	No more than mild ILD on HRCT.	60 (10.8)	Time from 1st non-RP	83
ACA 67 (42.68%) Scl-70 6 (3.82%) U1-RNP 4 (2.55%)														
Launay 2013	Prospective registry (French PAH Network)	SSc patients with newly diagnosed PAH. SSc – ACR/LeRoy classification criteria	Screening registry – all underwent RFT, NYHA functional class assessment, 6MWD, RHC.	France	Yes, 17 centres	Median follow-up 2.31 years (2006 to 2009) Mean follow-up 2.33 years (SD 1.09 years)	85	PAH (mPAP ≥ 25mmHg, PCWP ≤ 15mmHg during RHC at rest.	HRCT evidence of ILD. Overlap syndromes. Patients who received PH-specific therapy prior to RHC.	64.9 (12.2)	LcSSc 87% Scl70 3%	90 (95% CI 81 – 95)	78 (95% CI 67 – 86)	56 (95% CI 42 – 68)

[1] SD – standard deviation
[2] Survival - Overall survival
[3] PHAROS – Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Registry
[4] Events restricted to PAH-related deaths. Short term (< 4 years) deaths related to PAH 61%, however long term (≥ 4 years) 17%. PAH-related deaths at combined 5- and 8-year 76%.

Table 2
Descriptions of screening methods evaluated, study population and outcomes of evaluation.

	Study type	Participants	Intervention/Screening applied	Country	Multicentre	Duration mean (SD)	Number of Participants	Exclusion Criteria
Soukup et al.	Retrospective cross-sectional study	SSc (ACR criteria)[2] attending University Hospital Hradec Kralove in Czech Republic	Annual TTE. Retrospective appraisal of complete clinical data required for modified DETECT.	Czech Republic	No	Mean follow-up 31 months (2009 to 2014)	58	Pre-existing PAH or incomplete data.
Iudici et al.	Prospective registry (inception cohort)	Adults with ACR/LeRoy classification criteria for SSc	"All patients investigated, at admission, for core set variables considered in EUSTAR clinical chart. In particular, patients underwent a careful clinical history, a complete physical examination, ECG, HRCT of lungs, RFT, TTE and RHC, if indicated. Patients were then visited every 6 – 12 months in order to assess the course of the disease. In addition 237 of 867 had NT-proBNP at admission…"	Italy	Yes, 4 tertiary centres	Mean follow-up 51.7 months (34.3 months) (1st November 2000 to 31st December 2010)	867	N/A
Coghlan 2014	Prospective cross-sectional study (The DETECT)	Age ≥ 18 years with ACR classification criteria for SSc (including other CTDs)	112 variables assessed, all patients underwent RHC. Disease duration > 3 years from 1st non-RP symptom and DLCO <60% predicted.	North America, Europe, Asia	Yes, 62 centres	Unclear	488 (466 underwent RHC)	pH on RHC prior to enrolment. Receiving pH-specific therapy. FVC <40% predicted. Renal insufficiency. Evidence of LHD. Pregnancy.
Khanna et al.	Prospective cross-sectional study	Age ≥ 18 years with ACR classification criteria for SSc.	Structured guidelines provided to clinicians based on consensus for the diagnosis and management of PAH.	United States	Yes, 27 centres	Follow-up to 3 years. (Recruited July 2006 to December 2007)	207	Unavailable for follow-up. Previously documented pH/PAH (diagnosed by RHC, mPAP > 25 mmHg, PVR > 3 WU, PCWP <15). Severe ILD (FVC <45% predicted). Overlap with other CTD.
Ancuta et al.	Prospective cross-sectional study (abstract)	Patients with SSc recruited in the EUSTAR cohort.	Standard assessments per EUSTAR minimal data set. Annual TTE, RFT, ECG, biomarkers (urate, NT-proBNP). DETECT Algorithm.	Romania	No	2 visits in 6 months. (January 2013 to December 2016)	41	N/A
Coirier et al.	Prospective cross-sectional study (abstract in English)	Consecutive patients with SSc meeting ACR/EULAR 2013 classification criteria.	Annual assessment by usual practice (examination, pathology, ECG, RFT, TTE). Discussed in multidisciplinary meeting to determine referral for RHC.	France	No	Recruited over 6 months.	117 (note 106 met ACR/EULAR criteria for SSc)	Missing data necessary to complete DETECT.
Koutsianas et al.	Prospective cross-sectional study (abstract)	Diagnosis of SSc with at least one visit to Russell Hall Scleroderma Clinic	History, examination, immunological status, RFT, NT-proBNP, urate, ECG, TTE, CXR, HRCT.	United Kingdom	No	10 months. (February to November 2016)	31	Incomplete data
Hoffmann-Vold et al.	Cohort study	All patients from Oslo University Hospital (OUH) Scleroderma cohort meeting 2013 ACR/EULAR Classification criteria for SSc and had undergone a primary RHC between 2009 and 2017.	2009 to 2013: OUH protocol annual examination, TTE, 6MWT, NT-proBNP. 2014 to 2017: OUH protocol plus DETECT.	Norway	No	2.9 years (2.4 years)	161	N/A
Guillen-Del Castillo et al.	Retrospective cohort study	Patients with SSc (100% LeRoy classification criteria) who had undergone at least one RHC. Disease duration > 3 years from 1st non-	Annual RFT and TTE. DETECT compared to ESC/ERS 2009 Guidelines.	Barcelona	Unclear	Unclear	78	FVC >40% and DLCO ≤ 60%.

(*continued on next page*)

Table 2 (*Continued*)

	Study type	Participants	Intervention/Screening applied	Country	Multicentre	Duration mean (SD)	Number of Participants	Exclusion Criteria
		RP symptom and DLCO <60% predicted. (61 patients fulfilled ACR/EULAR 2013 classification criteria for SSc).						
Hao et al.	Retrospective cross-sectional study	Consecutive adults with SSc enroled in the Australian Sclero-derma Cohort Study (ASCS) who had undergone RHC.	Annual examination, TTE and RFT. DETECT compared to ASIG algorithm and ESC/ERS 2009 Guidelines.	Australia	No	Participants attending between 2007 and 2012	73	PH confirmed by RHC prior to enrolment. Receiving PH-specific therapy. FVC <40% predicted. Renal insufficiency Pregnancy >1 missing variable. No detectable TRV

Age, years (mean & SD)[1]	Disease characteristics, n (%)	Incidence of PAH, n (%)	Frequency of RHC referral, n (%)	Efficacy			
				Sensitivity	Specificity	NPV	PPV
61.1 (12.1)	DcSSc 33 (56.9%) LcSSc 23 (39.7%) Overlap 2 (3.4%)	6 (10.3%)	2009 ESC/ERS 14 (24.1%)	DETECT 24 (41.4%)	11 patients underwent RHC, PAH in 7, PH-ILD in 2		
Median (range) 59 (12 – 89)	Disease duration median (range) 4 years (0.2 – 55) LcSSc 676 (78%) Scl70 274 (31.4%) ACA 358 (41.2%)	29 (3.34%)	139 (16%)	N/A			
Non-pH group 54.7 (11.8) (n = 321) PAH group 61.1 (9.8) (n = 87)	PAH group disease duration 163 months (130.3 months)	87 (19%)	466 (95.5%)	The DETECT Algorithm (n = 319)			
				96%	48%	35%	98%
				The ESC/ERS Guidelines 71%	69%	40%	89%
	DcSSc 20.9% LcSSc 70.9% Overlap/MCTD 8.1%						
Median (range) 57 (49–66)	Median time from diagnosis of SSc 5 years (IQR 1 - 10) LcSSc 126 (60.9%) DcSSc 66 (31.9%)	10 patients had confir-matory PAH (4.8%)	27 (13%)	N/A			
N/A	DcSSc 63.41% Scl70 Ab positive in up to half. ACA positive in about 1/3.	8 (19.51%)	ESC/ERS 2009 9 (21.95%)	DETECT 14 (34.14%)	N/A		
Median (range) 55 (19–80)	Median (range) Disease duration 6 years (0–48) ACA 65 (56%)	7 (6%)	Usual practice 15 (12.8%)	DETECT 70 (59.8%) *DETECT applied to DLCO <60% & disease duration >3 years 31 (26.5%)	N/A		
64.4 (12.9)	Mean time from diagnosis 6.2 years (3.2years) LcSSc 87% ACA 58.1%	N/A	ESC/ERS 2015 4 (13%)	DETECT 18 (58%)	N/A		
61 (11.8)	LcSSc 125 (78.1%) ACA 78 (48.8%)	15 (9.32%)	All patients had under-gone RHC for inclusion.	OUH – RHC diagnostic of PAH in 16 (20.8%) DETECT – RHC diag-nostic of PAH in 15 (17.9%)			

(*continued on next page*)

Table 2 (*Continued*)

Age, years (mean & SD)[1]	Disease characteristics, n (%)	Incidence of PAH, n (%)	Frequency of RHC referral, n (%)	Efficacy				
				Sensitivity	Specificity	NPV	PPV	
62.4 (11.6)	Time from 1st non-RP symptom (mean SD) 10.5 years (8.9)	35 (44.8%)	ESC/ESR 2009 36 (57.1%)	DETECT 35 (44.9%)	ESC/ERS 2009 Guidelines% (95% CI) 91.4 (77.6 – 97) DETECT% (95% CI) 100 (90.1 – 100)	85.7 (68.2 – 94.3) 42.9 (26.5 – 60.9)	88.9 (71.9 – 96.1) 100 (75.7 – 100)	No statistical significant difference As above.
	ACA 34 (54%) Scl70 12 (19%) LcSSc 45 (71.4%) DcSSc 10 (15.9%)							
Non-PH patients (n = 34) 61.2 (11.9)	PAH patients LcSSc 23 (85%) DcSSc 4 (15%)	26 (35.6%)	All patients had undergone RHC for inclusion.	ASIG Algorithm (n = 37)% (95% CI)				
PAH patients (n = 27) 66.8 (8.3)	ACA 17 (63%) Scl70 1 (4%)			100 (78.2 – 100) DETECT (n = 61)% (95% CI)	54.5 (32.2 – 75.6)	100 (73.5 – 100)	60 (38.7 – 78.8)	
				100 (87.2 – 100) ESC/ERS 2009 (n = 58)% (95% CI)	35.3 (19.7 – 53.5)	100 (63.1 – 100)	55.1 (40.2 – 69.3)	
				96.3 (81 – 99.9)	32.3 (16.7 – 51.4)	90.9 (58.7 – 99.8)	55.3 (40.1 – 69.8)	

[1] SD – standard deviation.
[2] 2013 ACR/EULAR classification criteria.

publications regarding investigations for screening and diagnosis of PAH in patients with CTD. Young et al. was undertaken prior to the 6th WSPH in order to update guidelines for the screening and diagnosis of PAH and identified three commonly evaluated composite screening algorithms. The evaluations of composite screening measures from each of these three systematic reviews are summarised in Table 3.

Of the composite measures for PAH screening, the two most frequently evaluated were the DETECT and the ASIG algorithms [13].

Survival in screened versus control cohorts

Kolstad et al. reported outcomes for 160 patients with incident SSc-PAH during a median follow-up time of 7.1 years. When events were restricted to PAH-related deaths, the 1-, 3-, and 5- and 8-year survival rates after diagnosis were 97%, 83% and 76%, these results are shown in Table 1.

Launay et al. reported outcomes for 85 consecutive patients with incident SSc-PAH or "pre-PAH" enroled in the FPHN multicentre prospective registry between 2006 and 2009 in France. Patients with SSc fulfilled ACR/EULAR criteria and/or Le Roy classification criteria and PAH was defined as mPAP $\geq$ 25 mmHg at rest and PAWP $\leq$ 15 mmHg at rest. Patients with an overlap syndrome with another CTD were excluded, and patients with evidence of ground glass change on HRCT were excluded to focus on patients without any ILD. The mean follow up after PAH diagnosis was 2.33 $\pm$ 1.09 years. At 1, 2 and 3 years from PAH diagnosis, overall survival was 90% (95% CI 81 to 95%), 78% (95% CI 67 to 86%) and 56% (95% CI 42 to 68%).

2015 ESC/ERS Risk stratification (prognostic) factors at diagnosis

Kolstad et al. reported median haemodynamic parameters for patients diagnosed with SSc-PAH, NYHA FC and median 6MWD. This study reported that 43.67% of patients were diagnosed in NYHA FC II and that the median 6MWD for patients with incident SSc-PAH was 365.9 m. These results are summarised in Table 4.

Launay et al. reported the mean right atrial pressure (mRAP) at diagnosis with PAH was 7 $\pm$ 5 mmHg and mean CI 2.64 $\pm$ 0.78 l /min/ m^2. Sixty-seven percent of patients diagnosed with PAH were classified as NYHA FC III and the mean 6MWD was 259 m ($\pm$ 126 m). The mean serum BNP for patients diagnosed with SSc-PAH at baseline was 463 $\pm$ 573 ng/L.

Coghlan et al. reported WHO FC at baseline in 87 patients with SSc diagnosed with group 1 PAH; 18.4% of patients were diagnosed in WHO FC I, 46% in FC II and 44.6% in FC III or IV. For 66 patients diagnosed with SSc-PAH, the mean 6MWD was 389.7 m $\pm$ 106.6 m.

Hoffmann-Vold et al. reported WHO FC prior to referral for RHC in patients who had undergone systematic screening for PAH and subsequently diagnosed with PAH. Of 15 patients, 7 (46.7%) were classified as FC I and II, and 8 patients (53.3%) with FC III and IV. The mean 6MWD in 15 patients diagnosed with PAH as a result of screening was 356 m ($\pm$ 207.9 m) and the mean NT-proBNP was 189 μmol/L ($\pm$ 221.9 μmol/L). At the time of PAH diagnosis there was a similar distribution of patients across 2015 ESC/ERS risk stratification groups (low, intermediate and high risk) using the OUH protocol for screening compared to the DETECT algorithm. However, the authors noted that at the time of diagnosis with borderline PAH (defined as mPAP 20–24 mmHg) there was a trend towards better FC and lower risk levels at diagnosis in the DETECT cohort.

Iudici et al. reported that increased serum levels of NT-proBNP at admission were predictive of development of PAH on univariate though not in multivariable analysis.

Soukup et al. reported the mean mPAP at diagnosis with PAH in a cross-sectional study of patients was 59 mmHg ($\pm$ 19.5 mmHg).

Hao et al. reported that the mean 6MWD for 27 patients diagnosed with PAH through screening was 310.4 m ($\pm$ 115.8 m), the mean NT-proBNP was 1919.6 ng/L ($\pm$ 2063.6 ng/L) and the mean mRAP was 9.7 mmHg ($\pm$ 3.9 mmHg).

Table 3
Summary of evaluation of composite screening algorithms evaluated in three systematic reviews.

	Thakkar 2013	Gladue 2013	Young 2018
Aim	Identify and evaluate screening algorithms for PAH in patients with scleroderma	Identify the best evidence for screening & diagnosis of PAH in CTDs.	Systematic review of screening and diagnosis of PAH in patients with CTD.
Participants	Adults with SSc meeting ACR or LeRoy criteria	Patients with CTDs (CTD, collagen vascular disease, collagen diseases, dermatomyositis, inflammatory myositis, polymyositis, lupus, MCTD, rheumatic disease, rheumatoid arthritis, scleroderma/SSc, Sjogren syndrome, vasculitis)	Adults with diagnosis of CTD (based on ACR classification criteria) who underwent RHC.
Intervention	Applied a pre-defined screening test(s) and cut point(s) to consecutive patients without PAH. Diagnosis of pre-capilllary PH based on RHC mPAP at rest >25mmHg and PCWP ≤ 15mmHg)	Diagnosis or screening to detect PAH (pulmonary function tests, echocardiogram, ECG, CXR, NT-proBNP)	Any intervention to screen or diagnose CTD-PAH.
Publications	9	4	8
	Composite Screening Algorithms		
Study	Avouac et al.	Thakkar et al.	Guillen-Del Castillo et al.
Screening Algorithm	TTE and RFT. TTE sPAP >40mmHg or DLCO 50% or unexplained SOB.	RFT and NT-proBNP. DLCO <70.3% and FVC/DLCO ≥ 1.82 and NT-proBNP ≥ 209.8pg/mL.	DETECT and ESC/ERS 2009 (annual TTE)
Evaluation	PPV 20.4%	Sensitivity 100% Specificity 77.8%	DETECT sensitivity 100% NPV 100% ESC/ERS 2009 sensitivity 91% NPV 89%
Study	Hachulla1 et al.	Allanore et al.	Hao et al.
Screening Algorithm	TTE and RFT. TG >35mmHg or DLCO <50% or DLCO fall by 20% or unexplained SOB.	RFT and NT-proBNP. DLCO/VA ratio <70% and NT-proBNP > 75th percentile of normal.	ASIG and DETECT and ESC/ERS 2009
Evaluation	PPV 48.3%	Sensitivity 75% Specificity 97%	ASIG Sens 100% Spec 54.9% PPV 60% NPV 100% DETECT Sens 100% Spec 35.3% PPV 55.1% NPV 100% ESC/ERS 2009 Sens 96% Spec 32.3% PPV 55.3% NPV 91%
Study	Cavagna et al.	Meune et al.	Vandecasteele et al.
Screening Algorithm	TTE alone. VTR > 3m/sec or VTR 2.5 – 3/msec & unexplained SOB.	Cochin RPS score Cut off 2.73	DETECT and ESC/ERS 2009
Evaluation	PPV 87%	Sensitivity 89.5% Specificity 74.1%	DETECT PPV 6% (95% CI 2 – 17%) ESC/ERS 2009 PPV 18% (95% CI 6 – 41%) DETECT & ESC/ERS PPV 23% (95% CI 8 – 50%)
Study	Hachulla2 et al.	Coghlan et al.	Soukup et al.
Screening Algorithm	TTE alone. VTR >3m/sec. or VTR 2.8 – 3m/sec with unexplained SOB	DETECT algorithm	Modified DETECT and ESC/ERS 2009
Evaluation	PPV 30.7%	Sensitivity 96% Specificity 48%	12% patients diagnosed with PAH RHC in 41% of patients by DETECT RHC in 24% of patients by ESC/ERS 2009
Study	Jansa et al.		Morrisroe1 et al.
Screening Algorithm	TTE alone TG > 30mmHg		Six variable model (ACA, oesophageal stricture, calcinosis, digital ulcers, mild ILD, sicca symptoms)
Evaluation	PPV 35.8%		Sensitivity 100% (95% CI 99.7 – 100%) Specificity 99.9% (95% CI 99.3 – 99.9%) PPV 100% (95% CI 15.8 – 100%) NPV 91.8% (95% CI 90.3 – 93.1%)
Study	Cizuynski et al.		Gladue et al.
Screening Algorithm	TTE alone TG >31mmHg or		TTE and RFT TRV 3.16 m/sec and FVC/DLCO ratio ≥ 1.6

(*continued*)

Table 3 (*Continued*)

	Thakkar 2013	Gladue 2013	Young 2018
	elevated TG by 20mmHg on exercise		
Evaluation	PPV 14.3%		91% of PAH cases captured
Study	Mukerjhee et al.		Morrisroe2 et al.
Screening Algorithm			TTE and RFT sPAP ≥ 40mmHg or DLCO ≤ 50% & FVC > 85% or annual fall in DLCO ≥ 20% or unexplained SOB.
Evaluation	PPV 59.2%		9.7% of patients developed PAH
Study	Allanore et al.		
Screening Algorithm	TTE and RFT sPAP >40mmHg or DLCO <50% or unexplained SOB.		
Evaluation	PPV 42.1%		

Frequency of RHC referrals

Coghlan et al. referred 466 (95.5%) patients for RHC based upon a standardised procedure for referrals. Khanna et al. reported a structured algorithm based on a consensus of clinical evidence and expert opinion on when to refer for RHC resulted in a total of 27 patients (13% of the cohort) referred for RHC during a 3-year period. The investigators noted that only six patients referred for RHC met the recommended "trigger" criteria for referral for RHC. Ancuta et al. applied the DETECT algorithm to patients attending a single centre and 14 patients (34.14%) of a total of 41 were referred for RHC, with 8 patients being diagnosed with PAH (19.51% of the total cohort).

Coirier et al. compared the frequency of RHC referrals for patients with SSc whose case was discussed in a multidisciplinary meeting compared to the recommended referral frequency when the DETECT algorithm was applied. When the DETECT algorithm was applied RHC was recommended for 59.8% of patients. However, when the DETECT algorithm was only applied to those patients with disease duration > 3 years and DLCO% <60%, RHC was recommended for 26% of patients. The authors noted that application of the DETECT algorithm resulted in an increase in RHC referrals by three times the background rate based on referral for RHC following multidisciplinary meeting.

Koutsianas et al. also prospectively evaluated the frequency of RHC referrals when the DETECT algorithm was applied to a cohort of patients attending the Russells Hall Hospital scleroderma clinic and found that RHC was recommended for 58% of patients based on a positive DETECT score compared to 13% based on TR jet velocity according to the 2015 ESC/ERS guidelines.

Soukup et al. reported that 12% of a cohort of 58 SSc patients were diagnosed with PAH (7 patients), 14 patients were recommended for RHC according to the 2015 ESC/ERS guidelines and 41.4% (24 patients) according to the modified DETECT algorithm.

Summary of findings from systematic reviews

Thakkar et al. performed a systematic review evaluating predefined screening tests and cut-offs in patients with SSc. This identified nine studies, of which TTE was included in all studies; five publications used TTE alone and four included DLCO in 'composite' screening algorithms. The results of these 'composite' screening algorithms are summarised in Table 3.

Gladue et al. sought to identify the best evidence for screening and diagnosis of PAH in patients with CTDs. This study identified 22 publications, 12 of which focussed on TTE parameters and were predominantly undertaken in cohorts of patients with SSc, four regarding RFTs, five evaluated serum NT-proBNP and four evaluated composite measures. A summary of the publications of composite measures evaluated in this review is included in Table 3. The authors also identified single publications each regarding the use of ECG, and cardiac magnetic resonance imaging and computed tomography for diagnosis of SSc-PAH. There were also single publications regarding arterial oxygen partial pressure, chest radiographs, brain natriuretic peptide, erythrocyte sedimentation rate, autoantibodies in patients with systemic lupus erythematosus (SLE) and nail fold capillaroscopy.

Gladue et al. concluded that when using TTE for screening, the TR velocity or equivalent RVSP were most commonly evaluated and the usefulness of TTE for screening was supported. However three publications reported issues with TR velocity, which was unable to be estimated in 3/8 patients with PAH in one cohort, and 13–15% of the total cohort in two other studies. The most evidence existed for the use of TTE, RFT and NT-proBNP for screening.

Young et al. was performed by the same group of investigators in order to update guidelines for screening and diagnosis of CTD-PAH. This study identified 22 publications, of which eight examined composite measures to screen patients for PAH. The three most frequently evaluated composite screening algorithms were the DETECT algorithm, the 2009 ESC/ERS guidelines and the ASIG algorithm. This systematic review also evaluated other publications investigating the role of RFT, laboratory biomarkers including troponin and anti-cardiolipin antibodies in patient cohorts with SSc and SLE. Again, the authors noted that the majority of the literature regarding screening and diagnosis of PAH is in cohorts with SSc and that there is increasing evidence for incorporating TTE into novel screening algorithms (like DETECT or ASIG) to improve screening outcomes.

Meta-analysis

We included six studies in the meta-analysis. Humbert et al., Jansa et al. and Morrisroe et al. were prospective multicentre studies. Phung et al. and Vandecasteele et al. were prospective single tertiary centre study cohorts. Hesselstrand et al. was a retrospective single tertiary centre cohort study. The studies included for meta-analysis are summarised in Table 5.

Humbert et al. compared two incident multicentre cohorts of patients with SSc-PAH from the same management era (2002 to 2003). The first cohort, from the FPHN, comprised patients in whom PAH was diagnosed using a standardised diagnostic approach, including patients with SSc-PAH, that were compared to a second cohort of patients (ItinérAIR-Sclérodermie program) with SSc defined as meeting American Rheumatism Association criteria and/or Le Roy classification criteria who were diagnosed with PAH by a systematic detection program. Patients who had undergone confirmatory RHC were included in the analysis, and patients with risk factors for PH not classified as Group 1 PAH (for example with evidence of severe obstructive or restrictive ventilatory defects) were excluded. PAH was defined as a mPAP ≥ 25 mmHg at rest, mPAWP ≤ 15 mmHg during RHC. To ensure a homogeneous study population, case report forms of all patients were reviewed by an adjudication panel prior to inclusion in a cohort and analysis. The study included 16 patients in

Table 4
Summary of ESC/ERS 2015 Risk Stratification table parameters at diagnosis with PAH from studies included in systematic review.

	Participants, n	Number of patients diagnosed with PAH	Functional class at diagnosis or baseline	6-minute walk distance at diagnosis or baseline (metres) mean (SD)	Respiratory function parameters at diagnosis or baseline mean (SD)	Haemodynamic parameters at diagnosis or baseline by RHC mPAP (mmHg) mean (SD)	CI (L/min/m^2) mean (SD)	mRAP (mmHg) mean (SD)	mPCWP (mmHg) mean (SD)	PVR (WU) mean (SD)	Haemodynamic parameters at diagnosis or baseline by TTE	Serum NT-proBNP (or BNP) at diagnosis or baseline mean (SD)
Launay 2013	85	85	79% of patients in NYHA FC III/IV (n = 75)	259 (126) (n = 137)	N/A	41 (11)	2.64 (0.78) (n = 83)	N/A	N/A	N/A	N/A	BNP (ng/L) 463 (573) (n = 48)
Kolstad 2018	160	160	NYHA FC I 25 (15.82%) NYHA FC II 69 (43.67%) NYHA FC III 57 (36.08%) NYHA FC IV 7 (4.43%) (n = 158)	Median (range) 365.9 (20 – 960.4)	Median (range) FVC/DLCO ratio 2.1 (1 – 6.1) (n = 136)	Median (range) 35 (25 – 70)	N/A	N/A	Median (range) 10 (1 – 15)	Median (range) 4.8 (1.7 – 29.96)	Median (range) sPAP 55.5 (15 – 123) (n = 134)	N/A
Soukup 2016	58	7	N/A	N/A	FVC/DLCO ratio 1.88 (0.5)	48.9 (15.5)	N/A	N/A	N/A	N/A	sPAP 62.1 (9.4)	NT-proBNP (pmol/L) 307.1 (359.3)
Iudici 2013	867	40 (29 with PAH, 11 with pre-capillary ILD-PH)	N/A	N/A	N/A	37.91 (10.27)	2.51 (0.84)	N/A	10 (3.59)	N/A	N/A	NT-proBNP noted to be higher than normal range in 7 of 16 patients with PAH (43.7%) compared to 35 of 221 (15.8%) without PAH
Coghlan 2014	488	87	NYHA FC I 16 (18.4%) NYHA FC II 40 (46%) NYHA FC III 30 (34.5%) NYHA FC IV 1 (1.1%) (n = 66)	389.7 (106.6)	FVC/DLCO ratio 2.2 (0.7)	32.5 (8.3)	2.9 (0.6) (n = 86)	N/A	10.3 (3.2)	N/A	TR velocity (m/sec) 3.1 (0.7) (n = 78)	NT-proBNP (pg/mL) 516.4 (805) (n = 80)
Khanna 2014	207	30 physician reported PH diagnosis.	NYHA FC I 97 (46.9%) NYHA FC II 72 (34.8%) NYHA FC III 14 (6.8%) NYHA FC IV 3 (1.4%) Missing 21 (10.1%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	RVSP (sPAP) (mmHg) Median (IQR) 30 (24 – 38) (n = 123) TR velocity (m/sec) 2.3 (2 – 2.6) (n = 45)	N/A
Hoffmann-Vold 2018	161 (OUH protocol 2009-2013 = 77) (OUH & NYHA III & IV 8 (53.3%)	DETECT = 84) NT-proBNP (μmol/L) 189 (221.9)	15	NYHA FC I & 2 7 (46.7%)	356 (207.9)	FVC/DLCO ratio 2.9 (1.2)	N/A	N/A	N/A	N/A	N/A	sPAP (mmHg) 52 (26)
Guillen-Del Castillo 2017	78 (n = 63 included for DETECT analysis)	35	WHO FC III & IV 15 (42.9%)	232.8 (76.7)	FVC/DLCO ratio 2.0 (0.7)	Median (IQR) 42 (33 – 50)	N/A	N/A	9.7 (4.8)	9.9 (4.6)	RVSP (mmHg) Median (IQR) 73 (61 – 85) TR velocity (m/sec) 4.0 (0.6)	NT-proBNP (pg/mL) Median (IQR) 1271 (580 – 3154)
Hao 2015	73	27	N/A	310.4 (115.8)	FVC/DLCO ratio 2.0 (0.5)	36.4 (10.1)	N/A	9.7 (3.9)	N/A	5.7 (3.3)	sPAP (mmHg) 57.7 (19.6) TR velocity (m/sec) 3.4 (0.6)	NT-proBNP (pg/mL) 1919.6 (2063.6)

Table 5
Summary of studies included for meta-analysis.

	Year	Country	Participants	Screening	Control
Humbert *et al.*	2011	France	32	Annual echocardiography (TTE) with RHC based on TRV.	Routine practice, PAH diagnosed on basis of symptoms.
Morrisroe *et al.*	2017	Australia	160	Annual clinical assessment, TTE and RFT. RHC referral based on all 3 and ESC/ERS guidelines.	PAH diagnosed at 1st screening visit. Presumed delayed diagnosis or 'prevalent' PAH.
Vandecasteele *et al.*	2017	Belgium	362	Annual TTE based on 2009 ESC/ERS guidelines & the DETECT algorithm from 2015. (2010-2015)	Historical control referred for RHC on physician discretion (2006-2009).
Hesselstrand *et al.*	2011	Sweden	30	Collaboration with cardiology to screen by annual TTE. RHC if sPAP > 36mmHg. (2002-2009)	PAH diagnosed at 1st screening visit, presumed delayed diagnosis or 'prevalent' PAH.
Jansa et al.	2012	Czech Republic	203	Annual TTE with RHC if TR gradient > 30mmHg. (Between Jan-Dec 2007)	Patients previously diagnosed with PAH based on symptoms.
Phung et al.	2009	Australia	184	Annual clinical assessment, RFT, TTE, 6MWT. RHC if estimated RVSP > 40mmHg, symptomatic and RVSP 35 – 40mmHg, other of PH. (2005-2007)	Patients referred to PH centre with a probable diagnosis of PAH.

each cohort designated as the routine clinical practice cohort and the systematic detection cohort. Reported outcomes included 1, 3, 5, and 8 year survival rates, and risk stratification factors at diagnosis including NYHA FC, 6MWD and haemodynamic parameters [10].

Jansa et al. included 203 patients with SSc (classified as limited, overlap syndrome or sine scleroderma) attending rheumatology practices in the Czech Republic who were offered TTE as a routine investigation. Important exclusion criteria included severe pulmonary function abnormalities (FVC, total lung capacity (TLC) or forced expiratory volume in one second (FEV1) < 60% predicted) and those with cardiac disorders including significant valvular heart disease or left ventricular ejection fracture (LVEF) < 50% predicted. Haemodynamic parameters of patients diagnosed via the screening programme were compared with those of patients with PAH diagnosed before 2007 based on symptoms [37].

Morrisroe et al. reported data from patients enroled in the Australian Scleroderma Cohort Study (ASCS) in which patients with SSc are assessed annually by a mandated PAH screening algorithm based on the ESC/ERS guidelines and comprehensive demographic and disease-related data are collected at each visit. This analysis compared 38 patients with a diagnosis of PAH made at their first visit for screening with 122 patients who were subsequently diagnosed through systematic screening within the same defined period. Three-year survival from the time of PAH diagnosis in the cohort who were diagnosed at their first screening visit ('prevalent PAH') was compared to survival in patients whose PAH was diagnosed as a result of subsequent screening ('incident PAH'). Clinical, functional and haemodynamic parameters at the time of diagnosis with PAH for each cohort was also reported [3].

Phung et al. conducted a prospective cross-sectional study at a tertiary centre in Perth, Australia. The investigators compared patients with SSc meeting the American Rheumatology Association (ARA) classification criteria (including six with mixed connective tissue disease) who had been referred with a clinical suspicion of PAH to those who had been referred specifically for screening for PAH [19]. Outcomes for 170 patients who had been referred for screening and 14 patients who had been referred for diagnosis were evaluated including clinical, functional and haemodynamic parameters for 17 patients with PAH diagnosed by screening who were compared to 7 with PAH diagnosed based on clinical suspicion [38].

Vandecasteele et al. evaluated data from consecutive patients with SSc included in the Ghent University Systemic Sclerosis Cohort from May 2006 to December 2015. Using a historical control they compared outcomes between a cohort of 157 patients seen between 2006 and December 2009 during which time referral for RHC was at the discretion of the treating physician, and a cohort of 205 patients screened for SSc-PAH from 2010 to 2015 according to the 2009 ESC/ERS guidelines. Additionally, patients seen from 2015 were screened by both the 2009 ESC/ERS and the DETECT algorithms. The outcomes of this study included the prevalence and incidence of PAH in both cohorts and the frequency of referral for RHC using both screening mechanisms [39].

Hesselstrand et al. evaluated survival in a cohort of 30 patients diagnosed with SSc-PAH between 2002 and 2009 as a result of an improved screening programme implemented at Skåne University Hospital in Sweden in collaboration with the Department of Cardiology and compared them each to five control patients from the total SSc cohort without PAH. Controls were matched by year of first examination in the department. Reported outcomes included overall survival for patients with SSc-PAH at 1-, 2-, 3- and 4 years, as well as clinical, functional, serological and haemodynamic parameters at the time of diagnosis with PAH comparing patients who were diagnosed at their first visit with those diagnosed during follow up [40].

Survival

Of the six studies included for meta-analysis, three reported survival in screened compared to unscreened cohorts. There was a statistically significant better survival in screened cohorts compared to an unscreened cohort in two multicentre studies. Humbert et al. reported the hazard ratio (HR) for mortality in the routine practice cohort relative to the detection (screened) cohort was 4.15 (95% CI 1.47–11.71). Inversing the HR for Humbert et al. reveals the HR for mortality in the screened compared to routine practice cohort was 0.24 (95% CI 0.09–0.68). Morrisroe et al. reported improved three-year survival from the time of diagnosis with PAH in the screened compared to unscreened cohort (94.7% vs 42.7%, $p < 0.001$) with longer mean time to death in those diagnosed as a result of screening (4.7 ± 2.3 vs 2.3 ± 2.3, $p < 0.001$). Using the methods described, the HR for mortality risk in the patients diagnosed as a result of subsequent screening relative to those diagnosed at first visit was 0.34 (95% CI 0.18–0.64). This resulted in a pooled HR for mortality of 0.31 (95% CI 0.19–0.52, $p < 0.0001$) favouring screening (Fig. 2).

Hesselstrand et al. descriptively reported no difference in survival between 11 patients who already had PAH at the time of inclusion and 19 who developed PAH during the time period from 1st July 2002 to 30th September 2009, although the data required to include this paper in the meta-analysis of survival were not provided. From the time of diagnosis with SSc, the 5-year survival rate of the combined cohort of 30 patients with SSc-PAH was 67%, and 10-year survival rate was 43%.

Functional class at diagnosis of PAH

Four studies reported functional class at diagnosis of PAH in a total of 222 patients with SSc who were screened compared to those who

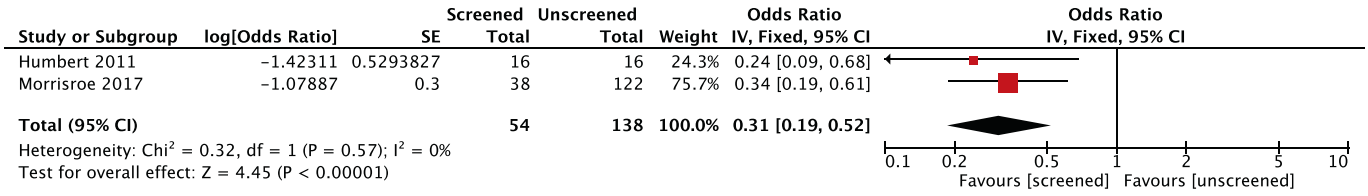


Fig. 2. Forest plot mortality.

were not. The risk ratio (RR) of having a functional class of I or II at diagnosis with PAH was 1.84 (95% CI 0.84 to 4.06, $p = 0.13$) favouring the screened cohort, however there was statistically significant heterogeneity amongst the included studies ($I^2 = 56\%$, $p = 0.08$) (Fig. 3). Jansa et al. reported the mean ± SD NYHA functional class in patients diagnosed during screening 2.67 ± 0.52 compared to 2.89 ± 0.33 in patients who were diagnosed with SSc-PAH and were not screened.

Sensitivity analysis was performed by excluding Hesselstrand et al. which revealed a statistically significant RR of having functional class of I or II at diagnosis of 2.33 (95% CI 1.45 to 3.73, $p = 0.0004$) favouring the screened cohorts with no statistically significant heterogeneity ($I^2 = 0\%$, $p = 0.58$) (Fig. 4).

Haemodynamic parameters at diagnosis with PAH

Four studies including 237 participants reported better haemodynamic parameters at the time of diagnosis of PAH in patients with SSc diagnosed as a result of screening. Using a random-effects model for analysis the mean difference in mean pulmonary artery pressure (mPAP) in mmHg between screened compared to unscreened patients was −8.15 (95% CI −15.56 to −0.73, $p = 0.03$). There was significant heterogeneity between trials ($I^2 = 83\%$, $p = 0.0005$), (Fig. 5). Performing sensitivity analysis by excluding Hesselstrand et al. from the analysis demonstrated a mean difference in mPAP of −11.51 (95% CI −18.94 to −4.09, $p = 0.002$), however heterogeneity remained significant ($I^2 = 78\%$, $p = 0.010$) (Fig. 6).

Three multicentre studies including 222 participants reported statistically significant improvement/reduction in right atrial pressure (mRAP) in mmHg. The mRAP was lower in screened patients compared to unscreened patients with a mean difference of −1.98 favouring screening, which did not reach statistical significance (95% CI −4.08 to 0.11, $p = 0.06$) ($I^2 = 36\%$, $p = 0.21$). There was statistically significant heterogeneity amongst the included studies (Fig. 7).

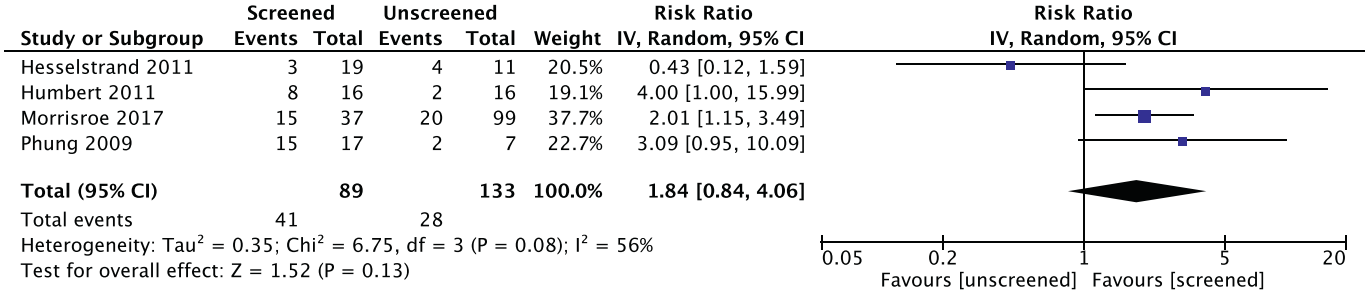


Fig. 3. Forest plot FC.

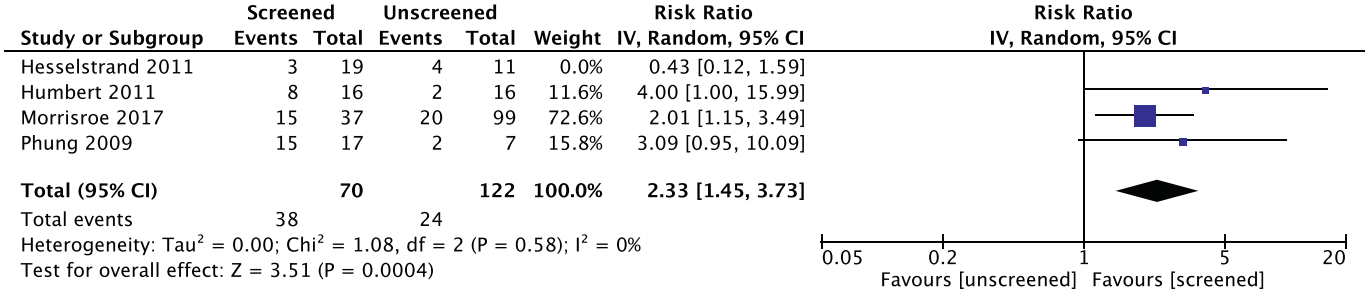


Fig. 4. Forest plot FC sens.

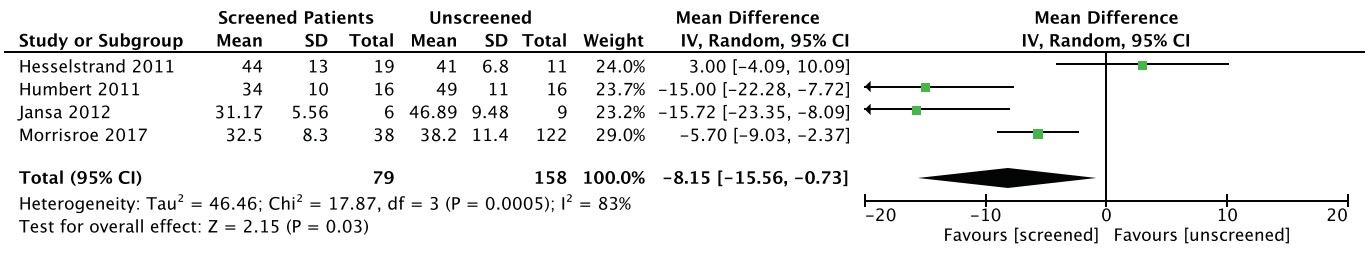


Fig. 5. Forest plot mPAP.

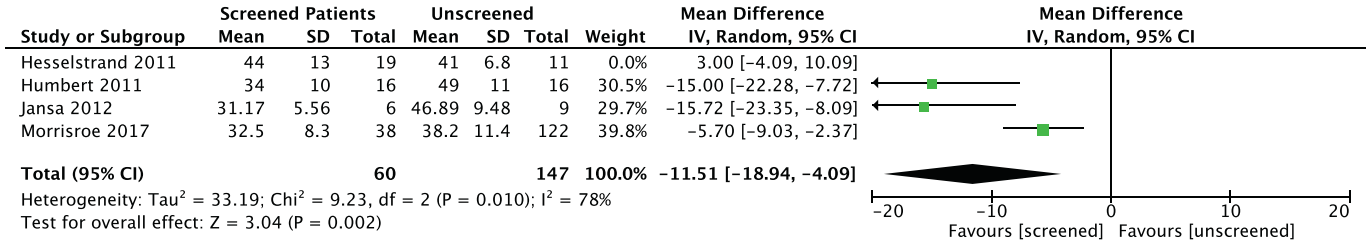


Fig. 6. Forest plot mPAP sens.

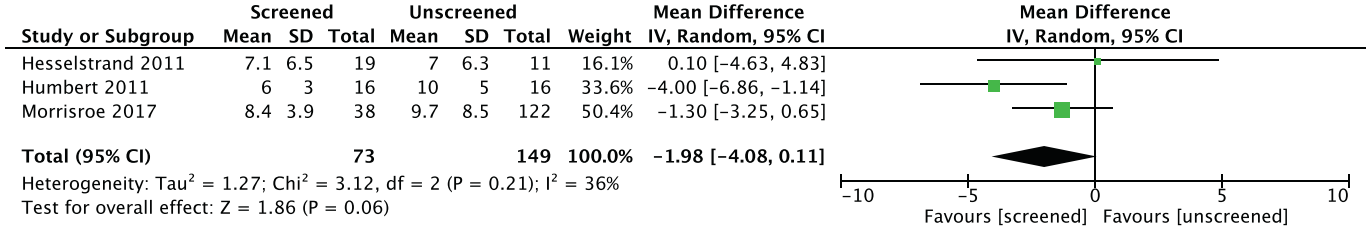


Fig. 7. Forest plot mRAP.

Sensitivity analysis by performing the analysis using a random effects model and excluding Hesselstrand et al. revealed a mean difference of −2.44 (95% CI −5.05 to 0.17, $p = 0.07$), however significant heterogeneity remained ($I^2 = 57\%$, $p = 0.13$) (Fig. 8).

The mean difference in pulmonary vascular resistance (PVR) in Woods Units was −3.09 (95% CI −6.50 to 0.33, $p = 0.08$) with significant heterogeneity between studies ($I^2 = 88\%$, $p < 0.0001$), (Fig. 9). Mean difference in cardiac index (CI) in L/min/m^2 did not reach statistical significance and was 0.25 (95% CI −0.25 to 0.75, $p = 0.33$) with significant heterogeneity ($I^2 = 69\%$, $p = 0.02$), (Fig. 10).

Sensitivity analyses by the methods above did not result in improved heterogeneity regarding PVR and CI, however did result in a statistically significant mean difference in PVR favouring screening, with mean difference in PVR of −4.83 (95% CI −9.30 to −0.37, $p = 0.03$) (Fig. 11).

6 min walk distance at diagnosis with PAH

Three studies including 222 participants reported a statistically significant improvement in 6MWD measured in metres in patients diagnosed with SSc-PAH in a screened cohort compared to unscreened patients. The mean difference favouring screening was 75.42 m (95% CI 39.32 to 111.53, $p < 0.0001$) ($I^2 = 0\%$, $p = 0.85$), (Fig. 12). This exceeds the minimal clinically important difference (MCID) in PAH which is 41 metres [41].

Respiratory function test parameters at diagnosis with PAH

One study with 30 participants reported DLCO% predicted at the time of diagnosis with PAH in screened compared to unscreened patients with SSc, however there was no statistically significant difference (41% compared to 33%, p 0.069) [40].

NT-proBNP

Hesselstrand et al. study of 30 participants reported serum NT-proBNP in ng/L at the time of PAH confirmation in patients diagnosed as a result of screening compared to those who had not been screened. There was a trend towards lower NT-proBNP in screened patients at diagnosis, although this did not reach statistical significance (mean difference −693 ng/L (95% CI −2535.38 to 1149.38). However, there was a statistically significant difference in mean serum NT-proBNP measured at the 'first visit' of the screening programme (starting from 1 July 2002 to 30 September 2009) between patients who subsequently developed PAH during follow-up and

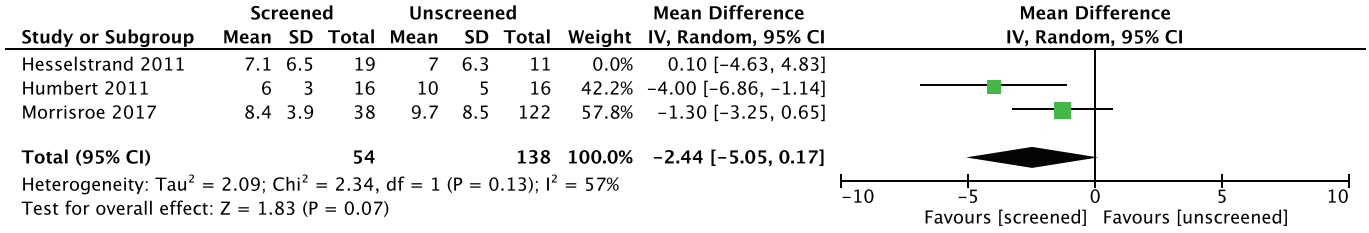


Fig. 8. Forest plot mRAP sens.

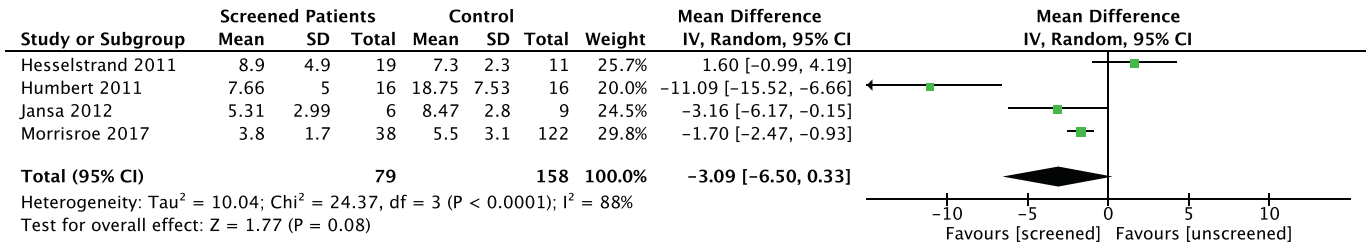


Fig. 9. Forest plot PVR.

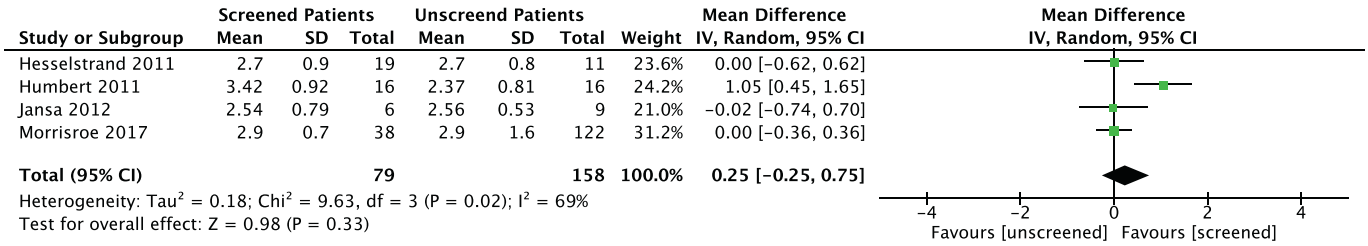


Fig. 10. Forest plot CI.

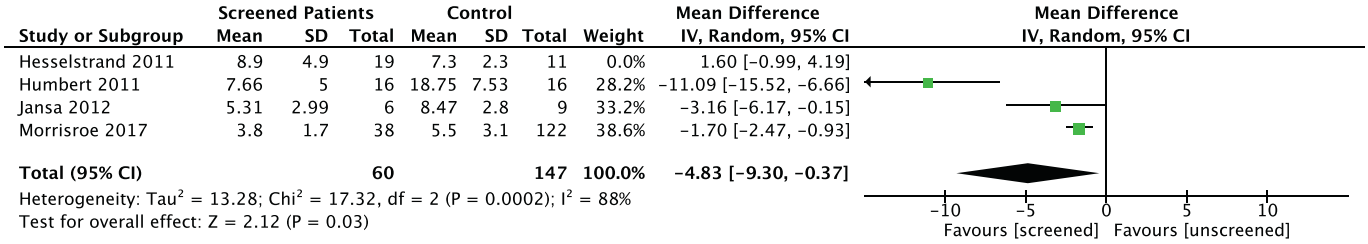


Fig. 11. Forest plot PVR sens.

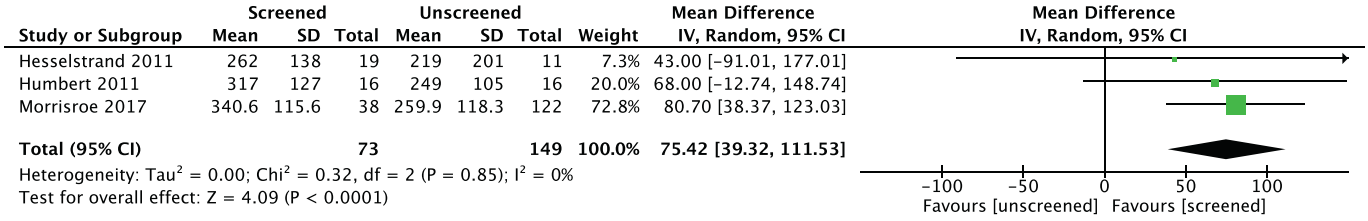


Fig. 12. _Forest plot 6MWD.

those without PAH (mean NT-proBNP 1859 ng/L ± 3785 vs 696 ± 4149, $P < 0.001$) [40].

Frequency of detection of PAH with mPAP ≤ 20 mmHg

Following the 6th WSPH, an updated definition of pre-capillary pulmonary hypertension (PH) has been published. Based on a scientific approach, pre-capillary PH is best defined by a mPAP > 20 mmHg, pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and PVR ≥ 3 Woods Units (WU) [4].

Vandecasteele et al., addressed this by evaluating the frequency of a diagnosis of 'borderline PH' defined as a mPAP of 21 to 24 mmHg during RHC using the DETECT algorithm compared to screening with annual echocardiography according to the 2015 ESC/ERS guidelines. Based on the DETECT algorithm, 13 of 14 patients (93%) with borderline PH were referred for diagnostic RHC, and 10 of 14 patients with borderline PH (71%) were referred for RHC by screening with annual echocardiography.

Hoffman-Vold et al. likewise evaluated the incidence of borderline PH diagnosed as a result of screening annually by complete clinical examination, echocardiogram, RFT, 6MWT and NT-proBNP compared to screening following implementation of the DETECT algorithm. In the DETECT cohort, 26 patients (31.0%) were diagnosed with borderline PH compared to 13 (16.9%) in the cohort screened prior to implementation of the DETECT algorithm.

Risk of bias within studies

Systematic review

Studies by Kolstad et al., Launay et al. and Hoffman-Vold et al. reported data collected from patients enroled in registries and were assessed at low risk of detection bias.

However, the remaining studies included in the systematic review were observational cohort or cross-sectional studies and felt to be at high risk of bias and confounding.

Meta-analysis

We assessed the risks of bias in the included studies using the QUADAS-2 tool ('Summary of QUADAS-2 evaluation' in the appendices). Overall, publications included in the meta-analysis were assessed at low risk of bias, particularly for domains regarding comparison to the index test and reference standard. Hesselstrand et al. was assessed at high risk of bias during patient selection as patients were compared to controls without PAH. Vandecasteele et al. used a historical cohort as a control group who had undergone assessment for PAH between 2006 and 2009. Overall, there was low concern regarding the applicability domain for all publications included in the meta-analysis, as shown in Fig. 13.

Risk of bias across studies

The cumulative evidence presented in this systematic review and meta-analysis is derived predominantly from observational registries, cohort studies and cross-sectional studies and may be at risk of confounding. With regard to survival analysis, the included publications analysed patients with varying disease duration which may introduce the risk of survivor bias. Additionally, when evaluating screening algorithms, lead-time and length-time biases cannot be excluded when cases detected in the screened group have a longer duration of disease.

Discussion

Summary of evidence

This review demonstrates statistical and clinical long-term benefit for patients with SSc who have been systematically screened for the early detection of PAH.

The systematic review revealed that there are a number of protocols in use to screen patients with SSc for PAH. Annual TTE according to the ESC/ERS guidelines is widely used and screening algorithms

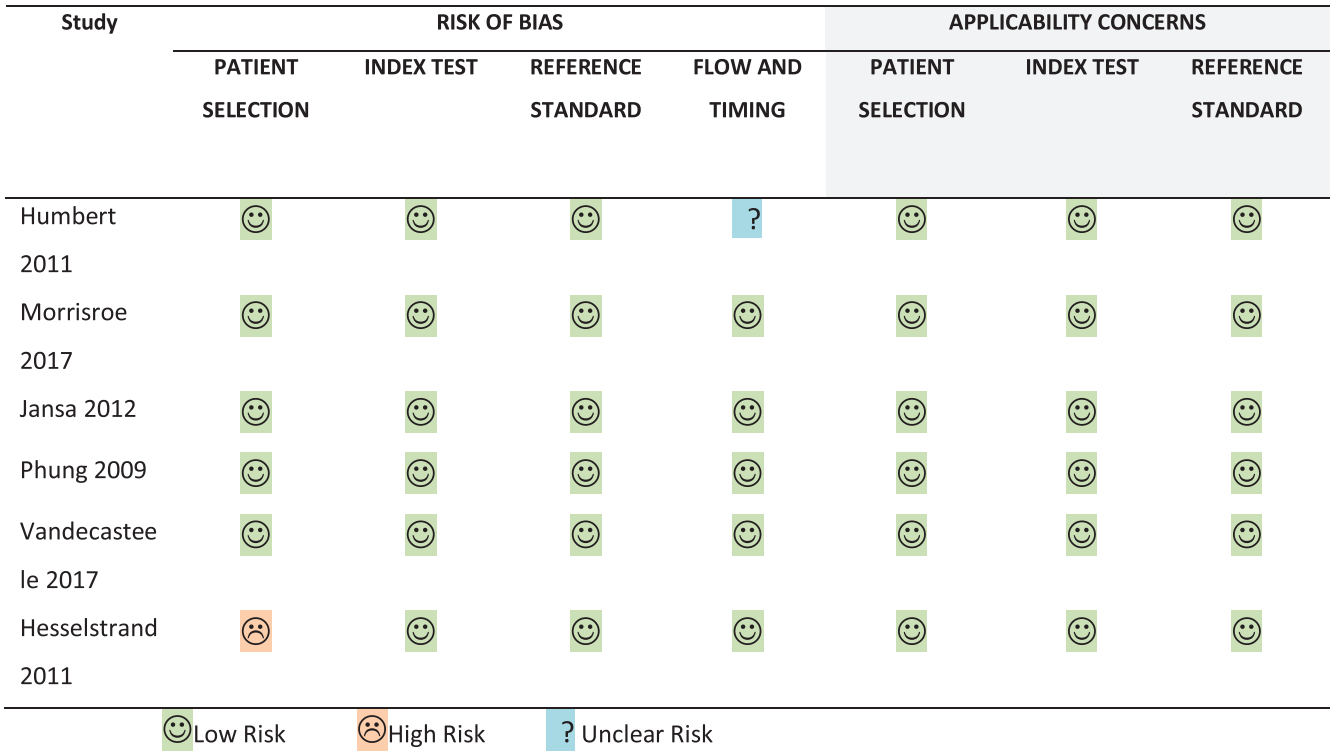


Fig. 13. QUADAS-2 results of assessment for risk of bias and applicability.

which rely on multidimensional assessments including annual assessments of RFTs and biomarkers prior to TTE have been evaluated. A number of studies included in the systematic review evaluated known PAH risk stratification (prognostic) parameters at diagnosis with PAH in patients diagnosed as a result of screening.

The meta-analysis, which included six studies of patients undergoing screening to detect SSc-PAH when compared to cohorts who had not been screened according to current guidelines, favoured screening with regards to survival, with a statistically significant better survival using data from two prospective multicentre registries. 6MWD at diagnosis was also statistically significantly better, which has been shown to be a predictor of mortality and is included in multidimensional risk assessment tools [42–44].

Screening also resulted in trends towards better clinical, functional, haemodynamic and serological prognostic parameters at the time of PAH diagnosis in both the systematic review and meta-analysis. Five studies included in the meta-analysis reported more patients diagnosed with functional class I or II at the time of diagnosis with PAH in screened versus unscreened patients. Four studies reported significant differences favouring screening for improved haemodynamic parameters, including mPAP and RAP, at the time of diagnosis with PAH in patients with SSc whose PAH was diagnosed as a result of screening.

Overall completeness and applicability of the evidence

The numbers of patients included in the meta-analysis of survival are small and there were no randomised studies for inclusion; however, the direction of effect is consistent across studies and demonstrates improved long-term outcomes for patients with SSc diagnosed with PAH as a result of systematic screening. This is concordant with current ESC/ERS guidelines which recommend annual screening of asymptomatic individuals at risk of developing PAH, including those with SSc and SSc-spectrum disorders.

The secondary outcomes evaluated including clinical, functional, serological and haemodynamic parameters at the time of diagnosis with PAH are characteristics which are included in the 2015 ESC/ERS risk stratification table.

The 2015 ESC/ERS guidelines stratify patients at low, intermediate or high risk (equating to $a > 10\%$ estimated 1-year morality) based on the assessment of clinical signs of right heart failure, progression of symptoms, syncope, WHO functional class, cardiopulmonary exercise testing, serum NT-proBNP levels, right atrial area or presence of pericardial effusion, haemodynamics including right atrial pressure (RAP), cardiac index (CI) or mixed venous oxygen saturation (SvO2) [12]. Low-risk criteria are defined as WHO/NYHA FC I or II, 6MWD $>$ 440 m, RAP $<$ 8 mmHg and CI $\geq$ 2.5 L/min/m^2 [12]. The number of low-risk criteria present at diagnosis and first re-evaluation have been shown to correlate with survival and lung transplantation. [44,45].

This review showed that screening detected more patients with FC I or II, and demonstrated increased 6MWD at the time of diagnosis with PAH. Overall, patients with SSc-PAH diagnosed as a result of screening had more favourable haemodynamic parameters at diagnosis, including RAP. It can be postulated that these findings will correlate with improved survival in patients diagnosed early with SSc-PAH as a result of screening.

This systematic review highlights differing protocols in use for PAH screening in SSc. Three systematic reviews (Thakkar et al., Gladue et al. and Young et al.) have evaluated screening and diagnosis of PAH in patients with CTD and SSc. Three commonly evaluated algorithms for screening, the 2015 ESC/ERS guidelines, the DETECT algorithm and the ASIG algorithm have subsequently been included in the updated guidelines for screening following the 6th WSPH.

Two papers included in this review undertook cost analysis, and a third has been performed evaluating cost-savings associated with the ASIG algorithm and suggest that composite screening programs for the detection of PAH in patients with SSc can be cost saving [10,39,46]. True cost-effective analysis, incorporating survival data and health-related quality of life data, are needed.

Two papers undertook an evaluation of the frequency of diagnoses of 'borderline pH' or PAH with a mPAP $>$ 20 mmHg as a result of

screening, though further prospective evaluation of the efficacy of screening to detect patients with the updated definition of PAH will be important to inform guidelines.

Strength/Quality of the evidence

The quality of evidence for survival in patients undergoing screening was high due to the inclusion of two real-world registries with low heterogeneity and comparison of outcomes between contemporaneous cohorts, thereby reducing the effect of confounding. In Morrisroe et al., 100% of deaths in the cohort with SSc-PAH were attributable to SSc-PAH and in Humbert et al. the majority of deaths were related to refractory right-sided heart failure while only one death in the screened cohort was due to gastrointestinal bleeding.

The quality of the evidence regarding risk stratification parameters at the time of diagnosis of PAH is reduced due to heterogeneity amongst the studies, although the effect was consistent across studies in the meta-analysis and systematic review.

Limitations

Survival analysis based on pooled data includes patients with different disease durations and is subject to survivor bias. Previous registry data comparing survival in prevalent compared to incident cohorts of patients with PAH (for example from the REVEAL registry and the FPHN) confirms the effect of survivor bias, where patients with stable prevalent disease have better survival when compared to an incident cohort [11,47]. This may negatively affect the magnitude of the observed intervention effect, as this analysis evaluates the outcomes of patients with incident PAH.

The evaluation of screening programs may be subject to lead-time and length-time bias; however, evaluation of mortality rates which do not consider the time from diagnosis to death are felt to be less subject to length-time bias [48].

The authors have made an attempt to systematically appraise methodology of the included studies, although the inclusion of non-randomised observational data is subject to confounding.

Conclusions

Data from this review demonstrate long-term benefit from the systematic screening of patients with SSc of varying disease duration for the early detection of PAH. Screened cohorts had improved survival, and were more likely to have low-risk criteria prognostic factors at the time of diagnosis with PAH when compared to cohorts who were not screened.

Systematic review reveals that there are variations of screening protocols in practice and that they are based upon guidelines produced by the ESC/ERS, with increasing use of multidimensional or composite evaluation with TTE as a second tier investigation. Screening in these publications detected patients with more favourable risk stratification characteristics at diagnosis with PAH.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2021.03.011.

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