

Echocardiography as an outcome measure in scleroderma-related pulmonary arterial hypertension

Results of a systematic literature analysis by the EPOSS group

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ABSTRACT

Aim: To assess the validation status of echo-Doppler as an outcome measure in pulmonary arterial hypertension associated with systemic sclerosis (PAH-SSc).

Methods: Structured literature review on full-text English articles was performed using the PubMed and Cochrane databases. The assessment of validation of echo-Doppler was based on the “OMERACT filter” criteria with the domains *truth (face, content, construct, and criterion validity), discrimination, and feasibility.*

Results: Out of 35 studies eligible for analysis, only 5 included well-defined (according to the World Health Organization criteria) PAH-SSc subgroups. Echo was considered as having *face validity* based on expert opinion and high number of studies using echo for evaluation of SSc patients. Echo was considered partially validated with respect to *criterion validity* based on significant correlations between echo measures and right heart catheterization in SSc patients being at risk of PAH/PH. However, echo was found to lack specificity (lack of *content validity*), since measurements of echo pulmonary pressure may be influenced by left heart disease and interstitial lung disease. Data from general populations of scleroderma patients indicate that evaluation of pulmonary artery pressure by echo might not be available in all PAH-SSc patients because of technical factors. No studies enabling evaluation of the *discriminant capacity* over time and treatment of echo in PAH-SSc could be identified.

Conclusions: Further studies are needed to fully validate echo-Doppler as an outcome measure in PAH-SSc. These studies include cross-sectional analysis of baseline measures and longitudinal data of placebo and verum groups in randomized controlled trials of patients with PAH-SSc.

Key Indexing Terms: Scleroderma, Echo-Doppler, EPOSS, Outcomes, Clinical Trials

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Abbreviations used in the text

CTD	Connective tissue disease
echo-Doppler	Echocardiography with continuous Doppler
EPOSS	Expert Panel on Outcomes Measures in PAH related to Systemic Sclerosis
FVC	Forced vital Capacity
HRCT	High resolution computed tomography
NYHA	New York Heart Association
OMERACT	The Outcome Measure in Rheumatology
PAH	Pulmonary arterial hypertension
PAH-SSc	Pulmonary arterial hypertension associated with systemic sclerosis
PH-SSc	Pulmonary hypertension associated with systemic sclerosis
PAP	Pulmonary artery pressure
PASP	Pulmonary artery systolic pressure
PH	Pulmonary hypertension
RCT	Randomized controlled trial
RHC	Right heart catheterization
SSc	Systemic sclerosis
VTR	Velocity of tricuspid regurgitation
WHO	World Health Organization

INTRODUCTION

Pulmonary arterial hypertension (PAH) associated with systemic sclerosis (scleroderma, SSc) is one of the most frequent causes of death in SSc patients. PAH develops on the basis of obstructive proliferative vasculopathy of small and medium-sized pulmonary arteries. In the setting of SSc, other causes than primary pulmonary vasculopathy may also lead to an increase in pulmonary artery pressure (PAP). Indeed, significant lung disease, which might lead to pulmonary hypertension (PH) due to hypoxemia, was found in up to 30-75% of SSc patients with elevated PAP [1-2]. Left heart dysfunction, which might cause postcapillary/venous PH, was found in up to 13%-19% of SSc patients suspected of having PAH [3-4].

So far only intravenous epoprostenol has been proven to be beneficial in a randomized controlled trial (RCT) exclusively in PAH-SSc patients [5]. In contrast, the other therapies were investigated in more general PAH populations, where PAH-SSc contributed approximately a quarter of patients. Although numbers were always small and statistical power calculations may have confounded the SSc-specific results, post-hoc analyses of these studies showed that the PAH-SSc subgroup was usually less responsive than patients with idiopathic PAH [6]. Thus, there is an urgent need for clinical studies aimed at evaluation of new therapeutics specifically in PAH-SSc patients.

Since appropriate outcome measures are of key importance for the correct evaluation of clinical trials, the OMERACT (Outcome Measures in Rheumatology Clinical Trials) consensus group has developed a set of criteria for the validation of endpoints in rheumatic diseases. These criteria are known as the “OMERACT filter” and include: *truth* (face, content, construct, and criterion validity), *discrimination* (reliability/reproducibility and sensitivity to

change), and *feasibility* [7]. These OMERACT criteria should be fulfilled before a specific outcome measure is fully validated and recommended for use in clinical trials.

Among 11 measures identified by a recent expert panel on outcome measures in PAH-SSc (EPOSS) utilizing a Delphi process among 74 interdisciplinary experts [8], only right heart catheterization (RHC) has so far been considered validated according to the “OMERACT filter criteria” and therefore judged “ready for use in clinical trials” [9]. However, RHC is often not feasible for repeated measures due to its invasiveness. Echocardiography including assessment of pulmonary arterial pressures by continuous Doppler (echo-Doppler) is another endpoint indicated for consideration by the EPOSS group. However, echo requires full validation before it can be recommended for clinical trials in PAH-SSc. The aim of the present study was therefore to assess the current status of validation of echo in PAH-SSc according to the OMERACT criteria using a systematic literature search. The identification of specific aspects of echo that need further validation in PAH-SSc is the basis for the design of further validation studies.

METHODS

Systematic literature review

Studies in which echo was used for the evaluation of patients with PAH/PH-SSc were searched in PubMed and Cochrane Controlled Trial Register databases using combinations of predefined key words. The key words used were “systemic sclerosis OR scleroderma OR CREST” AND “pulmonary arterial hypertension OR pulmonary hypertension” AND “echocardiography OR echo”. To identify other relevant articles, references of the retrieved papers and most recent review articles published within the last two years were analyzed. In addition, the “related article” tool in PubMed was used. All original studies published between 1966 and 15th of January 2008 were selected if they involved ≥ 5 PAH/PH-SSc patients. Abstracts or congress reports were not included. Studies with mixed populations of PAH patients or patients with different connective tissue diseases were eligible if the subset of patients with SSc was separately analyzed, or if $> 45\%$ of the patients in the study had SSc. The literature analysis was limited to studies published in English and those pertaining to humans and adults only.

Studies were excluded, if they were not an original study, if by definition only patients with other forms of PH than PAH were analyzed, if $\geq 55\%$ of patients had other diseases than SSc, and if the studies did not include a separate analysis of SSc patients. Studies including < 5 PAH/PH-SSc patients and those for which there was no information given as to whether any PAH/PH-SSc patients were analyzed, were also excluded. Studies concerning exercise echo were also not considered for the analysis, because exercise echo was not part of the core set recommended by the EPOSS group after the Delphi exercise [8].

The systematic literature search and the analysis of retrieved documents were performed independently by two trained reviewers (OKB, JA). If differences in the judgment occurred, they were solved by discussion.

Quality evaluation of identified manuscripts according to the methodological quality and level of evidence

The quality of studies fulfilling our inclusion criteria was rated by using the impact factor of the journal in which the study was published (ISI Journal Citation Reports 2006) and by the Jadad scale [10]. The Jadad scale contains 2 questions to determine appropriate randomisation and study masking and 1 question evaluating the reporting of withdrawals and dropouts. Each question requires a yes or no response. Five total points can be awarded with a higher score indicating superior quality.

The level of evidence was assessed according to established criteria based on study design using a hierarchy of evidence in descending order according to qualities [11]. In brief, meta-analyses of RCTs were considered the highest level of evidence (1a), followed by RCTs (1b), non-randomized controlled studies (2a), quasi-experimental studies (2b), descriptive studies (3) and expert committee reports or opinions (4).

Quality evaluation of identified manuscripts according to the definition of pulmonary hypertension

Because this analysis aimed to look at the validation of echo for pulmonary arterial hypertension, and because other forms of pulmonary hypertension have different pathophysiologies, clinical courses and clinical presentations, we also rated the respective studies according to their definition of PAH. The criteria for this quality assessment are summarized in Table 1.

Based on the tests used for the diagnosis of PAH/PH in the respective studies, the following rating was applied: PAH/PH confirmed by RHC (mean PAP higher than 25 mmHg at rest and/or higher than 30 mmHg with exercise per WHO definition), was assigned category A; PAH/PH assessed by echo with pulmonary artery systolic pressure PASP \geq 45 mmHg, which has 97% specificity versus RHC [13], or pulmonary artery systolic pressure (PASP) $>$ 30 mmHg by RHC was assigned category B; PAH/PH assessed by echo with 45 mmHg $>$ PASP/tricuspid gradient \geq 35 mmHg, was assigned category C, and all other definitions were considered category D.

In addition, studies were analyzed regarding whether clinically significant interstitial lung disease and postcapillary pulmonary hypertension/left heart disease were excluded. Interstitial lung disease and left heart disease are considered the most frequent causes of pulmonary hypertension other than PAH in SSc. Interstitial lung disease was considered clinically significant when restrictive ventilatory defects and/or advanced radiological changes were present. Postcapillary pulmonary hypertension was judged based on the wedge pressure higher than 15 mmHg on right heart catheterization. Accordingly, studies in which the definition of PAH included these exclusions were assigned category 1, while all other studies were considered category 2.

Application of the OMERACT filter

To assess the current status of validation of echo, the OMERACT criteria were used. These include: *truth* (face, content, construct, and criterion validity), *discrimination* (reliability/reproducibility and sensitivity to change), and *feasibility* [7,9]. Definitions of the OMERACT criteria are given in Table 2.

The OMERCT criteria were applied on the manuscripts retrieved from the systematic literature review. For the final assessment of validation, the quality of the manuscript was taken into consideration (see also Table 1):

Echo was considered valid (V) or not valid (NV) only if high quality studies were available with a definition of PAH according to the WHO criteria and if severe interstitial lung disease and post-capillary pulmonary hypertension/left heart disease were excluded. This corresponds to the “A1” level of the quality assessment as defined above.

Echo was considered partially validated (PV) if lower quality studies indicated that echo was valid. “Lower quality studies” were defined as all studies with a quality assessment below A1. These strict criteria were used because these studies might include patients with forms of PH other than PAH (e.g. associated with left heart disease, interstitial fibrosis) and a number of false positives (PAH not confirmed by RHC). This is relevant for the assessment of outcome measures because forms of PH other than PAH have a different pathogenesis, disease presentation, disease symptoms and prognosis than patients with PAH.

Validation status of echo was considered unclear/possibly not valid (U), if “lower quality studies” indicated that echo was not valid. Again, lower quality studies were defined as studies with a quality assessment below A1.

Moreover, validation of echo with respect to the sensitivity to change over time required longitudinal studies for which parallel data on RHC and echo at two different time points were available. Validation of sensitivity to change over treatment required in addition data from RCT.

The application of the OMERACT criteria was discussed at three face-to-face meetings of the EPOSS steering committee. If there was disagreement on the status of validation, it was solved by discussion.

RESULTS

Results of the systematic literature search

Out of 124 articles identified, 87 were excluded based on predefined inclusion/exclusion criteria, two studies could not be retrieved for full text review, and 35/124 articles were included for further analysis [references 1-4,12-42]. The search strategy of the systematic literature research including reasons for exclusions is presented in Figure 1.

Quality assessment of retrieved articles

The 35 retrieved studies were next evaluated according to their level of quality. The results of the quality assessment are summarized in Table. Only 5 (14%) studies included well-defined PAH-SSc subgroups according to the WHO criteria (quality level A1). Five other studies involved patients with PAH/PH diagnosed with RHC, but without excluding lung fibrosis or left heart disease (quality level A2). One study reported subgroup analyses corresponding to A1 or A2 quality levels [12]. The remaining 25 studies corresponded to lower quality levels: 3 studies were classified as B2, 13 studies as C2, 9 studies as D2, and one study included subgroup analyses of patients classified as C2 or D2 [42].

No RCTs fulfilling the inclusion criteria could be identified. Four uncontrolled studies [21-23, 30] represented level of evidence 2b, while the remaining studies were classified as level of evidence 3. The impact factor of the identified studies varied from 0 to 7.421 (mean 3.39).

Status of validation according to the OMERACT criteria

The current status of validation of echo according to the OMERACT criteria and based on the systematic literature review and its quality assessment is summarized in Table 4.

I. Truth

1. Face validity

Echocardiography was selected by the experts during the recent Delphi study [8] as an appropriate measure for the evaluation of PAP, heart structure and function in PAH-SSc patients. Thus, by definition, it was considered credible (having *face validity*).

2. Content validity

Several studies indicated that echo does not differentiate between different forms of PH associated with SSc and is thus not specific for PAH-SSc. Accordingly, left heart disease/postcapillary PH were found in up to 19% of SSc patients with increased tricuspid velocity (> 2.5 m/s) and in up to 13% of SSc patients considered at high risk of PAH/PH by clinical evaluation including echo examination, radiographic studies and lung function tests [3-4].

Several studies including SSc patients with and without PAH/PH revealed significant associations between higher PASP/tricuspid gradient and the presence of interstitial lung disease, as evaluated by lung function tests [13, 15, 26-27], or high resolution computed tomography (HRCT) of the lungs [1-2, 23, 24]. Significant lung disease (defined by TLC < 70 -80%, and/or diffuse interstitial fibrosis/alveolitis by HRCT) was found in up to 30 - 75% of SSc patients with elevated PAP [1,2].

Thus, it can be anticipated that measurements of PASP by echo-Doppler might reflect the presence of interstitial lung disease or left heart disease and not only the pulmonary vasculopathy underlying true PAH.

Another aspect of content validity is whether the outcome measure of interest covers the whole spectrum of disease severity. Denton et al looked at a broad range of PAH/PH patients [34]. The range of PAP by RHC in the 6 patients with PAH/PH and no tricuspid regurgitation was similar (30-80 mmHg) to that seen in the 15 patients with PAH/PH in whom echo-Doppler measurement revealed increased PAP (34-109 mmHg), indicating that even in patients with moderate/severe PAH/PH, tricuspid regurgitation might not be present.

Taken together, these results show that echo is not specific for PAH and thus does not fulfill this aspect of the *content validity* criterion of the OMERACT filter. The highest quality level of studies evaluated for this criterion was A1 [4]. *Content validity* according to the OMERACT filter was therefore rated as “not valid” by the expert group.

3. Criterion validity

Sensitivity and specificity of echo versus RHC

The sensitivity of echo-Doppler for identification of SSc patients with PAH/PH ranged from 39% to 100%, and its specificity from 42% to 97% in comparison with RHC as the “gold standard” measure. Sensitivity and specificity depended strongly on the definition of PAH/PH by echo and the population of SSc patients [1,12,34,41]. The specificity of echo increased with the higher PASP thresholds, reaching 97% for PASP/tricuspid gradient ≥ 45 mmHg. Opposite, the sensitivity was highest when the lower cut-off values were used being 90% in SSc patients with PASP > 30 mmHg [12,34]. Thus, there is an inverse relationship between specificity and sensitivity of echo in identifying patients with PAH/PH-SSc.

Of note, the majority of studies comparing echo with RHC used in their definition of PAH/PH a combination of tricuspid gradient/PASP and, particularly if PASP was not measurable or

suggestive of PAH/PH, evaluation of right heart dimensions and function and/or clinical assessment including evaluation of dyspnea, pulmonary function tests and/or chest x rays.

Correlation of parameters measured by echo with PAP measured by RHC

Three studies involving SSc patients considered to be at high risk of PAH/PH, including those with significant interstitial lung disease, showed significant correlations between PASP (tricuspid gradient) measured by echo-Doppler and PASP/mean PAP measured by RHC. However, r-values were only low to moderate ($r^2 = 0.5$ for PASP and $r^2 = 0.5$ for mPAP, respectively) [1,12,34]. Similarly, a study by Murata et al. including 77 patients with connective tissue diseases (CTD) of whom 55% were SSc patients showed significant correlation between PASP by echo and by direct measurement during RHC ($p < 0.01$) [40]. Depending on the diagnostic criteria, the presence of pulmonary fibrosis by HRCT or pulmonary function test was reported in 38% to 75% of patients evaluated in these studies.

Another study compared the right ventricular myocardial performance index also known as Tei index, which is calculated based on echo measurements (the isovolumic contraction time and isovolumic relaxation time divided by the ejection time) and RHC measures in a group of 35 SSc patients with elevated $PASP \geq 35$ mmHg, of whom 28 patients had mPAP by RHC consistent with the WHO definition of PAH. The right ventricular Tei index significantly correlated with the mean PAP by RHC at low r-values ($r^2 = 0.21$, $p = 0.01$), but not with the pulmonary vascular resistance measured during catheterization ($r^2 = 0.11$, $p = 0.08$). Similarly to the two previous studies, patients with interstitial lung disease were also included [17].

Taken together, echo showed - depending on the cut-off value for PASP - an acceptable sensitivity and specificity and a significant, but rather weak correlation with right heart catheterization. The highest quality level of studies evaluated for sensitivity/specificity and

correlation of echo with RHC was A2. The criterion validity was therefore rated “partially validated”.

4. Construct validity

Association with survival/mortality

Only one study including SSc patients with PAH defined according to the WHO criteria (A1) was identified and showed that the presence of pericardial effusion is associated with higher number of deaths in PAH-SSc (hazard ratio = 2.35, 95%CI: 1.06 - 5.2, p = 0.04) [19]. The presence of pericardial effusion of any size (odds ratio = 10.7, p = 0.001) or significant pericardial effusion were also associated with higher mortality in the general SSc population [15, 36, 42].

Another retrospective, case-control study involving 206 patients with limited cutaneous SSc showed that the presence of PH (PASP > 30mmHg by echo in combination with clinical symptoms) was associated with lower survival (50% at 2 years and 10% at 5 years) in comparison with well matched controls without PH (88% and 80%, respectively) [28].

In the study by McGregor et al., high PASP (> 60 mmHg) by echo was associated with higher mortality in the overall population of SSc patients with PH (PASP > 30 mmHg by echo), in SSc patients with isolated PH (PH without significant lung disease by LFTs/HRCT) and in those with PH and lung disease. The risk of death in the whole PH population increased significantly (hazard ratio = 3.6; 95%CI: 1.42-9.15) for PASP > 60mmHg. The 2-year mortality in SSc patients with isolated PH was 8%, 33% and 67%, and in those with PH and lung disease 0%, 15%, and 67%, for PASP < 30 mmHg, 30-60 mmHg and > 60 mmHg, respectively. In the overall SSc population (with and without PAH/PH), high initial PASP (> 60mmHg) by echo was an independent risk factor for mortality (by multivariate analysis)

[31]. Similarly, the presence of PH by echo was associated with lower survival in the overall SSc population combining those with and without PH (odds ratio = 9.8, $p = 0.002$ for PH versus those without PH) in the study by Simeon [36], and in early diffuse SSc patients (PASP ≥ 45 mmHg, $p = 0.001$ versus those without PH) in the study by Trad [22].

Associations with dyspnea/functional capacity, exercise tolerance (six minute walk test (6MWT), oxyhemoglobin desaturation after exercise ($\Delta O_2\text{Sat}$), and maximal oxygen consumption during exercise testing)

In 67 SSc patients with and without PH, in whom interstitial lung disease had been excluded (by HRCT), greater dyspnea (by NYHA classification) appeared as an independent factor associated with PH defined as PASP > 50 mmHg by echo ($p = 0.0001$ by multivariate analysis) [14]. In an overall population of SSc patients, frequency of dyspnea (NHYA class II, III, or IV) increased with the levels of velocity of tricuspid regurgitation (VTR) measured by echo-Doppler [4]. Accordingly, dyspnea was present in 29.3% of patients with VTR ≤ 2.5 meters/second, 40.6% with VTR = 2.5 - 3 meters/second, and 72% with VTR > 3 meters/second.

One study involving SSc patients with and without PH, 42% of whom had restrictive pulmonary function tests, indicated that the presence of PH by echo (PASP > 30 mmHg) was significantly associated with abnormal (< 400 m) 6MWT and $\Delta O_2\text{Sat}$ in univariate but not multivariate analysis (multiple regression analysis) [16].

In another study, baseline PASP by echo was the only parameter that independently correlated with maximal oxygen consumption ($r = -0.66$) and anaerobic threshold ($r = -0.52$) in stress test [33]

Associations with heart structure/function

In a SSc population including those with pulmonary fibrosis, right ventricular and right atrial enlargement were more frequent in SSc patients with PH by echo $PASP \geq 36-40$ mmHg than in those without PH ($p = 0.03$ and $p < 0.0001$, respectively) [13,25]. PAP by echo-Doppler was independently correlated with tricuspid E/A ratio, an index of the right ventricular relaxation ($r = -0.35$, $p < 0.003$, by multiple regression analysis) [32]. No correlation was found between PASP and right ventricular ejection fraction (RVEF) [20]

In summary, only an association between the presence of pericardial effusion on echo and survival/mortality, was supported with the highest quality study (level A1) [19]. For this aspect of the construct validity, echo was rated as validated.

Although two studies reporting association between echo measurements and dyspnea/functional class used the WHO definition of PAH (A1 level) [4,14], analyses concerning PASP and functional class included heterogeneous populations of SSc patients with and without PAH/PH. For all other aspects of construct validity including associations of PASP with survival/mortality, functional capacity, and right heart parameters, only studies with a less stringent definition of PH were available (highest quality level A2). Thus, while these studies in patients with PH-SSc indicate that echo passes the *construct validity* criterion of the OMERACT filter, it can only be rated as partially validated as long as A1 studies involving PAH-SSc patients do not exist.

II. Discrimination

Discriminant capacity over time and treatment

To assess the validity of discriminant capacity over time, longitudinal studies with parallel data on RHC and echo at two different time points are required, and for validation of

discriminant capacity over treatment it has to be a RCT in addition. However, such trials were not available according to our inclusion criteria of the systematic literature review.

Reliability

One study (quality level B2), including SSc patients with and without PH, showed a low intra- and interobserver variability in evaluation of right ventricular ejection fraction and left ventricular ejection fraction (range from 3.5% to 5.3%, depending on the parameters) [20]. However, there was no study available analyzing intra- or interobserver variability of parameters relevant for the assessment of PAH in SSc-patients.

In view of the lack of appropriate longitudinal studies including RCTs it was concluded that there are no data available to assess the discrimination criterion. Reliability was analyzed only in a study of quality level B2 and was therefore judged “partially validated”.

III. Feasibility

The high number of studies using echo as a diagnostic tool indicates that this method is feasible in the clinical assessment of PAH patients. It is ubiquitously available in all centers with a cardiology department or a cardiology consultant and the cost-effectiveness for clinical studies is reasonable.

However, it is not possible to obtain PASP values in some patients because of technical limitations. Inability to evaluate PASP due to the lack of tricuspid regurgitation and/or due to insufficient quality of the images obtained was reported in several studies – Table 5 [4, 13, 24-25, 29, 32, 34-35, 37-40, 42]. The percentage of patients in whom evaluation of PASP was not possible ranged from 3% in the study by Battle et al up to 74% in the study by Candell-

Reira et al [37, 39]. It should be noted that all studies reported above included SSc patients without PAH/PH, in whom the presence of tricuspid regurgitation might be less frequent. Of interest, in the study by Denton et al, involving SSc patients considered at high risk of PAH/PH, PASP could not be evaluated due to the lack of tricuspid regurgitation in 13 out of 33 (39%) including 6 out of 21 (29%) patients with PAH/PH by RHC [34].

In summary, inability to evaluate PASP by echo-Doppler was shown in several studies including different populations of SSc patients. All these studies evaluated heterogeneous populations of patients with and without PAH/PH or, if including separate analyses of PAH/PH patients, were of quality levels below A1 (highest quality level A2) [34,38]. Thus, until studies on the ability of echo-Doppler to evaluate PASP exclusively in PAH-SSc (level A1) are available, this aspect of *feasibility* was judged “unclear”.

DISCUSSION

This is the first study addressing the validity of ECHO as an outcome measure in PAH-SSc according to a systematic literature review, while recent assessments were based on expert opinion only. In addition, one of our main tasks was to consider the quality of available studies, which largely depend on the definition of PAH in this patient population. Surprisingly, only 5 out of 35 studies (14%) used the current WHO definition of PAH (diagnosis confirmed by RHC) and excluded other forms of PH such as left heart disease and interstitial lung disease. Based on the analysis of these few studies, a final evaluation regarding validity of echo for PAH-SSc could only be completed for the *content validity* criterion of the “OMERACT filter”. In addition, face validity could be evaluated, because this criterion does not require studies in PAH-SSc patients. For some other aspects of the OMERACT filter, indirect information could be obtained from studies with more heterogeneous SSc populations, including SSc patients with and without PAH/PH. Finally, the OMERACT criteria “sensitivity to change over time and treatment” could not be evaluated at all, because of lack of appropriate data.

Most importantly, the structured literature review and the assessment of identified papers according to the OMERACT filter revealed several aspects of echo that need further validation in additional studies. This defines a specific research agenda which needs to be addressed to allow full validation of echo as an outcome measure in PAH-SSc. This research agenda can be summarized as follows (Table 6):

Truth

Face validity is the only OMERACT criterion that is fully validated based on the consensus of experts who selected echo as an appropriate outcome measure for evaluation of PAH-SSc [8] as well as based on its frequent use as an evaluation tool in PAH/PH-SSc studies. There are no further studies required.

Echo is not valid with respect to its *content validity* because measurements of pulmonary pressures using echo might be influenced by co-morbidities including left heart dysfunction and/or lung fibrosis in SSc patients. There are no further studies required, because available data were of sufficient quality (quality level A1) to allow final evaluation of its validation status.

Does the lack of content validity exclude echo as an outcome measure in PAH-SSc? Not necessarily, because the lack of specificity of echo could be overcome by excluding relevant co-morbidities before SSc patients enter clinical trials. For instance, clinically relevant pulmonary fibrosis can be excluded by pulmonary function tests and/or computed tomography. Indeed, this strategy has already been utilized in many of the randomized controlled trials in PAH, where lung fibrosis as documented by decreased FVC was an exclusion criterion [43-44]. Left heart dysfunction such as valvular diseases can be partially excluded by echo itself, although there are controversies whether definite diagnosis of diastolic dysfunction, which is more frequent in SSc patients [45], requires invasive testing [46]. Other co-morbidities such as pulmonary venous occlusive disease (PVOD) are more difficult to exclude, and it is currently unknown if PVOD is of relevant prevalence in PAH-SSc or limited to certain patients with a very severe clinical course of pulmonary hypertension [47].

The impact scleroderma lung disease and other comorbidities may have on the correlations between echo and RHC in SSc is unclear, however evaluation of RVSP by echo has been

found inaccurate in patients with idiopathic pulmonary fibrosis [48]. Therefore, definite validation of the *criterion and construct validity* is required through evaluation of echo versus RHC and other outcomes specifically in PAH-SSc. This can be achieved for example by cross-sectional studies in PAH-SSc patients performing RHC and other relevant outcome measures in parallel with echo (Table 6). Although these data are unpublished, they are actually available as part of the baseline measurements in randomized controlled treatment trials in PAH. Thus, subanalysis of the baseline measurements in the PAH-SSc population of these trials is likely sufficient to fully validate content and construct validity of echo.

Discrimination

The type of studies required to assess the validity of echo with respect to the *discriminant capacity over time* are longitudinal studies including PAH-SSc patients without treatment and parallel echo and RHC evaluations at different time points (Table 6). Again, they are already available as unpublished data from the placebo groups of randomized controlled trials with RHC and echo performed at baseline and end of study. Although it might be argued that placebo-treatment is an intervention and thus patients from the placebo group are not true untreated patients, analysis of the PAH-SSc subpopulation of these trials would further contribute to the validation of discriminant capacity over time. Similarly, to assess the *discriminant capacity over treatment*, subanalysis of PAH-SSc patients in the verum group of these trials is appropriate (Table 6). Validation of *reliability* of echo in PAH-SSc requires comparisons of repeated echo assessments performed within a short time period by the same investigator (intra-observer variability) and by two independent investigators (inter-observer variability) at the same time in patients with well defined PAH-SSc (Table 6).

Feasibility

The validation status of echo with respect to its *feasibility* was considered unclear since evaluation of pulmonary pressures was impossible in a significant proportion of SSc patients including PAH/PH-SSc. This was due to the lack of tricuspid regurgitation but also due to insufficient quality of echo imaging caused by skin thickening or concomitant severe lung disease. Formally, further studies including exclusively PAH-SSc patients are required to fully validate *feasibility* of echo in the evaluation of PAH-SSc. Studies required for full validation are cross-sectional analysis of PAH-SSc-patients and are thus similar to studies required for other aspects such as criterion and construct validity (Table 6). However, it appears rather unlikely that pulmonary pressures can be measured in all patients, because some of the limitations such as skin thickening can still be operative in this population. Thus, it is likely that echo cannot be used as a single outcome measure and needs to be combined with other measures to allow assessment of all patients.

Many of the studies identified by this systematic literature review focused on PASP, while other parameters were rarely considered. However, it needs to be emphasized that other echo parameters might be more relevant for certain aspects of PAH-SSc than PASP alone. For instance, as shown in patients with severe idiopathic PAH, reduction in PASP may reflect disease progression and right-ventricle failure rather than improvement of PAH [49]. In addition, although correlations between PASP by echo-Doppler and PASP/mean PAP by RHC were statistically significant, they showed low r-values, reflecting the clinical experience that PASP by Doppler are not necessarily accurate when compared to directly measured pressures in PAH-SSc. Thus, assessment of PASP alone is unlikely to reach full validation in PAH-SSc for discriminant capacity of time and treatment. Additional measures such as tricuspid annular plane systolic excursion (TAPSE) are promising [50, 51] and should be considered for further validation studies in PAH-SSc.

In conclusion, this systematic literature analysis demonstrated that echo in PAH-SSc fulfills the OMERACT criteria for *face* validity and partially for criterion and construct validity as well as reliability. Other forms of PH such as PH associated with lung fibrosis or left heart disease need to be excluded if echo is used as an outcome measure, because the content validity criterion is not fulfilled. Validation studies for echo in PAH-SSc should not be limited to PASP alone, but should also include other measures such as TAPSE, in particular for the assessment of discriminant capacity over time and treatment. Studies required for further validation of the OMERACT criteria are largely performed already as part of randomized controlled treatment trials in PAH patients. However, subanalyses of PAH-SSc with regard to echo as an outcome measure have not been published. Because echo pulmonary pressures cannot be measured technically in all patients, echo needs to be combined with other outcomes in trials with PAH-SSc patients.

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Figure legend

Figure 1: Results of the systematic literature search