Primary Systemic Sclerosis heart involvement: a systematic literature review and preliminary consensus-based WSF/HFA definition.

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ABSTRACT

Background: primary heart involvement in systemic sclerosis (SSc-pHI) may cause morpho functional and electrical cardiac abnormalities and is a common cause of death. The absence of a clear definition of SSc-pHI limits our understanding and ability of focussed research. We aimed to create an expert consensus definition for SSc-pHI.

Methods: a systematic literature review of cardiac involvement and manifestations in systemic sclerosis (SSc) was conducted using PubMed, Web of Science and Embase, including articles from inception to December 31st 2018. An international and multi-disciplinary task force discussed the data following which a nominal group technique (NGT) was used to derive a definition that was then subject to voting. Sixteen clinical cases were evaluated to test face validity, feasibility, reliability and criterion validity (gold standard set by agreed evaluation from expert rheumatologist, cardiologist and methodologist) of the newly created definition.

Results: 171 publications met eligibility criteria. Using the NGT, experts added their opinion, provided statements to consider and ranked them to create the consensus definition, which received 100% agreement on face validity, a median 60 (5-300) seconds taken for the feasibility on a single case. Inter-rater agreement was moderate [mKappa(95%CI) 0.56(0.46-1.00) for first and 0.55(0.44-1.00) for second round] and intra-rater agreement was good [mKappa(95%CI) 0.77(0.47-1,00)]. Criterion validity showed a 78(73-84) % correctness versus gold standard.

Conclusion: a preliminary SSc-pHI consensus-based definition and preliminary validation process was developed for future application in research.

MAIN TEXT

INTRODUCTION

Systemic sclerosis (SSc) is a complex autoimmune multi-organ disease and its pathogenesis is still unclear (1). The disease has an initial vascular component, which facilitates homing of inflammatory cells and cytokine production in the tissues (2), and activation of pro-fibrotic pathways, involving the skin, the lung and the heart. Myocardial disease is among the most frequent causes of death in SSc (3), including both primary and secondary cardiac involvement. The largest survey made by the European Scleroderma Trials and Research (EUSTAR) group showed that 12% of death may relate to heart disease (ref?). The prevalence of clinical SSc primary heart involvement (SSc-pHI) is still unclear, as most studies have not sought to distinguish primary from secondary heart involvement. Cardiac involvement varies from 7% to more than 39% of SSc patients (4). The most frequent clinical cardiac features may include impaired contractility, arrhythmias, myocarditis and pericardial/valvular disease?; prevalence of cardiac involvement can be much higher when autopsy findings are included, in particular due to initially asymptomatic cases (5). Possible risk factors include older age at disease onset (6, 7), male gender (8), anti-topoisomerase antibodies positivity (7) and history of digital ulcers (9). The use of vasodilators (such as calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers) and low-dose aspirin has been associated with lower frequency of primary cardiac disease (10).

Several consensus recommendations and management algorithms have been published to enable early detection, tailored monitoring and treatment of patients with SSc cardiac involvement. The UK SSc Study Group was the first to provide a pathway for physicians in assessing both asymptomatic and symptomatic patients for cardiac disease, taking into consideration the possible concomitant presence of classical cardiovascular disease risk factors (11). Moreover, a timing for investigations and assessment was proposed. A similar management algorithm was suggested by a Greek cardiology-rheumatology collaboration group, based on a two-step approach to assess patients with cardiac symptoms (12). More recently, despite not primarily focussed on primary cardiac disease, a set of agreed domains and variables for a longitudinal annual assessment of organ involvement was proposed by experts from the EUSTARgroup and Scleroderma Clinical

Trial Consortium (SCTC), including heart domain, with dyspnoea as assessed by the New York Heart Association (NYHA) functional class, leg oedema, ECG, doppler echocardiography, heart rate, blood pressure and concurrent (non-SSc related) heart disease as variables (13).

Despite all these resources, a definition to identify patients with SSc-pHI is lacking. A recent Systematic Literature Review (SLR) found high heterogeneity of the definitions of SSc heart involvement, and highlighted the unmet need of a uniform and agreed definition of SSc-pHI, as well as the need for consensus classification criteria to establish its real prevalence, prognostic impact and therapeutic effect (14).

Under the auspices of the World Scleroderma Foundation and the Heart Failure Association (of the European Society of Cardiology), we aimed to create and validate a data-driven definition of primary heart involvement.

METHODS

Literature search

Considering the absence of a validated definition to use as comparator (14), the project core team (CB, MHB, PS, MMC) identified 6 domains: signs, symptoms, pathological changes, anatomical site involved, altered physiological function, prognostic outcomes. In each domain, a list of variables was noted. A list of PEO questions were created accordingly (see Appendix 1) (15). We subsequently performed an SLR, following the methodology recently used for the development of another consensus definition (16). A single author (CB) performed MEDLINE, EMBASE and PubMed databases searches, using the same search terms previously proposed (14), for articles from inception to December 31st 2018, to identify manuscripts on SSc-pHI manifestations. All references were imported to a dedicated ENDNOTE (version X8) database. Review articles references were evaluated by extractors and articles were manually selected according to title and added to the total references database, if not already present. PRISMA recommendations were followed where applicable.

Study selection and data abstraction

Study selection was performed in a three-step approach. After de-duplication being performed by a single author using the reference software (CB), articles were selected according to title evaluation by two authors

(CB, GDL), with a third author contribution in case of disagreement (MHB). The same three authors acted in the second round, with abstracts evaluation. In the third round, full text evaluation was performed by seven pairs of authors each including cardiology and SSc expertise (GH and MP, YAS and AB, GDL and KB, AL and AD, RBD and GMM, AG and IM, YI and AX), with a third author (CB) to achieve consensus in case of disagreement. Papers were evaluated according to inclusion/exclusion criteria listed in Appendix 2 and the reason for exclusion was recorded. Cross-revision of papers and data extracted on 5% of articles was used for consistency.

Outcomes

Data were extracted according to the PEO questions formulated, the 6 identified domains and the pre-set variables. A variable called "other" was present in each domain, in order to capture variables which were not covered. For each article selected from step three, study nature, patients' selection criteria, number of patients with number/percentage of female gender, the presence of domains and variables with number of patients presenting/reporting it, were extracted. The SLR extracted data were analyzed by a biostatistician (LT), as explained below.

Task Force

The task force consisted of 16 senior experts from Europe (n=13), North America (n=2) and Asia (n=1), including 8 cardiologists (EB, LG, SM, ALPC, SP, CT, AD, AR), 1 cardio-immunologist (RM), 1 cardio-pathologist (KK), 1 dermatologist (TK) and 5 rheumatologists (YA, CD, DK, DEF, MK). A face to face meeting was held in Rome in June 2019. A patient research partner (PRP – IG) also took part to give a patient's point of view and input.

Definition Formulation

The task force was informed of the SLR results and the domains and variables presented. The Nominal Group Technique (NGT) was applied that comprised 4 steps (moderated by MHB). Experts were asked how to define SSc-pHI, each of them silently and independently generating (up to 3) ideas/thoughts in brief phrases or statements, without any discussion. The next step included round-robin feedback to record each idea without

discussion. In the third step, statements were merged into domains and with discussion and clarification as needed, a single group statement was derived from each domain. Experts confidentially voted to prioritise final statements, ranking the top half ideas and each member voting on these to establish a further ranking. A consensus was attained when agreement was >70% (17).

Preliminary validation

During the validation process, OMERACT criteria were followed (18). Face validity was defined as the credibility of the measure determined by the experts. Sixteen real-life clinical cases were created. Feasibility was tested during the face-to-face meeting, with each expert evaluating whether the definition was plausible on each case, using a stopwatch to measure the time spent. Reliability was tested with evaluation of case reports during the face-to-face meeting and during a second round of case report evaluation, which was performed online. These comprised the same clinical cases in a different random order; inter- and intra-rater agreements were tested. Criterion validity reflects the agreement with a gold-standard evaluation. In the absence of a reference standard definition and to take a pragmatic approach, the agreed evaluation of two senior experts in cardiology and SSc (PS and MMC) was used as gold standard and experts' evaluations were tested against it.

Analysis

For continuous variable median and standard deviation are reported, while for categorical variables absolute frequencies and percentage for each category are presented. To asses criterion validity, the proportion of correct assessments against gold standard and its 95% confidence interval was calculated. In order to evaluate inter-rater and intra-rater agreement Cohen's kappa coefficient adjusted for multiple raters and its 95% confidence interval was used.

RESULTS

SLR data

From the database search, a total of 2,593 papers were identified. Once duplicates were removed (n=725), first step evaluation included 1,863 abstracts, that were further reduced to 251 full-texts for evaluation. Out

of 251, 171 were eligible for data extraction, consisting of 23 retrospective studies, 49 prospective, 81 cross-sectional, 4 case series, 2 clinical trials, 1 case-control study and 3 non-specified study type. The 171 studies provided a total of 23,276 patients, with female prevalence ranging from 82.1-83.6%. The majority of studies (n=72) enrolled patients according to the 1980 ARA preliminary classification criteria (19), with the 2013 ACR/EULAR criteria (20) being used by 41 papers. Forty-seven studies included patients with no known cardiac disease or pulmonary arterial hypertension (PAH) or asymptomatic patients, 10 manuscripts focussed on patients with already diagnosed cardiac involvement or symptoms suggestive for cardiac involvement and 3 studies were autoptic evaluations. Details for each domain were collected from at least one paper; in particular 60 papers had data on symptoms (Table 1), 22 on signs (table 2), 15 on pathological changes (table 3), 135 on anatomical site involvement (table 4), 157 on altered physiological function (table 5) and, finally, 37 on prognostic outcome (table 6). Data revealed almost all variables being reported at least once.

Formulation of a new definition

The domains and variables were presented to the 16 experts and, following the NGT process detailed earlier, silent generation of ideas was undertaken. The round-robin phase generated 27 statements, as listed in Appendix 3. These statements were grouped and 4 clusters were identified, focussed on pathogenesis, aetiology, clinical and diagnostics and timing. Further discussion was carried on and one statement was generated, refined and derived for each domain. The four final statements were voted individually on a scale of agreement ranging from 0 to 100%, then ranked from higher to lower percent. The final definition which was reached, including statements with agreement>70% and ranked according to prioritization, was as follows:

"*SSc-pHI comprises cardiac abnormalities that are predominantly attributable to SSc rather than other causes and/or complications*. SSc-pHI may be sub-clinical and must be confirmed through diagnostic investigation. The pathogenesis of SSc-pHI comprises one or more of inflammation, fibrosis and vasculopathy.*

**Non SSc-specific cardiac conditions (e.g. Ischemic heart disease, arterial hypertension, drug toxicity, other cardiomyopathy, primary valvular disease) and/or SSc non-cardiac conditions (e.g. PAH, renal involvement, interstitial lung disease, ILD).”*

Validation of the new definition

100% agreement on credibility of the proposed definition against the sixteen pre-identified case reports was recorded. A median 60 (5-300) seconds was taken per case to decide if the definition could correctly identify SSc-pHI or other. Using the same sixteen clinical cases in different order, the inter-rater agreement was moderate during the face-to-face meeting and the web-based evaluation respectively, with mKappa (95%CI) of 0.56 (0.46-1.00) and 0.55 (0.44-1.00); the intra-rater agreement was good, with a mKappa (95%CI) of 0.77 (0.47-1,00) between face-to-face and web-based evaluation. Interestingly, there was no significant difference between cardiologists and non-cardiologists, when evaluated separately, in terms of inter- and intra-rater agreement levels. For criterion validity, when the assessments of the experts were compared to the cardiology-rheumatology agreed evaluations, a 78 (73-84) % correctness versus gold standard was achieved.

DISCUSSION

Studies on SSc-associated cardiac disease comprise heterogeneous populations defined by different combinations of signs/symptoms, diagnostic tools and definitions and serum biomarkers (14). This has implications on our understanding of SSc-pHI and the ability to improve outcomes. Our initiative used an international and multi-disciplinary task force of cardiology and rheumatology experts to develop a first definition of SSc-pHI for application in future clinical research and practice.

Today, it is well known that SSc-pHI is a frequent organ complication associated with varied clinical manifestations. In SSc, advances in the management of other major organ complications have focussed the attention on the significant cardiac-related morbidity and mortality. To date, studies report strikingly variable prevalence of SSc-heart involvement (4, 14, 14 a?), largely attributable to the lack of a clear definition. Therefore, a SLR of current available evidence was first performed but employed different outcomes

compared to previous reviews (4, 14). We categorised the possible manifestations of SSc-pHI into several domains: clinical expression, anatomical and patho-physiological involvement, pathological findings and cardiac-related prognostic outcomes. This strategy allowed the expert group to create a consensus definition, which was based on applicable and generalisable concepts. The NGT methodology is an established approach to ensure all experts contribute and intervene in equal measure, allowing the different expertise to inform the process and ultimately merge to a single consensus agreed result. This enabled effective input from rheumatologists, fundamental in highlighting SSc non-cardiac conditions, which may masquerade as cardiac manifestations. Similarly, cardiologists' expertise was pivotal in identifying traditional non-SSc specific cardiac diseases, such as atherosclerosis. The multi-disciplinary team approach was a necessary strategy and we consolidated this with the input of PRP that advised the committee on the importance of also capturing asymptomatic patients and early disease stages, often excluded in research studies.

Our SSc-pHI consensus definition has undergone the first step of validation according to the OMERACT criteria. Face validity, feasibility, reliability and criterion validity were evaluated: the intra-rater reliability was good and the inter-rater reliability was moderate. According to this, the same evaluator should assess the case when participating in a longitudinal evaluation and, to accurately select patients, confounding conditions should be excluded. Moreover, to effectively disseminate the definition and explain to the wider community, teaching sessions and standardisation may be useful and supportive, as shown for other operator-dependent evaluations (21). Finally, the correctness of the application of the definition was still good against our pre-set gold standard.

This is the first literature-based multidisciplinary consensus definition of SSc-pHI, gathering rheumatology, cardiology, immunology and pathology expertise. Similar initiatives supported by the SCTC to create a working definition and classification criteria are ongoing (22). Future studies will evaluate for complementarity of these two definitions, any added value of combined use of both definitions in widening the uniformity in clinical research.

To detect organ involvement, a minimal annual systematic set of assessments has been proposed by a joint initiative from EUSTAR/SCTC (13). These include basic clinical assessment and cardiac investigation. A similar

set or recommended testing was proposed by the UK SSc Study group consensus, including frequency of the recommended testing, minimum dataset for echocardiography assessment (11). The use of wider tools, such as 24-hour Holter monitoring, other electrophysiological testing and more sensitive and functional imaging such as cardiac magnetic resonance imaging and stress tests rely on cardiology consultation and expertise (11, 12). These suggestions may be now reviewed in the light of this novel proposed SSc-pHI definition. Our future research agenda includes optimising and tailoring use of cardiac assessments in the early diagnosis and follow-up of SSc-pHI, as well as the studies on prevalence and prognostic impact in early SSc stages.

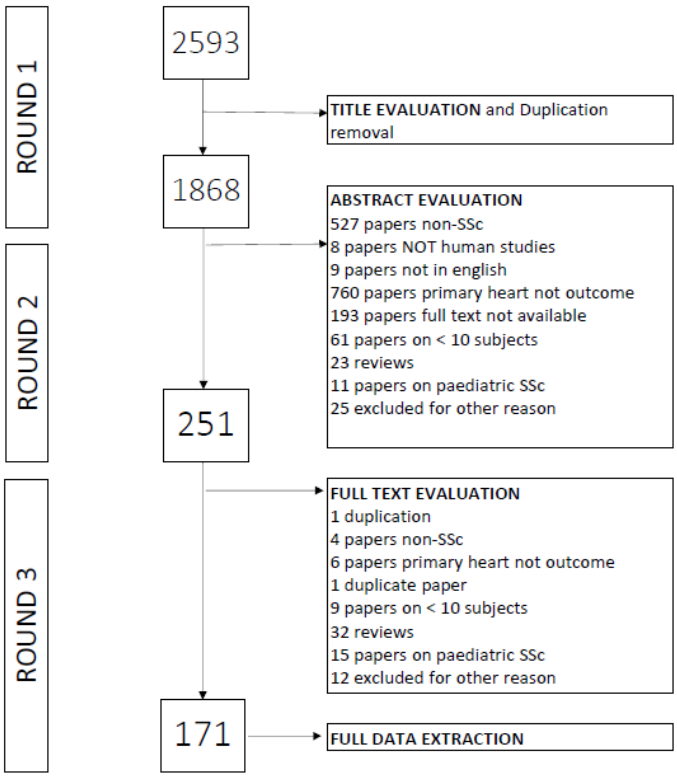
A key concept that also emerged in the definition is that of subclinical heart involvement. Sensitive imaging studies highlight the presence of abnormalities in asymptomatic individuals in up to 70% of the studied cohorts, whilst only a subgroup of them progress to clinically meaningful pathology. Nevertheless, our definition captures this subgroup, providing a basis for their further evaluation in prognostic studies.

The strengths of our study include the application of a standardized SLR to inform on the nature of cardiac involvement. We deliberately decided not to include cut-offs or findings derived from specific diagnostic tools, in order to make this SSc-pHI definition applicable worldwide and independent from local facilities or health systems. Different specialists that may clinically interface with SSc-pHI were included, in particular cardiologists (with subspecialist expertise in electrophysiology, echocardiography, cardiac MRI), rheumatologists, immunologists and cardio-pathologists. Moreover, we received valuable input from our patient representation on the definition, underlying the importance of PRP participation to such initiatives. Our study however holds some limitations. The number of clinical cases was limited and this might have impaired the reliability exercise. Moreover, the lack of an established standardised gold standard warrants cautious interpretation of the criterion validity assessment. We tried to overcome this with a pragmatic approach of multi-disciplinary team evaluation, which is used in clinical practice. Content, construct and response/discrimination exercise remains to be evaluated in the future steps of the validation.

In conclusion, we report on an underpinning SLR and NGT to create a consensus-based definition of SSc related primary heart involvement, demonstrating face validity, feasibility, reliability and preliminary data

for criterion validity. This initiative is ongoing for the next steps of the validation and future research agenda initiatives.

Figure 1. Study selection flow diagram, with reasons for exclusion.



SSc= systemic sclerosis

Appendix 1. **Patient-Exposure-Outcome (PEO) questions**

A) Symptoms

- In patients with SSc, can the presence of *palpitation* be defined as primary heart involvement?
- In patients with SSc, the presence of *syncope* can be defined as primary heart involvement?
- In patients with SSc, the presence of *dizziness* can be defined as primary heart involvement?
- In patients with SSc, the presence of *dyspnoea* can be defined as primary heart involvement?
- In patients with SSc, the presence of *chest pain* can be defined as primary heart involvement?
- In patients with SSc, the presence of *other symptoms* can be defined as primary heart involvement?

B) Signs

- In patients with SSc, the presence of *hypoxia* can be defined as primary heart involvement?
- In patients with SSc, the presence of *cyanosis* can be defined as primary heart involvement?
- In patients with SSc, the presence of *ankle swelling* can be defined as primary heart involvement?
- In patients with SSc, the presence of *s3/s4 sounds* can be defined as primary heart involvement?
- In patients with SSc, the presence of *bibasal lung crepitations* can be defined as primary heart involvement?
- In patients with SSc, the presence of *other clinical signs* can be defined as primary heart involvement?

C) Anatomical site involved

- In patients with SSc, the alteration of *pericardium* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *epicardium* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *endocardium* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *myocardium* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *valves* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *atria* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *ventricles* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *coronary circulation* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *intramural circulation* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *heart size* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *impulse origin* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *conduction system* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *other anatomical site* can be defined as primary heart involvement?

D) Altered Physiologic function

- In patients with SSc, the alteration of *muscle contraction* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *muscle relaxation* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *conduction* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *automaticity* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *atrial depolarization* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *ventricular depolarization* can be defined as primary heart involvement?

- In patients with SSc, the alteration of *ventricular re-polarization* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *wall motion* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *perfusion* can be defined as primary heart involvement?
- In patients with SSc, the alteration of *other physiological function* can be defined as primary heart involvement?

E) Pathological changes

- In patients with SSc, the presence of *cardiac cellular hypertrophy* can be defined as primary heart involvement?
- In patients with SSc, the presence of *cardiac cellular hypotrophy* can be defined as primary heart involvement?
- In patients with SSc, the presence of *cardiac cellular atrophy* can be defined as primary heart involvement?
- In patients with SSc, the presence of *cardiac cellular necrosis* can be defined as primary heart involvement?
- In patients with SSc, the presence of *cardiac fibrosis* can be defined as primary heart involvement?
- In patients with SSc, the presence of *cardiac inflammation* can be defined as primary heart involvement?
- In patients with SSc, the presence of *cardiac collagen deposition* can be defined as primary heart involvement?
- In patients with SSc, the presence of *pericardial inflammation* can be defined as primary heart involvement?
- In patients with SSc, the presence of *pericardial haemorrhage* can be defined as primary heart involvement?
- In patients with SSc, the presence of *pericardial fluid alteration* can be defined as primary heart involvement?
- In patients with SSc, the presence of *cardiac vasculitis* can be defined as primary heart involvement?
- In patients with SSc, the presence of *cardiac vasculopathy* can be defined as primary heart involvement?
- In patients with SSc, the presence of *other cardiac pathologic change* of can be defined as primary heart involvement?

F) Prognostic outcomes

- In patients with SSc, the development of *myocarditis* can be defined as primary heart involvement?
- In patients with SSc, the development of *heart failure* can be defined as primary heart involvement?
- In patients with SSc, the development of *acute coronary syndrome* can be defined as primary heart involvement?
- In patients with SSc, the development of *arrhythmia* can be defined as primary heart involvement?
- In patients with SSc, the development of *sudden death* can be defined as primary heart involvement?

Appendix 2. Inclusion and exclusion criteria in evaluating publications.

Inclusion criteria:

1. Articles on Systemic sclerosis or in which SSc patients can be separately identified
2. Articles with heart involvement as main topic
3. Articles published from inception to October 31st 2018
4. Articles with full text in English or Italian or Romanian or French or Arabic or Serbian.
5. Randomised clinical trials, retrospective or observational studies, registries, case series with and without controls and case reports with ≥ 10 patients
6. Reviews will be examined to search the articles that are not available otherwise

Exclusion criteria:

1. Non-human studies
2. Studies without clinical or imaging outcomes (genetic, in vitro data)
3. Articles including only patients with overlap syndrome by ACR/EULAR classification criteria
4. Case reports/series of < 10 patients
5. Heart involvement secondary to pulmonary hypertension or other SSc related organ involvement, drug toxicity, infections or other comorbidities clearly identifiable and distinguishable from systemic sclerosis

Appendix 3. Statements derived from the three rounds of the Nominal Groups technique, with the derived statements for the four clusters and its level of agreement among the 16 experts.

A) PATHOGENESIS CLUSTER

1. A combination pattern of inflammation, fibrosis, micro-vascular vasculopathy after exclusion of other known heart diseases.
2. SSc-pHI includes inflammation, fibrosis and vasculopathy.
3. Presence of cardiac fibrosis of non-ischemic origin.
4. Inflammatory/fibrotic process of the heart after excluding other causes.

Statement: ***SSc-pHI pathogenesis comprises one or more of inflammation, fibrosis and/or vasculopathy. (73%)***

B) ETIOLOGY CLUSTER

5. Cardiac abnormalities directly attributable to SSc.
6. Cardiac abnormalities not due to drug induced cardio-toxicity.
7. For symptomatic patients, primary is exclusion of cardiac involvement secondary is atherosclerosis, ischemic heart disease, severe kidney disease, pulmonary hypertension.
8. Exclude all other causes of heart disease (including infections, ischaemic) to define primary.
9. Cardiac abnormalities not entirely explained by other cardiovascular (CV) and non-cardiovascular causes and likely to be due to pathological processes characteristics of SSc.
10. Evidence of histopathological or imaging assessment of acute or chronic heart involvement which is not clearly secondary to non-SSc cardiac conditions and/or extra cardiac conditions.
11. Significant cardiac conduction defects in the absence of systemic hypertension.
12. Other causes can be background but not fully explain the cause.
13. Requiring as much as possible the exclusion of non-cardiac and non SSc signs and symptoms.
14. Additional part of algorithm after exclusion of PAH and borderline PAH, in addition to other general population CV factors, other cardiomyopathies and myocarditis to perform differential diagnosis for SSc-pHI.
15. Structural functional heart impairment without known disease or comorbidity.

Statement: ***SSc-pHI comprises cardiac abnormalities that are predominantly attributable to SSc rather than other causes*. (91%)***

Non SSc specific cardiac (Atherosclerosis, Ischaemic heart disease Systemic hypertension…) and SSc non-cardiac (PAH, Renal involvement, ILD)

C) CLINICAL AND DIAGNOSTIC CLUSTER

16. Systolic or diastolic dysfunction, pericarditis or arrhythmias, both symptomatic and asymptomatic, excluding other causes.
17. Dysfunction of the heart predominantly caused by SSc.
18. Systolic/diastolic dysfunction or alteration of conduction system excluding other conditions.
19. Definition requires all symptoms, signs and physiological measures.
20. Presence of heart failure symptoms and exclusion of cardiac and non-cardiac causes.
21. Not only heart failure, but also primary arrhythmias and chest pain.
22. Signs and symptoms of heart failure, excluding mimickers.
23. Evidence of ventricular ectopy on ECG monitoring and ambulatory monitoring.
24. Symptoms to start the suspicion, followed by algorithmic diagnostic pathway.

25. Involvement due to SSc that is clinically meaningful and may be symptomatic or impact on prognosis
26. SSc-pHI includes valve disease

Statement: ***SSc-pHI may be sub-clinical and must be detected and/or confirmed through diagnostic investigations. (77%)***

D) TIMING CLUSTER

27. Cardiac involvement can manifest also at disease onset

Statement: ***SSc-pHI may be present at time of disease onset. (51%)***

Table 1. Data extracted from the “Symptoms” domain and its variables.

Symptoms	**N° PAPERS**	**References**	**N° PATIENTS**	**References**
PALPITATION	28	(23-50)	1265 / 4684 (27 %)	from 25 papers (23, 26, 28-32, 36, 37, 39-51)
SYNCOPE	8	(23-26, 28, 38, 41, 52)	9 / 112 (8 %)	from 3 papers (26, 41, 52)
DIZZINESS	5	(24, 25, 28, 48, 53)	10 / 83 (12 %)	from 2 papers (28, 48)
DYSPNOEA	37	(23-25, 27, 29-32, 36-40, 43-46, 48, 50, 52-69)	2178 / 5091 (43 %)	from 28 papers (23, 30-32, 37-40, 43-46, 48, 50, 52-54, 56-58, 62-69)
CHEST PAIN	32	(23-30, 32-35, 37, 39, 42, 43, 45, 46, 48, 52-54, 56, 61, 64, 70-76)	103 / 859 (12 %)	from 23 papers (26, 28-30, 33-35, 37, 39, 42, 43, 45, 46, 48, 52-54, 56, 64, 70, 74-76)
Non specified	5	(59, 77-80)	15/48 (31%)	From 1 paper (77)

Table 2. Data extracted from the “Signs” domain and its variables.

Signs	**N° papers**	**References**	**N° patients**	**References**
HYPOXIA	2	(59, 64)	10 / 37 (27 %)	from 2 papers (59, 64)
CYANOSIS	0			
ANKLE SWELLING	4	(39, 46, 59, 69)	33 / 148 (22 %)	from 4 papers (39, 46, 59, 69)
S3/S4 SOUNDS	5	(41, 53, 59, 69, 81)	25 / 125 (20 %)	from 5 papers (41, 53, 59, 69, 81)
BIBASAL CREPITATIONS	3	(41, 59, 69)	22 / 61 (36 %)	from 3 papers (41, 59, 69)
OTHER CLINICAL SIGNS	10			
Signs of CHF	4	(30, 32, 39, 52)	38 / 93 (41 %)	from 4 papers (30, 32, 39, 52)
Systemic Hypotension	2	(38, 82)	3 / 54 (6 %)	from 1 paper (82)
Systemic Hypertension	1	(29)	4 / 22 (18 %)	from 1 paper (29)
Valvular murmur	2	(59, 69)	6 / 10 (60 %)	from 1 paper (69)
Fatigue	1	(58)	16 / 16 (100 %)	from 1 paper (58)

Table 3. Data extracted from the “Pathological changes” domain and its variables.

Pathological Changes	**N° PAPERS**	**References**	**N° PATIENTS**	**References**	**Comments / details**
INFLAMMATION	3	(54, 57, 83)	45 / 56 (80 %)	from 3 papers (54, 57, 83)	15 grade I, 18 grade II, 9 grade III (83) Lymphocytic myocardial infiltrate in 1 patient (54)
FIBROSIS	11	(5, 27, 52, 54, 57, 70, 83-87)	187 / 322 (58 %)	from 11 papers (5, 27, 52, 54, 57, 70, 83-87)	Myocardium/endocardium in 26 patients (70) Myocardium in 60 patients (5, 52, 84, 85) Endocardium in 7 patients (85) Midwall 21 patients Epicardial in 12 patients (85) Perivascular in 17 patients (27, 54) Bi-ventricular in 3 patients (87) Mean degree 12.3 ± 6.3 % in 20 patients (83) Range from 8 to 32 % in 25 patients (57)
COLLAGEN DEPOSITION	2	(27, 81)	3 / 15 (20 %)	from 1 papers (81)	Interstitium, between muscle fibers (27, 81)
VESSEL ABNORMALITIES	2	(5, 86)	8 / 55 (15 %)	from 2 papers (5, 86)	Coronary atherosclerosis in 5 patients(5) Myocardial vessels in 3 patients (86)
CELLULAR HYPERTHROPHY	1	(52)	5 / 25 (20 %)	from 1 paper (52)	Located in myocardial microvessels (52)
CELLULAR ATROPY	0				
CELLULAR NECROSIS	1	(70)	16 / 52 (30 %)	from 1 paper (70)	Myocardium (70)

HAEMORRHAGE	0				
PERICARDIUM alteration	4	(42, 70, 84, 86)	87 / 184 (47 %)	from 4 papers (42, 70, 84, 86)	Focal or diffuse fibrous or fibrinous pericarditis in 17 patients (70) Fibrinous, fibrous pericarditis and pericardial adhesions in 31 patients (84) Pericarditis with chronic inflammatory cells in 31 patients (86) Pericardial fibrosis in 4 patients (42) Granulomatous pericarditis in 2 patients (42) Non-specific inflammation in 2 patients (42)
PERICARDIAL FLUID alteration	1	(42)	9 / 30 (30%)	from 1 paper (42)	Presence of exhudate
OTHER (Conduction System)	1	(70)	15 / 52 (29 %)	from 1 paper (70)	Varying degrees of SA node fibrosis in 13 pts (70) Interruption in proximal bundle branches in 2 patients (70)

Table 4. Data extracted from the “Anatomical site involved” domain and its variables.

Anatomical site involved	**N ° papers**	**References**	**N° Patients**	**References**	**COMMENTS/DETAILS**
HEART SIZE	54	(5, 23-27, 34, 37, 44-46, 54, 56, 58, 59, 69, 70, 76, 80, 83, 85, 87-118)	247 / 1289 (19 %)	from 26 papers (5, 37, 44-46, 54, 56, 58, 59, 69, 70, 76, 83, 97, 102, 103, 105, 107, 108, 112-116, 118)	Increased heart weight in 1 patient (5) Enlarged cardiac shadow in 31 pts (56, 97) Increased Cardio-thoracic ratio in 35 patients (58, 59, 102, 105) Cardiomegaly in 29 patients (37, 76, 112)
LEFT ATRIUM	40	(24, 31, 44, 55, 59, 69, 76, 79, 80, 85, 87, 89, 91-96, 98, 100, 101, 103, 104, 106-108, 114, 116-126)	129 / 1090 (12 %)	from 14 papers (44, 59, 69, 76, 85, 87, 89, 93, 103, 114, 116, 118, 124, 125)	Enlarged LA in 11 patients (103)
LEFT VENTRICLE	91	(5, 23-31, 34, 36, 38, 39, 42, 44, 46, 51, 52, 54, 56-60, 68-70, 72-74, 76, 78-80, 83, 87-104, 106-109, 111, 113-116, 118, 119, 121-125, 127-147)	1140 / 10571 (11 %)	from 52 papers (5, 28, 30, 34, 39, 42, 44, 46, 51, 52, 54, 58-60, 69, 70, 72, 76, 83, 87, 89, 97, 102, 103, 107-109, 113-116, 118, 123-125, 127, 129-133, 135, 138-140, 142, 144-147)	LV/RV Hypertrophy in 36 patients (70) LV/RV dilation in 39 patients (83, 113) LV Hypertrophy in 42 patients (44, 54, 114, 115) LV enlargement in 24 patients (46)
RIGHT ATRIUM	14	(5, 24, 44, 79, 80, 92, 98, 100, 104, 106, 125, 133, 148, 149)	22 / 96 (23 %)	from 2 papers (44, 125)	
RIGHT VENTRICLE	50	(23-27, 29, 30, 37, 42, 45, 51, 55-60, 68-70, 73, 76, 79, 80, 83, 85, 87, 91,	262 / 1340 (20 %)	from 26 papers (29, 30, 37, 42, 45, 51, 58-60, 69, 70, 76, 83,	LV/RV Hypertrophy in 36 patients (70)

		92, 94, 96-100, 103, 104, 106, 109-111, 113, 114, 116, 121, 123, 130, 133, 150)		85, 87, 103, 104, 106, 113, 114, 116, 123, 130, 133, 150)	LV/RV dilation in 39 patients (83, 113)
INTERVENTRICULAR SEPTUM	33	(27, 28, 31, 38, 45, 56, 60, 69, 72, 76, 79, 80, 83, 88, 94, 98, 99, 101, 103, 104, 106-108, 115, 116, 118, 119, 123, 128, 132-134, 147)	112 / 1061 (11 %)	from 12 papers (38, 45, 60, 69, 72, 76, 106, 115, 116, 123, 132)	
VALVES	41	(25, 27, 28, 37, 43, 56, 59, 70, 76, 79, 80, 84, 85, 87, 90, 93, 94, 98, 100, 103-105, 107, 108, 110, 114, 116, 118, 123-126, 130, 132-134, 139, 140, 142, 143, 151-153)	386 / 1051 (37 %)	from 22 papers (27, 37, 43, 70, 76, 84, 87, 93, 103, 105, 114, 116, 123-125, 130, 139, 140, 142, 143, 152, 153)	
Mitral Valve	34	(25, 27, 28, 37, 41, 43, 53, 56, 59, 76, 79, 80, 84, 85, 93, 94, 98, 104, 105, 107, 114, 116, 118, 123-125, 130, 132-134, 139, 142, 151, 152)	339 / 1529 (22 %)	from 25 papers (27, 28, 37, 41, 43, 53, 56, 59, 76, 84, 85, 93, 98, 105, 114, 116, 124, 125, 130, 132, 134, 139, 142, 151, 152)	
Tricuspid Valve	23	(25, 37, 41, 53, 56, 79, 80, 84, 94, 100, 103-105, 110, 114, 116, 123, 130, 133, 134, 139, 142, 153)	269 / 860 (31 %)	from 17 papers (37, 41, 53, 56, 84, 100, 103, 105, 114, 116, 123, 130, 133, 134, 139, 142, 153)	
Pulmonary Valve	12	(25, 41, 59, 79, 94, 103-105, 110, 114, 133, 134)	12 / 326 (4 %)	from 5 papers (41, 59, 103, 105, 114)	

Aortic Valve	26	(25, 27, 37, 41, 59, 79, 80, 84, 93, 94, 98, 103-105, 108, 114, 116, 124, 130, 132-134, 139, 151, 152)	132 / 1194 (11 %)	from 16 papers (27, 37, 41, 59, 84, 93, 98, 105, 114, 116, 124, 130, 132, 139, 151, 152)	
CORONARY VESSELS					
Epicardial	13	(5, 30, 35, 52, 54, 70, 80, 84, 87, 90, 116, 125, 154)	43 / 177 (37%)	from 6 papers (30, 54, 70, 84, 116, 125)	
Intramural	15	(29, 30, 33, 35, 44, 52, 61, 70, 79, 80, 87, 128, 136, 137, 154)	98 / 338 (29 %)	from 10 papers (29, 30, 33, 35, 44, 52, 61, 79, 136, 137)	
SINUS-ATRIAL NODE	14	(25, 28, 32, 43, 48, 67, 70, 80, 94, 105, 114, 153, 155, 156)	228 / 726 (31 %)	from 10 papers (28, 32, 43, 48, 67, 70, 94, 153, 155, 156)	
ATRIUM-VENTRICULAR NODE	18	(25, 28, 44, 47, 52, 58, 67, 70, 80, 93, 94, 105, 112, 114, 116, 155)	129 / 720 (18 %)	from 13 papers (28, 44, 47, 52, 58, 67, 93, 94, 105, 112, 114, 116, 155)	
CONDUCTION SYSTEM	48	(24, 25, 28, 29, 33-36, 39, 44-48, 52, 56, 59, 60, 67, 70, 73, 76, 77, 80, 85, 87, 92-94, 97, 101, 102, 105, 112, 115, 116, 123, 125, 131, 132, 134, 143, 147, 153, 156-159)	683 / 2734 (25 %)	from 42 papers (24, 28, 29, 33-36, 39, 44-48, 52, 56, 59, 67, 70, 73, 77, 85, 87, 93, 94, 97, 102, 105, 112, 115, 116, 123, 125, 131, 132, 134, 143, 147, 153, 156-159)	
EPICARDIUM	8	(38, 70, 79, 80, 85, 104, 144, 160)	26 / 230 (11 %)	from 3 papers (38, 85, 144)	

ENDOCARDIUM	8	(38, 60, 79, 80, 85, 104, 136, 160)	18 / 331 (5 %)	from 5 papers (38, 60, 85, 136, 160)	
MYOCARDIUM	43	(5, 26, 36, 38, 44, 46, 51, 53, 57, 60, 61, 70, 73, 75, 77, 79, 80, 83-85, 87, 104, 113-117, 124, 131, 136, 137, 139, 143-145, 147, 159-165)	548 / 1999 (27 %)	from 35 papers (38, 44, 46, 51, 53, 57, 60, 61, 70, 73, 77, 83, 85, 87, 114-116, 124, 131, 136, 137, 139, 143-145, 147, 159-165)	
PERICARDIUM	62	(25, 27-30, 32-38, 41-45, 51, 53, 56, 59, 60, 62, 64, 69, 70, 76, 79-81, 83-86, 93, 94, 97, 98, 103-105, 112-114, 116, 123, 124, 130-134, 140, 143, 151, 152, 157, 159, 160, 164, 166, 167)	511 / 3216 (16 %)	from 53 papers (28-30, 33-38, 41-45, 51, 53, 56, 59, 60, 64, 69, 70, 76, 81, 83, 85, 86, 93, 94, 97, 98, 103, 105, 112-114, 116, 123, 124, 130-132, 134, 140, 143, 151, 152, 157, 159, 160, 164, 166, 167)	

Table 5. Data extracted for the “Altered Physiological Function” domain and its variables.

Altered Physiologic Function	**N° papers**	**references**	**N° patients**	**references**
SYSTOLE / CONTRACTION / EJECTION / DEPOLARIZATION	109	(23-25, 27-38, 40, 42, 44, 45, 50-52, 55-60, 62, 63, 68, 74, 78-81, 83, 88-108, 110-124, 126-141, 143, 144, 147, 150, 152, 159, 160, 164, 167-176)	1182 / 16554 (7 %)	from 55 papers (29, 30, 33-35, 37, 38, 40, 42, 44, 45, 50-52, 58, 60, 62, 78, 81, 83, 89, 106-108, 113-116, 118, 123, 124, 127-135, 138, 139, 143, 144, 150, 152, 159, 160, 164, 171-173, 176)
DIASTOLE / FILLING / RELAXATION / REPOLARIZATION	90	(25, 31, 32, 37, 43, 44, 48, 50, 51, 55-57, 59, 62, 63, 68, 71, 80-83, 85, 88-93, 95, 96, 98-104, 106-111, 114-126, 128-130, 132-135, 138-142, 148, 151, 152, 157, 164, 167-180)	2198 / 9349 (24 %)	from 56 papers (25, 26, 32, 37, 43, 44, 48, 50, 51, 59, 62, 63, 71, 81-83, 85, 89, 100, 102, 106-109, 114-118, 123-126, 129, 130, 132-135, 138-140, 142, 151, 152, 157, 164, 167, 171-173, 175-178, 180)
RHYTHM CONDUCTION	51	(25, 26, 28, 32, 33, 35, 36, 39, 43-48, 50, 52, 54, 58, 60, 61, 63, 67, 70, 72, 85, 87, 92-94, 97, 101, 102, 105, 112, 114-116, 123, 125, 128, 131, 134, 143, 147, 153, 156, 157, 178, 181, 182)	799 / 5877 (14 %)	from 41 papers (26, 32, 33, 35, 36, 39, 43, 44, 46-48, 50, 52, 54, 58, 61, 63, 67, 70, 85, 87, 93, 97, 102, 105, 112, 114-116, 123, 125, 131, 134, 143, 147, 153, 156, 157, 178, 181)
RHYTHM AUTOMATICITY	33	(28, 32, 43-46, 48, 56, 59, 63, 67, 71, 72, 74, 80, 87, 101, 105, 109, 112, 114-116, 125, 143, 147, 153, 155, 156, 158, 172, 178)	411 / 1615 (25 %)	from 28 papers (28, 32, 43, 45, 48, 56, 59, 63, 67, 71, 74, 87, 101, 105, 109, 112, 115, 116, 125, 143, 147, 153, 155, 156, 158, 172, 178)
MYOCARDIAL PERFUSION	38	(29-31, 33, 35, 36, 38, 43, 51, 52, 56, 61, 69, 72, 75, 77, 79, 87, 88, 114, 116, 136, 137, 139, 150, 154, 161, 165, 168, 171, 172, 174, 178, 183-185)	365 / 954 (38 %)	from 27 papers (29, 30, 33, 35, 36, 38, 43, 52, 56, 61, 69, 72, 75, 77, 79, 87, 116, 136, 137, 139, 150, 154, 161, 171, 172, 185)
WALL MOTION	31	(25, 29, 30, 33-35, 37, 38, 44, 51, 69, 72, 74, 79, 83, 87, 94, 95, 103, 104, 107, 108, 113, 116, 118, 123-125, 146, 163)	154 / 638 (24 %)	from 23 papers (29, 30, 33, 35, 37, 38, 44, 51, 69, 72, 74, 83, 87, 94, 107, 108, 113, 116, 118, 124, 125, 146, 163)
VALVE FUNCTION	38	(25, 27, 28, 37, 56, 59, 79, 85, 89, 93, 94, 98, 103-108, 114, 116, 118, 123-126, 130, 132, 133, 135, 139, 140, 142, 143, 151-153, 160, 167)	778 / 2213 (35 %)	from 25 papers (27, 28, 59, 85, 89, 93, 98, 103, 105, 114, 116, 123-125, 130, 132, 139, 140, 142, 143, 151-153, 160, 167)
OTHER FUNCTION	8			
Response to exercise (heart rate, LVEF, stroke volume)	3	(30, 58, 186)	26 / 42 (62 %)	from 2 papers (30, 58)
Reduced coronary flow reserve	1	(187)	24 / 44 (55 %)	from 1 paper (187)

Heart rate variability	4	(47-49, 188)	34 / 34 (100 %)	from 1 paper (49)

Table 6. Data extracted for the “Prognostic Outcome” domain and its variables.

Prognostic outcome	**N° papers**	**references**	**N° patients**	**references**
MYOCARDITIS	1	(161)	2 / 46 (4 %)	from 1 paper (161)
HEART FAILURE	23	(52, 57, 65, 70, 74, 76, 77, 87, 113, 130, 132, 135, 143, 144, 151, 164, 166, 176, 179, 189-192)	138 / 1814 (8 %)	from 15 papers (52, 65, 70, 76, 87, 135, 143, 144, 151, 164, 166, 176, 179, 189, 190)
ACUTE CORONARY SYNDROME	7	(54, 67, 70, 125, 143, 189, 190)	29 / 687 (4 %)	from 7 papers (54, 67, 70, 77, 143, 189, 190)
SIGNIFICANT ARRHYTHMIAS	18	(46, 52, 54, 57, 70, 71, 76, 77, 116, 125, 143, 151, 166, 173, 174, 176, 189, 190)	197 / 3106 (6 %)	from 16 papers (46, 52, 54, 57, 70, 71, 76, 77, 116, 143, 151, 166, 173, 176, 189, 190)
SUDDEN DEATH	11	(40, 46, 52, 65, 67, 70, 98, 122, 125, 131, 132)	119 / 1063 (11 %)	from 10 papers (40, 46, 52, 65, 67, 70, 122, 125, 131, 132)

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