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

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ABSTRACT

Introduction: 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 to focus clinical research. We aimed to create an expert consensus definition for SSc-pHI.

Methods: A systematic literature review of cardiac involvement and manifestations in SSc was conducted to inform an international and multi-disciplinary task-force. In addition, the 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 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 was 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 was created and partially validated, for use in future clinical research.

KEY MESSAGES:

* We performed a systematic literature review and used the nominal technique group to create a data and consensus-driven definition of SSc-pHI.
* Preliminary validation of the definition was performed in terms of face validity, feasibility, reliability and criterion validity.
* Future research agenda includes prevalence studies and diagnostic suggestion according to the proposed definition.

**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 (3). Myocardial disease is among the most frequent causes of death in SSc (4), including both primary and secondary cardiac involvement (5). The largest survey carried out by the European Scleroderma Trials and Research (EUSTAR), including almost 12000 patients and almost 1000 deaths. In this significant population, Elhai et al showed that 12% of SSc-death were related to primary heart disease, although this was a physician-based adjudication and a specific definition was not provided to the investigators at the time of data collection (6). 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, due to other SSc-related (i.e. renal, pulmonary vascular or pulmonary parenchymal disease)(7-11) or non-SSc related condition (i.e. ischemic heart disease) (12). Cardiac involvement varies from 7% to more than 39% of SSc patients and this range is linked to both the lack of consensual definition and the wide sensitivity of detecting tools (13, 14). Still, the prevalence of cardiac involvement can be much higher when autopsy findings are included, in particular due to early asymptomatic cases (15). The most frequent clinical cardiac features may include impaired contractility and relaxation, arrhythmias, myocarditis, and pericardial disease (16). Despite the plethora of possible different manifestations, primary cardiac involvement shares the main overall disease pathogenetic features, with variable combination of inflammatory, fibrotic and vasculopathic changes (17). These may explain why certain demographic or SSc-features may act as risk factors for specific SSc-cardiac manifestations, such as older age at disease onset (18, 19), male gender (20), auto-antibodies positivity (19, 21), diffuse cutaneous subset (22), musculoskeletal involvement (22) for more inflammatory involvements including myocarditis, while history of digital ulcers (23) may increase the risk of vasculopathic and subsequent fibrotic and dysfunctional changes. Despite this, the same risk factor may not impact on the development of other typical manifestation of heart involvement, such as diastolic disfunction (24). Finally, the use of drugs such as calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and low-dose aspirin has been associated with a lower incidence of primary cardiac disease (25).

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 cardiac disease, taking into consideration the possible concomitant presence of classical cardiovascular disease risk factors (26). Moreover, the 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 (27). More recently, although not being primarily focussed on primary cardiac disease, a set of domains and variables for a longitudinal annual assessment of organ involvement was proposed by experts from the EUSTAR group and Scleroderma Clinical Trial Consortium (SCTC), including heart domain. The latter included 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 (28).

Despite all these resources (29), 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 need of a uniform data- and consensus-driven definition of SSc-pHI, as well as the need for consensus classification criteria to establish the real prevalence, prognostic impact and therapeutic effect (30).

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 consensus-based, data-driven definition of primary heart involvement.

**METHODS**

*Literature search*

Considering the absence of a validated definition to use as comparator (30), the project core team (CB, MHB, PS, MMC) identified 6 domains for SSc-pHI: signs, symptoms, pathological changes, anatomical site involved, altered physiological function, prognostic outcomes. At this stage, the domains were created to facilitate data collection and presentation. In each domain, a list of variables was noted. A list of Patient-Exposure-Outcome (PEO) questions were created accordingly (see Supplementary Data S1) (31). We subsequently performed a systematic literature review (SLR), following the methodology recently used for the development of another consensus definition (32). A single author (CB) performed MEDLINE, EMBASE and PubMed databases searches, 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 contributing in case of disagreement (MHB). The same three authors acted in the second round, during 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 the inclusion/exclusion criteria listed in Supplementary Data S2 and the reasons for exclusion was recorded. To document consistency, 5% of the papers underwent selection and data extraction by all the 14 extractors.

*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 to capture variables which were not covered. For each article selected from step three, the following were extracted: study nature, patients’ selection criteria, number of patients with number/percentage of female gender, the presence of the pre-selected domains and variables with the number of patients presenting/reporting them. The extracted data were analyzed by a biostatistician (LT), as explained below. Two external assessors (EZ, rheumatologist, and FT, cardiologist, both with experience in SSc), not aware of the pre-defined domains and PEOs, reviewed the data extracted from the SLR and presented after analysis, and identified similar domains, providing validation to our preliminary clustering.

*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 (ERB, 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 the 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 utilized. This consisted of 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 newly defined domains specifically oriented to the creation of the definition, with discussion and clarification as needed. A single group statement was then derived from 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. Statements were specifically re-discussed in case of agreement <70%, then re-voted. The final definition included statements with agreement>70% and ranked according to prioritization. A final consensus on the proposed definition was attained when agreement was >70% (33).

*Preliminary validation*

During the validation process, OMERACT criteria were followed (34). 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 and 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 with the same clinical cases presented in a different random order (an example of the case report forms is presented in Supplement Data 3). These comprised the same clinical cases in a different random order; inter- and intra-rater agreements were tested. Criterion concurrent 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 (35) and the single experts’ evaluations were tested against it.

*Analysis*

Data were analysed using SAS software, version 9.3. For continuous variable median and standard deviation are reported, while for categorical variables absolute frequencies and percentage for each category are presented. To assess 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. Level of agreement was evaluated as previously proposed (36).

**RESULTS**

Among 2,593 identified papers, 171 were eligible for data extraction (Figure 1 includes reasons for exclusion in the three steps), consisting of 23 retrospective, 49 prospective, 81 cross-sectional, 4 case series, 2 clinical trials, 1 case-control and 3 non-specified studies. The 171 studies provided a total of 23,276 patients, with female prevalence ranging from 82.1-83.6%, mainly enrolled according to the 1980 ARA SSc preliminary classification criteria (n=72) (37) or with the 2013 ACR/EULAR SSc classification criteria (n=41) (38). Forty-seven studies included SSc patients with no-known cardiac disease or pulmonary arterial hypertension (PAH) or asymptomatic patients, 10 manuscripts focussed on SSc patients with previously diagnosed cardiac involvement or symptoms suggestive of cardiac involvement and 3 studies were autopsy evaluations. Details for each domain and almost all variables were collected from at least one paper (Supplementary Tables S1-S6).

Details for each domain were collected from at least one paper; in particular 60 papers had data on symptoms (Supplementary Table 1), 22 on signs (Supplementary table 2), 15 on pathological changes (Supplementary table 3), 135 on anatomical site involvement (Supplementary table 4), 157 on altered physiological function (Supplementary table 5) and, finally, 37 on prognostic outcome (Supplementary table 6). Wide heterogeneity was detected in terms of information collected, with almost all variables being reported at least once; this further highlighted the need for a comprehensive definition which should include pathological, anatomical, and functional involvement simultaneously.

The SLR results were presented to the 16 experts, who carried separate data-driven discussion regarding the data of the 6 abovementioned domains. Following the NGT process, silent generation of ideas was then undertaken. The round-robin phase generated 27 statements, clustered into 4 domains according to common themes: aetiology, clinical and diagnostic, pathogenesis, and timing (see Table 1). Further discussion was undertaken, and one statement was generated, refined and derived for each domain. The final definition which was reached, including statements with agreement>70% and ranked according to prioritization, then refined 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)].”*

A 100% agreement was noted on the proposed definition when tested among the sixteen pre-identified case reports, with a median 60 (5-300) seconds was taken per case to decide if the definition could correctly identify SSc-pHI or other disease, therefore supporting face validity. The inter-rater agreement was moderate, with mKappa (95%CI) of 0.56 (0.46-1.00) and 0.55 (0.44-1.00) respectively; the intra-rater agreement was good, with a mKappa (95%CI) of 0.77 (0.47-1,00). The higher rate of disagreement was among cases with features of both primary and secondary heart involvement. Interestingly, there was no significant difference between cardiologists and non-cardiologists, when evaluated separately, in terms of inter- and intra-rater agreement. The definition was created based on the data derived from more than 23000 patients, including variable expression of gender, age, and disease manifestations, therefore supporting content validity. For criterion concurrent validity, a 78 (73-84) % correctness versus gold-standard was found.

**DISCUSSION**

Studies on SSc-associated cardiac disease comprise heterogeneous populations defined by different combinations of signs/symptoms, diagnostic tools, definitions, and serum biomarkers (30). This has implications for our understanding and diagnosis of SSc-pHI and the ability to improve outcomes. Our initiative used an international and multi-disciplinary task force of experts from cardiology, pathology and different SSc medical specialties (rheumatology, immunology, dermatology), to develop a first definition of SSc-pHI for application in future clinical research.

It is well known that SSc-pHI is a frequent organ complication associated with varied clinical manifestations and significant morbidity and mortality. To date, studies report a strikingly variable prevalence of SSc-heart involvement (13, 30), 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 (13, 30). 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 to equal measure, allowing all and varied expertise to inform the process and ultimately merge to a single consensus agreed result. 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. Rheumatologists enabled effective input in considering SSc non-cardiac conditions, which may masquerade as cardiac manifestations. Similarly, cardiologists’ expertise was pivotal in the consideration of 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 the PRP who highlighted the importance of capturing asymptomatic patients and early disease stages, often excluded in research studies.

Our SSc-pHI consensus definition has undergone preliminary validation according to the OMERACT criteria. Face validity and feasibility were reached, the intra-rater reliability was good and the inter-rater reliability was moderate. Although reliability was sufficient, it is not surprising that it was not higher, as the need to include asymptomatic patients will naturally increase variability. This highlights the complexity of SSc-pHI and emphasises the importance of consistent physician evaluation when participating in a longitudinal evaluation. The validation process also suggests that confounding conditions should be excluded to accurately select patients. Finally, the correctness of the application of the definition (i.e., criterion validity) was 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 for primary SSc heart involvement are ongoing (39). Future studies will evaluate for complementarity of these two definitions and/or any added value of combined use of both definitions in improving the accuracy and uniformity of SSc-pHI identification in clinical research.

Currently proposed diagnostic sets of assessments (28), frequency of the recommended testing and minimum dataset(26) and experience-based suggestion for use of wider tools (such as cardiac magnetic resonance imaging and stress tests) (26, 27), can be reviewed in the light of this new proposed SSc-pHI definition. Our future research agenda includes studies to better capture prevalence and prognostic impact including in early SSc stages when SSc-pHI may be asymptomatic and subclinical (40); as well as optimising and tailoring use of cardiac assessments in the early diagnosis and follow-up of SSc-pHI (41).

The strengths of our study include the multi-disciplinary input and 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 widely applicable and independent from local facilities or health systems.

Our study however holds some limitations. The initial definition of the disease domains was performed among a small committee, not including a patient representative; this was anyway intended to guide the literature review and the data presentation to the experts’ board, not as a basis for the definition itself, which have would have then required a different methodological approach. The limited number of clinical cases might have impaired the reliability exercise; the lack of an established standardised gold standard warrants cautious interpretation of the evaluation of criterion validity. We tried to overcome this with a pragmatic approach of multi-disciplinary team evaluation, which is also used in clinical practice, although more physicians could have been involved in creating the “gold-standard” agreed assessment. Moreover, the level of agreement was assessed among the same experts who created the definition, which might have biased the evaluation. Finally, we applied the OMERACT filter, which was created for outcome measures, to validate our definition. Although this may not be globally applicable, it showed that our definition has internal face validity, content validity and partial criterion validity. Further feasibility, construct and response/discrimination exercises remain to be evaluated in the future steps of the validation, including a second assessment for agreement in an external cohort of experts.

In conclusion, we report on an underpinning SLR and NGT to create a consensus-based, data-driven definition of SSc 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.

Legend

Figure 1. Study selection flow diagram, with reasons for exclusion. (SSc= systemic sclerosis)

Table 1. Domains and statement derived from the face to face meeting, with level of agreement between experts.

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