# DOTTORATO DI RICERCA IN SCIENZE CLINICHE

CICLO XXXIV

COORDINATORE Prof. Lorenzo Cosmi

# To develop a definition and validated expert recommendations to diagnose primary heart involvement in Systemic sclerosis - Preliminary pathway to a T2T approach

Settore Scientifico Disciplinare MED/16


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Anni 2018/2021

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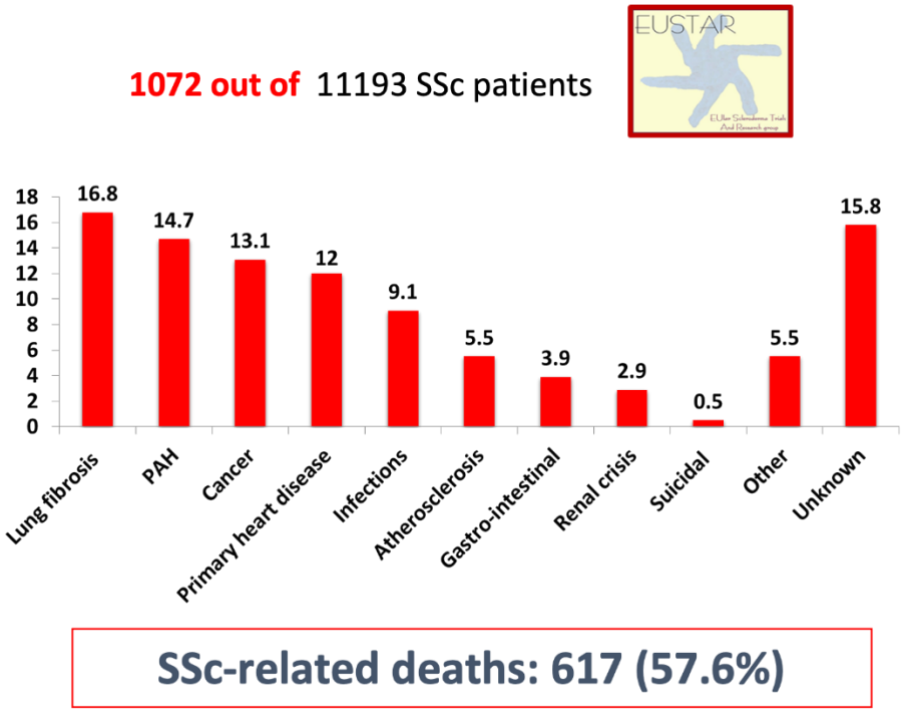
## 1. Introduction

Systemic sclerosis (SSc) is a chronic connective tissue disorder, in which the pathways of vasculopathy, inflammation/autoimmunity and fibrosis are pathogenetically involved (1). The combination of the three processes manifests differently among the affected patients, in terms of clinical expression and severity. Among them, lung parenchymal involvement (interstitial lung disease – ILD) and lung vascular involvement (pulmonary hypertension – PH- and pulmonary arterial hypertension - PAH) represent the leading causes of mortality (Figure 1), as shown by various publications among different study populations (2, 3). In this light, great effort has been spent so far for the early detection, identification and treatment of such complications, in order to limit their morbidity and mortality burden, as well as the consequently impaired quality of life. In the context of PH, different screening algorithms have been proposed in the last two decades, mostly based on the combination of multi-domains parameters and risk attribution (4). A rational for these was found on the previous demonstration that the standardized application of screening methods for early PAH detection determined a positive impact on PAH-related mortality events in the years after the diagnosis (5).

Figure 1 – Attributed causes of mortality in the EUSTAR SSc cohort study. Reproduced from Elhai et al (2).



Despite less evidence is available for a standardized screening approach to SSc-ILD, a similar pathway has also been undertaken for this topic. A recent European consensus of experts deriving from the Rheumatology, Pulmonology and Internal Medicine specialties, agreed that patients with SSc should be screened for ILD at the time of diagnosis, using high resolution computed tomography (HRCT), in combination with pulmonary function tests to provide baseline values of the respiratory functional impairment (6). This was particularly stressed in case of presence of evidence-based risk factors, such as gender, ethnicity and positivity of certain autoantibodies (6). Currently, no data derived from a standardized baseline application of HRCT to screen for SSc-ILD are available, and doubt remain on the best approach to follow-up patients with initially negative chest HRCT.

Various awareness campaigns have been performed in the last decade to stress the importance of screening for both SSc-ILD and SSc-PAH. The rational of screening for specific disease or complication relies on different factors, including the improvement of the outcome in comparison to when the condition is detected randomly, the possibility of improving the prognosis through acts or medications, and a balanced risk/benefit ratio with rationalization of the screening application (7). Despite with different entities, both SSc-PAH and SSc-ILD studies have shown improvement of outcome with the currently available medications and the different algorithms take risk factors into account, therefore optimizing the application of the screening procedures.

Cardiac involvement in SSc is frequently referred to as “the silent killer”. In the EUSTAR cohort study from Elhai et al, “primary cardiac involvement” (SSc-pHI) was deemed as the 4$^{th}$ cause of mortality, accounting for 12% of the events (Figure 1). Similar data were also seen in the combined Australian-Canadian cohort by Hao et al, who identified 9% of the mortality events in their prevalent cohort as being related to “myocardial involvement” (3). In both studies, cardiac involvement was not defined according to pre-set criteria and the adjudication was left to the caring physician’s opinion.

The problem of the definition of SSc-related cardiac involvement has been a challenge in the last decade. Indeed, SSc-associated cardiac involvement may include different kind of events, such as contractility/relaxation defects, arrhythmias, pericardial disease and valve disease (8, 9). These can be determined by the primary involvement of the myocardial/pericardial tissue, as part of the pathogenetic SSc-related processes, but also secondary to other conditions. This might be the case of cardiac and cardiovascular comorbidities, which may occur in the general population, such as systemic arterial hypertension, age associated diastolic dysfunction and coronary artery disease (10). At the same time, cardiac manifestations in SSc may derive from other SSc-associated complications, such as ILD and PAH, which appear

mostly on a later stage (11, 12), or Scleroderma Renal Crisis (SRC), in which the cardiac complication is more acute and may manifests from the onset (13).

Given this etiological heterogeneity, the prevalence of SSc-heart involvement and SSc-pHI have been variably reported in the literature, ranging from 7-39% (14). This wide variability is also in line with the lack of standardized definition and classification criteria to identify patients with SSc heart involvement and in particular with SSc-pHI (15). A recent systematic literature review from Ross et al tried to identify previously used definitions of SSc heart involvement. The high heterogeneity of the definitions found highlighted the unmet need of a comprehensive and agreed definition of SSc-pHI, as well as the need for classification criteria to establish its real prevalence, prognosis and treatment strategies (16, 17).

Different sets of Expert consensus algorithms are available to detect, follow-up and treat patients with SSc-pHI. Among them, the UK Systemic Sclerosis Study Group first provided a guidance for physicians, stressing the importance of examining both symptomatic and asymptomatic patients, as well as the need to take general population's cardiovascular risk factors into account (18). More recently, a Greek cardiology-rheumatology collaboration group proposed a management algorithm that was also based on a two-steps approach to evaluate SSc patients, and placing the different tests in different tiers of priority (19).

Indeed, there is a plethora of first, second and third levels tests which can be performed on SSc patients for the identification and follow-up of cardiac complications, but each of them is sometimes specifically oriented to one of the possible manifestations of SSc-cardiac involvement. For example, resting electrocardiography mostly picks fixed conduction defects, resting trans-thoracic echocardiography identifies motion abnormality and contractility impairment, cardiac magnetic resonance detects inflammatory and fibrotic changes (15). Given the heterogeneity of manifestations included in the "cardiac scleroderma spectrum", the different tests should determine a broad-spectrum evaluation, which still needs to be optimized mostly for feasibility (time, costs, availability).

This Doctoral project was aimed at collecting the evidence from the literature and use them to create a data-driven and consensus-based definition of SSc-pHI, then starting its validation process. Once the definition was available to define our target, we used the evidence from the literature to create a list of consensus guidance for the screening, diagnosis and follow-up of SSc-pHI. Finally, we performed a retroactive evaluation of the application of the consensus guidance, to test its feasibility, added value and possible implications in a cohort of SSc patient followed up longitudinally.

## 2. Objective:

To implement the daily care of systemic sclerosis-associated primary heart involvement (SSc-pHI), supporting caring physicians in its identification and diagnosis.

## 3. Aims:

To achieve the objective, the workflow was divided into multiple aims, as also summarized in Flowchart 1.

*a) To assess the impact of cardiac involvement from SSc patients' perspective.*

This aim will be achieved using patients' interviews, investigating the perception and feelings related to a diagnosis of SSc heart involvement (see section 4.b.)

*b) To scope the literature for heart involvement features in SSc.*

This aim will include a systematic literature review investigating the possible manifestations of SSc primary heart involvement; this will be seen from different perspectives including anatomy, pathology, pathophysiology (see section 4.c.)

*c) To develop and validate a definition of SSc-pHI.*

The information derived from aims 3a and 3b will create the basis of discussion for the Experts committee, aiming at creating a definition of SSc-pHI and performing the initial validation on a pre-defined set of clinical cases (see section 4.d.)

*d) To scope the literature for cardiac diagnostic tests in SSc.*

A second systematic literature review will collect information about the tests and the parameters used in SSc patients for the screening, diagnosis and monitoring of SSc-pHI, with pre-defined attention on certain assessments including electrocardiography, echocardiography and cardiac magnetic resonance (see section 4.e.)

*e) To develop a guidance for the screening, diagnosis and monitoring of SSc-pHI.*

The data derived from aim 4d will be discussed by the expert committee and merged with their personal experience in the management of SSc-pHI. This will result in a

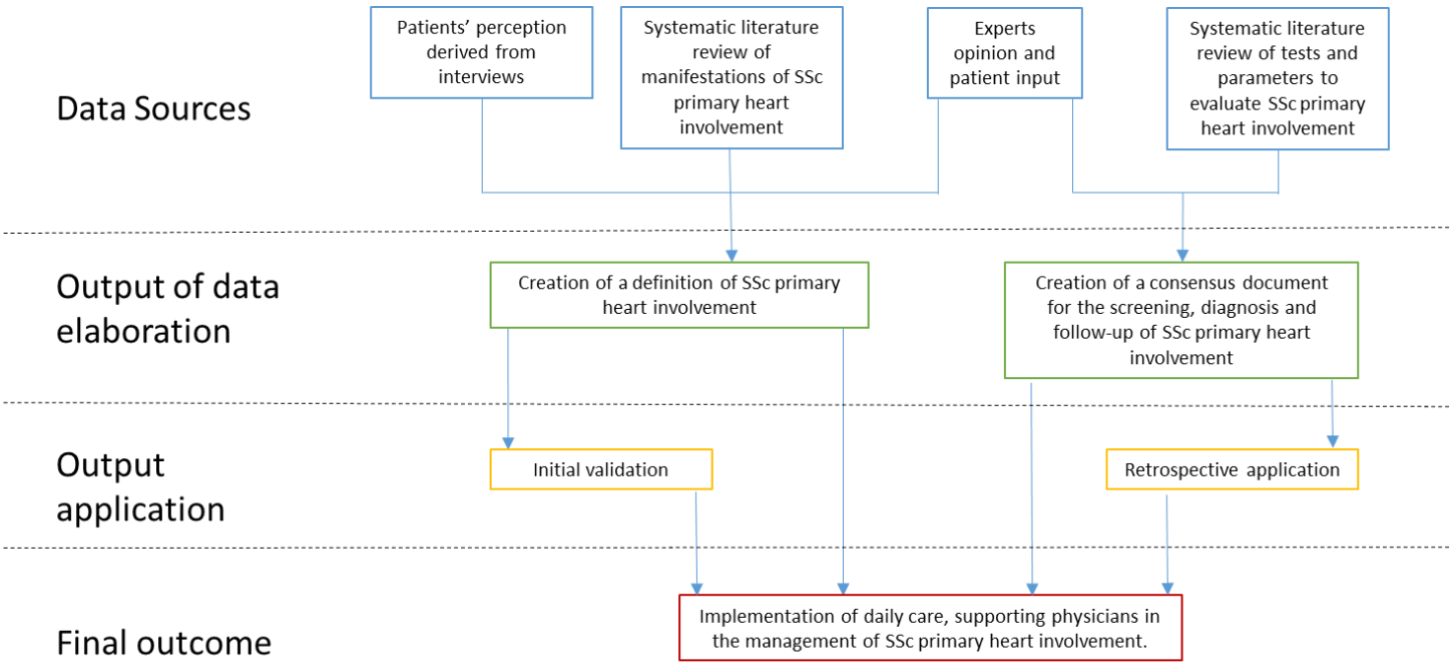
consensus document guiding the clinicians in the screening, diagnosis and management of SSc-pHI. In addition, SSc-dedicated protocols for echocardiography and cardiac magnetic resonance will be proposed, aiming at homogenizing reporting and interpretation (see section 4.f.).

*f) To assess the feasibility and usefulness of the application of the definition and the guidance statements in a real-life clinical context.*

The definition and the consensus statements will be tested retrospectively in a single centre cohort of SSc patients, followed up longitudinally. As explained in further details in section 4.g., the retrospective study will:

i. test the prevalence of SSc-cardiac involvement and SSc-pHI;
ii. test the impact of SSc-PHI on mortality;
iii. identify the risk factors for SSc-pHI;
iv. test the impact of the consensus guidance on the detection of SSc-pHI;
v. test the impact of the consensus guidance on the performance of additional 2nd and 3rd level assessments;
vi. test the impact of cardiovascular medications on SSc-cardiac events and mortality.

Flowchart 1 – Project reasoning flow.



## 4. Materials and Methods

### 4.a. Teams

The first part of the project led to the creation of a task force of SSc and SSc-pHI experts, belonging to prestigious support and research associations, such as the World Scleroderma Foundation (WSF), European Scleroderma Trial and Research Group (EUSTAR) and the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Each expert suggested at least one young collaborator to contribute to the systematic literature review (SLR) section of the project. In addition, a representative of the Italian SSc patient association (Gruppo Italiano Lotta alla Sclerodermia - GILS) was identified and involved. The participating members were divided into different groups, according to their roles in the project.

The following groups and roles were therefore identified:

**Core Leadership team**:

Prof Marco Matucci Cerinic (Rheumatologist - I)

Prof Peter Seferovic (Cardiologist - Sr)

Prof. Maya Buch (Rheumatologist, Methodologist - UK)

Dr Cosimo Bruni (Rheumatologist, Project Coordinator – I)

**Expert panel**:

**Cardiologist:** Prof.ssa Sophie Mavrogeni (GR), Dr. Luna Gargani (I), Prof. Alida Caforio (I), Prof. Carsten Tschoepe (D), Prof. Arsen Ristic (Sr), Prof. Sven Plein (UK), Prof. Elijah Behr (UK), Prof. Aleksandra Djokovic (Ser), Dr. Alessia Pepe (I),

**Cardio-pathologist**: Prof. Karin Klingel (D)

**Rheumatologist:** Prof. Yannick Allanore (F), Prof. Masataka Kuwana (Jp), Prof. Christopher Denton (UK), Prof. Daniel E Furst (USA), Prof. Dinesh Khanna (USA), Prof. Petros Sfikakis (GR), Prof. Oliver Distler (CH)

**Dermatologist**: Prof. Thomas Krieg (D)

**Cardio-Immunologist**: Dr. Renzo Marcolongo (I)

**Patient representative:** Ilaria Galetti (I)

**Systematic Literaturature Review (SLR) team:**

**Rheumatology:** Dr. Ghadeer Hasan (USA), Dr. Yossra Atef Suliman (Eg), Dr. Giacomo De Luca (I), Dr. Alexia Steelandt (F), Dr. Bianca R. Dumitru (RO), Dr. Alessandro Giollo, (I), Dr. Yohei Isomura (JAP), Dr. Cosimo Bruni (I).

**Cardiologia**: Dr. Marija Polovina (Ser), Dr. Ivan Milinkovic (Ser), Dr. Costas Bratis (GR), Dr. Anna Baritussio (I), Dr. George Markousis- Mavrogenis (GR), Dr. Anastasia Xintarakou (GR).

**Antropologist:** Prof. Cameron Hay-Rollins (USA)

### 4.b. Patients Interviews

Patient interviews represent a qualitative research method in which participants can express their perceptions and feelings, usually in response to questions stimulated by a moderator. The audio of the interview is recorded, transcribed, and analyzed for the identification of key concepts.

The aim of Patient Interviews is, first of all, is to obtain information about the perceptions, feelings and sensations of patients suffering from SSc-pHI. The patient is not asked questions like "Did you experience angina or atypical chest pain?", but rather focus on “how did you feel, how this sensation made you feel?”, looking for informative details that, for example, led the patient to seek help from their family or health provider.

In order to define the questions that are part of the official interviews, a preliminary version of the interview was drawn up (prepared by CB, CHR, DEF), as follows:

1. *Let’s talk about the time you started having your heart problem.*
    a. *What did you feel?*
    b. *In thinking about your sensations, did you notice a rapid heartbeat that seemed out of place? Tell me about that.*
    c. *How did it make you feel?*
    d. *When did it occur? Did it occur repeatedly?*
    e. *Was there anything you associated as a cause? Anything making it better or worse?*
    f. *What did you do about it?*
    g. *Did you talk to someone soon? Was it your doctor/nurse or a family/friend?*
    h. *Did you do it soon or wait until severe? Tell me about what prompted you to begin to think that there was something worth mentioning to a physician.*

2. *Thinking about the time you were diagnosed:*
    a. *How did you feel when you were told?*
    b. *Once diagnosed, what was your expectation for treatment?*
    c. *Once diagnosed, what was your expectation for how the cardiac condition would affect your life?*
    d. *Now, how does your cardiac condition, and the ways you treat it, affect your life?*

e. *If there was one thing that in hind sight, you wish you had known, what would it be?*

The interview was performed via phone on SSc patients with diagnosed heart involvement, followed up at the Rheumatology Unit of the University of Florence – Careggi Hospital.

### 4.c. First systematic literature review: heart involvement in SSc

The first SLR focused on identifying the possible anatomical, clinical and pathological expressions of SSc-pHI. During the preliminary phase, the Core Leadership T processed the PEO (Population-Exposure-Outcome) questions. Six domains (with the relevant parameters included) were pre-identified and used to compose the PEOs:

•Symptoms
o In patients with SSc, can the presence of palpitations be defined as SSc-pHI?
o In patients with SSc, can the presence of syncope be defined as SSc-pHI?
o In patients with SSc, can the presence of vertigo be defined as SSc-pHI?
o In patients with SSc, can the presence of dyspnea be defined as SSc-pHI?
o In patients with SSc, can the presence of chest pain be defined as SSc-pHI?
o In patients with SSc, can the presence of other symptoms be defined as SSc-pHI?

• Clinical Signs
o In patients with SSc, can the presence of hypoxia be defined as SSc-pHI?
o In patients with SSc, can the presence of cyanosis be defined as SSc-pHI?
o In patients with SSc, can the presence of declining edema be defined as SSc-pHI?
o In patients with SSc, can the presence of the third and / or fourth tone be defined as SSc-pHI?
o In patients with SSc, can the presence of bibasal crackles be defined as SSc-pHI?
o In patients with SSc, can the presence of other clinical signs be defined as SSc-pHI?

• Cardiac Anatomy
o In patients with SSc, can the alteration of the pericardium be defined as SSc-pHI?
o In patients with SSc, can the alteration of the epicardium be defined as SSc-pHI?
o In patients with SSc, can the alteration of the endocardium be defined as SSc-pHI?
o In patients with SSc, can the myocardial alteration be defined as SSc-pHI?
o In patients with SSc, can the alteration of the heart valves be defined as SSc-pHI?
o In patients with SSc, can the alteration of the heart chambers be defined as SSc-pHI?
o In patients with SSc, can the alteration of coronary circulation be defined as SSc-pHI?
o In patients with SSc, can the alteration of intramural circulation be defined as SSc-pHI?

o In patients with SSc, can the alteration of the pericardium be defined as SSc-pHI?
o In patients with SSc, can the alteration in cardiac size be defined as SSc-pHI?
o In patients with SSc, can the alteration of the impulse origin be defined as SSc-pHI?
o In patients with SSc, can the alteration of rhythm conduction be defined as SSc-pHI?

• Cardiac Physiology
o In patients with SSc, can the alteration of muscle contraction be defined as SSc-pHI?
o In patients with SSc, can the alteration of muscle relaxation be defined as SSc-pHI?
o In patients with SSc, can the conduction alteration be defined as SSc-pHI?
o In patients with SSc, can the alteration of the automatism be defined as SSc-pHI?
o In patients with SSc, can the alteration of atrial depolarization be defined as SSc-pHI?
o In patients with SSc, can the alteration of ventricular depolarization be defined as SSc-pHI?
o In patients with SSc, can the alteration of ventricular repolarization be defined as SSc-pHI?

• Heart Pathology
o In patients with SSc, can the presence of myocardiocyte hypertrophy be defined as SSc-pHI?
o In patients with SSc, can the presence of myocardiocyte hypotrophy be defined as SSc-pHI?
o In patients with SSc, can the presence of myocardial collagen deposition be defined as SSc-pHI?
o In patients with SSc, can the presence of myocardial necrosis be defined as SSc-pHI?
o In patients with SSc, can the presence of myocardiocyte atrophy be defined as SSc-pHI?
o In patients with SSc, can the presence of myocardial fibrosis be defined as SSc-pHI?
o In patients with SSc, can the presence of pericardial haemorrhage be defined as SSc-pHI?
o In patients with SSc, can the presence of pericardial inflammation be defined as SSc-pHI?
o In patients with SSc, can the presence of pericardial infection be defined as SSc-pHI?
o In patients with SSc, can the pericardial fluid alteration be defined as SSc-pHI?
o In patients with SSc, can the presence of cardiac vasculitis be defined as SSc-pHI?
o In patients with SSc, can the presence of cardiac vasculopathy be defined as SSc-pHI?

• Prognosis
o In patients with SSc, can the development of myocarditis be defined as SSc-pHI?
o In patients with SSc, can the development of heart failure be defined as SSc-pHI?
o In patients with SSc, can the development of acute coronary syndrome be defined as SSc-pHI?
o In patients with SSc, can the development of arrhythmias be defined as SSc-pHI?
o In patients with SSc, can the development of sudden death be defined as SSc-pHI?

Once the PEOs were set, the literature research was performed to verify the presence of information that could answer these questions, passing through some preliminary preparatory steps:

• Creation of a list of MESH terms, to be used to search for scientific works: ((((((((((((((((((((((((((((((((((((((((“cardiac disease”[TW]) OR “heart disease”[TW]) OR “cardiac diseases”[TW]) OR “heart diseases”[TW]) OR “cardiac dysfunction”[TW]) OR “heart dysfunction”[TW]) OR “cardiac dysfunctioning”[TW]) OR “heart dysfunctioning”[TW]) OR “cardiac injury”[TW]) OR “heart injury”[TW]) OR “cardiac injuries”[TW]) OR “heart injuries”[TW]) OR “cardiac involvement”[TW]) OR “heart involvement”[TW]) OR “cardiac involvements”[TW]) OR “heart involvements”[TW]) OR “cardiac impairment”[TW]) OR “heart impairment”[TW]) OR “cardiac dysfunction”[TW]) OR “heart dysfunction”[TW]) OR “myocardial dysfunction”[TW]) OR “myocardial involvement”[TW]) OR “cardiac impairment”[TW]) OR “heart impairment”[TW]) OR “myocardial impairment”[TW]) OR “cardiac pathology”[TW]) OR “heart pathology”[TW]) OR “myocardial pathology”[TW]) OR “cardiac disorder”[TW]) OR “heart disorder”[TW]) OR “myocardial disorder”[TW]) OR “myocardial disease”[TW]) OR “cardiac disorders”[TW]) OR “heart disorders”[TW]) OR “myocardial disorders”[TW]) OR “myocarditis”[TW]) OR “pericarditis”[TW]) OR “pericardial effusion”[TW]) OR “electrocardiograph”[TW]) OR “ECG”[TW]) OR “conduction defect”[TW]) OR “conduction defects”[TW]) OR “conduction abnormality”[TW]) OR “conduction abnormalities”[TW]) AND ((((((((((((("scleroderma"[TW] OR "sclerodermas"[TW]) OR "sclerodermatous"[TW]) OR "sclerodermal"[TW]) OR "sclerodermic"[TW]) OR "sclerodermia"[TW]) OR "sclerodermy"[TW]) OR "sclerodermias"[TW]) OR "systemic sclerosis"[TW]) OR "systemic sclerotic patients"[TW]) OR "systemic sclerotic skin"[TW]) OR "crest syndrome"[TW]) OR "sclerosis/crest"[TW]) OR "crest syndromes"[TW]) OR "progressive systemic sclerotic"[TW])) NOT (("animals"[MeSH Terms:noexp] OR animals[All Fields]) NOT ("humans"[MeSH Terms] OR "humans"[All Fields])).

• Selection of databases: EMBASE, Pubmed, Web of Science.

• Definition of the timing of publication: from inception to 31/12/18.

• Inclusion Criteria: articles on adult patients, affected by Systemic Sclerosis or enrolled in cohorts in which SSc patient data could be extracted / evaluated separately, cardiac involvement or cardiac evaluation as primary target of the work, articles with case series ≥ 10 patients, articles in English / Italian / Romanian / Greek / Arabic / Serbo-Croatian.

• Exclusion criteria: non-human studies (pre-clinical, genetics, in vitro), paediatric subjects, articles with patients suffering from overlap syndromes, case series <10 patients, secondary cardiac involvement, article in a language other than those listed above, full - text not available, another reason why the examiner considered the work not to be included (to be specified), duplicates, literature reviews (after careful checking of the bibliography for any articles not included in the evaluation).

Finally, a CRF (Case Report Form) was prepared on Excel computer support, to support the extraction and processing of data.

A single author (CB) performed the literature search and the publications retrieved from the 3 databases underwent removal of duplicates, using the software EndNote. Subsequently the articles were subjected to title/abstract evaluation, and finally to the full-text evaluation of the selected ones. The two evaluations were conducted in duplicate by two “blinded” evaluators (7 couples of extractors from the SLR Team, with balanced coupling of Rheumatology and Cardiology expertise), whose discrepancies were resolved by direct comparison or through the opinion of a third evaluator (CB). A reproducibility exercise was conducted on the first 5 articles derived from the selection and performed by all 14 extractors, to ensure homogeneity in manuscript evaluation and data extraction.

### 4.d. Methodology for Meeting 1: Creating the Definition of SSc-pHI

The Expert Committee was informed of the data derived from the patients’ interviews and the SLR, whose domains and variables were presented. The Nominal Group Technique (NGT) was utilized during the meeting and this consisted of 3 steps. First, the Experts were asked how they defined SSc-pHI, each of them silently and independently generating up to 3 ideas in brief phrases or statements, without any discussion. The second step included round-robin feedback to record each idea without discussion. In the third step, statements were merged into domains, with discussion and clarification as needed; a single group statement was derived from each domain. The Experts voted in confidence to prioritise final statements, ranking the top 50% of the ideas and each member voting on these to establish a further ranking. A consensus was attained when agreement was >70% (20).

During the validation process, the OMERACT criteria were followed. Face validity was defined as the credibility of the measure determined by the experts. Seventeen real-life clinical cases were created from patient files, not taken care of by any of the participants. 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 for its application to

the single case. Reliability was tested with the evaluation of case reports during the face-to-face meeting and repeated during a second round, 4 weeks apart, 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 SSc-pHI (PS and MMC from the Core Leadership team) was used as gold standard and experts' evaluations were tested against it.

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.

### 4.e. Second systematic literature review: diagnostic tests

The second SLR focused on the different techniques, tests and parameters applied to SSc patients in the screening, diagnosis or evaluation of SSc-pHI. As for the first SLR, the Core Leadership Team processed the PEO questions and pre-identified 6 domains, with the respective parameters, through which the PEO questionss were composed:

- Conventional radiology
  - Is conventional radiology used to diagnose SSc-pHI?
  - Which parameters of Conventional radiology are used to diagnose SSc-pHI?
  - Which alterations detected on Conventional radiology are useful to diagnose SSc-pHI?

- Nuclear medicine techniques
  - Is Cardiac Scintigraphy used to diagnose SSc-pHI?
  - Which parameters of Cardiac Scintigraphy are used to diagnose SSc-pHI?
  - Which alterations detected on Cardiac Scintigraphy are useful to diagnose SSc-pHI?
  - Is SPECT used to diagnose SSc-pHI?
  - Which parameters of SPECT are used to diagnose SSc-pHI?
  - Which alterations detected on SPECT are useful to diagnose SSc-pHI?
  - Is PET used to diagnose SSc-pHI?
  - Which parameters of PET are used to diagnose SSc-pHI?
  - Which alterations detected on PET are useful to diagnose SSc-pHI?

- Peripheral blood Biomarkers
  - Are blood biomarkers used to diagnose SSc-pHI?
  - Which blood biomarkers are used to diagnose SSc-pHI?
  - What cut-off with respect to a blood biomarker is useful to diagnose SSc-pHI?

- Coronary angiography/arteriography
  - Is Coronary angiography/arteriography used to diagnose SSc-pHI?
  - Which parameters of Coronary angiography/arteriography are used to diagnose SSc-pHI?
  - Which alterations detected on Coronary angiography/arteriography are useful to diagnose SSc-pHI?

- Cardiac Magnetic Resonance (CMR)
  - Is CMR used to diagnose SSc-pHI?
  - Which parameters of CMR are used to diagnose SSc-pHI?
  - Which alterations detected on CMR are useful to diagnose SSc-pHI?

- Electrocardiography (ECG)/ 24h Holter monitoring / stress ECG.
  - Is ECG used to diagnose SSc-pHI?
  - Which parameters of ECG are used to diagnose SSc-pHI?
  - Which alterations detected on ECG are useful to diagnose SSc-pHI?

- Echocardiography
  - Is Echocardiography used to diagnose SSc-pHI?
  - Which parameters of Echocardiography are used to diagnose SSc-pHI?
  - Which alterations detected on Echocardiography are useful to diagnose SSc-pHI?

- Other tests
  - Are other tests used to diagnose SSc-pHI?
  - Which parameters of Other tests are used to diagnose SSc-pHI?
  - Which alterations detected on other tests are useful to diagnose SSc-pHI?

• Research string: same as used for the first SLR, see section 4.b.

• Performed on three databases: EMBASE, Pubmed, Web of Science.

• Definition of the timing of publication: from inception to 31/12/19.

• Inclusion Criteria: articles on adult patients, affected by Systemic Sclerosis or enrolled in cohorts in which SSc patient data could be extracted / evaluated separately, cardiac involvement or cardiac evaluation as primary target of the work, articles with case series ≥ 10 patients, articles in English / Italian / Romanian / Greek / Arabic / Serbo-Croatian.

• Exclusion criteria: non-human studies (pre-clinical, genetics, in vitro), pediatric subjects, articles with patients suffering from overlap syndromes, case series <10 patients, secondary cardiac involvement, article in a language other than those listed above, full -text not available, another reason why the examiner considered the work not to be included (to be specified), duplicates, literature reviews (after careful checking of the bibliography for any articles not included in the evaluation).

• Preparation of a CRF (Case Report Form) on Excel computer support, to support the extraction and processing of data.

The methodology for the selection of the manuscript was the same applied to the first SLR, see section 4.b.

### 4.f. Methodology of Meeting 2: creating a consensus guidance

The results of the second SLR were presented to the Experts Committee during three meetings, covering different topics (Laboratory and ECG for the first; ECHO for the second, CMR and other tests for the third). During each session, the data were presented reporting separately if the studies included patients with previously diagnosed or high suspicion of heart involvement (therefore with diagnostic/monitoring purposes) or without (therefore screening purposes). If reported, the comparison with the control group was also presented.

Following each session's presentation, the data were discussed by the Expert Committee, that was then asked to specifically indicate which of the discussed tests/parameters they would suggest to be performed, in which category of patients and when (both in terms of timing in the disease course and frequency during the follow-up evaluation). In addition, previously proposed protocols for laboratory assessments (18), transthoracic resting Echo (21) and CMR (22) where used as a basis, asking the Expert Committee to indicate if they would modify the protocol by adding or removing some assessment/parameter or change the timing of their application, in the light of the SLR results.

The results of each meeting were then summarized into statements by the Core Leadership Team. The overall consensus guidance document was then reviewed and commented by the Expert Committee during two consecutive meetings: during the first, the statements were reviewed and discussed in terms of content, using the Nominal Group Technique, as previously

described (see section 4.d.). During the second meeting, the revised statements were finalized in terms of clarity and voted upon for agreement, with a scale ranging from 1 (=strongly disagree) to 10 (strongly agree). Each statement required a mean agreement ≥7/10 and agreement ≥7 from ≥70% of voters to be included in the final version of the document.

### 4.g. Real-life retrospective application of the consensus guidance

The scientific application of the Consensus Guidance was performed during the academic stay at the Department of Rheumatology, University Hospital Zurich, University of Zurich.
The local cohort of SSc patients is enrolled in the European Scleroderma Trials and Research (EUSTAR) group database and can be exploited for research purposes.
It already includes most of the demographic, clinical, laboratory, instrumental assessments and therapies used for the treatment of SSc patients.

The databased was censored at July 31, 2020 and exported in Excel Format.

Through manual checking of the patients' files, the following items were collected ex novo:

- Medical history: previous Coronary Arteries Disease (CAD), previous non-ischemic cardiac disease (related and not related to SSc), recent history of cardio-specific signs and symptoms (syncope, chest pain, leg edema)
- Laboratory parameters: high-sensitivity troponin T (hsTnT)
- Second and third level cardiac assessments: cardiology specialist consultation, Holter ECG, stress-ECG, stress-ECHO, cardiac MRI, SPECT, PET, myocardial scintigraphy, endomyocardial biopsy.
- Cardio-vascular treatments: alpha-receptors blockers, beta-receptors blockers, calcium channel blockers, angiotensin receptors blockers (ARB), angiotensin converting enzyme inhibitors (ACEi), platelet aggregation inhibitors, oral anti-coagulant, diuretics.
- Outcomes and date of outcome: diagnosis of myocarditis, pericarditis, arrhythmia, need for anti-arrhythmic medication, congestive heart failure, need for intravenous diuretics, need for immunosuppression (initiation or titration) for cardiac disease, death.

At the same time, missing data for the following variables already part of the database were searched and collected, if identified:

- Medical history: recent history of cardio-specific signs and symptoms (dyspnea NYHA functional status, palpitations)

- Physical examination: heart rate, systemic arterial pressure.
- Laboratory parameters: creatine-kinase (CK), N-terminal fraction of the pro-peptide natriuretic B (NT-proBNP)
- First level assessments: resting transthoracic ECHO, resting ECG.

Descriptive analysis was used to show the prevalence of disease related manifestations, performance of tests and occurrence of outcomes, and presented as number (%), mean ± SD or median (IQR). Odds Ratios (OR) were used to present the risk carried by each predictor, accompanied by 95% Confidence Interval (95% CI). ROC curve analysis was used to evaluate the performance of the different models created for the prediction of the outcome, and presented as Area Under the Curve (AUC). Significance level was set at 5% ($p<0.05$).

To test the prevalence of SSc-heart involvement and SSc-pHI (Aim 5.f.i.), the data were modelled to isolate primary from secondary SSc cardiac involvement. This allowed the creation of data on the whole cohort (targeting SSc heart involvement, therefore primary, secondary and mixed) and the sub-group without the leading causes of secondary SSc-heart involvement (targeting SSc-pHI, both as isolated primary or mixed). Given the longitudinal prospective nature of the database, including repeated assessments over time, the impact of covariates on binary outcomes (SSc-cardiac involvement) was tested through General Linear Mixed Model (GLMM).

To test the impact of SSc-heart involvement and SSc-pHI on mortality (Aim 5.f.ii), we analyzed different general population and SSc-specific risk factors, considering the last available visit of each patient as time-point. Logistic Regression considering mortality as outcome, was used to establish the association of co-variates (including SSc cardiac involvement) with mortality.

To achieve Aim 5.f.iii, general population and SSc-specific risk factors were modelled in a GLMM, considering SSc-pHI as outcome. This determined the creation of a model to predict the presence of SSc-pHI, as a basis to test the added value of the consensus guidance to clinical practice.

To achieve Aim 5.f.iv, we first tested the prevalence of the use of the tests/parameters suggested in the Consensus guidance; then, we divided the visits into screening, diagnosis and monitoring of SSc-pHI. Consequently, we tested different prediction models (risk factors and physical examination – Basic model; risk factors, physical examination, medical history, ECG, ECHO and NT-proBNP – the Detect-like Model; risk factors, physical examination, medical history, ECG, Echo, NT-proBNP, hsTNT, CK, ESR/CRP. The three models were

tested first in the whole population with SSc-heart involvement as outcome (and separated according to the screening/diagnostic purpose), then in the sub-group depurated from secondary heart involvement causes with SSc-pHI as outcome (first the whole subgroup, then again separated into diagnostic and screening purposes groups). Given the repeated observations of the same patients over time, the models were obtained using GLMM regression method.

For aim 5.f.v, we considered the second and third level assessments targeting the heart which were performed following the annual visit. Again, we created a basic model, a Detect-like and a Consensus model, to test the impact of different first level algorithm on the request of any second/third level assessment. As for aim 5.f.iv, the models were separately tested in the whole group, the subgroup without secondary causes, and respectively according to screening or diagnosis purposes, still using the GLMM regression method. In addition, we tested the added value of the second/third level tests (named Consensus Plus model) versus the Detect-like and the Consensus models, in predicting the presence of SSc-pHI cases, still using the GLMM regression model.

Finally, for the aim 5.f.vi, we tested the association of exposure to certain cardio-active medication on the diagnosis of SSc-heart involvement or SSc-pHI events after the visit (before the next one), and their possible effect on mortality. The former was tested using the GLMM regression model and including all the visits of each patients, the latter through a Logistic Regression model testing the ongoing medications at last visit as covariates.

## 5. Results

### 5.a. Patient Interviews: feelings and perceptions

Interviews were conducted over telephone on 4 patients, who volunteered to participate anonymously. The patients were recruited from the Rheumatology Unit, Departement of Geriatric Medicine, Careggi University Hospital of Florence, Italy. They were all affected by some form of SSc-pHI. The transcriptions of the interviews are shown below.

**PILOT INTERVIEW 1**

1. Let's talk about the time you started having your heart problem.
    a. What did you feel? *To be honest, I never experienced real problems, every now and then some weird squeezing, some sort of vibration in my chest, elbows and thighs, as if my mobile was vibrating. Later on, I felt short of breath, some burning feeling and felt my heart was beating funny.*
    b. How did it make you feel? *I had no particular feeling about it as I was more worried about other problems I was going though, such as pain in other parts of my body.*
    c. When did it occur? Did it occur repeatedly? Was there anything you associated as a cause? Anything making it better or worse? *I realised no association with anything, at the beginning I did not realize that much being connected with it, except for this random fast heart beating. Nothing was causing it or making it worse or better, it was just there random.*
    d. What did you do about it? *Initially I did not talk about it, mostly because people did not believe in what I was feeling, even if then I was admitted every time I saw doctors about these issues.*
    e. Did you talk to someone soon? Was it your doctor/nurse or a family/friend? *I initially spoke with my colleagues, friends and family, but I had the feeling they minimized. I thought this was because it was not something they could see from outside; people see you in your whole body, that was not something they could see or perceive from outside.*
    *f.* Did you do it soon or wait until severe? *I used to report these issues soon when I felt them, but people did not consider me that much; I was smiling from outside and this may be the reason why it got minimized, in particular in my family environment, where many people did and have not even accepted my condition.*
2. Thinking about the time you were diagnosed,

a. How did you feel when you were told? Did you have any feeling or expectation for the future regarding it? *When I was told about my heart issues, I felt like I was slowed and I was going with the break (of the car) pushed. Initially I told myself I could still make many things and that I could have lived with it, but also cope with not being possible for me to do certain things such as biking, running or going to the beach. I pleased myself just by going out with friends and seeing them, which were things I was not told to avoid, and therefore I thought I could handle it all just by taking pills. When I had my first cardiac DC shock and I was later told I could be a candidate for heart transplant, I cried all the afternoon. I had been in perfect health for all my life and my acceptance was different compared to that of one person who had been sick for all life. For this kind of people, a certain solution, even if drastic, could bring back light in their eyes. When I was later told to take it's an opportunity and not as a court sentence, I look behind and saw friends I had already lost, then I considered I could have made it myself without undergoing the transplant and I would have improved. I was looking at old people having tours in my city, as tourists, climbing up hills like Olympic heroes, OMG such strong people, as it was absolutely impossible for me to do it and it was normal for me not do to it while it was normal for others to make it. By the way, I felt protected by the fact I had been undergoing so many tests even if I had had no symptoms, which made me feel somehow protected and looked after by my doctors.*

**PILOT INTERVIEW 2**

1. Let's talk about the time you started having your heart problem.
    a. What did you feel? *In general, I used to feel tired and fatigued, as I never used to. I blamed I had just started going to the gym and I was doing exercises the wrong way. But that was not as feeling tired after gym, it was something long lasting, which was not ending. Then I started feeling accelerated heartbeat.*
    b. How did it make you feel? *Initially I blamed myself for being quite an anxious person, but then as things were not getting better, I felt hesitant about it, as if I felt something was going wrong.*
    c. When did it occur? Did it occur repeatedly? *It had been ongoing for about two months, after I started going to the gym, and I felt it continuously in all the joints.*
    d. Was there anything you associated as a cause? Anything making it better or worse? *I found no specific association with any action or activity; as I was not a trained sporty person, I blamed myself for pushing too hard in the gym. But then I started feeling my legs week and I had to seat all the time; when I had to walk*

*to the gym, which is like 10 minutes from where I live, it took me 45 minutes, as I had to stop frequently to rest, as if something was blocking my movements.*

e. What did you do about it? Did you talk to someone soon? Was it your doctor/nurse or a family/friend? *Initially I did not give it so much importance, I used to think it would have stopped. Then I started thinking about it to my mother and she brought me to the family doctor. When I spoke to him about it, he told my mother she was exaggerating.*

f. Did you do it soon or wait until severe? *It never got severe, fortunately.*

2. Thinking about the time you were diagnosed,
    a. How did you feel when you were told? *On one hand, I felt reassured when I was told this was due to scleroderma, my disease, and not related to other problems or diseases. I know this sounds a bit masochist, but i felt like it was something that could happen in the disease course, therefore reassured I did not suffer from an additional condition.*
    b. Did you have any feeling or expectation for the future regarding it? *I am coping better with it now, since I started taking drugs for it and they are working, and I am ending up not paying too much attention to it. Seeing that the treatment is giving me good results I try to be positive, for what I can.*

**PILOT INTERVIEW 3**

1. Let's talk about the time you started having your heart problem.
    *a.* What did you feel? *At the beginning I had no symptoms at all. When I was first told about having heath issues related to scleroderma. I was undergoing assessments for haematopoietic stem cell transplantation. I had no feelings or perceptions at all about it, but then the doctors made additional tests and they saw I already das heart problems. I could not believe it, but they finally agreed to do the HSCT to me anyway and that I would have been further tests afterwards. Later I started feeling palpitations, quite random, but I associated it to anxiety problem and the burden of workload and its rhythm.*
    b. How did it make you feel? *I was a bit afraid, a bit anxious, a feeling if I was short of breath.*
    c. When did it occur? Did it occur repeatedly? *Nothing happened until August this year, when my cardioverter first gave me a shock, which happened again last October.*
    d. Was there anything you associated as a cause? *Sincerely not, the first time I had this shock I was coming from a very stressful event, while the second time i was at home preparing pizza very quiet.*

e. What did you do about it? *I went to AE, spent the night in there the first episode, while I was admitted after the second episode.*
f. Did you talk to someone soon? Was it your doctor/nurse or a family/friend? Did you do it soon or wait until severe? *I spoke to my husband and we went straight to the AE department close to home.*

2. Thinking about the time you were diagnosed,
    a. How did you feel when you were told? *I felt very sceptic, as I had not symptoms at all at the beginning; but then I said myself "ok, let's have the defibrillator implanted", although I was still a bit surrendered as I was globally feeling ok.*
    b. Did you have any feeling or expectation for the future regarding it? *It was not causing me particular anxiety or stress at the beginning; but now, since I had these two events last year, I am afraid on going far away, such as going abroad on holidays. For the problem itself, I think it is a matter of chance and you have to trust destiny, I don't put myself down and don't cry on myself, I take things the way they go.*

**PILOT INTERVIEW 4**

1. Let's talk about the time you started having your heart problem.
    *a.* What did you feel? *Initially I started paying attention on my heart as I was feeling my beats being irregular, as if some of them was missing, like a hit on my chest. When their number increased with time, I started feeling very tires.*
    *b. How did it make you feel? Initially I said myself something like "hey, what's happening!?" but I did not limit myself regarding any activity, I did not stop because I was afraid of what could happen. Maybe I was simply paying more attention listening to myself and my body, as I usually don't pay attention to many things. Despite this, no specific physiologic consequence.*
    c. When did it occur? Did it occur repeatedly? *At the beginning it was a random rare feeling, same as when you are anxious or excited, and I thought this was due to the fact that I still had not accepted the diagnosis of scleroderma I was given 1 year before. I was feeling generally ok though, therefore not paying too much attention to it, until they become more frequent.*
    d. Was there anything you associated as a cause? Anything making it better or worse? *Nothing really associated, the irregular beat does what it wants.*
    e. What did you do about it? Did you talk to someone soon? Was it your doctor/nurse or a family/friend? Did you do it soon or wait until severe? *I initially spoke to my husband about this feeling, despite the fact I was not recognizing*

*it properly, so I got used to it. Then I referred it to my doctors and they started doing many-many additional tests to me.*

2. Thinking about the time you were diagnosed,
    a. How did you feel when you were told? *Once I reported my symptoms to my rheumatologist, I felt the problem was solved. I used to be very irresponsible, even when I was told I had to get a pacemaker implanted. But generally, I felt better than when I did not know clearly about it, as I finally knew where to go and how to act to solve it. I said myself "ok, let's have the pacemaker implanted", also because I was told it was a security procedure to prevent the consequences of the haematopoietic stem cell transplant, I was getting prepared for.*
    b. Did you have any feeling or expectation for the future regarding it? *I take it very easily, I am in peace, maybe I am crazy, but I am ok like this.*

These pilot interviews confirmed the applicability of the pre-set questions and their efficacy in bringing out patients' feelings and emotions about SSc-pHI. A variable mix of surprise, uncertainty and anxiety emerged from these interviews.

These pilot interviews would have been the base to create Focus Groups, another qualitative research methodology that considers discussion between participants on a certain topic, letting every participant express the personal opinion. As a result, similar to the interviews, recordings are transcribed and analysed with dedicated software to identify the most prioritized emerged concepts. As per previous experience, it was planned to perform 6 Focus Groups, each with a maximum of 5-6 participants, conducting 3 in the USA (University of California in Los Angeles) and 3 in the UK (Manchester University). This would have also ensured a certain ethnic and geographical variability, to make the results more applicable. Unfortunately, this excluded Italy from the procedure due to the need to include patients with English as their mother language. Although the process had continued until the submission of the documentation to the ethics committee of the University of Miami (OH - USA), unfortunately the Coronavirus Pandemic did not make it possible to put these meetings into practice on time for the next steps of the project.

Therefore, the concepts derived from the pilot interviews and the active participations of the Patient Research Partner were used to enrich the scientific and Experts' inputs with the voice of the patient.

### 5.b. First systematic literature review: heart involvement in SSc

Overall, 2953 publications were retrieved from the three databases: these underwent evaluation by removal of duplicates, leading to the exclusion of 725 manuscripts; 1868 articles were subjected to title/abstract evaluation. This led to the selection of 251 articles, whose full texts were then evaluated. From the latter, 172 scientific publications were included in the data extraction phase (see PRISMA graph - Figure 2). The reproducibility exercise was conducted on the first 5 articles derived from the selection obtained a level of agreement of 93%.

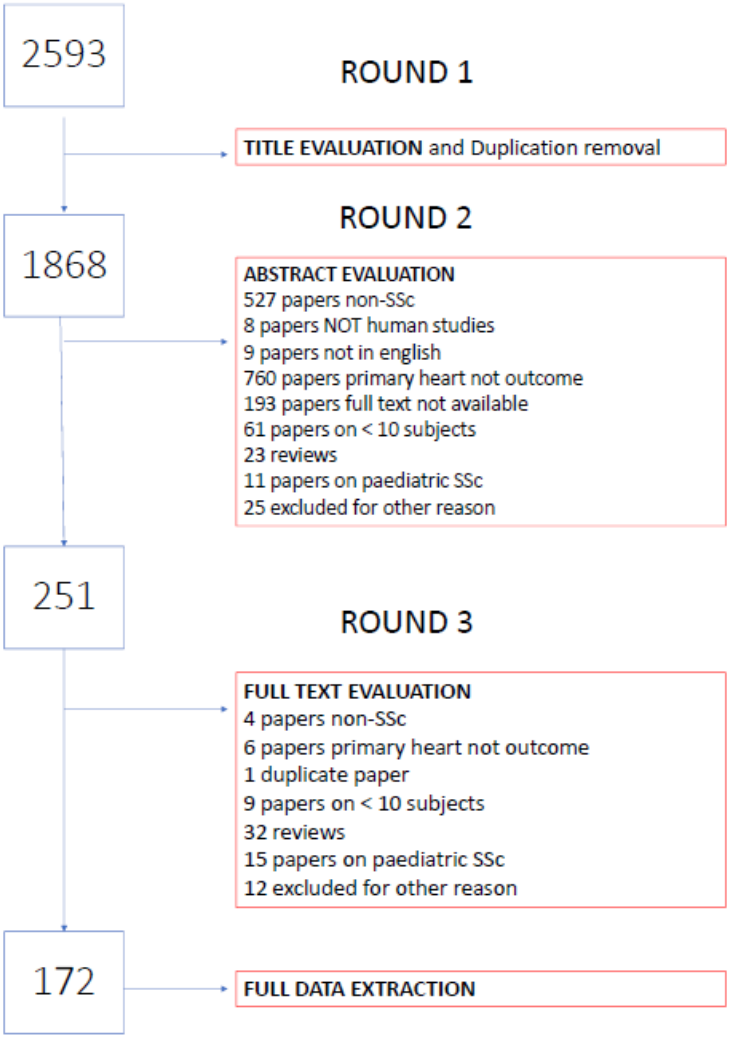
Following the completion of the data extraction, a descriptive analysis of the data was performed, divided for the domains initially set. This led to highlighting how variable and heterogeneous was the prevalence of the individual parameters examined and how scarce was the evidence present in the literature for many of them.

The 172 articles were largely represented by cross-sectional (n=81), prospective (n=49), retrospective (n=23) studies, case series (n=4), studies with an unspecified design (n=4), clinical trials (n=2), case-control studies (n=1).

In total, these studies involved 23,276 patients, predominantly female (n=19458, 82.1% of 166 articles), classified as SSc through the ACR / EULAR 2013 criteria (n=41), or ARA 1980 criteria (n=73), through multiple sets of criteria (n=35) or through unspecified criteria (n=23).

Patients were mostly enrolled in the studies as consecutive cases (n = 112), as subgroups of patients without cardiac involvement or PAH or symptoms suspected for cardiac involvement (n=47), with cardiac involvement or known cardiologic symptoms (n=10) or as autopsy studies (n = 3).

Figura 2 – PRISMA chart of the evaluation and selection of manuscripts for the first systematic literature review.



Data on the “Symptoms” domain were obtained from 60 (30.9%) articles, in which 2678/4091 patients (65.5% from 29 articles) reported unspecified symptoms. Dyspnea and palpitation represented, otherwise, the most frequently reported specific symptoms (table 1).

Table 1. Data extracted for the “Symptoms” domain and its variables, derived from 55 papers.

| **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) |

The “Clinical Signs” domain was populated through data from 22 (12.8%) articles, in which no-nspecific clinical signs were reported for 32/225 (14.2%) patients from 6 articles. It was interesting to observe that none of the remaining manuscripts reported the presence of cyanosis and, in any case, a low prevalence of the remaining specific clinical signs (Table 2).

Table 2. Data extracted for the “Signs” domain and its variables, derived from 15 papers.

| **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 Congestive Heart Failure | 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) |

The histopathological domain contained a great deal of information (Table 3), although it was the least frequently analyzed in the articles (15.9%). Despite the small number of reports, the simultaneous presence of inflammatory and fibrotic phenomena of different locations and histotypes emerged.

Table 3. Data extracted for the “Pathological changes” domain and its variables, derived from 13 papers.

| **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)<br>Lymphocytic myocardial infiltrate in 1 patient (54) |
| Fibrosis | 11 | (27, 52, 54, 57, 70, 83-88) | 187 / 322 (58 %) | from 11 papers (27, 52, 54, 57, 70, 83-88) | Myocardium/endocardium in 26 patients (70)<br>Myocardium in 60 patients (52, 84-86)<br>Endocardium in 7 patients (86)<br>Midwall 21 patients<br>Epicardial in 12 patients (86)<br>Perivascular in 17 patients (27, 54)<br>Bi-ventricular in 3 patients (88)<br>Mean degree 12.3 ± 6.3 % in 20 patients (83)<br>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 | (85, 87) | 8 / 55 (15 %) | from 2 papers (85, 87) | Coronary atherosclerosis in 5 patients(85)<br>Myocardial vessels in 3 patients (87) |
| 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, 87) | 87 / 184 (47 %) | from 4 papers (42, 70, 84, 87) | Focal or diffuse fibrous or fibrinous pericarditis in 17 patients (70)<br>Fibrinous, fibrous pericarditis and pericardial adhesions in 31 patients (84)<br>Pericarditis with chronic inflammatory cells in 31 patients (87)<br>Pericardial fibrosis in 4 patients (42)<br>Granulomatous pericarditis in 2 patients (42)<br>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 Sinus-Atrial node fibrosis in 13 pts (70)<br>Interruption in proximal bundle branches in 2 patients (70) |

Information on the “Anatomical” domain was obtained from about three quarters of the evaluated literature (78.5%), showing how practically all cardiac sites and structures can be involved in SSc (table 4).

Table 4. Data extracted for the “Anatomical site involved” domain and its variables, derived from 138 papers.

| **Anatomical site involved** | **N ° papers** | **References** | **N° Patients** | **References** | **COMMENTS/DETAILS** |
|---|---|---|---|---|---|
| Heart size | 54 | (23-27, 34, 37, 44-46, 54, 56, 58, 59, 69, 70, 76, 80, 83, 85, 86, 88-119) | 247 / 1289 (19 %) | from 26 papers (37, 44-46, 54, 56, 58, 59, 69, 70, 76, 83, 85, 98, 103, 104, 106, 108, 109, 113-117, 119) | Increased heart weight in 1 patient (85)<br>Enlarged cardiac shadow in 31 pts (56, 98)<br>Increased Cardio-thoracic ratio in 35 patients (58, 59, 103, 106)<br>Cardiomegaly in 29 patients (37, 76, 113) |
| Left atrium (LA) | 40 | (24, 31, 44, 55, 59, 69, 76, 79, 80, 86, 88, 90, 92-97, 99, 101, 102, 104, 105, 107-109, 115, 117-127) | 129 / 1090 (12 %) | from 14 papers (44, 59, 69, 76, 86, 88, 90, 94, 104, 115, 117, 119, 125, 126) | Enlarged LA in 11 patients (104) |
| Left ventricle (LV) | 91 | (23-31, 34, 36, 38, 39, 42, 44, 46, 51, 52, 54, 56-60, 68-70, 72-74, 76, 78-80, 83, 85, 88-105, 107-110, 112, 114-117, 119, 120, 122-126, 128-148) | 1140 / 10571 (11 %) | from 52 papers (28, 30, 34, 39, 42, 44, 46, 51, 52, 54, 58-60, 69, 70, 72, 76, 83, 85, 88, 90, 98, 103, 104, 108-110, 114-117, 119, 124-126, 128, 130-134, 136, 139-141, 143, 145-148) | LV/RV Hypertrophy in 36 patients (70)<br>LV/RV dilation in 39 patients (83, 114)<br>LV Hypertrophy in 42 patients (44, 54, 115, 116)<br>LV enlargement in 24 patients (46) |

| | | | | | |
|---|---|---|---|---|---|
| Right atrium (RA) | 14 | (24, 44, 79, 80, 85, 93, 99, 101, 105, 107, 126, 134, 149, 150) | 22 / 96 (23 %) | from 2 papers (44, 126) | |
| Right ventricle (RV) | 50 | (23-27, 29, 30, 37, 42, 45, 51, 55-60, 68-70, 73, 76, 79, 80, 83, 86, 88, 92, 93, 95, 97-101, 104, 105, 107, 110-112, 114, 115, 117, 122, 124, 131, 134, 151) | 262 / 1340 (20 %) | from 26 papers (29, 30, 37, 42, 45, 51, 58-60, 69, 70, 76, 83, 86, 88, 104, 105, 107, 114, 115, 117, 124, 131, 134, 151) | LV/RV Hypertrophy in 36 patients (70)<br>LV/RV dilation in 39 patients (83, 114) |
| Interventricular septum | 33 | (27, 28, 31, 38, 45, 56, 60, 69, 72, 76, 79, 80, 83, 89, 95, 99, 100, 102, 104, 105, 107-109, 116, 117, 119, 120, 124, 129, 133-135, 148) | 112 / 1061 (11 %) | from 12 papers (38, 45, 60, 69, 72, 76, 107, 116, 117, 124, 133) | |
| Valves | 41 | (25, 27, 28, 37, 43, 56, 59, 70, 76, 79, 80, 84, 86, 88, 91, 94, 95, 99, 101, 104-106, 108, 109, 111, 115, 117, 119, 124-127, 131, 133-135, 140, 141, 143, 144, 152-154) | 386 / 1051 (37 %) | from 22 papers (27, 37, 43, 70, 76, 84, 88, 94, 104, 106, 115, 117, 124-126, 131, 140, 141, 143, 144, 153, 154) | |
| Mitral Valve | 34 | (25, 27, 28, 37, 41, 43, 53, 56, 59, 76, 79, 80, 84, 86, 94, 95, 99, 105, 106, 108, 115, 117, 119, 124-126, 131, 133-135, 140, 143, 152, 153) | 339 / 1529 (22 %) | from 25 papers (27, 28, 37, 41, 43, 53, 56, 59, 76, 84, 86, 94, 99, 106, 115, 117, 125, 126, 131, 133, 135, 140, 143, 152, 153) | |

| | | | | | |
|---|---|---|---|---|---|
| Tricuspid Valve | 23 | (25, 37, 41, 53, 56, 79, 80, 84, 95, 101, 104-106, 111, 115, 117, 124, 131, 134, 135, 140, 143, 154) | 269 / 860 (31 %) | from 17 papers (37, 41, 53, 56, 84, 101, 104, 106, 115, 117, 124, 131, 134, 135, 140, 143, 154) | |
| Pulmonary Valve | 12 | (25, 41, 59, 79, 95, 104-106, 111, 115, 134, 135) | 12 / 326 (4 %) | from 5 papers (41, 59, 104, 106, 115) | |
| Aortic Valve | 26 | (25, 27, 37, 41, 59, 79, 80, 84, 94, 95, 99, 104-106, 109, 115, 117, 125, 131, 133-135, 140, 152, 153) | 132 / 1194 (11 %) | from 16 papers (27, 37, 41, 59, 84, 94, 99, 106, 115, 117, 125, 131, 133, 140, 152, 153) | |
| Coronary vessels | | | | | |
| Epicardial | 13 | (30, 35, 52, 54, 70, 80, 84, 85, 88, 91, 117, 126, 155) | 43 / 177 (37%) | from 6 papers (30, 54, 70, 84, 117, 126) | |
| Intramural | 15 | (29, 30, 33, 35, 44, 52, 61, 70, 79, 80, 88, 129, 137, 138, 155) | 98 / 338 (29 %) | from 10 papers (29, 30, 33, 35, 44, 52, 61, 79, 137, 138) | |
| Sinus-atrial node | 14 | (25, 28, 32, 43, 48, 67, 70, 80, 95, 106, 115, 154, 156, 157) | 228 / 726 (31 %) | from 10 papers (28, 32, 43, 48, 67, 70, 95, 154, 156, 157) | |
| Atrium-ventricular node | 18 | (25, 28, 44, 47, 52, 58, 67, 70, 80, 94, 95, 106, 113, 115, 117, 156) | 129 / 720 (18 %) | from 13 papers (28, 44, 47, 52, 58, 67, 94, 95, 106, 113, 115, 117, 156) | |
| Conduction system | 48 | (24, 25, 28, 29, 33-36, 39, 44-48, 52, 56, 59, 60, 67, 70, | 683 / 2734 (25 %) | from 42 papers (24, 28, 29, 33-36, 39, 44-48, 52, 56, 59, 67, | |

| | | | | | |
|---|---|---|---|---|---|
| | | 73, 76, 77, 80, 86, 88, 93-95, 98, 102, 103, 106, 113, 116, 117, 124, 126, 132, 133, 135, 144, 148, 154, 157-160) | | 70, 73, 77, 86, 88, 94, 95, 98, 103, 106, 113, 116, 117, 124, 126, 132, 133, 135, 144, 148, 154, 157-160) | |
| Epicardium | 8 | (38, 70, 79, 80, 86, 105, 145, 161) | 26 / 230 (11 %) | from 3 papers (38, 86, 145) | |
| Endocardium | 8 | (38, 60, 79, 80, 86, 105, 137, 161) | 18 / 331 (5 %) | from 5 papers (38, 60, 86, 137, 161) | |
| Myocardium | 43 | (26, 36, 38, 44, 46, 51, 53, 57, 60, 61, 70, 73, 75, 77, 79, 80, 83-86, 88, 105, 114-118, 125, 132, 137, 138, 140, 144-146, 148, 160-166) | 548 / 1999 (27 %) | from 35 papers (38, 44, 46, 51, 53, 57, 60, 61, 70, 73, 77, 83, 86, 88, 115-117, 125, 132, 137, 138, 140, 144-146, 148, 160-166) | |
| Pericardium | 62 | (25, 27-30, 32-38, 41-45, 51, 53, 56, 59, 60, 62, 64, 69, 70, 76, 79-81, 83, 84, 86, 87, 94, 95, 98, 99, 104-106, 113-115, 117, 124, 125, 131-135, 141, 144, 152, 153, 158, 160, 161, 165, 167, 168) | 511 / 3216 (16 %) | from 53 papers (28-30, 33-38, 41-45, 51, 53, 56, 59, 60, 64, 69, 70, 76, 81, 83, 86, 87, 94, 95, 98, 99, 104, 106, 113-115, 117, 124, 125, 131-133, 135, 141, 144, 152, 153, 158, 160, 161, 165, 167, 168) | |

The “Cardiac Physiology” domain showed many data, coming from the overwhelming majority of the evaluated works (91.3%). Although there were extremely variable definitions of the impairment of physiological cardiac functions, it emerged that SSc-pHI can manifest itself with both contraction / relaxation, perfusion and rhythmic alterations (Table 5).

Table 5. Data extracted for the “Altered Physiological Function” domain and its variables, derived from 153 papers.

| **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, 89-109, 111-125, 127-142, 144, 145, 148, 151, 153, 160, 161, 165, 168-177) | 1182 / 16554 (7 %) | from 55 papers (29, 30, 33-35, 37, 38, 40, 42, 44, 45, 50-52, 58, 60, 62, 78, 81, 83, 90, 107-109, 114-117, 119, 124, 125, 128-136, 139, 140, 144, 145, 151, 153, 160, 161, 165, 172-174, 177) |
| Diastole / filling / relaxation / repolarization | 90 | (25, 31, 32, 37, 43, 44, 48, 50, 51, 55-57, 59, 62, 63, 68, 71, 80-83, 86, 89-94, 96, 97, 99-105, 107-112, 115-127, 129-131, 133-136, 139-143, 149, 152, 153, 158, 165, 168-181) | 2198 / 9349 (24 %) | from 56 papers (25, 26, 32, 37, 43, 44, 48, 50, 51, 59, 62, 63, 71, 81-83, 86, 90, 101, 103, 107-110, 115-119, 124-127, 130, 131, 133-136, 139-141, 143, 152, 153, 158, 165, 168, 172-174, 176-179, 181) |
| Rhythm conduction | 51 | (25, 26, 28, 32, 33, 35, 36, 39, 43-48, 50, 52, 54, 58, 60, 61, 63, 67, 70, 72, 86, 88, 93-95, 98, 102, 103, 106, 113, 115-117, 124, 126, 129, 132, 135, 144, 148, 154, 157, 158, 179, 182, 183) | 799 / 5877 (14 %) | from 41 papers (26, 32, 33, 35, 36, 39, 43, 44, 46-48, 50, 52, 54, 58, 61, 63, 67, 70, 86, 88, 94, 98, 103, 106, 113, 115-117, 124, 126, 132, 135, 144, 148, 154, 157, 158, 179, 182) |
| Rhythm automaticity | 33 | (28, 32, 43-46, 48, 56, 59, 63, 67, 71, 72, 74, 80, 88, 102, 106, 110, 113, 115-117, 126, 144, 148, 154, 156, 157, 159, 173, 179) | 411 / 1615 (25 %) | from 28 papers (28, 32, 43, 45, 48, 56, 59, 63, 67, 71, 74, 88, 102, 106, 110, 113, 116, 117, 126, 144, 148, 154, 156, 157, 159, 173, 179) |
| Myocardial perfusion | 36 | (29-31, 33, 35, 36, 38, 43, 51, 52, 56, 61, 69, 72, 75, 77, 79, 88, 115, 117, 137, 138, 140, 151, 155, 162, 166, 169, 172, 173, 175, 179, 184, 185) | 351 / 940(37 %) | from 26 papers (29, 30, 33, 35, 36, 38, 43, 52, 56, 61, 69, 72, 75, 77, 79, 88, 117, 137, 138, 140, 151, 155, 162, 172, 173) |
| Wall motion | 31 | (25, 29, 30, 33-35, 37, 38, 44, 51, 69, 72, 74, 79, 83, 88, 95, 96, 104, 105, 108, 109, 114, 117, 119, 124-126, 147, 164) | 154 / 638 (24 %) | from 23 papers (29, 30, 33, 35, 37, 38, 44, 51, 69, 72, 74, 83, 88, 95, 108, 109, 114, 117, 119, 125, 126, 147, 164) |
| Valve function | 38 | (25, 27, 28, 37, 56, 59, 79, 86, 90, 94, 95, 99, 104-109, 115, 117, 119, 124-127, 131, 133, 134, 136, 140, 141, 143, 144, 152-154, 161, 168) | 778 / 2213 (35 %) | from 25 papers (27, 28, 59, 86, 90, 94, 99, 104, 106, 115, 117, 124-126, 131, 133, 140, 141, 143, 144, 152-154, 161, 168) |

| | | | | |
|---|---|---|---|---|
| Other function | 8 | | | |
| Response to exercise (heart rate, left ventricle ejection fraction, stroke volume) | 3 | (30, 58, 186) | 26 / 42 (62 %) | from 2 papers (30, 58) |
| Reduced coronary flow reserve | 3 | (89, 187, 188) | 38 / 71 (54 %) | from 2 paper (187, 188) |
| Heart rate variability | 4 | (47-49, 189) | 34 / 34 (100 %) | from 1 paper (49) |

Finally, the "Prognostic" domain showed how cardiac events of variable manifestation and severity could occur, in percentages ranging from 4 to 11% of the population of the few articles that could be analyzed (Table 6).

Table 6. Data extracted for the "Prognostic Outcome" domain and its variables, derived from 36 papers.

| **Prognostic outcome** | **N° papers** | **references** | **N° patients** | **references** |
|---|---|---|---|---|
| Myocarditis | 1 | (162) | 2 / 46 (4 %) | from 1 paper (162) |
| Heart failure | 23 | (52, 57, 65, 70, 74, 76, 77, 88, 114, 131, 133, 136, 144, 145, 152, 165, 167, 177, 180, 190-193) | 138 / 1814 (8 %) | from 15 papers (52, 65, 70, 76, 88, 136, 144, 145, 152, 165, 167, 177, 180, 190, 191) |
| Acute coronary syndrome | 7 | (54, 67, 70, 126, 144, 190, 191) | 29 / 687 (4 %) | from 7 papers (54, 67, 70, 77, 144, 190, 191) |
| Significant arrhythmias | 18 | (46, 52, 54, 57, 70, 71, 76, 77, 117, 126, 144, 152, 167, 174, 175, 177, 190, 191) | 197 / 3106 (6 %) | from 16 papers (46, 52, 54, 57, 70, 71, 76, 77, 117, 144, 152, 167, 174, 177, 190, 191) |
| Sudden death | 11 | (40, 46, 52, 65, 67, 70, 99, 123, 126, 132, 133) | 119 / 1063 (11 %) | from 10 papers (40, 46, 52, 65, 67, 70, 123, 126, 132, 133) |

### 5.c. Meeting 1: Creating the Definition of SSc-pHI

On June 28, 2019, the first face-to-face meeting of the project took place. All members of the Core Leadership Team and the Expert Committee participated, as well as the Patient Research Patients.

The meeting began with the presentation of the abovementioned SLR data, which were provided both on paper and presented orally, as well as of the patients' interviews.

Under the guidance of the methodologist, the meeting was conducted with the NTG, in which space was left for each of the participants to intervene, in consecutive order.

The first phase of the meeting was characterized by 3 rounds of idea generation and concept creation. Each participant expressed, for a maximum of three times, what he/she believed to be his own definition of SSc-pHI or one of its fundamental characteristics, with the possibility of adding a new concept, or of reshaping one already expressed previously.

This first phase led to the generation of 27 statements, which partial overlap of the different concepts. Through a conceptual qualitative analysis, 4 recurring/basic themes emerged, through which the 27 statements were clustered (Table 7):

- Pathogenesis

- Etiology

- Clinical manifestation / instrumental detection

- Timing of presentation

Table 7. Clustering of the statements created during the first round of the nominal group technique meeting.

***A) Pathogenesis (green)***

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

***B) Etiology (yellow)***

5. Cardiac abnormalities directly attributable to SSc
6. Not due to drug induced cardio-toxicity
7. For symptomatic patients, primary is exclusion Secondary is atherosclerosis, ischemic heart, severe kidney, PH
8. Exclude all other heart disease (including infections, ischaemic) to define primary
9. Cardiac abnormalities not entirely explained by other CV and non-CV 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 explaining

***C) Clinical manifestation / instrumental detection (grey)***

16. Systolic or diastolic disfunction, pericarditis or arrhythymias, both symptomatic and asymptomatic, excluding other causes
17. Dysfunction of the heart predominantly caused by SSc
18. Syst/diastolic disfunction or alteration of conduction system excluding other conditions
19. Definition requires all symptoms, signs and physiological measures
20. HF symptoms and exclusion of cardiac and non-cardiac causes
21. Not only HF, but primary arrhythmias and chest pain
22. Signs and symptoms of HF, excluding mimickers
23. Evidence of ventricular ectopy on ECG monitoring and ambulatory monitoring
24. Symptoms to start followed by algorithmic pathway
25. Due to SSc that is clinically meaningful and may be symptomatic or impact on prognosis
26. Valvular disease

D) ***Timing of presentation (light purple)***

27. SSc-pHI may be present at time of disease

A Statement was generated from each cluster, in order to summarize and include the various concepts contained in each group. The four statements then underwent evaluation by all participating members, expressing what, according to them, was the “weight” of the single statement. After calculating the average of the weights attributed by the individual evaluators, the statements were then sorted in descending order.

From these, the statements with priority lower than 70% were excluded (specifically the one coming from cluster D). In addition, the statement from cluster C, the first in order of priority, was split into a main component (as part of the definition) and an appendix to the definition itself (Table 8).

Table 8. Statements and their ranking for the formulation of the definition.

| Cluster | Statement | Mean ranking |
|---|---|---|
| C | *SSc-pHI comprises cardiac abnormalities that are predominantly attributable to SSc rather than other causes (including Non SSc specific cardiac (Atherosclerosis, Ischaemic heart disease Systemic hypertension…) and SSc non-cardiac (PAH, Renal involvement, ILD)* | 90,9 |
| B | *SSc-pHI may be sub-clinical and must be detected and/or confirmed through diagnostic investigation* | 77,3 |
| A | *SSc-pHI pathogenesis comprises one or more of inflammation, fibrosis and/or vasculopathy* | 72,7 |
| D | *Future research agenda: SSc-pHI may be present at time of disease onset* | 50,9 |

A provisional definition of SSc-pHI was therefore proposed, as follows:

**"Primary SSc heart involvement (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 valve disease) and / or SSc non-cardiac conditions (e.g. PAH, Renal involvement, ILD). "**

This definition was unanimously approved by the Expert Panel, the Patient Representative and the Core Leadership Team (Agreement 100%).

In line with the OMERACT criteria for the validation of an outcome measure and with the provisions of the initial project, a partial validation of the definition was carried out, in regards to:

• Face validity - reflects the "intrinsic logic" of the definition itself, how much it "makes sense". The provisional definition was presented to 20 experts (not involved in its creation), who determined that the definition was credible.

• Criterion validity (Consistency) - indicates the comparison between the definition / method used and the gold standard to obtain the same measure. As there is currently no proven definition against which to test the proposed one, the Core Leadership Team decided to test the applicability of the definition by the members of the Expert Panel vs that of the Core Leadership Team. In this case, a correctness in the application of the definition with respect to the "gold standard" of 78 (73-84)% was observed.

• Feasibility - indicates the applicability of the definition itself, specifically the time taken to establish it. This validation was carried out by the members of the Expert Panel participating in the meeting on 7 clinical cases created and approved by the Core Leadership team. Each expert measured the time taken for the evaluation of the clinical case and therefore for the applicability of the definition, with a stopwatch. The median time to establish the applicability of the definition was 60 seconds (IQR 5-300).

• Reliability - reflects the repeatability and reproducibility of the definition, leading to the same result on repeated measurements in the absence of a change in the context or in the condition in which the definition is applied. This part of the validation was conducted regarding both:

o Reproducibility (inter-rater agreement): the assessments of applicability or otherwise of the definition made by the members of the Expert Panel during the F2F meeting. It was analyzed by testing the applicability of the definition on 17 clinical cases submitted to the attention of experts during clinical cases. This calculation was performed using the modified Kappa coefficient, resulting in a moderate agreement between the evaluators, with an average coefficient of 0.56 (95% CI 0.46-1.00) during the first evaluation.

o The inter-observer agreement on the second evaluation of clinical cases was again calculated using the modified Kappa coefficient, demonstrating a good level of agreement, with a coefficient of 0.77 (95% CI 0.47-1.00).

o Repeatability (intra-rater agreement): the members of the Expert Panel applied the definition on the 17 clinical cases on two separate occasions, first during the F2F

meeting and then electronically after about 1 month. During the second evaluation, the cases were presented in random order, different from that of the first evaluation. A moderate agreement was confirmed, with a modified Kappa coefficient of 0.55 (95% CI 0.44-1.00).

o It was interesting to observe how the cases with the highest level of disagreement were those involving patients with both primary cardiac involvement from SSc and secondary cardiac complication related to another conditions or other SSc-associated organ involvement. Furthermore, no statistically significant difference was observed by repeating the analysis for the cardiologist vs non-cardiologist evaluators alone, showing similar level of agreement between the experts of the two groups.

### 5.d. Second systematic literature review: diagnostic tests

A total of 2650 publications were obtained from the 3 databases, subjected to duplicates removal, leading to the exclusion of 736 manuscripts. The remaining 1914 articles were evaluated through title and abstract. This led to the selection of 271 articles, which then underwent a third evaluation on a full text. From the latter, 168 scientific papers were included in the data extraction (see PRISMA graph - Figure 3). Again, the reproducibility exercise performed on the first 5 articles derived from the selection showed a level of agreement of 94%.

The descriptive analysis of the collected, divided by the individual domains initially set, highlighted the variability and heterogeneity of the prevalence of the individual parameters examined, as well as the paucity of evidence present in the for many parameters.

The 168 articles were largely represented by cross-sectional studies (n=70), therefore with decreasing prevalence from prospective (n=50), retrospective (n=23), case series (n=7), studies with unspecified design (n=4), clinical trials (n=2), case-control studies (n=12).

In total, these studies involved 28723 patients, predominantly female (n=23396, 83.3% out of 164 articles, range from 15.1% to 100%), classified as SSc by the ACR / EULAR 2013 criteria (n=45), or ARA 1980 criteria (n=75), through multiple sets of criteria (n=24) or through unspecified criteria (n=24).

Patients were mostly enrolled in the studies as consecutive cases (n=100), as subgroups of patients without cardiac involvement or PAH or symptoms suspected for cardiac involvement (n=54), with cardiac involvement or known cardiologic symptoms (n=11) or involving both (n=3).

A control group was present in 101 articles and represented by:

- age- and sex-matched healthy controls (97 articles with 2964 patients)

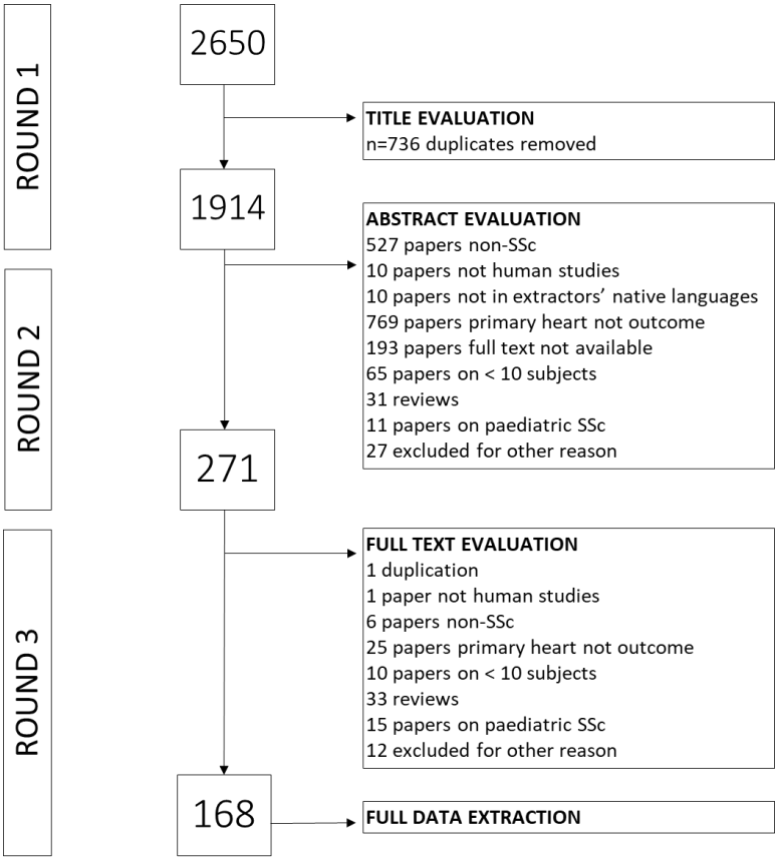
- patients with rheumatoid arthritis and systemic lupus erythematosus (1 article with 13 patients)

- rheumatology patients with arthritis (1 article with 19 patients)

- patients undergoing myocardial bypass or myoma excision (1 article with 10 patients)

- patients with acute coronary disease (1 article on 20 patients).

Figure 3 - PRISMA scheme of the evaluation and selection procedure of scientific articles for the second systematic review of the literature.




The results of the second SLR are reported herein (tables 9-13), divided according to the pre-defined domains used, thus listing the parameters reported for the single method. In addition, the category of SSc patients (c=consecutive, w=with cardiac involvement or cardiac symptoms; w/o= no symptoms or known cardiac involvement) are reported. Data are also highlighted in gray if a control group was present, in green if the comparison was statistically significant and in blue if this was not.

Table 9. Conventional Radiology

Including 1201 patients (28, 30, 33, 35, 37, 39, 47, 53, 54, 56, 58, 67, 69, 72, 73, 77, 79, 81, 86, 98, 102, 103, 106, 113, 132, 135, 137, 156, 162) e 240 controls (56, 87, 102, 106, 110, 122, 156).

- Chest X-ray

| **Finding** | **N° PAPERS** | **References** | **N° PATIENTS** | **References** | **N° controls** | **References** |
|---|---|---|---|---|---|---|
| cardiomegaly | 19 | (28, 33, 37, 53, 56, 58, 67, 69, 72, 73, 77, 98, 102, 103, 106, 113, 132, 135, 137) | 120/1201 (10%) | (28, 37, 53, 56, 58, 67, 69, 77, 98, 103, 106, 113) | 4/88 (4.5%) | (106) |
| Pleural effusion | 2 | (37, 54) | 4/39 (10%) | (37, 106) | Not reported | |
| Signs of pulmonary oedema | 4 | (54, 69, 135, 137) | 10/40 (25%) | (54, 69, 135) | Not reported | |
| Sings of interstitial lung disease | 12 | (33, 35, 37, 39, 53, 54, 58, 67, 69, 81, 135, 137, 162) | 143/455 (31.4%) | (33, 35, 37, 39, 53, 54, 58, 67, 69, 81, 135, 162) | Not reported | |
| Hilar enlargement | 1 | (137) | Not specified | | Not reported | |

- Chest computed tomography

| **Finding** | **N° PAPERS** | **References** | **N° PATIENTS** | **References** | **N° controls** | **References** |
|---|---|---|---|---|---|---|
| cardiomegaly | 1 | (37) | 5/28 (17.9%) | (37) | | |

Table 10. Myocardial scintigraphy

Reported in 26 manuscripts including 1072 patients (29-34, 52, 56, 62, 69, 72, 75, 77, 88, 129, 133, 139, 140, 151, 159, 173, 179, 194) and 128 controls (56, 72, 129, 139, 151, 156, 179).

| **Finding** | **N° papers** | **References** | **N° patients** | **References** | **N° controls** | **References** |
|---|---|---|---|---|---|---|
| Decreased perfusion | | | | | | |
| *At rest* | 5 | (29, 30, 33, 35, 52) | 83/196 (42.3%) | (29, 30, 33, 35, 52) | Not reported | |
| *On stress* | 3 | (32, 56, 88) | 49/105 (46.6%) | (32, 56, 88) | 1/20 (5%) | (56) |
| *Both rest and stress* | 1 | (88) | 3/24 (12.5%) | (88) | Not reported | |
| *Not specified* | 10 | (29, 34, 62, 69, 72, 77, 133, 140, 151) | 113/514 (22%) | (29, 34, 62, 69, 72, 77, 133, 140, 151) | 1/128 (0.7%) | (56, 72, 129, 139, 151, 156, 179) |
| Motion Abnormalities | 6 | (29, 33-35, 69, 139) | 17/73 (23.3.%) | (29, 33, 35, 69) | Not reported | |
| Functional impairment | 10 | (29, 30, 33, 62, 69, 129, 139, 151, 173, 179) | 50/239 (20.9%) | (29, 30, 33, 62, 69, 129, 139, 151, 173, 179) | Not reported | |
| Inflammation | 3 | (29, 75, 194) | 15/75 (20%) | (29, 75, 194) | Not reported | |
| Other | | | | | | |
| *Pathologically increased activity* | 1 | (159) | 7/17 (41.2%) | (159) | Not reported | |
| *Ischaemic ST tract changes* | 1 | (129) | 1/24 | (32) | Not reported | |
| *Improvement after dipyridamole or nifedipine* | 2 | (33, 35) | 43/43 | (54, 122) | Not reported | |

Table 11. Laboratory biomarkers

Derived from 45 manuscripts including 16266 patients (29, 37, 39, 40, 65, 66, 68, 69, 71, 75, 94, 96, 100, 103, 106, 107, 109, 112, 115, 119, 121, 122, 131, 132, 136, 143, 145, 146, 149, 150, 153, 158, 160, 162, 164, 171, 185, 194-201) and 447 controls (40, 66, 68, 107, 109, 119, 122, 149, 164, 196, 198, 201).

| **Finding** | **N° PAPERS** | **N° patients** | **Value/ prevalence in patients** | **N° controls** | **Value/ prevalence in controls** | **Statistically significant difference** | **References** |
|---|---|---|---|---|---|---|---|
| NT-proBNP | 17 | 1383 | | | | | |
| *mean* | 1 | 42 c | 122±135 pg/l | | | | (121) |
| *mean* | 1 | 50 c | 275±536 pg/ml | | | | (171) |
| *mean* | 1 | 69 w/o | 229±447 pg/ml | | | | (131) |
| *mean* | 1 | 144 c | 138±130 pmol/l | | | | (145) |
| *mean* | 1 | 70 w/o | 192±163 pg/ml | | | | (150) |
| *mean* | | 19 c | 145±130 ng/l | | | | (200) |
| *median* | 1 | 78 late vs 37 early onset | 172.6 vs 73.3 pg/ml | | | yes | (160) |
| *median* | 1 | 21 w vs 42 w/o | 219 vs 11 pg/l | | | yes | (132) |
| *median* | 1 | 33 w/o | 127 ng/l | 20 hc | 47 ng/l | yes | (164) |
| *median* | 1 | 110 c | 147 ng/l | 105 hc | 87 ng/l | yes | (196) |
| *median* | 1 | 195 c | 85 pg/ml | 30 hc | 54 | no | |
| median | 1 | 31 w/o | 11.6 pmol/ml | 32 hc | 9.6 pmol/ml | no | (107) |
| >450 in >50yo, >900 in 50-75yo, >1800 in >75yo | 1 | w/o | 38/103 (36.7%) | | | | (103) |
| >125 pg/ml | 3 | w/o | 28/69 (40.6%) | | | | (131) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | c | 29/65 (44.6%) | | | | (158) |
| | | c | 62/195 (31.8%) | hc | 4/30 (13.3%) | yes | (40) |
| *>300 ng/l* | 1 | c | 34/234 (15%) | | | | (199) |
| *BNP* | 7 | 357 | | | | | |
| *mean* | 1 | 153 c | 37.5±28.5 pg/ml | 17 hc | 23.1±16.0 pg/ml | yes | (66) |
| *median* | 3 | 24 w | 56.5 pg/ml | | | | (39) |
| | | 47 w/o | 111 mg/dl | 36 hc | 70 mg/dl | yes | (198) |
| *Within SSc, for future cardiac events* | | 11 w vs 22 w/o | 166.2±151-2 vs 102.0±101.7 pg/ml | | | No | (194) |
| *Hs-Troponin I* | | | | | | | |
| *median* | 2 | 110 c | 5.1 ng/L | 105 hc | 3.7 ng/L | yes | (196) |
| | | 33 w/o | 3.7 ng/L | 20 hc | 8.0 ng/L | no | (164) |
| *mean* | 1 | 19 c | 76±137 ng/L | | | | (200) |
| *Hs-Troponin T* | 2 | | NA | | NA | | (162, 201) |
| *>14 ng/L* | 3 | c | 23/65 (35.4%) | | | | (158) |
| | | w/o | 38/103 (36.7%) | | | | (103) |
| | | c | 63/195 (32.3%) | hc | 0/30 (0.0%) | yes | (40) |
| *median* | 1 | 195 c | 11 ng/L | 30 hc | 5 ng/L | no | (40) |
| *CK* | | | | | | | (194) |
| *Elevated* | 2 | Depressed vs normal LVEF | 44/383 (11.4%) vs 535/6690 (8.0%) | | | yes | (195) |
| | | w | 21/25 (84%) | | | | (29) |
| | | c | 0/16 (0%) | | | | (75) |
| *>190 mg/dl* | 1 | c | 16/195 (8.2%) | | | | (40) |
| *>500 mg/dl* | 1 | *Within SSc,* Late | 13/78 (16.7%) vs | | | no | (160) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | vs early onset | 6/37 (29.7%) | | | | |
| *mean* | 3 | 69 w/o | 146±161 mg/dl | | | | (131) |
| | | 100 w/o | 176±247 mg/dl | | | | (153) |
| | | 19 c | 141±148 mg/dl | | | | (200) |
| *CK-MB* | | | | | | | |
| *elevated* | | w/o | 2/25 (8%) | | | | (52) |
| *>4 mg/dl* | | c | 36/195 (18.5%) | | | | (40) |
| *>25 U/L* | | w/o | 38/103 (36.7%) | | | | (103) |
| *Other* | | | | | | | |
| *TIMP-1* | 1 | 111 c | 167±63 ng/ml | 21 hc | 183±29 nl/ml | No | (122) |
| *ET-1* | 1 | 30 c | 2.6±0.2 pmol/L | 48 hc | 1.8±0.1 pmol/L | Yes | (109) |
| *IL-6 median* | 1 | 31 w/o | 3.2 pg/ml | 32 hc | 2.2 pg/ml | Yes | (107) |
| *ANP mean* | 1 | 30 c | 239±59 pmol/l | 48 hc | 172.8±36 pmol/L | Yes | (119) |
| *NT-proANP* | | | | | | | |
| *mean* | 1 | 144 c | 648.8±383.1 pmol/l | | | | (96) |
| *Proposed cut-off for future cardiac event* | 1 | 144 c | 822.5 pmol/l | | | | (98) |
| *ESR* | 2 | | | | | | |
| *median* | | 110 c | 13 mm/h | 105 hc | 10 mm/h | Yes | |
| *mean* | | 30 w/o | 21.5±13.5 mm/h | 30 hc | 11.3±7.1 | Yes | (68) |
| *Hs-CRP* | 2 | | | | | | |
| *median* | | 110 c | 2.2 mg/L | 105 hc | 1.7 mg/L | Yes | |
| *mean* | | 30 w/o | 5.3±4.4 mg/dl | 30 hc | 3.9±1.8 | No | (68) |

Table 11. Coronary angiography, arteriography and computed tomography.

Data obtained from 21 papers including 1746 patients (29, 30, 33, 36, 46, 54, 56, 57, 70, 74, 77, 88, 133, 145, 146, 169, 177, 185, 191, 202) and 88 controls (87, 156, 162, 169).

| **Finding** | **N° PAPERS** | **References** | **N° PATIENTS** | **References** | **N° controls** | **References** |
|---|---|---|---|---|---|---|
| Coronary arteries abnormalities | 20 | (29, 30, 33, 36, 46, 54, 56, 57, 70, 74, 77, 79, 88, 89, 133, 145, 169, 177, 191, 202) | 189/1711 (11%) | (29, 30, 33, 36, 46, 54, 56, 57, 70, 74, 77, 88, 133, 169, 177, 191, 202) | 0/68 (0%) HC<br>20/20 (100%) CAD | (87, 156, 162, 169) |
| Coronary flow reserve on Coronary Angiography | 1 | 17 c | Severity of coronary atherosclerosis was similar using WCA and SYNTHAX scores. Similar values of coronary flow velocity. | (169) | 17 hc | |

Table 12. Cardiac magnetic resonance imaging

Data obtained from 28 publications including 1326 patients (22, 23, 25, 36, 38, 39, 51, 60, 73, 75, 79, 83, 114, 118, 136-138, 146, 148, 155, 162-164, 166, 185, 194, 200, 201, 203) and 207 controls (23, 25, 39, 118, 138, 162-164, 166, 185, 201).

| **Finding** | **N° PAPERS** | **N° patients** | **Value/prevalence in patients** | **N° controls** | **Value/prevalence in controls** | **Statistically significant difference** | **References** |
|---|---|---|---|---|---|---|---|
| LA abnormalities | 1 | 19 | | | | | (163) |
| *LA diameter (mm)* | 1 | 19 w/o | 37±6 | 20 hc | 28±5 | Yes | (163) |
| RA abnormalities | 0 | | | | | | Not reported |
| LV abnormalities | 10 | | | | | | (25, 38, 39, 51, 83, 114, 138, 146, 162, 203) |
| **LV dilation** | 1 | c | 3/52 (5.7%) | | | | (51) |
| | 2 | w/o | 14/46 (30.4%) | | | | (83, 114) |
| | 1 | w | 22/50 (48.9%) | | | | (38) |
| **LV-EDV (ml)** | | | | | | | |
| *Mean* | 1 | 50 c | 96.5±18.6 | 31 hc | 126.8±29.5 | Yes | (25) |
| *Mean* | 1 | 46 c | 122±29 | 20 hc<br>20 CAD | 127±32<br>237±77 | No vs HC<br>Yes vs CAD | (162) |
| *Mean* | 1 | 62 d vs 20 l c | 118±28 vs 120±19 | | | No | (146) |
| *Mean* | 1 | 19 w/o | 69±11 | 20 hc | 77±16 | No | (163) |
| *Median* | 1 | 150 c | 88 (72-126) | | | Different among risk categories | (203) |
| **LV-EDV-I (ml/m2)** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Mean* | 1 | 24 c | 77.8±23.7 | 12 hc | 75.1±16.5 | No | (39) |
| *>95 in females, >100 in males* | 1 | w/o | 4/20 (20%) | | | | (83) |
| **LV hypertrophy** | | | | | | | |
| *LV septum* | 2 | w and w/o | 9/70 (12.9%) | | | | (38, 83) |
| *LV infero-lateral wall* | 1 | w/o | 7/20 (35%) | | | | (83) |
| *LVMI (g/m2)* | | | | | | | |
| *Mean* | 3 | | | | | No | (39, 163, 166) |
| **LV anatomical or structural changes** | | | | | | | |
| *Present* | 1 | c | 15/52 (28.8%) | | | | (51) |
| >77 g/m$_2$ (f); >91 g/m$_2$ (m) +2SD | 1 | w/o | 2/20 (10%) | | | | (83) |
| **Global LV systolic disfunction** | | | | | | | |
| Not defined | 2 | w/o | 23/227 (10.1%) | | | | (60, 114) |
| LVEF < 55% | 2 | C | 24/170 (14.1%) | | | | (83, 203) |
| LVEF (%) | | | | | | | |
| Median | 1 | 150 w and w/o | 64.5 (610. – 69.7) | | | | (203) |
| mean | 1 | 46 c | 62.8±11 | 20 hc<br>20 CAD | 61.8±15.2<br>42±12 | No vs HC<br>Yes vs CAD | (162) |
| mean | 1 | 50 w/o | 60.8±6.7 | 31 hc | 65.2±7.1 | Yes | (25) |
| **LV wall motion abnormalities** | 1 | c | 15/52 (28.8%) | | | | (51) |
| hypokinesia | 2 | w/o | 27/46 (58.7%) | | | | (83, 114) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | w | 12/50 (24%) | | | | (38) |
| **LV diastolic disfunction** | | | | | | | |
| | 1 | c | 11/46 (23.9%) | | | | (162) |
| | 1 | w/o | 17/20 (85%) | | | | (83) |
| Peak diastolic strain rate (1/s) | 1 | 19 c | 83±26 | 20 hc | 114±16 | Yes | (163) |
| **LV GLS abnormalities** | | | | | | | |
| Present | 1 | W | 2/50 (4%) | | | | (38) |
| Radial strain | 1 | | | | | Significantly reduced in SSc vs HC | (138) |
| Circumferential stran | 1 | | | | | Significantly higher in SSc vs HC | (138) |
| Mid SA circumferential strain | 1 | 19 w/o | -16.8 ± 1.6 | 20 hc | -18.6 ± 1.0 | Yes | (163) |
| **LV myocardial perfusion abnormalities** | | | | | | | |
| Present | 5 | c or w/o | 31/85 (36.4%) | | | | (79, 114, 137, 138, 155) |
| MPR | 1 | 46 c | 0.6±0.4 | 20 HC | 3.1±0.3 | Yes | (162) |
| MPRI | 1 | 19 c | 3.1±0.9 | 22 HC | 4.2±1.3 | Yes | (166) |
| RV abnormalities | | | | | | | |
| **RV dyskinesia** | 1 | C | 5/52 (9.6%) | | | | (51) |
| **RV dilatation** | | | | | | | |
| *prevalence* | 3 | c or w/o | 36/124 (29.0%) | | | | (51, 114, 162) |
| *Median* | 1 | 150 w and w/o | 86.5 (67-119) | | | | (203) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *RV-EDV (ml)* | 1 | 50 c | 80.5 ± 19.3 | 31 hc | 105.4 ± 12.6 | Yes | (25) |
| | 1 | 46 c | 114.3±32.4 | 20 HC<br>20 CAD | 108.2±33.8<br>132.6±33 | No vs HC<br>Yes vs CAD | (162) |
| *RV-EDV-I (ml/m2) >96 for females, >111 for males* | 1 | w/o | 6/20 (30%) | | | | (83) |
| ***RV hypertrophy*** | | | | | | | |
| *Thickness >5mm* | 1 | w/o | 2/20 (10%) | | | | (83) |
| *RV mass index (g/m2)* | 1 | 24 w | 19.4 ± 5.6 | 12 hc | 16.6 ± 3.1 | No | (39) |
| **RVEF (%)** | | | | | | | |
| Median | 1 | 150 w + w/o | 62 (56-68) | | | | (203) |
| Reduced | 4 | C + w/o | 44/299 (14.7%) | | | | (51, 60, 83, 114) |
| Mean | 3 | 100 c + w/o | | 63 hc | | No | (23, 39, 162) |
| | 1 | 50 w | | 31 hc | | Yes | (25) |
| ***EGE – Range median of LV mass (%)*** | *Within SSc* | Higher in patients with myocarditis defined with Lake Louis criteria | | | | Not reported | (162) |
| | *Within SSc, for future cardiac events* | 31 w vs 19 w/o arrhythmic events | 3.8 (2.0, 6.0) vs 1.9 (1.4, 3.4) | | | Yes | (201) |
| ***LGE*** | | | | | | | |
| *Present* | 4 | C | 75/173 (43.3%) | | | | (73, 162, 166, 200, 201) |
| | 8 | w/o | 166/499 (33.2%) | | | | (36, 46, 60, 79, 83, 114, 137, 138, 146, 148, 163, 164) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 5 | W | 158/362 (43.6%) | | | | (38, 39, 162, 194, 203) |
| *distribution* | *Of the prevalent cases* | Linear | 64/183 (34.9%) | | | | (36, 51, 73, 83, 148) |
| | | Nodular | 14/183 (7.6%) | | | | (36, 73, 79, 83) |
| | | Diffuse | 105/183 (57.4%) | | | | (22, 83, 137, 162, 163, 200, 201) |
| | | Not specified | 383/517 (74.1%) | | | | |
| *Location* | *Of the prevalent cases* | subendocardial | 19/120 (15.8%) | | | | (83, 137) |
| | | midmiocardial | 93/120 (77.5%) | | | | (22, 23, 51, 79, 114, 148, 163, 201) |
| | | epicardial | 8/120 (6.7%) | | | | (114) |
| | | Not specified | 384/504 (76.2%) | | | | |
| *Pattern* | *Of the prevalent cases* | Ischemic | 4/94 (4.2%) | | | | (22, 60) |
| | | Not ischemic | 90/94 (95.8%) | | | | |
| | | Not reported | 410/504 (81.3%) | | | | |
| *Range Mean of LV mass (%)* | | 301 c+ w/o+ w | From 2.0±2.9 to 9.3±8.7 | 20 hc | 0.002±0.01 | Yes | (52, 146, 162, 203) |
| *Rage median of LV mass (%)* | | 31 w vs 19 w/o arrhythmic events | 6.0 (5.0, 12.0) vs 3.0 (0.0, 5.0) | | | Yes | (201) |
| ***Native T1 Mapping (ms)*** | | | | | | | |
| *mean* | 1 | 24 w | 1005±63 | 12 hc | 951±46 | Yes | (39) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 33 w/o | 1258.9± 51.2 | 20 hc | 1192.2±32. 6 | Yes | (164) |
| | 1 | 19 w/o | 1007±2 9 | 20 hc | 958 ± 20 | Yes | (163) |
| *Within SSc, for future cardiac events* | 1 | 31 ssc w event | 1135.0 (1117.0, 1202.0) | 19 ssc w/o events | 1065.0 (1018.0, 1126.0) | Yes | (201) |
| ***Extracellular volume fraction (ECV) – (%)*** | | | | | | | |
| *Mean* | 1 | 19 w/o | 35.4±4. 8 | 20 hc | 27.6±2.5 | Yes | (163) |
| | 1 | 33 w/o | 27.5 ± 2.8 | 20 hc | 22.8 ± 1.9 | Yes | (164) |
| | 1 | 24 w | 30.0 ± 4.2 | 12 hc | 24.1 ± 3.5 | Yes | (39) |
| | 1 | 30 c | 30±4 | 10 hc | 28±4 | Yes | (23) |
| *Median* | 1 | 33 w/o | 30.0 (28.0-31.9) | 16 hc | 26.8 (25.4-29.1) | Yes | (118) |
| *Within SSc, for future cardiac events* | 1 | 8 w vs 11 w/o significant arrhythmia | 30±2 vs 29±4 | | | Not reported | (200) |
| | | 31 w vs 19 w/o arrhythmic events | 32.0 (31.0-34.0) vs 30.5 (28.0-32.0) | | | Yes | (201) |
| ***T2/STIR alteration*** | | | | | | | |
| *Presence of abnormality/ oedema* | 1 | c | 6/52 (11.5%) | | | | (51) |
| | 2 | w/o | 5/201 (2.4%) | | | | (60) |
| | | w/o | 10/26 (41.7%) | | | | (114) |
| | 1 | W | 5/50 (10.0%) | | | | (38) |
| *T2 signal ratio* | 1 | w + w/o | 2.0 ± 0.5 | | | | (203) |
| | 1 | 46 c | 3.5 ± 0.5 | 20 hc | 1.25±0.12 | Yes | (201) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Within SSc, for future cardiac events* | 31 w vs 19 w/o arrhythmic events | 2.4 (2.0, 2.7) vs 2.2 (1.8, 2.3) | | | Yes | (201) |
| *T2 mapping (ms) - Within SSc, for future cardiac events* | 1 | 31 w vs 19 w/o arrhythmic events | 63.0 (55.0-65.0) vs 55.0 (49.0-58.0) | | | Yes | (203) |
| ***Valvular abnormalities*** | | | | | | | Not reported |
| **Pericardial effusion** | | | | | | | |
| *Present* | 1 | C | 10/52 (19.2%) | | | | (51) |
| | 1 | w/o | 32/201 (15.9%) | | | | (60) |
| *<5 mm* | 2 | w/o + w | 23/70 (32.8%) | | | | (38, 83) |
| *≥ 5 mm* | 2 | w/o + w | 15/70 (21.4%) | | | | (38, 83) |

Table 13. Rest electrocardiography

Data derived from 75 manuscripts involving 22866 patients (22-24, 28, 29, 32-37, 39, 40, 43-48, 50, 52-54, 56, 58, 66, 67, 69, 73-75, 77, 79, 81, 86, 88, 93, 94, 97, 98, 102, 103, 106, 109, 113, 115, 116, 124, 128, 129, 132, 133, 135, 137, 154, 156-160, 172, 178, 181, 184, 186-189, 194, 197, 200, 204-207)) and 799 controls (23, 24, 43, 44, 47, 56, 58, 66, 72, 93, 94, 106, 109, 116, 122, 124, 156, 178, 179, 181, 188, 189).

| **Finding** | **N° papers** | **N° patients** | **Value/prevalence in patients** | **N° controls** | **Value/prevalence in controls** | **Statistically significant difference** | **References** |
|---|---|---|---|---|---|---|---|
| 12 leads ECG abnormality | 29 | 1638 | 468 (28.6%) | 20 | 3 (15.0%) | | |
| 15 leads ECG abnormality | 1 | 36 | 15 (41.7%) | | | | (86) |
| No specified ECG abnormality | 45 | 15773 | 1246 (7.9%) | 759 | 34 (4.7%) | | |
| Sinus rhythm | 22 | 1050 | 804 (76.6%) | 105 | 99 (94.3%)(116) | | (24, 28, 34, 39, 47, 53, 54, 58, 72, 73, 86, 93, 94, 103, 124, 154, 157, 172, 184, 187, 200, 206) |
| Sinus bradycardia | 2 | 86 | 11 (12.8%) | | | | (37, 73) |
| Sinus tachycardia | 2 | 58 | 24 (41.4%) | | | | (37, 197) |
| Mobitz type I AV conduction block | 10 | 808 | 27 (3.3%) | | | | (44, 45, 48, 58, 103, 157, 184, 187, 194) |
| Mobitz type II AV conduction block | 10 | 571 | 1 (0.1%) | | | | (44, 48, 58, 103, 160, 184, 187, 194) |
| Third degree AV block | 12 | 763 | 7 (0.09%) | | | | (28, 44, 45, 53, 77, 88, 103, 160, 184, 187, 194) |
| Sinus arrhythmia | 9 | 459 | 14 (3.1%) | 105 | 6 (5.7%) (116) | | (32, 44, 48, 58, 103, 115, 184, 187, 194) |
| Atrial Fibrillation | 14 | 663 | 13 (2.0%) | | | | (28, 44, 48, 52, 53, 58, 103, 115, 184, 187, 194, 206) |
| Atrial Flutter | 9 | 405 | 11 (2.7%) | | | | (44, 48, 52, 53, 58, 103, 184, 187, 194) |
| Atrial Tachycardia | 10 | 404 | 11 (2.7%) | | | | (39, 44, 48, 52, 58, 88, |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | 103, 184, 187, 194) |
| Supraventricular Tachycardia | 9 | 558 | 20 (3.6%) | | | | (44, 48, 52, 58, 77, 103, 115, 184, 187) |
| Ventricular Tachycardia – monomorphic | 14 | 1384 | 30 (2.7%) | | | | (44, 45, 48, 52, 58, 77, 88, 98, 103, 115, 184, 187, 194, 207) |
| Ventricular Tachycardia – polymorphic | 7 | 425 | 0 (0.0%) | | | | (44, 48, 103, 115, 184, 187, 194) |
| Ventricular fibrillation | 9 | 490 | 1 (<0.1%) | 66 | 0 (0.0%) | | (48, 53, 58, 103, 115, 184, 187, 194) |
| Atrial ectopies | 15 | 1098 | 63 (5.7%) | 154 | 9 (5.8%) (44, 106) | | (28, 32, 44, 46, 53, 56, 58, 86, 103, 106, 115, 157, 184, 206) |
| Ventricular ectopies | 18 | 908 | 80 (8.8%) | 177 | 2 (1.1%) (44, 47, 106) | | (28, 32, 44, 46, 47, 52, 53, 58, 72, 74, 86, 88, 103, 106, 115, 184, 194, 206) |
| Right bundle branch block | 36 | 6329 | 175 (2.8%) | 302 | 17 (5.6%)(44, 47, 116) | | (28, 34, 39, 40, 44-48, 50, 52, 53, 56, 58, 72-74, 86, 88, 94, 98, 103, 113, 115, 124, 154, 157, 160, 172, 184, 187, 194, 200, 205-207) |
| Left bundle branch block | 26 | 5138 | 52 (1.0%) | 307 | 2 (0.6%) (44, 106, 109, 116) | | (28, 33, 43-45, 48, 50, 52, 53, 58, 72, 86, 98, 103, 113, 115, 124, 154, 157, 160, 184, 187, 194, 200, 205, 206) |
| Left Ventricle hypertrophy | 2 | 131 | 8 (6.1%) | | | | (86, 206) |
| Right Ventricle hypertrophy | 14 | 975 | 30 (3.1%) | 154 | 3 (1.9%) (44, 106) | | (33, 44, 45, 53, 58, 69, 94, 98, 115, 124, 157, 184, 187, 206) |
| Left Atrium Enlargement | 7 | 564 | 9 (1.6%) | 186 | 0 (0.0%) (44, 106, 156) | | (44, 69, 115, 156, 157, 184, 187) |
| Right Atrium Enlargement | 6 | 551 | 11 (2.0%) | 186 | 1 (0.5%) (44, 106, 156) | | (44, 47, 115, 157, 184, 187) |
| WPW pattern | 1 | 29 | 0 (0.0%) | | | | (184) |
| T wave morphology alternation | 16 | 946 | 102 (10.8%) | 75 | 3 (4.0%) (44, 72) | | (28, 29, 32, 34, 37, 44, 69, 74, 81, 94, |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | 115, 157, 184, 187, 197, 206) |
| Brugada pattern | 1 | 29 | 0 (0.0%) (184) | | | | |
| Heart rate | | | | | | | |
| *Abnormal (<60/bpm or >100 bpm)* | 1 | 110 c | 13 (11.8%) | | | | (115) |
| *Mean* | 1 | 24 w | 73±18 | | | | (39) |
| *Median* | 1 | 22 c | 82 (607-106) | | | | (43) |
| RR interval | | | | | | | |
| *Mean (ms)* | 1 | 35 c | 859±135 | 35 hc | 903±120 | No | (94) |
| PR interval | | | | | | | |
| *Mean* | 1 | 35 c | 158±21 | 35 hc | 157±21 | No | (94) |
| | 1 | 76 c | 148±21 | 66 hc | 152±38 | No | (44) |
| *Abnormal* | 5 | 301 c | 13 (4.3%) | | | | (53, 94, 103, 106, 184) |
| QRS interval | | | | | | | |
| *Mean* | 1 | 76 c | 87±10 | 66 hc | 90±14 | No | (44) |
| | 1 | 15 c | 95±13 | 18 hc | 95±7 | No | (181) |
| *Anterior left hemiblock* | 3 | 90 c | 12 (13.3%) | | | | (32, 47, 154) |
| *Abnormal* | 9 | 588 c | 70 (11.9%) | | | | (28, 77, 94, 103, 160, 184, 196, 205, 206) |
| QT interval | | | | | | | |
| QTc (ms) Mean | 2 | 72 c | 423±17 | 74 c | 408±14 | Yes | (44) |
| | | 110 c | 419±25 | 105 hc | 413±25 | No (p=0.06) | (116) |
| Mean | 1 | 36 c | 404±22 | | | | (86) |
| >440 ms | 3 | 398 c + w/o | 43 (10.8%) | | | | (40, 46, 103) |
| >440 ms | 1 | 110 c | 21 (20%) | 105 hc | 10 (9%) | Yes | (116) |
| QTcd (ms) Mean | 1 | 27 c | 58±30.3 | 17 hc | 55.8±18.6 | No | (66) |
| Other | | | | | | | |
| ST tract depression | 2 | 120 c | 37 (30.8%) | | | | (33, 46) |

Table 14. Transthoracic rest Echocardiography

Data retrieved from 139 manuscripts on 20790 patients (23-28, 31-35, 37, 39-41, 43, 44, 46-48, 50-52, 54, 56-58, 60, 62, 64-66, 68, 69, 71-73, 75, 77-82, 86, 88-94, 96-98, 100-115, 118-122, 124, 125, 127-129, 131-138, 140-143, 145, 147, 149, 150, 152-156, 158, 160, 163, 164, 168-172, 176-178, 180, 181, 183-188, 191, 192, 194, 196-202, 204, 206-211)) and 2448 controls (23-25, 27, 41, 44, 47, 56, 58, 62, 66, 68, 71, 72, 78, 80, 81, 91-94, 96, 97, 100-102, 104-107, 109-112, 118-122, 124, 125, 127, 129, 134, 135, 140, 142, 149, 150, 152-154, 156, 163, 164, 168-170, 172, 173, 176-181, 183-185, 187, 188, 192, 196, 198, 201, 208, 210).

| **Finding** | **N° papers** | **N° patients** | **Value/prevalence in patients** | **N° controls** | **Value/prevalence in controls** | **Statistically significant difference** | **References** |
|---|---|---|---|---|---|---|---|
| LA Dilatation | 26 | | | | | | (25, 44, 48, 65, 69, 81, 82, 86, 88, 90, 94, 96, 104, 105, 109, 119, 121, 122, 125, 127, 131, 135, 152, 153, 176, 194, 208) |
| **Present, not specified** | 8 | C+w/o+w | 27/404 (6.7%) | Hc | 3/251 (1.2%) (44, 81, 119, 180) | | (44, 48, 69, 81, 86, 88, 115, 119, 180) |
| **LA Index Volume (mL/m2)** | 8 | | | | | | (39, 65, 82, 96, 108, 121, 127, 176) |
| *Normal cut-off <34* | 1 | | | | | | (82) |
| *Mean (SD)* | | 42 c | 24.9±5.3 | 42 hc | 24.7±4.4 | No | (121) |
| | | 45 c | 28.4±8.7 | 20 hc | 19.3±4.6 | Yes | (96) |
| | | 22 c | 22.4±4.5 | | | | (108) |
| | | 52 w/o | 23.7±5.7 | 52 hc | 23.3±6.2 | No | (176) |
| | | 54 w/o | 27±8 | | | | (82) |
| | | 24 w | 27±7.2 | | | | (39) |
| **LA Area** | 3 | | | | | | (101, 109, 177) |
| *M-mode (cm2) – Mean (SD)* | 1 | 40 c | 14.7±3.5 | 40 hc | 15.0±2.0 | No | (101) |
| | 1 | 46 w diastolic dysf | 21±5 | 195 ssc w/o diastolic dysf 66 hc | 17±4<br>18±3 | Yes<br>Yes | (177) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *2D area (mm2/m2) – Mean (SD)* | 1 | 30 c | 913±43 | 48 hc | 748±25 | Yes | (109) |
| **LA Diameter (mm)** | 21 | | | | | | (31, 65, 66, 80, 82, 90, 93, 94, 97, 104, 105, 107, 108, 120, 131, 135, 141, 152, 153, 194, 199, 208) |
| >40mm | 2 | C+w/o | 74/650 (11.4%) | | | | (90, 104) |
| Mean (SD) value range | 6 | 1052 c | From 34.6±5.2 to 38.7±6.1 | | | | (82, 90, 108, 131, 141, 199) |
| Mean (SD) value range | 1 | 35 c | 34±6 | 35 hc | 29±5 | Yes | (94) |
| | 1 | 100 c | 34±0.5 | 45 hc | 31.9±2.6 | Yes | (153) |
| Mean (SD) value range | 10 | 334 c + w/o | From 28.8±2.0 to 36.2±4.1 | 306 hc | From 27.3±5.9 to 35.8±3.7 | No | (66, 80, 93, 97, 102, 105, 120, 129, 135, 152) |
| Median (IQR) value range | 1 | 17 c | 38.5 (32-41) | 23 hc | 37 (33.8-39) | No | (208) |
| | 1 | 31 w/o | 38 (35-43) | 32 hc | 36.5 (32.38) | Yes | (107) |
| RA dilatation | 8 | | | | | | (44, 48, 93, 101, 109, 149, 150, 176) |
| **Dilated RA** | 1 | C | 18/76 (23.7%) | Hc | 0/66 (0.0%) | Yes | (44) |
| **RA indexed Volume (mL/m2)** | 1 | 70 w/o | 19.4±5.5 | 25 hc | 19.5±5.9 | No | (150) |
| **RA area** | | | | | | | |
| *M-mode (cm2) – Mean (SD)* | 1 | 52 c | 20.7±9.0 | 52 hc | 19.7±6.4 | No | (176) |
| *M-mode (cm2) – Mean* | 1 | 40 c | 13 | 40 hc | 14.2 | No | (101) |
| *2D area (mm2/m2) – Mean (SD)* | 1 | 30 c | 929±56 | 48 hc | 917±30 | No | (109) |
| **RA diameter (mm)** | | | | | | | |
| *Not specified* | 1 | 26 c | 29.2±2.4 | 24 hc | 29.9±2.6 | No | (93) |
| *Major Axis* | 1 | 42 w/o | 44.5±5.6 | 40 hc | 43.3±4.9 | No | (149) |
| *Minor Axis* | 1 | 42 w/o | 34.8±4.2 | 40 hc | 31.9±3.6 | Yes | (149) |
| LA impaired emptying | 2 | | | | | | (93, 129) |
| Present | 1 | c | 14/24 (58.3%) | | | | (129) |
| Decreased LA Passive Emptying | 2 | | | | | | (65, 93) |
| Present | 1 | C | 16/40 (40%) | | | | (65) |
| RV Dilation | | | | | | | |
| Present | 10 | C+w/o+ w | 56/547 (10.2%) | | | | (27, 48, 69, 86, 104, |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | 114, 115, 124, 196, 206) |
| RV diameter ≥23 mm | 1 | C | 17/80 (21.3%) | Hc | 3/18 (16.7%) | Not reported | (104) |
| RV diameter ≥26 mm | 1 | C | 9/110 (8.1%) | | | | (115) |
| RV diameter (mm) – Median | 1 | 31 w/o | 24.3 (22-26) | 32 hc | 21.8 (21-23) | Yes | (107) |
| RV diameter (mm) – Mean | 1 | 76 c | 21.5±5.5 | 66 hc | 21.4±2.5 | No | (44) |
| RV diameter Indexed mm/m2 | 1 | 63 c | 9.5±4.7 | 40 hc | 8.9±2.8 | No | (56) |
| RV basal diameter | 1 | 46 with diastolic dysfunction | 43±9 | 195 w/o diastolic dynsfunction 65 hc | 38±6 37±5 | Yes Yes | (177) |
| RV Basal diameter indexed (mm/m2) | 1 | 70 c | 18.4±2.4 | 25 hc | 17.5±1.6 | No | (150) |
| RVEDD (mm) – Mean | 1 | 23 c | 26.4±2.2 | 25 hc | 21.2±3.8 | Yes | (100) |
| RVED Area (mm2) – median | 1 | 95 w/o | 9.7 (8.5-10.7) | 54 hc | 9.6 (6.8-10.5) | No | (210) |
| | 1 | 42 c | 10.5 (9.2-13.5) | 40 hc | 12.2 (9.4-13.1) | No | (149) |
| RVES Area (mm2) – Median | 1 | 95 w/o | 5.2 (4.6-5.8) | 54 hc | 4.6 (4.2-5.5) | No | (210) |
| | 1 | 42 c | 5.6 (4.5-8.3) | 40 hc | 5.9 (4.4-6.9) | No | (163) |
| LV Dilation | | | | | | | (27, 48, 56-58, 69, 71, 81, 89, 90, 96, 100, 102, 104, 105, 107, 112, 114, 115, 120, 124, 125, 133, 152, 177, 178, 196, 210) |
| Present | 14 | C+ w/o | 41/1072 (3.8%) | HC | 6/775 (0.8%) | | (27, 48, 58, 69, 81, 100, 104, 114, 115, 120, 124, 125, 133, 177) |
| LV diameter (mm) | 1 | 124 c | 44.8±5.5 | 41 hc | 44.2±4.0 | No | (91) |
| LV Internal Dimension – diastolic (mm) | 4 | 179 c | From 40.6±4.2 to 47.0±2.2 | 135 hc | From 42.0±4.4 to 48.4±3.8 | No | (105, 135, 152, 178) |
| LV Internal Dimension – systolic (mm) | 4 | 179 c | From 24.9±2.6 to 28.6±3.8 | 135 hc | From 25.2±4.4 to 29.0±5.1 | No | (104, 105, 152, 178) |
| LVEDD (mm) | 1 | 25 w | 46.7±5.9 | | | | (57) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mean | 5 | 383 c | From 42.8±3.9 to 51.2±5.1 | 210 hc | From 40.4±4.8 to 50.3±2.5 | No | (66, 92-94, 153, 183, 188) |
| Median | 1 | 47 c | 44 (42-47) | 36 hc | 45 (42-48) | No | (198) |
| | | 17 w/o | 44 (44-47) | 22 hc | 47 (42-49) | No | (208) |
| ≥55 mm | 1 | c | 7/80 (8.8%) | | | | (104) |
| LVEDD Index (mm/m2) | 1 | 63 c | 16.9±2.8 | 40 hc | 17.3±3.1 | No | (56) |
| LVESD (mm) - Mean | 1 | 47 c | 26±3.3 | 36 hc | 25±3.4 | No | (198) |
| Median | 1 | 17 w/o | 26 (22-29) | 20 hc | 27 (25-29) | No | (208) |
| LVESD Index (mm/m2) | 1 | 63 c | 26.9±3.3 | 40 hc | 27.4±3.0 | No | (56) |
| LVEDV (ml) – Mean (SD) | 1 | 104 w/o | 76.0±25.4 | 37 hc | 70.6±20.6 | No | (71) |
| | 1 | 45 c | 80.6±20.2 | 20 hc | 70.7±4.2 | No | (96) |
| | 1 | 35 c | 80.8±9.2 | 35 hc | 80.8±14 | No | (178) |
| Median (IQR) | 1 | 47 c | 89 (79-103) | 36 hc | 93 (79-108) | No | (198) |
| LVEDV Index (ml/m2) – Median (IQR) | 1 | 95 w/o | 40.3 (35.6-45.4) | 54 hc | 43.8 (39.6-49.0) | Yes | (210) |
| LVESV (ml) - Mean | 1 | 104 w/o | 29.1±13.1 | 37 hc | 26.6±5.7 | No | (71) |
| | 1 | 35 c | 28.0±4.1 | 35 hc | 27.1±7.1 | No | (178) |
| Median | 1 | 47 c | 26±3.3 | 36 hc | 25±3.4 | No | (198) |
| LVESV Index (ml/m2) – Median (IQR) | 1 | 95 w/o | 16 (12.8-18.7) | 54 hc | 16.3 (14.3-19.8) | No | [27] |
| Increased wall thickness | 28 | | | | | | (37, 43, 44, 47, 56, 62, 69, 82, 91, 94, 96, 97, 100, 102, 112, 115, 119, 124, 131, 135, 140, 150, 153, 168, 178, 188, 194, 196, 206) |
| Hypertrophy of the wall (not specified) ≥13 mm | 1 | C | 15/80 (18.8%) | | | | (104) |
| ED-IVS thickness (mm) – Mean | 1 | 69 c | 9.3±2.1 | | | | (131) |
| | 1 | 124 c | 10.3±1.8 | 41 hc | 8.9±1.1 | Yes | (91) |
| | 1 | 35 c | 9.3±1.1 | 25 hc | 8.2±1.1 | Yes | (102) |
| | 1 | 19 c | 8.7±1.6 | 10 hc | 6.6±2.0 | Yes | (135) |
| | 1 | 30 c | 12.2±0.5 | 48 hc | 9.9±0.3 | Yes | (119) |
| | 1 | 42 w/o | 9.2±2.0 | 20 hc | 7.9±1.6 | Yes | (62) |
| | 11 | 530 c + w/o | From 6.2±1.2 to 10.8±2.4 | 406 hc | From 5.5±0.9 to 10.1±0.4 | No | (27, 56, 94, 97, 100, 105, 112, 153, 168, 178, 188, 196) |
| | 1 | 25 w diastolic | 9.9±1.3 | 25 w/o diastoli | 9.5±1.1 | No | (82) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | dysfunction | | c dysfunction | | | |
| | 1 | 24 w ILD | 11±2.6 | 10 w/o ILD | 9±1 | Yes | (124) |
| >11 mm | 4 | C + w | 43/240 (17.9%) | Hc | 4/66 (6.1%) (44) | | (44, 47, 115, 140) |
| ≥12mm | 1 | C | 12/95 (12.6%) | | | | (206) |
| ED-Posterior wall thickness (mm) - Mean | 1 | 69 c | 8.6±2.1 | | | | (131) |
| | 1 | 124 c | 9.7±1.4 | 41 hc | 8.9±1.2 | Yes | (91) |
| | 1 | 19 c | 8.7±1.7 | 10 hc | 6.6±1.3 | Yes | (135) |
| | 1 | 30 c | 10.1±0.4 | 48 hc | 9.1±0.3 | Yes | (119) |
| | 1 | 42 w/o | 8.9±1.6 | 20 hc | 7.9±1.4 | Yes | (62) |
| | 10 | 462 c + w/o | From 6.0±1.0 to 10.0±0.6 | 339 hc | From 5.5±0.9 to 9.8±0.7 | No | (27, 56, 94, 100, 102, 112, 153, 168, 178, 196) |
| | 1 | 25 w diastolic dysfunction | 9.9±1.3 | 25 w/o diastolic dysfunction | 9.5±1.1 | No | (82) |
| | 1 | 24 w ILD | 10.2±2.0 | 10 w/o ILD | 9±2 | Yes | (124) |
| >9 mm | 1 | C | 7/28 (25%) | | | | (37) |
| RV wall thickness (mm) - mean | 1 | 70 c | 5.0±1.0 | 25 hc | 4.8±0.8 | No | (150) |
| LV Mass | | | | | | | |
| LV Mass Index (g/m2) | | | | | | | |
| Mean | 1 | 570 w/o | 97±33 | | | | (90) |
| | 1 | 124 c | 99±31 | 41 hc | 84±25 | Yes | (91) |
| | 1 | 30 c | 116±7 | 48 hc | 95±3 | Yes | (119) |
| | 1 | 72 c | 96.9±19.5 | 30 hc | 83.3±11.6 | Yes | (127) |
| | 1 | 24 w | 42.7±6.2 | 12 hc | 43.9±12.1 | No | (39) |
| | 7 | 261 c | From 70.0±22.4 to 105.9±26.1 | 180 hc | From 72±15 to 99.0±25.9 | No | (56, 93, 94, 96, 100, 102, 198) |
| | 1 | 16 w IAMD | 107.1±21.7 | 24 w/o IAMD | 82.5±19.9 | Yes | (65) |
| | 1 | 25 w DD | 90±34 | 25 w/o DD | 87±20 | No | (82) |
| Median | 1 | 103 w/o | 82 (70-95) | 103 hc | 80 (69-99) | No | (180) |
| | 1 | 95 W/o | 70 (59-79) | 54 hc | 68 (57-81) | No | (210) |
| Wall Motion Abnormalities | | | | | | | |
| Not defined | 1 | c | 11/72 (15.2%) | HC | 1/64 (1.5%) | Yes | (44) |
| Segmental hypokinesia | 9 | C | 29/505 (5.7%) | Hc | 2/221 (0.9%) (44, 125, 196) | | (25, 27, 28, 44, 48, 88, 125, 196, 206) |
| | 1 | w | 3/10 (30%) | | | | (69) |
| | 1 | After cold | 12/13 (92.3%) | | | | (72) |

| | | challenge | | | | | |
|---|---|---|---|---|---|---|---|
| Global hypokinesia | 1 | C | 0/30 (0.0%) | | | | (48) |
| | 1 | W | 1/10 | | | | (69) |
| Akinesia | 5 | C + w | 0/182 (0.0%) | Hc | 0/97 (0.0%) (25, 44) | | (25, 27, 44, 48, 69) |
| Valvular Lesion | | | | | | | |
| Valve Sclerosis | 1 | C | 19/110 (17.3%) | | | | (196) |
| Mitral Valve | | | | | | | |
| Any abnormality | 1 | C | 8/22 (36.4%) | | | | (43) |
| Thickening / Stenosis | 5 | C + W7o | 26/312 (8.3%) | Hc | 8/76 (20.5%) (125, 153) | | (27, 94, 115, 125, 153) |
| Regurgitation | 15 | C+w/o | 313/1459 (21.5%) | Hc | 84/558 (15.1%) (44, 56, 109, 119, 125, 127, 135, 153, 196) | | (37, 44, 56, 86, 90, 109, 115, 119, 125, 127, 131, 135, 153, 196, 206) |
| Prolapse | 6 | C + W/o | 23/377 (6.1%) | Hc | 2/76 (2.6%) | | (28, 37, 94, 115, 125, 153) |
| Aortic Valve | | | | | | | |
| Sclerosis | 1 | C | 6/37 (16.2%) | | | | (41) |
| Thickening / Stenosis | 7 | C + w/o | 37/210 (17.6%) | Hc | 6/167 (3.5%) (25, 41, 47, 106, 125, 140, 153, 196) | | (27, 37, 90, 94, 115, 125, 153) |
| Regurgitation | 11 | C+w/o+w | 73/1280 (5.7%) | Hc | 15/397 (3.8%) (25, 41, 47, 106, 125, 140, 153, 196) | | (37, 90, 106, 115, 125, 131, 140, 153, 168, 196, 206) |
| Prolapse | Not reported | | | | | | |
| Tricuspid Valve | | | | | | | |
| Any abnormality | 3 | C | 45/172 (26.2%) | Hc | 41/230 (17.8%) (25, 41, 47, 106, 124, 170) | | (25, 41, 106) |
| Thickening / Stenosis | Not reported | | | | | | |
| Regurgitation | 15 | c+w/o | 216/1142 (18.9%) | Hc | 22/326 (6.7%) (44, 56, 101, 135, 177, 196) | | (37, 44, 47, 56, 86, 101, 104, 115, 124, 135, 154, 170, 177, 196, 206) |
| | 1 | W | 27/37 (72.9%) | Hc | 21/37 (56.8%) | Not reported | (140) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Prolapse | Not reported | | | | | | |
| Pulmonary Valve | | | | | | | |
| Any abnormality | 1 | C | 1/37 (2.7%) | Hc | 2/37 (6.5%) | No | (41) |
| Thickening / Stenosis | 1 | C | 3/110 (2.7%) | | | | (115) |
| Regurgitation | 2 | C | 7/165 (4.2) | Hc | 0/111 (0.0%) | | (104, 106) |
| Prolapse | | | | | | | |
| LV systolic function | | | | | | | |
| LV Ejection fraction (%) | | | | | | | |
| < 55% | 10 | C + w/o | 471/8483 (5.6%) | HC | 1/94 (1.1%) (25, 140, 153) | | (25, 40, 46, 62, 115, 128, 129, 131, 136, 140) |
| < 50 % | 6 | C | 27/341 (7.9%) | HC | 1/341 (5.2%) (134, 178, 196) | | (52, 89, 134, 160, 178, 196) |
| < 45% | 1 | w/o | 8/570 (1.4%) | | | | (90) |
| Mean±SD | 57 | 2305 c | from 54±5±4.9 to 78.2±5.7 | 1287 hc | 55.6±5.8 to 76.6±5.6 | No | (27, 39, 43, 46, 57, 68, 71, 72, 80, 82, 86, 89-93, 96, 97, 101, 107-109, 112, 114, 115, 120, 121, 125, 131, 134, 136, 138, 141, 145, 150, 152, 160, 168-170, 176-178, 180, 181, 183, 186, 188, 191, 192, 194, 196-200, 202, 209-211) |
| Mean±SD | 5 | 323c + w/o | From 54.1±6.7 to 68.5±7.9 | 205 hc | From 59.6±6.8 to 72.4±5.0 | Yes | (62, 104, 105, 150, 196) |
| | 1 | 46 w DD 195 w/o DD | 57±10<br><br>58±7 | 65 hc | 62±4 | Yes | (177) |
| Fractional shortening (%) | 1 | 80 c | 19.7±6.2 | 18 hc | 23.7±6.0 | Yes | (104) |
| | 1 | 35 c | 38±5 | 35 hc | 36±5 | Not reported | (94) |
| | 1 | 63 c | 40±10 | 40 hc | 38±5 | No | (56) |
| | 1 | 35 c | 39.2±6.4 | 25 hc | 40.7±6.2 | No | (102) |
| LV Stroke volume (ml) | | | | | | | (73, 81) |
| Mean | 1 | 23 c | 64.7±12.5 | 25 hc | 69.6±6.9 | No | (100) |
| | 1 | 30 c | 80.4±5.0 | 48 hc | 94.5±4.9 | No | (109) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 35 c | 53.7±10.2 | 35 hc | 52.9±8.2 | No | (178) |
| LV Stroke volume Indices (ml) | | | | | | | |
| Mean | 1 | 25 c | 38±2 | 25 hc | 42±2 | No | (58) |
| LV Stroke work (kg cm) | | | | | | | |
| Median | 1 | 95 c | 4.2 (3.6-4.8) | 54 hc | 5.4 (4.2-6.6) | Yes | (210) |
| LV Stroke Work Index (gg/cm2) | | | | | | | |
| Mean | 1 | 95 c | 60.3±10.3 | 54 hc | 70.0±11.9 | Yes | (210) |
| RV systolic function | | | | | | | |
| RV ejection fraction (RVEF) – (%) | 1 | 30 c | 56.7±7.7 | 30 hc | 50.45±8.4 | Yes | (68) |
| | 1 | 40 c | 39.2±6.7 | 45 hc | 49.6±6.8 | Yes | (105) |
| < 35% | 1 | C | 16/42 (38.1%) | | | | (62) |
| Fractional Area Change (FAC) – (%) | 1 | 70 w/o | 47.5±7.2 | 25 hc | 54.1±6.6 | Yes | (150) |
| | 1 | 45 w/o | 46±6 | 43 hc | 52±6 | Yes | (111) |
| | 1 | 42 c | 49.2±12.9 | 40 hc | 48.8±8.8 | No | (149) |
| | 1 | 52 c | 49.3±12.4 | 52 hc | 42.9±9.3 | No | (176) |
| | 1 | 12 w DD | 31.5±5.2 | 28 w/o DD | 33.5±3.4 | No | (101) |
| <35% | 1 | C | 4/115 (3.5%) | | | | (160) |
| TAPSE | | | | | | | |
| < 20mm | 1 | 25 w | 2/25 (8.0%) | | | | (57) |
| < 17 mm | 2 | C | 12/220 (5.4%) | Hc | 105 (0.0%) | | (115, 196) |
| < 16 mm | 1 | C | 4/115 (3.5%) | | | | (160) |
| < 15 mm | 1 | w/o | 0/37 (0.0%) | Hc | 0/37 (0.0%) | | (140) |
| Mean±SD | 1 | 20 c | 23.1±3.5 | 20 HC | 26.5±1.9 | Yes | (92) |
| | 1 | 50 c | 20.4±4.3 | 44 hc | 24.4±3.6 | Yes | (171) |
| | 1 | 26 c | 23.3±1.6 | 24 hc | 25.8±2.8 | Yes | (93) |
| | 1 | 40 c | 21.1±3.2 | 40 hc | 24.3±3.4 | Yes | (101) |
| | 1 | 111 c | 22.2±3.2 | 21 hc | 24.1±2.4 | Yes | (122) |
| | 1 | 45 c | 23±3 | 43 hc | 26±2 | Yes | (111) |
| | 1 | 70 c | 21.1±2.6 | 25 hc | 23.6±1.6 | Yes | (150) |
| | 1 | 42 c | 24.7±3.9 | 40 hc | 22.1±3.3 | Yes | (149) |
| | 1 | 47 c | 21.0±3.9 | 36 hc | 21.0±4.6 | No | (198) |
| | 1 | 52 c | 22.2±4.3 | 52 hc | 23.0±3.6 | No | (176) |
| | 1 | 23 c | 19.1±3.5 | 25 hc | 20.1±2.6 | No | (100) |
| | 1 | 46 w DD | 20±6 | 195 w/o DD<br>65 HC | 24±5<br>25±4 | Yes<br>Yes | (177) |
| | 1 | 12 w DD | 21.1±2.8 | 28 w/o DD | 21.0±3.5 | No | (101) |
| Systolic Pulmonary Arterial Pressure (mmHg) | | | | | | | (23, 39, 46, 57, 91, 131, 170, 185, 194, 199, 211) |
| >35 mmHg | 8 | C + W/o | 150/674 (22.3%) | Hc | 1/202 (0.5%) (25, 44, 196) | | (25, 44, 100, 115, 168, 170, 196, 199) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| >40 mmHg | 6 | C + W/o + w | 240/7504 (3.2%) | Hc | 0/78 (0.0%) (140, 153, 172) | | (40, 128, 131, 140, 153, 197) |
| >45 mmHg | 1 | C | 44/124 (35.5%) | | | | (91) |
| >50 mmHg | 1 | C | 6/115 (5.2%) | | | | (160) |
| Mean (SD) | 1 | 104 c | 28.9±8.7 | 37 hc | 21.7±6.3 | Yes | (71) |
| | 1 | 50 c | 32.3±17.1 | 44 hc | 20.7±5.6 | Yes | (171) |
| | 1 | 45 c | 25.4±8.7 | 20 hc | 20.2±3.4 | Yes | (96) |
| | 1 | 23 c | 43.2±9.8 | 25 hc | 23.2±5.8 | Yes | (100) |
| | 1 | 40 c | 24.2±5.7 | 40 hc | 19.8±6.2 | Yes | (101) |
| | 1 | 40 w/o | 35.2±5.8 | 45 hc | 19.9±6.0 | Yes | (105) |
| | 1 | 17 w/o | 33.1±6.0 | 15 hc | 27.7±3.8 | Yes | (172) |
| | 1 | 51 w/o | 25.0±4.8 | 20 hc | 20.1±2.3 | Yes | (192) |
| | 1 | 45 w/o | 33±14 | 43 hc | 22±5 | Yes | (111) |
| | 1 | 30 w/o | 29.9±8.8 | 30 hc | 22.9±9.8 | Yes | (68) |
| | 1 | 72 c | 40.9±16.4 | 64 hc | 30.1±2.5 | Yes | (44) |
| | 1 | 100 w/o | 33.3±0.6 | 26 hc | 30.8±1.0 | No | (153) |
| | 1 | 42 c | 24.1±8 | 42 hc | 21±7 | No | (121) |
| | 1 | 35 c | 24.0±23.3 | 35 hc | 23.3±6.4 | No | (186) |
| | 1 | 70 w/o | 26.2±5.7 | 25 hc | 25.8±2.9 | No | (150) |
| | 1 | 72 w/o | 26.6±7.5 | 30 hc | 25.5±2.8 | No | (127) |
| | 1 | 42 w/o | 30.3±5.4 | 20 hc | 27.6±3.8 | No P=0.078 | (62) |
| | 1 | 35 w DD | 33±11 | 118 w/o DD | 31±15 | No | (136) |
| | 1 | 25 w DD | 35±17 | 25 w/o DD | 25±7 | Yes | (82) |
| | 1 | 202 AA | 39.3±17.2 | 200 non-AA | 32.8±14.2 | Yes | (202) |
| Median | 1 | 31 c | 26 (20-36) | 41 hc | 20 (18-24) | Yes | (24) |
| | 1 | 31 w/o | 36.5 (31-44.5) | 32 hc | 26 (22-29) | Yes | (107) |
| | 1 | 37 w | 30 (20-51) | 37 hc | 20 (14-28) | Yes | (140) |
| | 1 | 103 w/o | 27 (22-35) | 103 hc | 23 (10-27) | Yes | (180) |
| Right ventricle systolic pressure (mmHg) | | | | | | | (145) |
| Mean±SD | 1 | 14 c | 25±4.3 | | | | (89) |
| | 1 | 42 w/o | 33.5±8,7 | 40 hc | 28.8±4.4 | Yes | (149) |
| | 1 | 17 c | 34.4±7.1 | 17 hc | 35.3±6.0 | No | (169) |
| | 1 | | 34.3±5.9 | | 31.2±2.3 | No | (188) |
| | | | | | | | |
| Median (IQR) | 1 | 14 c | 25 (19-35) | | | | (89) |
| | 1 | 95 c | 28.6 (23.5-33.1) | 54 hc | 13.4 (11.8-14.6) | Yes | (210) |
| RV/RA gradient (mmHg) | | | | | | | |
| Mean±SD | 1 | 110 c | 28±11 | 105 hc | 23±4 | Yes | (196) |
| Mean Pulmonary Arterial Pressure (mmHg) | | | | | | | |
| | 1 | 30 c | 17.8±6.3 | 30 hc | 14.4±6.9 | No (p=0.054) | (68) |
| Pulmonary Acceleration Time (m/s) | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 26 c | 119±11 | 24 c | 142±13 | Yes | (93) |
| | 1 | 110 c | 105±32 | 105 hc | 114±35 | Not reported | (196) |
| | 1 | 10 w/o ILD | 125±30 | 24 w ILD<br>21 hc | 105±30<br>135±15 | No<br>No | (124) |
| <90 | 1 | W | 4/37 (10.8%) | Hc | 0/37 (0.0%) | Yes | (140) |
| Isovolumetric Acceleration (m/s2) | | | | | | | |
| | 1 | 22 c | 2.3±0.4 | 22 hc | 4.1±0.8 | Yes | (142) |
| Pulmonary Ejection time (ms) | | | | | | | |
| | 1 | 17 c | 360 (320-388) | 23 hc | 340 (320-350) | Yes | (208) |
| RV diastolic dysfunction | | | | | | | |
| Tricuspid E (cm/s) | | | | | | | |
| *Mean±SD* | 1 | 111 c | 52.2±11.4 | 21 hc | 58.8±11.2 | Yes | (122) |
| | 1 | 70 c | 47.5±9.2 | 25 hc | 54.3±8.9 | Yes | (150) |
| | 1 | 63 c | 56±10 | 40 c | 60±10 | No | (56) |
| | 1 | 77 c | 41.4±14.1 | 36 hc | 45.1±8.5 | No | (134) |
| | 1 | 23 c | 49±2 | 25 hc | 55±1 | No | (100) |
| *Median (IQR)* | 1 | 42 w/o | 55.9 (46.9-59.6) | 40 hc | 56.8 (53.9-62.4) | Yes | (149) |
| Tricuspid A (cm/s) | | | | | | | |
| *Mean±SD* | 1 | 63 c | 54±20 | 40 hc | 43±10 | Yes | (56) |
| | 1 | 111 c | 50.5±13.5 | 21 hc | 46.4±10.4 | No | (122) |
| | 1 | 77 c | 37.9±15.2 | 36 hc | 36.5±9.7 | No | (134) |
| | 1 | 70 c | 39.5±8.8 | 25 hc | 39.0±5.6 | No | (150) |
| | 1 | 23 c | 47±0.9 | 25 hc | 46±2 | No | (100) |
| *Median (IQR)* | 1 | 42 w/o | 38 (353.1-39.8) | 40 hc | 44.2 (41.5-49.5) | Yes | (149) |
| Tricuspid E/A | | | | | | | |
| *Mean±SD* | 1 | 111 c | 1.05±0.24 | 21 hc | 1.3±0.3 | Yes | (122) |
| | 1 | 20 c | 1.08±0.48 | 15 hc | 1.5±0.6 | Yes | (112) |
| | 1 | 30 w/o | 1.01±1.3 | 30 hc | 1.19±0.89 | Yes | (68) |
| | 1 | 63 c | 1.04±0.3 | 40 hc | 1.36±0.4 | Yes | (56) |
| | 1 | 77 c | 1.2±0.4 | 36 hc | 1.2±0.2 | No | (134) |
| | 1 | 52 w/o | 1.2±0.4 | 52 hc | 1.4±0.4 | No | (176) |
| *Median (IQR)* | 1 | 42 w/o | 1.4 (1.3-1.7) | 40 hc | 1.30 (1.14-1.38) | Yes | (149) |
| Tricuspid E’ | | | | | | | |
| *Mean±SD* | 1 | 111 c | 12.0±3.6 | 21 hc | 12.7±2.7 | No | (122) |
| | 1 | 31 w/o | 11.7 (9.7-14.6) | 32 hc | 13.7 (12.3-15) | Yes | (107) |
| | 1 | 70 c | 9.5±2.3 | 25 hc | 11.7±2.8 | Yes | (150) |
| Tricuspid E/E’ (cm/s) | | | | | | | |
| *Mean±SD* | 1 | 111 c | 4.8±1.8 | 21 hc | 4.7±0.8 | No | (122) |
| | 1 | 70 c | 5.3±1.5 | 25 hc | 4.9±1.4 | No | (150) |
| | 1 | 52 w/o | 3.9±1.9 | 52 hc | 9.0±5.0 | Yes | (176) |
| *Median (IQR)* | 1 | 31 w/o | 4.3 (3.3-5.2) | 32 hc | 3.4 (2.9-3.9) | Yes | (107) |
| | 1 | 95 W/o | 4.8 (3.8-5.9) | 54 hc | 4.15 (3.4-4.8) | Yes | (210) |
| | 1 | 42 w/o | 5.20 (4.19-6.35) | 40 hc | 4.60 (4.10-4.90) | Yes | (149) |
| RV Tei Index | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Mean±SD* | 1 | 111 c | 0.38±0.08 | 21 hc | 0.29±0.02 | Yes | (122) |
| *Median (IQR)* | 1 | 42 w/o | 0.40 (0.30-0.43) | 40 hc | 0.30 (0.30-0.40) | No (p=0.09) | (149) |
| LV diastolic dysfunction | | | | | | | (82, 160) |
| Present | 1 | C | 35/153 (22.9%) | | | | (136) |
| | 1 | C | 47/110 (42.7%) | | | | (115) |
| Mitral E/A <1 | 1 | C | 10/19 (52.6%) | | | | (143) |
| | 1 | C | 4/30 (13.3%) | | | | (48) |
| | 1 | C | 16/35 (46.0 %) | hc | 5/35 (14.0%) | Yes | (178) |
| | 1 | W | 17/37 (45.9%) | Hc | 15/37 (40.5%) | No | (140) |
| | 1 | C | 7/25 (28%) | Hc | 2/25 (8%) | No (p=0.06) | (168) |
| Mitral E/A | | | | | | | (39, 125, 141, 152) |
| *Mean* | 1 | 14 c | 1.03±0.3 | | | | (89) |
| | 1 | 120 c | 1.0±0.4 | | | | (191) |
| | 1 | 570 c | 1.1±0.4 | | | | (90) |
| | 1 | 243 c | 1.13±0.36 | | | | (199) |
| | 1 | 42 c | 1.1±0.4 | 42 hc | 1.3±0.4 | No | (121) |
| | 1 | 124 c | 1.14±0.46 | 41 hc | 1.26±0.20 | No | (91) |
| | 1 | 17 c | 1.01±0.39 | 17 hc | 0.75±0.23 | No | (169) |
| | 1 | 35 c | 1.1±0.4 | 35 hc | 1.2±0.3 | No | (120) |
| | 1 | 35 c | 1.3±0.4 | 35 hc | 1.3±0.4 | No | (94) |
| | 1 | 24 w/o | 1.1±0.3 | 24 hc | 1.2±0.2 | No | (97) |
| | 1 | 23 c | 1.04±0.4 | 25 hc | 1.2±0.8 | No | (100) |
| | 1 | 27 c | 1.04±0.24 | 26 hc | 1.29±0.61 | No | (80) |
| | 1 | 17 w/o | 1.18±0.3 | 15 hc | 1.21±0.5 | No | (172) |
| | 1 | 110 c | 1.1±0.3 | 105 hc | 1.1±0.3 | No | (196) |
| | 1 | 35 c | 1.18±0.38 | 35 hc | 1.13±0.27 | No | (186) |
| | 1 | 30 w/o | 1.28±0.52 | 30 hc | 1.39±1.29 | No | (68) |
| | 1 | 52 w/o | 1.2±0.4 | 52 hc | 1.1±0.4 | No | (176) |
| | 1 | 27 c | 1.05±0.3 | 27 hc | 0.90±0.02 | No | (186) |
| | 1 | 42 w/o | 1.02±0.6 | 20 hc | 1.24±0.51 | No (p=0.07) | (62) |
| | 1 | 72 w/o | 1.08±0.3 | 30 hc | 1.37±0.3 | Yes | (127) |
| | 1 | 20 w/o | 1.02±0.42 | 15 hc | 1.48±0.26 | Yes | (112) |
| | 1 | 100 w/o | 1.0±0.3 | 26 hc | 1.2±0.6 | Yes | (153) |
| | 1 | 30 c | 1.09±.01 | 48 hc | 1.33±0.06 | Yes | (119) |
| | 1 | 18 c | 1.36±0.49 | 10 hc | 1.75±0.53 | Yes | (135) |
| | 1 | 77 c | 1.2±0.5 | 36 hc | 1.5±0.1 | Yes | (134) |
| | 1 | 35 w/o | 1.03±0.42 | 25 hc | 1.44±0.28 | Yes | (102) |
| | 1 | 50 w/o | 1.04±0.4 | 25 hc | 1.45±0.2 | Yes | (26) |
| | 1 | 45 c | 0.89±0.16 | 20 hc | 1.04±0.21 | Yes | (96) |
| | 1 | 41 c | 0.87±0.2 | 30 hc | 1.38±0.5 | Yes | (170) |
| | 1 | 20 c | 1.10±0.04 | 20 hc | 1.34±0.19 | Yes | (92) |
| | 1 | 26 c | 0.94±0.37 | 24 hc | 1.18±0.34 | Yes | (93) |
| | 1 | 50 c | 1.2±0.9 | 31 hc | 1.35±0.1 | Yes | (25) |
| | 1 | 63 c | 1.02±0.3 | 40 hc | 1.37±0.4 | Yes | (56) |
| | 1 | 111 c | 0.98±0.3 | 21 hc | 1.21±0.28 | Yes | (122) |
| | 1 | 15 c | 1.23±0.37 | 18 hc | 1.72±0.31 | Yes | (181) |
| | 1 | 11 w CVE | 0.8±0.3 | 22 w/o CVE | 0.9±0.3 | No | (194) |
| *Median* | 1 | 14 c | 1 (0.7-1.8) | | | | (89) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 33 w/o | 1.2 (0.9-1.4) | 16 hc | 1.2 (0.9-1.6) | No | (118) |
| | 1 | 31 w/o | 1 (0.8-1.2) | 32 hc | 1.1 (0.9-1.4) | No | (107) |
| | 1 | 47 w/o | 0.88 (0.72-1.35) | 36 hc | 1.16 (0.i87-1.36) | No | (198) |
| | 1 | 103 w/o | 1.03 (0.83-1.30) | 103 hc | 1.05 (0.87-1.27) | | (180) |
| Mitral E (cm/s) | | | | | | | |
| *Mean* | 1 | 570 w/o | 75±19 | | | | (90) |
| | 1 | 24 c | 59.2±15.7 | 24 hc | 65.3±8 | Yes | (129) |
| | 1 | 20 c | 78±13 | 20 hc | 85±17 | Yes | (92) |
| | 1 | 18 c | 88.5±17.8 | 18 hc | 75.9±17.1 | Yes | (135) |
| | 1 | 35 c | 70±30 | 35 hc | 60±20 | No (p=0.06) | (120) |
| | 1 | 35 w/o | 69±22 | 25 hc | 80±21 | No (p=0.07) | (102) |
| | 1 | 27 c | 74±14 | 26 hc | 79±19 | No | (80) |
| | 1 | 77 c | 65.7±17.0 | 36 c | 70.0±8.5 | No | (134) |
| | 1 | 50 w/o | 71±20 | 25 hc | 80±21 | No | (26) |
| | 1 | 23 c | 68±9 | 25 hc | 70±20 | No | (100) |
| | 1 | 111 c | 73.2±17.0 | 21 hc | 87.4±14.3 | No | (122) |
| | 1 | 24 w/o | 76.4±15.8 | 24 hc | 78.2±9.2 | No | (97) |
| | 1 | 50 c | 81.1±15.8 | 31 hc | 85.2±18.2 | No | (25) |
| | 1 | 124 c | 66.6±12.3 | 41 hc | 70.2±10.2 | No | (91) |
| | 1 | 26 c | 67±14 | 24 hc | 73±15 | No | (93) |
| | 1 | 63 c | 78±20 | 40 hc | 82±20 | No | (56) |
| *Median* | 1 | 47 w/o | 78 (70-87) | 36 hc | 85 (70-95) | No | (198) |
| Mitral A (cm/s) | | | | | | | |
| *Mean* | 1 | 570 c | 73±21 | | | | (90) |
| | 1 | 35 w/o | 70±12 | 25 hc | 57±13 | Yes | (102) |
| | 1 | 77 c | 57.5±17.4 | 36 hc | 46.6±8.8 | Yes | (134) |
| | 1 | 24 c | 56.2±19.9 | 24 hc | 36.7±4.9 | Yes | (129) |
| | 1 | 35 c | 70±20 | 35 hc | 50±10 | Yes | (120) |
| | 1 | 124 c | 64.5±18.7 | 41 hc | 55.9±14.2 | Yes | (91) |
| | 1 | 20 c | 73±11 | 20 hc | 63±39 | Yes | (92) |
| | 1 | 50 c | 70.2±16.2 | 31 hc | 63.8±7.8 | Yes | (25) |
| | 1 | 63 c | 81±39 | 40 hc | 61±10 | Yes | (56) |
| | 1 | 111 c | 76.9±18.6 | 21 hc | 66.5±16.2 | Yes | (122) |
| | 1 | 50 w/o | 72±16 | 25 hc | 57±16 | Yes | (26) |
| | 1 | 24 w/o | 74.2±16.3 | 24 hc | 65.4±13.9 | No (p=0.09) | (97) |
| | 1 | 26 c | 76±15 | 24 hc | 65±16 | No (p=0.09) | (93) |
| | 1 | 27 c | 71±13 | 26 hc | 67±20 | No | (80) |
| | 1 | 23 c | 65±6 | 25 hc | 62±10 | No | (100) |
| | 1 | 18 c | 55.2±5.3 | 10 hc | 59.4±16.1 | No | (135) |
| *Median* | 1 | 47 w/o | 80 (63-93) | 36 hc | 71 (64-83) | No | (198) |
| Mitral e’ | | | | | | | |
| *Median* | 1 | 42 w/o | 10.8 (8.2-14.2) | 40 hc | 12.1 (10.5-12.7) | No | (149) |
| Mitral E’ (cm/s) | | | | | | | |
| *< 10* | 1 | c | 75/234 (32%) | | | | (199) |
| *Mean* | 1 | 234 c | 11.2±2.8 | | | | (199) |
| | 1 | 35 c | 10.6±4.2 | 35 hc | 8.8±2.2 | Yes | (120) |
| | 1 | 72 w7o | 10.9±1.4 | 30 hc | 9.8±2.8 | Yes | (127) |
| *Median* | 1 | 31 w/o | 9.04 (7.2-11.6) | 32 hc | 7.37 (6.2-7.99) | Yes | (107) |
| Mitral a’ | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Median* | 1 | 42 w/o | 13.2 (11.9-15.8) | 40 hc | 9.4 (8.7-10.1) | No | (149) |
| Mitral A' (cm/s) | | | | | | | |
| *Mean* | 1 | 35 c | 8.8±2.6 | 35 hc | 7.6±1.8 | Yes | (120) |
| Mitral e'/a' | | | | | | | |
| *Median* | 1 | 42 w/o | 0.7 (0.5-1.0) | 40 hc | 1.1 (0.9-1.3) | No | (149) |
| Mitral E/E' | | | | | | | |
| *Mean* | 1 | 35 c | 7.2±2.1 | 35 hc | 7.3±2.3 | No | (120) |
| | 1 | 111 c | 7.55±2.85 | 21 hc | 6.9±2.3 | No | (122) |
| | 1 | 110 c | 9.8±3.9 | 105 hc | 8.7±3.4 | Yes | (196) |
| | 1 | 42 c | 7.6±2.4 | 42 hc | 6.5±1.5 | Yes | (121) |
| | 1 | 72 w/o | 9.3±2.8 | 30 hc | 7.4±1.4 | Yes | (127) |
| | 1 | 52 c | 6.6±2.6 | 52 hc | 7.8±2.5 | Yes | (176) |
| | 1 | 11 w CVE | 9.2±3.3 | 22 w/o CVE | 9.3±7.9 | No | (194) |
| *Median* | 1 | 103 w/o | 8.8 (7.1-10.4) | 103 hc | 9.0 (7.6-10.9) | No | (180) |
| | 1 | 47 w/o | 9 (7.1-11) | 36 hc | 8.9 (7.1-9.6) | No | (198) |
| Mitral s' | | | | | | | |
| *Median* | 1 | 42 w/o | 12.9 (11.5-15.7) | 40 hc | 12.0 (11.3-12.7) | No | (149) |
| Mitral S' | | | | | | | |
| *Mean* | 1 | 35 c | 7.5±2.1 | 35 hc | 6.9±1.3 | No | (120) |
| *Median* | 1 | 31 w/o | 7.7 (6.7-7.5) | 32 hc | 9.3 (8.1-10.5) | Yes | (107) |
| LV Tei Index | 1 | 111 c | 0.46±0.09 | 21 hc | 0.39±0.06 | Yes | (122) |
| Isovolumetric relaxation time (IVRT) – ms | | | | | | | (149, 212) |
| *Mean* | 1 | 20 c | 35.4±12.7 | 20 hc | 19.2±6.3 | Yes | (92) |
| | 1 | 77 c | 78.5±1.4 | 36 hc | 59.3±0.9 | Yes | (134) |
| | 1 | 111 c | 73.2±12.0 | 21 hc | 64.3±7.8 | Yes | (122) |
| | 1 | 27 c | 97.6±13.1 | 26 hc | 91.2±5.3 | Yes | (80) |
| | 1 | 77 c | 77.7±14.4 | 45 hc | 60.0±6.4 | Yes | (152) |
| | 1 | 22 c | 62.4±34.6 | 22 hc | 11.7±18.2 | Yes | (142) |
| | 1 | 23 c | 80±11 | 25 hc | 78.5±9.7 | No | (100) |
| | 1 | 35 c | 61±14 | 35 hc | 66±15 | No | (94) |
| | 1 | 40 w/o | 63.2±11.2 | 46 hc | 65.4±9.0 | No | (105) |
| | 1 | 110 c | 84±19 | 105 hc | 85±15 | No | (196) |
| | 1 | 35 c | 98.8±13.8 | 35 hc | 97.6±15.5 | No | (186) |
| | 1 | 27 c | 111±20 | 17 hc | 110±21 | No | (66) |
| *Median* | 1 | 33 c | 87 (78-95) | 16 hc | 87 (82-97) | No | (118) |
| Pulmonary Vascular Resistances (WU) | | | | | | | |
| Median | 1 | 103 c | 1.5 (1.2-1.8) | 103 hc | 1.1 (0.9-1.4) | Yes | (180) |
| | | 42 c | 1.56 (1.28-1.99) | 40 hc | 1.10 (0.99-1.30) | Yes | (149) |
| Pericardium Alteration | | | | | | | |
| Non specified – Present | 5 | C | 58/487 (11.9%) | | 1/50 (2.0%) (125) | | (27, 34, 35, 94, 133) |
| Pericardial Thickening | | | | | | | |
| Present | 1 | W | 2/10 (20.0%) | | | | (69) |
| ≥7mm | 1 | C | 14/80 (17.5%) | | | | (104) |
| Pericardial effusion | 20 | C | 135/1363 (9.9%) | | 2/446 (0.4%) (25, 44, 56, 58, 106, 124, | | (28, 33, 41, 43, 44, 56, 58, 81, 86, |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 135, 140, 153, 196) | | 91, 104, 106, 115, 125, 135, 141, 160, 196, 197, 199) |
| | 6 | w/o | 27/300 (9.0%) | | | | (37, 124, 131, 153, 168, 187) |
| | 4 | W | 35/128 (27.3%) | | | | (64, 69, 113, 140) |
| Tamponade | 1 | W | 4/23 (17.4%) | | | | (64) |
| Inferior Vena Cava | | | | | | | |
| Diameter (mm) | 1 | 17 c | 14.5 (12.3-17) | 22 hc | 14 (10-17) | No | (208) |
| | 1 | 70 w/o | 14.0±3.8 | 25 hc | 14.8±4.7 | No | (150) |
| | 1 | 25 c | 15.7±3.0 | 25 hc | 14.0±3.9 | No | (168) |
| | 1 | 23 c | 16±3 | 25 hc | 15±3 | No | (100) |
| | 1 | 42 w/o | 15.0 (11.3-17.0) | 40 hc | 11.9 (10.2-15.6) | Yes | (149) |
| Respiratory variation (%) | 1 | 17 c | 65 (59-68.5) | 22 hc | 100 (66.8-100) | Yes | (208) |
| | 1 | 70 c | 55.5±11.5 | 25 hc | 55.0±13.4 | No | (150) |
| Strain Echo | | | | | | | |
| Peak Myocardial systolic velocity on STRAIN Echo (cm/s) | 1 | 22 c | 11.6±2.3 | 22 hc | 13.9±2.7 | Yes(142) | |
| | 1 | 35 c | 5.3±0.7 | 35 hc | 5.6±0.6 | No | (178) |
| Peak systolic velocity on STRAIN Echo (cm/s) | 1 | 27 w/o | 10.7±1.8 | 17 hc | 11.4±1.4 | No | (66) |
| Tricuspid anular peak systolic velocity (cm/s) | 1 | 103 c | 6.4±1.8 | 103 hc | 6.9±1.7 | No | (180) |
| Peak systolic Strain Rate (/s) | 1 | 18 c | 2.1 (1.3-3.1) | | | | (185) |
| | 1 | 17 w/o | 1.7±0.5 | 15 hc | 3.8±1.7 | Yes | (172) |
| *Global* | 1 | 45 c | 1.1±0.1 | 20 hc | 0.9±0.2 | Yes | (96) |
| | 1 | 35 w/o | -1.3±0.1 | 35 hc | -1.6±0.1 | Yes | (178) |
| *RV* | 1 | 17 c | -5.5 (-6.4-2.6) | 23 hc | -1.8 (-3.9 - 1.4) | Yes | (208) |
| | 1 | 27 c | -2.9±0.6 | 26 hc | -3.2±0.7 | No | (80) |
| *Basal IVS* | 1 | 17 c | -1.0 (-1.6-0.7) | 15 hc | -1.1 (-1.6-0.8) | No | (208) |
| Peak diastolic Strain Rate (/s) | 1 | 18 c | 2.6 (1.4-6.7) | | | | (185) |
| | 1 | 17 w/o | 3.7±1.5 | 15 hc | 5.6±1.2 | Yes | (172) |
| Early diastolic Strain Rate (/s) | 1 | 95 w/o | 1.5 (1.2-1.7) | 54 hc | 1.5 (1.3-1.8) | No | (210) |
| Basal IVS longitudinal strain (%) | 1 | 17 c | -18.6 (-27.9-6.0) | 15 c | -17.1 (-20.6-3.6) | No | (208) |
| Free wall RV longitudinal strain (%) | 1 | 45 w/o | -30±5 | 43 hc | -31.3±4 | No | (111) |
| | 1 | 17 c | -25.2 (-53.7 - 6.8) | 23 hc | -28.6 (-43.3-21-2) | No | (208) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 46 w DD | -20±7 | 195 w/o DD | -25±5 | Yes | (177) |
| Positive peak LA longitudinal strain (%) | 1 | 42 c | 18.4±4 | 42 hc | 21.4±7.6 | Yes | (121) |
| Negative peak LA longitudinal strain (%) | 1 | 42 c | 31.3±4.2 | 42 hc | 35.0±7.6 | Yes | (121) |
| Global Longitudinal strain (%) | 1 | 234 c baseline | -20.9±2.0 | 234 c f/u | -19.3±2.5 | Yes | (199) |
| | 1 | 45 c | -13.6±2.7 | 20 hc | -12.2±2.9 | No | (96) |
| | 1 | 35 W/o | -19.5±2.3 | 35 hc | -26.1±2.4 | Yes | (178) |
| | 1 | 95 w/o | -20.4±2 | 54 hc | -21.5±1.9 | Yes | (210) |
| LV | 1 | 104 w/o | -18.2±1.8 | 37 hc | -21.3±1.7 | Yes | (71) |
| | 1 | 25 w/o | -17.4±1.6 | 25 hc | -19.2±8.8 | Yes | (168) |
| | 1 | 52 w/o | -19.2±4.4 | 52 hc | -21.1±2.5 | Yes | (176) |
| | 1 | 72 w/o | -19.3±1.5 | 30 hc | -17.2±2.3 | Yes | (127) |
| | 1 | 33 w/o | -18.6±1.6 | 20 hc | -21.1±1.2 | Yes | (164) |
| | 1 | 47 w/o | -17.5±5.7 | 36 hc | -20.6±2.7 | Yes | (198) |
| | 1 | 27 c | -19.8±3.0 | 26 hc | -23.4±2.8 | Yes | (80) |
| | 1 | 40 c | -20.5±3.4 | 40 hc | -20.9±2.7 | No | (101) |
| RV | 1 | 25 w/o | -20.3±5.4 | 25 hc | -24.9±3.6 | Yes | (168) |
| | 1 | 52 w/o | -18.2±9.1 | 52 hc | -22.2±7.1 | Yes | (176) |
| | 1 | 45 w/o | -24.8±4 | 43 hc | -25.6±3 | No | (111) |
| | 1 | 47 w/o | -17.5±4.2 | 36 hc | -18.9±3.9 | No | (198) |
| | 1 | 27 c | -28.2±6.8 | 26 hc | -30.7±6.4 | No | (80) |
| Global Circumferential Strain (%) | | | | | | | |
| LV | 1 | 104 w/o | -18.2±2.3 | 37 hc | -21.3±2.1 | Yes | (71) |
| | 1 | 33 w/o | -18.7±1.7 | 20 hc | -20.7±1.4 | Yes | (164) |
| | 1 | 47 w/o | -18.2±3.2 | 36 hc | -19.8±2.7 | Yes | (198) |
| | 1 | 95 w/o | -22.7 (-25-21.2) | 54 hc | -25.3 (-28.3-23.3) | Yes | (210) |
| | 1 | 40 c | -17.5±5.5 | 40 hc | -18.8±4.8 | No | (101) |
| Global radial strain (%) | | | | | | | |
| LV | 1 | 104 w/o | 37.0±13.9 | 37 hc | 40.3±12.4 | No | (71) |
| | 1 | 40 c | 39.4±18.6 | 40 hc | 42.2±13.1 | No | (101) |
| Coronary flow reserve | | | | | | | |
| ≥ 2.00 | 1 | w/o | 24/44 (54.5%) | | | | (187) |
| | 1 | C | 14/29 (48.3%) | | | | (184) |
| Mean | 1 | 29 c | 1.93±0.56 | 11 hc | 1.81±0.56 | Yes | (184) |

Table 15 – Other tests.

Data reported from 16 publications, including 443 patients (27, 37, 57, 58, 79, 88, 89, 132, 142, 150, 169, 181, 186, 197, 209) and 146 controls (58, 142, 169, 181, 186, 209).

| **Test** | **N° papers** | **N° patients** | **Value/prevalence in patients** | **N° controls** | **Value/prevalence in controls** | **Statistically significant difference** | **References** |
|---|---|---|---|---|---|---|---|
| Biopsy | | | | | | | |
| Endo-myocardial | 2 | 41 | Various degrees of myocardial fibrosis and inflammatory infiltrate, with increase in collagen and perivascular fibrosis. | | | | (27, 57) |
| Pericardial | 1 | 8 | 4 pts with fibrosis, 2 with granulomatous lesions, 2 with inflammation. | | | | (197) |
| Six minutes walking test | | | | | | | |
| Six minutes walking distance (m) | 1 | 70 | 391±95 | | | | (150) |
| Exercise Heart Rate Recovery (bpm) | | | | | | | |
| 1 minutes after stress | 1 | 35 c | 21.8±4.4 | 35 hc | 27.7±4.3 | Yes | (186) |
| 2 minutes after stress | 1 | 35 c | 43.8±6.3 | 35 hc | 47.6±4.4 | Yes | (186) |
| 3 minutes after stress | 1 | 35 c | 58.8±10.3 | 35 hc | 63.6±7.3 | Yes | (186) |
| Ventriculography | | | | | | | |
| With cold test | 1 | 16 c | | | | | (74) |
| Signal-averaged ECG | | | | | | | |
| Ventricular Late potentials | 1 | W | 11/24 (45.8%) | Hc | 2/24 (8.3%) | Yes | (181) |

### 5.e. Meeting session 2: creating a consensus guidance

Five virtual meeting were held online between November 2020 and July 2021, involving the Core Leadership Team and the Expert Committee.

During the first three meetings, in which the results of the second systematic literature review were presented and discussed, the Expert Committee reviewed and proposed changed to already available echocardiography and cardiac magnetic resonance procotols, adapting them to SSc patients. Finally, consensus for the evaluation of cardiac involvement in SSc was released.

Overall, various topics were stressed by general considerations. First of all, the importance of detecting SSc-pHI and including cardiac evaluations as part of regular SSc patient assessment in the light of the non-invasive nature of the tests and given its prognostic importance. History or presence of symptoms (cardiac red flags) arising the suspicion for cardiac involvement (such as dyspnea, chest pain, palpitations, syncope, dizziness) should be always part of the medical interview and patients should be educated/motivated to report such symptoms. In addition to medical history, cardiovascular physical examination/assessment should be part of the SSc rheumatology consultation, as a basis.

The identification of patients at higher risk of SSc-pHI is an area of outmost importance, where we lack an evidence base data: there is an unmet need to define and refine clinical suspicion more effectively, in order to translate it into clinical practice. High-risk SSc clinical profile in the literature includes male gender, diffuse cutaneous skin subset, the positivity of specific auto-antibodies, early disease duration, presence of peripheral myopathy and other inflammatory manifestations.

A multi-disciplinary working (cardiologist and non-cardiologist scleroderma expert) was strongly recommended, when possible and feasible. SSc-caring physicians should share the high-risk “scleroderma” profile features with cardiologists to support a tighter timing for assessments. Similarly, cardiologists should give inputs if the normal screening time would be too long and advice for a shorter-term assessment based on specific alterations. As for other assessments, evaluation from an SSc-experienced cardiologist and follow-up by the same cardiologist are recommended.

In the light of the application of laboratory and instrumental tests, the Experts Committee agreed that “Screening” refers to assessing patients belonging to a group with non-increased risk of developing heart involvement at present, as well as those whom we may feel the risk but are asymptomatic. Conversely, “Diagnosis” refers to assessing patients presenting with symptoms/signs compatible with SSc-pHI.

Regarding the use of laboratory tests, the previously proposed protocol from Bissell et al reported suggestion for CK, Troponin and NT-proBNP annually in asymptomatic/uninvolved patients, while 6-monthly for at risk/symptomatic/involved cases (18) (Table 16).

Table 16. Recommended testing and frequency of testing for SSc cardiomyopathy, according to the United Kingdom Systemic Sclerosis Study group. Adapted from Bissell et al (18).

| Baseline Test | Monitoring | | |
|---|---|---|---|
| | Asymptomatic/ uninvolved | At risk | Symptomatic/ Involved |
| Resting ECG | Annual | 6-monthly | 6-monthly |
| Echocardiography | Annual | 6-monthly | 6-monthly |
| Troponin, CK | Annual | 6-monthly | 6-monthly |
| NTpro-BNP | Annual | 6-monthly | 6-monthly |
| Targeted questioning for red flag symptoms | Each visit | Each visit andcardiology referral | Each visit |

Despite overall agreement with the previous consensus guidance, the Expert Committee indicated BNP as more reliable in case of patients with renal failure when compared to NT-proBNP (which is instead recommended in patients with systolic heart failure). In addition, they suggested considering the use of Statins when evaluating CK levels.

For unselected stable - asymptomatic patient, the Expert Committee suggested at least one annual assessment including Hs-Troponin and NT-proBNP, to identify patients with some abnormalities and try to guide the cardiologists on which patients to search for sub-abnormalities. C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and CK were also suggested to be performed every year, as a cardiac non-specific workup. In particular, this considered the performance of these three tests for other purposes (such as inflammatory articular or muscular involvement), therefore helpful when considering confounders and differential diagnosis.

In patients with symptoms or unstable clinical presentation, the same abovementioned laboratory tests were suggested as a minimum annual evaluation, with timing and additional tests also guided by weather there had been any previous or current evidence of ongoing cardiomyopathy, otherwise symptoms-guided and diagnostic tests-guided.

Regarding the use of electrocardiography - ECG, Bissell et al (18) still suggested an annual rest ECG to asymptomatic/uninvolved patients and 6-montly test to at risk/ symptomatic/ involved cases. As a general consideration, the Expert Committee stressed the importance of taking concomitant medications (i.e. β-blockers, anti-depressants) and metabolic disorders (such as potassium disorders) into account, in particular when evaluating conduction abnormalities such as QTc interval. Moreover, there was a suggestion to focus more thoroughly on alterations that might change the treatment of the patient, such as atrial fibrillation, malignant arrhythmias (i.e., non-sustained or sustained ventricular tachycardia) and major conduction disorders (leading to pace-maker or implantable cardiac defibrillator implantation), while all other alterations might be considered minor (as requiring minor treatments, such as β-blockers).

For unselected stable - asymptomatic patient, the Expert Committee considered annual resting ECG to pick up fixed abnormalities, while annual ECG-Holter may be considered in selected patients with higher risk profile, if feasible according to local availability. There was no clear background position to identify a risk model to implement Holter/prolonged monitoring as a routine base for all patients, although not invasive and carrying prognostic significance. Overall, the Expert Committee agreed that Holter ECG should report alterations both qualitatively (presence) and quantitatively (number).

For patients with symptoms or unstable clinical presentation, rest ECG should then eventually repeated during/immediately before the Cardiology consultation. In case of “cardiac” symptoms, an Holter ECG was also deemed important before the Cardiology consultation. These tests would be mostly driven on an individual basis, by integrating the clinical context. Merging physical examination, symptoms and other laboratory/imaging biomarkers should guide to a Cardiology consultation to individualize the further workup. Other electrocardiographic modalities should be considered as research agenda for prospective studies, such as loop-recorder implantation or cardio-pulmonary exercise test (CPET). For patients with already symptomatic atrial/ventricular arrhythmias, Holter ECG would represent the most promising assessment to evaluate the burden of atrial and/or ventricular arrhythmia. This still requires evaluation in a prospective systematic registry. In general, based on pre-existing cardiology management and known diagnosis, the cardiologist should guide the choice of the appropriate frequency of monitoring and nature of ECG testing.

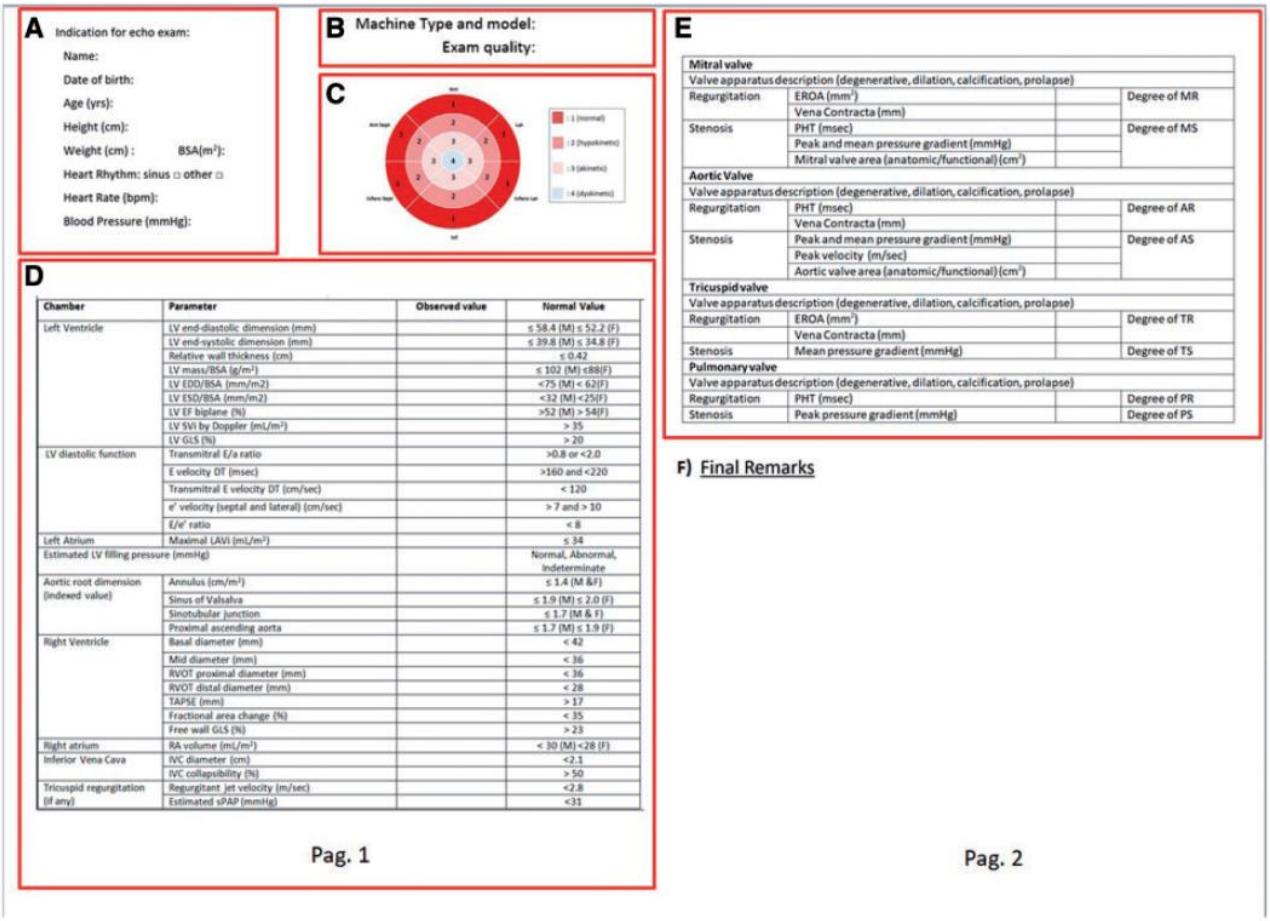
The previous consensus guidance from Bissell et al recommended the use of echocardiography - ECHO annually in asymptomatic/uninvolved patients and 6-montly to at risk/symptomatic/involved cases (18). As general concerns, the Expert Committee stressed the importance of ECHO to include both 2-chambers and 4-chambers (biplane) and advocated high-skill training of sonographers. This was deemed necessary to ensure consistency among

tests performed at tertiary centers or peripheral centers, still acknowledging that, in case of any doubt, the expertise of a tertiary center should be invoked.

The in-depth ECHO protocol proposed by Galderisi et al from the European Association of Cardiovascular Imaging (EACVI) (21) was reviewed and commented upon, in the light of the specific evidence on ECHO assessments in Scleroderma patients derived from the SLR.

Considering feasibility, the Experts Committee indicated that the addition of more parameters to be assessed would increase the time needed for the overall examination, but not the price of the test itself. In this view, a standard and an optional/research-oriented ECHO protocols were proposed.

Figure 4. EACVI proposal for transthoracic echocardiography reporting. Reproduced from Galderisi et al (21).




The standard ECHO protocol included the majority of the parameters of the EACVI protocol (Figure 4).

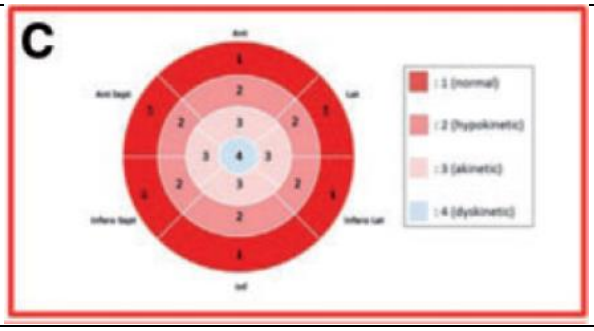
Particular attention was pointed at the evaluation of regional wall motion abnormalities, in the light of its usefulness to consider ischemic comorbidities. For valve disease, the Expert Committee stressed the importance of specifying the absence of valve disease, otherwise if

minimal or significant when present. If significant, it should be described semi-quantitatively (degree of regurgitation/stenosis 1-4) or quantitatively (using measurements such as EROA, PHT). In addition to the EACVI protocol, pericardial evaluation was added as a basic assessment. In particular, pericardial effusion, that should be measured if present during diastolic phase. This could be reported as the diastolic size of the effusion (maximal size) or according to Horowitz classification (213), clearly detailing in which view it was measured and where it is distributed (i.e., circumferential or along the RV free wall).

In the optional/research agenda protocol, additional parameters were added. This included a more detailed assessment of left ventricle diastolic dysfunction, referring to the protocols suggested by the HFA (214) and the EACVI (215). Regarding right heart disease, it included the Tricuspid valve assessment on tissue Doppler (E, A, E/A, E', E/E'), secondary to Global Longitudinal Strain for a time-wise point of view. In fact, Strain ECHO was not considered a standard of case, also as not available in every machine. If available, it could be part of the optional/research agenda, to support its future inclusion as a screening assessment to detect early heart dysfunction (table 17).

Regardless of the chosen protocol, an annual ECHO assessment was suggested, in line with PAH screening. For patients at higher risk or in case of patients developing other organ manifestations/involvement or in case or borderline results on the previous assessment or non-otherwise explained symptoms (dyspnea of non-respiratory origin), a case-by-case personalized evaluation should be performed to increase the frequency of assessments, if possible in accordance with a cardiologist assessment. For patients with cardiac symptoms or unstable clinical presentation, therefore for an ECHO with diagnostic purposes, the same proposed protocols were deemed valid, although the Experts Committee suggested that a case-by-case personalized evaluation of ECHO abnormalities should be performed to trigger cardiologist consultation and then guide a patient-tailored case re-evaluation.

Table 17. Proposed standard and Optional/Research agenda ECHO protocols.

| Structure | Standard ECHO Protocol | Optional/ Research agenda ECHO Protocol |
|---|---|---|
| Left Atrium | Maximal LAVI (mL/m²) | |
| | LA diameter – parasternal long axes view (mm) | |
| | | LA emptying assessment |
| Right Atrium | RA Volume (mL/m²) | |
| | RA Area (cm²) | |
| Left Ventricle | LV end-diastolic dimension (mm) | |
| | LV end-diastolic volume/BSA (mL/m²) | |
| | LV EDD/BSA (mm/m²) | |
| | LV-end-systolic dimension (mm) | |
| | LV end-systolic volume/BSA (mL/m²) | |
| | LV ESD/BSA (mm/m²) | |
| | LV posterior wall and interventricular septum thickness (mm) | |
| | Left ventricular mass index (LVMI, g/m$^2$) | |
| | Relative wall thickness | |
| | LV EF biplane (%) | |
| | LV SVI by Doppler (mL/m²) | |
| | LV Fractional shortening (%) | |
| | | LV GSL (%) |
| | | LV stroke volume (ml) |
| Aortic root dimension (indexed value) | Annulus (mm/m²)<br>Proximal ascending aorta (mm/m$^2$) | |
| Right Ventricle | Basal diameter (mm) | |
| | Mid Diameter (mm) | |
| | RV free wall thickness | |
| | RVOT proximal diameter (mm) | |
| | RVOT distal diameter (mm) | |
| | TAPSE (mm) | |
| | Fractional area change (%) | |
| | | Free Wall GLS |
| Tricuspid regurgitation (if any) | Regurgitation jet velocity (cm/sec)<br>Estimated sPAP (mmHg) | |
| Wall Motion Score Index |  | |
| Valves | To clearly specify if valve disease/abnormality is present/absent, if present then specify is minimal or significant. If significant, it should be described semi- | |

| | | |
|---|---|---|
| | quantitatively (i.e. degree of regurgitation/stenosis 1-4, if present) and/or quantitatively (i.e. using measurements such as EROA, PHT, etc). | |
| LV diastolic function | Transmitral E<br>Transmitral A<br>Transmitral E/A ratio | |
| | E velocity DT (msec) | |
| | Transmitral E velocity DT (cm/sec) | |
| | e' velocity (septal and lateral) (cm/sec) | |
| | E/e' ratio | |
| | | For more in-depth assessment, refer to HFA (214) and EACVI (215). |
| RV diastolic function | | Tricuspid assessment on TDI (E, A, E/A, e', E/e', etc) |
| Inferior Vena cava | IVC diameter (cm)<br>IVS collapsibility (%) | |
| Pericardium | Presence of pericardial effusion (PE) during diastolic phase, specifying in which view it was detected and the distribution (circumferential, along the RV free wall, etc) | |
| | If present, PE should be measured during diastolic phase and reported as maximal size, or according to the Horowitz classification | |
| Other | | PVR (W.U.) |

Finally, the CMR parameters evaluation suggested by Mavrogeni et al for the assessment of patients with rheumatic disease was used as a guidance and reviewed in the light of the advances in the literature (22) (Table 18).

Table 18. Previously proposed protocol for rest cardiac magnetic resonance imaging in patients with rheumatic diseases. Adapted from Mavrogeni et al (22).

| Parameter evaluated | CMR methodology for rest study |
|---|---|
| Anatomy + Function | LVEDV, LVESV, LVEF, RVEDV, RVESV, RVEF, wall motion changes using SSFP |
| Myocardial inflammation and/or necrosis | T2 STIR, early (EGE) and late (LGE) gadolinium (Gd) enhanced T1 images (according to JACC White paper) T1 and T2 mapping |

LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; RVEDV = right ventricular end-diastolic volume; RVESV = right ventricular end-systolic volume; RVEF = right ventricular ejection fraction; SSFP = steady state free precession; T2 STIR = T2-weighted short tau inversion recovery.

In the previous consensus guidance, Bissell et al stated that “although reports to date demonstrate the utility of CMR in SSc, there is no consensus for the development of a meaningful algorithm” (18).

General consideration on CMR from the Experts Committee indicated that there is need for a standardized protocol in terms of views and sequences, with sequences in the short axis needing to cover the whole heart. Similar to the ECHO protocols, a core-set and an optional/research agenda protocols were proposed also for CMR. The standard protocol with good compliant patients would last 35 minutes in a realistic duration of protocol, 45 minutes if including optional / research agenda assessments. In addition, CMR under sedation may be performed if high clinical suspicion but patients with difficulty in tolerating the exam.

For an anatomical and functional evaluation, all the parameters from the previously suggested protocol were supported and deemed important to be measured. The Experts Committee underlined that the comparison with normal values adjusted for age/gender/body surface area is essential, giving much more information compared to absolute values. Local values are not needed, as consistent normal values are available. In addition to the proposed protocol, the evaluation of Atria was considered as an essential part of CMR report and should therefore be performed and reportedl. Same consideration was given for the assessment of the pericardium, which should be part of the Core protocol not just on the cine images but also

localizers and T1 anatomical images. Its description should include the presence of thickened pericardium or effusion. Finally, for Strain CMR there is active research ongoing, which could have important relevance in scleroderma, for early diagnosis, also in patients with normal CMR.

For the evaluation of myocardial inflammation and necrosis, changes in T2 STIR sequences were indicated, as they can give a qualitative or semi-quantitative evaluation, therefore a first impression for myocardial inflammation. Despite its important limitations, T2 STIR data currently have prognostic implication data in the literature, which were not available for T2 mapping. T2 mapping measures mainly inflammation, although nonspecific: in its evaluation, it is important to acquire a basal, a mid and an apical slice, then examine each quartile of the short axis of the ventricle, give a mean quantitative number (ms) to be used as a value to compare also over longitudinal evaluation (sensitivity to change, response to treatment). Early gadolinium enhancement (EGE) would be acquired as part of the standard protocol and it is useful as a diagnostic parameter only in case of negativity of the other tissue characterization parameters. An alternative would be represented by post contrast steady state sequence for hyperemia/oedema, in a time-sparing shorter protocol. Late gadolinium enhancement (LGE) is commonly observed in asymptomatic and symptomatic/affected SSc patients. It gives a visual impressive image, in particular for focal fibrosis. Multiple software are available to quantify LGE, although no standard agreement on the cut-off for positive value (proposed >5 folds standard deviations of the value of unaffected areas). As for T2-STIR, LGE is also predictive value for future cardiac events from other diseases. Native T1 mapping measures mainly inflammation, although relatively nonspecific. It may be included as part of the Core CMR protocol if LGE cannot be acquired (for reasons such as difficulty in cannulation, contraindication to gadolinium). For its evaluation, it requires healthy controls normal values, which should be center specific. Finally, the evaluation of extra-cellular volume (ECV, which represents the difference between post-contrast and native T1 mapping) measures mainly inflammation, although relatively nonspecific. It is useful to quantify diffuse changes in the myocardium, representing what is the extracellular component of the myocardium. If possible, a basal, mid and apical slice should be acquired (as micro fibrosis is not the same everywhere), to perform a segmental analysis and obtain each quartile of the short axis of the ventricle, give a mean quantitative number (ms). As for T2 mapping, T1 mapping values can also compared in time (sensitivity to change, response to treatment). ECV carries some technical limitation, such as the not so robust methodology when acquired through a 3 Tesla machine, relying mostly on a one-slice mid approach. Despite this, the Experts Committee suggested that it should be included in the optional/research agenda where available and where expertise is sufficient.

The Experts Committee proposed a CMR protocol for SSc patients, which included a first section, with specific details on the views and sequences to be used for specific aims/assessments, as well as technical tips (Table 19).

Table 19. Views, sequences, tips and aims of assessment for the application of cardiac magnetic resonance imaging in systemic sclerosis.

| **View and sequence** | **Tips** | **Assessment** |
|---|---|---|
| Localizer bSSFP | | Anatomical overview |
| BB T1w or cine bSSFP axial stack covering thorax | | Pleural effusion, large vessel, pulmonary and mediastinal lesions, interstitial disease |
| 2, 4, 3 C bSSFP | At least 25 phases for temporal resolution < 40 ms | Planning of SAX and assessment of chamber morphology and function, valves, pericardium |
| SAX stack bSSFP | At least 25 phases for temporal resolution < 40 ms 8-10mm, no gap | Chamber morphology and function, pericardium |
| RVOT and stack of axial cines if the RV is of concern | At least 25 phases for temporal resolution < 40 ms, 6mm slices | RV morphology and function |
| Flow velocity encoded imaging if valve disease suspected | In aortic root for AV<br>In PA for PV<br>Consider in plane for TV and MV | Valve regurgitation and maximal velocity |
| SAX STIR T2w | Surface coil may induce signal inhomogeneity → consider body coil<br>May fail for arrhythmias and low compliance→ consider single shot T2w (but lower spatial resolution and SNR) | Oedema |
| T2 mapping (if available)<br>SAX stack plus 4ch/2ch | | Oedema |

| | | |
|---|---|---|
| Pre and post contrast T1 mapping if available<br>SAX stack plus 4ch/2ch | Normal cut off value to be adapted according to local laboratories (attention not to create false positive) | Oedema, diffuse fibrosis (ECV) |
| EGE in SAX stack, 2,4,3 ch | Single slice single breath-hold is the gold standard, SS in low compliance (lower spatial resolution). | Hyperaemia, thrombus |
| LGE in 2, 4, 3 C and SAX stack | Single slice single breath-hold is the gold standard, SS in low compliance (lower spatial resolution). 3D available in some centres | Macroscopic fibrosis (very small areas) + thrombus |
| CEMRA | Optional, if required. | Aorta and PA |

The second section included parameters to be evaluated, for both the Core and the Optional/Research agenda CMR protocols (table 20).

As for the previous consensus guidance, there was lack of both agreement and robust evidence regarding the performance of CMR. Although completely asymptomatic patients may also have CMR abnormalities and these abnormalities may carry a prognostic impact, CMR cannot be currently recommend as a standard screening for different reasons including availability, feasibility and costs. Regarding patients with cardiac symptoms or unstable clinical presentation, the Experts Committee agreed on the identification of patients to send for CMR according to selected triggers and on the multi-disciplinary team discussion to consider additional diagnostic tests and differential diagnosis (including ischemic, infective, metabolic causes).

Additional tests, such as Nuclear medicine tests (Scintigraphy, PET scan) or Coronary angiography and coronary CT were considered by the Expert Committee if suggested after the cardiologist evaluation. Regarding endo-myocardial and pericardial biopsy, these tests should be performed according to the according to ESC guidelines, i.e., in patients with repeated oedema findings on CMR without other explanation.

Table 20. Proposed core and optional/research agenda cardiac magnetic resonance imaging protocols for the evaluation of patients with systemic sclerosis.

| **Parameters evaluated** | **Core CMR protocol** | **Optional/Research agenda CMR protocol** | **Comments** |
|---|---|---|---|
| Anatomy and Function | LVEDV, LVESV, LVEF, RVEDV, RVESV, RVEF, wall motion changes using SSFP | LVEDV, LVESV, LVEF, RVEDV, RVESV, RVEF, wall motion changes using SSFP | Age-gender-BSA adjusted normal values are available from the literature |
| | Atria assessment | Atria assessment | |
| | Pericardial assessment on both cine, localizers and T1 anatomical images, including thickened pericardium and effusion. | Pericardial assessment on both cine, localizers and T1 anatomical images, including thickened pericardium and effusion. | |
| | | Strain CMR | More research is needed to support it. |
| Myocardial inflammation or necrosis | T2 STIR | T2 STIR, | |
| | | T2 mapping | |
| | EGE | EGE (optional if T1 mapping is available) | |
| | LGE | LGE | |
| | T1 mapping (if LGE cannot be acquired) | T1 mapping | Center-specific healthy controls normal values |
| | | ECV | Where available and with sufficient expertise |

The discussion held during the three virtual meetings was used as a base for the Core Leadership team in the generation of a list of statements to summarize the content. These were divided into “overarching principles” and “consensus guidance statements” and presented to the Experts Committee during two virtual meetings, held between March and June 2021.

The overall discussion around the statements was intense and determined a significant amount of re-wording, to obtain a semantically clear message to deliver to the audience.

After content and linguistic revision, both the 7 overarching principles and the 10 consensus guidance statements were voted for agreement by the Core Leadership team and the Experts Committee (Tables 21-22).

None of the originally created statements was discarded by the committee, neither for agreement lower than the established threshold or for low number of voters above the pre-defined cut-off. The overall mean agreement of the guidance points was 9.1/10, with mean 93% of experts voting above 7/10.

Table 21. Overarching principles of the consensus guidance for the screening, diagnosis and follow-up of systemic sclerosis primary heart involvement.

| | Overarching Principles | n voting | mean agreement (ok if ≥7) | % voters <7 (ok if ≤30) |
|---|---|---|---|---|
| OP1 | These recommendations refer to the definition of systemic sclerosis-related primary heart involvement (SSc-pHI). | 12 | 8,42 | 17% |
| OP2 | SSc-pHI should be considered particularly in the early stages of the disease, but it may also be present and develop throughout the disease course of a patient with SSc. | 13 | 9,38 | 8% |
| OP3 | The patient should be counselled about the symptoms and consequences of SSc-pHI to raise their awareness and to ensure the importance of reporting symptoms to the physician. | 14 | 9,71 | 7% |
| OP4 | Where suspicion for SSc-pHI exists, acute and chronic coronary syndromes should be considered and managed in line with current guidelines. | 14 | 9,21 | 0% |
| OP5 | The differential diagnosis and management of SSc-pHI should be undertaken by a multi-disciplinary team that comprises cardiologist(s) (with necessary subspecialist expertise as indicated) and rheumatologists with SSc expertise. | 15 | 9,00 | 7% |
| OP6 | Screening refers to the assessment of asymptomatic patients with no known SSc-pHI, who can be further stratified into those who are considered ‘at higher risk’ and those who should be considered ‘at lower risk’ of developing heart involvement. | 14 | 8,43 | 14% |
| OP7 | Diagnosis refers to the assessment of patients presenting with symptoms and/or signs and/or investigations compatible with possible SSc-pHI. | 15 | 8,47 | 13% |

Table 22. Statements of the consensus guidance for the screening, diagnosis and follow-up of systemic sclerosis primary heart involvement.

| | Consensus Guidance Statements | n voting | mean agreement (ok if ≥7) | % voters <7 (ok if ≤30%) |
|---|---|---|---|---|
| ST1 | The diagnostic workup of SSc-pHI should comprise an integration of history (cardiac red flag symptoms), physical examination and laboratory/imaging/ECG results and should be tailored to the individual. | 14 | 9.86 | 0% |
| ST2 | Physicians should counsel patients and caregivers in layperson language, providing detailed information on SSc-pHI, its symptoms and signs, diagnostic and monitoring procedures. The information should highlight the importance of reporting symptoms to the multidisciplinary team. | 14 | 9.86 | 0% |
| ST3 | Screening for SSc-pHI should be performed in every patient at time of SSc diagnosis. Follow-up evaluations should be considered. | 15 | 8.80 | 7% |
| ST4 | Asymptomatic SSc patients with no history of heart involvement should have a core annual assessment, which may coincide with annual pulmonary arterial hypertension (PAH) surveillance.<br>Core assessment would comprise ECG, standard Transthoracic Echocardiography and serum cardiac biomarkers such as hs-Troponin, NT-pro-BNP or BNP. | 15 | 9.33 | 0% |
| ST5 | Screening with Cardiac Magnetic Resonance (CMR) may be considered in asymptomatic patients with no history of heart involvement and on a case-by-case basis. | 14 | 8.21 | 21% |
| ST6 | Symptoms suggestive of SSc-pHI should trigger specific assessment. This includes initial core evaluation with ECG, standard Transthoracic Echocardiography and serum cardiac biomarkers such as hs-Troponin, NT-pro-BNP or BNP. | 14 | 9.93 | 0% |
| ST7 | CMR should be included as part of the diagnostic work up where suspicion for SSc-pHI remains following positive findings from the initial core evaluation. | 13 | 9.23 | 0% |
| ST8 | Where SSc-pHI is confirmed, Holter monitoring is recommended as the first-line assessment to evaluate for the arrhythmia burden and Echocardiography for the evaluation of the cardiac chambers and function. Other tests may be considered in consultation with appropriate cardiology expertise. | 12 | 8.50 | 0% |
| ST9 | In patients with confirmed SSc-pHI or clinically suspected myocarditis, with or without myocardial abnormalities on CMR, endomyocardial biopsy may be indicated in line with ESC guidelines and position statements, after exclusion of coronary artery disease. | 12 | 8.67 | 17% |
| ST10 | Management of confirmed SSc-pHI (including frequency of monitoring and nature of testing) should be tailored to the individual patient's clinical scenario, discussed, and agreed by the multi-disciplinary team. | 13 | 9.31 | 0% |

### 5.f. – Real life application of definition of SSc-PHI and consensus guidance

From August 2003 to July 2020, 530 patients were enrolled in the EUSTAR Scleroderma Cohort database of the Department of Rheumatology, University Hospital Zurich. A baseline description of the study population are presented in table 23.

Table 23. Baseline description of the study population.

| **Parameter** | **Distribution** |
|---|---|
| Age, years, mean±SD | 56.3±13.9 |
| Female gender, n (%) | 432 (81.5) |
| Disease duration, years, median (IQR) | 4.5 (1.4-9.2) |
| Anti-centromere antibody positive, n (%) | 224 (42.3) |
| Anti-topoisomerase I antibody positive, n (%) | 135 (25.5) |
| Anti-RNA polymerase III antibody positive, n (%) | 40 (7.5) |
| Diffuse cutaneous skin subset, n (%) | 128 (24.2) |
| Modified Rodnan skin score, median (IQR) | 4 (0-10) |
| Esophageal symptoms, n (%) | 296 (55.8) |
| Stomach symptoms, n (%) | 134 (25.3) |
| Intestinal symptoms, n (%) | 150 (28.3) |
| Pulmonary arterial hypertension, n (%) | 32 (6.0) |
| Interstitial lung disease, n (%) | 223 (42.1) |
| Scleroderma renal crisis, n (%) | 13 (2.5) |
| Digital ulcers, n (%) | 100 (18.9) |
| Arthritis, n (%) | 147 (27.7) |
| Myositis, n (%) | 48 (9.1) |
| Scleroderma related heart involvement, n (%) | 11 (2.1) |
| Body mass index, kg/m², mean±SD | 24.3±4.6 |
| Arterial Hypertension, n (%) | 142 (26.8) |
| Smoking exposure, n (%) | 154 (29.1) |
| Diabetes mellitus, n (%) | 22 (4.2) |
| Dyslipidemia, n (%) | 49 (9.2) |
| Coronary artery disease, n (%) | 21 (4.0) |
| Non-ischemic cardiac disease, n (%) | 75 (14.2) |
| NYHA functional class, I / II / III / IV, n (%) | 294 (55.5) / 183 (34.5) / 46 (8.7) / 7 (1.3) |
| Palpitations, n (%) | 79 (14.9) |
| Chest pain, n (%) | 12 (2.3) |
| Syncope, n (%) | 3 (0.6) |
| Clinical signs of heart failure, n (%) | 21 (4.0) |

| | |
|---|---|
| Heart rate, beats/minute, mean±SD | 78±15 |
| Systolic arterial pressure, mmHg, mean±SD | 124±18 |
| Diastolic arterial pressure, mmHg, mean±SD | 76±11 |
| Conduction blocks, n (%) | 71 (13.4) |
| Right bundle bunch block, n (%) | 28 (5.3) |
| Right axis deviation, n (%) | 6 (1.1) |
| Auricular arrhythmias, n (%) | 14 (2.6) |
| Ventricular arrhythmias, n (%) | 4 (0.8) |
| Left ventricular ejection fraction, %, mean±SD | 62±5 |
| Pericardial effusion, n (%) | 27 (5.1) |
| Diastolic dysfunction, n (%) | 160 (30.2) |
| sPAP on ECHO, mmHg, mean±SD | 27±10 |
| C-reactive protein, mg/dl, median (IQR) | 0.2 (0.1-0.6) |
| ESR, mm/min, median (IQR) | 14 (8-26) |
| Serum creatinine, mg/dl, median (IQR) | 0.8 (0.7-0.9) |
| Hemoglobin, mg/dl, mean±SD | 13.1±1.4 |
| CK, mg/dl, median (IQR) | 84 (62-125) |
| NT-proBNP, pg/ml, median (IQR) | 118 (73-291) |
| hsTnT, median (IQR) | 10 (6-22) |
| FVC, % predicted, mean±SD | 96±20 |
| TLC, % predicted, mean±SD | 95±21 |
| DLCO/SB, % predicted, mean±SD | 74±22 |
| DLCO/VA, % predicted, mean±SD | 82±19 |
| Alpha-receptors blockers, n (%) | 3 (0.6) |
| Beta-receptors blockers, n (%) | 41 (7.7) |
| Angiotensin-receptors blockers, n (%) | 45 (8.5) |
| Angiotensin converting enzyme inhibitors, n (%) | 52 (9.8) |
| Verapamil, n (%) | 12 (2.3) |
| Calcium channel blockers – others, n (%) | 140 (26.4) |
| Anti-platelet aggregants, n (%) | 139 (26.2) |
| Oral anti-coagulant, n (%) | 34 (6.4) |
| Diuretics, n (%) | 54 (10.2) |

CK=creatine kinase; DLCO=diffusion capacity of carbone oxide; ESR=erythrocyte sedimentation rate; FVC= forced vital capacity; hsTNT= high sensitivity troponin T; sPAP= systolic pulmonary arterial pressure

Overall, 1828 visits were available: 154 patients presented only one visit, while the remaining 376 at least one follow-up visit. Prognostic outcome data were available for all patients.

### 5.f.i - The prevalence of SSc-pHI

At baseline visit, 11/530 (2.1%) patients were previously diagnosed with some form of SSc-heart involvement. After a median follow-up of 4.7 (2.1-7.8) years, the prevalence of SSc-heart involvement increased to 102/530 (19.2%) cases.

Table 24. Prevalence of cardiac comorbidities and causes of secondary heart manifestations in the study population

| | Baseline visit | Last follow-up |
|---|---|---|
| Pulmonary arterial hypertension, n (%) | 32 (6.0) | 47 (8.9) |
| Interstitial lung disease, n (%) | 223 (42.1) | 255 (48.1) |
| Scleroderma renal crisis, n (%) | 13 (2.5) | 17 (3.2) |
| Scleroderma related heart involvement, n (%) | 11 (2.1) | 102 (19.2) |
| Coronary artery disease, n (%) | 21 (4.0) | 34 (6.4) |
| Non-ischemic cardiac disease, n (%) | 75 (14.2) | 104 (19.6) |

Table 24 presents the prevalence of cardiac comorbidities and causes of secondary heart manifestations in the study population. From baseline to end of follow-up, there was a slight increase in all prevalences, which was particularly meaningful for cardiac complications. Taking these into account, the prevalence of SSc-heart involvement was higher among the patients with PAH (40.4% versus 17.2% for non-PAH patients, $p<0.001$), ILD (25.4% versus 14.1% for non-ILD patients, $p<0.001$), SRC (52.9% versus 18.1% in non-SRC, $p<0.001$), CAD (50.0% versus 17.2% in non-CAD cases, $p<0.001$) and non-ischemic cardiac disease cases (46.2% versus 12.8% for patients without non-ischemic cardiac disease, $p<0.001$). Overall, 92/102 (90.2%) cases of SSc-heart involvement presented in patients with at least one cause of secondary heart involvement, while 10/102 (9.8%) in patients without cardiac comorbidities or other causes of possible secondary involvement.

Considering visits, 133/1823 (7.3%) visits contributed to the detection of some sort of SSc-cardiac involvement event (detailed in Table 25).

Table 25. Cardiac diagnosis and events detected overall during the follow-up observation.

| **Parameter** | **Prevalence among 1828 visits (530 patients)** | **Prevalence among 1472 visits (392 patients)** |
|---|---|---|
| Myocarditis, n (%) | 17 (0.9) | 12 (0.8) |
| Pericarditis, n (%) | 24 (1.3) | 21 (1.4) |
| Arrhythmia, n (%) | 53 (2.9) | 30 (2.0) |
| Need for major anti-arrhythmic drug, n (%) | 6 (0.3) | 3 (0.2) |
| Need for cardiac interventional procedure, n (%) | 35 (1.9) | 13 (0.9) |
| Need for PM or ICD implantation, n (%) | 3 (0.2) | 2 0.1) |
| Congestive heart failure, n (%) | 46 (2.5) | 14 (1.0) |
| Need for hospitalization or intravenous diuretics, n (%) | 14 (0.8) | 5 (0.3) |
| Need for initiation or titration of immunosuppression for the treatment of heart disease, n (%) | 14 (0.8) | 11 (0.7) |
| Other non-primary SSc cardiac diseases (i.e., PAH, CAD, etc) | 53 (2.9) | 39 (2.6) |

CAD=coronary artery disease; ICD= implantable cardiac defibrillator; PAH=pulmonary arterial hypertension; PM=pacemaker.

Similarly to the previous comparison of prevalence at patient level, there was a higher number of cardiac events in patients with cardiac comorbidities or possible SSc-related causes of secondary heart involvement: 104 events (9.7%) versus 29 events (3.8%) in the groups without those conditions (p<0.001). This significant highly prevalence of SSc-cardiac events was confirmed for visits of patients with:

- PAH 23/104 (22.1%) versus non-PAH 110/1614 (6.4%), p<0.001.
- ILD 77/855 (9.0%) versus non-ILD 56/962 (5.8%), p=0.011.
- SRC 9/43 (20.9%) versus non-SRC 124/1785 (6.9%), p=0.003
- SSc-pHI 43/155 (27.7%) versus non SSc-pHI 90/1673 (5.4%), p<0.001
- CAD 12/94 (12.8%) versus non CAD 121/1607 (7.0%), p=0.043
- Non ischemic cardiac disease 51/282 (18.1%) versus absent 82/1540 (5.3%), p<0.001

Specifically describing the different events, a new diagnosis of myocarditis was statistically more prevalent in visits of patients with ILD (1.5% versus 0.4%, p=0.016) and previous diagnosis of SSc-heart involvement (3.9% versus 0.7%, p=0.002). Pericarditis was more prevalent in patients with previous diagnosis of SSc-pHI (10.3% vs 0.5%, p<0.001). Diagnosis of arrhythmias was more prevalent in visits of patients with PAH (8.7% vs 2.6%, p=0.002), ILD (4.6% vs 1.5%, p<0.001), previous SSc-pHI (6.5% vs 2.6%, p=0.011) and concomitant non-

ischemic cardiac disorders (6.7% vs 2.2%, p<0.001). Patient with PAH showed also higher prevalence of need for major anti-arrhythmic drugs (1.9% vs 0.2%, p=0.041) and cardio-interventional procedures (9.6% vs 1.5%, p<0.001). Similarly, visits of patients with SSc-pHI (6.5% vs 1.5%, p<0.001), CAD (6.4% vs 1.7%, p=0.008) and non-ischemic cardiac disease (6.7% vs 1.0%, p<0.001) showed higher need for cardio-interventional procedures.

Congestive heart failure events were seen with high frequency in patients with PAH (11.5% vs 2.0%, p<0.001), SRC (11.6% vs 2.3%, p=0.004), previous SSc-PHI (6.5% vs 2.2%), CAD (6.4% vs 2.3%, p=0.028) and non-ischemic heart disease (8.9% vs 1.4%, p<0.001). In line with this, only PAH patients showed higher prevalence of need for hospitalization for intravenous diuretics (3.8% vs 0.6%, p=0.006). Need for immunosuppression initiation or titration was instead more prevalent in patients with ILD (1.4% vs 0.2%, p=0.003), SRC (4.7% vs 0.7%, p=0.041) and previous SSc-pHI diagnosis (2.6% vs 0.6%, p=0.025).

Given the difficulty in understanding and differentiating the presence of primary and secondary components of SSc-pHI, we run a GLMM model including the cardiac comorbidities and SSc-related causes of possible secondary heart involvement as co/variates and SSc-heart events as dependent variable (Table 26). This identified PAH, non-ischemic cardiac disease and SSc-pHI as statistically independent causes of cardiac events.

Table 26. Prediction model for SSc cardiac outcomes, using cardiac comorbidities and SSc-related causes of possible secondary heart involvement as covariates.

| | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Intercept | 0.188 | 0.283 | 0.042 | 1.916 |
| PAH | **0.047** | 2.760 | 1.016 | 7.496 |
| CAD | 0.924 | 1.062 | 0.296 | 3.801 |
| Non ischemic cardiac disease | **0.035** | 2.286 | 1.064 | 4.911 |
| ILD | 0.394 | 1.332 | 0.677 | 2.622 |
| SRC | 0.250 | 2.372 | 0.527 | 10.672 |
| SSc-pHI | **0.001** | 4.366 | 1.898 | 10.040 |

CAD=coronary artery disease; ILD=interstitial lung disease; PAH=pulmonary arterial hypertension; SRC=scleroderma renal crisis; SSc-pHI= systemic sclerosis primary heart involvement.

Overall, after excluding PAH and non-ischemic cardiac diseases (n=138), we obtained a sub-population of 392 patients/1472 visits in which we could consider SSc cardiac events as very likely related to SSc/pHI, either as a pure isolated primary form or combined with possible other causes. In this subgroup, we observed 5/392 (1.3%) patients with SSc-pHI at baseline and 45/392 (11.5%) at follow up, for a total of 73 events in 1472 visits (5.0%).

### 5.f.ii - To test the impact of SSc-pHI on mortality

Death was recorded for 84/530 (15.8%) patients in the overall population and 44/392 (11.2%) of patients without PAH/non-ischemic cardiac diseases. Considering last visit data, the impact of general population cardio-vascular risk factors and comorbidities was analyzed separately from the SSc-associated organ complications. As shown in Table 27 and Table 28, certain risk factors were identified, specifically age and male gender from the general population factors, while mRSS and SSc-cardiac involvement from the SSc-related ones. In addition, there was a trend for significant prediction of death for PAH, SRC and arthritis.

When the variables were merged in the same multivariate prediction model including co-variates with p<0.1 (Table 29), mRSS, SSc cardiac involvement and age were confirmed as independent predictors of deaths.

Table 27. Logistic regression prediction model for mortality, including general population cardiovascular risk factors and comorbidities as covariates.

| Model Term | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Male gender | **<0.001** | 3.629 | 1.775 | 7.420 |
| Age | **<0.001** | 1.076 | 1.042 | 1.111 |
| BMI | 0.200 | 0.955 | 0.890 | 1.025 |
| Systemic arterial hypertension | 0.271 | 1.435 | 0.755 | 2.729 |
| Diabetes Mellitus | 0.192 | 2.218 | 0.670 | 7.342 |
| Dislipidemia | 0.277 | 0.628 | 0.271 | 1.453 |
| Smoking | 0.160 | 1.636 | 0.823 | 3.250 |
| Coronary artery disease | 0.642 | 1.251 | 0.486 | 3.222 |
| Non-Ischemic cardiac disease | 0.145 | 1.671 | 0.838 | 3.335 |
| Constant | **<0.001** | 0.002 | | |

BMI= body mass index.

Table 28. Logistic regression prediction model for mortality, including SSc-associated organ involvements and complications as covariates.

| | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| PAH | **0.060** | 2.056 | 0.971 | 4.351 |
| ILD | 0.884 | 1.042 | 0.600 | 1.810 |
| SRC | **0.088** | 2.566 | 0.870 | 7.568 |
| Digital ulcers | 0.707 | 1.112 | 0.639 | 1.933 |
| Arthritis | **0.067** | 0.583 | 0.327 | 1.039 |
| Myositis | 0.184 | 1.718 | 0.773 | 3.819 |
| Disease duration | 0.928 | 1.001 | 0.972 | 1.031 |
| mRSS | **<0.001** | 1.077 | 1.041 | 1.115 |
| SSc cardiac involvement | **<0.001** | 2.910 | 1.646 | 5.146 |
| Constant | <0.001 | 0.085 | | |

ILD=interstitial lung disease; PAH=pulmonary arterial hypertension; mRSS=modified Rodnan skin score; SRC=scleroderma renal crisis.

Table 29. Logistic regression prediction model for mortality combining general population and SSc specific comorbidities as covariate in the overall study population.

| | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| PAH | 0.075 | 2.050 | 0.931 | 4.516 |
| SRC | 0.100 | 2.607 | 0.832 | 8.166 |
| Arthritis | 0.212 | 0.686 | 0.379 | 1.240 |
| mRSS | **<0.001** | 1.098 | 1.057 | 1.140 |
| SSc cardiac involvement | **<0.001** | 2.853 | 1.590 | 5.119 |
| Age | **<0.001** | 1.094 | 1.064 | 1.125 |
| Male sex | 0.064 | 1.850 | 0.966 | 3.545 |
| Constant | **<0.001** | 0.000 | | |

PAH=pulmonary arterial hypertension; mRSS=modified Rodnan skin score; SRC=scleroderma renal crisis.

When repeating the same procedure including the 392 patients without PAH/non-ischemic cardiac diseases, including the significant covariates of the model in Table 29, mRSS and age were confirmed as independent predictor (table 30). In addition, male sex emerged as an independent predictor, while a trend towards statistical significance was still identified for SSc-pHI as a risk factor for mortality in SSc.

Table 30. Logistic regression prediction model for mortality combining general population and SSc specific comorbidities as covariate in the population without PAH or non-ischemic cardiac comorbidities.

| | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| mRSS | **<0.001** | 1.093 | 1.043 | 1.145 |
| SSc-pHI | 0.075 | 2.210 | 0.923 | 5.293 |
| age | **<0.001** | 1.086 | 1.050 | 1.124 |
| Male sex | **0.007** | 2.852 | 1.327 | 6.132 |
| Constant | **<0.001** | 0.000 | | |

mRSS=modified Rodnan skin score; SSc-pHI=systemic sclerosis primary heart involvement

### 5.f.iii - To identify the risk factors for SSc-pHI

This analysis was focused on the visits of patients who did not have PAH or other non-ischemic cardiac diseases at the time of the visits (n=392 patients, 1472 visits).
Given the number of visits with SSc-pHI events (n=73), general cardiovascular risk factors and SSc manifestations were tested first separately and then merged in a single prediction model. Among general population risk factors, a trend for statistical significance was observed for systemic arterial hypertension and for male gender (Table 31).

Table 31. GLMM prediction model for SSc-pHI events, using general population risk factors as covariates.

| Model Term | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Intercept | 0.420 | 3.280 | 0.183 | 58.871 |
| Age | 0.931 | 0.999 | 0.978 | 1.021 |
| Male gender | **0.051** | 1.813 | 0.999 | 3.291 |
| BMI | 0.244 | 1.035 | 0.977 | 1.096 |
| Systemic arterial hypertension | **0.050** | 1.804 | 1.001 | 3.251 |
| Diabetes mellitus | 0.744 | 0.767 | 0.156 | 3.772 |
| Dislipidaemia | 0.963 | 0.980 | 0.416 | 2.306 |
| Smoking | 0.339 | 0.745 | 0.408 | 1.363 |
| Coronary artery disease | 0.357 | 1.589 | 0.592 | 4.264 |

BMI= body mass index.

Among SSc manifestations and complications, again, it was interesting to see signals for other SSc-related possible causes of secondary heart involvement as risk factors. In this case, these events could represent examples of concomitant/mixed primary and secondary heart involvements (Table 32). This was the case of ILD and SRC, while mRSS emerged for the first time.

The combined model merging both groups of predictors, including those co-variates with $p<0.1$ from previous sub-models, removed male sex and confirmed the other factors as independent predictors of SSc-pHI events, creating a statistically significant risk factor model (Table 33).

Table 32. GLMM prediction model for SSc-pHI events, using SSc manifestations and organ involvements as covariates.

| Model Term | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Intercept | 0.116 | 3.744 | 0.722 | 19.426 |
| Disease duration | 0.197 | 0.976 | 0.942 | 1.012 |
| ILD | **0.073** | 1.856 | 0.944 | 3.650 |
| SRC | **0.001** | 7.879 | 2.303 | 26.961 |
| Digital ulcers | 0.576 | 1.184 | 0.654 | 2.145 |
| mRSS | **0.021** | 0.959 | 0.926 | 0.994 |
| Arthritis | 0.565 | 1.205 | 0.638 | 2.275 |
| Myositis | 0.601 | 0.758 | 0.267 | 2.148 |
| Anti-Scl 70 antibody positive | 0.689 | 1.158 | 0.566 | 2.369 |

ILD=interstitial lung disease; mRSS=modified Rodnan skin score; SRC=scleroderma renal crisis.

Table 33. GLMM prediction model for SSc-pHI events, combining general population cardio-vascular risk factors and SSc-specific risk factors as covariates.

| Model Term | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Intercept | 0.125 | 2.738 | 0.756 | 9.915 |
| ILD | **0.038** | 1.931 | 1.037 | 3.596 |
| SRC | **0.029** | 4.165 | 1.155 | 15.018 |
| mRSS | **0.012** | 0.957 | 0.924 | 0.990 |
| Male gender | 0.258 | 1.531 | 0.732 | 3.203 |
| Systemic arterial hypertension | **0.038** | 2.001 | 1.039 | 3.853 |

ILD=interstitial lung disease; mRSS=modified Rodnan skin score; SRC=scleroderma renal crisis.

**5.f.iv - To test the impact of the consensus guidance on the detection of SSc-pHI.**

Data on the first level assessments suggested by the consensus guidance were investigated among the 1828 visits available. While signs and symptoms, as part of medical history and physical examinations, were always present in the database, certain assessments were not performed in all visits, in particular during the first decade of the 21st century. In addition, even if the test was performed, not all parameters were specifically reported for every visit, therefore the different prevalence shown in table 34.

Table 34. Prevalence of fist level assessments and detected alteration among the overall database.

| | Prevalence among 1828 visits (530 patients) | Prevalence among 1472 visits (392 patients) |
|---|---|---|
| *Medical history and physical examination performed, n (%)* | 1828 (100) | 1472 (100) |
| Palpitations reported, n (%) | 259 (14.2) | 162 (11.0) |
| NYHA functional class, I/II/III/IV, n (%) | 939 (51.4)/ 661 (36.2)/ 167 (9.1) / 24 (1.3) | 842 (58.5) / 504 (35.0) / 89 (6.2) / 4 (0.3) |
| Chest pain reported, (%) | 57 (3.1) | 32 (2.2) |
| Syncope reported, n (%) | 19 (1.0) | 11 (0.7) |
| Sings of heart failure detected, n (%) | 95 (5.2) | 42 (2.9) |
| Altered systolic blood pressure detected, n (%) | 345 (18.9) | 261 (17.7) |
| Altered diastolic blood pressure detected, n (%) | 244 (13.3) | 201 (13.7) |
| Altered heart rate detected, n (%) | 205 (11.2) | 162 (11.0) |
| *Laboratory Tests performed, n (%)* | 1811 (99.1) | 1456 (98.9) |
| CK performed, n (%) | 1662 (90.9) | 1359 (92.3) |
| Increased CK > ULN, n (%) | 206/1662 (12.2) | 163/1359 (12.0) |
| NT-proBNP performed, n (%) | 1616 (88.4) | 1320 (89.7) |
| Increased NT-proBNP > ULN, n (%) | 319/1616 (19.7) | 165/1320 (12.5) |
| hsTnT performed, n (%) | 1206 (66.0) | 966 (65.6) |
| Increased hsTnT > ULN, n (%) | 244/1206 (20.2) | 137/966 (14.2) |
| Inflammatory serum biomarkers performed, n (%) | 1807 (98.6) | 1453 (98.7) |

| | | |
|---|---|---|
| Increased inflammatory serum biomarkers > ULN, n (%) | 604/1807 (33.4) | 454/1453 (31.2) |
| *Rest ECG performed, n (%)* | 1776 (97.2) | 1431 (97.2) |
| Conduction blocks detected, n (%) | 330/1635 (20.2) | 213/1309 (16.3) |
| Right bundle branch block detected, n (%) | 125/1236 (10.1) | 96/982 (9.8) |
| Right axis deviation detected, n (%) | 27/1237 (2.2) | 16/982 (1.6) |
| Right ventricular hypertrophy detected, n (%) | 11 /1238 (0.9) | 4/1984 (0.4) |
| Auricular arrhythmias detected, n (%) | 85/1239 (6.9) | 36/987 (3.6) |
| Ventricular arrhythmias detected, n (%) | 49/1262 (2.7) | 23/1004 (2.3) |
| *Transthoracic rest Echocardiography performed, n (%)* | 1802 (98.6) | 1451 (98.6) |
| Abnormal LV diastolic function detected, n (%) | 493/1637 (30.1) | 359/1351 (26.6) |
| Abnormal LV systolic function detected, n (%) | 41/1622 (7.0) | 18/1343 (1.3) |
| Pericardial effusion detected, n (%) | 113/1622 (7.0) | 82/1314 (6.2) |
| Increased sPAP>35mmHg, n (%) | 141/1250 (11.3) | 66/981 (4.5) |

CK= creatin-kinase; ECG= electrocardiogram; ECHO=echocardiography; hsTnT=high sensitivity troponin T; LV= left ventricle; sPAP=systolic pulmonary arterial pressure; ULN=upper level of normality.

Considering the distribution of clinical and anamnestic features, in line with OP6 and OP7 defining screening and diagnostic purposes for the SSc-pHI assessment, we counted for:

- 583 visits of patients without sings/symptoms (screening group)
- 1090 visits of patients with signs/symptoms (diagnosis group)
- 155 visits of patients with already diagnosed SSc-pHI (monitoring group)

In line with ST4 and ST6, suggesting the first level assessments to be performed regularly in SSc patients to screen or diagnose SSc-pHI, 89.2% of visits had both ECG, ECHO, and lab parameters (NT-proBNP and/or hsTnT) being performed; conversely, 6.9% of visits had ECG and ECHO without laboratory tests done and 3.9% had missing ECG or ECHO, regardless of laboratory assessments. The distribution of the core annual assessment was similar between the screening, diagnostic and monitoring visits (p=0.948). Regarding ST3, 88.5% of baseline visits and 94.6% of follow up visits had a full core set-up, with increasing number in recent years.

Taking into consideration the 133/1828 cardiac events detected during the overall study period and described in Table 25, we created different prediction models considering SSc-heart events as dependent variable, analyzing the predictive power of the independent variables described below:

- Basic model: risk factors for SSc-pHI (Table 33), physical examination and medical history
- Detect-like model: risk factors for SSc-pHI (Table 33), physical examination and medical history, ECG, Echo, NT-proBNP
- Consensus model: risk factors for SSc-pHI (Table 33), physical examination and medical history, ECG, Echo, NT-proBNP, hsTnT, CK, ESR/CRP.

The basic model confirmed the overall predictive power of the risk factors identified from the model in Table 33, showing additional significance as risk factors for NYHA functional class, palpitations, chest pain and signs of heart failure (Table 35).

Table 35. GLMM prediction model for SSc-related cardiac events, including variables from the "basic model" as covariates.

| Model Term | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Intercept | **<0.001** | 0.000 | 2.544E-06 | 0.008 |
| Risk Factors | **<0.001** | 1203.338 | 24.458 | 59203.456 |
| NYHA class I | **<0.001** | 9.302 | 3.406 | 25.401 |
| NYHA class II | **<0.001** | 5.887 | 2.217 | 15.638 |
| NYHA class III | 0.060 | 2.661 | 0.959 | 7.381 |
| Palpitations | **0.001** | 2.227 | 1.410 | 3.518 |
| Chest pain | **<0.001** | 3.968 | 2.002 | 7.865 |
| Syncope | 0.334 | 1.987 | 0.494 | 7.999 |
| Signs of heart failure | **0.003** | 2.512 | 1.376 | 4.586 |
| Altered SBP | 0.969 | 0.989 | 0.572 | 1.709 |
| Altered DBP | 0.291 | 0.686 | 0.341 | 1.382 |
| Altered HR | 0.977 | 0.991 | 0.536 | 1.832 |

SBP=systolic blood pressure; DBP= diastolic blood pressure; HR= heart rate.

In comparison to the "basic model", the "Detect-like" model showed additional predictive power from right axis deviation, pericardial effusion and increased NT-proBNP levels (table 36).

Table 36. GLMM prediction model for SSc-related cardiac events, including variables from the "Detect-like model" as covariates.

| Model Term | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Intercept | **<0.001** | 0.001 | 9.458E-05 | 0.016 |
| Basic model | **<0.001** | 130.019 | 24.815 | 681.226 |
| Conduction blocks | 0.838 | 0.936 | 0.497 | 1.763 |
| RBBB | 0.297 | 1.557 | 0.677 | 3.581 |
| Right axis deviation | **<0.001** | 8.202 | 2.939 | 22.885 |
| Right ventricular hyperteophy | 0.556 | 0.576 | 0.092 | 3.617 |
| Ventricular arrhythmias | 0.172 | 1.859 | 0.763 | 4.527 |
| Auricular arrhythmias | 0.497 | 1.280 | 0.627 | 2.613 |
| Pericardial effusion | **0.004** | 2.442 | 1.327 | 4.494 |
| LV Diastolic dysfunction | 0.239 | 1.319 | 0.832 | 2.092 |
| LV Systolic dysfunction | 0.473 | 1.514 | 0.488 | 4.700 |
| Increased sPAP>35mmHg | 0.386 | 1.323 | 0.702 | 2.494 |
| Increased NT-proBNP | **<0.001** | 2.929 | 1.792 | 4.789 |

LV=left ventricle; RBBB=right bundle branch block; sPAP=systolic pulmonary artery pressure.

Finally, the addition of the three laboratory biomarkers included in the "Consensus model", showed further value as risk factor for increased high-sensitivity troponin T values, while a trend towards statistical significance for increased inflammatory biomarkers (Table 37)

Table 37. GLMM prediction model for for SSc-related cardiac events, including variables from the "Consensus model" as covariates.

| Model Term | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Intercept | **<0.001** | 0.035 | 0.013 | 0.096 |
| Detect-like model | **<0.001** | 290.128 | 89.492 | 940.586 |
| Increased hsTnT | **<0.001** | 3.629 | 2.325 | 5.662 |
| Increased inflammatory biomarkers | 0.090 | 1.445 | 0.944 | 2.213 |
| Increased CK | 0.487 | 1.235 | 0.681 | 2.242 |

CK=creatin-kinase, hsTnT=high sensitivity troponin T

In comparison to the simple evaluation of the risk factor, each model applied to the overall population showed an increased in the Area Under the Curve predicting SSc-heart events, therefore representing an increase in the predictive power of the model (Figure 5, Table 38). When comparing the predictive power of the different models, all three models were significantly better than the simple evaluation of the risk factors in the prediction of SSc-associated cardiac events. In addition, while both the "Detect-like" and the "Consensus" models were significantly superior to the "Basic model", the increase in the area under the ROC curve from the "Detect-like" to the "Consensus" model was not statistically significant (Table 39).

Figure 5. ROC curves for the prediction of the detection of SSc-related cardiac events in the whole study population (n=530 patients, 1828 visits)

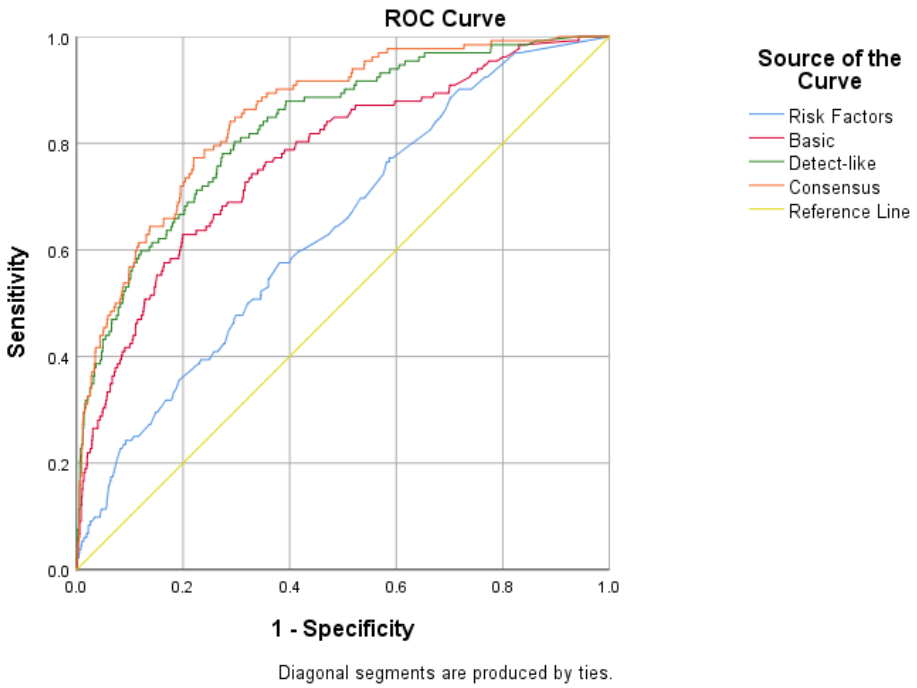



Table 38. Area under the ROC curves for the risk factors, Basic, Detect-like and Consensus prediction model for SSc-related cardiac events.

| | Area under the curve | Standard error | Asymptotic Sig. | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk Factors | 0.639 | 0.024 | **<0.001** | 0.592 | 0.686 |
| Basic | 0.771 | 0.022 | **<0.001** | 0.727 | 0.814 |
| Detect-like | 0.830 | 0.019 | **<0.001** | 0.794 | 0.867 |
| Consensus | 0.853 | 0.016 | **<0.001** | 0.821 | 0.885 |

Table 39. Paired comparison of the area under the ROC curves between the risk factors, basic, Detect-like and consensus prediction model for SSc-related cardiac events.

| Test Result Pair(s) | Asymptotic Sig. | AUC Difference | Std. Error Difference | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk factors vs Basic | **<0.001** | -0.132 | 0.214 | -0.182 | -0.082 |
| Risk factors vs Detect-like | **<0.001** | -0.192 | 0.206 | -0.244 | -0.140 |
| Risk factors vs Consensus | **<0.001** | -0.215 | 0.201 | -0.264 | -0.165 |
| Basic vs Detect-like | **0.001** | -0.060 | 0.201 | -0.095 | -0.024 |
| Basic vs Consensus | **<0.001** | -0.083 | 0.196 | -0.124 | -0.041 |
| Detect-like vs Consensus | 0.114 | -0.023 | 0.186 | -0.051 | 0.006 |

When applying the same models to the sub-group without PAH or non-cardiac ischemic disease, aiming at the prediction of SSc-pHI events, similar results were confirmed (Figure 6, Table 40). In addition, there was a trend towards statistical significance for the comparison between the “Detect-like” and the “Consensus” models, possibly supporting the more-PAH oriented target of the former versus the more “primary cardiac”-oriented target of the latter model (Table 41).

Figure 6. ROC curves for the risk factors, basic, Detect-like and consensus prediction model for SSc-pHI events (n=392 patients, 1472 visits).

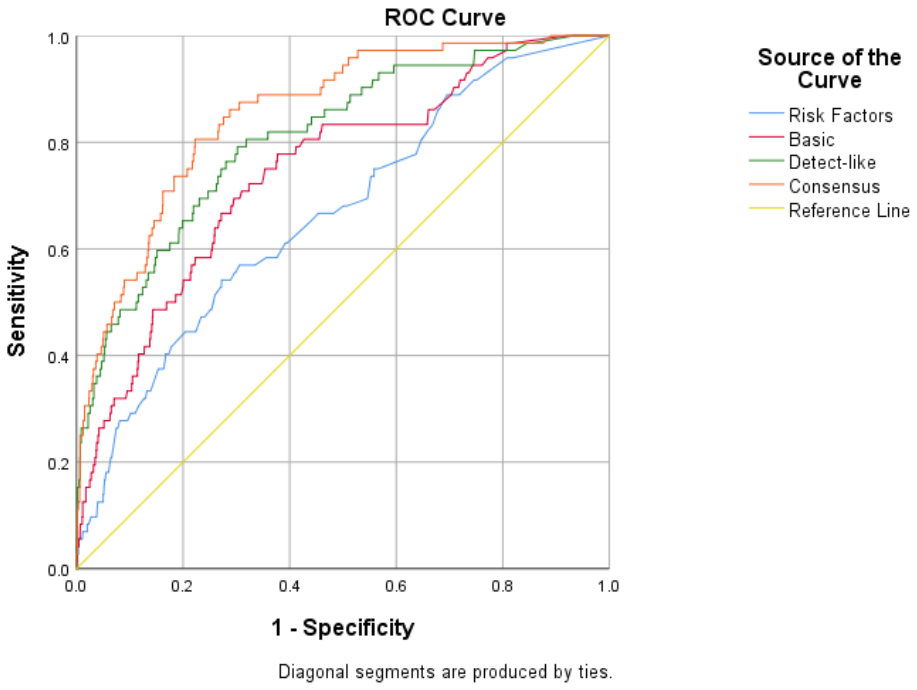



Table 40. Area under the ROC curves for the risk factors, Basic, Detect-like and Consensus prediction model for SSc-pHI events.

| | Area under the curve | Standard error | Asymptotic Sig. | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk Factors | 0.666 | 0.033 | **<0.001** | 0.601 | 0.731 |
| Basic | 0.746 | 0.030 | **<0.001** | 0.687 | 0.805 |
| Detect-like | 0.809 | 0.027 | **<0.001** | 0.756 | 0.862 |
| Consensus | 0.855 | 0.022 | **<0.001** | 0.813 | 0.898 |

Table 41. Paired comparison of Area under the ROC curves for the risk factors, basic, Detect-like and consensus prediction model for SSc-pHI events.

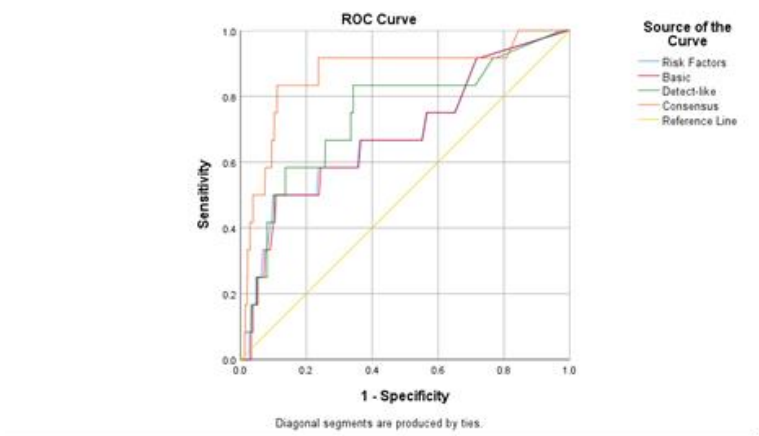
| Test Result Pair(s) | Asymptotic Sig. | AUC Difference | Std. Error Difference | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk factors vs Basic | **0.010** | -0.080 | 0.250 | -0.141 | -0.019 |
| Risk factors vs Detect-like | **<0.001** | -0.144 | 0.245 | -0.214 | -0.073 |
| Risk factors vs Consensus | **<0.001** | -0.189 | 0.234 | -0.257 | -0.122 |
| Basic vs Detect-like | **0.019** | -0.064 | 0.238 | -0.116 | -0.011 |
| Basic vs Consensus | **<0.001** | -0.109 | 0.227 | -0.170 | -0.049 |
| Detect-like vs Consensus | 0.054 | -0.046 | 0.220 | -0.093 | 0.001 |

We then differentiated the application of the models according to diagnostic or screening groups; the monitoring group was not analysed, given the low number of observations and events, not allowing further testing. Figure 7 shows similar distribution of ROC curves when the models were applied separately in the screening (upper panels) and diagnostic purposes (lower panels), in the whole population (left panels) and the sub-population without PAH or non-ischemic cardiac diseases (right panels) subgroups.

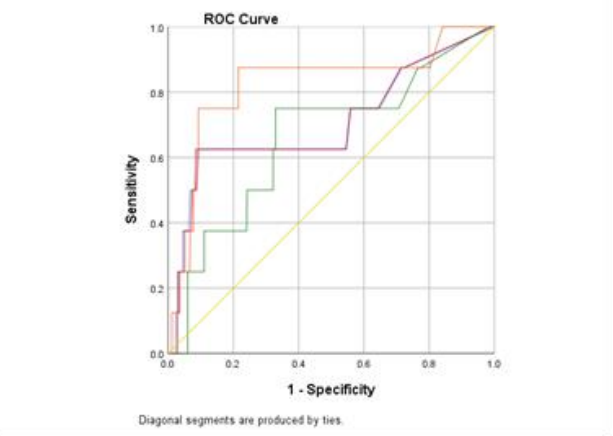
In the screening populations (upper left and upper right panels of Figure 7), there was a trend towards statistical significance in the whole study group (upper left panel) when comparing the "Consensus" versus "Risk factors" model (AUC difference -0.180, p=0.059), of the "Consensus" versus "Basic" model (AUC difference -0.184, p=0.051), and of the "Consensus" versus the "Detect-like model" (AUC difference -0.122, p=0.070). Only the latter was partially confirmed also in the sub-group without PAH or non-ischemic cardiac disease (AUC difference -0.167, p=0.095), see Upper right panel of Figure 7.

When analyzing the application of the models for diagnostic purposes, all the three "Basic", "Detect-like" and "Consensus" models showed statistically significant additional benefit compared to the simple assessment of "Risk Factors" in the overall population (AUC delta ranging from -0.104 to -0.181, p<0.001). Similarly, the same statistically significant difference was observed in the sub-group without PAH/non-ischemic cardiac disease (AUC difference ranging from -0.104 and -0.130, p values ranging from 0.002 and 0.013), as graphically represented in the bottom right section of Figure 7. Conversely, there was no statistically significant difference between the three models, both in the overall and in the PAH/cardiac disease-free subgroups.

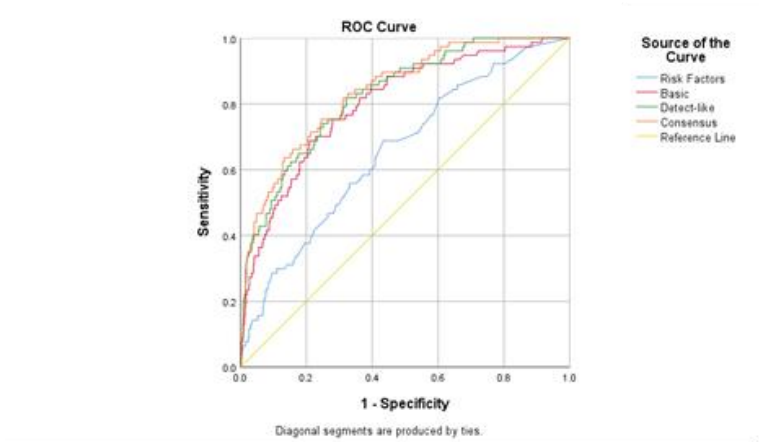
Figure 7. ROC curves for the prediction of SSc-associated cardiac events in the overall population for screening (upper left) and diagnostic (lower left) purposes, and in the sub-group without PAH and non-ischemic cardiac disease, still for screening (upper right) and diagnosis (lower right) of SSc-pHI events.



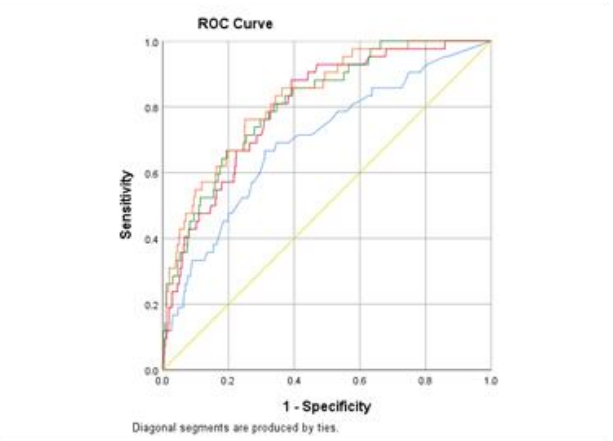

| Test Result Variable(s) | Area under the curve | Standard error | Asymptotic Sig. | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk Factors | 0.688 | 0.086 | 0.025 | 0.520 | 0.857 |
| Basic | 0.685 | 0.085 | 0.029 | 0.518 | 0.851 |
| Detect-like | 0.746 | 0.079 | 0.003 | 0.591 | 0.901 |
| Consensus | 0.868 | 0.063 | 0.000 | 0.744 | 0.993 |




| Test Result Variable(s) | Area under the curve | Standard error | Asymptotic Sig. | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk Factors | 0.707 | 0.116 | 0.044 | 0.480 | 0.934 |
| Basic | 0.704 | 0.114 | 0.047 | 0.481 | 0.928 |
| Detect-like | 0.658 | 0.103 | 0.125 | 0.456 | 0.860 |
| Consensus | 0.825 | 0.089 | 0.002 | 0.650 | 1.000 |




| Test Result Variable(s) | Area under the curve | Standard error | Asymptotic Sig. | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk Factors | 0.657 | 0.032 | 0.000 | 0.594 | 0.719 |
| Basic | 0.801 | 0.026 | 0.000 | 0.749 | 0.852 |
| Detect-like | 0.826 | 0.023 | 0.000 | 0.781 | 0.872 |
| Consensus | 0.838 | 0.023 | 0.000 | 0.793 | 0.882 |




| Test Result Variable(s) | Area under the curve | Standard error | Asymptotic Sig. | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk Factors | 0.696 | 0.043 | 0.000 | 0.611 | 0.781 |
| Basic | 0.800 | 0.032 | 0.000 | 0.737 | 0.862 |
| Detect-like | 0.812 | 0.031 | 0.000 | 0.750 | 0.873 |
| Consensus | 0.826 | 0.031 | 0.000 | 0.765 | 0.886 |

### 5.f.v - To test the impact of the consensus guidance on the performance of additional 2nd and 3rd level assessments

The evaluation of the 1828 visits showed a variable performance of second and third levels cardiac investigations, which are described in detail in Table 42.

Table 42. Second and third level cardiac assessments performed in the whole study population among the observed study period.

| | Prevalence among 530 patients/ 1828 visits | Prevalence among 392 patients/ 1472 visits |
|---|---|---|
| Any second/third level assessment | 432 (23.6) | 295 (20.0) |
| Cardiology consultation, n (%) | 218 (11.9) | 119 (8.1) |
| Right heart catheterization, n (%) | 85 (4.6) | 66 (4.5) |
| Stress ECG, n (%) | 74 (4.0) | 51 (3.5) |
| Holter ECG, n (%) | 108 (5.9) | 65 (4.4) |
| Stress ECHO, n (%) | 8 (0.4) | 7 (0.5) |
| Coronary angiography/CT, n (%) | 37 (2.0) | 27 (4.4) |
| Cardiac magnetic resonance, n (%) | 147 (8.0) | 119 (8.1) |
| SPECT/PET or Myocardial Scintigraphy, n (%) | 20 (1.1) | 12 (0.8) |
| Endomyocardial Biopsy, n (%) | 1 (0.1) | 0 (0.0) |

CT=computed tomography; ECG=electrocardiogram; ECHO= echocardiography; PET= positron emission tomography; SPECT=single positron emission computed tomography.

In line with the ST6, ST8 and ST10, visits of patients with signs/symptoms suspicious of cardiac involvement or known cardiac disease determined an increasing performance of at least one second/third level assessments, moving from the screening group (11.8% of visits) to the diagnostic group (27.3% of visits) and to the monitoring group (41.9% of visits) ($p<0.001$).

Regarding a possible multi-disciplinary team approach (reflected by a cardiologist consultations), this also showed a progressive increase among the groups, from 3.3% to 14.5% to 26.5% of visits, moving from the screening to the diagnostic to the monitoring group. This was in line with the data on Holter ECG, requested in 2.4% of screening, 6.3% of diagnostic and 16.1% of monitoring visits ($p<0.001$; in line with ST9).

In line with ST5, ST7, ST8 and ST10, CMR was also applied among all groups, still with increasing prevalence, from 6.3% of visits in the screening, 8.1% in the diagnostic and 14.1% in the monitoring groups ($p=0.044$).

We therefore investigated if performing additional tests using the “Basic”, the “Detect-like” or the “Consensus” models determined differences in predicting the performance of second/third level assessments, therefore representing an additional request of tests, with possible organizational, ethical and economic burdens.

The Risk factors model applied to the request of second and third level assessment confirmed Systemic arterial hypertension, mRSS and SRC as significant predictor, while this was not the case for presence of ILD on HRCT (Table 43).

Table 43. GLMM model to predict the performance of second/third level cardiac assessments, using the SSc-associated cardiac involvement risk factors as co-variates.

| Model Term | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Intercept | 0.747 | 1.112 | 0.581 | 2.127 |
| Systemic arterial hypertension | **<0.001** | 1.705 | 1.344 | 2.162 |
| ILD | 0.457 | 1.090 | 0.867 | 1.371 |
| SRC | **0.008** | 2.378 | 1.254 | 4.509 |
| mRSS | **<0.001** | 0.970 | 0.956 | 0.985 |

ILD=interstitial lung disease; mRSS= modified Rodnan skin score; SRC=scleroderma renal crisis.

When the Basic model variables were added, NYHA functional class, palpitations, chest pain, syncope and clinical signs of heart failure were shown as independent predictors of second/third level cardiac assessments (Table 44).

Table 44. GLMM model to predict the performance of second/third level cardiac assessments, using the Basic model variables as co-variates.

| Model Term | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Intercept | **<0.001** | 0.001 | 7.249E-05 | 0.004 |
| Risk Factors | **<0.001** | 46.715 | 9.426 | 231.505 |
| NYHA functional class I | **<0.001** | 6.758 | 2.658 | 17.183 |
| NYHA functional class II | **0.001** | 4.628 | 1.825 | 11.735 |
| NYHA functional class III | 0.059 | 2.548 | 0.964 | 6.731 |
| Palpitations | **<0.001** | 2.367 | 1.736 | 3.227 |
| Chest pain | **<0.001** | 3.509 | 1.902 | 6.474 |
| Syncope | **0.009** | 4.010 | 1.418 | 11.336 |
| Signs of heart failure | **0.046** | 1.630 | 1.009 | 2.634 |
| Altered SBP | 0.533 | 1.108 | 0.803 | 1.527 |
| Altered DBP | 0.579 | 1.110 | 0.767 | 1.606 |
| Altered HR | 0.152 | 1.302 | 0.907 | 1.870 |

SBP=systolic blood pressure; DBP= diastolic blood pressure; HR= heart rate.

Among the Detect-like model variables, the presence of conduction blocks on resting ECG and increased NT-proBNP levels were the only significant additional predictors of second/third level assessments, with a trend towards statistical significance for the presence of LV diastolic dysfunction or increase sPAP on ECHO (Table 45).

Table 45. GLMM model to predict the performance of second/third level cardiac assessments, using the Detect-like model variables as co-variates.

| Model Term | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Intercept | **<0.001** | 0.025 | 0.004 | 0.153 |
| Basic model | **<0.001** | 42.473 | 18.276 | 98.703 |
| Conduction blocks | **0.012** | 1.583 | 1.108 | 2.263 |
| RBBB | 0.891 | 1.036 | 0.621 | 1.728 |
| Right axis deviation | 0.852 | 1.091 | 0.437 | 2.723 |
| Right ventricular hypertrophy | 0.801 | 0.832 | 0.198 | 3.502 |
| Ventricular arrhythmias | 0.691 | 1.143 | 0.591 | 2.211 |
| Auricular arrhythmias | 0.888 | 0.963 | 0.570 | 1.628 |
| Pericardial effusion | 0.745 | 1.081 | 0.675 | 1.732 |
| Altered LV diastolic function | 0.062 | 1.283 | 0.988 | 1.666 |
| Altered LV systolic function | 0.101 | 1.994 | 0.873 | 4.555 |
| Increased sPAP>35 mmHg | 0.054 | 1.529 | 0.992 | 2.357 |
| Increased NT-proBNP | **<0.001** | 1.706 | 1.266 | 2.299 |

LV=left ventricle; RBBB= right bundle branch block; sPAP=systolic pulmonary arterial pressure.

Further independent predictive power was gained when the variables of the Consensus model were added. This showed statistically significant prediction for high sensitivity Troponin, but not for increased CK or increased inflammatory biomarkers (Table 46).

Table 46. GLMM model to predict the performance of second/third level cardiac assessments, using the Consensus model variables as co-variates.

| Model Term | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Intercept | **<0.001** | 0.091 | 0.054 | 0.154 |
| Detect-like model | **<0.001** | 74.648 | 35.365 | 157.568 |
| Increased hsTnT | **0.005** | 1.473 | 1.122 | 1.933 |
| Increased inflammatory biomarkers | 0.152 | 1.201 | 0.935 | 1.542 |
| Increased CK | 0.218 | 1.262 | 0.871 | 1.823 |

CK=creatine-kinase.

The comparison of the different discriminative power of the models showed increasing predictive values with the increasing number of variables, as expected, with AUC progressively increasing from 0.608 to 0.746 in the overall population, and from 0.615 to 0.729 in the sub-group without PAH or non-ischemic cardiac comorbidities (Figure 8 and Figure 9, Tables 47 and 49). Both in the whole study population and in the sub-group without PAH/non-ischemic cardiac diseases, there was a statistically significant increase in the prediction of request of second/third levels cardiac assessments when any of the three models was applied, in comparison to the sole evaluation of risk-factors. In addition, the difference in the AUC was still statistically significant when applying the Detect-like or the Consensus models versus the Basic model (Tables 48 and 50). Despite this, no statistically significant increase in the request of second and third level assessment was shown when comparing the Detect-like and the consensus models (tables 48 and 50).

There was a trend towards statistical significance for better prediction of second and third level assessment in the screening group of the whole population when applying the Consensus versus the Detect-like model (AUC difference -0.047, p=0.071) (Figure 10, upper left panel), which was not confirmed in the diagnostic group (AUC difference -0.002, p=0.792) (Figure 10, lower left panel). When analyzing the subgroup without PAH or non-ischemic cardiac diseases, still trend for better prediction of request of second/third levels assessments when using the Consensus versus the Detect-like model was confirmed for screening (AUC difference -0.052, p=0.089) (Figure 10, upper right panel), but not for diagnostic purposes (AUC difference 0.009, p=0.256) (Figure 10, lower right panel).

Figure 8. ROC curves for the prediction of the request of second/third level cardiac assessments in the whole study population (n=530 patients, 1828 visits)

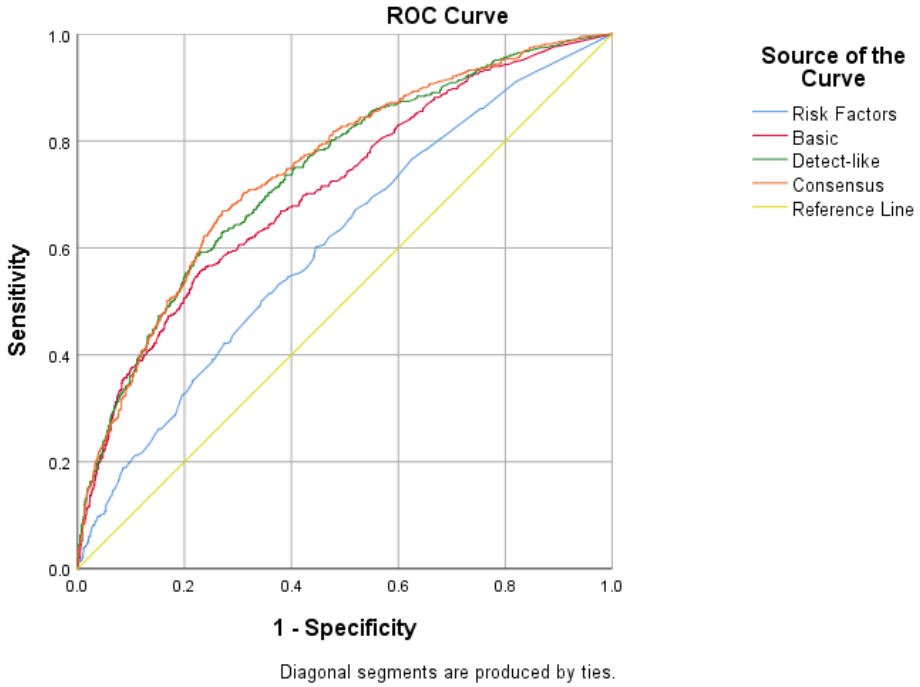



Table 47. Area under the ROC curves for the risk factors, basic, Detect-like and consensus prediction model for the request of second/third level cardiac assessments in the whole study population.

| | Area under the curve | Standard error | Asymptotic Sig. | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk Factors | 0.608 | 0.016 | 0.000 | 0.578 | 0.639 |
| Basic | 0.708 | 0.015 | 0.000 | 0.680 | 0.737 |
| Detect-like | 0.738 | 0.014 | 0.000 | 0.711 | 0.765 |
| Consensus | 0.746 | 0.014 | 0.000 | 0.720 | 0.773 |

Table 48. Paired comparison of Area under the ROC curves for the risk factors, basic, Detect-like and Consensus prediction model for the request of second/third level cardiac assessments in the whole study population.

| Test Result Pair(s) | Asymptotic Sig. | AUC Difference | Std. Error Difference | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk factors vs Basic | **<0.001** | -0.100 | 0.173 | -0.131 | -0.069 |
| Risk factors vs Detect-like | **<0.001** | -0.130 | 0.171 | -0.161 | -0.099 |
| Risk factors vs Consensus | **<0.001** | -0.138 | 0.170 | -0.168 | -0.108 |
| Basic vs Detect-like | **<0.001** | -0.030 | 0.168 | -0.047 | -0.014 |
| Basic vs Consensus | **<0.001** | -0.038 | 0.167 | -0.057 | -0.019 |
| Detect-like vs Consensus | 0.197 | -0.008 | 0.164 | -0.020 | 0.004 |

Figure 9. ROC curves for the prediction of the request of second/third level cardiac assessments in the PAH/non-ischemic cardiac disease-free sub-group (n=392 patients, 1472 visits).

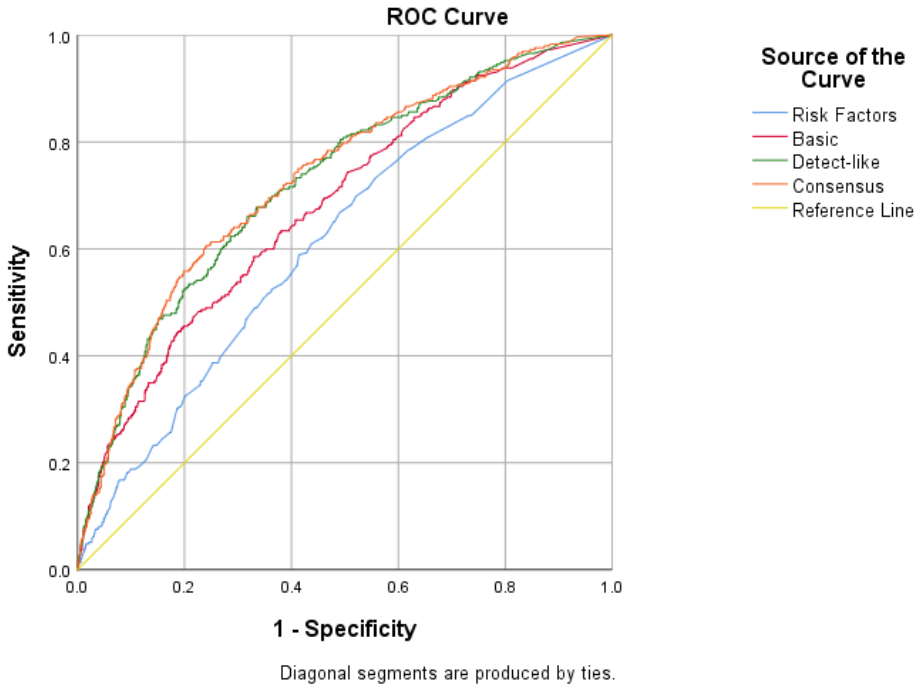


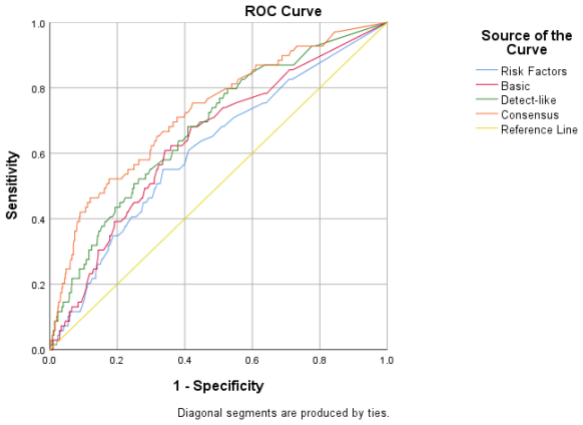

Table 49. Area under the ROC curves for the risk factors, basic, Detect-like and consensus prediction model for the request of second/third level cardiac assessments in the PAH/non-ischemic cardiac disease-free sub-group.

| | Area under the curve | Standard error | Asymptotic Sig. | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk Factors | 0.615 | 0.018 | 0.000 | 0.579 | 0.650 |
| Basic | 0.681 | 0.017 | 0.000 | 0.647 | 0.715 |
| Detect-like | 0.723 | 0.017 | 0.000 | 0.690 | 0.756 |
| Consensus | 0.729 | 0.017 | 0.000 | 0.697 | 0.762 |

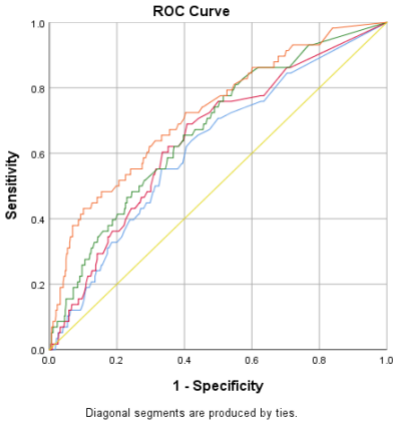
Table 50. Paired comparison of Area under the ROC curves for the risk factors, basic, Detect-like and consensus prediction model for the request of second/third level cardiac assessments in the PAH/non-ischemic cardiac disease-free sub-group.

| Test Result Pair(s) | Asymptotic Sig. | AUC Difference | Std. Error Difference | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk factors vs Basic | **<0.001** | -0.067 | 0.187 | -0.101 | -0.032 |
| Risk factors vs Detect-like | **<0.001** | -0.108 | 0.185 | -0.144 | -0.073 |
| Risk factors vs Consensus | **<0.001** | -0.115 | 0.185 | -0.149 | -0.081 |
| Basic vs Detect-like | **<0.001** | -0.042 | 0.184 | -0.063 | -0.020 |
| Basic vs Consensus | **<0.001** | -0.048 | 0.183 | -0.074 | -0.023 |
| Detect-like vs Consensus | 0.451 | -0.006 | 0.181 | -0.023 | 0.010 |

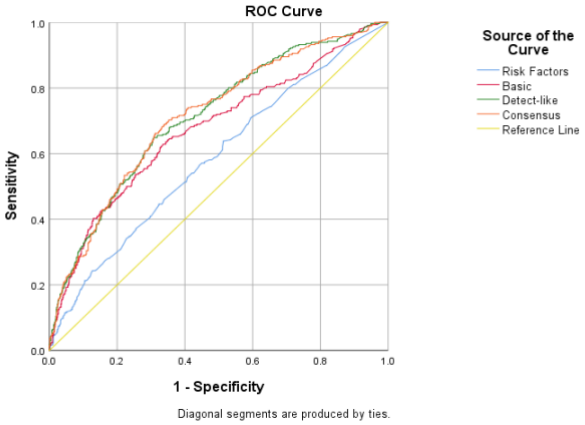
Figure 10. ROC curves for the prediction of request of second/third level cardiac tests in the overall population for screening (upper left) and diagnostic (lower left) purposes, and in the sub-group without PAH and non-ischemic cardiac disease, still for screening (upper right) and diagnosis (lower right) of SSc-pHI events.



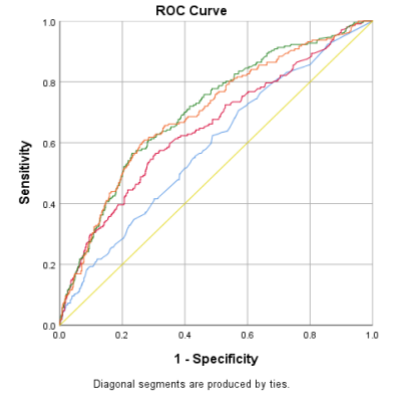

| Test Result Variable(s) | Area under the curve | Standard error | Asymptotic Sig. | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk Factors | 0.611 | 0.036 | 0.003 | 0.540 | 0.683 |
| Basic | 0.641 | 0.035 | 0.000 | 0.572 | 0.710 |
| Detect-like | 0.679 | 0.034 | 0.000 | 0.612 | 0.746 |
| Consensus | 0.726 | 0.034 | 0.000 | 0.660 | 0.792 |




| Test Result Variable(s) | Area under the curve | Standard error | Asymptotic Sig. | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk Factors | 0.619 | 0.038 | 0.003 | 0.543 | 0.694 |
| Basic | 0.645 | 0.038 | 0.000 | 0.571 | 0.719 |
| Detect-like | 0.671 | 0.037 | 0.000 | 0.600 | 0.743 |
| Consensus | 0.724 | 0.036 | 0.000 | 0.653 | 0.795 |




| Test Result Variable(s) | Area under the curve | Standard error | Asymptotic Sig. | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk Factors | 0.586 | 0.020 | 0.000 | 0.547 | 0.624 |
| Basic | 0.674 | 0.019 | 0.000 | 0.636 | 0.711 |
| Detect-like | 0.711 | 0.018 | 0.000 | 0.676 | 0.745 |
| Consensus | 0.713 | 0.018 | 0.000 | 0.678 | 0.747 |




| Test Result Variable(s) | Area under the curve | Standard error | Asymptotic Sig. | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Risk Factors | 0.588 | 0.023 | 0.000 | 0.543 | 0.632 |
| Basic | 0.649 | 0.023 | 0.000 | 0.605 | 0.694 |
| Detect-like | 0.705 | 0.021 | 0.000 | 0.665 | 0.746 |
| Consensus | 0.697 | 0.021 | 0.000 | 0.655 | 0.738 |

In this light, given the trend for increased request of second and third level cardiac assessments when applying the Consensus model in the screening population, we investigated the added value of those additional tests for the diagnosis of SSc-related cardiac events and SSc-pHI events. Endomyocardial biopsy was excluded from the analysis as only one event was recorded. Cardiology consultations, Holter ECG, Coronary arteries studies and Nuclear medicine tests were positively associated with diagnosis of SSc-cardiac events, while CMR was negatively associated with a possible role in the exclusion of such complications (Table 51).

Table 51. GLMM model to predict SSc-related cardiac events, using the Consensus model variables and the second/third level assessments as co-variates.

| Model Term | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Intercept | **<0.001** | 2.334E-14 | 1.980E-15 | 2.752E-13 |
| Consensus model | **<0.001** | 292.444 | 89.348 | 957.203 |
| RHC | 0.336 | 0.652 | 0.273 | 1.559 |
| Cardiology consultation | **<0.001** | 2.829 | 1.677 | 4.772 |
| Stress ECG | 0.842 | 0.920 | 0.403 | 2.100 |
| Stress ECHO | 0.291 | 2.611 | 0.440 | 15.501 |
| Holter ECG | **<0.001** | 4.650 | 2.623 | 8.245 |
| Coronary arteries studies | **0.001** | 4.240 | 1.747 | 10.294 |
| CMR | **<0.001** | 0.368 | 0.212 | 0.639 |
| Nuclear medicine tests | **0.022** | 4.149 | 1.233 | 13.965 |

CMR=cardiac magnetic resonance; ECG= electrocardiogram; ECHO= echocardiography; RHC= right heart catheterization.

This additional model, named “Consensus plus”, confirmed the additional value of second/third level cardiac assessments in the prediction of diagnosis of SSc-cardiac events, as showed in Figure 11 and Table 52 for the whole population, while in Figure 12 and Table 54 for the subpopulation without PAH/non-ischemic cardiac diseases. The “Consensus plus” model was statistically significant superior in the prediction of SSc-associated cardiac events and SSc-pHI events in the two populations analyzed compared to the other three models (Tables 53 and 55).

Figure 11. ROC curves for the prediction of SSc-associated cardiac events in whole study population, comparing the Basic, Detect-like, Consensus and Consensus plus models (n=530 patients, 1828 visits).

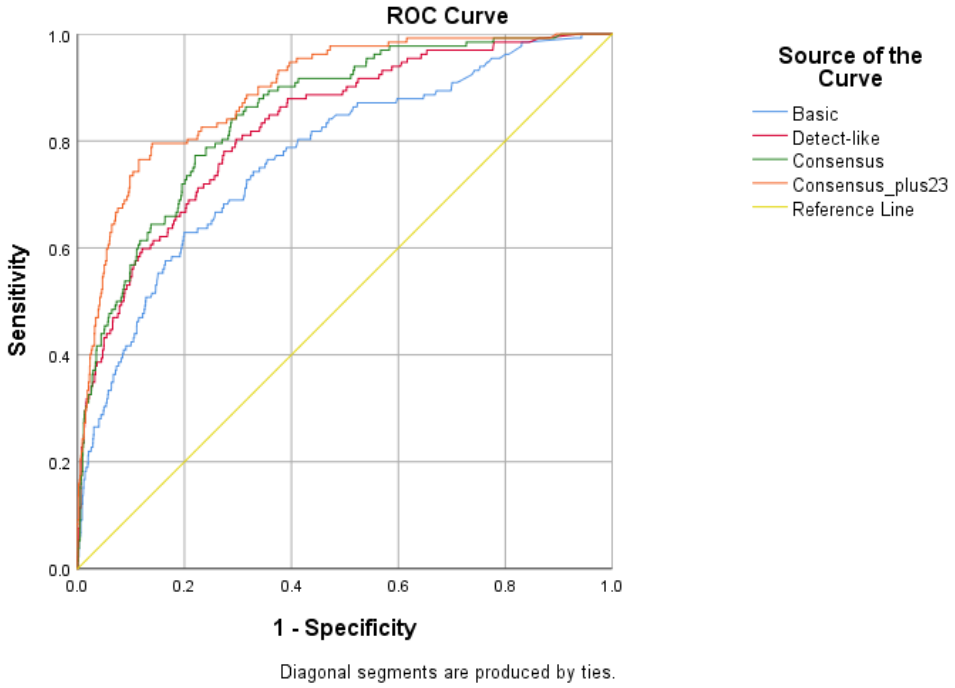



Table 52. Area under the ROC curves for the Basic, Detect-like, Consensus and Consensus plus prediction model for the detection of SSc-associated cardiac events in the whole population.

| | Area under the curve | Standard error | Asymptotic Sig. | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Basic | 0.771 | 0.022 | **<0.001** | 0.727 | 0.814 |
| Detect-like | 0.830 | 0.019 | **<0.001** | 0.794 | 0.867 |
| Consensus | 0.853 | 0.016 | **<0.001** | 0.821 | 0.885 |
| Consensus plus 2nd/3rd | 0.894 | 0.014 | **<0.001** | 0.866 | 0.921 |

Table 54. Paired comparison of Area under the ROC curves for the Basic, Detect-like, Consensus and Consensus plus prediction model for the detection of SSc-associated cardiac events in the whole population.

| Test Result Pair(s) | Asymptotic Sig. | AUC Difference | Std. Error Difference | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Basic vs Consensus plus 2nd/3rd | **<0.001** | -0.123 | 0.190 | -0.162 | -0.084 |
| Detect-like vs Consensus plus 2nd/3rd | **<0.001** | -0.063 | 0.180 | -0.095 | -0.032 |
| Consensus vs Consensus plus 2nd/3rd | **0.004** | -0.040 | 0.173 | -0.068 | -0.013 |

Figure 12. ROC curves for the prediction of SSc-pHI events in the PAH/non-ischemic cardiac disease-free sub-group, comparing the Basic, Detect-like, Consensus and Consensus plus models (n=392 patients, 1472 visits).

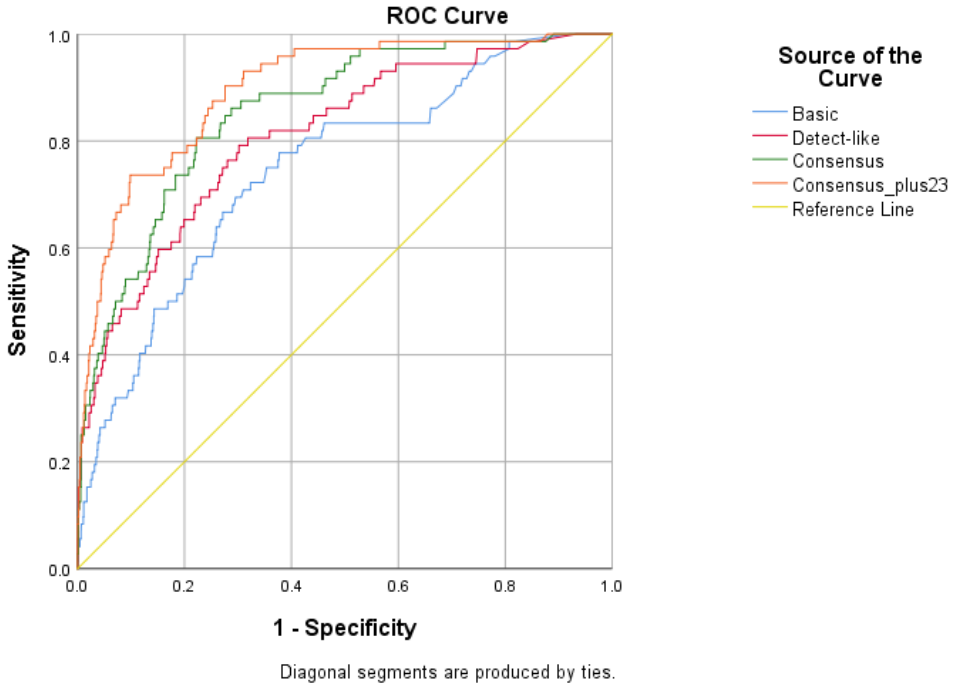



Table 54. Area under the ROC curves for the Basic, Detect-like, Consensus and Consensus plus prediction model for the prediction of SSc-pHI events in the PAH/non-ischemic cardiac disease-free sub-group.

| | Area under the curve | Standard error | Asymptotic Sig. | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Basic | 0.746 | 0.030 | **<0.001** | 0.687 | 0.805 |
| Detect-like | 0.809 | 0.027 | **<0.001** | 0.756 | 0.862 |
| Consensus | 0.855 | 0.022 | **<0.001** | 0.813 | 0.898 |
| Consensus plus 2nd/3rd | 0.896 | 0.018 | **<0.001** | 0.860 | 0.932 |

Table 55. Paired comparison of Area under the ROC curves for the Basic, Detect-like, Consensus and Consensus plus prediction model for the detection of SSc-PHI events in the PAH/non-ischemic cardiac disease-free sub-group.

| Test Result Pair(s) | Asymptotic Sig. | AUC Difference | Std. Error Difference | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| Basic vs Consensus plus 2nd/3rd | **<0.001** | -0.151 | 0.219 | -0.204 | -0.097 |
| Detect-like vs Consensus plus 2nd/3rd | **<0.001** | -0.087 | 0.212 | -0.131 | -0.043 |
| Consensus vs Consensus plus 2nd/3rd | **0.032** | -0.041 | 0.199 | -0.079 | -0.004 |

**5.f.vi - To test the impact of cardiovascular medications on developing SSc-cardiac events and mortality.**

The exposure to cardio-active medications along the overall visits is presented in Table 56, with a lower prevalence of beta-blockers, ACE inhibitors, anti-coagulants, and diuretics in the population without PAH/non-ischemic cardiac disease.

Table 56. Prevalence of cardio-vascular medications among visits, in the whole study population and in the subgroup without PAH/non-ischemic cardiac diseases.

| Medication | **Prevalence among 1828 visits (530 patients)** | **Prevalence among 1472 visits (392 patients)** |
|---|---|---|
| Alpha-receptors blockers, n (%) | 6 (0.3) | 5 (0.3) |
| Beta-receptors blockers, n (%) | 192 (10.5) | 97 (6.6) |
| Angiotensin-receptors blockers, n (%) | 181 (9.9) | 116 (7.9) |
| Angiotensin converting enzyme inhibitors, n (%) | 203 (11.1) | 126 (8.6) |
| Verapamil, n (%) | 35 (1.9) | 23 (1.6) |
| Calcium channel blockers – others, n (%) | 592 (32.4) | 490 (33.3) |
| Platelet anti-aggregants, n (%) | 637 (34.8) | 506 (34.4) |
| Oral anti-coagulant, n (%) | 140 (7.7) | 37 (2.5) |
| Diuretics, n (%) | 290 (15.9) | 130 (8.8) |

Given the low prevalence in both cohorts, alpha-receptors blockers were excluded from the analysis.

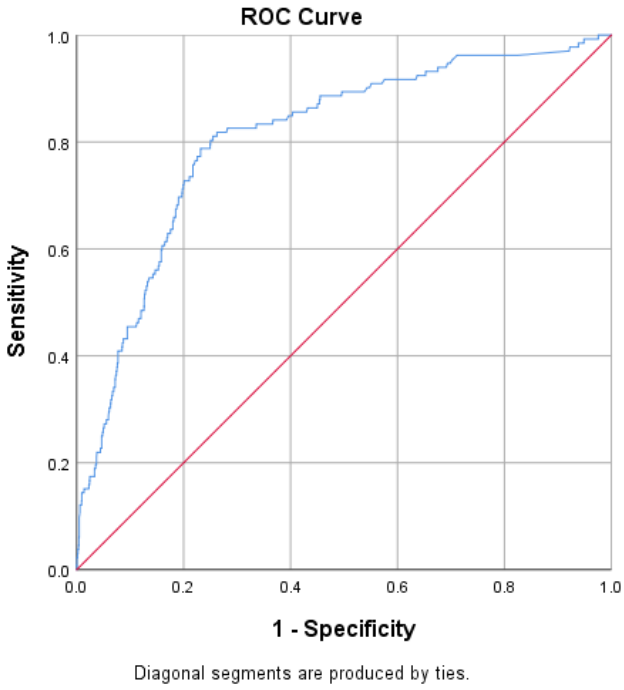
Adjusted for risk factors for the development of SSc-cardiac events (Table 33), the exposure to ARB and ACEi was associated with reduced risk of development of SSc-associated cardiac events in the overall population, being also statistically significant for the former drug. The other medications showed a positive association with events, being statistically significant for oral anticoagulant and diuretics (Table 57). This model showed good prediction, with area under the ROC curve of 0.807 (95% CI 0.768-0.847, p<0.001), as presented in Figure 13.

Table 57. GLMM model to predict SSc-associated cardiac events in the overall population, using background risk factors (see Table 33) and cardio-vascular medications as co-variates.

| Model Term | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Intercept | **0.002** | 0.043 | 0.006 | 0.323 |
| Background risk of SSc-cardiac events | **<0.001** | 135.324 | 18.760 | 976.162 |
| ARB | **0.031** | 0.399 | 0.173 | 0.921 |
| ACEi | 0.207 | 0.641 | 0.321 | 1.280 |
| Verapamil | 0.240 | 2.132 | 0.603 | 7.539 |
| CCB - others | 0.474 | 1.197 | 0.731 | 1.961 |
| Beta blockers | 0.443 | 1.286 | 0.675 | 2.450 |
| Anti-aggregants | 0.617 | 1.140 | 0.681 | 1.910 |
| OAC | **0.049** | 1.997 | 1.002 | 3.981 |
| Diuretics | **0.001** | 2.643 | 1.487 | 4.699 |

ARB=angiotensin receptor blockers; ACEi= angiotensin converting enzyme inhibitors; CCB=calcium channels blockers; OAC=oral anti-coagulants

Figure 13. ROC curve of the model in Table 57, predicting the development of SSc-associated cardiac events in the whole study population.




When the same model was applied in the sub-group without PAH or non-ischemic cardiac comorbidities (Table 58), ARB and ACEi were confirmed as protective factors, and this was shown also for CCB and anti-aggregants, while the other medications had signals as risk factors. Among medications, only diuretics reached statistical significance. The model showed

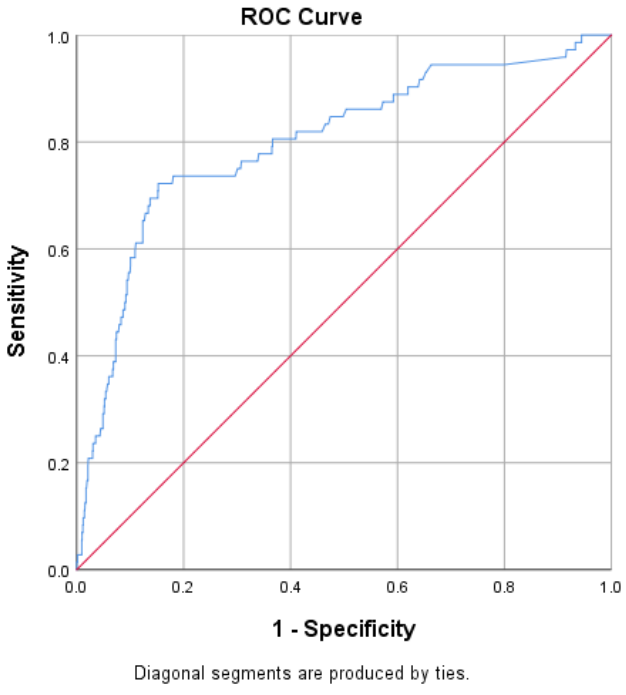
again good prediction, with area under the ROC curve of 0.800 (95% CI 0.741-0.858, p<0.001), as presented in Figure 14.

Table 58. GLMM model to predict SSc-associated cardiac events in the subgroup without PAH or non-ischemic cardiac comorbidities, using background risk factors (see Table 33) and cardio-vascular medications as co-variates.

| Model Term | Sig. | OR | LCI 95% | UCI 95% |
|---|---|---|---|---|
| Intercept | **<0.001** | 6.974E-06 | 1.020E-07 | 0.000 |
| Background risk of SSc-pHI events | **<0.001** | 949087.339 | 13821.491 | 65171462.468 |
| ARB | 0.157 | 0.451 | 0.150 | 1.358 |
| ACEi | 0.475 | 0.724 | 0.298 | 1.757 |
| Verapamil | 0.468 | 1.892 | 0.337 | 10.606 |
| CCB - others | 0.865 | 0.947 | 0.506 | 1.773 |
| Beta blockers | 0.174 | 1.824 | 0.766 | 4.345 |
| Anti-aggregants | 0.613 | 0.849 | 0.450 | 1.603 |
| OAC | 0.181 | 2.158 | 0.699 | 6.663 |
| Diuretics | **<0.001** | 4.321 | 2.051 | 9.105 |

ARB=angiotensin receptor blockers; ACEi= angiotensin converting enzyme inhibitors; CCB=calcium channels blockers; OAC=oral anti-coagulants

Figure 14. ROC curve of the model in Table 58, predicting the development of SSc-associated cardiac events in the subgroup without PAH or non-ischemic cardiac comorbidities.



When investigating mortality, the last visit was considered as the observation starting point, with exposure to medication recorded on that visit as co-variate for the prediction model. The prevalence of medications use is presented in Table 59 and is in line with the numbers along the whole dataset of visits.

Table 59. Distribution of cardiovascular medications at last visit, for the whole study population and the sub-group without PAH or non-ischemic cardiac disease.

| Medication ongoing at last visit | **Prevalence among 530 patients** | **Prevalence among 392 patients** |
|---|---|---|
| Alpha-receptors blockers, n (%) | 4 (0.8) | 3 (0.8) |
| Beta-receptors blockers, n (%) | 55 (10.4) | 23 (5.9) |
| Angiotensin-receptors blockers, n (%) | 58 (10.9) | 34 (8.7) |
| Angiotensin converting enzyme inhibitors, n (%) | 66 (12.5) | 32 (8.2) |
| Verapamil, n (%) | 16 (3.0) | 9 (2.3) |
| Calcium channel blockers – others, n (%) | 155 (29.2) | 118 (30.1) |
| Platelet anti-aggregants, n (%) | 185 (34.9) | 130 (33.2) |
| Oral anti-coagulant, n (%) | 48 (9.1) | 14 (3.6) |
| Diuretics, n (%) | 95 (18.0) | 38 (9.7) |

When the model adjusted for the risk factors of mortality presented in Table 30 and combined with exposure to cardio-active medications was applied to all patients, ARB and beta-blockers were associated with lower risk of mortality, although this did not reach statistical significance. Conversely, all other medication showed an Odds Ratio>1, representing a positive association with mortality: among them, only diuretics reached statistical significance (Table 60). The model presented a good predictive power, with area under the ROC curve of 0.840 (95% CI 0.795-0.885, p<0.001), as graphically presented in Figure 15.

When patients with PAH or non-ischemic cardiac diseases were excluded from the analysis, the same model confirmed association as protective factors for ARB, beta blockers and other CCB, although none reached statistical significance (Table 61). All other medications carried an increased risk for mortality, with ACEi, Verapamil and diuretics showing a statistically significant association with the outcome. Again, the model showed good predictive power, with area under the ROC curve of 0.825 (95% CI 0.761-0.890, p<0.001), as presented in Figure 16.

Table 60. Logistic regression model to predict mortality in the overall population, using background risk factors (see Table 30) and cardio-vascular medications as co-variates.

| | Sig. | OR | 95% LCI | 95% UCI |
|---|---|---|---|---|
| Background risk of death | **<0.001** | 251.754 | 57.002 | 1111.898 |
| ARB | 0.054 | 0.393 | 0.152 | 1.016 |
| ACEi | 0.393 | 1.368 | 0.666 | 2.810 |
| Verapamil | 0.053 | 3.359 | 0.983 | 11.472 |
| CCB - others | 0.814 | 1.076 | 0.585 | 1.978 |
| Beta blockers | 0.160 | 0.543 | 0.232 | 1.272 |
| Anti-aggregants | 0.088 | 1.700 | 0.924 | 3.129 |
| OAC | 0.548 | 1.322 | 0.532 | 3.280 |
| Diuretics | **0.002** | 2.967 | 1.483 | 5.935 |
| Constant | **<0.001** | 0.036 | | |

ARB=angiotensin receptor blockers; ACEi= angiotensin converting enzyme inhibitors; CCB=calcium channels blockers; OAC=oral anti-coagulants

Figure 15. ROC curve of the model in Table 60, predicting mortality in the whole study population.

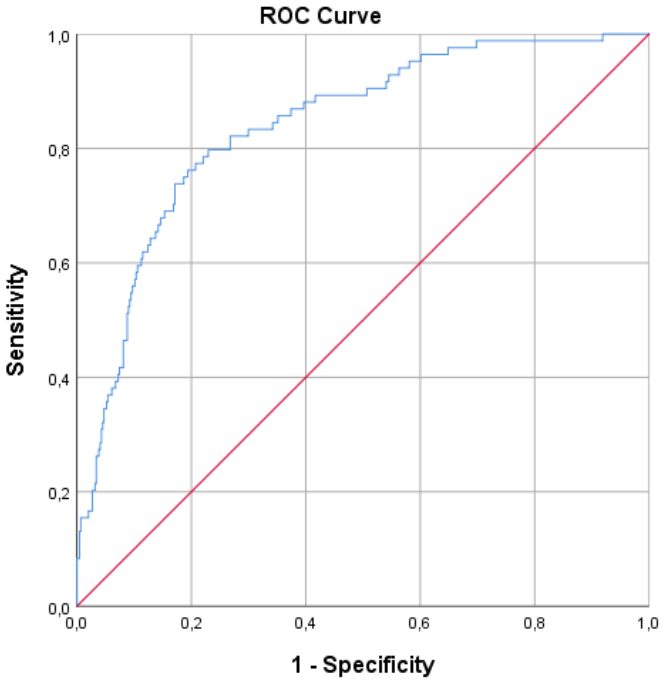
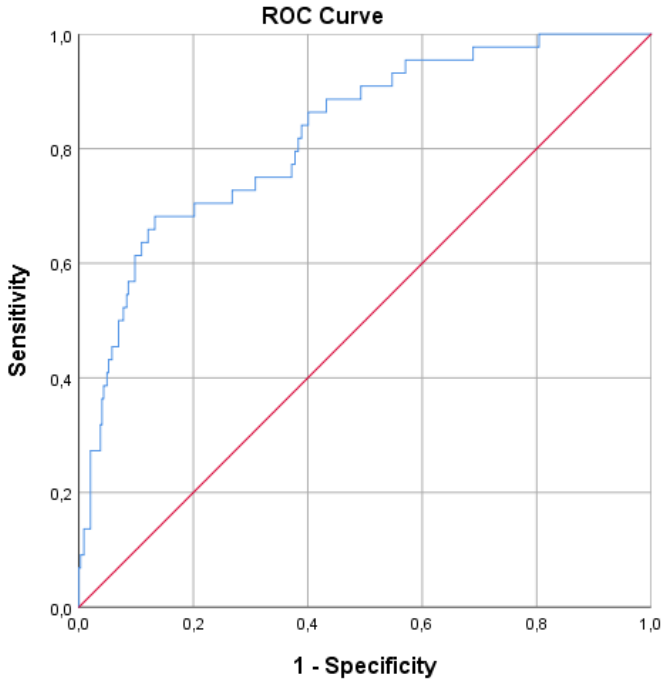


Table 61. Logistic regression model to predict mortality in the subgroup without PAH or non-ischemic cardiac comorbidities, using background risk factors (see Table 30) and cardio-vascular medications as co-variates.

| | Sig. | OR | 95% LCI | 95% UCI |
|---|---|---|---|---|
| Background risk of death | **<0.001** | 201.309 | 28.360 | 1428.966 |
| ARB | 0.622 | 0.728 | 0.206 | 2.574 |
| ACEi | **0.043** | 2,815 | 1,032 | 7,678 |
| Verapamil | **0,046** | 4,935 | 1,026 | 23,728 |
| CCB - others | 0,273 | 0,626 | 0,271 | 1,447 |
| Beta blockers | 0,403 | 0,554 | 0,139 | 2,211 |
| Anti-aggregants | 0,395 | 1,398 | 0,646 | 3,028 |
| OAC | 0,578 | 1,566 | 0,323 | 7,601 |
| Diuretics | **0,021** | 3,385 | 1,201 | 9,539 |
| Constant | **<0.001** | 0,036 | | |

ARB=angiotensin receptor blockers; ACEi= angiotensin converting enzyme inhibitors; CCB=calcium channels blockers; OAC=oral anti-coagulants

Figure 16. ROC curve of the model in Table 61, predicting mortality in the subgroup without PAH or non-ischemic cardiac comorbidities



## 6. Discussion

Overall, the project resulted in the creation and initial validation of a data-driven and consensus-based definition of SSc-pHI, the development of a Consensus Guidance on the screening, diagnosis and follow-up assessments for SSc-pHI, with a real-life retro-active evaluation of the feasibility of their application and the added value in comparison to current standard of practice.

*Heart involvement> creation and validation of the definition*

In SSc, SSc-pHI represents a relatively frequent organ complication, with variable clinical picture. Among the possible cardiac manifestations, the impairment of muscle relaxation or contractility, the alteration of origin or conduction of the rhythm, as well as inflammatory and fibrotic changes have been described, with variable prevalence (14, 17). According to the definition applied, the prevalence of SSc-pHI may range from less than 10% of cases up to 40% of SSc-patients. In fact, previous studies relied on the application of criteria based on presence of cardiac specific or non-specific signs and symptoms (i.e., dyspnoea, palpitations, leg oedema), presence of pre-determined altered values on cardiac tests or imaging techniques (i.e., arrhythmias on ECG, reduction of LVEF on ECHO, presence of LGE on CMR), or the increase of specific circulating biomarkers (such as NT-proBNP or troponin) (14, 17). Although this showed the important prevalence of certain specific alterations, the use of a specific diagnostic test with pre-defined cut-off may limit the detection of SSc-pHI, which manifests heterogeneously. In fact, ECG is indeed not capable of detecting contractility or relaxation defects, ECHO and CMR do not catch arrhythmias, the use of NT-proBNP or Troponin reflects the release of cardiac specific markers in the blood stream but do not explain the processes behind it.

For this reason, our study was indeed based on a SLR of current available evidence, which we pre-set differently in comparison to previous reviews (14, 17). In fact, we decided to consider the different aspects of SSc-cardiac involvement and to collect data regarding the clinical manifestations reported, the anatomic sites involved, the physiological functions affected, the findings identified on histopathology studies and the prognostic outcomes. Although these were arbitrarily chosen, we considered the basis of medical thinking trying to answer the basic rational questions: “what”, “where”, “when”, “why” and “how” SSc-pHI may manifest. Our first SLR confirmed that all cardiac chambers and structures might be affected during the disease course: while the left heart was affected in 11-12% of patients, the prevalence of right heart involvement was 20-23%. This may indeed reflect pulmonary vasculopathy, although our exclusion criteria ruled out manuscripts describing changes related to PAH and other secondary causes. Similarly, valve diseases were frequently reported in the

manuscripts, affecting around 37% of SSc patients. Still in this context, the presence of underlying non-SSc related valvulopathies could not be ruled out, unless specified in the manuscripts. The conduction system was involved in 25% of cases and also coronary vessels in around 30% of patients, both when considering epicardial or intramural vessels. While the myocardium was reported as the most frequently involved cardiac layer in 27% of the cases, a considerable percentage of patients (16%) presented with pericardial disease, which is more frequently looked for in other connective tissue diseases. Consequently, also all cardiac functions were possible targets of SSc-pHI: contraction was indeed rarer than relaxation impairments (7% vs 24% of reporting papers), and rhythm automaticity more frequent than rhythm conduction defects (25% vs 14%), while myocardial perfusion defects and valve abnormalities were detected to a similar extent (35-37%). Pathologically, myocardial inflammation, myocardial fibrosis and pericardial alterations were the most frequently detected changes in biopsy or autopsy samples, in 80%, 58% and 47% of patients respectively. Despite this relatively high prevalence of anatomical and functional involvement, our literature search showed quite heterogeneous clinical manifestations, with symptoms ranging 8-43% and signs 6-100% of prevalence and major cardiac events were developed by 4-11% of patients during the follow-up.

Keeping in mind these results, our Expert Committee and the PRP created a definition that could take all these aspects into account and that was not relying on a single test or on test-related parameters, stressing the importance of investigating also asymptomatic and early patients. The latter point was particularly stressed, although not included in the final definition. In fact, the research agenda should take into consideration the evaluation of cardiac disease in the early SSc stage and, in particular, in the diffuse cutaneous subset of the disease, when the inflammatory component is at its peak and cellular extravasation and tissue invasion may happen in all organs and systems, including cardiac structures (216).

The final definition of SSc-pHI stressed three points: first, the need to consider as primary SSc-pHI those cardiac abnormalities that are predominantly attributable to SSc, rather than other conditions. SSc patients, in fact, may have cardiac abnormalities as part of the general population, therefore atherosclerosis and coronary artery disease may manifest because of known cardiovascular risk factors (i.e., smoke, hyperlipidaemia). Moreover, the heart may be secondarily involved in non-cardiac SSc manifestations, such as lung vasculopathy. This can manifest as a primary condition in the context of PAH, or secondary to ILD and the consequent increase in pulmonary vessel structures pressure not fulfilling the criteria for pre-capillary-PH. In addition, SRC may manifest with acute cardiac failure and pericardial effusion, because of vascular overload and acute malignant systemic hypertension. As a second milestone, our definition included the important concepts of sub-clinical involvement and the need for investigations to confirm the presence of SSc-pHI. As for other organ involvements, such as

PAH and ILD, SSc-pHI may be completely asymptomatic but still be detectable when diagnostic tests are performed. This section of the definition is, indeed, one of the bases to support the screening of SSc-pHI: the investigations performed on asymptomatic patients can determine an earlier diagnosis and, therefore, both an earlier therapeutic approach and possible positive impact on the prognosis. Finally, we clearly included in the definition the pillars of the pathogenesis of SSc: vasculopathy, inflammation and fibrosis were in fact detected with different extent in the pathology studies, reflecting the systemic nature of the disease.

The NTG we used is a standardized methodology that allows all the participants to intervene in equal measure: this reflected one of the main concepts that later emerged from the consensus guidance, which is the need for a multi-disciplinary approach to SSc-pHI. As the different expertise were combined and merged to a single agreed result (the definition), the cooperation between specialists is pivotal during clinical practice: first of all, to exclude secondary causes and adapt the treatment to the disease stage. To these aims, a team approach is the winning strategy.

To the best of our knowledge, this is the first literature-based consensus definition of SSc-pHI, derived from combined rheumatology, cardiology, immunology and pathology expertise. While the previous review from Ross et al highlighted how different and heterogeneous were the criteria used to identify heart involvement, we created a definition which is independent from the tests used to detect it, therefore repeatable and applicable in different geographical, economic and social contexts. Currently, a parallel initiative supported by the Scleroderma Clinical Trials Consortium (SCTC) is ongoing, regarding the creation of classification criteria for Scleroderma heart involvement (16). While some may see these two initiatives as in competition, there is indeed a hypothetical benefit of combining the definition, the consensus guidance, and a set of classification criteria in the homogenization of study populations and in clinical practice.

*Diagnostic tests in SSc-pHI: data from the literature*

The performance of diagnostic tests in SSc patients has been widely reported in the literature, including different study populations, mostly consecutive patients, while other publications were focused mostly on patients without cardiac involvement or with known cardiologic involvement or cardiac symptoms.

The majority of the manuscripts included the so-called “first line” assessments, namely laboratory biomarkers, electrocardiography and echocardiography. A growing evidence is further accumulating from cardiac magnetic resonance studies, allowing anatomical, functional

and tissue characterization. In comparison to this, lower amount of evidence was collected for conventional radiology, myocardial scintigraphy and coronary arteries studies.

Most of the cardiac specific laboratory biomarkers, such as NT-proBNP, BNP and Troponin I showed increased values in SSc patients compared to healthy controls (66, 164, 196, 198), while non cardiac-specific markers, such as CK, ESR, CRP showed conflicting results, including statistically different values but no clinically meaningful differences (196). In line with the data we collected in the first SLR, ECG, ECHO and CMR confirmed the presence of different kinds of cardiac involvement, at different site levels and affecting different physiological functions. CMR and ECHO, indeed, confirmed that all cardiac chambers and structures may be involved in SSc-pHI, in particular with impariment in mobility, contraction and relaxation. In addition, CMR data were in line with the possible alterations dected by pathology evaluatuion of biopsy and autopsy samples. EGE and LGE, as well as native T1 mapping and ECV studies confirmed increased prevalence or values of fibrotic changes in SSc-pHI patients versus SSc patients without cardiac involvement (201) or versus healthy controls (23, 39, 118, 163, 164). On the inflammatory component of cardiac involvement, still CMR studies testing T2-STIR was performed in a relevant percentage of patients, with increased values compared to healthy controls and carrying prognostic implications for future cardiac events (60, 201). ECG studies detected a meaningful number of arrhythmias, ranging from isolated ectopic extra-beats to major malignant ventricular arrhythmias, although no studies directly comparing the reports with healthy controls or between cardiac involved and non-involved SSc patients were available. In line with the higher prevalence of right chambers versus left chambers involvement, ECHO demonstrated significantly different values of right ventricular function and tissue Doppler data, compared to healthy controls (68, 92, 112, 122, 149, 150).

Regarding the other tests, conventional radiology did not show a real benefit for diagnostic purposes of SSc-pHI. Nuclear medicine evaluations, such as myocardial scintigraphy, showed perfusion defect both at rest and after stress in a high percentage of SSc patients (42-46%) (29, 30, 32, 33, 35, 52, 56, 88), while motion abnormalities, functional impairment and signs of inflammation were detected in almost 20% of cases (29, 30, 33-35, 62, 69, 129, 139, 151, 173, 179). In line with the perfusion defects on myocardial scintigraphy, coronary arteries abnormalities were seen in 11% of SSc patients, compared to absent detection in healthy controls (29, 30, 33, 36, 46, 54, 56, 57, 70, 74, 77, 87, 88, 133, 156, 162, 169, 177, 191, 202).

*Creation of consensus guidance on screening, diagnosis, and follow-up evaluation of SSc-pHI.*

A minimal set of assessments has been proposed as an annual systematic assessment by a joint initiative from EUSTAR/SCTC, aimed to detect organ involvement (217). This included basic clinical and instrumental cardiac assessments, mostly for longitudinal research purposes.

A similar set of recommended tests was proposed by the UK Systemic Sclerosis Study group consensus, including frequency of the recommended testing and minimum dataset for echocardiography assessment and CMR evaluation (18). The use of more advanced tools, such as 24-hours Holter monitoring, CMR imaging and stress tests, mostly relied on cardiology consultations and expertise (18, 19).

The details of the cohorts and nature of the patients identified in the second SLR were not clear and there was a meaningful granularity of information. Some cardiac imaging studies identified underlying pathology but not necessarily clinically overt disease, and most evidence was derived from simple association studies. This resulted in the Consensus Agreement being more the art than the science, also given that the local organization of the different Health Systems environment may be extremely variable.

Two concepts were deemed as extremely important and, therefore, played a strong role in the Consensus guidance: the active participation of the Patient in the care process and the pivotal role of the multi-disciplinary management. Patient involvement in clinical practice and clinical research is a well-established factor, contributing to understanding which meaningful interventions may have a positive impact on quality of life (as well as morbidity and mortality) (218). Both from the patient's interview and through the active participation of the PRP to the creation of the SSc-pHI definition and consensus guidance, it was clear that the concepts of surprise, uncertainty and anxiety were present in this context, mostly related to the possibility of the presence of sub-clinical disease without patient's awareness. In this light, attention was put on the second statement of the definition, which clearly stated the possible sub-clinical nature of SSc-pHI and the need to confirm its presence through diagnostic testing. This was also important to raise further the awareness of the clinician, together with statements from the Consensus guidance regarding the suggestion to screen at baseline and repeat the assessments during the disease course, given the possibility of SSc-pHI to manifest in the early as well as late disease stage. Given the heterogeneity of SSc-pHI presentation, particular attention was placed on the need to counsel patients in a lay language to inform about possible cardiac symptoms and diagnostic procedures, as well as the importance to report to the multidisciplinary team.

Multidisciplinary approach to SSc-pHI was indeed the other pivotal feature in the Consensus Guidance: previous data showed the added value of a multi-specialist approach in SSc-PAH, another life-threatening complication of SSc (219). Rheumatologist, Internal Medicine specialists, Immunologists would indeed be the Experts in the overall care of SSc patients, but the specialist knowledge of the Cardiologists (and its different sub-specialties) is pivotal in considering and excluding differential or concomitant diagnosis, such as coronary artery disease, as well as in suggesting second/third level assessments in patients with confirmed SSc-pHI or unclear clinical pictures, on a clinical case-by-case basis.

Other screening programs are currently of practice in SSc, such as the screening for PAH recommended once a year by the ESC/ERS (220). As for other screening procedures, the evaluation of cardiac status may be performed more frequently in patients with cardiac symptoms, or known cardiac disease or heart failure, depending on the clinical presentation. This would indeed be the case for laboratory tests and for resting ECG, which can pick fixed conduction disturbances. Previous consensus statements from Bissell et al did not include Holter ECG and focussed its use only in the clinical context. Holter ECG and stress electrophysiology do not have the scientific basis to be supported as routine screening practice, while mostly based on triggers (symptoms or other tests). Holter ECG may be the most promising or powerful technique for this aim, but it needs to be validated in a systematic prospective registry, including the testing for cut-offs with diagnostic or prognostic values. Although electrophysiology is a non-invasive methodology that is possibly well accepted by the patient, performing Holter ECGs on every SSc patients finds important feasibility issues. It is therefore part of the research agenda to support its standardized application at baseline or on annual routine assessment.

The EACVI echocardiography protocol was designed for the general population and it was reviewed by the Experts committee in the light of the literature and their personal experience. In terms of feasibility and availability, two protocols were derived from the revision of the EACVI protocol, one as a standard clinical practice and the other as an optional/research agenda protocol. The protocols were derived through the removal of certain parameters that were not considered to be pivotal in the assessment of SSc-pHI patients. For example, this is the case of Strain ECHO, requiring machines that are more sophisticated. However, Strain ECHO can provide more details especially for the detection of early changes: ideally, it should be done in all asymptomatic patients to detect early myocardial involvement. Currently, some centres may be undertaking Strain ECHO where they have that capability; still this is very much part of a research agenda that could inform future protocols. For valve diseases, trivial minimal alterations can be detected in a high percentage of the general population: as a conclusion, it was agreed that the alterations that are present should be quantified and measured, while clearly stated if absent. Lot of discussion was placed on the pericardium, which is not included

in the standard EACVI protocol. The pericardium, as also seen in the first SLR, can be quite frequently involved in SSc patients: for this reason, its assessment should be included in the periodical ECHO evaluation, in particular regarding the presence of pericardial effusion, but with a specific standardization of the reporting also in the light of longitudinal comparison. If not standardized, the heterogeneity of the reporting could indeed generate uncertainty for the patient and non-clarity for the non-cardiologist physician. Although tertiary cardiology centres with SSc expertise would be the ideal setting for the performance of the ECHO, this would indeed generate issues in terms of accessibility and feasibility. In this light, given the differences among health systems, the Scientific Community should be advocating highly skilled training of sonographers to ensure consistency in the reporting whether a tertiary or a peripheral centre is performing the exam. Timing for screening was set to once a year, also in line with the PAH-screening standard, with possible shortening of the timing on a case-by-case base according to clinical judgment. Of course, this should be considered from both a cardiologist and a rheumatologist point of view, who may integrate their knowledge in indicating patients needing a tighter control.

Bi-ventricular and bi-atrial morphology and function are important and are still nowadays cornerstones of the CMR assessment, with indexation of measurements being essential. Regarding tissue characterization, LGE or T2-STIR signal alteration are considered the basis, while T1 mapping, ECV and T2 mapping represent the new quantitative techniques that can detect subtle changes. Despite the additional data on fibrotic or inflammatory changes, none of these techniques detect SSc-specific alterations, as the tool cannot distinguish between the possible etiologies of the detect changes. LGE is for focal fibrosis, T1 mapping pre- and post-contrast (and the consequent ECV) give a quantitative estimate of the fibrotic burden, although its interpretation as normal/pathologic relies on normal values for each center. Still for LGE there are software that can quantify the intensity of the signal, with different methods for indicating pathologic cut-offs, although it is not clear if this has prognostic relevance in SSc. This is in contract with the reality and infrastructure/expertise variability, as the newer techniques may not be available in every center. As for the ECHO, the use of Strain CMR is still part of the research agenda, as the impairment in its values does not have a clear interpretation and impact on the prognosis.

Despite the growing evidence on the added value of CMR, there was a big discussion between the Experts Committee members regarding its application in clinical practice. In the previous UK SSc study group consensus paper, the use of CMR was based on clear triggers of cardiac involvements (signs/symptoms, ECG, ECHO, laboratory alterations) and still today the level of evidence to standardize its screening use is lacking, although even completely asymptomatic patients may show CMR abnormalities. CMR represents the surrogate for the gold-standard of tissue characterization, which is endomyocardial biopsy; despite its indirect results, CMR

does not provide etiological information, i.e., when cardiac edema is detected. In this context, the current Consensus Guidance included CMR as an assessment to be considered on a case-by-case basis also in asymptomatic patients without history of heart involvement, and to be included as part of the diagnostic work up where suspicion remains following positive findings in the initial core evaluation.

The diagnostic work-up from Bournia et al included, similar to our Consensus guidance, three levels of evaluation (19): the “basis” was constituted by medical history and physical examination, specifically focusing on cardiac signs and symptoms, which was suggested twice a year in all SSc patients. As first level assessments, ECG, chest X-ray, laboratory biomarkers (NT-proBNP or BNP and Troponin I) and ECHO were suggested yearly. Finally, the second level evaluation included stress echocardiography, SPECT, CMR, right heart catheterization and Coronary angiography, to be performed under the Cardiologist guidance. In comparison to this algorithm, our consensus guidance was fully oriented to primary heart involvement and did not consider chest X-ray as a first line evaluation. Similarly, we did not clearly indicate which assessment should be included as second level evaluation, as they should be decided on a case-by-case basis according to diagnostic and differential diagnosis purposes, in line with the concept of the multidisciplinary team management that we introduced. Bournia et al suggested physical examination, ECG and ECHO once a year for the screening evaluation of asymptomatic patients: in comparison to this, we stressed the importance of evaluating also laboratory biomarkers annually, given the increasing evidence on their role for the evaluation of myocardial stress and microvasculopathy (221, 222). This is particularly the case of high sensitivity Troponin, which has been proposed as a promising biomarker for the detection of myocardial involvement (221-223). In addition, NT-proBNP and BNP are already part of the screening algorithm for SSc-PAH, making this datum already available to the physician as a useful guidance to further understand the cardiac picture (224).

The Consensus best practice from Bissell et al stressed from the very beginning the importance of multi-disciplinary team, including overall cardiac disease and a focus on primary cardiac disease (18). In line with what also our Consensus Guidance suggested, medical history and physical examination were indicated in all SSc patients to identify those at higher risk of heart involvement, who would represent what we named “diagnostic purpose” patients. In asymptomatic cases, Bissell et al suggested annual ECG (±Holter as indicated), ECHO and blood tests, similar to our Consensus guidance. Comparing the two Consensus documents, we considered acute and chronic CAD as a necessary differential diagnosis to be always considered and carried out following specific guidelines and recommendations. Moreover, Bissell et al included specific statements, such as the need to test annually for lipid profile and glycate hemoglobin, attributing an active role to the caring rheumatologist in the evaluation for coronary artery disease. Regarding diagnostic patients, therefore these cases with signs or

symptoms suspicious of cardiac involvement, as well as in cases already affected by heart disease, Bissell et al suggested 6 monthly laboratory, ECG (±Holter) and ECHO evaluations, then the performance of additional tests according to the cardiology guidance. In our Consensus paper, we still proposed a yearly assessment also of symptomatic patients, with further adjustment of timing and kind of assessments guided by the case-to-case scenario evaluation in the context of the multidisciplinary team. In fact, different cardiac-specific or SSc-specific factors may determine a different impact on both timing and type of evaluation, which therefore may benefit from the shared decision-making process. This was even more stressed in our paper for the cases with definite cardiac involvement diagnosis, in which no early screening/diagnostic test was suggested and the whole decisional algorithm was patient-tailored by the multi-specialty team.

In comparison to both Bournia et al and Bissell et al, our manuscript proposed specific statements for the use of CMR. There was an increasing evidence on the use of CMR and the possible parameters tested with this evaluation compared to few years ago, when the other two manuscripts were published (60). Indeed, there are prognostic data for CMR detectable parameters, even for asymptomatic sub-clinical detections (203). Despite the growing knowledge in the field, the overall evaluation of feasibility, generalizability, costs and scientific robustness of the data was not deemed sufficient to justify the use of CMR on a screening or global diagnostic approach. However, our Consensus guidance proposes that CMR may be considered for screening purposes and should be included in the diagnostic work-up where suspicion remains after the core evaluation with biomarkers, ECG and ECHO. This remains part of the research agenda, although recent publications have identified possible risk factors for the detection of CMR changes: this is the case of higher mRSS, presence of digital ulcers and increased cardiac biomarkers (225). Moreover, the same UK group has also published recent data on the prognostic value of CMR changes for future cardiac events (226). These results further support the performance of a multidisciplinary team evaluation, with the role of the Rheumatologist being pivotal for the evaluation of skin involvement and peripheral vasculopathy, the role of biomarkers in the annual cardiac assessment and the added value of CMR from a diagnostic and prognostic perspective.

*Testing the application of the definition of SSc-pHI and the consensus guidance in a real-life scenario*

The SSc database of the Rheumatology Department at Zurich University Hospital (USZ) accounted for 530 patients at the time of censoring and data were prospectively collected in line with the parameters present in the EUSTAR database and the suggested annual evaluation (217).

In line with the so-far heterogeneous definition of SSc-cardiac disease and SSc-pHI, this item has not been included in the prospective standardized data collection, which was instead the case of other organ complications (i.e., ILD, SRC, DU).

The application of the definition of SSc-pHI to the USZ cohort resulted on an overall prevalence of almost 19% of cardiac involvement, with possible primary and secondary components. Excluding the cases with complete absence of possible SSc and non-SSc causes of possible secondary heart involvement, which represented a minority, we adopted a statistical model to understand the significant predictors of cardiac disease among these complications and identified PAH and non-ischemic cardiac disease as possible independent causes of cardiac events, therefore as significant sources of secondary cardiac disease. Although artificial, we applied this definition of "secondary heart involvement" to our cohort to identify the cases with sure SSc-pHI and combined primary and secondary heart disease. This lead to identify 45 cases of isolated or combined SSc-pHI, accounting for a 11.5% prevalence. This is in line with the wide range of prevalence of cardiac involvement identified by both Bissell et al (14) and Ross et al (17), although a direct comparison is not possible. In fact, both other manuscripts relied on data derived from systematic literature reviews, including manuscripts in which cardiac involvement was defined through the application of single tests or specific imaging/laboratory/diagnostic parameters. Our definition of SSc-pHI was indeed more general and inclusive and not relying on stringent ECHO or ECG or CMR parameters, therefore allowing a global inclusion of rhythm, muscle, and inflammatory/fibrotic cardiac complication, and being more in line with the real nature of SSc cardiac involvement and its possible manifestations.

Elhai et al identified 12% of SSc-related deaths as attributable to primary heart disease and elaborated a 3-years mortality prediction model based on the EUSTAR database parameters (2). Among them, certain cardiac variables were included as independent predictors of mortality, such as prominent dyspnoea and LVEF<50%, and other suspicious features such as increased CRP. As a limitation, arrhythmic events or ECG changes were not included in the model, although some data could be derived from the EUSTAR dataset. In our prediction model for mortality, we included SSc cardiac disease, both as a global entity (primary and secondary) or in the restricted group of isolated or combined SSc-pHI. Moreover, given the small number of events, we included cardiovascular general population risk factors and major SSc-related organ complications as co-variates. Age, higher mRSS and SRC were confirmed both in Elhai et al and in our model, while we newly identified SSc-cardiac involvement as a significant predictive factor. This was particularly evident in the overall population (including secondary and primary heart disease) and reached a trend towards independent statistical significance in the isolated or combined primary sub-cohort. Although our initiative was mostly focussed on SSc-pHI, these data highlight the importance of assessing and managing cardiac

involvement in SSc independently from its primary or secondary nature, given the significant prognostic role it carries.

Different risk factors for the development of cardiac involvement in SSc were previously identified, such as older age at disease onset (204, 227), male gender (228), certain auto-antibodies positivity (227, 229), diffuse cutaneous subset (128) and inflammatory musculoskeletal involvement (128) for more cardiac involvements with inflammatory features such as myocarditis, while history of digital ulcers (230) was identified as a risk factor for fibrotic and dysfunctional changes. Our prediction model identified both fibrotic (mRSS and ILD) and vascular (SRC and systemic arterial hypertension) features as predictors of the heterogeneously defined SSc-pHI. Although not included in the final model, also male gender initially resulted as a significant predictive factor, in line with previous results. This again in line with the mixed pathogenesis of SSc-pHI and its possible manifestations and could be used, once validated, as the definition of the “high risk” profile, according to which the screening and diagnostic procedures may be adapted.

The applicability and the feasibility of the Consensus Guidance was tested retrospectively in the USZ SSc cohort. Despite it was oriented to the specific screening, detection and monitoring of SSc-pHI, it was tested both the overall cohort (primary and secondary heart involvement) and in the primary heart involvement cohort (prevalent isolated or combined primary and secondary heart involvement). The annual core assessment, proposed for both screening and diagnostic purposes, showed high feasibility: medical history for symptoms and physical examination for signs raising suspicion of cardiac involvement were reported in all visits evaluated (100%), laboratory tests in almost 99% of visits (89% for NT-proBNP and 66% for high resolution troponin), resting ECG in 97.2% and ECHO in 98.6% of visits. This is in line with the standardized application of the DETECT score (224), a screening algorithm for the early detection of SSc-PAH, that requires laboratory, ECG and ECHO parameters for the calculation of the first and second steps of the risk score. In line with the EUSTAR data collection, but also with the ESC/ERS guidelines for the screening of PAH (220), the screening was performed annually to most of the patients, excluding of course loss of follow-ups. In addition to the DETECT algorithm, only additional laboratory tests would be part of the annual assessment: this would be the case of high sensitivity troponin, with added value in the detection of SSc-pHI, while CK or CRP/ESR supporting the differential diagnosis as part of the overall work-up.

In the real-life study application of the Consensus Guidance, 4 different algorithms were compared for their predictive value to associate with SSc-cardiac events (both primary and secondary) and, separately, SSc-pHI events: the “risk factors” model, the “basic model”, composed of risk factor and signs/symptoms, the “Detect-like”, including NTproBNP, ECHO

and ECG available parameters, and the “Consensus-like”, with added the three abovementioned laboratory parameters. In comparison to the sole evaluation of risk factors, NYHA functional class, palpitations, chest pain and clinical signs of heart failure showed additional predictive value, then further by right axis deviation on ECG, pericardial effusion on ECHO and increased NT-proBNP, finally additional value by increased high sensitivity Troponin. The further added value of the progressive increase of parameters tested was paralleled by an increase of the AUC when progressively escalating from the basic to the Consensus models.

Regardless of which model was used, both the Basic, the Detect-like and the Consensus models showed a statistically significant increase in the AUC compared to the sole assessment of risk factors, further supporting the application of a screening/diagnostic protocol. In addition, both the Detect-like and the Consensus models showed further significant added value of laboratory, ECG and ECHO to the basic model (association of risk factors and clinical consultation). A trend towards statistical significance was observed when comparing the Detect-like and the Consensus models, which almost reached statistical significance when focussing on the patients without PAH and non-ischemic cardiac disease. In fact, the Basic and the Detect-like models showed higher AUC when tested in the global population, while the Consensus model was similar or slightly higher when tested in the SSc-pHI sub-analysis population. This might support the additional value of high sensitivity Troponin, CK and ESR/CRP for the detection of primary heart disease, leaving to sole NT-proBNP evaluation to a more PAH oriented role. In addition, the separation of visits performed for Screening or for diagnostic purposes confirmed the increased detection power of the Consensus model, which reached a statistically significant difference in screening cohorts of the global and the sub-group populations, but not in the diagnostic subgroup. This might be related also to the strong reduction in number of events when further dividing the patients into sub-groups.

Along the 1828 visits, 23.8% of them resulted in the prescription of at least one second or third level assessment, being represented in most of the cases by cardiology specialist consultation, CMR or Holter ECG. In line with the statements 6, 8 and 10 of the Consensus guidance, additional tests were more frequently requested in patients with already diagnosed cardiac disease (monitoring group) or with sings/symptoms suggestive of cardiac disease (diagnostic group). This was also the case of the cardiologist consultation, which represented a surrogate for the multidisciplinary team evaluation, applied more frequently in the diagnostic and monitoring visits. Although ECG and ECHO are pivotal instruments of the Core set evaluation of heart function an involvement, most of the diagnosis rely on second and third level evaluations, allowing an in-depth evaluation of inflammatory/fibrotic conditions and of the nature/severity of arrhythmic burden. Still comparing the risk factors, the Basic, the Detect-like and the Consensus models, we observed a progressive and statistically significant increase in

the AUC of the different models. Both the Basic, Detect-like and Consensus models predicted the performance of second/third level tests better than the model constituted by risk factors, and the Detect-like and Consensus better than the Basic model. Interestingly, the Comparison between the Detect-like and the Consensus models did not show a statistically significant difference in both the overall population and in the sub-population without PAH or non-ischemic cardiac disease, regarding the subsequent request/performance of second and third level tests. This indicated that the performance of the additional first level laboratory biomarkers (high sensitivity troponin, CK and ESR/CRP) was not associated with a higher performance of second and third level assessments. This was instead seen in the screening subgroups of both populations, in which the application of the Consensus algorithm predicted the performance of second/third level assessments significantly better than the Detect-like model.

Although outside the aim of this study, we made an economic consideration for this latter results. If the Consensus model was applied in the screening population and this determined a significantly higher performance of additional second/third level tests, this would determine a higher expense for the health systems and higher burden for the patients. With our subsequent analysis and the creation of the Consensus-plus model (which included also second and third level evaluations), we justified the performance of the second/third level tests and supported their additional value of these further evaluations in the detection of SSc-cardiac disease and SSc-pHI.

Once corroborated the value of screening and diagnostic use of our consensus guidance, although again outside of the current stage of this project, we tried to lead the basis for the treat to target strategy of SSc-pHI. A recent publication from Valentini et al on behalf of the EUSTAR Group, analysed the role of vasodilators and low-dose acetylsalicylic acid in patients free from cardiac disease or any possible cause of secondary SSc- and non SSc-related cardiac involvements (207). In comparison to our population, they analysed 603 patients with follow-up data and observed a total of 72 events attributable to SSc-pHI. When testing the possible preventive effect of cardio-active medications in our whole population, on top of background risk factors, we observed a protective effect for angiotensin receptor blockers against SSc-cardiac events, which was not then replicated in the population without PAH or non-ischemic cardiac disease against SSc-pHI events. The same class of medications showed also a protective effect against mortality (with trend towards statistical significance) in the whole population, which was weaker but still pointing towards a protective effect also for beta-blockers. Different medications showed an increased risk for cardiac events, such as diuretics and oral anti-coagulants for cardiac events, but also ACE-inhibitors and verapamil for the prediction of mortality. These results do not speak for an increased risk for these medications, determining the onset of cardiac events or mortality, and may instead represent confounders by indication.

Although our results cannot be directly compared with the study of Valentini et al, given the different populations studied and the different nature of the outcomes, there is signal for potential beneficial effect of cardio-active medications. The replication of the same analysis of Valentini et al in our population could not be performed, given the very low number of patients/visits/events left after excluding all the possible organ complications and comorbidities. In addition, other medications such as major vasoactive-vasodilating drugs (i.e., anti-endothelin, phosphodiesterase 5 inhibitors, prostacyclin analogues) as well as immunosuppressive medications, were not considered in the current analysis. They may play indeed a role in the prevention or in the treatment of cardiac disease and the consequent reduction of mortality events, given their effect on the pathogenetic determinants on SSc-pHI, and should therefore be studied in future projects.

*Strenghts*

Our project globally presents strengths. In particular, our SSc-pHI definition was derived from information gathered through a standardized SLR investigating the basis of cardiac involvement, including semeiotic, clinical, anatomy, physiology and pathology background. It was in fact a decision of the Core Leadership team not to include cut-offs or findings derived from specific diagnostic tools, in order to make the currently proposed definition of SSc-pHI applicable in different geographic, economic and healthcare systems, independent from local facilities. In the creation of the definition, as well as during the creation of the Consensus guidance, we included different specialists dealing with SSc-pHI, including cardiologists (with different expertise in ECG, ECHO, CMR), rheumatologists, immunologists, and cardio-pathologists. Moreover, we had the pleasure to receive valuable inputs from the patients' pilot interviews and the active participation of the PRP to all the meetings of this initiative. In comparison to other studies or definitions, which relied exclusively on "pure" SSc patients without any other cardiac condition or SSc-causes of secondary cardiac involvement, we considered the possibility of the simultaneous presence of primary and non-primary cardiac disease in our SSc-patients. This allowed the demonstration of the importance of regularly assessing those patients, with at least an annual core cardiac evaluation, showing its added value in detecting/predicting primary and non-primary cardiac events. Moreover, this study represents the first application of a Consensus guidance for the detection of SSc-cardiac disease and SSc-pHI. This showed first the feasibility of the screening and diagnostic approach, the added value of the multidisciplinary team and the importance of screening/diagnosing SSc-cardiac disease, given the strong impact on mortality events.

*Limitations*

Of course, the overall study and all its phases present also with limitations. Regarding the definition of SSc-pHI, the validation process was only partially performed, the number of clinical cases used was limited and this might have impaired the reliability exercise. In addition, the absence of a real gold standard for the detection of SSc-pHI suggests a cautious interpretation of its criterion validity assessment. We tried to overcome this using the real-life approach of the multi-disciplinary team evaluation. The validation of the definition needs to be completed (including sensitivity to change). The creation of the Consensus guidance, given the granularity of available data, represents more an Eminence than an Evidence-based product, similarly to the previous UK SSc study group consensus document (18). Regarding the real-life application of the Consensus guidance, the USZ database presented also differences in terms of available variables (prospectively collected) and those who were retrospectively searched for. In fact, high sensitivity troponin or standard troponin are not part of the yearly EUSTAR assessment, therefore not included in the original database. Conversely, BNP and NT-proBNP are both included in the local dataset, but BNP is not routinely performed in the centre, except for rare cases. Regarding the ECHO protocol, the list of parameters in the EUSTAR/USZ dataset was essential (LVEF, diastolic disfunction, sPAP, pericardial effusion) with additional although more PAH-oriented parameters having been included in the recent years (TRV, RV/LV ratio, TAPSE, right atrium and right ventricle areas). Although the ECHO evaluation at the cardiology department of USZ goes more in depth in the cardiac assessment and many other parameters included in our standard ECHO suggested protocol are regularly collected, these were not part of the current study data collection, as the dataset was designed earlier, while the protocol was finalized only when the data collection was almost finished. This left out meaningful components of the ECHO evaluation, such as atria assessment, valve evaluation and the assessment of wall motion abnormalities. In addition, the right heart function data, which are frequently reported as impaired in SSc patients, could not be evaluated for the high percentage of missing data related to the recent addition to the local database, which resulted in the impossibility to handle them with imputation. CMR data were not included in USZ dataset at all and, in line with previous lack of guidance, there was no standardized use of CMR at USZ for SSc patients, except for research purposes or in cases with high clinical suspicion. As for the ECHO, we could not compare the current practice of CMR data acquisition with the proposed CMR protocol, still for the time gap reason. To solve this gap, aiming at corroborating the application of the Consensus guidance and the proposed ECHO/CMR protocols, a multi-centre prospective longitudinal study should be designed. This could also determine the possibility of creating a screening algorithm/score for the presence of SSc-pHI, based on first level assessments, to further support the performance of second/third level assessments and, consequently, increase the detection of cardiac complications. Given the high number of clinical, ECHO, ECG and laboratory parameters included, this would require a very high

number of patients, in order to reach a meaningful number of events during the follow-up to support the statistical analysis.

## 7. Conclusions

The current study has led the basis for a treat-to-target approach for SSc-pHI: this project has led to the creation of a definition of SSc-pHI, provided a Consensus guidance for its detection both as screening and diagnosis application, which was further corroborated with a retrospective application in a real-life clinical context. As next steps of this initiative, the Consensus guidance and the definition will be first tested with a field study of acceptability and feasibility targeting the practicing physicians; later, they should be further validated in a real-life multi-centre prospective longitudinal registry. In a longer-term perspective, this could be the basis to test specific medications aiming at preventing or treating SSc-pHI, this life-threatening complication and its manifestations.

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