Consensus on the assessment of Systemic Sclerosis-associated primary Heart Involvement (SSc-pHI): WSF/HFA guidance on screening, diagnosis, and follow-up assessment.

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A patient research partner (IG) was involved in the project.

Abstract - Word count: 248/250

Introduction: Heart involvement is a common problem in systemic sclerosis (SSc). Recently, a definition of SSc primary heart involvement (SSc-pHI) has been proposed and our aim was to establish a consensus guidance on the screening, diagnosis and follow-up of SSc-pHI patients.

Methods: A systematic literature review was performed to investigate the tests used to evaluate cardiac involvement in SSc. The extracted data were categorized into relevant domains (conventional radiology, electrocardiography, echocardiography, cardiac magnetic resonance imaging, laboratory, others) and presented to experts and one patient research partner, who discussed the data and added their opinion. This led to the formulation of overarching principles and guidance statements, then reviewed and voted on for agreement. Consensus was attained when mean agreement was ≥7/10 and of ≥70% of voters.

Results: Among 2650 publications, 168 met eligibility criteria; the data extracted were discussed over three meetings. Seven Overarching Principles and 10 Guidance Points were created, revised and voted on. The Consensus highlighted the importance of patient counselling, differential diagnosis, and multi-disciplinary team management, as well as defining screening and diagnostic approaches. The initial core evaluation should integrate history, physical examination, rest electrocardiography, transthoracic echocardiography and standard serum cardiac biomarkers. Further investigations should be individually tailored and decided through a multi-disciplinary management. Overall mean agreement was 9.1/10, with mean 93% of experts voting above 7/10.

Conclusion: This consensus-based guidance on screening, diagnosis and follow-up of SSc-pHI provides a foundation for standard of care and future feasibility studies that are ongoing to support its application in clinical practice.

Main Text (=4880)

Introduction

Systemic sclerosis (SSc) is a chronic connective tissue disorder characterized by vasculopathy, inflammation/autoimmunity and fibrosis (1) that may be present in different organs and at different times during the disease evolution, resulting in heterogeneous clinical scenarios. Cardiac involvement in SSc is frequently referred to as "the silent killer". In the EUSTAR cohort study from Elhai et al, SSc primary heart involvement (SSc-pHI) was deemed to be the cause of 12% of SSc-related deaths (2). Similar data were also seen in a 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-defined criteria and the adjudication was by physician opinion.

Different sets of expert consensus algorithms are available for the detection, follow-up and treatment of SSc-pHI patients. 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 the general population's cardiovascular risk factors into account (4). 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 (5).

Indeed, there is a plethora of first, second and third level tests that can be performed on patients with SSc for the identification and follow-up of cardiac complications. However, each of them identifies only one or a few specific manifestations of SSc-cardiac involvement: for example, resting electrocardiography (ECG) and monitoring mostly detects fixed conduction defects and arrhythmia, resting trans-thoracic echocardiography (ECHO) identifies motion abnormality and contractility impairment, while cardiac magnetic resonance is a more sensitive multiparametric test that can also detect tissue characteristics indicative of inflammatory and fibrotic changes (6). Given the diverse manifestations included in the "cardiac scleroderma spectrum", the different tests should allow for comprehensive but feasible evaluation, taking into consideration time, costs and availability.

This paper will support physicians in identifying SSc-pHI in daily practice by providing, 1) a review of the literature for cardiac diagnostic tests used in SSc, and 2) providing consensus guidance for the screening, diagnosis and monitoring of SSc-pHI.

Methods

Systematic literature review

Patient-Exposure-Outcome (PEO) questions were formulated, investigating the use of assessments to evaluate cardiac structure and function in SSc (Supplement Annex 1). Using the search string applied for our recent literature review providing evidence for the creation of the definition of SSc-pHI (7), a systematic literature review was performed on three databases (EMBASE, Pubmed, Web of Science), from inception to 31/12/19. Papers in English / Italian / Romanian / Greek / Arabic / Serbo-Croatian, including ≥ 10 adult SSc patients, or cohorts in which SSc patient data could be separately extracted, with cardiac involvement or cardiac evaluation as primary target, were included. Non-human studies, pediatric age (<18 years), secondary cardiac involvement, articles in a language other than those listed above, full -text not available and literature reviews (after careful checking of the bibliography for any articles not included in the evaluation) represented the main exclusion criteria. PRISMA recommendations were followed where applicable.

Study selection and data abstraction

A single author (CB) performed the de-duplication using the reference software EndNote. The articles were then screened according to title and abstract evaluation by two reviewers (CB, GDL), with a third author giving inputs when disagreements occurred (MHB). Finally, full texts were evaluated by authors in pairs (GH and KB, YAS and AB, GDL and CB, AL and AD, RBD and GMM, AG and IM, YI and AX), with a third evaluator (MHB) resolving disagreements. To test for consistency, 5% of the papers were evaluated for both title, abstract and full texts by all extractors.

Outcomes

Data were extracted in agreement with the formulated PEO questions. The design of the study, the criteria used to select the patients, number of patients and female prevalence were additionally extracted from all manuscripts. In addition, data regarding the test used in the cardiac evaluation and the specific parameters were also extracted. Data were presented in terms of absolute frequencies (percentage), mean ± standard deviation, median (interquartile range) according to the terms used in the manuscript of origin.

Expert committee meetings

Aside from the convenors (PS and MMC) and methodologists (CB and MHB), the expert committee included 18 senior members from Europe (n=16), North America (n=2) and Asia (n=1), comprising 9 cardiologists (ERB, LG, SM, AP, ALPC, SP, CT, AD, AR) and 9 SSc experts (RM, PS, TK, OD, YA, CD, DK, DEF, MK). The committee participated in a series of virtual meetings between November 2020 and July 2021. Input from a patient research partner (PRP – IG) was also provided during all meetings and voting process.

Methodology of formulation of each statement

The results of the SLR were presented to the expert committee during three meetings, covering different topics (Laboratory and ECG for the first; ECHO for the second, cardiovascular magnetic resonance (CMR) and 'other tests' for the third). The data were separated according to the nature of the patients included, namely whether there was a high suspicion of or previously diagnosed heart involvement (with investigations therefore applied for diagnostic or monitoring purposes respectively) or no known heart involvement (with tests therefore screening in nature). If reported, the comparison with the control group was also presented.

The data were presented and discussed by the expert committee, whose members were asked to specify which of the discussed tests they would recommend, in which category of patients and when (both in terms of timing in the disease course and frequency).

The results of each meeting were then summarized into statements (CB, MHB, MMC, PS), which underwent further revision by the expert committee: first in terms of content, then for

clarity. Finally, the revised statements were 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 by ≥70% of voters to be accepted as a consensus statement.

Results

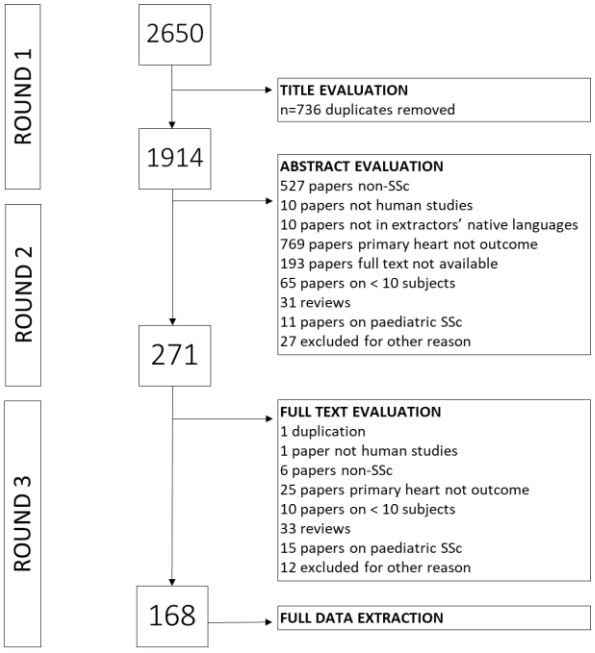
Data from the systematic literature review

Among 2650 publications retrieved from the 3 databases, 168 manuscripts underwent data extraction (see PRISMA graph - Figure 1). The reproducibility exercise confirmed a level of agreement of 94% on manuscript selection and data extraction.

The 168 articles reported cross-sectional (n=70), prospective (n=50) and retrospective (n=23) studies. Among 28723 patients included in the manuscripts, (n=23396, 83.3% were female) from 164 articles, 15.1% to 100% were classified as SSc by the ACR / EULAR 2013 criteria (n=45), or ARA 1980 criteria (n=75), although multiple sets of criteria (n=24) or unspecified criteria (n=24) were also recorded. Patients were mostly enrolled in the studies as consecutive cases (n=100), as subgroups of patients without cardiac involvement or PAH or suspicion of presence of either one or the other (n=54). The remaining studies comprised patients with present cardiac involvement or known cardiac symptoms (n=11). Among 97 manuscripts with controls, 2964 age- and sex-matched healthy individuals constituted the control group.

The results of the SLR are reported in the supplementary files (supplementary table 1-8), divided according to the pre-defined domains used, thus listing the parameters reported for the single test category. Overall, heterogeneity of data was observed, in terms of both tests used and parameters reported, which were frequently derived from small samples of patients involved.

Figure 1 - PRISMA scheme of the evaluation and selection procedure of scientific articles for the systematic review of the literature.



Meeting sessions: creating a consensus guidance

The discussion held during the three virtual meetings allowed the generation of a list of 17 statements which were divided into "overarching principles" and "consensus guidance statements". After content and linguistic revision, the 7 overarching principles and the 10 consensus guidance statements were voted on to reach agreement by the whole committee (Tables 1-3). None of the originally created statements were discarded, either for agreement lower than the established threshold (<70% agreement) or for low number of voters above the pre-defined cut-off (<70% of the committee). The overall mean agreement of the guidance points was 9.1/10, with mean 93% of experts voting above 7/10.

Overarching principles

1. *These recommendations refer to the definition of systemic sclerosis-related primary heart involvement (SSc-pHI) (7).*
2. *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.*
3. *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.*

In addition, the committee supported the previously proposed definition of SSc-pHI, which was the main target population of this initiative. Also, the committee underlined the possibility for SSc-pHI to manifest at any stage of the disease, but with closer attention in the early disease phase in diffuse cutaneous SSc. Finally, there was overall agreement that the patient should be actively and specifically questioned about cardiac red flag symptoms and be educated and motivated to patients to report such symptoms during medical consultations.

4. *Where suspicion for SSc-pHI exists, acute and chronic coronary syndromes should be considered and managed in line with current guidelines.*
5. *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.*

Multi-disciplinary management between cardiologists and non-cardiologist SSc experts was strongly recommended, when possible and feasible. Physicians caring for patients with SSc may bring those with high-risk “scleroderma” profile features to the attention of cardiologists to support more rapid cardiac assessment as indicated. Similarly, cardiologists may recommend a more timely assessment based on specific signs or symptoms, taking into consideration the differential diagnosis and other cardiac complications not primarily related to SSc. The

evaluation and ongoing management of patients by a cardiologist experienced with SSc was suggested where feasible.

6. *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.*
7. *Diagnosis refers to the assessment of patients presenting with symptoms and/or signs and/or investigations compatible with possible SSc-pHI.*

The expert committee agreed that "*Screening*" refers to the assessment of patients with no known history of heart involvement and/or those considered to be at higher risk of SSc-pHI. "*Diagnosis*" refers to the assessment of patients presenting with symptoms/signs compatible with SSc-pHI. The identification of patients at higher risk of SSc-pHI was highlighted as an area of particular importance, with more effective definition and refinement of clinical suspicion considered important unmet needs. From the literature to date, a high-risk SSc-pHI clinical profile includes male gender, diffuse cutaneous skin subset, positive scleroderma-specific autoantibodies (in particular, anti-topoisomerase I), early disease, presence of interstitial lung disease, peripheral myopathy and other inflammatory manifestations.

Consensus statements

1. *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.*

The importance of including cardiac evaluation as part of regular SSc patient assessment to detect SSc-pHI early was stressed, supported by the availability of non-invasive tests and the prognostic importance. Presence of symptoms (cardiac red flags such as dyspnea, chest pain, palpitations, syncope, dizziness) and cardiovascular physical examination raising the suspicion for cardiac involvement were deemed a pivotal part of the medical consultation.

2. *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.*

Further emphasizing overarching principle 3, the committee agreed on a specific statement on the importance of promoting the understanding of the patients about cardiac SSc related complications, educating and motivating the patients to report such symptoms; as well as on the assessments needed for its screening, diagnosis, and follow-up evaluation.

3. *Screening for SSc-pHI should be performed in every patient at time of SSc diagnosis. Follow-up evaluations should be considered.*
4. *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. Core assessment would comprise ECG, standard Transthoracic Echocardiography and serum cardiac biomarkers such as hs-Troponin, NT-pro-BNP or BNP.*
5. *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.*

Given the possibility of SSc-pHI in the early inflammatory stages of SSc, the expert committee suggested assessment for pHI should take place from the time of SSc diagnosis. The expert committee advised at least one annual assessment with hs-Troponin and NT-proBNP for unselected stable/asymptomatic patients to identify patients with possible subclinical abnormalities if appropriate. C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and CK were also suggested every year, as a non-specific workup which could indicate cardiac disease (acknowledging articular and/or inflammatory muscle involvement may confound these tests). The expert committee indicated BNP as more reliable in patients with renal failure when compared to NT-proBNP (which is recommended in patients with systolic heart failure). It was also recommended that physicians should be aware of statin use and elevated CK levels, often asymptomatic. Regarding ECG, the expert committee suggested annual resting ECG to pick up fixed abnormalities, while annual ECG-Holter may be considered in selected patients with a

higher risk profile, if feasible. 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, when evaluating conduction parameters, such as QTc interval. Moreover, there was a suggestion to focus more thoroughly on alterations that need a prompt change of the treatment, such as atrial fibrillation, malignant arrhythmias (i.e., non-sustained or sustained ventricular tachycardia) and major conduction disorders (leading to pacemaker or cardiac defibrillator implantation). All other alterations might be considered minor (as requiring treatments, such as β-blockers). As with previous consensus guidance papers, there was no agreement regarding the performance of CMR due to the lack of robust evidence. Although asymptomatic patients may have CMR abnormalities, the prognostic significance has not been fully established, consequently CMR as part of standard screening cannot be recommended despite its unquestionable potential for detailed assessment of structural and functional manifestations of SSc-pHI. Although availability, feasibility and cost have also limited this as a general screening measure, access in a number of centres has paved the way for acquiring and capitalizing on an unprecedented level of data so far. Regarding ECHO, an annual assessment was suggested in line with PAH screening of asymptomatic patients. For those patients with a high-risk profile and development of other organ involvement, borderline results in a previous assessment, case-by-case evaluation was recommended, in accordance with a cardiology assessment. In general, the expert committee stressed the importance of ECHO to include both 2-chamber and 4-chamber (biplane) and advocated high-skill training of sonographers to ensure consistency among tests performed at tertiary centers or peripheral centers. In case of doubt, the expertise of a tertiary center should be considered.

6. *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.*

7. *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.*

8. *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.*

In patients with symptoms or unstable clinical presentation, the same above-mentioned laboratory tests were suggested as a minimum annual evaluation, with timing and additional laboratory tests guided by history and other diagnostic assessments. For patients with symptoms or unstable clinical presentation, resting ECG should be repeated during or immediately before the Cardiology consultation, linked with a Holter ECG, with frequency and modality tailored to the clinical context and specific need as per the cardiologist's evaluation. The expert committee agreed that Holter ECG should report both qualitative (presence) and quantitative (number) alterations. Regarding patients with cardiac symptoms or unstable clinical presentation, a similar personalized evaluation of ECHO abnormalities was suggested to trigger cardiologist consultation and guide further re-evaluation. Similarly, the expert committee agreed on patient selection and on the need for multi-disciplinary team discussion to consider additional diagnostic tests (including CMR) and differential diagnosis (including ischemic, infective, metabolic causes). Additional tests, such as nuclear medicine tests (Scintigraphy, PET scan), coronary angiography and coronary CT, were considered as appropriate after cardiology evaluation. Endomyocardial and pericardial biopsy should be performed according to European Society of Cardiology (ESC) guidelines, e.g., in patients with repeated oedema findings on CMR without other explanation and with appropriate cardiology expertise.

9. *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.*

10. *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.*

Finally, the expert committee recommended importance of multi-disciplinary care when following up patients with a diagnosis SSc-pHI. This included both the nature of the testing (mostly relying on milestone assessments such as ECHO and Holter-ECG in relation to the specific cardiac manifestation) to be further adopted to the individual case, as well as the frequency of the monitoring to be performed.

Table 1. 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 2. Guidance 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. 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	14	8.21	21%

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	on a case-by-case basis.			
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%

Table 3 – Flowchart of the assessments of SSc patients, according to their cardiac disease status.

	Status	Medical history	Clinical examination	Laboratory biomarkers	ECG	ECHO	CMR	Further tests
No prior diagnosis of SSc-pHI	Asymptomatic – low risk	Annual	Annual	Annual	Annual resting ECG	Annual	May be considered on a case-by-case basis	To be guided by the MDT according to the results of the core assessment, on a case-by-case evaluation.
	Asymptomatic – high risk	Annual	Annual	Annual	Annual – ECG Holter may be considered	Annual	May be considered on a case-by-case basis	
	Symptomatic	Annual, unless timing adjusted by the MDT.	Annual, unless timing adjusted by the MDT.	Annual, unless timing adjusted by the MDT.	Annual ECG/ECG Holter, unless timing adjusted by the MDT.	Annual	Should be considered if suspicion remains.	
Diagnosed with SSc-pHI		Annual, unless timing adjusted by the MDT. Specific follow-up assessments set tailored by the MDT.					To be guided by the MDT according to the diagnosis and treatment, on a case-by-case evaluation.	

Discussion

This initiative led to the development of a Consensus Guidance on the screening, diagnosis and follow-up assessments for SSc-pHI.

Diagnostic tests in SSc-pHI: data from the literature

Most of the current literature included the "first line" assessments for SSc-pHI, including patients with or without cardiac involvement or cardiac symptoms. Growing evidence is also accumulating from CMR studies, allowing concomitant anatomical, functional and tissue characterization. However, less evidence was available for conventional radiology, myocardial scintigraphy and coronary artery studies.

Most of the cardiac specific laboratory biomarkers, such as NT-proBNP and Troponin I, had higher concentrations in SSc patients compared to healthy controls (8-11). Studies using CMR and ECHO confirmed that all cardiac chambers and structures may be involved in SSc-pHI, in particular with impariment in motion, contraction and relaxation. In addition, ECHO demonstrated significantly abnormal values of right ventricular function and tissue doppler data (18-23), while CMR data were consistent with histopathological evaluation of endomyocardial biopsy and autopsy samples, regarding inflammatory and fibrotic tissue changes (12)(8, 13-16)(12, 17). ECG studies detected a meaningful number of arrhythmias, although the definition ranged from benign isolated ectopic extra-beats to major malignant ventricular arrhythmias, and no studies have compared a SSc group with matched healthy controls or between cardiac involved and non-involved SSc patients.

The details of the cohorts and nature of the patients identified in the SLR were not clear, and there was significant heterogeneity of information, in terms of both tests/parameters applied on patients and details given. Some cardiac imaging studies identified underlying pathology but not necessarily with clinically overt disease and were mostly derived from simple association studies. This relatively low quality of evidence means the Consensus Agreement is based more on eminence than evidence, also influenced by the fact that the local organization of the different Health Systems in countries in Europe, North America and Asia may be extremely variable.

Principles of SSc-pHI management

The *need for the active participation of the patient in the care process* emerged as a pillar in the management of SSc-PHI: Patient involvement in clinical practice and clinical research is well-established and contributes to our understanding on which interventions may have a positive impact on quality of life, morbidity and mortality (24). This was also important to further raise the awareness of the clinician, with particular emphasis on the need to counsel patients in a lay language, to inform them about possible cardiac symptoms and diagnostic procedures, as well as the importance to report to the multidisciplinary team.

The *pivotal role of multi-disciplinary management* of SSc-pHI was another central feature, whose additional value has been previously shown for SSc-PAH (25). Scleroderma and Cardiology expertise are both pivotal in considering and excluding differential or concomitant diagnoses, as well as in suggesting second/third level assessments on a case-by-case basis.

S*creening, diagnosis, and follow-up evaluation of SSc-pHI*

Other screening programs are currently practiced in SSc, such as the screening for PAH, which is recommended once a year by the European Society of Cardiology/European Respiratory Society (26). As for other screening procedures, the evaluation of cardiac status may be performed more frequently depending on the clinical presentation. In comparison to the core assessment including clinical examination, ECHO, rest ECG and laboratory tests, Holter and stress electrophysiology do not have the basis to be supported as routine screening practice and their use is driven by symptoms or other tests. Holter ECG may be the most promising or powerful technique for this aim, and it is probably well accepted by the patient given its non-invasive nature. Therefore, it remains part of the research agenda to be validated in a systematic prospective registry, including testing for cut-offs with diagnostic or prognostic value, to support its standardized application as routine screening assessment.

Timing for ECHO application as screening was recommended as once a year, also in line with the PAH-screening standard, with possible shortening of the timing on a case-by-case basis according to cardiologist and rheumatologist judgment. Although tertiary cardiology centres with SSc expertise would be the ideal setting for the performance of the ECHO, this is unrealistic and not necessarily in the patient's interest. Given the differences among health systems, the

scientific community should be advocating highly skilled training of echocardiographers to ensure consistency in the reporting whether a tertiary or a peripheral centre is performing the exam.

Despite growing evidence for the potential role of CMR in detecting several manifestations of SSc-PHI, currently available data do not yet allow a recommendation for a standardized use of the modality. It is recognized that even completely asymptomatic patients may show CMR abnormalities and that CMR represents the surrogate for the gold-standard, endomyocardial biopsy. Furthermore, CMR provides important data on tissue characterization with preliminary data suggesting prognostic implication, but these findings require confirmation in larger prospective studies. Against this background, the current consensus guidance included CMR to 1. be considered on a case-by-case basis, including in asymptomatic patients without history of heart involvement, 2. to be included as part of the diagnostic work up where suspicion remains following positive findings in the initial core evaluation.

Comparison with current approaches

In comparison to the diagnostic work-up proposed by Bournia et al, we did not clearly indicate which assessments should be included in the second tier, to be decided on a case-by-case basis in line with a tailored approach managed by a multidisciplinary team. Our consensus included laboratory biomarkers in the annual cardiac workup, ECG and ECHO for the screening of asymptomatic patients, given the increasing evidence of their role for the evaluation of myocardial stress and microvasculopathy (27, 28). This is particularly the case of high sensitivity Troponin, which is a promising biomarker for the detection of myocardial involvement (27-29). In addition, NT-proBNP and BNP are already part of the screening algorithm for SSc-PAH and are already available to the physician as a useful guidance to further understand the cardiac context (30).

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The consensus best practice from Bissell et al stressed the importance of the multi-disciplinary team in the management of SSc-pHI, including recognition of wider cardiac disease, attributing an active role to the caring rheumatologist in the evaluation for coronary artery disease (CAD), lipid profile and glycate hemoglobin (4). In contrast, our consensus guidance considered acute and chronic CAD as a necessary differential diagnosis to be always considered and tested according to specific guidelines and recommendations. In addition, we continue to recommend

yearly assessment even in the symptomatic patients, with further adjustment of timing and kind of assessments on a case-to-case evaluation. This was even stressed more in our paper for the patients with definite cardiac involvement, in which the whole decision algorithm was patient-tailored by the multi-specialty team.

In comparison to both Bournia et al and Bissell et al, our manuscript had the benefit of increasing evidence on the use of CMR (4, 5)(17) and therefore proposes that it may be considered by the multidisciplinary team for screening purposes and should be included in the diagnostic work-up where suspicion remains after the core evaluation. This remains part of the research agenda, although recent publications have identified possible risk factors for the detection of CMR changes, such as higher mRSS, presence of digital ulcers and increased cardiac biomarkers (33). These results further support the multidisciplinary team evaluation, with the rheumatologist being pivotal to assess 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.

Strengths and limitations

Our study has some clear strengths. The expert panel comprised of specialists dealing with the breadth of SSc-pHI, including cardiologists with sub-specialty expertise, rheumatologists and immunologists. Moreover, we included patient research partners throughout this initiative.

Limitations of this document includes that much of the guidance given is in part based on poorly detailed and inconsistent data with a clear lack of well-controlled prospective data in this field. Guidance on state-of-the-art tests was largely based on expertise (rather than a sizeable evidence base), similar to the previous consensus document (4). Unfortunately, no validation is currently available to support the statements provided, either retrospective or prospective. We recommend ongoing research to refine the suggested guidance, in particular the investigations that would not be captured by routinely assessment of other indications, such as the screening for PAH.

Conclusions

This consensus initiative for SSc-pHI provides guidance for screening and diagnostic work up. A next step will be validation in a real-life cohort with the future ambition of evaluating interventions to prevent and treat this life-threatening complication and its manifestations.

Supplement Annex 1 – The formulated Patients-Exposure-Outcome questions created as basis for the systematic literature review.

- 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?

Supplement Table 1. Data extracted during through the systematic literature review, regarding the Conventional Radiology domain.

Including 1201 patients (13, 34-61) e 240 controls (21, 44, 51, 52, 57, 62, 63).

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.

- Chest X-ray

Finding	N° PAPERS	References	N° PATIENTS	References	N° controls	References
cardiomegaly	19	(35-38, 40, 43-46, 48-55, 59, 61)	120/1201 (10%)	(35, 38, 40, 46, 49-55, 61)	4/88 (4.5%)	(51)
Pleural effusion	2	(38, 60)	4/39 (10%)	(38, 51)	Not reported	
Signs of pulmonary oedema	4	(36, 45, 50, 60)	10/40 (25%)	(45, 50, 60)	Not reported	
Sings of interstitial lung disease	12	(13, 35, 36, 38, 41-43, 45-47, 50, 53, 60)	143/455 (31.4%)	(13, 35, 38, 41-43, 45-47, 50, 53, 60)	Not reported	
Hilar enlargement	1	(36)	Not specified		Not reported	

- Chest computed tomography

Finding	N° PAPERS	References	N° PATIENTS	References	N° controls	References
cardiomegaly	1	(38)	5/28 (17.9%)	(38)		

Supplement Table 2. Data extracted during through the systematic literature review, regarding the myocardial scintigraphy domain.

Reported in 26 manuscripts including 1072 patients (34, 43, 48, 50, 52, 61, 64-80) and 128 controls (48, 52, 57, 69, 70, 77, 79).

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.

Finding	N° papers	References	N° patients	References	N° controls	References
Decreased perfusion						
At rest	5	(34, 42, 43, 68, 72)	83/196 (42.3%)	(34, 42, 43, 68, 72)	Not reported	
On stress	3	(52, 66, 80)	49/105 (46.6%)	(52, 66, 80)	1/20 (5%)	(52)
Both rest and stress	1	(66)	3/24 (12.5%)	(66)	Not reported	
Not specified	10	(48, 50, 61, 65, 70, 72-75)	113/514 (22%)	(48, 50, 61, 65, 70, 72-75)	1/128 (0.7%)	(48, 52, 57, 69, 70, 77, 79)
Motion Abnormalities	6	(42, 43, 50, 65, 72, 79)	17/73 (23.3.%)	(42, 43, 50, 72)	Not reported	
Functional impairment	10	(34, 43, 50, 69, 70, 72, 73, 76, 77, 79)	50/239 (20.9%)	(34, 43, 50, 69, 70, 72, 73, 76, 77, 79)	Not reported	
Inflammation	3	(64, 72, 78)	15/75 (20%)	(64, 72, 78)	Not reported	
Other						

Pathologically increased activity	1	(67)	7/17 (41.2%)	(67)	Not reported	
Ischaemic ST tract changes	1	(77)	1/24	(80)	Not reported	
Improvement after dipyridamole or nifedipine	2	(42, 43)	43/43	(21, 60)	Not reported	

Supplement Table 3. Data extracted during through the systematic literature review, regarding the Laboratory biomarkers domain.

Derived from 45 manuscripts including 16266 patients (8-13, 18, 19, 21-23, 38, 41, 50, 51, 55, 59, 64, 72, 78, 81-105) and 447 controls (8-12, 19, 21, 23, 92-94, 102).

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.

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				(84)
mean	1	50 c	275±536 pg/ml				(85)
mean	1	69 w/o	229±447 pg/ml				(86)
mean	1	144 c	138±130 pmol/l				(98)
mean	1	70 w/o	192±163 pg/ml				(18)
mean		19 c	145±130 ng/l				(105)
median	1	78 late vs 37 early onset	172.6 vs 73.3 pg/ml			yes	(103)
median	1	21 w vs 42	219 vs 11 pg/l			yes	(59)

		w/o					
median	1	33 w/o	127 ng/l	20 hc	47 ng/l	yes	(8)
median	1	110 c	147 ng/l	105 hc	87 ng/l	yes	(9)
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	(92)
>450 in >50yo, >900 in 50-75yo, >1800 in >75yo	1	w/o	38/103 (36.7%)				(55)
>125 pg/ml	3	w/o	28/69 (40.6%)				(86)
		c	29/65 (44.6%)				(88)
		c	62/195 (31.8%)	hc	4/30 (13.3%)	yes	(102)
>300 ng/l	1	c	34/234 (15%)				(104)
BNP	7	357					
mean	1	153 c	37.5±28.5 pg/ml	17 hc	23.1±16.0 pg/ml	yes	(10)
median	3	24 w	56.5 pg/ml				(13)
		47 w/o	111 mg/dl	36 hc	70 mg/dl	yes	(11)
Within SSc, for future cardiac events		11 w vs 22 w/o	166.2±151-2 vs 102.0±101.7 pg/ml			No	(64)
Hs-Troponin I							
median	2	110 c	5.1 ng/L	105 hc	3.7 ng/L	yes	(9)
		33 w/o	3.7 ng/L	20 hc	8.0 ng/L	no	(8)

mean	1	19 c	76±137 ng/L				(105)
Hs-Troponin T	2		NA		NA		(12, 41)
>14 ng/L	3	c	23/65 (35.4%)				(88)
		w/o	38/103 (36.7%)				(55)
		c	63/195 (32.3%)	hc	0/30 (0.0%)	yes	(102)
median	1	195 c	11 ng/L	30 hc	5 ng/L	no	(102)
CK							(64)
Elevated	2	Depressed vs normal LVEF	44/383 (11.4%) vs 535/6690 (8.0%)			yes	(81)
		w	21/25 (84%)				(72)
		c	0/16 (0%)				(78)
>190 mg/dl	1	c	16/195 (8.2%)				(102)
>500 mg/dl	1	*Within SSc,* Late vs early onset	13/78 (16.7%) vs 6/37 (29.7%)			no	(103)
mean	3	69 w/o	146±161 mg/dl				(86)
		100 w/o	176±247 mg/dl				(95)
		19 c	141±148 mg/dl				(105)

CK-MB							
elevated		w/o	2/25 (8%)				(68)
>4 mg/dl		c	36/195 (18.5%)				(102)
>25 U/L		w/o	38/103 (36.7%)				(55)
Other							
TIMP-1	1	111 c	167±63 ng/ml	21 hc	183±29 nl/ml	No	(21)
ET-1	1	30 c	2.6±0.2 pmol/L	48 hc	1.8±0.1 pmol/L	Yes	(93)
IL-6 median	1	31 w/o	3.2 pg/ml	32 hc	2.2 pg/ml	Yes	(92)
ANP mean	1	30 c	239±59 pmol/l	48 hc	172.8±36 pmol/L	Yes	(94)
NT-proANP							
mean	1	144 c	648.8±383.1 pmol/l				(89)
Proposed cut-off for future cardiac event	1	144 c	822.5 pmol/l				(49)
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	(19)
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	(19)

Supplement Table 4. Data extracted during through the systematic literature review, regarding the Coronary studies (angiography, CT) domain.

Data obtained from 21 papers including 1746 patients (34, 43, 52, 60, 61, 66, 72, 75, 83, 97, 98, 106-114) and 88 controls (41, 57, 63, 108).

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.

Finding	N° PAPERS	References	N° PATIENTS	References	N° controls	References
Coronary arteries abnormalities	20	(34, 39, 43, 52, 60, 61, 66, 72, 75, 98, 106-115)	189/1711 (11%)	(34, 43, 52, 60, 61, 66, 72, 75, 106-114)	0/68 (0%) HC 20/20 (100%) CAD	(41, 57, 63, 108)
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.	(108)	17 hc	

Supplement Table 5. Data extracted during through the systematic literature review, regarding the Cardiac Magnetic Resonance domain.

Data obtained from 28 publications including 1326 patients (8, 12-17, 31, 36, 37, 39, 41, 64, 78, 83, 91, 97, 105, 114, 116-125) and 207 controls (8, 12-16, 41, 83, 122, 123, 125).

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.

Finding	N° PAPERS	N° patients	Value/prevalence in patients	N° controls	Value/prevalence in controls	Statistically significant difference	References
LA abnormalities	1	19					(14)
LA diameter (mm)	1	19 w/o	37±6	20 hc	28±5	Yes	(14)
RA abnormalities	0						Not reported
LV abnormalities	10						(13, 31, 41, 97, 116, 117, 120, 121, 123, 125)
LV dilation	1	c	3/52 (5.7%)				(116)
	2	w/o	14/46 (30.4%)				(117, 120)
	1	w	22/50 (48.9%)				(121)

LV-EDV (ml)							
Mean	1	50 c	96.5±18.6	31 hc	126.8±29.5	Yes	(123)
Mean	1	46 c	122±29	20 hc 20 CAD	127±32 237±77	No vs HC Yes vs CAD	(41)
Mean	1	62 d vs 20 l c	118±28 vs 120±19			No	(97)
Mean	1	19 w/o	69±11	20 hc	77±16	No	(14)
Median	1	150 c	88 (72-126)			Different among risk categories	(31)
LV-EDV-I (ml/m2)							
Mean	1	24 c	77.8±23.7	12 hc	75.1±16.5	No	(13)
>95 in females, >100 in males	1	w/o	4/20 (20%)				(117)
LV hypertrophy							
LV septum	2	w and w/o	9/70 (12.9%)				(117, 121)
LV infero-lateral wall	1	w/o	7/20 (35%)				(117)
LVMI (g/m2)							
Mean	3					No	(13, 14, 122)
LV anatomical or structural changes							

Present	1	c	15/52 (28.8%)				(116)
>77 g/m2 (f); >91 g/m2 (m) +2SD	1	w/o	2/20 (10%)				(117)
Global LV systolic disfunction							
Not defined	2	w/o	23/227 (10.1%)				(17, 120)
LVEF < 55%	2	C	24/170 (14.1%)				(31, 117)
LVEF (%)							
Median	1	150 w and w/o	64.5 (610. – 69.7)				(31)
mean	1	46 c	62.8±11	20 hc 20 CAD	61.8±15.2 42±12	No vs HC Yes vs CAD	(41)
mean	1	50 w/o	60.8±6.7	31 hc	65.2±7.1	Yes	(123)
LV wall motion abnormalities	1	c	15/52 (28.8%)				(116)
hypokinesia	2	w/o	27/46 (58.7%)				(117, 120)
	1	w	12/50 (24%)				(121)
LV diastolic disfunction							
	1	c	11/46 (23.9%)				(41)
	1	w/o	17/20 (85%)				(117)

Peak diastolic strain rate (1/s)	1	19 c	83±26	20 hc	114±16	Yes	(14)
LV GLS abnormalities							
Present	1	W	2/50 (4%)				(121)
Radial strain	1					Significantly reduced in SSc vs HC	(125)
Circumferential stran	1					Significantly higher in SSc vs HC	(125)
Mid SA circumferential strain	1	19 w/o	-16.8 ± 1.6	20 hc	-18.6 ± 1.0	Yes	(14)
LV myocardial perfusion abnormalities							
Present	5	c or w/o	31/85 (36.4%)				(36, 39, 118, 120, 125)
MPR	1	46 c	0.6±0.4	20 HC	3.1±0.3	Yes	(41)
MPRI	1	19 c	3.1±0.9	22 HC	4.2±1.3	Yes	(122)
RV abnormalities							
RV dyskinesia	1	C	5/52 (9.6%)				(116)
RV dilatation							
prevalence	3	c or w/o	36/124 (29.0%)				(41, 116, 120)
Median	1	150 w and	86.5				(31)

		w/o	(67-119)				
RV-EDV (ml)	1	50 c	80.5 ± 19.3	31 hc	105.4 ± 12.6	Yes	(123)
	1	46 c	114.3±32.4	20 HC 20 CAD	108.2±33.8 132.6±33	No vs HC Yes vs CAD	(41)
RV-EDV-I (ml/m2) >96 for females, >111 for males	1	w/o	6/20 (30%)				(117)
RV hypertrophy							
Thickness >5mm	1	w/o	2/20 (10%)				(117)
RV mass index (g/m2)	1	24 w	19.4 ± 5.6	12 hc	16.6 ± 3.1	No	(13)
RVEF (%)							
Median	1	150 w + w/o	62 (56-68)				(31)
Reduced	4	C + w/o	44/299 (14.7%)				(17, 116, 117, 120)
Mean	3	100 c + w/o		63 hc		No	(13, 15, 41)
	1	50 w		31 hc		Yes	(123)
EGE – Range median of LV mass (%)	*Within SSc*	Higher in patients with myocarditis defined with Lake Louis criteria				Not reported	(41)

	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	(12)
LGE							
Present	4	C	75/173 (43.3%)				(12, 37, 41, 105, 122)
	8	w/o	166/499 (33.2%)				(8, 14, 17, 36, 39, 97, 111, 114, 117, 119, 120, 125)
	5	W	158/362 (43.6%)				(13, 31, 41, 64, 121)
distribution	*Of the prevalent cases*	Linear	64/183 (34.9%)				(37, 114, 116, 117, 119)
		Nodular	14/183 (7.6%)				(37, 39, 114, 117)
		Diffuse	105/183 (57.4%)				(12, 14, 36, 41, 105, 117, 124)
		Not specified	383/517 (74.1%)				
Location	*Of the prevalent cases*	subendocardial	19/120 (15.8%)				(36, 117)
		midmiocardial	93/120 (77.5%)				(12, 14, 15, 39, 116, 119, 120, 124)
		epicardial	8/120 (6.7%)				(120)

		Not specified	384/504 (76.2%)				
Pattern	*Of the prevalent cases*	Ischemic	4/94 (4.2%)				(17, 124)
		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	(31, 41, 68, 97)
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	(12)
Native T1 Mapping (ms)							
mean	1	24 w	1005±63	12 hc	951±46	Yes	(13)
	1	33 w/o	1258.9±51.2	20 hc	1192.2±32.6	Yes	(8)
	1	19 w/o	1007±29	20 hc	958 ± 20	Yes	(14)
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	(12)
Extracellular volume fraction (ECV) – (%)							
Mean	1	19 w/o	35.4±4.8	20 hc	27.6±2.5	Yes	(14)

	1	33 w/o	27.5 ± 2.8	20 hc	22.8 ± 1.9	Yes	(8)
	1	24 w	30.0 ± 4.2	12 hc	24.1 ± 3.5	Yes	(13)
	1	30 c	30±4	10 hc	28±4	Yes	(15)
Median	1	33 w/o	30.0 (28.0-31.9)	16 hc	26.8 (25.4-29.1)	Yes	(16)
Within SSc, for future cardiac events	1	8 w vs 11 w/o significant arrhythmia	30±2 vs 29±4			Not reported	(105)
		31 w vs 19 w/o arrhythmic events	32.0 (31.0-34.0) vs 30.5 (28.0-32.0)			Yes	(12)
T2/STIR alteration							
Presence of abnormality/ oedema	1	c	6/52 (11.5%)				(116)
	2	w/o	5/201 (2.4%)				(17)
		w/o	10/26 (41.7%)				(120)
	1	W	5/50 (10.0%)				(121)
T2 signal ratio	1	w + w/o	2.0 ± 0.5				(31)
	1	46 c	3.5 ± 0.5	20 hc	1.25±0.12	Yes	(12)
	Within SSc, for	31 w vs 19 w/o	2.4 (2.0, 2.7) vs			Yes	(12)

	future cardiac events	arrhythmic events	2.2 (1.8, 2.3)				
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	(31)
Valvular abnormalities							Not reported
Pericardial effusion							
Present	1	C	10/52 (19.2%)				(116)
	1	w/o	32/201 (15.9%)				(17)
<5 mm	2	w/o + w	23/70 (32.8%)				(117, 121)
≥ 5 mm	2	w/o + w	15/70 (21.4%)				(117, 121)

Supplement Table 6. Data extracted during through the systematic literature review, regarding the Electrocardiography domain.

Data derived from 75 manuscripts involving 22866 patients (10, 13, 15, 35-40, 42-47, 49-61, 64-68, 72, 75, 77, 78, 80, 87, 88, 93, 100-103, 105, 109, 111, 114, 124, 126-150)) and 799 controls (10, 15, 21, 46, 48, 51, 52, 57, 58, 69, 87, 93, 126, 128, 132, 136, 139, 141, 142, 144, 145, 149).

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%)				(56)
No specified ECG abnormality	45	15773	1246 (7.9%)	759	34 (4.7%)		
Sinus rhythm	22	1050	804 (76.6%)	105	99 (94.3%)(144)		(13, 35, 37, 46, 48, 54-56, 58, 60, 65, 87, 105, 126, 128, 129, 133, 136, 140, 143, 146, 150)
Sinus bradycardia	2	86	11 (12.8%)				(37, 38)
Sinus tachycardia	2	58	24 (41.4%)				(38, 101)
Mobitz type I AV conduction block	10	808	27 (3.3%)				(46, 55, 64, 133-135, 142, 146, 150)
Mobitz type II AV conduction block	10	571	1 (0.1%)				(46, 55, 64, 103, 134, 142, 146, 150)
Third degree AV block	12	763	7 (0.09%)				(35, 54, 55, 61, 64, 66, 103, 135, 142, 146, 150)

Sinus arrhythmia	9	459	14 (3.1%)	105	6 (5.7%) (144)		(46, 55, 64, 80, 100, 134, 142, 146, 150)
Atrial Fibrillation	14	663	13 (2.0%)				(35, 46, 54, 55, 64, 68, 100, 134, 142, 143, 146, 150)
Atrial Flutter	9	405	11 (2.7%)				(35, 46, 55, 64, 68, 134, 142, 146, 150)
Atrial Tachycardia	10	404	11 (2.7%)				(13, 46, 55, 64, 66, 68, 134, 142, 146, 150)
Supraventricular Tachycardia	9	558	20 (3.6%)				(46, 55, 61, 68, 100, 134, 142, 146, 150)
Ventricular Tachycardia – monomorphic	14	1384	30 (2.7%)				(46, 49, 55, 61, 64, 66, 68, 100, 134, 135, 142, 146, 147, 150)
Ventricular Tachycardia – polymorphic	7	425	0 (0.0%)				(55, 64, 100, 134, 142, 146, 150)
Ventricular fibrillation	9	490	1 (<0.1%)	66	0 (0.0%)		(35, 46, 55, 64, 100, 134, 146, 150)
Atrial ectopies	15	1098	63 (5.7%)	154	9 (5.8%) (51, 142)		(35, 46, 51, 52, 54-56, 80, 100, 111, 133, 142, 143, 146)
Ventricular ectopies	18	908	80 (8.8%)	177	2 (1.1%) (51, 58, 142)		(35, 46, 48, 51, 54-56, 58, 64, 66, 68, 80, 100, 109, 111, 142, 143, 146)
Right bundle branch block	36	6329	175 (2.8%)	302	17 (5.6%)(58, 142, 144)		(13, 35, 37, 40, 46, 48, 49, 52, 54-56, 58, 64-66, 68, 87, 100, 102, 103, 105, 109, 111, 129, 133-137, 140, 142, 143, 146-148, 150)
Left bundle branch block	26	5138	52 (1.0%)	307	2 (0.6%) (51, 93, 142, 144)		(35, 40, 43, 46, 48, 49, 54-

							56, 64, 68, 100, 103, 105, 129, 133-137, 142, 143, 146, 148-150)
Left Ventricle hypertrophy	2	131	8 (6.1%)				(56, 143)
Right Ventricle hypertrophy	14	975	30 (3.1%)	154	3 (1.9%) (51, 142)		(35, 43, 46, 49, 50, 87, 100, 133, 135, 136, 142, 143, 146, 150)
Left Atrium Enlargement	7	564	9 (1.6%)	186	0 (0.0%) (51, 57, 142)		(50, 57, 100, 133, 142, 146, 150)
Right Atrium Enlargement	6	551	11 (2.0%)	186	1 (0.5%) (51, 57, 142)		(58, 100, 133, 142, 146, 150)
WPW pattern	1	29	0 (0.0%)				(146)
T wave morphology alternation	16	946	102 (10.8%)	75	3 (4.0%) (48, 142)		(38, 47, 50, 54, 65, 72, 80, 87, 100, 101, 109, 133, 142, 143, 146, 150)
Brugada pattern	1	29	0 (0.0%) (146)				
Heart rate							
Abnormal (<60/bpm or >100 bpm)	1	110 c	13 (11.8%)				(100)
Mean	1	24 w	73±18				(13)
Median	1	22 c	82 (607-106)				(149)
RR interval							
Mean (ms)	1	35 c	859±135	35 hc	903±120	No	(87)
PR interval							
Mean	1	35 c	158±21	35 hc	157±21	No	(87)
	1	76 c	148±21	66 hc	152±38	No	(142)
Abnormal	5	301 c	13 (4.3%)				(35, 51, 55, 87, 146)
QRS interval							
Mean	1	76 c	87±10	66 hc	90±14	No	(142)
	1	15 c	95±13	18 hc	95±7	No	(145)
Anterior left hemiblock	3	90 c	12 (13.3%)				(58, 80, 129)
Abnormal	9	588 c	70 (11.9%)				(9, 54, 55, 61, 87, 103, 137, 143, 146)
QT interval							

QTc (ms) Mean	2	72 c	423±17	74 c	408±14	Yes	(142)
		110 c	419±25	105 hc	413±25	No (p=0.06)	(144)
Mean	1	36 c	404±22				(56)
>440 ms	3	398 c + w/o	43 (10.8%)				(55, 102, 111)
>440 ms	1	110 c	21 (20%)	105 hc	10 (9%)	Yes	(144)
QTcd (ms) Mean	1	27 c	58±30.3	17 hc	55.8±18.6	No	(10)
Other							
ST tract depression	2	120 c	37 (30.8%)				(43, 111)

Supplement Table 7. Data extracted during through the systematic literature review, regarding the Echocardiography domain.

Data retrieved from 139 manuscripts on 20790 patients (8-23, 36-40, 42-52, 54-62, 64-66, 68, 71, 73-75, 77, 78, 80, 82-96, 98-106, 108, 110-113, 115, 116, 118, 120, 123, 125-131, 134, 136, 138-143, 145-182)) and 2448 controls (8-12, 14-16, 18-23, 44-48, 51, 52, 57, 58, 62, 69, 73, 74, 76, 77, 82-84, 87, 89, 90, 92-95, 108, 110, 123, 126, 128-130, 136, 139-142, 145, 146, 150-153, 156-159, 161, 163-171, 175-178, 181, 182).

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.

Finding	N° papers	N° patients	Value/prevalence in patients	N° controls	Value/prevalence in controls	Statistically significant difference	References
LA Dilatation	26						(21, 45, 47, 50, 56, 64, 66, 84, 86, 87, 89, 93-95, 99, 123, 134, 142, 154, 158, 159, 161, 165-167, 171, 173)
Present, not specified	8	C+w/o+w	27/404 (6.7%)	Hc	3/251 (1.2%) (47, 94, 142, 175)		(47, 50, 56, 66, 94, 100, 134, 142, 175)
LA Index Volume (mL/m2)	8						(13, 84, 89, 99, 158, 162, 171, 173)
Normal cut-off <34	1						(173)
Mean (SD)		42 c	24.9±5.3	42 hc	24.7±4.4	No	(84)
		45 c	28.4±8.7	20 hc	19.3±4.6	Yes	(89)
		22 c	22.4±4.5				(162)

		52 w/o	23.7±5.7	52 hc	23.3±6.2	No	(158)
		54 w/o	27±8				(173)
		24 w	27±7.2				(13)
LA Area	3						(93, 110, 156)
M-mode (cm2) – Mean (SD)	1	40 c	14.7±3.5	40 hc	15.0±2.0	No	(156)
	1	46 w diastolic dysf	21±5	195 ssc w/o diastolic dysf 66 hc	17±4 18±3	Yes Yes	(110)
2D area (mm2/m2) – Mean (SD)	1	30 c	913±43	48 hc	748±25	Yes	(93)
LA Diameter (mm)	21						(10, 45, 64, 71, 86, 87, 92, 95, 99, 104, 126, 130, 154, 159, 161-164, 166, 167, 173, 174)
>40mm	2	C+w/o	74/650 (11.4%)				(154, 159)
Mean (SD) value range	6	1052 c	From 34.6±5.2 to 38.7±6.1				(86, 104, 154, 162, 173, 174)
Mean (SD) value range	1	35 c	34±6	35 hc	29±5	Yes	(87)
	1	100 c	34±0.5	45 hc	31.9±2.6	Yes	(95)
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	(10, 44, 45, 77, 126, 130, 161, 163, 164, 166)
Median (IQR) value range	1	17 c	38.5 (32-41)	23 hc	37 (33.8-39)	No	(167)
	1	31 w/o	38 (35-43)	32 hc	36.5 (32.38)	Yes	(92)
RA dilatation	8						(18, 23, 93, 126, 134, 142, 156, 158)
Dilated RA	1	C	18/76 (23.7%)	Hc	0/66 (0.0%)	Yes	(142)
RA indexed	1	70 w/o	19.4±5.5	25 hc	19.5±5.9	No	(18)

Volume (mL/m2)							
RA area							
M-mode (cm2) – Mean (SD)	1	52 c	20.7±9.0	52 hc	19.7±6.4	No	(158)
M-mode (cm2) – Mean	1	40 c	13	40 hc	14.2	No	(156)
2D area (mm2/m2) – Mean (SD)	1	30 c	929±56	48 hc	917±30	No	(93)
RA diameter (mm)							
Not specified	1	26 c	29.2±2.4	24 hc	29.9±2.6	No	(126)
Major Axis	1	42 w/o	44.5±5.6	40 hc	43.3±4.9	No	(23)
Minor Axis	1	42 w/o	34.8±4.2	40 hc	31.9±3.6	Yes	(23)
LA impaired emptying	2						(77, 126)
Present	1	c	14/24 (58.3%)				(77)
Decreased LA Passive Emptying	2						(99, 126)
Present	1	C	16/40 (40%)				(99)
RV Dilation							
Present	10	C+w/o+w	56/547 (10.2%)				(9, 50, 56, 100, 120, 134, 136, 143, 157, 159)
RV diameter ≥23 mm	1	C	17/80 (21.3%)	Hc	3/18 (16.7%)	Not reported	(159)
RV diameter ≥26 mm	1	C	9/110 (8.1%)				(100)
RV diameter (mm) – Median	1	31 w/o	24.3 (22-26)	32 hc	21.8 (21-23)	Yes	(92)
RV diameter (mm) – Mean	1	76 c	21.5±5.5	66 hc	21.4±2.5	No	(142)
RV diameter Indexed mm/m2	1	63 c	9.5±4.7	40 hc	8.9±2.8	No	(52)
RV basal diameter	1	46 with diastolic dysfunction	43±9	195 w/o diastolic dynsfunction 65 hc	38±6 37±5	Yes Yes	(110)
RV Basal diameter indexed (mm/m2)	1	70 c	18.4±2.4	25 hc	17.5±1.6	No	(18)

RVEDD (mm) – Mean	1	23 c	26.4±2.2	25 hc	21.2±3.8	Yes	(90)
RVED Area (mm2) – median	1	95 w/o	9.7 (8.5-10.7)	54 hc	9.6 (6.8-10.5)	No	(178)
	1	42 c	10.5 (9.2-13.5)	40 hc	12.2 (9.4-13.1)	No	(23)
RVES Area (mm2) – Median	1	95 w/o	5.2 (4.6-5.8)	54 hc	4.6 (4.2-5.5)	No	(178)
	1	42 c	5.6 (4.5-8.3)	40 hc	5.9 (4.4-6.9)	No	(14)
LV Dilation							(9, 22, 44, 46, 47, 50, 52, 75, 82, 89, 90, 92, 100, 106, 110, 115, 120, 134, 136, 139, 154, 157, 159, 161, 164-166, 178)
Present	14	C+ w/o	41/1072 (3.8%)	HC	6/775 (0.8%)		(46, 47, 50, 75, 90, 100, 110, 120, 134, 136, 157, 159, 164, 165)
LV diameter (mm)	1	124 c	44.8±5.5	41 hc	44.2±4.0	No	(151)
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	(45, 139, 161, 166)
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	(139, 159, 161, 166)
LVEDD (mm)	1	25 w	46.7±5.9				(106)
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	(10, 20, 87, 95, 126, 141, 153)
Median	1	47 c	44 (42-47)	36 hc	45 (42-48)	No	(11)
		17 w/o	44 (44-47)	22 hc	47 (42-49)	No	(167)
≥55 mm	1	c	7/80 (8.8%)				(159)
LVEDD Index (mm/m2)	1	63 c	16.9±2.8	40 hc	17.3±3.1	No	(52)
LVESD (mm) - Mean	1	47 c	26±3.3	36 hc	25±3.4	No	(11)
Median	1	17 w/o	26 (22-29)	20 hc	27 (25-29)	No	(167)
LVESD Index	1	63 c	26.9±3.3	40 hc	27.4±3.0	No	(52)

(mm/m2)							
LVEDV (ml) – Mean (SD)	1	104 w/o	76.0±25.4	37 hc	70.6±20.6	No	(82)
	1	45 c	80.6±20.2	20 hc	70.7±4.2	No	(89)
	1	35 c	80.8±9.2	35 hc	80.8±14	No	(139)
Median (IQR)	1	47 c	89 (79-103)	36 hc	93 (79-108)	No	(11)
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	(178)
LVESV (ml) -Mean	1	104 w/o	29.1±13.1	37 hc	26.6±5.7	No	(82)
	1	35 c	28.0±4.1	35 hc	27.1±7.1	No	(139)
Median	1	47 c	26±3.3	36 hc	25±3.4	No	(11)
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						(9, 18, 22, 38, 44, 45, 50, 52, 58, 64, 73, 74, 86, 87, 89, 90, 94, 95, 100, 130, 136, 139, 141-143, 149, 151, 173, 181)
Hypertrophy of the wall (not specified) ≥13 mm	1	C	15/80 (18.8%)				(159)
ED-IVS thickness (mm) – Mean	1	69 c	9.3±2.1				(86)
	1	124 c	10.3±1.8	41 hc	8.9±1.1	Yes	(151)
	1	35 c	9.3±1.1	25 hc	8.2±1.1	Yes	(44)
	1	19 c	8.7±1.6	10 hc	6.6±2.0	Yes	(45)
	1	30 c	12.2±0.5	48 hc	9.9±0.3	Yes	(94)
	1	42 w/o	9.2±2.0	20 hc	7.9±1.6	Yes	(73)
	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	(9, 22, 52, 87, 90, 95, 130, 139, 141, 157, 161, 181)
	1	25 w diastolic dysfunction	9.9±1.3	25 w/o diastolic dysfunction	9.5±1.1	No	(173)
	1	24 w ILD	11±2.6	10 w/o	9±1	Yes	(136)

				ILD			
>11 mm	4	C + w	43/240 (17.9%)	Hc	4/66 (6.1%) (142)		(58, 74, 100, 142)
≥12mm	1	C	12/95 (12.6%)				(143)
ED-Posterior wall thickness (mm) - Mean	1	69 c	8.6±2.1				(86)
	1	124 c	9.7±1.4	41 hc	8.9±1.2	Yes	(151)
	1	19 c	8.7±1.7	10 hc	6.6±1.3	Yes	(45)
	1	30 c	10.1±0.4	48 hc	9.1±0.3	Yes	(94)
	1	42 w/o	8.9±1.6	20 hc	7.9±1.4	Yes	(73)
	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	(9, 22, 44, 52, 87, 90, 95, 139, 157, 181)
	1	25 w diastolic dysfunction	9.9±1.3	25 w/o diastolic dysfunction	9.5±1.1	No	(173)
	1	24 w ILD	10.2±2.0	10 w/o ILD	9±2	Yes	(136)
>9 mm	1	C	7/28 (25%)				(38)
RV wall thickness (mm) - mean	1	70 c	5.0±1.0	25 hc	4.8±0.8	No	(18)
LV Mass							
LV Mass Index (g/m2)							
Mean	1	570 w/o	97±33				(154)
	1	124 c	99±31	41 hc	84±25	Yes	(151)
	1	30 c	116±7	48 hc	95±3	Yes	(94)
	1	72 c	96.9±19.5	30 hc	83.3±11.6	Yes	(171)
	1	24 w	42.7±6.2	12 hc	43.9±12.1	No	(13)
	7	261 c	From 70.0±22.4 to 105.9±26.1	180 hc	From 72±15 to 99.0±25.9	No	(11, 44, 52, 87, 89, 90, 126)
	1	16 w IAMD	107.1±21.7	24 w/o IAMD	82.5±19.9	Yes	(99)
	1	25 w DD	90±34	25 w/o DD	87±20	No	(173)
Median	1	103 w/o	82 (70-95)	103 hc	80 (69-99)	No	(175)
	1	95 W/o	70 (59-79)	54 hc	68 (57-81)	No	(178)
Wall Motion Abnormalities							
Not defined	1	c	11/72 (15.2%)	HC	1/64 (1.5%)	Yes	(142)

Segmental hypokinesia	9	C	29/505 (5.7%)	Hc	2/221 (0.9%) (9, 142, 165)		(9, 54, 66, 123, 134, 142, 143, 157, 165)
	1	w	3/10 (30%)				(50)
	1	After cold challenge	12/13 (92.3%)				(48)
Global hypokinesia	1	C	0/30 (0.0%)				(134)
	1	W	1/10				(50)
Akinesia	5	C + w	0/182 (0.0%)	Hc	0/97 (0.0%) (123, 142)		(50, 123, 134, 142, 157)
Valvular Lesion							
Valve Sclerosis	1	C	19/110 (17.3%)				(9)
Mitral Valve							
Any abnormality	1	C	8/22 (36.4%)				(149)
Thickening / Stenosis	5	C + W7o	26/312 (8.3%)	Hc	8/76 (20.5%) (95, 165)		(87, 95, 100, 157, 165)
Regurgitation	15	C+w/o	313/1459 (21.5%)	Hc	84/558 (15.1%) (9, 45, 52, 93-95, 142, 165, 171)		(9, 38, 45, 52, 56, 86, 93-95, 100, 142, 143, 154, 165, 171)
Prolapse	6	C + W/o	23/377 (6.1%)	Hc	2/76 (2.6%)		(38, 54, 87, 95, 100, 165)
Aortic Valve							
Sclerosis	1	C	6/37 (16.2%)				(177)
Thickening / Stenosis	7	C + w/o	37/210 (17.6%)	Hc	6/167 (3.5%) (9, 51, 58, 74, 95, 123, 165, 177)		(38, 87, 95, 100, 154, 157, 165)
Regurgitation	11	C+w/o+w	73/1280 (5.7%)	Hc	15/397 (3.8%) (9, 51, 58, 74, 95, 123, 165, 177)		(9, 38, 51, 74, 86, 95, 100, 143, 154, 165, 181)
Prolapse	Not reported						
Tricuspid Valve							
Any abnormality	3	C	45/172	Hc	41/230		(51, 123,

			(26.2%)		(17.8%) (51, 58, 123, 136, 170, 177)		177)
Thickening / Stenosis	Not reported						
Regurgitation	15	c+w/o	216/1142 (18.9%)	Hc	22/326 (6.7%) (9, 45, 52, 110, 142, 156)		(9, 38, 45, 52, 56, 58, 100, 110, 129, 136, 142, 143, 156, 159, 170)
	1	W	27/37 (72.9%)	Hc	21/37 (56.8%)	Not reported	(74)
Prolapse	Not reported						
Pulmonary Valve							
Any abnormality	1	C	1/37 (2.7%)	Hc	2/37 (6.5%)	No	(177)
Thickening / Stenosis	1	C	3/110 (2.7%)				(100)
Regurgitation	2	C	7/165 (4.2)	Hc	0/111 (0.0%)		(51, 159)
Prolapse							
LV systolic function							
LV Ejection fraction (%)							
< 55%	10	C + w/o	471/8483 (5.6%)	HC	1/94 (1.1%) (74, 95, 123)		(73, 74, 77, 86, 91, 100, 102, 111, 123, 127)
< 50 %	6	C	27/341 (7.9%)	HC	1/341 (5.2%) (9, 139, 182)		(9, 68, 103, 115, 139, 182)
< 45%	1	w/o	8/570 (1.4%)				(154)
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	(9, 11, 13, 18-20, 22, 48, 56, 64, 82, 84, 86, 89, 91-93, 98, 100, 101, 103-106, 108, 110-113, 115, 120,

							125, 126, 130, 138, 139, 141, 145, 149, 151, 153, 154, 156-158, 162-166, 168, 170, 172-175, 178, 180-182)
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	(9, 18, 73, 159, 161)
	1	46 w DD 195 w/o DD	57±10 58±7	65 hc	62±4	Yes	(110)
Fractional shortening (%)	1	80 c	19.7±6.2	18 hc	23.7±6.0	Yes	(159)
	1	35 c	38±5	35 hc	36±5	Not reported	(87)
	1	63 c	40±10	40 hc	38±5	No	(52)
	1	35 c	39.2±6.4	25 hc	40.7±6.2	No	(44)
LV Stroke volume (ml)							(37, 47)
Mean	1	23 c	64.7±12.5	25 hc	69.6±6.9	No	(90)
	1	30 c	80.4±5.0	48 hc	94.5±4.9	No	(93)
	1	35 c	53.7±10.2	35 hc	52.9±8.2	No	(139)
LV Stroke volume Indices (ml)							
Mean	1	25 c	38±2	25 hc	42±2	No	(46)
LV Stroke work (kg cm)							
Median	1	95 c	4.2 (3.6-4.8)	54 hc	5.4 (4.2-6.6)	Yes	(178)
LV Stroke Work Index (gg/cm2)							
Mean	1	95 c	60.3±10.3	54 hc	70.0±11.9	Yes	(178)
RV systolic function							
RV ejection fraction (RVEF) – (%)	1	30 c	56.7±7.7	30 hc	50.45±8.4	Yes	(19)
	1	40 c	39.2±6.7	45 hc	49.6±6.8	Yes	(161)
< 35%	1	C	16/42 (38.1%)				(73)
Fractional Area Change (FAC) –	1	70 w/o	47.5±7.2	25 hc	54.1±6.6	Yes	(18)

(%)							
	1	45 w/o	46±6	43 hc	52±6	Yes	(169)
	1	42 c	49.2±12.9	40 hc	48.8±8.8	No	(23)
	1	52 c	49.3±12.4	52 hc	42.9±9.3	No	(158)
	1	12 w DD	31.5±5.2	28 w/o DD	33.5±3.4	No	(156)
<35%	1	C	4/115 (3.5%)				(103)
TAPSE							
< 20mm	1	25 w	2/25 (8.0%)				(106)
< 17 mm	2	C	12/220 (5.4%)	Hc	105 (0.0%)		(9, 100)
< 16 mm	1	C	4/115 (3.5%)				(103)
< 15 mm	1	w/o	0/37 (0.0%)	Hc	0/37 (0.0%)		(74)
Mean±SD	1	20 c	23.1±3.5	20 HC	26.5±1.9	Yes	(20)
	1	50 c	20.4±4.3	44 hc	24.4±3.6	Yes	(85)
	1	26 c	23.3±1.6	24 hc	25.8±2.8	Yes	(126)
	1	40 c	21.1±3.2	40 hc	24.3±3.4	Yes	(156)
	1	111 c	22.2±3.2	21 hc	24.1±2.4	Yes	(21)
	1	45 c	23±3	43 hc	26±2	Yes	(169)
	1	70 c	21.1±2.6	25 hc	23.6±1.6	Yes	(18)
	1	42 c	24.7±3.9	40 hc	22.1±3.3	Yes	(23)
	1	47 c	21.0±3.9	36 hc	21.0±4.6	No	(11)
	1	52 c	22.2±4.3	52 hc	23.0±3.6	No	(158)
	1	23 c	19.1±3.5	25 hc	20.1±2.6	No	(90)
	1	46 w DD	20±6	195 w/o DD 65 HC	24±5 25±4	Yes Yes	(110)
	1	12 w DD	21.1±2.8	28 w/o DD	21.0±3.5	No	(156)
Systolic Pulmonary Arterial Pressure (mmHg)							(13, 15, 64, 83, 86, 104, 106, 111, 151, 170, 180)
>35 mmHg	8	C + W/o	150/674 (22.3%)	Hc	1/202 (0.5%) (9, 123, 142)		(9, 90, 100, 104, 123, 142, 170, 181)
>40 mmHg	6	C + W/o + w	240/7504 (3.2%)	Hc	0/78 (0.0%) (74, 95, 140)		(74, 86, 95, 101, 102, 127)
>45 mmHg	1	C	44/124 (35.5%)				(151)
>50 mmHg	1	C	6/115 (5.2%)				(103)
Mean (SD)	1	104 c	28.9±8.7	37 hc	21.7±6.3	Yes	(82)
	1	50 c	32.3±17.1	44 hc	20.7±5.6	Yes	(85)

	1	45 c	25.4±8.7	20 hc	20.2±3.4	Yes	(89)
	1	23 c	43.2±9.8	25 hc	23.2±5.8	Yes	(90)
	1	40 c	24.2±5.7	40 hc	19.8±6.2	Yes	(156)
	1	40 w/o	35.2±5.8	45 hc	19.9±6.0	Yes	(161)
	1	17 w/o	33.1±6.0	15 hc	27.7±3.8	Yes	(140)
	1	51 w/o	25.0±4.8	20 hc	20.1±2.3	Yes	(168)
	1	45 w/o	33±14	43 hc	22±5	Yes	(169)
	1	30 w/o	29.9±8.8	30 hc	22.9±9.8	Yes	(19)
	1	72 c	40.9±16.4	64 hc	30.1±2.5	Yes	(142)
	1	100 w/o	33.3±0.6	26 hc	30.8±1.0	No	(95)
	1	42 c	24.1±8	42 hc	21±7	No	(84)
	1	35 c	24.0±23.3	35 hc	23.3±6.4	No	(138)
	1	70 w/o	26.2±5.7	25 hc	25.8±2.9	No	(18)
	1	72 w/o	26.6±7.5	30 hc	25.5±2.8	No	(171)
	1	42 w/o	30.3±5.4	20 hc	27.6±3.8	No P=0.078	(73)
	1	35 w DD	33±11	118 w/o DD	31±15	No	(91)
	1	25 w DD	35±17	25 w/o DD	25±7	Yes	(173)
	1	202 AA	39.3±17.2	200 non-AA	32.8±14.2	Yes	(112)
Median	1	31 c	26 (20-36)	41 hc	20 (18-24)	Yes	(128)
	1	31 w/o	36.5 (31-44.5)	32 hc	26 (22-29)	Yes	(92)
	1	37 w	30 (20-51)	37 hc	20 (14-28)	Yes	(74)
	1	103 w/o	27 (22-35)	103 hc	23 (10-27)	Yes	(175)
Right ventricle systolic pressure (mmHg)							(98)
Mean±SD	1	14 c	25±4.3				(115)
	1	42 w/o	33.5±8,7	40 hc	28.8±4.4	Yes	(23)
	1	17 c	34.4±7.1	17 hc	35.3±6.0	No	(108)
	1		34.3±5.9		31.2±2.3	No	(141)
Median (IQR)	1	14 c	25 (19-35)				(115)
	1	95 c	28.6 (23.5-33.1)	54 hc	13.4 (11.8-14.6)	Yes	(178)
RV/RA gradient (mmHg)							
Mean±SD	1	110 c	28±11	105 hc	23±4	Yes	(9)
Mean Pulmonary Arterial Pressure (mmHg)							
	1	30 c	17.8±6.3	30 hc	14.4±6.9	No	(19)

						(p=0.054)	
Pulmonary Acceleration Time (m/s)							
	1	26 c	119±11	24 c	142±13	Yes	(126)
	1	110 c	105±32	105 hc	114±35	Not reported	(9)
	1	10 w/o ILD	125±30	24 w ILD 21 hc	105±30 135±15	No No	(136)
<90	1	W	4/37 (10.8%)	Hc	0/37 (0.0%)	Yes	(74)
Isovolumetric Acceleration (m/s2)							
	1	22 c	2.3±0.4	22 hc	4.1±0.8	Yes	(176)
Pulmonary Ejection time (ms)							
	1	17 c	360 (320-388)	23 hc	340 (320-350)	Yes	(167)
RV diastolic dysfunction							
Tricuspid E (cm/s)							
Mean±SD	1	111 c	52.2±11.4	21 hc	58.8±11.2	Yes	(21)
	1	70 c	47.5±9.2	25 hc	54.3±8.9	Yes	(18)
	1	63 c	56±10	40 c	60±10	No	(52)
	1	77 c	41.4±14.1	36 hc	45.1±8.5	No	(182)
	1	23 c	49±2	25 hc	55±1	No	(90)
Median (IQR)	1	42 w/o	55.9 (46.9-59.6)	40 hc	56.8 (53.9-62.4)	Yes	(23)
Tricuspid A (cm/s)							
Mean±SD	1	63 c	54±20	40 hc	43±10	Yes	(52)
	1	111 c	50.5±13.5	21 hc	46.4±10.4	No	(21)
	1	77 c	37.9±15.2	36 hc	36.5±9.7	No	(182)
	1	70 c	39.5±8.8	25 hc	39.0±5.6	No	(18)
	1	23 c	47±0.9	25 hc	46±2	No	(90)
Median (IQR)	1	42 w/o	38 (353.1-39.8)	40 hc	44.2 (41.5-49.5)	Yes	(23)
Tricuspid E/A							
Mean±SD	1	111 c	1.05±0.24	21 hc	1.3±0.3	Yes	(21)
	1	20 c	1.08±0.48	15 hc	1.5±0.6	Yes	(22)
	1	30 w/o	1.01±1.3	30 hc	1.19±0.89	Yes	(19)
	1	63 c	1.04±0.3	40 hc	1.36±0.4	Yes	(52)
	1	77 c	1.2±0.4	36 hc	1.2±0.2	No	(182)
	1	52 w/o	1.2±0.4	52 hc	1.4±0.4	No	(158)

Median (IQR)	1	42 w/o	1.4 (1.3-1.7)	40 hc	1.30 (1.14-1.38)	Yes	(23)
Tricuspid E'							
Mean±SD	1	111 c	12.0±3.6	21 hc	12.7±2.7	No	(21)
	1	31 w/o	11.7 (9.7-14.6)	32 hc	13.7 (12.3-15)	Yes	(92)
	1	70 c	9.5±2.3	25 hc	11.7±2.8	Yes	(18)
Tricuspid E/E' (cm/s)							
Mean±SD	1	111 c	4.8±1.8	21 hc	4.7±0.8	No	(21)
	1	70 c	5.3±1.5	25 hc	4.9±1.4	No	(18)
	1	52 w/o	3.9±1.9	52 hc	9.0±5.0	Yes	(158)
Median (IQR)	1	31 w/o	4.3 (3.3-5.2)	32 hc	3.4 (2.9-3.9)	Yes	(92)
	1	95 W/o	4.8 (3.8-5.9)	54 hc	4.15 (3.4-4.8)	Yes	(178)
	1	42 w/o	5.20 (4.19-6.35)	40 hc	4.60 (4.10-4.90)	Yes	(23)
RV Tei Index							
Mean±SD	1	111 c	0.38±0.08	21 hc	0.29±0.02	Yes	(21)
Median (IQR)	1	42 w/o	0.40 (0.30-0.43)	40 hc	0.30 (0.30-0.40)	No (p=0.09)	(23)
LV diastolic dysfunction							(103, 173)
Present	1	C	35/153 (22.9%)				(91)
	1	C	47/110 (42.7%)				(100)
Mitral E/A <1	1	C	10/19 (52.6%)				(96)
	1	C	4/30 (13.3%)				(134)
	1	C	16/35 (46.0 %)	hc	5/35 (14.0%)	Yes	(139)
	1	W	17/37 (45.9%)	Hc	15/37 (40.5%)	No	(74)
	1	C	7/25 (28%)	Hc	2/25 (8%)	No (p=0.06)	(181)
Mitral E/A							(13, 165, 166, 174)
Mean	1	14 c	1.03±0.3				(115)
	1	120 c	1.0±0.4				(113)
	1	570 c	1.1±0.4				(154)
	1	243 c	1.13±0.36				(104)
	1	42 c	1.1±0.4	42 hc	1.3±0.4	No	(84)
	1	124 c	1.14±0.46	41 hc	1.26±0.20	No	(151)
	1	17 c	1.01±0.39	17 hc	0.75±0.23	No	(108)
	1	35 c	1.1±0.4	35 hc	1.2±0.3	No	(164)
	1	35 c	1.3±0.4	35 hc	1.3±0.4	No	(87)
	1	24 w/o	1.1±0.3	24 hc	1.2±0.2	No	(130)

	1	23 c	1.04±0.4	25 hc	1.2±0.8	No	(90)
	1	27 c	1.04±0.24	26 hc	1.29±0.61	No	(163)
	1	17 w/o	1.18±0.3	15 hc	1.21±0.5	No	(140)
	1	110 c	1.1±0.3	105 hc	1.1±0.3	No	(9)
	1	35 c	1.18±0.38	35 hc	1.13±0.27	No	(138)
	1	30 w/o	1.28±0.52	30 hc	1.39±1.29	No	(19)
	1	52 w/o	1.2±0.4	52 hc	1.1±0.4	No	(158)
	1	27 c	1.05±0.3	27 hc	0.90±0.02	No	(138)
	1	42 w/o	1.02±0.6	20 hc	1.24±0.51	No (p=0.07)	(73)
	1	72 w/o	1.08±0.3	30 hc	1.37±0.3	Yes	(171)
	1	20 w/o	1.02±0.42	15 hc	1.48±0.26	Yes	(22)
	1	100 w/o	1.0±0.3	26 hc	1.2±0.6	Yes	(95)
	1	30 c	1.09±.01	48 hc	1.33±0.06	Yes	(94)
	1	18 c	1.36±0.49	10 hc	1.75±0.53	Yes	(45)
	1	77 c	1.2±0.5	36 hc	1.5±0.1	Yes	(182)
	1	35 w/o	1.03±0.42	25 hc	1.44±0.28	Yes	(44)
	1	50 w/o	1.04±0.4	25 hc	1.45±0.2	Yes	(155)
	1	45 c	0.89±0.16	20 hc	1.04±0.21	Yes	(89)
	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	(20)
	1	26 c	0.94±0.37	24 hc	1.18±0.34	Yes	(126)
	1	50 c	1.2±0.9	31 hc	1.35±0.1	Yes	(123)
	1	63 c	1.02±0.3	40 hc	1.37±0.4	Yes	(52)
	1	111 c	0.98±0.3	21 hc	1.21±0.28	Yes	(21)
	1	15 c	1.23±0.37	18 hc	1.72±0.31	Yes	(145)
	1	11 w CVE	0.8±0.3	22 w/o CVE	0.9±0.3	No	(64)
Median	1	14 c	1 (0.7-1.8)				(115)
	1	33 w/o	1.2 (0.9-1.4)	16 hc	1.2 (0.9-1.6)	No	(16)
	1	31 w/o	1 (0.8-1.2)	32 hc	1.1 (0.9-1.4)	No	(92)
	1	47 w/o	0.88 (0.72-1.35)	36 hc	1.16 (0.i87-1.36)	No	(11)
	1	103 w/o	1.03 (0.83-1.30)	103 hc	1.05 (0.87-1.27)		(175)
Mitral E (cm/s)							
Mean	1	570 w/o	75±19				(154)
	1	24 c	59.2±15.7	24 hc	65.3±8	Yes	(77)
	1	20 c	78±13	20 hc	85±17	Yes	(20)
	1	18 c	88.5±17.8	18 hc	75.9±17.1	Yes	(45)
	1	35 c	70±30	35 hc	60±20	No (p=0.06)	(164)
	1	35 w/o	69±22	25 hc	80±21	No (p=0.07)	(44)
	1	27 c	74±14	26 hc	79±19	No	(163)
	1	77 c	65.7±17.0	36 c	70.0±8.5	No	(182)
	1	50 w/o	71±20	25 hc	80±21	No	(155)

	1	23 c	68±9	25 hc	70±20	No	(90)
	1	111 c	73.2±17.0	21 hc	87.4±14.3	No	(21)
	1	24 w/o	76.4±15.8	24 hc	78.2±9.2	No	(130)
	1	50 c	81.1±15.8	31 hc	85.2±18.2	No	(123)
	1	124 c	66.6±12.3	41 hc	70.2±10.2	No	(151)
	1	26 c	67±14	24 hc	73±15	No	(126)
	1	63 c	78±20	40 hc	82±20	No	(52)
Median	1	47 w/o	78 (70-87)	36 hc	85 (70-95)	No	(11)
Mitral A (cm/s)							
Mean	1	570 c	73±21				(154)
	1	35 w/o	70±12	25 hc	57±13	Yes	(44)
	1	77 c	57.5±17.4	36 hc	46.6±8.8	Yes	(182)
	1	24 c	56.2±19.9	24 hc	36.7±4.9	Yes	(77)
	1	35 c	70±20	35 hc	50±10	Yes	(164)
	1	124 c	64.5±18.7	41 hc	55.9±14.2	Yes	(151)
	1	20 c	73±11	20 hc	63±39	Yes	(20)
	1	50 c	70.2±16.2	31 hc	63.8±7.8	Yes	(123)
	1	63 c	81±39	40 hc	61±10	Yes	(52)
	1	111 c	76.9±18.6	21 hc	66.5±16.2	Yes	(21)
	1	50 w/o	72±16	25 hc	57±16	Yes	(155)
	1	24 w/o	74.2±16.3	24 hc	65.4±13.9	No (p=0.09)	(130)
	1	26 c	76±15	24 hc	65±16	No (p=0.09)	(126)
	1	27 c	71±13	26 hc	67±20	No	(163)
	1	23 c	65±6	25 hc	62±10	No	(90)
	1	18 c	55.2±5.3	10 hc	59.4±16.1	No	(45)
Median	1	47 w/o	80 (63-93)	36 hc	71 (64-83)	No	(11)
Mitral e'							
Median	1	42 w/o	10.8 (8.2-14.2)	40 hc	12.1 (10.5-12.7)	No	(23)
Mitral E' (cm/s)							
< 10	1	c	75/234 (32%)				(104)
Mean	1	234 c	11.2±2.8				(104)
	1	35 c	10.6±4.2	35 hc	8.8±2.2	Yes	(164)
	1	72 w7o	10.9±1.4	30 hc	9.8±2.8	Yes	(171)
Median	1	31 w/o	9.04 (7.2-11.6)	32 hc	7.37 (6.2-7.99)	Yes	(92)
Mitral a'							
Median	1	42 w/o	13.2 (11.9-15.8)	40 hc	9.4 (8.7-10.1)	No	(23)
Mitral A' (cm/s)							
Mean	1	35 c	8.8±2.6	35 hc	7.6±1.8	Yes	(164)
Mitral e'/a'							
Median	1	42 w/o	0.7 (0.5-1.0)	40 hc	1.1 (0.9-1.3)	No	(23)
Mitral E/E'							

Mean	1	35 c	7.2±2.1	35 hc	7.3±2.3	No	(164)
	1	111 c	7.55±2.85	21 hc	6.9±2.3	No	(21)
	1	110 c	9.8±3.9	105 hc	8.7±3.4	Yes	(9)
	1	42 c	7.6±2.4	42 hc	6.5±1.5	Yes	(84)
	1	72 w/o	9.3±2.8	30 hc	7.4±1.4	Yes	(171)
	1	52 c	6.6±2.6	52 hc	7.8±2.5	Yes	(158)
	1	11 w CVE	9.2±3.3	22 w/o CVE	9.3±7.9	No	(64)
Median	1	103 w/o	8.8 (7.1-10.4)	103 hc	9.0 (7.6-10.9)	No	(175)
	1	47 w/o	9 (7.1-11)	36 hc	8.9 (7.1-9.6)	No	(11)
Mitral s'							
Median	1	42 w/o	12.9 (11.5-15.7)	40 hc	12.0 (11.3-12.7)	No	(23)
Mitral S'							
Mean	1	35 c	7.5±2.1	35 hc	6.9±1.3	No	(164)
Median	1	31 w/o	7.7 (6.7-7.5)	32 hc	9.3 (8.1-10.5)	Yes	(92)
LV Tei Index	1	111 c	0.46±0.09	21 hc	0.39±0.06	Yes	(21)
Isovolumetric relaxation time (IVRT) – ms							(23, 183)
Mean	1	20 c	35.4±12.7	20 hc	19.2±6.3	Yes	(20)
	1	77 c	78.5±1.4	36 hc	59.3±0.9	Yes	(182)
	1	111 c	73.2±12.0	21 hc	64.3±7.8	Yes	(21)
	1	27 c	97.6±13.1	26 hc	91.2±5.3	Yes	(163)
	1	77 c	77.7±14.4	45 hc	60.0±6.4	Yes	(166)
	1	22 c	62.4±34.6	22 hc	11.7±18.2	Yes	(176)
	1	23 c	80±11	25 hc	78.5±9.7	No	(90)
	1	35 c	61±14	35 hc	66±15	No	(87)
	1	40 w/o	63.2±11.2	46 hc	65.4±9.0	No	(161)
	1	110 c	84±19	105 hc	85±15	No	(9)
	1	35 c	98.8±13.8	35 hc	97.6±15.5	No	(138)
	1	27 c	111±20	17 hc	110±21	No	(10)
Median	1	33 c	87 (78-95)	16 hc	87 (82-97)	No	(16)
Pulmonary Vascular Resistances (WU)							
Median	1	103 c	1.5 (1.2-1.8)	103 hc	1.1 (0.9-1.4)	Yes	(175)
		42 c	1.56 (1.28-1.99)	40 hc	1.10 (0.99-1.30)	Yes	(23)
Pericardium Alteration							
Non specified – Present	5	C	58/487 (11.9%)		1/50 (2.0%) (165)		(42, 65, 75, 87, 157)
Pericardial Thickening							
Present	1	W	2/10 (20.0%)				(50)

≥7mm	1	C	14/80 (17.5%)				(159)
Pericardial effusion	20	C	135/1363 (9.9%)		2/446 (0.4%) (9, 45, 46, 51, 52, 74, 95, 123, 136, 142)		(9, 43, 45-47, 51, 52, 54, 56, 100, 101, 103, 104, 142, 149, 151, 159, 165, 174, 177)
	6	w/o	27/300 (9.0%)				(38, 86, 95, 136, 150, 181)
	4	W	35/128 (27.3%)				(40, 50, 74, 160)
Tamponade	1	W	4/23 (17.4%)				(160)
Inferior Vena Cava							
Diameter (mm)	1	17 c	14.5 (12.3-17)	22 hc	14 (10-17)	No	(167)
	1	70 w/o	14.0±3.8	25 hc	14.8±4.7	No	(18)
	1	25 c	15.7±3.0	25 hc	14.0±3.9	No	(181)
	1	23 c	16±3	25 hc	15±3	No	(90)
	1	42 w/o	15.0 (11.3-17.0)	40 hc	11.9 (10.2-15.6)	Yes	(23)
Respiratory variation (%)	1	17 c	65 (59-68.5)	22 hc	100 (66.8-100)	Yes	(167)
	1	70 c	55.5±11.5	25 hc	55.0±13.4	No	(18)
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(176)	
	1	35 c	5.3±0.7	35 hc	5.6±0.6	No	(139)
Peak systolic velocity on STRAIN Echo (cm/s)	1	27 w/o	10.7±1.8	17 hc	11.4±1.4	No	(10)
Tricuspid anular peak systolic velocity (cm/s)	1	103 c	6.4±1.8	103 hc	6.9±1.7	No	(175)
Peak systolic Strain Rate (/s)	1	18 c	2.1 (1.3-3.1)				(83)
	1	17 w/o	1.7±0.5	15 hc	3.8±1.7	Yes	(140)
Global	1	45 c	1.1±0.1	20 hc	0.9±0.2	Yes	(89)
	1	35 w/o	-1.3±0.1	35 hc	-1.6±0.1	Yes	(139)
RV	1	17 c	-5.5 (-6.4-	23 hc	-1.8 (-3.9 -	Yes	(167)

			2.6)		1.4)		
	1	27 c	-2.9±0.6	26 hc	-3.2±0.7	No	(163)
Basal IVS	1	17 c	-1.0 (-1.6-0.7)	15 hc	-1.1 (-1.6-0.8)	No	(167)
Peak diastolic Strain Rate (/s)	1	18 c	2.6 (1.4-6.7)				(83)
	1	17 w/o	3.7±1.5	15 hc	5.6±1.2	Yes	(140)
Early diastolic Strain Rate (/s)	1	95 w/o	1.5 (1.2-1.7)	54 hc	1.5 (1.3-1.8)	No	(178)
Basal IVS longitudinal strain (%)	1	17 c	-18.6 (-27.9-6.0)	15 c	-17.1 (-20.6-3.6)	No	(167)
Free wall RV longitudinal strain (%)	1	45 w/o	-30±5	43 hc	-31.3±4	No	(169)
	1	17 c	-25.2 (-53.7 - 6.8)	23 hc	-28.6 (-43.3-21-2)	No	(167)
	1	46 w DD	-20±7	195 w/o DD	-25±5	Yes	(110)
Positive peak LA longitudinal strain (%)	1	42 c	18.4±4	42 hc	21.4±7.6	Yes	(84)
Negative peak LA longitudinal strain (%)	1	42 c	31.3±4.2	42 hc	35.0±7.6	Yes	(84)
Global Longitudinal strain (%)	1	234 c baseline	-20.9±2.0	234 c f/u	-19.3±2.5	Yes	(104)
	1	45 c	-13.6±2.7	20 hc	-12.2±2.9	No	(89)
	1	35 W/o	-19.5±2.3	35 hc	-26.1±2.4	Yes	(139)
	1	95 w/o	-20.4±2	54 hc	-21.5±1.9	Yes	(178)
LV	1	104 w/o	-18.2±1.8	37 hc	-21.3±1.7	Yes	(82)
	1	25 w/o	-17.4±1.6	25 hc	-19.2±8.8	Yes	(181)
	1	52 w/o	-19.2±4.4	52 hc	-21.1±2.5	Yes	(158)
	1	72 w/o	-19.3±1.5	30 hc	-17.2±2.3	Yes	(171)
	1	33 w/o	-18.6±1.6	20 hc	-21.1±1.2	Yes	(8)
	1	47 w/o	-17.5±5.7	36 hc	-20.6±2.7	Yes	(11)
	1	27 c	-19.8±3.0	26 hc	-23.4±2.8	Yes	(163)
	1	40 c	-20.5±3.4	40 hc	-20.9±2.7	No	(156)
RV	1	25 w/o	-20.3±5.4	25 hc	-24.9±3.6	Yes	(181)
	1	52 w/o	-18.2±9.1	52 hc	-22.2±7.1	Yes	(158)
	1	45 w/o	-24.8±4	43 hc	-25.6±3	No	(169)
	1	47 w/o	-17.5±4.2	36 hc	-18.9±3.9	No	(11)
	1	27 c	-28.2±6.8	26 hc	-30.7±6.4	No	(163)
Global Circumferential							

Strain (%)							
LV	1	104 w/o	-18.2±2.3	37 hc	-21.3±2.1	Yes	(82)
	1	33 w/o	-18.7±1.7	20 hc	-20.7±1.4	Yes	(8)
	1	47 w/o	-18.2±3.2	36 hc	-19.8±2.7	Yes	(11)
	1	95 w/o	-22.7 (-25-21.2)	54 hc	-25.3 (-28.3-23.3)	Yes	(178)
	1	40 c	-17.5±5.5	40 hc	-18.8±4.8	No	(156)
Global radial strain (%)							
LV	1	104 w/o	37.0±13.9	37 hc	40.3±12.4	No	(82)
	1	40 c	39.4±18.6	40 hc	42.2±13.1	No	(156)
Coronary flow reserve							
≥ 2.00	1	w/o	24/44 (54.5%)				(150)
	1	C	14/29 (48.3%)				(146)
Mean	1	29 c	1.93±0.56	11 hc	1.81±0.56	Yes	(146)

Supplement Table 8. Data extracted during through the systematic literature review, regarding the "other tests" domain.

Data reported from 16 publications, including 443 patients (18, 38, 39, 46, 59, 66, 101, 106, 108, 115, 138, 145, 157, 172, 176) and 146 controls (46, 108, 138, 145, 172, 176).

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.

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.				(106, 157)
Pericardial	1	8	4 pts with fibrosis, 2 with granulomatous lesions, 2 with inflammation.				(101)
Six minutes walking test							
Six minutes walking distance (m)	1	70	391±95				(18)
Exercise Heart Rate Recovery (bpm)							
1 minutes after stress	1	35 c	21.8±4.4	35 hc	27.7±4.3	Yes	(138)
2 minutes after stress	1	35 c	43.8±6.3	35 hc	47.6±4.4	Yes	(138)
3 minutes after stress	1	35 c	58.8±10.3	35 hc	63.6±7.3	Yes	(138)
Ventriculography							
With cold test	1	16 c					(109)
Signal-averaged ECG							
Ventricular Late potentials	1	W	11/24 (45.8%)	Hc	2/24 (8.3%)	Yes	(145)

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