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REVIEW ARTICLES

Clinical spectrum and outcomes of pericardial and myocardial disease in systemic sclerosis: a multicentre case series and literature review

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ABSTRACT

Objectives: Cardiac involvement is a leading cause of morbidity and mortality in systemic sclerosis (SSc) yet is often underdiagnosed. Early recognition is crucial but published data remains limited. This study aimed to characterize the clinical presentation, diagnostic features, and outcomes of SSc patients with acute primary heart involvement.
Methods: This multicentre retrospective case series included patients meeting the 2013 ACR/EULAR SSc classification criteria with clinically significant pericardial effusion or myocardial involvement, identified across tertiary rheumatology centres in Portugal (Coimbra, Lisbon, and Porto) and Spain (León). A complementary literature review was performed to identify additional published cases.
Results: Of 23 screened cases, 6 met the inclusion criteria. The literature review identified 13 additional reports, totalling 19 patients. In 8 (42.1%) of patients, heart involvement was either the initial manifestation or occurred concurrently with the diagnosis of SSc. Pericardial disease (n=6) often presented as tamponade requiring emergent pericardiocentesis. Myocardial involvement (n=13) was classified as acute myocarditis (AM) in 9 (69.2%) and chronic inflammatory cardiomyopathy (CIC) in 4 (30.8%). Cardiac magnetic resonance showed late gadolinium enhancement in 9 (72.7%) and myocardial oedema in 4 (36.4%); however, both were absent in two biopsy-confirmed AM cases. Cyclophosphamide was the second most common therapy after corticosteroids. Two patients died during hospitalization, with three more deaths during long-term follow-up.
Conclusion: Severe cardiac manifestations in SSc frequently occur early in the disease, presenting as tamponade or myocardial involvement. Reliance solely on imaging may lead to myocarditis underdiagnosis. Distinct clinical profiles between AM and CIC point toward separate phenotypes with unique prognostic and therapeutic considerations. Large-scale, prospective studies are essential to refine early diagnostic approaches and optimize treatment.

Keywords: Systemic sclerosis; Primary heart involvement; Pericarditis; Myocarditis

INTRODUCTION

Cardiac involvement is a major determinant of morbidity and mortality in systemic sclerosis (SSc)[1]. However, it remains frequently underdiagnosed due to its often subclinical presentation and overlap with other cardiopulmonary manifestations[2-4]. The spectrum of SSc-related cardiac manifestations is heterogeneous varying from pericardial effusion, myocarditis, myocardial fibrosis, conduction disturbances, and arrhythmias[4]. Importantly, acute and severe cardiac events, such as pericardial tamponade, may precede hallmark features of SSc[5].

Recently, it has been highlighted that acute myocarditis and chronic inflammatory cardiomyopathy represent a continuum of myocardial inflammation, where persistent inflammatory injury leads to progressive dysfunction and remodelling[6]. However, few studies have specifically examined both these entities, and current guidelines provide limited direction for their differential diagnosis and management in SSc population[7-9]. Despite the clinical significance of acute cardiac events in SSc, published data on their timing, presentation, and outcomes, published literature remain scarce, largely limited to case reports and small series[5, 10, 11].

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This fragmented evidence base hinders timely diagnosis and tailored therapeutic strategies.

In this evolving landscape, the 2025 ESC Guidelines for the management of myocarditis and pericarditis offer updated recommendations on the diagnostic and therapeutic workup of myocardial inflammation, emphasising early detection, multimodality imaging, particularly cardiac MRI and risk-based management[12]. While these guidelines standardise the general approach to myocarditis, their applicability to SSc is limited, as they do not address the distinct mechanisms, overlap with microvascular dysfunction, or high burden of subclinical fibrosis characteristic of SSc. This gap reinforces the need for disease-specific guidance tailored to the unique presentation and progression of cardiac involvement in SSc.

To address these gaps, we conducted a multicentre retrospective case series complemented by a literature review. The objectives of this study were (i) to characterize the full spectrum of both acute and non-acute clinically significant myocardial and pericardial involvement in systemic sclerosis, (ii) to describe diagnostic pathways across different clinical presentations, and (iii) to evaluate short- and longer-term outcomes according to the mode of cardiac involvement. By integrating real-world data with published evidence, we aimed to provide a comprehensive framework for recognizing, investigating, and managing cardiac inflammatory manifestations of SSc beyond exclusively acute events, an underrecognized yet potentially life-threatening complication of the disease.

METHODS

We performed a retrospective observational multicentre study including patients diagnosed and evaluated between January 2010 and August 2022 across tertiary rheumatology centres in Portugal (Unidade Local de Saúde de Coimbra; Unidade Local de Saúde Santa Maria, Lisbon; Unidade Local de Saúde São João, Porto) and Spain (Complejo Asistencial Universitario de León). Eligible participants were adults (≥18 years) fulfilling the 2013 ACR/EULAR classification criteria for systemic sclerosis (SSc) with clinically significant pericardial effusion or myocardial involvement, the latter defined as acute myocarditis (AM) or chronic inflammatory cardiomyopathy (CIC). Clinically significant was defined as leading to hospitalization or worsening of New York Heart Association Functional Classification. This study was conducted in accordance with ethical standards and was approved by the Ethics Committee of the Unidade Local de Saúde de Coimbra (Comissão de Ética da ULS Coimbra) under protocol PI 2025-ESI.SF-120, with approval granted on 28 October 2025. Written informed consent was obtained from all participants prior to inclusion. Clinically suspected myocarditis was defined according to European Society of Cardiology (ESC) criteria, requiring at least one clinical presentation (e.g., chest pain, new-onset heart failure, palpitations or syncope) in combination with at least one diagnostic criterion (elevated troponin, abnormal electrocardiogram [ECG] or cardiac magnetic resonance [CMR] suggestive of myocardial inflammation, or histopathology)[13]. Definitive myocarditis on biopsy was defined by histological Dallas criteria and immunohistochemical criteria[13]. Acute myocarditis was defined as symptomatic myocarditis of recent onset (< 1month), while chronic inflammatory cardiomyopathy was defined as persistent structural and functional myocardial abnormalities for >1 month with fibrosis[14]. Acute pericarditis was defined according to ESC criteria, requiring at least 2 of the following 4 items: pericarditic chest pain; pericardial rubs, new widespread ST-elevation or PR depression on ECG; pericardial effusion (new or worsening)[15]. Pericardial fluid was classified as an exudate if it met any of the following criteria: protein fluid/serum ratio >0.5, LDH >200 IU/L, fluid/serum LDH ratio >0.6[15]. Left ventricular dysfunction was defined as an LVEF <50% on echocardiography or CMR[12].

To ensure primary heart involvement as defined by the World Scleroderma Foundation/Heart Failure Association (WSF/HFA)[16] was captured, we excluded patients with alternative plausible causes for the cardiac event (e.g., infection, neoplasm, ischemic heart disease, pulmonary hypertension, scleroderma renal crisis, other autoimmune diseases), as well those with incomplete clinical data.

In parallel, a literature review of clinical cases and case series written in English was conducted in PubMed and Embase (January 1956–April 2025) using predefined search terms (Supplementary Data S1). Inclusion and exclusion criteria mirrored those of the retrospective series, diagnostic approaches, definitions, and reporting standards varied across published studies, reflecting changes in imaging availability, biomarker use, and clinical practice over time. Conference abstracts without full-text availability were excluded. Literature records were independently reviewed by two investigators. Reporting followed the PRISMA 2020 statement[17], where applicable. The review protocol was not registered.

Given the rarity of clinically significant myocardial and pericardial involvement in SSc, data from the multicentre cohort and published cases were analysed together to illustrate the spectrum of disease rather than to derive pooled estimates or comparative inferences.

The following data was extracted from both cohorts:

demographic characteristics, SSc subtype, cumulative organ involvement, autoantibody profiles, cardiovascular symptoms, diagnostic tests (including ECG, echocardiography, CMR, endomyocardial biopsy), treatment strategies, and clinical outcomes.

STATISTICAL ANALYSIS

All statistical analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as absolute frequencies and percentages, and continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the distribution assessed using the Shapiro–Wilk test. For continuous variables, comparisons between groups were made using the t-test or Mann-Whitney U test, according to the normality of their distribution. For categorical variables, $\chi 2$ or Fischer's exact test were used, the latter when any expected cell frequency was five or less. Statistical significance was set at $p < 0.05$ for all tests.

RESULTS

Case selection

During the screening phase, 23 cases were submitted by 15 centres. After application of predefined eligibility criteria, 9 cases were excluded due to absence of clinically significant cardiac involvement, most commonly small pericardial effusions without haemodynamic compromise or other cardiac manifestations not included in this study (e.g. isolated arrhythmias). A further 8 cases were excluded after detailed review, owing to a more likely alternative cause for the cardiac event—pulmonary hypertension in 6 cases—or insufficient clinical data in 2 cases.

Consequently, 6 patients fulfilled all inclusion criteria and constituted the final multicentre cohort. The centres contributing eligible cases were Unidade Local de Saúde de Coimbra (n=2), Unidade Local de Saúde Santa Maria, Lisbon (n=1), Unidade Local de Saúde São João, Porto (n=2), and Complejo Asistencial Universitario de León (n=1).

The literature review identified 13 additional eligible cases, resulting in a final study population of 19 patients. Figure 1 illustrates the PRISMA 2020 flow diagram for the literature review, and Table I summarises the clinical characteristics of all included cases.

Demographic and clinical features

Table II summarizes clinical and immunological features of the study cohort, stratified by case origin and primary heart involvement. No statistically significant differences were observed between patients from the multicentre cohort and those identified through the literature review, nor between patients with pericardial versus myocardial involvement.

In the overall cohort of 19 patients, 13 (68.4%) were female, with a mean age of 47.1 ± 17.8 years at SSc diagnosis and 48.5 ± 17.2 years at the time of the cardiac event. Diffuse cutaneous SSc was the predominant subtype, observed in 14 patients (73.7%). The median interval from SSc diagnosis to cardiac involvement was 4.5 months (IQR 36). In 8 patients (42.1%), cardiac involvement either preceded or was simultaneous with the diagnosis of SSc; excluding these cases, the median interval increased to 30 months (IQR 35.2).

Cardiac involvement was classified as pericardial disease in 6 patients and myocardial disease in 13. Patients with pericardial disease were older at both SSc diagnosis (50.0 ± 19.5 vs 45.7 ± 17.7 years) and at the time of the cardiac event (50.0 ± 18.3 vs 47.7 ± 17.4 years). Female predominance was higher in the pericardial group (5/6, 83.3%) compared with myocardial disease (8/13, 61.5%). Diffuse cutaneous SSc was observed in the majority of patients in both groups (5/6 [83.3%] vs 9/13 [69.2%]).

The median time from SSc diagnosis to cardiac event was shorter in the pericardial group (0 months [IQR 11.3]) compared to the myocardial group (17.5 months [IQR 36]). Approximately two-thirds of pericardial effusion cases and a third of myocardial involvement patients presented simultaneously or preceded SSc diagnosis. Isolated instances of cardiac involvement preceding Raynaud's phenomenon (patient 3) and skin thickening (patients 3 and 6) were reported in the pericardial group, while no such cases were reported in the myocardial group. Follow-up duration after the cardiac event was longer for patients with pericardial disease (median 17.5 months [IQR 29]) compared to those with myocardial disease (median 6.0 months [IQR 11.1]).

Among patients presenting with initial pericardial tamponade without overt SSc-specific manifestations (n = 5), cardiac involvement preceded or coincided with the diagnosis of SSc in 4 cases (80.0%). At presentation, Raynaud's phenomenon was absent in 2/5 patients (40.0%), and cardiac involvement preceded the onset of Raynaud's phenomenon in 1 patient (20.0%) and skin thickening in 2 patients (40.0%).

Despite the lack of classical SSc features at initial presentation, subsequent clinical characterisation revealed that 4/5 patients (80.0%) developed a diffuse cutaneous SSc phenotype. Immunologically, all patients were antinuclear antibody–positive (5/5, 100%), and anti–Scl-70 antibodies were detected in 3/5 patients (60.0%), while anti-centromere antibodies were present in 1/5

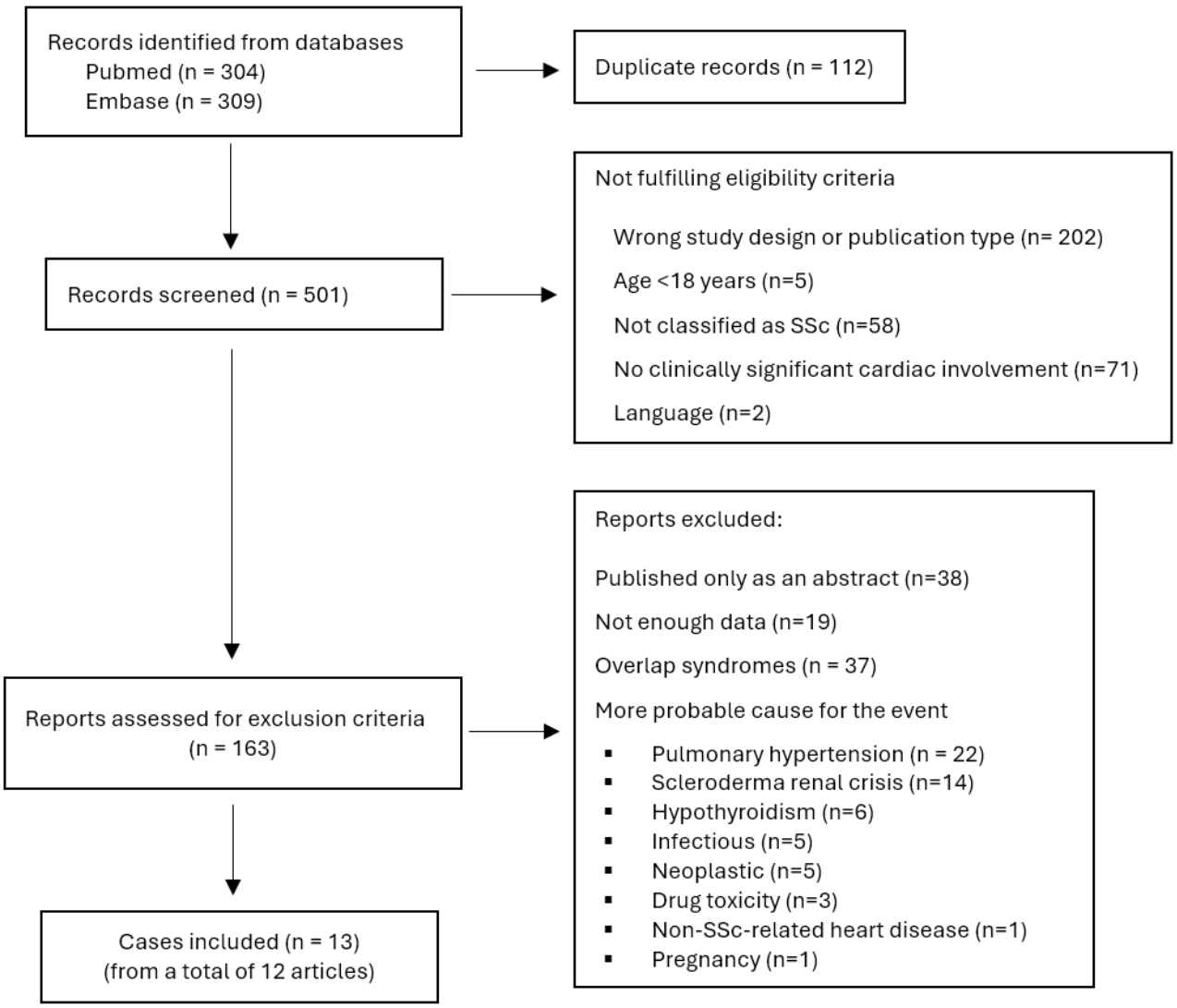

Figure 1. PRISMA 2020 flow diagram for study inclusion in the literature review

patients (20.0%).

Pericardial disease

One third (n=6) of the patients presented with severe pericardial effusion, five of which with tamponade. All five tamponade cases fulfilled clinical criteria supported by echocardiographic features of haemodynamic compromise. In four patients, emergent pericardiocentesis was performed based on clinical instability. Right heart catheterization was performed in one case (patient 4), with elevated right atrium pressure and loss of the normal "y" descent of the jugular venous pressure waveform. All patients were submitted to pericardiocentesis. The median volume drained was 925 mL (range: 200–1700 mL), and all effusions were exudative. The procedure was emergent in 4 patients, with favourable immediate outcomes.

Myocardial disease

Among patients with myocardial involvement (n=13), 69.2% were classified as acute myocarditis (AM) and 30.8% as chronic inflammatory cardiomyopathy (CIC). CIC patients were older at the time of the event (mean 58.0 vs 43.0, p=0.146). AM was an inaugural SSc manifestation more often (44.4% vs 25.0%, p=1.00). Troponin elevation was frequent among patients with myocardial involvement, observed in 61.5% (n=8/13) overall. Elevated troponin was slightly more common in acute myocarditis (66.7%, n=6/9) than in chronic inflammatory cardiomyopathy (50%, n=2/4). Clinically suspected myocarditis was common (92.3%), with similar rates between acute myocarditis and CIC. Table

TABLE I. Selected cases from the retrospective case series and literature review.

Patient Nr.	Event	Sex	Age (SSc diagnosis)	Age (event)	SSc subtype	Source
1	Tamponade	M	37	37	Diffuse	Case series
2	Tamponade	F	24	25	Limited	Case series
3	Tamponade	F	64	63	Diffuse	Case series
4	Tamponade	F	72	72	Diffuse	(18)
5	Severe effusion	F	38	41	Diffuse	(31)
6	Tamponade	F	65	62	Diffuse	(17)
7	AM	F	31	31	Diffuse	Case series
8	AM	F	27	29	Diffuse	Case series
9	CIC	M	61	64	Limited	Case series
10	AM	F	66	66	Diffuse	(32)
11	AM	M	38	38	Diffuse	(33)
12	AM	M	37	38	Diffuse	(22)
13	AM	M	42	42	Limited	(20)
14	AM	M	22	22	Diffuse	(34)
15	CIC	F	69	72	Limited	(35)
16	CIC	F	48	51	Diffuse	(21)
17	CIC	F	45	47	Diffuse	(21)
18	AM	F	30	43	Diffuse	(36)
19	AM	F	78	78	Missing	(25)

AM – acute myocarditis; CIC – chronic inflammatory cardiomyopathy; SSc – systemic sclerosis

III summarizes the clinical and diagnostic criteria for clinically suspected myocarditis.

Five patients with AM underwent endomyocardial biopsy, all showing histological evidence of myocardial inflammation and necrosis, and infiltrating mononucleated cells in immunohistochemistry. Endomyocardial biopsy was performed in one patient with CIC, revealing fibrosis without inflammatory infiltrate.

Cardiac magnetic resonance (CMR) showed oedema or late gadolinium enhancement (LGE) suggestive of myocarditis in 72.7% of the cases. Among the 11 patients who underwent CMR, LGE was present in all of those with CIC (Table IV), and in 57.1% of those with AM (p=0.236). Myocardial oedema was more prevalent among patients with CIC compared to AM (50% vs 29%, p=0.576). Notably, in two patients with biopsy proven myocarditis, CMR did not show LGE or oedema (patients 8 and 18). Left ventricular dysfunction was common, seen in 73% of patients, with similar frequencies between acute and chronic myocarditis groups.

Treatment and outcomes

Sixteen patients were hospitalized and all patients with pericardial involvement underwent pericardiocentesis, four of which emergent. Initial immunosuppressive therapy stratified by type of cardiac involvement is described in Table V.

Among patients with myocardial involvement, endomyocardial biopsy was performed in selected cases with high clinical suspicion despite negative or non-diagnostic CMR, driven by persistent symptoms (chest pain or heart failure), sustained troponin elevation, ventricular dysfunction, and/or malignant arrhythmias unexplained by alternative diagnoses. EMB provided a definitive diagnosis in these cases and informed subsequent therapeutic decisions.

Two fatalities occurred during hospitalisation, both in patients with biopsy-confirmed myocarditis (patients 10 and 14). Overall outcomes were favourable among patients surviving the acute event. Over a median follow-up of 12.0 months, 11 patients experienced complete resolution of cardiac involvement and 4 showed significant improvement. Two patients died during follow-up due to progressive heart failure (patients 8 and 9). Additionally, one patient initially diagnosed with cardiac tamponade died due to SSc-related complications (patient 1), and another patient (patient 5), initially diagnosed with a large pericardial effusion, died from unrelated lung cancer.

Diagnostic and management algorithm for suspected primary cardiac involvement in systemic sclerosis

Figure 2 summarises a structured, risk-stratified diag-

TABLE II. Demographic, clinical, and serological characteristics of patients according to case origin and pericardial versus myocardial involvement

	Total n = 19	Case series n=6	Literature review n=13	Pericardial disease n=6	Myocardial disease n=13
Age (mean ± DP)					
at SSc diagnosis	47.1 ± 17.8	40.7 ± 17.5	50.0 ± 17.9	50.0 ± 19.5	45.7 ± 17.7
at cardiac event	48.5 ± 17.2	41.5 ± 17.5	51.7 ± 16.8	50.0 ± 18.3	47.7 ± 17.4
Female sex, n (%)	13 (68.4)	4 (66.7)	8 (66.7)	5 (83.3)	8 (61.5)
SSc cutaneous subtype, n (%)					
Diffuse	14 (73.7)	4 (66.7)	10 (76.9)	5 (83.3)	9 (69.2)
Limited	4 (21.1)	2 (33.3)	2 (15.4)	1(16.7)	3 (23.1)
Not reported	1 (5.0)	0 (0.0)	1 (7.7)	0 (0)	1 (7.7)
Clinical features, n (%)					
Raynaud´s Phenomenon	15 (78.9) [4]	4 (66.7) [2]	11 (84.6) [2]	4 (66.7) [2]	11 (84.6) [2]
Skin thickening	18 (100)	6 (100)	13 (100)	6 (100)	12 (100)
Rodnan (mean ± DP)	16.9 ± 9.9 [12]	9.3 ± 6.5 [3]	22.5 ± 8.2 [9]	15.0 ± 5.6 [3]	18.3 ± 12.9 [9]
Telangiectasia	2 (10.5) [13]	2 (33.3) [2]	0 (0) [11]	1 (16.7) [5]	1 (7.7) [8]
Digital ulcers or pitting scars	7 (36.8) [9]	4 (66.7)	3 (23.1) [9]	2 (33.3) [2]	5 (38.5) [7]
Articular involvement	8 (42.1) [8]	4 (66.7)	4 (30.8) [8]	2 (33,3) [2]	6 (46.2) [6]
Gastrointestinal involvement	10 (52.6) [6]	3 (50.0)	7 (53.8) [6]	3 (50.0) [1]	7 (53.8) [5]
Interstitial lung disease	7 (36.8) [7]	2 (33.3) [2]	5 (38.5) [5]	2 (33.3) [2]	5 (38.5) [5]
Antinuclear antibodies, n (%)	19 (100)	6 (100)	13 (100)	6 (100)	13 (100)
Anti-Scl-70	11 (57.9)	5 (83.3)	6 (46.2)	4 (66.7)	7 (53.8)
Anti-centromere	2 (10.5)	0 (0)	2 (15.4)	1 (16.7)	1 (7.7)
Anti-PM/Scl	1 (5.3)	0 (0)	1 (7.7)	0 (0)	1 (7.7)
Anti-RNP	1 (5.3)	0 (0)	1 (7.7)	0 (0)	1 (7.7)
Anti-RNApol-III	1 (5.3)	0 (0)	1 (7.7)	0 (0)	1 (7.7)
Not specified	3 (15.8)	1 (16.7)	2 (15.4)	1 (16.7)	2 (15.4)
Timing of cardiac event					
Time from SSc diagnosis, months, median (IQR)	4.5 (36) [1]	1.5 (27)	8.5 (36)[1]	0 (11.3)	17.5 (36)[1]
Simultaneous to SSc diagnosis, n (%)	6 (31.6)	2 (33.3)	4 (30.8)	4 (66.7)	4 (30.8)
Preceding SSc diagnosis, n(%)	2 (10.5)	1 (16.7)	1 (7.7)	2 (33.3)	0 (0)
Preceding Raynaud's, n (%)	1 (6.7) [4]	1 (16.6) [2]	0 (0)[2]	1 (20.0)[1]	0 (0)[3]
Preceding scleroderma, n (%)	2 (12.5) [3]	1 (16.6) [2]	1 (7.7)[1]	2 (40.0) [1]	0 (0) [2]
Follow-up time, months, median (IQR)	12.0 (10.5)	13.5 (11.5)	6 (11.6)	17.5 (29.0)	6.0 (11.1)
Main Cardiac diagnosis, n (%)					
Severe pericardial effusion	6 (31.6)	3 (50.0)	3 (23.1)		
with tamponade	5 (83.3)	3 (100.0)	2 (66.7)		
Acute Myocarditis	9 (47.4)	2 (33.3)	7 (53.8)		
Chronic inflammatory cardiomyopathy	2 (21.1)	1 (16.7)	3 (23.1)		

Superscript number = number of cases on which variable was not reported. Missing data treated as if absent clinical characteristic.

nostic and management algorithm for suspected primary cardiac involvement in SSc, informed by the clinical patterns observed in this cohort and supported by existing evidence. The pathway clearly distinguishes routine screening from diagnostic escalation and integrates recognised clinical, serological, and disease-related risk factors associated with cardiac involvement.

All patients undergo systematic evaluation for cardiac symptoms and recognised clinical "red flags," alongside physical examination and patient education regarding early cardiac manifestations. Baseline screening is performed annually and includes electrocardiography, cardiac biomarkers (hs-troponin and NT-proBNP/BNP), and transthoracic echocardiography, with parallel exclusion of alternative causes of cardiac dysfunction, including coronary artery disease, pulmonary arterial hypertension, scleroderma renal crisis, and infection[12,16].

Asymptomatic patients at low clinical risk continue routine annual surveillance. In contrast, asymptomatic patients with high-risk features or persistent clinical concern, such as diffuse cutaneous SSc, abnormal cardiac biomarkers, or disease characteristics associated with cardiac involvement are escalated to cardiovascular magnetic resonance (CMR) on a case-by-case basis.

TABLE III. Clinically suspected myocarditis criteria in patients with myocardial involvement

	Total – N (%) (N=13)	AM - N (%) (N=9)	CIC – N (%) (N=4)
Clinically suspected myocarditis	12 (92.3)	8 (88.9)	4 (100)
Clinical presentation			
Acute chest pain	0 (0)	0 (0)	0 (0)
New-onset or worsening of dyspnoea and/or fatigue	6 (46.2)	4 (44.4)	2 (50.0)
Subacute/chronic dyspnoea and/or fatigue	6 (46.2)	4 (44.4)	2 (50.0)
Palpitation and/or unexplained arrhythmia symptoms and/or syncope and/or aborted sudden cardiac death	5 (38.5)	4 (44.4)	1 (25.0)
Unexplained cardiogenic shock	3 (23.1)	3 (33.3)	0 (0)
Diagnostic criteria			
ECG / Holter/stress test features	6 (46.2) [4]	5 (55.6) [2]	1 (25.0) [2]
Elevated Troponin T / Troponin I	8 (61.5) [1]	6 (66.7) [1]	2 (50.0) [2]
Functional and structural abnormalities on echo/angiography/CMR)	8 (61.5)	5 (55.6)	3 (75.0)
Oedema and/or LGE of classical myocarditic pattern on CMR	9 (69.2) [2]	5 (55.6) [2]	4 (100)

Superscript number = number of cases on which variable was not reported. Missing data treated as if absent clinical characteristic. AM – acute myocarditis; CIC – chronic inflammatory cardiomyopathy; CMR - cardiac magnetic resonance; ECG – electrocardiogram; LGE – late gadolinium enhancement

Symptomatic patients or those with abnormal screening results undergo targeted CMR to assess myocardial inflammation, fibrosis, and ventricular function.

Endomyocardial biopsy (EMB) is reserved for selected cases and applied within a nuanced, risk-stratified framework. Given its invasive nature, EMB is not performed routinely nor when CMR findings are clearly diagnostic. In line with ESC guidance, EMB should be considered when ESC-defined high-risk clinical features are present and CMR findings are non-diagnostic or expected to influence management, following exclusion of coronary artery disease and alternative causes. High-risk scenarios include acute coronary syndrome–like presentations with troponin elevation and unobstructed coronary arteries, new-onset or rapidly progressive heart failure, recurrent heart failure exacerbations suggestive of inflammatory cardiomyopathy, and life-threatening presentations such as malignant ventricular arrhythmias, cardiogenic shock, or severe ventricular dysfunction[12].

This algorithm is informed by established risk factors for cardiac involvement in SSc reported in previous studies, including demographic factors (male sex, older age at disease onset), disease phenotype (diffuse cutaneous SSc, higher modified Rodnan skin score, digital ulcers, tendon friction rubs, myositis, lung involvement, late nailfold videocapillaroscopy patterns), and serological profiles (including anti–topoisomerase I, anti–RNA polymerase III, anti-Ku, anti-U3RNP, and anti-histone antibodies)[16]. These features have been associated with myocardial dysfunction, arrhythmias, pericardial disease, and abnormal cardiac imaging, and should inform clinical judgement when determining escalation beyond routine screening.

By combining baseline surveillance with dynamic risk stratification and selective use of advanced imaging and biopsy, this approach acknowledges the heterogeneity of SSc-related cardiac disease and avoids reliance on disease stage or a single diagnostic modality. Overall, the algorithm supports timely identification of clinically relevant cardiac involvement while minimising unnecessary investigations and invasive procedures, thereby enhancing both clinical applicability and patient safety.

DISCUSSION

This multicentre retrospective analysis, complemented by a literature review, provides a comprehensive overview of clinically significant primary heart involvement in SSc, with a specific focus on acute myocarditis (AM), chronic inflammatory cardiomyopathy (CIC), and pericardial disease. Our findings Our findings reinforce the early, heterogeneous, and often life-threatening nature of cardiac involvement in SSc. Integrating real-world cases from multiple tertiary centres with published reports allowed us to explore the clinical variability, diagnostic challenges, and prognostic implications of these

TABLE IV. Cardiac magnetic resonance imaging features in patients with myocardial involvement

	Total – N (%) (N=11)	AM – N (%) (N=7)	CIC – N (%) (N=4)
LGE	8 (72.7)	4 (57.1)	4 (100)
Myocardial oedema	4 (36.4) [3]	1 (28.6)[1]	2 (50) [2]
LV dysfunction	8 (72.7) [2]	5 (71.4) [2]	3 (75.0)
Pericardial effusion	6 (54.5) [5]	4 (57.1) [3]	2 (50) [3]

Superscript number = number of cases on which variable was not reported. Missing data treated as if absent clinical characteristic. AM – acute myocarditis; CIC – chronic inflammatory cardiomyopathy; LGE – late gadolinium enhancement; LV – left ventricle

TABLE V. Immunosuppressive treatment stratified by cardiac involvement.

	Total – N (%)	Pericardial involvement – N (%)	Myocardial involvement – N (%)	CIC – N (%)	AM – N (%)
Oral GCs	12 (63.2)	4 (66.7)	8 (61.5)	0 (0)	8 (88.9)
Pulse GCs	4 (21.1)	0 (0)	4 (30.8)	0 (0)	4 (44.4)
CYC	7 (36.8)	0 (0)	7 (53.8)	2 (50.0)	5 (55.6)
TCZ	3 (15.8)	0 (0)	3 (23.1)	2 (50.0)	1 (11.1)
MMF	2 (10.5)	2 (33.3)	0 (0)	0 (0)	0 (0)
AZA	2 (10.5)	0 (0)	2 (15.4)	0 (0)	2 (22.2)
IgEV	1 (5.3)	0 (0)	1 (7.7)	0 (0)	1 (11.1)

AM – acute myocarditis; AZA – azathioprine; CIC – chronic inflammatory cardiomyopathy; CYC – Cyclophosphamide; GCs – glucocorticoids; IgEV – Intravenous immunoglobulin; MMF - Mycophenolate mofetil; TCZ - tocilizumab

manifestations.

In 42% of cases, the cardiac event preceded or coincided with the diagnosis of SSc, corroborating earlier reports that cardiac involvement may represent an inaugural or early disease feature[1, 5, 18, 19]. Several patients presented with pericardial tamponade before developing Raynaud's phenomenon or cutaneous signs of SSc, highlighting the need to consider SSc within the differential diagnosis of unexplained pericardial or myocardial inflammation. Although tamponade dominated the pericardial presentations in our cohort, this should not be interpreted as representative of prevalence; tamponade remains extremely rare in SSc (~0.2%), and our enriched cohort reflects purposeful selection of clinically severe cases at participating centres.

Pericardiocentesis demonstrated exudative fluid in all pericardial cases, supporting an immune-mediated mechanism. Notably, only one patient fulfilled ESC criteria for acute pericarditis, underscoring that contemporary definitions may lack sensitivity for SSc-related inflammatory pericardial syndromes. The 2025 ESC Guidelines' concept of *inflammatory myopericardial syndrome*, recognising myocarditis and pericarditis as manifestations along a shared inflammatory spectrum, may offer a more appropriate framework for interpreting SSc cardiac involvement; however, these guidelines do not account for SSc-specific mechanisms such as microvascular dysfunction, fibrotic remodelling, or immune-mediated vasculopathy[12].

Stratification into AM and CIC was clinically informative. These phenotypes likely represent distinct yet overlapping points along a continuum of inflammation and fibrosis[6, 20]. AM tended to affect younger patients and often represented the first manifestation of SSc, consistent with active myocardial inflammation. CIC occurred later and in older individuals, supporting the hypothesis that cumulative subclinical injury and microvascular disease contribute to progressive fibrotic cardiomyopathy. Treatment responses appeared to differ between groups: inflammation-driven AM showed evidence of reversibility with immunosuppression—including corticosteroids, cyclophosphamide, and IL-6 inhibitors—whereas CIC appeared more refractory, consistent with fibrotic myocardial remodelling. One patient undergoing AHSCT demonstrated resolution of inflammatory changes, in line with evidence supporting AHSCT in selected cases of severe SSc heart involvement[23, 24]. These observations suggest that timely recognition and immunomodulatory therapy may be particularly impactful in AM, though therapeutic guid-

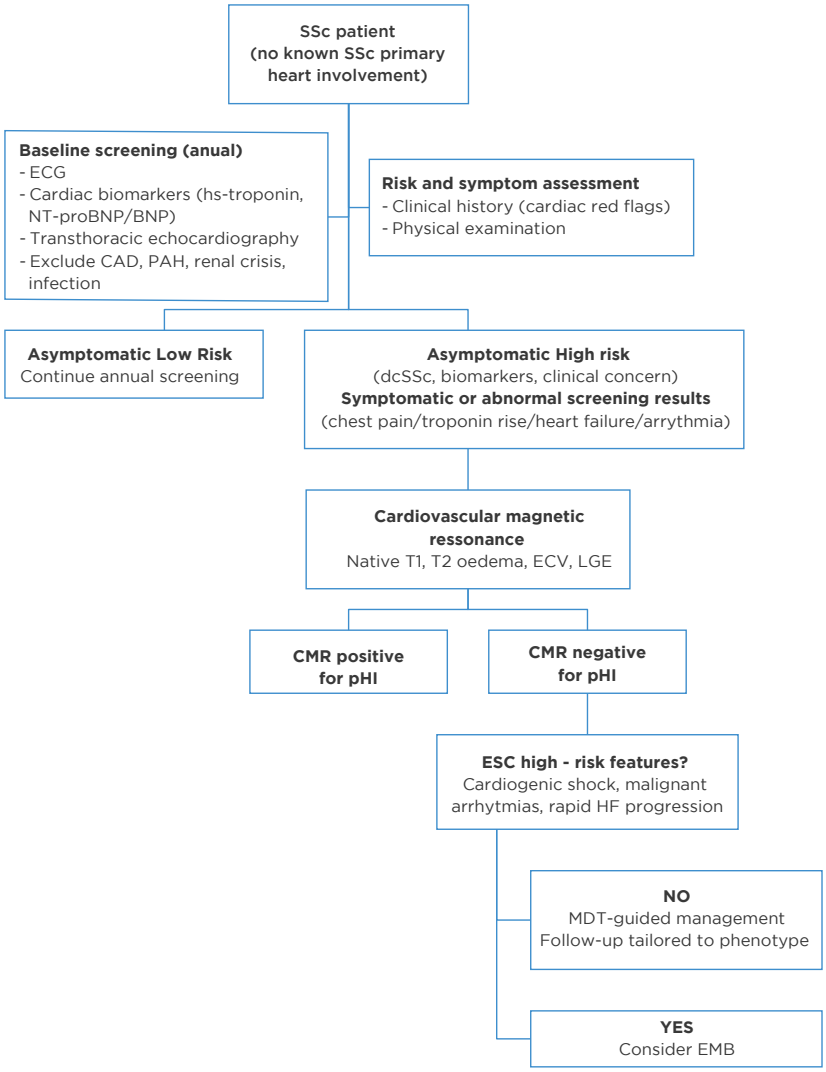

Figure 2. Risk-stratified diagnostic and management algorithm for suspected primary cardiac involvement in systemic sclerosis (SSc). SSc, systemic sclerosis; pHI, primary heart involvement; ECG, electrocardiography; NT-proBNP, N-terminal pro-brain natriuretic peptide; CAD, coronary artery disease; PAH, pulmonary arterial hypertension; CMR, cardiovascular magnetic resonance; T1, native T1 mapping; T2, T2 mapping; ECV, extracellular volume; LGE, late gadolinium enhancement; ESC, European Society of Cardiology; HF, heart failure; EMB, endomyocardial biopsy; MDT, multidisciplinary team; dcSSc, diffuse cutaneous systemic sclerosis.

ance remains empirical and based on limited evidence.

Importantly, substantial and clinically relevant phenotypic differences were observed between patients in our multicentre case series and those identified through the literature review. Literature-derived cases were older at both SSc diagnosis and cardiac event (mean age at cardiac event ~52 vs ~42 years), had a higher prevalence of diffuse cutaneous disease, and demonstrated markedly higher modified Rodnan skin scores, indicating more advanced cutaneous involvement. Despite this, the prevalence of anti–Scl-70 antibodies was lower in literature cases, an unexpected finding given the association between anti–Scl-70 positivity and diffuse disease. These differences likely reflect publication and referral bias, with literature cases enriched for advanced, established disease and late cardiac complications. In contrast, our cohort, derived from systematic adjudication across tertiary centres, captures earlier and more inflammatory cardiac presentations, often occurring close to or even before SSc diagnosis and in patients with less extensive skin involvement. Clinically, this suggests that significant cardiac involvement in SSc is not confined to advanced diffuse disease, and that reliance on skin extent or autoantibody profile alone may underestimate cardiac risk.

CMR was abnormal in most of the cases, especially in CIC, where late gadolinium enhancement (LGE) was consistently present. However, two biopsy-confirmed

AM cases lacked oedema or LGE on CMR. This discordance, previously described in myocarditis literature, likely reflects patchy or early inflammation below CMR resolution thresholds and underscores the limitations of imaging alone. These findings are consistent with previous studies showing the utility of LGE and T2-weighted sequences in differentiating active inflammation from fibrosis[8, 25, 26]. Nevertheless, the limitations of CMR must be acknowledged. Previous studies, including those by Lurz *et al.*, have demonstrated that the diagnostic performance of cardiac magnetic resonance (CMR) varies according to the clinical phenotype of myocardial involvement. The best diagnostic performance was observed in patients with suspected acute myocarditis, with a sensitivity of 81%, specificity of 71%, and overall accuracy of 79%, whereas CMR performance in suspected chronic inflammatory cardiomyopathy was substantially lower (sensitivity 63%, specificity 40%, accuracy 52%)[13,27]. Thus, while CMR remains central to non-invasive assessment, a normal or inconclusive CMR does not exclude clinically relevant inflammatory myocardial disease, particularly in SSc.

Accordingly, the role of endomyocardial biopsy (EMB) requires a nuanced, risk-stratified approach. Given its invasive nature, EMB should not be performed routinely nor when CMR findings are clearly diagnostic. In line with ESC and WSF/HFA guidance, EMB should be considered in patients with ESC-defined high-risk clinical presentations when CMR findings are non-diagnostic or inconclusive, following exclusion of coronary artery disease and alternative causes[12, 16]. High-risk scenarios include acute coronary syndrome–like presentations with troponin elevation and unobstructed coronaries, new-onset or rapidly progressive heart failure, recurrent heart failure exacerbations suggestive of inflammatory cardiomyopathy, and life-threatening presentations such as malignant ventricular arrhythmias, cardiogenic shock, or severe ventricular dysfunction. In our cohort, EMB provided definitive diagnosis in five cases of AM and contributed to CIC classification in one case, supporting its value when guided by clinical context rather than imaging alone.

Cardiac biomarkers complemented imaging and clinical assessment. Troponin elevation was common, particularly in AM, reinforcing its role as an accessible marker of myocardial injury and a useful trigger for further investigation in appropriate clinical settings. The relatively high proportion of male patients in our cohort (~32%) is also noteworthy and consistent with prior evidence that male sex is associated with more severe organ involvement and poorer prognosis in SSc, including cardiac disease[28,29].

This study benefits from detailed phenotyping, central adjudication, and rigorous exclusion of alternative causes of cardiac dysfunction, strengthening diagnostic specificity for SSc primary heart involvement. Nevertheless, limitations include its retrospective design, over-representation of severe cases, and heterogeneity introduced by combining multicentre cohort data with literature-derived cases. As such, analyses were intentionally descriptive, and findings should be interpreted as hypothesis-generating rather than inferential.

CONCLUSIONS

Clinically significant myocardial and pericardial involvement in systemic sclerosis is rare but often severe, frequently occurring early and occasionally preceding classical disease manifestations. Reliance on cardiac magnetic resonance alone may lead to under-recognition of inflammatory myocardial disease, particularly in early or focal presentations.

A key clinical implication is that endomyocardial biopsy should be considered in patients with ESC-defined high-risk clinical features when CMR findings are non-diagnostic or inconclusive, rather than applied routinely irrespective of imaging results. A clinically driven, risk-stratified diagnostic approach, integrating biomarkers, CMR, and selective biopsy, is essential for accurate phenotypic classification and timely initiation of immunomodulatory therapy.

Prospective multicentre studies with harmonised diagnostic algorithms are urgently needed to validate this approach, refine risk stratification, and improve outcomes in SSc-associated primary heart involvement.

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