Received: 26 March 2025 | Accepted: 14 June 2025

DOI: 10.1111/eci.70094

ORIGINAL ARTICLE

WILEY

First-line diagnostic tests to intercept primary heart involvement in systemic sclerosis: Clinical associations from the SPRING-SIR registry

Antonio Tonutti[1,2] | Francesca Motta[1,2] | Rossella De Angelis[3,4] | Edoardo Cipolletta[3] | Clodoveo Ferri[5,6] | Gianluigi Bajocchi[7] | Silvia Bellando-Randone[8] | Cosimo Bruni[8] | Martina Orlandi[6] | Giovanni Zanframundo[9] | Rosario Foti[10] | Giovanna Cuomo[11] | Alarico Ariani[12] | Edoardo Rosato[13] | Gemma Lepri[8] | Francesco Girelli[14] | Elisabetta Zanatta[15,16] | Silvia Laura Bosello[17] | Ilaria Cavazzana[18] | Francesca Ingegnoli[19] | Fabio Cacciapaglia[20] | Giuseppe Murdaca[21] | Giuseppina Abignano[22] | Giorgio Pettiti[23] | Alessandra Della Rossa[24] | Maurizio Caminiti[25] | Anna Maria Iuliano[26] | Giovanni Ciano[27] | Lorenzo Beretta[28] | Gianluca Bagnato[29] | Ennio Lubrano[30] | Ilenia De Andres[31] | Luca Idolazzi[32] | Marta Saracco[33] | Cecilia Agnes[34] | Corrado Campochiaro[35] | Marco Fornaro[36] | Federica Lumetti[6] | Amelia Spinella[6] | Luca Magnani[7] | Giacomo De Luca[35,36] | Veronica Codullo[9] | Elisa Visalli[10] | Carlo Iandoli[11] | Antonietta Gigante[13] | Greta Pellegrino[37] | Erika Pigatto[38] | Maria Grazia Lazzaroni[18] | Enrico De Lorenzis[17] | Gianna Mennillo[22] | Marco Di Battista[24] | Giuseppa Pagano-Mariano[25] | Federica Furini[39] | Licia Vultaggio[39] | Simone Parisi[40] | Clara Lisa Peroni[40] | Gerolamo Bianchi[41] | Enrico Fusaro[40] | Gian Domenico Sebastiani[26] | Marcello Govoni[39] | Salvatore D'Angelo[22,42] | Franco Cozzi[38] | Franco Franceschini[18] | Serena Guiducci[8] | Lorenzo Dagna[35,36] | Andrea Doria[15] | Dilia Giuggioli[6] | Valeria Riccieri[37] | Carlo Salvarani[43] | Florenzo Iannone[20] | Marco Matucci-Cerinic[35,36] | Carlo Selmi[1,2] | Maria De Santis[1,2] | on behalf of SPRING-SIR (Systemic Sclerosis PRogression INvestiGation group of the Italian Society for Rheumatology)

See Appendix for SPRING-SIR (Systemic Sclerosis PRogression INvestiGation group of the Italian Society for Rheumatology).

For affiliations refer to page 9.

Correspondence
Francesca Motta, Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy; Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Milan, Italy.
Email: francesca.motta2@humanitas.it

Abstract

Introduction: Primary heart involvement (pHI) is an overlooked and poorly characterised complication of systemic sclerosis (SSc), associated with the risk of heart failure, arrhythmia and death. Despite consensus definition by the World Scleroderma Foundation/Heart Failure Association (WSF/HFA), diagnostic criteria and risk factors remain poorly elucidated.

Methods: Out of 1922 patients in the Italian national SPRING registry, we excluded those with potentially confounding conditions according to WSF/HFA, and those with incomplete ECG or echocardiographic assessment, resulting in 600 subjects with clearly defined parameters to intercept SSc-pHI. Cross-sectional and longitudinal analyses were performed to identify factors associated with pHI.

Results: ECG and/or echocardiographic signs of SSc-pHI were identified in 25% of patients at enrollment and were associated with older age (OR 1.04; 95% CI 1.02–1.06), diffuse cutaneous SSc (OR 1.85; 95% CI 1.05–3.26) and intestinal symptoms (OR 1.79; 95% CI 1.03–3.08). Diastolic dysfunction (62%) and conduction disturbances (34%) were the most frequent phenotypes, while diffuse hypokinesia with reduced ejection fraction was the least common (3%). During follow-up, new-onset signs of pHI were observed in an additional 25% of patients, particularly in those with skeletal muscle involvement (HR 2.83; 95% CI 1.01–7.73).

Conclusions: pHI is a severe complication potentially affecting one-quarter of patients with SSc. Early detection is crucial, particularly in those with diffuse skin fibrosis, muscular involvement and intestinal manifestations.

KEYWORDS
autoimmunity, connective tissue disease, echocardiography, immunology, risk factors, systemic sclerosis

1 | INTRODUCTION

Primary heart involvement (pHI) is an often overlooked manifestation of systemic sclerosis (SSc) and is associated with the risk of arrhythmias, heart failure and sudden cardiac death.[1,2] Despite its prognostic implications, SSc-pHI remains poorly characterised. First, there are limited data on the prevalence and incidence of pHI in SSc, and considerable heterogeneity has been reported among studies, largely due to the different detection methods.[3,4] Second, despite consensus definition[5,6] and ongoing initiatives,[7] standard diagnostic criteria remain unavailable. Cardiac magnetic resonance (CMR) is the reference for detecting myocardial inflammation, fibrosis and microvascular alterations,[8,9] but its availability is limited to referral centres.[1] Nevertheless, SSc-pHI encompasses a spectrum of myocardial alterations, including functional and electrical abnormalities that can be detected through echocardiographic and ECG evaluation.[1,5] Third, while risk factors for other complications of SSc, such as interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are well known,[10,11] predictors of SSc-pHI remain elusive. A recent attempt to define risk factors for SSc-pHI was pursued in the European Scleroderma Trials and Investigation Cohort (EUSTAR), seeking validation.[12]

The SPRING (Systemic sclerosis PRogression INvestiGation) registry was established by the Italian Society for Rheumatology (SIR) in 2014 and represents one of the largest national multicentric datasets including demographic, clinical, laboratory and instrumental data on patients with SSc.[13] The aim of the present study is to evaluate the prevalence, incidence and risk factors of pHI, defined through specific ECG and echocardiographic alterations, in SSc patients within the SPRING cohort.

2 | METHODS

2.1 | Study design, data source and study setting

This was a retrospective, multicenter, nationwide cohort study. Data collection was conducted using the REDCap (Research Electronic Data Capture) platform. Clear

definitions of all variables were established a priori to minimise heterogeneity among the various centres participating in the SPRING study, and periodic quality checks were performed by the coordinators.[13] The study was approved by reference number OSS 15.10, Azienda Ospedaliera Universitaria Careggi (Firenze); participants gave informed consent to participate in the study before taking part. We extracted data from the SPRING registry on 15th July 2022.

2.2 | Population

Patients from the SPRING registry were included if they (i) were ≥18 years old at the time of enrolment, (ii) fulfilled the 2013 ACR/EULAR classification criteria for SSc,[13] (iii) had all ECG and echocardiographic parameters required for the definition of SSc-pHI clearly available (see below) and (iv) did not meet the following exclusion criteria: systemic arterial hypertension, diabetes mellitus, ischaemic heart disease, chronic pulmonary diseases (excluding SSc-ILD), PAH, echocardiographic evidence of pulmonary artery systolic pressure (PASP) ≥40 mmHg, renal impairment or a history of scleroderma renal crisis. In accordance with the definition of SSc-pHI,[5,6] exclusion criteria were designed to minimise interference from cardiac findings and potential overlapping conditions (including both comorbidities and SSc-related features) associated with myocardial alterations that could act as confounders.

Patients were included in the longitudinal analysis if they did not meet the SSc-pHI criteria at baseline and had at least one follow-up visit at 12 (±2) months.

2.3 | Exposure

The exposures of interest included demographic and clinical variables, laboratory data (autoantibodies and routine chemistries), pulmonary function tests (predicted value of forced vital capacity—FVC, and diffusion capacity for carbon monoxide—DLCO), and high-resolution chest computed tomography (HRCT) scan findings. Information on previous and current treatments was recorded, including immunosuppressants (cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, rituximab, tocilizumab), endothelin receptor antagonists (bosentan, macitentan), phosphodiesterase-5 inhibitors (sildenafil, tadalafil), intravenous iloprost, calcium channel blockers and antiplatelet agents.

2.4 | Outcomes

The primary outcome was the presence of at least one of the following ECG or echocardiographic domains suggestive of SSc-pHI: (i) non-ischemic hypokinesia, defined as left ventricular (LV) ejection fraction (LVEF) <50% or diffusely reduced wall thickening with reduced systolic inward excursion, either diffuse or not related to coronary artery territories; (ii) LV dilatation; (iii) LV diastolic dysfunction[14]; (iv) arrhythmia, including atrial/auricular arrhythmias, ventricular tachycardia, a burden of ventricular ectopic beats judged as clinically relevant, or the need for antiarrhythmic therapy[15,16]; (v) conduction block in the absence of other explaining causes.

2.5 | Follow-up

In the SPRING registry, visits were recorded annually (±2 months) after the baseline visit, with a maximum follow-up duration of 5 years. In this study, each patient was followed from the date of enrolment in the SPRING registry until the occurrence of the primary outcome or the date of the last available visit in the registry.

2.6 | Statistical analysis

Continuous variables were reported as means (standard deviation) or medians (interquartile range, IQR), depending on their distribution, while categorical variables were reported as proportions and percentages. For variables with missing data, the prevalence of which is reflected by the denominators in the tables, statistical analysis was performed exclusively on patients with complete data for those variables.

A cross-sectional analysis was conducted to identify factors associated with SSc-pHI at baseline. Categorical variables were compared between groups using the chi-square test or Fisher's exact test, while continuous variables were compared using the *t*-test or Mann–Whitney *U*-test, as appropriate. The Benjamini-Hochberg correction was applied for multiple testing. Logistic regression was used to assess factors associated with SSc-pHI; variables were included in the multivariable model based on clinical judgement or if they showed a p-value <.10 in the univariable analysis.

Survival analysis was performed to evaluate the incidence of SSc-pHI in patients with at least one follow-up visit after baseline. Cox proportional hazards regression was applied to identify candidate risk factors for the development of SSc-pHI during follow-up, with the multivariable model adjusted for covariates considered clinically relevant or showing $p < .10$ in the univariable analysis.

Since variables included in the SSc-pHI definition were not mutually exclusive, correlations between these variables and other relevant echocardiographic parameters

available in the registry were calculated using Spearman's correlation. The *p*-values for each pair of variables were calculated using Spearman's significance test, with *p*-values less than .05 indicating statistically significant correlations.

Statistical significance was defined as *p*-values <.05. All analyses were performed using RStudio (Version 2024.12.0+467).

3 | RESULTS

3.1 | Patients' characteristics

Figure 1 illustrates the patient selection process: out of 1922 patients with SSc included in the SPRING database, 677 were excluded due to the presence of at least one exclusion criterion, and 645 were further excluded due to the absence of information on at least one of the five ECG or echocardiographic domains used for SSc-pHI. This resulted in 600 patients being included in the baseline risk factor analysis.

The characteristics of the baseline patient cohort are presented in Table 1. The cohort was predominantly female (89.8%), with a median age at SSc onset of 45 years (IQR 35–55) and a median disease duration of 8 years (IQR 4–14). In terms of organ manifestations, 22% of patients had dcSSc, 43% had ILD and 24% had digital ulcers. Musculoskeletal manifestations, defined through physical examination as per clinical practice, included arthritis in 12%, muscle weakness in 16% and muscle atrophy in 6.5%. Gastrointestinal involvement was observed in 53% of patients with oesophageal symptoms (gastro-oesophageal reflux, oesophageal dysphagia) and in 22% with intestinal symptoms (diarrhoea, constipation, bloating, or malabsorption syndrome). Anti-topoisomerase I antibodies were positive in 41% of patients, and anticentromere antibodies were positive in 39%.

3.2 | Prevalence and characteristics of patients with signs of SSc-pHI at baseline

At the time of enrolment in the SPRING registry, 149 out of 600 patients (25%) were classified as having SSc-pHI according to the adopted definition. Diastolic dysfunction was the most common alteration, being reported in 93/149 (62%) patients, followed by conduction block in 50/149 (34%), and arrhythmia in 16/149 (11%). LV dilation was reported in 13/149 (9%) patients, and non-ischaemic hypokinesia in 4/149 (3%). As shown in the Venn diagram in Figure 2A, these alterations were not mutually exclusive. The median value of LVEF was 60% (IQR 60%–65%) in patients with SSc-pHI and did not significantly differ from that of patients without SSc-pHI. Echocardiography-assessed PASP values were slightly but significantly higher in patients with SSc-pHI [27 mmHg (IQR 18–30)] compared to those without SSc-pHI [25 mmHg (IQR 15–30); $p < .001$]. Remarkably, all PASP values were within the normal range according to the adopted inclusion criteria. The prevalence of pericardial effusion, as estimated by echocardiography, was similar between the two groups (7% vs. 5%; $p = .343$).

Results of the Spearman's correlation analysis are shown in Figure 2B, accounting for domains included in the SSc-pHI definition, along with other available relevant echocardiographic parameters, including the presence of pericardial effusion, LVEF and PASP values. Weak but significant positive

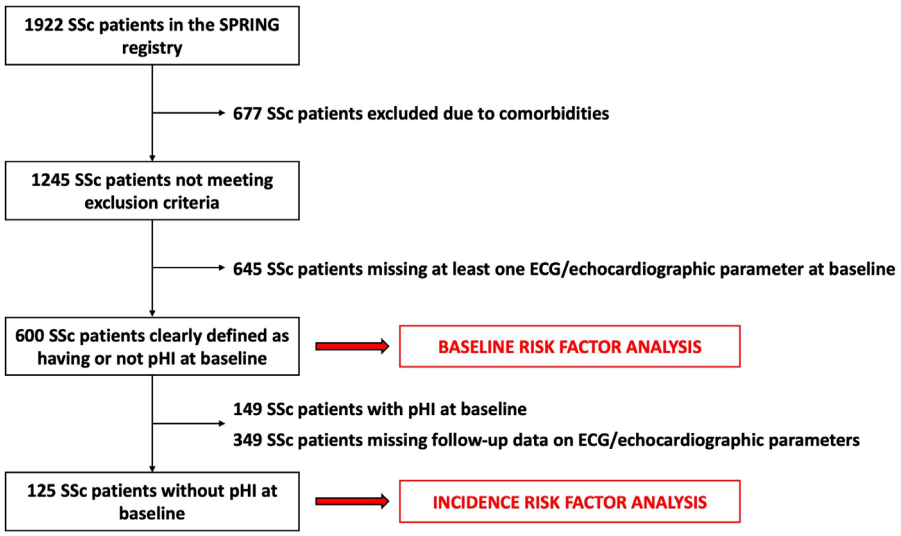

FIGURE 1 Selection of the study population, according to the established criteria. pHI, Primary heart involvement; SSc, Systemic sclerosis.

TABLE 1 Cross-sectional comparison of patients with SSc with and without ECG and echocardiographic signs of pHI at baseline.

Variable	Whole cohort *N* = 600	SSc-pHI *N* = 149	SSc without pHI *N* = 451	*p*-Value	Adj. *p*
Demographic features					
Age at SSc onset, years	45 [35–55]	50.5 [38–59]	43 [34–53]	<.001*	.004*
Duration, years	8 [4–14]	9 [4–16]	8 [4–14]	.123	.289
Female sex	539/600 (90%)	133/149 (89.3%)	406/451 (90%)	.912	.988
Smoking	115/540 (21%)	31/126 (25%)	84/414 (20%)	.362	.589
BMI, kg/m^2	23.2 [21.1–25.6]	24.3 [21.5–26.2]	23.2 [21.3–25.6]	.142	.309
Clinical features					
dcSSc	129/595 (22%)	41/147 (28%)	88/448 (20%)	.047*	.165
mRSS	4 [2–9]	5 [2–12]	4 [2–9]	.035*	.138
Pitting scars	308/597 (22%)	84/149 (56%)	224/448 (50%)	.210	.372
Digital ulcers	144/599 (24%)	36/149 (24%)	108/450 (24%)	1.000	1.000
Teleangectasia	386/597 (65%)	111/148 (75%)	275/449 (61%)	.003*	.032*
Calcinosis	75/597 (13%)	25/148 (17%)	50/449 (11%)	.091	.274
Tendon friction rubs	76/598 (13%)	24/149 (16%)	52/449 (12%)	.195	.363
Muscle weakness	95/597 (16%)	36/149 (24%)	59/448 (13%)	.002*	.030*
Muscle atrophy	39/596 (6.5%)	17/148 (12%)	22/448 (5%)	.009*	.070
Arthritis	73/595 (12%)	24/147 (16%)	49/448 (11%)	.113	.289
Oesophageal symptoms	317/598 (53%)	92/149 (62%)	225/449 (50%)	.018*	.077
Intestinal symptoms	132/598 (22%)	48/149 (32%)	84/449 (19%)	<.001*	.018*
Sicca syndrome	196/597 (33%)	61/148 (41%)	135/449 (30%)	.016*	.077
NTproBNP >125 pg/mL	29/64 (45%)	10/19 (53%)	19/45 (42%)	.625	.805
ILD at HRCT	257/600 (43%)	77/149 (52%)	180/451 (40%)	.016*	.077
DLCO, %predicted	71 [60–83]	65 [50–79.5]	71 [59–83]	.015*	.077
FVC, %predicted	103 [90–117]	97.4 (23.8)	102 (20.8)	.057	.185
Autoantibodies					
ACA	233/600 (39%)	50/149 (34%)	183/451 (41%)	.154	.315
Anti-TOPO1	246/600 (41%)	60/149 (40%)	186/451 (41%)	.910	.988
Anti-RNAPOL3	8/600 (1.3%)	4/149 (3%)	4/451 (1%)	.110	.289
Anti-SSA	64/600 (11%)	13/149 (9%)	51/451 (11%)	.464	.646
ANA nucleolar	103/600 (17%)	25/149 (17%)	78/451 (17%)	.984	1.000
Therapeutic exposure					
Glucocorticoids	87/547 (16%)	19/137 (14%)	68/410 (17%)	.537	.722
Cyclophosphamide	68/533 (13%)	16/138 (12%)	52/395 (13%)	.743	.878
Methotrexate	93/537 (17%)	27/135 (20%)	66/402 (16%)	.412	.643
Azathioprine	65/530 (12%)	17/133 (13%)	48/397 (12%)	.954	1.000
Mycophenolate mofetil	85/533 (16%)	28/137 (20%)	57/396 (14%)	.126	.289
Rituximab	35/529 (6.6%)	13/137 (9.5%)	22/392 (5.6%)	.170	.332
Tocilizumab	8/524 (1.5%)	3/135 (2.2%)	5/389 (1.3%)	.431	.644
ERA	179/544 (33%)	43/139 (31%)	136/405 (34%)	.640	.805
PDE5-inhibitors	23/527 (4.4%)	8/136 (6%)	15/391 (4%)	.446	.644
Calcium channel blockers	395/569 (69%)	104/141 (74%)	291/428 (68%)	.236	.401
Iloprost	358/583 (61%)	87/146 (60%)	271/437 (62%)	.672	.820
Antiplatelet agents	349/571 (61%)	90/144 (63%)	259/427 (61%)	.770	.882

Abbreviations: ACA, anticentromere autoantibodies; ANA, antinuclear antibodies; anti-TOPO1, anti-Topoisomerase-I; anti-RNAPOL3, anti-RNA polymerase III; BMI, body mass index; dcSSc, diffuse cutaneous systemic sclerosis; DLCO, diffusion capacity of carbon monoxide; ERA, endothelin receptor antagonists; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; mRSS, modified Rodnan skin score; PDE5, phosphodiesterase 5; SSc, systemic sclerosis; SSc-pHI, systemic sclerosis-associated primary heart involvement.

*p-value < 0.05

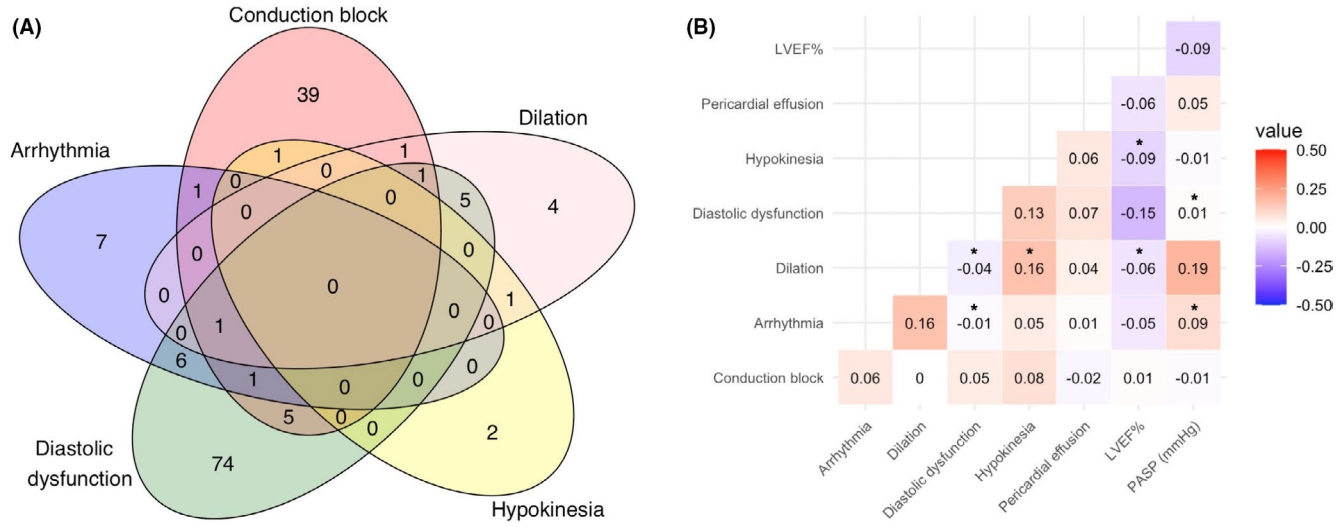

FIGURE 2 Echocardiographic and ECG characteristics defining SSc-pHI in the SPRING cohort. (Panel A) presents a Venn diagram illustrating the distribution of SSc-pHI-defining alterations at baseline, highlighting the absence of mutual exclusivity among different domains. (Panel B) displays the correlation matrix of clinically relevant echocardiographic and ECG alterations in patients with SSc-pHI. This includes the five defining domains (non-ischemic hypokinesia, LV dilation, diastolic dysfunction, conduction block and arrhythmia), along with pericardial effusion, left ventricular ejection fraction (LVEF, %) and pulmonary artery systolic pressure (PASP, mmHg) as estimated by echocardiography. Spearman's rho correlation coefficients are reported within the matrix cells, with statistically significant correlations ($p < .05$) indicated by asterisks (*).

correlations were found between increasing PASP and arrhythmia, increasing PASP and diastolic dysfunction, and LV dilation and non-ischaemic hypokinesia. On the other hand, diastolic dysfunction negatively correlated with LV dilation and arrhythmia. Unsurprisingly, lower LVEF correlated with LV dilation and hypokinesia.

3.3 | Risk factors for signs of SSc-pHI at baseline

The cross-sectional comparison between patients with and without pHI is presented in Table 1. Patients with SSc-pHI were older at the onset of the first non-Raynaud's symptom [median age 50.5 years (IQR 38–59) vs. 44 years (IQR 35–54); $p = .004$] and tended to have more frequently dcSSc (27.9% vs. 19.6%) and ILD (51.7% vs. 39.9%), although these clinical features did not reach statistical significance after adjusting for multiple comparisons. Skin thickening, as measured by the modified Rodnan skin score (mRSS), was comparable between the two groups: 5 (IQR 2–12) and 4 (IQR 2–9), respectively. Pulmonary function tests revealed slightly lower values of FVC and DLCO in patients with SSc-pHI, but these differences did not reach statistical significance after correction. Telangiectasias were more frequently observed in patients with SSc-pHI compared to the other group (75% vs. 61.2%; $p = .032$). Additionally, these patients more often reported muscle weakness (24.2% vs. 13.2%; $p = .030$) and muscle atrophy (11.5% vs. 4.9%; $p = .070$). Gastrointestinal involvement was more common in patients with signs of SSc-pHI, particularly intestinal symptoms (32.2% vs. 18.7%; $p = .018$), with a similar trend observed for oesophageal involvement and sicca syndrome, although these did not reach statistical significance. Exposure to various immunosuppressive and vasoactive treatments did not differ significantly between patients with and without signs of SSc-pHI.

In the multivariable logistic regression model (adjusted for age at SSc onset, sex and disease duration), the risk of finding signs of SSc-pHI was more pronounced in patients with dcSSc (OR 1.85; 95% CI: 1.05–3.26; $p = .033$), intestinal symptoms (OR 1.79; 95% CI: 1.03–3.08; $p = .038$) and increasing age at SSc onset (OR 1.04; 95% CI: 1.02–1.06; $p < .001$). The other covariates did not show statistical significance (Figure 3; Table S1).

3.4 | Incidence and risk factors incident SSc-pHI

Out of 451 patients without SSc-pHI at baseline, follow-up data on the five echocardiographic and ECG parameters included in the pHI definition were available for 125 subjects. Among them, 31 new cases of SSc-pHI were recorded, resulting in a cumulative incidence of 25%. Specifically, 20 (65%) new cases were diagnosed within the 12-month follow-up, 7 (22%) within the 24-month follow-up, and 4

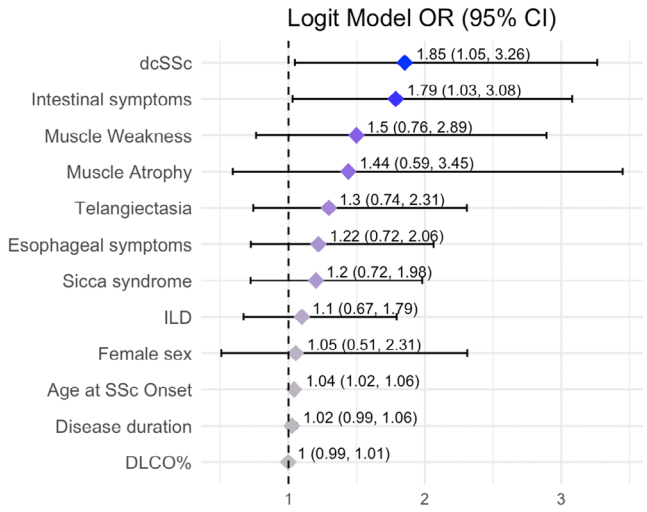

FIGURE 3 Odds ratios (OR) for covariates included in the multivariable logistic regression model assessing the risk of SSc-pHI at baseline in patients with SSc. dcSSc, Diffuse cutaneous SSc; DLCO, Diffusion capacity of carbon monoxide; ILD, Interstitial lung disease; OR (95% CI), Odds ratio (95% confidence interval); pHI, Primary heart involvement; SSc, Systemic sclerosis.

(13%) within the 36-month follow-up. Survival analysis of incident cases of SSc-pHI is summarised in the Kaplan–Meier curve in Figure S1. Overall mortality did not differ between patients with and without incident SSc-pHI, with two and six deaths observed during the follow-up, respectively.

Table 2 summarizes the results of the Cox proportional hazards regression model assessing risk factors for incident SSc-pHI. In both the univariable and multivariable models (adjusted for age at SSc onset, disease duration and sex), muscle atrophy was confirmed as the only risk factor for new onset of signs of SSc-pHI, with a hazard ratio (HR) of 2.83 (95% CI 1.01–7.73; $p = .043$). Treatment exposure did not seem to influence the risk of developing incident SSc-pHI (Table S2).

4 | DISCUSSION

We report a prevalence of SSc-pHI, defined through selected echocardiographic and ECG alterations not

TABLE 2 Results of the univariable and multivariable Cox proportional hazards model assessing risk factors for incident onset of ECG and echocardiographic signs of SSc-pHI in the analysed cohort.

	Univariable Cox model			Multivariable Cox model		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age at SSc onset	1.00	.97–1.03	.913	1.02	.98–1.05	.338
Disease duration	1.03	.99–1.08	.148	1.05	.99–1.10	.111
Sex	.63	.22–1.81	.391	.97	.21–2.36	.562
Smoke	.64	.22–1.85	.408			
dcSSc	1.16	.53–2.52	.714			
Pitting scars	1.55	.63–3.78	.339			
Digital ulcers	1.62	.80–3.30	.179			
Telangectasia	.80	.38–1.71	.572			
Calcinosis	1.76	.75–4.09	.191			
Tendon friction rubs	.79	.30–2.05	.622			
ILD	1.81	.88–3.72	.104			
Muscle weakness	1.06	.46–2.46	.894			
Muscle atrophy	2.62	1.01–6.84	.048	2.83	1.01–7.73	.043
Arthritis	.81	.24–2.67	.727			
Oesophageal symptoms	1.40	.66–2.98	.380			
Intestinal symptoms	1.46	.69–3.10	.325			
Sicca syndrome	.88	.43–1.81	.720			
ACA	.93	.44–1.94	.842			
Anti-TOPO1	.97	.48–1.96	.926			
Anti-SSA	.90	.31–2.58	.839			

Abbreviations: ACA, anticentromere autoantibodies; anti-TOPO1, anti-Topoisomerase-I; dcSSc, diffuse cutaneous systemic sclerosis; ILD, interstitial lung disease.

otherwise explainable, reaching 25% in a large multicentric national Italian cohort of patients with SSc, with a similar cumulative incidence over a five-year follow-up. These alterations are not mutually exclusive within each patient and show weak but occasionally significant correlations. To support patient stratification according to different risk profiles, we identified disease features and phenotypes specifically associated with prevalent and incident SSc-pHI, namely dcSSc and intestinal involvement for the former and skeletal muscle atrophy for the latter.

Our findings on the prevalence of SSc-pHI, based on the adopted definition, align with previous studies.[3,17] Notably, previous research confirmed the correlation between such alterations and CMR findings.[5,18–20] In the absence of established classification criteria, we acknowledge that the adopted criteria may underestimate the burden of CMR-detected abnormalities that do not lead to electrical or echocardiographic alterations,[18] while potentially overestimating pHI in specific scenarios, primarily in ageing populations. However, by excluding major comorbidities and conditions that could lead to confounding cardiac disease, our results likely reflect alterations primarily attributable to SSc.[5,6] These findings also reflect a real-world clinical scenario, underscoring the need for a treatable-trait approach in patients with cardiac alterations suggestive of SSc-pHI.[21] In this regard, efforts to implement and integrate CMR data should be prioritised.

From a precision and stratified medicine perspective, we identified specific disease features as risk factors for ECG or echocardiographic alterations suggesting SSc-pHI. Prevalent SSc-pHI was associated with age, dcSSc and intestinal symptoms, while the incidence of SSc-pHI was higher in patients with skeletal muscle atrophy. Our findings on the association between dcSSc and pHI align with previous evidence from monocentric and national cohorts adopting similar inclusion criteria.[22,23] Interestingly, while this observation was not confirmed in patients with CMR-defined subclinical SSc-pHI, an association with increased skin thickness (measured as mRSS) was reported.[19] Thus, while acknowledging the risk of pHI across different skin subsets,[24] we emphasize the need for particular attention in patients with more extensive skin fibrosis. While the association between intestinal symptoms and SSc-pHI remains unclear, our findings corroborate recent observations from the EUSTAR cohort.[12] Although elucidating the mechanisms underlying this association is beyond the scope of the present research, our results may support the well-theorized existence of a 'gut-heart' axis[25] even in SSc. We confirm muscle involvement, particularly in the form of muscle atrophy, as a significant predictor of SSc-pHI, consistent with previous reports.[12,22] Finally and in agreement with several previous studies,[12,19,22] older age was associated with an increased risk of SSc-pHI. Importantly, the effect of age appears to be independent of concurrent comorbidities potentially affecting cardiac function, as per our exclusion criteria.

In our cohort, LV diastolic dysfunction and conduction defects were the most common alterations. Overall, the distribution of alterations defining SSc-pHI was similar to that reported in some previous studies,[12,26] but lower compared to others.[27–29] This discrepancy may be due to the strict exclusion criteria adopted, which aimed to eliminate potential confounders (including comorbidities and SSc manifestations) that could be responsible for the observed abnormalities.[28,30] Most importantly, caution should also be exercised regarding the potential confounding role of aging, despite showing consistent impact across several cohorts of patients evaluated for SSc-pHI.

Among the strengths of our study, SPRING represents one of the largest multicentric SSc cohorts, characterised by detailed clinical profiling and robust follow-up. Comprehensive data recording, standardisation of diagnostic labels, statistical adjustment for multiple testing, confounders, and covariates helped minimise bias. Strict inclusion and exclusion criteria were adopted to eliminate comorbidities or complications that could confound the assessment of cardiac alterations, according to the consensus definition of SSc-pHI.[5,6] Notably, patients were included in the analysis only if complete information was available for each ECG and echocardiographic variable considered in the adopted definition of SSc-pHI.

We also must acknowledge some limitations beyond the retrospective nature of the study. First, the criteria adopted for SSc-pHI were based on data collection predating the consensus definition.[5] Stringent exclusion criteria were applied to minimise potential interference from secondary causes of heart involvement, but we acknowledge that this can also limit our findings to a select patient population. Additionally, the marked female predominance, while typical of an SSc cohort, restricts the generalisability of our findings to male patients. The absence of CMR data may have led to an underestimation of myocardial alterations not associated with functional or ECG abnormalities. Overestimation of cardiac abnormalities unrelated to SSc could have resulted in misclassification bias, particularly in the case of age-related changes or subclinical ischaemic heart disease, which warrant further investigation. While CMR plays a central role in characterising SSc-pHI, its availability is largely restricted to referral centres. Most importantly, efforts should be made to validate the predictive role of our findings on first-line diagnostic modalities in patients with CMR-confirmed SSc-pHI. Second, since right heart catheterisation is performed to exclude PAH in only a minority of SSc patients, we used PASP ≥40 mmHg on echocardiography as an

additional exclusion criterion. This may have led to the inadvertent omission of cases of pulmonary hypertension secondary to SSc-pHI. Notably, we observed higher PASP values (even within the normal range) in patients with SSc-pHI compared to those without, consistent with findings from other cohorts.[22] Third, longitudinal data were available for only a subset of patients, with significant loss to follow-up and heterogeneous follow-up durations, limiting the power of our analysis. Therefore, selection bias should be acknowledged in the longitudinal cohort, as it may have contributed to an increased incidence of SSc-pHI. Sample size at follow-up was reduced, and this can potentially lead to missing information since patients who developed severe SSc-pHI might have been missed from the analysis because they died before being diagnosed with cardiac disease. In the follow-up population, two deaths were observed in patients with incident SSc-pHI, while six deaths occurred in the counterpart, resulting in a non-statistically significant difference; however, the sample size limited our ability to estimate the survival in the two subsets. Fourth, the proportion of missing data for natriuretic peptides prevented their inclusion in the analysis, while serum troponins were not recorded in SPRING. According to the registry case report form, a detailed breakdown of the observed alterations was not available, limiting the assessment of the various nuances of these abnormalities (e.g. degree of conduction blocks, severity of arrhythmias) which could have provided important prognostic information; further focused studies are warranted on this point. Similarly, muscle involvement was assessed solely through clinical examination, which could introduce measurement bias. In our analysis, immunosuppressive and vasoactive treatments were not associated with prevalent and incident SSc-pHI alterations, despite the retrospective design and the associated confounding bias preventing us from drawing any conclusion in this regard. Lastly, as the SPRING registry includes multiple referral centres across Italy, referral bias may have led to the selection of a cohort with more severe disease, potentially overestimating the prevalence of pHI in the general SSc population. Leveraging this potentially 'higher risk' cohort, we identified risk factors to be considered for all patients referring to Rheumatology units.

In conclusion, by adopting an ECG- and echocardiography-based definition of SSc-pHI in line with consensus recommendations, we identified a prevalence of SSc-pHI reaching 25% in a large, multicenter Italian cohort. This complication was more frequent in older patients and in those with dcSSc, intestinal involvement and muscle atrophy. Integration of CMR data for the detection and correlation of myocardial fibrosis, inflammation and microvascular changes could enable earlier diagnosis and improved risk stratification. This approach may further refine patient selection for targeted management strategies,[31] enhancing our ability to identify those most at risk for specific SSc-pHI phenotypes.

AUTHOR CONTRIBUTIONS

Conceptualization and methodology: A. Tonutti, F. Motta, C. Selmi, M. De Santis. Research and data curation; Writing – revision and editing: A. Tonutti, F. Motta, R. De Angelis, E. Cipolletta, C. Ferri, G. Bajocchi, S. Bellando-Randone, C. Bruni, M. Orlandi, G. Zanframundo, R. Foti, G. Cuomo, A. Ariani, E. Rosato, G. Lepri, F. Girelli, E. Zanatta, S. L. Bosello, I. Cavazzana, F. Ingegnoli, F. Cacciapaglia, G. Murdaca, G. Abignano, G. Pettiti, A. Della Rossa, M. Caminiti, A. M. Iuliano, G. Ciano, L. Beretta, G. Bagnato, E. Lubrano, I. De Andres, L. Idolazzi, M. Saracco, C. Agnes, C. Campochiaro, M. Fornaro, F. Lumetti, A. Spinella, L. Magnani, G. De Luca, V. Codullo, E. Visalli, C. Iandoli, A. Gigante, G. Pellegrino, E. Pigatto, M. G. Lazzaroni, E. De Lorenzis, G. Mennillo, M. Di Battista, G. Pagano-Mariano, F. Furini, L. Vultaggio, S. Parisi, C. L. Peroni, G. Bianchi, E. Fusaro, G. D. Sebastiani, M. Govoni, S. D'Angelo, F. Cozzi, F. Franceschini, S. Guiducci, L. Dagna, A. Doria, D. Giuggioli, V. Riccieri, C. Salvarani, F. Iannone, M. Matucci-Cerinic, C. Selmi, M. De Santis. Data analysis: A. Tonutti, F. Motta, R. De Angelis, E. Cipolletta, M. De Santis. Writing – original draft: A. Tonutti, F. Motta, C. Selmi, M. De Santis, C. Ferri, R. De Angelis, M. Matucci-Cerinic.

AFFILIATIONS

[1]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy
[2]Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Milan, Italy
[3]Rheumatology Unit, Department of Clinical and Molecular Sciences, Polytechnic University of Marche, Ancona, Italy
[4]IRCSS INRCA, Ancona, Italy
[5]Rheumatology Clinic 'Madonna dello Scoglio', Cotronei, Crotone, Italy
[6]Department of Medical and Surgical Sciences for Children and Adults, University Hospital of Modena and Reggio Emilia School of Medicine, Modena, Italy
[7]Rheumatology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
[8]Division of Rheumatology, Department of Experimental and Clinical Medicine, AOU Careggi, University of Florence, Florence, Italy
[9]Division of Rheumatology, IRCCS Foundation Policlinico San Matteo, Pavia, Italy
[10]Reumatology Unit, AOU Policlinico San Marco, Catania, Italy
[11]Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy
[12]Department of Medicine, Internal Medicine and Rheumatology, Azienda Ospedaliero Universitaria di Parma, Parma, Italy
[13]Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy
[14]Rheumatology Unit, Ospedale GB Morgagni, AUSL Romagna, Forlì, Italy

[15]Department of Medicine, University of Padua, Padova, Italy
[16]Department of Cardiac, Thoracic, and Vascular Sciences and Public Health, Padova University Hospital, Padova, Italy
[17]Division of Rheumatology, Catholic University of the Sacred Heart, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[18]Rheumatology and Clinical Immunology, ASST Spedali Civili of Brescia; Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
[19]Division of Clinical Rheumatology, ASST Pini, Department of Clinical Sciences & Community Health, Research Center for Adult and Pediatric Rheumatic Diseases, Research Center for Environmental Health, Università Degli Studi di Milano, Milan, Italy
[20]Rheumatology Unit, Department of Precision and Regenerative Medicine, Area Jonica (DiMePRe-J), University of Bari, Bari, Italy
[21]Department of Internal Medicine, University of Genoa, Genoa and IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[22]Department of Health of Science, University of Basilicata, Potenza, Italy
[23]Rheumatology Unit, S. Croce e Carle Hospital, Cuneo, Italy
[24]Department of Rheumatology, University of Pisa, Pisa, Italy
[25]Departmental Rheumatology Unit, Grande Ospedale Metropolitano, Reggio Calabria, Italy
[26]Rheumatology Unit, San Camillo–Forlanini Hospital, Rome, Italy
[27]Local Health Department, Ariano Irpino Hospital, Avellino, Italy
[28]Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico di Milano, Milan, Italy
[29]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[30]Department of Rheumatology, University of Molise, Campobasso, Italy
[31]Rheumatology Unit, Azienda Ospedaliera di Rilievo Nazionale Ed Alta Specializzazione Garibaldi, Catania, Italy
[32]Rheumatology Section, Department of Medicine, University of Verona, Verona, Italy
[33]Rheumatology Unit, Mauriziano-Umberto I Hospital, Turin, Italy
[34]Department of Medicine, Division of Rehabilitation, Turin, ASL TO5, Carmagnola, Italy
[35]Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), & Inflammation, Fibrosis and Ageing Initiative (INFLAGE), IRCCS San Raffaele Hospital, Milan, Italy
[36]Vita-Salute San Raffaele University, Milan, Italy
[37]Department of Clinical, Internal, Anesthesiologic and Cardiological Sciences, Sapienza University of Rome, Rome, Italy
[38]Department of Medicine, Villa Salus Hospital, Venice, Italy
[39]Rheumatology Unit, Department of Medical Sciences, University of Ferrara and Azienda Ospedaliera-Universitaria S. Anna di Ferrara, Ferrara, Italy
[40]Rheumatology Unit, Azienda Ospedaliera Universitaria Città Della Salute e Della Scienza, Turin, Italy
[41]Rheumatology Unit, Department of Medical Specialities, Local Health Trust 3, Genoa, Italy
[42]Rheumatology Institute of Lucania (IReL) and Rheumatology Department of Lucania, San Carlo Hospital, Potenza, Italy
[43]Azienda USL-IRCCS di Reggio Emilia and Università di Modena e Reggio Emilia, Reggio Emilia, Italy

ACKNOWLEDGEMENTS

This work was partially supported by "Ricerca Corrente" of the Italian Ministry of Health for IRCCS Humanitas Research Hospital.

CONFLICT OF INTEREST STATEMENT

CB: consultant for Boehringer Ingelheim; Grant/research support from: Gruppo Italiano Lotta alla Sclerodermia (GILS), European Scleroderma Trials and Research Group (EUSTAR), Foundation for Research in Rheumatology (FOREUM), Scleroderma Clinical Trials Consortium (SCTC), Scleroderma Research Foundation (SRF), Novartis Foundation for Bio-Medical Research, EMDO Foundation. Educational grants from AbbVie and Wellcome Trust. Congress support from Boehringer Ingelheim. The other authors have no relevant disclosure to declare.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article or uploaded as Appendix S1.

ORCID

Antonio Tonutti https://orcid.org/0009-0000-9534-6853
Giovanna Cuomo https://orcid.org/0000-0002-4292-3589
Marco Fornaro https://orcid.org/0000-0003-1716-7432
Marco Di Battista https://orcid.org/0000-0002-4788-5729
Florenzo Iannone https://orcid.org/0000-0003-0474-5344

REFERENCES

1. De Luca G, Matucci-Cerinic M, Mavrogeni SI. Diagnosis and management of primary heart involvement in systemic sclerosis. *Curr Opin Rheumatol*. 2024;36(1):76-93.
2. Allanore Y, Meune C, Kahan A. Outcome measures for heart involvement in systemic sclerosis. *Rheumatology (Oxford)*. 2008;47(Suppl 5):v51-v53.
3. Meune C, Vignaux O, Kahan A, Allanore Y. Heart involvement in systemic sclerosis: evolving concept and diagnostic methodologies. *Arch Cardiovasc Dis*. 2010;103(1):46-52.
4. Bruni C, Ross L. Cardiac involvement in systemic sclerosis: getting to the heart of the matter. *Best Pract Res Clin Rheumatol*. 2021;35(3):101668.
5. Bruni C, Buch MH, Furst DE, et al. Primary systemic sclerosis heart involvement: a systematic literature review and preliminary data-driven, consensus-based WSF/HFA definition. *J Scleroderma Relat Disord*. 2022;7(1):24-32.
6. Bruni C, Buch MH, Djokovic A, et al. Consensus on the assessment of systemic sclerosis-associated primary heart involvement: world Scleroderma Foundation/heart failure association guidance on screening, diagnosis, and follow-up assessment. *J Scleroderma Relat Disord*. 2023;8(3):169-182.
7. Baron M, Kahaleh B, Bernstein EJ, et al. An interim report of the scleroderma clinical trials consortium working groups. *J Scleroderma Relat Disord*. 2019;4(1):17-27.
8. Mavrogeni S, Pepe A, Gargani L, et al. Cardiac inflammation and fibrosis patterns in systemic sclerosis, evaluated by magnetic resonance imaging: an update. *Semin Arthritis Rheum*. 2022;58:152126.

9. De Luca G, Bombace S, Monti L. Heart involvement in systemic sclerosis: the role of magnetic resonance imaging. *Clin Rev Allergy Immunol*. 2023;64(3):343-357.
10. Coghlan JG, Denton CP, Grünig E, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis*. 2014;73(7):1340-1349.
11. Perelas A, Silver RM, Arrossi AV, Highland KB. Systemic sclerosis-associated interstitial lung disease. *Lancet Respir Med*. 2020;8(3):304-320.
12. Györfi AH, Filla T, Polzin A, et al. Evaluation of systemic sclerosis primary heart involvement and chronic heart failure in the European scleroderma trials and research cohort. *J Am Heart Assoc*. 2025;14(5):e036730.
13. Ferri C, Giuggioli D, Guiducci S, et al. Systemic sclerosis progression INvestiGation (SPRING) Italian registry: demographic and clinico-serological features of the scleroderma spectrum. *Clin Exp Rheumatol*. 2020;38 Suppl 125(3):40-47.
14. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277-314.
15. Ferri C, Bernini L, Bongiorni MG, et al. Noninvasive evaluation of cardiac dysrhythmias, and their relationship with multisystemic symptoms, in progressive systemic sclerosis patients. *Arthritis Rheum*. 1985;28(11):1259-1266.
16. Bairkdar M, Dong Z, Andell P, Hesselstrand R, Holmqvist M. Arrhythmia in patients with systemic sclerosis: incidence, risk factors and impact on mortality in a Swedish register-based study. *RMD Open*. 2024;10(3):e004532.
17. Fairley JL, Ross L, Nikpour M. Heart involvement in systemic sclerosis: emerging concepts. *Curr Opin Rheumatol*. 2024;36:393-400.
18. Gotschy A, Jordan S, Stoeck CT, et al. Diffuse myocardial fibrosis precedes subclinical functional myocardial impairment and provides prognostic information in systemic sclerosis. *Eur Heart J Cardiovasc Imaging*. 2023;24(3):373-382.
19. Dumitru RB, Bissell LA, Erhayiem B, et al. Predictors of subclinical systemic sclerosis primary heart involvement characterised by microvasculopathy and myocardial fibrosis. *Rheumatology (Oxford)*. 2021;60(6):2934-2945.
20. Purevsuren M, Uehara M, Ishizuka M, et al. Native T1 mapping in early diffuse and limited systemic sclerosis, and its association with diastolic function. *J Cardiol*. 2023;82(2):100-107.
21. Amati F, Bongiovanni G, Tonutti A, et al. Treatable traits in systemic sclerosis. *Clin Rev Allergy Immunol*. 2023;65:251-276.
22. Guédon AF, Carrat F, Mouthon L, et al. Heart and systemic sclerosis-findings from a national cohort study. *Rheumatology (Oxford)*. 2024;63(12):3380-3389.
23. Fernández-Codina A, Simeón-Aznar CP, Pinal-Fernandez I, et al. Cardiac involvement in systemic sclerosis: differences between clinical subsets and influence on survival. *Rheumatol Int*. 2017;37(1):75-84.
24. De Luca G, Campochiaro C, Peretto G, Busnardo E, Matucci-Cerinic M, Dagna L. Cardiac involvement, a threatening very early manifestation of systemic sclerosis: evidence from VEDOSS patients. *Clin Exp Rheumatol*. 2023;41(8):1723-1724.
25. Herisson FM, Cluzel GL, Llopis-Grimalt MA, et al. Targeting the gut-heart Axis improves cardiac remodeling in a clinical scale model of cardiometabolic syndrome. *JACC Basic Transl Sci*. 2025;10(1):1-15.
26. Ferri C, Di Bello V, Martini A, et al. Heart involvement in systemic sclerosis: an ultrasonic tissue characterisation study. *Ann Rheum Dis*. 1998;57(5):296-302.
27. Faludi R, Költő G, Bartos B, Csima G, Czirják L, Komócsi A. Five-year follow-up of left ventricular diastolic function in systemic sclerosis patients: determinants of mortality and disease progression. *Semin Arthritis Rheum*. 2014;44(2):220-227.
28. Hui M, Zhou J, Zhang L, et al. Prevalence and risk factors for left ventricular diastolic dysfunction in systemic sclerosis: a multi-center study of CRDC cohort in China. *Clin Rheumatol*. 2021;40(11):4589-4596.
29. Foocharoen C, Pussadhamma B, Mahakkanukrauh A, Suwannaroj S, Nanagara R. Asymptomatic cardiac involvement in Thai systemic sclerosis: prevalence and clinical correlations with non-cardiac manifestations (preliminary report). *Rheumatology (Oxford)*. 2015;54(9):1616-1621.
30. Maione S, Cuomo G, Giunta A, et al. Echocardiographic alterations in systemic sclerosis: a longitudinal study. *Semin Arthritis Rheum*. 2005;34(5):721-727.
31. De Santis M, Tonutti A, Motta F, et al. Add-on rituximab for primary heart involvement associated with systemic sclerosis: a step forward in the tailored treatment of myocarditis? *Eur J Heart Fail*. 2024;27:473-475.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Tonutti A, Motta F, De Angelis R, et al. First-line diagnostic tests to intercept primary heart involvement in systemic sclerosis: Clinical associations from the SPRING-SIR registry. *Eur J Clin Invest*. 2025;00:e70094. doi:10.1111/eci.70094

APPENDIX

SPRING-SIR (Systemic Sclerosis PRogression INvestiGation group of the Italian Society for Rheumatology): Giorgio Amato (AOU Policlinico – Vittorio Emanuele, Catania; giorgioamato@hotmail.it). Alessia Benenati (AOU 'Policlinico – Vittorio Emanuele, Catania; alessia.benenati@libero.it). Francesca Calabrese (SSD Reumatologia, Reggio Calabria; francescacalabrese81@virgilio.it). Renato Carignola (AOU San Luigi Gonzaga, Orbassano-TO; renatocarigno@gmail.com). Francesca Dall'Ara (UO Medicina Interna-Ambulatorio Reumatologia, Ospedale di Lodi; francesca.dall'ara@gmail.com). Angelo De Cata (Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG); a.decata@operapadrepio.it). Claudio Di Vico (Università

degli Studi della Campania 'Luigi Vanvitelli'; claudio.divico@unicampania.it). Marica Doveri (ASL3 Genova; marica.doveri@asl3.liguria.it). Nicoletta Romeo (Rheumatology Unit, Santa Croce e Carle Hospital, Cuneo; romeo.n@ospedale.cuneo.it). Elena Generali (IRCCS Humanitas Research Hospital, Rozzano). Gianluca Sambataro (Azienda Ospedaliera Cannizzaro, Catania; dottorsambataro@gmail.com). Rossella Talotta (L.Sacco Hospital, Milan; talotta1@virgilio.it). Alberto Lo Gullo (Azienda Ospedaliera "Papardo", Messina, Italy; albertologullo@virgilio.it). Study Center of the Italian Society for Rheumatology (SIR): Carlo Scirè (Università degli Studi, Milano-Bicocca, Milan; c.scire@reumatologia.it). Greta Carrara (Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy; g.carrara@reumatologia.it). Giampiero Landolfi (Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy; g.landolfi@reumatologia.it). Davide Rozza (Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy; d.rozza@reumatologia.it). Anna Zanetti (Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy; a.zanetti@reumatologia.it).