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# Thermographic abnormalities associate with electrocardiogram/echocardiographic changes and mortality in systemic sclerosis: a retrospective cohort study

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**Objectives:**

Cardiac involvement is common in systemic sclerosis (SSc) and associated with high mortality, yet challenging to detect. Our aim was to investigate relationships between cardiac involvement, as assessed by electrocardiogram (ECG) and transthoracic echocardiography (TTE), and thermographic abnormalities.

**Methods:**

A retrospective (2015–2023) study of SSc patients attending a UK referral center. Relevant patient characteristic/demographic data were collected. Logistic regression models were used to evaluate the association between thermographic impairment and ECG/TTE abnormalities. Thermography data were categorized by the presence/absence of 'cold fingers' at baseline (defined as one or more distal digits being more than 1°C colder than the dorsum – a distal-dorsal difference [DDD]); and impairment with rewarming: 'mild', 'moderate', 'severe'). Kaplan-Meier analysis described differences in survival based on thermographic abnormalities.

**Results:**

We included 266 patients (84% female, mean age 57 years). Cardiac abnormalities (≥1) were identified in ~one-third by ECG (39%) and TTE (34%). Baseline DDD were observed in 83% and severe thermographic impairment of rewarming in 58% of patients. Baseline DDDs were associated with ECG (OR 1.18, p=0.047) and TTE (OR 1.19, p=0.008) in univariable analysis, with stronger associations in multivariable analysis for ECG (OR 2.36, p=0.073) and TTE (OR 9.08, p=0.05). Cox Proportional Hazard regression analysis revealed higher mortality risk in patients with baseline DDD (HR 6.04), male sex (HR 2.86), older age (HR 1.06), and cardiovascular comorbidities (HR 3.73). Baseline DDD was associated with significantly shorter survival (chi-squared 4.04, p=0.047).

**Conclusions:**

Thermographic abnormalities were associated with cardiac abnormalities and increased mortality in SSc patients.

**Key words: systemic sclerosis; thermography; echocardiography, ECG, mortality, vasculopathy**

**Key messages**

- Electrocardiogram and echocardiographic abnormalities are frequently found in patients with SSc.
- Thermographic abnormalities were associated with electrocardiogram and echocardiographic abnormalities and death in patients with SSc.
- Predictors of death were thermographic baseline distal-dorsal difference, age, male sex, traditional cardiovascular risk factors.

## Introduction

Systemic sclerosis (SSc) is a complex rheumatic disease characterised by widespread vascular dysfunction, immune system activation, and fibrosis (1–3). Progressive digital and systemic organ-based vascular disease ('vasculopathy') results in progressive detrimental vessel remodelling, with endoluminal fibrosis and neointima proliferation. These phenomena impair downstream perfusion, leading to a profibrotic local hypoxic environment, and driving ischaemic organ dysfunction (4). Peripheral vasculopathy is almost universal in patients with SSc, including symptoms incorporating vasospastic Raynaud's phenomenon (RP) (5,6), and can be complicated by persistent ischaemic tissue injury encompassing pitting scars, digital ulcers (DUs), and gangrene (7,8). Systemic organ-based vasculopathy including pulmonary artery hypertension (PAH), primary cardiac involvement, and scleroderma renal crisis (SRC), are associated with significant disease-related morbidity and mortality (9,10).

There have been significant improvements observed over time in the treatment of major life-threatening vascular complications associated with the disease (e.g., PAH and SRC), which have translated into major patient benefit, such as longer survival (10). Furthermore, there are a number of effective therapies for the management of SSc-associated digital vasculopathy, including DU prevention and healing (11,12). A unified endovascular phenotype in SSc has been proposed, in which common pathological drivers likely exist across different vascular beds, and are potentially amenable to shared treatment approaches (13–15). In SSc, microvascular pathology impairs myocardial perfusion resulting in tissue ischaemia, which is of particular importance to the development of heart failure with preserved ejection fraction (16). However, little is known regarding the complex relationships between cardiac microangiopathy with myocardial inflammation and fibrosis in SSc (17).

Cardiac involvement is increasingly recognised in patients with SSc and may occur primarily to the disease itself, or secondary to interstitial lung disease, PAH, and renal disease (18). Nonetheless, heart involvement is likely still underappreciated and therefore the true prevalence of its primary involvement in SSc remains ill-defined, reflecting challenges in definition, methods used for detection, and the process of attributing abnormalities to the disease itself (19). In SSc, cardiac involvement may manifest as a myriad of clinical features including heart failure, and

arrhythmias, or can be asymptomatic. Patients are potentially at risk of sudden cardiac death (20), and therefore, early detection of cardiac involvement should be considered a clinical priority for improving outcomes in patients with SSc (14). Previous post-mortem studies have demonstrated a higher prevalence of cardiac abnormalities in up to 80% of patients with SSc (21).

Infrared thermography allows measurement of cutaneous temperature regulation (often incorporating a dynamic challenge) and provides complementary insights to nailfold capillaroscopy (NFC), although its correlation with capillary density is moderate (22). NFC abnormalities are predictive of future internal organ and peripheral cutaneous, including vascular, complications (e.g., DUs) in SSc (23,24). Furthermore, NFC abnormalities have been reported to be associated with interstitial lung disease (ILD) (25,26). In our previous retrospective cohort study, NFC abnormalities were associated with future DUs and death in patients with SSc (27).

Against this background, our aims were to 1) describe electrocardiogram (ECG) and transthoracic echocardiogram (TTE) abnormalities in patients with SSc, and 2) to examine for relationships between cardiac abnormalities and thermography. Ours can be considered an exploratory analysis to examine for tentative associations between peripheral and cardiac vascular involvements in SSc, and to further explore the role of thermography as a novel biomarker of disease severity in SSc.

## Methods

### Study design and patients

Ours was a retrospective, cross-sectional analysis of patients newly referred to the Salford Scleroderma outpatient clinic (a national UK tertiary referral centre for SSc), where they were diagnosed with SSc, and fulfilling the 2013 ACR/EULAR Classification Criteria for SSc, between December 2015 and May 2023. Data collected included patient demographics, disease-related information, cardiovascular (CV) comorbidities namely smoking status (previous or current), dyslipidaemia, diabetes, and systemic hypertension, as well as relevant (including vascular) medications.

Data on mortality were collected through chart review for exploratory time-to-event analysis. A total of 301 patients with SSc were eligible for inclusion. Of these, 35 patients had missing

thermography data and were excluded, leaving 266 patients included in our final analysis. The study was registered and approved as a Health Improvement Project (ID: 23HIP35) with the Northern Care Alliance NHS Foundation Trust. Explicit patient consent was not required by the Trust for this type of project.

**ECG and TTE**

Cardiac abnormalities as detected by ECG and TTE were recorded. For our study, we defined an abnormal ECG as at least one of these findings: atrial fibrillation, QT prolongation, left bundle block, atrioventricular block, PR prolongation, signs of previous infarct, abnormal r wave, and sinus bradycardia. While arrhythmias such as atrioventricular blocks and atrial fibrillation are of higher interest due to their clinical significance, we did not limit our analysis to these events. Given the hypothesis-generating nature of the study and considering the high incidence of myocardial involvement in SSc, we also included the mentioned ECG abnormalities, including conduction delays and repolarization disturbances, thus applying a lower threshold for identifying relevant abnormalities in this patient population. Abnormal TTE was defined as any of the following: moderate or severe valvular (aortic, mitral, pulmonary, or tricuspid) insufficiency/regurgitation or stenosis, left or right atrium dilation, left or right ventricular dilation, segmental hypokinesia, and US heart failure, diagnosed in the presence of a left ventricular ejection fraction ≤40%.

**Nailfold capillaroscopy and thermography**

Microcirculation structure and function was assessed using NFC and thermography, respectively. These tests were typically carried out a median (inter-quartile range) of 0.9 (0 to 3.6) years prior to ECG/TTE. NFC was assessed in 8 fingers using either a Nikon stereomicroscope and attached DSLR camera, or latterly a Dino-Lite device, model MEDL4N Pro. In either instance NFC was performed according to our established local protocol (Supplementary Table S1): assessing/subjectively grading capillary density (normal, mild changes, definitive low density or avascular area), dimension (normal, wide, giant), morphology (normal, SSc pattern), and presence of haemorrhages (yes or no). Infrared thermography was performed using several camera models over the time span of the study, all FLIR devices (models included T460, T540, and A655sc). Thermography data were captured using custom software designed specifically for the cold challenge protocol in use. Measurements and analyses of thermal images were conducted by

trained vascular technicians according to our local Raynaud's protocol (Supplementary Table S2). We acknowledge that while thermography protocols can be standardised and reproduced, their application is currently more feasible in specialist centres due to technical and training requirements.

Briefly, a baseline image was followed by a cold challenge (15°C water immersion of gloved hands for 1 minute). Baseline thermographic impairment was assessed via the distal-dorsal temperature difference (DDD) in all 8 fingers – if the DDD in any single digit was <-1°C (i.e. fingers significantly cooler than dorsum) then the baseline is classified as "low" or impaired. Recovery of finger temperature after the cold challenge was monitored for 15 minutes. Severe rewarming impairment in this case is defined as finger temperatures failing to recover 80% of the baseline values in 15 minutes, partial recovery as ≥80% recovery between 5 and 15 minutes, and good recovery as ≥80% of baseline finger temperature values within 5 minutes.

**Statistical analysis**

Descriptive statistics for demographic and clinical characteristics were reported stratifying by the presence of severe rewarming impairment. Continuous variables were expressed as means with standard deviation (SD) or medians with interquartile ranges (IQR) as appropriate, and categorical variables as frequencies and percentages. Chi-square or Fisher's exact tests were employed for categorical variables and Student's or Kruskal-Wallis's test was used for continuous variables, depending on the distribution. All the tests were two-sided, and a p-value<0.05 was considered statistically significant. Univariable and multivariable logistic regression models were used to evaluate the association between thermographic impairment indicators (including both baseline DDD and rewarming impairment) and both ECG and echocardiographic abnormalities; an exploratory association was reported with particular focus on right valve abnormality as particularly relevant for SSc. The same univariable models were also applied to evaluate the association of these cardiovascular abnormalities with demographic and clinical predictors. Variables with a significant association in the univariable analysis (p<0.05) were then included in multivariable logistic regression models to determine whether the associations observed with thermographic indicators remained significant after adjusting for potential confounders. Results are reported as odds ratios (OR) with corresponding 95% confidence intervals (CI) to quantify the

strength and reliability of the associations. Univariable Cox Proportional Hazard regression was deployed to explore the association of clinical and demographic features, ECG, and TTE findings with mortality. Lastly, exploratory Kaplan-Meier survival curves for all-cause mortality were plotted stratified by the presence of a severe rewarming impairment and survival distributions were compared via log-rank test**.** NFC size and density were transformed into semi quantitative scales from 1 (normal) to 3 (giant capillaries for size and avascular areas for density). Data analysis was performed using R version 4.3.4 (R Core Team, 2024. R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Patient- and disease-related characteristics

The clinical and demographic features of the study cohort are presented in Table 1. Of the 266 included patients with SSc, 223 (84%) were female, with a mean (SD) age of 57 (18) years. Two-hundred and six patients (77%) presented the limited cutaneous subset of disease, according to LeRoy et al (28). PAH and ILD were present in 35 (14%) and 59 (22%) patients, respectively, with 59 (22%) patients presenting a history of DUs. Over half of patients received treatment with vasodilator therapies (n=153, 58%), and one-quarter or less with either PDE type-5 inhibitors (n=66, 25%) or antiplatelet agents (n=46, 17%). One-hundred and fifty-three (58%) were on vasoactive drugs and 73 patients (27%) were on conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (Table 1).

Most patients had either severe (n=153, 57%) or moderate (n=68, 26%) thermographic rewarming impairment, while fewer had no impairment (n=45, 17%). The majority (n=220, 83%) of patients had evidence of baseline DDD; with an expected significantly higher proportion (93%) seen in those with more severe thermographic rewarming impairment ($p<0.001$) (Table 1). Capillaroscopy was assessed in 266 patients, of these, 189 (71%) presented either a reduced capillary density or avascular areas, and 148 (56%) presented giant capillaries. Haemorrhages were present in 115 (43%) patients. Overall, 251 (95%) patients were classified as having a scleroderma pattern (either early, active, or late) according to Cutolo et al (29).

**Traditional cardiovascular risk factors**

Half of patients (n=137, 52%) had at least one CV risk factor, and these were often multiple: 2 (n=40, 15%), 3 or more (n=5, 1.9%). Specifically, approximately one-fifth had either recorded dyslipidaemia (n=48, 18%) or hypertension (n=44, 17%), while diabetes was less common (n=16, 6%). Around one-third of the patients were either current (n=30, 11%) or former (n=66, 25%) smokers. Twenty-two (8.2%) patients had a known history of ischaemic heart disease, 10 (3.8%) had a known history of cerebrovascular accident, and 3 (1.1%) had a history of aortic aneurysm.

**ECG and TTE abnormalities**

Of the 266 patients, 265 had available TTE, whereas 169 had available ECG. Over-one third of patients had abnormal (defined as the presence of at least one abnormality) ECG (n=66, 39%) or TTE (n=73, 41%) (Table 2). The most common ECG abnormalities were signs of previous infarct (13%), left atrial enlargement (11%), and left ventricular hypertrophy (7.2%). Other important ECG findings (found in between 3-5% of patients) were atrial fibrillation (3.6%), right bundle branch block (3.6%), and premature atrial complexes (3.0%).

**Predictors of ECG abnormalities**

The univariable and multivariable analyses of predictors for ECG abnormalities are presented in Table 3. In univariable logistic regression analysis, baseline DDD on thermography was significantly associated with the presence of ECG abnormalities (OR 1.18, p=0.047). Age also showed a significant association with ECG abnormalities (OR 1.01, p=0.014) (Table 3). Conversely, conventional CV risk factors were not significantly associated with ECG abnormalities in our cohort. NFC parameters (e.g., haemorrhages, capillary density, and pattern), autoantibody type, medication use, and disease subset were not significantly associated with ECG abnormalities, and thus not included in multivariable models. In multivariable analysis, after adjusting for the factors significantly associated in univariable analysis (i.e., age, ILD, and US heart failure), baseline DDD on thermography showed a borderline significant positive association (OR 2.36, p=0.073) with ECG abnormalities. Of the other predictors, only age remained a marginally significant predictor (OR 1.02, p=0.065) (Table 3).

**Predictors of TTE abnormalities**

The univariable and multivariable analyses of predictor for TTE abnormalities are presented in Table 4. In univariable logistic regression analysis, there was a significant association between baseline DDD on thermography (OR 1.19, p=0.008) with TTE abnormalities. Scl70 antibodies (OR 1.16, p=0.009) and male sex (OR 1.14, p=0.027) were also significant positive predictors for TTE abnormalities (Table 4). Similar to ECG abnormalities, NFC parameters, medication use, and disease subset were not significantly associated with echocardiogram abnormalities, and thus not included in multivariable models. In multivariable analysis, after adjusting for significantly associated predictors in univariable regressions (namely sex, Scl70 presence, PAH, and US heart failure), baseline DDD on thermography remained positively associated with TTE abnormalities, with an OR of 9.08 (p=0.052) (Table 4). Other variables that maintained significant association were US heart failure (OR 10.8, p=0.002), PAH (OR 6.21, p<0.001), and, marginally, Scl70 positivity (OR 2.45, p=0.07).

**Survival analysis**

Thirty-four patients (13%) died during the follow-up period. The median (IQR) follow-up time was 53.5 (45) months for the overall cohort, with a median (IQR) censoring time of 56.5 (43) months, and a median time to event of 38 (43.5) months for the patients who died during follow-up.

Univariable Cox Proportional Hazard regression analysis revealed a significant positive association for age (HR 1.06, p<0.001), disease duration (HR 1.01, p=0.038), and male sex, with men being nearly three times more likely to die compared to women (HR 2.86, p=0.009). Conventional CV risk factors, namely, were strongly associated with mortality, with patients presenting with any of these showing a more than three-times higher mortality risk (HR 3.73, p=0.002). Being in the diffuse cutaneous Leroy subset conferred a more than 2-fold higher mortality risk (HR 2.63, p=0.01) (See Supplementary Table S2).

***Thermography parameters and mortality***

The exploratory analysis for the association of thermography parameters with mortality revealed a trend towards a significantly higher risk in patients with baseline DDD on thermography (HR 6.04, p=0.067), while no association was found for severe rewarming impairment (Supplementary Table S2). Among patients with baseline DDD on thermography (n=220), 33 events were observed, compared to 1 event in patients without baseline DDD (n=46). The log-rank test indicated a statistically significant shorter survival distribution for the patients with baseline DDD on thermography (chi-squared 4.04, p=0.047) (Figure 1).

## Discussion

The key finding of our study is that, taken together, thermographic abnormalities (especially baseline DDD) were associated with ECG and TTE abnormalities, and tentatively, with death. Conceptually, these data may lend further support towards a unifying endovascular phenotype in SSc, in which shared disease effector mechanisms likely exist across peripheral and central vascular beds and are associated with organ manifestations. Our data further support investigation of thermography as a novel biomarker of disease severity in patients with SSc. Although thermography is currently limited to use in specialist centers, the availability of low-cost, handheld, thermography equipment may allow wider access to the technology (30).

Our study can be considered as exploratory. That is, ECG and TTE capture broad ranging cardiovascular pathology including (but not limited to) hypertensive, ischaemic, valvular, inflammatory, and fibrotic aetiologies. In particular, many of the TTE findings were concerning abnormalities, which aside from tricuspid regurgitation (i.e., related to PAH), are unlikely primarily SSc-related in the majority of cases (that is mainly from degenerative valve disease and functional in some patients). Arrythmia has been reported to be an important cause of death in patients with SSc (31). Specifically, ECG abnormalities have been observed in varying frequency (between 25-75%) in patients with SSc (32), and are associated with increased mortality (33). Given the challenges in defining pathological versus incidental findings in ECG of SSc patients, studies often adopt broader criteria to capture a wide spectrum of abnormalities, acknowledging that some may not necessarily indicate overt disease (e.g., sinus bradycardia in otherwise well athletic individuals), but could reflect subclinical pathologic myocardial involvement. Nonetheless, the role of thermography as a non-invasive biomarker of cardiovascular involvement

in SSc could be a useful tool warranting further investigation. The underlying pathobiological mechanisms, including myocardial fibrosis, autonomic dysfunction and/or inflammation, may contribute in varying degrees to these ECG findings. Although our data do not allow us to distinguish among these mechanisms, we propose that future studies integrate cardiac imaging and validated tools such as the COMPASS-31 questionnaire to assess autonomic involvement (42,43).

Specifically, in our study, baseline DDD on thermography was consistently and significantly associated with ECG and TTE abnormalities. The mechanistic importance of these observations is largely unknown, but taken together, likely attest to the central importance of vascular alterations in the complex aetiopathogenesis of SSc. To highlight, although different measurements can be made from thermographic assessment/images at baseline (i.e., akin to 'cold' or cyanotic fingers observed in clinic) and following dynamic challenge, these remain the subject of ongoing international debate, yet likely provide conceptually related (but not necessarily interchangeable) information.

In our previous retrospective SSc cohort study, patients (n=138) with abnormal (compared to normal) thermography were more likely (OR 2.84) to develop future DUs (including multiple DU episodes) (27). Furthermore, patients with abnormal thermography were found to be significantly more likely to die (OR 5.42). Although NFC abnormalities have been widely reported to be predictive of disease outcomes and severity (e.g., DUs and PAH) in SSc (24), in our study we did not find an association between different NFC alterations and either ECG or TTE abnormalities. This likely reflects intrinsic differences between these potentially complementary vascular techniques. Specifically, NFC findings reflect progressive microangiopathy, whereas thermography to a greater extent assesses larger vessel (thermoregulatory) function. In our present (retrospective) study we were not able to assess the prevalence and/or impact of other potentially important (and more common) cardiorespiratory (e.g., COPD and obstructive sleep apnoea) conditions. Furthermore, the impact of other forms of systemic autoimmunity (e.g., idiopathic inflammatory myopathies, autoimmune thyroid disease and antiphospholipid syndrome), and these should be considered in the design of future (prospective) studies.

Our study provides some important clinical insights. As might be expected, patients with PAH were more likely to have TTE abnormalities, including right-sided valvular insufficiency. In our study, 14% of patients had PAH, which is comparable to general prevalence estimates (that have remained stable over time) of around 10% (10). Taken together, this highlights the need for regular and proactive cardiopulmonary detection strategies for SSc-PAH (14,34,35). Patients with SSc have been reported to have an increased risk of CV disease (although this remains a topic of ongoing debate) (36,37). Despite patients having a significantly higher risk, the prevalence of traditional CV risk factors has been reported to be lower or similar to that of the general population (14). The presence of traditional CV risk factors was not uncommon in our patient cohort, and was significantly associated with mortality (OR 3.73). These data highlight the likely importance of other mechanisms of vascular disease in SSc, which are not necessarily influenced by classic CV risk factors (38). With recognition of an ever-ageing population and improvements in the treatment of SSc, age remained significantly associated, including in multivariable analyses, with ECG abnormalities. The well documented poorer outcomes, including from cardiac involvement, in men with SSc (39,40) was also confirmed in our study, with men bring almost three times more likely to die compared to women.

Our study benefited from a large number of well phenotyped patients allowing for analysis of the predictors of broad-ranging ECG and TTE abnormalities, and tentatively examination of mortality. Our retrospective study design was based on our standardised routinely collected clinical data. However, the retrospective nature of our data prevents us from establishing definitive causal relationships between the studied variables and the observed clinical outcomes, including to establish the cause of death (e.g., from cardiovascular causes). We adopted a pragmatic approach to defining an abnormal ECG and TTE, and therefore this potentially included benign findings, of no clinical relevance, including in the context of SSc. Another limitation of our study is that standard ECG, unlike Holter monitoring, may not capture transient arrhythmias such as ventricular ectopic beats or episodes of non-sustained ventricular tachycardia, both of which have been associated with increased cardiovascular mortality in SSc. To mitigate this limitation and achieve an optimal trade-off between sensitivity to cardiac SSc disease and specificity for true myocardial pathology, we considered all detected ECG abnormalities, with the exception of supraventricular ectopics and premature atrial complexes, which are generally common and non-specific, as well

as right bundle branch block, which is generally considered as benign in the general population, and in SSc, is more likely indicative of PAH rather than primary myocardial disease. We observed a relatively lower prevalence (~75%) of ANA positivity compared to most reported cohorts (often ~90% or greater) (5). However, some cohorts have also reported a comparable lower ANA prevalence of around 70-80% (41), particularly in those including a greater proportion of the limited cutaneous subset, which aligns with our patient cohort disposition (77% limited cutaneous SSc). Furthermore, ours was a monocentric study from a UK tertiary SSc referral center and therefore our findings might not be generalisable to other patient cohorts, requiring further exploration and validation in larger assembled numbers of patients, including confirmation of prognostic relevance.

In conclusion, abnormalities as assessed by thermography were associated with broad ranging ECG and TTE abnormalities, and tentatively with death, in our cohort of patients with SSc. Future research should explore thermography as a valuable novel biomarker to identify patients with cardiac involvement from SSc, including to facilitate early diagnosis. Our data also lends support to the emerging concept of a unified endovascular phenotype in SSc, in which anatomically distinct involvement from shared vascular disease mechanisms might be amenable to common treatment strategies.

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**Conflicts of interest**

MJV: Speaker fees from Astrazeneca, Janssen , Pfizer and Bristol Myers Squibb. MH: Speaker fees and Research funding from Janssen. SDD: none. ALH has received consultancy fees from Arena, Boehringer Ingelheim, Camurus, Galderma, Gesynta Pharma, and Janssen and speaker fees

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**Author disclosure statement**

The data underlying this article will be shared upon reasonable request to the corresponding author.

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Table 1. Clinical and demographic features of the study cohort divided by the degree of thermography impairment. cs DMARD: conventional synthetic disease modifying anti-rheumatic drug; CV: cardiovascular; dcSSc: diffuse cutaneous SSc; cDMARDs: conventional Disease-Modifying Anti Rheumatic Drugs; DUs: digital ulcers; ILD: interstitial lung disease; lcSSc: limited cutaneous SSc; NFC: nailfold capillaroscopy; PAH: pulmonary arterial hypertension.

| **Characteristic** | **Overall** N = 266[1] | **No thermography impairment** N = 45[1] | **Moderate thermography impairment** N = 68[1] | **Severe thermography impairment** N = 153[1] | **p-value**[2] |
|---|---|---|---|---|---|
| Age (Mean, SD) | 57 (18) | 54 (20) | 51 (17) | 60 (15) | 0.017 |
| Sex | | | | | 0.3 |
| Female | 223 (84%) | 38 (84%) | 53 (78%) | 132 (86%) | |
| Male | 43 (16%) | 7 (16%) | 15 (22%) | 21 (14%) | |
| Disease duration (months) | 102 (66, 138) | 102 (78, 126) | 102 (66, 162) | 90 (66, 138) | 0.6 |
| dcSSc | 60 (23%) | 11 (24%) | 16 (24%) | 33 (22%) | 0.9 |
| lcSSc | 206 (77%) | 34 (76%) | 52 (76%) | 120 (78%) | 0.9 |
| ANA | 199 (75%) | 28 (62%) | 50 (74%) | 121 (79%) | 0.070 |
| Anticentromere antibodies | 133 (50%) | 23 (51%) | 31 (46%) | 79 (52%) | 0.7 |
| Anti-Scl70 antibodies | 49 (18%) | 5 (11%) | 15 (22%) | 29 (19%) | 0.3 |
| Anti-PmScl75/100 | 18 (6.8%) | 5 (11%) | 4 (5.9%) | 9 (5.9%) | 0.5 |
| Anti-Ro52 | 54 (20%) | 4 (8.9%) | 16 (24%) | 34 (22%) | 0.11 |
| Anti-platelets | 46 (17%) | 7 (16%) | 9 (13%) | 30 (20%) | 0.5 |
| Vasodilators | 153 (58%) | 21 (47%) | 44 (65%) | 88 (58%) | 0.2 |
| PDE5 inhibitors | 66 (25%) | 10 (22%) | 15 (22%) | 41 (27%) | 0.7 |
| cs DMARD | 73 (27%) | 10 (22%) | 19 (28%) | 44 (29%) | 0.7 |
| DUs history | 59 (22%) | 11 (24%) | 15 (22%) | 36 (24%) | >0.9 |
| Smoking | | | | | 0.8 |

| | | | | | |
|---|---|---|---|---|---|
| Never | 169 (64%) | 29 (64%) | 43 (63%) | 97 (64%) | |
| Current | 30 (11%) | 7 (16%) | 6 (8.8%) | 17 (11%) | |
| Former | 66 (25%) | 9 (20%) | 19 (28%) | 38 (25%) | |
| Dyslipidaemia | 48 (18%) | 5 (11%) | 12 (18%) | 31 (20%) | 0.4 |
| Diabetes | 16 (6.0%) | 1 (2.2%) | 4 (5.9%) | 11 (7.2%) | 0.6 |
| Systemic hypertension | 44 (16%) | 4 (8.9%) | 11 (16%) | 29 (19%) | 0.5 |
| Ischaemic heart disease | 22 (8.3%) | 3 (6.6%) | 8 (13%) | 11 (7.2%) | 0.7 |
| Cerebrovascular accident | 10 (3.8%) | 1 (2.2%) | 2 (3.0%) | 7 (4.6%) | 0.6 |
| At least one CV risk factor | 137 (52%) | 22 (49%) | 36 (53%) | 79 (52%) | >0.9 |
| Abnormal ECG (at least one finding) | 66 (39%) | 7 (26%) | 20 (38%) | 39 (44%) | 0.2 |
| Abnormal TTE (at least one finding) | 73 (41%) | 7 (26%) | 16 (31%) | 50 (50%) | 0.020 |
| Baseline DDD on thermography | 220 (83%) | 28 (62%) | 50 (74%) | 142 (93%) | <0.001 |
| NFC haemorrhages | 115 (43%) | 20 (42%) | 32 (47%) | 63 (41%) | 0.8 |
| NFC SSc pattern | 251 (95%) | 41 (93%) | 63 (94%) | 147 (96%) | 0.6 |
| NFC capillary size | | | | | 0.1 |
| Normal capillaries | 47 (18%) | 11 (24%) | 12 (18%) | 24 (16%) | |
| Enlarged capillaries | 71 (27%) | 11 (24%) | 11 (16%) | 49 (32%) | |
| Giant capillaries | 148 (56%) | 23 (51%) | 45 (66%) | 80 (52%) | |
| NFC capillary density | | | | | 0.04 |
| Normal density | 77 (29%) | 15 (33%) | 9 (13%) | 53 (35%) | |
| Reduced density | 118 (44%) | 19 (42%) | 38 (56%) | 61 (40%) | |
| Avascular areas | 71 (27%) | 11 (24%) | 21 (31%) | 39 (25%) | |
| PAH | 35 (14%) | 5 (13%) | 8 (13%) | 22 (16%) | 0.8 |
| ILD | 59 (22%) | 13 (29%) | 11 (16%) | 35 (23%) | 0.3 |
| Deaths during follow up | 32 (12%) | 8 (18%) | 6 (8.8%) | 18 (12%) | 0.4 |
| cDMARDs use | 73 (27%) | 10 (22%) | 19 (28%) | 44 (29%) | 0.7 |
| Vasoactive drugs use | 153 (58%) | 21 (47%) | 44 (65%) | 88 (58%) | 0.2 |

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Student's t test; Pearson's Chi-squared test; Fisher's exact test

Table 2. Prevalence of the individual TTE and ECG abnormalities in the overall cohort, expressed as absolute count and relative frequency.

| Characteristic | Overall, n (%) |
|---|---|
| **Electrocardiogram (ECG) abnormalities** | |
| Atrial fibrillation | 6 (3.6%) |
| QT prolongation | 4 (2.4%) |
| Premature atrial complexes | 5 (3.0%) |
| Supraventricular ectopics | 1 (0.6%) |
| Left bundle block | 7 (4.2%) |
| Right bundle block | 6 (3.6%) |
| Atrioventricular block | 1 (0.6%) |
| PR prolongation | 1 (0.6%) |
| Signs of previous infarct | 22 (13%) |
| Left atrial enlargement | 18 (11%) |
| Left ventricular hypertrophy | 12 (7.2%) |
| Right ventricular hypertrophy | 4 (2.4%) |
| Right atrial enlargement | 3 (1.8%) |
| Abnormal r wave | 4 (2.4%) |
| Sinus Bradycardia | 1 (0.6%) |
| Abnormal ECG (at least one finding) | 66 (39%) |
| **Transthoracic echocardiogram (TTE) abnormalities** | |
| Moderate Pulmonary insufficiency | 1 (0.4%) |
| Mild Pulmonary insufficiency | 11 (4.6%) |

| | |
|---|---|
| Trivial Pulmonary insufficiency | 1 (0.4%) |
| Moderate Tricuspid insufficiency | 9 (3.8%) |
| Mild Tricuspid insufficiency | 28 (12%) |
| Trivial Tricuspid insufficiency | 14 (5.9%) |
| Severe Aortic insufficiency | 1 (0.4%) |
| Moderate Aortic insufficiency | 2 (0.8%) |
| Mild Aortic insufficiency | 13 (5.5%) |
| Trivial Aortic insufficiency | 3 (1.3%) |
| Moderate Mitral insufficiency | 7 (2.9%) |
| Mild Mitral insufficiency | 23 (9.7%) |
| Trivial Mitral insufficiency | 5 (2.1%) |
| Moderate Aortic stenosis* | 2 (0.8%) |
| Mild Aortic stenosis* | 3 (1.2%) |
| Mild Mitral stenosis* | 1 (0.4%) |
| Any right valve dysfunction | 40 (17%) |
| Any left valve dysfunction | 40 (17%) |
| Right atrium dilation | 10 (4.2%) |
| Right ventricular dilation | 9 (3.8%) |
| Left atrium dilation | 15 (6.3%) |
| Left ventricular dilation | 3 (1.3%) |
| Segmental hypokinesia | 5 (2.1%) |
| US heart failure** | 14 (5.9%) |
| Abnormal TTE (at least one finding) | 73 (41%) |

**Data only presented for valvular stenotic lesions where observed in the studied cohort.*

***Defined as reduced ejection fraction with left ventricular EF <40%.*

Table 3. Univariable and Multivariable logistic regressions assessing the association of clinical and demographic features with specific ECG abnormality presence. ANA: antinuclear antibody; cDMARDs: conventional Disease-Modifying Anti-Rheumatic Drugs; CV: cardiovascular; dcSSc: diffuse cutaneous systemic sclerosis; DDD: distal-dorsal temperature difference; DUs: digital ulcers; ILD: interstitial lung disease; NFC: nailfold capillaroscopy; PAH: pulmonary arterial hypertension.

| Characteristic | Univariable logistic regression | | | Multivariable logistic regression | | |
|---|---|---|---|---|---|---|
| | OR[1] | 95% CI[1] | p-value | OR[1] | 95% CI[1] | p-value |
| Age | 1.01 | 1.00, 1.01 | 0.014 | 1.02 | 1.00, 1.05 | 0.065 |
| Male sex | 1.15 | 0.97, 1.38 | 0.1 | | | |
| ANA positivity | 1.00 | 0.88, 1.12 | 0.9 | | | |
| Anticentromere | 0.90 | 0.81, 1.04 | 0.1 | | | |
| Anti-PmScl75/100 | 0.99 | 0.81, 1.21 | >0.9 | | | |
| Anti-Scl70 | 1.18 | 0.94, 1.34 | 0.4 | | | |
| Anti-Ro52 | 1.03 | 0.91, 1.17 | 0.6 | | | |
| Leroy (28) – dcSSc | 1.16 | 0.98, 1.31 | 0.08 | | | |
| Disease duration (months) | 1.00 | 1.00, 1.00 | 0.8 | | | |
| Raynaud's Phenomenon | 1.13 | 0.86, 1.50 | 0.4 | | | |
| DUs history | 0.98 | 0.87, 1.11 | 0.8 | | | |
| ILD | 1.12 | 1.00, 1.27 | 0.053 | 1.53 | 0.73, 3.09 | 0.2 |
| Conventional CV risk factors (any) | 1.01 | 0.92, 1.12 | 0.8 | | | |
| PAH | 1.10 | 0.95, 1.28 | 0.2 | | | |
| US heart failure | 1.34 | 1.13, 1.55 | 0.006 | 2.22 | 0.69, 6.80 | 0.2 |
| Baseline DDD on thermography | 1.18 | 1.02, 1.27 | 0.047 | 2.36 | 0.97, 7.23 | 0.073 |
| Any rewarming impairment on thermography | 1.10 | 0.96, 1.26 | 0.2 | | | |
| Severe rewarming impairment on thermography | 1.01 | 0.91, 1.11 | >0.9 | | | |
| Moderate rewarming impairment on thermography | 1.06 | 0.95, 1.20 | 0.3 | | | |

| | | | |
|---|---|---|---|
| NFC density – semi quantitative | 1.01 | 0.95, 1.07 | >0.9 |
| NFC size – semi quantitative | 1.02 | 0.97, 1.08 | 0.7 |
| NFC haemorrhages | 1.09 | 0.99, 1.21 | 0.088 |
| NFC SSc pattern | 0.93 | 0.73, 1.17 | 0.5 |
| Use of cDMARDs | 0.98 | 0.88, 1.10 | 0.7 |
| Use of vasoactive drugs | 1.01 | 0.91, 1.11 | >0.9 |

[1] CI = Confidence Interval, OR = Odds Ratio

Table 4. Univariable and Multivariable logistic regressions assessing the association of clinical and demographic features with echocardiogram abnormalities presence. ANA: antinuclear antibody; CV: cardiovascular; dcSSc: diffuse cutaneous systemic sclerosis; DDD: distal-dorsal temperature difference; DUs: digital ulcers; ILD: interstitial lung disease; NFC: nailfold capillaroscopy; PAH: pulmonary arterial hypertension. US: ultrasound.

| **Characteristic** | **Univariable logistic regression** | | | **Multivariable logistic regression** | | |
|---|---|---|---|---|---|---|
| | **OR[1]** | **95% CI[1]** | **p-value** | **OR[1]** | **95% CI[1]** | **p-value** |
| Age | 1.00 | 1.00, 1.01 | 0.062 | | | |
| Male sex | 1.14 | 1.02, 1.28 | 0.027 | 1.38 | 0.45, 3.81 | 0.6 |
| ANA positivity | 1.00 | 0.90, 1.10 | >0.9 | | | |
| Anticentromere | 0.98 | 0.90, 1.06 | 0.6 | | | |
| Anti-PmScl75/100 | 1.02 | 0.86, 1.21 | 0.8 | | | |
| Anti-Scl70 | 1.16 | 1.04, 1.29 | 0.009 | 2.45 | 0.90, 6.41 | 0.07 |
| Anti-Ro52 | 0.98 | 0.88, 1.09 | 0.7 | | | |
| Leroy (28) – dcSSc | 1.05 | 0.95, 1.16 | 0.4 | | | |
| Disease duration (months) | 1.00 | 1.00, 1.00 | >0.9 | | | |
| Raynaud's Phenomenon | 1.18 | 0.72, 1.92 | 0.5 | | | |
| DUs history | 1.05 | 0.95, 1.17 | 0.3 | | | |
| ILD | 1.03 | 0.93, 1.14 | 0.6 | | | |
| Conventional CV risk factors (any) | 1.00 | 0.92, 1.09 | >0.9 | | | |
| PAH | 1.48 | 1.31, 1.66 | <0.001 | 6.21 | 2.33, 16.5 | <0.001 |
| US heart failure | 1.95 | 1.64, 2.33 | <0.001 | 10.8 | 2.52, 39.6 | 0.002 |
| Baseline DDD on thermography | 1.19 | 1.07, 1.33 | 0.008 | 9.08 | 1.53, 88.1 | 0.052 |
| Any rewarming impairment on thermography | 1.07 | 0.96, 1.20 | 0.2 | | | |
| Severe rewarming impairment on thermography | 1.04 | 0.95, 1.13 | 0.4 | | | |
| Moderate rewarming impairment on thermography | 1.00 | 0.91, 1.10 | >0.9 | | | |

| | | | |
|---|---|---|---|
| NFC density – semi quantitative | 1.01 | 0.96, 1.06 | 0.7 |
| NFC size – semi quantitative | 1.00 | 0.92, 1.08 | 0.8 |
| NFC haemorrhages | 1.00 | 0.92, 1.10 | >0.9 |
| NVC SSc pattern | 0.85 | 0.69, 1.03 | 0.10 |
| Use of cDMARDs | 0.99 | 0.90, 1.09 | 0.8 |
| Use of vasoactive drugs | 1.01 | 0.93, 1.10 | 0.8 |

[1] CI = Confidence Interval, OR = Odds Ratio

Figure 1:

Kaplan-Meier survival curves showing all-cause mortality in patients with systemic sclerosis, stratified by presence (red curve) or absence (green curve) of baseline distal-dorsal temperature difference (DDD) on thermography. The red curve shows significantly lower survival compared to the green curve. Time is shown in months.

Alt text: A Kaplan-Meier survival plot is shown with the vertical axis labelled ‘survival probability’ (from 0.0 to 1.0), and the horizontal axis labelled ‘time’ (in months, from 0 to 120). Two curves are shown: one for normal baseline thermography, and one for baseline DDD on thermography. A table below the axes shows the number of patients at risk in these two groups

over 20 month intervals. A p-value of 0.047 is superimposed on the axes highlighting the significant difference in survival between the two groups.