Seminars in Arthritis and Rheumatism 73 (2025) 152723

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Subclinical coronary artery calcification in systemic sclerosis using high-resolution chest CT: Identification, extent, and disease-specific risk factors

Esben U. Næser [a,*,1], Frederik C. Enevoldsen [a,b,1], Simon Winther [b,c], Morten Bøttcher [b,c], Klaus Søndergaard [a,b], Ellen-Margrethe Hauge [a,b]

[a] Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark
[b] Department of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark
[c] Department of Cardiology, Gødstrup Hospital, Herning, Denmark

ARTICLE INFO

Keywords (MESH):
Systemic sclerosis
Atherosclerosis
Coronary artery disease / diagnostic imaging*
Vascular calcification / diagnostic imaging
Tomography
X-ray computed
Middle aged

ABSTRACT

Objectives: Early detection of subclinical atherosclerosis is pivotal for preventing symptomatic coronary artery disease. This study aimed to compare the proportion of patients with systemic sclerosis (SSc) having an Agatston coronary artery calcification (CAC) score ≥100 using high-resolution computed tomography (HRCT) chest scans to a background population using cardiac CT scans, and to identify disease-specific risk factors for subclinical CAC in patients with SSc.

Methods: Logistic regression models, adjusted for cardiovascular risk factors, evaluated the odds ratio of patients having a CAC score ≥100. CAC scores for the background population were derived from two cardiac CT screening cohorts. CAC scores by HRCT chest scans were calibrated using a conversion factor to adjust for overestimation in comparison to CAC scores obtained from dedicated cardiac CT scans.

Results: HRCT chest scans from 394 patients with SSc were evaluated. In total, 116 (29.4 %) had a CAC score of 0, while 162 (41.1 %) had a CAC score ≥100. Disease duration (OR=1.05, 95 % CI 1.01–1.09) and a history of digital ulcers (OR=2.25, 95 % CI 1.31; 3.86) were independently associated with a CAC score ≥100. Compared to the background population, a significantly higher proportion of SSc patients had a CAC score ≥100 (35.0 % vs. 23.2 %, p<0.001).

Conclusion: The identification of subclinical atherosclerosis using routine HRCT chest scans in patients with SSc offers the potential to detect individuals at increased risk of developing CAD and guide preventive treatment strategies. Additionally, digital ulcers appear to be a novel risk factor for subclinical CAD in these patients.

Introduction

Patients with systemic sclerosis (SSc) have an increased risk of coronary artery disease (CAD) compared to the general population [1–7], with an approximately two-fold increased risk of myocardial infarction [8]. Evidence indicates that the increased risk of CAD in patients with SSc is independent of traditional cardiovascular risk factors [1,3–7,9], and a recent nationwide study suggested that patients with SSc have the highest incidence of CAD among patients with autoimmune diseases [7].

While symptomatic CAD in patients with SSc can result from microvascular disease and vasospasms of the coronary arteries [10], several studies have demonstrated an increased prevalence of macrovascular disease and arteriosclerosis of the coronary arteries in patients with SSc compared to reference individuals [11]. Endothelial injury is central to both the development of arteriosclerosis and the pathogenesis of SSc [12]. In SSc, endothelial dysfunction and defective angiogenesis lead to intimal hyperplasia and media thickening in medium-sized vessels, as well as structural changes in capillaries characterized by enlargement and progressive loss of capillaries. The widespread obliterative vasculopathy and impaired neoangiogenesis result in reduced tissue perfusion, and clinical manifestations, such as poor digital perfusion and ischemic digital ulcers [12].

* Corresponding author at: Department of Rheumatology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 45, 8200 Aarhus N, Denmark.
E-mail address: esben.naeser@clin.au.dk (E.U. Næser).
[1] Esben U. Næser and Frederik C. Enevoldsen contributed equally to this study.

https://doi.org/10.1016/j.semarthrit.2025.152723

Available online 10 April 2025

Coronary artery calcification (CAC) of the epicardial coronary arteries is a surrogate marker for atherosclerotic plaque burden [13]. The Agatston CAC score, traditionally computed from non-contrast electrocardiography (ECG)-gated computed tomography (CT) scans of the heart, is the strongest predictor of atherosclerotic cardiovascular events in asymptomatic individuals with an intermediate risk of CVD [14,15]. In the St. Francis Heart Study, a CAC score threshold above 100 versus below 100 was associated with 9.6 times the risk of atherosclerotic cardiovascular events in asymptomatic individuals [15]. In contrast, an Agatston CAC score of 0 is associated with a very low 10-year risk of developing atherosclerotic cardiovascular disease events, even in the presence of traditional risk factors [16].

In patients with SSc, high-resolution CT (HRCT) scans of the chest are recommended for the early detection and monitoring of systemic sclerosis-associated interstitial lung disease (SSc-ILD) [17,18]. These scans differ from dedicated cardiac CT-scans in multiple parameters, as HRCT chest scans are non-ECG-gated, have a thinner slice thickness (<1.5 mm compared to ~3 mm), and different reconstruction algorithms [19]. In both SSc and non-SSc patients, CAC scores on regular chest CT scans provide reliable estimates that independently predict CV events and death [20–23]. Thus, cardiovascular risk stratification of SSc patients based on opportunistic CAC scoring using HRCT chest scans holds the potential to guide primary prevention treatment.

The primary aims were (1) to evaluate the prevalence and severity of CAC using HRCT chest scans in a large single center cohort of SSc patients, (2) to evaluate the agreement between the Agatston CAC score and a simple visual assessment of CAC, and (3) to identify disease-specific risk factors for higher values of CAC in SSc patients.

Methods

Design and study population

We conducted a retrospective, single-center, cross-sectional cohort study on middle-aged patients aged 50 to 75 years who were diagnosed with SSc according to the 2013 ACR/EULAR classification criteria [24]. Data were collected using electronic health records and radiological electronic archiving systems.

The hospital registry was used to identify patients aged between 50 and 75 years who were registered with an SSc diagnosis (ICD-10 code M34) between 1 January 2012 and 1 December 2022. Inclusion criteria were fulfilment of the 2013 ACR/EULAR SSc classification criteria [24] and having an HRCT chest scan performed during the inclusion period. Exclusion criteria included a history of myocardial infarction or prior coronary intervention, and the inability to retrieve of HRCT chest scan images or poor image quality (Fig. 1).

As references for the CAC scores in the SSc patients, we used CAC scores from 17,252 individuals aged 50-75 years from a population with a low risk of CVD in the same geographical area [25]. Individuals in the background population had participated in two separate population-based studies (DANCAVAS and DanRisk) using ECG-gated cardiac CT scan to examine the prevalence of CAC [26,27]. The computed population-based CAC percentiles have been published [25] and are freely available through an online calculator (http://flscripts.dk/cacscore/).

HRCT chest scan

We retrieved the first HRCT chest scan performed during the inclusion period from the regional electronic archiving systems. The date of the HRCT chest scan was chosen as the index date.

HRCT chest scans were analyzed using the original slice thickness (median of 0.9 mm [range 0.625 mm–1.25 mm]) [28]. CAC was assessed using two different methods: (1) the continuous Agatston calcium score [13], and (2) a simple categorical visual scoring method ranging from no calcium to minimal and moderate to heavy calcium burden corresponding to estimated CAC scores of 0, 1– 99, 100–999, and ≥ 1000, respectively (Supplementary Figure 1) [22]. When using the Agatston method, CAC was defined as voxels contained within the coronary arteries with a value greater than or equal to 130 Hounsfield Units using a semiautomatic scoring system [13]. The left main coronary artery, left anterior descending artery, left circumflex artery, and right coronary artery were evaluated. Assessment of CAC was carried out using VitreaCore 6.5.1 (Canon Medical Systems Corporation).

CAC scoring was performed by two readers (EN and FE). Prior to the analyses, the readers had received supervised training from an experienced cardiologist (SW) and had subsequently performed CAC score analyses of more than 200 ECG-gated CT and HRCT chest scans each. To assess the efficacy of the training, ECG-gated CT scans from a subset of SSc patients (N=43) were analyzed randomly by one of the readers and the cardiologist. The mean difference between the Agatston CAC scores assessed by a cardiologist and the readers was 11.9 (95 % limits of

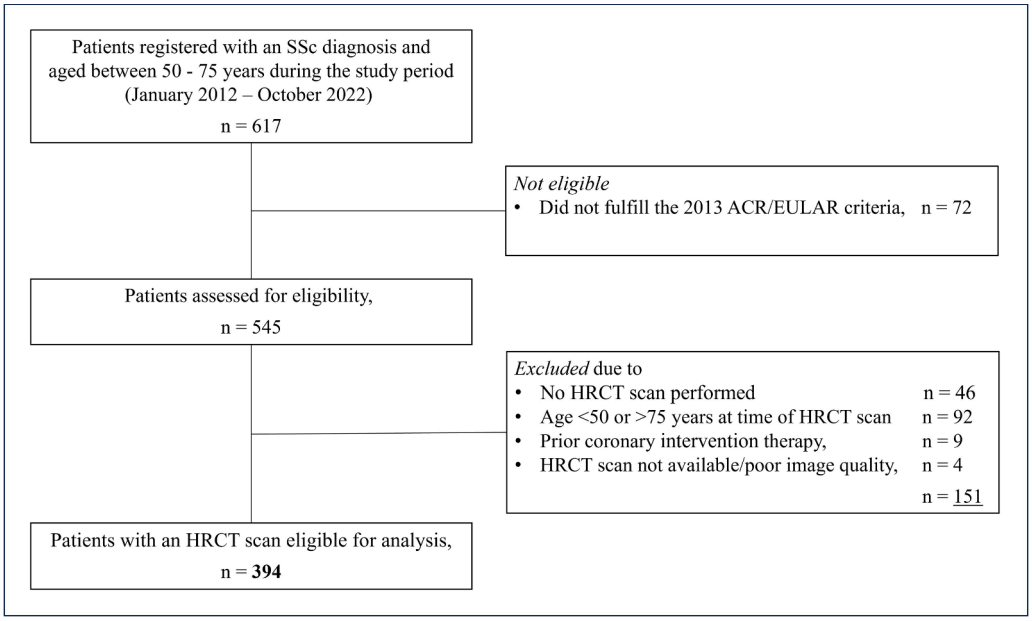

Fig. 1. Flowchart depicting the identification of patients, the assessment of eligibility, and exclusion due to different criteria.

agreement: -70.9; 94.7), and the corresponding intraclass correlation coefficient (ICC) showed an excellent correlation between the respective CAC scores (ICC 0.99 (95 % confidence interval: 0.99–0.99)) [29] (Supplementary Figure 2).

Covariates

Demographics, SSc disease characteristics, and CVD risk factors registered in the electronic health records within ± one year of the index date were collected using predefined criteria (Supplementary Table 1). The following cardiovascular risk factors were collected from the electronic health records: smoking history, body mass index (BMI), hypertension, diabetes mellitus, dyslipidemia, kidney failure, and known arteriosclerotic CVD. Hypertension was defined as the use of antihypertensive medication or SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg based on repeated home measurements of blood pressure. Dyslipidemia was defined based on active lipid-lowering treatment, while kidney failure was defined as eGFR < 60. Diabetes mellitus (DM) was defined as a documented history of DM, and/or the use of anti-diabetic medications. Arteriosclerotic CVD was defined as previous stroke or peripheral arterial surgery.

Statistical analysis

Continuous variables are presented as means and standard deviations (SD) or medians and interquartile ranges (IQR). Categorical variables are presented as counts and percentages (%). The Shapiro-Wilk test and QQ-plots were used to assess the Gaussian distribution of data. Logistic regression models, both crude and adjusted for traditional CVD risk factors (age, gender, BMI, diabetes, hypertension, dyslipidemia, smoking, and arteriosclerotic CVD) evaluated odds ratios for an Agatston CAC score >100. The correlation between the Agatston CAC score and the visual score of CAC was assessed using the weighted Cohen's kappa coefficient (κ) with standard error (SE).

The age-specific 50th, 75th, and 90th percentiles of the background population's CAC scores were plotted against the observed CAC scores in patients with SSc, stratified by gender. Based on the age- and gender-composition of our study population, we calculated the expected proportion of individuals in the background population with a CAC score ≥100 stratified for each age band between 50 and 75. We used a two-tailed one-sample z-test for proportions to compare the proportion of individuals with a CAC score ≥100 in the background population to the observed proportion of patients with SSc who had a CAC score ≥100. To account for the systematic overestimation of CAC by HRCT chest scan compared to ECG-gated CT, the CAC scores in SSc patients obtained by HRCT chest scans were calibrated using a conversion equation, which was calculated based on the results from a previous validation of CAC score by HRCT chest scan [28]. The calibration equation was calculated from Bland-Altman plots of $\log_{10}$-transformed mean difference of the Agatston CAC scores from ECG-gated gated CT scan against HRCT chest scan. Details are provided in Supplementary Figure 3. All analyses were carried out in Stata 18.0 (StataCorp).

Ethical permission

Access to the electronic health records was approved by the regional committee in Central Region Denmark and the Danish Data Protection Agency (case number: 1-16-02-344-22). According to Danish law, no approval was required from the Danish health research ethics committees for this type of study.

Results

Patient inclusion and characteristics

We identified 545 patients aged 50 to 75 years who fulfilled the 2013 ACR/ EULAR SSc classification criteria [24]. Of these, 394 were eligible for CAC scoring using HRCT chest scans (Fig. 1). The median age among SSc patients was 62 years (IQR 56-68) and the majority were females (73.9 %) (Table 1). Sixty-six (16.8 %) patients were current smokers, and 222 patients (56.4 %) had one or more risk factors for CVD. Although the demographics were similar between eligible and ineligible patients (Supplementary Table 1), the eligible SSc patients had a shorter disease duration, more frequent use of immunosuppressive medications, and a greater disease burden, including more pronounced microvascular involvement of the digits, increased SSc-related gastrointestinal symptoms, and more severe SSc-ILD.

Severity of coronary artery calcification in SSc

The median Agatston CAC score in the SSc patients was 52 (IQR: 0; 410). Agatston CAC scores were significantly higher in male subjects compared to female subjects (139 (IQR: 15-605) vs. 30 (IQR: 0-304), p<0.001) (Table 2). CAC scores of 0, 1 to 99, and ≥100 were present in 116 (29.4 %), 116 (29.4 %), and 162 (41.1 %) patients, respectively.

Table 3 shows a comparison of characteristics between patients with Agatston CACS ≥100 and Agatston CACS <100. Patients with an Agatston CAC score ≥100 were older and had a higher burden of traditional cardiovascular risk factors, including hypertension (48.1 % vs. 31.6 %, p=0.001), dyslipidemia (21.6 % vs. 12.5 %, p=0.02), diabetes mellitus (14.2 % vs. 3.0 %, p<0.001), arteriosclerotic cardiovascular disease (9.9 % vs. 4.3 %, p=0.03), and smoking history (72.2 % vs. 53.9 %, p<0.001). A higher proportion of patients with CACS ≥100 had a history of digital ischemic ulcers (30.2 % vs. 19.0 %, p=0.01).

Impact of SSc-specific disease parameters on the presence of coronary artery calcification

Table 4 shows the SSc-specific disease parameters associated with an Agatston CAC score of ≥100. Both disease duration and digital ulcers were associated with an Agatston CAC score of ≥100 in both univariate and multivariate analyses (adjusted OR=1.05 (95 % CI 1.01; 1.09) and adjusted OR= 2.25 (95 % CI 1.31; 3.86), respectively). We found no associations with cutaneous subsets, immunological profile, or any other clinical SSc characteristics.

Agreement between Agatston CAC score and visual assessment of CAC score on HRCT chest scan

Table 5 shows the agreement between the Agatston CAC score and the simple visual assessment of CAC on HRCT chest scans. Supplementary Figure 1 illustrates four examples of different severities of CAC scores based on the Agatston CAC score and their corresponding simple visual scores on HRCT chest scans.

When compared to the Agatston CAC score, the simple visual score showed a strong correlation (κ = 0.93 [SE = 0.04]). A total of 30 patients (7.6 %) had discordant CAC categories between the visual score and the corresponding Agatston CAC score. Only 1 patient (0.3 %) was misclassified by more than one CAC category. In agreement with the findings using the Agatston CAC score, only disease duration and digital ulcers were associated with moderate to severe calcification using visual assessment in both univariate and multivariate analyses (Supplementary Table 2).

Distribution of coronary arterY calcifications in SSc compared to the background population

The proportion of patients with SSc with CAC scores ≥100 was significantly higher in the background population (35.0 % versus 23.2 %, p<0.001). When stratified by gender, the proportion of female SSc patients with CAC score ≥100 was significantly higher than that of the female in the background population (30.6 % versus 17.8 %, p<0.001)

Table 1
Baseline characteristics and cardiovascular risk factors in patients with SSc.

	Total (n=394)		Females (n=291)		Males (n=103)	
Demographics						
Age, median (IQI)	62	(56; 68)	62	(56; 68)	62	(56; 67)
Body mass index, median (IQI)	24.9	(22.4; 28.7)	24.5	(22.1;28.8)	25.1	(23.1; 28.7)
Body mass index classification, n (%)						
Underweight (BMI<18.5)	18	(4.6)	16	(5.6)	2	(2.0)
Normal (BMI 18.5–24.9 kg/m^2)	179	(46.0)	134	(46.7)	45	(44.1)
Overweight (BMI 25–29.9 kg/m^2)	111	(28.2)	76	(26.1)	35	(34.0)
Obese (BMI≥30)	81	(20.6)	61	(21.0)	20	(19.4)
Smoking history, n (%)						
Never smoker	150	(38.1)	125	(43.0)	25	(24.3)
Ex-smoker	174	(44.2)	124	(42.6)	50	(48.5)
Current smoker	66	(16.8)	40	(13.7)	26	(25.2)
Unknown	4	(1.0)	2	(0.7)	2	(1.9)
Cardiovascular risk factors						
Hypertension, n (%)	151	(38.4)	113	(38.8)	38	(37.3)
Dyslipidaemia, n (%)	64	(16.2)	45	(15.5)	19	(18.4)
Kidney failure, n (%)	34	(8.6)	25	(8.6)	9	(8.7)
Diabetes mellitus, n (%)	30	(7.6)	17	(5.8)	13	(12.5)
Arteriosclerotic CVD, n (%)	26	(6.6)	18	(6.2)	8	(7.8)
Stroke	19	(4.8)	13	(4.5)	6	(5.8)
Peripheral arterial surgery	8	(2.0)	6	(2.1))	2	(1.9)
SSc characteristics						
Disease duration since first non-RS symptom, years median (IQI)[1]	4.5	(1.4; 11.4)	5.0	(1.7; 12.0)	2.7	(0.7; 7.8)
Time duration since diagnosis of SSc, years, median (IQI)	0.1	(0.0; 4.8)	0.14	(0.0; 6.2)	0.0	(0.0; 1.9)
Modified Rodnan skin score, median (IQI)	4	(2; 9)	4	(2; 8)	6	(4; 12.3)
Cutaneous subset, n (%)						
Limited	218	(55.3)	176	(60.5)	42	(40.8)
Diffuse	146	(37.1)	89	(30.6)	57	(55.3)
No skin involvement	30	(7.6)	26	(8.9)	4	(3.9)
Autoantibodies, n (%)						
Anti-centromere	157	(39.7)	133	(45.7)	24	(23.3)
Anti-topoisomerase l	47	(11.9)	37	(12.7)	11	(10.7)
Anti-RNA polymerase III	31	(7.9)	25	(8.6)	6	(5.8)
Other SSc related autoantibodies[2]	75	(19.0)	54	(18.6)	21	(20.4)
No SSc specific autoantibodies	84	(21.3)	43	(14.8)	41	(39.8)
Organ involvement						
Raynaud's phenomenon, n (%)	359	(90.9)	270	(92.8)	88	(85.4)
Gastrointestinal involvement, n (%)	265	(67.3)	206	(70.8)	59	(57.3)
Interstitial lung disease, n (%)	193	(49.0)	139	(47.8)	54	(52.4)
Digital ischemic ulcers, n (%)	93	(23.6)	63	(21.6)	30	(29.1)
Arthritis, n (%)	82	(20.8)	59	(20.3)	23	(22.3)
Myositis, n (%)	42	(10.7)	24	(8.3)	18	(17.5)
Myocarditis, n (%)	9	(2.3)	2	(0.7)	7	(6.8)
Pulmonary arterial hypertension, n (%)	22	(5.6)	16	(5.5)	6	(5.8)
Previous renal SSc crisis, n (%)	11	(2.8)	7	2.4	4	(3.9)
Current medical treatment						
Prednisolone, n (%)	71	(18.0)	46	(16.0)	25	(25.0)
Immunosuppressive medicine, n (%)	101	(25.6)	67	(23.0	34	(33.0)
Methotrexate	49	(12.4)	37	(12.7)	12	(11.7)
Mycophenolate	25	(6.4)	13	(4.5)	12	(11.7)
Hydroxychloroquine	13	(3.3)	10	(3.4)	3	(2.9)
Other immunosuppressive treatments[3]	35	(8.9)	24	(8.3)	11	(10.7)

Abbreviations:Arteriosclerotic CVD, Arteriosclerotic cardiovascular disease; IQR, interquartile range.
[1] 284 valid responses.
[2] Including Anti-U3RNP, Anti Th/To, Anti-U1-RNP, Anti-PM-Scl and Anti-KU.
[3] Other immunosuppressives used in less than 10 patients, including azathioprine, abatacept, cyclophosphamide, ciclosporin, leflunomide, interleukin 1 inhibitor, rituximab, salazopyrine, tocilizumab, and tumor necrosis factor inhibitor.

(see Fig. 2, lower panel). However, while the proportion of male SSc patients with a CAC score ≥100 was higher than that of male individuals in the background population, the difference was not statistically significant (47.6 % vs. 38.3 %, p=0.052).

Discussion

This study found a significantly higher burden of subclinical coronary artery calcification in a cohort of systemic sclerosis (SSc) patients compared to the background population. It also demonstrated that CAC scoring can easily be performed using a simple visual assessment of existing HRCT chest scans. Furthermore, we observed an association between digital ulcers and coronary artery calcification, suggesting a link between peripheral vascular disease and subclinical macrovascular coronary arteriosclerosis.

Patients with SSc have an increased risk of premature CAD [1–7], and it is important to be aware of early signs of CAD. The CAC score is superior to other methods for risk stratification of CVD among asymptomatic individuals (e.g. SCORE2, Framingham Risk Score, carotid intima media thickness or biomarkers), and has been suggested to better identify individuals at high risk who would benefit from primary cardiovascular preventive intervention, including treatment with statins and aspirin [30–32]. CAC quantified on non-gated CT scans has good agreement with CAC on ECG-gated CT scans [33] and several radiological societies recommend reporting CAC scores on routinely performed CT chest scans [34,35].

Table 2
Coronary artery calcifications in patients with SSc stratified by sex.

	Total		Female subjects (n= 291)		Male subjects (n=103)	
Coronary calcifications						
Agatston CAC score, median (IQR)	52	(0; 410)	30	(0; 304)	139	(15; 605)
Plaque present						
No plaques	116	(29.4)	101	(34.7)	15	(14.6)
1-vessel	102	(25.9)	74	(25.4)	28	(27.2)
2-vessels	97	(24.6)	63	(21.7)	34	(33.0)
3-vessels	79	(20.1)	53	(18.2)	26	(25.2)
Agatston CAC score, categorial, n (%)						
0	116	(29.4)	101	(34.7)	15	(14.6)
1-99	116	(29.4)	85	(29.2)	31	(30.1)
100- 999	111	(28.2)	71	(24.4)	40	(38.8)
>1000	51	(12.9)	34	(11.7)	17	(16.5)
Visual assessment of CAC score, n (%)						
None	115	(29.2)	100	(34.4)	15	(14.6)
mild	118	(30.0)	86	(29.6)	32	(31.1)
Moderate	113	(28.7)	73	(25.1)	40	(38.8)
Heavy	48	(12.2)	32	(11.0)	16	(15.5)

Abbreviations: CAC score; coronary artery calcium score, IQR, interquartile range.

Expert recommendations for the utilization of HRCT chest scans suggest screening for SSc-ILD at the time of diagnosis, particularly in patients at high risk of SSc-ILD progression, or in cases with declining pulmonary function tests or the onset of new respiratory symptoms [18]. Consequently, the majority of SSc patients undergo one or more HRCT chest scans during their disease course, presenting an opportunity for opportunistic analysis of CAC [36,37]. Such analysis could potentially guide preventive cardiovascular medical treatment and interventions. While the Agatston CAC score stands out as the gold standard for evaluating CAC, it requires dedicated software and the absolute Agatston CAC score is often overestimated on non-gated CT chest scans [28,38]. Chiles et al. have demonstrated that a simple visual assessment of CAC is comparable to the Agatston CAC score on non-gated low-dose chest CT scans to predict cardiovascular mortality in 1,575 smokers [22], allowing easy stratification of cardiovascular disease risk. Using HRCT chest scans, we demonstrate that the Agatston CAC score and this simple visual score strongly correlate. Moreover, the recent development of deep learning-based computer vision technologies enables the automatic quantification of coronary artery calcification from non-ECG-gated chest CT scans. This method has demonstrated a strong agreement with visual CAC scoring in SSc [39] and holds promise for routine reporting of CAC from HRCT chest scans in patients with SSc. Still, it should be emphasized that CAC scoring on HRCT chest scans may vary [28] and should not replace the use of dedicated cardiac CT.

Previous studies on subclinical calcifications detected by dedicated cardiac CT scans in patients with systemic sclerosis (SSc) have yielded conflicting results. Three studies found that SSc was an independent risk factor for CAC [40–42], while one study found no difference in CAC between SSc patients and controls [43]. Furthermore, two prior studies have suggested that the SSc disease duration is independently associated with CAC [41,42]. The results of these studies are not directly comparable to our study due to differences in study population and methods used to assess CAC. Our study included middle-aged patients with SSc and showed significantly higher calibrated CAC score from routinely collected HRCT-scans in comparison to CAC score using ECG-gated cardiac CT scan. Likewise, we observed a high prevalence of CAC scores >100 in male patients with SSc, but the prevalence of CAC score >100 was not significantly different from the background population, which may be explained by the smaller number of male patients with SSc in the study.

Table 3
Comparison of characteristics in patients with Agatston CACS ≥100 and Agatston CACS <100.

	Agatston CACS ≥100 (n=162)		Agatston CACS <100 (n= 232)		P-value
Demographics					
Age group median (IQI)					**0.001**
50-59	41	(25.3)	151	(49.6)	
60-69	80	(49.4)	88	(37.9)	
70-75	41	(25.3)	29	(12.5)	
Males, n (%)	57	(35.2)	46	(19.8)	**0.001**
Obesity (BMI≥30)	31	(19.1)	50	(21.6)	**0.34**
Smoking history, n (%)[1]					**<0.001**
Never smoker	44	(27.5)	106	(46.1)	
Current or ex-smoker	116	(72.5)	124	(53.9)	
Cardiovascular risk factors					
Hypertension, n (%)	78	(48.1)	73	(31.6)	**0.001**
Dyslipidaemia, n (%)	35	(21.6)	29	(12.5)	**0.023**
Diabetes mellitus n (%)	23	(14.2)	7	(3.0)	**<0.001**
Kidney failure, n (%)	17	(10.5)	17	(7.3)	0.27
Arteriosclerotic CVD, n (%)	16	(9.9)	10	(4.3)	**0.03**
Number of cardiovascular risk factors, n (%)					**<0.001**
0	50	(30.9)	115	(49.6)	
1-2	88	(53.3)	106	(45.7)	
≥3	24	(14.8)	11	(4.7)	
SSc characteristics					
Disease duration since first non-RS symptom, n (%)[2]					0.18
0-5 years	50	(35.8)	101	(43.5)	
>5 years	54	(33.3)	78	(33.6)	
Modified Rodnan skin score, n (%)					0.25
<15	139	(85.8)	208	(86.7)	
≥15	23	(14.2)	24	(10.3)	
Cutaneous subset, n (%)					0.19
Limited	89	(54.9)	129	(55.6)	
Diffuse	65	(40.1)	81	(34.9)	
No skin involvement	8	(4.9)	22	(9.5)	
Autoantibodies, n (%)					0.13
Anti-centromere antibody	65	(40.1)	92	(39.7)	
Anti-topoisomerase l	16	(9.9)	31	(13.4)	
Anti-RNA polymerase III	11	(6.8)	20	(8.6)	
Other SSc related autoantibodies[3]	26	(16.0)	49	(21.1)	
No autoantibodies	44	(27.2)	40	(17.2)	
Organ involvement					
Raynaud's phenonemon, n (%)	145	(89.5)	213	(91.8)	0.43
Gastrointestinal involvement, n (%)	111	(68.5)	154	(66.4)	0.66
Interstitial lung disease, n (%)	86	(53.1)	107	(46.1)	0.17
Digital ischemic ulcers, n (%)	49	(30.2)	44	(19.0)	**0.01**
Arthritis, n (%)	31	(19.1)	51	(22.0)	0.49
Pulmonary arterial hypertension, n (%)	13	(8.0)	9	(3.9)	0.08
Previous renal SSc crisis, n (%)	5	(3.1)	6	(2.6)	0.77
Myositis, n (%)	22	(13.6)	20	(8.6)	0.12
Myocarditis	5	(3.1)	4	(1.7)	0.37
Current medical treatment					
Prednisolone, n (%)	32	(20.6)	39	(16.8)	0.34
Immunosuppresive medicine, n (%)	45	(27.8)	56	(24.1)	0.42

Abbreviations: Arteriosclerotic CVD, Arteriosclerotic cardiovascular disease; IQR, interquartile range.
[1] 390 valid responses.
[2] 283 valid responses.
[3] Including Anti-U3RNP, Anti Th/To, Anti-U1-RNP, Anti-PM-Scl and Anti-KU.

Consistent with the findings of Rossdale et al., who reported a 58 % prevalence of CAC by routine CT chest scans in patients with SSc [23], we also found a high prevalence of CAC in our cohort. Rossdale et al. noted a particularly high risk in patients with pulmonary arterial hypertension, while we observed high CAC scores particularly associated with digital ulcers and longer disease duration. Similarly, the findings from the deep-learning-based approach mentioned above further supported an association between CAC prevalence and markers of severe microvascular disease, including fingertip ischemic ulcers, digital pitting scars, and pulmonary arterial hypertension [39]. Conversely, a

Table 4
Determinants of coronary artery calcium burden represented by an Agatston CAC score of ≥100 on HRCT in systemic sclerosis.

	Crude			Adjusted*		
	OR	(95 % CI)	P-value	OR	(95 % CI)	P-value
Disease duration in years	1.03	(1.01; 1.06)	0.02	1.05	(1.01; 1.09)	0.01
Anti-centromere antibodies	1.02	(0.67; 1.54)	0.96	1.04	(0.65; 1.66)	0.88
Anti SCL 70 antibodies	0.68	(0.36; 1.29)	0.23	0.79	(0.39; 1.58)	0.50
Anti RNA polymerase III antibodies	0.77	(0.36; 1.66)	0.49	0.47	(0.33; 1.69)	0.47
Limited skin involvement	1.02	(0.68; 1.54)	0.93	1.02	(0.65; 1.62)	0.93
Diffuse skin involvement	1.25	(0.83; 1.89)	0.31	1.15	(0.72; 1.86)	0.57
Raynauds phenomenon	0.76	(0.39; 1.51)	0.45	1.01	(0.46; 2.23)	0.98
Digital ulcers	1.85	(1.16; 2.96)	0.01	2.25	(1.31; 3.86)	0.01
Pulmonary arteriel hypertension	2.16	(0.90; 5.19)	0.09	1.54	(0.59; 4.10)	0.38
Renal crisis	1.20	(0.36; 4.00)	0.78	0.90	(0.24; 3.35)	0.87
Interstitial lung disease	1.32	(0.88; 1.98)	0.16	1.30	(0.83; 2.04)	0.26
Gastrointestinal involvement	1.10	(0.72; 1.69)	0.63	1.10	(0.67; 1.78)	0.71
Myositis	1.67	(0.88; 3.17)	0.12	1.50	(0.73; 3.07)	0.27
Myocarditis	1.82	(0.48; 6.87)	0.38	0.65	(0.15; 2.92)	0.58
Arthritis	0.84	(0.51; 1.38)	0.57	0.95	(0.54; 1.66)	0.86

* Adjusted for traditional cardiovascular risk factors (age, gender, diabetes, hypertension, dyslipidemia, BMI, smoking, and existing arteriosclerotic cardiovascular disease.)

Table 5
Agreement between the Agatston CAC score and the visual assessment of CAC on HRCT scan.

	Visual score				
Agatston CAC category	*None*	*Mild*	*Moderate*	*Heavy*	Total, n (%)
None (<1)	114	2	0	0	116 (29)
Mild (1-99)	1	110	5	0	116 (29)
Moderate (100-999)	0	5	99	7	111 (28)
Heavy (≥1000)	0	1	9	41	51 (13)
Total, n (%)	115 (29)	118 (30)	113 (29)	48 (12)	395

small observational study including 67 patients identified an association between only digital ulcers and CAC in univariate regression analysis [44]. However, this association did not persist in multivariate analysis, where adjustments were made for e.g. traditional risk factors and carotid plaques – suggesting that CAD might be primarily influenced by common atherogenic mechanisms rather than SSc-specific factors. While we did not have data on the presence of carotid plaques, this method is currently not recommended for cardiovascular risk assessment due to the absence of added value in predicting CVD events [45]. Together, these findings suggest that certain SSc phenotypes may predispose patients to a higher burden of CAC. This insight could be valuable for tailoring cardiovascular monitoring and interventions based on individual SSc characteristics.

Understanding the mechanisms behind accelerated subclinical arteriosclerosis in SSc is crucial for developing targeted interventions to manage and mitigate cardiovascular risks in the individual patient with SSc. The risk is presumably caused by a complex interplay between traditional risk factors and disease-specific mechanics, including endothelial damage and dysfunction, thrombogenesis, and chronic inflammation. Emerging evidence indicates an association between proximal large vessel vasculopathy and the presence of peripheral vasculopathy of micro- and medium-sized vessels in SSc. Color Doppler ultrasonography studies have linked ulnar artery occlusion and ischemic digital ulcers [46,47], while nailfold capillaroscopy studies have shown correlation between microvascular abnormalities and macrovascular indices, such as arterial stiffness [48] and aorta root dilation [49]. A large Italian multicenter study involving 613 patients with SSc found that ischemic digital ulcers were independently associated with both CVD and subclinical arteriosclerosis of the carotid arteries and the limbs, as assessed by Color Doppler ultrasonography [50]. Recently, elevated plasma desphospho-uncarboxylated matrix Gla-protein (dp-ucMGP) levels were reported in SSc patients compared to controls [51], correlating with increased CVD risk in both SSc patients and the general population [51,52]. Dp-ucMGP, the inactive form of matrix Gla-protein (a vitamin K-dependent inhibitor of vascular calcification), is synthesized by endothelial and vascular smooth muscle cells, linking it to vascular dysfunction and increased calcifications. These findings suggest a connection between microvascular and macrovascular dysfunction in SSc, contributing to the elevated risk of cardiovascular disease among these patients.

Atherosclerosis may be driven by autoimmune processes, involving both humoral factors and immune cells. However, the role of specific SSc autoantibodies in subclinical atherosclerosis remains unclear as conflicting results have been reported in the literature [2,23,40–44,50,53]. Two previous studies have suggested an association between anti-centromere antibodies (ACA) and ischemic arterial events as well as large vessel disease [2,53]. However, in our cohort, although most patients were ACA-positive, we found no association between autoantibody status and CAC severity. This discrepancy may reflect differences in study populations or sample sizes and warrants further investigation.

This study is not without limitations. Firstly, the retrospective design and reliance on electronic health records introduce the risk of incomplete or inconsistent documentation, potentially leading to biases in the analysis. Specifically, key cardiovascular risk factors such as hypertension, dyslipidemia, arteriosclerotic CVD, and diabetes may not have been completely registered in the electronic health records, potentially causing residual biases in the regression analysis. Moreover, the absence of systematic examinations for calcinosis and nailfold capillaroscopy, as well as evaluation of SSc heart involvement (fibrosis and arrhythmia), in all registered outpatients limits the ability to explore the associations between these characteristics and the extent of calcium burden in the coronary arteries. Secondly, we collected routinely performed HRCT chest scans performed after different SSc disease durations. Still, the median disease duration at the time of the HRCT chest scan was only 0.1 years (IQR: 0.0 years; 4.8 years) suggesting that most scans were baseline scans performed at time of diagnosis. Thirdly, we did not adjust for disease severity, including immunosuppressive medication and prednisolone use, as most HRCT chest scans served as baseline assessments. Since these scan results informed treatment decisions, this may have resulted in an underestimation of disease severity at the index date. Fourthly, patients with SSc were scanned using HRCT chest scans, while individuals in DANCAVAS and DanRisk were scanned using ECG-gated cardiac CT scans. To overcome these differences, we calibrated the CAC score from the HRCT chest scans to facilitate comparison with Agatston CAC derived from ECG-gated cardiac CT scans. However, this calibration was based on a small dataset [28], leading to substantial variation in CAC scores, making it difficult to account for this variability. Nevertheless, our aim was not to demonstrate interchangeability between the methods but rather to provide a comparative analysis with ECG-gated cardiac CT in this study. Lastly, our study population consisted primarily of SSc patients with a relatively short disease duration and high SSc-specific disease burden (Supplementary Table 1). Hence,

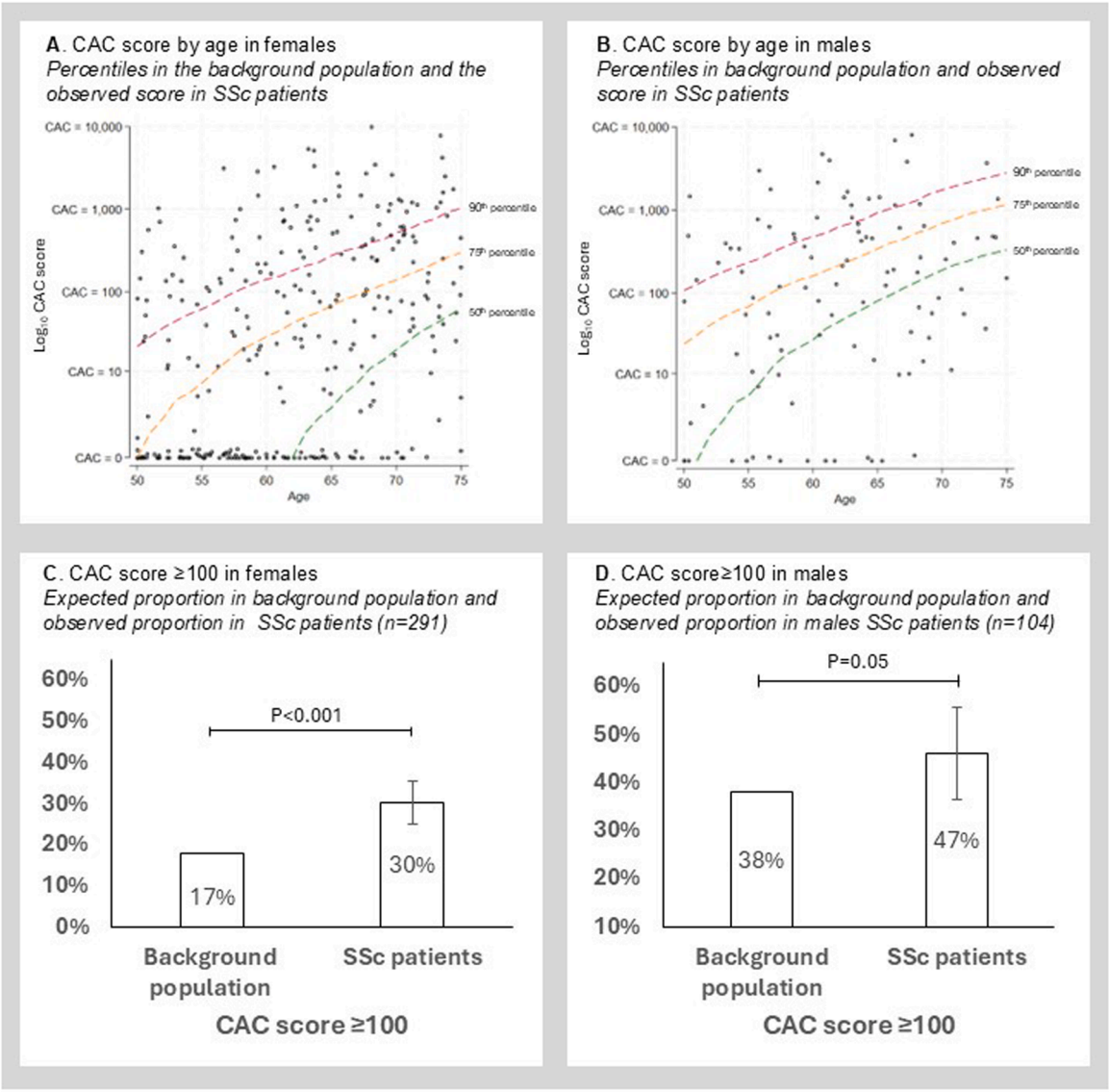

Fig. 2. Calibrated CAC scores in SSc patients and age- and gender specific CAC score in background population. Upper panel: Plot of calibrated CAC score for each SSc patient by gender and age-specific CAC score percentiles in the background population. The colored dashed lines show the gender- and age-specific 50th, 75th and 90th CAC score percentiles in background population. The solid black line represents the CAC score=100 Figure A: Female patients (n=291), Figure B: male patients (n=104). Lower panel: Proportion CAC score≥100 in the background population and observed proportion of SSc patients with CAC score ≥100 by HRCT scan. C: female patients (n=291), figure D: male patients (n=104). Vertical black lines represent the 95 % confidence intervals for the SSc patients.

our results may not be generalizable to the entire spectrum of SSc patients.

Despite these limitations, the strengths of our study lies in the large cohort of SSc patients, as well as the significant number of available HRCT chest scans for analysis. These strengths enhance the precision of the calculations and increase the generalizability of the findings. Furthermore, we were able to compare our findings with a large reference population.

Clinical implications

While medium- and small-vessel changes are characteristic of the vasculopathy in SSc, the presence of macrovascular atherosclerotic disease can substantially worsen the prognosis of patients [54]. The detection of CAC on routine chest CT scans is associated with more than a twofold increase in mortality risk for SSc patients [23]. Although non-gated CT scans differ in technical parameters and are more prone to artifacts compared to ECG-gated scans CT scans, emerging evidence suggests that the presence of CAC on these scans holds independent prognostic value in SSc [23,28]. Opportunistic screening for subclinical CAC using routinely performed HRCT chest scans, when integrated with conventional risk stratification tools, might refine CAD risk assessment and guide diagnostic and preventive strategies. While it should not replace ECG-gated CT scans, this approach could enhance CAD risk assessment and may offer clinical utility in managing patients with SSc.

Conclusion

Routinely performed HRCT chest scans can provide information on the presence of calcified plaques in patients with SSc, enabling the identification of individuals at increased risk for coronary artery disease and guiding further preventive diagnostic and treatment strategies. Additionally, digital ulcers appear to be a novel risk factor for the presence of coronary artery calcification.

Statements

None.

Ethics

The study was approved by the Danish Data Protection Agency (J. no. 1-16-02-344-22) and received permission from the Regional Committee in Central Region Denmark to access electronic medical records (case number: 1-45-70-80-22). In accordance with Danish law, approval from the Regional Committee on Health Research Ethics in the Central Denmark Region was not required, as the study did not involve any biomedical intervention.

Artificial intelligence

ChatGPT was used to improve the readability and clarity of the manuscript by refining sentence structure, grammar, and word choice.

Data availability

All data supporting the findings of this study are securely stored and managed in a REDCap database. As the data includes sensitive information that could compromise the privacy of the research participants, access is restricted to collaborative partners and is not available to the public.

CRediT authorship contribution statement

Esben U. Næser: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Frederik C. Enevoldsen:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Simon Winther:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Methodology, Formal analysis, Conceptualization. **Morten Bøttcher:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Formal analysis, Conceptualization. **Klaus Søndergaard:** Writing – review & editing, Supervision, Resources, Methodology. **Ellen-Margrethe Hauge:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Esben Uggerby Naeser reports financial support was provided by Danish Rheumatism Association. Frederik Enevoldsen reports financial support was provided by Royal Hofbuntmager Aage Bangs Fund. Esben Uggerby Naeser reports a relationship with Boehringer Ingelheim GmbH that includes: speaking and lecture fees. Morten Boettcher reports a relationship with Novo Nordisk Inc that includes: consulting or advisory. Morten Boettcher reports a relationship with AstraZeneca that includes: consulting or advisory. Morten Boettcher reports a relationship with Novartis that includes: consulting or advisory. Morten Boettcher reports a relationship with Boehringer Ingelheim GmbH that includes: consulting or advisory. Morten Boettcher reports a relationship with Sanofi SA that includes: consulting or advisory. Morten Boettcher reports a relationship with Amarin Switzerland GmbH that includes: consulting or advisory. Morten Boettcher reports a relationship with Acarix that includes: consulting or advisory. Simon Winther reports a relationship with Novo Nordisk Foundation that includes: funding grants. Klaus Soendergaard reports a relationship with Boehringer Ingelheim GmbH that includes: consulting or advisory, funding grants, and speaking and lecture fees. Klaus Soendergaard reports a relationship with The Danish Rheumatism Association that includes: funding grants. Klaus Soendergaard reports a relationship with UCB Inc that includes: consulting or advisory and speaking and lecture fees. Ellen-Margrethe Hauge reports a relationship with Novo Nordisk Inc that includes: consulting or advisory and funding grants. Ellen-Margrethe Hauge reports a relationship with Novartis that includes: consulting or advisory and travel reimbursement. Ellen-Margrethe Hauge reports a relationship with SynACT Pharma that includes: consulting or advisory. Ellen-Margrethe Hauge reports a relationship with Aarhus University Hospital that includes: funding grants. Ellen-Margrethe Hauge reports a relationship with Independent Research Fund Denmark that includes: funding grants. Ellen-Margrethe Hauge reports a relationship with Danish Rheumatism Association that includes: funding grants. Ellen-Margrethe Hauge reports a relationship with Aarhus University that includes: funding grants. Ellen-Margrethe Hauge reports a relationship with Danish Regions Medicine Grants that includes: funding grants. Ellen-Margrethe Hauge reports a relationship with Galapagos that includes: funding grants. Ellen-Margrethe Hauge reports a relationship with AbbVie Inc that includes: funding grants and travel reimbursement. Ellen-Margrethe Hauge reports a relationship with Sobi Inc that includes: travel reimbursement. Ellen-Margrethe Hauge reports a relationship with Boehringer Ingelheim GmbH that includes: travel reimbursement. Ellen-Margrethe Hauge has been a principal investigator in trials by SynACT Pharma, and a site principal investigator in trials by AbbVie, Novartis, Novo Nordisk, and Sanofi If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding sources

This work was supported by the Danish Rheumatism Association (Grant number: R217-A8011 & R224-A8291) and Aage Bangs Fond. The funding sources had no role in the study design, data collection, data analysis and interpretation, writing of the report, or the decision to submit the article for publication.

Acknowledgements

The authors are grateful for important technical assistance from Jette Barlach, René Møller Sørensen, Britta Hjaltason Jeppesen, and Anders Frodo Stegmann Mikkelsen. We also thank Asger Roer Pedersen for his statistical assistance.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2025.152723.

References

[1] Ngian GS, Sahhar J, Proudman SM, Stevens W, Wicks IP, Van Doornum S. Prevalence of coronary heart disease and cardiovascular risk factors in a national cross-sectional cohort study of systemic sclerosis. Ann Rheum Dis 2012;71:1980–3. https://doi.org/10.1136/annrheumdis-2011-201176.

[2] Nordin A, Jensen-Urstad K, Björnådal L, Pettersson S, Larsson A, Svenungsson E. Ischemic arterial events and atherosclerosis in patients with systemic sclerosis: A population-based case-control study. Arthritis Res Ther 2013;15. https://doi.org/10.1186/ar4267. R87.

[3] Man A, Zhu Y, Zhang Y, Dubreuil M, Rho YH, Peloquin C, et al. The risk of cardiovascular disease in systemic sclerosis: A population-based cohort study. Ann Rheum Dis 2013;72:1188–93. https://doi.org/10.1136/annrheumdis-2012-202007.

[4] Chu SY, Chen YJ, Liu CJ, Tseng WC, Lin MW, Hwang CY, et al. Increased risk of acute myocardial infarction in systemic sclerosis: A nationwide population-based study. Am J Med 2013;126:982–8. https://doi.org/10.1016/j.amjmed.2013.06.025.

[5] Antonio Aviña-Zubieta J, Man A, Yurkovich M, Huang K, Sayre EC, Choi HK. Early cardiovascular disease after the diagnosis of systemic sclerosis. Am J Med 2016; 129:324–31. https://doi.org/10.1016/j.amjmed.2015.10.037.

[6] Butt SA, Jeppesen JL, Torp-Pedersen C, Sam F, Gislason GH, Jacobsen S, et al. Cardiovascular Manifestations of systemic sclerosis: A Danish nationwide cohort study. J Am Heart Assoc 2019;8:e013405. https://doi.org/10.1161/JAHA.119.013405.

[7] Chen F-Y, Huo A-P, Wei JC-C. The risk of major adverse cardiovascular events in patients with systemic sclerosis: a nationwide, population-based cohort study. Rheumatology 2024;63:1–8. https://doi.org/10.1093/rheumatology/keae037.

[8] Chen IW, Wang WT, Lai YC, Lin CM, Liu PH, Wu SZ, et al. Association between systemic sclerosis and risk of cerebrovascular and cardiovascular disease: a meta-analysis. Sci Rep 2024;14:1–10. https://doi.org/10.1038/s41598-024-57275-9.

[9] Lai EC-C, Huang Y-C, Liao T-C, Weng M-Y. Premature coronary artery disease in patients with immune-mediated inflammatory disease: A population-based study. RMD Open 2022;8. https://doi.org/10.1136/rmdopen-2021-001993.

[10] Derk CT, Jimenez SA. Acute myocardial infarction in systemic sclerosis patients: A case series. Clin Rheumatol 2007;26:965–8. https://doi.org/10.1007/s10067-006-0211-8.

[11] Meiszterics Z, Tímár O, Gaszner B, Faludi R, Kehl D, Czirják L, et al. Early morphologic and functional changes of atherosclerosis in systemic sclerosis-a systematic review and meta-analysis. Rheumatology 2016;55:2119–30. https://doi.org/10.1093/rheumatology/kew236.

[12] Murdaca G, Colombo BM, Cagnati P, Gulli R, Spanò F, Puppo F. Endothelial dysfunction in rheumatic autoimmune diseases. Atherosclerosis 2012;224:309–17. https://doi.org/10.1016/j.atherosclerosis.2012.05.013.

[13] Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32. https://doi.org/10.1016/0735-1097(90)90282-T.

[14] Okwuosa TM, Greenland P, Ning H, Liu K, Bild DE, Burke GL, et al. Distribution of coronary artery calcium scores by Framingham 10-year risk strata in the MESA (Multi-Ethnic Study of Atherosclerosis): potential implications for coronary risk assessment. J Am Coll Cardiol 2011;57:1838–45. https://doi.org/10.1016/j.jacc.2010.11.053.

[15] Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, Coronary calcification, Coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. J Am Coll Cardiol 2005;46:158–65. https://doi.org/10.1016/j.jacc.2005.02.088.

[16] Budoff MJ, Young R, Burke G, Carr JJ, Detrano RC, Folsom AR, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). Eur Heart J 2018;39:2401–8. https://doi.org/10.1093/eurheartj/ehy217.

[17] Bernstein EJ, Khanna D, Lederer DJ. Screening high-resolution computed tomography of the chest to detect interstitial lung disease in systemic sclerosis: A global survey of rheumatologists. Arthritis and Rheumatol 2018;70:971–2. https://doi.org/10.1002/art.40441.

[18] Khanna D, Distler O, Cottin V, Brown KK, Chung L, Goldin JG, et al. Diagnosis and monitoring of systemic sclerosis-associated interstitial lung disease using high-resolution computed tomography. J Scleroderma Relat Disord 2022;7:168–78. https://doi.org/10.1177/23971983211064463.

[19] Gotway MB, Reddy GP, Webb WR, Elicker BM, Leung JWT. High-resolution CT of the lung: patterns of disease and differential diagnoses. Radiol Clin North Am 2005; 43:513–42. https://doi.org/10.1016/j.rcl.2005.01.010.

[20] Hughes-Austin JM, Dominguez A, Allison MA, Wassel CL, Rifkin DE, Morgan CG, et al. Relationship of coronary calcium on standard chest CT scans with mortality. JACC Cardiovasc Imaging 2016;9:152–9. https://doi.org/10.1016/j.jcmg.2015.06.030.

[21] Mets OM, Vliegenthart R, Gondrie MJ, Viergever MA, Oudkerk M, De Koning HJ, et al. Lung cancer screening CT-based prediction of cardiovascular events. JACC Cardiovasc Imaging 2013;6:899–907. https://doi.org/10.1016/j.jcmg.2013.02.008.

[22] Chiles C, Ravenel JG, Baginski SG, Snyder BS, Demello S, Desjardins SS, et al. Association of coronary crtery calcification and mortality in the National lung screening Trial: A comparison of three scoring methods. Radiology 2015;276:82–90.

[23] Rossdale J, Graby J, Harris M, Jones C, Greenish D, Bartlett J, et al. Coronary artery calcification is prevalent in systemic sclerosis and is associated with adverse prognosis. J Scleroderma Relat Disord 2024;9:192–202. https://doi.org/10.1177/23971983241264090.

[24] Van Den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: An american college of rheumatology/European league against rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737–47. https://doi.org/10.1002/art.38098.

[25] Gerke O, Lindholt JS, Abdo BH, Lambrechtsen J, Frost L, Steffensen FH, et al. Prevalence and extent of coronary artery calcification in the middle-aged and elderly population. Eur J Prev Cardiol 2021;28:2048–55. https://doi.org/10.1093/eurjpc/zwab111.

[26] Lindholt JS, Rasmussen LM, Søgaard R, Lambrechtsen J, Steffensen FH, Frost L, et al. Baseline findings of the population-based, randomized, multifaceted Danish cardiovascular screening trial (DANCAVAS) of men aged 65–74 years. British J Surg 2019;106:862–71. https://doi.org/10.1002/bjs.11135.

[27] Diederichsen ACP, Sand NP, Nørgaard B, Lambrechtsen J, Jensen JM, Munkholm H, et al. Discrepancy between coronary artery calcium score and HeartScore in middle-aged Danes: the DanRisk study. Eur J Prev Cardiol 2012;19:558–64. https://doi.org/10.1177/1741826711409172.

[28] Enevoldsen FC, Næser EU, Winther S, Bøttcher M, Søndergaard K, Hauge EM. Validation of routine high-resolution computed tomography scans against gated cardiac CT for the assessment of coronary artery calcification. J Cardiovasc Comput Tomogr 2024;18:311–3. https://doi.org/10.1016/j.jcct.2024.01.017.

[29] Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med 2016;15:155–63. https://doi.org/10.1016/j.jcm.2016.02.012.

[30] Martin SS, Blaha MJ, Blankstein R, Agatston A, Rivera JJ, Virani SS, et al. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the multi-ethnic study of atherosclerosis. Circulation 2014;129:77–86. https://doi.org/10.1161/CIRCULATIONAHA.113.003625.

[31] Patel J, Pallazola VA, Dudum R, Greenland P, McEvoy JW, Blumenthal RS, et al. Assessment of coronary artery calcium scoring to guide statin therapy allocation according to risk-enhancing factors: the multi-ethnic study of atherosclerosis. JAMA Cardiol 2021;6:1161–70. https://doi.org/10.1001/jamacardio.2021.2321.

[32] Lindholt JS, Søgaard R, Rasmussen LM, Mejldal A, Lambrechtsen J, Steffensen FH, et al. Five-year outcomes of the Danish cardiovascular screening (DANCAVAS) trial. New England J Med 2022;387:1385–94. https://doi.org/10.1056/nejmoa2208681.

[33] Xie X, Zhao Y, De Bock GH, De Jong PA, Mali WP, Oudkerk M, et al. Validation and prognosis of coronary artery calcium scoring in nontriggered thoracic computed tomography: systematic review and meta-analysis. Circ Cardiovasc Imaging 2013; 6:514–21. https://doi.org/10.1161/CIRCIMAGING.113.000092.

[34] Hecht HS, Cronin P, Blaha MJ, Budoff MJ, Kazerooni EA, Narula J, et al. 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: A report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. J Cardiovasc Comput Tomogr 2017;11:74–84. https://doi.org/10.1016/j.jcct.2016.11.003.

[35] Williams MC, Abbas A, Tirr E, Alam S, Nicol E, Shambrook J, et al. Reporting incidental coronary, aortic valve and cardiac calcification on non-gated thoracic computed tomography, a consensus statement from the BSCI/BSCCT and BSTI. British J Radiol 2021;94:20210302. https://doi.org/10.1259/bjr.20200894.

[36] Hoffmann-Vold AM, Fretheim H, Halse AK, Seip M, Bitter H, Wallenius M, et al. Tracking impact of interstitial lung disease in systemic sclerosis in a complete nationwide cohort. Am J Respir Crit Care Med 2019;200:1258–66. https://doi.org/10.1164/rccm.201903-0486OC.

[37] Forestier A, Le Gouellec N, Béhal H, Kramer G, Perez T, Sobanski V, et al. Evolution of high-resolution CT-scan in systemic sclerosis-associated interstitial lung disease: description and prognosis factors. Semin Arthritis Rheum 2020;20:1406–13.

[38] Kim JY, Suh YJ, Han K, Choi BW. Reliability of coronary artery calcium severity assessment on non-electrocardiogram-gated CT: A meta-analysis. Korean J Radiol 2021;22:1034–43. https://doi.org/10.3348/kjr.2020.1047.

[39] Luo Y, Hanuska D, Xu J, Salvatore MM, Bernstein EJ. Quantification of coronary artery calcification in systemic sclerosis using visual ordinal and deep learning scoring: association with systemic sclerosis clinical features. Semin Arthritis Rheum 2025;70. https://doi.org/10.1016/j.semarthrit.2024.152598.

[40] Khurma V, Meyer C, Park GS, McMahon M, Lin J, Singh RR, et al. A pilot study of subclinical coronary atherosclerosis in systemic sclerosis: coronary artery calcification in cases and controls. Arthritis Care Res 2008;59:591–7. https://doi.org/10.1002/ART.23540.

[41] Mok MY, Lau CS, Chiu SSH, Tso AWK, Lo Y, Law LSC, et al. Systemic sclerosis is an independent risk factor for increased coronary artery calcium deposition. Arthritis Rheum 2011;63:1387–95. https://doi.org/10.1002/ART.30283/FORMAT/PDF.

[42] Afifi N, Khalifa MMM, Al Anany AAMMM, Hassan HGEMA. Cardiac calcium score in systemic sclerosis. Clin Rheumatol 2022;41:105–14. https://doi.org/10.1007/s10067-021-05887-1.

[43] Seung-Geun L, Young-Eun P, Su-Yeon C, Eun-Kyung P, Geun-Tae K, Ki-Seok C, et al. Systemic sclerosis is not associated with increased coronary artery calcium deposition. Turkish J Rheumatol 2013;28:242–50. https://doi.org/10.5606/tjr.2013.3625.

[44] Rotondo C, Sciacca S, Rella V, Busto G, Colia R, Cantatore FP, et al. Subclinical coronary atherosclerosis, detected by computer tomography with coronary calcium score, and the occurrence of major cardiovascular events at 5 years of follow-up in a cohort of patients with systemic sclerosis. Eur J Intern Med 2023;115:62–9. https://doi.org/10.1016/j.ejim.2023.06.003.

[45] Visseren F, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227–337. https://doi.org/10.1093/eurheartj/ehab484.

[46] Lüders S, Friedrich S, Ohrndorf S, Glimm AM, Burmester GR, Riemekasten G, et al. Detection of severe digital vasculopathy in systemic sclerosis by colour Doppler sonography is associated with digital ulcers. Rheumatology 2017;56:1865–73. https://doi.org/10.1093/rheumatology/kex045.

[47] Lescoat A, Yelnik CM, Coiffier G, Wargny M, Lamotte C, Cazalets C, et al. Ulnar artery occlusion and severity markers of vasculopathy in systemic sclerosis: A multicenter cross-sectional study. Arthritis Rheumatol 2019;71:983–90. https://doi.org/10.1002/art.40799.

[48] Pagkopoulou E, Soulaidopoulos S, Triantafyllidou E, Arvanitaki A, Katsiki N, Loutradis C, et al. Peripheral microcirculatory abnormalities are associated with cardiovascular risk in systemic sclerosis: a nailfold video capillaroscopy study. Clin Rheumatol 2021;40:4957–68. https://doi.org/10.1007/s10067-021-05795-4.

[49] Colaci M, Dal Bosco Y, Schinocca C, Ronsivalle G, Guggino G, De Andres I, et al. Aortic root dilation in associated with the reduction in capillary density observed at nailfold capillaroscopy in SSc patients. Clin Rheumatol 2021;40:1185–9. https://doi.org/10.1007/s10067-020-05201-5.

[50] Liakouli V, Verde I, Ruscitti P, Di Vico C, Ruggiero A, Mauro D, et al. Clinical and subclinical atherosclerosis in patients with systemic sclerosis: an observational, multicentre study of GIRRCS (Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale). Clin Exp Rheumatol 2024;42:1645–55. https://doi.org/10.55563/clinexprheumatol/zr8j5p.

[51] Potjewijd J, Tobal R, Boomars KA, van Empel VVPM, de Vries F, Damoiseaux JGMC, et al. Plasma dephosphorylated-uncarboxylated matrix gla-protein in systemic sclerosis patients: biomarker potential for vascular calcification and inflammation. Diagnostics 2023;13:1–13. https://doi.org/10.3390/diagnostics13233526.

[52] Wei FF, Trenson S, Verhamme P, Vermeer C, Staessen JA. Vitamin K-dependent matrix gla protein as multifaceted protector of vascular and tissue integrity. Hypertension 2019;73:1160–9. https://doi.org/10.1161/HYPERTENSIONAHA.119.12412.

[53] Wan MC, Moore T, Hollis S, Herrick AL. Ankle brachial pressure index in systemic sclerosis: influence of disease subtype and anticentromere antibody. Rheumatology 2001;40:1102–5. https://doi.org/10.1093/rheumatology/40.10.1102.

[54] Komócsi A, Pintér T, Faludi R, Magyari B, Bozó J, Kumánovics G, et al. Overlap of coronary disease and pulmonary arterial hypertension in systemic sclerosis. Ann Rheum Dis 2010;69:202–5. https://doi.org/10.1136/ard.2008.096255.