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Original Article

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Aslihan Avanoglu-Guler[1,2], Michael Hughes[3,4,5], Giacomo De Luca[2,6], Silvia Bellando Randone[7], David Launay[8,9], Anna Wojteczek[10], Simona Rednic[11,12], Emmanuel Chatelus[13], Alexandra Balbir-Gurman[14], Liala Moschetti[15], Ulf Müller-Ladner[16], Petros P. Sfikakis[17], Luca Idolazzi[18], Nicoletta Del Papa[19], Oliver Distler[20], Lorenzo Dagna[2,6], Marie Elise Truchetet[21,22], Madelon C. Vonk[23], Francesco Del Galdo[24,25], Marco Matucci-Cerinic[2,26], Corrado Campochiaro[2,6,*], for EUSTAR Collaborators[†]

[1]Division of Rheumatology, Department of Internal Medicine, Ufuk University Faculty of Medicine, Ufuk University Dr Rıdvan Ege Hospital, Ankara, Türkiye
[2]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Hospital, Milan, Italy
[3]Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Science, School of Biological Sciences, Faculty of Biological Medicine and Health, The University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom
[4]Department of Rheumatology, Northern Care Alliance NHS Foundation Trust, Salford Care Organisation, Salford, United Kingdom
[5]NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester, United Kingdom
[6]Vita Salute San Raffaele University, Milan, Italy
[7]Department of Experimental and Clinical Medicine, University of Florence, Division of Rheumatology Scleroderma Unit, Careggi Hospital, Florence, Italy
[8]University of Lille, Inserm, CHU Lille, U1286 – INFINITE—Institute for Translational Research in Inflammation, Lille, France
[9]Département de Médecine Interne et Immunologie Clinique, CHU Lille, Centre de Référence des Maladies Auto-Immunes et Auto-Inflammatoires Rares du Nord, Nord-Ouest, Méditerranée et Guadeloupe (CeRAINOM), Lille, France
[10]Department of Rheumatology, Clinical Immunology, Geriatrics and Internal Medicine, Medical University of Gdańsk, University Clinical Centre in Gdańsk, Gdańsk, Poland
[11]Department of Rheumatology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
[12]Department of Rheumatology, County Emergency Hospital, Cluj-Napoca, Romania
[13]Rheumatology Department, Strasbourg University Hospital, Hautepierre Hospital, Strasbourg, France
[14]Rambam Health Care Campus and The Rappaport Faculty of Medicine, Rheumatology Institute, Haifa, Israel
[15]Rheumatology and Clinical Immunology Unit, ASST Spedali Civili and University of Brescia, Italy
[16]Campus Kerckhoff, Department of Rheumatology and Clinical Immunology, Justus Liebig University Giessen, Bad Nauheim, Germany
[17]Rheumatology Unit, First Department of Propaedeutic Internal Medicine, Joint Academic Rheumatology Program, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece
[18]Section of Rheumatology, Department of Medicine, University of Verona, Verona, Italy
[19]Scleroderma Clinic, Rheumatology Department, ASST G. Pini-CTO, Università degli Studi di Milano, Milano, Italy
[20]Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[21]Bordeaux University, CNRS, ImmunoConcEpT, UMR 5164, Bordeaux, France
[22]Rheumatology department, Bordeaux University Hospital, Centre National de référence Des Maladies Autoimmunes et Systémiques Rares Est/Sud-Ouest (RESO), Bordeaux, France
[23]Department of Rheumatology, Radboud University Njmegen Medical Center, Nijmegen, The Netherlands
[24]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom
[25]NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals Trust, Leeds, United Kingdom
[26]Inflammation Fibrosis and Ageing Initiative (INFLAGE), Division of Genetics and Cell Biology, IRCCS San Raffaele Scientific Institute, Milan, Italy
*Correspondence to: Corrado Campochiaro, Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), San Raffaele Scientific Institute, IRCCS San Raffaele Hospital, Milan, Via Olgettina, 60, 20132 Milano (MI), Italy. E-mail: campochiaro.corrado@hsr.it
[†]See supplementary material available at *Rheumatology* online for a list of the EUSTAR Collaborators.

Abstract

Objectives: **Calcinosis Cutis (CaC) represents one of the most frequent and disabling non-lethal manifestations in SSc. Our objectives were to evaluate (1) associations of CaC with SSc clinical characteristics and (2) identify risk factors for CaC development.**

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Methods: **EUSTAR database–registered SSc patients with available information on their CaC status were included. We compared baseline patient characteristics (with *vs* without CaC at baseline) and investigated predictors of CaC development at 5 and 10 years (in those without baseline CaC) with logistic regression analyses.**

Results: **A total of 7114 SSc patients were included. At baseline, 11.9% had CaC. Among 1010 and 997 patients without baseline CaC, 40% and 46% developed CaC within 5 years and 10 years, respectively. Patients with CaC were more frequently female, had longer disease duration, higher modified Rodnan Skin Score, telangiectasia, digital ischaemia, late capillaroscopy patterns, joint contractures, tendon friction rubs, gastrointestinal involvement (all $P < 0.001$), pulmonary arterial hypertension (PAH) ($P = 0.02$), joint synovitis, and renal crisis (both $P = 0.04$). CaC patients had a higher frequency of ACA and anti-PM/Scl antibody positivity ($P < 0.001$; $P = 0.03$, respectively). Predictors for the development of CaC at 5 years included longer disease duration [odds ratio (OR) 1.04], cardiac involvement (OR 1.63), late capillaroscopy pattern (OR 1.70), telangiectasia (OR 1.92), digital ulcers (OR 2.60), and PAH (OR 2.10). Predictors at 10 years included longer disease duration (OR 1.03), dcSSc (OR 1.51), female gender (OR 1.85), telangiectasia (OR 1.92), and digital ulcers (OR 2.92).**

Conclusion: **CaC is common and progressive; clinical risk factors may provide insights into the pathogenesis.**

Keywords calcinosis cutis, clinical characteristics, predictor, risk factor, systemic sclerosis

Rheumatology key messages

- Calcinosis cutis is common and often progressive over time in systemic sclerosis.
- Vasculopathic findings, particularly in digital ulcers and telangiectasia, independently predict calcinosis development.
- Longer disease duration is significantly associated with calcinosis development.

Introduction

Calcinosis Cutis (CaC), a form of dystrophic calcification of soft tissue, is a commonly observed manifestation in SSc patients. Dystrophic calcification can be defined as soft tissue calcinosis with normal serum calcium and phosphorous levels, while in SSc the crystalline component of calcinosis is mainly represented by calcium hydroxyapatite [1, 2].

In SSc, the most frequent sites of calcinosis are the hands (particularly the distal phalanges), elbows, and knees, which are more exposed to pressure and repetitive trauma [3, 4]. In SSc, more unusual areas, such as the facial or spinal regions of the body, can also be affected by calcinosis [1].

The prevalence of CaC in SSc has been reported to range between 18% and 49% [5–8]. However, calcinosis is often subclinical and may be detected coincidentally on otherwise performed imaging procedures; therefore, its presence (and extent) may be underestimated by clinical examination alone [9, 10]. However, in a subset of patients, this represents a major burden associated with the disease, because CaC can be complicated with pain, infection, or ulceration that significantly reduce the quality of life [11–13]. Moreover, CaC is independently related to physical impairment and pain in SSc patients [7, 11, 14].

Although its pathogenesis is still largely unknown, vascular ischaemia and mechanical stress/repetitive microtrauma have been proposed as key drivers of CaC development, and may differ in contribution according to the anatomical site [4, 5, 7]. In SSc, the severity of digital ischaemia (e.g. as assessed by nailfold capillaroscopy) and longer disease duration are closely associated with CaC [7, 9, 15]. The limited cutaneous subset and ACA / anti-Pml/Scl antibodies have been suggested as CaC risk factors, but these findings are still debated, as the observations were only in small cohorts [7, 9, 15–19].

The management of CaC remains a major clinical challenge with no known disease-modifying treatments, including preventative approaches. Various pharmacological approaches (topical, intralesional, systemic) and surgical interventions have been proposed [3, 5]. However, most treatment modalities for CaC are not curative, and this field remains remarkably debated due to the anecdotal evidence in the existing studies. Surgical excision is considered as a final resort, as CaC can often regrow, and wound healing can be challenging.

Against this background, our primary objective was to investigate the prevalence of CaC, within the multicentre cohort of the European Scleroderma Trials and Research Group (EUSTAR) database. Our secondary objectives were to identify the clinical features characterizing CaC patients and the risk factors for CaC development.

Material and methods

Data sampling

Patients registered in the international EUSTAR database were analysed. Patients who met the 2013 ACR/EULAR SSc classification criteria and who had at least one visit recording data on calcinosis were included in the study (EUSTAR Clinical Project number: CP 136) [20].

The definition and evaluation of variables

The structure and collected variables of the EUSTAR database have been well described [21]. For the EUSTAR database, calcinosis is defined as a deposit of insoluble calcium salts in soft tissues confirmed through physical examination or imaging

modalities, such as plain radiography and CT. In the dataset, the first visit, which documented the presence or absence of calcinosis, was designated as the study baseline.

Recorded demographic data, clinical features and laboratory findings were systematically extracted from the baseline visit and comprehensively assessed. The variables extracted were: age, gender, smoking habits, SSc-related features, including disease duration (since the onset of first non-RP manifestation and onset of RP), SSc cutaneous subset, digital ischaemic findings [digital ulcers (DUs), gangrene, and amputation], capillaroscopic pattern, modified Rodnan skin score (mRSS), interstitial lung disease (presence of lung fibrosis on chest radiography and/or high-resolution CT), pulmonary arterial hypertension (PAH), muscle involvement (proximal limb muscle strength deficit on physical examination as judged by the physician not explainable by other causes), cardiac involvement (presence of arrhythmias/conduction blocks, left ventricular ejection fraction $\leq 49\%$, diastolic dysfunction, and pericardial effusion) renal crisis, gastrointestinal involvement (presence of oesophageal, stomach or intestinal symptoms), joint synovitis (clinical evidence of joint swelling/tenderness), joint contractures, tendon friction rubs, and death.

The elevation of CRP and the antibody profile were evaluated. SSc-specific treatments, including proton pump inhibitors, calcium channel blockers, ET-1 receptor antagonists, phosphodiesterase-5 inhibitors, prostanoids, glucocorticosteroids, immunosuppressive/immunomodulators, antiplatelet drugs, and anticoagulants, were assessed.

All variables at the baseline visit were examined by means of a comparison between the CaC and non-CaC groups. After the initial baseline assessment, the development of new calcinosis in the non-CaC group at 5 and 10 years was evaluated using longitudinal data.

Statistical analysis

Age, following a normal distribution, was presented as the mean and standard deviation (S.D.). Non-parametric variables were described using the median and interquartile range (IQR) for continuous data, including disease duration and mRSS, and proportions and frequencies for categorical variables, as appropriate. The comparison of variables between the CaC and non-CaC group at baseline, as well as between those with new calcinosis development over 5 and 10 years and those without calcinosis, was analysed by using Student's t, χ^2, Fisher's exact, or the Mann–Whitney U test as appropriate.

The risk factors for new calcinosis development were determined using univariate logistic regression analyses and described as a crude odds ratio (OR) with 95% CIs. Variables found statistically significant in the univariate analyses ($P < 0.05$) were subsequently included in a multivariate regression model, in addition to age and gender, to detect independent risk factors. The effect of CaC on patient survival was evaluated using the log-rank (Kaplan–Meier) test.

Results

A total of 7114 SSc patients with available CaC information at baseline were analysed. The mean (S.D.) age of patients was 57.2 ± 13.5 years, and the majority (83.8%) were female. One-third of patients (36.4%) had a diffuse subset of SSc. At baseline, 850 patients (11.9%) had CaC.

The association of clinical features with the presence of CaC at the baseline visit

The baseline characteristics of SSc patients with respect to the presence of CaC are presented in Table 1. Patients with (*vs* without) CaC were more likely to be female (89.4% *vs* 83%, $P < 0.001$) and older (58.5 ± 12.9 *vs* 57.0 ± 13.6 years, $P = 0.002$). Moreover, SSc patients with CaC had a significantly longer disease duration [12.8 (13) *vs* 6.3 (10) years, $P < 0.001$]. Similarly, the disease duration since RP onset (information available for 1092 patients) was higher in patients with CaC compared with those without CaC [15.8 (18) *vs* 7 (13) years, $P < 0.001$].

The assessment of clinical characteristics of SSc patients showed that patients with CaC had more frequently telangiectasia (74.5% *vs* 56.3% $P < 0.001$), musculoskeletal manifestations, including muscle involvement (19% *vs* 13% $P < 0.001$), joint synovitis (12.2% *vs* 10.2% $P = 0.04$), joint contractures (35.4% *vs* 20.7% $P < 0.001$), and tendon friction rubs (7.8% *vs* 4.7% $P < 0.001$). The frequency of digital ischaemia findings, including the presence of previous/current ulcers, gangrene, and amputation, was significantly higher in SSc patients with CaC (Table 1). In addition, the nailfold capillaroscopy pattern differed notably, as patients with CaC exhibited a higher frequency of the late pattern (52.9% *vs* 29.1%, $P < 0.001$). The median mRSS (IQR) was numerically higher in patients with CaC compared with patients without CaC [4 (11) *vs* 3 (9), $P < 0.001$], while the the presence of CaC did not differ in the disease subsets.

The evaluation of organ involvement showed that the prevalence of gastrointestinal involvement and renal crisis was more prevalent in patients with CaC (67.6% *vs* 58.9%, $P < 0.001$; 2.6% *vs* 1.6% $P = 0.04$, respectively). Similarly, PAH was more commonly observed in patients with CaC (20.6% *vs* 14.5%, $P = 0.023$). There were no meaningful differences in interstitial lung disease (ILD) or cardiac involvement between the two groups. ACA and anti-PM/Scl antibodies were more frequent in CaC patients (47.3% *vs* 37.8% $P < 0.001$ and 7.9% *vs* 3.5% $P = 0.03$, respectively), whereas anti-Scl-70 positivity was more common in those without CaC (29.9% *vs* 39.5% $P < 0.001$). Among patients with CaC, those who were anti-Scl-70 positive more frequently exhibited tendon friction rub (19% *vs* 4%), and joint contractures (54% *vs* 30%) and had a higher median mRSS [7 (15) *vs* 4 (11)] (all $P < 0.001$). Moreover, as expected, CaC patients with tendon friction rub had significantly lower frequency of ACA positivity compared with those without tendon friction rub (22.6% *vs* 50%, $P < 0.001$). Furthermore, the frequency of anti-Scl-70 positivity was notably higher in CaC patients with tendon friction rub (68.5% *vs* 26.5%, $P < 0.01$). Similarly CaC patients with joint contracture had a significantly higher frequency of anti-Scl-70 (43% *vs* 22%, $P < 0.001$), whereas CaC patients without joint contracture had increased positivity of ACA compared with those with joint contractures (55% *vs* 35% $P < 0.001$). The overall mortality rate was higher in CaC patients compared with patients without CaC (7.6% *vs* 5.4%, $P = 0.007$). The univariate logistic regression analysis showed that the presence of CaC was related to all-cause mortality (crude OR = 1.5, 95% CI: 1.10–1.90, $P = 0.008$). However, this association was not statistically

Table 1 Baseline characteristics of SSc patients in comparison with the presence of calcinosis

	Patients with calcinosis ($n = 850$)	Patients without calcinosis ($n = 6264$)	*P*
Age, mean (S.D.), years[a]	58.53 (12.91)	57.03 (13.58)	0.002
Sex, female (%)	760 (89.4)	5200 (83)	<0.001
Disease duration, median (IQR), years	12.8 (13)	6.3 (10)	<0.001
Smoking, current (%)	85 (10)	705 (11.3)	0.546
Subtype (%)			0.23
dcSSc	253 (34.4)	2012 (36.7)	
lcSSc/sine	482 (65.6)	3473 (63.3)	
mRSS (IQR)	4 (11)	3 (9)	<0.001
Telangiectasia (%)	633 (74.5)	3529 (56.3)	<0.001
Digital ulcers (%)			<0.001
Never	257 (30.2)	3567 (56.9)	
Previous	349 (41.1)	1515 (24.2)	
Current	215 (25.3)	847 (13.5)	
Gangrene (%)			<0.001
Never	471 (87.7)	3856 (94.2)	
Previous	44 (8.2)	160 (3.9)	
Current	22 (4.1)	78 (1.9)	
Amputation (%)	22 (12.9)	30 (5)	<0.001
Capillaroscopy (%)[b]			<0.001
Early	48 (14.7)	753 (29.1)	
Active	106 (32.4)	1081 (41.8)	
Late	173 (52.9)	754 (29.1)	
Muscle involvement (%)	152 (19)	755 (13)	<0.001
Joint synovitis (%)	104 (12.2)	636 (10.2)	0.041
Joint contractures (%)	301 (35.4)	1294 (20.7)	<0.001
Tendon friction rub (%)	66 (7.8)	293 (4.7)	<0.001
GI involvement (%)	575 (67.6)	3668 (58.9)	<0.001
Cardiac involvement (%)	218 (69.9)	1406 (67.7)	0.44
Interstitial lung disease (%)	334 (53.6)	2504 (53.9)	0.89
Pulmonary arterial hypertension (%)	43 (20.6)	191 (14.5)	0.023
Renal crisis (%)	22 (2.6)	100 (1.6)	0.038
Positivity of antibodies (%)			
Anti-Scl-70	204 (29.9)	2055 (39.5)	<0.001
ACA	322 (47.3)	1917 (37.8)	<0.001
Anti-RNA-pol-3	46 (9.8)	306 (8.1)	0.197
Anti-SSA	46 (13.3)	439 (15)	0.404
Anti-SSB	13 (3.8)	74 (2.6)	0.184
Anti-PM/Scl[a]	15 (7.9)	56 (3.5)	0.03
Elevated CRP (%)[a]	88 (32.6)	470 (28)	0.121
Treatments (%)			
Proton pump inhibitors	540 (63.5)	3617 (57.7)	<0.001
Calcium channel blockers	348 (40.9)	2525 (40.3)	0.978
ET-1 receptor antagonists	165 (19.4)	793 (12.7)	<0.001
Phosphodiesterase 5 inhibitors	107 (12.6)	535 (8.5)	<0.001
Prostanoids	150 (17.5)	883 (14.1)	0.009
Glucocorticosteroids	244 (28.7)	1641 (26.2)	0.130
Immunosuppressive/immunomodulators	301 (35.4)	2452 (39.1)	0.012
Antiplatelets	225 (26.5)	1622 (25.9)	0.910
Oral anticoagulants	51 (6)	244 (3.9)	0.05

[a] Age was calculated based on the date of the study baseline visit.
[b] Number of patients included for capillaroscopy, $n = 2915$ (41%); anti-PM/Scl, $n = 1792$ (25%) and elevated CRP, $n = 1949$ (27%). GI: gastrointestinal; IQR: interquartile range; mRSS: modified Rodnan skin score.

significant after adjustment in the multivariate model. In Kaplan–Meier analyses, survival tended to be lower in patients with CaC, although the difference did not reach statistical significance (log-rank $\chi^2 = 3.73$, $P = 0.053$).

CaC patients also had higher use of proton pump inhibitors (PPIs), vasoactive treatments, prostanoids, and anticoagulants (Table 1). Patients without CaC had a higher frequency of immunosuppressive/immunomodulator therapy use (39% *vs* 35.4%, $P = 0.01$). The use of calcium channel blockers (CACBs) was similar in both groups.

The development of CaC and its potential risk factors at the fifth and tenth years

Five-year follow-up

Five-year longitudinal data were available for 1010 SSc patients without CaC at baseline. Among these, 403 (40%) developed CaC within 5 years. These patients were significantly older and had longer disease duration than those who did not develop CaC (Supplementary Table S1). The dcSSc subset was more frequently observed in patients developing CaC (40.4% *vs* 31.6% $P < 0.01$). Patients who developed CaC had numerically higher skin scores [5 (12) *vs* 4 (9), $P = 0.02$]. The presence of ILD was associated with the development of CaC, but only at univariate analyses (crude OR = 1.47, 95% CI: 1.10–1.96, $P = 0.008$, Supplementary Table S1). There was no meaningful relationship between positivity of antibodies and CaC development. The frequency of elevated CRP levels was not statistically different between the two groups (29.7% *vs* 22.7% $P = 0.06$).

Multivariate logistic regression analysis identified, as independent risk factors for the development of CaC at 5 years, longer disease duration [OR 1.04 (95% CI: 1.01–1.06)], cardiac involvement [OR 1.63 (95% CI: 1.02–2.58)], late capillaroscopy pattern [OR 1.70 (95% CI: 1.00–2.90)], telangiectasia [OR 1.92 (95% CI: 1.36–2.71)], digital ulcers [OR 2.60 (95% CI: 1.88–3.60)], and PAH [OR 2.10 (95% CI: 1.08–4.11)].

Ten-year follow-up

Among 997 patients followed up for 10 years, 46.2% developed CaC. The median mRSS was higher in patients with developed CaC than in those who did not develop CaC [5 (12) *vs* 4 (9), $P = 0.01$]. Similar to the 5-year results, the development of CaC was associated with the presence of ILD: OR = 1.47 (95% CI: 1.11–1.94), cardiac involvement: OR = 1.62 (95% CI: 1.11–2.35), PAH: OR = 2.42 (95% CI: 1.34–4.37), and late capillaroscopy pattern: OR = 2.19 (95% CI: 1.40–3.42) in univariate analyses (Supplementary Table S2). However, these associations did not reach statistical significance in adjusted multivariate analysis. No substantial differences were shown between the two groups regarding CRP elevation or autoantibody positivity.

In multivariate logistic regression analyses, independent risk factors for the development of CaC at 10 years were longer disease duration [OR 1.03 (95% CI: 1.01–1.05)], dcSSc [OR 1.51 (95% CI: 1.02–2.22)], female gender [OR 1.85 (95% CI: 1.21–2.83)], telangiectasia [OR 1.92 (95% CI: 1.36–2.71)] and digital ulcers [OR 2.92 (95% CI: 2.12–4.02)] (Fig. 1).

Discussion

Our large study leveraging the power of the international EUSTAR cohort highlights that CaC is common in patients with SSc, and is often progressive over time. We have identified meaningful associations with CaC relevant to clinical practice, including risk factors for progression over time. Our data also provides important insights into pathogenesis.

The baseline prevalence of CaC in SSc patients in our cohort study was 11.9%, which is lower than has been previously reported (with rates varying from 18% to 49%) [5–8]. However, our observed prevalence CaC rates at 5 and 10 years of 40% and 46%, respectively, are more consistent with those of previously reported cohorts. This makes sense, as longer disease duration has been reported to be associated with CaC in SSc [7, 9, 15]. Therefore, a key result from our study is that the burden of CaC

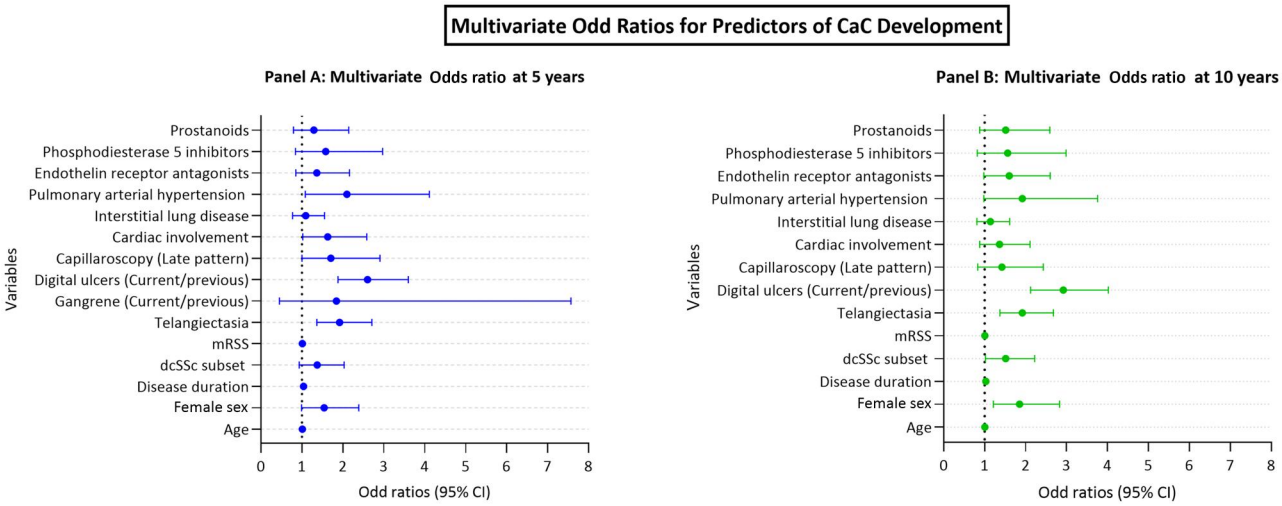

Figure 1 Multivariate odds ratios for predictors of CaC development at (A) 5 and (B) 10 years. CaC: calcinosis cutis; CI: confidence interval; dcSSc: diffuse cutaneous systemic sclerosis; mRSS: modified Rodnan skin score

increases over time, emphasizing the necessity for detailed long-term follow-up and sustained clinical vigilance.

The relationship between the cutaneous subset and CaC in SSc is still debated. Previous studies have suggested that the limited cutaneous disease subset might be a predictor for calcinosis [9, 16], whereas others have not found associations with the subset. For example, in a multicentre (10 centres), international study, which included 568 SSc patients, 38% of whom had calcinosis, there was no significant association between disease subset and CaC [7]. Moreover, a multicentre study on 1305 SSc patients (baseline 30% CaC) did not detect a meaningful relationship between CaC and the disease subset [15]. Another smaller ($n = 109$) cohort study evaluating the characteristics of CaC in Mexican patients (63% with calcinosis) observed that the diffuse cutaneous subset was strongly associated with CaC (OR: 2.4) [17]. In accordance with the literature, we have found that at baseline the disease subset does not significantly differ depending on CaC presence. However, regarding disease evolution at 5 and 10 years, the patients with dcSSC are those who developed CaC. This evidence corroborates the fact that the SSc subset is an independent predictor of the development of CaC within the disease progression.

In the literature, ACA and anti-PM/Scl autoantibodies are more frequently associated with CaC, consistent with our results [18, 19]. Furthermore, these autoantibodies were considered strong predictors of CaC in previous studies, in contrast to our results [15, 18, 19]. Nonetheless, several reports have proven that there is no remarkable association of CaC with the positivity of SSc-specific autoantibodies [7, 9, 17]. Therefore, the role of autoantibodies in CaC genesis remains unknown. Interestingly, our analyses demonstrated that CaC with positive anti-Scl-70 was related to the presence of tendon friction rubs, joint contractures, and higher skin score, which suggests that the antibody profile may help to determine the disease severity in calcinosis patients. Further prospective investigations are needed to elucidate the underlying mechanisms. In SSc, another challenging aspect is the influence of gender on CaC development in SSc: in our cohort, the frequency of female gender was higher in CaC patients at baseline, in line with the results of multicentre cohorts [9, 19]. However, gender has not been identified as a specific predictor for CaC in Canadian and Mexican cohort studies [15, 17]. In addition, our study has shown female gender to be a prominent risk factor (OR: 1.85) for CaC development at 10 years. However, the assessment of hand lesions as detected by hand X-ray in 103 SSc patients identified that male gender was the strongest predictor for calcinosis radiological progression (defined as an incident or worsened calcinosis), followed by DUs [22]. Therefore, further longitudinal studies are needed to clarify the exact effect of gender on calcinosis development.

Ischaemia is believed to play a key role in the aetiopathogenesis of SSc-CaC development. Mechanistically, it could be considered that endothelial cells may follow a mesenchymal transition into an osteogenic phenotype, which can be induced by inflammatory cytokines, hypoxia, and reactive oxygen species [1]. As a consequence of chronic vascular ischaemia, an increase in hypoxia-related molecules and reactive oxygen species might therefore play a role in the calcification process [23–26]. Furthermore, ischaemia can induce osteoclast activation and osteolysis, resulting in the local release of calcium and phosphorus; primary components in soft tissue calcification. In SSc, acro-osteolysis (characteristic distal shortening of the digits) due to osteolysis, is well recognized to be markedly associated with calcinosis [1, 7]. Our results identified that systemic vasculopathic-type features, including DUs, late nailfold capillaroscopy pattern, telangiectasia, and PAH, are more prevalent in patients with CaC, in accordance with the findings of previous studies [7, 9, 15, 19]. Furthermore, all these vasculopathic-type manifestations were identified as independent risk factors for the development of CaC within 5 years. Moreover, at multivariate analyses, DUs and telangiectasia were the most substantial risk factors for the development of CaC within 10 years. In the literature, DU has been considered as the most prominent predictor for calcinosis in SSc by several clinical studies assessing cross-sectional data [7, 9, 19]. However, there is a paucity of longitudinal studies evaluating the association between SSc-related features and the development of calcinosis [15, 22]. The results of a study including 805 SSc patients without calcinosis have demonstrated that 26.7% of patients developed calcinosis in the follow-up period (mean of 3.8 years), and digital ischaemia was found to be one of the most significant risks for the development of calcinosis after SSc-specific autoantibodies (ACA and anti-RNA polymerase III) [15]. Taken together, these data suggest a significant vasculopathic/ischaemic drive to CaC pathogenesis in SSc.

Assessment of calcinosis, based on morphology and physical examination, to determine the subtype of calcinosis in SSc, has demonstrated that patients with stone calcinosis, defined by palpable or hard consistency, have a higher frequency of lung involvement and lower prevalence of PAH compared with those with mousse calcinosis, defined by a soft consistency [13]. A retrospective study involving a small number of patients with CTDs has shown that the presence of calcinosis is related to severe gastrointestinal disease and higher disease activity in SSc [27]. At baseline, our CaC patients were more likely to have musculoskeletal and gastrointestinal involvement, PAH, a higher skin score, and renal crises. Moreover, univariate analyses identified a higher skin score, ILD, and cardiac involvement as risk factors for the development of CaC within 5 and 10 years. However, multivariate analyses identified cardiac involvement as the only independent risk factor for the development of CaC within 5 years, among organ involvement. Similarly, the evaluation of a retrospective multicentre cohort, including 5218 SSc patients with 24.7% calcinosis, has revealed that gastrointestinal involvement, cardiac involvement, and arthritis are related to calcinosis, and that, notably, cardiac involvement is independently associated with the presence of calcinosis [19]. Another large multicentre cohort has shown a higher frequency of cardiac involvement in SSc patients with calcinosis [7]. The analysis of the Portuguese cohort has detected gastrointestinal involvement as significantly more prominent in SSc patients with calcinosis, and oesophageal involvement as an independent risk factor for hand calcinosis, while other organ involvements are not found to be predictors for calcinosis [9]. Even though CaC is a prevalent symptom of SSc, there is a lack of evidence assessing its association with mortality. In our cohort, the mortality rate was found to be higher in CaC patients. Considering the strong relationship between CaC and major organ involvement, the presence of CaC was not identified as an independent predictor of

mortality, as expected. Therefore, CaC may indicate a more severe disease profile and act as a prognostic indicator rather than being a risk factor for mortality. Further studies are needed to confirm and better understand this relationship.

Treatment modalities for SSc-CaC lack evidence and are largely based on anecdotal reports/experience [3, 5]. CACBs are sometimes considered, likely reflecting a therapeutic rationale to reduce tissue ischaemia (through vasodilation), as this is considered important in SSc-CaC pathogenesis [5]. Some authors have reported beneficial CaC amelioration with CACBs use [15]. However, findings from the Canadian cohort showed that CACBs were only of benefit when used in patients with shorter (<5 years) disease duration [28]. In our cohort, we did not observe a favourable effect of CACBs on CaC at baseline and/or throughout the follow-up period, similar to results already seen in a previous multicentre study [7]. The impact of immunosuppressive treatments on SSc with CaC has not yet been evaluated in prospective studies or randomized controlled trials, although several case series, particularly in refractory SSc with CaC, have been reported [29, 30]. The exact role of inflammation in the pathogenesis of CaC is still unknown; however, inflammatory cytokines, such as IL-6, IL-1 or TNF-α, can promote osteogenic differentiation of mesenchymal stromal cells and endothelial cells [1]. In our cohort, patients without CaC were more likely to take immunosuppressive/immunomodulator therapies, while treatment exposure was not linked to the development of CaC. This observation may suggest a potential role for immunosuppressive therapy in preventing the development of CaC in patients with SSc. However, given the retrospective design of our study and the heterogeneity of immunosuppressive regimens used across the cohort, these findings should be considered exploratory. Prospective, well-designed studies will be essential to clarify whether immunosuppression truly exerts a protective effect against CaC in SSc.

Another critical consideration in calcinosis is the long-term use of PPIs, due to the high prevalence of gastrointestinal involvement seen in patients with SSc. A deleterious association between PPI use and increased vascular calcification has been described, and has been attributed to hypomagnesemia induced by PPI use disrupting bone metabolism and accelerating calcification [31, 32]. A recent investigation assessed the impact of PPI use on CaC in a retrospective SSc cohort (199 patients) and a prospective cohort (215 SSc patients). In the retrospective cohort, the prevalence of high-dose PPI use was higher among CaC patients. In this study, it has also been prospectively shown that cumulative PPI exposure is an independent risk factor for CaC [33]. In our study, the frequency of PPI use was higher in patients with CaC than in those without CaC, but PPI use was not detected as a predictor for the development of CaC. If further confirmed, research is required to determine the optimal therapeutic strategy concerning PPI use in the context of a significant CaC burden [34].

To date, our study represents the most extensive investigation in SSc, comprehensively evaluating the clinical features of CaC and risk factors for its development. Our study has a few limitations. The most significant limitation is that calcinosis status was previously identified in EUSTAR through physical examination and/or plain radiography or CT. Therefore, this may systematically miss subclinical calcinosis, which could result in an underestimation of the actual prevalence of incident and/or new CaC development. We also did not have data on the presence of acro-osteolysis, information on the anatomical distribution of calcinosis, or patients' occupational histories, precluding assessment of a possible association with repetitive microtrauma. In future studies, these could be important to understand pathobiology and impact. Another important issue is the absence of data on specific therapeutics for CaC in the cohort; consequently, the effects of treatments on incident CaC and/or development of CaC were not assessed.

In conclusion, we have benchmarked the prevalence of and identified risk factors for CaC in patients with SSc. CaC is likely underappreciated by clinician examination alone, and is often progressive over time. Our data also supports that vascular disease/ischaemia plays an important role in CaC aetiology. The identification of SSc patients at risk for CaC may provide a rationale and targeting for early intervention to contain CaC evolution and the development of related complications.

All patients included in this analysis provided written informed consent to participate in the EUSTAR cohort, using consent forms approved by the local ethics committees of the participating centres.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data that support the findings are available upon reasonable request.

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