Ultrasonography involvement of carotid, upper and lower limb arteries in a large cohort of systemic sclerosis patients

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Abstract

Objectives: Data on macrovascular involvement in systemic sclerosis (SSc) are still debatable. The aim of this study was to estimate its prevalence and possible determinants in a large cohort.

Methods: One hundred and fifty-five outpatients with SSc were enrolled. Data about disease characteristics and cardiovascular risk factors were collected and patients underwent ecocolor Doppler ultrasonography of arteries of the neck and lower (LL) and upper (UL) limbs.

Results: Mean age was 57.9 ± 14.5 years and most were female (88.4%) with a limited subset (63.2%). Mean disease duration was 11.4 ± 8.1 years. Twenty-three (14.8%) had hypertension, 7 (4.8%) diabetes, 64 (41.3%) hypercholesterolemia and 63 (40.6%) were active/past smokers. Seventy-nine (49%) patients had plaques at carotids, 49 (32.9%) at LL and 7 (4.9%) at UL. In multivariate analysis, patients with carotid plaques had more often a limited pattern \(P = .001\), patients with distal LL plaques pulmonary arterial hypertension \(P = .006\) and patients with proximal LL plaques lower diffusing capacity for carbon monoxide adjusted to hemoglobin and its ratio to alveolar volume \(P = .004\). In patients with UL plaques traditional cardiovascular risk factors were not more common, while forced vital capacity was lower \(P = .023\). Finally, upper limb and proximal LL plaques were as common in early disease patients as in longstanding ones, although the former were younger.

Conclusions: This study shows that macrovascular involvement is quite common in SSc and that some disease characteristics linked to microvascular involvement are associated with atherosclerotic plaques, which can be present even in early disease. Our study suggests that a complete evaluation of macrocirculation is mandatory for rheumatologists treating SSc patients.

KEYWORDS
macrovascular involvement, systemic sclerosis, ultrasonography
1 | INTRODUCTION

Skin and visceral microvasculopathy is a typical characteristic of systemic sclerosis (SSc), together with abnormal widespread deposition of collagen and other proteins of extracellular matrix, as shown by some threatening and severe clinical manifestations such as digital ulcers, pulmonary artery hypertension (PAH) and scleroderma renal crisis.\textsuperscript{1,2}

Whether macrovasculopathy affects scleroderma patients has been the object of some studies leading to contrasting results. A possible reason is the great heterogeneity between studies, as underlined by a meta-analysis published in 2011.\textsuperscript{3} The same paper showed that carotid intima-media thickness (cIMT) was found higher in SSc than controls in 6 out of 14 studies.\textsuperscript{3} In those showing higher cIMT, differences with controls were found comparable to those shown in other diseases characterized by an increased cardiovascular risk such as rheumatoid arthritis (0.09 mm),\textsuperscript{4} diabetes mellitus (0.13 mm)\textsuperscript{5} and familial hypercholesterolemia (0.12 mm),\textsuperscript{6} so the burden of carotid atherosclerosis in SSc may be of some relevance, although still debatable.

Also, data on peripheral artery disease at lower limbs (LL) were discordant. Ho et al\textsuperscript{7} found evidence of atherosclerosis in 9 out of 53 SSc cases (17%) compared with no controls, whereas Bartoli et al\textsuperscript{8} and Nordin et al\textsuperscript{9} did not show any difference in ankle-brachial pressure index (ABPI) between patients and healthy subjects.

Some studies underlined the involvement of ulnar artery in SSc. In previous studies, Doppler examination showed that the diameter of ulnar artery was narrower in 20 SSc patients compared to 20 controls\textsuperscript{10} and an occlusion of ulnar artery was found in 17 out of 79 SSc patients.\textsuperscript{11}

The aim of the present study was to assess macrovascular involvement in a large and well-defined cohort of SSc patients by contemporaneously evaluating, by Doppler ultrasonography, 3 different arterial districts, that is carotid arteries and arteries of upper limbs (UL) and LL; in addition, we evaluated a great number of clinical features in order to study if any of them may be useful to select those SSc patients at increased atherosclerotic risk.

2 | PATIENTS AND METHODS

For the present study we enrolled 155 consecutive outpatients affected by SSc followed at the Rheumatology Unit of Verona, Roma and Modena. All patients fulfilled the American College of Rheumatology/European League Against Rheumatism classification criteria for SSc.\textsuperscript{12} The distinction between limited and diffuse cutaneous SSc was made according to LeRoy et al\textsuperscript{13} criteria. Skin involvement was assessed by modified Rodnan skin score (mRSS).\textsuperscript{14} Antinuclear antibodies (ANA) and anticientromere antibodies (ACA) were tested by indirect immunofluorescence on HEp-2 cells, and anti-Sc170 antibodies were searched by enzyme-linked immunosorbent assay method.

Laboratory evaluation also included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine with estimated glomerular filtration rate (eGFR), total, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, triglycerides, glucose and homocysteine levels. Each patient underwent pulmonary function tests with diffusing capacity for carbon monoxide adjusted to hemoglobin (DLCO) and ratio of DLCO to alveolar volume (DLCO/AV). At the same time body mass index (BMI) was calculated and disease severity score was assessed, as proposed by Medsger et al.\textsuperscript{15} The diagnosis of interstitial lung disease (ILD) and PAH was based upon lung high-resolution computed tomography and right heart catheterization, respectively. Digital ulcers were defined as ischemic ulcers located at the digit tip. Evaluation of the cardiovascular risk was made in agreement with the European Low Risk Chart proposed by the European Society of Cardiology (ESC),\textsuperscript{16} which considers the following parameters: gender, age, systolic blood pressure, total cholesterol value and smoking habits.

All patients underwent Doppler ultrasonography (DUS) of the carotid arteries and of the UL and LL arteries. The following arteries were analyzed: common carotid, internal and external carotid, subclavian artery, humeral artery, ulnar artery, radial artery, common femoral artery, profunda femoral artery, superficial femoral artery, popliteal artery, anterior and posterior tibial artery. cIMT measurements were carried out after a 15-minutes resting interval and no intravenous vasodilators were given the day of the examination and during the 3 previous days. Patients underwent ultrasound measurement of cIMT at both common carotid arteries on the distal wall. cIMT was examined by a skilled operator using a high-resolution linear probe (7.5 MHz) by means of automatic ultrasound detection of cIMT (Esaote MyLab 30 Gold—QIMT). Common carotids were examined at standard angles bilaterally: 1 cm proximally to the bulb, a segment of 2 cm was selected with the cursor of the system and IMT was automatically calculated. Median IMT for each common carotid artery was calculated and expressed in centimeters.

Plaques were defined as a localized increase of vessel wall profile of more than 1.5 mm. Stenoses were calculated in accordance with the Consensus Panel Gray-Scale and Doppler Ultrasound Criteria for Diagnosis reported by Grant et al.\textsuperscript{17}

A written informed consent was obtained from all the participants in the study. The protocol study was approved by the local Ethical Committee (protocol no. 55946 for Verona University, protocol no. 3822/14 for Catholic University of the Sacred Heart of Rome, protocol no. 10693 of 25/05/2016 for Modena and Reggio Emilia University).

2.1 | Statistics

Continuous variables were expressed as mean ± standard deviation if they were normally distributed and as median with interquartile range if they were not normally distributed. Categorical variables were expressed as percentage. Comparisons between groups were performed using t test, Mann-Whitney or Chi-square tests/Fisher’s test, as appropriate. The determinants of macrovascular involvement were explored with logistic multivariate regression. Receiver
operating characteristic analysis was run to evaluate the performance of ESC score in predicting subclinical atherosclerosis. A \( P \) value < .05 was considered significant. Statistical analysis was performed by SPSS 17.0 (SPSS Inc).

### RESULTS

#### 3.1 | SSc cohort

The study population was composed of 155 subjects, 18 male and 137 female, of which 95 (69.3%) were in menopause status. Mean age was 57.9 ± 14.5 years; the disease duration was 11.4 ± 8.1 years and the time from onset of Raynaud's phenomena was 16.4 ± 11.7 years. The main clinical characteristics are reported in Table 1.

#### 3.2 | Carotid atherosclerosis

Seventy-five patients (49%) had carotid plaques. The artery stenosis was <50% in the majority of subjects (51 cases); 4 and 2 patients showed a hemodynamically significant stenosis comprised between 50% and 60% and between 60% and 70%, respectively. The mean value of IMT was 0.09 mm.

In univariate analysis we found the following differences: scleroderma patients with plaques were older (\( P < .001 \)), more frequently had a limited cutaneous pattern of disease (\( P = .030 \)) and hypertension (\( P = .032 \)), showed higher values of glucose (\( P = .005 \)), disease severity score (\( P = .009 \)), homocysteine (\( P = .014 \)) and ESR (\( P = .001 \)) and lower values of eGFR (\( P = .002 \)). Current immunosuppressive therapy was negatively associated with the presence of carotid plaques (\( P = .017 \)). In terms of autoantibodies, ACAs were more frequent in patients with plaques (58% vs 42%, \( P = .045 \)). These data are shown in Table 2.
|                  | Carotid plaques | Upper limb plaques | P  |
|------------------|-----------------|--------------------|----|
| **Age**          |                 |                    |    |
| No               | 52.2 (14.2)     | 63.5 (12.3)        | <.001 |
| Yes              | 60.2 (21.0)     | 52.6 (26.0)        | ns  |
| **Disease duration, y** |                 |                    |    |
| No               | 9 (10.3)        | 12 (9)             | ns  |
| Yes              | 10.0 (10.0)     | 14.0 (11.0)        | ns  |
| **BMI, kg/m²**   |                 |                    |    |
| No               | 23.4 (4.1)      | 24.6 (4.1)         | 0.067 |
| Yes              | 24.0 (6.1)      | 20.3 (8.2)         | ns  |
| **FVC, predicted (%)** |                 |                    |    |
| No               | 103 (21)        | 100 (24)           | ns  |
| Yes              | 104 (26)        | 87 (49)            | .021 |
| **DLCO, predicted (%)** |                 |                    |    |
| No               | 68 (21)         | 65 (23)            | ns  |
| Yes              | 66 (27)         | 48 (25)            | .023 |
| **DLCO/AV, predicted (%)** |             |                    |    |
| No               | 74 (21)         | 74 (24)            | ns  |
| Yes              | 77 (29)         | 56 (43)            | .022 |
| **mRSS**         |                 |                    |    |
| No               | 7 (8)           | 8 (7)              | ns  |
| Yes              | 7 (7)           | 8 (11)             | ns  |
| **Disease severity score, 15** |                 |                    |      |
| No               | 5 (2.5)         | 6 (4)              | .009 |
| Yes              | 5 (3)           | p                  | .043 |
| **Creatinine, mg/dL** |                 |                    |    |
| No               | 0.7 (0.1)       | 0.8 (0.3)          | ns  |
| Yes              | 0.72 (0.19)     | 0.63 (0.2)         | ns  |
| **eGFR using CKD-EPI formula, mL/min/1.73 m²** |             |                    |    |
| No               | 95 (20)         | 82 (20)            | .002 |
| Yes              | 89 (18)         |                   | ns  |
| **Total cholesterol, mg/dL** |             |                    |    |
| No               | 189 (36)        | 186 (33)           | ns  |
| Yes              | 187 (44)        | 177 (37)           | ns  |
| **HDL cholesterol, mg/dL** |             |                    |    |
| No               | 61 (20)         | 59 (15)            | ns  |
| Yes              | 58 (21)         | 52 (20)            | ns  |
| **LDL cholesterol, mg/dL** |             |                    |    |
| No               | 109 (30)        | 107 (31)           | ns  |
| Yes              | 104 (43)        | 95 (23)            | ns  |
| **Triglycerides, mg/dL** |             |                    |    |
| No               | 98 (32)         | 107 (53)           | ns  |
| Yes              | 93 (56)         | 77 (64)            | ns  |
| **Glucose, mg/dL** |                 |                    |    |
| No               | 82 (13)         | 88 (14)            | .005 |
| Yes              | 84 (16)         | 88 (39)            | ns  |
| **Homocysteine, μmol/L** |           |                    |    |
| No               | 12.8 (6.4)      | 16.4 (8.8)         | .014 |
| Yes              | 12.4 (6.4)      | 9.8 (-)            | ns  |
| **ESR, mm/h**    |                 |                    |    |
| No               | 19 (13)         | 28 (17)            | .001 |
| Yes              | 18 (22)         | 35 (46)            | ns  |
| **CRP, mg/L**    |                 |                    |    |
| No               | 3 (1)           | 3 (1)              | ns  |
| Yes              | 3.0 (0.0)       | 2.0 (4.6)          | ns  |
| **ESC score**    |                 |                    |    |
| No               | 1 (2)           | 2 (1)              | .054 |
| Yes              | 1 (2.0)         |                   | ns  |
| **Female**       |                 |                    |    |
| No               | 73 (93.6)       | 63 (84.0)          | .059 |
| Yes              | 126 (88.1)      | 7 (100.0)          | ns  |
| **Smoker**       |                 |                    |    |
| Never            | 50 (64.1)       | 42 (56.0)          | ns  |
| Previous         | 20 (25.6)       | 26 (34.7)          | ns  |
| Active           | 8 (10.3)        | 7 (9.3)            | ns  |
| **Endothelin receptor antagonists** |             |                    |    |
| No               | 11 (14.5)       | 9 (12.0)           | ns  |
| Yes              | 17 (11.9)       | 3 (42.9)           | .050 |
| **Iloprost**     |                 |                    |    |
| No               | 72 (93.5)       | 69 (92.0)          | ns  |
| Yes              | 132 (93.0)      | 7 (100.0)          | ns  |
| **Current immunosuppressants** |             |                    |    |
| No               | 31 (40.8)       | 17 (22.7)          | .017 |
| Yes              | 46 (67.8)       | 5 (71.4)           | ns  |
| **Previous immunosuppressants** |             |                    |    |
| No               | 32 (41.0)       | 24 (32.0)          | ns  |
| Yes              | 53 (37.1)       | 3 (42.9)           | ns  |
| **HCQ**          |                 |                    |    |
| No               | 16 (20.5)       | 15 (20.0)          | ns  |
| Yes              | 30 (21.0)       | 0 (0.0)            | ns  |
| **Current steroid treatment** |             |                    |    |
| No               | 12 (15.8)       | 18 (24.0)          | ns  |
| Yes              | 28 (19.6)       | 1 (14.3)           | ns  |
| **Autoantibodies** |                 |                    |    |
| **Scl70**        | 34 (43.6)       | 24 (32.0)          | ns  |
| **ACA**          | 29 (37.2)       | 40 (53.3)          | ns  |
| **ANA**          | 15 (19.2)       | 11 (14.7)          | ns  |
| **Cutaneous pattern** |               |                    |    |
| **Limited**      | 43 (55.1)       | 54 (72.0)          | .030 |
| **Diffuse**      | 35 (44.9)       | 21 (28.0)          | .030 |
| **ILD**          | 30 (38.5)       | 22 (29.3)          | ns  |
| **PAH**          | 2 (2.7)         | 5 (6.8)            | ns  |
| **Active ischemic digital ulcers** |             |                    |    |
| No               | 7 (9.0)         | 5 (6.7)            | ns  |
| Yes              | 9 (6.3)         | 3 (42.9)           | ns  |
| **Previous ischemic digital ulcers** |             |                    |    |
| No               | 28 (35.9)       | 19 (25.3)          | ns  |
| Yes              | 41 (28.7)       | 6 (85.7)           | .004 |
| **Scleroderma renal crisis** |           |                    |    |
| No               | 0 (0.0)         | 1 (1.4)            | ns  |
| Yes              | 1 (0.7)         | 0 (0.0)            | ns  |
| **Statin**       |                 |                    |    |
| No               | 9 (11.5)        | 14 (18.7)          | ns  |
| Yes              | 20 (14.0)       | 2 (28.6)           | ns  |

(Continues)
TABLE 2 (Continued)

| Carotid plaques | Upper limb plaques |
|-----------------|--------------------|
|                 | No    | Yes   | P       | No    | Yes   | P       |
| Hypercholesterolemia<sup>c</sup> | 30 (38.5) | 27 (36.0) | ns | 52 (36.4) | 4 (57.1) | ns |
| Blood hypertension<sup>c</sup> | 7 (9.0) | 16 (21.3) | .032 | 22 (15.4) | 0 (0.0) | ns |
| Diabetes mellitus<sup>c</sup> | 2 (2.6) | 5 (6.7) | ns | 7 (4.9) | 0 (0.0) | ns |

Abbreviations: ACA, anticentromere antibodies; ANA, antinuclear antibodies; BMI, body mass index; CDK-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; DLCO, diffusion lung for carbon monoxide; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; HCQ, hydroxychloroquine; HDL, high density lipoproteins; ILD, interstitial lung disease; IMT, intima-media thickness; LDL, low density lipoprotein; mRSS, modified Rodnan skin score; PAH, pulmonary artery hypertension; RCS, Raynaud’s condition score; VA, alveolar volume; VAS, visual analog scale.

<sup>a</sup>Values expressed as mean (SD).
<sup>b</sup>Values expressed as median (interquartile range).
<sup>c</sup>Values expressed as absolute number (%).
Statistically significant values (P<.05) are indicated in bold.

We performed 2 multivariate models (Table 4). The first one considered all the variables with a \( P < .1 \) in univariate analysis (except ESC) and showed that older age \( (P = .001) \), higher disease severity scores \( (P = .034) \) and limited cutaneous pattern \( (P = .001) \) were significantly associated with carotid plaques. The second model considered the variables with a \( P < .1 \) in the first one with the addition of ESC score and diabetes mellitus and confirmed the significance of cutaneous pattern \( (P = .001) \) and ESR \( (P = .010) \) with only a trend for ESC \( (P = .074) \).

3.3 | LL artery involvement

The data were collected in 140 patients. Forty-nine patients (32.9%) had plaques at the LL arteries. The artery stenosis was <50% in the majority of subjects (32 cases), but 1 patient had a hemodynamically significant stenosis between 50% and 60% and 1 between 80% and 90%. Moreover, occlusion of the anterior tibial artery was found in three cases.

We divided LL involvement in proximal or distal accordingly to the localization of plaques, that is, proximal (43, 30.7%) or distal (14, 9.3%) to the popliteal artery.

Patients with proximal LLs were older \( (P = .007) \) than patients with no plaques, more frequently of male gender \( (P = .007) \), with higher disease severity score \( (P = .025) \) and with a higher prevalence of PAH \( (P = .032) \) and diabetes \( (P = .028) \); in addition they were more frequently on statins \( (P = .014) \), had lower predicted DLCO \( (P = .044) \), lower eGFR \( (P = .005) \), higher total and LDL cholesterol levels \( (P = .022 \text{ and } 0.011, \text{ respectively}) \), glycemia \( (P = .037) \), ESC scores \( (P = .002) \) and homocysteine \( (P = .009) \) (Table 3).

In multivariate analysis, predicted DLCO/AV \( (P = .004) \) was found lower in patients with plaques, while ESC score was higher \( (P = .005) \) (Table 4).

Patients with distal LLs were older \( (P = .049) \) than patients with no plaques, with a higher mRSS \( (P = .007) \), with lower HDL cholesterol \( (P = .018) \), more often ACA positive \( (P = .021) \), with ILD \( (P = .035) \) and PAH \( (P = .020) \) (Table 3).

Multivariate analysis (Table 4) showed that only PAH was significantly more frequent in patients with plaques \( (P = .027 \text{ in model 1 and } P = .006 \text{ in model 2}) \), also after correcting for ESC and diabetes.

3.4 | UL artery involvement

Only seven patients showed UL plaques. All had ulnar involvement and 2 had also radial and humeral plaques. No patients had subclavian involvement. In univariate analysis, patients with plaques had worse predicted FVC, DLCO and DLCO/VA \( (P = .021, .023 \text{ and } .02, \text{ respectively}) \), more frequent ulcers \( (P = .012 \text{ for active and } P = .004 \text{ for previous}) \), higher disease severity score \( (P = .043) \) and were more often on anti-endothelin treatment \( (P = .050) \) (Table 2).

In multivariate analysis we performed 2 models as previously explained (Table 4). We preferred previous to active ulcers for the analysis given the bigger sample size in this group. Model 1 showed that only a trend for lower predicted FVC and DLCO/VA to be associated with UL plaques \( (P = .066 \text{ and } P = .078, \text{ respectively}) \). In model 2 predicted FVC was shown to be significantly associated with plaques \( (P = .023) \).

3.5 | Combined analysis

We then analyzed data according to the number of vascular sites involved, that is, carotid and/or proximal LLs and/or distal LLs. We did not consider UL involvement since no differences in its prevalence were found between patients with and without plaques in other sites. Scleroderma patients with carotid plaques more frequently had also plaques at the LLs: 37 out of 73 cases (50.7%) vs 12 out of 67 cases (17.9%), \( P < .001 \). Table 5 summarizes univariate analysis that showed both traditional cardiovascular risk factors and disease characteristics to be associated with an increased number of sites involved. When we performed the multivariate analysis only male gender was found to be a risk factor for multi-site involvement (data not shown).
### TABLE 3  Differences between patients with plaques at lower limb arteries and those without

|                                | Proximal lower limbs plaques | Distal lower limb plaques |
|--------------------------------|-----------------------------|---------------------------|
|                                | No (Mean [SD])              | Yes (Mean [SD])           | No (Mean [SD])     | Yes (Mean [SD])     | P    |
| Agea                          | 53.8 (14.6)                 | 64.5 (12.2)               | .007              | 56.9 (21.0)         | 62.2 (11.0) | .049 |
| Disease duration, yb           | 10 (10)                     | 12 (10)                   | .074              | 10.0 (11.0)         | 15.5 (14)  | ns   |
| BMI, kg/m²a                    | 23.9 (4.2)                  | 24.9 (3.6)                | ns                | 23.7 (6.1)          | 24.4 (8.0) | ns   |
| FVC, predicted (%)a           | 101 (23)                    | 104 (22)                  | ns                | 102 (26)            | 101 (29)  | ns   |
| DLCO, predicted (%)a          | 70 (21)                     | 61 (19)                   | .044              | 66 (27)             | 55 (45)   | ns   |
| DLCO/AV, predicted (%)a       | 77 (21)                     | 68 (23)                   | .094              | 74 (21)             | 74 (31)   | ns   |
| mRSSb                          | 7.5 (8.5)                   | 7.0 (6.0)                 | ns                | 7 (7)               | 9 (5)     | .007 |
| Disease severity score, 15b   | 5 (3)                       | 6 (3)                     | .025              | 5 (3)               | 7 (4.5)   | ns   |
| Creatinine, mg/dL²            | 0.7 (0.2)                   | 0.8 (0.3)                 | .06               | 0.7 (0.2)           | 0.8 (0.2) | .044 |
| eGFR using CKD-EPI formula, mL/min/1.73 m²a | 91 (19) | 79 (18) | .005 | 91 (15) | 78 (19) | .07 |
| Total cholesterol, mg/dL³     | 183 (39)                    | 197 (33)                  | .022              | 188 (34)            | 187 (37)  | ns   |
| HDL cholesterol, mg/dL³       | 58 (20)                     | 60 (28)                   | ns                | 60 (20)             | 52 (13)   | .018 |
| LDL cholesterol, mg/dL³       | 103 (28)                    | 118 (33)                  | .111              | 103 (40)            | 111 (46)  | ns   |
| Triglycerides, mg/dL³         | 90 (54)                     | 95 (66)                   | ns                | 91 (57)             | 100 (57)  | ns   |
| Glucose, mg/dL³               | 83 (12)                     | 89 (16)                   | .037              | 84 (16)             | 89 (19)   | ns   |
| Homocysteine, μmol/L³         | 12.0 (22.8)                 | 16.6 (10.2)               | .009              | 11.8 (6.7)          | 15.9 (11.5)| .056 |
| ESR, mm/h²                    | 17 (23)                     | 23 (27)                   | .081              | 19 (22)             | 31 (42)   | ns   |
| CRP, mg/Lb                    | 3 (p)                       | 3 (0)                     | ns                | 3 (1)               | 3 (2)     | ns   |
| ESC scoreb                    | 1 (2)                       | 2 (2)                     | .002              | 1 (2)               | 2 (2)     | ns   |
| Femalec                       | 91 (93.8)                   | 33 (76.7)                 | .007              | 123 (90.4)          | 10 (71.4) | .056 |
| Smokerd                       |                            |                           |                   |                     |         |
| Never                         | 65 (67.0)                   | 22 (51.2)                 | ns                | 83 (61.0)           | 7 (50.0)  | ns   |
| Previous                      | 24 (24.7)                   | 15 (34.9)                 | 39 (28.7)         | 6 (42.9)            | 3 (7.1)   |    |
| Active                        | 8 (8.2)                     | 6 (14.0)                  | 14 (10.3)         | 1 (7.1)             |         |    |
| Endothelin receptor antagonistsc | 10 (10.3) | 5 (11.6) | ns | 16 (11.8) | 4 (28.6) | .095 |
| Iloprost                      | 90 (92.8)                   | 39 (92.9)                 | ns                | 125 (92.6)          | 14 (100.0)| ns   |
| Current immunosuppressants     | 33 (34.0)                   | 13 (30.2)                 | ns                | 45 (33.1)           | 3 (21.4)  | ns   |
| Previous immunosuppressants   | 39 (40.2)                   | 15 (34.9)                 | ns                | 53 (39.0)           | 3 (21.4)  | ns   |
| HCQc                          | 24 (24.7)                   | 6 (14.0)                  | ns                | 27 (19.9)           | 3 (21.4)  | ns   |
| Current steroid treatment     | 16 (16.5)                   | 12 (27.9)                 | ns                | 28 (20.6)           | 1 (7.1)   | ns   |
| Autoantibodiesc               |                            |                           |                   |                     |         |
| Scl70                         | 40 (41.2)                   | 14 (32.6)                 | ns                | 54 (39.7)           | 3 (21.4)  | .021 |
| ACA                           | 39 (40.2)                   | 22 (51.2)                 | ns                | 56 (41.2)           | 11 (78.6)| ns   |
| ANA                           | 18 (18.6)                   | 7 (16.3)                  | ns                | 26 (19.1)           | 0 (0.0)   |    |
| Cutaneous patternc            |                            |                           |                   |                     |         |
| Limited                       | 58 (59.8)                   | 28 (65.1)                 | ns                | 84 (61.8)           | 11 (78.6) | ns   |
| Diffuse                       | 39 (40.2)                   | 15 (34.9)                 | ns                | 52 (38.2)           | 3 (21.4)  |    |
| ILDc                          | 29 (29.9)                   | 16 (37.2)                 | ns                | 49 (36.0)           | 1 (7.1)   | .035 |
| PAHf                          | 1 (1.1)                     | 4 (9.5)                   | .032              | 4 (3.0)             | 3 (21.4)  | .02 |
| Active ischemic digital ulcers | 9 (9.3)                     | 3 (7.0)                   | ns                | 10 (7.4)            | 2 (14.3)  |    |
| Previous ischemic digital ulcers | 29 (29.9) | 12 (27.9) | ns | 42 (30.9) | 5 (35.7) | ns   |
| Scleroderma renal crisisc     | 1 (1.1)                     | 0.0 (0.0)                 | ns                | 1 (0.8)             | 0 (0.0)   | ns   |
| Statinc                       | 8 (8.2)                     | 10 (23.3)                 | .014              | 18 (13.2)           | 4 (28.6)  | ns   |

(Continues)
In addition, cIMT was higher in patients with proximal and/or distal LL involvement (0.10 ± 0.04 vs 0.09 ± 0.02, P < .001) and patients with a cIMT > 0.09 had 2.6-fold increased risk of having a multi-district vasculopathy (95% CI 1.3-5.3, P < .001). No differences in cIMT were found for UL involvement.

### 3.6 | ESC

We studied ESC score to predict cIMT as surrogate of developing atherosclerotic events. A significant correlation between cIMT and ESC was found (Spearman’s correlation .300, P < .001) and patients with a cIMT > 0.09 cm had higher ESC scores (0 ± 2 vs 1 ± 2, P = .002). Indeed, ESC score was found to perform fairly in predicting a cIMT > 0.09 cm (area under the curve [AUC] 0.646, P = .003) and showed a very low sensitivity but a high specificity in identifying patients at high risk, that is with an ESC score ≥5% (49.2% and 97.4%, respectively). When considering an ESC score ≥1% as a marker of increased cIMT, it showed a specificity of 53.8% and a sensitivity of 70.5%.

### 3.7 | Early disease

Patients were divided according to the disease duration, that is ≤5 years or >5 years. Those with an early disease (39, 25.2%) were significantly younger than those with a longstanding disease (46.2 ± 14.0 vs 61.9 ± 12.5, P < .001). Carotid and distal LL plaques were more common in the latter (54.4% vs 33.3%, P = .023, and 12.6% vs 0.0%, P = .020, respectively). In contrast, UL and proximal limb plaques were as common in early disease patients as in longstanding ones (5%-2% vs 2.6%, P = .677 and 32.4% vs. 25.7%, P = .459).

### 4 | DISCUSSION

In this study we have evaluated the macrovascular involvement in patients with SSC by performing a DUS of carotid, UL and LL and by collecting information on disease and cardiovascular risk factors (CRF). We have found that macrovascular involvement is quite common and that traditional CRF and some disease characteristics are associated with the development of plaques, not only in the univariate analysis that may be affected by age and disease duration, but also in multivariate models. In addition, we have confirmed that cIMT may be a useful red flag for macrovasculopathy also at LLs. Finally, ESC was found to perform fairly also in identifying SSC patients with subclinical atherosclerosis.

Table 6 summarizes the most important and recent studies on macrovascular involvement in SSC. Prevalence of carotid plaques was significantly variable, ranging from 11.8% to 65.5% with our study showing results in line with Nordin et al.\(^6\) and Schiopu et al.\(^\text{18}\) Comparing the prevalence of LL and UL involvement is not easy given the use of different methods to define these manifestations. It is worth noticing that, although the prevalence of plaques is not uncommon, only a small proportion of patients had hemodynamically significant stenosis.

In our cohort we found that carotid and LL involvement is quite common and that, in multivariate analysis, traditional CRF are important determinants of proximal LL atherosclerosis with a trend for carotid and distal LL involvement. Similar results, although with a less complete evaluation of traditional CRF, have been reported in other studies.\(^11\)\(^19\)\(^20\) Traditional CRF may play a role in macrovasculopathy, especially at proximal LLs, also in SSC, so the rheumatologist should always assess cardiovascular risk in these patients in order to prevent the development of its possible complications. When treating cardiovascular risk in SSC the rheumatologist should keep in mind there is some evidence that statins, apart from lowering blood cholesterol, may have favorable effects also on the fibrotic and vascular mechanisms involved in SSC pathogenesis.\(^21\)

In addition, ESR was found to be higher in patients with carotid plaques. There is strong evidence that inflammation increases the risk of atherosclerosis not only in the general population,\(^22\) but also in SSC patients.\(^18\) In particular, Ozen et al\(^19\) and Sedky et al\(^20\) have recently found an increase in ESR in SSC patients with subclinical atherosclerosis. Although ESR is more variable than CRP in assessing...
### TABLE 4 Multivariate analysis of possible determinants of plaques

| Carotid | B      | Wald  | Significance | Exp(B) | 95% CI for Exp(B) | Inferior | Superior |
|---------|--------|-------|-------------|--------|-------------------|----------|----------|
|         |        |       |             |        |                   | Inferior | Superior |
| **Model 1** |        |       |             |        |                   | Inferior | Superior |
| Age     | 0.148  | 10.604| .001        | 1.16   | 1.061             | 1.268    |          |
| Disease severity score (15) | 0.284  | 4.488 | .034        | 1.328  | 1.021             | 1.726    |          |
| eGFR    | 0.023  | 1.517 | .218        | 1.024  | 0.986             | 1.063    |          |
| Glucose (mg/dL) | 0.019  | 0.571 | .450        | 1.019  | 0.971             | 1.069    |          |
| ESR (mm/h) | 0.043  | 3.564 | .059        | 1.044  | 0.998             | 1.091    |          |
| Homocysteine (μmol/L) | -0.036 | 0.768 | .381        | 0.965  | 0.89              | 1.046    |          |
| Female gender | -1.246 | 2.201 | .138        | 0.288  | 0.055             | 1.492    |          |
| Cutaneous pattern (limited) | 2.514  | 11.654| .001        | 12.35  | 2.917             | 52.294   |          |
| Blood hypertension | 0.328  | 0.166 | .684        | 1.388  | 0.286             | 6.734    |          |
| ESC     | 0.302  | 3.194 | .074        | 1.044  |                   |          | 1.884    |
| Diabetes mellitus | 0.476  | 0.24  | .886        | 1.353  | 0.971             | 1.884    |          |
| ESR (mm/h) | 0.038  | 6.642 | .010        | 1.039  | 1.009             | 1.069    |          |
| Cutaneous pattern (limited) | 1.456  | 10.587| .001        | 4.290  | 1.784             | 10.314   |          |
| Disease severity score (15) | 0.124  | 2.298 | .130        | 1.132  | 0.964             | 1.328    |          |
| **Model 1 PAH** | -1.401 | 1.502 | .351        | 0.246  | 0.013             | 4.683    |          |
| Statin  | -0.595 | 0.737 | .420        | 0.552  | 0.130             | 2.338    |          |
| Diabetes mellitus | -1.413 | 1.109 | .203        | 0.243  | 0.028             | 2.139    |          |
| Female gender | -1.942 | 0.989 | .050        | 0.143  | 0.021             | 0.997    |          |
| Age     | 0.064  | 0.037 | .839        | 1.066  | 0.992             | 1.146    |          |
| DLCO/AV (predicted, %) | -0.039 | 0.019 | .040        | 0.961  | 0.926             | 0.998    |          |
| Creatinine (mg/dL) | 0.219  | 1.524 | .886        | 1.245  | 0.063             | 24.697   |          |
| LDL cholesterol | 0.011  | 0.009 | .243        | 1.011  | 0.993             | 1.030    |          |
| Glucose (mg/dL) | -0.001 | 0.028 | .977        | 0.999  | 0.946             | 1.056    |          |
| Homocysteine (μmol/L) | 0.040  | 0.044 | .359        | 1.041  | 0.955             | 1.135    |          |
| ESR (mm/h) | 0.023  | 0.019 | .224        | 1.024  | 0.986             | 1.063    |          |
| Disease severity score (15) | -0.070 | 0.145 | .629        | 0.932  | 0.702             | 1.239    |          |
| ESC     | 0.474  | 7.900 | .005        | 1.606  | 1.154             | 2.234    |          |
| Diabetes mellitus | -1.626 | 3.196 | .074        | 0.197  | 0.033             | 1.170    |          |
| DLCO/AV (predicted, %) | -0.028 | 8.080 | .004        | 0.972  | 0.954             | 0.991    |          |
| **Model 1** |        |       |             |        |                   | Inferior | Superior |
| Age     | -0.033 | 0.367 | .544        | 0.968  | 0.870             | 1.076    |          |
| Disease duration | -0.099 | 1.161 | .281        | 0.906  | 0.756             | 1.085    |          |
| mRSS    | 0.121  | 0.715 | .398        | 1.129  | 0.852             | 1.495    |          |
| eGFR    | -0.039 | 1.491 | .222        | 0.961  | 0.902             | 1.024    |          |
| HDL cholesterol (mg/dL) | -0.055 | 1.777 | .182        | 0.947  | 0.873             | 1.026    |          |
| ESR (mm/h) | -0.003 | 0.006 | .939        | 0.997  | 0.927             | 1.072    |          |
| Homocysteine (μmol/L) | 0.077  | 2.479 | .115        | 1.080  | 0.981             | 1.189    |          |
| Female gender | -0.566 | 0.272 | .602        | 0.568  | 0.068             | 4.762    |          |
| Endothelin receptor antagonists | 0.012  | 0.000 | .995        | 1.012  | 0.032             | 31.708   |          |
| Autoantibodies | -0.789 | 0.534 | .465        | 0.454  | 0.055             | 3.770    |          |
| ILD     | 20.279 | 0.000 | .998        | 6.413 × 108 | 0.000 |          |          |          |
| PAH     | 4.237  | 4.900 | .027        | 71.429 | 1.623             |          |          |
| **Model 2** |        |       |             |        |                   | Inferior | Superior |
| ESC     | 0.370  | 2.926 | .087        | 1.448  | 0.947             | 2.213    |          |
| Diabetes mellitus | -0.248 | 0.045 | .833        | 0.780  | 0.078             | 7.800    |          |
| PAH     | 2.422  | 7.486 | .006        | 11.264 | 1.988             | 63.832   |          |

(Continues)
inflammation and may be affected by many factors, such as age and gender, our result was confirmed also after correcting for them, so its increase in vasculopathy patients may be actually related to the role of inflammation in atherosclerosis.

Some disease characteristics have been found to increase the risk of macrovascular involvement independently from traditional CRF. Subjects with limited pattern were shown to have an increased risk of carotid plaques. Nordin et al9 has previously reported a similar result for anti-centromere antibodies after correction for gender, age and disease duration. These antibodies have been shown to be also associated with a lower ABPI.23 Although in our cohort ACAs were showed to be more frequent in patients with carotid plaques only in univariate analysis, our results on limited pattern seems to support that those patients with a more pronounced microvascular than fibrotic process have an increased risk of carotid atherosclerosis, supporting a possible link between micro- and macrovascular involvement. On the other hand, one may argue that patients with a diffuse pattern or anti-Scl70 antibody positivity are more often on immunosuppressive drugs; it is worth noticing that, in our cohort, this treatment was found to be protective against carotid plaques in univariate analysis. Although the role of inflammation in atherosclerosis is well known, there is still a lack of data on the possible role of immunotherapy to prevent its progression.24 We speculate that the higher prevalence of carotid plaques in limited SSc may be related to different factors, such as a possible role of microvascular damage or a less frequent use of immunosuppressive treatment, although other factors, such as other treatments or the degree of inflammation, cannot be ruled out and further studies are needed. Also, for proximal and distal LLs a possible link with microvasculopathy could be hypothesized. Indeed, low DLCO/AV and PAH, both markers of microvascular disease, were more frequent in patients with proximal or distal LL involvement. No data in the literature are available for a proper comparison since different methodologies were used to assess LL arteriopathy. Nevertheless, SSc patients were reported to have an increased risk of vasculopathy in 2 out 3 studies present in the literature. Again, Nordin et al9 have found that ACA + patients suffered more often from ischemic peripheral vascular disease defined as intermittent claudication + ankle-brachial index (ABI) <0.9 or peripheral arterial thrombosis/embolus (confirmed by angiogram or Doppler flow studies). ACAs are a well-known risk factor for PAH but no analysis on this was reported probably because of the small number of patients with both or either of these characteristics. In addition, Ozen et al25 have recently found that PAH was more common in patients with increased cIMT, further supporting a possible link between micro- and macrovasculopathy via a common pathologic pathway such as endothelial dysfunction.25,26 Although these data support an intriguing link between micro- and macrovasculopathy, there is contrasting evidence on videocapillaroscopy. It was found to be related to ulnar involvement by Lescoat et al28 while Schioppo et al29 found no correlation. It is worth noticing that these vessels are not a usual target of atherosclerosis and do not clearly reflect large vessel involvement, so further studies are needed to clarify this issue. Indeed, also in our study, traditional risk factors were not found to be independently associated with UL involvement. This could be expected since ulnar involvement is an unusual finding in atherosclerosis, whereas it may be a possible peculiar manifestation of SSc given its high prevalence.10,29 as partially supported by significantly higher disease severity scores in patients with plaques in univariate analysis. In our experience the involvement of UL arteries was observed in a very little subgroup of patients, different from the results previously reported in other studies.10,29 Although our data showed that ulnar vasculopathy is a risk factor for digital ulcers only in univariate analysis, that may be affected by disease duration, this may further support other previous studies since the lack of significance in multivariate analysis may be caused by both the small number of patients with UL vasculopathy and the correlation between disease severity score and ulcers (actually when we re-run the analysis without Medsger score, ulcers showed statistical

### TABLE 4 (Continued)

| Carotid | B    | Wald | Significance | Exp(B) | 95% CI for Exp(B) |
|---------|------|------|--------------|--------|------------------|
| Model 1 |      |      |              |        |                  |
| FVC (predicted, %) | -0.101 | 3.371 | .066          | 0.904  | 0.811 – 1.007    |
| Previous ischemic digital ulcers | 18.813 | 3.105 | 0.092        | .978    | 0.912 – 1.010    |
| Disease severity score (15) | 4.142 | 1.541 | .215        | 62.903  | 0.091 – 4.353 × 104 |
| Model 2 |      |      |              |        |                  |
| ESC    | -0.592 | 0.940 | .332         | 0.553  | 0.167 – 1.830    |
| Diabetes mellitus | 17.152 | 3.261 | .039        | 3.621  | 0.922 – 1.003    |
| FVC (predicted, %) | -0.049 | 5.181 | .023         | 0.952  | 0.912 – 0.993    |
| DLCO/AV (predicted, %) | -0.039 | 3.261 | .071         | 0.962  | 0.922 – 1.003    |

Abbreviations: DLCO, diffusion lung for carbon monoxide; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; HDL, high density lipoproteins; ILD, interstitial lung disease; LDL, low density lipoproteins; mRSS, modified Rodnan skin score; PAH, pulmonary artery hypertension; VA, alveolar volume; VAS, visual analog scale. Statistically significant values (P<.05) are indicated in bold.
TABLE 5 Differences between patients with 0 or 1 site with plaques and those with 2 or 3 sites involved

| Sites with plaques | 0 or 1 | 2 or 3 | P    |
|--------------------|--------|--------|------|
| Age                | 53.9 (14.3) | 66.1 (11.9) | <.001 |
| Disease duration, y | 10 (10) | 12 (10) | .094 |
| BMI, kg/m²         | 23.9 (4.1) | 25.1 (3.9) |    |
| FVC, predicted (%) | 102 (21) | 102 (26) |    |
| DLCO, predicted (%) | 69 (20) | 61 (22) | .046 |
| DLCO/AV, predicted (%) | 76 (20) | 69 (26) |    |
| mRSS               | 8 (7) | 8 (7) |    |
| Disease severity score, 15 | 5 (3) | 6 (3) | .023 |
| Creatinine, mg/dL² | 0.7 (0.2) | 0.8 (0.3) | .031 |
| eGFR using CKD-EPI formula, mL/min/1.73 m² | 91 (19) | 79 (18) | .007 |
| Total cholesterol, mg/dL | 185 (34) | 191 (34) |    |
| HDL cholesterol, mg/dL² | 60 (19) | 61 (15) |    |
| LDL cholesterol, mg/dL² | 106 (28) | 113 (34) |    |
| Triglycerides, mg/dL² | 99 (47) | 110 (47) |    |
| Glucose, mg/dL² | 83 (12) | 91 (16) | .001 |
| Homocysteine, μmol/L² | 13.7 (6.6) | 18.4 (10.3) | .007 |
| ESR, mm/h³ | 17 (23) | 24 (30) | .038 |
| CRP, mg/L² | 3 (0) | 3 (0) |    |
| ESC score² | 0 (2) | 2 (1) | <.001 |
| Female³ | F | 97 (94.2) | 27 (73.0) | <.001 |
| Smoker³ | Never | 68 (66.0) | 19 (51.4) |    |
| Previous | 26 (25.2) | 13 (35.1) |    |
| Active | 9 (8.7) | 5 (13.5) |    |
| Endothelin receptor antagonists⁴ | 9 (8.7) | 6 (16.2) |    |
| Iloprost | 94 (92.2) | 35 (94.6) |    |
| Current immunosuppressants⁴ | 36 (35.0) | 10 (27.0) |    |
| Previous immunosuppressants⁴ | 43 (41.7) | 11 (29.7) |    |
| HCQ⁴ | 25 (24.3) | 5 (13.5) |    |
| Current steroid treatment | 19 (18.4) | 9 (24.3) |    |
| Autoantibodies⁴ | Scl70 | 45 (43.7) | 9 (24.3) | .060 |
| ACA | 39 (37.9) | 22 (59.5) |    |
| ANA | 19 (18.4) | 6 (16.2) |    |
| Cutaneous pattern⁵ | Limited | 60 (58.3) | 26 (70.3) |    |
| Diffuse | 43 (41.7) | 11 (29.7) |    |

TABLE 5 (Continued)

| Sites with plaques | 0 or 1 | 2 or 3 | P    |
|--------------------|--------|--------|------|
| ILD⁶ | 0 | 33 (32.0) | 12 (32.4) | ns |
| PAH⁶ | 0 | 0 (0.0) | 5 (13.9) | <.001 |
| Active ischemic digital ulcers⁶ | 0 | 8 (7.8) | 4 (10.8) | ns |
| Previous ischemic digital ulcers⁶ | 0 | 32 (31.1) | 9 (24.3) |    |
| Scleroderma renal crisis⁶ | 0 | 1 (1.0) | 0 (0.0) | ns |
| Statin⁶ | 0 | 9 (8.7) | 9 (24.3) | .015 |
| Hypercholesterolemia⁶ | 0 | 39 (37.9) | 11 (29.7) | ns |
| Blood hypertension⁶ | 0 | 14. (13.6) | 8 (21.6) | ns |
| Diabetes mellitus⁶ | 0 | 3 (2.9) | 4 (10.8) | .059 |

*Abbreviations: ACA, anticentromere antibodies; ANA, antinuclear antibodies; BMI, body mass index; CDK-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; DLCO, diffusion lung for carbon monoxide; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; HCQ, hydroxychloroquine; HDL, high density lipoproteins; ILD, interstitial lung disease; IMT, intima-media thickness; LDL, low density lipoprotein; mRSS, modified Rodnan skin score; PAH, pulmonary artery hypertension; RCS, Raynaud’s condition score; VA, alveolar volume; VAS, visual analog scale.

²Values expressed as mean (SD).
³Values expressed as median (interquartile range).
⁴Values expressed as absolute number (%).
⁵Values expressed as absolute number (%).

Statistically significant values (P<.05) are indicated in bold.

significance). Indeed, both our group and other authors previously reported a positive association between necrosis at LL extremities and concomitant peripheral artery disease⁶; together these data suggest that a concomitant micro- and macrovascular involvement may favor the development of ischemic complications in SSc. To the best of our knowledge, the link between reduced FVC and ulnar plaques is a finding not previously reported. A possible explanation is that the fibrotic process may be also involved in ulnar artery involvement. Interestingly the result that patients with early disease do not seem to have a lower risk of UL and proximal LL plaques than patients with a longer disease, although they are at a significantly younger age. We think more studies are needed to confirm this data that may further shed a light upon a possible role of SSc itself in causing macrovascular involvement. We have confirmed that carotid atherosclerosis increases the risk of LL involvement. In particular, a cIMT > 0.09 gives a more than 2.6-fold increased risk of having plaques at the LLs. Given the high prevalence of macrovasculopathy in SSc patients, these data further stress the importance of performing a wide evaluation involving not only a carotid DUS but also of other sites. Finally, ESC was found to fairly predict subclinical atherosclerosis with AUC of 0.646. This result differs from that reported by Ozen et al⁵ who showed a poor performance of different cardiovascular...
risk scores in SSc patients. This difference may be explained by the significantly lower cIMT and prevalence of carotid plaques in their cohort as compared to our population.

Given that atherosclerosis is quite common also in SSc patients and that carotid DUS is a good screening tool, since cIMT correlates well with both ESC score and macrovasculopathy in other sites, our study further stresses that a thorough cardiovascular screening of SSc patients may be effective and very important in particular if we consider that peripheral atherosclerosis is a well-known risk factor for cardiovascular events in the general population and statins and aspirin are recommended in its treatment.\(^\text{32}\) In addition, cardiovascular events accounted for about 29% of non-SSc-related deaths in the large EUSTAR cohort,\(^\text{33}\) so its prevention is an issue also in SSc.

In conclusion, this study shows that macrovascular involvement is quite common in SSc patients and that, apart from a possible role of traditional risk factors, some disease characteristics are significantly associated with atherosclerotic plaques. In addition, we further underline the importance of screening for macrovascular involvement at LLs in those SSc patients with an increased cIMT. Finally, ESC score was found to have a fair performance in predicting subclinical atherosclerosis also in SSc patients. Our study suggests that a complete evaluation of patients is mandatory for rheumatologists for a comprehensive approach to this disease, that is still without a specific treatment, and a multidisciplinary and tailored therapy may allow longer survival.

**AUTHORS’ CONTRIBUTION**
The authors meet all 4 International Committee of Medical Journal Editors criteria for authorship. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by C. Caimmi, S. De Marchi, SL Bosello, A. Di Giorgio, A. Spinella, G. Astarino, G. Canestrari, E. Cocchiara. The first draft of the manuscript was written by C. Caimmi and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**How to cite this article:** Caimmi C, De Marchi S, Bosello SL, et al. Ultrasonography involvement of carotid, upper and lower limb arteries in a large cohort of systemic sclerosis patients. *Int J Rheum Dis*. 2020;23:681–692. [https://doi.org/10.1111/1756-185X.13824](https://doi.org/10.1111/1756-185X.13824)