Progression of patients with Raynaud's phenomenon to systemic sclerosis: a five-year analysis of the European Scleroderma Trial and Research group multicentre, longitudinal registry study for Very Early Diagnosis of Systemic Sclerosis (VEDOSS)

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Summary

Background Preliminary criteria for the very early diagnosis of systemic sclerosis (VEDOSS) have been previously proposed to identify signs and symptoms in patients with Raynaud's phenomenon. Patients with all signs or symptoms of the VEDOSS criteria already fulfil the 2013 American College of Rheumatology–European League Against Rheumatism (ACR–EULAR) classification criteria for systemic sclerosis. However, prospective data for the evolution to fulfilling these criteria do not exist. We therefore aimed to determine the clinical value of the VEDOSS criteria to identify patients with Raynaud's phenomenon who progress to systemic sclerosis within 5 years.

Methods The VEDOSS project was a multicentre, longitudinal registry study done in 42 European Scleroderma Trial and Research group centres located in 20 countries in Europe, North America, and South America. Patients with Raynaud's phenomenon were eligible for enrolment. Those who had fulfilled the 1980 ACR or the 2013 ACR–EULAR classification criteria for systemic sclerosis, as well as of any other ACR or EULAR classification criteria for other definite connective tissue diseases at enrolment were excluded. Data were recorded each year during follow-up visits and included the four VEDOSS criteria (ie, positivity for antinuclear antibodies [ANAs], puffy fingers, systemic sclerosis-specific autoantibodies, and abnormal nailfold capillaroscopy). The primary endpoint was the fulfilment of the 2013 ACR–EULAR classification criteria for systemic sclerosis (ie, progression from enrolment to follow-up). Proportion of progressors and VEDOSS criteria interaction were reported descriptively. Predictors of progression of the distinct VEDOSS criteria interactions were determined based on the point prevalence at 5 years. To investigate the intermediate course of progression of the distinct VEDOSS criteria and their combinations, Kaplan-Meier analysis was done.

Results Between March 1, 2010, and Oct 4, 2018, we enrolled 1150 patients with Raynaud's phenomenon in the VEDOSS database. 764 (66·4%) of 1150 patients met the VEDOSS criteria for study inclusion. Of the 764 patients, 553 (72·4%) had at least one available follow-up visit and the median duration of follow-up was 3·6 years (IQR 1·7–5·8). The mean age was 45·9 years (SD 15·0), 507 (91·7%) of 553 participants were female, and the median time since the onset of Raynaud's phenomenon was 4·0 years (IQR 1·7–10·0). At baseline, 401 (73·7%) of 544 patients with Raynaud's phenomenon had detectable ANA, with 208 (39·5%) of 527 patients positive for systemic sclerosis-specific autoantibodies. Nailfold capillaroscopy abnormalities were present in 182 (36·0%) of 505 patients and puffy fingers were detected in 96 (17·8%) of 540 at baseline. 1885 follow-up visits were recorded. 254 (45·9%) of 553 patients completed the study with progression or a 5-year follow-up; of whom, 133 reached the primary endpoint, resulting in an overall progression rate of 52·4%. The absence of ANA at baseline was the factor most strongly associated with a lack of progression within 5 years, with only four (10·8%) of 37 ANA-negative patients progressing. Conversely, positivity at baseline for systemic sclerosis-specific autoantibodies and puffy fingers was the combination having the highest risk of progression (16 [94·1%] of 17).

Interpretation Our results from the VEDOSS project offers a useful tool for a stratified risk approach to patients with Raynaud's phenomenon. The absence of ANA is a strong protective factor that identifies patients with very low risk of developing systemic sclerosis whereas the presence of one or two VEDOSS criteria in patients with Raynaud's phenomenon confers a progressively higher risk for systemic sclerosis over time. This stratification tool can be used both for clinical management and to inform early interventional trials.

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Research in context

Evidence before this study

In the past 15 years, numerous single centre studies have evaluated the relative risk of antinuclear antibody (ANA) or nailfold capillaroscopic abnormalities for progression to systemic sclerosis. Although this topic has generated increased attention in recent years, evidence has remained limited to retrospective analysis of single centre cohorts. The preliminary validation of the Very Early Diagnosis of Systemic Sclerosis criteria has helped to inform the 2013 American College of Rheumatology–European League Against Rheumatism (ACR–EULAR) classification criteria for systemic sclerosis, but the relative risk of the criteria—single or in combination—has never been analysed prospectively in patients with Raynaud's phenomenon.

Added value of this study

To the best of our knowledge, this is the first multicentre study of this nature, capturing real-life progression within the context of a registry. We analysed the relative risk of progression to fulfil the 2013 ACR–EULAR criteria for systemic sclerosis at 5 years and within the 5 years. We found that the presence of one or more VEDOSS criteria at first assessment can be interpreted in a progressive risk score for progression to fulfil 2013 criteria within 5 years.

Implications of all the available evidence

The confirmation in a multicentre prospective setting of the high negative predictive value for future systemic sclerosis in the absence of ANA is very important in assessing risk and planning extensive screening and clinical follow-up in patients with Raynaud's phenomenon. Furthermore, the risk metre offered within our results can be a valuable tool both for stratified medicine approaches and for translational studies aimed at understanding disease progression. Additionally, the longitudinal analysis offers insights with regard to the stable versus progressive nature of the criteria contributing to the classification of systemic sclerosis, which might be useful in the identification of surrogate endpoints in future prevention studies.

Introduction

Systemic sclerosis is an autoimmune disease characterised by high clinical heterogeneity in morbidity and mortality.[1,2] This disease represents a great challenge for rheumatologists because of its unpredictable course. Despite the advances in understanding the pathogenesis of systemic sclerosis[1] and the development of new targeted therapies,[3–5] the disease has a high socioeconomic burden. This issue is particularly true in patients with complications that might have been avoided if an early diagnosis had been made.[6–7] In fact, an early diagnosis of systemic sclerosis is of particular importance, as therapy can be started before skin fibrosis progresses and other organs are damaged.[8] Population-based studies showed that mild systemic sclerosis occurs more frequently than previously suspected[9] and that organ involvement is already present in the preclinical stage.[10–13]

In 1980, the first classification criteria for systemic sclerosis were published and widely used as diagnostic criteria[14] despite poor sensitivity for an early classification of patients with systemic sclerosis.[15] In 1988, LeRoy and colleagues proposed new criteria that included clinical features, autoantibodies, and capillaroscopy, underlying the differences between the two main subsets of systemic sclerosis.[16] In 2001, LeRoy and Medsger proposed a revision of the classification criteria to include early cases of systemic sclerosis, making use of the nail fold capillary pattern and systemic sclerosis-specific autoantibodies.[6] These criteria have been validated and reveal the positive predictive value of the presence of systemic sclerosis-specific autoantibodies and the pattern of systemic sclerosis on capillaroscopy.[17] Finally, the revised American College of Rheumatology–European League Against Rheumatism (ACR–EULAR) classification criteria were published in 2013, showing an increased sensitivity to classify patients with systemic sclerosis who have less apparent skin involvement.[8]

Raynaud's phenomenon is a fundamental sentinel sign identifying patients at higher risk of developing systemic sclerosis or other connective tissue diseases.[17,18] The preliminary criteria for the very early diagnosis of systemic sclerosis (VEDOSS) were developed in 2011 as a result of a multicentre Delphi exercise among experts in systemic sclerosis.[19] The study identified Raynaud's phenomenon, positivity for antinuclear antibodies (ANAs), and puffy fingers as so-called red flags or level 1 signs to raise suspicion for the very early diagnosis of systemic sclerosis.[18,19] In the presence of these red flags, in the level 2 assessment, the positivity of systemic sclerosis-specific autoantibodies (ie, anticentromere, antiscleroderma-70, and anti-RNA polymerase III antibodies) or the detection of abnormal nailfold capillaroscopy, or both, could allow the identification of a patient affected by very early systemic sclerosis.[15,19]

To validate this approach, patients with Raynaud's phenomenon not fulfilling the 2013 ACR–EULAR classification criteria for systemic sclerosis were enrolled in a prospective, multicentre, longitudinal registry (ie, the Very Early Diagnosis of Systemic Sclerosis [VEDOSS] project), supported by the European Scleroderma Trial and Research (EUSTAR) group. In this study, we therefore aimed to determine the clinical value of the VEDOSS criteria to identify patients with Raynaud's phenomenon who progress to fulfil the 2013 ACR–EULAR criteria for systemic sclerosis within 5 years.

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See Online for appendix

Methods

Study design and participants

The VEDOSS project was a multicentre, longitudinal registry study done in 42 EUSTAR centres located in 20 countries in Europe, North America, and South America. Patient enrolment was opened on March 1, 2010. Patients with Raynaud's phenomenon—defined as a history of at least two of three colour changes (ie, white, blue, or red), usually induced by cold exposure, and involving at least one finger of each hand—were eligible for enrolment in the VEDOSS project.[19] Patients who had fulfilled the 1980 ACR[14] or the 2013 ACR–EULAR classification[8] criteria for systemic sclerosis, as well as of any other ACR or EULAR classification criteria for other definite connective tissue diseases (ie, overlap syndromes) at enrolment were excluded.

We obtained written informed consent from all eligible and enrolled participants. The respective Local Ethical Committee of the 42 EUSTAR centres approved this study.

Procedures

Data were recorded each year during follow-up visits in a centralised database within the EUSTAR database infrastructure. Database export for the current analysis was done on Oct 4, 2018. Data recorded in the database included demographics, medical history and clinical or serological data, results from laboratory and imaging examinations, current medications, and capillaroscopic characteristics as per the clinical research form. The other data recorded included the four VEDOSS criteria: ANA-positivity (according to local laboratory assays), puffy fingers, systemic sclerosis-specific autoantibodies, and abnormal nailfold capillaroscopy.

The systemic sclerosis-specific autoantibodies were defined by a positive test for anticentromere, anti-scleroderma-70, or anti-RNA polymerase III antibodies, either alone or in combination. The nailfold capillaroscopy abnormalities were based on the 2013 ACR definition: either giant capillaries or capillary loss with or without haemorrhages.[8] To this end, capillaroscopic evaluations that had been described in the VEDOSS database as giant capillaries (ie, as rare, moderate, or severe) or any capillary loss (ie, rare, moderate, or severe) were categorised as abnormal nailfold capillaroscopy, which potentially also comprises aspecific images with rare loss of capillaries.[20–21]

Outcomes

The primary outcome of this study was to provide estimates of the 5-year progression rates of patients in the VEDOSS project, which was defined as fulfilment of the 2013 ACR–EULAR classification criteria or so-called progression from enrolment to follow-up.[8] Frequency of single and combined items at inclusion and at follow-up was descriptively analysed. The analysis was limited to 5 years of follow-up. For the calculation of 5-year event rates, patients not reaching the endpoint, those who had an observation duration of less than 5 years, or both, were not included. Accordingly, progression events after 5 years were censored.

Statistical analysis

To answer various questions about the disease course of the patients in the VEDOSS project, we planned to include 1000 patients in the study. The collection of data was started as a registry without predefined termination rules. At the point of the intermediate database freeze for this analysis, at least one follow-up was available for 553 (72·4%) of 764 enrolled patients. Among the 211 patients without follow-up, 197 (93·4%) had a baseline visit at least 3 years before the database freeze, so the chance to ever see these patients again was low. Of the remaining 553 patients with follow-up, the 5-year observation criterion or progression was fulfilled in more than 50%. Therefore, we considered 764 patients as a reasonable number to describe baseline characteristics of our VEDOSS cohort and 533 with follow-up as a reasonable basis to provide first estimates for progression rates of this patient population. This decision was not driven by case number calculations of predefined hypotheses.

To investigate the course of progression based on the fully available follow-up data, the time to fulfilling classification of systemic sclerosis was evaluated with Kaplan-Meier analysis; the Breslow tests accounting for decreasing case numbers and thereby censored data was used. To identify baseline predictors of progression to definite systemic sclerosis for different combinations of the four baseline criteria in the same cohort, missing values for the four criteria were imputed with ten repetitions. Logistic regression on the 5-year events and Cox regression on the fully available follow-up data were run for all combinations of baseline criteria; pooled results of the imputed data are reported. For continuous data, mean (SD) or median (IQR) are shown. For categorical data, counts and percentages are shown. Because of the exploratory nature of the study, no adjustment for multiple testing was done.

We did all the statistical analyses using SPSS (version 24).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 1, 2010, and Oct 4, 2018, we included 1150 patients with Raynaud's phenomenon in the VEDOSS database on the basis of available baseline data. 764 (66·4%) of 1150 patients fulfilled the VEDOSS criteria (ie, ANA positive, puffy fingers, systemic sclerosis-specific autoantibody positive, abnormal nailfold capillaroscopy). Of the 764 patients, 553 (72·4%) had at

least one available follow-up visit and the median duration of follow-up was 3·6 years (IQR 1·7–5·8). 1885 follow-up visits were recorded. Figure 1A summarises the patient selection of this study. The mean age was 45·9 years (SD 15·0) and 507 (91·7%) of 553 participants were female (table). The median time since the onset of Raynaud's phenomenon was 4·0 years (IQR 1·7–10·0; table), which was no different from the 211 (27·6%) of 764 patients without follow-up (4·2 years [1·9–8·0]).

Complete 5-year follow-up data were available for 254 (45·9%) of 553 patients. The number of patients with data for each VEDOSS criterion are available in the table. Of the 553 patients with at least one follow-up, 401 (73·7%) of 544 patients with Raynaud's phenomenon had detectable ANA at baseline, with 208 (39·5%) of 527 patients positive for systemic sclerosis-specific autoantibodies. 164 (31·6%) of 519 patients were positive for anticentromere antibodies, 39 (7·4%) of 525 were positive for antiscleroderma-70 antibodies, and six (3·3%) of 180 were positive for anti-RNA polymerase III antibodies (table; figure 1B). Nailfold capillaroscopy abnormalities were present in 182 (36·0%) of 505 patients. Puffy fingers were detected in 96 (17·8%) of 540 patients with available data.

In patients with more than one VEDOSS criterion in addition to Raynaud's phenomenon at baseline, the case number with available information about the respective item combinations varied between 505 and 553. The summary of criteria interactions is shown in figure 1B, in which the intersection of a matrix of interactions are plotted in the bar graph. The most common combination was the presence of ANA and nailfold capillaroscopy abnormalities, recorded in 149 (29·3%) of 509 patients, followed by the combination of systemic sclerosis-specific autoantibodies, and nailfold capillaroscopy abnormalities, which was recorded in 80 (15·6%) of 514 patients. The third most common was the combination of ANA and puffy fingers recorded in 69 (12·8%) of 538 patients. Systemic sclerosis-specific autoantibodies and puffy fingers were recorded in 27 (5·0%) of 535, and nailfold capillaroscopy abnormalities and puffy fingers in the absence of systemic sclerosis-specific autoantibodies was noted in 30 (5·6%) of 532 (figure 1B).

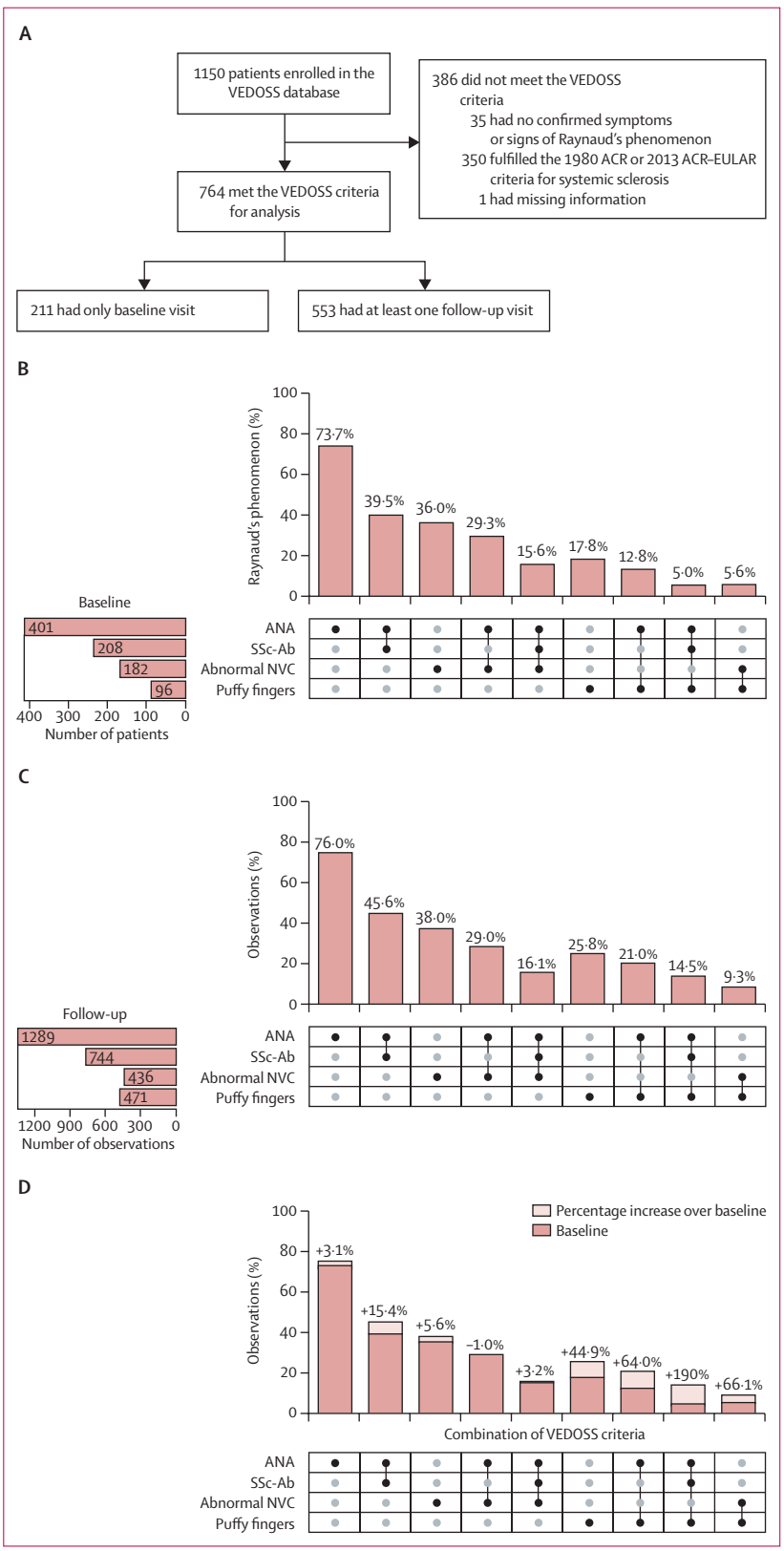


Figure 1: **Patient selection and distribution of the VEDOSS criteria with relative interactions**

(A) Patient selection flowchart; total sample size was 553 patients at baseline and 6067 observations were made during follow-up. (B) Baseline distribution and interaction in the 553 patients included in the analysis. (C) Follow-up distribution of the criteria by event recorded. (D) Bar graph summarising the relative change of interaction size between baseline and follow-up. VEDOSS criteria present at the same time are shown as black dots connected by vertical lines in the table and their size of interaction is described in the horizontal bars; grey dots indicate the absence of this VEDOSS criterion. ACR=American College of Rheumatology. ANA=antinuclear antibody. EULAR=European League Against Rheumatism. NVC=nailfold capillaroscopy. SSc-Ab=systemic sclerosis-specific autoantibody. VEDOSS=Very Early Diagnosis of Systemic Sclerosis.

During follow-up, ANA data were available for 1695 visits, with 1630 events recorded for systemic sclerosis-specific autoantibodies. The nailfold capillaroscopy evaluation was available for 1146 visits and the presence of puffy fingers in 1823 visits (figure 1C). The distribution of the VEDOSS criteria during follow-up visits showed that the prevalence of ANA was stable with a marginal 3·1% relative increase compared with baseline prevalence (difference of 2·3% divided by 73·7%; figure 1D). Similarly, nailfold capillaroscopy abnormalities remained largely stable, with a 5·6% relative increase (difference of 2% divided by 38·0% at baseline). On the contrary, puffy fingers were recorded in 96 (17·8%) of 540 observations at baseline compared with 471 (25·8%) of 1823 at follow-up, showing a 44·9% relative increase in prevalence during follow-up. Systemic sclerosis-specific autoantibodies were also reported more frequently during follow-up (744 [45·6%] of 1630 observations at follow-up compared with 208 [39·5%] of 527 at baseline), with a relative increase of 15·4% over baseline prevalence. This increase was associated with a 190·0% relative increase in prevalence of observations including all of ANA, systemic sclerosis-specific autoantibodies, and puffy fingers; a 64·1% relative increase in the combination of ANA and puffy fingers and 66·1% increase in nailfold capillaroscopy abnormalities and puffy fingers were also observed (figure 1D).

	Censored before 5 years (n=299)	5-year follow-up completers (n=254)	p value	Total (n=553)
Male	29 (9·7%)	17 (6·7%)	0·22	46 (8·3%)
Female	270 (90·3%)	237 (93·3%)	0·22	507 (91·7%)
Age	43·63 (14·4)	48·7 (15·2)	<0·001	45·9 (15·0)
Duration of Raynaud's phenomenon (years)	4·0 (1·7–10·0)	4·0 (1·5–10·3)	0·98	4·0 (1·7–10·0)
ANA positive	187/293 (63·8%)	214/251 (85·3%)	<0·001	401/544 (73·7%)
Systemic sclerosis-specific autoantibody positive	77/280 (27·5%)	131/247 (53·0%)	<0·001	208/527 (39·5%)
Anticentromere antibody positive	64/275 (23·3%)	100/244 (41·0%)	<0·001	164/519 (31·6%)
Anti-scleroderma-70 positive	11/280 (3·9%)	28/245 (11·4%)	<0·001	39/525 (7·4%)
Anti-RNA polymerase III positive	2/109 (1·8%)	4/71 (5·6%)	0·21	6/180 (3·3%)
Puffy fingers	48/298 (16·1%)	48/242 (19·8%)	0·31	96/540 (17·8%)
Nailfold capillaroscopy abnormalities	105/286 (36·7%)	77/219 (35·2%)	0·78	182/505 (36·0%)
Combinations*				
None	75 (25·1%)	25 (9·8%)	..	100 (18·1%)
ANA only†	56 (18·7%)	48 (18·9%)	..	104 (18·8%)
ANA and nailfold capillaroscopy	33 (11·0%)	14 (5·5%)	..	47 (8·5%)
ANA, nailfold capillaroscopy, and puffy fingers	13 (4·3%)	9 (3·5%)	..	22 (4·0%)
ANA and puffy fingers	8 (2·7%)	12 (4·7%)	..	20 (3·6%)
ANA and systemic sclerosis-specific autoantibody	32 (10·7%)	69 (27·2%)	..	101 (18·3%)
ANA, systemic sclerosis-specific autoantibody, and nailfold capillaroscopy	35 (11·7%)	45 (17·7%)	..	80 (14·5%)
ANA, systemic sclerosis-specific autoantibody, and puffy fingers	10 (3·3%)	17 (6·7%)	..	27 (4·9%)
Nailfold capillaroscopy	20 (6·7%)	5 (2·0%)	..	25 (4·5%)
Nailfold capillaroscopy and puffy fingers	4 (1·3%)	4 (1·6%)	..	8 (1·4%)
Puffy fingers	13 (4·3%)	6 (2·4%)	..	19 (3·4%)

Data are n (%), mean (SD), median (IQR), or n/N (%), unless otherwise specified. Data are of patients in the VEDOSS project at inclusion with at least one follow-up split by progression to the endpoint within or follow-up of 5 years or more (ie, completers) or duration of observation of less than 5 years without progression (ie, censored). ANA=antinuclear antibody. VEDOSS=Very Early Diagnosis of Systemic Sclerosis. *Missing values in single items were assumed as not present if other criteria were recorded for the allocation to combination categories. †ANA positive, but no other criteria (systemic sclerosis-specific antibodies, puffy fingers, or nailfold capillary abnormalities).

Table: **Characteristics of patients in the VEDOSS project**

The increase in detection of systemic sclerosis-specific autoantibodies over time was interesting and to our knowledge has not been reported before. To determine whether this observation was linked to a bias in obtaining specific information about these antibodies, we analysed the proportion of unknown or missing systemic sclerosis-specific autoantibodies over time. Anticentromere antibody was reported as missing or unknown in 72 (9·4%) of 764 at baseline and antiscleroderma-70 antibody was reported as missing or unknown in 58 (7·6%) of 764 at baseline. In all cases, these proportions did not decrease over time. On the contrary, we observed a slight increase in the proportion of missing data in subsequent visits from 9·4% to 15·0% for anticentromere antibody and from 7·6% to 15·7% for antiscleroderma-70 antibody.

In our population of patients with Raynaud's phenomenon, the analysis of progression over 5 years by baseline criteria offered the opportunity to examine risk stratification. The proportion of progressors stratified by the VEDOSS criteria and their interaction is summarised in figures 2, 3A–B. Follow-up data beyond or progression within 5 years were available for 254 (45·9%) of 553 patients; of whom, 133 reached the primary endpoint, resulting in an overall progression rate of 52·4%. 126 (94·7%) of 133 progressors were ANA positive, which corresponded to 126 (58·9%) of 214 ANA-positive patients. The absence of ANA at baseline was a strongly protective factor against progression, with only four (10·8%) of 37 ANA-negative patients progressing. This finding translates to a relative risk (RR) of 0·18 (95% CI 3·0–25·4). 92 (70·2%) of 131 patients with systemic sclerosis-specific autoantibodies at baseline progressed compared with 36 (31·0%) of 116 progressing in patients that did not have systemic sclerosis-specific autoantibodies at baseline. The presence of nailfold capillaroscopy abnormalities (54 [70·1%] of 77) or puffy fingers (34 [70·8%] of 48) at baseline conferred a similar risk of patients progressing (figures 2, 3; appendix p 2).

When looking at combinations of the VEDOSS criteria, patients with Raynaud's phenomenon who have ANA,

systemic sclerosis-specific autoantibodies, and puffy fingers at baseline represented the highest proportion of progressors (16 [94·1%] of 17). The coexistence of ANA, systemic sclerosis-specific autoantibodies, and nailfold capillaroscopy abnormalities had the second highest proportion of progressors (37 [82·2%] of 45; figure 3A). A colour-coded distribution of progression risk, according to the presence or absence of one or two VEDOSS criterion in combination is summarised in figure 3B.

For comparison of the predictive value of different VEDOSS criteria combinations, missing baseline values were imputed: nine (1·6%) of 553 values were missing for ANA, 13 (2·4%) were missing for puffy fingers, 26 (4·7%) were missing for systemic sclerosis-specific autoantibodies, and 48 (8·7%) were missing for nailfold capillaroscopy abnormalities.

When focusing on the percentage of correct prediction of 5-year progression, univariable logistic regression provided the best prediction for systemic sclerosis-specific autoantibodies, with a 69·2% correct prediction overall comparing both non-progression and progression. Among the significant singles or combinations, the best prediction of progression was for ANA with 96·2%, although with a low correct rate for non-progressions (27·3%; appendix p 3). When testing the four single criteria in a multivariable logistic regression model, with stepwise backward selection, the pooled results confirmed all criteria with significant predictive values: RR 6·21 (95% CI 1·57–24·6; p=0·010) for ANA, 5·83 (2·40–14·2; p=0·0001) for puffy fingers, 4·20 (2·21–7·99; p<0·0001) for systemic sclerosis-specific autoantibodies, and 2·52 (1·35–4·72; p=0·004) for nailfold capillaroscopy abnormalities (appendix p 1).

In the univariable Cox regression, incorporating the fully available follow-up data, the presence of systemic sclerosis-specific autoantibodies was the best predictor for progression. When testing the four single criteria in a multivariable Cox regression model, with stepwise backward selection, the pooled results confirmed all criteria with significant predictive values: RR 5·05 (95% CI 1·71–14·95; p=0·004) for ANA, 3·02 (2·00–4·55; p<0·0001) for systemic sclerosis-specific autoantibodies, 2·92 (1·91–4·46; p<0·0001) for puffy fingers, and 1·70 (1·18–2·46; p=0·004) for nailfold capillaroscopy abnormalities.

The overall comparison of time to fulfil the 2013 ACR–EULAR classification criteria for all combinations is shown in figure 4A. Subgroup analyses comparing progression with single or combined criteria versus those without progression are shown in figure 4B–C, and the appendix (p 1). Consistent with the baseline data analysis, the lowest risk category was patients without ANA. Comparison of groups with or without ANA showed a significantly different progression course (p<0·0001; figure 4C). Similarly, the group with the highest progression rate was the patients with systemic sclerosis-specific autoantibodies and puffy fingers; comparison of the population with this combination versus those with either only a single feature or none of the two features showed a steeper progression (p<0·0001; figure 4B). The presence of any single criterion or dual combination was always associated with a significantly higher progression than the comparison group without the single or dual feature, although by differing magnitudes. Kaplan-Meier analysis, taking also censored cases into account, showed that the largest 5-year difference was seen for the presence versus absence of systemic sclerosis-specific autoantibodies and puffy fingers (91·3% *vs* 32·8%), the smallest difference was seen for the presence versus absence of abnormal nailfold capillaroscopy (46·0% *vs* 28·3%; figure 4A; appendix p 1).

The course of progression analysis also offered the opportunity to determine the proportion of progression at each of the earlier timepoints. The combination of puffy fingers with ANA or systemic sclerosis-specific autoantibodies, or the combination of systemic sclerosis-specific autoantibodies and nailfold capillaroscopy abnormalities were associated with a 35–40% rate of progression at 24 months, increasing to about 50% at 36 months.

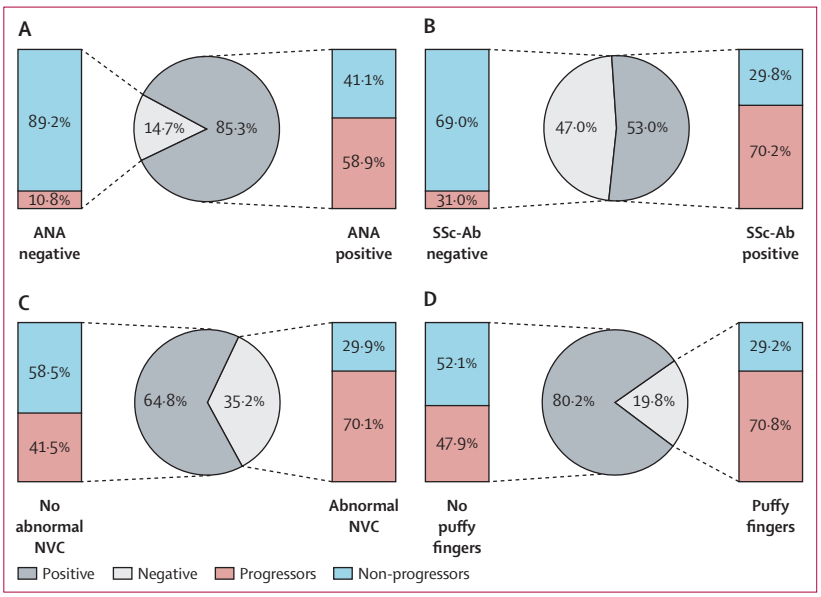
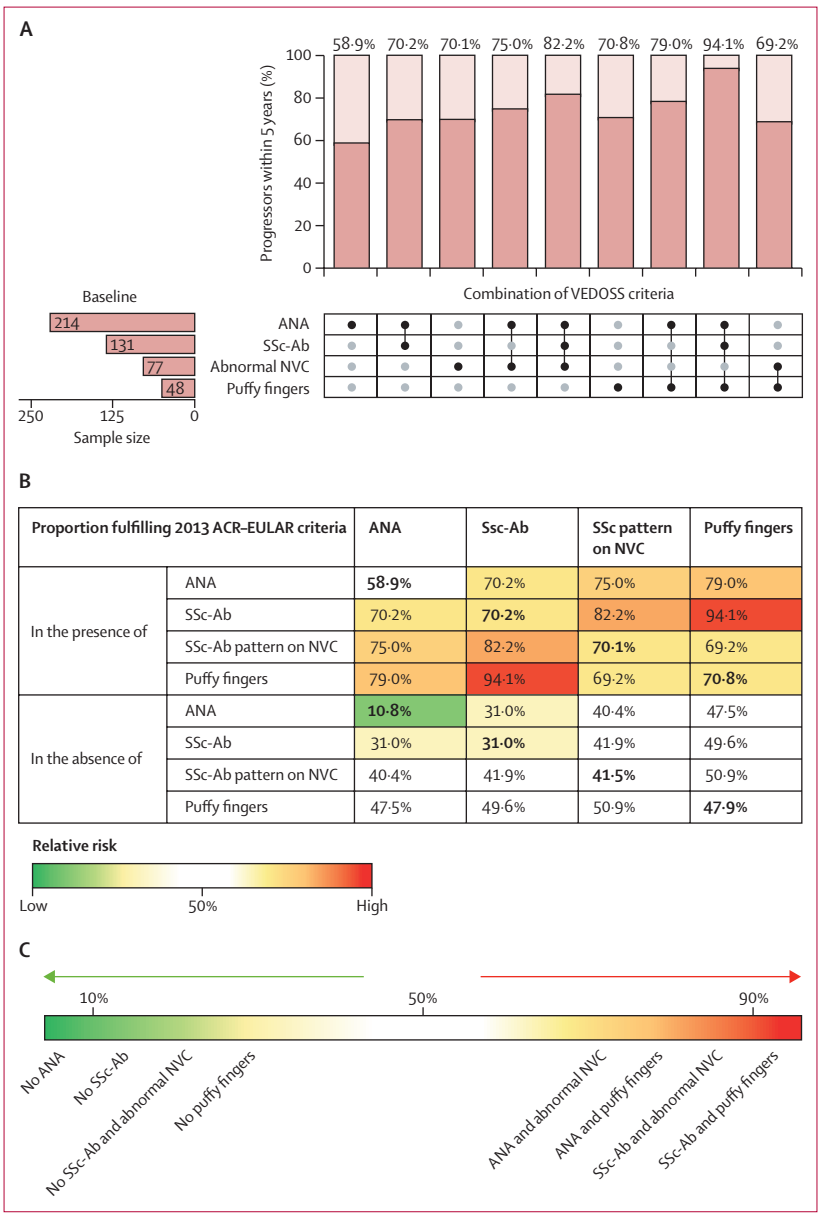


Figure 2: **Progression to fulfil the 2013 ACR–EULAR classification of systemic sclerosis by the VEDOSS criteria at baseline**

Only patients with 5-year follow-up or progression to the endpoint were included (n=254). The bar graphs represent proportion of progressors and non-progressors within the given subgroup. (A) Proportion of patients presenting at baseline observation with or without ANA. (B) Proportion of patients presenting at baseline observation with or without systemic sclerosis-specific autoantibodies. (C) Proportion of patients presenting at baseline observation with or without abnormal nailfold capillaroscopy. (D) Proportion of patients presenting at baseline observation with or without puffy fingers. ACR=American College of Rheumatology. ANA=antinuclear antibodies. EULAR=European League Against Rheumatism. NVC=nailfold capillaroscopy. SSc-Ab=systemic sclerosis-specific autoantibody. VEDOSS=Very Early Diagnosis of Systemic Sclerosis.

Discussion

This analysis has allowed us to evaluate the clinical, laboratory, and imaging features of patients with Raynaud's phenomenon in a large, prospective, multicentre cohort.



Proportion fulfilling 2013 ACR–EULAR criteria		ANA	Ssc-Ab	SSc pattern on NVC	Puffy fingers
In the presence of	ANA	**58·9%**	70·2%	75·0%	79·0%
	SSc-Ab	70·2%	**70·2%**	82·2%	94·1%
	SSc-Ab pattern on NVC	75·0%	82·2%	**70·1%**	69·2%
	Puffy fingers	79·0%	94·1%	69·2%	**70·8%**
In the absence of	ANA	**10·8%**	31·0%	40·4%	47·5%
	SSc-Ab	31·0%	**31·0%**	41·9%	49·6%
	SSc-Ab pattern on NVC	40·4%	41·9%	**41·5%**	50·9%
	Puffy fingers	47·5%	49·6%	50·9%	**47·9%**

Relative risk: Low — 50% — High

Figure 3: **Proportion of patients with 5 years of complete follow-up or progressing to fulfil the 2013 ACR–EULAR criteria (n=254) according to the VEDOSS criteria at baseline**

(A) UpSet plot showing proportion of progressor according to the VEDOSS criteria and their interaction. The sample sizes are shown on bottom left of the graph. VEDOSS criteria present at the same time are shown as black dots connected by vertical lines in the table and their size of interaction is described in the horizontal bars; grey dots indicate the absence of this VEDOSS criterion. (B) Frequency of progression as calculated in the presence or absence of the VEDOSS criteria alone or in combination. Absence for combinations comprises none or just one of two criteria. Frequencies are colour-ranked according to low and high risk of progression. Presence and absence of single criteria on the diagonal of the table are highlighted in bold font. (C) Diagram summarising the progressively higher or lower proportion of patients progressing to fulfil criteria within 5 years as per figure 3B. ACR=American College of Rheumatology. ANA=antinuclear antibody. EULAR=European League Against Rheumatism. NVC=nailfold capillaroscopy. SSc-Ab=systemic sclerosis-specific autoantibody. VEDOSS=Very Early Diagnosis of Systemic Sclerosis.

The purpose of this study was to identify, on top of Raynaud's phenomenon, signs that might best predict progression to the fulfilment of the classification criteria for systemic sclerosis. Our results confirm the clinical value of Raynaud's phenomenon, puffy fingers, and ANA positivity[17–19] among the pivotal signs and biomarkers to raise the suspicion of systemic sclerosis. These signs together with the positivity of systemic sclerosis-specific autoantibodies or an abnormal nailfold capillaroscopy, or both, might identify patients with Raynaud's phenomenon who have a very early systemic sclerosis that is characterised by the highest risk to evolve to definite systemic sclerosis, as defined by the 2013 ACR–EULAR classification criteria.[8] The present data offer also a clinical validation of the VEDOSS criteria since each one of these increases the risk of fulfilling the 2013 ACR–EULAR classification criteria for systemic sclerosis within 5 years.

In 2008, Koenig and colleagues found, in a 20-year single centre prospective study of 586 patients with Raynaud's phenomenon, that those with systemic sclerosis-specific autoantibodies or systemic sclerosis-specific nailfold capillaroscopy abnormalities without any other systemic sclerosis clinical manifestations had an increased risk to develop systemic sclerosis, classified according to the 1980 ACR criteria, compared with other patients with Raynaud's phenomenon.[17] At 5 years of follow-up, they found that 47% of patients with Raynaud's phenomenon were classified as having definite systemic sclerosis, according to the 1980 ACR criteria. The data from Koenig and colleagues' study used systemic sclerosis-specific nailfold capillaroscopy changes and pinpointed the relevance of the combination of systemic sclerosis-specific autoantibodies and nailfold capillaroscopy in centres specialised in such analysis. Our data show a similar proportion of patients fulfilling the newer ACR–EULAR criteria at 5 years (133 [52·4%] of 254 patients). Consistent with the registry approach, our data closely reflect daily practice and are based mainly on clinical signs and antibody detection. No central analysis of nailfold capillaroscopy images were done, and the nail capillaroscopy procedures and interpretation of results were not monitored. The definition of abnormal nailfold capillaroscopy changes in our analysis is broader than the one used in Koenig and colleagues' study. This difference might have under evaluated the role of nailfold capillaroscopy interpretation by including some non-specific abnormalities. However, our findings revealed the importance of ANA as a sign of evolving autoimmunity in this at-risk population and the role of puffy fingers.[22,23]

The strong negative predictive value of the absence of ANA could be considered when monitoring patients for the risk of progression to systemic sclerosis. It is also interesting to note that ANA did not change over time. We speculated that the increase in the proportion of missing data for anticentromere and antiscleroderma-70 antibodies in subsequent visits could be explained by a diminishing eagerness to document antibody status once this finding had been documented before. Regardless of the putative explanation, the observation of increased prevalence of systemic sclerosis-specific autoantibodies over time remained supported by the data. Notably, the absence of

anti-Th/To and anti-U3-RNP autoantibodies in the 2013 ACR–EULAR criteria might underestimate the effect of these specific autoantibodies in our analysis of progression. Nevertheless, patients with these specific autoantibodies still cannot be classified as having systemic sclerosis with the current criteria and therefore we did not do a specific sub-analysis in our study.

Similarly, the prevalence of nailfold capillaroscopy abnormalities were rather stable, increasing only 5·6% over 5 years, thus making both ANA and nailfold capillaroscopy abnormalities strong stratification points for clinical management. By contrast, the prevalence of puffy fingers increased by 44·9% over the 5 years. Similarly, the prevalence of systemic sclerosis-specific autoantibodies increased; this increasing prevalence of systemic sclerosis-specific autoantibodies over time is analogous to the increasing prevalence of anticyclic citrullinated peptide antibodies and rheumatoid factor in patients with rheumatoid arthritis, which is thought to reflect epitope spreading.[24] These observations might lead individuals to speculate that systemic sclerosis-specific autoantibodies and puffy fingers might reflect antigen spreading and progressive vascular damage in patients with autoimmunity (eg, ANA) and initial capillary abnormalities.[25] Although the higher risk of progression was in patients with the highest 2013 ACR–EULAR score at baseline (8 points in patients with systemic sclerosis-specific autoantibodies and either puffy fingers or nailfold capillaroscopy abnormalities), the presence of ANA, while not adding any points to the score, increased the RR to each of the other criteria. Further studies, in which only systemic sclerosis-specific nailfold capillaroscopy changes will be evaluated, will elucidate the role of these specific systemic sclerosis nailfold patterns in this population with Raynaud's phenomenon.

Our data are in agreement with Ricciardi and colleagues' study,[26] in which they reported similar results in a population of 102 patients with undifferentiated connective tissue disease at risk for systemic sclerosis, a condition characterised by Raynaud's phenomenon and either the presence of systemic sclerosis-specific autoantibodies and distinct nailfold capillaroscopy alterations or both. In the study by Ricciardi and colleagues,[26] patients showed a low risk of progression to any condition other than systemic sclerosis, suggesting that the risk of systemic sclerosis is perhaps more

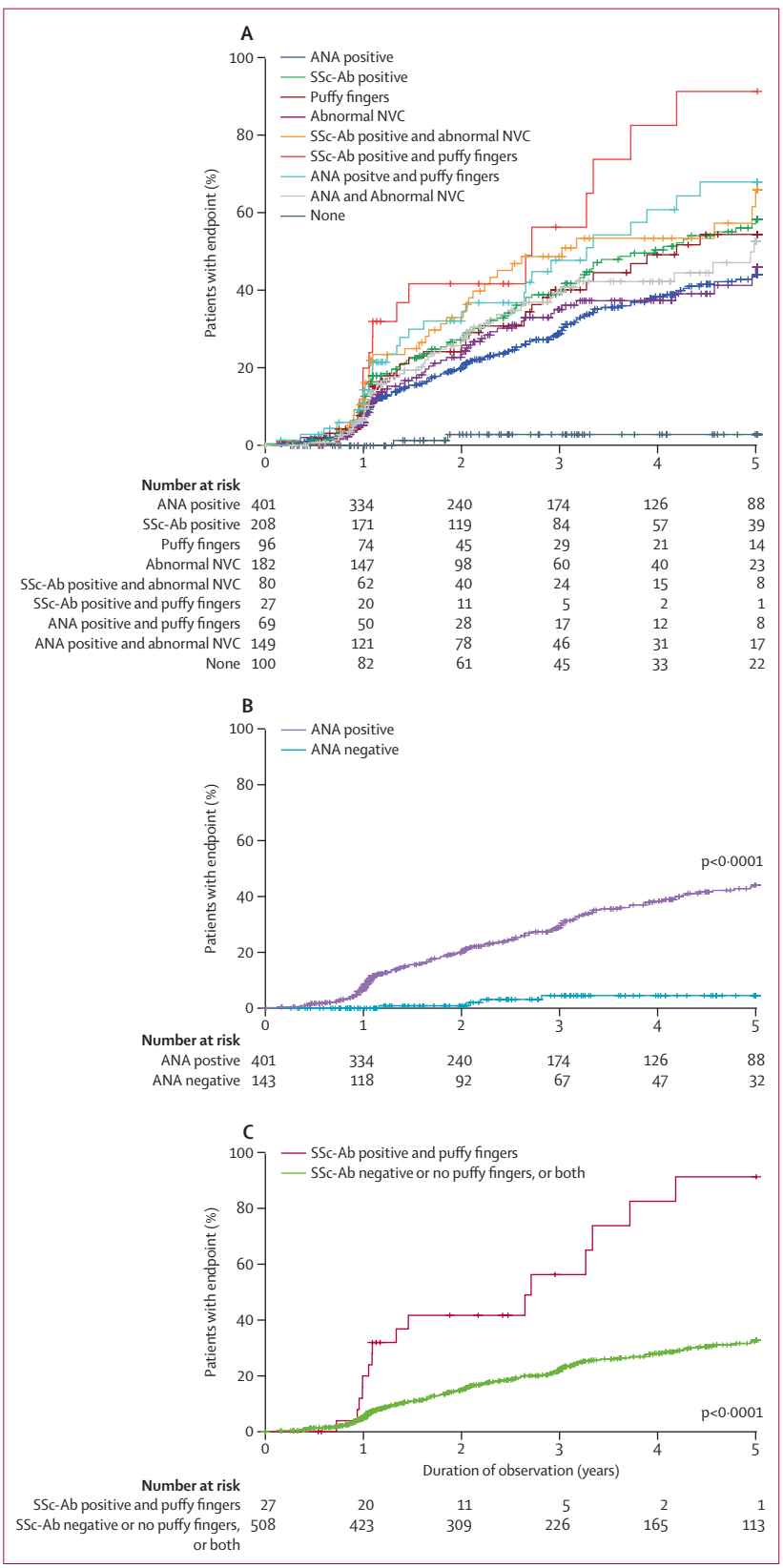


Figure 4: **Kaplan-Meier graphs showing progression over time startified by VEDOSS criteria**

(A) Progression to fulfil the 2013 ACR–EULAR classification of systemic sclerosis by different single VEDOSS criterion or combinations of the VEDOSS criteria at baseline. (B) Comparison of progression of patients with or without ANA positivity. (C) Comparison of progression of systemic sclerosis-specific autoantibody-negative patients with puffy fingers versus those with only a single feature or neither of these features. ACR=American College of Rheumatology. ANA=antinuclear antibody. EULAR=European League Against Rheumatism. NVC=nailfold capillaroscopy. SSc-Ab=systemic sclerosis-specific autoantibody. VEDOSS=Very Early Diagnosis of Systemic Sclerosis.

appropriate than a diagnosis of undifferentiated connective tissue disease for this cohort of patients.

One of the major strengths of our study is that it is the first prospective, multicentre, international study on this at-risk population, which suggest that the data are generalisable. Furthermore, the data have been obtained from specialised tertiary referral centres for systemic sclerosis, suggesting that patients were likely to be correctly and uniformly evaluated.

Our study, however, has some limitations, which are inherent to large international registry studies with a large number of centres. Koenig and colleagues reported from a single centre that the mean time between the onset of Raynaud's phenomenon and the first non-Raynaud's phenomenon symptom or sign was 4·8 years in limited cutaneous systemic sclerosis and 1·9 years in diffuse cutaneous systemic sclerosis.[17] This observation, if confirmed, might lead to a bias towards the diagnosis of limited cutaneous systemic sclerosis in our population. Despite the historical clinical subset, the definition has been recently challenged by the community.[27] A detailed sub-analysis of the VEDOSS criteria to provide a more predictive course of progression to the diffuse subset versus the limited subsets is currently an important point in the research agenda.

Perhaps the most important limitation is the low frequency of patients with follow-up (<50%). From our analysis, we observed that patients with no ANA and normal nailfold capillaroscopy were more likely to be lost at follow-up. This observation could reflect the lack of clinical need for follow-up in these patients but might have resulted in an overestimation of the proportion of progressors.

Of particular importance were the difficulties relating to measuring nailfold capillaroscopy changes. Our study had been initiated in an era before the consensus on how to categorise images as a pattern of systemic sclerosis or not, on a fast-track basis. Hence non-specific as well as specific changes of systemic sclerosis in capillaroscopic characteristics have been taken into account in this analysis, reflecting daily practice in which rheumatologists with any capillaroscopy training level had participated. Further studies taking the recently published Scleroderma Clinical Trials Consortium–EULAR consensus on evaluation of capillaroscopy and concerning classification of an image as having scleroderma pattern or not will elucidate the role of specific changes of systemic sclerosis in such a cohort.[28] Another limitation might be the potential differences in the detection of ANA and systemic sclerosis-specific autoantibodies. Since the detection of these antibodies was done locally, we cannot exclude a variability in sensitivity of the different methods used and the potential bias in unknown anti-RNA polymerase III status in the majority of centres. Nevertheless, this effect is likely to be minor as methods for doing these tests are generally uniform, although not exactly alike. Furthermore, the measures were used as dichotomous variables, so that titre differences are not of concern and limits of detection should not be a major methodological issue given the large number of patients in our study.

Another important limitation of our study was that wide heterogeneity in the follow-up rates were observed. In fact, complete 5-year follow-up data were available for 254 (45·9%) of 553 patients; and among 211 patients without follow-up, 95 (45·0%) were without specific features at baseline, showing that, at least in part, the missing follow-up could reflect an absence of progression bias and be due to patients having a mild disease course or no progression at all. Despite this limitation, the number of patients was sufficient for an appropriate analysis.

In conclusion, our data show that a substantial proportion of patients that met the VEDOSS criteria progressed to a definite classification of systemic sclerosis according to the 2013 ACR–EULAR criteria within 5 years of follow-up. The results of this study provide a simple and effective risk stratification model that might be relevant in clinical practice thus allowing an earlier therapeutic intervention to stop the progression of systemic sclerosis to fibrosis. In fact, the direct reference scale we propose might help physicians to stratify the risk and tailor the regularity of follow-up in patients with a higher risk versus a lower risk of progression, focusing frequent and expensive screening procedures on those at higher risk. The implementation of this risk stratification model in a clinical trial setting might also inform sample size calculations for early therapeutic trials aimed at preventing the progression of patients with very early diagnosis of systemic sclerosis to definite systemic sclerosis, and help to improve long-term outcomes and prevent organ damage.

Contributors

SBR and FDG conceived the analysis plan and drafted the manuscript and figures. DH did all the statistical analysis and contributed to the manuscript draft. GL, TM, LC, CB, SG, JA, MC, and VS contributed to the data interpretation and revised the manuscript. DEF, YA, OD, and MM-C conceived and contributed to all aspects of the study. SBR and DH verified the underlying data.

Declaration of interests

LC has had consultancy relationships with Boehringer Ingelheim, Actelion, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Lilly. FdG has had consultancy relationships or has received research funding, or both, from Actelion, AstraZeneca, Boehringer Ingelheim, Capella Biosciences, Chemomab, GlaxoSmithKline, Kymab, and Mitsubishi-Tanabe in the area of potential treatments of scleroderma and its complications. DEF has received grant or research support from Actelion, Amgen, BMS Corbus, CSL Behring, Galapagos Gilead, GlaxoSmithKline, National Institutes of Health, Novartis, Kadmon, PICORI, Pfizer, Sanofi, Roche–Genentech, Talaris, and Mitsubishi; and consultancy relationships with AbbVie, Acetelion, Amgen, BMS Corbus, Galapagos, Novartis, Pfizer, Talaris, R-Pharm, Sanofi, CSL Behring, and Boehringer Ingelheim; and speakers bureau from CME. YA has had consultancy relationships or has received research funding, or both, from Actelion, Bayer, Boehringer Ingelheim, Genentech–Roche, Inventiva, Medsenic, and Sanofi in the area of potential treatments of scleroderma and its complications. OD reports receiving personal fees from AbbVie, Acceleron Pharma, Amgen, AnaMar, Arxx Therapeutics, Baecon Discovery, Blade Therapeutics, Bayer, Boehringer Ingelheim, ChemomAb, Corbus, CSL Behring, Galapagos NV, Glenmark, GlaxoSmithKline, Horizon, Inventiva, IQvia, Italfarmaco, Iqone, Kymera Therapeutics, Lilly, Medac, Medscape, Merck Sharp & Dohme, Novartis,

Pfizer, Roche, Roivant Siences, Sanofi, Serodapharm, Topadur, Target Bioscience, and UCB, during the conduct of the study; and grants from Mitsubishi Tanabe; and a patent issued mir-29 for the treatment of systemic sclerosis (US8247389, EP2331143). MMC has received consulting fees or honorarium from Actelion, Janssen, Inventiva, Bayer, Biogen, Boehringer Ingelheim, CSL Behring, Corbus, Galapagos, Mitsubishi, Samsung, Regeneron, Acceleron, Merck Sharp & Dohme, Chemomab, Lilly, Pfizer, and Roche. DH has received travel funding from Actelion, Boehringer Ingelheim, and Shire. VS reports grants and personal fees from Boehringer Ingelheim and Janssen-Cilag NV; grants from Flanders, the Belgian Fund for Scientific Research in Rheumatic diseases; and personal fees from Accord Healthcare, Celgene, and UCB, outside the submitted work. VS is also the chair (unpaid) of the European League Against Rheumatism Study group on Microcirculation in Rheumatic Diseases, co-chair (unpaid) of the American College of Rheumatology Study Group on Microcirculation, co-chair (unpaid) of the Scleroderma Clinical Trials Consortium Working Group on capillaroscopy, and is a steering committee member (unpaid) of the European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases. TM has received honoraria and fees for lectures from Actelion, Janssen, Boehringer Ingelheim, Lilly, Pfizer, Roche, AbbVie, and Richter. CB reports personal fees from Actelion and Eli Lilly; and grants from the European Scleroderma Trial and Research group, New Horizon Fellowship, the Foundation for Research in Rheumatology, and Fondazione Italiana per la Ricerca sull'Artrite, outside the submitted work All other authors declare no competing interests.

Data sharing

A data dictionary will be made available upon request. Deidentified individual participant data could be made available upon a clinical project request following the standard operating procedures of the World Scleroderma Foundation–European Scleroderma Trial and Research).

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