# MRI Digital Artery Volume Index (DAVIX) as a surrogate outcome measure of digital ulcer disease in patients with systemic sclerosis: a prospective cohort study

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## Summary

**Background** Vascular fibrosis is a key manifestation of systemic sclerosis that leads to the narrowing of small and medium arteries, causing vascular clinical manifestations including digital ulcers and pulmonary arterial hypertension. We investigated the potential of the MRI-based Digital Artery Volume Index (DAVIX) as a surrogate outcome measure of vascular fibrosis by using it to quantify and predict the burden of digital ulcer disease in patients with systemic sclerosis.

**Methods** Two independent cohorts of patients participating in the prospective observational study STRIKE were consecutively enrolled from the Scleroderma Clinic of the Leeds Teaching Hospitals Trust, Leeds, UK. Eligible patients were aged 18 years or older and fulfilled the very early diagnosis of systemic sclerosis (VEDOSS) or the 2013 American College of Rheumatology (ACR)–European Alliance of Associations for Rheumatology (EULAR) systemic sclerosis classification criteria. DAVIX was calculated as the percentage mean of the ratio of digital artery volume to finger volume in the four fingers of the dominant hand. Data were collected at baseline and 12-month follow-up, and the primary outcome was the presence of digital ulcers at 12-month follow-up.

**Findings** Between Feb 7, 2018, and April 11, 2022, we included 85 patients in the exploratory cohort and 150 in the validation cohort. In the exploratory cohort, the mean age was 54·5 years (SD 11·6), 75 (88%) of 85 patients were women, ten (12%) were men, and 69 (82%) were White. In the validation cohort, the mean age was 53·5 years (SD 13·8), 136 (91%) of 150 patients were women, 14 (9%) were men, and 127 (85%) were White. In the exploratory cohort, DAVIX was significantly lower in patients with previous or active digital ulcers (0·34% [IQR 0·16–0·69]) than in those without digital ulcer disease (0·65% [0·42–0·88]; p=0·015); this finding was substantiated in the validation cohort (0·43% [0·20–0·73] *vs* 0·73% [0·53–0·97]; p<0·0001). Patients who developed new digital ulcers during 12-month follow-up had a lower DAVIX (0·23% [0·10–0·66]) than those who did not (0·65% [0·45–0·91]; p=0·0039). DAVIX was negatively correlated with disease duration ($r$=–0·415; p<0·0001), the ratio of forced vital capacity to the diffusing capacity of the lungs for carbon monoxide ($r$=–0·334; p=0·0091), nailfold capillaroscopy pattern ($r$=–0·447; p<0·0001), and baseline modified Rodnan skin score ($r$=–0·305; p=0·014) and was positively correlated with the diffusing capacity of carbon monoxide ($r$=0·368; p=0·0041). DAVIX was negatively correlated with change in score on the Scleroderma Health Assessment Questionnaire-Disability Index ($r$=–0·308; p=0·024), Visual Analogue Scale (VAS) Raynaud's ($r$=–0·271; p=0·044), and VAS digital ulcers ($r$=–0·291; p=0·044).

**Interpretation** DAVIX is a promising surrogate outcome measure of digital ulcer disease in patients with systemic sclerosis. The ability of DAVIX to non-invasively predict future digital ulcers and worsening of patient-reported outcomes could aid patient enrichment and stratification in clinical trials. Clinically, DAVIX could offer insights into the assessment of vascular activity. The sensitivity of DAVIX to change over time and with treatment will establish its value as an imaging outcome measure of vascular disease.

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## Introduction

In patients with systemic sclerosis, digital and systemic vasculopathy is associated with substantial morbidity and mortality throughout the disease course.[1,2] Fibroproliferative vasculopathy, which is caused by neointima proliferation and results in arterial vessel narrowing, affects multiple organs and is a hallmark of the disease.[1,2]

Digital vasculopathy is a key feature of systemic sclerosis, with a range of manifestations from Raynaud's phenomenon to persistent tissue ischaemia including digital ulcers, pitting scars, and gangrene.[3,4] Although

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## Research in context

### Evidence before this study

To find existing evidence of macrovascular impairment in systemic sclerosis and its visualisation through MRI, we searched PubMed, Google Scholar, Cochrane Library, and Web of Science, without language restriction, for studies published from Jan 1, 2005, until Sept 30, 2022, with the search terms "Systemic Sclerosis" or "Scleroderma" and "vascular disease" or "vascular manifestation" or "MRI" or "MRI angiography" in the title or abstract. Individual searches were then combined. The resulting studies showed that patients with systemic sclerosis have an apparently smaller digital artery lumen than healthy controls. In one study, the majority of patients with systemic sclerosis had at least one digital artery that did not reach the first phalanx and more than half had an abnormal venous return. These findings supported the possibility of using MRI angiography of finger vessels to assess vascular involvement in patients with systemic sclerosis; we therefore decided to further explore the relationship of such vascular involvement with disease manifestations.

### Added value of this study

We used a non-invasive, quantitative, artificial intelligence-based assessment of digital artery volume in patients with systemic sclerosis, using MRI time-of-flight angiography without the need for a contrast agent. The Digital Artery Volume Index (DAVIX) quantifies the odds of worsening digital ulcer disease, which correlates with changes in patient-reported outcomes over the following 12 months and with disease duration. The correlation of DAVIX with existing measures of vascular activity in systemic sclerosis—such as nailfold capillaroscopy and the ratio of forced vital capacity to the diffusing capacity of the lungs for carbon monoxide—suggests its value as a surrogate outcome measure of the activity and severity of vascular disease.

### Implications of all the available evidence

The ability of DAVIX to predict the worsening of digital ulcer disease in systemic sclerosis could aid patient enrichment and stratification in clinical trials. The index is now being tested as an outcome measure of vascular disease in two randomised, placebo-controlled trials in patients with systemic sclerosis. Clinically, the index offers insights into the severity of vascular fibrosis, which aids in the assessment of vascular disease activity in systemic sclerosis. Ongoing studies will establish the value of DAVIX in identifying preclinical stages of vascular manifestations (such as digital ulcers and pulmonary arterial hypertension), in enriching for patients with active vascular disease, and as a surrogate endpoint in interventional trials.

still debated, large-vessel (macrovascular) disease has been reported to be over-represented in patients with systemic sclerosis,[5] which is likely to further compound the effect of progressive microangiopathy.

To date, there is no validated, non-invasive imaging technique to assess the severity of arterial involvement in patients with systemic sclerosis and, in turn, to inform patient stratification and assess the effect of treatment. Although obliterative microvascular disease can be easily visualised by non-invasive nailfold capillaroscopy, assessing the involvement of deeper medium and large vessels is more challenging. In particular, the proper digital arteries are very small, with an average diameter of approximately 1·5 mm,[6] requiring high-resolution imaging for visualisation.

We aimed to assess the ability of the Digital Artery Volume Index (DAVIX)[7]—a quantitative, non-invasive imaging score based on time-of-flight MRI—for early detection of digital ulcer disease and predicting the onset of digital ulcers. The association of DAVIX with worsening patient-reported outcomes and clinical manifestations in patients with systemic sclerosis were studied as exploratory analyses.

## Methods

### Study design and patients

This prospective observational cohort study included consecutive participants recruited to an MRI substudy of the Stratification for Risk of Progression in Systemic Sclerosis (STRIKE) study (ID 178638). Patients who attended the Scleroderma Clinic of the Leeds Teaching Hospitals Trust, Leeds, UK, were recruited to the study between February 7, 2018, and April 4, 2019 (exploratory cohort) and between April 17, 2019, and April 11, 2022 (validation cohort).

Eligible patients were aged 18 years or older and fulfilled the very early diagnosis of systemic sclerosis (VEDOSS)[8] or the 2013 American College of Rheumatology (ACR)–European Alliance of Associations for Rheumatology (EULAR) systemic sclerosis classification criteria.[9] The study protocol was approved by the NHS Health Research Authority (Research Ethics Committee reference 15/NE/0211, ID 178638).[10] All patients provided written informed consent.

### Procedures and outcomes

To investigate whether DAVIX could quantify and predict the worsening of digital ulcer disease in patients with systemic sclerosis or VEDOSS during a 12-month follow-up, all patients had an MRI scan of their dominant hand at the time of enrolment and DAVIX of the hand was calculated. Patients in the exploratory cohort were followed up longitudinally and assessed for the presence of digital ulcers at 12 months (the primary endpoint). Longitudinal follow-up of the validation cohort is still ongoing; baseline data for this cohort are presented.

Baseline data on sex, age, presence of anti-nuclear antibodies, anti-topoisomerase I (Scl-70) or

anti-centromere specific autoantibodies, and drug therapies were collected for each participant from medical records. Systemic sclerosis was divided into diffuse cutaneous and limited cutaneous disease subtypes, as defined by LeRoy and colleagues.[11] Disease duration was defined as the time since the onset of the first non-Raynaud's phenomenon systemic sclerosis symptom.

Patients were assessed at baseline and at 12-month follow-up, including for the presence of digital ulcers. Digital ulcers were defined as a loss of skin continuity involving at least the epidermis, the basal membrane, and the dermis, localised on the fingertip or close to the nails, according to the definition endorsed by the World Scleroderma Foundation. History of digital ulcers were collected from patient records in the STRIKE cohort database.

Additional clinical parameters collected at both baseline and at 12-month follow-up were modified Rodnan skin score, for the quantification of skin fibrosis (scored on a continuous integer scale from 0 to 51); pulmonary function tests (forced vital capacity [FVC] and diffusing capacity of the lungs for carbon monoxide [DLCO]); percentage predicted FVC and DLCO value for age, sex, height, and weight; systolic pulmonary artery pressure obtained through echocardiographic estimation; and nailfold capillaroscopy pattern (normal, non-specific, early, active, or late;[12] Optilia, VCAP [Optilia Medical, Vällingby, Sweden]).

Patient-reported outcomes were collected at baseline and at 12-month follow-up. The Scleroderma Health Assessment Questionnaire-Disability Index (SHAQ-DI) was given to participants at both timepoints. In addition to the HAQ visual analogue scale (VAS) for pain and the VAS for patient global assessment, this questionnaire also contains other VAS for systemic sclerosis-related domains: VAS arthritis, VAS intestinal function, VAS breathing, VAS Raynaud's phenomenon, and VAS digital ulcers.[13] All VAS were presented to patients as a 15 cm, doubly anchored horizontal line scored from 0 (very well) to 100 (very poor). The Cochin Hand Function Scale, a score ranging from 0 to 90 on which a higher score indicates more difficulty in hand function,[14] and the Borg rating of perceived exertion scale, ranging from 1 to 10, were also completed by participants at both baseline and 12-month assessment visits.[15]

Similar to previous studies, we studied the four fingers and excluded the thumb.[16,17] We used a time-of-flight MRI angiography sequence as previously described.[7] This flow-compensated, gradient-echo MRI sequence is mainly used to visualise blood flow within vessels in other regions of the body (eg, brain) without the need to administer an MR-specific contrast agent.[18] Time-of-flight enables the visualisation of vessels by enhancing the signal of flowing blood and suppressing the signal from surrounding stationary tissue in a definite volume. The volume of blood moving is then approximated to the patent portion of the vessels. We detected the blood volume using established approaches in image processing that have previously been used in the automatic detection of lung nodules or for coronary artery segmentation.[19]

MRI scans were done on a 3T Magnetom Verio (Siemens Healthineers, Erlangen, Germany). A volumetric interpolated breath-hold examination (VIBE) three-dimensional (3D) T1 scan of 3 min and a two-dimensional (2D) time-of-flight sequence of around 10 min (two identical time-of-flight scans are run in case of movement; each 4 min 52 s) were performed using a time to echo of 5 ms and repetition times ranging from 24 ms to 72 ms as needed. Semi-automated post-processing analysis was done on the Dynamika platform (Image Analysis Group), as previously described.[7] In brief, the method incorporated into the platform uses a region-growing algorithm[20] to semi-automatically detect the anatomy of the arteries and fingers. To mitigate the risk of vasospasm, the temperature of the MRI acquisition room was controlled at 22°C. Patients were asked to avoid any caffeine or nicotine for at least 1 h before MRI acquisition and left to acclimatise to the room for at least 30 min, as described in the acquisition protocol.[7] Further detailed description of the methods is provided in the appendix (pp 1–2).

See Online for appendix

An overview of the finger and vessel segmentation is reported in the appendix (pp 1–2). After volume rendering and quantification, the volumes of the two arteries detected in each finger are summed and divided by the volume of the finger. This ratio (expressed as a percentage) is defined as the DAVIX of the single finger. DAVIX of the dominant hand was calculated as the mean of the values of the four fingers.

### Statistical analysis

The primary hypothesis we aimed to test was that DAVIX could differentiate patients with digital ulcer disease from those without, and predict the onset of digital ulcers in the following 12 months. We found no previous literature to inform an effect size. Pilot data from 15 patients with systemic sclerosis who fulfilled the 2013 ACR–EULAR criteria and 15 patients with primary Raynaud's phenomenon showed that the mean DAVIX for the two groups was significantly different (0·30% [SD 0·04] *vs* 1·46% [0·14]; p<0·0001) and the effect size, computed through Cohen's *d*, was –10·88 (95% CI –13·83 to –7·89). To be conservative, we used a Cohen's *d* of 0·8, for a large effect size, for the sample size calculation.[21] Considering a power of 95% and an α of 0·05, we estimated a sample size of 84 patients, to which we added 10% to account for missing data and loss to follow-up, leading to an estimated sample of 92 patients. On the basis of this estimation, we aimed to start the analysis of the observational cohort as soon as we had 12-month clinical follow-up data available for at least 90 patients enrolled in the STRIKE MRI substudy.

The distribution of the data was analysed with the D'Agostino-Pearson normality test. Comparisons between two groups were made using the unpaired

Student's *t* test or the Mann-Whitney-Wilcoxon test as appropriate. When DAVIX was compared in the same patient cohort, regrouped according to digital ulcer disease or new digital ulcer development, a Bonferroni correction factor of M=2 was applied to the p significance level, to correct for multiple testing to maintain the type I error threshold below 0·05 ($p_{adj}$). To compare DAVIX among diagnostic categories of systemic sclerosis, an ANOVA was conducted with a Tukey honestly significant difference test to show which group differed significantly. The assumptions of constancy of variance and normality of errors were checked graphically. The ability of DAVIX to predict the onset of new digital ulcers at 12 months was assessed using a receiver–operating characteristic (ROC) curve, plotted using DAVIX as the binary classifier mapped to the presence or absence of new digital ulcers at 12-month follow-up. The optimal DAVIX threshold was estimated through the highest Youden index. The odds ratio (OR) for the development of new digital ulcers at 12 months was calculated in patients with DAVIX above and below the estimated threshold.

Correlations of DAVIX with clinical manifestations were assessed using Spearman's or Pearson's tests, as appropriate. The correlation between DAVIX and nailfold capillaroscopy was scored on a semi-quantitative integer scale ranging from 0 to 4 (0 normal, 1 non-specific, 2 early, 3 active, and 4 late).

The correlations of DAVIX with clinical parameters and patient-reported outcomes and with their differences between baseline and 12-month follow-up (expressed as Δ, ie, the absolute difference between the 12-month values and the baseline values) were studied as additional exploratory analyses. Correlation coefficients and their relative p values were summarised in a correlation matrix. We did not correct for multiple comparisons as the clinical parameters and patient-reported outcomes we investigated were not mutually exclusive and sample size was not calculated for this purpose. Data were analysed using R Core Team software and RStudio.

### 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 Feb 7, 2018, and April 11, 2022, a total of 241 participants were recruited to the study. 91 patients were recruited to the exploratory cohort, of whom 85 (93%) had 12-month follow-up data and were included in subsequent analyses (appendix p 3). 150 patients were recruited to the validation cohort, for which longitudinal follow-up is ongoing. From these 235 patients we studied 912 fingers; 28 fingers were excluded (28 from the exploratory cohort, none from the validation cohort) because of an image quality below the

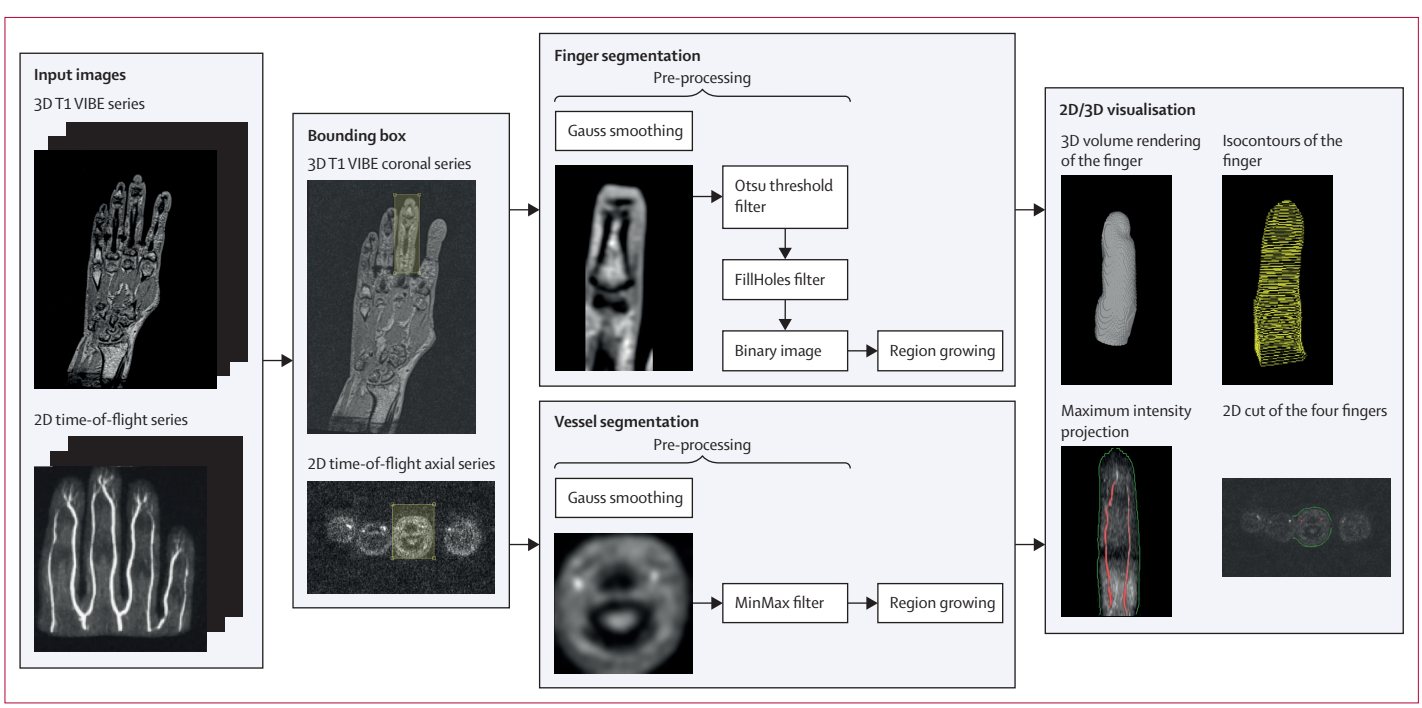



***Figure 1:*** **Workflow of finger and vessel segmentation**
Workflow on the Dynamika platform. In the first stage, the 3D T1 VIBE and 2D time-of-flight input images are uploaded. Next, the target finger is identified and outlined with a bounding box. A finger segmentation model is then applied to calculate the volume of the finger, and a vessel segmentation model is used to calculate the volume of the arteries within the finger. Finally, 3D rendering of the segmented finger and arteries enables visualisation for clinical validation. 2D=two-dimensional. 3D=three-dimensional. VIBE=Volumetric Interpolated Breath-hold Examination.

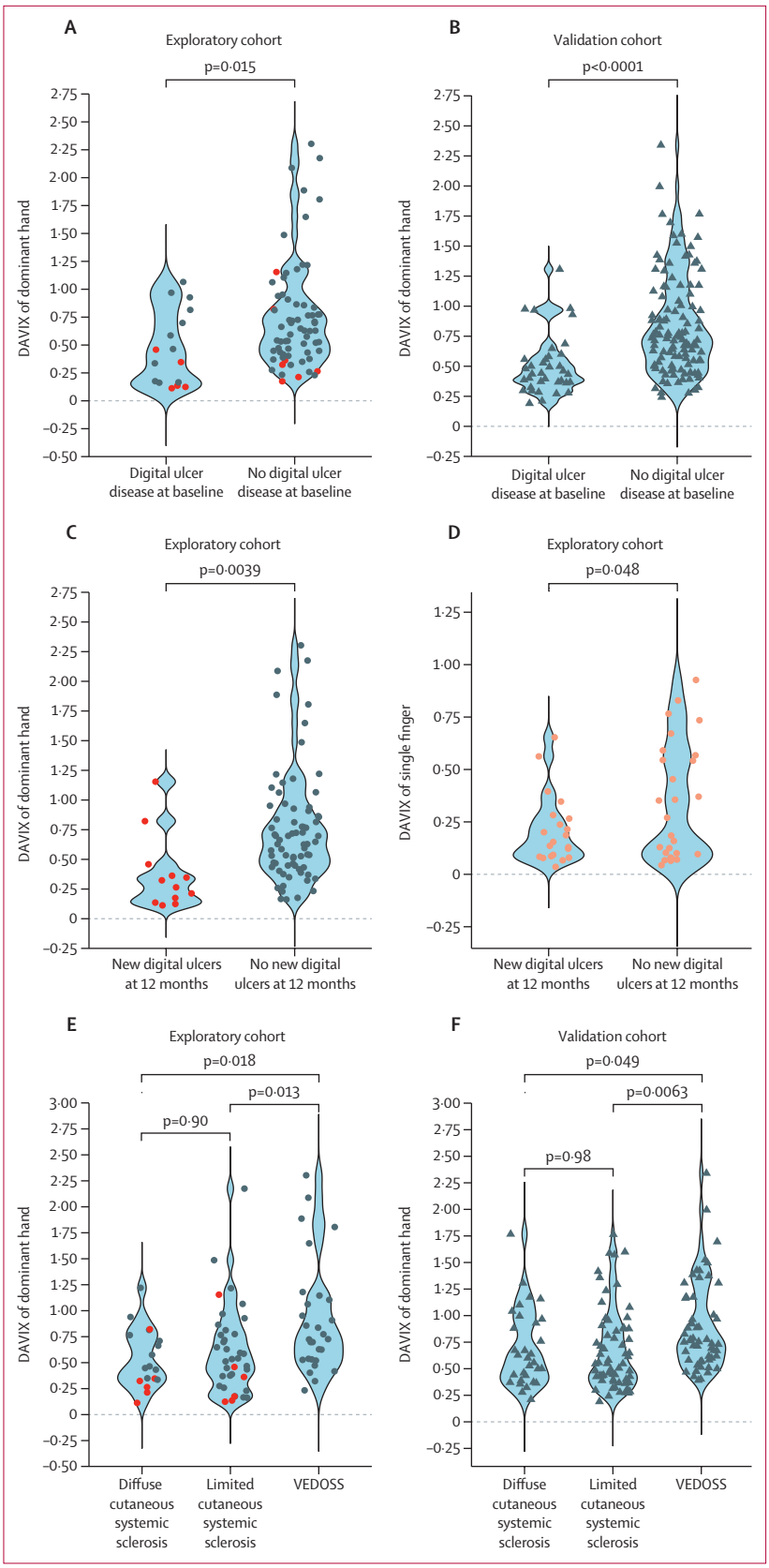
quality control standards (n=17),[7] no visible digital artery (n=5), deforming osteoarthritis (n=5), and finger amputation (n=1). A representative workflow of finger and vessel segmentation informing DAVIX is shown in figure 1.

Baseline patient and disease-related characteristics are presented in the table. 152 (65%) of 235 patients (56 [66%] of 85 in the exploratory cohort and 96 [64%] of 150 in the validation cohort) fulfilled the 2013 ACR–EULAR systemic sclerosis classification criteria,[9] whereas 83 (35%) patients (29 [34%] of 85 in the exploratory cohort and 54 [36%] of 150 in the validation cohort) had a score of less than 9 on this scale and therefore fulfilled VEDOSS criteria. Overall, 211 (90%) of 235 patients were women and 24 (10%) were men, and the median disease duration (measured from the first non-Raynaud's symptom) for patients fulfilling the 2013 ACR–EULAR systemic sclerosis classification criteria was 72 (IQR 36–120) months (exploratory cohort 71 months [IQR 35–119], validation cohort 72 months [IQR 36–120]). The median duration of Raynaud's phenomenon for all patients across the two cohorts—including patients with VEDOSS—was 34 months (IQR 0–84; exploratory cohort 35 months [IQR 0–86], validation cohort 24 months [IQR 0–84]). In the exploratory cohort, 75 (88%) of 85 patients were women,

| | Exploratory cohort | | | Validation cohort | | |
|---|---|---|---|---|---|---|
| | Overall cohort (n=85) | Digital ulcer disease (n=17) | No digital ulcer disease (n=68) | Overall cohort (n=150) | Digital ulcer disease (n=36) | No digital ulcer disease (n=114) |
| Age, years | 54·5 (11·6) | 54·8 (12·2) | 54·5 (11·5) | 53·5 (13·8) | 57·8 (12·7) | 53·2 (13·9) |
| Sex | | | | | | |
| Female | 75 (88%) | 13 (77%) | 62 (91%) | 136 (91%) | 31 (86%) | 105 (92%) |
| Male | 10 (12%) | 4 (24%) | 6 (9%) | 14 (9%) | 5 (14%) | 9 (8%) |
| Race/ethnicity | | | | | | |
| African | 2 (2%) | 1 (6%) | 1 (1%) | 3 (2%) | 2 (5%) | 1 (1%) |
| South Asian | 14 (16%) | 5 (29%) | 9 (13%) | 20 (13%) | 6 (17%) | 14 (12%) |
| White | 69 (81%) | 11 (65%) | 58 (85%) | 127 (85%) | 28 (78%) | 99 (87%) |
| Disease duration, months | 71 (35–119) | 97 (75–188) | 51 (31–100) | 72 (36–120) | 84 (60–174) | 72 (34–93) |
| Disease duration at time of first digital ulcer, months | .. | 65 (48–90) | .. | .. | 56 (40–78) | .. |
| Systemic sclerosis subtype | | | | | | |
| Diffuse cutaneous | 18 (21%) | 5 (29%) | 13 (19%) | 31 (21%) | 14 (39%) | 17 (15%) |
| Limited cutaneous | 38 (45%) | 12 (71%) | 26 (38%) | 65 (43%) | 22 (61%) | 43 (38%) |
| VEDOSS | 29 (34%) | 0 | 29 (43%) | 54 (36%) | 0 | 54 (47%) |
| Autoantibodies | | | | | | |
| Antinuclear | 83 (98%) | 16 (94%) | 67 (99%) | 143 (95%) | 35 (97%) | 108 (95%) |
| Antitopoisomerase I | 18 (21%) | 5 (29%) | 13 (19%) | 31 (21%) | 9 (25%) | 22 (19%) |
| Anticentromere | 44 (52%) | 8 (47%) | 36 (53%) | 67 (45%) | 12 (33%) | 55 (48%) |
| DAVIX, % | 0·59% (0·38–0·86) | 0·34% (0·16–0·69) | 0·65% (0·42–0·88) | 0·66% (0·45–0·96) | 0·43% (0·20–0·73) | 0·73% (0·53–0·97) |
| Nailfold capillaroscopy pattern | | | | | | |
| Normal | 14 (17%) | 0 | 14 (21%) | 10 (7%) | 0 | 10 (9%) |
| Non-specific | 22 (26%) | 4 (24%) | 18 (26%) | 47 (31%) | 5 (14%) | 42 (37%) |
| Early | 18 (21%) | 4 (24%) | 14 (21%) | 36 (24%) | 11 (31%) | 25 (22%) |
| Active | 16 (19%) | 3 (18%) | 13 (19%) | 33 (22%) | 14 (39%) | 19 (17%) |
| Late | 15 (18%) | 6 (35%) | 9 (13%) | 24 (16%) | 6 (17%) | 18 (16%) |
| Drug therapies | | | | | | |
| Calcium-channel blockers | 44 (52%) | 10 (59%) | 34 (50%) | 76 (51%) | 14 (39%) | 62 (54%) |
| Sildenafil | 26 (31%) | 10 (59%) | 16 (24%) | 45 (30%) | 16 (44%) | 29 (25%) |
| ACE inhibitor | 22 (26%) | 4 (24%) | 18 (26%) | 26 (17%) | 12 (33%) | 14 (12%) |
| Bosentan | 9 (11%) | 6 (35%) | 3 (4%) | 17 (11%) | 12 (33%) | 5 (4%) |
| Iloprost | 10 (12%) | 4 (24%) | 6 (9%) | 18 (12%) | 12 (33%) | 6 (5%) |

Data are mean (SD), median (IQR), or n (%). Percentages may not total 100 owing to rounding. ACE=angiotensin-converting enyzme. DAVIX=Digital Artery Volume Index. VEDOSS=very early diagnosis of systemic sclerosis.

***Table:*** **Baseline characteristics**




ten (12%) were men, and the mean age was 54·5 years (SD 11·6); two (2%) patients were African, 14 (16%) were south Asian, and 69 (82%) were White. In the validation cohort, 136 (91%) of 150 patients were women, 14 (9%) were men, and the mean age was 53·5 years (SD 13·8); three (2%) patients were African, 20 (13%) were south Asian, and 127 (85%) were White.

For the purpose of this study, patients presenting with current digital ulcers at baseline or with a history of previous digital ulcers were considered to be affected by digital ulcer disease. In the exploratory cohort, 17 (20%) of 85 patients were affected by digital ulcer disease, with a median time between the first non-Raynaud's symptom and onset of the first ulcer of 65 months (IQR 48–90). Seven (41%) of these 17 patients developed new digital ulcers during the 12-month follow up. Of the six patients with digital ulcer disease presenting with a current ulcer at baseline, none had the same digital ulcer still present at follow-up. 68 (80%) of 85 patients had neither a positive history of digital ulcers nor a baseline ulcer; five (7%) of these 68 patients developed new digital ulcers during the 12-month follow-up whereas 63 (93%) did not. A complete history of digital ulcers could not be obtained from the central STRIKE database for five (6%) of 85 patients; these patients were therefore excluded from the subanalyses involving history of digital ulcers and DAVIX. None of these five patients had a digital ulcer at the baseline visit or at the 12-month follow-up.

In the validation cohort, 36 (24%) of 150 patients were affected by digital ulcer disease; the median time from the first non-Raynaud's symptom to the onset of the first ulcer for these patients was 56 months (IQR 40–78). 114 (76%) of 150 patients had no history of digital ulcers and did not present with digital ulcers at baseline.

For the 80 patients in the exploratory cohort for whom data on the history of digital ulcers were available, median

***Figure 2:*** **Violin plots of DAVIX by presence of digital ulcer disease and subtype of systemic sclerosis**

DAVIX of the dominant hand in patients with digital ulcer disease versus patients without digital ulcer disease in the exploratory cohort (A; n=80) and the validation cohort (B; n=150). DAVIX of the dominant hand of patients in the exploratory cohort who developed new digital ulcers during 12-month follow-up (n=12) versus those who did not (n=73; C) and, for those who developed new ulcers, DAVIX of the individual fingers that developed ulcers (n=21) during follow-up versus the fingers that did not (n=27; D). DAVIX of the dominant hand in patients who fulfilled the ACR–EULAR 2013 systemic sclerosis classification criteria—grouped by disease subtype (diffuse cutaneous and limited cutaneous) according to LeRoy's classification—and those with VEDOSS in the exploratory cohort (n=85, comprising 18 patients with diffuse cutaneous disease, 38 with limited cutaneous disease, and 29 with VEDOSS; E) and the validation cohort (n=150, comprising 31 patients with diffuse cutaneous disease, 65 with limited cutaneous disease, and 54 with VEDOSS; F). Red dots in panels A, C, and E show DAVIX of the dominant hand of patients who developed new digital ulcers during 12-month follow-up. Comparisons in A–D used the Wilcoxon rank sum test; those in E and F used ANOVA with Tukey's honestly significant difference test. ACR=American College of Rheumatology. DAVIX=Digital Artery Volume Index. EULAR=European League Against Rheumatism. VEDOSS=very early diagnosis of systemic sclerosis.

DAVIX was significantly lower in patients with digital ulcer disease (0·34% [IQR 0·16–0·69]) than in those without (0·65% [IQR 0·42–0·88]; p=0·0074, $p_{adj}$=0·015; figure 2A). This finding was substantiated in the validation cohort for patients with (0·43% [IQR 0·20–0·73]) and without (0·73% [IQR 0·53–0·97]) digital ulcer disease (p<0·0001; figure 2B).

In the exploratory cohort, the median DAVIX of patients who developed new digital ulcers within 12 months was significantly lower (0·23% [IQR 0·10–0·66]) than that of patients who did not (0·65% [IQR 0·45–0·91]; p=0·0019, $p_{adj}$=0·0039; figure 2C). This finding shows the predictive value of DAVIX.

We compared DAVIX of individual fingers affected by new digital ulcers during the 12-month follow-up with fingers of the same hand that did not develop ulcers during this timeframe. 48 fingers were included in this subanalysis, of which 21 (44%) developed new digital ulcers. The median value of DAVIX in these 21 fingers was significantly lower (0·15% [IQR 0·09–0·25]) than that of fingers that did not develop digital ulcers over 12 months (0·27% [IQR 0·09–0·67]; p=0·048; figure 2D).

A ROC curve was plotted using DAVIX as a binary classifier, mapped to the presence or absence of new digital ulcers at 12-month follow-up. A DAVIX threshold of 0·37%, estimated by the highest Youden index (appendix p 4), had a specificity of 84% and a sensitivity of 67% for identifying patients who would develop a digital ulcer within 12 months (area under the ROC curve (AUC)=0·75 [95% CI 0·57–0·94]; p=0·049 (figure 3). Accordingly, patients with DAVIX below the 0·37% threshold had higher odds of developing new digital ulcers than patients with DAVIX greater than 0·37% (OR 18·6 [95% CI 4·7–95·6]; p<0·0001]). By comparison, a history of digital ulcers conferred higher odds of a patient developing new digital ulcers than did no history of ulcers (OR 4·4 [1·1–16.8]; p=0·028]). Of note, for 26 (90%) of 29 patients with VEDOSS, DAVIX was greater than the 0·37% cutoff.

The median DAVIX of the hand in all study participants was 0·64% (IQR 0·43–0·92) and no significant difference was found between the median DAVIX of patients in the exploratory cohort (0·59% [IQR 0·38–0·86]) and those in the validation cohort (0·66% [IQR 0·45–0·96]; p=0·31).

A one-way ANOVA was conducted to compare DAVIX of the hand among patients with different systemic sclerosis clinical subsets. A significant difference in DAVIX was observed in at least two clinical subsets in the exploratory cohort ($F$ [2, 82]=5·489; p=0·0057) and in the validation cohort ($F$ [2, 147]=5·424; p=0·0053). In particular, in the exploratory cohort, Tukey's honestly significant difference test for multiple comparisons showed that the mean value of DAVIX was significantly different between patients with diffuse cutaneous systemic sclerosis and patients with VEDOSS (difference=0·37 [95% CI 0·05–0·69]; p=0·018) and between patients with limited cutaneous systemic sclerosis and patients with VEDOSS (difference=0·31 [0·06–0·58]; p=0·013; figure 2E). The results were substantiated in the validation cohort for patients with diffuse cutaneous systemic sclerosis and patients with VEDOSS (difference=0·21 [0·01–0·41]; p=0·049) and patients with limited cutaneous systemic sclerosis and patients with VEDOSS (difference=0·22 [0·01–0·39]; p=0·0063; figure 2F).

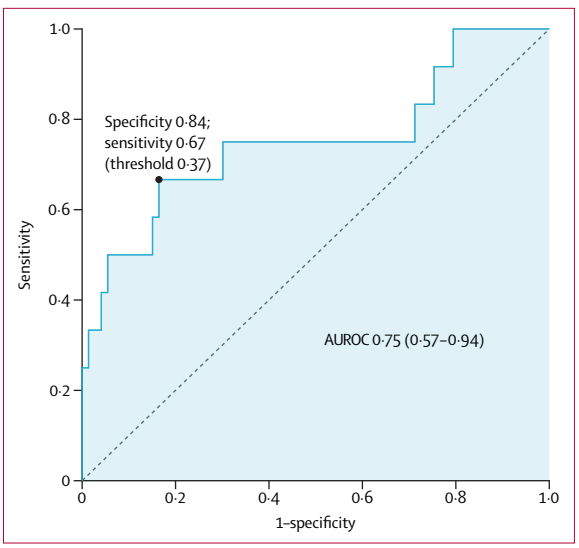



***Figure 3:*** **ROC curve and AUC for the performance of DAVIX in the detection of new digital ulcers at 12 months**
DAVIX is plotted as a binary classifier against the presence or absence of new digital ulcers at 12-month follow-up. The 0·37% threshold has a specificity of 84% and a sensitivity of 67% in identifying patients who went on to develop new digital ulcers during the 12-month follow-up. AUC=area under the curve. DAVIX=Digital Artery Volume Index. ROC=receiver–operator characteristic.

We conducted exploratory analyses of DAVIX with the available clinical parameters and with patient-reported outcomes relevant to hand involvement, vascular involvement, and disease severity (figure 4). All baseline correlations were then assessed in the validation cohort. DAVIX was positively correlated with baseline DLCO (exploratory cohort $r$=0·368, p=0·0041; validation cohort $r$=0·332, p=0·0042) and, in the exploratory cohort, the correlation was stronger in patients with digital ulcer disease than in those without ($r$=0·883, p=0·008). In both exploratory and validation cohorts, DAVIX had a negative correlation with disease duration (exploratory cohort $r$=–0·415, p<0·0001; validation cohort $r$=–0·284, p<0·0001), baseline FVC-to-DLCO ratio (exploratory cohort $r$=–0·334, p=0·0091; validation cohort $r$=–0·272, p=0·033), and nailfold capillaroscopy pattern (exploratory cohort $r$=–0·447, p<0·0001; validation cohort $r$=–0·335, p<0·0001; figure 4). Baseline modified Rodnan skin score was significantly correlated with DAVIX in the exploratory cohort ($r$=–0·305, p=0·014) but not in the validation cohort.

In terms of patient-reported outcomes, DAVIX correlated with worsening of SHAQ-DI score ($r$=–0·308, p=0·024), VAS Raynaud's ($r$=–0·271, p=0·044), and VAS

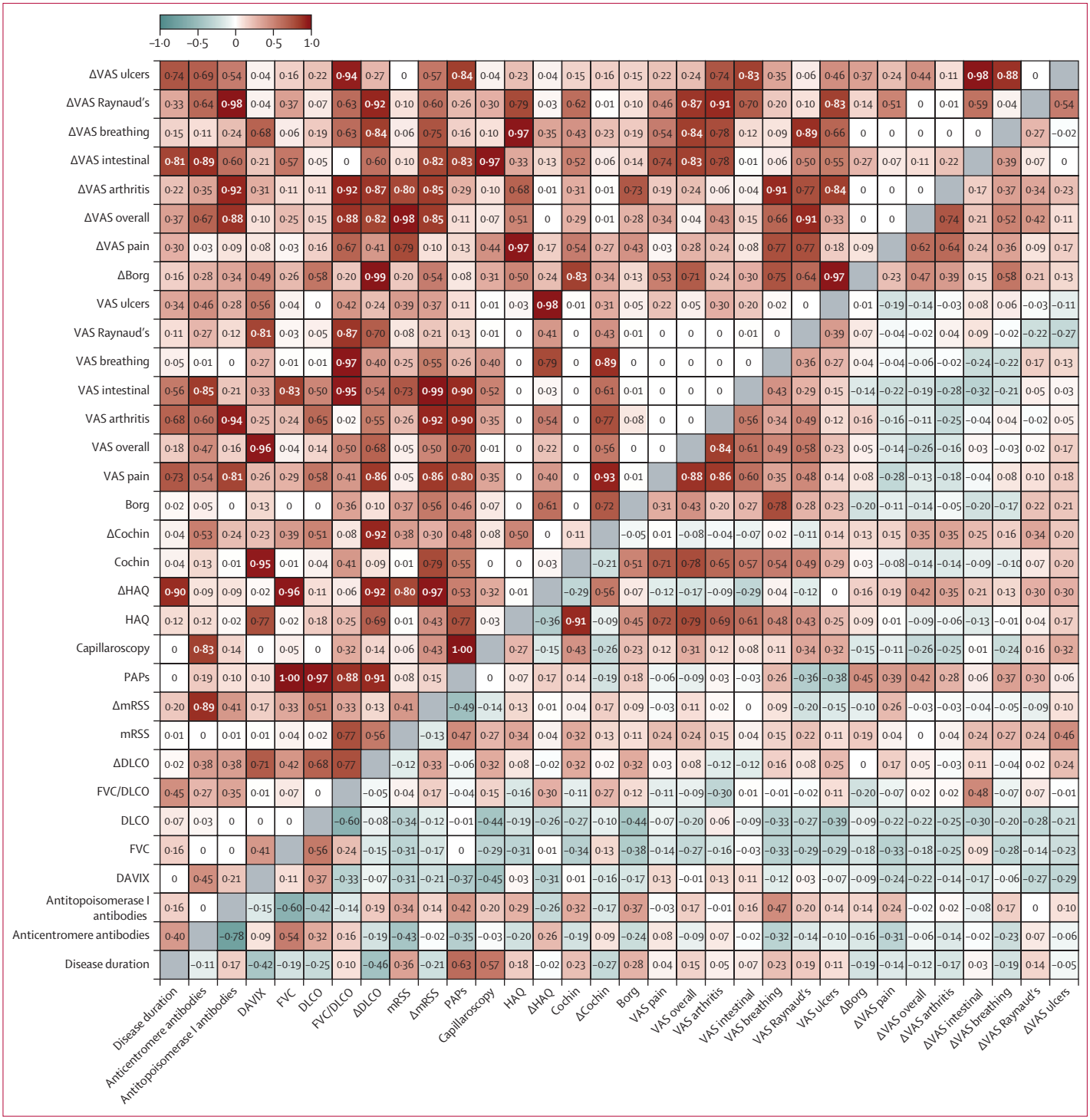



***Figure 4:*** **Correlation matrix for DAVIX, disease domains, and patient-reported outcomes in the exploratory cohort**

The top left half of the graph shows p values, and the corresponding *r* values (from Spearman's test) are shown in the bottom right half of the graph. p values shown are not corrected for multiple comparisons and are reported for descriptive purposes. The matrix uses an approximation to two decimal places; p<0·01 is reported as zero. Δ represents the absolute difference between the 12-month values and the baseline values. Borg=Borg rating of perceived exertion scale. Cochin=Cochin Hand Function Scale. DAVIX=Digital Artery Volume Index. DLCO=diffusing capacity of the lungs for carbon monoxide. FVC=forced vital capacity. HAQ=Health Assessment Questionnaire. mRSS=modified Rodnan skin score. PAPs=systolic pulmonary artery pressure. VAS=visual analogue scale.

digital ulcers ($r$=–0·291, p=0·044) at 12 months in the exploratory cohort (figure 4). Consistent with these findings, patients in the exploratory cohort who showed clinically significant worsening on the Cochin Hand Function Scale at 12 months (defined as a minimal clinically important difference worsening of the score of more than 21·6% compared with the baseline value[22]) had a significantly lower median DAVIX of the hand (0·43% [IQR 0·26–0·74]) than patients for whom hand function did not worsen (0·69% [0·42–0·88]; p=0·031; appendix p 5).

## Discussion

To our knowledge, this study is the first to use a semi-automated, MRI time-of-flight based technique to quantitatively assess digital artery disease in patients with systemic sclerosis and to explore its clinical value by correlating the resulting index with clinical parameters and patient-reported outcomes.

We show that DAVIX can differentiate between patients with digital ulcer disease and those without and can predict the appearance of new digital ulcers. This finding supports previous studies using colour Doppler ultrasound and MRI-based techniques that showed a strong association between the severity of digital artery disease and its occurrence alongside systemic sclerosis.[16,23,24] Additionally, reports suggest that, over time, patients with systemic sclerosis have difficulty in distinguishing between discrete Raynaud's phenomenon attacks and persistent ischaemia,[25] highlighting the need to objectively characterise peripheral vascular disease in patients with systemic sclerosis.[26] To this end, DAVIX could be promising because measuring the inner volume of digital arteries could be considered an indirect outcome measure of neointima proliferation in the fingers. Furthermore, the inverse correlation of DAVIX with the FVC-to-DLCO ratio supports the idea that digital ulcer disease and pulmonary artery hypertension are two clinical manifestations of the same pathological process in systemic sclerosis that lead to vascular fibrosis.

Another key finding is that the digital artery volume measured by DAVIX correlated with disease severity within the same patient, as assessed by patient-reported outcomes and clinical manifestations. This finding could have implications for future studies, including in patients at high risk of developing systemic sclerosis before the onset of clinically relevant skin fibrosis. Furthermore, DAVIX was correlated with DLCO and with the FVC-to-DLCO ratio, but not with FVC. Although these two findings warrant further independent validation, we speculate that the digital artery vessel lumen could be used as an indicator of overall vascular disease activity and predict early abnormalities in the pulmonary vasculature. If these data are independently validated, DAVIX could be considered as a non-invasive biomarker of preclinical pulmonary arterial hypertension.

The negative correlation between DAVIX and the duration of systemic sclerosis suggests that DAVIX could be a useful tool to measure the accrual of vascular damage, which is important in observational and interventional studies. Consistent with our findings, Zhang and colleagues[17] reported that the severity of digital artery abnormalities was strongly correlated with disease duration (from the onset of Raynaud's phenomenon), also suggesting that vascular disease is progressive in systemic sclerosis. Future research should explore the quantification of vascular damage in a unified vascular endotype in which vascular therapies could be used to support disease modification.[2,27,28]

Although recognised for several decades,[29] studies of severe morphological abnormalities of the digital arteries and ischaemic sequelae in patients with systemic sclerosis are scarce. Allanore and colleagues[16] examined vascular involvement in the hands of 38 patients with systemic sclerosis using magnetic resonance angiography (MRA) and found that 23 (61%) patients had evidence of four or more damaged arteries. Different methods have been used to image the digital arteries of patients with systemic sclerosis, each of which has relative benefits and challenges. Colour Doppler ultrasound and 3D ultrasound are easy to perform and are non-invasive, but can be technically challenging and time consuming.[30] MRA enables an accurate visualisation of vessels without any image processing, but requires the administration of a gadolinium-based intravascular contrast agent.[16,17] Independent of the tools used, numerous data support an association between the severity of digital artery disease and the development of digital ulcers in patients with systemic sclerosis.[15,23,24,31]

Compared with other studies using MRA and 3D-MRI time-of-flight to assess digital arteries, ours had a considerably (around three times) larger sample size and used a semi-automated, centralised, and standardised quantification method. We also explored several patient-reported outcomes and clinical outcomes relevant to systemic sclerosis. Although definite validation with matched tissue biopsies is unlikely to be feasible, the correlation of DAVIX with digital ulcers and other surrogate measures of disease severity in patients with systemic sclerosis strongly supports the face and content validity of the index. Whether DAVIX is sensitive to change over time remains to be established. In this context, follow-up studies in the same cohorts, and the use of DAVIX as an exploratory endpoint in randomised controlled trials, will be a crucial step in defining its clinical value.

Our study has several limitations. As a new technique for estimation of the vessel-to-tissue ratio, no previous data were available to inform the expected effect size in patients with primary Raynaud's phenomenon and in those with systemic sclerosis. The study was therefore powered conservatively to detect the ability of this technique to predict the onset of new digital ulcers in

patients with systemic sclerosis, with and without a known history of vascular manifestations. In the exploratory cohort, five of the 85 patients analysed did not have data on the history of digital ulcers. Although this factor could potentially inform a recall bias, these patients had no new digital ulcers throughout the 12-month follow-up, and therefore this potential bias is minimal.

The digital arteries could be detected in the majority (around 95%) of fingers of patients in both the exploratory and validation cohorts. However, multiple reasons for a lack of visualisation—including a blood flow speed below the limit of detection—should be considered in future studies.

Another limitation of our study is that patients in both cohorts were recruited from one centre and images were acquired with the same machine. Data on the variability of results from different geographical locations or using different types of MRI magnet are therefore not available. Nevertheless, DAVIX is currently being used in two multicentre randomised controlled trials (NCT05559580 and CM101 in systemic sclerosis). Both studies will investigate the feasibility of adopting DAVIX as a surrogate imaging outcome measure of peripheral vascular disease and consider the effects of using different MRI magnets and recruiting from different geographical locations, among other endpoints.

For more on the **trial of CM101 in systemic sclerosis** see https://www.chemomab.com/pipeline/#ssc

A further limitation is that our observational study did not consistently track lifestyle changes. Patients could have differed in their implementation of lifestyle changes after diagnosis with systemic sclerosis or after developing their first digital ulcer, and this factor should be considered in future studies on the natural history of digital ulcer disease.

In conclusion, the potential of DAVIX to detect and predict digital ulcer disease could render it a useful stratification tool in clinical trials. Furthermore, by predicting the worsening of patient-reported outcomes and clinical manifestations in all patients—including those at high risk—DAVIX could provide insights into the role of vascular disease activity in the overall progression of systemic sclerosis.

#### Contributors

GA, GL, and FDG conceptualised the study, and FDG and GL conceived the DAVIX methodology. SDD conducted the literature search. SDD, KG, FD, EDL, and DB curated the data and SDD and MH analysed the data. SDD conducted statistical analysis and contributed to creating figures relating to statistical analysis. PO'C developed the imaging methodology and interpreted the data, and supervised the imaging work. OK and JD developed the software. DB, PO'C, and FDG were responsible for project administration and DB and FDG for project supervision. PO'C and FDG acquired funding. MH, SDD, OK, JD, and GL wrote the original draft of the manuscript, which was reviewed and edited by MH, SDD, GL, PO'C, OK, JD, and GL. KG, SDD, and FDG, accessed and verified the data. All authors had full access to all data in the study, and had final responsibility for the decision to submit for publication.

#### Declaration of interests

MH reports speaking fees from Actelion Pharmaceuticals, Eli Lilly, and Pfizer, outside of the submitted work and he is a member of a data and safety monitoring board for Certa Therapeutics. OK and JD are employees and shareholders of Image Analysis Group and co-developers of DAVIX. OK reports speaking fees from Takeda Pharmaceuticals and is on scientific advisory boards for Werfen and MiMedx. FDG reports consulting fees from Argenx, Arxx Therapeutics, AstraZeneca, Ergomed, GSK, Image Analysis Group, Janssen Pharmaceuticals, and Novartis and research support from AbbVie, AstraZeneca, Boehringer-Ingelheim, Capella Biosciences, Chemomab Therapeutics, and Mitsubishi Tanabe Pharma. All other authors declare no competing interests.

#### Data sharing

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

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