




BMJ Open Hand function impairment in Systemic sclerosis: Outcomes, Mechanisms and Experience (HANDSOME) – a longitudinal observational multicentre study protocol

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ABSTRACT

Introduction The majority of all patients with systemic sclerosis (SSc) experience hand function impairment. The exact cause for this impairment is yet unknown. As impaired hand function hugely impacts daily functioning and quality of life, there is a high unmet need for effective treatments. With the availability of new imaging modalities, biomarkers and laboratory techniques, opportunities arise to increase insights into the factors contributing to hand function impairment. The objective of this study is to identify risk factors and underlying mechanisms leading to hand function impairment in SSc.

Methods and analysis This is a longitudinal observational multicentre study in patients with very early diagnosis of systemic sclerosis and SSc under care of the Department of Rheumatology and Clinical Immunology of the University Medical Centre Utrecht (UMCU), St Antonius Hospital Nieuwegein, UMC Groningen (UMCG), Leiden UMC (LUMC), Radboudumc or Royal Free Hospital (RFH) London. Patients will be followed for 2 years. Medical history, clinical status, nailfold capillaroscopy, skin assessments, serum biomarker analysis, ultrasound, elastography and MRI will be performed, and results related to hand function measurements will be analysed.

Ethics and dissemination This study was approved by the Medical Research Ethics Committee NedMec (MREC NedMec) in the Netherlands and by HRA and Health and Care Research Wales in the UK. Results will be published in scientific journals and presented at scientific congresses and patient meetings.

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INTRODUCTION

Background and rationale

Systemic sclerosis (SSc) is a rare disease characterised by inflammation, fibrosis and vasculopathy.¹ Clinical presentation is heterogeneous and includes Raynaud phenomenon,

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first study that extensively assesses hand function in patients with systemic sclerosis.
- ⇒ This is a large prospective international multidisciplinary study with a follow-up of 2 years in 300 patients.
- ⇒ This is the first study that explores elastography of tendons in the hand.
- ⇒ The study is conducted in collaboration with patient associations.
- ⇒ Conclusions can be limited due to the lack of prior research for comparison and the heterogeneity of the disease.

cutaneous manifestations, musculoskeletal manifestations, gastrointestinal manifestations, pulmonary manifestations, cardiac manifestations and renal manifestations. Thus far, studies in SSc mainly focused on organ damage and mortality. However, other disease manifestations have a tremendous impact on quality of life and daily functioning.

Around 90% of patients with SSc experience hand function limitation, which leads to impaired daily functioning and work participation.^{2–3} An important cause of impaired hand function is contractures of the hand, which are reported in half of the patients.⁴ Contractures are reported more frequently in patients with diffuse cutaneous systemic sclerosis and associated with anti-topoisomerase I positivity.⁵ Only a few studies explored imaging techniques in SSc hands. Thickening of the A1 pulley and flexor tendons was associated with hand disability in a small group of patients (n=29).

Soft tissue calcifications were seen in affected tendons, but this has not been studied in more detail.^{6,7} In other small studies, ultrasound and MRI showed subclinical synovitis or tendinitis and bone erosions, which could also contribute to impaired hand function.^{7,8} Shear wave elastography (SWE), a new imaging modality to assess the elastic properties and stiffness of soft tissue, has been studied in SSc skin and muscles, but no studies have assessed hand tendons. Moreover, no studies explored tenosynovial changes and underlying biological mechanisms, especially in correlation with imaging or functional tests. This leaves clinicians ‘in the dark’ regarding diagnostic work-up and effective management. Current management for hand symptoms includes exercises, splints and sometimes immunosuppressive therapies. However, it is unknown which treatment is suitable for which patient and the efficacy of immunosuppressive drugs has not been confirmed in trials. As impaired hand function in SSc hugely affects daily functioning and, with that, quality of life, there is a high unmet need for effective treatments.⁹ With the availability of improved imaging modalities such as ultrasound, MRI and elastography, biomarkers in serum and plasma and laboratory techniques such as proteomics, opportunities arise to study this problem in more detail to guide optimal treatment development.

This study aims to enhance the understanding of the mechanisms underlying hand function impairment in patients with SSc, including development from the early phase in very early disease of systemic sclerosis (VEDOSS). The study is based on three key hypotheses: (1) Hand function in SSc is affected through various pathways involving joints, tendons, skin and/or microcirculation. (2) Prior to the development of contractures, tissue changes—such as inflammation, fibrosis or decreased elasticity—can be detected using imaging techniques. (3) Patients with hand impairment can be categorised into distinct subgroups based on clinical and imaging features, as well as protein markers, which may reflect different activated biological pathways.

Objectives

Primary objective

To identify underlying mechanisms responsible for hand function impairment in patients with SSc.

Secondary objectives

To determine risk factors and categorise patients with hand function impairment into subgroups based on clinical, immunological and/or imaging characteristics, thereby guiding future research towards personalised treatment strategies.

To assess the impact of hand function impairment on quality of life, daily functioning, work and participation and explore how these impacts relate to the identified mechanisms and patient subgroups.

METHODS

Patient and public involvement statement

Members of the Dutch (NVLE) and UK (SRUK) systemic sclerosis patient organisations are involved in every step of this project. They have been involved in the study design, and during the development of the protocol, a qualitative study was performed to explore patients’ functional concerns and (unmet) needs. The study protocol has been co-produced to ensure representation and input from those with personal experiences. All questionnaires have been checked on content and feasibility. During all meetings with the entire research team, patients will be involved to share their opinions on decisions being made and provide advice on recruitment and dissemination of results.

Study setting

This is a longitudinal observational international study in patients with VEDOSS and SSc who are under care at the Department of Rheumatology and Clinical Immunology of the University Medical Centre Utrecht (UMCU), St Antonius Hospital Nieuwegein, UMC Groningen (UMCG), Leiden UMC (LUMC), Radboud UMC or Royal Free Hospital (RFH) London. Patients will be followed for 2 years. Inclusion started in April 2024 and is open until April 2026; the expected end date is April 2028.

Study population

Patients (n=300; 18 years and older) with the following:

1. SSc with hand contractures regardless of disease duration (n=50).
2. Patients with SSc without hand contractures (n=200) and disease duration of <4 years.
3. Patients with VEDOSS (n=50).

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Age>18 years.
2. Willing and able to understand the study information and sign the informed consent form.
3. For patient populations (1) and (2):
 - a. Diagnosis of SSc according to the 2013 EULAR-ACR (The European League Against Rheumatism and the American College of Rheumatology) classification criteria for SSc.¹⁰
4. For the patient population (3):
 - a. Diagnosis of VEDOSS, defined as the presence of RP, puffy fingers, SSc-specific autoantibodies and abnormal nailfold capillaroscopy, while not fulfilling the 2013 EULAR-ACR classification criteria for SSc.¹¹
5. Only for patient population (1):
 - a. Hand contractures are defined as a range of motion <75% of the normal range of at least one small hand joint.¹²

Table 1 Overview of study procedures

	Baseline	6 months	12 months	24 months
Informed consent	x			
Medical history	x			
Nailfold capillaroscopy	x			x
Clinical status	x	x	x	x
Skin assessment	x	x	x	x
PROMs	x	x	x	x
Serum and plasma collection	x	x	x	x
Hand function assessment	x	x	x	x
Ultrasound	x	x	x	x
Elastography*	x	x	x	x
MRI*	x			
Vascular imaging†	x	x	x	x

*Subanalysis comparing MRI with ultrasound features. UMC Utrecht only.

†Subanalysis assessing hand circulation extensively with ultrasound using a 70-mHz probe. UMC Groningen only.
PROMs, patient-related outcome measurements; UMC, University Medical Centre.

Exclusion criteria

Subjects who meet any of the following criteria will be excluded from participation:

1. Age <18 years.
2. Patients with diabetic cheiroarthropathy and Dupuytren's disease, based on expert opinion. (Other diseases or overlap syndromes are not excluded).

Study procedures

Three patient groups are included and then followed for 24 months. Table 1 shows the study procedures and data collection in these three groups.

Medical history

Clinical data collected in routine care will be retrieved at baseline. Age, sex, height, educational level, ethnicity and autoantibody status (ANA (Antinuclear Antibody) negative/positive, line blot and scleroderma blot autoantibodies) are collected.

In addition, data will be collected on previous tobacco use, vasoactive and immunosuppressive medication use and dosage, digital ulcers, pitting scars, gangrene, clinical arthritis, myositis, interstitial lung disease, pulmonary hypertension and scleroderma renal crisis.

Nailfold capillaroscopy

A capillaroscope with a magnification of 200× is used to assess all fingers, including the thumbs. At least two adjacent fields of a linear millimetre in the middle of each finger are captured and stored. Images will be scored according to EULAR criteria centrally on normal or abnormal/scleroderma patterns.¹³

Clinical status

- Weight, blood pressure, changes in tobacco use, changes in occupation, changes in immunosuppressive and/or vasoactive medication use and dosage.

- New onset interstitial lung disease (y/n), pulmonary hypertension (y/n), scleroderma renal crisis (y/n)
- Hb (hemoglobin in mmol/L), ESR (erythrocyte sedimentation rate in mm/hour), CRP (C-reactive protein in mg/L), CK (creatinine kinase in IU/L).

Skin assessment

The modified Rodnan skin score (assessed by trained investigators), presence of digital ulcers (if yes: count, location), pitting scars (if yes: count, location), gangrene (if yes: location), calcinosis cutis in the hands (if yes: location), clinical arthritis (if yes: site and joint count) and myositis will be assessed/recorded.¹⁴

Patient-related outcome measurements

Patient-related outcome measurements will be collected in the week of the study visit, and the following questionnaires will be collected:

- Cochin Hand Function Scale (CHFS), containing 18 questions, structured in five distinct categories, designed to evaluate hand function in kitchen activities, dressing, personal hygiene, office and other generic activities.¹⁵
- Brief Satisfaction with Appearance Scale, containing six questions about subjective body image dissatisfaction and the perceived social impact.¹⁶
- IMTA Productivity Cost Questionnaire (IPCQ), a standardised instrument for measuring and valuing health-related productivity losses.¹⁷
- Utrecht Scale for Evaluation of Rehabilitation (-Participation) (USER-P), which measures both subjective and objective participation in the community.¹⁸
- Health-related quality of life (EQ-5D-5L), that defines health in terms of five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression.¹⁹

- Self-assessment of skin thickening, a self-reported measure of skin thickness in the upper limb.²⁰
- Scleroderma Health Assessment Questionnaire (SHAQ), which measures disease status changes.²¹

Serum and plasma collection

Two blood samples will be collected (both a maximum of 10 mL) to obtain both serum and plasma samples during each visit. The venepuncture is performed at routine outpatient or daycare unit visits according to standard protocol in a non-fasted state and not taking diurnal changes into account due to practical feasibility.²² Aliquots of both serum and plasma samples will be stored at -80°C . Serum and plasma analysis will include measurement of levels of immunological markers (including cytokines) and fibrotic markers.

Hand function assessment

At all study visits, hand function will be assessed by trained investigators. Hand mobility is assessed with the range of motion of the wrist joint, range of motion of the finger joints, delta Finger-to-Palm distance,²³ and the Modified Hand Mobility in Scleroderma test (mHAMIS).²⁴ Grip strength is measured with the JAMAR dynamometer and JAMAR pinch dynamometer for the two-point pinch, three-point pinch and lateral pinch.

Ultrasound

Ultrasound will be performed by an operator/physician trained in musculoskeletal ultrasound. An ultrasound machine with a high-frequency probe (linear or hockey stick with 8–24 MHz) will be used. Images of all study sites will be stored and rated centrally by the coordinating researcher in conjunction with ultrasound experts afterwards. The presence of arthritis of the wrist, distal radioulnar joint, metacarpophalangeal (MCP) and proximal interphalangeal joints will be assessed using validated semiquantitative methods in B-mode and power Doppler setting if there was grey-scale evidence of inflammation. Furthermore, the presence of osteophytes is assessed. The first to fifth flexor and extensor tendons of both hands will be assessed longitudinally. Tenosynovitis and sclerotic thickening of tendon(-sheaths) and calcifications within tendons will be evaluated. The pulley and tendons are measured at the MCP joint. The fingers of the dominant hand will be assessed with ultrasound for vascular involvement. Dig 2 will be assessed standardly. In addition, fingers with ulceration, if present on other fingers, will be assessed. Additionally, intima media thickness (IMT) will be measured in dig 2. All arteries per finger will be assessed at the proximal phalangeal part. Qualitative scoring is performed. See online supplemental appendix 1, imaging protocol, for the full ultrasound protocol.

Elastography

In addition to the ultrasound assessment, fibrosis of the first to fifth flexor and extensor tendons of both hands will be measured quantitatively using SWE in a subgroup of patients at the UMC Utrecht ($n=100$).²⁵ SWE is measured

with the ultrasound machine GE healthcare LOGIQ E10s using the linear ML4-20 transducer.

Vascular imaging

Another addition to the ultrasound assessment is the extensive vascular evaluation performed on patients in the UMC Groningen ($n=35$). The vascular protocol entails ultrasound measurements of IMT performed with the Visual Sonics Vevo MD (FujiFilm, Tokyo, Japan) which uses an ultra-high frequency ultrasound transducer (max 70 MHz). Finger pressures will be measured with photoelectric plethysmography (Biopac MP-160, Biopac Systems, Goleta, California, USA) and pressure cuffs on five fingers simultaneously.²⁶ Doppler spectral analysis will be performed with the SMT Vicorder II (Wave Medical Heerenveen, the Netherlands).²⁷

Magnetic resonance imaging

In a subgroup of patients included at the UMC Utrecht ($n=50$), a contrast-enhanced 3 Tesla MRI of the dominant hand will be done at baseline, recording the presence of synovitis, joint capsule thickening of the wrist, MCP and PIPs, and thickness or inflammation of tendons and tendon sheaths of the hands. The researcher will determine whether there are no contraindications according to the MRI screening form used in the UMC Utrecht. The entire MRI protocol is shown in online supplemental appendix 1, imaging protocol.

Outcomes

Main study parameter/endpoints

The correlation between the CHFS scores and circulating biomarkers, as well as changes observed through imaging, over a 2-year follow-up period will be assessed.

Secondary study parameters/endpoints

- The change in hand function at 2 years, reflected by the CHFS and hand function measures.
- Predictive value of imaging features and circulating biomarkers at baseline for change of hand impairment at follow-up.
- Distinct subgroups of patients based on clinical, immunological and imaging characteristics.
- Health-related quality of life (EQ-5D-5L), daily functioning (SHAQ), work (IPCQ) and participation (USER-P) in relation to CHFS.

Sample size

For multivariable regression analysis with a continuous outcome, we need at least 10 patients per variable studied according to the rule of thumb. As we anticipate including 300 patients we will be able to validly study 30 variables for their association with the (progressive) hand impairment (including patient subgroup as a covariate in the analysis) with sufficient power. We will also perform more explorative subgroup analyses per patient population and calculate variance inflation factors as well as use data reduction techniques (eg, principal component analysis) and/or analysis techniques more suitable for analysing outcomes

with many independent variables compared with the number of patients (like partial least squares regression or Lasso regression). Furthermore, we will explore clusters of patients developing hand function impairment using imaging and protein biomarkers to inform our multivariable analyses. Missing data will be accounted for using multiple imputations. With the above calculation and strategy, we think our cohort of 300 patients will be sufficient to obtain meaningful results.

Recruitment and consent

Subjects will be informed about the study by their treating physician and receive an information letter. Thereafter, they will have the possibility to ask questions, either during a face-to-face appointment or over the phone with the investigator or research nurses. They will be allowed sufficient time, but at least 24 hours, to consider their participation. If the subject wants to participate, a meeting will be set for signing the consent form and explaining the study procedure. This will take place at a day/time suitable for the patients, ideally combined with routine care appointments.

Data management

Data handling is described in detail in the data management plan. This has been approved by the data manager of the UMC Utrecht.

Data from patients will be handled with care, taking into consideration the required confidentiality as stated by the Dutch 'AVG' ('Law for the Protection of Personal Information'), the 'Wet Gemeenschappelijke Behandelingen Overeenkomst' ('Law Common Treatment Agreement') and the privacy policy of the UMC Utrecht. The electronic patient files will be used as the source for the clinical data. Data will be pseudonymised and the key will be stored in a separate secured folder at each clinical site.

Patient material will be encoded and stored at the UMC Utrecht, Department of Rheumatology and Clinical Immunology. Patient material is only used to answer the questions in this study; material is not stored for biobank purposes. Only the local investigators are permitted access to the code key. Research documents, from which patient identity can be deduced, will only be accessible for third parties (eg, monitors, auditors and inspection by competent authorities) after specific consent by the participant in the informed consent document. Research documents will be kept up to 15 years after ending the research.

In all local centres, images and patient material will be stored according to local protocol and collected and analysed centrally.

Monitoring and quality assurance

A central independent monitor will perform yearly monitoring according to the monitoring plan.

Statistical methods

To predict decline in hand function (defined as an increase in CHFS) at 6, 12 and 24 months, we will use linear/logistic regression analysis, with baseline patient

characteristics as independent variables/predictors, as well as short-term (over 6 months) changes in clinical scores, imaging markers and biomarkers. When needed, we will use (regression) techniques suitable for a high variable to patient/outcome ratio (see section Statistics/power calculation).

Characteristics at baseline and changes over time seen on ultrasound will be reported for the number of patients with tenosynovitis, arthritis and/or calcifications in tendons, the mean thickness and elastography of tendons and the A1 pulley. Linear mixed models will be used to analyse changes over time (both with time defined as follow-up time or as time since early disease/VEDOSS) regarding hand function scores and to relate these changes to changes in ultrasound and serum/plasma biomarkers.

Also, joint modelling of the multivariate longitudinal data (ie, the clinical scores, imaging and biomarkers measured over time) and time-to-event (ie, development of limitations of hand function) will be performed. In this analysis, so-called 'latent trajectories' in the longitudinal markers (ie, not directly observed subgroups of patients with a distinct course in longitudinally measured 'markers') will be related to the development of the outcome (in this case, limitations in hand function). Results can be used to obtain more insight into the development of limitations in hand function and the possible existence of subgroups regarding the development of hand function limitations. Models may also be used to 'dynamically' predict the outcome over time. The patient subgroups (VEDOSS/SSc with/without hand impairment) will be taken appropriately into account in all analyses and/or subgroup analyses will be performed.

To further explore subgroups in patients with/without hand function limitations. Baseline clinical, imaging and biomarkers, as well as changes over time in markers, will be used in a cluster analysis. As most likely different types of variables (ie, linear, binary and categorical) will be included, we will use an algorithm suitable for this, like k-medoids cluster analysis using partitioning around medoids. The validity of different solutions regarding the number of clusters will be evaluated using statistical criteria (eg, silhouette width, calculated based on Gower distances) as well as clinical relevance by expert opinion (also considering the results of the above analyses) to derive a final solution. Possible confounders will be assessed and corrected.

ETHICS AND DISSEMINATION

The Medical Research Ethics Committee NedMec (MREC NedMec) reviewed the study in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and other applicable Dutch and European regulations. Based on the requirements, the MREC NedMec issued an approval for the Netherlands. HRA and Health and Care Research Wales have approved the study in the UK. The study will be conducted according to the

principles of the Declaration of Helsinki (2013). Results will be published in scientific journals and presented at scientific congresses and patient meetings.

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Contributors JS is the project's guarantor and initiator, and she has been involved in every step of the process. MG contributed to writing the protocol and was involved in the methodology for the study procedures. VHO, CD, AH, DJM, MCV, JKdV-B, PW and SM participated in setting up the study and writing the protocol. WF and MK were responsible for the imaging procedures. NJ-O and RS served as patient representatives during the study setup. IM was involved in the hand function measures. Primary research team (University Medical Centre Utrecht, The Netherlands), responsible for study design, data collection, data management, data analysis, data interpretation, report writing, and decision to submit: Dr J Spierings, PI; Dr SC Mastbergen, co-PI; Drs MJ Greveling, coordinating researcher). Participating research team sponsor (University Medical Centre Utrecht, The Netherlands), advising on study design, collaborating on data collection, data management, data analysis, and data interpretation: Dr P Welsing, methodologist; Dr A Marijnissen, study coordinator; Dr W Foppen, radiologist; R Boot, research nurse; S Mast, specialist nurse; I Masselink, occupational therapist; A Conception, lab analyst; Dr MP Jansen, MRI-expert. External participating research team, advising on study design, collaborating on data collection, data management, data analysis, and data interpretation: Dr DJ Mulder, internist, Groningen University Medical Centre, The Netherlands; Dr JK De Vries-Bouwstra, rheumatologist, Leiden University Medical Centre, The Netherlands; Dr MC Vonk, rheumatologist, Radboud University Medical Centre, The Netherlands; Dr A Herman, rheumatologist, St. Antonius hospital Nieuwegein, The Netherlands; Dr MC Kortekaas, rheumatologist and MSUS expert, Leiden University Medical Centre, The Netherlands; Professor CP Denton, rheumatologist, Royal Free Hospital – University College London, United Kingdom; Dr VH Ong, rheumatologist, Royal Free Hospital – University College London, United Kingdom; Professor D Abraham, Royal Free Hospital – University College London, United Kingdom; Drs S Rodolphi, clinical research fellow, Royal Free Hospital – University College London, United Kingdom. External advisors, advising on study design, data collection and data analysis: Drs MR Schriemer, Dutch systemic sclerosis patient organisation (NVLE); D Dittmar, Dutch systemic sclerosis patient organisation (NVLE); E Blamont, UK systemic sclerosis patient organisation (SRUK); N Jeffries-Owen, UK systemic sclerosis patient organisation (SRUK); K Fligelstone, Royal Free Hospital patient partner.

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