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DE DOCTEUR EN MEDECINE

Épaississement cutané au cours de la sclérodermie systémique : modélisation et caractérisation des trajectoires du score cutané de Rodnan modifié au cours du temps.

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“Everything should be made as simple as possible, but not simpler”

Albert Einstein

ABREVIATIONS

Utilisées dans la thèse

ET	Écart-type
LCMM	Latent class mixed modelling
MMF	Mycophénolate mofétil
MRSS	Modified Rodnan skin score
ScS	Sclérodermie systémique
ScScl	Sclérodermie systémique cutanée limitée
ScScd	Sclérodermie systémique cutanée diffuse
STPR	Skin thickening progression rate

Utilisées dans l'article

ACA	Anti-centromere antibodies
ARA	Anti-RNA polymerase III antibodies
BIC	Bayesian information criteria
CRP	C-reactive protein
dcSSc	Diffuse cutaneous systemic sclerosis
DU	Digital ulcers
GIT	Gastrointestinal tracts
ILD	Interstitial lung disease
lcSSc	Limited cutaneous systemic sclerosis
LCMM	Latent class mixed modelling
MMF	Mycophenolate mofetil
MRSS	Modified Rodnan skin score
SSc	Systemic sclerosis
PH	Pulmonary hypertension
RP	Raynaud phenomena
SRC	Scleroderma renal crisis
SD	Standard deviation
STPR	Skin thickening progression rate
TOPO	Anti-topoisomerase antibodies

I. TITRE DE LA THESE

Épaississement cutané au cours de la sclérodermie systémique : modélisation et caractérisation des trajectoires du score cutané de Rodnan modifié au cours du temps.

II. TABLE DES MATIERES

III. INTRODUCTION GENERALE

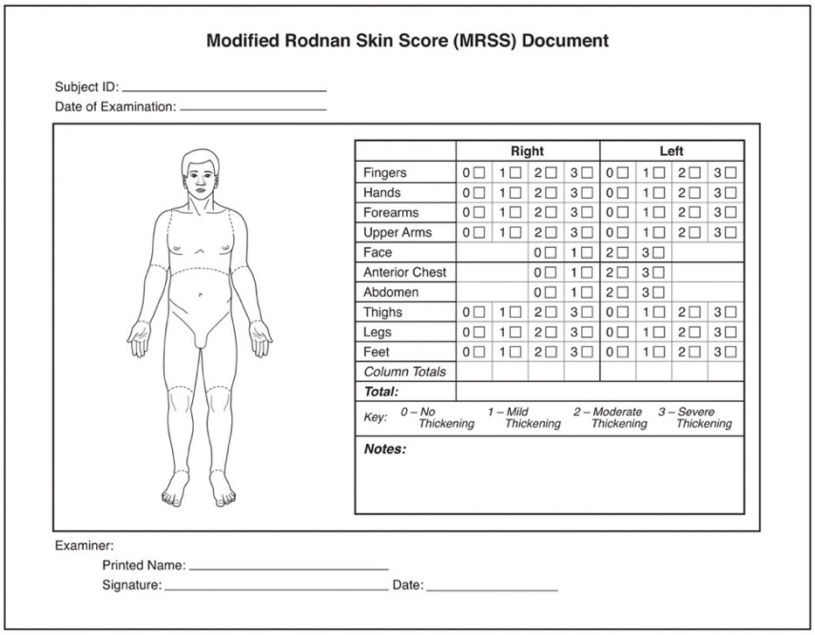
La sclérodermie systémique (ScS) est une maladie auto-immune caractérisée par une fibrose systémique touchant la peau et les organes internes.(1) En France, à partir d'une étude réalisée en Seine-Saint-Denis, la prévalence a été estimée à 158,3 [IC95% : 129 ; 187] cas par million d'habitants.(2) Il s'agit d'une maladie rare inscrite aux affections de longue durée (ALD 21), dont la prise en charge a fait l'objet d'un protocole national de soins réactualisé en 2017. Bien que la pathogenèse ne soit pas entièrement élucidée, elle implique des interactions complexes entre une microangiopathie, une production excessive de matrice extracellulaire par des myofibroblastes, et des anomalies des réponses immunitaires innées et adaptatives (**annexe n°1**).(3)

La ScS est une maladie hétérogène.(4) L'épaississement cutané est un critère important de la classification ACR-EULAR 2013 de la maladie (**annexe n°2**).(5) L'histoire naturelle de l'épaississement cutané est complexe et pourrait être influencée par de nombreux facteurs tels que : le sexe, l'origine ethnique, l'exposition à la silice et aux solvants, la présence d'un contexte néoplasique ou d'un syndrome de chevauchement, ou encore le type d'auto-anticorps.(6-9) Pour quantifier l'épaississement cutané, on utilise le score cutané de Rodnan modifié (MRSS : modified Rodnan skin score). Il s'agit d'un score semi-quantitatif détaillé dans la **figure 1** et l'**annexe 3**. Sa facilité de réalisation, sa fiabilité, et sa reproductibilité en ont fait un outil incontournable dans la pratique clinique et dans les essais thérapeutiques.(10) La différence minimale cliniquement relevante du MRSS a été estimée entre 3 et 5 points dans les formes cutanées diffuses.(11,12) Il a été également rapporté qu'un MRSS >20/51, une vitesse initiale de progression élevée

(STPR[1] ≥40 unités/an), et une aggravation du MRSS pendant le suivi étaient associés à la sévérité de la maladie.[13-16]

Figure 1. *Score cutané de Rodnan modifié*

Reproduit à partir de Khanna *et al.*[10]



Modified Rodnan Skin Score (MRSS) Document

Subject ID: _____

Date of Examination: _____

	Right				Left			
Fingers	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Hands	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Forearms	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Upper Arms	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Face			0☐	1☐	2☐	3☐		
Anterior Chest			0☐	1☐	2☐	3☐		
Abdomen			0☐	1☐	2☐	3☐		
Thighs	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Legs	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Feet	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Column Totals								
Total:								

Key: 0 – No Thickening 1 – Mild Thickening 2 – Moderate Thickening 3 – Severe Thickening

Notes:

Examiner:

Printed Name: _____

Signature: _____ Date: _____

On distingue classiquement trois formes selon l'étendue de l'atteinte cutanée : les formes « cutanée limitée » (ScScl), « cutanée diffuse » (ScScd) et « sine scleroderma » (**figure 2**).[17] Cette classification est utile pour prédire les risques d'atteintes d'organes et la sévérité de la maladie.

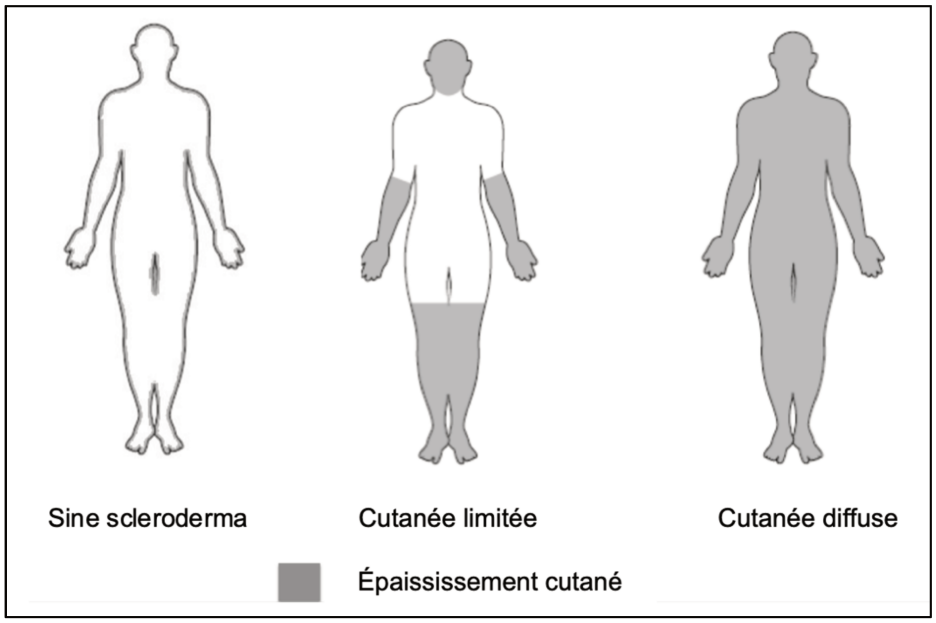
La ScScl est définie par un épaississement cutané qui affecte les extrémités en distalité des coudes et des genoux, associé ou non à une atteinte du visage. L'histoire naturelle de l'atteinte cutanée au cours des ScScl est caractérisée par un épaississement cutané relativement stable au cours du temps.[13] Cette forme est classiquement associée à des manifestations microvasculaires de type télangiectasies muco-cutanées et hypertension artérielle pulmonaire. Dans la cohorte EUSTAR (EUropean Scleroderma Trials And

[1] STPR : Skin Thickening Progression Rate : MRSS initial divisé par la durée d'évolution de la maladie depuis le début de l'atteinte cutanée rapporté par le patient (exprimée en année).

Research), les patients atteints de ScScl étaient majoritairement des femmes (90,9%), caucasiennes, âgées de 57,4 ±13,1 ans (moyenne ±ET). La plupart d'entre eux avaient des auto-anticorps anti-centromères (46,7%) ou anti-Scl70 (23,4%). Le MRSS moyen ±ET des ScScl était de 8,1 ±5,3 après une durée moyenne d'évolution de 9,6 ±8,1ans.[18] Récemment, la survie à 10 ans a été estimée à 91,5% [IC95% : 90,1 ; 92,9].[4]

Figure 2. Classification adaptée selon Leroy et Medsger

Adaptée à partir de Leroy et Medsger[17]



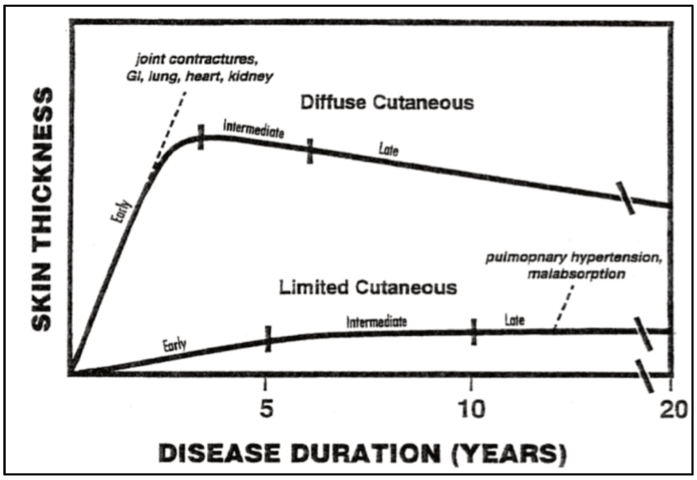
Dans la forme ScScd, l'épaississement cutané s'étend de manière centripète jusqu'aux bras, aux cuisses et au tronc au cours des premiers mois de la maladie avec un pic entre le 12ème et 18ème mois, puis le plus souvent régresse partiellement (**Figure 3**).[19-21] Les complications pulmonaires, rénales et cardiaques sont plus fréquentes et plus sévères que dans les ScScl.[18,22,23] Dans la cohorte EUSTAR, les patients atteints ScScd étaient majoritairement des femmes (81,1%), âgées (moyenne ±ET) de 52,3 ±13,7 ans. Ces patients avaient principalement des auto-anticorps anti-Scl70 (60,8%). Le MRSS moyen

±ET des ScScd était de 19,0 ±10,0 après une durée moyenne de la maladie de 7,4 ±6,9.[18] Récemment, la survie à 10 ans a été estimée à 80,0% [IC95% : 77,8 ; 82,4].[4]

Les patients avec une forme sine scleroderma remplissent les critères de classification ACR-EULAR 2013 de la ScS mais ne présentent pas d'épaississement cutané objectivable à l'examen clinique. Le profil de morbi-mortalité est similaire à celui des ScScl.[24]

Figure 3. *Représentation schématique de l'évolution de l'épaississement cutané au cours du temps dans la ScS.*

Reproduit à partir de Medsger[25]



L'épaississement cutané est le symptôme pivot de la ScS et se révèle aussi hétérogène entre les patients que dynamique chez un même patient.[15,22] Bien que des facteurs prédictifs d'aggravation du MRSS (≥ 5 unités et ≥ 25%) ont été identifiés dans de grandes cohortes,[20,21,26] il reste difficile de prédire avec précision l'évolution du MRSS chez un patient donné. De plus, les données concernant les associations potentielles entre l'évolution longitudinale du MRSS au cours du temps et la morbi-mortalité de la maladie restent limitées. Une meilleure caractérisation de l'hétérogénéité de la ScS semble nécessaire afin de mieux sélectionner les patients à inclure dans les essais thérapeutiques.

Notre objectif principal était de mettre en évidence, sans *a priori,* des groupes (appelés classes de trajectoires) distincts de patients définis par une trajectoire similaire de MRSS au cours du temps, dans une population de formes récentes de ScS issues de la cohorte nationale française. Notre objectif secondaire était d'étudier les associations entre les classes de trajectoires identifiées et les caractéristiques de la maladie.

IV. ARTICLE

1. Title

Manuscript title: Early Trajectories of Skin Thickening Are Associated with Severity and Mortality in Systemic Sclerosis

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2. Abstract

Objectives. To delineate classes of patients with early similar skin thickening trajectories in SSc without any *a priori* assumptions.

Methods. From the French SSc national cohort, patients with a disease duration less than 2 years at inclusion and with at least 2 modified Rodnan skin score (MRSS) available within the first 4 years of follow-up were included. Classes of patients with similar MRSS trajectories were identified with a latent class mixed model. Clinical characteristics and survival were compared between the identified classes.

Results. A total of 198 patients fulfilled inclusion criteria, with a total of 641 MRSS available. Median disease duration and follow-up were respectively 0.8 (IQR: 0.4; 1.2) and 4.4 (2.9; 6.1) years. Individual trajectories of MRSS were highly heterogeneous between patients. Models with one to six latent classes of trajectories were sequentially assessed and the 5-class model represented the best fit to data. Each class was characterized by a unique global trajectory of MRSS. The median disease duration did not differ significantly between classes. Organ involvement were more frequent in classes with significant change over time (classes 2 to 5) than in class 1 (low baseline MRSS without significant change over time). Using Cox regression, we observed a progressive increasing risk of death from classes 1 to 5.

Conclusion. Early identification of clinical phenotype based on skin thickening trajectories could predict morbi-mortality in SSc. This study suggested that MRSS trajectories characterization might be pivotal for clinical practice and future trials design.

3. Article

a. Introduction

Systemic sclerosis (SSc) is a chronic connective tissue disease characterized by a widespread fibrosis of skin and/or internal organs.[1] Among the hallmarks of SSc, skin thickening is one of the pivotal symptoms and is used in routine practice to classify patients within subsets: limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) SSc.[2] Modified Rodnan skin score (MRSS) is a semi-quantitative score evaluating the skin thickness from 0 (normal) to 3 (severe) at 17 different cutaneous sites (for a total score from 0 to 51), and is correlated with histological skin thickness.[3] MRSS is a validated clinical instrument[4] often used as primary or secondary outcomes in clinical trials.[5]

Few studies have focused on the evolution of MRSS over time. Using latent trajectory modeling, Shand *et al.*[6] described 3 subgroups in early dcSSc patients (less than 2 years after disease onset): “low baseline / improvers”, “high baseline / improvers”, and “high baseline / non improvers”. Survival was associated to the subsequent MRSS trajectories, albeit only 68% of patients included could be classed in one of these three groups. Perera *et al.*[7] described 5 skin thickening profiles in early SSc associated with anti-topoisomerase I antibodies: 3 subgroups in dcSSc patients based on their skin thickening progression rate (STPR): rapid (≥40 units per year); intermediate (15–40 units per year); and slow (≤15 units per year); and 2 subgroups in lcSSc patients: one where the skin clinical phenotype subsequently became diffuse, and one remaining limited throughout follow-up. These works underlined the well-known heterogeneity of the skin thickening evolution in SSc, and the complexity of the relations between MRSS at baseline and the skin thickening course (improvers / non-improvers and STPR). Some predictive factors of MRSS progression (defined as >5 units and ≥25% increment in MRSS at 1-year follow-up) have been identified such as tendon friction rubs, joint

synovitis, MRSS at baseline ≤22/51, disease duration <15 months, and antibody status.[8-10] Nevertheless, it remains difficult to accurately predict the trajectory of MRSS in a given patient which might limit the homogeneity and thus comparability of patients included in clinical trials.[10] Deciphering the skin thickening trajectories is therefore of utmost importance considering the wide use of MRSS as primary outcome and the potential impact on prognosis assessment.[11-13]

We herein sought to identify early MRSS longitudinal trajectories in SSc patients from the prospective French SSc national database without any *a priori* assumptions and examined their associations with organ involvement and survival.

b. Patients and methods

Study population and inclusion criteria

The French SSc national database is a multicenter cohort conducted in 42 French hospital centers. Data are collected prospectively using a standardized form. According to French legislation, the database is declared to the CNIL (number 914607) and patients gave informed consent before entering the database. Inclusion criteria for this study were: (i) adult SSc patients fulfilling the 2013-ACR/EULAR SSc classification criteria;[14] (ii) inclusion visit occurred less than 2 years after the first non-Raynaud Phenomenon (RP) symptom; (iii) baseline MRSS available and at least one MRSS available during follow-up.

Data collection and variables

Baseline was defined as the date of inclusion in the database and follow-up as the time between the inclusion and the last available visit at the time of the extraction in August 2015. Data collected were demographics, dates of first RP and first non-RP symptom, cutaneous subset, telangiectasia, calcinosis, and autoantibody status (anti-centromere (ACA), anti-topoisomerase I (ATA), anti-RNA polymerase III (ARA), anti-U1-RNP, anti-PM/Scl, other autoantibodies). Disease duration was defined as the time between the first non-RP symptom by patient report and inclusion visit. Organ involvements were defined by the occurrence of clinical events at baseline and/or during follow-up as: skin involvement: MRSS, STPR defined as the MRSS at the first visit, divided by the disease duration (in years);[7,15] joint involvement: arthritis, arthralgia, friction rubs or synovitis; muscle involvement: myalgia, myositis, or rhabdomyolysis; lung involvement: lung fibrosis on high-resolution computerized tomography and forced vital capacity <70% (predicted value) and/or total lung capacity <80% (predicted value); heart involvement: arrhythmia or conduction block or systolic dysfunction (left ventricular

fraction ejection ≤45% of predicted value) or pericardial effusion; pulmonary hypertension (PH): mean pulmonary arterial pressure measured by right heart catheterization >25mmHg at rest; gastrointestinal tract (GIT) involvement: esophageal reflux, dysmotility, constipation, diarrhea, signs of bacterial overgrowth and/or malabsorption, abnormal esophageal manometry and/or endoscopy test; digital ulcer (DU): history or active DU, digital tip, pitting scar or digital ischemia; scleroderma renal crisis (SRC): by new onset hypertension (≥150/85 mmHg) associated with a decrease in renal function defined by a decrement of at least 10% in the estimated glomerular filtration rate. C-reactive protein elevation was defined as level >6 mg/L. All immunosuppressive drugs were recorded. Death was also recorded.

Statistical analyses

The primary objective of this study was to delineate groups of patients according to their skin thickening trajectories (classes) as measured by MRSS over time using Latent Class Mixed Modeling (LCMM).[16,17] LCMM consists in assuming that the population is divided in a finite number of groups called latent classes. Each latent class is characterized by a specific mean trajectory which is described by a class-specific linear mixed model. In a given latent class, the individual trajectories of patients are close to each other while the individual trajectories of patients of different classes tend to be dissimilar. In LCMM, latent classes correspond to an unknown categorical variable which is identified from data using a multinomial logistic model, and trajectories of MRSS are analyzed using the mixed model with random coefficients to take into account individual trajectories. The random effects (linear or quadratic) are determined from the analysis of residuals according to Verbeke & Molenberghs.[17] To identify the number of classes, several LCMM are performed. Each model predicts the shape of the trajectory of each class, estimates the probability for each individual of class membership and assigns each

of them to the class for which the likelihood is the highest. Time 0 was defined by the date of baseline MRSS recorded. Trajectories were censored after 4 years of follow-up because of substantial missing records after this duration. To determine the best number of latent classes that represented the heterogeneity of developmental trajectories, we considered both formal statistical criteria (such as Bayes information criterion (BIC)) and model adequacy. A lower value of BIC corresponds to a better model, and average posterior probabilities of class membership should be greater than 0.7-0.8.[18,19]

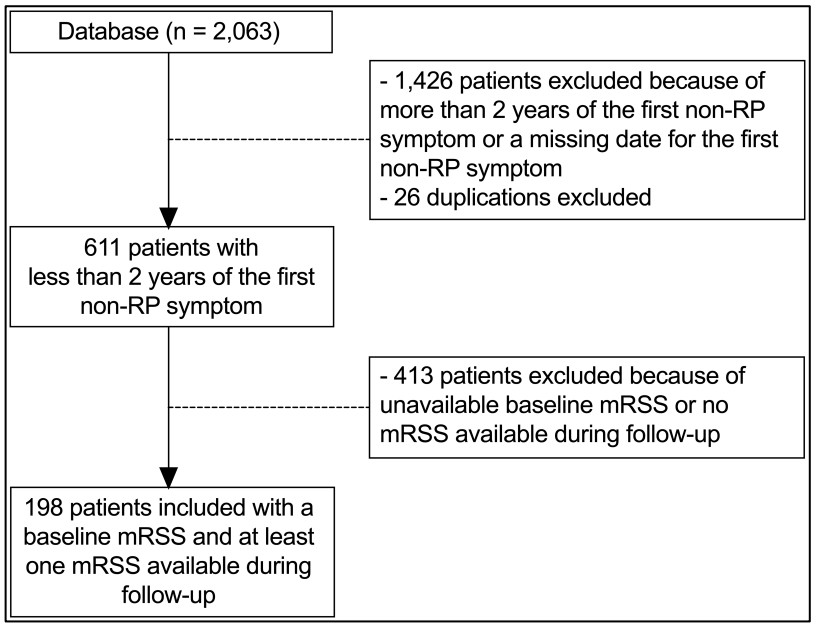
Continuous variables were expressed by the mean ±SD (standard deviation) or median (IQR) (interquartile range) to describe classes, and by the mean with [95% Confidence Interval] to describe trajectory shapes. The normality of distribution was checked graphically and using the Shapiro-Wilk test. Categorical variables were expressed as frequencies and percentages. Comparisons of classes were performed by using the analysis of variance or the Kruskal-Wallis test for quantitative variables and the Fisher Exact test or the Chi-square test for categorical variables. In case of significant result, pairwise comparisons were performed, and a Bonferroni correction was applied. Survival rate in every classes were estimated using the Kaplan–Meier method and compared by the Cox regression adjusted for age and sex. All statistical tests were performed at 2-tailed α level of 0.05 and data analysis were performed using the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and the R software (Package LCMM).

c. Results

Baseline characteristics

Of the 2,063 patients in the database, 611 patients had a disease duration of less than 2 years at the time of inclusion (median disease duration (IQR): 0.72 (0.3; 1.2) years) (**eTable 1**). Among them, 198 patients had a baseline MRSS available and at least one MRSS available within the first 4 years of follow-up and were included **(Figure 1)**.

Figure 1. *Flow-chart of the study.*



RP: Raynaud phenomenon; MRSS: modified Rodnan skin score.

The mean age of included patients was 51.1 ±14.3 years with a majority of Caucasian patients and a ratio 3:1 of women to men. The median disease duration and follow-up were respectively 0.8 (IQR: 0.4; 1.2) years and 4.4 (2.9; 6.1) years. The proportion of dcSSc patients was 49.7%. Nearly 95.0% of patients were positive for antinuclear antibodies (ACA: 28.3%, ATA: 55.9%, and ARA: 5.3%) (**Table 1**). A total of 641 MRSS values were available and 55.0% of patients had at least three MRSS records (**eTable 2**). The median baseline MRSS was 8 (2; 18).

Table 1. *Demographics and systemic sclerosis characteristics of included patients.*

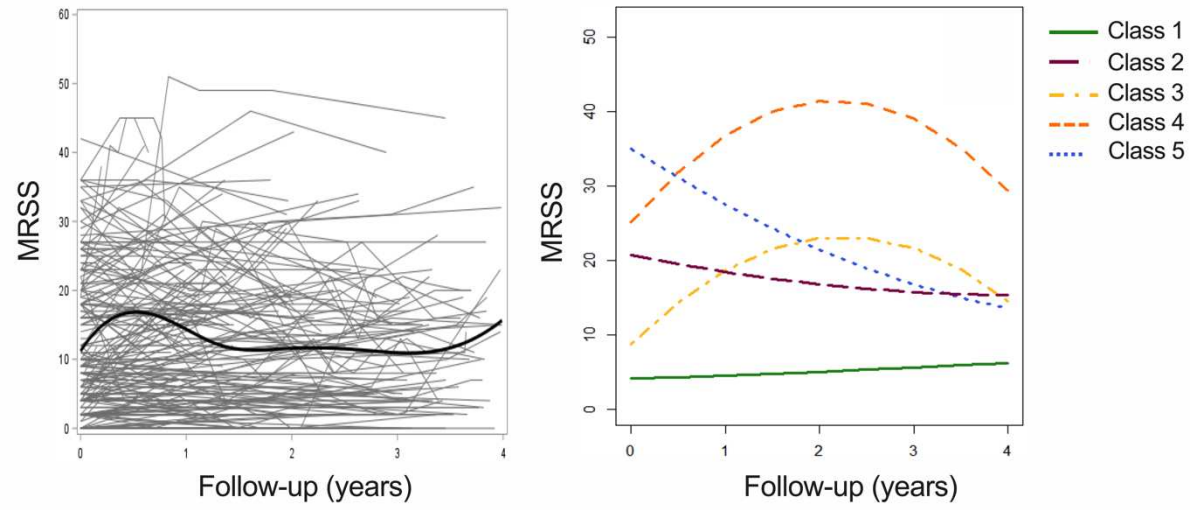
	No. with available data	Included patients
Demographics		
Sex, No. (%)		
Female	198	145 (73.2)
Male	198	53 (26.8)
Ethnicity, No. (%)		
White	161	140 (87.0)
Black	161	16 (9.9)
Asian	161	5 (3.1)
Age, mean ±SD, y	198	51.1 ±14.3
Diseases characteristics		
Autoantibody status[a], No. (%)		
ANA	165	156 (94.5)
ACA	152	43 (28.3)
ATA	152	85 (55.9)
ARA	152	8 (5.3)
Anti-U1RNP	152	9 (5.9)
Anti-PM/Scl	152	6 (4.0)
Disease duration, median (IQR), y	198	0.8 (0.4; 1.2)
Duration from RP, median (IQR), y	187	1.3 (0.6; 3.9)
Follow-up, median (IQR), y	198	4.4 (2.9; 6.1)
Skin variables		
Cutaneous subset, No. (%)		
Limited	195	98 (50.3)
Diffuse	195	97 (49.7)
MRSS, baseline, median (IQR)	198	8 (2; 18)
Organ involvement[b], No. (%)		
Telangiectasia	183	76 (41.5)
Calcinosis	175	20 (11.4)
Joints	191	114 (59.7)
Muscles	194	53 (27.3)
Digital ulcers	181	76 (42.0)
Gastrointestinal tracts	187	99 (52.9)
Interstitial lung disease	123	27 (22.0)
Heart	187	15 (8.0)
Pulmonary hypertension	194	15 (7.7)
Renal crisis	123	12 (9.8)
Biological variable, No. (%)		
CRP level[b], ≥ 6mg/L	148	51 (34.5)

ACA: anticentromere antibodies; ANA: antinuclear antibodies; ARA: anti-RNA polymerase III antibodies; ATA: antitopoisomerase I antibodies; CRP: C-reactive protein; Disease duration: duration from the first non-RP symptom; RP: Raynaud phenomenon; y: years; [a] the sum of % may be different from 100% because some patients had either ANA with no specific SSc target antibodies or multiple specific SSc target antibodies; [b] during follow-up.

Model fit evaluation

Individual trajectories of 198 patients included are presented on **Figure 2** and showed a notable heterogeneity between patients. Models with one to six latent classes were sequentially performed (**A to F, eFigure 1**). The 5-class model (E) had the lowest value of BIC index meaning that it represented the best fit to data (**Figure 2, eTable 3**). Averages of posterior probabilities of belonging to a class were respectively 0.96, 0.88, 0.92, 0.95 and 0.93 for classes 1 to 5 meaning that the modelled trajectories gathered individuals with similar patterns of skin change and discriminated between individuals with dissimilar patterns of skin change (**eTables 4-5**). The median disease duration did not differ significantly between classes (p=0.21).

Figure 2. *The 5-class LCMM results.*



(Left) All individual trajectories and the average trend estimated using B-splines. **(Right)** Results of the 5-class LCMM. Time 0 was defined by the date of baseline MRSS record (within 2 years of the first non-Raynaud Phenomenon symptom). MRSS: modified Rodnan skin score.

Demographics and clinical characteristics of the 5 MRSS trajectories classes (Table 2, Figure 3)

Class 1 was characterized by a low baseline MRSS (mean MRSS: 4.1 [95%CI: 3.2; 5.0]) with no significant change over time (mean MRSS at 4 years: 6.2 [3.8; 8.6]). This class gathered 117 patients mainly composed of lcSSc (82.6%) affecting Caucasian women with ACA (42.3%) or ATA (42.3%). A third of these patients were affected by joint, GIT and DU complications. The median STPR was 3.9 (IQR: 1.2; 9.3) units/year.

Class 2 slightly improved from a mean baseline MRSS of 20.8 [19.0; 22.5] to a mean MRSS at 4 years of 15.4 [11.0; 19.8]. This class gathered 43 patients composed of Caucasian (87.5%) women (65.1%) with dcSSc (97.6%) associated with ATA (75.0%). Joint, DU and GIT symptoms were common. SRC was found in 7 patients (22.6%). The median STPR was 21.8 (IQR: 16.0; 35.9) units/year.

Class 3 was characterized by a two-step trajectory with a low baseline MRSS (mean MRSS: 8.7 [6.0; 11.5]) rapidly increasing to a mean estimated peak MRSS of 23.2 [18.8; 27.6] at 2.3 years of follow-up, then followed by an improvement (mean MRSS at 4 years: 14.5 [8.4; 20.7]). There were 11 dcSSc and 2 lcSSc with a majority of ATA. Two-thirds of them were affected by joint, DU and GIT involvements. Three were African. The median STPR was 7.8 (IQR: 5.7; 13.4) units/year.

Class 4 was characterized by a two-step trajectory with a mean baseline MRSS of 25.1 [22.6; 27.6] rapidly increasing to a mean estimated peak MRSS of 41.6 [37.2; 46.0] at 2.2 years of follow-up, then followed by an improvement (mean MRSS at 4 years: 29.5 [22.7; 36.2]). This class was composed of 13 patients including 6 men and 3 of African ethnicity. ATA, joint and GIT involvements were frequent. The median STPR was 38.5 (IQR: 29.0; 131.3) units/year.

Class 5 was characterized by a mean baseline MRSS of 35.1 [32.2; 37.9] subsequently improving (mean MRSS at 4 years: 13.5 [0; 29.5]). All of 12 patients had dcSSc mainly associated with ATA. Most of them had joint and DU involvements. The median STPR was 34.4 (IQR: 27.6; 74.9) units/year.

Steroids and immunosuppressive treatments were more frequently used in classes 2 to 5 than in 1 (from 83.5% to 100% versus 53.3% in class 1; p<.001). No significant difference was noted between classes 2 to 5 in terms of steroids, methotrexate, azathioprine, cyclophosphamide, and rituximab. Mycophenolate mofetil (MMF) was used more often in class 5 (90.0%) compared to 2 (44.1%; p=0.013) and 3 (41.7%; p=0.031). No significant difference was found between with classes 4 (72.7%) and 5 (90.0%).

Table 2. *Demographics and systemic sclerosis characteristics of the 5 MRSS trajectories classes.*

	No. with available data	Class 1 (n = 117)	Class 2 (n = 43)	Class 3 (n = 13)	Class 4 (n = 13)	Class 5 (n = 12)	p
Demographics							
Sex, No. (%)							
Female	198	93/117 (79.5)	28/43 (65.1)	9/13 (69.2)	7/13 (53.9)	8/12 (66.7)	0.13
Male	198	24/117 (20.5)	15/43 (34.9)	4/13 (30.8)	6/13 (46.1)	4/12 (33.3)	
Ethnicity, No. (%)							
White	161	88/98 (89.8)	28/32 (87.5)	8/11 (72.7)	8/11 (72.7)	8/9 (88.9)	
Black	161	6/98 (6.1)	3/32 (9.4)	3/11 (27.3)	3/11 (27.3)	1/9 (11.1)	<.001
Asian	161	4/98 (4.1)	1/32 (3.1)	0/11 (0.0)	0/11 (0.0)	0/9 (0.0)	
Age, mean ±SD, y	198	52.9 ±13.9	49.2 ±14.1	43.6 ±17.0	47.8 ±14.6	51.9 ±14.5	0.15
Disease characteristics							
Disease duration, median (IQR), y	198	0.8 (0.4; 1.3)	0.9 (0.5; 1.2)	0.9 (0.5; 1.1)	0.6 (0.2; 0.9)	1.1 (0.4; 1.3)	0.21
Duration from RP, median (IQR), y	187	1.6 (0.6; 6.0)	1.3 (0.6; 1.7)	0.8 (0.8; 2.0)	0.6 (0.2; 0.9)	1.3 (0.4; 3.3)	0.018
Follow-up, mean ±SD, y	198	4.9 ±0.2	5.0 ±0.6	6.8 ±1.0	7.4 ±1.5	4.1 ±0.4	0.10
Antibodies, No. (%)[a]							
ANA	165	89/93 (95.7)	37/39 (94.8)	9/11 (81.8)	11/12 (91.7)	10/10 (100)	0.32
ACA	152	41/97 (42.3)	1/28 (3.6)	0/9 (0.0)	1/10 (10.0)	0/8 (0.0)	<.001
ATA	152	41/97 (42.3)	21/28 (75.0)	8/9 (88.9)	8/10 (80.0)	7/8 (87.5)	<.001
ARA	152	3/97 (3.1)	4/28 (14.3)	0/9 (0.0)	0/10 (0.0)	1/8 (12.5)	0.11
Anti-U1RNP	152	7/97 (7.2)	2/28 (7.1)	0/9 (0.0)	0/10 (0.0)	0/8 (0.0)	>.99
Anti-PM/Scl	152	5/97 (5.2)	1/28 (3.6)	0/9 (0.0)	0/10 (0.0)	0/8 (0.0)	NA
Only others	152	4/97 (4.1)	1/28 (3.6)	1/9 (11.1)	2/8 (20.0)	0/8 (0.0)	0.19
Treatment[b], No. (%)							
Steroids and/or IS	185	57/107 (53.3)	33/40 (82.5)	13/13 (100)	12/13(92.3)	12/12 (100)	<.001

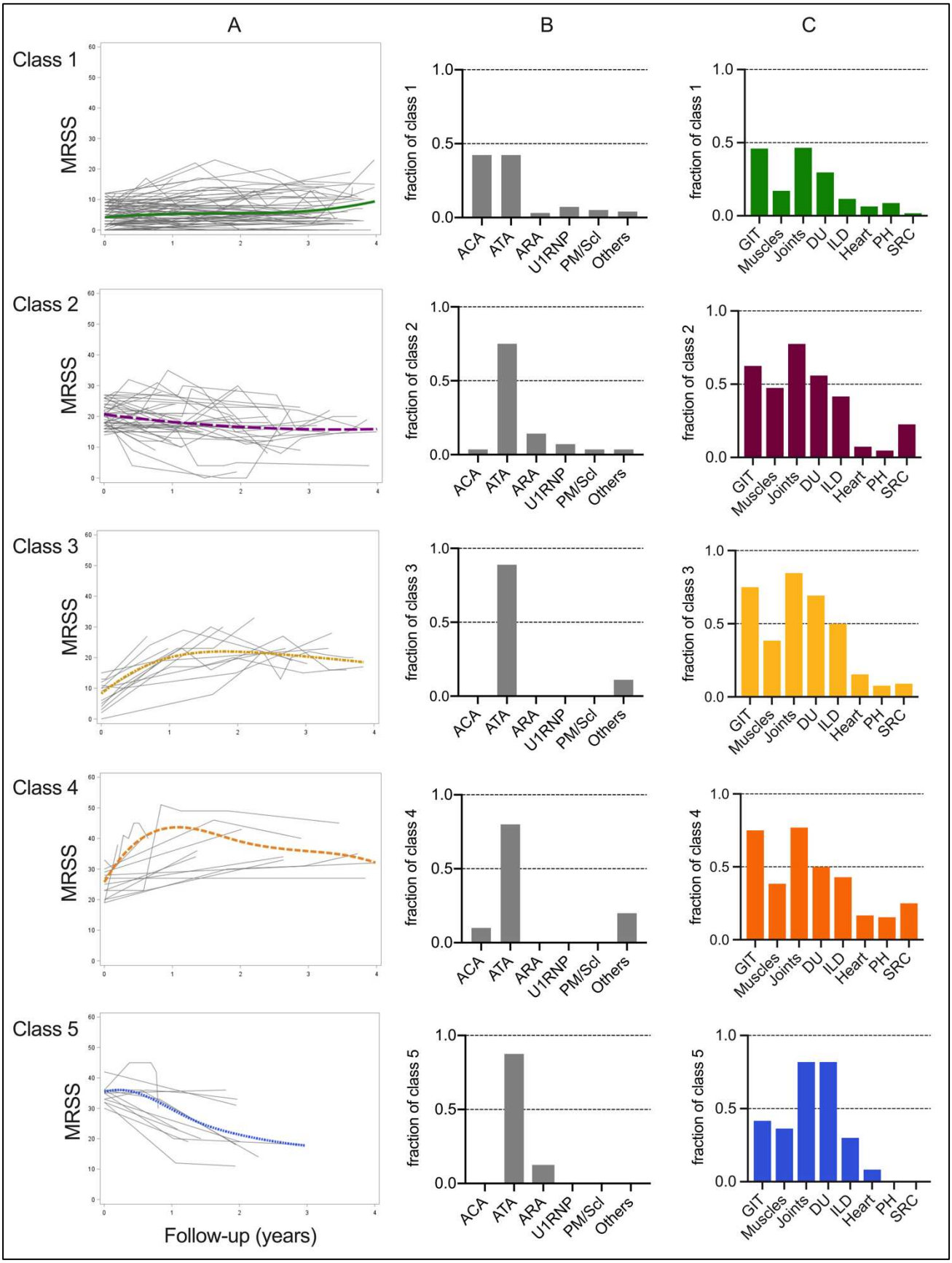
- Continued –

Table 2. *(Continued)*

	No. With Available Data	Class 1 (n = 117)	Class 2 (n = 43)	Class 3 (n = 13)	Class 4 (n = 13)	Class 5 (n = 12)	p
Skin variables							
Cutaneous subtype, No (%)							
Limited	195	95/115 (82.6)	1/42 (2.4)	2/13 (15.4)	0/13 (0.0)	0/12 (0.0)	<.001
Diffuse	195	20/115 (17.4)	41/42 (97.6)	11/13 (84.6)	13/13 (100)	12/12 (100)	
STPR[c], median (IQR); units per y	198	3.9 (1.2; 9.3)	21.8 (16.0; 35.9)	7.8 (5.7; 13.4)	38.5 (29.0; 131.3)	34.4 (27.6; 74.9)	<.001
MRSS trajectories							
Mean baseline MRSS [95%CI]	198	4.1 [3.2; 5.0]	20.8 [19.0; 22.5]	8.7 [6.0; 11.5]	25.1 [22.6; 27.6]	35.1 [32.2; 37.9]	
Mean peak MRSS [95%CI]	198	NA	NA	23.2 [18.8; 27.6]	41.6 [37.2; 46.0]	NA	NA
Mean MRSS at 4-years [95%CI]	198	6.2 [3.8; 8.6]	15.4 [11.0; 19.8]	14.5 [8.4; 20.7]	29.5 [22.7; 36.2]	13.5 [0; 29.5]	
Organ involvement[b], No. (%)							
Telangiectasia	183	48/109 (44.0)	15/38 (39.5)	4/12 (33.3)	4/13 (30.8)	5/11 (45.5)	0.85
Calcinosis	175	13/104 (12.5)	3/37 (8.1)	2/11 (18.2)	2/12 (16.7)	0/11 (0.0)	0.57
Joints	191	53/114 (46.5)	31/40 (77.5)	11/13 (84.6)	10/13 (76.9)	9/11 (81.8)	<.001
Muscles	194	20/117 (17.1)	19/40 (47.5)	5/13 (38.5)	5/13 (38.5)	4/11 (36.4)	0.001
Digital ulcers	181	33/111 (29.7)	19/34 (55.9)	9/13 (69.2)	6/12 (50.0)	9/11 (81.8)	<.001
Gastrointestinal tracts	187	51/111 (46.0)	25/40 (62.5)	9/12 (75.0)	9/12 (75.0)	5/12 (41.7)	0.062
Interstitial lung disease	123	9/78 (11.5)	10/24 (41.7)	2/4 (50.0)	3/7 (42.9)	3/10 (30.0)	0.003
Heart	187	7/109 (6.4)	3/41 (7.3)	2/13 (15.4)	2/12 (16.7)	1/12 (8.3)	0.40
Pulmonary hypertension	194	10/114 (8.8)	2/42 (4.8)	1/13 (7.7)	2/13 (15.4)	0/12 (0.0)	0.58
Renal crisis	123	1/59 (1.7)	7/31 (22.6)	1/11 (9.1)	3/12 (25.0)	0/10 (0.0)	0.003
Biological variable No. (%)							
CRP level[b], ≥ 6mg/L	148	19/85 (22.4)	15/32 (46.9)	5/11 (45.5)	7/10 (70.0)	5/10 (50.0)	0.003

ACA: anticentromere antibodies; ANA: antinuclear antibodies; ARA: anti-RNA polymerase III antibodies; ATA: antitopoisomerase I antibodies; CRP: C-reactive protein; Disease duration: duration from the first non-RP symptom; IS: immunosuppressive treatment; NA: not applicable; RP: Raynaud phenomenon; STPR: skin thickening progression rate; y: years; [a] the sum of % may be different from 100% because some patients had either ANA with no specific SSc target antibodies or multiple specific SSc target antibodies; [b] during follow-up; [c] at baseline.

Figure 3. *Clinical characteristics of the 5 trajectories classes of the 5-class LCMM.*

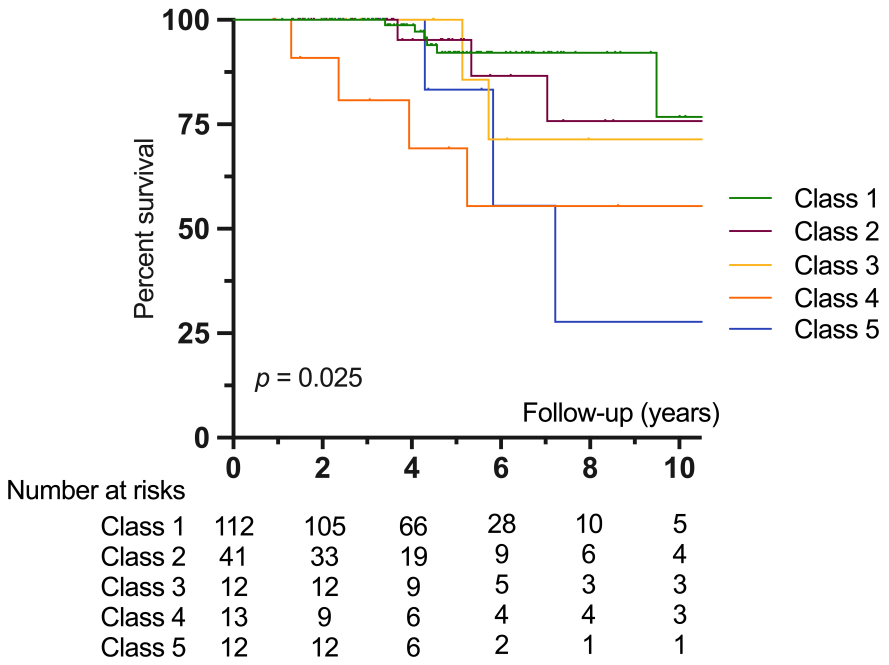


(1) Each class' spaghetti-plot of the 5-class LCMM with the modeled trajectory estimated using B-splines. Time 0 was defined by the date of baseline MRSS record (within 2 years of the first non-Raynaud Phenomenon symptom). MRSS: modified Rodnan skin score. **(2)** Graphs representing the autoantibodies in each class. ACA: anti-centromere antibodies; ARA: anti-RNA polymerase III antibodies; ATA: anti-topoisomerase I antibodies; Others: no specific SSc target antibodies. **(3)** Graphs describing the main organ involvements in each class. DU: digital ulcers; GIT: gastrointestinal tracts; ILD: interstitial lung disease; PH: pulmonary hypertension; SRC: scleroderma renal crisis.

Survival analysis

Kaplan-Meier curves are given in **Figure 4**. Survival was different according to the trajectories classes (p=0.025). Using Cox regression analysis (**eTables 6-7**), we observed a progressive increasing risk of death from classes 2 to 5 compared with class 1 (reference): Hazard Ratio (HR) (class 2) = 1.35 [CI95% 0.33; 5.46], HR (class 3) = 2.99 [0.74; 12.07], HR (class 4) = 3.93 [1.04; 14.90], and HR (class 5) = 5.14 [1.32; 19.94]. Results were similar after adjustment for age and sex.

Figure 4. *Survival of the 5 trajectories classes of the 5-class LCMM.*



Kaplan-Meier curves of 5-class LCMM (p=0.025). Time 0 was defined by the date of the first non-Raynaud Phenomenon symptom.

d. Discussion

The main results were: (i) LCMM identified without any *a priori* assumptions 5 distinct trajectories of MRSS during the follow-up in early SSc patients (inclusion within 2 years of the first non-RP symptom); (ii) the MRSS trajectories classes were associated with different organ involvement and survival.

The natural evolution of skin thickening is very heterogenous, yet it is generally accepted that it tends to worsen at the beginning of dcSSc to a maximum that usually occurs 12-18 months after disease onset, then followed by improving at the advanced stage.[10,20,21] However, data are scarce and complex. Modelling the evolution of MRSS has only been performed in a few studies. Shand *et al.*[6] classified 131/192 (68%) early dcSSc patients in 3 subgroups using latent trajectory modeling over the first 3 years of follow-up. Those 3 subgroups: “low baseline (mean MRSS: 20 ±6) / improvers”, “high baseline (mean MRSS: 42 ±8) / non-improvers” and “high baseline (mean MRSS: 35 ±7) / improvers” had similar trajectories than classes 2, 4 and 5 found in our study, respectively. The survival in the “high baseline / non-improvers” (similar to the class 4 in our work) subgroup was significantly worse than in the two other subgroups of their study. In our work, we observed the worst survival in classes 4 and 5. Moreover, we found two additional trajectories: one mainly composed by lcSSc (class 1), and another one characterized by a two-step trajectory with a low baseline MRSS rapidly increasing to a mean estimated peak MRSS of 23.2 [18.8; 27.6] before improving (class 3). We may have captured this last trajectory for the following reasons: (i) we included patients with lcSSc; (ii) the very short disease duration in our study allowed us to discriminate these individual trajectories with different patterns of early skin change. By using a prespecified definition of progressive skin disease (increase of MRSS >5 points and ≥25% from baseline), Maurer *et al.*[9] identified several independent factors associated with skin thickening

progression as baseline MRSS ≤22/51, low baseline STPR, and disease duration ≤15 months. The best prediction model of worsening performed correctly in only 44.4% of cases, suggesting that it is still not easy to accurately predict the skin thickening progression. To our knowledge, no study has tried to model the evolution of MRSS without any *a priori* assumptions or prespecified definition.

Our approach identified 5 original distinct trajectories over time meeting the fittest formal statistical criteria, model adequacy and clinical relevance of discriminated trajectories. Class 1 had low values of MRSS and STPR at baseline, less of organ involvements, and the better survival, as reported in lcSSc.[22,23] Most patients with ACA (95%) were assigned to class 1. However, 42% of patients in class 1 had ATA, which is a higher proportion than usually observed in lcSSc.[22,24,25] In addition to lcSSc, there was also 20 dcSSc (17%) associated with ATA whose the median baseline MRSS was 9 (IQR: 6.5; 9.5). Low values of MRSS have been already reported in dcSSc[26-28] and some limitations have been identified about the current classification,[25,29] especially when the forearms are involved. Their assignation to class 1 were probably related to the modelled trajectory shape of class 1 that was fitter to their individual trajectories than the other modelled trajectories classes.

Organ involvement were more frequent in classes 2 to 5 than in class 1. As expected, the immunosuppressive drug use was also more frequent in classes 2 to 5 compared to class 1. With respect to survival, we found that an increasing risk of death from classes 2 to 5 compared to class 1, especially in classes with either an intermediate baseline MRSS which increased before an improvement (class 4) or a high baseline MRSS (class 5). These two classes also shared a rapid STPR at baseline (median >30 units/years) compared to others. Recently, Wu *et al.*[30] reported in dcSSc that the skin progression within 1 year was independently associated with forced vital capacity decline

and all-cause death. Taken together, these results emphasis the importance to consider the skin thickening trajectory (progressor / regressor) and the rate of skin thickening (slow / rapid) in the patient risk stratification.

Our study has strengths and limitations. The strengths are that we used prospective data from a French multicenter cohort on SSc and included only patients with early disease duration from the first non-RP symptom. We also used an approach without any *a priori* assumptions in order to capture the heterogeneity of MRSS longitudinal trajectories. Then, the MRSS changes which occurred in the trajectories classes 2 to 5 were clinically relevant. Indeed, they were higher than the minimal clinically important difference for MRSS (≥3-4 units) estimated in the Scleroderma Lung Studies.[31] Finally, we identified 2 trajectories associated with the most unfavorable survival.

Study limitations include a potential inclusion bias, explaining a higher proportion of dcSSc analyzed. Skin involvement, which is an important outcome in dcSSc, could have been more frequently assessed in dcSSc patients. Second, missing data (patients lost to follow-up, unrecorded MRSS) precluded any determination of predictive factors of trajectory membership in multivariate analysis. Moreover, the small size of some classes and the unknown causes of death may limit the interpretation of data. Also, MRSS were not recorded by the same practitioner for each patient leading to potential inter-observer differences. Nevertheless, participating hospitals are SSc referral centers providing regular MRSS assessment training for physicians and it has been shown that MRSS can be reproducible between observers.[32,33] Our findings should be confirmed on an external validation cohort.

e. Conclusion

This study identified 5 distinct MRSS trajectories in early SSc patients. The MRSS trajectories classes were associated with organ involvement and survival. Early identification of clinical phenotype based on skin thickening trajectories could predict morbi-mortality in SSc and influence clinical management.

4. Supplemental information

eTable 1. *Clinical characteristics of patients with less than 2 years of the first non-RP symptom (n = 611).*

	No. with data available	≤ 1 MRSS available (n = 413)	No. with data available	Patients included (n = 198)	p
Demographics					
Sex, No. (%)					
Female	413	336 (81.4)	198	145 (73.2)	0.022
Male	413	77 (18.6)	198	53 (26.8)	
Ethnicity, No. (%)					
White	315	286 (90.8)	161	140 (87.0)	
Black	315	22 (7.0)	161	16 (9.9)	0.43
Asian	315	7 (2.2)	161	5 (3.1)	
Age, median (±SD), y	413	52.3 ±15.8	198	51.1 ±14.3	0.39
Disease characteristics					
Autoantibody status[a], No. (%)					
ANA	300	281 (93.7)	165	156 (94.5)	0.70
ACA	280	153 (54.6)	152	43 (28.3)	<0.001
ATA	280	97 (34.6)	152	85 (55.9)	<0.001
ARA	280	3 (1.1)	152	8 (5.3)	0.020
Anti-U1RNP	280	17 (6.1)	152	9 (5.9)	0.95
Anti-PM/Scl	280	11 (3.9)	152	6 (4.0)	0.99
Disease duration, median (IQR), y	413	0.7 (0.3; 1.2)	198	0.8 (0.4; 1.2)	0.018
Duration from RP, median (IQR), y	371	2.0 (0.7; 6.3)	187	1.3 (0.6; 3.9)	0.004
Skin variables					
Cutaneous subtype, No. (%)					
Limited	400	292 (73.0)	195	98 (50.3)	<0.001
Diffuse	400	108 (27.0)	195	97 (49.7)	
Organ involvement[b]					
Telangiectasia	367	168 (45.8)	183	76 (41.5)	0.35
Calcinosis	365	41 (11.2)	175	20 (11.4)	0.95
Joints	387	207 (53.5)	191	114 (59.7)	0.16
Muscles	401	104 (25.9)	194	53 (27.3)	0.72
Digital ulcers	322	135 (41.9)	181	76 (42.0)	0.99
Gastrointestinal tracts	379	135 (35.6)	187	99 (52.9)	<0.001
Interstitial lung disease	277	62 (22.4)	123	27 (22.0)	0.92
Heart	377	37 (9.8)	187	15 (8.0)	0.49
Pulmonary hypertension	388	31 (8.0)	194	15 (7.7)	0.91
Renal crisis	300	42 (14.0)	123	12 (9.8)	0.23
Biological variables, No. (%)					
CRP level[a], ≥ 6mg/L	278	89 (32.0)	148	51 (34.5)	0.61

Numbers are given as % or mean ±standard deviation or median (interquartile range). ACA: anticentromere antibodies; ANA: antinuclear antibodies; ARA: anti-RNA polymerase III antibodies; ATA: antitopoisomerase I antibodies; CRP: C-reactive protein; Disease duration: duration from the first non-RP symptom; RP: Raynaud phenomenon; y: years; [a] the sum of % may be different from 100% because some patients had either ANA with no specific SSc target antibodies or multiple specific SSc target antibodies; [b] during follow-up.

eTable 2. *Number of MRSS available in patients included in LCMM.*

MRSS recorded	Frequency	Cumulative percent (%)
2	89	45.0
3	45	67.7
4	32	83.9
5	14	90.9
6	8	95.0
7	5	97.5
8	1	98.0
9	2	99.0
10	1	99.5
11	1	100

MRSS: modified Rodnan skin score.

eTable 3. *Model fit evaluation information for each LCMM tested.*

	Maximum log-likelihood	**% reduction in log-likelihood from the previous model**	**Likelihood ratio test *p*-value**	**AIC**	**BIC**
One-class LCMM	-2170.0	-	-	4360	4393
Two-class LCMM	-2138.3	1.47	<.001	4305	4351
Three-class LCMM	-2115.6	1.06	<.001	4267	4326
Four-class LCMM	-2106.2	0.44	0.053	4256	4329
Five-class LCMM	**-2088.2**	**0.85**	**<.001**	**4228**	**4314**
Six-class LCMM	-2084.4	0.18	0.44	4229	4328

AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria; LCMM: latent class mixed modeling.

eTable 4. *Averages of posterior probabilities of belonging to a class in each LCMM tested.*

	Class 1	**Class 2**	**Class 3**	**Class 4**	**Class 5**	**Class 6**
One-class LCMM	-	-	-	-	-	-
Two-class LCMM	0.982	0.922	-	-	-	-
Three-class LCMM	0.891	0.968	0.841	-	-	-
Four-class LCMM	0.965	0.867	0.884	0.780	-	-
Five-class LCMM	**0.960**	**0.881**	**0.922**	**0.954**	**0.930**	**-**
Six-class LCMM	0.952	0.955	0.914	0.878	0.878	0.632

LCMM: latent class mixed modeling.

eTable 5. *Averages of posterior probabilities of belonging to a class in the 5-class LCMM.*

	Prob. A	Prob. B	Prob. C	Prob. D	Prob. E
Class 1	**0.960**	0.008	0.032	0.000	0.000
Class 2	0.027	**0.881**	0.035	0.039	0.018
Class 3	0.050	0.028	**0.922**	0.001	0.000
Class 4	0.000	0.033	0.011	**0.954**	0.002
Class 5	0.000	0.060	0.000	0.012	**0.930**

LCMM: latent class mixed modeling.

eTable 6. *Survival analyses using Cox regression analysis without adjustment in the 5-class LCMM.*

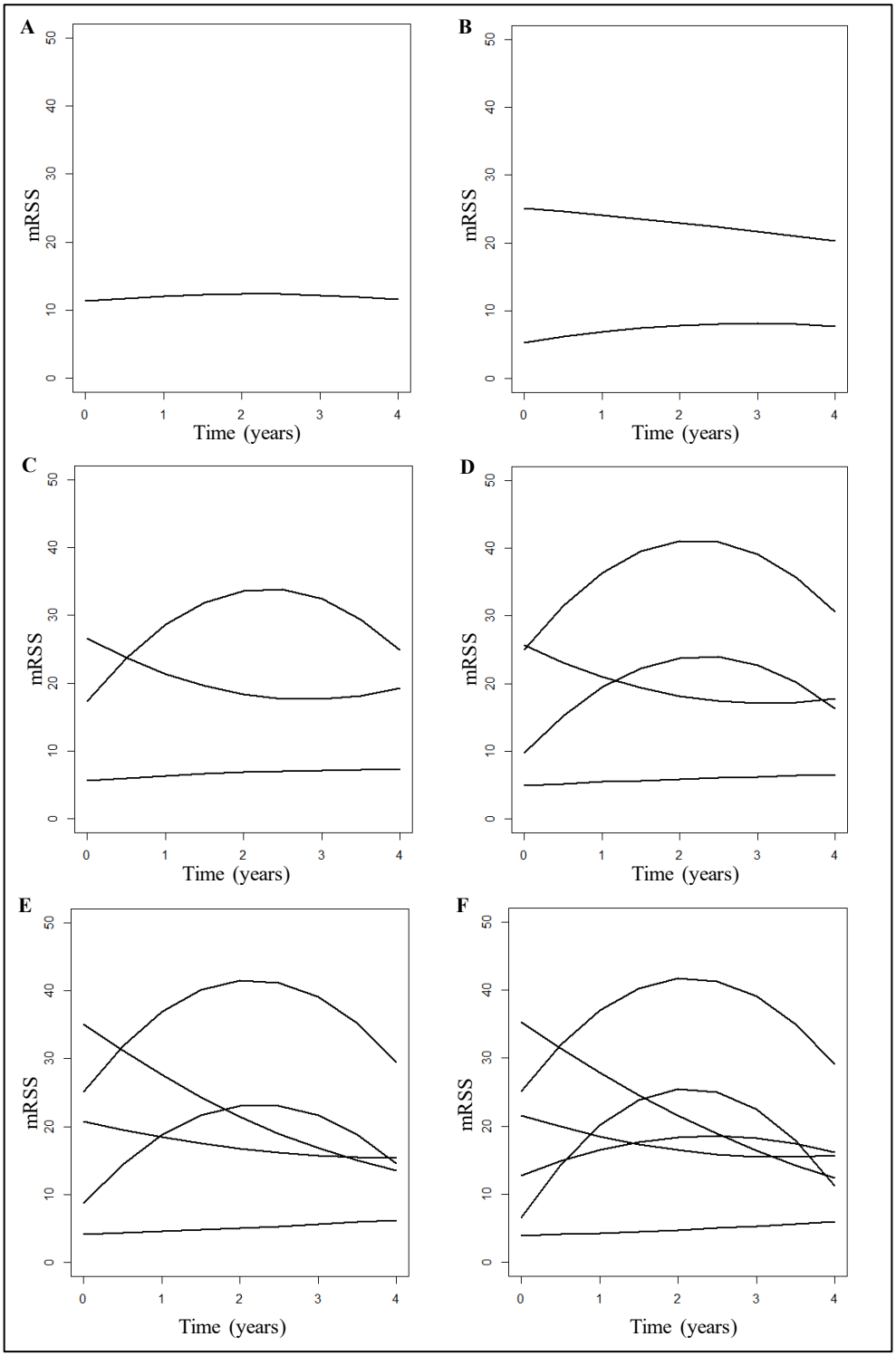
	Hazard ratio	**95%CI**	***p*-value**
Class 1	Reference	Reference	Reference
Class 2	1.35	[0.33; 5.46]	0.67
Class 3	2.99	[0.74; 12.07]	0.12
Class 4	4.05	[1.09; 15.13]	0.037
Class 5	5.85	[1.63; 21.03]	0.007

eTable 7. *Survival analyses using Cox regression analysis adjusted for age and sex in the 5-class LCMM.*

	Hazard ratio	**95%CI**	***p*-value**
Class 1	Reference	Reference	Reference
Class 2	1.32	[0.32; 5.36]	0.70
Class 3	2.84	[0.67; 11.99]	0.16
Class 4	3.93	[1.04; 14.90]	0.044
Class 5	5.14	[1.32; 19.94]	0.018

eFigure 1. *The 6 different LCMM tested.*

Number of patients: 198. (**A)** 1-class LCMM. (**B)** 2-class LCMM. (**C)** 3-class LCMM. (**D)** 4-class LCMM. (**E)** 5-class LCMM. (**F)** 6-class LCMM. LCMM: latent class mixed modeling. Time 0 was defined by the date of baseline MRSS record (within 2 years of the first non-Raynaud phenomenon symptom).



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V. DISCUSSION GENERALE

Cette étude avait pour objectif principal d'identifier sans *a priori* des classes distinctes de trajectoires de MRSS au cours des premières années d'évolution de la ScS. Le principal résultat a été la mise en évidence de 5 trajectoires de MRSS distinctes.

Afin d'identifier les potentielles classes de trajectoires, nous avons utilisé un modèle mixte à classes latentes (LCMM). Par rapport aux données longitudinales du MRSS précédemment rapportées,[13,19,27] nous avons choisi une approche sans *a priori* (c'est-à-dire que nous n'avons pas sélectionné les patients sur la forme cutanée ou le type d'autoanticorps) privilégiant une vision originale et globale de la maladie. Dans un LCMM, il est important de bien définir le temps T0. Nous avons fait le choix de la date d'inclusion dans la cohorte avec un MRSS disponible. Nous avons ensuite sélectionné uniquement les patients avec une durée d'évolution courte à l'inclusion (≤ 2 ans depuis le premier signe hors-Raynaud) puisque le pic de MRSS survient au cours des premières années d'évolution.[19-21] Nous avons d'ailleurs noté des médianes de durée d'évolution de la maladie similaires entre les classes identifiées. Cependant, un nombre important de patients ont été exclus faute d'un MRSS initial disponible (*cf. discussion de l'article*). Lors d'une approche par LCMM, on détermine initialement le nombre optimal de classes, en utilisant des mesures de qualité évaluant la vraisemblance du modèle. Nous avons ainsi séquentiellement évalué les modèles de 1 à 6 classes de trajectoires. Le modèle à 5 classes de trajectoires était statistiquement le plus pertinent. Ces résultats devront être confirmés sur une cohorte de validation externe.

Les classes de trajectoires identifiées étaient caractérisées par des profils de morbi-mortalité distincts. L'approche par LCMM pourrait permettre d'identifier des critères prédictifs d'appartenance d'un patient à une classe de trajectoire. Dans notre étude, la

proportion de données manquantes ne nous a pas permis de construire un modèle statistique robuste pour les déterminer. Il faut d'ailleurs remarquer que deux études récentes n'ont pas pu identifier avec précision des critères cliniques et biologiques prédictifs d'une « progression du MRSS ».[20,21] Parmi les biomarqueurs en cours de développement,[28] l'étude de l'expression génique des fibroblastes semble intéressante. Les patients du groupe placebo de l'étude faSScinate (MRSS initial ±ET : 25,1 ±5,2 après une durée moyenne de la maladie de 19,8 ±16,8 mois) avec une maladie active lors l'inclusion[2] ont été secondairement analysés avec une approche par LCMM.[27] Alors que les critères d'inclusion favorisaient l'inclusion de formes récentes et progressives sur le plan cutané, 3 trajectoires « spontanées » et distinctes du MRSS ont été identifiées au cours des 48 premières semaines de suivi : aggravative, stable, et régressive. L'étude de l'expression génique des fibroblastes cutanés de ces patients a permis d'identifier 5 gènes (CD14, IL13RA1, SERPINE1, OSMR et CTGF) dont les niveaux d'expression élevés étaient corrélés à la trajectoire aggravative du MRSS.[29] Dans l'essai clinique de phase II évaluant l'Abatacept dans la ScScd, on observait des trajectoires différentes du MRSS entre les signatures transcriptomiques « inflammatory », « normal-like » et « fibroproliferative » des fibroblastes à l'inclusion. Bien que le bénéfice de l'abatacept sur le MRSS n'était pas significatif dans l'ensemble de la population de l'étude, il semblait plus marqué chez les patients avec une signature « inflammatory ».[29] Il apparait ainsi qu'une classe de trajectoire de MRSS pourrait tirer davantage bénéfice d'un traitement par immunosuppresseur ou par biothérapie qu'une autre. D'ailleurs dans une petite cohorte de patients ScS traités par MMF, Hinchcliff *et al.* ont rapporté que la plupart des patients dont le MRSS s'était amélioré au cours des 12 derniers mois avaient des

[2] Maladie active au cours des 12 derniers mois lors de l'inclusion définie par : une augmentation du MRSS ≥3 points ou une augmentation du MRSS ≥2 points et atteinte d'une nouvelle zone cutanée ou une augmentation MRSS ≥1 point avec atteinte de 2 nouvelles zones cutanées ou ≥1 friction tendineuse avec un syndrome inflammatoire biologique.

signatures d'expression génique des fibroblastes cutanés de type « inflammatory » ou « inflammatory / fibroproliferative ».[30] Ces résultats suggèrent un plus grand bénéfice du MMF dans les signatures « inflammatory » que « normal-like » ou « fibroproliferative ».

Nos résultats suggèrent également que les objectifs thérapeutiques pourraient être adaptés aux caractéristiques intrinsèques des trajectoires. Ainsi, on propose qu'il faudrait plutôt évaluer le ralentissement de l'aggravation du MRSS pour les classes 3 et 4, et l'accélération de l'amélioration du MRSS pour les classes 2 et 5. L'effet d'un traitement devrait être également comparé à celui sur des patients « contrôles » d'une même trajectoire. De manière exploratoire, on pourrait imaginer utiliser une approche de type LCMM dans la cohorte ESOS[31] afin de déterminer s'il existe des classes distinctes de trajectoires d'épaississement cutané dans un même bras (cyclophosphamide, méthotrexate, mycophénolate mofétil, pas de traitement), puis comparer les patients traités et non traités appartenant à une même classe de trajectoire.

Le design de l'étude et les données manquantes n'ont pas permis d'évaluer la prévalence des critères prédictifs de sévérité déjà rapportés tels que les ulcères digitaux actifs ou les frictions tendineuses.[32-34] De plus, nous n'avons pas trouvé d'association entre la présence d'anticorps anti-ARNpol3 et l'assignation à l'une des trajectoires. En effet, la présence de ces anticorps a été rapportée comme associée à un pic plus précoce et plus élevé du MRSS comparé à celui observé avec les autres auto-anticorps.[21] La prévalence des anticorps anti-ARNpol3 était plus faible dans notre étude (5,3%) que les prévalences globale (11,0%),[35] et d'Herrick *et al.* (n=293 ; 20,2%)[21] ce qui limite la portée de nos résultats concernant ces formes associées aux anticorps anti-ARNpol3.

VI. CONCLUSION GENERALE

Cette approche sans *a priori* a permis d'identifier 5 trajectoires distinctes du MRSS au cours des premières années d'évolution de la ScS. Comme précédemment rapporté, un MRSS initial élevé et/ou une aggravation du MRSS après la première visite sont associés à une augmentation de la morbi-mortalité. Le principal message de ce travail est qu'il existe une hétérogénéité considérable en termes d'évolutivité de l'épaississement cutané qui peut potentiellement affecter la comparabilité des patients et les objectifs thérapeutiques. Une cohorte externe de validation et l'identification de nouveaux biomarqueurs seront primordiales pour confirmer ces résultats et établir des critères prédictifs d'appartenance à une classe de trajectoire.

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VIII. ANNEXES

Annexe n°1. Physiopathologie de la sclérodermie systémique

Reproduit à partir de Korman B.[3]

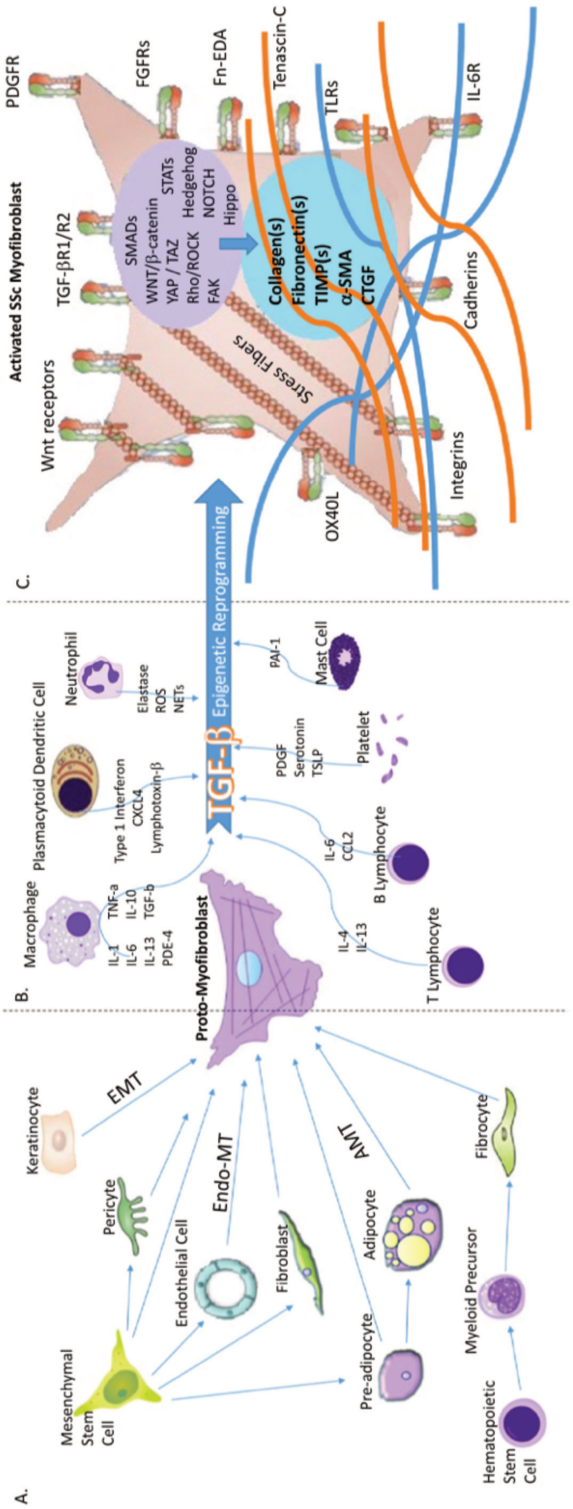


Fig. 1. Cellular source, immune interaction, and function of scleroderma myofibroblasts.

A, Cellular source of myofibroblasts. Myofibroblasts are derived from a diverse group of cells including mesenchymal cells (fibroblasts, endothelial cells, pericytes, adipocytes) and hematopoietic cells (fibrocytes). B, Immune cell interactions with proto-myofibroblasts. Secretion of cytokines by a variety of innate and adaptive immune cells leads to TGF-β activation and epigenetic reprogramming that leads fibroblasts to become activated and develop into activated scleroderma myofibroblasts. C, The myofibroblast in scleroderma. Activated myofibroblasts express a number of cell surface receptors and undergo signal transduction that leads to collagen and matrix deposition which drive fibrosis.

Annexe n°2. Critères de classification ACR/EULAR 2013 de la sclérodermie systémique

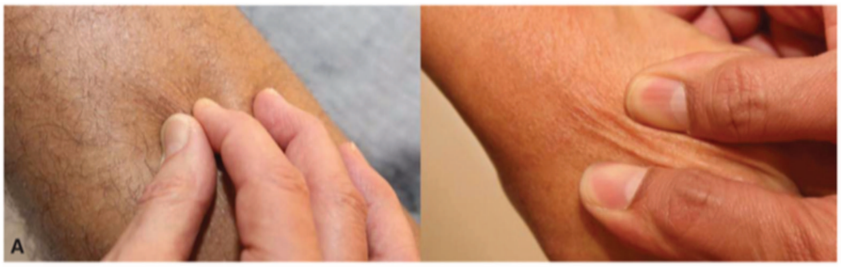
Reproduit à partir de : PNDS sclérodermie systémique 2017 (https://www.has-sante.fr/portail/upload/docs/application/pdf/2008-11/pnds__sclerodermie_web.pdf

Domaine	Critères *	Score #
Épaississement cutané (ne tenir compte que du score le plus élevé)	Épaississement cutané des doigts des mains s'étendant au-delà des articulations MCP	9
	Doigts boudinés	2
	Atteinte des doigts ne dépassant pas les articulations MCP	4
Lésions pulpaires (ne tenir compte que du score le plus élevé)	Ulcères pulpaires digitaux	2
	Cicatrices déprimées	3
Télangiectasies		2
Anomalies capillaroscopiques		2
Atteinte pulmonaire	HTAP et/ou fibrose pulmonaire	2
Phénomène de Raynaud		3
Anticorps spécifiques de la ScS	Anti-topoisomérase I Anticorps anti-centromères Anti-ARN polymerase de type III	3

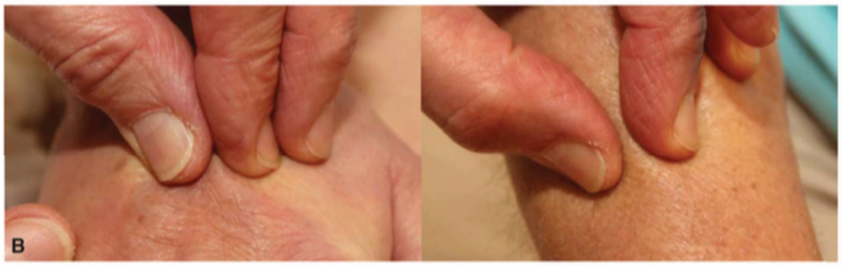
** Le critère peut être retenu s'il est présent à un moment au moins de l'histoire clinique.*
 # Le poids de chaque item présent doit être associé pour obtenir un score total. Un score de 9 ou au-delà permet de classer les patients comme atteints de ScS.
ARN : acide ribonucléïque ; MCP : métacarpo-phalangiennes ; ScS : sclérodermie systémique.

Annexe n°3. Score cutané de Rodnan modifié

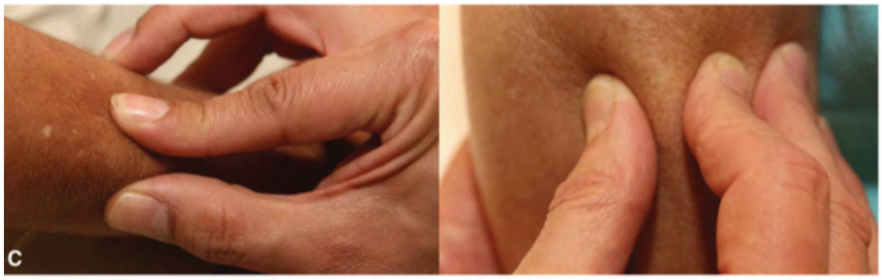
Reproduit à partir de Khanna *et al.*[10]



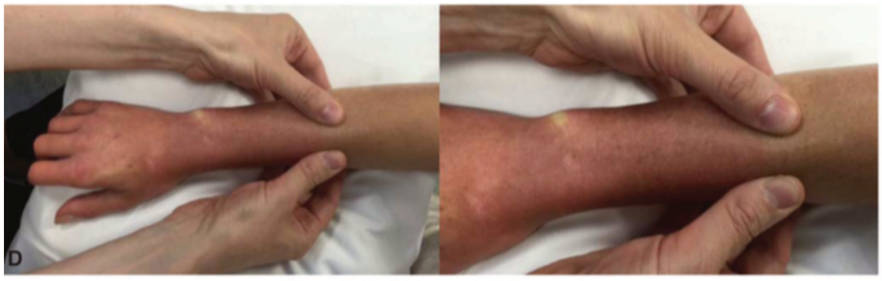
Fine wrinkles;
No thickness appreciated



"Mild" skin thickness; easily able to detect
a thickened skin fold between 2 fingers



"Moderate" skin thickness; difficulty in making
a skin fold and unable to appreciate fine wrinkles



"Severe" skin thickness; inability to make
skin folds between 2 fingers

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Date de Soutenance : 06 NOVEMBRE 2019

Titre de la Thèse : « Épaississement cutané au cours de la sclérodermie systémique : modélisation et caractérisation des trajectoires du score cutané de Rodnan modifié au cours du temps. »

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Résumé :

Objectifs. La sclérodermie systémique (ScS) est une maladie grave et hétérogène. Le score cutané de Rodnan modifié (MRSS) est un outil largement utilisé pour évaluer l'étendue et le degré d'épaisseur de la peau. Les trajectoires précoces de MRSS pourraient refléter la gravité future de la maladie et permettre une meilleure sélection des patients inclus dans les essais cliniques. Les objectifs de cette étude étaient de mettre en évidence, sans *a priori,* des groupes (appelées classes) de patients présentant une trajectoire similaire de MRSS, puis d'étudier leurs associations avec les caractéristiques et la sévérité de la maladie.

Matériels. Dans la cohorte nationale française de ScS, les patients avec une durée d'évolution de la maladie de moins de 2 ans à l'inclusion et pour lesquels au moins 2 MRSS étaient disponibles au cours des 4 premières années de suivi ont été inclus. Les patients avec des trajectoires similaires du MRSS ont été identifiés avec un modèle mixte de classes latentes. Les caractéristiques cliniques et la survie toutes causes confondues ont été comparées entre les classes identifiées.

Résultats. Un total de 198 patients remplissait les critères d'inclusion correspondant à 641 MRSS disponibles. La durée médiane de la maladie et du suivi étaient respectivement de 0,8 (IIQ : 0,4; 1,2) et de 4,4 (2,9; 6,1) années. Les trajectoires individuelles de MRSS étaient très hétérogènes entre les patients. Les modèles de une à six classes de trajectoires étaient séquentiellement testés et le modèle à 5 classes représentait le modèle le plus vraisemblable. La durée médiane de la maladie ne différait pas significativement entre les classes. Les atteintes d'organes étaient plus fréquentes dans les classes qui présentaient un changement dynamique du MRSS au cours du temps (classes 2 à 5) par rapport à la classe 1 (caractérisée par l'absence de changement significatif du MRSS). En utilisant un modèle de Cox, nous avons observé une augmentation progressive du risque de décès de la classe 1 à la classe 5.

Conclusion. Une identification précoce du phénotype clinique basée sur les trajectoires de MRSS pourrait contribuer à prédire la morbi-mortalité dans la ScS. Cette étude suggère que la caractérisation des trajectoires de MRSS pourrait être essentielle pour la pratique clinique et la conception des futurs essais.

Composition du Jury :

Président : Professeur Éric Hachulla

Assesseurs : Professeur David Launay, Docteur Alain Lescoat, Docteur Vincent Sobanski.