6ème Journée de la Sclérodermie des Centres de Référence des Maladies Auto-Immunes Systémiques Rares

Revue de la littérature des 12 derniers mois

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Méthodes

- Revue de la littérature scientifique de Novembre 2018 à Novembre 2019
- Mots de recherche (MeSH): ‘Systemic Sclerosis’ OR ‘Scleroderma’
- Moteur de recherche: Pubmed
- Focus sur pathogénèse, classification et clinique
- Critères d’exclusion: articles non en anglais ou sujet d’un thème abordé spécifiquement au cours de cette journée

- Pathogénèse
- Classification
- Clinique:
  - Suivi
  - Atteinte pulmonaire
  - Atteinte cardiaque
  - Atteinte Vasculaire périphérique
  - Atteinte rénale
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Etudes génétiques – meta-GWAS

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-12760-y OPEN

GWAS for systemic sclerosis identifies multiple risk loci and highlights fibrotic and vasculopathy pathways

Elena López-Isac et al.#

- 4 cohortes épidémiologiques indépendantes
- 28,179 individus non reliés génétiquement et génotypés genome-wide (9846 patients SSc et 18,333 controles sains)
- 9 nouvelles cohortes SSc GWAS et 5 cohortes SSc GWAS d'origine Européenne déjà décrites dans la littérature

Table 1 Twenty-seven signals independently associated with systemic sclerosis in the meta-GWAS

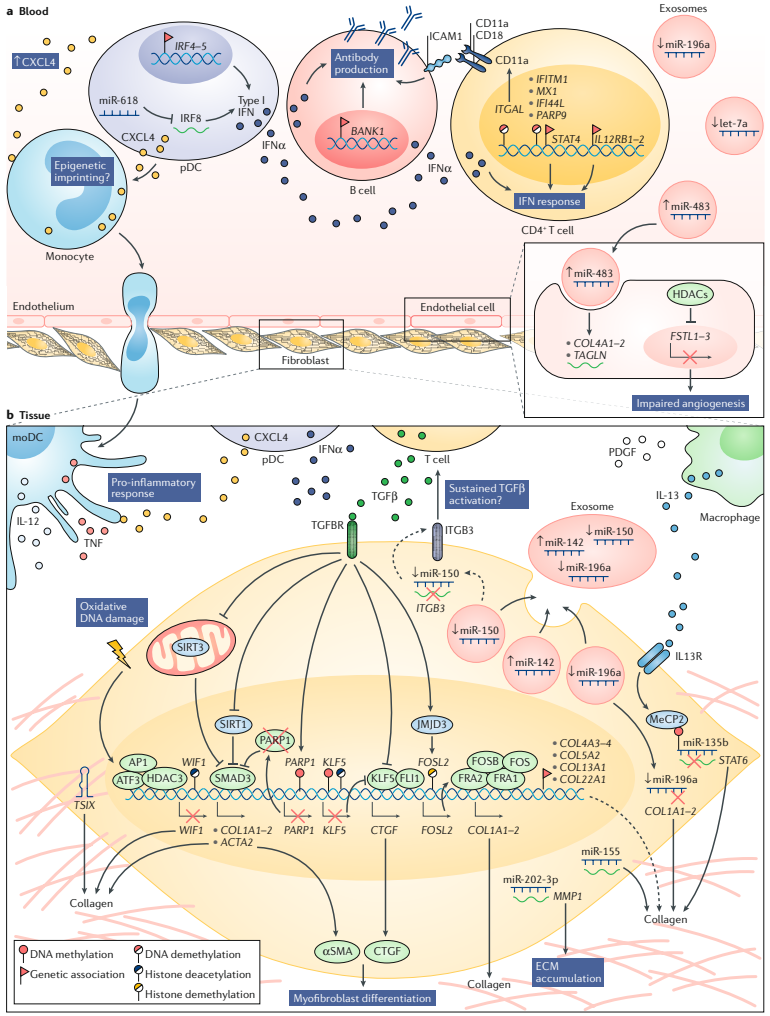
Chr	Locus	Bp	SNP	Index SNP	Ref.	MAF	N	P value	OR	Q	I	P_{cond}	Func refgene
1	*IL12RB2*	67814440	rs3790566	Yes	T	0.24	13	3.84E-10	1.16	0.80	0	-	Intronic
1	*CD247*	167420425	rs2056626	Yes	G	0.39	6	1.31E-11	0.81	0.57	0	-	Intronic
1	***TNFSF4-LOC100506023-PRDX6***	**173238736**	**rs2022449**	**No**	**T**	**0.23**	**12**	**6.28E-08**	**1.15**	**0.90**	**0**	**6.63E-08**	**Regulatory region**
1	***TNFSF4-LOC100506023-PRDX6***	**173332629**	**rs1857066**	**Yes**	**A**	**0.25**	**13**	**5.02E-09**	**0.87**	**0.84**	**0**	-	**ncRNA intronic**
2	***NAB1****	**191534372**	**rs16832798**	**Yes**	**C**	**0.14**	**14**	**5.20E-09**	**1.18**	**0.41**	**3.79**	3.84E-07	**Intronic**
2	*STAT4*	191902758	rs3821236	Yes	A	0.20	12	1.94E-23	1.31	0.03	48.21	-	Intronic
2	*STAT4*	191959489	rs4853458	No	A	0.23	9	4.86E-18	1.35	0.42	1.79	5.58E-08	Intronic
3	*FLNB-DNASE1L3-PXK*	58131515	rs7355798	No	T	0.24	13	1.24E-08	1.14	0.14	30.5	7.42E-07	Intronic
3	*FLNB-DNASE1L3-PXK*	58375286	rs4076852	Yes	G	0.26	13	1.04E-10	1.16	0.71	0	-	Intronic
3	***POGLUT1-TIMMDC1-CD80-ARHGAP31***	**119116150**	**rs9884090**	**Yes**	**A**	**0.16**	**13**	**1.89E-10**	**0.83**	**0.92**	**0**	-	**Intronic**
3	*IL12A*	159733527	rs589446	Yes	T	0.35	11	1.95E-10	0.86	0.85	0	-	ncRNA intronic
4	***DGKQ***	**965779**	**rs11724804**	**Yes**	**A**	**0.44**	**12**	**5.31E-11**	**1.17**	**0.24**	**21.04**	-	**Intronic**
4	***NFKB1***	**103449041**	**rs230534**	**Yes**	**T**	**0.34**	**10**	**5.38E-09**	**1.15**	**0.92**	**0**	-	**Intronic**
5	*TNIP1*	150455732	rs3792783	Yes	G	0.16	14	2.42E-12	1.20	0.03	47.41	-	Intronic
6	*ATG5*	106734040	rs633724	Yes	T	0.35	14	2.84E-09	1.13	0.31	13.41	-	Intronic
7	*IRF5-TNPO3*	128651522	rs36073657	Yes	T	0.10	12	3.10E-21	1.40	0.21	23.35	-	Intronic
7	*IRF5-TNPO3*	128658739	rs12155080	No	G	0.37	13	2.87E-13	0.85	0.69	0	2.22E-07	Intronic
8	***FAM167A-BLK***	**11343973**	**rs2736340**	**Yes**	**T**	**0.24**	**14**	**3.33E-21**	**1.24**	**0.17**	**26.76**	-	**Intergenic**
8	***RAB2A-CHD7***	**61564964**	**rs685985**	**Yes**	**T**	**0.47**	**11**	**3.82E-08**	**0.87**	**0.15**	**30.84**	-	**Intergenic**
11	***CDHR5-IRF7***	**618172**	**rs6598008**	**Yes**	**A**	**0.44**	**4**	**1.97E-08**	**0.80**	**0.16**	**42.27**	-	**Intronic**
11	***TSPAN32,CD81-AS1***	**2348619**	**rs2651804**	**Yes**	**T**	**0.17**	**12**	**2.54E-10**	**0.82**	**0.67**	**0**	-	**Intergenic**
11	***DDX6***	**118639353**	**rs11217020**	**Yes**	**A**	**0.20**	**14**	**2.08E-11**	**0.84**	**0.80**	**0**	-	**Intronic**
15	*CSK*	75077367	rs1378942	Yes	C	0.39	13	1.84E-14	1.18	0.90	0	-	Intronic
16	***IRF8***	**85971922**	**rs11117420**	**Yes**	**C**	**0.19**	**12**	**3.82E-15**	**0.81**	**0.47**	**0**	-	**Intergenic**
17	***IKZF3-GSDMB***	**38063381**	**rs883770**	**Yes**	**T**	**0.50**	**14**	**4.79E-09**	**1.13**	**0.75**	**0**	-	**Intronic**
17	***NUP85-GRB2***	**73224639**	**rs1005714**	**Yes**	**G**	**0.20**	**13**	**1.87E-08**	**0.85**	**0.68**	**0**	-	**Intronic**
19	*IL12RB1*	18193191	rs2305743	Yes	A	0.20	12	4.64E-10	0.83	0.28	16.88	-	Intronic

The new genome-wide significant loci for systemic sclerosis are highlighted in bold. *NAB1*-rs16832798 *p* value conditioned on conditioned on *STAT4*-rs3821236 and *STAT4*-rs4853458. For those intronic or regulatory SNPs that are located in a high gene density region, the gene they lie in was underlined

Bp base pair, *Chr* chromosome, *MAF* minor allele frequency in the 1000 Genome Project European Population, *N* number of cohorts, *OR* odds ratio, *Pcond p* value conditioned on index SNP, *Ref.* reference allele, *SNP* single-nucleotide polymorphism

Lopez-Isaac E et al. Nat Comm 2019

L’épigénétique – microARN et encore…



- Les mécanismes épigénétiques dérégulés dans la SSc sont encore loin d’ être précisés
- En dehors des microARN d’autres mécanismes sont impliqués comme la méthylation de l’ADN et les modifications des histones

Angiolilli C et al. Nat Rev Rheumatol 2019

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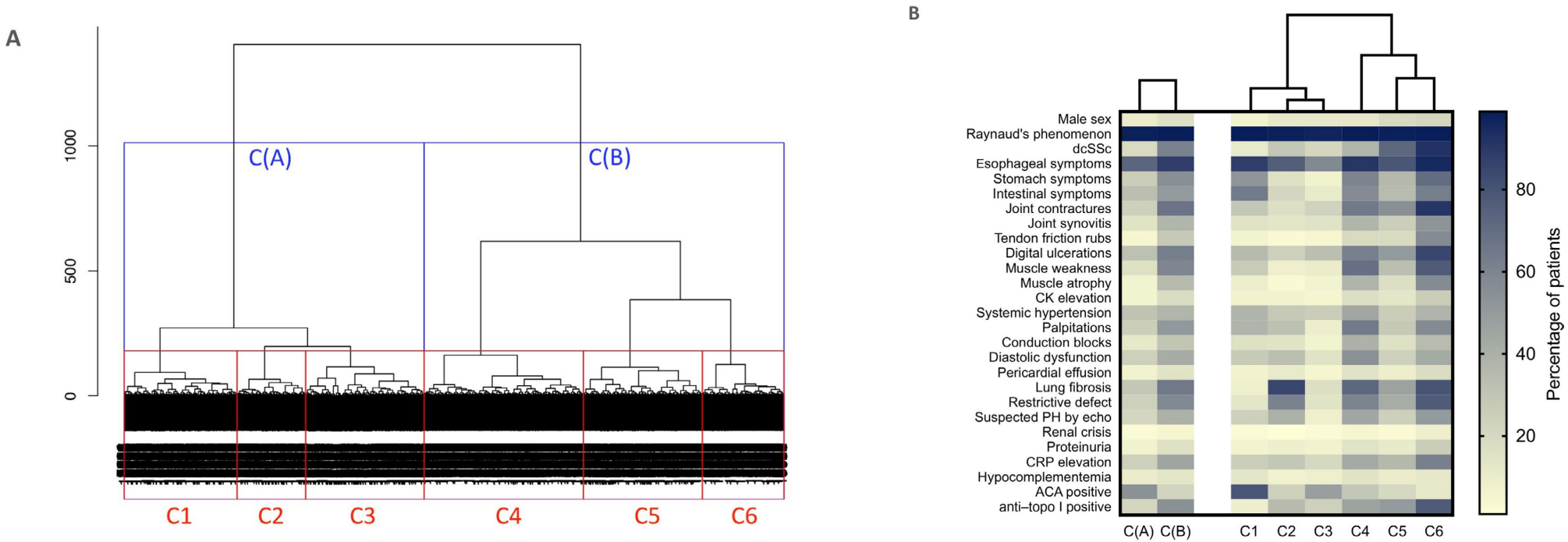
Une nouvelle classification ‘data-driven’

Arthritis & Rheumatology
Vol. 71, No. 9, September 2019, pp 1553–1570
DOI 10.1002/art.40906

American College of Rheumatology
Empowering Rheumatology Professionals

Phenotypes Determined by Cluster Analysis and Their Survival in the Prospective European Scleroderma Trials and Research Cohort of Patients With Systemic Sclerosis

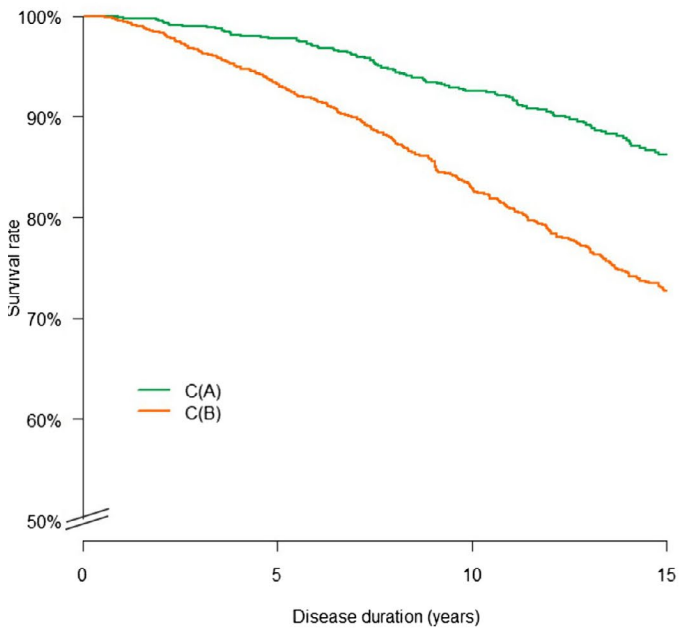
Vincent Sobanski,[1] Jonathan Giovannelli,[2] Yannick Allanore,[3] Gabriela Riemekasten,[4] Paolo Airò,[5] Serena Vettori,[6] Franco Cozzi,[7] Oliver Distler,[8] Marco Matucci-Cerinic,[9] Christopher Denton,[10] David Launay,[1] Eric Hachulla,[1] and the EUSTAR Collaborators



A

CLUSTER A 3149 PATIENTS	• < 1/3 of patients with complications such as intestinal symptoms, DU, joint, muscle and cardiac involvement
CLUSTER B 3778 PATIENTS	• Slightly younger patients • Lower age at disease onset • > 50% of patients with intestinal involvement, joint contractures, DU and ILD

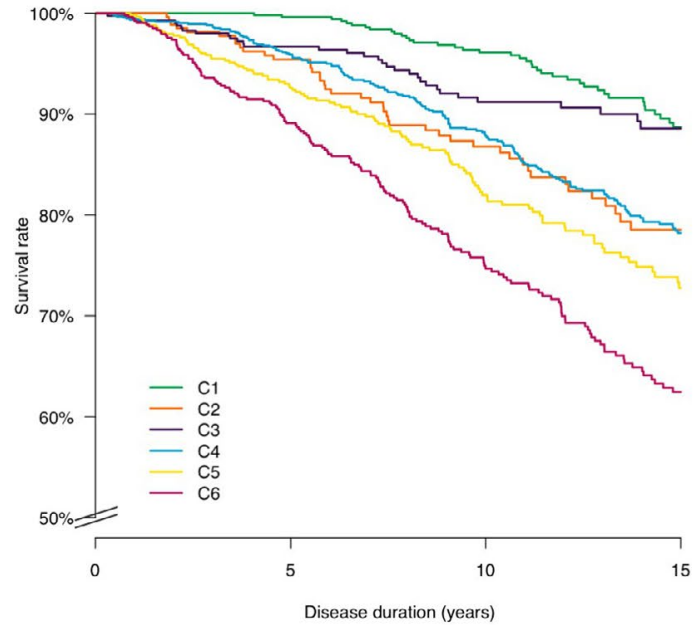
C



A

CLUSTER 1 1186 PATIENTS	• Highest percentage of females • Older onset • High rate of GI involvement • Lowest proportion of ILD
CLUSTER 2 720 PATIENTS	• High proportion of ILD • High rate of suspected PH • Lowest proportion of joint and muscular involvement
CLUSTER 3 1243 PATIENTS	• Younger onset • Lowest mRSS • Less aggressive disease • Highest DLCO % predicted
CLUSTER 4 1673 PATIENTS	• Older onset • High rate of DU • Highest proportion of cardiac involvement
CLUSTER 5 1249 PATIENTS	• Younger onset • Multiple and moderate organ involvements
CLUSTER 6 856 PATIENTS	• Youngest onset • Most aggressive disease • Highest proportion of joint contractures and renal crisis

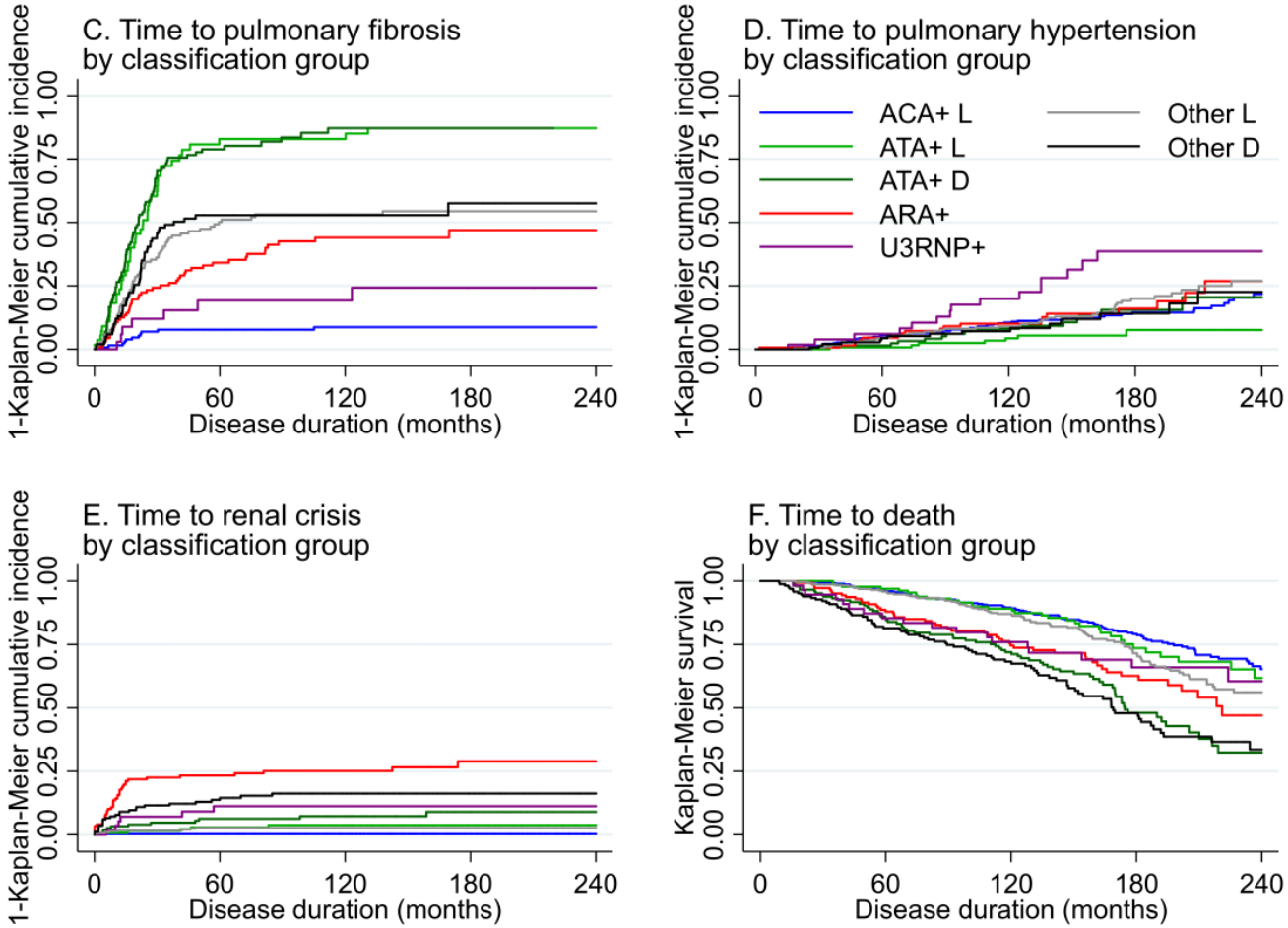
C



Sobanski V et al, Arthritis Rheumatol 2019

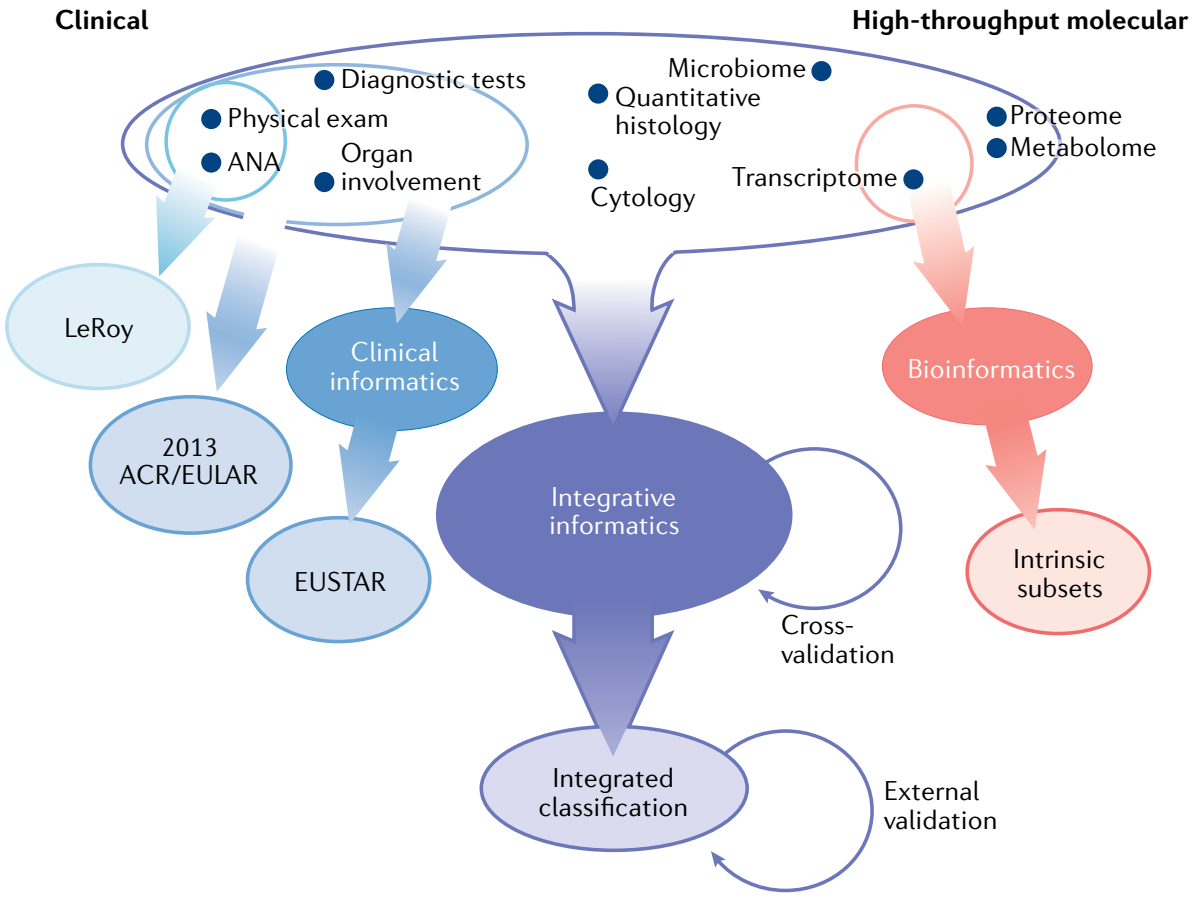
Reclassification sur la base des autoanticorps et du type d'atteinte cutanée

- Étude monocéntrique britannique
- Environ 1300 patients suivis
- 7 groups distincts sur la base de la survenue des complications d'organe et de la mortalité
  - ACA+ L
  - ATA+ L
  - ATA + D
  - ARA+
  - U3RNP+
  - Other L
  - Other D



Nithyianova et al, Arthritis Rheumatol 2019

Peut-on viser encore plus loin?



Hinchcliff M et al. Nat Rev Rheumatol 2019

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Consensus d'experts sur les mesures d'évaluation clinique dans le suivi

1. Domain: Raynaud's phenomenon
Symptoms: Frequency and severity of attacks

2. Domain: Skin and mucosa
Symptoms: Skin changes (worsening or improvement; patient reported)
Clinical assessment: Puffy fingers, modified Rodnan Skin Score (mRSS), telangiectasias, calcinosis

3. Domain: Musculoskeletal
Symptoms: Muscle weakness and stiffness
Clinical assessment: Puffy fingers, joint contractures, arthritis, calcinosis, tendon friction rub count

4. Domain: Digital ulcers
Symptoms: Fingertip ulcers, finger ulcers proximal of DIP joints, development of new ulcers during the last year, coexisting conditions relevant for perfusion (ie, diabetes), smoking status

5. Domain: Lung
Symptoms: Dyspnoea
Functional assessment: Functional class (NYHA 1–4)
Clinical assessment: Basal lung crackles on auscultation
Investigation: Lung function test and DLCO

6. Domain: Heart
Symptoms: Dyspnoea
Functional assessment: Functional class (NYHA 1–4),
Clinical assessment: Leg oedema
Investigation: ECG, Doppler-echocardiography, heart rate, blood pressure
Others: Concurrent heart disease

7. Domain: Gastrointestinal
Symptoms: Night and day time heart burn/reflux, dysphagia, diarrhoea, weight loss
Clinical assessment: Weight

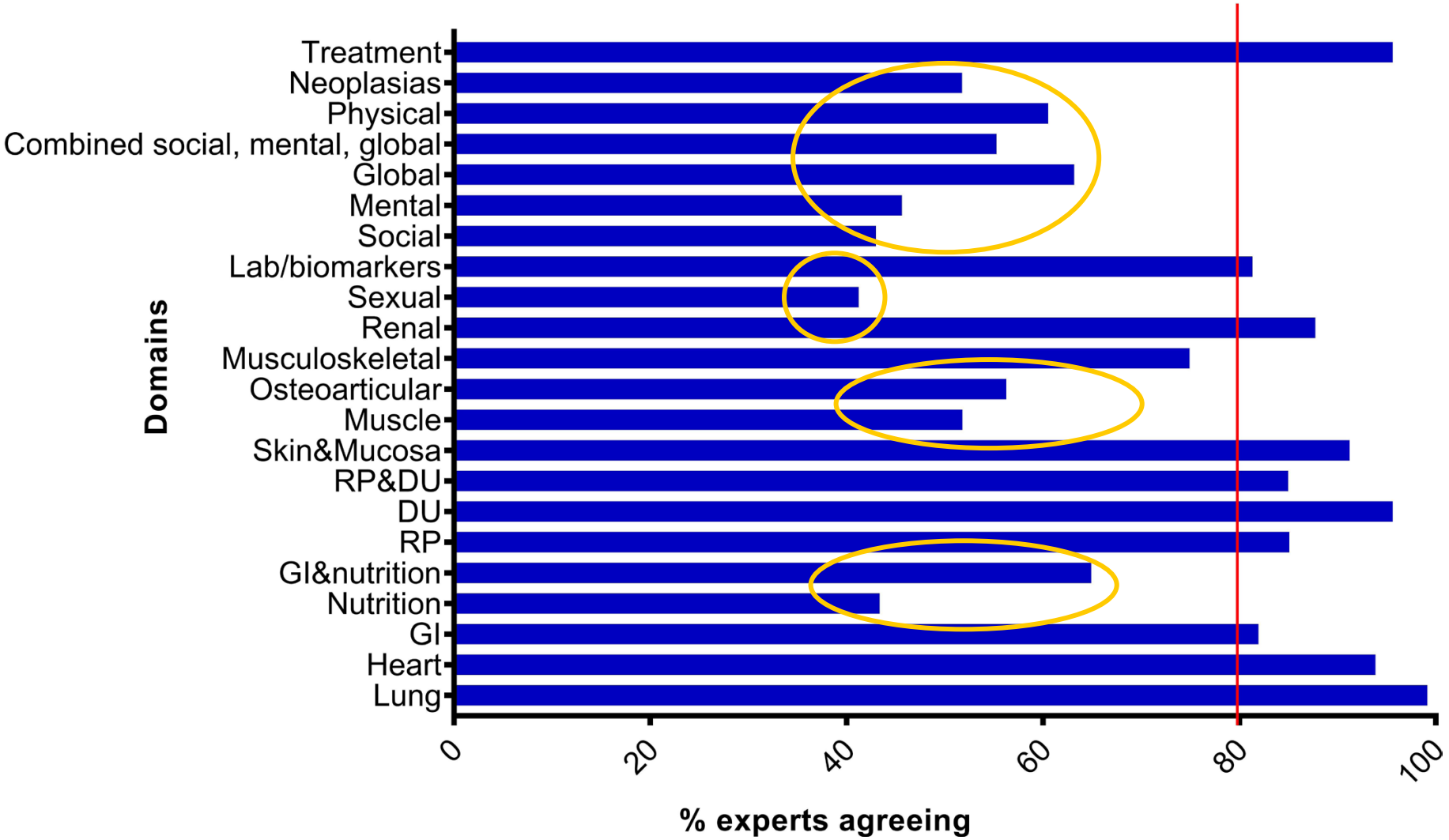
8. Domain: Renal
Investigation: Serum creatinine, eGFR, urine analysis, blood pressure

9. Domain: Laboratory
Investigation: Acute phase reactants, creatine kinases, haematology, renal function test, liver function test

10. Domain: Treatment
Type of treatment (generic and name of drug), date of initiation, date of finalisation of every medication

Hoffmann-Vold A et al, RMD 2019

Unmeet needs



Hoffmann-Vold A et al, RMD 2019

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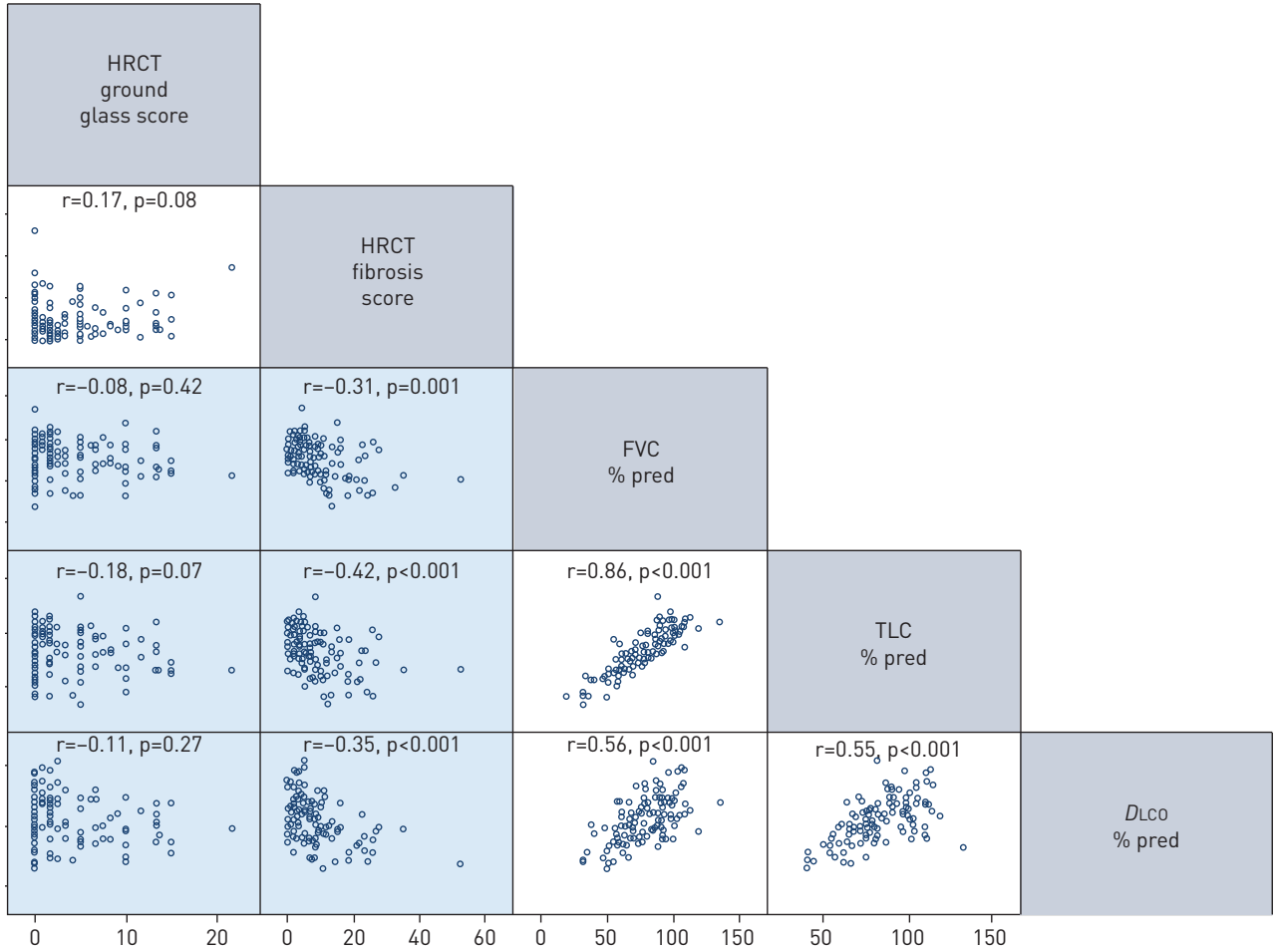
ILD dans la SSc: la valeur combinée du scanner et des EFRs



- Les algorithmes de traitement actuels sont fondés sur l'extension des altérations scannographiques et, si indéterminés, sur la valeur de la CVF
- Une étude Nord-Américaine nous révèle les associations entre des scores quantitatifs et la pathophysiologie pulmonaire
- Les associations entre scores HRCT et volumes sont significatives mais faibles (raisons intrinsèques, coexistence des altérations vasculaires pulmonaires, digestives (RGO), CPFE)
- Les informations fournies par ces examens sont complémentaires
- Le pattern radiographique devrait être analysé plus robustement dans les RCT comme mesure de sévérité

Jhajj A et al Eur Respir J 2019

The old “new kids on the block”: biomarkers

- Les Biomarqueurs d’intérêt: KL-6, SPD, CCL18, OXL40
- Ils sont discriminateurs au baseline pour le diagnostic
- En combinaison avec un biomarqueur sérologique (anti-Topo 1) sont très fortement associé à la sévérité de la maladie pulmonaire (surtout KL6 et CCl18) au baseline
- Dans le suivi ils sont prédicteurs d’une baisse significative de la CVF (>10%) (CCL18) ou de l’apparition *de novo* d’une maladie extensive (CCL18 et SP-D)
- Dans la cohorte SLS-II un taux élevé de CCL18 et KL-6 identifie les sujets plus à risque de progression à 12 mois
- CCL18 et KL-6 sont susceptibles de modifications après traitement

Elhai M, et al. A&R 2019
Volkmann ER et al. A&R 2019

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La cohorte DeSScipher: les vasodilatateurs et l'atteinte myocardique primitive

- L'atteinte cardiaque est la première cause de mortalité dans la sclérodermie
- La stratégie de prévention primaire spécifique pour la SSc n'est pas clarifiée
- Dans la cohorte DeSScipher sur environ 900 patients
  - L'utilisation des vasodilatateurs est associée à une mineure incidence de arythmies ventriculaires (HR 0.28 0.09-0.9; p=0.03)
  - Les IEC sont associés à une mineur incidence des bloques cardiaques, des anomalies ischémiques à l'ECG, d'implantation de PM (0.46 0.24-0.87; p=0.02)
- Étude internationale, prospective, observationnelle à support de la conduction d'ultérieures études RCT

Vaentini G et al Ann Rheum Dis 2019

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Vasculopathie digitale: consensus sur la classification

Classification, categorization and essential items for digital ulcer evaluation in systemic sclerosis: a DeSScipher/European Scleroderma Trials and Research group (EUSTAR) survey

- Episodic DU (rarely recurrent DU) defined as DU detected only at one follow-up visit and absence of DU at the remaining follow-up visits.
- Recurrent DU (frequently recurrent DU) defined as DU detected at two or more follow-up visits and absence of DU on at least one follow-up visit.
- Chronic DU defined as one or more DU and/or new DU detected at every follow-up visit.

Table 2 Essential clinical items for DU assessment and management

Item	Level of agreement regarding feasibility and usefulness of single items in clinical practice (%)
Number of DU defined as loss of tissue	*91.7*
Recurrent DU	*83.9*
Number of new DU	*73.6*
History of DU	60.9
Gangrene	60.9
Total number of DU	59.8
Infection of DU	58.6
DU distal to the proximal interphalangeal joints	50.6
Previous amputation	49.4
Number of DU due to calcinosis	46.4
Number of DU due to DPS	45.2
Number of healed DU	24.1

Blagojevic J et al Arthritis Res ther 2019

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Vasculopathie rénale

- No gold standard nor classification criteria for SRC
- Heterogeneity of definition in studies of SRC (40 original definitions of SRC identified in a recent literature review)
- The Scleroderma Clinical Trials Consortium (SCTC) SRC Working Group is charged of developing classification criteria for SRC

Butler EA et al, Arthritis Rheumatol 2019

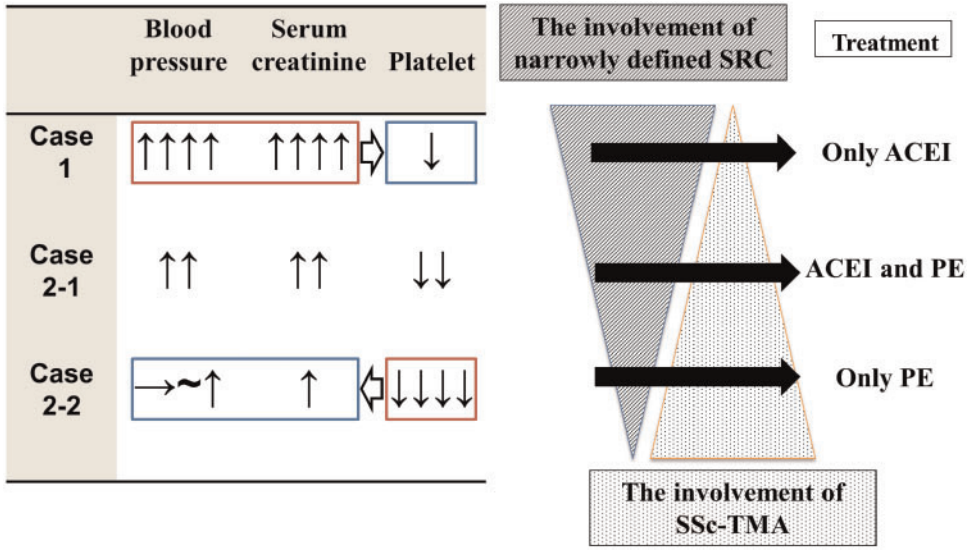
Core set retenu

- Blood pressure
  - Acute increase in blood pressure defined as any of the following:
    - Systolic blood pressure ≥140 mm Hg
    - Diastolic blood pressure ≥90 mm Hg
    - An increase in systolic blood pressure of ≥30 mm Hg above normal
    - An increase in diastolic blood pressure of ≥20 mm Hg above normal
  - Blood pressure measurement should be taken twice, separated by at least 5 minutes; if blood pressure readings are discordant, repeat readings should be taken until 2 consistent readings are obtained
- Kidney injury†
  - Acute kidney injury defined as any of the following:
    - Increase in serum creatinine of ≥26.5 μmoles/liter (≥0.3 mg/dl) within 48 hours
    - Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
    - Urine volume <0.5 ml/kg/hour for 6 hours
- Microangiopathic hemolytic anemia and thrombocytopenia
  - New or worsening anemia not due to other causes
  - Schistocytes or other red blood cell fragments on blood smear
  - Thrombocytopenia ≤100,000 platelets/mm^3, confirmed by manual smear
  - Laboratory evidence of hemolysis, including elevated lactate dehydrogenase, reticulocytosis, and/or low or absent haptoglobin
  - A negative direct antiglobulin test
- Target organ dysfunction
  - Hypertensive retinopathy (hemorrhages, hard and soft [cotton-wool] exudates, and/or disc edema, not attributable to other causes), confirmed by an ophthalmologist
  - Hypertensive encephalopathy, characterized by headache, altered mental status, seizures, visual disturbances, and/or other focal or diffuse neurologic signs not attributable to other causes
  - Acute heart failure, characterized by typical symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema)
  - Acute pericarditis, diagnosed with at least 2 of the 4 following criteria: 1) pericarditis chest pain; 2) pericardial rub; 3) new widespread ST segment elevation or PR segment depression on electrocardiography; 4) pericardial effusion (new or worsening) on cardiac echocardiography
- Renal histopathology
  - Histopathologic findings on kidney biopsy consistent with SRC, which may include the following: Small vessel (arcuate and interlobular arteries) changes that predominate over glomerular alterations. Glomerular changes of thrombotic microangiopathy may be present, with acute changes including fibrin thrombi and endothelial swelling, red blood cell fragments, and mesangiolysis, and chronic changes including double contours of the glomerular basement membrane. Nonspecific ischemic changes with corrugation of the glomerular basement membrane, and even segmental or global sclerosis of glomeruli may occur. Early vascular abnormalities include intimal accumulation of myxoid material, thrombosis, fibrinoid necrosis, and fragmented red blood cells, sometimes resulting in cortical necrosis. Narrowing and obliteration of the vascular lumen lead to glomerular ischemia. Juxtaglomerular apparatus hyperplasia, while relatively rare (10%), can be observed. Late changes are manifested by intimal thickening and proliferation (which lead to characteristic vascular "onion-skin" lesions), glomerulosclerosis, and interstitial fibrosis. Nonspecific tubular changes may also occur, including acute tubular injury in the early stage of injury, and later interstitial fibrosis and tubular atrophy. Since none of these findings are specific for SRC, the pathologic diagnosis must be supported by appropriate clinical and serologic data.

Butler EA et al, Arthritis Rheumatol 2019

Vasculopathie rénale

ISRCS	Expert consensus
Hypertensive SRC Any one of the following: (a) Systolic blood pressure > 140 mmHg, or (b) Diastolic blood pressure > 90 mmHg, or (c) Rise in systolic blood pressure > 30 mmHg compared to baseline, or (d) Rise in diastolic blood pressure > 20 mmHg compared to baseline, or AND One of the following features: (a) Increase in serum creatinine >50% over baseline or serum creatinine >120% of upper limit of normal for local laboratory (b) Proteinuria: >2+ by dipstick and confirmed by protein:creatinine ratio > upper limit of normal (c) Hematuria: >2+ by dipstick or >10 RBCs/HPF (without menstruation) (d) Thrombocytopenia: <100 000 platelets/mm^3 (e) Haemolysis: by blood smear or increased reticulocyte count (f) Hypertensive encephalopathy	*A. Hypertensive SRC (fulfills both A1 and A2)* 1. New onset hypertension, defined as any of the following: (a) Systolic blood pressure ⩾ 140 mgHg (b) Diastolic blood pressure ⩾ 90 mgHg (c) Rise in systolic blood pressure ⩾ 30 mmHg (d) d) Rise in diastolic blood pressure ⩾ 20 mmHg AND 2. One of the following five features: (a) Increase in serum creatinine by 50+% over baseline or serum creatinine ⩾120% of upper limit of normal for local laboratory (b) Proteinuria ⩾2+ by dipstick (c) Hematuria ⩾2+ by dipstick or ⩾10 RBCs/HPF (d) Thrombocytopenia: <100 000 platelets/mm^3 (e) Haemolysis defined as anaemia not due to other causes and either of the following: (i) Schistocytes or other RBC fragments seen on blood smear (ii) increased reticulocyte count
Normotensive SRC Increase in serum creatinine >50% over baseline OR serum creatinine >120% of upper limit of normal for local laboratory AND One of the following features: (a) Proteinuria: >2+ by dipstick and confirmed by protein:creatinine ratio > upper limits of normal (b) Hematuria: >2+ by dipstick or >10 RBCs/HPF (without menstruation) (c) Thrombocytopenia: <100 000 Platelets/mm^3 (d) Haemolysis: by blood smear or increased reticulocyte count (e) Hypertensive encephalopathy	*B. Normotensive SRC (fulfills both B1 and B2)* 1. Increase in serum creatinine >50% over baseline or serum creatinine ⩾120% of upper limit of normal for local laboratory AND 2. One of the following five features: (a) Proteinuria ⩾2+ by dipstick (b) Hematuria ⩾2+ by dipstick or ⩾10 RBCs/HPF (c) Thrombocytopenia: <100 000/mm^3 (d) Haemolysis defined as anaemia not due to other causes and either of the following: (i) Schistocytes or other RBC fragments seen on blood smear (ii) Increased reticulocyte counted renal biopsy findings consistent with scleroderma renal crisis (microangiopathy)



Yamashita H et al. Rheumatol 2019

- Pathogénèse
- Classification
- Clinique:
  - Atteinte pulmonaire
  - Atteinte cardiaque
  - Atteinte Vasculaire périphérique
  - Atteinte rénale
- **Facteurs prédictifs d'évolution défavorable**

L’indice d’activité EUSTAR

Table 4 Revised EUSTAR index

Item	Weight
Δ-Skin	1.5
Digital ulcers	1.5
mRss>18 or for mRss up to 18	1.5 Score×0.084
TFR	2.25
CRP>1 mg/dL	2.25
DLCO<70% of the predicted value	1.0

Valentini G et al. Ann Rheum Dis 2017

Table 1 Epidemiological, serological and clinical features at baseline (n=549)

Sex, F/M	445/104
Age at entry in the registry, years, mean (SD)	51.9 (±13.6)
Age at Raynaud’s onset, years, mean (SD)	46.5 (±14.3)
Age at first non-Raynaud’s feature, years, mean (SD)	49.8 (±13.7)
ANA positive (n, %)	529 (96.3)
Anti-Scl-70 positive (n, %)	217 (39.5)
Anticentromere positive (n, %)	178 (32.4)
Anti-PmScl positive (n, %)	10 (1.8)
Anti-U1RNP positive (n, %)	10 (1.8)
Anti-RNA polymerase III positive (n, %)	10 (1.8)
Limited SSc (n, %)	370 (67.3)
Diffuse SSc (n, %)	179 (32.6)

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L’indice d’activité EUSTAR

- L’indice d’activité est le meilleur prédicteur de progression de sévérité évalué à 2 ans par score de Medsger

Adjusted mean EUSTAR-AI	1.43 (1.23 to 1.66)	ΔMedsger’s severity score ≥1	0,002	9.49
Adjusted mean ESScG-AI	0.98(0.75 to 1.28)		0.92	0.007
Age	1.00 (0.99 to1.02)		0.32	0.95
ESR >25	1.01 (0.59 to 1.73)		0.95	0.003
Anti-Scl-70 Ab	1.51 (0.94 to2.44)		0.08	2.96
Subset diffuse	0.80 (0.48 to 1.31)		0.38	0.76
Adjusted mean EUSTAR-AI	1.23 (1.06 to 1.42)	ΔLung severity score ≥1	0.006	7.45
Adjusted mean ESScG-AI	1.09 (0.83 to 1.43)		0.11	0.44
Basal lung severity	0.57 (0.35 to 0.92)		0.01	0,006
Anti-Scl-70 Ab	1.27(0.75 to 2.15)		0.35	0.84
Subset diffuse	0.79 (0.46 to 1.36)		0.40	0.69
Adjusted mean EUSTAR-AI	1.96(1.10 to 3.50)	ΔHeart severity score ≥1	0.02	5.20
Adjusted mean ESScG-AI	0.52 (0.24 to 1.12)		0.09	2.75
Age	1.02 (0.98 to 1.07)		0.26	1.24
RNA polymerase III Ab	5.56 (0.65 to 6.98)		0.11	2.48
Subset diffuse	0.24 (0.04 to 1.42)		0.11	2.45
Basal vascular severity	1.08 (0.28 to 4.16)		0.90	0.01
Basal joint severity	2.71 (0.69 to 10.70)		0.15	2.04
Basal lung severity	1.04 (0.26 to 4.01)		0.95	3
Adjusted mean EUSTAR-AI	1.48 (1.21to1.82)	ΔSkin severity score ≥1	0,0002	14.29
Age	0.97 (0.95 to 0.99)		0.003	4.40
Baseline skin severity	0.21 (0.09 to 0.47)		0.0002	14.27
Adjusted mean ESScG-AI	1.34 (0.90 to 2.00)		0.13	2.17
Anti-Scl-70 Ab	2.16 (0.85 to 5.50)		0.10	2.65
Adjusted mean EUSTAR-AI	1.31 (1.13 to 1.52)	ΔPeripheral vascular severity score ≥1	0.0002	5.18
Adjusted mean ESScG-AI	1.02 (0.76 to 1.37)		0.87	0.02
Basal lung severity	1.94 (1.03 to 3.64)		0.03	4.26
Basal vascular severity	0.23 (0.13 to 0.39)		<0.0001	29.61
Anti-Scl-70 Ab	1.46 (0.75 to 2.48)		0.26	1.24
Subset diffuse	1.36 (0.74 to 2.48)		0.30	1.02
Adjusted mean EUSTAR-AI	0.86 (0.45 to 1.64)	ΔMuscle severity score ≥1	0.66	0.19
Adjusted mean ESScG-AI	1.49 (0.66 to 3.34)		0.33	0.94
Subset diffuse	0.69 (0.12 to 3.81)		0.67	0.17
RNA polymerase III Ab	8.32 (1.21 to 6.88)		0.03	4.66
Adjusted mean EUSTAR-AI	1.21 (0.15 to 9.32)	ΔKidney severity score ≥1	0.85	0.03
Adjusted mean ESScG-AI	1.24 (0.19 to 7.89)		0.59	0.28
Adjusted mean EUSTAR-AI	1.20 (0.40 to 3.53)	ΔGI tract severity score ≥1	0.73	0.11
Adjusted mean ESScG-AI	1.37 (0.32 to 5.76)		0.66	0.18

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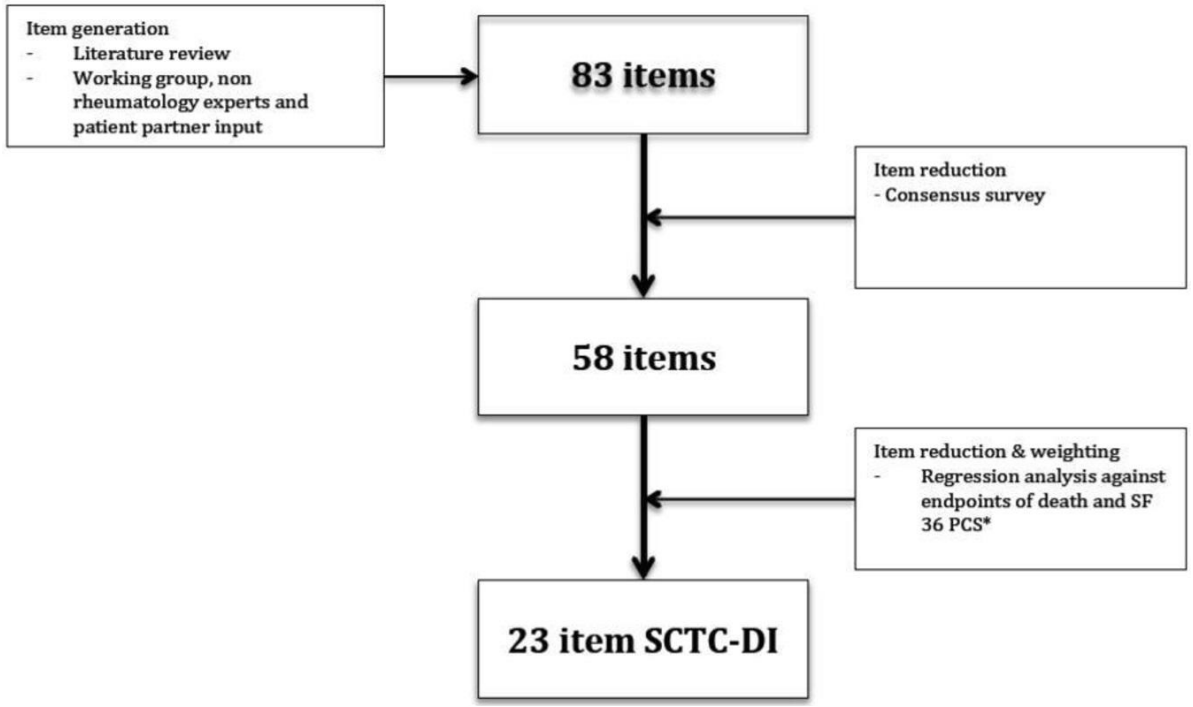
Development and validation of the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI): a novel instrument to quantify organ damage in systemic sclerosis

Nava Ferdowsi,[1,2] Molla Huq,[1,2] Wendy Stevens,[2] Marie Hudson,[3] Mianbo Wang,[4] Tien Tay,[1,2] Jodie L Burchell,[1] Sam Mancuso,[1] Candice Rabusa,[2] Vijaya Sundararajan,[5] David Prior,[1] Susanna M Proudman,[6] Murray Baron,[7] Mandana Nikpour,[1,2] The Scleroderma Clinical Trials Consortium Damage Index Working Group, The Australian Scleroderma Interest Group, Canadian Scleroderma Research Group



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Le score de dommage SCTC

Item	Score
Musculoskeletal and skin	
Joint contracture defined as any degree of contracture with the inability to reduce the joint to the anatomically neutral position in any small joint of the fingers.*†	2
Joint contracture defined as any degree of contracture with the inability to reduce the joint to the anatomically neutral position in the large joints, specifically elbows and knees.*†	2
Sicca symptoms defined as presence of dry eyes and/or dry mouth requiring treatment on a daily basis, for example, lubricant eye-drops, punctual plugs, saliva replacement.*	3
Proximal muscle weakness on clinical examination defined as shoulder abduction and/or hip or knee flexion less than 5/5 power (not due to contracture or pain).*	3
Calcinosis complicated by infection or requiring surgery.	4
Vascular	
Digital ulceration defined as loss of epithelialisation, of any degree, of the epidermis, the dermis and/or the subcutaneous tissue, distal to or at the proximal interphalangeal joint of the hands or feet not thought to be due to trauma and refractory to therapy* Add 1 if digital amputation required (surgical or autoamputation).	2 1
Gastrointestinal	
Oesophageal dysmotility defined as distal dysphagia refractory to treatment, with differential diagnoses (eg, oesophageal stricture or malignancy) excluded by endoscopy.	1
Oesophageal stricture confirmed on testing such as endoscopy or barium swallow.	1
Symptoms of gastro-oesophageal reflux disease (heart burn) refractory to treatment (eg, proton pump inhibitors) and confirmed on endoscopy.*	1
Gastric antral vascular ectasia confirmed on endoscopy.	2
Pseudo-obstruction with symptoms such as vomiting or constipation, with dilatation of the small and/or large bowel on imaging.	3
Low body mass index of <18.5 kg/m^2 or weight loss of >10% in the last 12 months.	2
Respiratory	
Moderate to severe interstitial lung disease >20% extent on HRCT of the chest Add 4 points if forced vital capacity <70% on lung function tests (not due to respiratory muscle weakness).*	2 4
Dependence on home oxygen.	5
Cardiovascular	
Pulmonary arterial hypertension (defined as mean pulmonary arterial pressure ≥25 mm Hg at rest and pulmonary arterial wedge pressure ≤15 mm Hg on right heart catheterisation) Add 5 if moderate to severe right ventricular dysfunction noted on echocardiography report based on assessment of any measure of RV function by experienced cardiologist.	2 5
Myocardial disease attributable to SSc based on a constellation of clinical features and supportive investigations, for example, syncope secondary to conduction abnormality, arrhythmia requiring defibrillator, heartblock requiring permanent pacemaker or ablation, systolic or diastolic dysfunction on TTE.	3
Presence of moderate to large pericardial effusion equivalent to greater than 1 cm on TTE.*	1
Renal	
History of scleroderma renal crisis (SRC), either hypertensive or normotensive, as defined by the International Scleroderma Renal Crisis Study Investigators.[45]	3
► Add 1 if history of SRC or other SSc-related kidney disease and persistent renal impairment with estimated glomerular filtration rate <45 mL/min/1.73 m^2	1
► Add 2 if SRC with stage 5 renal impairment and need for renal replacement therapy	2

- Score maximal 55
- low damage score <5,
- moderate damage score 6–12,
- high damage score ≥13

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Changement des mesures d'évaluation

- Le mRSS est-il une bonne mesure de outcome?
- Faut-il chercher des mesures composites d'outcome?
- Comment enrichir les cohortes avec les patients à risque?
- Proposition (consensus d'experts):
  - Survenue d'une crise rénale ; baisse de la CVF (CVF)≥10%; survenue d'une FEVG <45% ou diminution de la FEVG >10% pour ceux avec une FEVG initiale <45%; survenue d'une HTP diagnostiqué par ETT; ou décès

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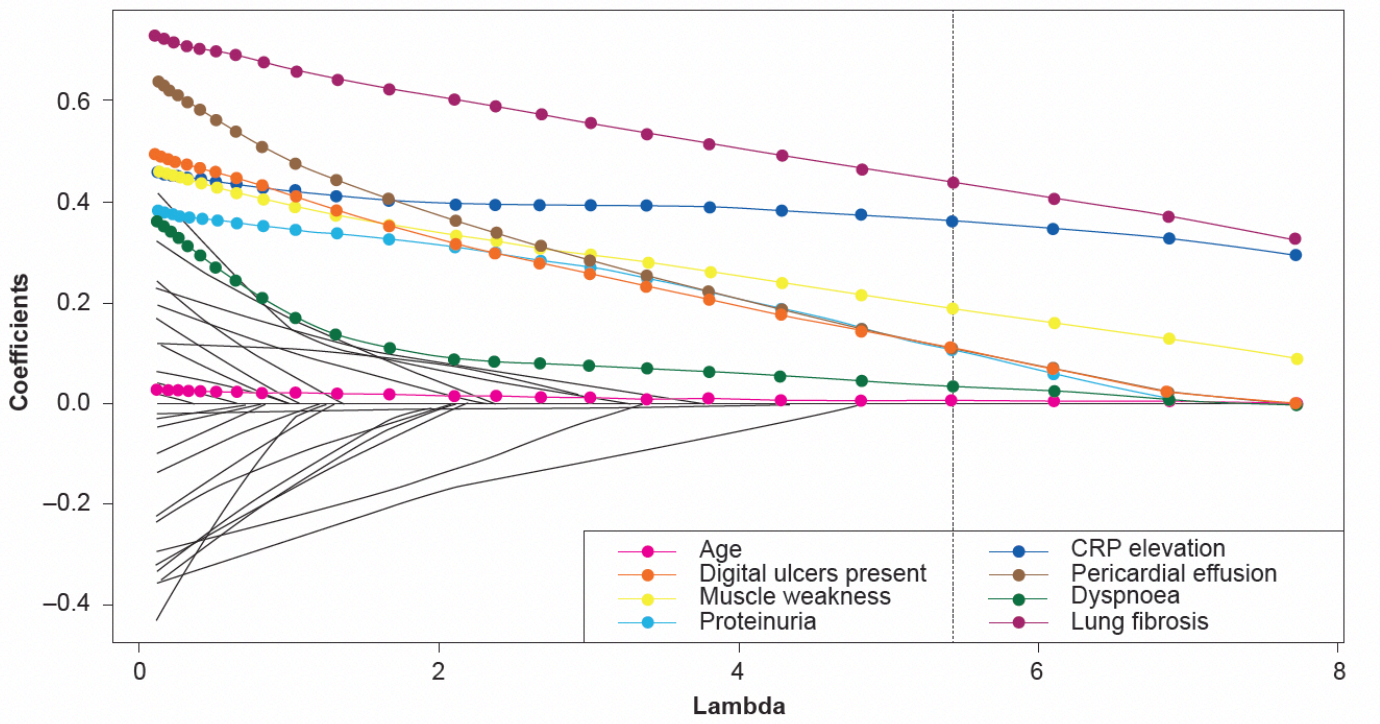
Database EUSTAR: subset diffus



Other risk factors*	Age			Patient numbers†
	60 years	65 years	70 years	
Lung fibrosis	37.5	40.4	43.3	131/666
Lung fibrosis and CRP elevation	52.0	55.0	57.9	47/650
Active DU	30.9	33.5	36.1	126/697
Lung fibrosis and active DU	49.7	52.6	55.6	31/662
Muscle weakness	30.9	33.5	36.2	164/701
Lung fibrosis, muscle weakness and active DU	61.8	64.6	67.3	16/660
Lung fibrosis, muscle weakness, CRP elevation and active DU	74.5	76.7	78.8	8/646

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Conclusions

- Révolution de la classification à partir des données cliniques (et possible futur rôle des –omiques avec l'analyse statistique informatisée des '*big data*')
- Rôle des centres de référence pour l'homogénéisation d'un suivi complexe et multidisciplinaire
- Amélioration des instruments clinimétriques pour la mise à point des nouvelles mesures d'outcome
- Enrichissement des cohortes pour une meilleure inclusion dans les RCT