Nouvelle classification des myopathies inflammatoires, implications pour le pneumologue

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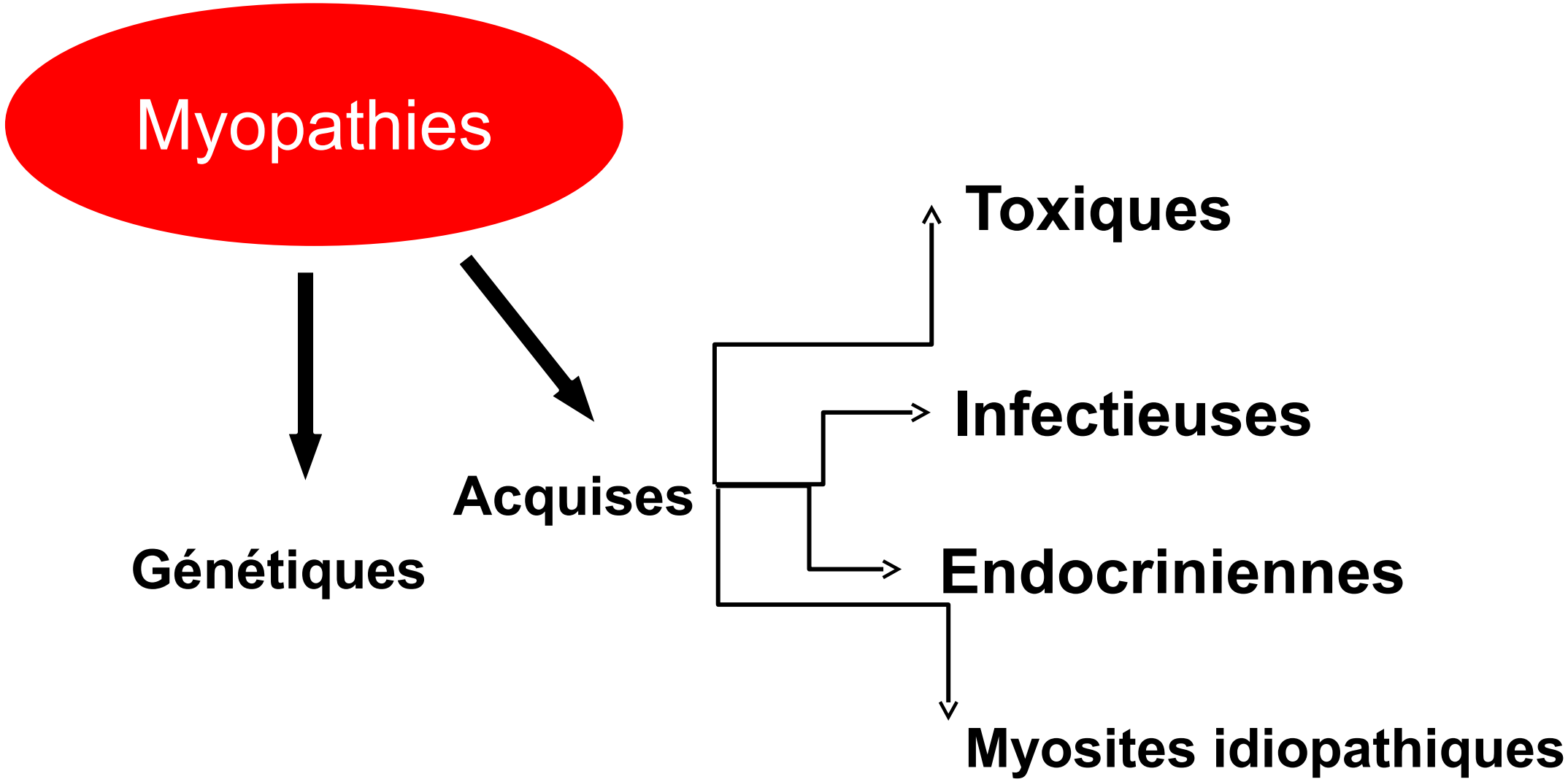
Département de Méde de référence Myosite


Myopathies
Génétiques
Acquises
Toxiques
Infectieuses
Endocriniennes
Myosites idiopathiques

The NEW ENGLAND JOURNAL of MEDICINE

February 13, 1975

N Engl J Med 1975; 292:344-347

DOI: 10.1056/NEJM197502132920706

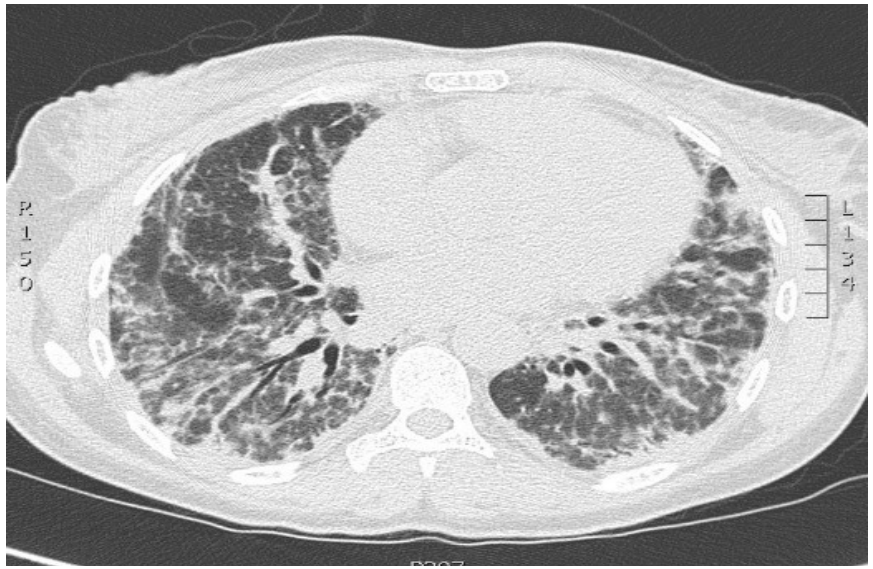
Polymyositis and Dermatomyositis

Anthony Bohan, M.D., and James B. Peter, M.D., Ph.D.

1. **Déficit musculaire bilatéral et symétrique**
2. **Elévation des enzymes musculaire (CK, Transaminases, LDH)**
3. **EMG (Myogène)**
4. **Anomalie à la biopsie musculaire (Nécrose/régénération, inflammation)**
5. **Erythéme typique**

Myopathies auto-immunes
Des maladies très hétérogènes

- Femme 42 ans
- Toux sèche – fébrile : 3,5 s
- Dyspnée : 2 s
- Hospitalisée en médecine : 1s
- Réanimation : 3 j

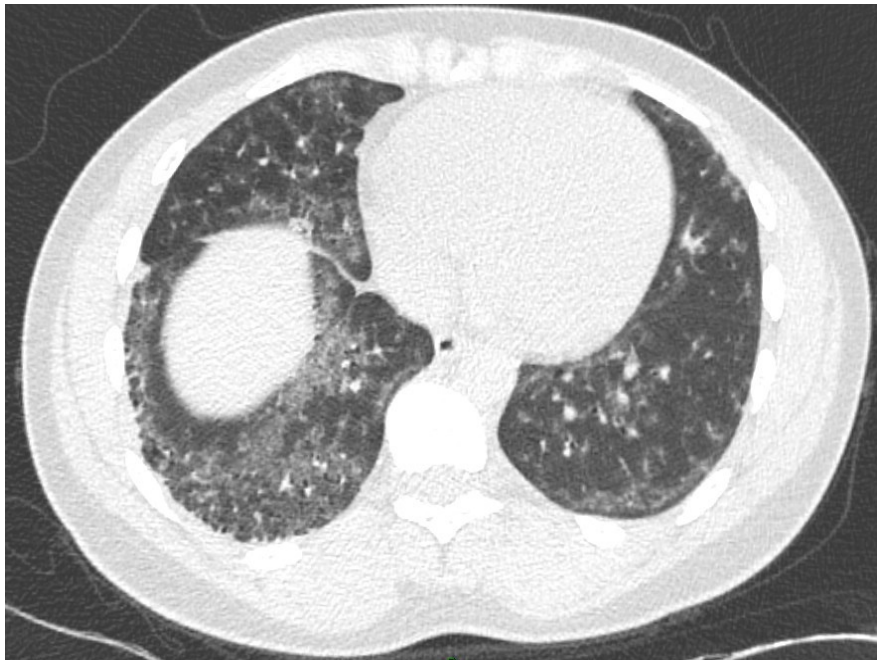


PaO2/Fio2 = 55% - DV - TDM DAD

DM MDA5+

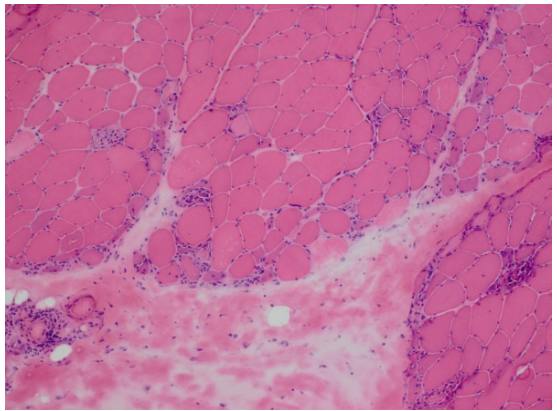
- 38,2 °C
- CRP 56 mg
- Cholestase
- CK normale

- F 21 ans Martiniquaise
- Dyspnée + Toux 3 mois
- NYHA II
- Crépitants aux bases
- PaO2 69 mmHg – PaCO2
- TVR – DLCO 72%

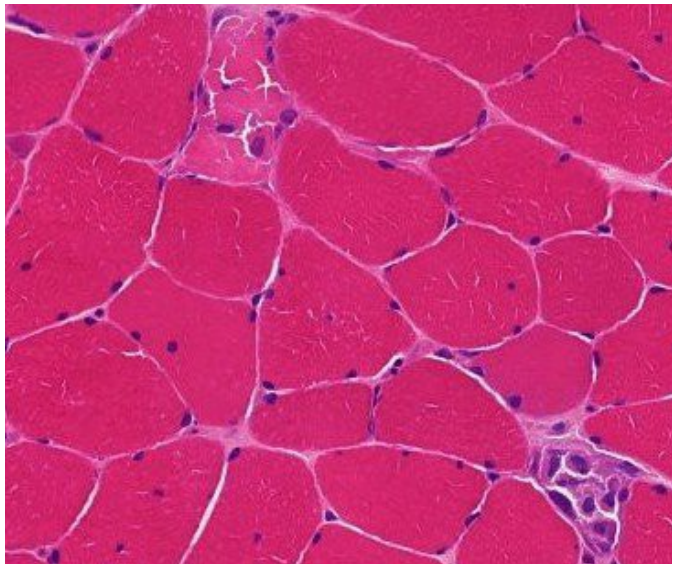


SAS – Jo-1

- Myalgies – CK 800
- Arthralgies
- Raynaud mains de Méca

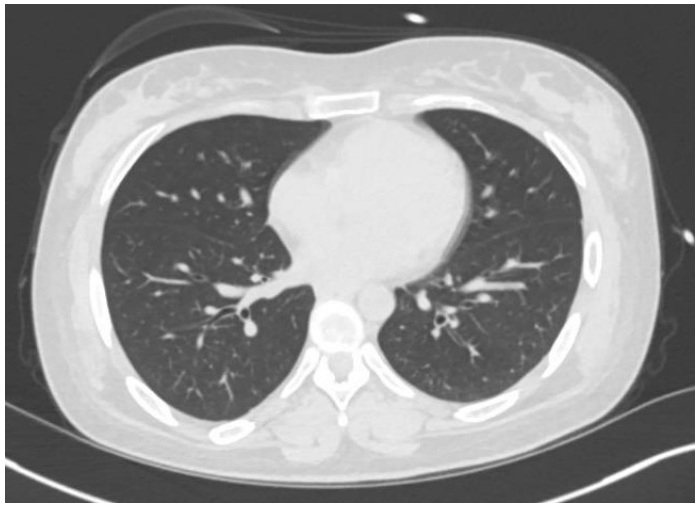


- H 32 ans
- tétraparésie (plusieurs mois)
- CK - 5000
- Dégradation sous traitement
- TVR1/5

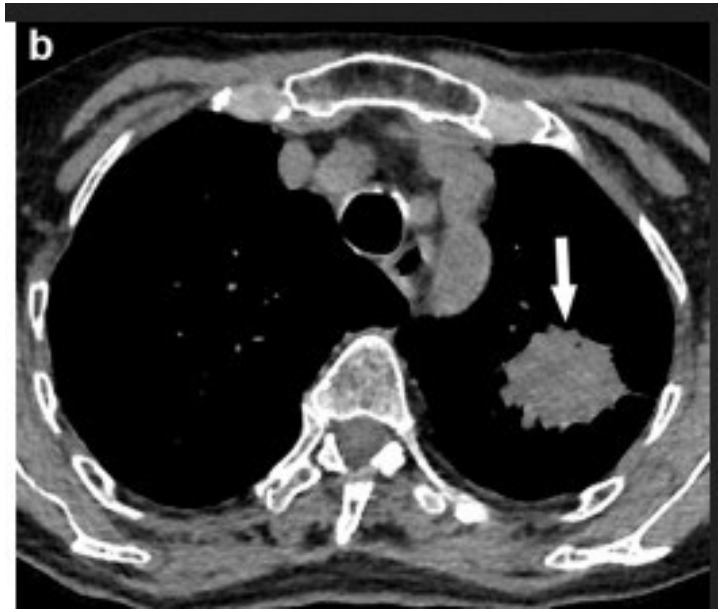


MNAI – SRP+

- Dyspnée repos
- PaO2 75 – PaCO2 56 – Ph 7,36
- IOT - trachéotomisé

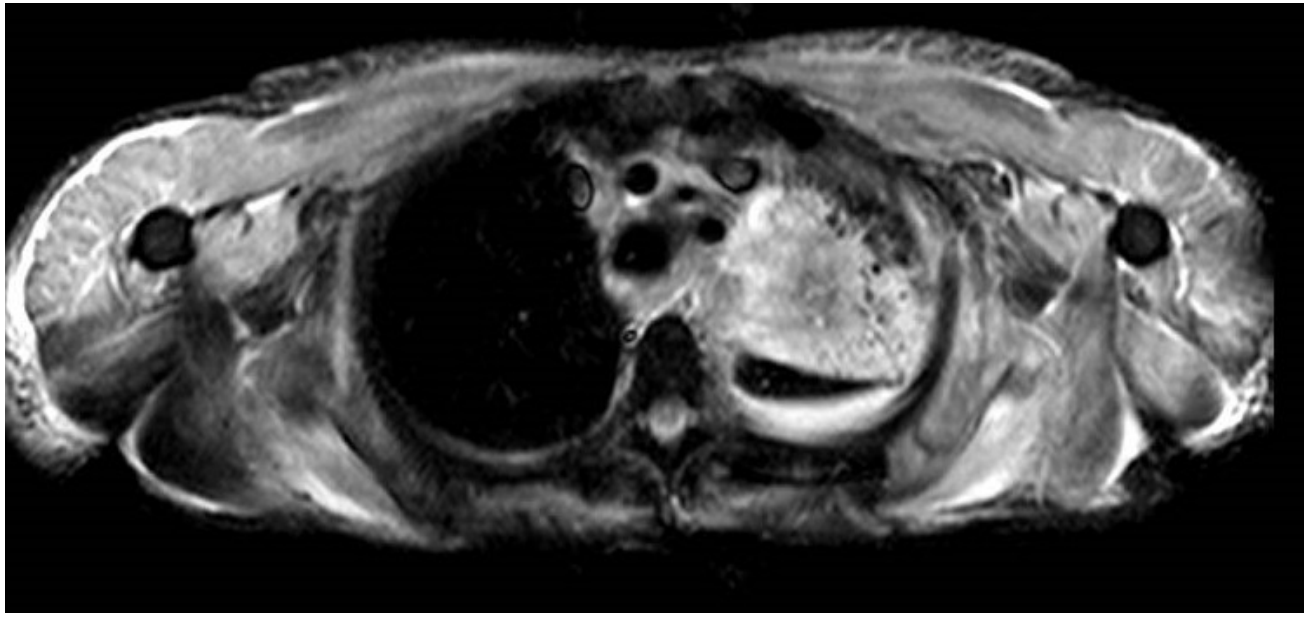


- H 61 ans
- adénocarcinome T3N0M0 au LSD

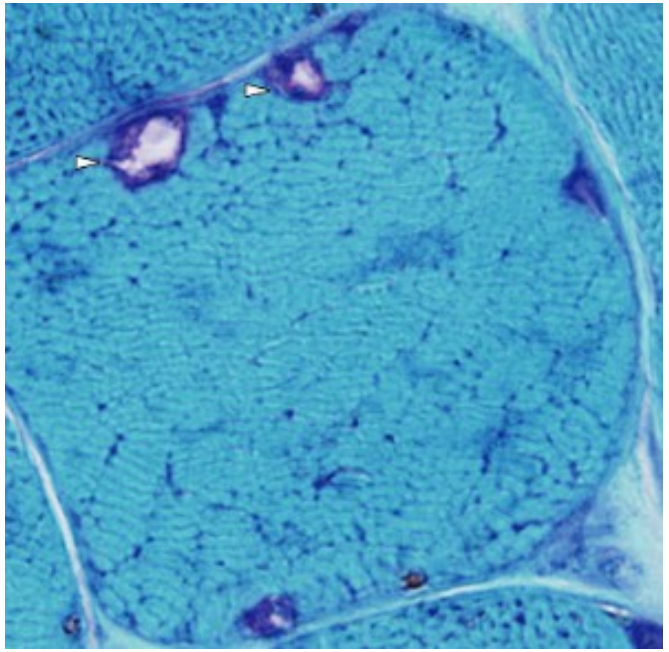


DM – NXP2 +CANCER

- Tétraparésie 2/5
- Fausse route
- CK 5000
- Oedème des 4 Membres

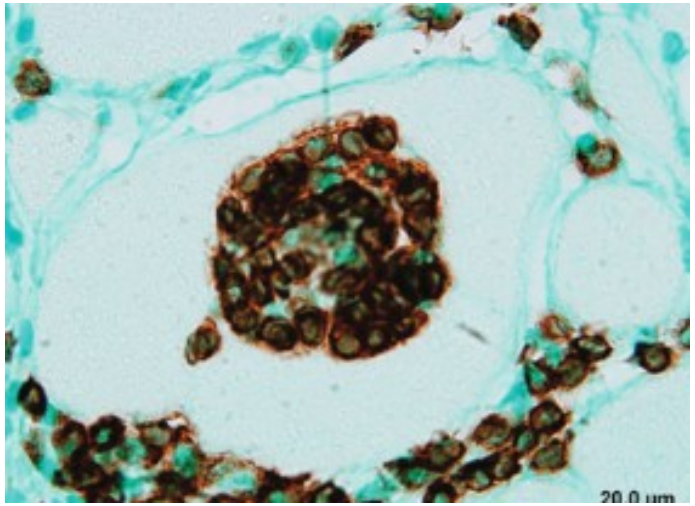


- H 68 ans
- Déficit moteur progressif
- Asymétrique
- Proximal et distal
- CK 500



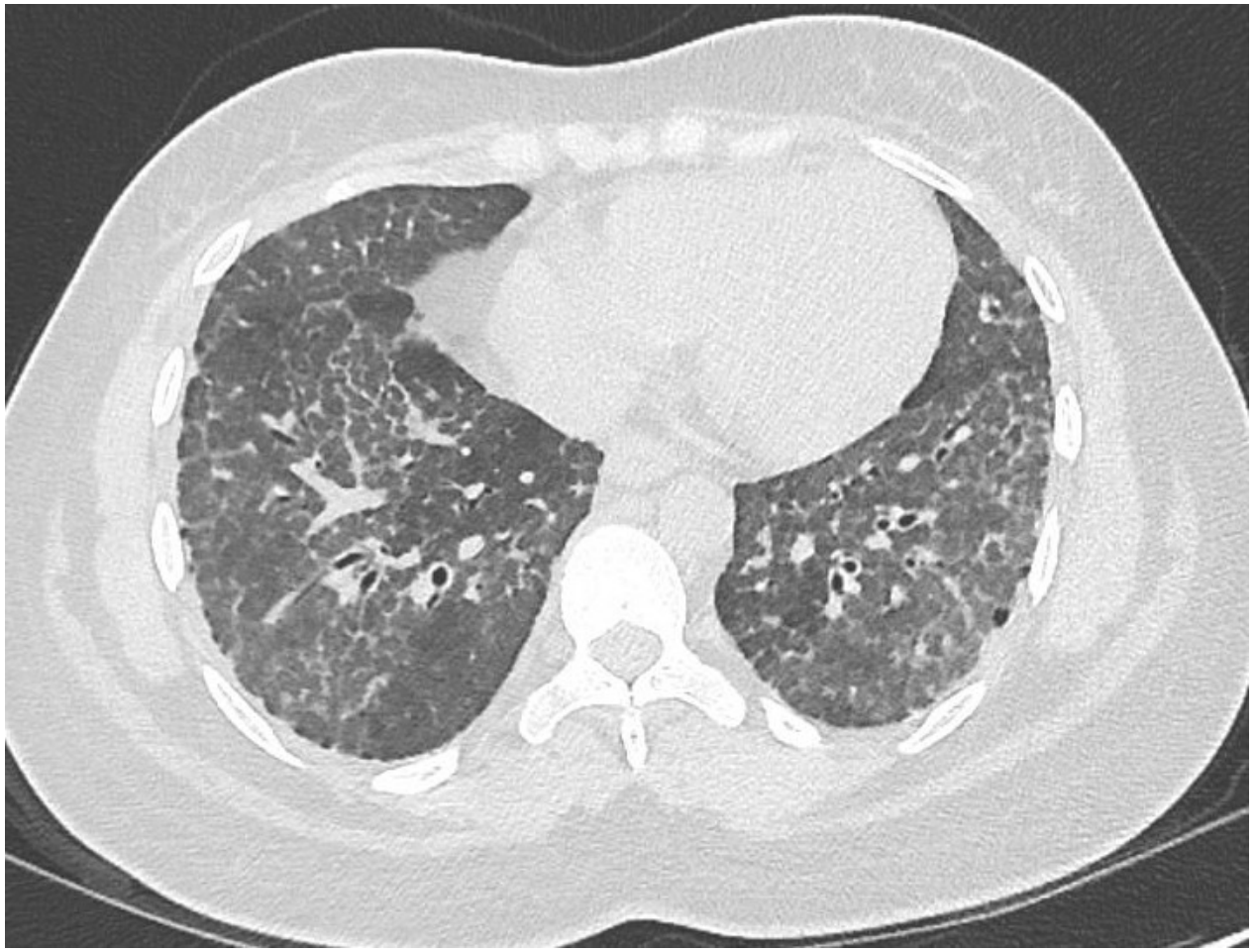
sIBM

- Dyspnée lentement évolutive III
- Céphalées matinales
- PaO2 71 – PCO 49 – Ph 7.39
- TVR

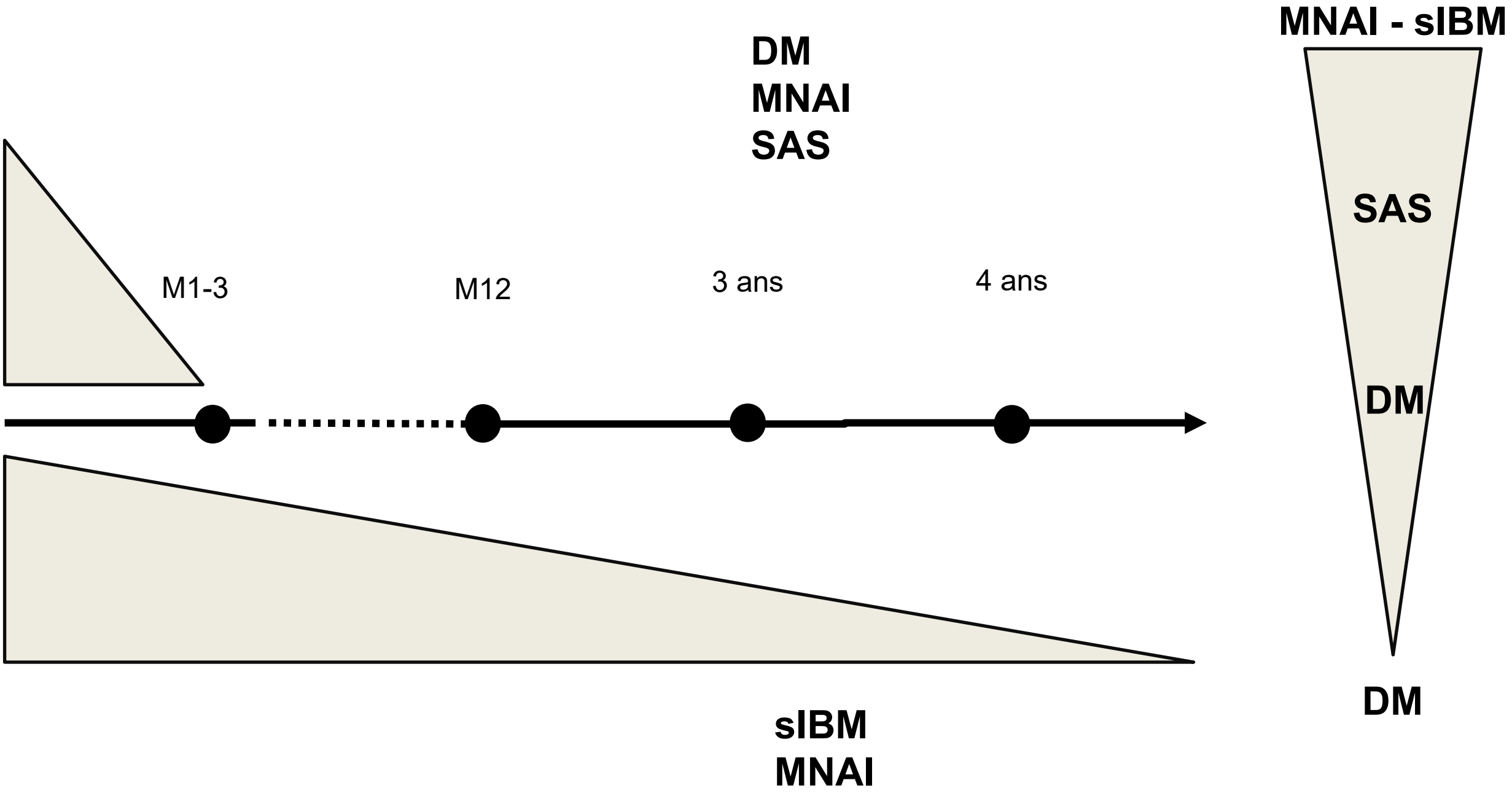


- H 29 ans
- PINS
- Myosite OJ+
- AZA + CT
- Dégradation clinico-morpho
- EDX 2 cures = Amélioration
- Nouvelle dégradation clinico-M

VRS+



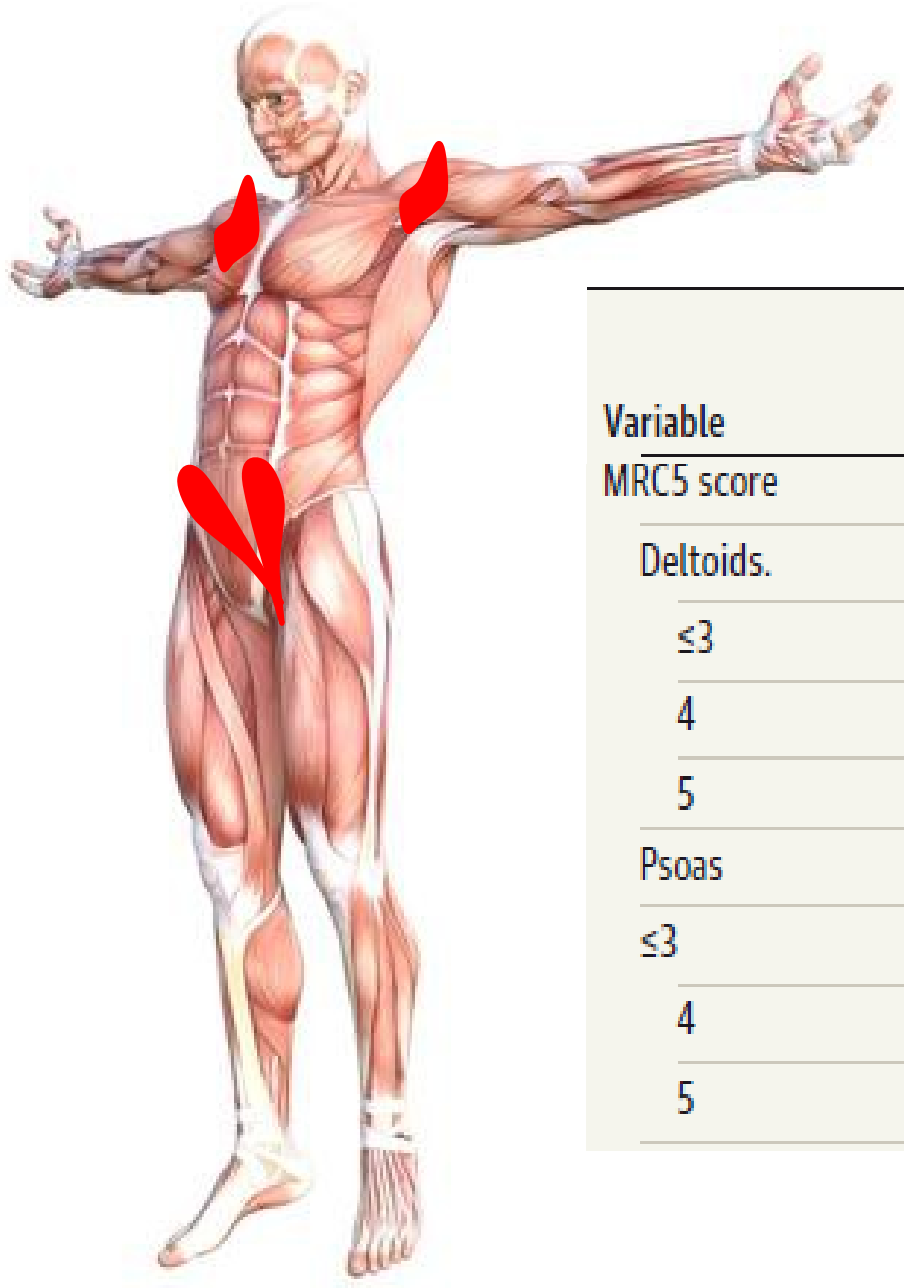
1- Myopathies auto-immunes
Des maladies très hétérogènes



Benveniste et al. 2011
Allenbach et al. 2015

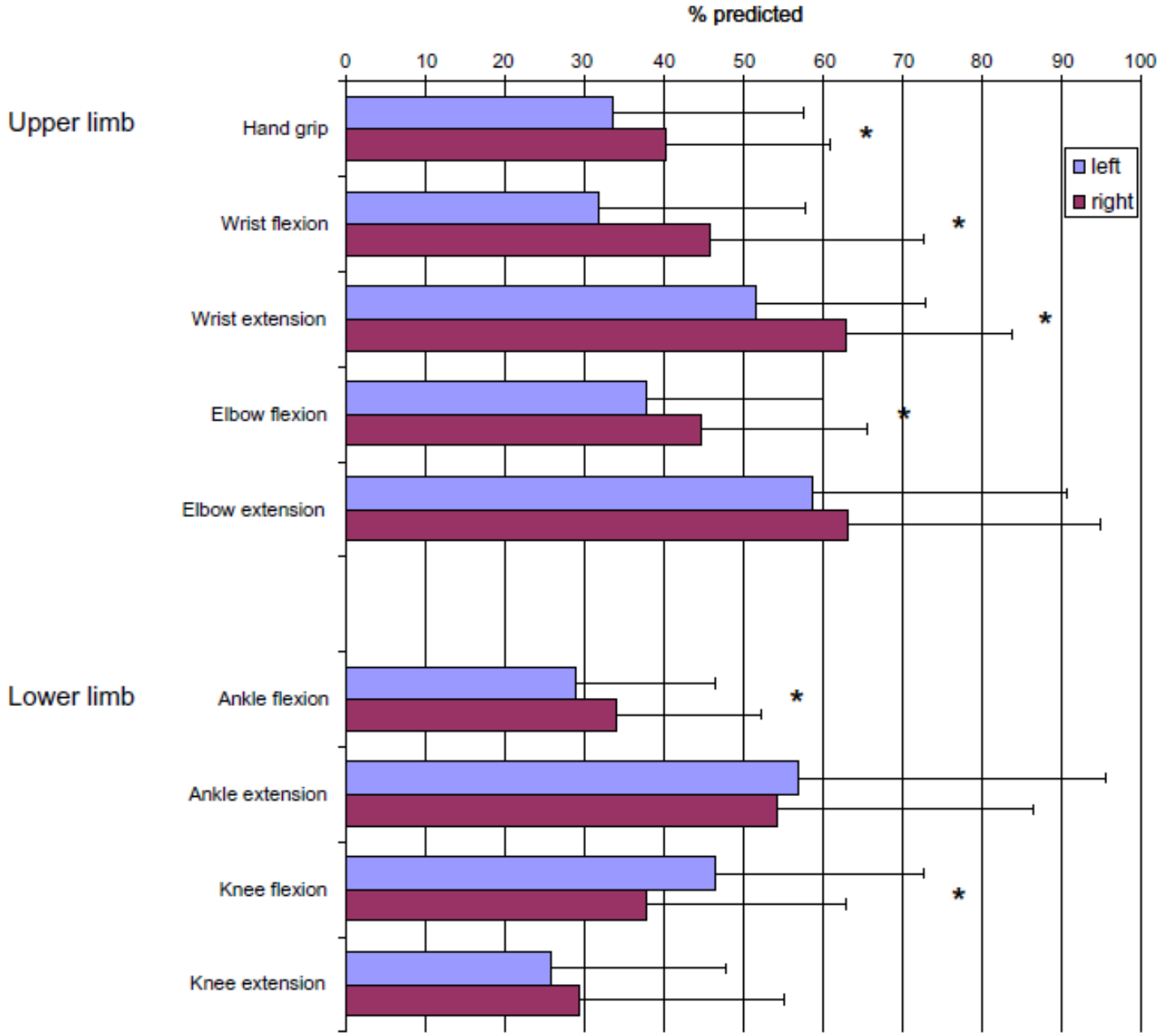
	Sex	
	Female	Male
Hip flexor strength at first visit	6.2	5.9
Follow-up hip flexor strength	7.2	7.4
Hip flexor strength at last visit	7.0	7.3
Arm abductor strength at first visit	8.1	8.4
Follow-up arm abductor strength	9.0	9.4
Arm abductor strength at last visit	9.0	9.5

Eleni Tiniakou et al. 2017
Pinal-Fernandez et al 2017
Mariampillai et al. 2018

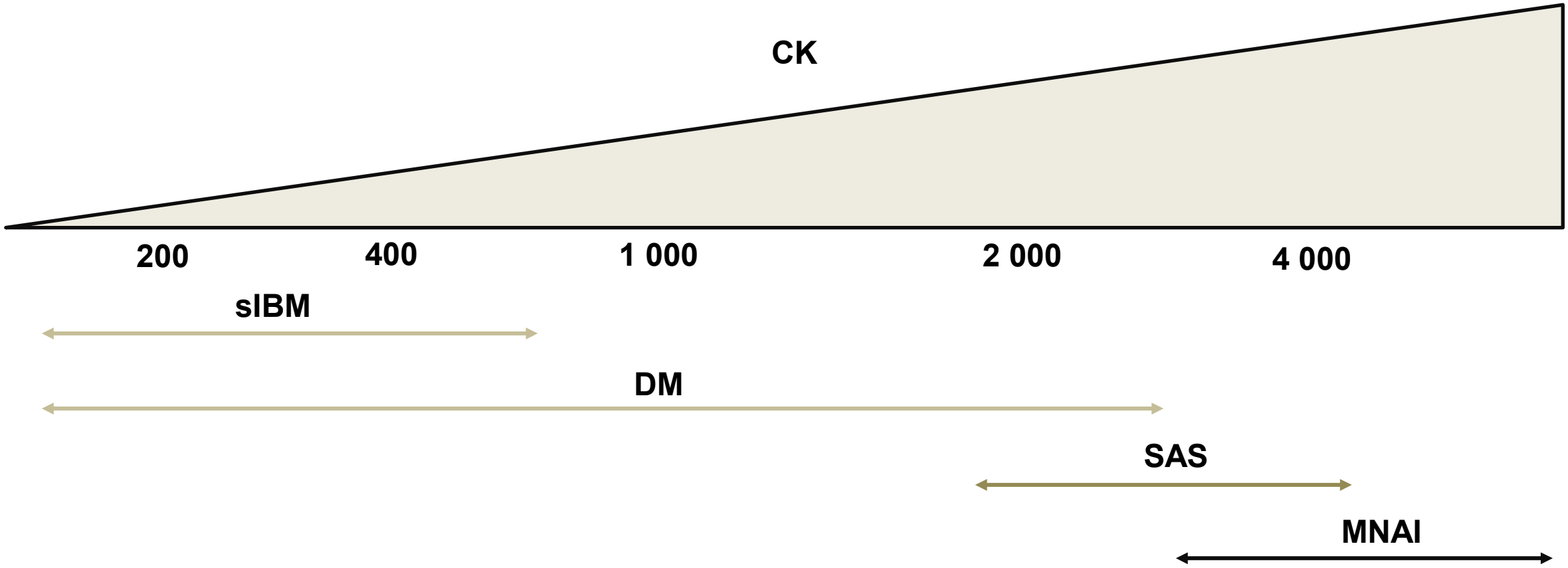


Variable	Cluster, No. (%) 1 (n = 77)	2 (n = 91)	DM 3 (n = 52)	4 (n = 40)	P Value[a]
MRC5 score					
Deltoids.					
≤3	23 (29.9)	40 (43.9)	29 (55.8)	8 (20.0)	
4	26 (33.8)	35 (38.4)	18 (34.6)	10 (25.0)	<.001
5	28 (36.4)	16 (17.6)	5 (9.6)	22 (55.0)	
Psoas					
≤3	38 (49.3)	57 (62.6)	31 (59.6)	14 (35.0)	
4	28 (36.4)	19 (20.9)	18 (34.6)	19 (47.5)	.02
5	11 (14.3)	15 (16.5)	3 (5.8)	7 (17.5)	

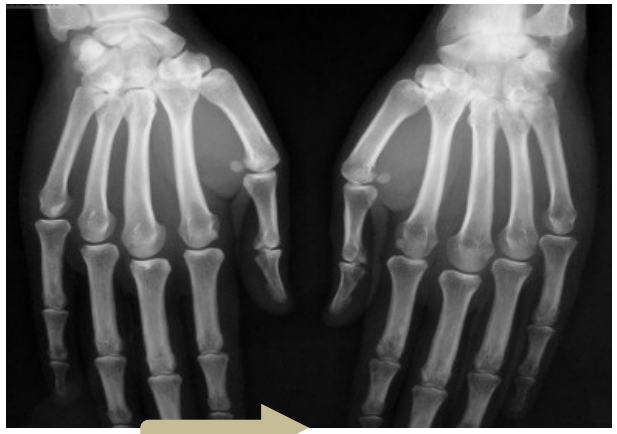
Mariampillai et al. 2018



Allenbach et al. 2011



Stanciu et al 2012
Allenbach et al. 2017
Eleni Tiniakou et al. 2017
Pinal-Fernandez et al 2017
Mariampillai et al. 2018



25-30%

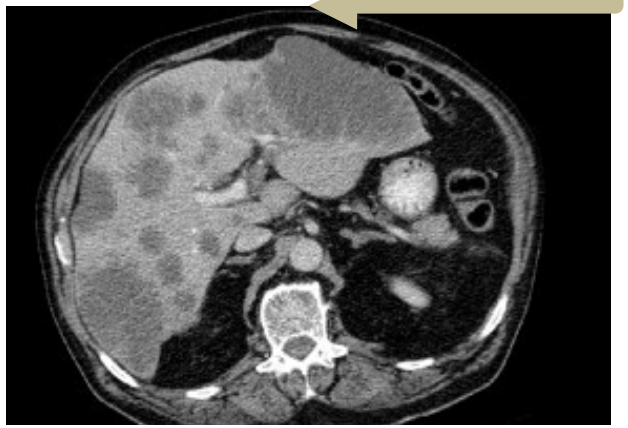
20%

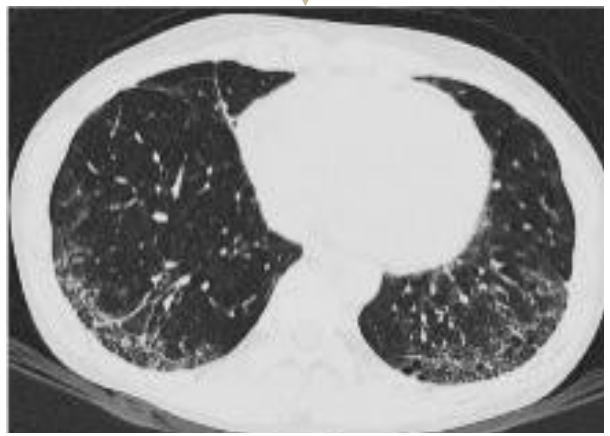
Manifestations extra-musculaires

10-20%

20-40%

4-50%





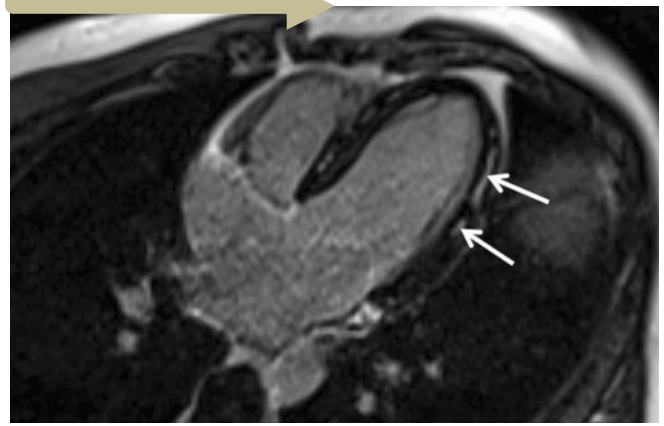
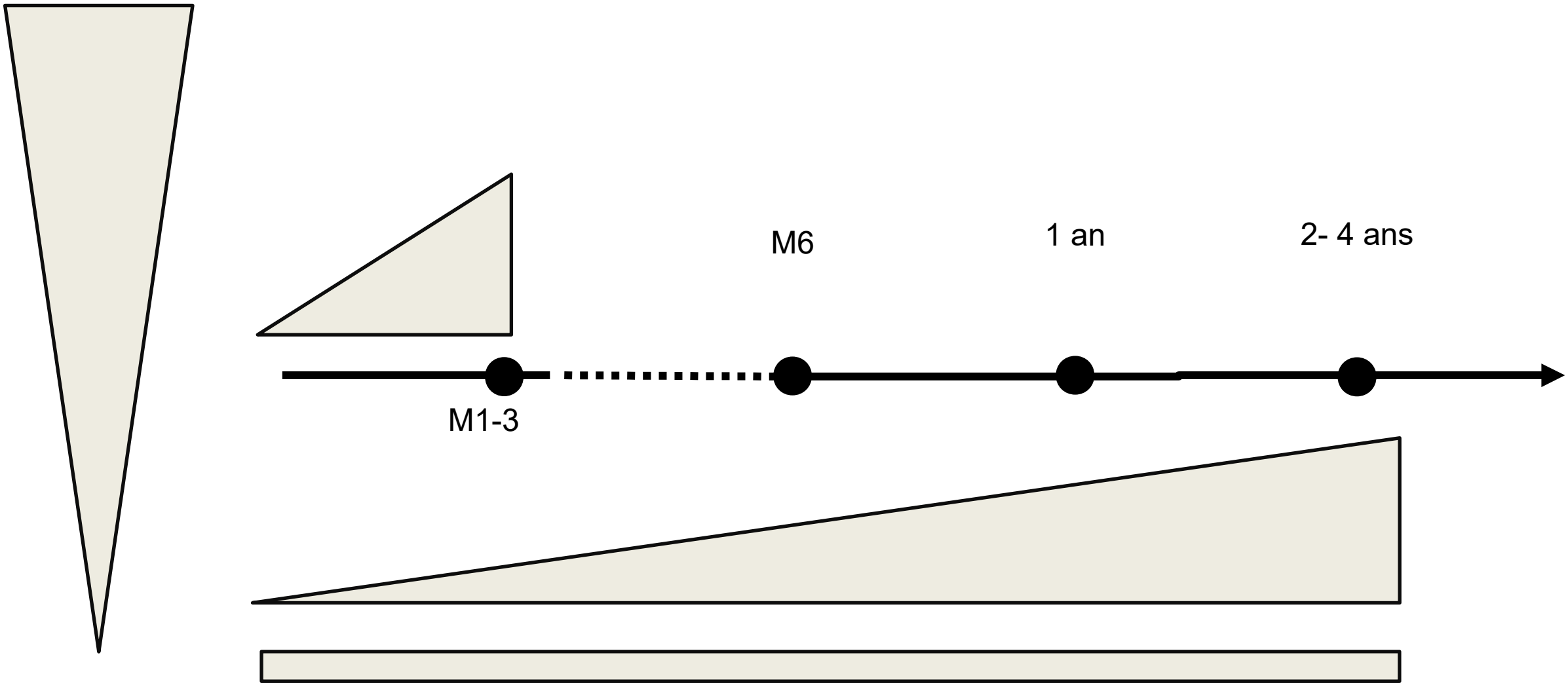
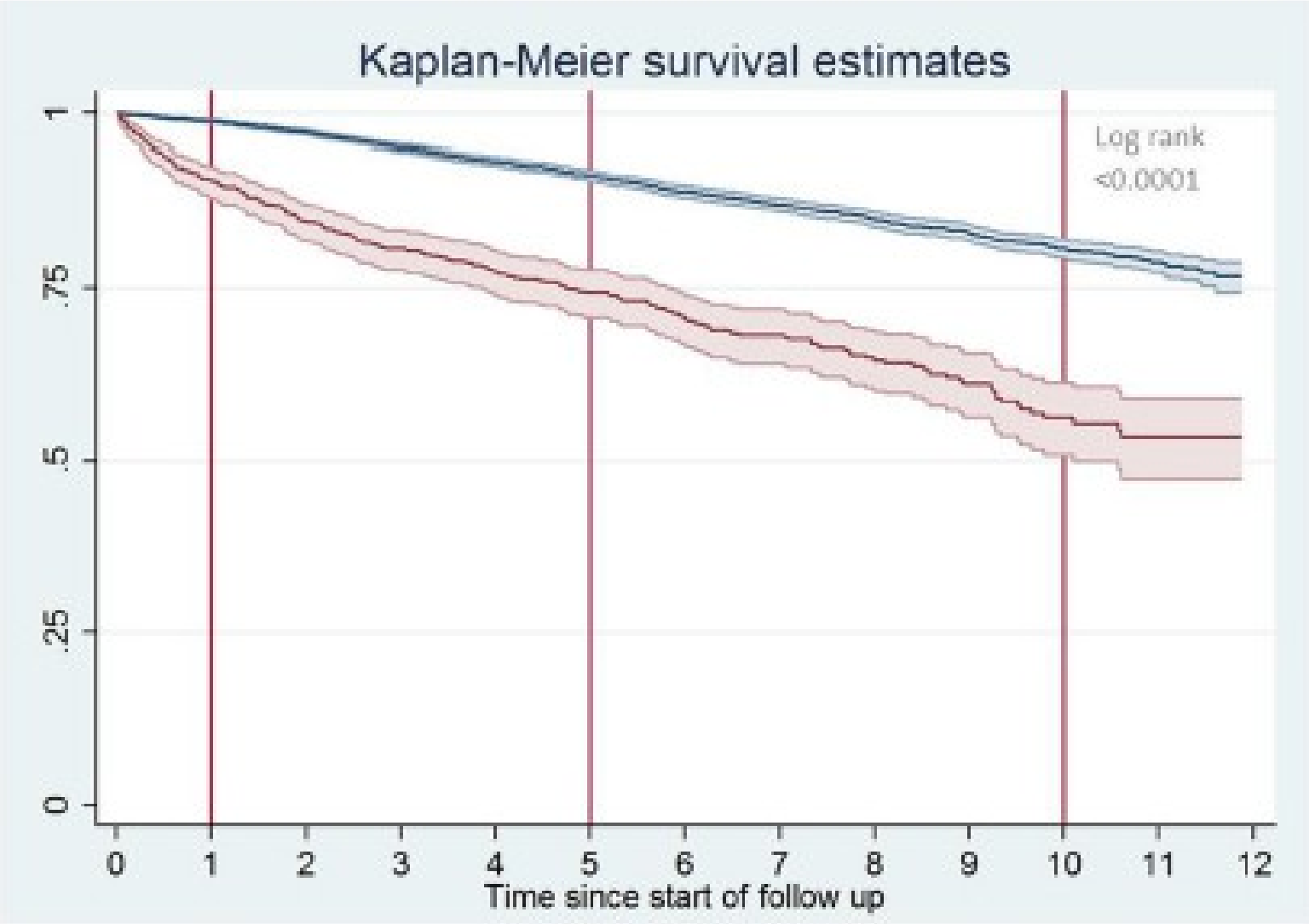


Table 2 Environmental exposures, extramuscular complications and disease severity assessments of cases in the EuroMyositis Registry

	Dermatomyositis	Polymyositis	Antisynthetase syndrome	Connective tissue disease-overlap myositis	Inclusion body myositis	Immune-mediated necrotising myopathy	Juvenile dermatomyositis	Total n (%)
Environmental exposures—% per diagnosis								
Current or previous smoker (n=1646)	33	39	42	45	35	29	20	611(37)
Environmental toxin exposure (n=930)	16	17	21	15	28	4	0	157 (17)
Extramuscular complications— % per diagnosis								
Interstitial lung disease (n=2442)	21	17	71	32	3	10	6	720 (30)

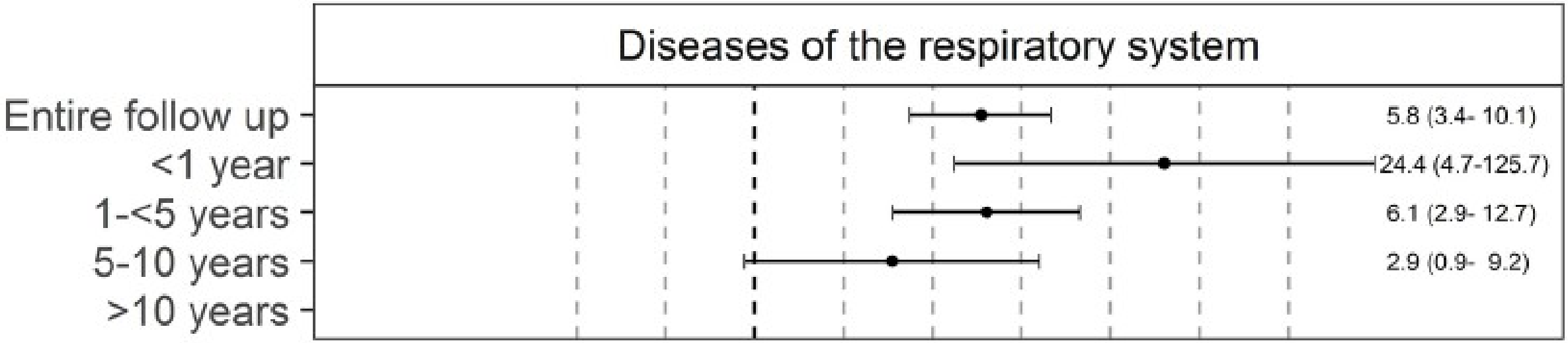
Lilleker JB et al. ARD 2018


M6
1 an
2- 4 ans
M1-3



At risk, n	716/7100	648/7013	327/4037
Dead at end of interval, n	66/77	100/448	53/318
Cumulative mortality, %	9/1	23/7	31/12

2 – 3 cause de mortalité



Myopathies auto-immunes : enjeux pneumlogiques

- Atteintes fréquentes
- Atteintes variées :
    - spécifiques
    - non spécifiques
    - Maladies pulmonaires ‘compliqées’ de myosites
- potentiellement graves

QUESTIONS:

- **Quelles sont les pathologies pulmonaires associées aux Myosites ?**
- **Evolution ?**
- **Comment faire le diagnostic ; imputabilité ?**

Spectres des manifestations respiratoires aux des myosites ?

DIAGNOSTIC ET CLASSIFICATION DES MYOSITES

2- Myopathies auto-immunes
Les variables de classifications
- Musculaires

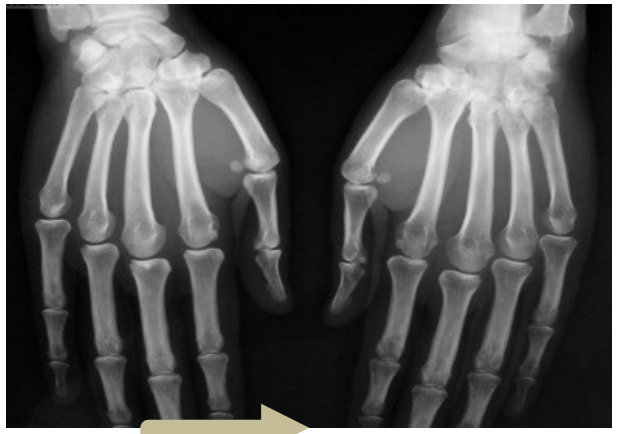
1- CLINIQUE : topographie du déficit
   EMG – IRM
2- BIOPSIE MUSCULAIRE

- Expertise
- Lésions élémentaires ?
  - Fibres
  - Vaisseaux
  - Conjonctif
- Répartition ?

2- Classification des Myopathies auto-immunes

Les variables de classifications

- Musculaires
- Extra-musculaires



25-30%

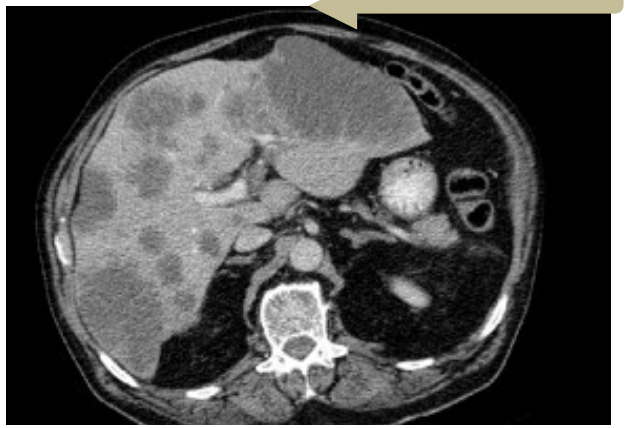
20%

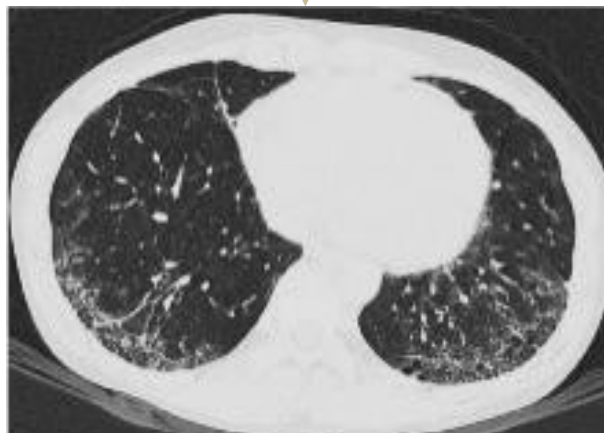
Manifestations extra-musculaires

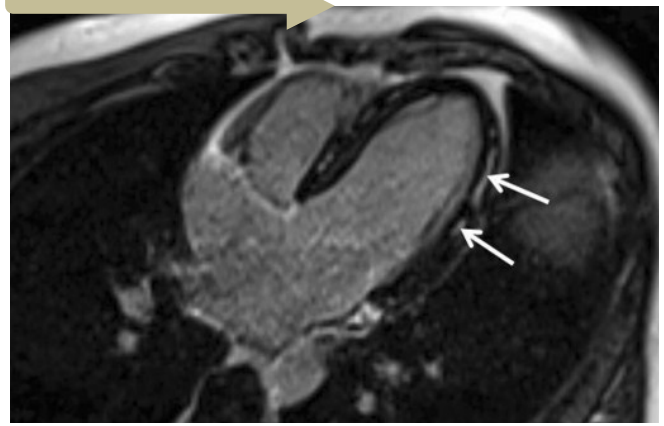
10-20%

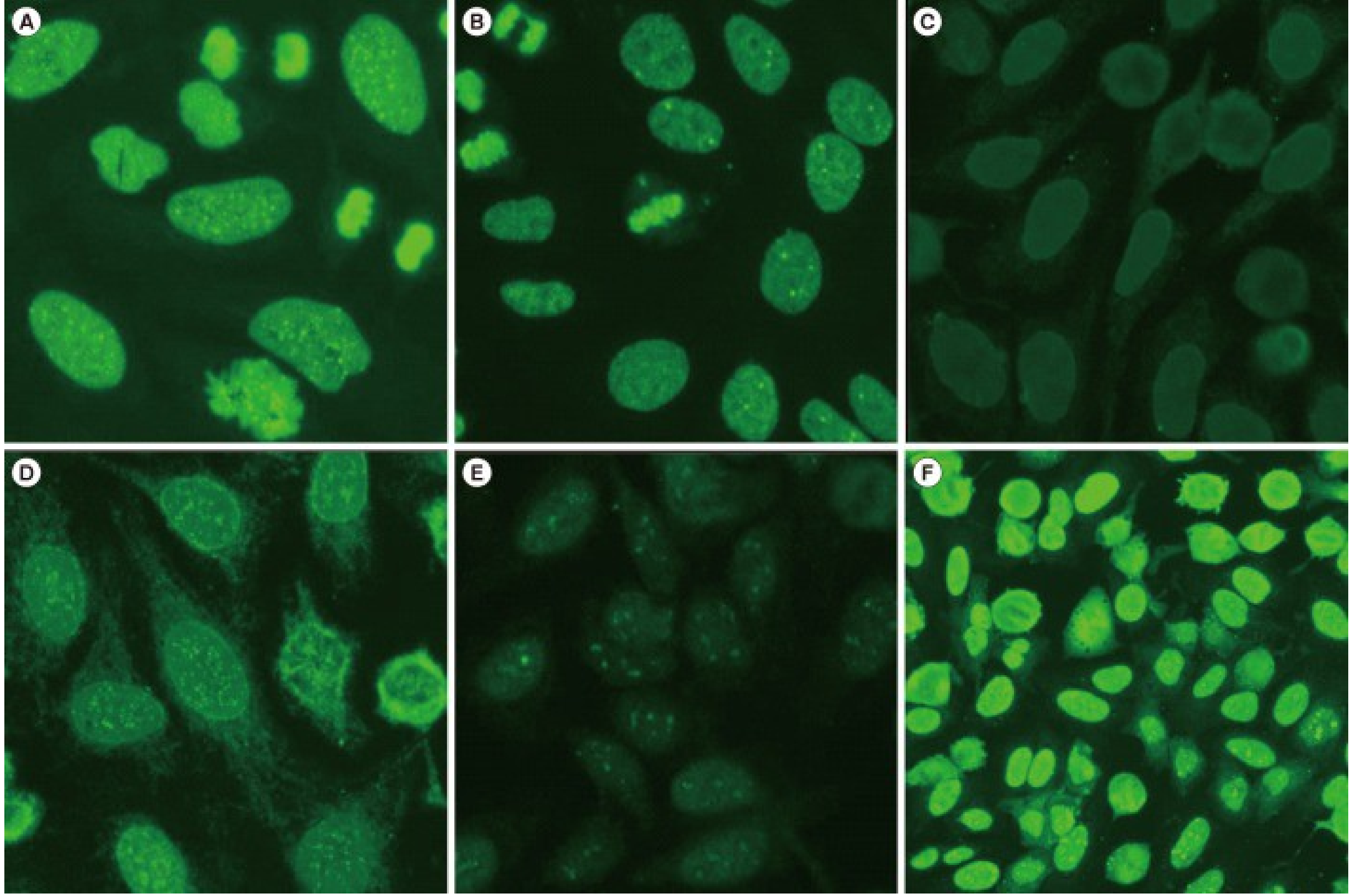
20-40%

4-50%

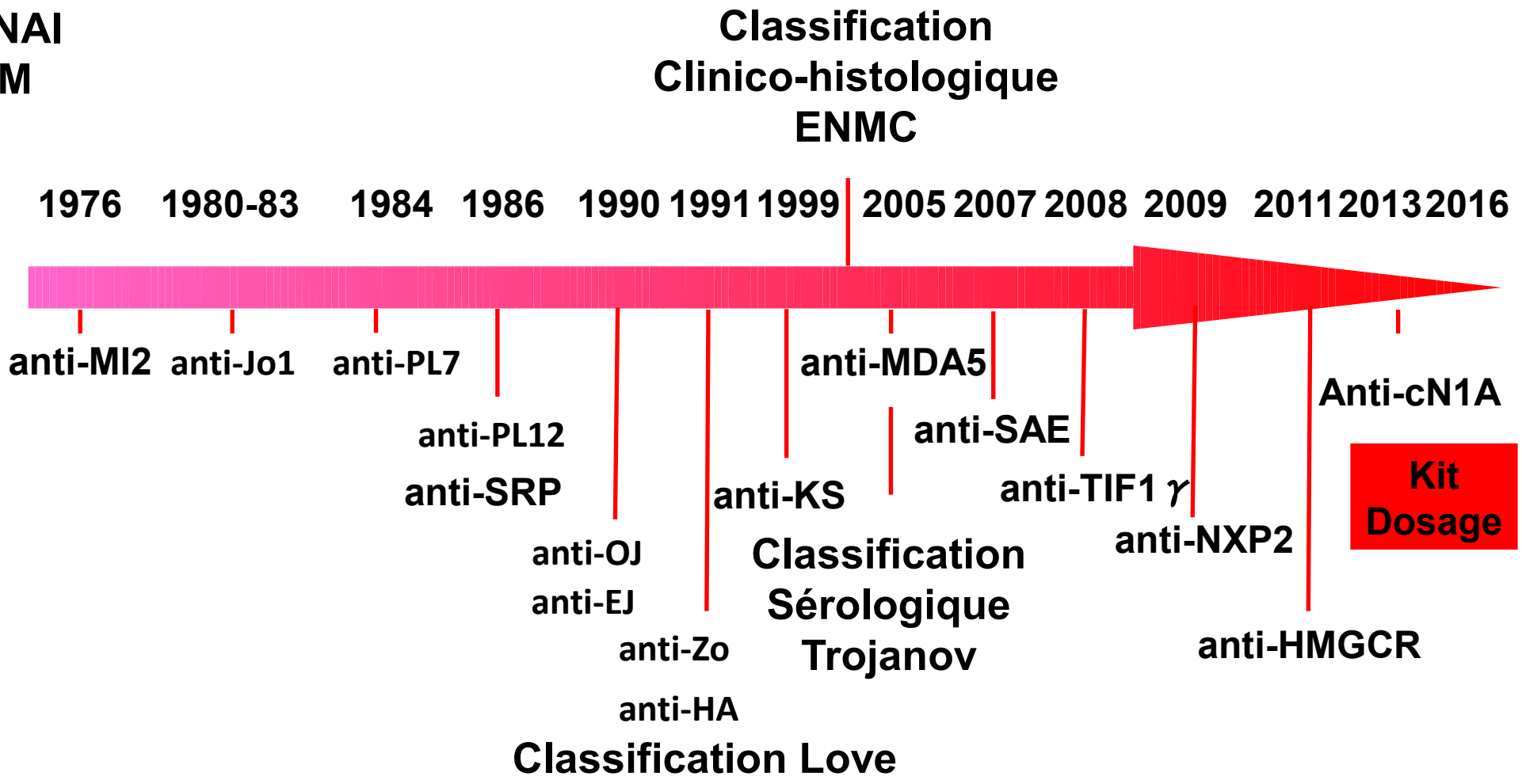




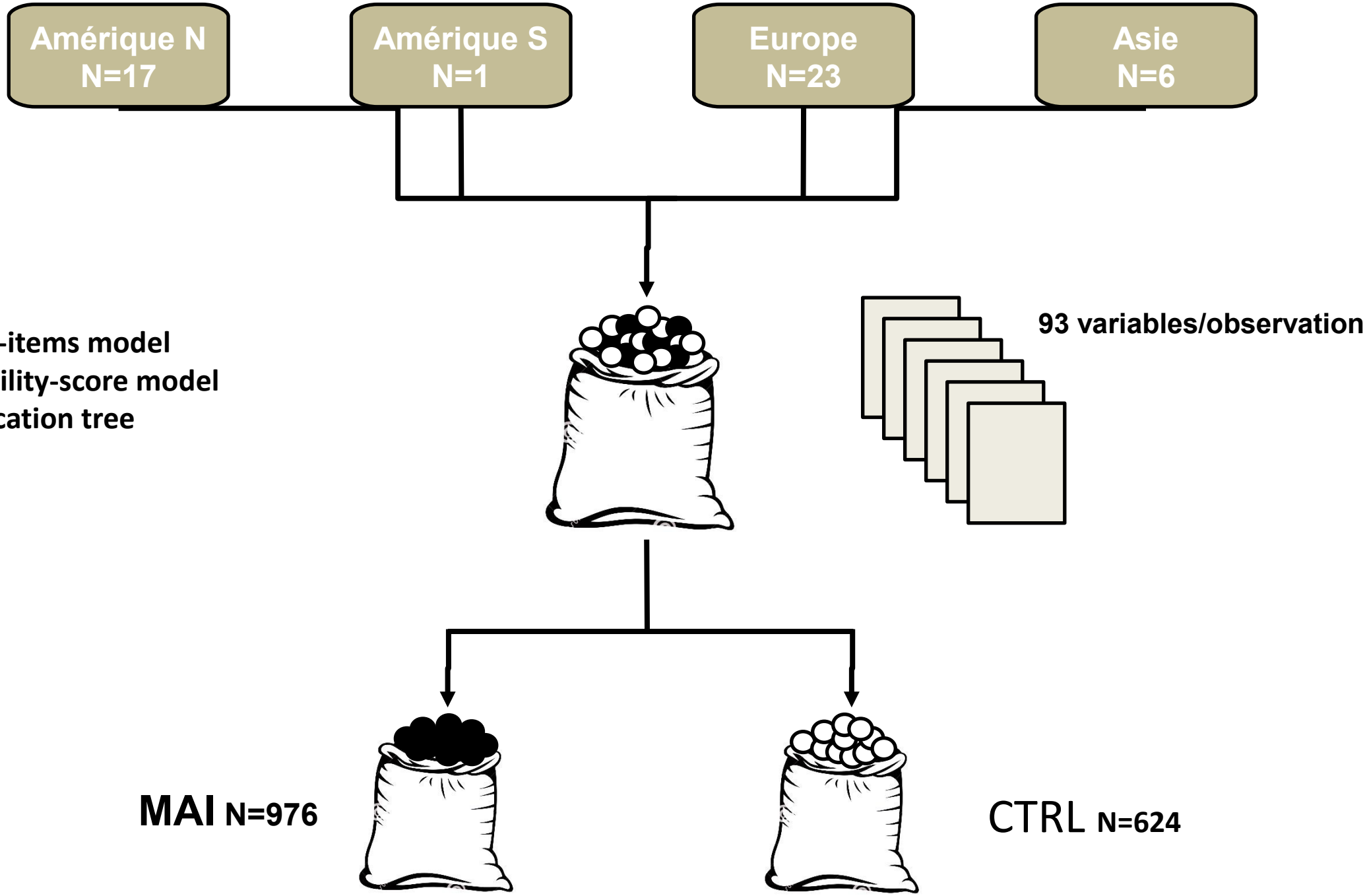



A
B
C
D
E
F

MSA & DM
MSA & SAS
MSA & MNAI
MSA & IBM



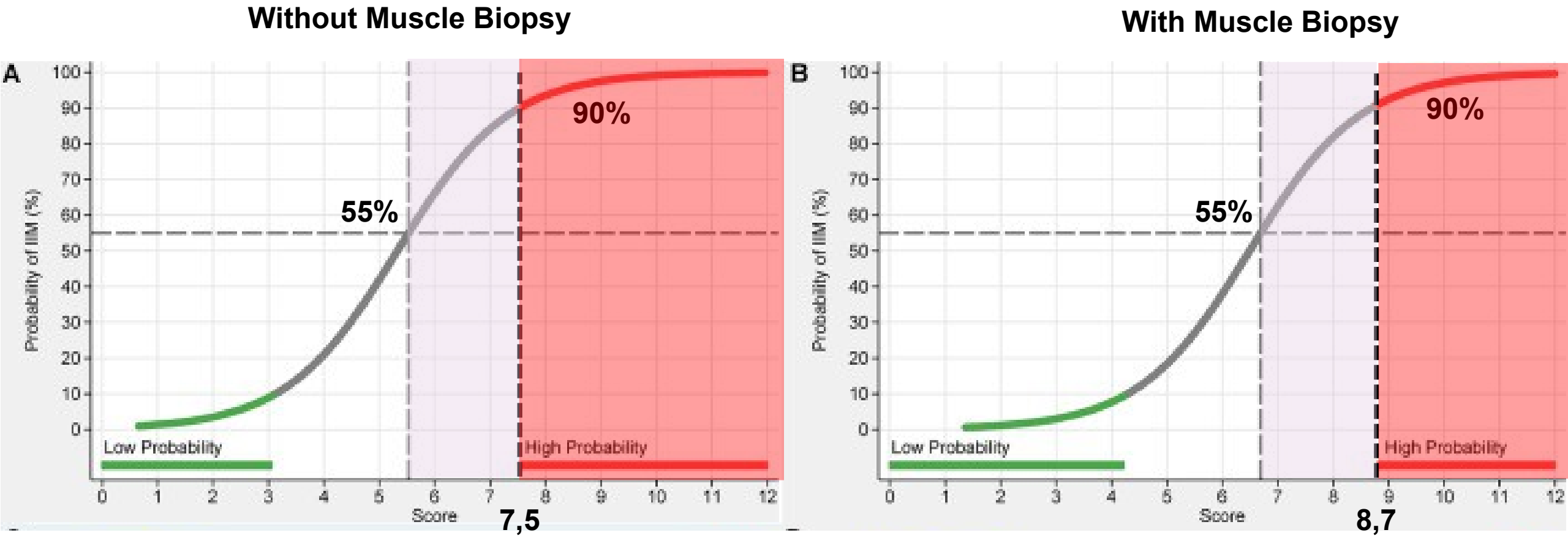
2- Classification des Myopathies auto-immunes
Variables de classification
Nouvelle classification



1) a sum-of-items model
2) a probability-score model
3) a classification tree

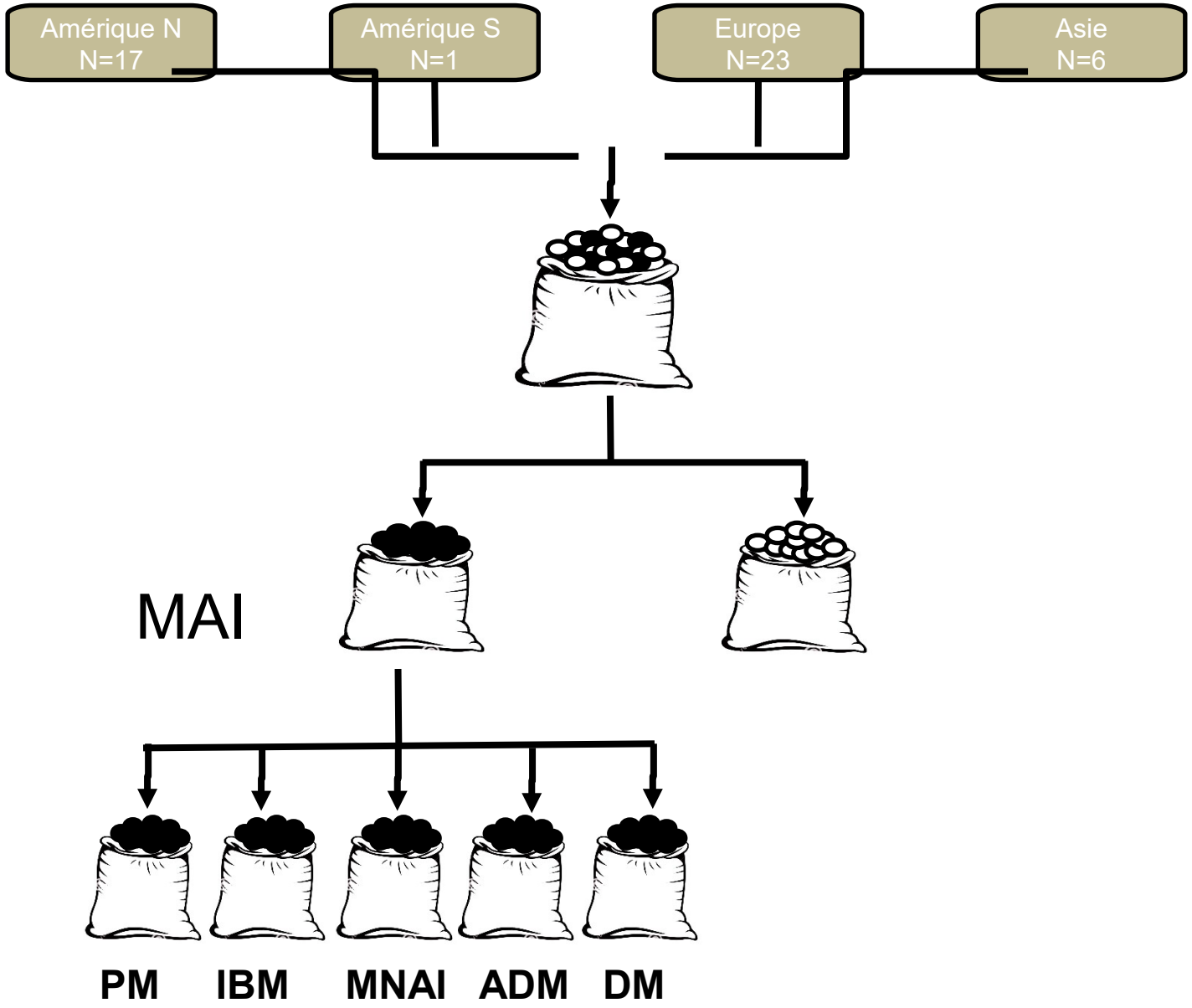
		Yes	No		
Age of onset of first symptom	0 – 17	☐		1.3	1.5
	18 – 39	☐		2.1	2.2
	40+	☐			
Objective symmetric weakness, usually progressive, of the proximal upper extremities		☐	☐	0.7	0.7
Objective symmetric weakness, usually progressive, of the proximal lower extremities		☐	☐	0.8	0.5
Neck flexors are relatively weaker than neck extensors		☐	☐	1.9	1.6
In the legs proximal muscles are relatively weaker than distal muscles		☐	☐	0.9	1.2
Heliotrope rash		☐	☐	3.1	3.2
Gottron's papules		☐	☐	2.1	2.7
Gottron's sign		☐	☐	3.3	3.7
Dysphagia or esophageal dysmotility		☐	☐	0.7	0.6
Anti-Jo-1 (anti-Histidyl-tRNA synthetase) autoantibody positivity		☐	☐	3.9	3.8
Elevated serum levels of creatine kinase (CK) or lactate dehydrogenase (LDH) or aspartate aminotransferase (ASAT/AST/SGOT) or alanine aminotransferase (ALAT/ALT/SGPT)		☐	☐	1.3	1.4
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		☐	☐		1.7
Perimysial and/or perivascular infiltration of mononuclear cells		☐	☐		1.2
Perifascicular atrophy		☐	☐		1.9
Rimmed vacuoles		☐	☐		3.1

www.imm.ki.se/biostatistics/calculators/iim



Probability score

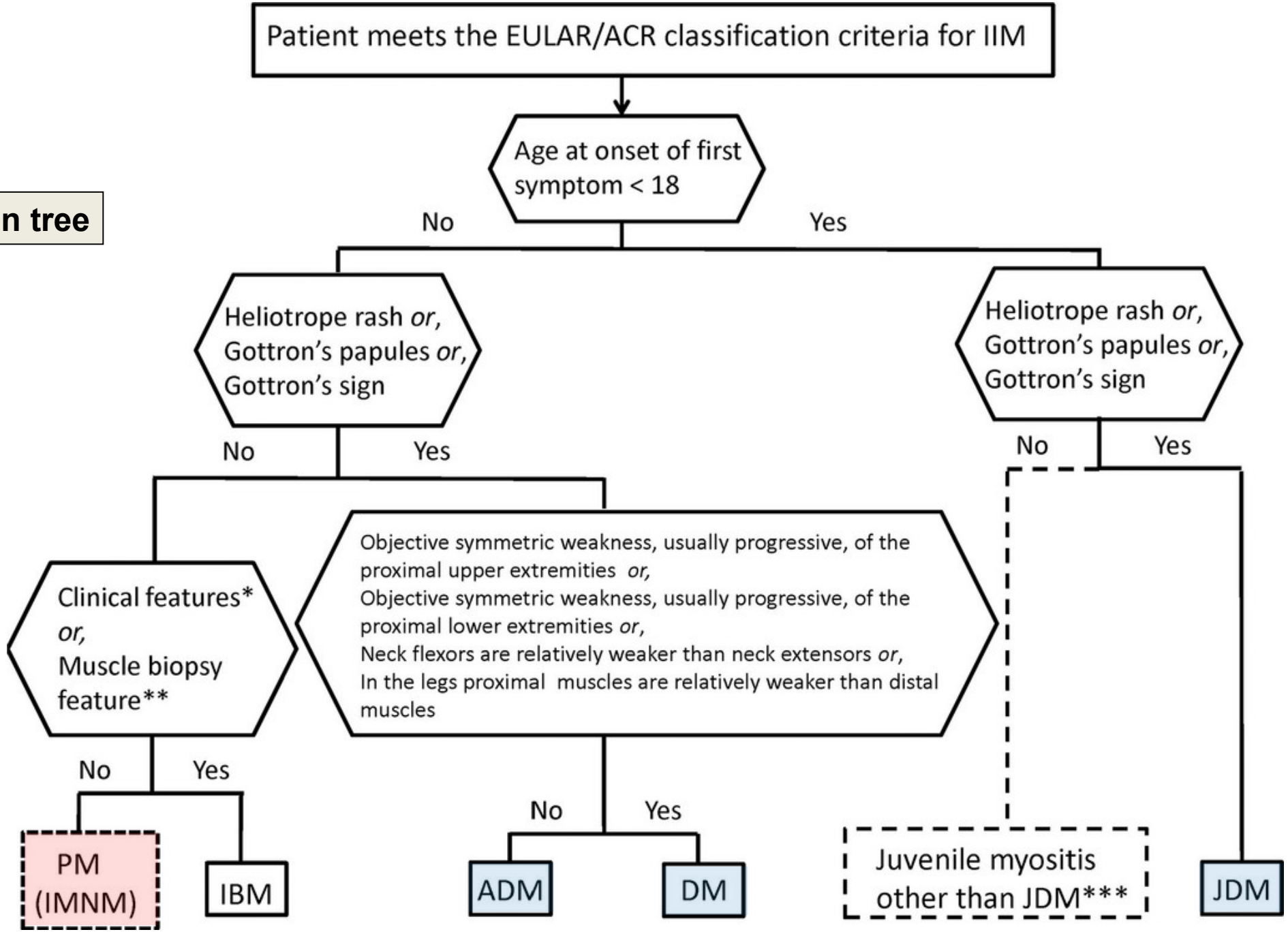
Classification des myopathies inflammatoires: CRITERES ACR/EULAR

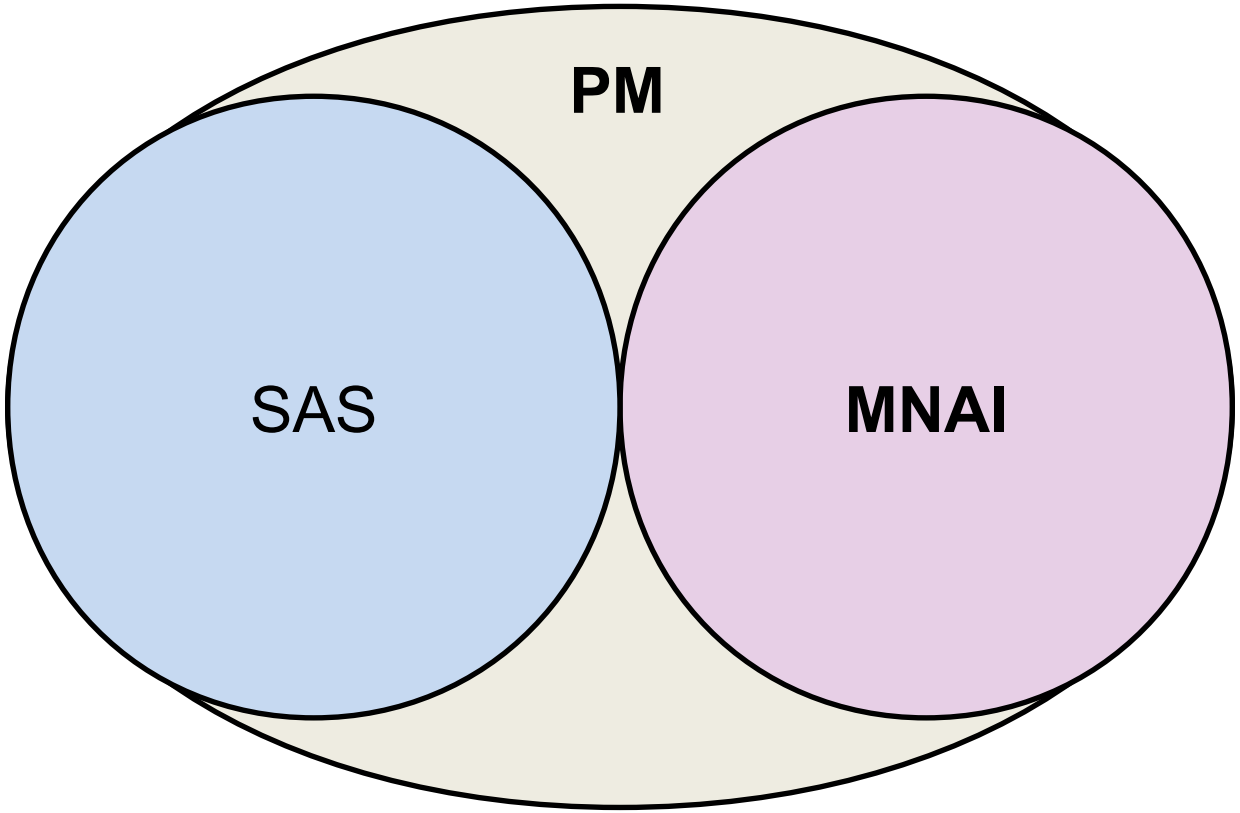

Amérique N
N=17
Amérique S
N=1
Europe
N=23
Asie
N=6
MAI
PM
IBM
MNAI
ADM
DM

Classification tree

PM
DM (am/j/a)

IBM

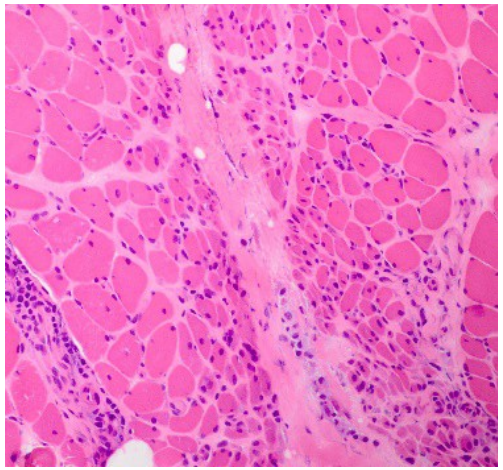



PM
SAS
MNAI

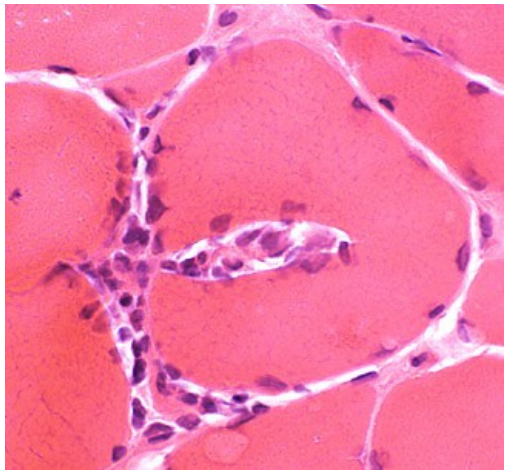
119th ENMC international workshop: Trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10–12 October 2003, Naarden, The Netherlands

Jessica E. Hoogendijk[a,*], Anthony A. Amato[b], Bryan R. Lecky[c], Ernest H. Choy[d], Ingrid E. Lundberg[e], Michael R. Rose[f], Jiri Vencovsky[g], Marianne de Visser[h], Richard A. Hughes[i,1]

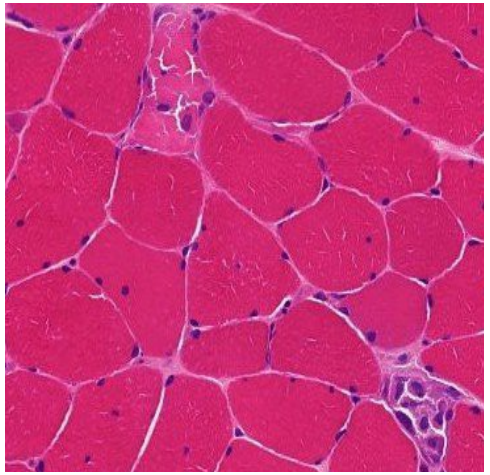
DM



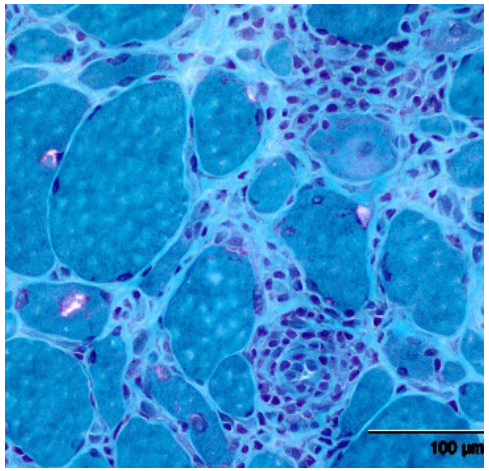
PM



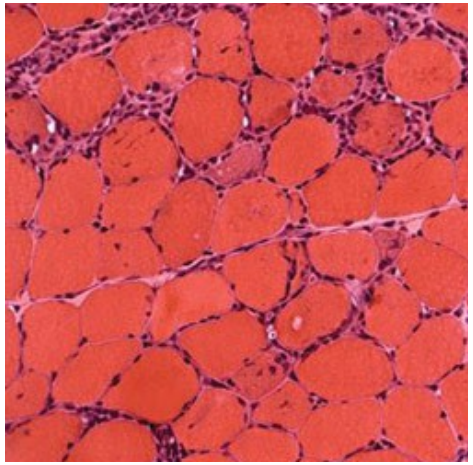
NAM



sIBM



Unspe myo



Hoogendjick et al. 2003

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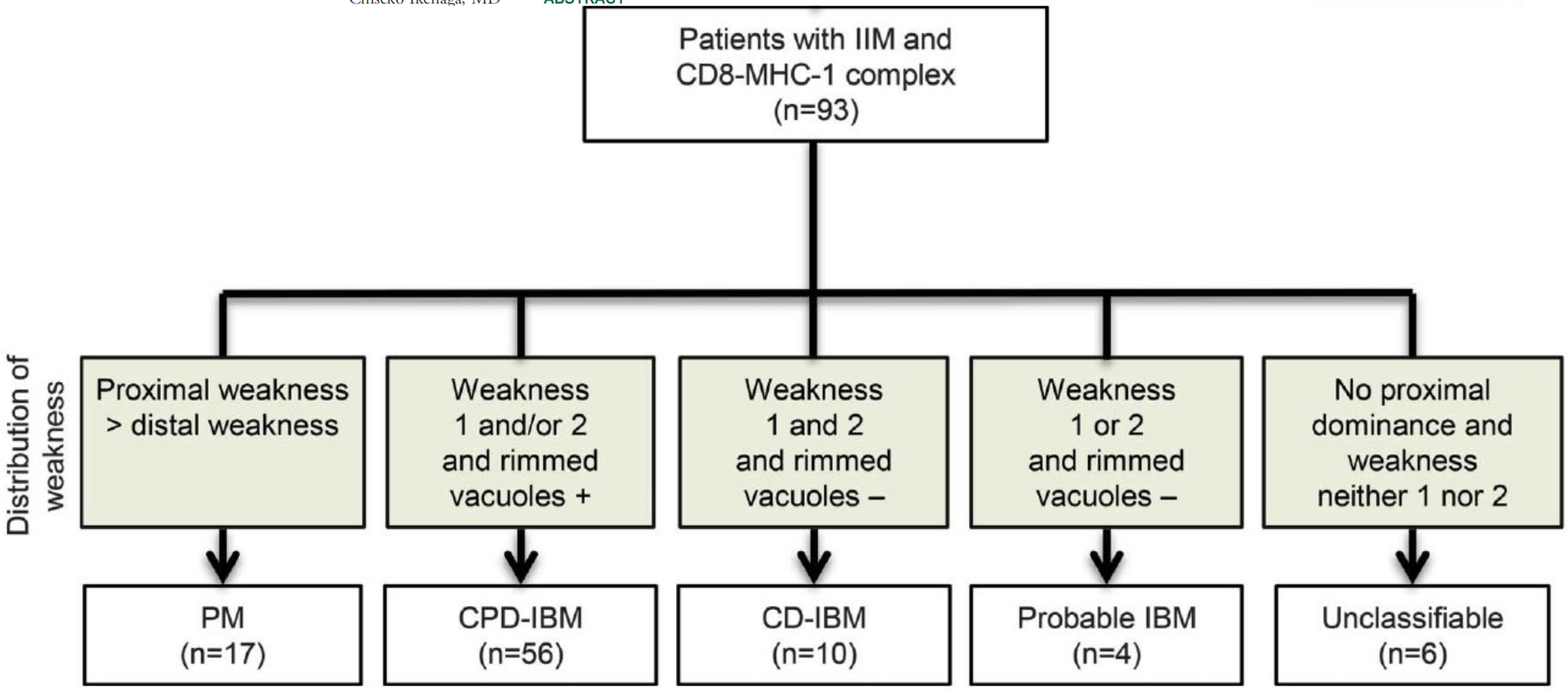
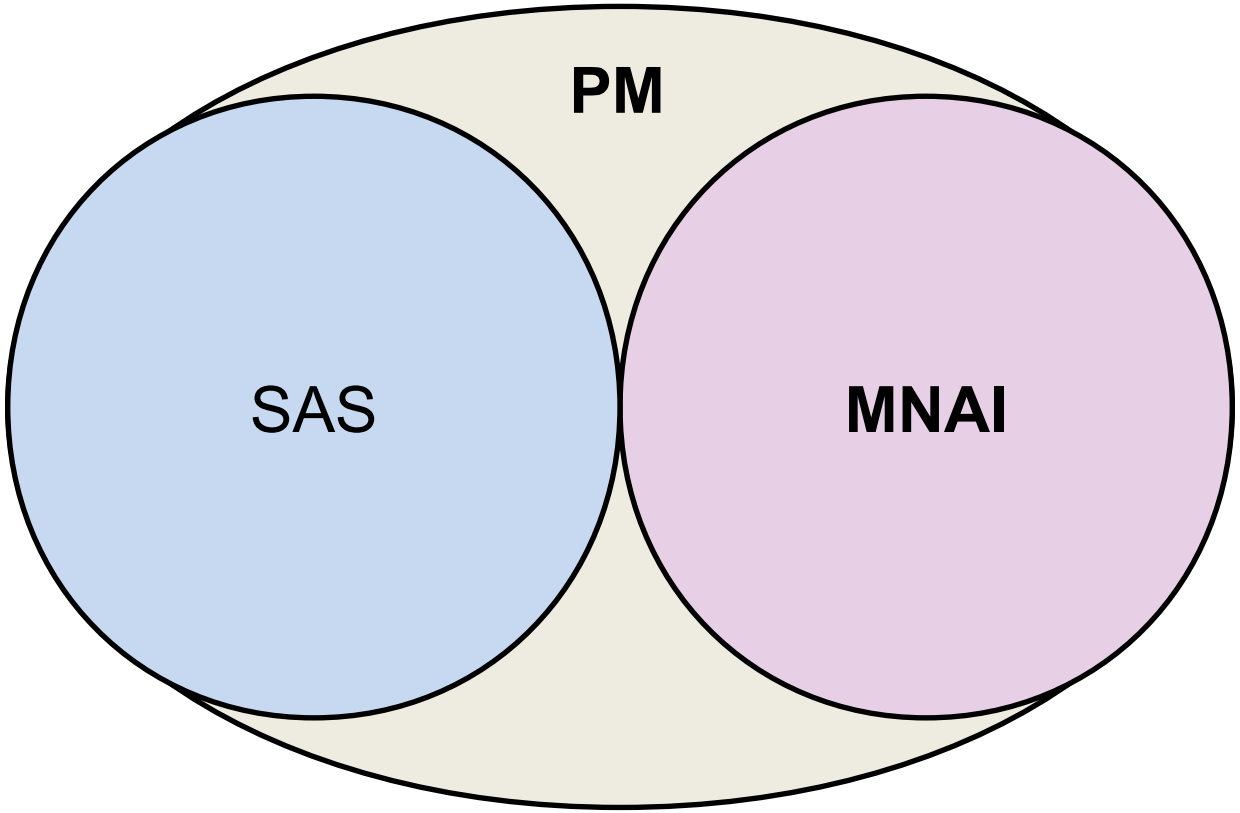
Clinicopathologic features of myositis patients with CD8-MHC-1 complex pathology

Chiseko Ikenaga, MD

ABSTRACT



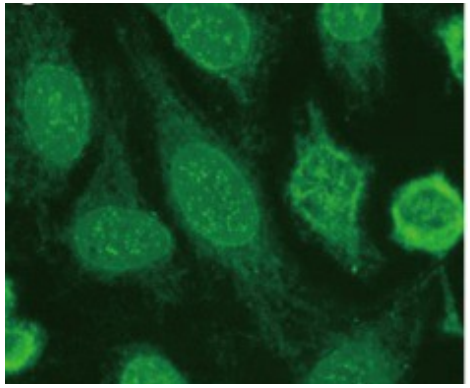

PM
SAS
MNAI

2- Classification des Myopathies auto-immunes

Variables de classification

Nouvelle classification

- ACR/EULAR
  - sérologique



708 Variables

↓

47 Variables

IIM registry of the myositis center (Paris)
N= 1150

→ Dot myositis not done (n= 643)

MSA panel evaluation performed
period 2003-2014
N=507

→ Bohan&Peter &Griggs criteria not satisfied (n=62)

Myositis defined according to historical classifications
N= 445

→ Files not available or lack of relevant data (n=84)

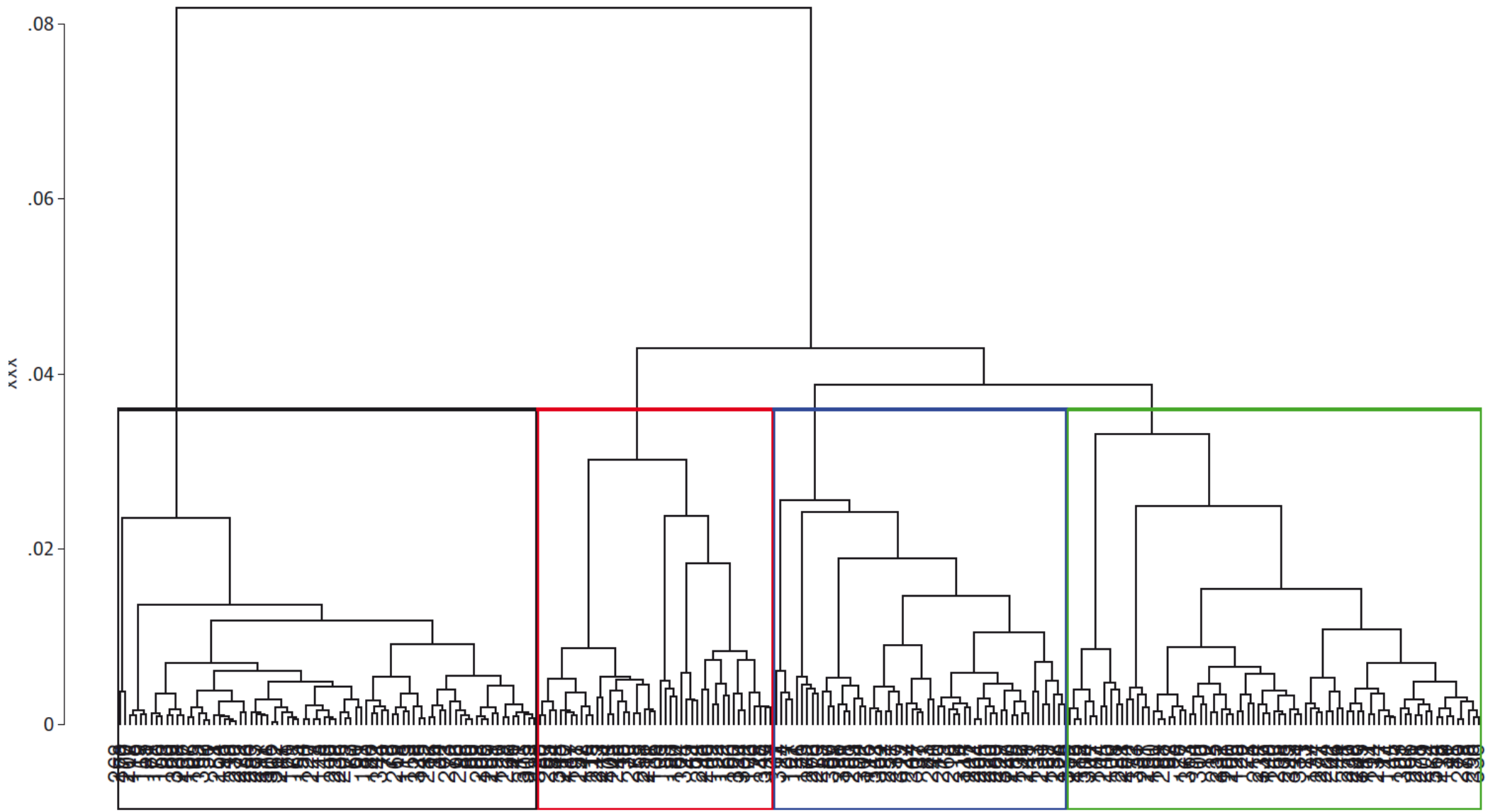
Patient's files included for pre-analytical phase (step 1)
N= 361 (708 variables)

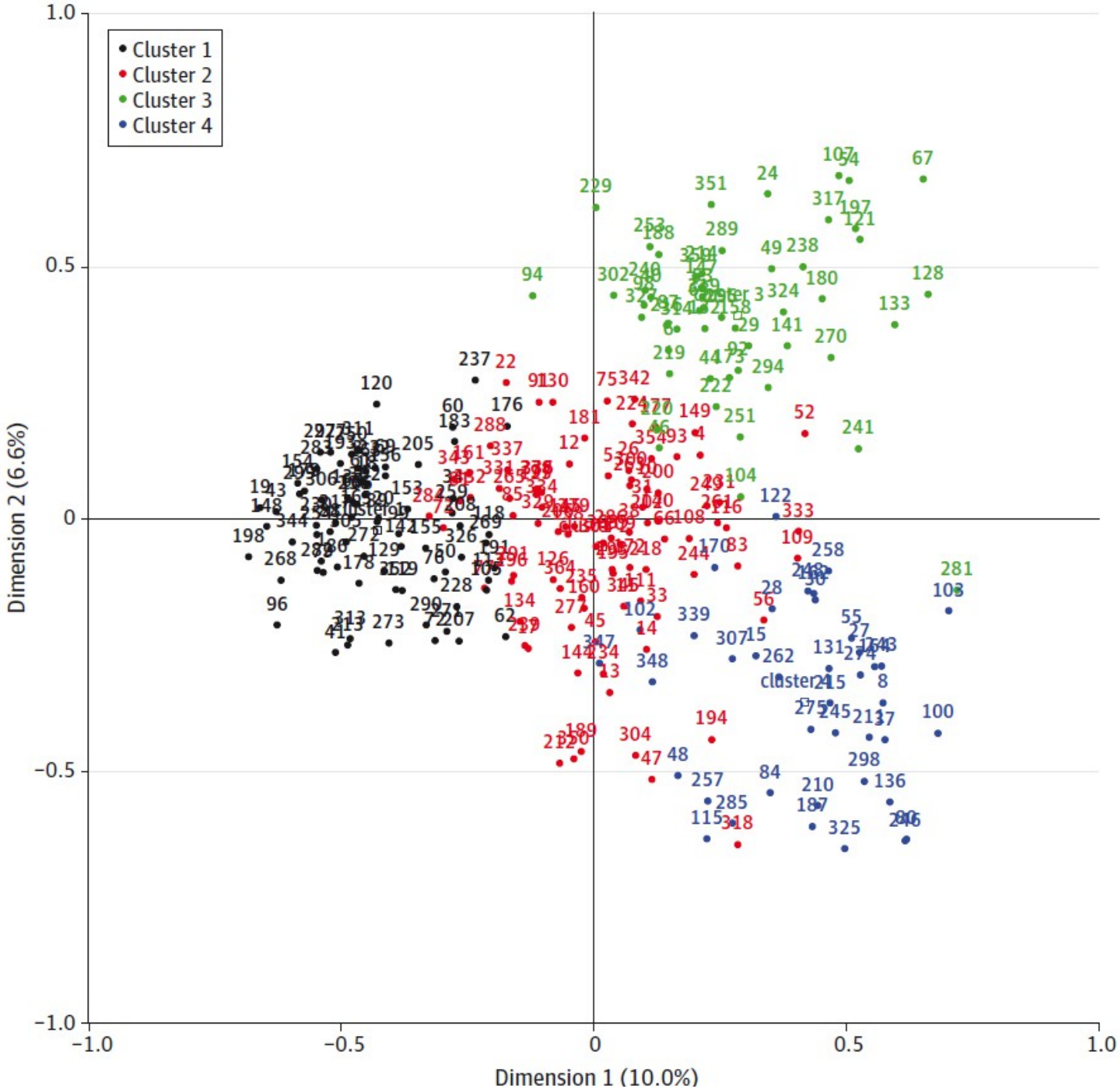
Patient's files included for analytical phase (step 2·1)
N=361 (47 variables)

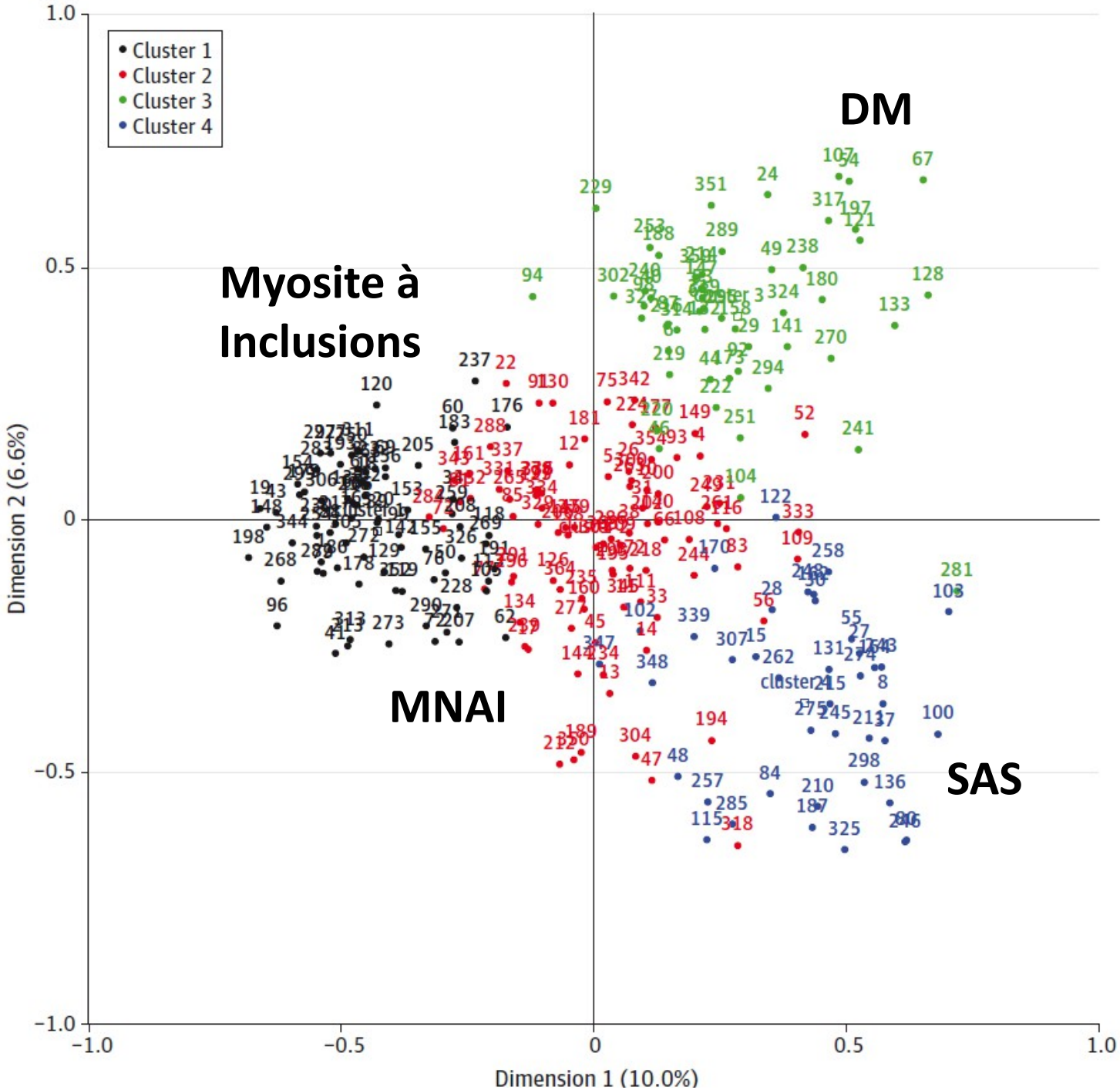
→ Patient's files with missing data (at least one, step 2·2, n=101)

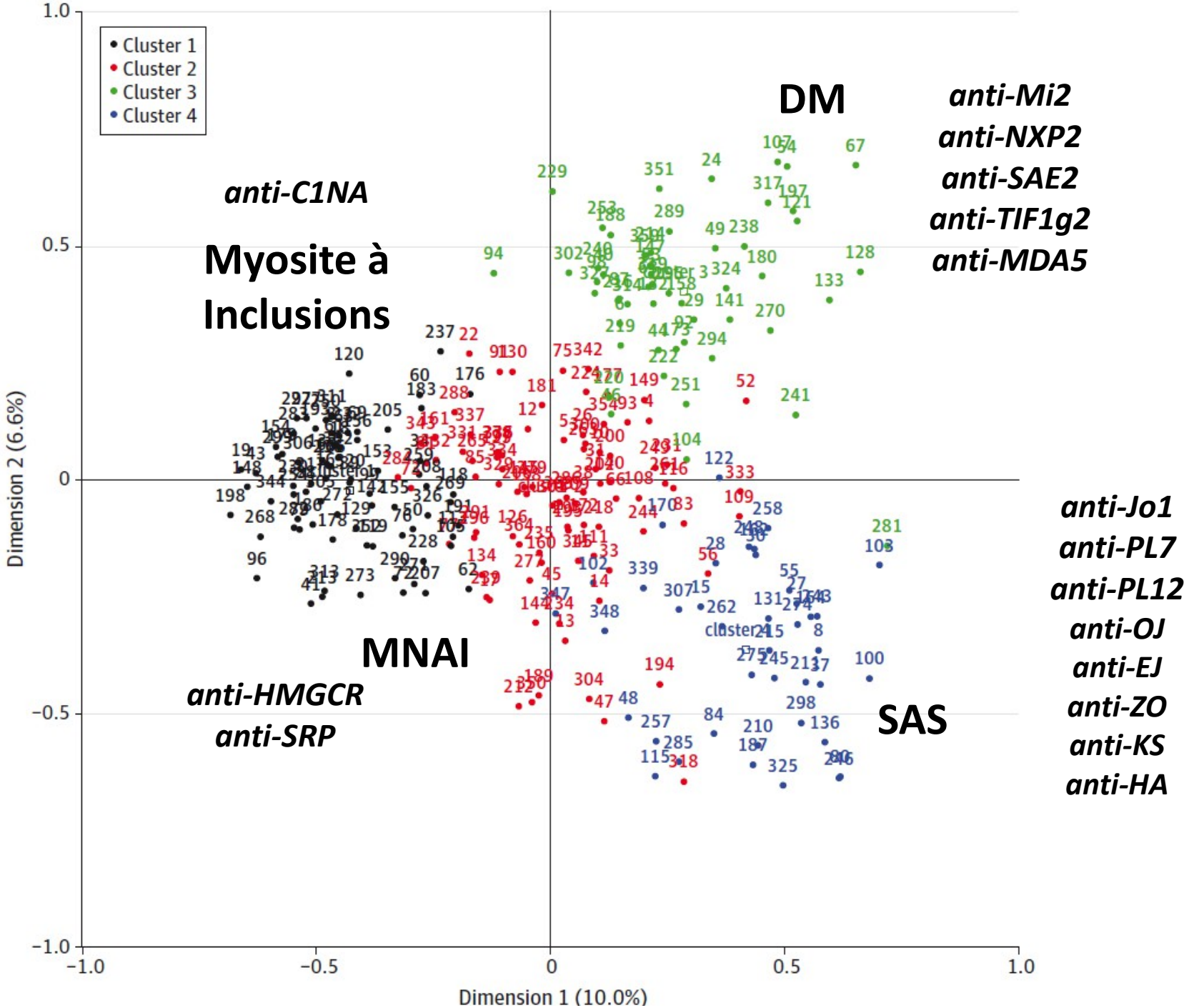
Patient's files for the new classification (MCA, HCA and CART)
N=260 (47 variables)

K. Mariampillay et al. JAMA Neuro 2018


.08
.06
.04
.02
0


Cluster 1
Cluster 2
Cluster 3
Cluster 4
Dimension 2 (6.6%)
Dimension 1 (10.0%)
1.0
0.5
0
−0.5
−1.0
−1.0
−0.5
0
0.5
1.0

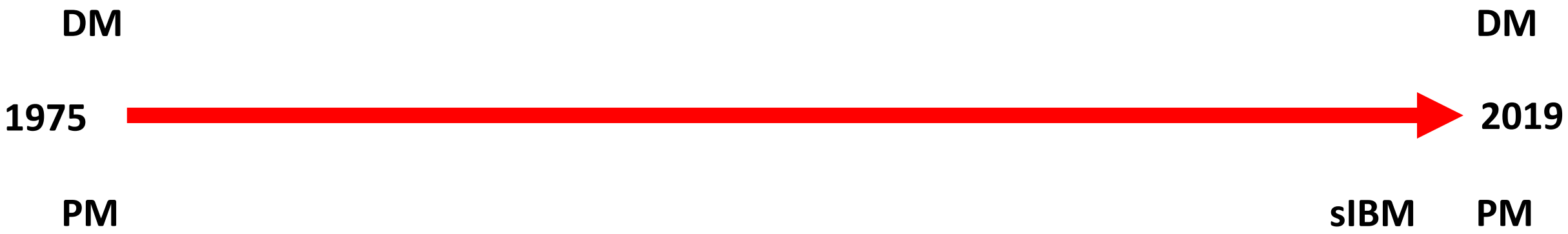

Cluster 1
Cluster 2
Cluster 3
Cluster 4
DM
Myosite à Inclusions
MNAI
SAS
Dimension 1 (10.0%)
Dimension 2 (6.6%)
1.0
0.5
0
−0.5
−1.0


Cluster 1
Cluster 2
Cluster 3
Cluster 4
DM
anti-Mi2
anti-NXP2
anti-SAE2
anti-TIF1g2
anti-MDA5
anti-C1NA
Myosite à Inclusions
MNAI
anti-HMGCR
anti-SRP
SAS
anti-Jo1
anti-PL7
anti-PL12
anti-OJ
anti-EJ
anti-ZO
anti-KS
anti-HA
Dimension 1 (10.0%)
Dimension 2 (6.6%)
1.0
0.5
0
−0.5
−1.0

DM

1975

PM


DM
1975
PM
DM
2019
sIBM
PM

DM

1975 → 2019

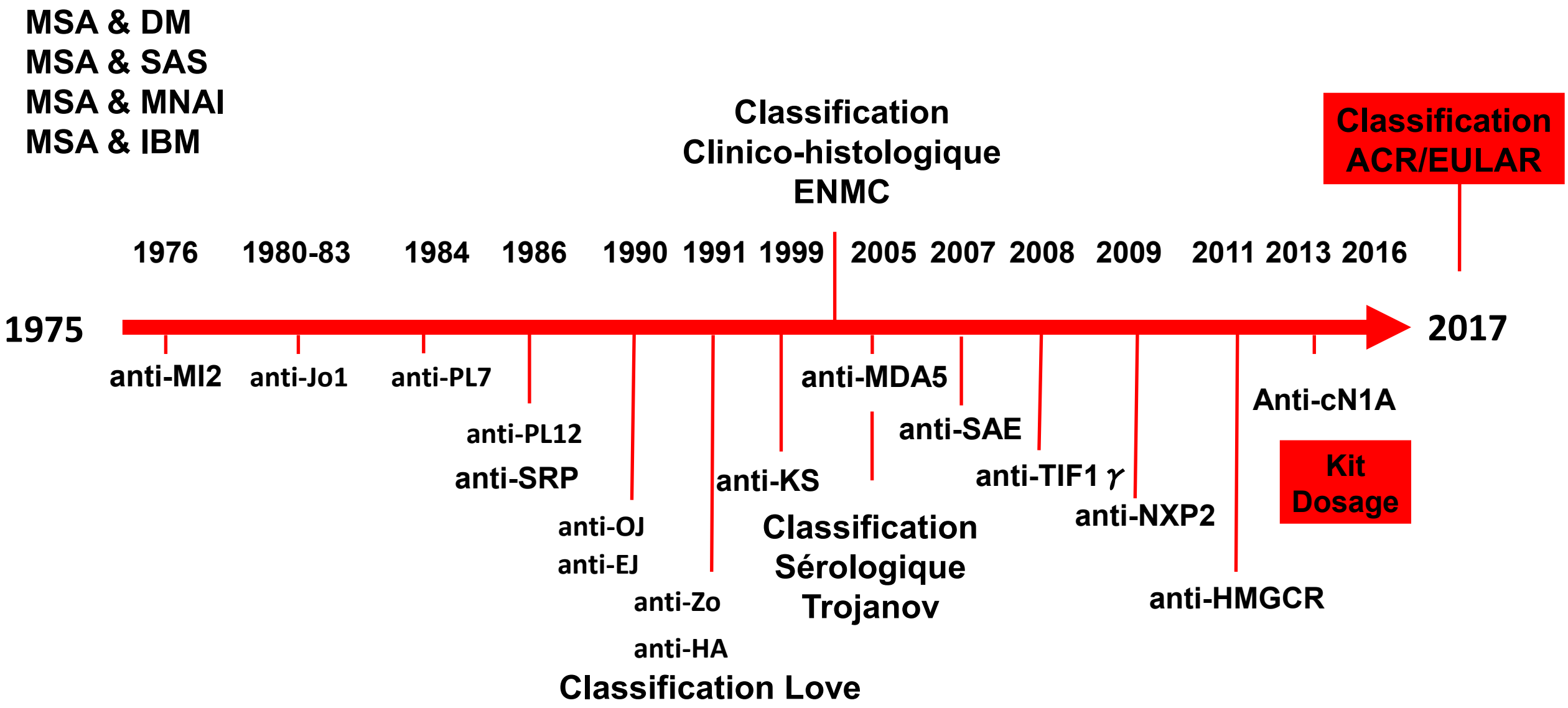
PM

SAS

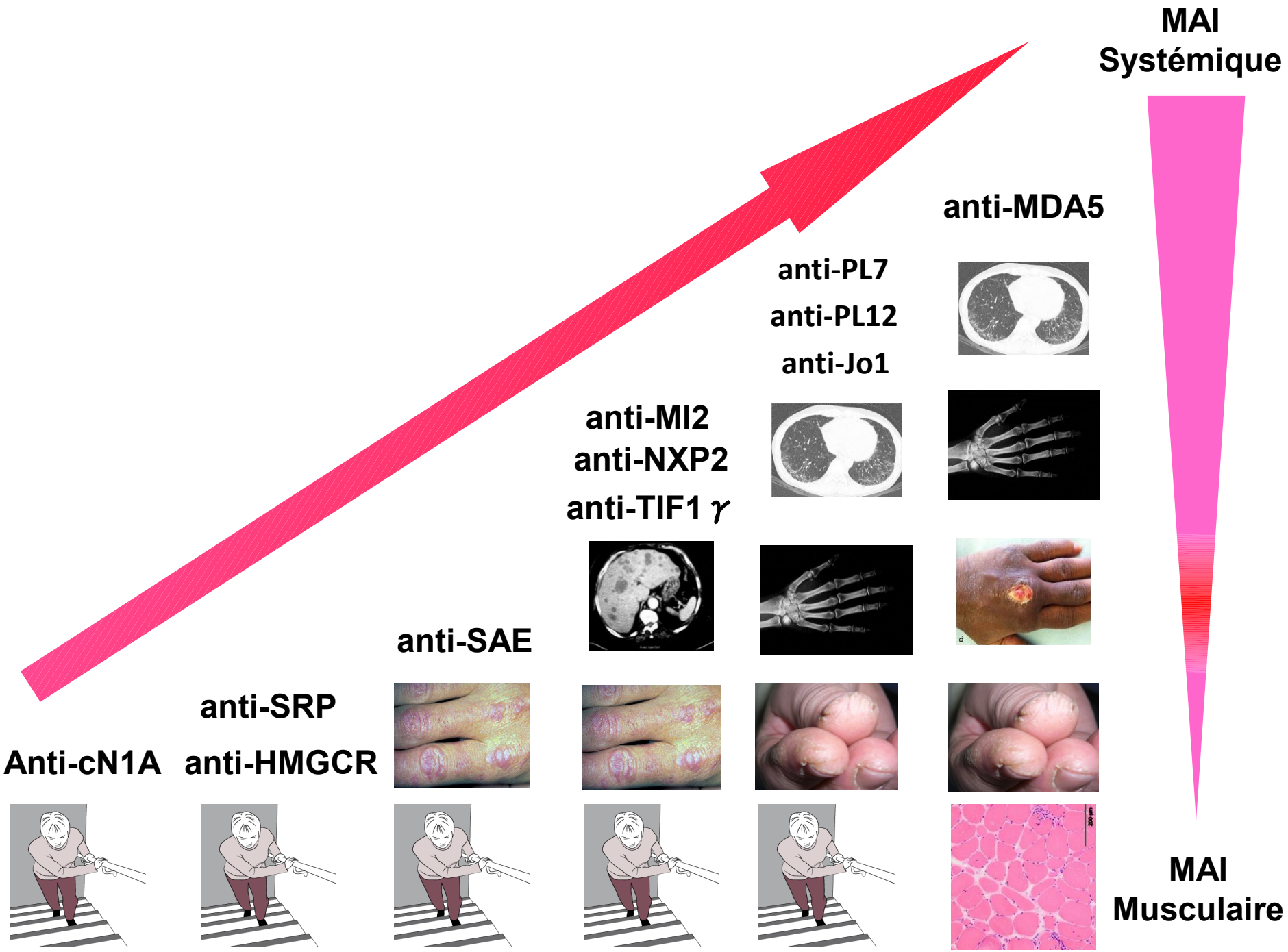
DM

sIBM

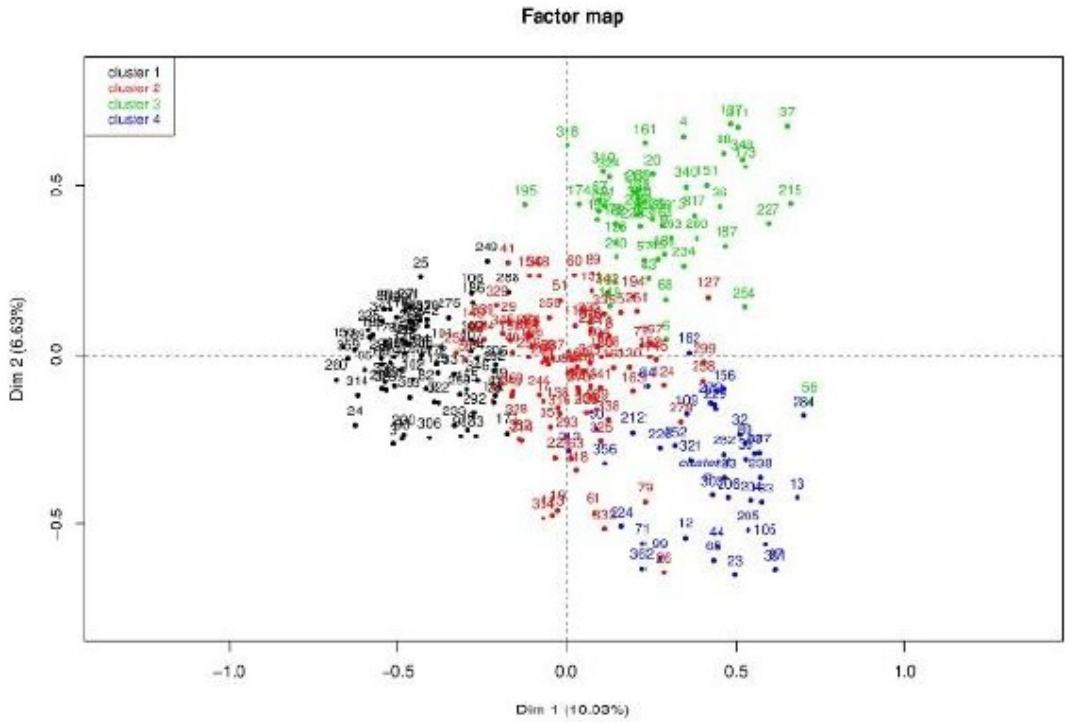
MNAI


MSA & DM
MSA & SAS
MSA & MNAI
MSA & IBM
Classification
Clinico-histologique
ENMC
Classification
ACR/EULAR
1976
1980-83
1984
1986
1990
1991
1999
2005
2007
2008
2009
2011
2013
2016
1975
2017
anti-MI2
anti-Jo1
anti-PL7
anti-PL12
anti-SRP
anti-OJ
anti-EJ
anti-Zo
anti-HA
Classification Love
anti-KS
anti-MDA5
Classification
Sérologique
Trojanov
anti-SAE
anti-TIF1 γ
anti-NXP2
anti-HMGCR
Anti-cN1A
Kit
Dosage

3- Un Ac un phénotype

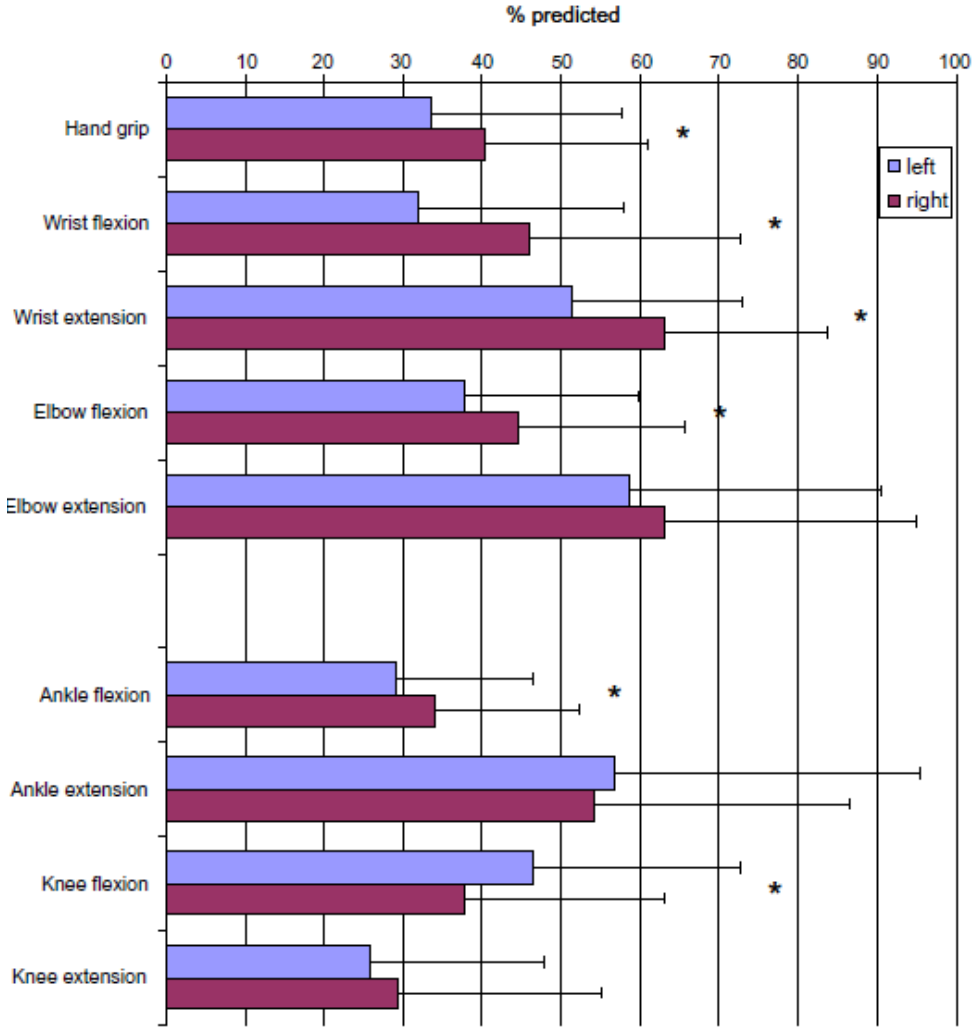

MAI
Systémique
anti-MDA5
anti-PL7
anti-PL12
anti-Jo1
anti-MI2
anti-NXP2
anti-TIF1 γ
anti-SAE
anti-SRP
anti-HMGCR
Anti-cN1A
MAI
Musculaire

1-Myosite à Inclusions



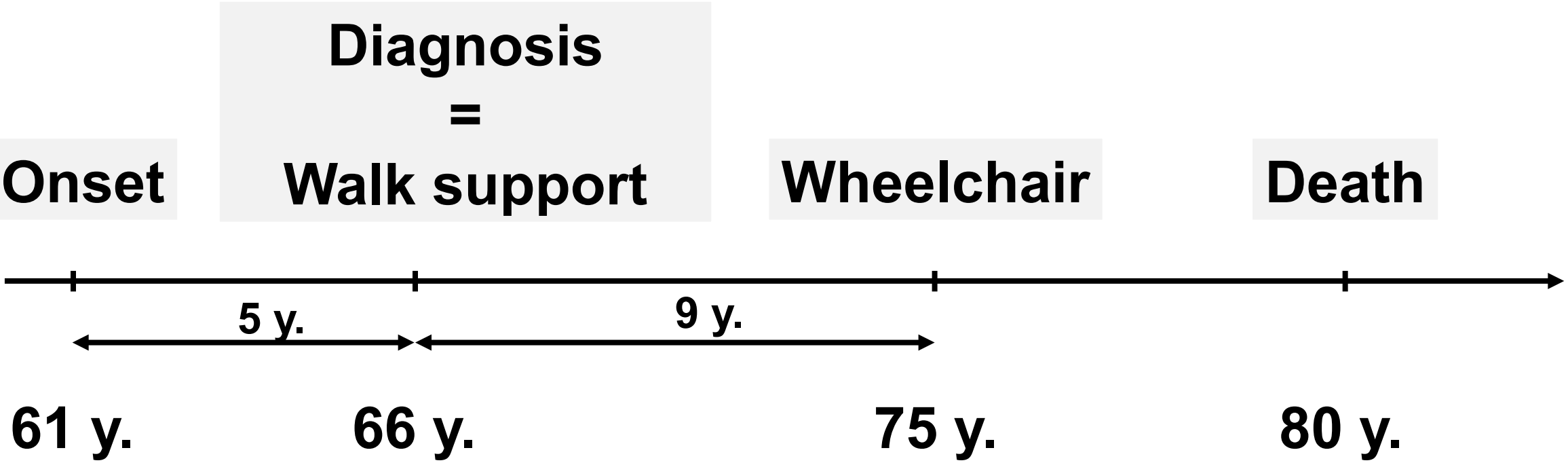
Anti-cN1A

Phénotype musculaire

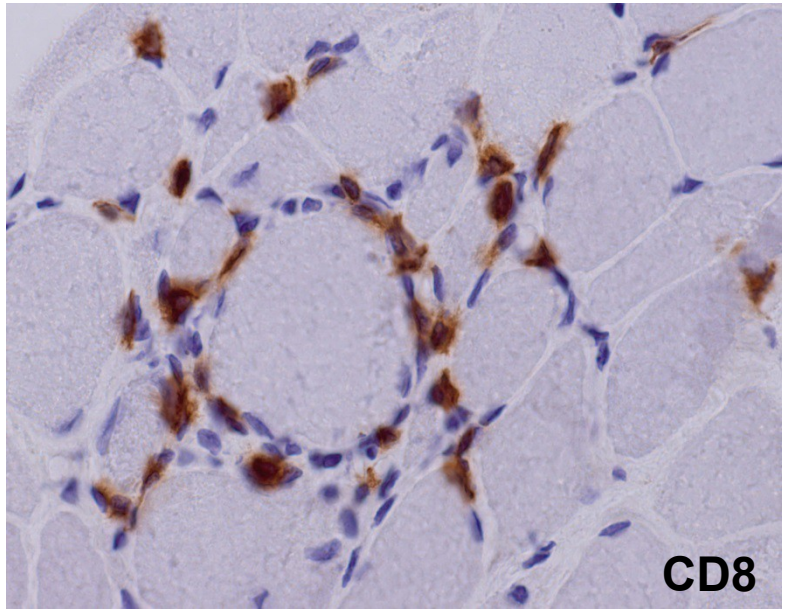


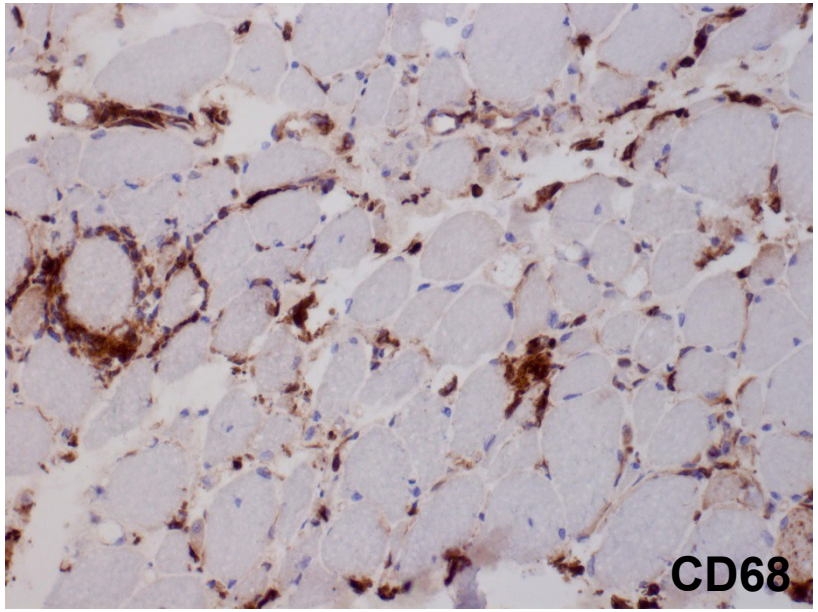
Tbs de la deglutition 40% des cas

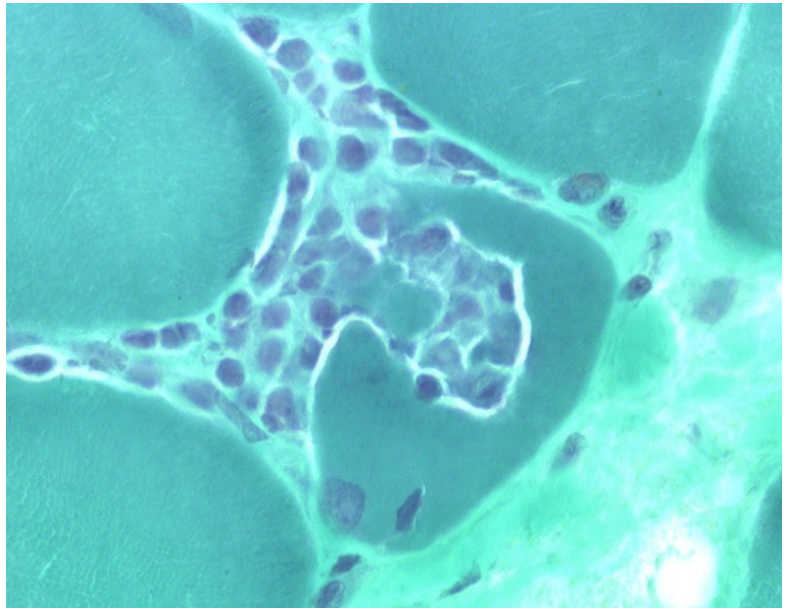
Allenbach et al. NMD 2015

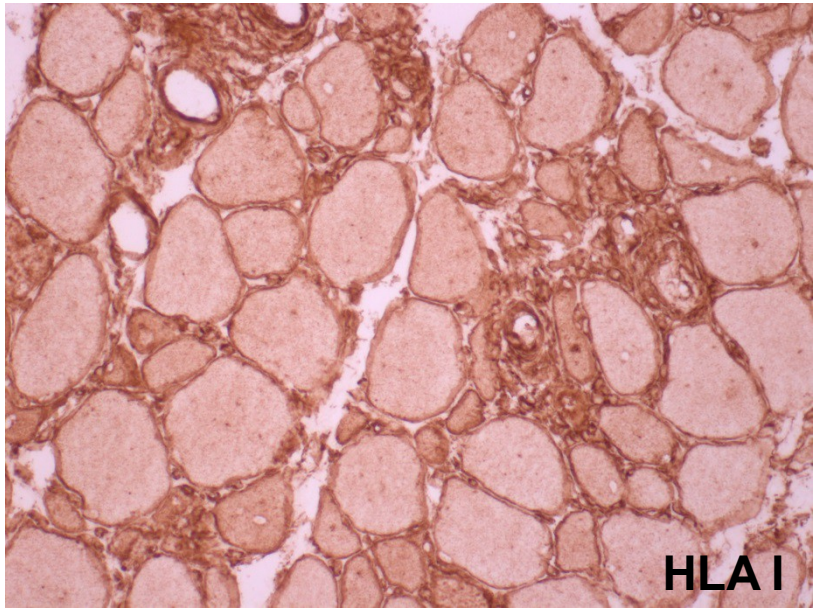


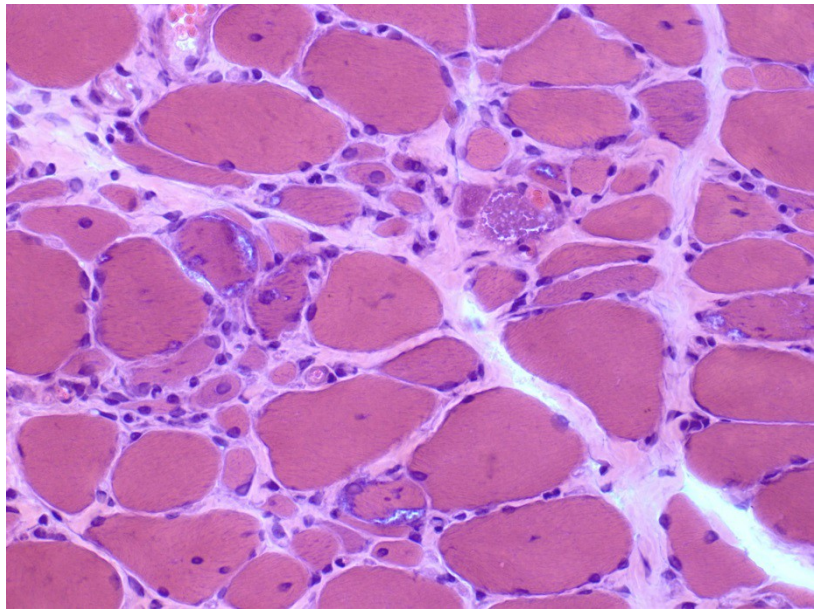
Benveniste et al. Brain

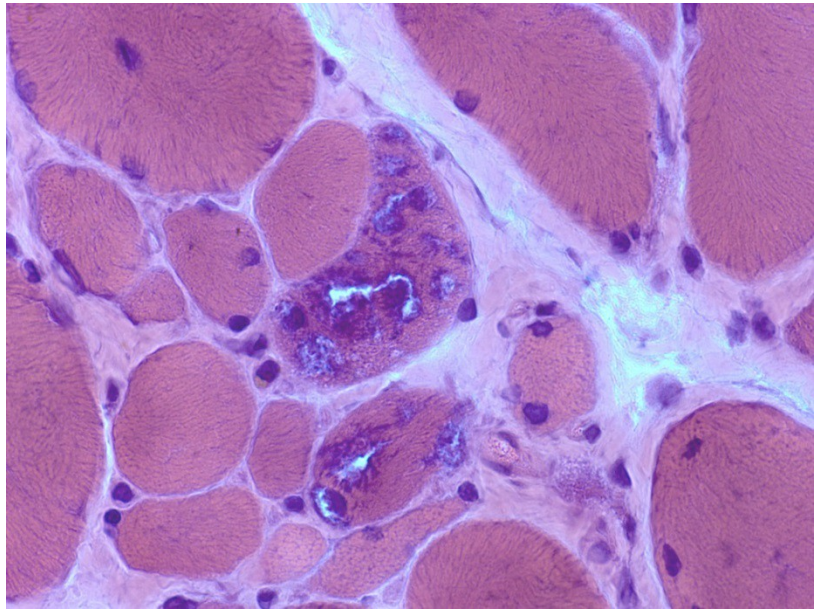

CD8

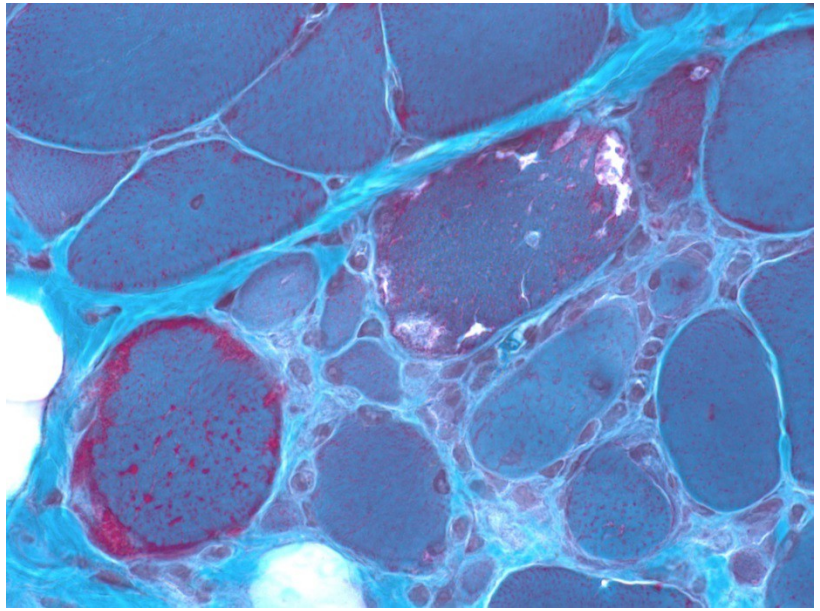

CD68

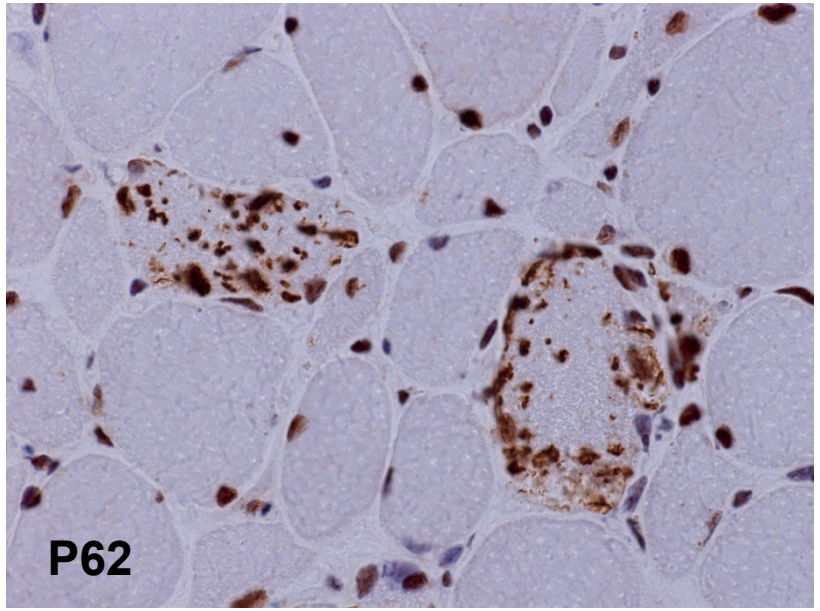



HLA I

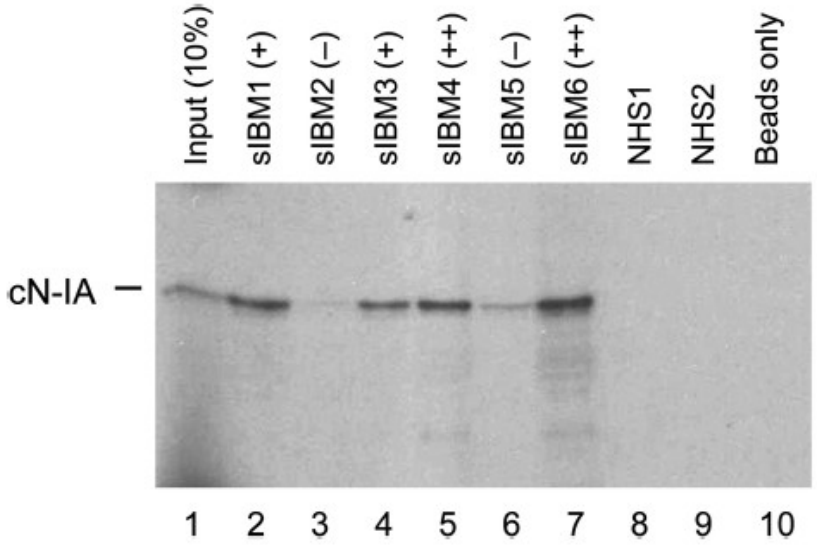


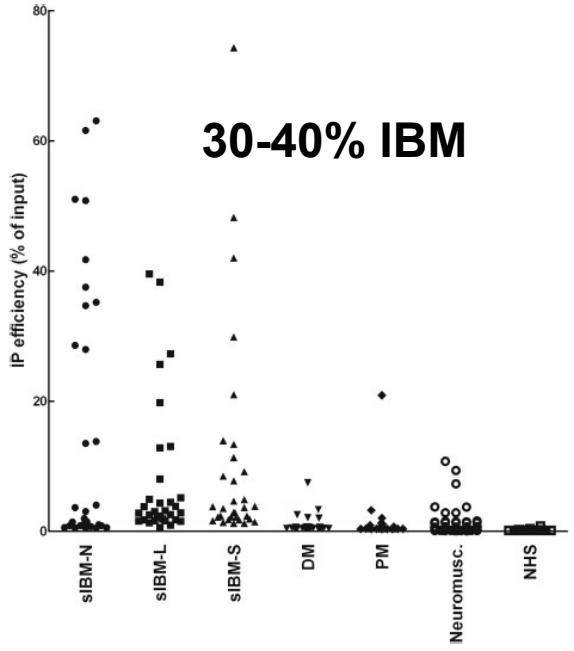


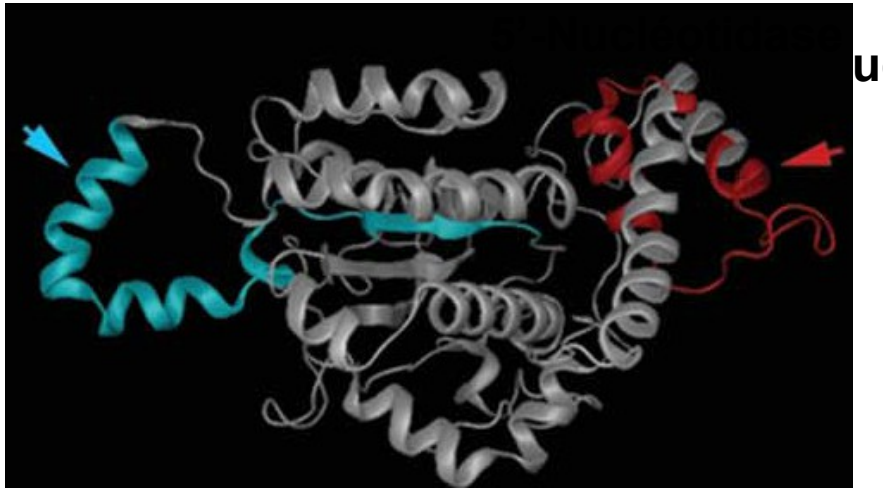



P62

Myosites à Inclusions : Ac spécifiques







ucléotidase

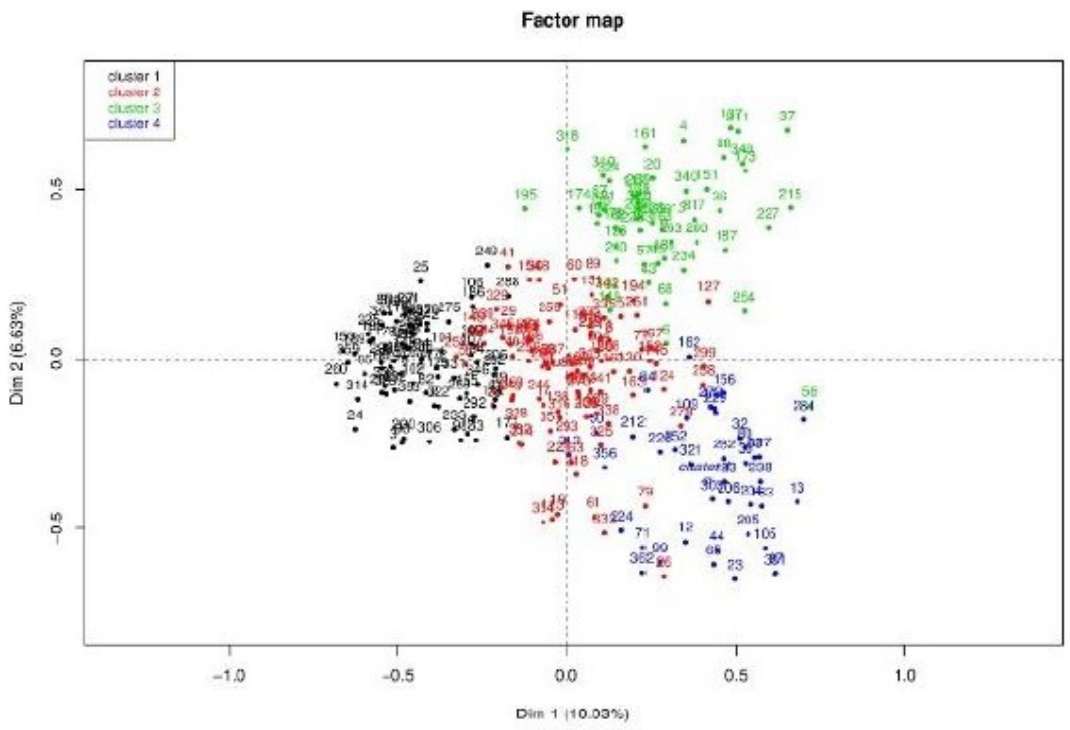
13.5% SLE (n=96)
22.7% SS (n=10)
jDM 30%

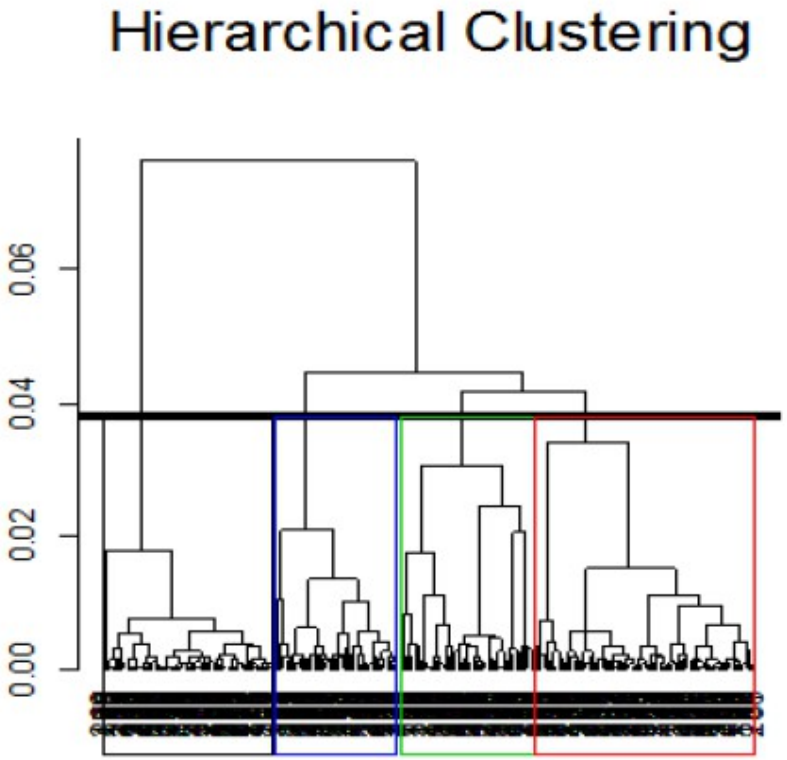
Van Engelen Ann. Neuro 2013
Greenberg Ann. Neuro 2013
Greenberg Muscle and Nerve 2014
TE. Lloyd Arthritis Ther res2015

sIBM et Poumon

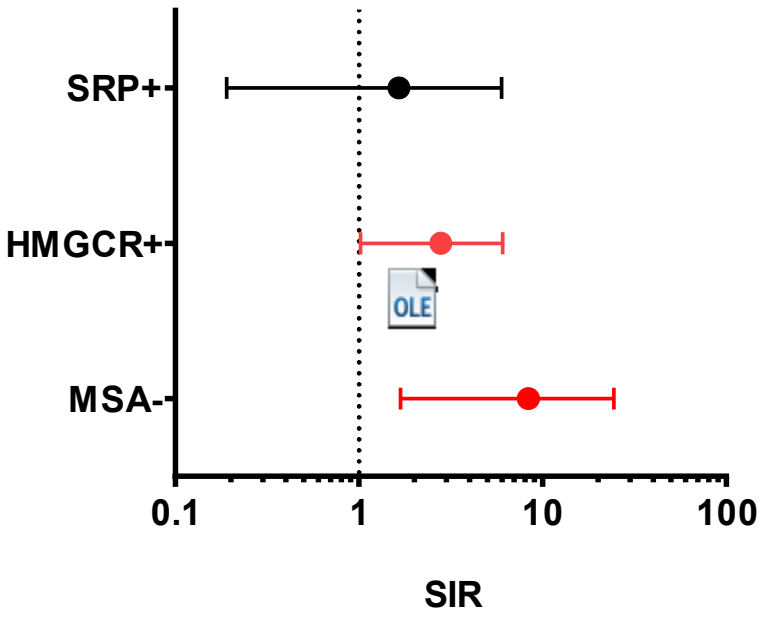
TVR – VNI en fin d’évolution

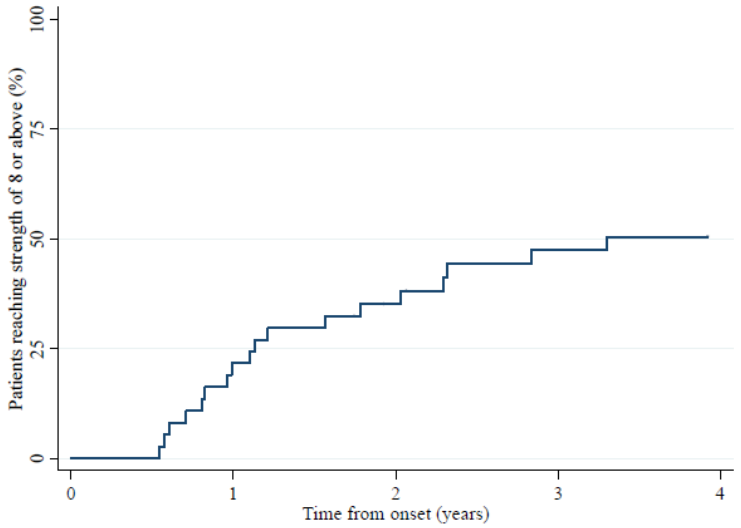
2-Myopathies Nécrosantes



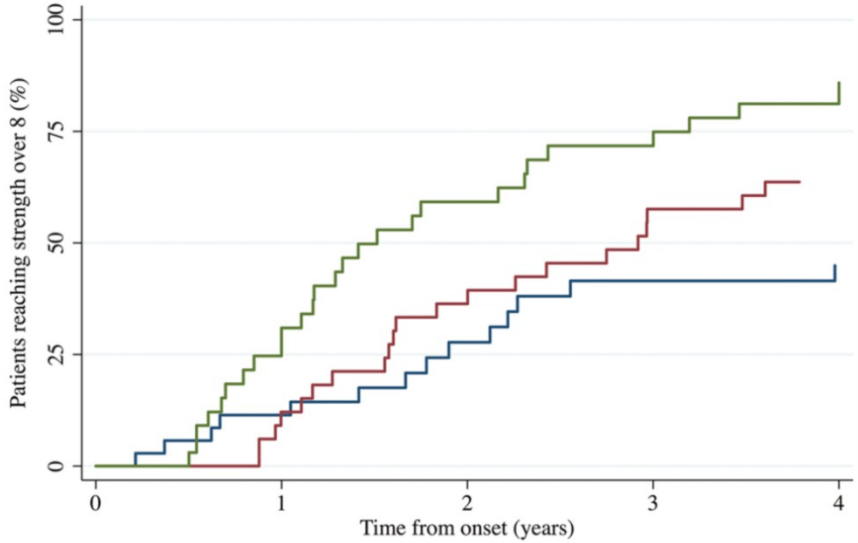


	MSA− patients $n = 14$	Anti-HMGCR+ patients $n = 52$	Anti-SRP+ patients $n = 49$	P-values
Age (years) at diagnosis of myopathy	53 ± 15	50 ± 22	47 ± 17	0.6
Statin exposure (%)	7.1 (1/14)	46.1 (24/52)	19.1 (5/26)	**0.004**
Percentage female (%)	73	73.1	67.3	0.8
Muscle strength (MRC)	2.9 ± 1	2.8 ± 0.9	2.1 ± 1.3	**0.0006**
Creatine kinase level (I.U/l)	10 156 ± 14 658	7012 ± 5944	8453 ± 6547	0.39
Dermatomyositis rash (%)	0 (0/14)	0 (0/37)	2.3 (1/44)	0.46





strength recovery over time in SRP+ patients



HMGCR+ patients

Allenbach, Benveniste et al. 2016

Tiniakou et al. 2015

Pinal-Fernandes et al. 2016

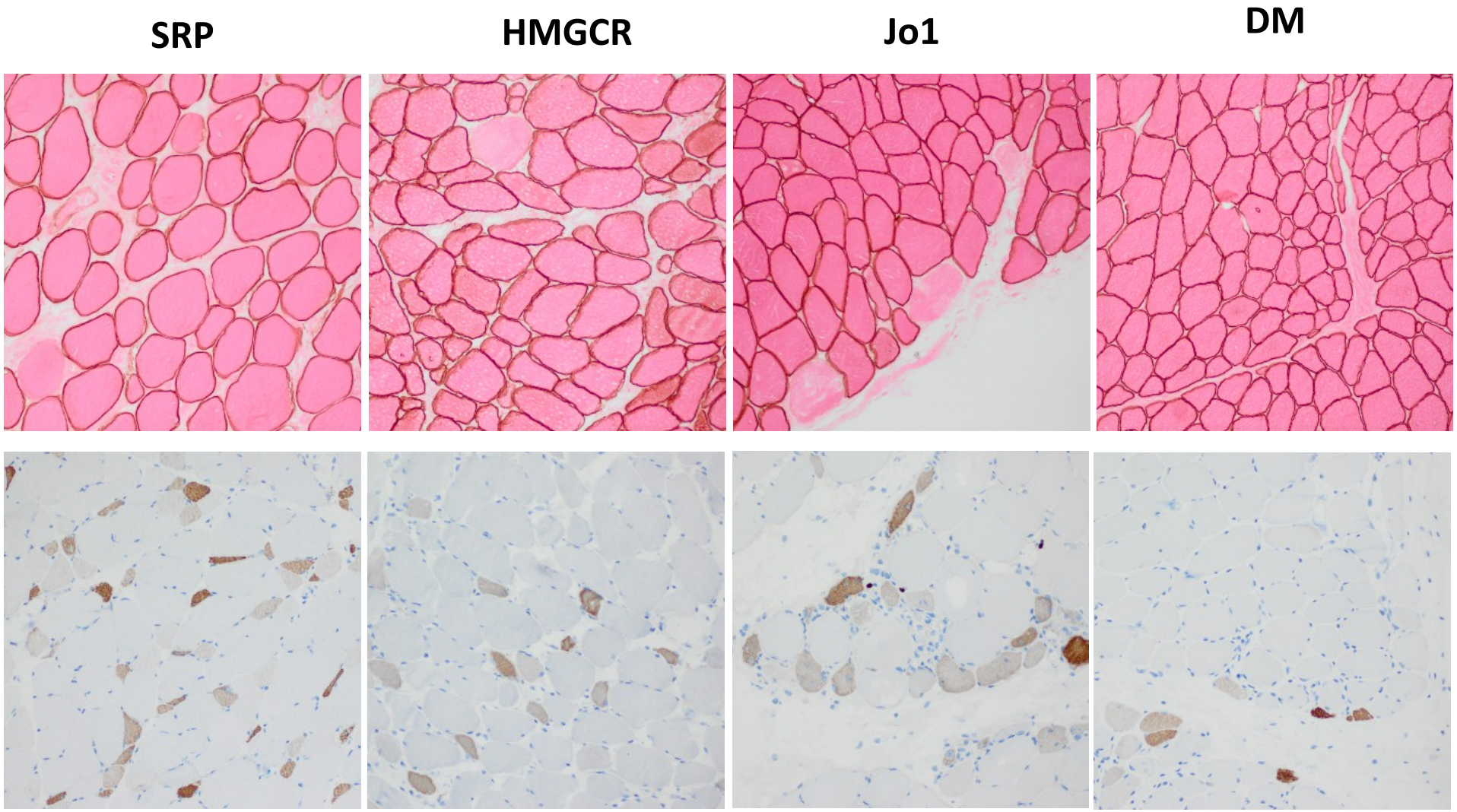
Table 2 Extent of thigh MRI findings among clinical subsets

	IMNM							
	Total (n=101) Mean (SD)	HMGCR (n=50) Mean (SD)	SRP (n=22) Mean (SD)	IBM (n=153) Mean (SD)	PM (n=176) Mean (SD)	DM (n=219) Mean (SD)	CADM (n=17) Mean (SD)	Total (n=666) Mean (SD)
Oedema	55.5 (32.2)***	58.9 (31.8)	65.8 (28.9)	48.1 (24.6)***	29.4 (30.5)***	30.1 (36.7)***	6.1 (18.5)***	37.3 (33.5)
Atrophy	23.2 (28.7)**	21.7 (28.9)*	38.2 (30.2)*	32.2 (26.7)***	12.7 (24.6)*	5.7 (16.7)***	2.5 (7.4)*	16.2 (25.5)
Fatty replacement	38.0 (33.1)*	34.4 (30.9)	49.1 (31.2)	50.1 (27.3)***	28.3 (31.1)	17.5 (27.0)***	7.1 (12.8)**	30.7 (31.6)
Fascial oedema	6.2 (15.1)*	5.1 (15.2)	6.0 (12.2)	6.0 (12.0)**	5.8 (11.8)**	16.5 (24.3)***	8.6 (17.0)	9.5 (18.1)

Mean percentage of each major clinical group (IMNM, IBM, PM, DM and CADM) compared with the rest of the sample using Student's t-test. In separate analyses, patients with anti-HMGCR and anti-SRP were compared to each other only.
*<0.05; **<0.01; ***<0.001.
CADM, clinically amyopathic dermatomyositis; DM, dermatomyositis; HMGCR, HMG-CoA reductase; IBM, inclusion body myositis; IMNM, immune-mediated necrotising myopathy; PM, polymyositis; SRP, signal recognition particle.

Christopher-Stine ARD 2016

NAM Ac anti SRP et HMGCR: histologie



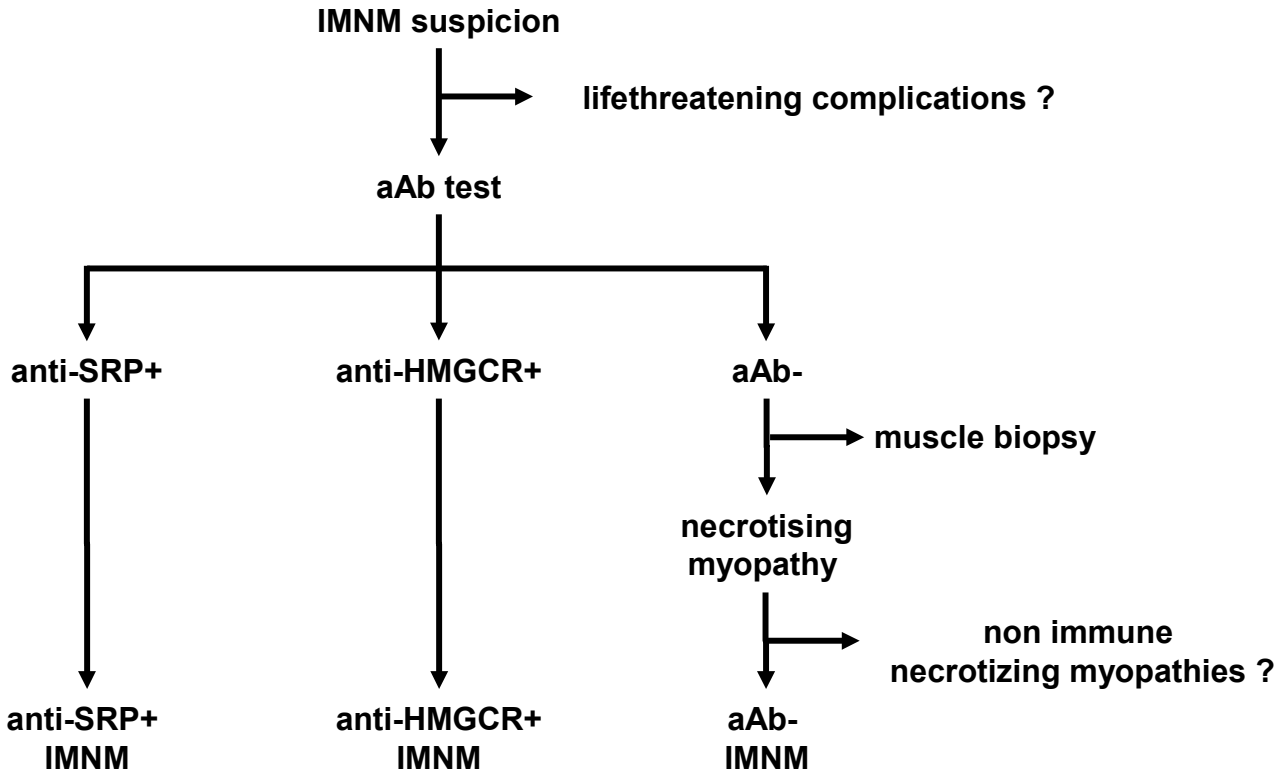
Allenbach et al. soumis

224th ENMC International Workshop:
Clinico-sero-pathological classification of immune-mediated necrotizing myopathies
Zandvoort, The Netherlands, 14–16 October 2016

Yves Allenbach [a,1], Andrew L. Mammen [b,1], Olivier Benveniste [a,2], Werner Stenzel [c,2,*] on behalf of the Immune-Mediated Necrotizing Myopathies Working Group [3]

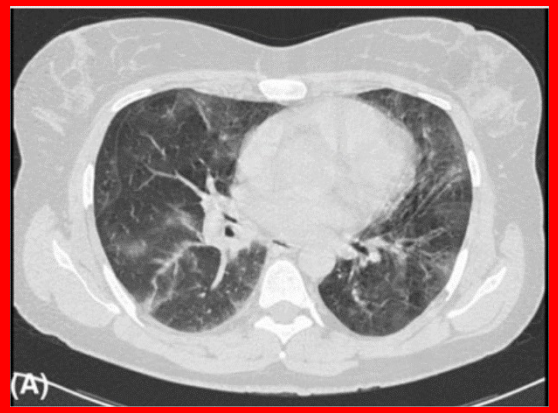
[a] *Department of Internal Medicine, Pitie Salpetrière Hospital, AP-HP Sorbonne university, Paris, France*
[b] *National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA*
[c] *Department of Neuropathology, Charité-Universitätsmedizin, Berlin, Germany*

Received 31 July 2017



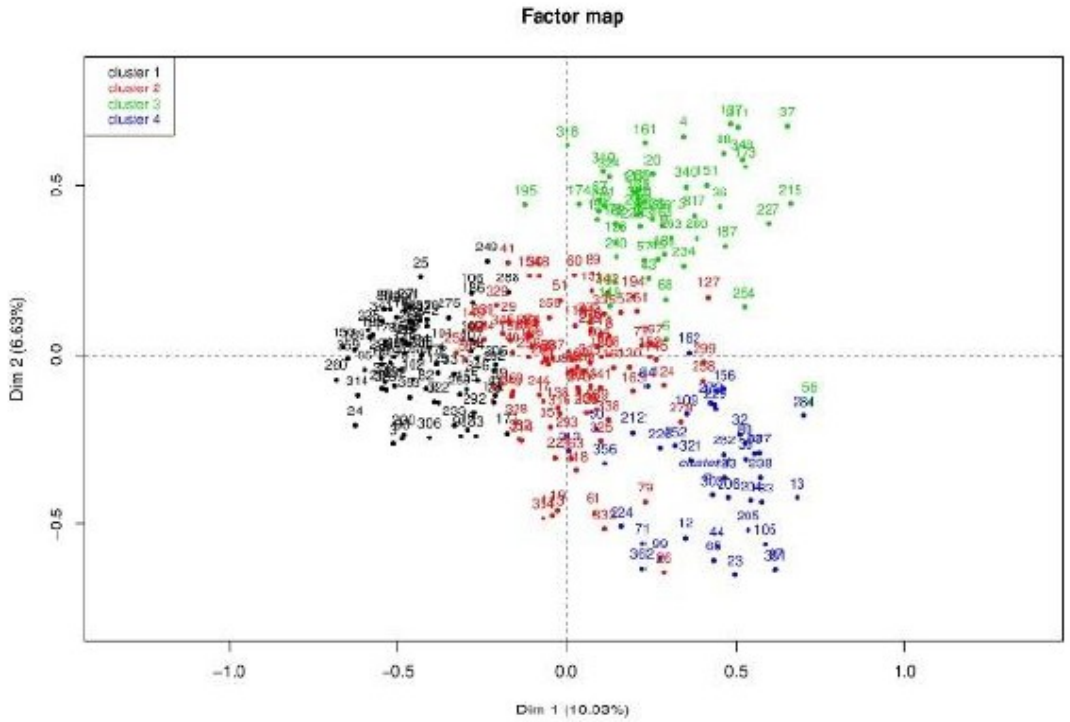
MNAI et Poumon

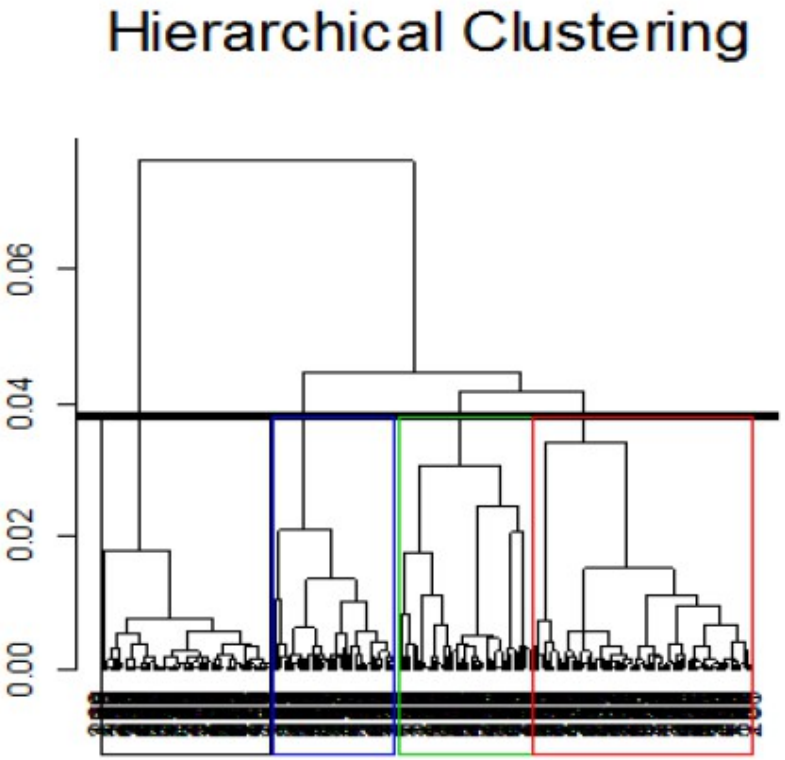
- TVR – VNI - IOT parfois précoce
- HMCGR+: PAS ILD
- SRP+: ILD Non sévère

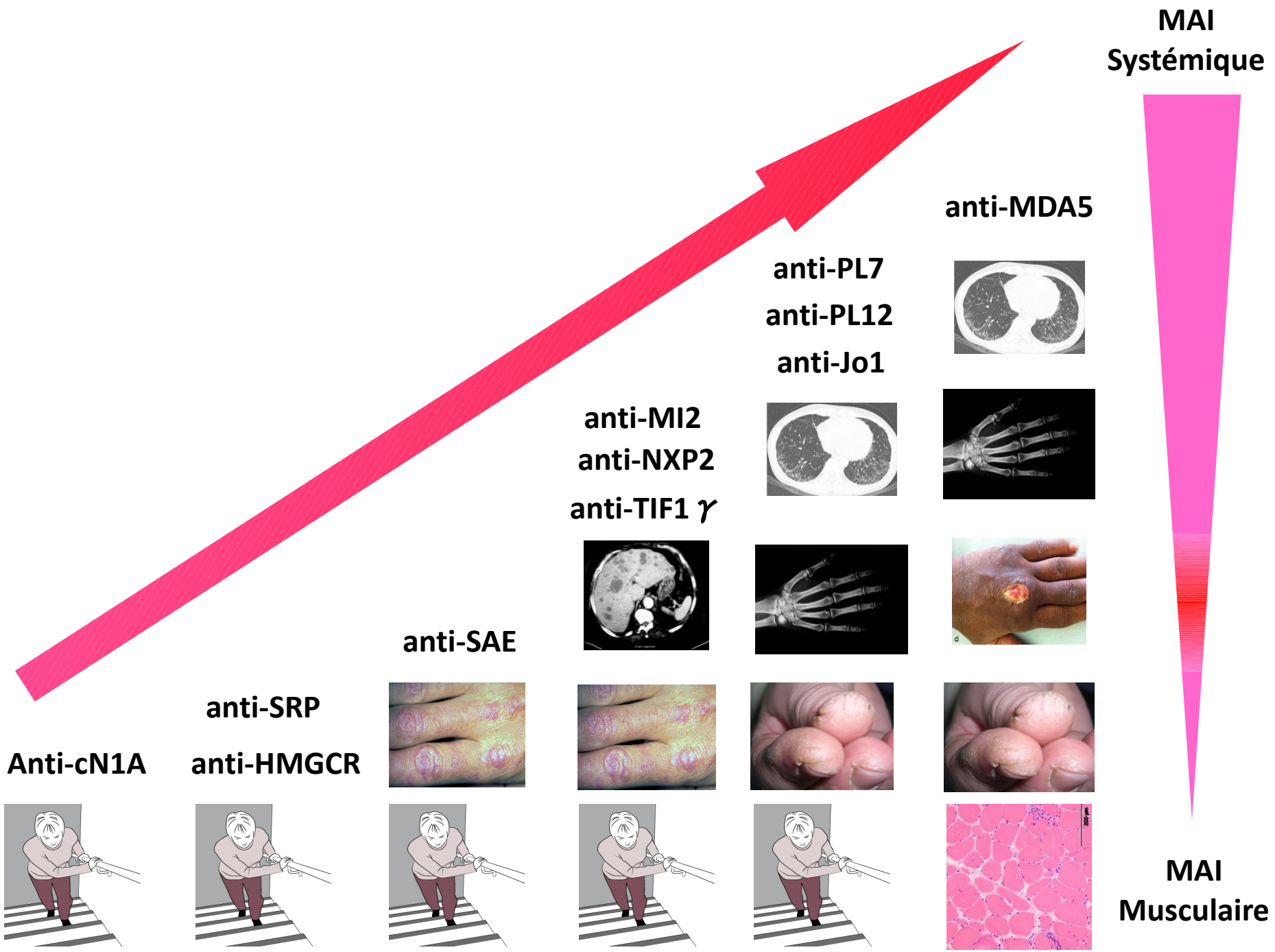


	Targoff	Miller	Kao	Hengstman	Suzuki	Takada	Wang	Basnayake	Suzuki	Pinal - Fernandez	Picard	Benveniste		
	1990	2002	2004	2006	2008	2009	2014	2014	2015	2016	2016	2016		
	USA	USA	USA	Europe	Asia	Asia	Asia	Australia	Asia	USA	Europe	Europe	Total	SD
n	13	7	19	23	8	23	16	5	100	37	36	147	434	
ILD	10	NA	19	22	38	24	19	0	13	NA	19	37	20,1	11,

2-Dermatomyosite



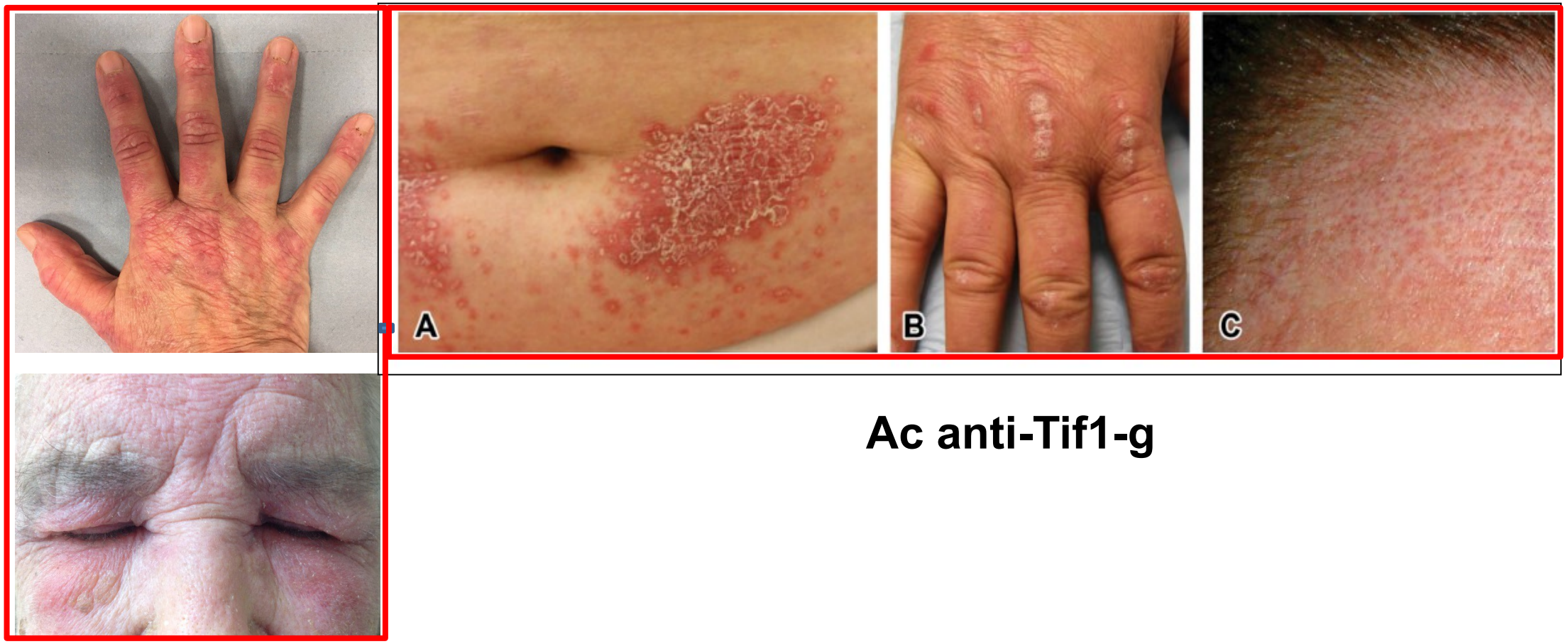



MAI
Systémique
anti-MDA5
anti-PL7
anti-PL12
anti-Jo1
anti-MI2
anti-NXP2
anti-TIF1 γ
anti-SAE
anti-SRP
anti-HMGCR
Anti-cN1A
MAI
Musculaire

Typique DM

Fiorentino et al. 2015

Typique DM

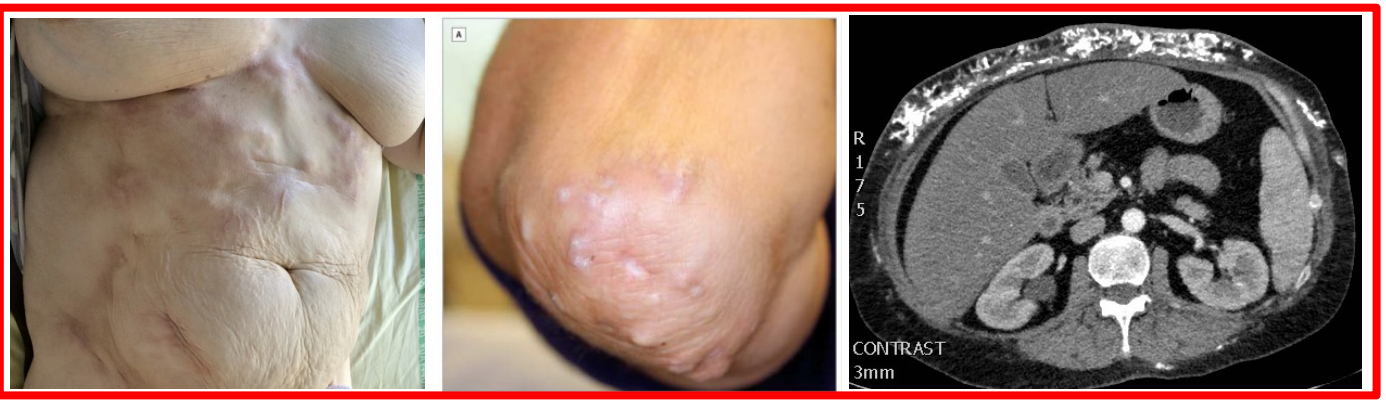


Ac anti-Tif1-g

Fiorentino et al. 2015

Typique DM

Ac anti-NXP2

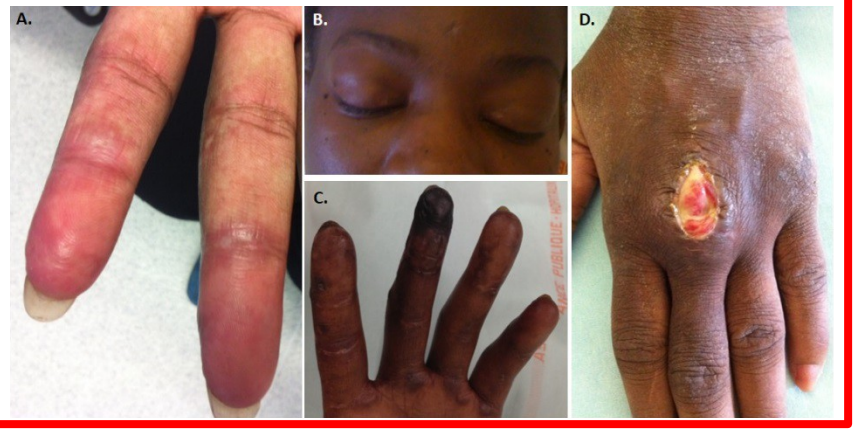


Fiorentino et al. 2012

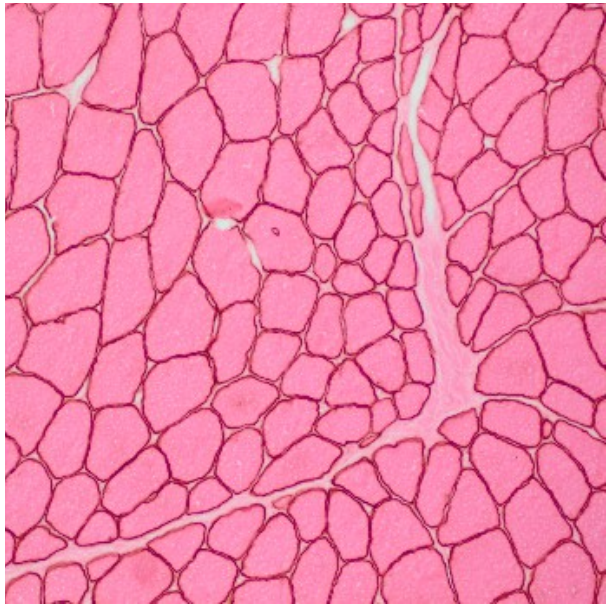
Fiorentino et al. 2015

Typique DM

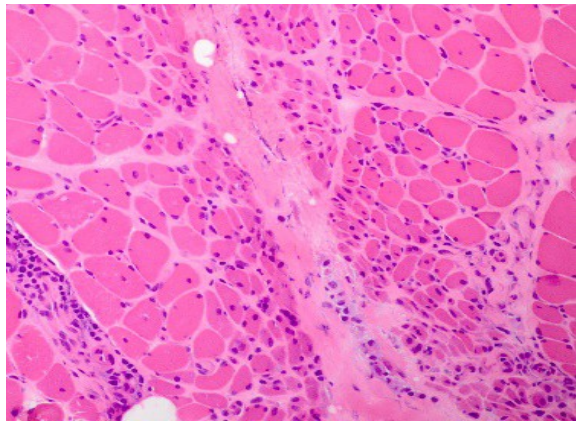
Ac anti-MDA5



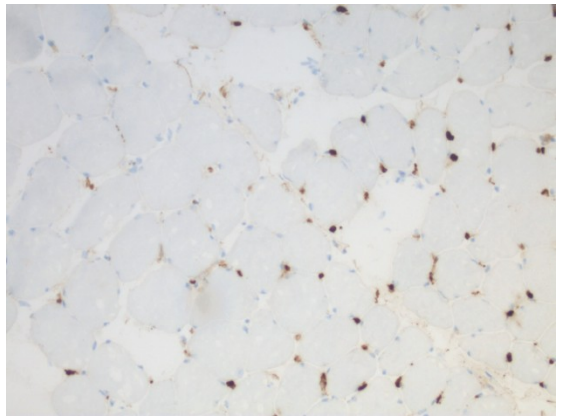
SAE



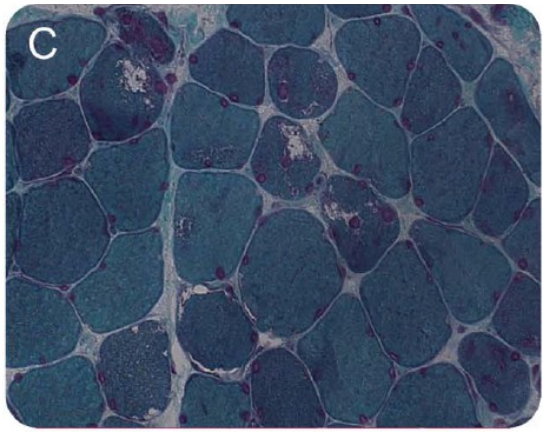
DM



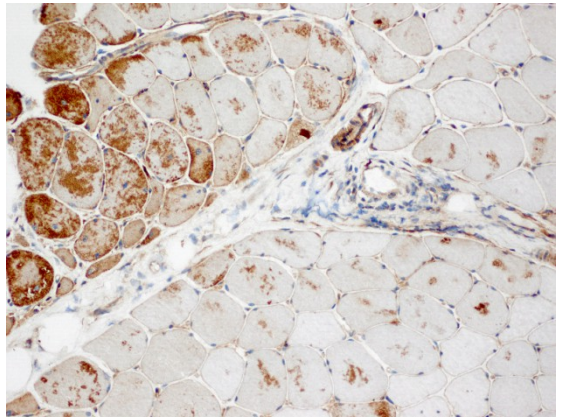
MI2



NXP2



TIF1 g



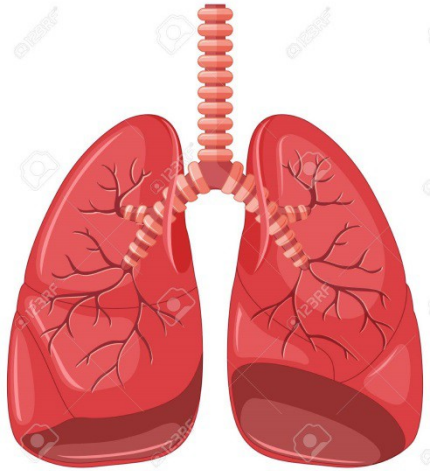
MDA5

W. Stenzel et al. 2016

	Dermatomyositis
Environmental exposures—% per diagnosis	
Current or previous smoker (n=1646)	33
Environmental toxin exposure (n=930)	16
Extramuscular complications— % per diagnosis	
Interstitial lung disease (n=2442)	21

DM

> 40 ans



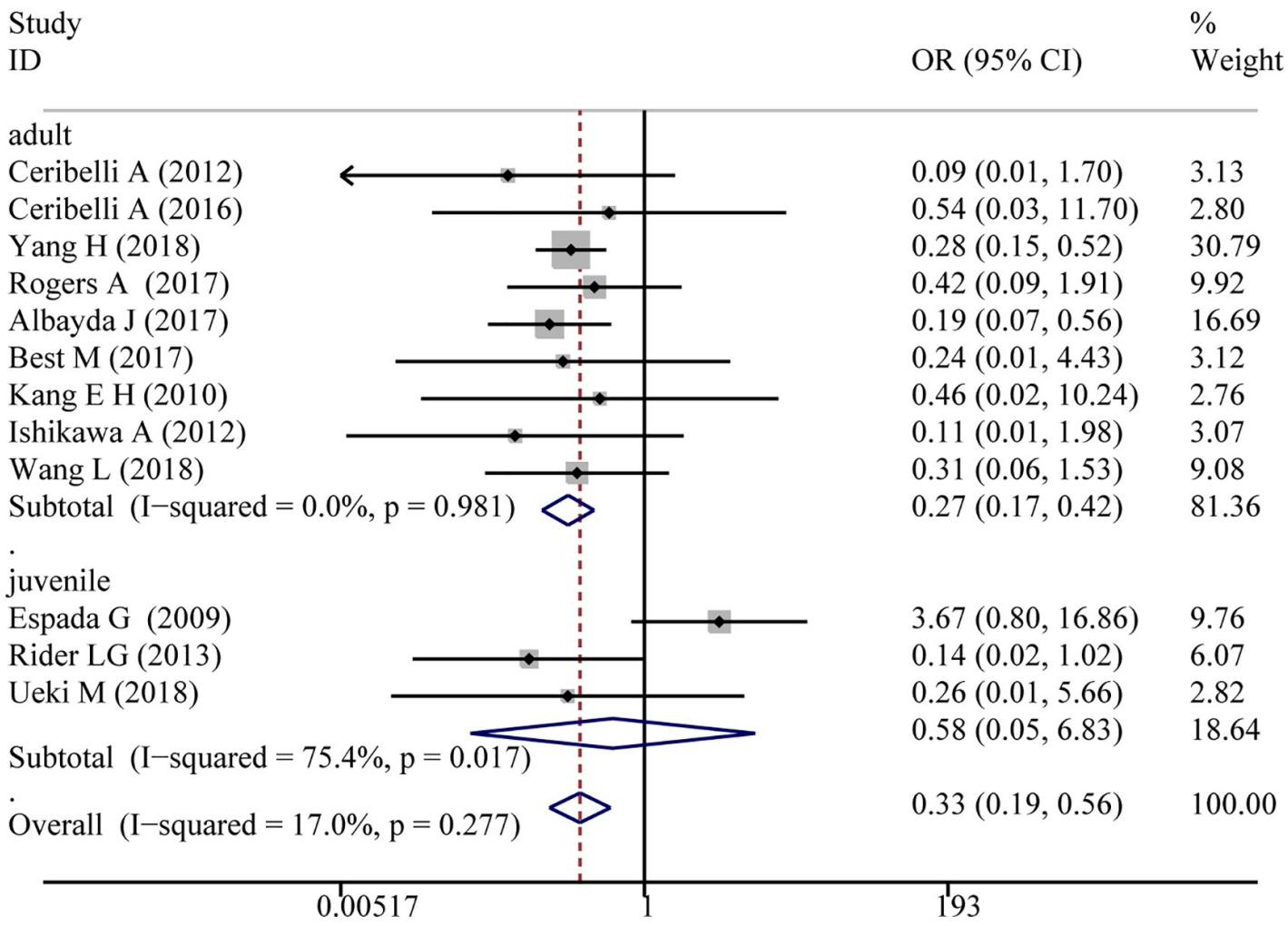
MI2

TIF1-γ

SAE

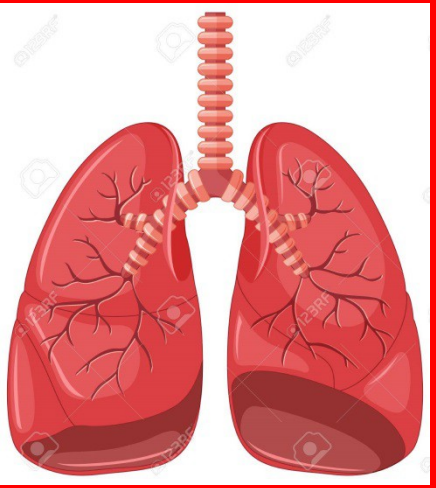
NXP-2

MDA5



Camille Rasmussen et al.
DM NXP2+ n = 30
ILD=0

DM



MI2

TIF1-γ

SAE

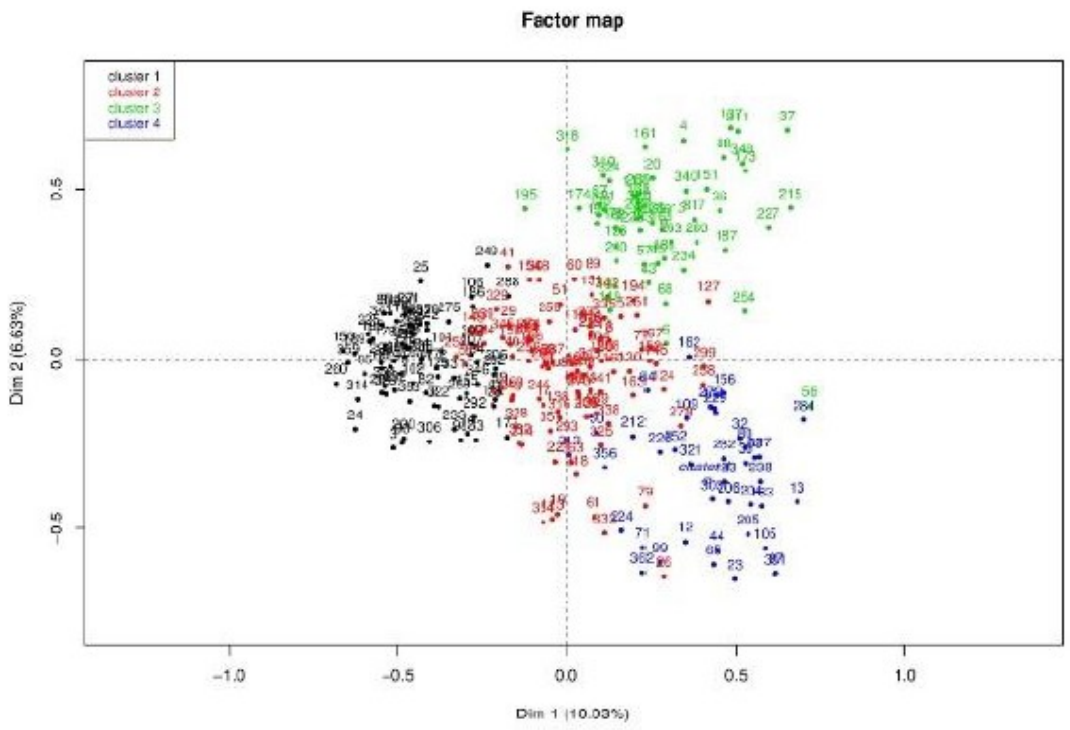
NXP-2

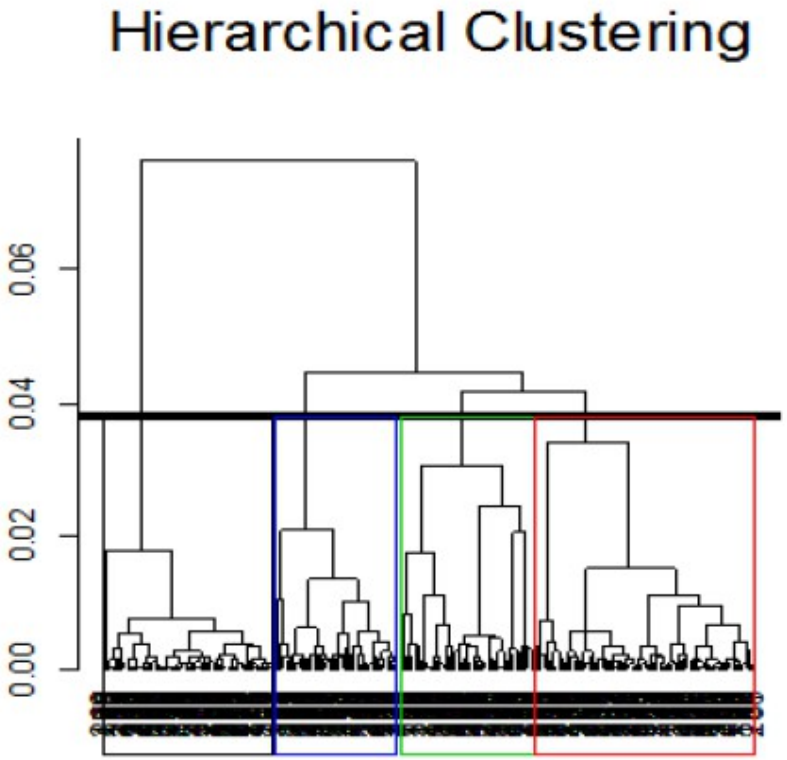
MDA5

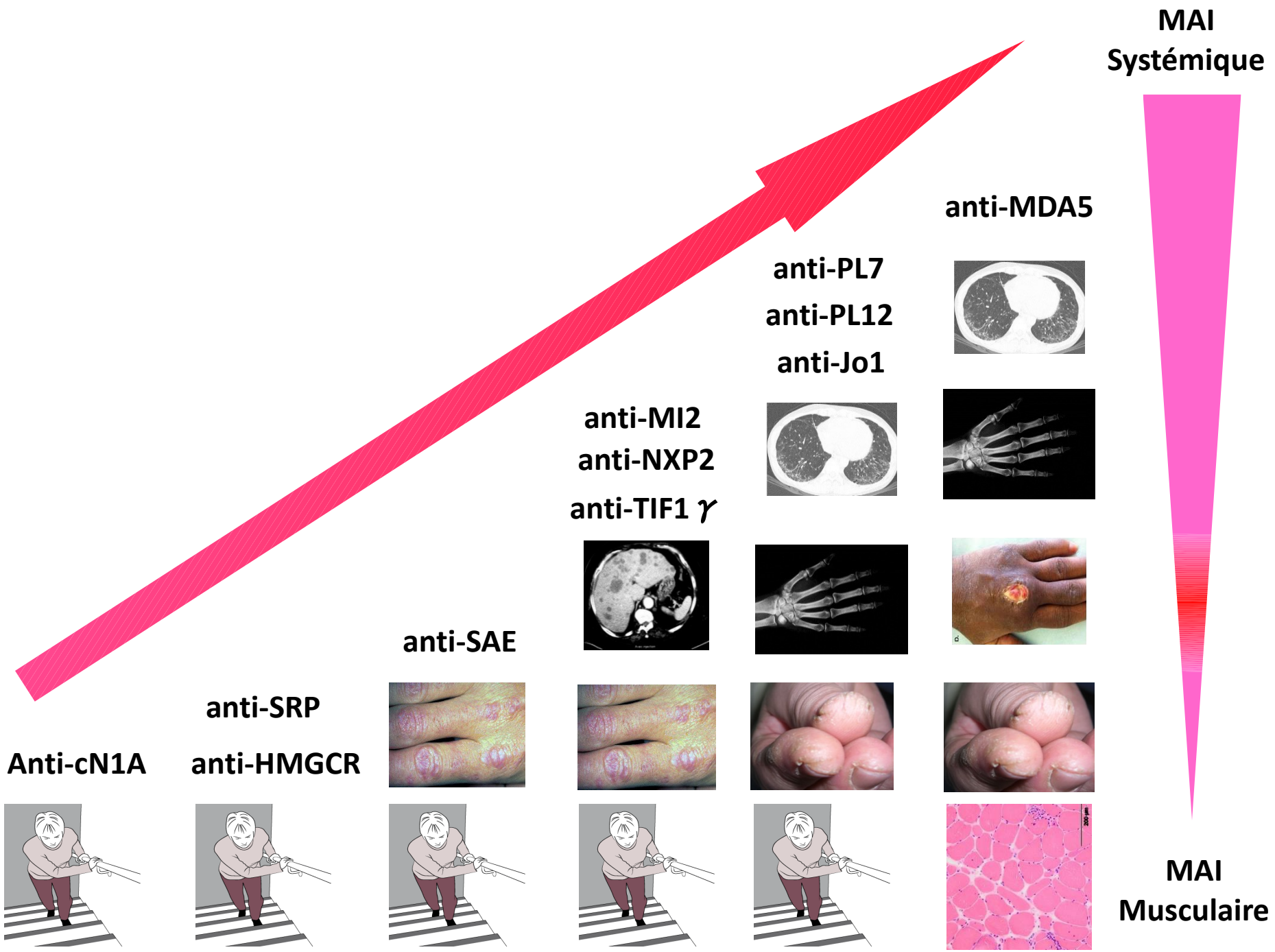
ILD et RPILD et Décés MDA5+

POC - DAD

4-Syndrome des anti-synthétases





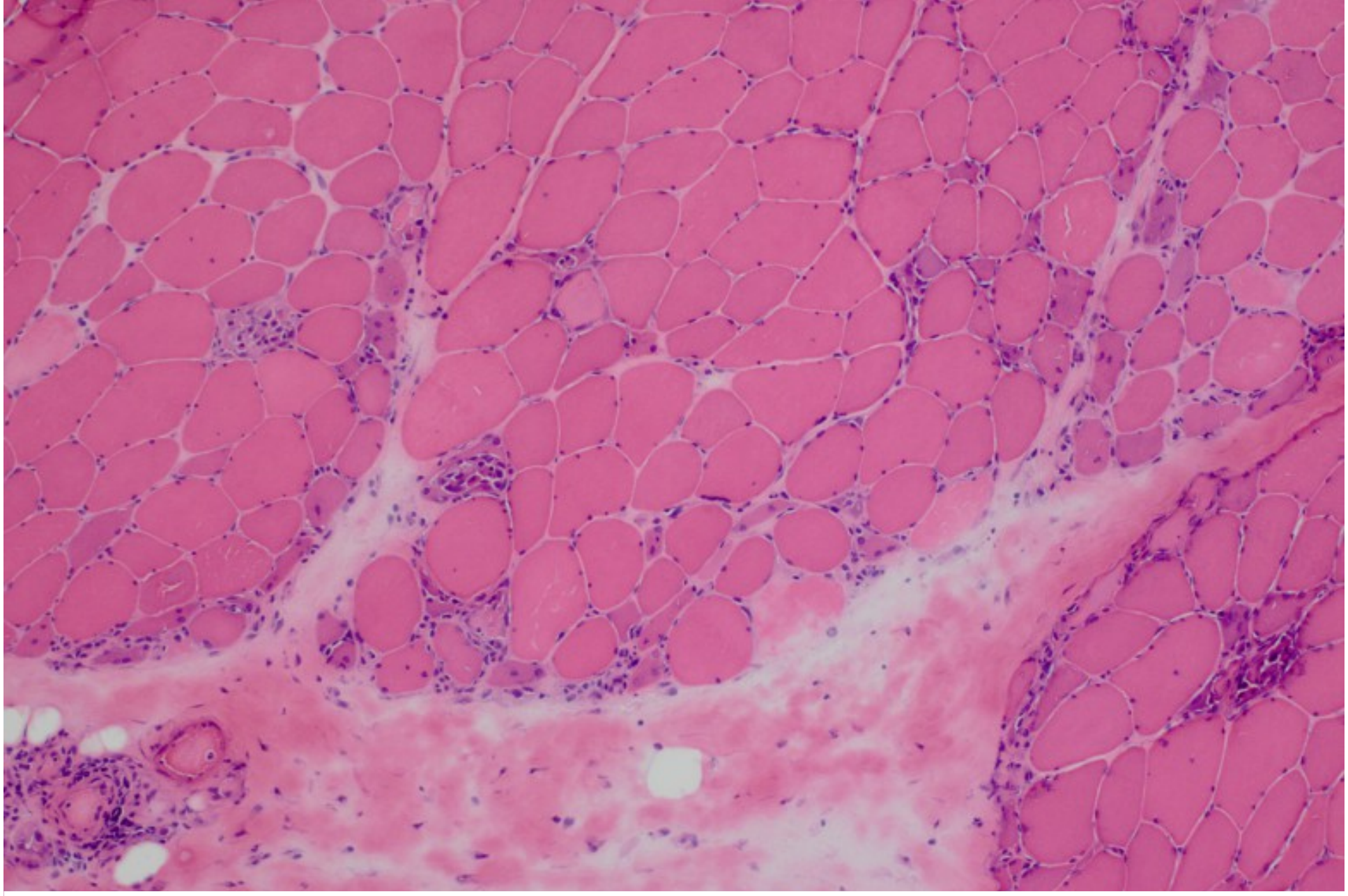

MAI
Systémique
anti-MDA5
anti-PL7
anti-PL12
anti-Jo1
anti-MI2
anti-NXP2
anti-TIF1 γ
anti-SAE
anti-SRP
anti-HMGCR
Anti-cN1A
MAI
Musculaire

Syndromes des Anti-synthétases Jo-1+




Tableau 2
Prévalence des différents signes cliniques au cours des différents syndromes des antisynthétases selon le sous type d'anticorps anti-aminoacyl-ARNt synthétase (AAS) : données moyennées à partir des séries les plus larges ou les plus récentes.

Nombre de séries	6	2	5	1	1
Références	[5,7,20,22,53,56]	[5,31]	[5,6,60–62]	[58]	[57]
Nombre de patients	435	79	71	7	6
Sous-type d'AAS	Jo-1	PL12	PL7	OJ	EJ
Femmes/Hommes	2,4	2,8	2,1	1,3	2
Fièvre (%)	31	41	43	43	–
Phénomène de Raynaud (%)	44	54	44	0	67
Myosite (%)	81	44	75	57	100
Atteinte articulaire (%)	72	51	51	57	83
Pneumopathie infiltrante diffuse (%)	75	89	80	100	83
Mains de mécaniciens (%)	27	11	26	–	–



Jo-1

H et E 10 x

Allenbach et al. Brain 2017

	Dermatomyositis	Polymyositis	Antisynthetase syndrome
Environmental exposures—% per diagnosis			
Current or previous smoker (n=1646)	33	39	42
Environmental toxin exposure (n=930)	16	17	21
Extramuscular complications— % per diagnosis			
Interstitial lung disease (n=2442)	21	17	71

Tableau 2
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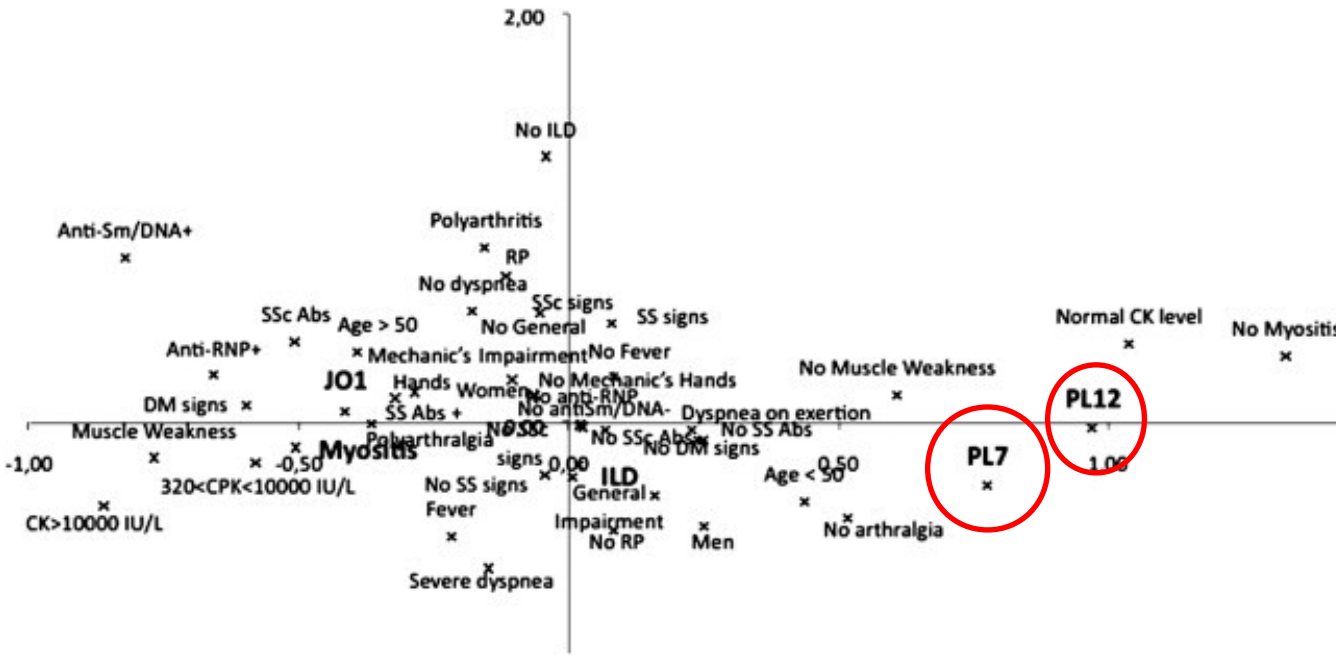
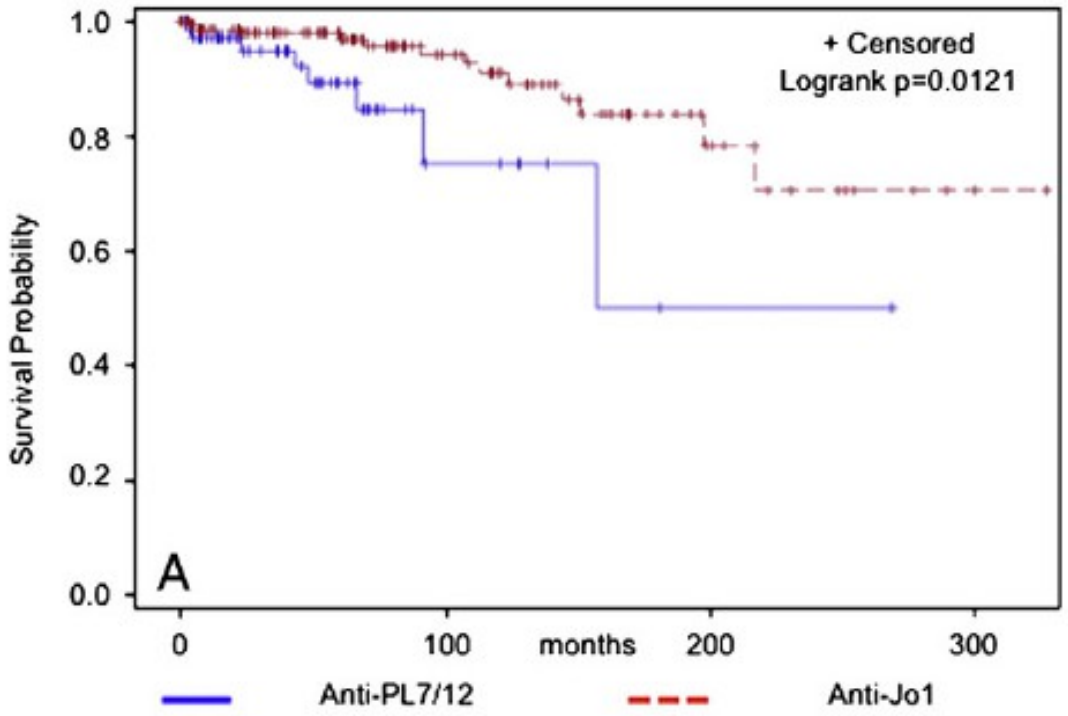
Hervier et al Hervier et al. 2015

Syndromes des Anti-synthétases Jo-1-
Signes extra-musculaires

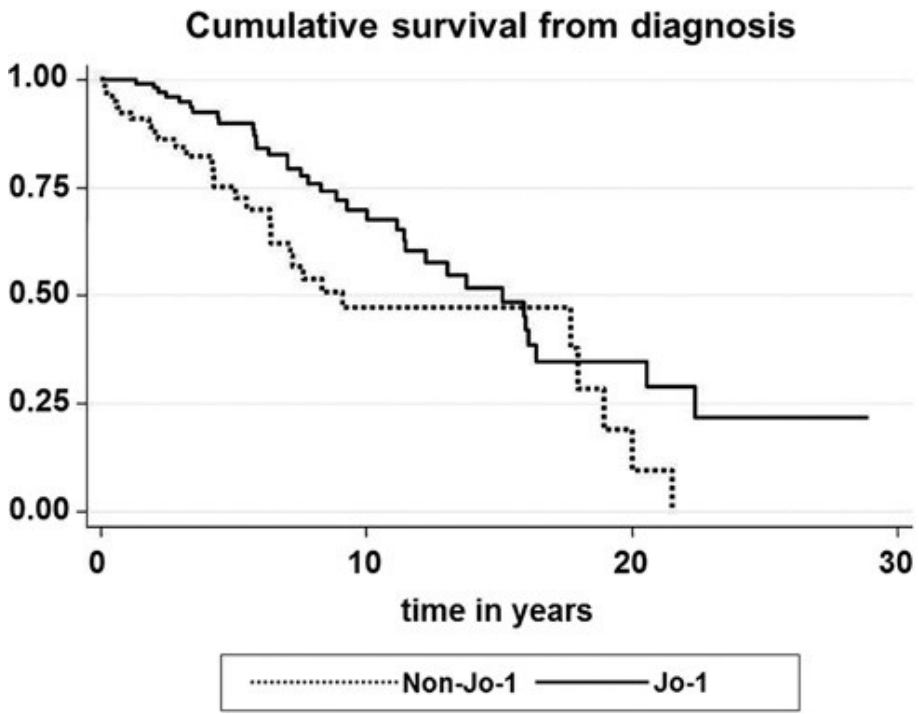




Aggrawal ARD 2014
Hervier Autoimmunity Reviews, 2012

Syndromes des Anti-synthétases Jo-1+
Signes extra-Musculaires

À 3ans 71% des SAS nécessitent intensification thérapeutiques

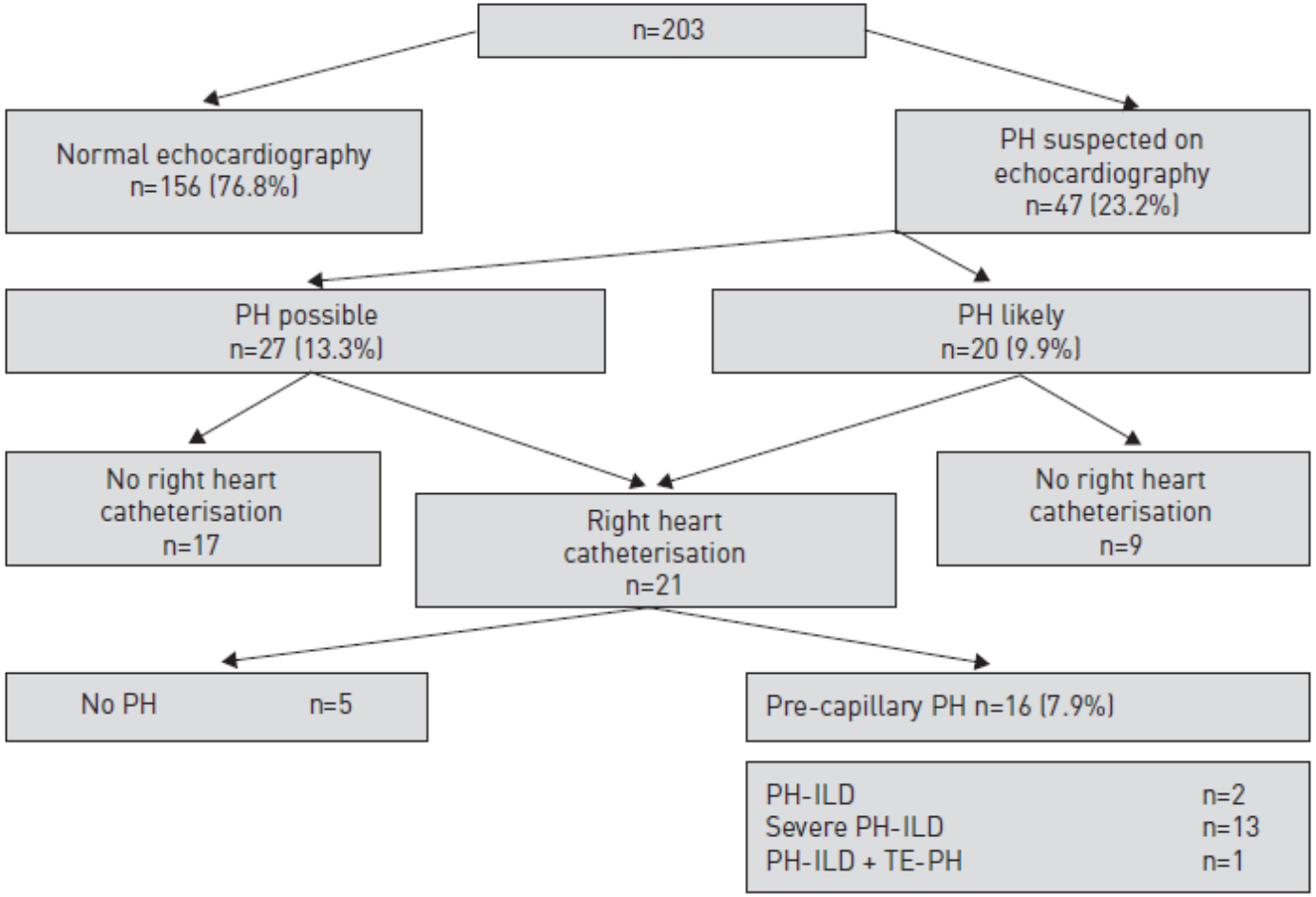


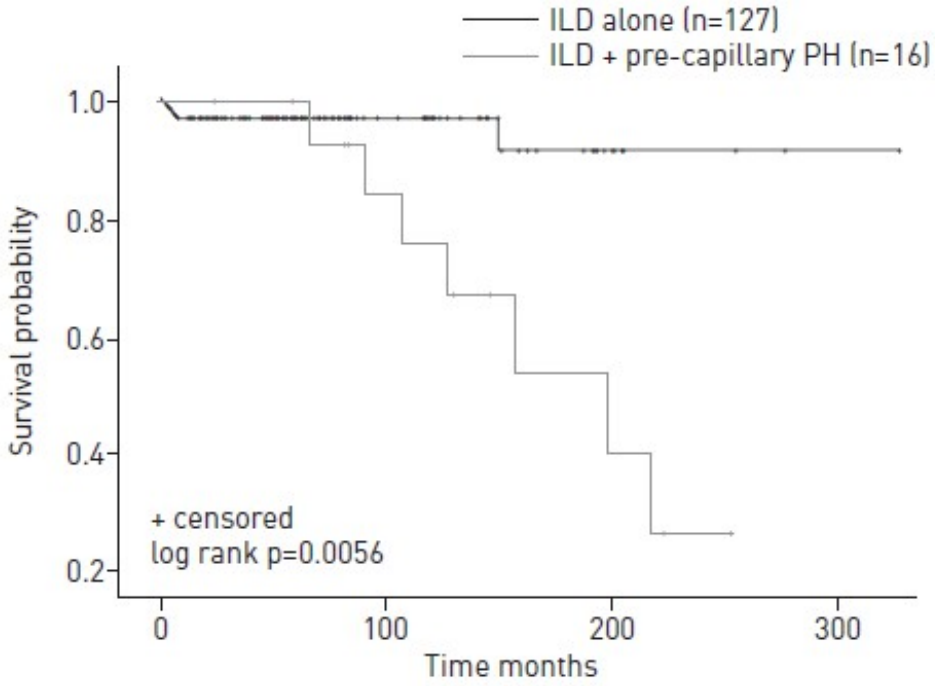
Stanciu R J Rheum 2012

Cause of death in Jo-1 and non-Jo-1 patients

	All patients N=66/202	Jo-1 N=36/122	non-Jo-1 N=30/80	p Value
Pulmonary fibrosis	32 (48.5%)	16 (44.4%)	16 (53.3%)	0.511
Pulmonary HTN	7 (10.6%)	3 (8.3%)	4 (13.3%)	0.472
CTD heart disease	3 (4.6%)	2 (5.6%)	1 (3.3%)	0.666
CTD kidney disease	2 (3.1%)	2 (5.6%)	0 (0.0%)	0.190
Cancer	6 (9.3%)	4 (11.1%)	2 (6.7%)	0.532
Infection	4 (6.2%)	3 (8.3%)	1 (3.3%)	0.397
Atherosclerosis	6 (9.3%)	5 (13.9%)	1 (3.5%)	0.138
Unknown	4 (6.2%)	1 (2.8%)	3 (10.0%)	0.221

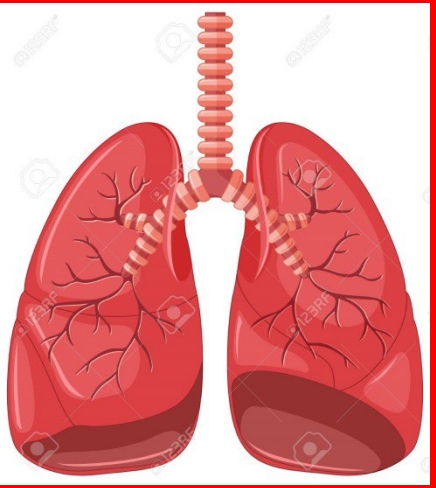
Aggrawl 2014 ARD





Hervier et al. 2015

DM



Jo1

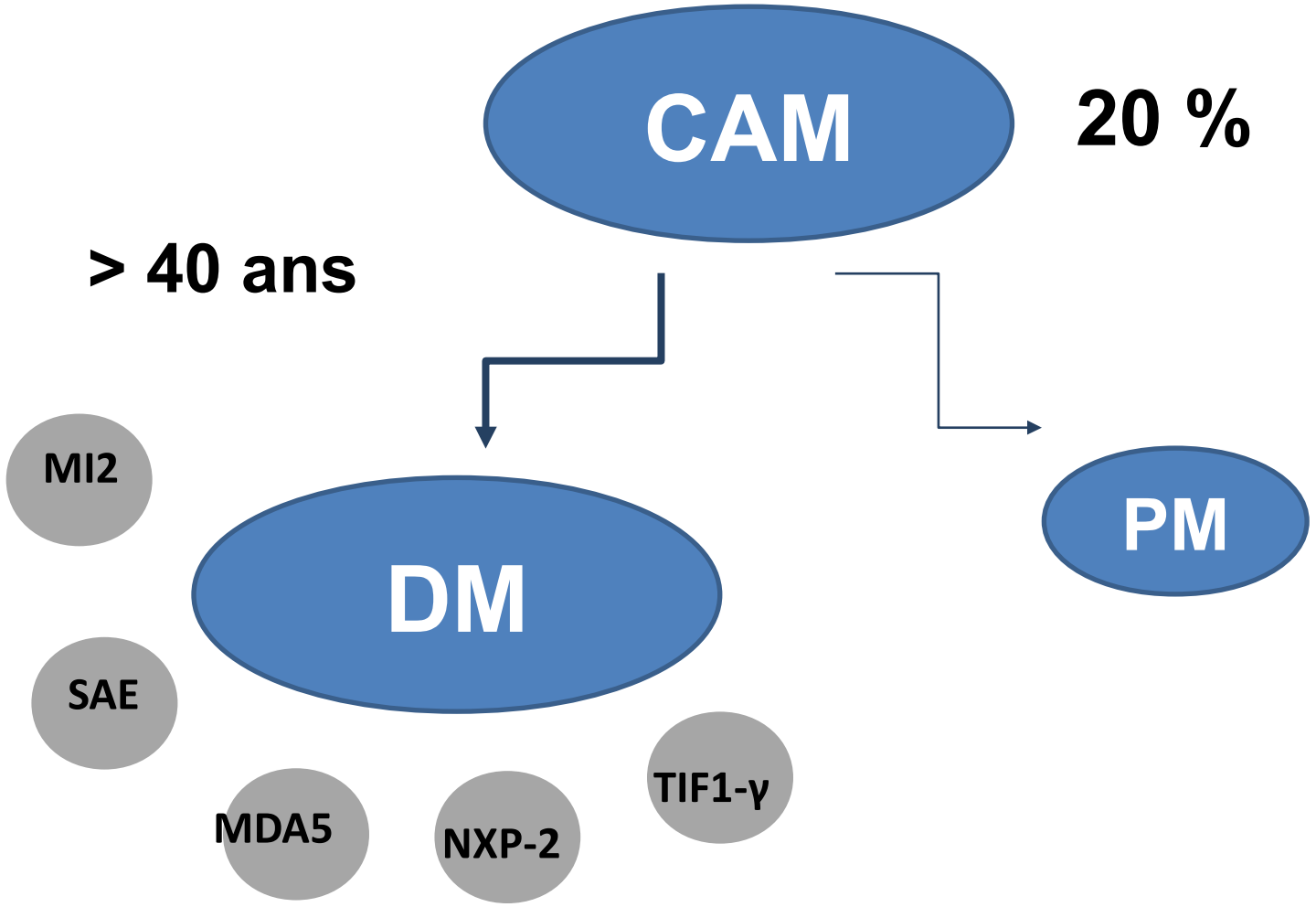
PL12

Pl7

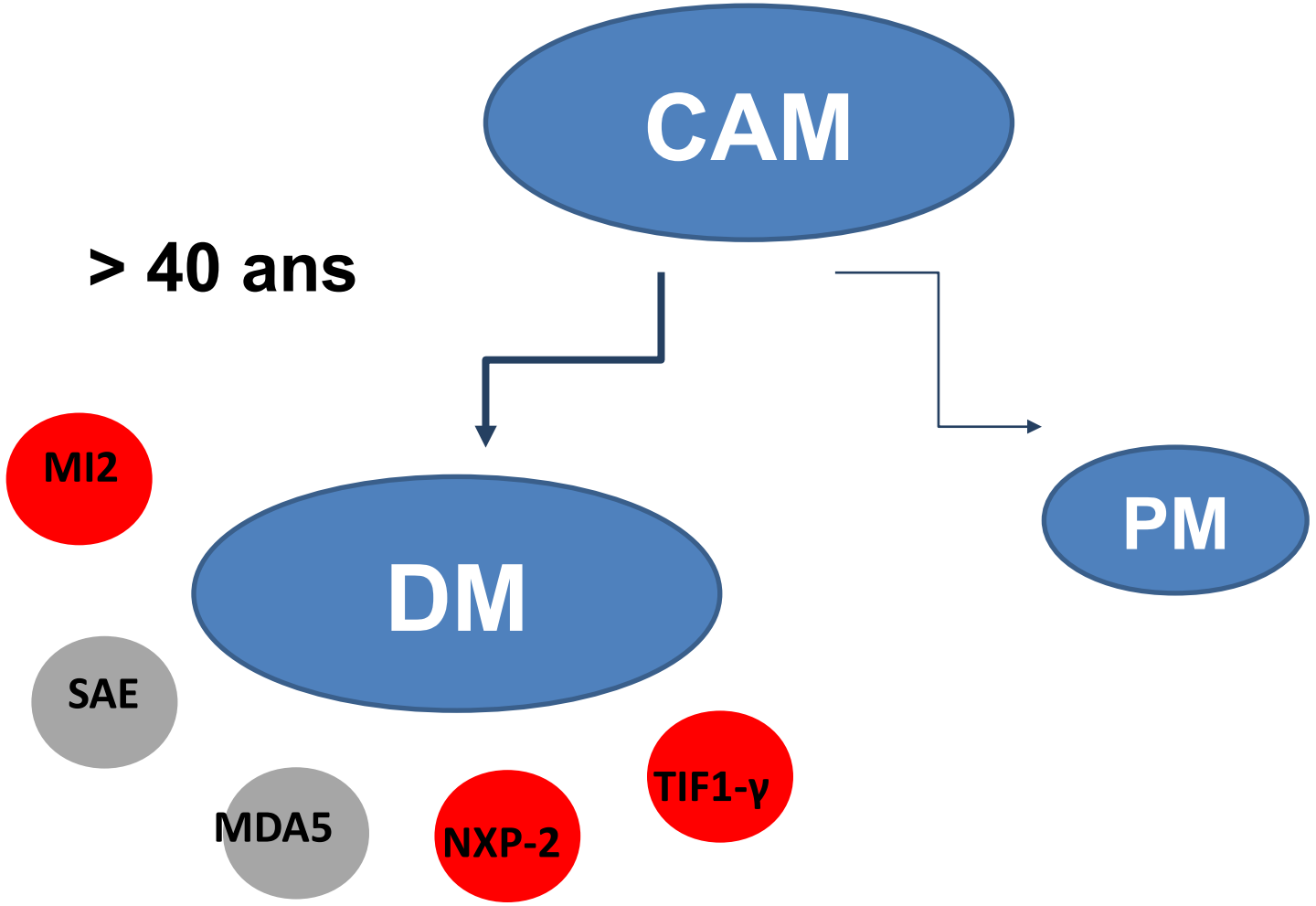
ILD Fréquente

Pronostic PL7-12 > Jo-1

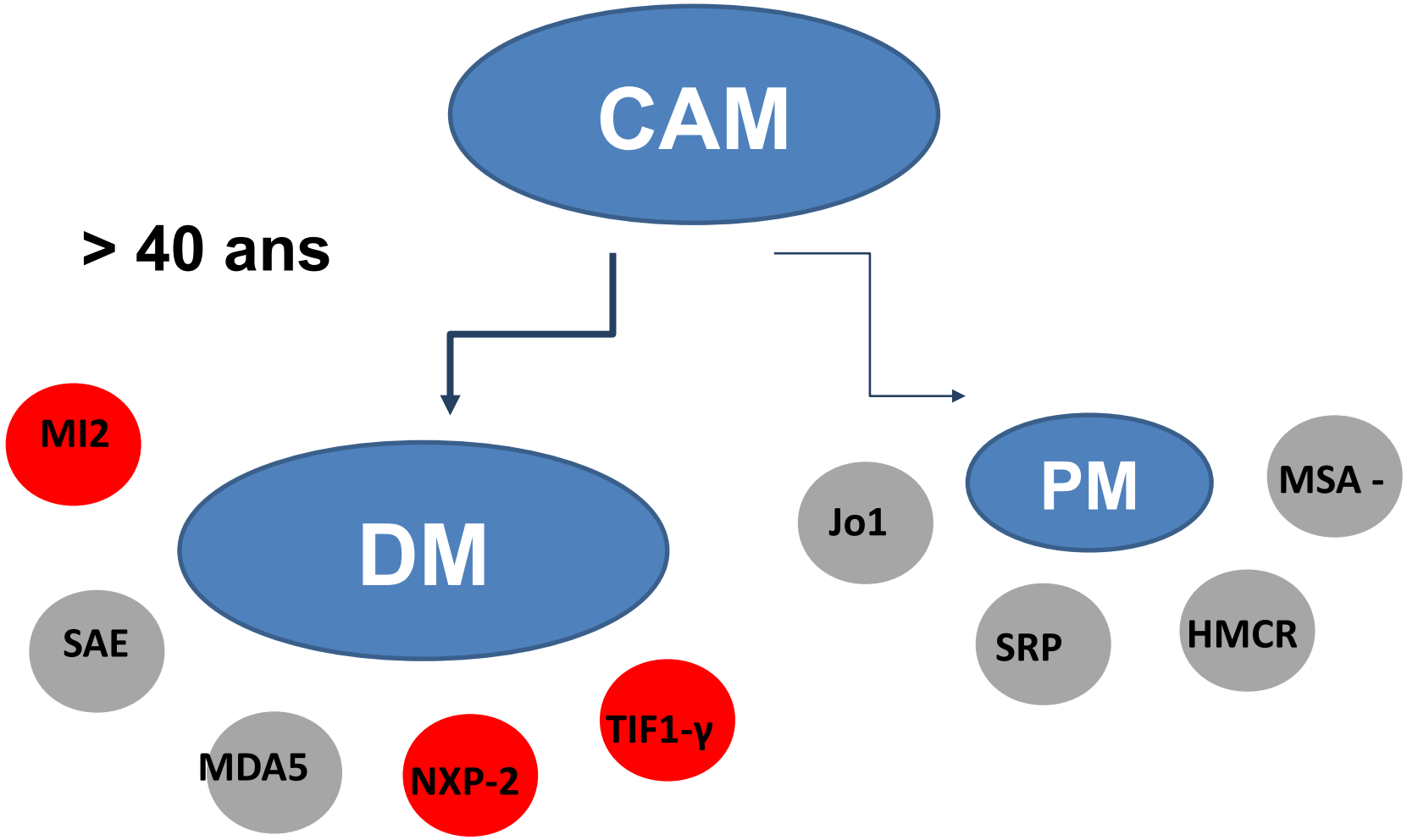
3- Myosite – cancer et poumon



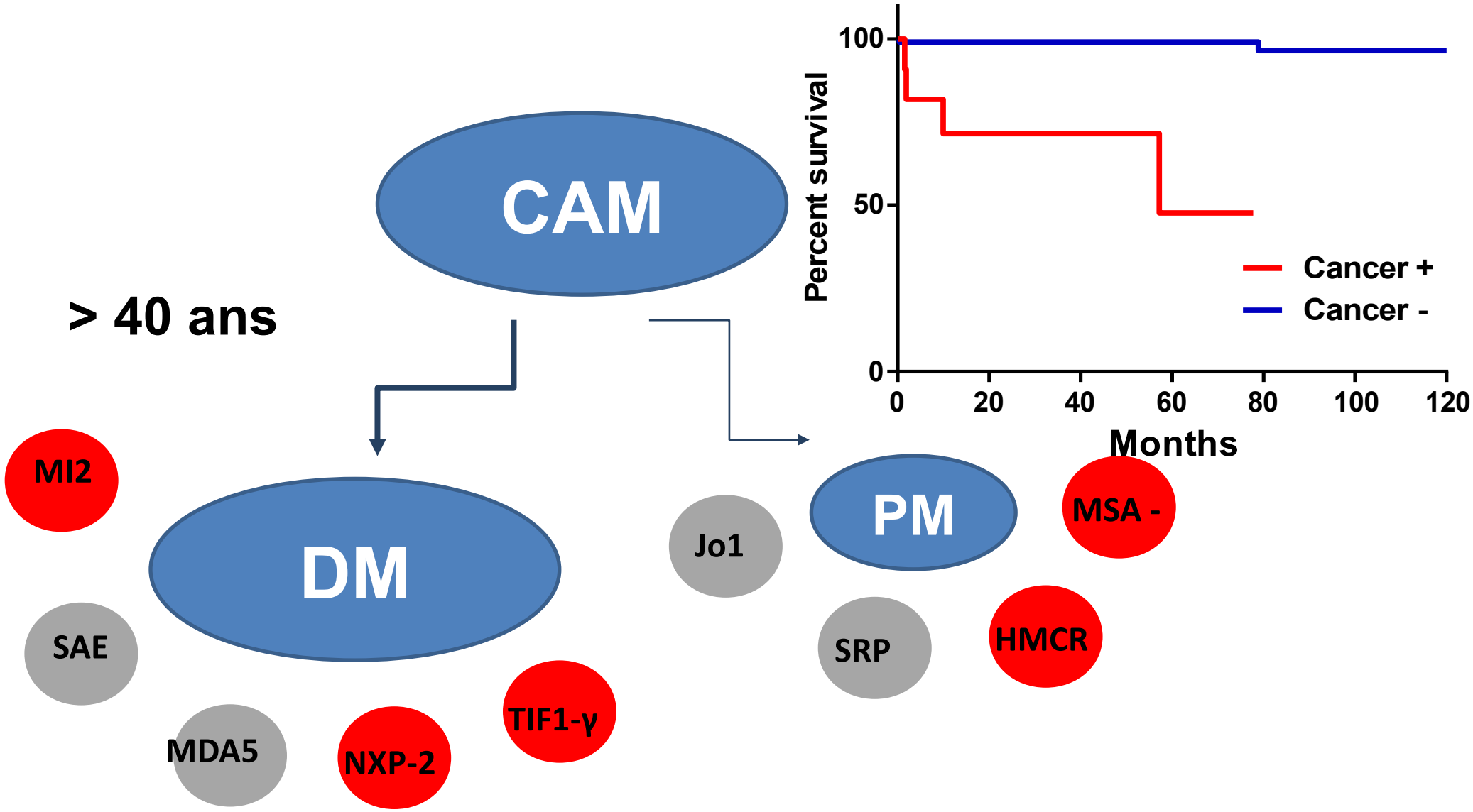
Fardet et al. Medicine 2009
Zahr et al. 2009



Fiorentino et al. 2014
Fardet et al. Medicine 2009
Hamaguchi et al. 2010



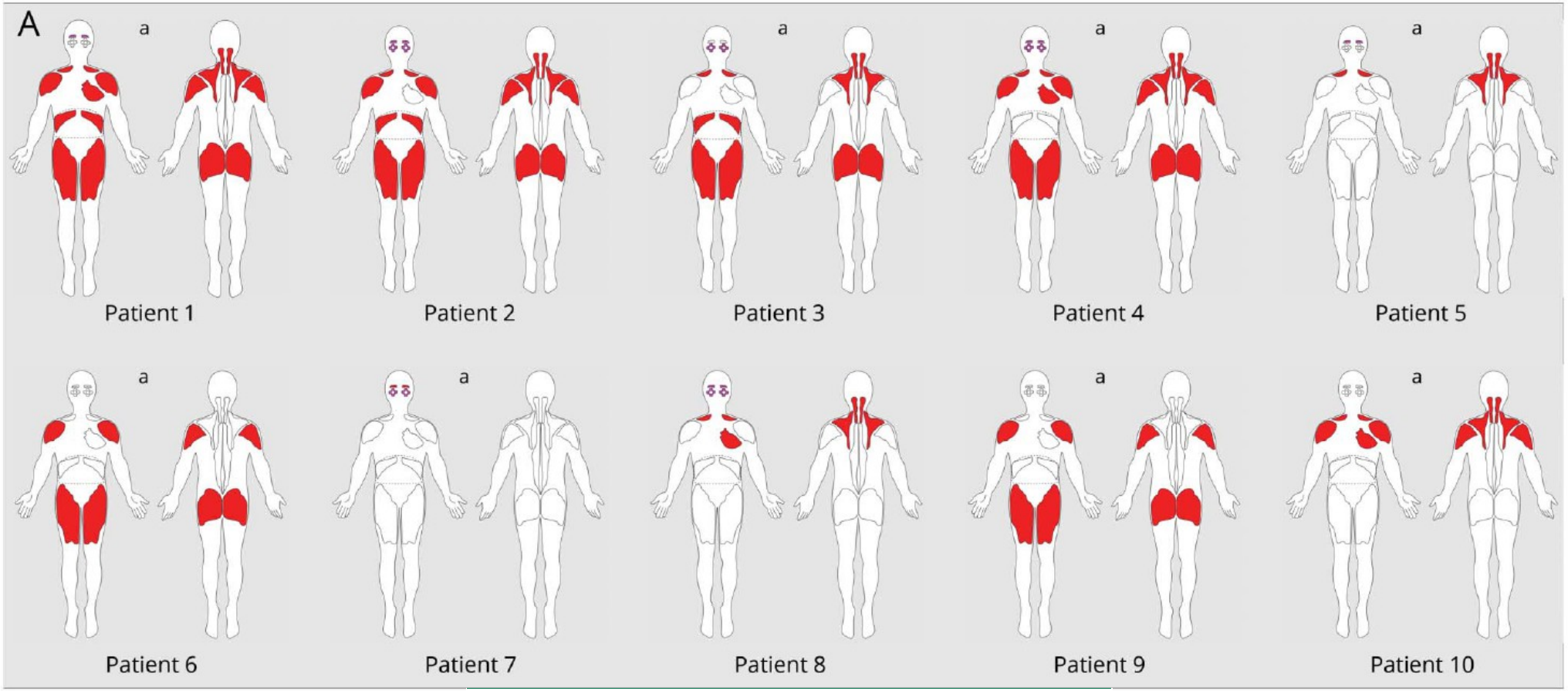
Fardet et al. Medicine 2009



Allenbach et al. 2016

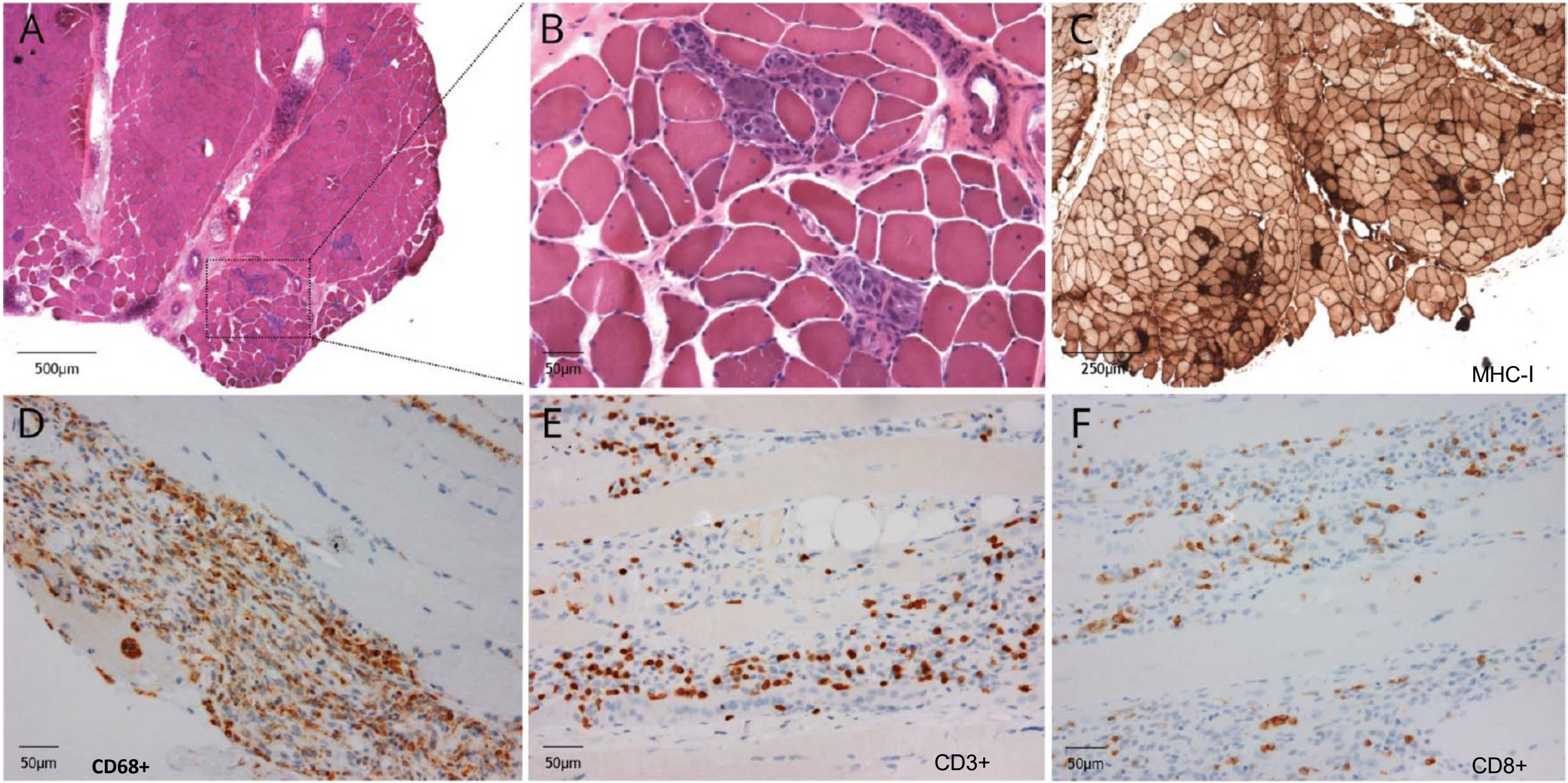
ICI regimen, n (%)	
Nivolumab (3 mg/kg, Q2W or Q3W)	6/10 (60)
Pembrolizumab (2 mg/kg, Q2W)	1/10 (10)
Durvalumab (10 mg/kg, Q2W)	1/10 (10)
Combined nivolumab (1 mg/kg Q3W) and ipilimumab (3 mg/kg Q3W)	2/10 (20)
Delay between ICI initiation and myositis onset, median (range), d	25 (5–87)
Phenotypic features and pattern of muscle weakness, n (%)	
Myalgias	8/10 (80)
Limb-girdle weakness (upper and/or lower)	7/10 (70)
Dropped head	7/10 (70)
Ocular motor dysfunction and/or ptosis	7/10 (70)
Dysphonia	2/10 (20)
Dyspnea	2/10 (20)
Fatigability	2/10 (20)

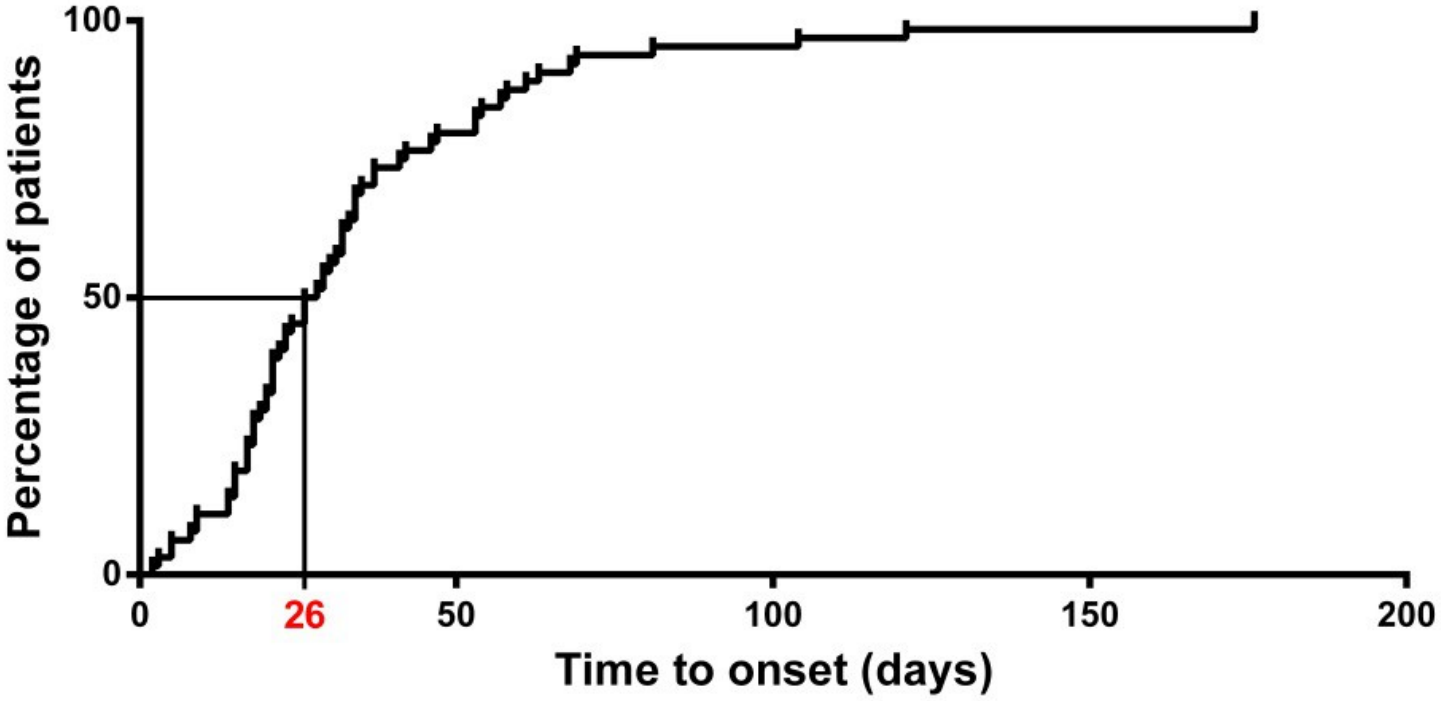
Touat et al. 2018 Neurology



Electromyoneurography, n (%)	
Abnormal test result	9/9 (100)
Electromyography suggestive of myopathic process[a]	9/9 (100)
Abnormal motor and/or sensory conduction	1/9 (11)
Decrement on repetitive stimulation	0/8 (0)
Laboratory tests	
Abnormal CK levels, n (%)	10/10 (100)
Median CK (range), U/L	2,668 (1,059–16,620)

Touat et al. 2018 Neurology

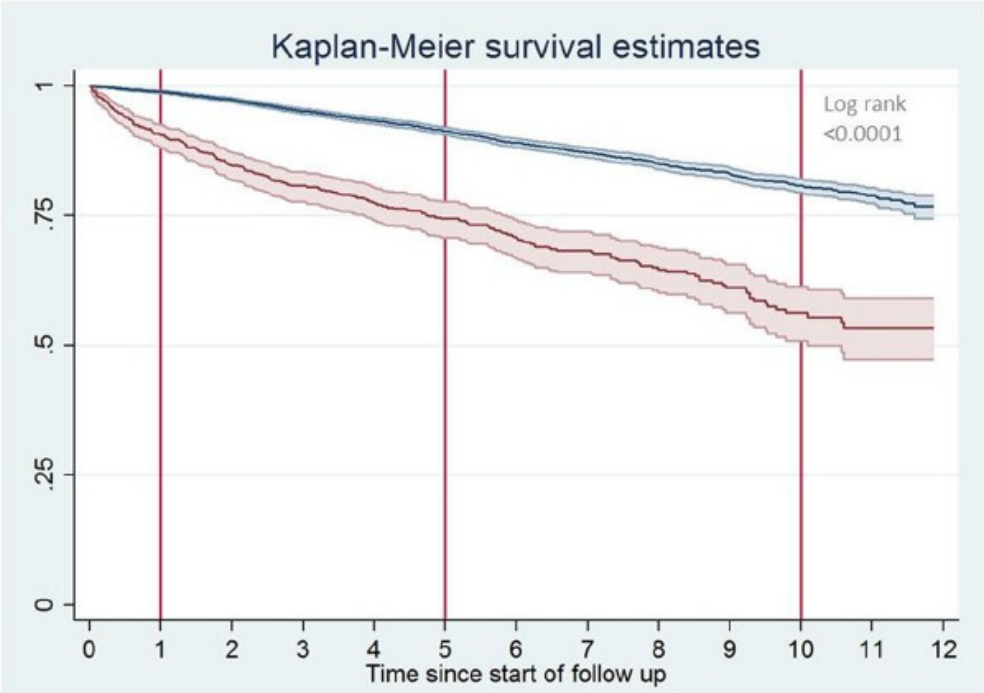

A
500µm
B
50µm
C
250µm
MHC-I
D
50µm
CD68+
E
50µm
CD3+
F
50µm
CD8+



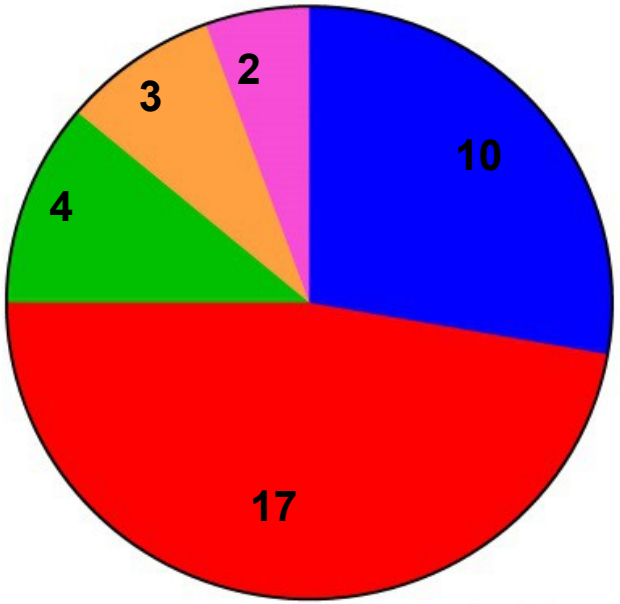
Associated irAEs	n/N (%)
Myasthenia gravis-like disorder	28/180 (15.6)
Myocarditis	29/180 (16.1)
Other irAE	25/180 (13.9)

Anquetil et al. 2018 Circulation

Outcome	n/N (%)
Severe complications	**84/170 (49.4)**
Death	**36/170 (21.2)**



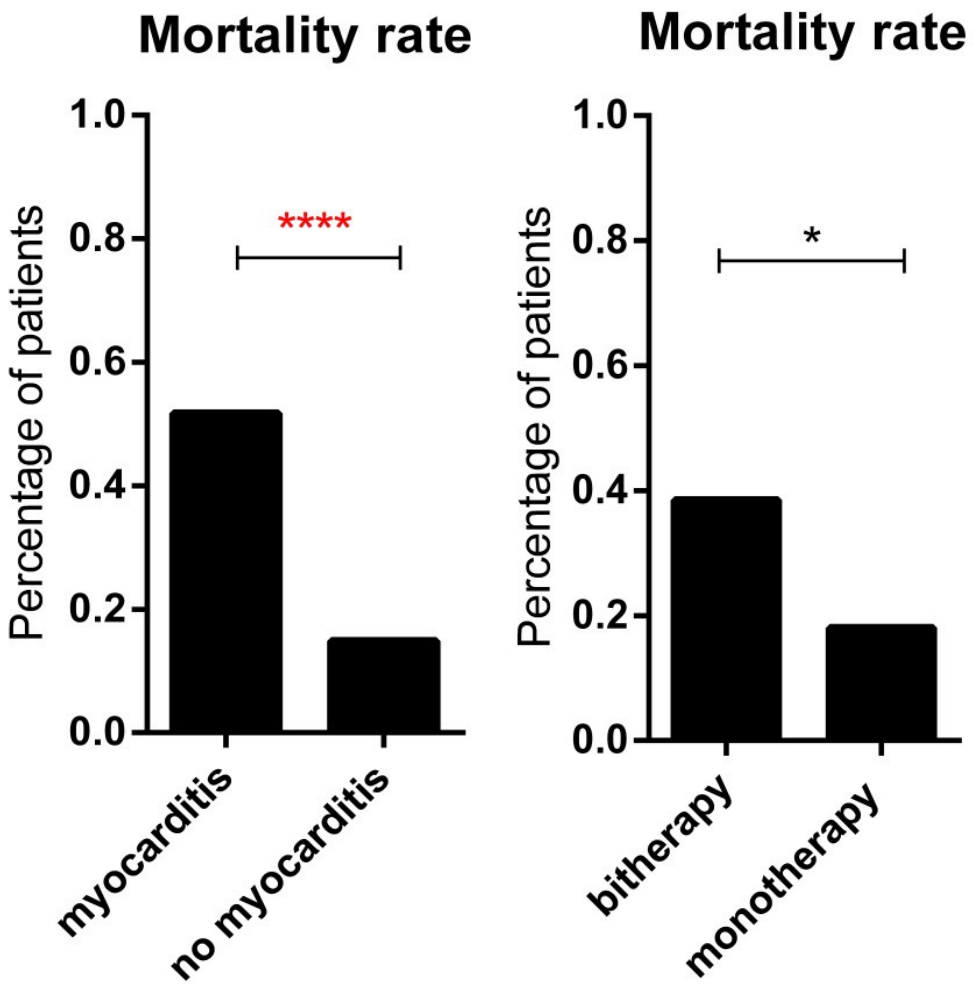
At risk, n	716/7100	648/7013	327/4037
Dead at end of interval, n	66/77	100/448	53/318
Cumulative mortality, %	9/1	23/7	31/12

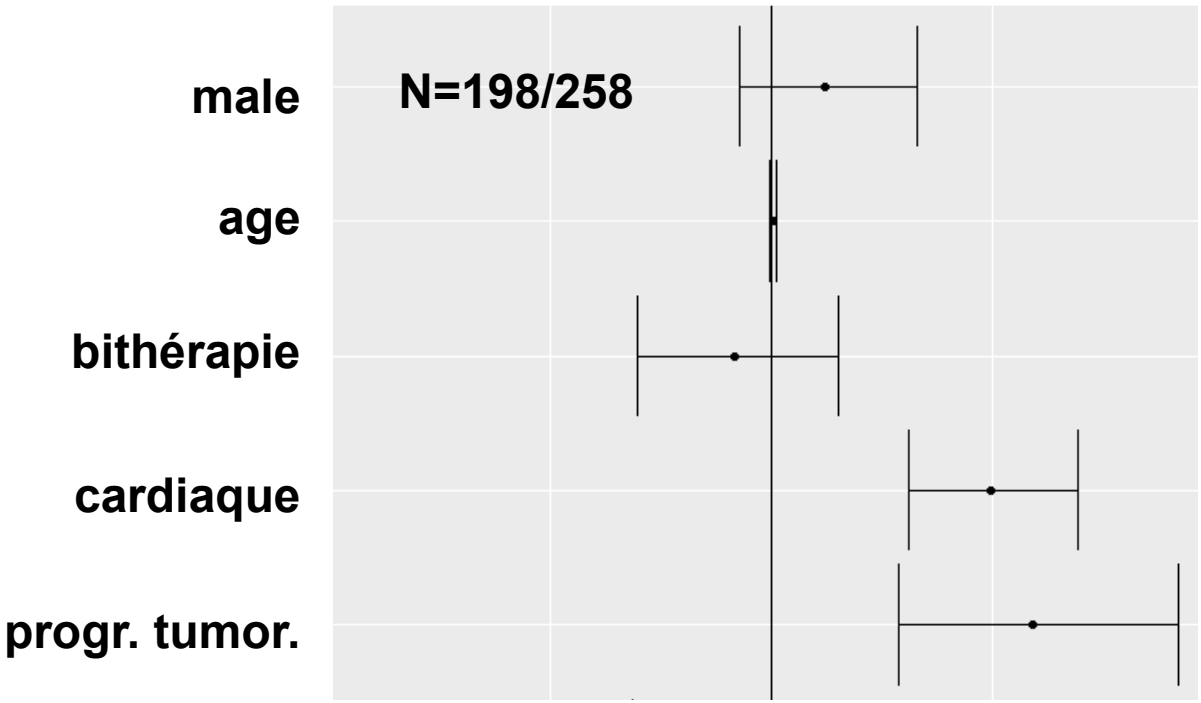


- Myositis
- Myocarditis
- Other irAE
- Cancer progression
- Cancer progression and other irAE

Fatal outcomes (n=36)

Anquetil et al. 2018 Circulation
Dobloug et al 2016 ARD





Délais ICI – Myosite

- **18 j [14.5-23.5] décès**
- **34 j [21-65] survie**

Anquetil et al. 2018 Circulation

CONCLUSION

- MAI hétérogène : 4 sous groupes et 15 Ac
- Poumon Pronostic
- Spécfique ou non

	sIBM	DM					SAS			MNAI		Myo - IrAE
	C1Na	MDA5	SAE	MI2	NXP2	TIF1G	JO1	PL7	PL12	SRP	HMGCR	-
Thorax	+	+++	+	+	-	-	+++	+++	+++	+	-	+
Sévérité	+/++	+++	+	-	-	-	+/++	++	++	-	-	+/++
TVR pur	+	-	-	+/-	+/-	-	-	-	-	++	++	+/++
ILD	-	+++ PO	+ PINS/PO	PINS	-	-	PINS	PINS	PINS	PINS	-	-
Cancer	-	-	-	-	++	++	-	-	-	-	+	++++
Rash	-	DM-Palm-U	DM	DM	DM-Calci	DM	Raynaud/HK	Raynaud/HK	Raynaud/HK	-	-	-
Deficit	++	+/-	+	++	++	+/++	++/+++	+/-	+/-	+++	+++	+/++
CK	+/-	+/-	+	++	++	+/++	++/+++	+/-	+/-	+++	+++	+/++