# I HAVE NO DISCLOSURES

UNIVERSITÀ DI PAVIA

PNEUMOMEDICINA 2022
Milano, 26 - 28 maggio 2022 · Centro Congressi Palazzo delle Stelline

# *ILD e sindrome anti-sintetasica: una "prepotente" entità clinica*


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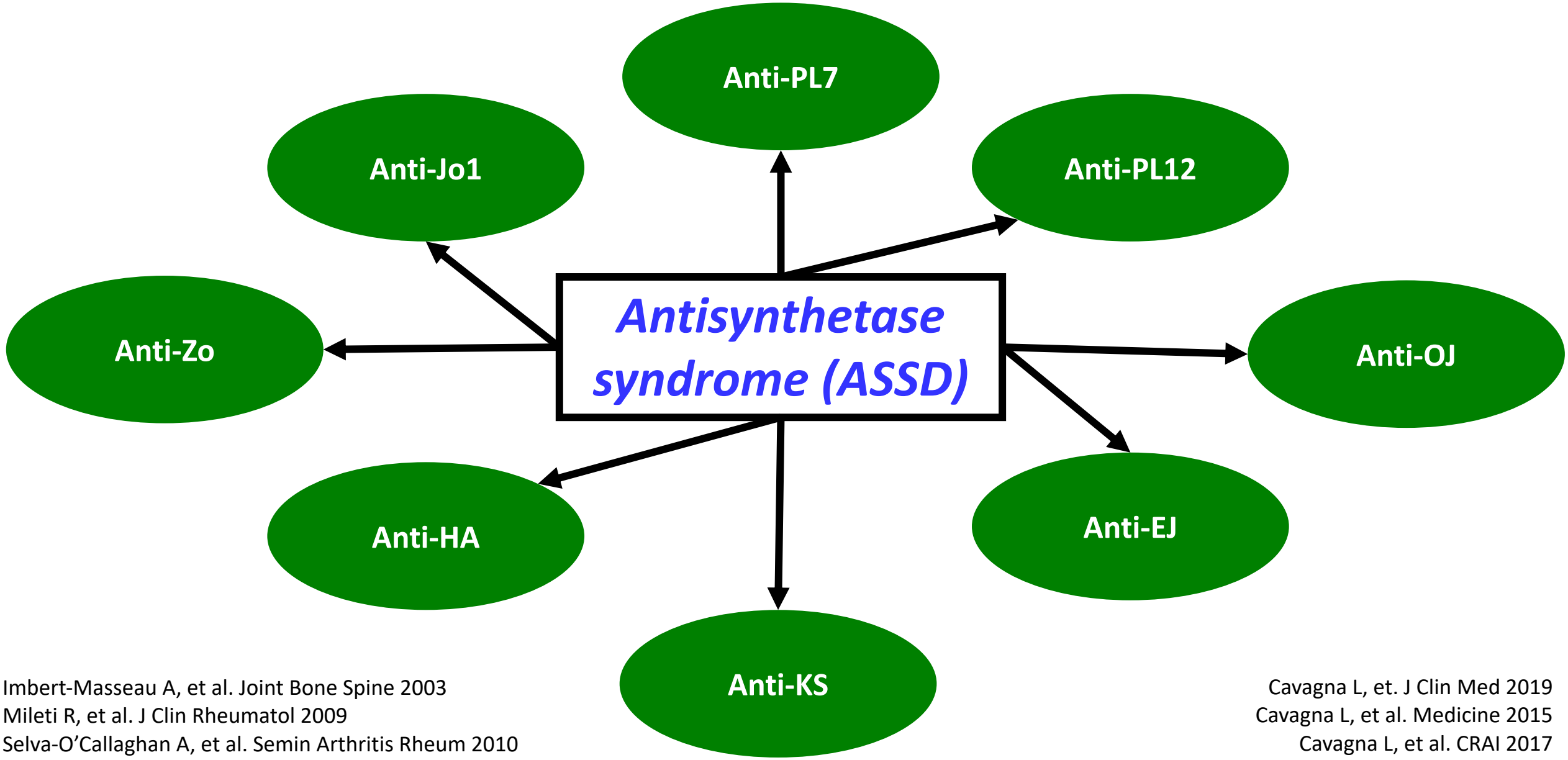
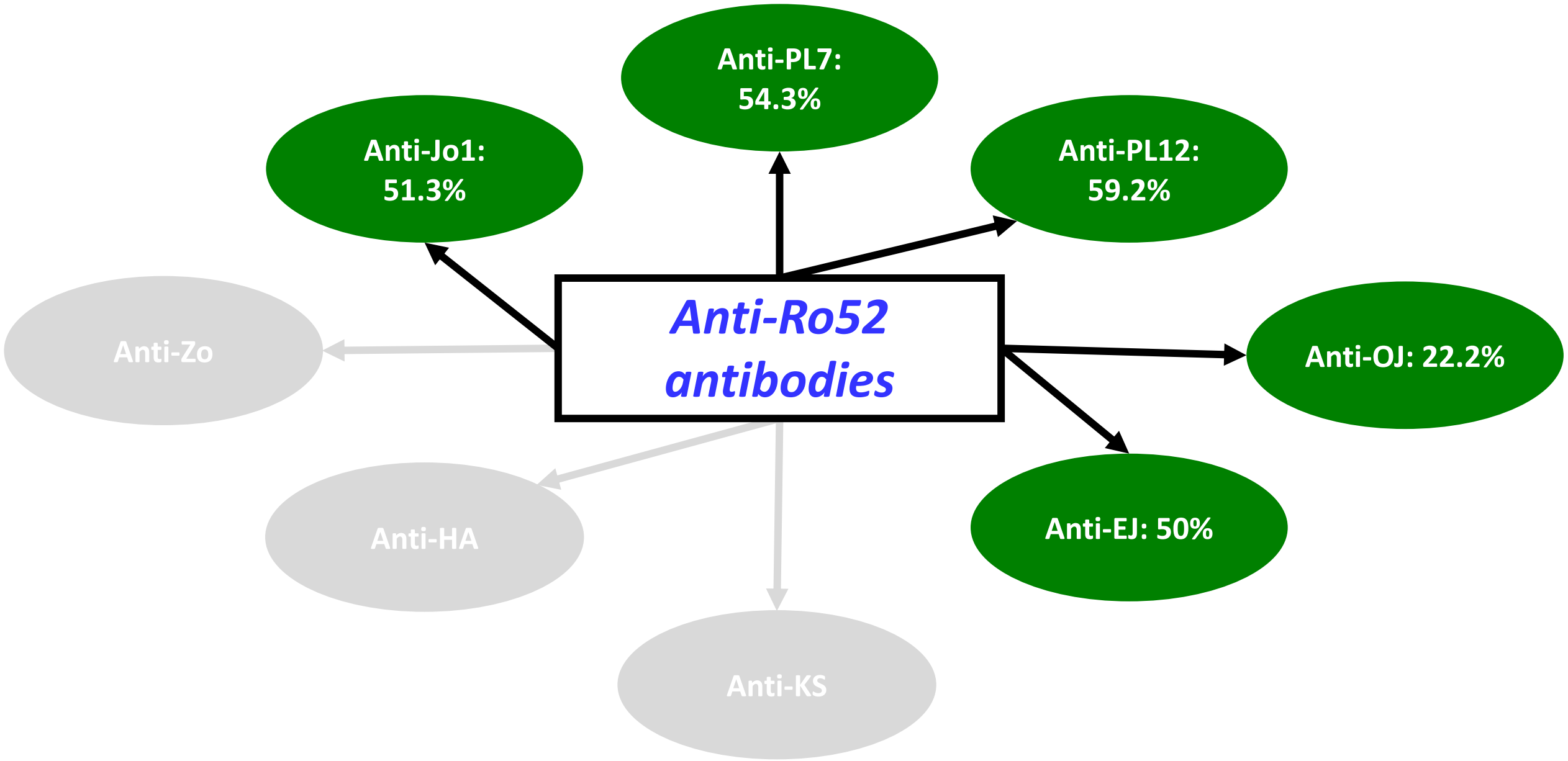



Imbert-Masseau A, et al. Joint Bone Spine 2003
Mileti R, et al. J Clin Rheumatol 2009
Selva-O'Callaghan A, et al. Semin Arthritis Rheum 2010
Hervier B, et al. Autoimmun Rev. 2012

Cavagna L, et. J Clin Med 2019
Cavagna L, et al. Medicine 2015
Cavagna L, et al. CRAI 2017
Bartoloni Bocci E,et a. Autoimmunity Rev, 2017




Cavagna L, et. J Clin Med 2019

## *Influence of Antisynthetase Antibodies Specificities on Antisynthetase Syndrome Clinical Spectrum Time Course*

| Onset Characteristics | Anti-Jo-1 ARS ($n$ = 593) | Anti-PL-7 ARS ($n$ = 95) | Anti-PL-12 ARS ($n$ = 84) | Anti-EJ ARS ($n$ = 38) | Anti-OJ ARS ($n$ = 18) |
|---|---|---|---|---|---|
| ANA positive (%) | 350 (60.3) | 58 (64.4) | 49 (59.4) | 21 (60.00) | 7 (38.9) |
| ANA negative (%) | 230 (39.7) | 32 (35.6) | 34 (41.0) | 14 (40.0) | 11 (61.1) |

*Cavagna et al, J. Clin. Med. 2019, 8, 2013*

Cytoplasmic positivity of ANA test (even isolated) is associated with ARS positivity

Aggarwal R, et al. J Rheumatol 2017

# *Clinical characteristics*

Arthritis 35-85% of cases

Myositis 60-80% of cases

Interstitial lung disease 50-95% of cases

Classic disease's triad

Raynaud's phenomenon up to 60% of cases

Fever up to 40% of cases

Mechanic's hands up to 40% of cases

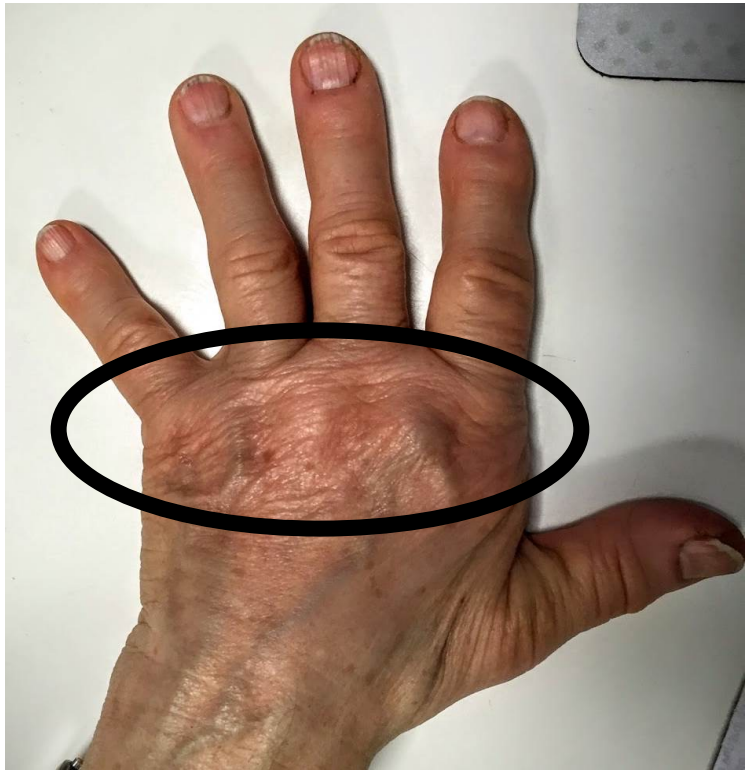
Accompanying features (for practical purpose)

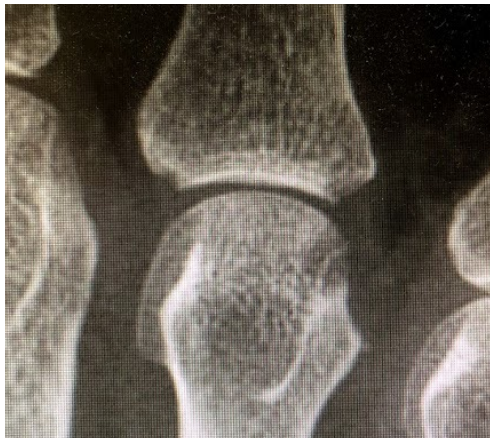
Cavagna L, et al. Medicine 2015, Cavagna L, et al. CRAI 2017, Bartoloni Bocci E,et al. Autoimmunity Rev, 2017

# *Joint involvement*

AENEAS collaborative group cohort 828 pts

- Patients with arthritis 552/828 (67%)
  - ❑ 367/534 (69%) Polyarticular/symmetrical
  - ❑ 134/521 (26%) RF positive
  - ❑ 49/449 (11%) ACPA positive
  - ❑ 69/457 (15%) joints' erosions
  - ❑ RA features mainly occurs in ASSD with arthritis from disease onset



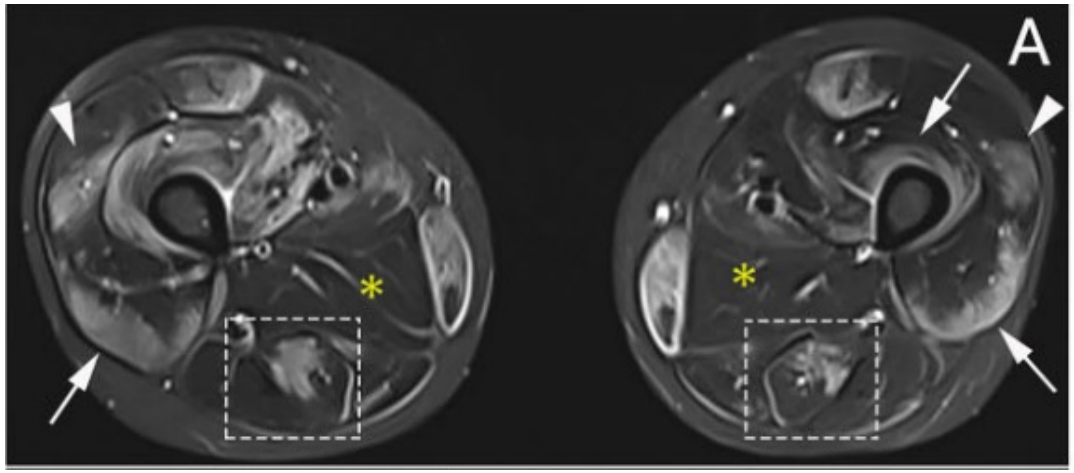


Imbert Masseau, et al. Joint Bone Spine 2003
Nagashima, et al. J Rheum 2009
Cavagna, et al. J Rheum 2010
Lefèvre, et al. Rheumatology 2014
Meyer, et al. Medicine 2015
Cavagna, et al. Medicine 2015
Gonzalez-Gay MA, et al. Clin Exp Rheum 2018
Cavagna et al. J Clin Med 2019

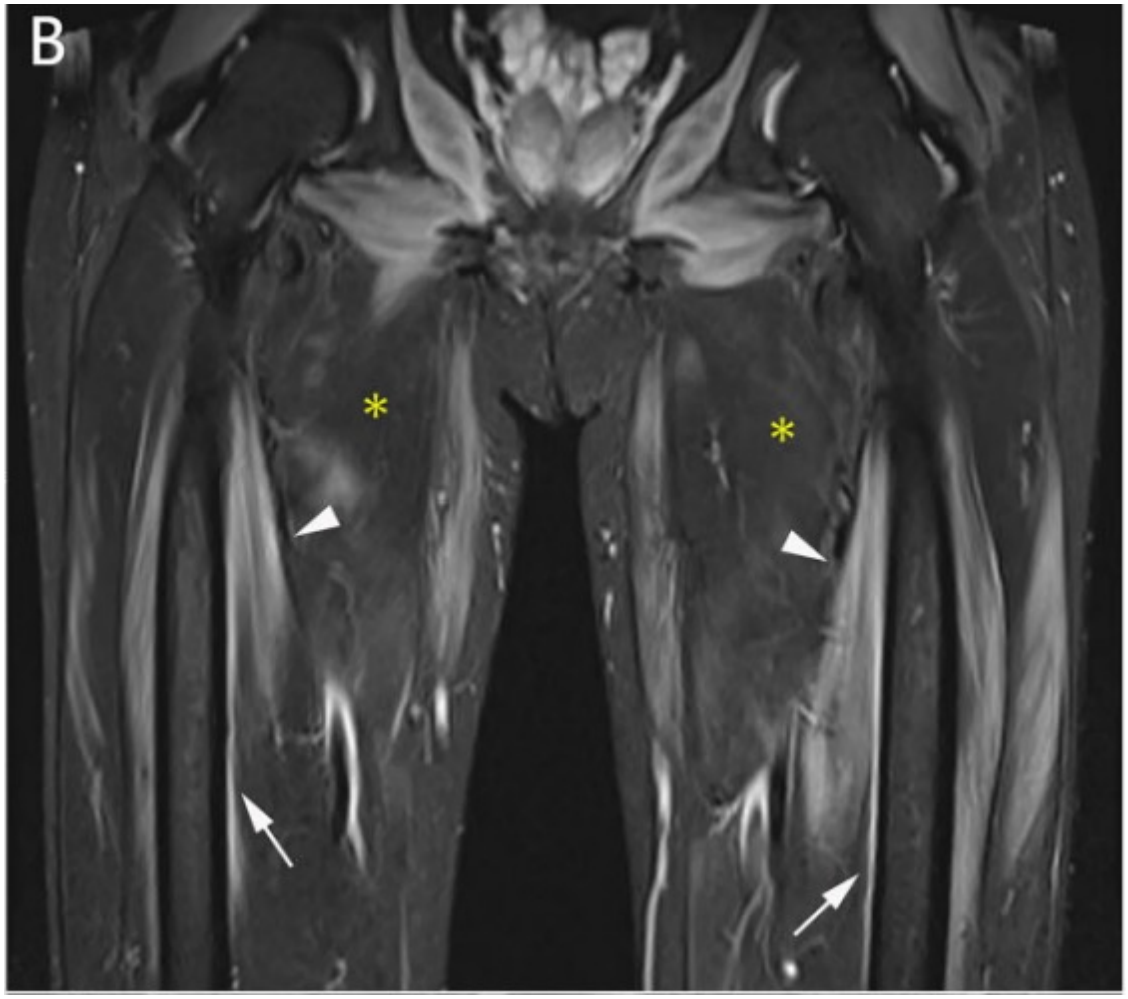
# *Muscle involvement characteristics*

AENEAS collaborative group cohort 828 pts

- Patients with muscle involvement: 652 (79%)
  - ❑ <u>Classic onset: 506 (78%)</u>
  - ❑ Hypomyopathic onset: 144 (22%)
  - ❑ Not reported: 2 patients (0%)



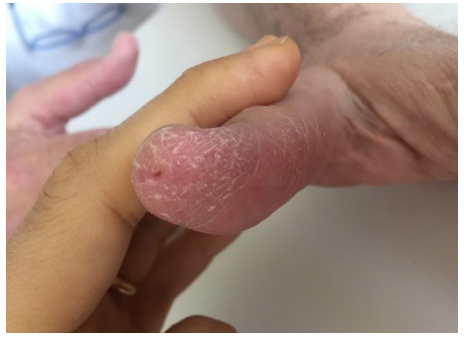

Distribution of muscle oedema is peripheral (arrows) and patchy (arrowheads). Signals of semitendinosus and corresponding muscular fasciae are prominent (dotted boxes), compared with adductor-muscle relative sparing (yellow stars) and other muscles of the posterior compartment

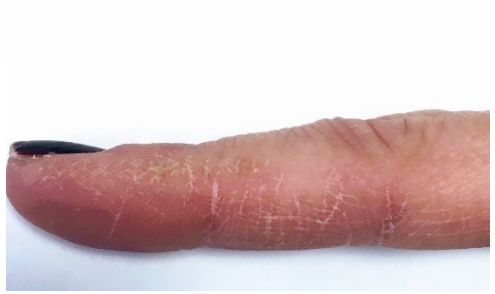


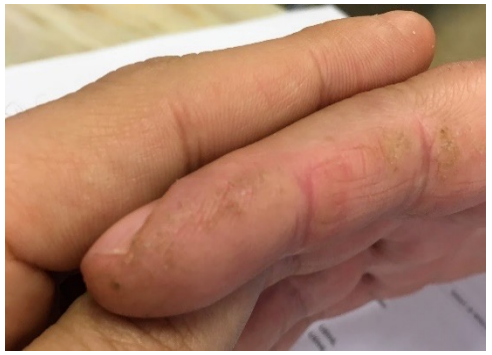

Oedema of muscular fasciae around the bone (arrows) and muscle attachment points (arrowheads) are shown. Adductor-muscle relative sparing is displayed (yellow stars).

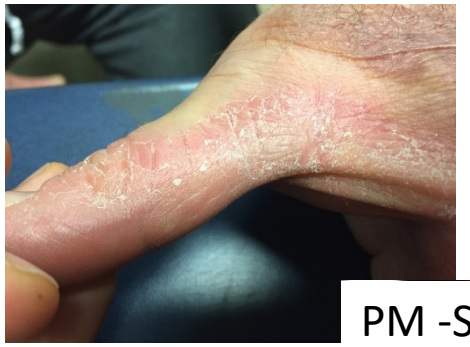
Cavagna L, et al. J Clin Med 2019
Zhang et al. Rheumatology (Oxford). 2022

# *Mechanic's hands*

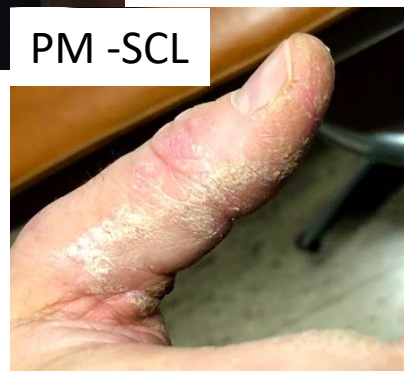


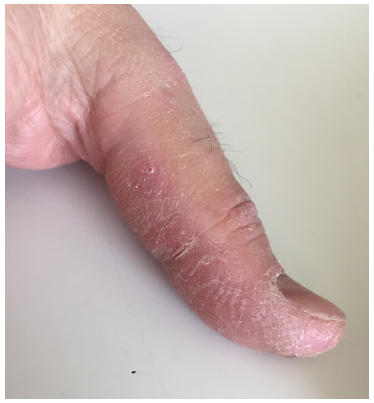




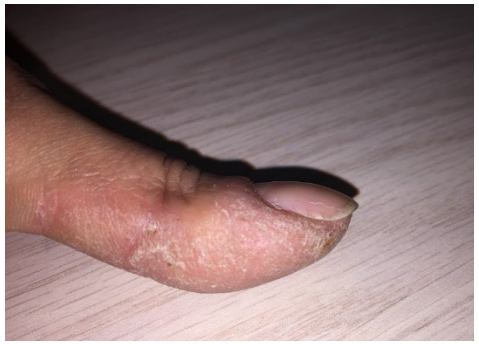


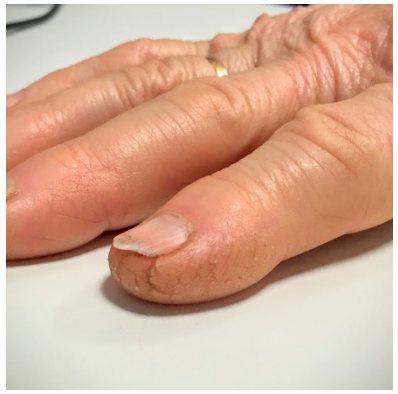
PM -SCL



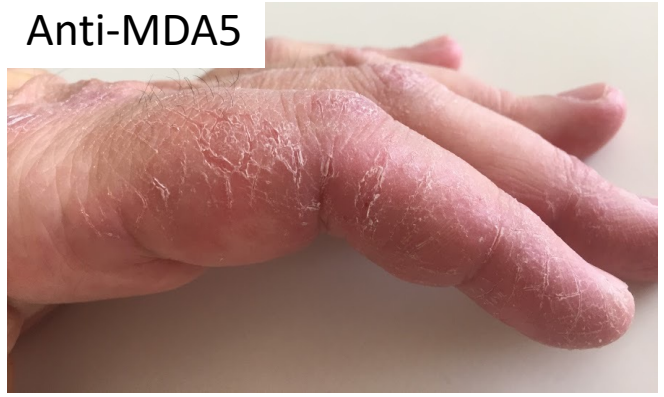


***Scaling or cracking of the skin over the lateral or palmar aspects of the fingers, and thumbs***

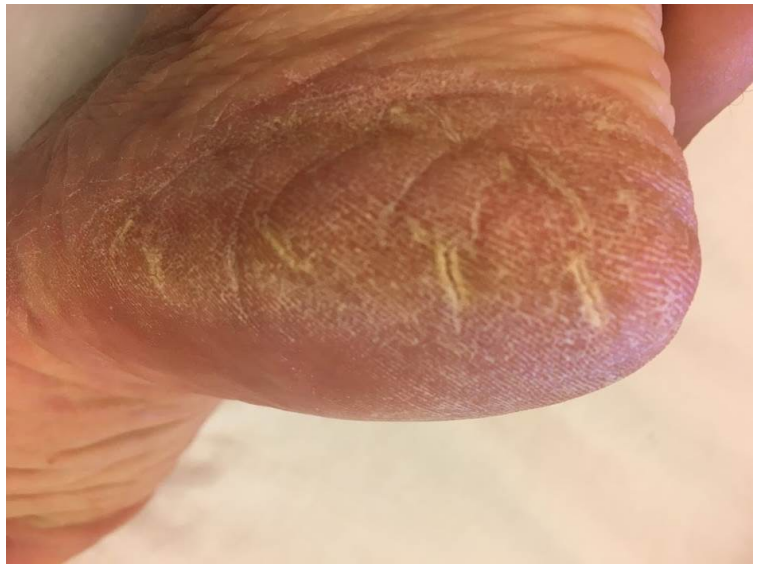


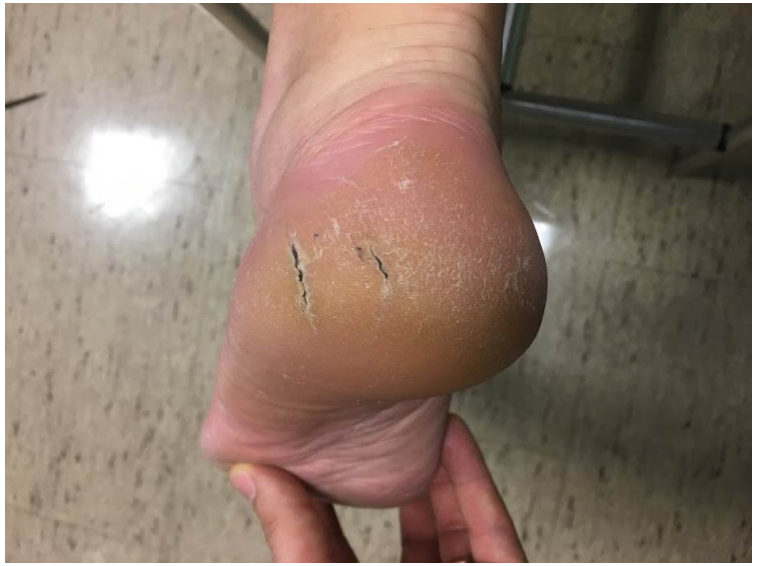


Anti-MDA5

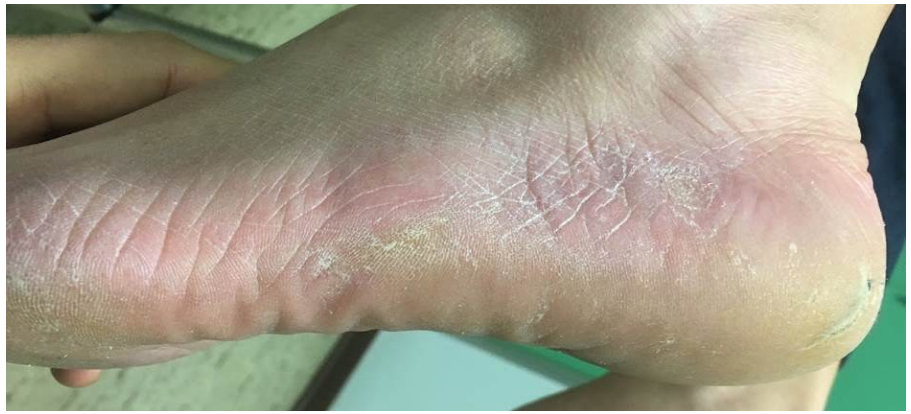


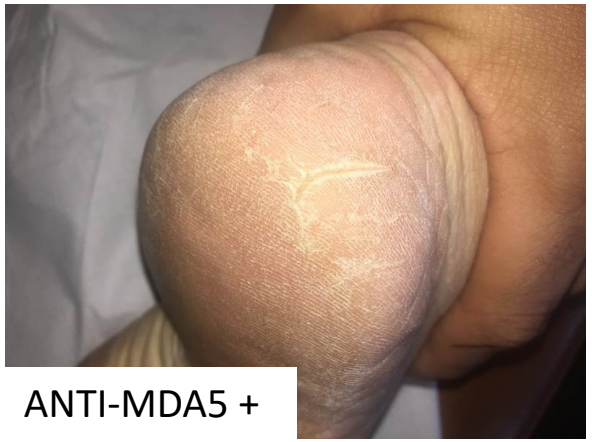
# *Hiker's feet*





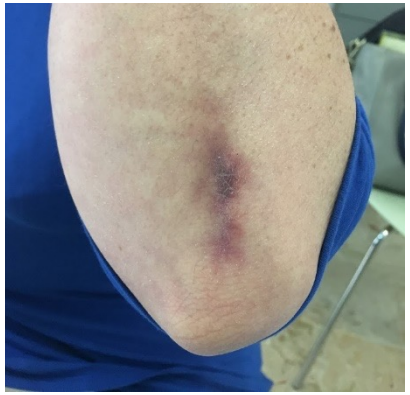
**Hyperkeratosis of the toes, plantar surface of the feet and heels**

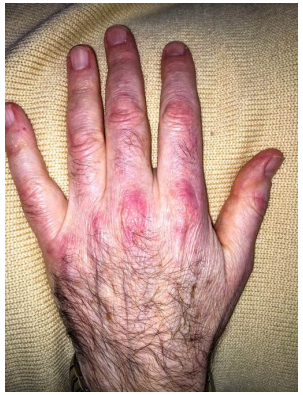




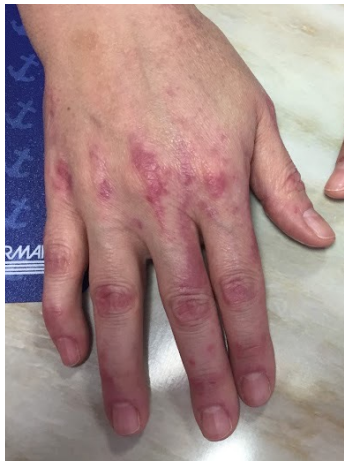
ANTI-MDA5 +

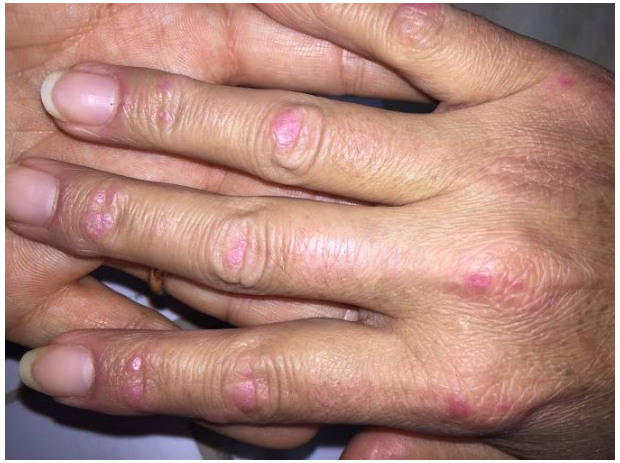
# Gottron's papules and sign





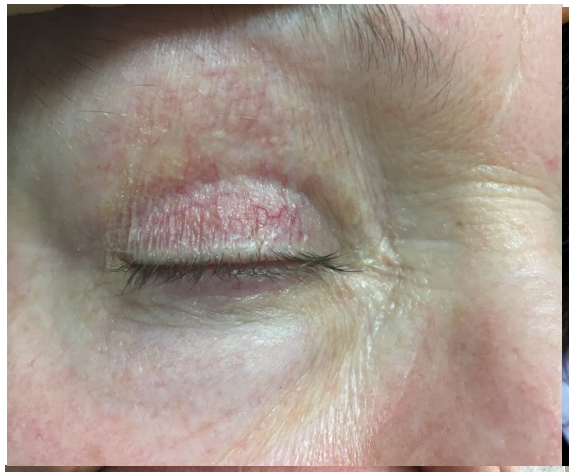
Erythematous to violaceous papules over the extensor surfaces of joints, which are sometimes scaly. May occur over the finger joints, elbows, knees, malleoli and toes

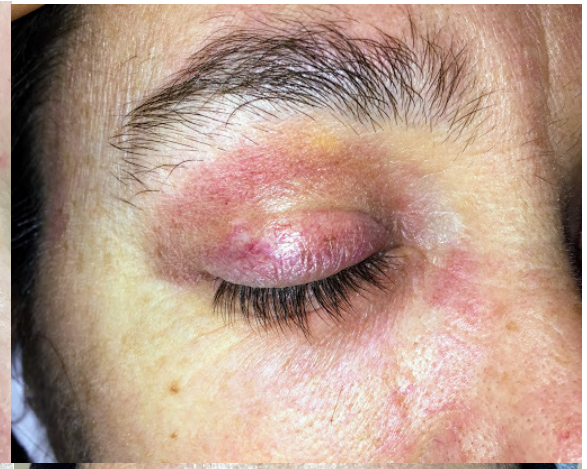


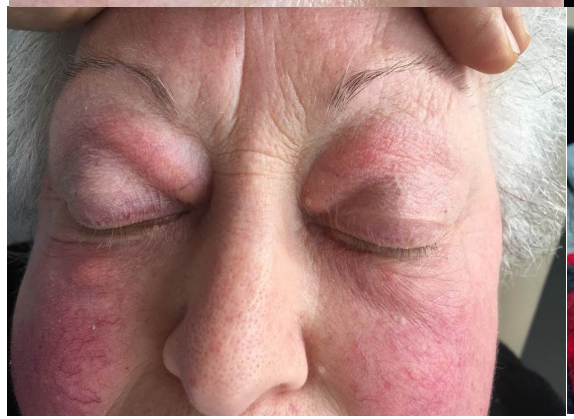


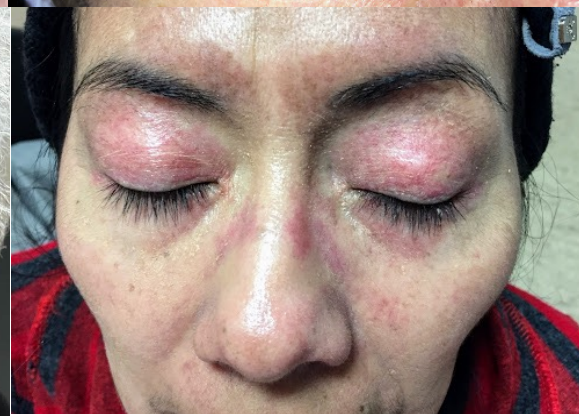
# Heliotrope rash

Purple, lilac-colored or erythematous patches over the eyelids or in a periorbital distribution, often associated with periorbital edema









The Journal of Rheumatology

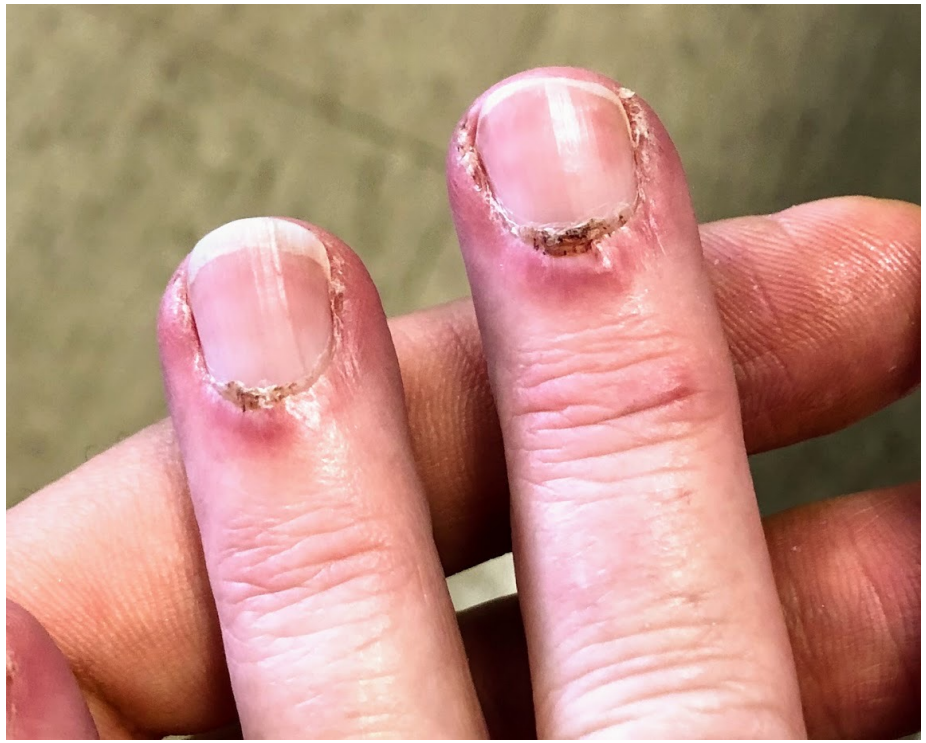
# Nailfold Capillaroscopy Characteristics of Antisynthetase Syndrome and Possible Clinical Associations: Results of a Multicenter International Study

Marco Sebastiani, Konstantinos Triantafyllias, Andreina Manfredi, Miguel Angel González-Gay, Natalia Palmou-Fontana, Giulia Cassone, Ulrich Drott, Christiane Delbrück, Jorge Rojas-Serrano, Chiara Bertolazzi, Laura Nuño, Margherita Giannini, Florenzo Iannone, Esther F. Vicente, Santos Castañeda, Albert Selva-O'Callaghan, Ernesto Trallero Araguas, Giacomo Emmi, Annamaria Iuliano, Jutta Bauhammer, Nikolaus Miehle, Simone Parisi, Lorenzo Cavagna, Veronica Codullo, Carlomaurizio Montecucco, Francisco Javier Lopez-Longo, Julia Martínez-Barrio, Juan Carlos Nieto-González, Silvia Vichi, Marco Confalonieri, Paola Tomietto, Raoul Bergner, Alberto Sulli, Francesco Bonella, Federica Furini, Carlo Alberto Scirè, Alessandra Bortoluzzi, Christof Specker, Simone Barsotti, Rossella Neri, Marta Mosca, Marzia Caproni, Julia Weinmann-Menke, Andreas Schwarting, Vanessa Smith and Maurizio Cutolo, on behalf of the American and European Network of Antisynthetase Syndrome Collaborative Group

DOI: 10.3899/jrheum.180355
http://www.jrheum.org/content/early/2018/11/12/jrheum.180355

***Results.*** NVC abnormalities were observed in 62.1% of AS patients compared with 29.3% of primary RP group ($p < 0.001$). An SSc-like pattern was detected in 67 patients (35.3%) and it was associated with anti-Jo1 antibodies ($p = 0.002$) and also with a longer disease duration ($p = 0.004$). Interestingly, there was no significant correlation between the presence of SSc-like pattern and RP, and only 47% of patients with SSc-like pattern had RP.

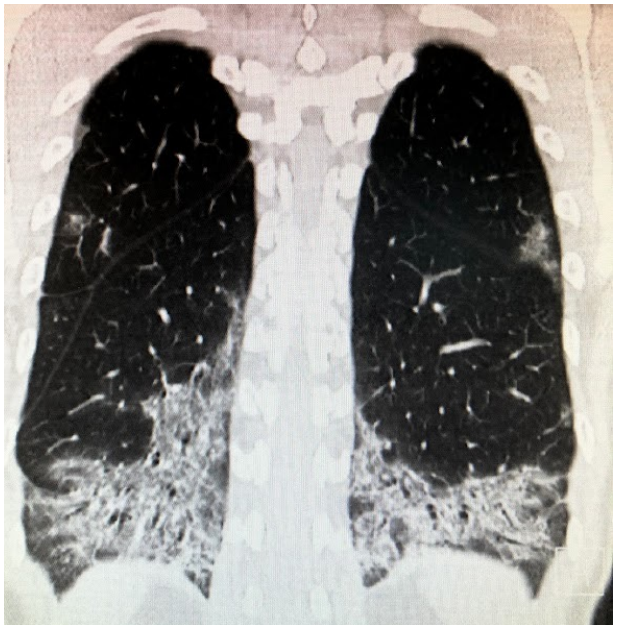
## *Nailfold bed abnormalities (macrohaemorrages)*

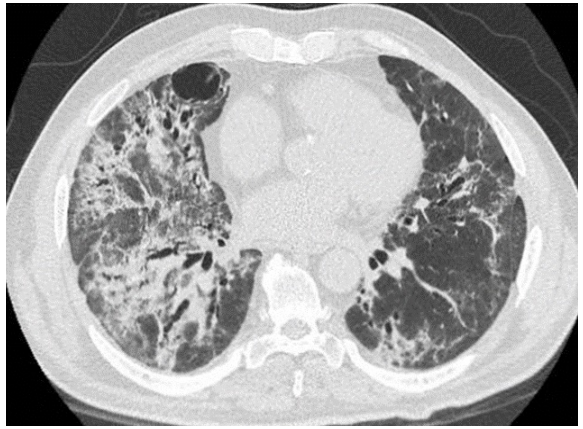


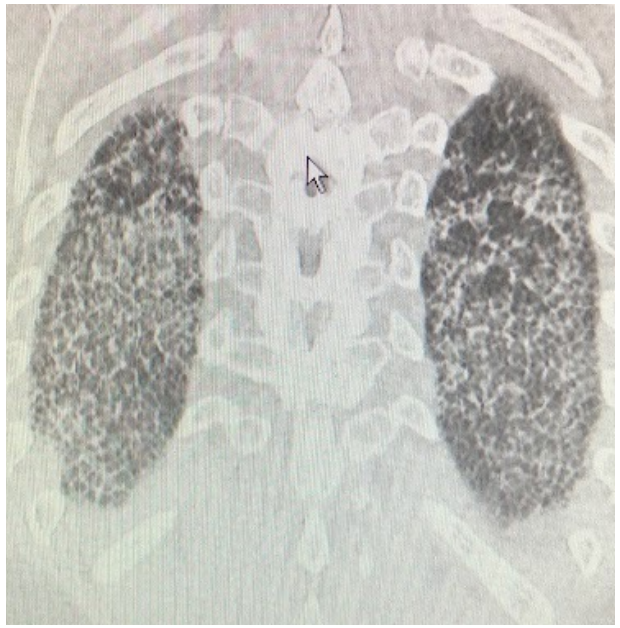
# *Interstitial Lung Disease*

AENEAS collaborative group cohort 828 pts

- Patients with ILD: 674 (81%, 486 anti Jo-1)
  - Acute onset: 266 (39%)
    - Dyspnea began acutely and progressed rapidly (4–6 weeks from symptom onset)
  - Chronic onset: 278 (41.5%)
    - Dyspnea began insidiously and progressed slowly
  - Asymptomatic: 122 (18%)
    - Lung involvement was not clinically evident
  - Not reported: 8 patients (1.5%)





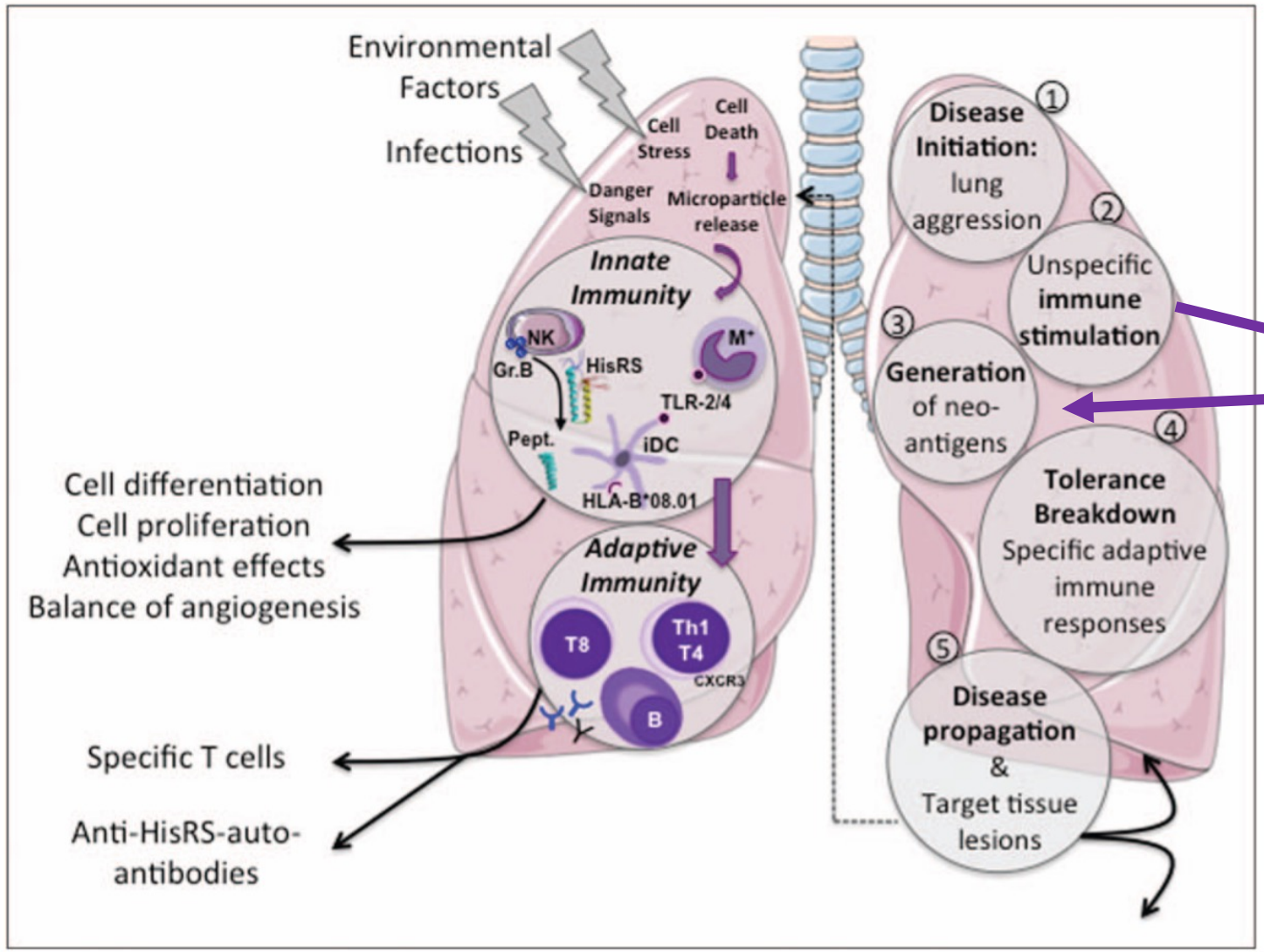


Cavagna L, et al. J Clin Med 2019

# *Interstitial Lung Disease*

- Is the lung involved in the disease's pathogenesis?
- Does the prevalence of ILD depend on ARS-specificity?
- What are the features of ASSD-ILD?
- Does ILD pattern depend on ARS-specificity?
- Is the survival affected by antibody specificty?

# *Is the lung involved in the disease's pathogenesis?*




NK cells could split HisRS into an immunogenic peptide

Gallay L et al, Curr Opin Rheumatol. 2018

# *Does the prevalence of ILD depend on ARS-specificity?*

233 pts
Cluster 2 describes a predominantly pulmonary disease

B. Hervier et al. Autoimmunity Reviews 12 (2012)

Mostly anti-Jo1

96% of anti-PL7 and anti-PL12

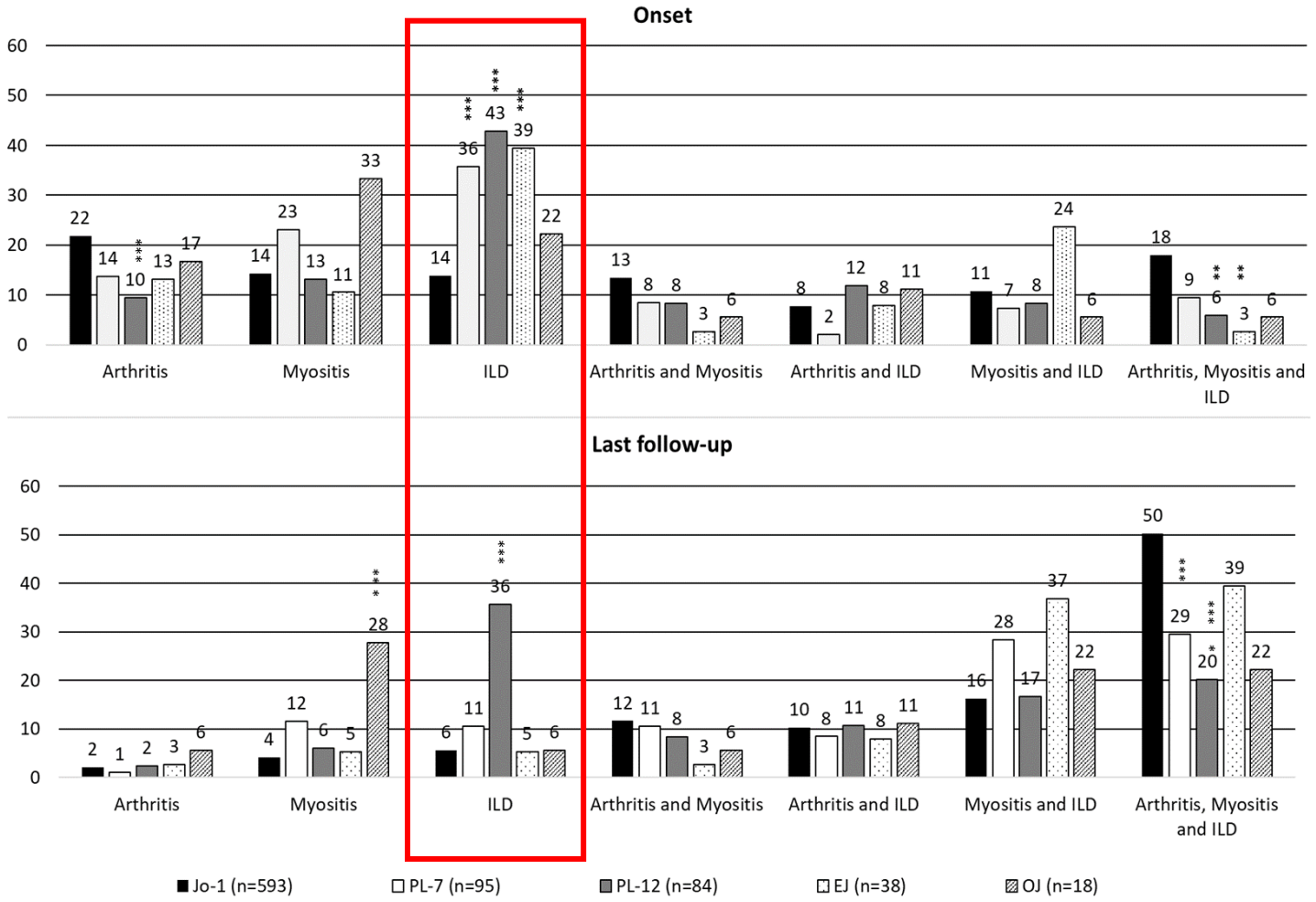
| | Cluster 1 ($n=175$) | Cluster 2 ($n=47$) | $p$-Value |
|---|---|---|---|
| Anti-Jo1 | 151 (86%) | 2 (4%) | <0.001 |
| Anti-PL12 | 17 (10%) | 28 (60%) | <0.001 |
| Anti-PL7 | 7 (4%) | 17 (36%) | <0.001 |
| Anti-RNP | 0 (0%) | 0 (0%) | <0.001 |
| Anti-Sm/anti-DNA | 0 (0%) | 0 (0%) | <0,001 |
| Evolution and outcome | | | |
| Myositis[d] | 143 (82%) | 18 (38%) | <0.001 |
| ILD[d] | 137 (78%) | 46 (98%) | 0.005 |

| Last Follow-Up Characteristics | Anti-Jo-1 ARS ($n$ = 593) | Anti-PL-7 ARS ($n$= 95) | Anti-PL-12 ARS ($n$ = 84) | Anti-EJ ARS ($n$ = 38) | Anti-OJ ARS ($n$= 18) | Test; $p$-Value; $df$ |
|---|---|---|---|---|---|---|
| Interstitial Lung Disease (%) | 486 (82.0) | 73 (76.8) | 70 (83.3) | 34 (89.5) | 11 (61.1) | $\chi2 = 8.16$; 0.086; 4 |
| Acute onset (%) | 179 (37.3) | 28 (38.9) | 34 (48.6) | 21 (63.6) | 4 (36.4) | Fisher exact test $p < 0.001$ |
| Chronic onset (%) | 201 (41.9) | 32 (44.4) | 28 (40.0) | 11 (33.3) | 6 (54.6) | |
| Asymptomatic onset (%) | 100 (20.8) | 12 (16.7) | 8 (11.4) | 1 (3.0) | 1 (9.1) | |
| comparison vs Anti-Jo-1 ARS | reference | 0.713 | 0.09 | *$p = 0.003$ | $p = 0.623$ | |

828 pts
No substantial differences in ILD prevalence

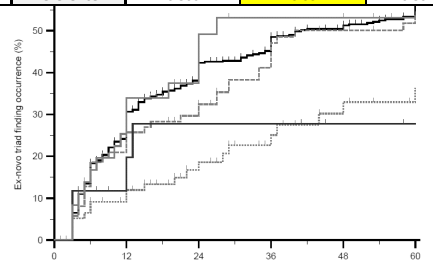
Cavagna L, et al. J Clin Med 2019

# *Influence of Antisynthetase Antibodies Specificities on Antisynthetase Syndrome Clinical Spectrum Time Course*




- Isolated ILD at onset is more common in non-anti-Jo1 ASSD
- Other disease manifestations eventually occurr during the disease course
- Anti-PL12 seems to remain more frequently associated with isolated ILD

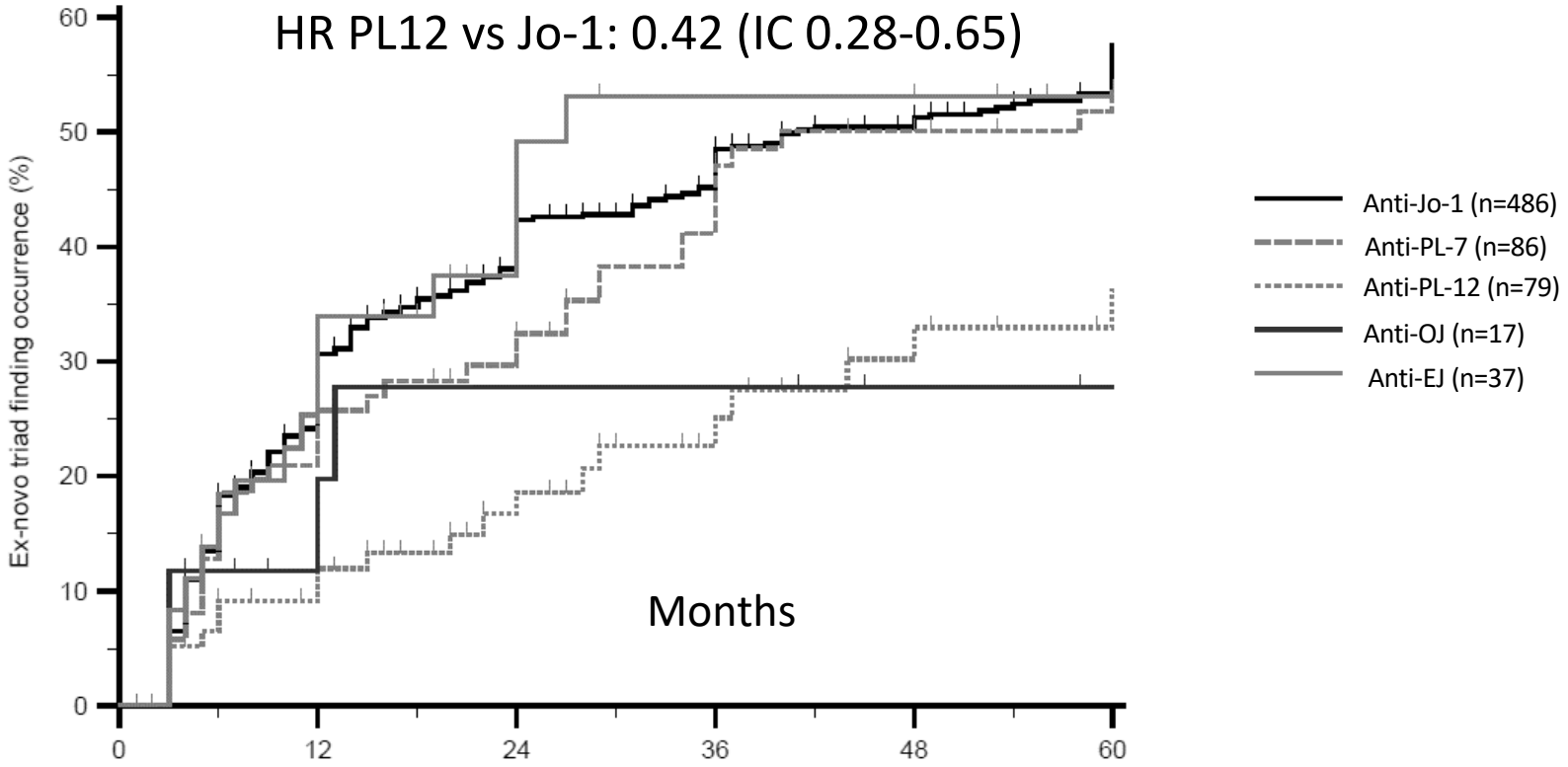
| | Anti Jo-1 + group | Anti PL-7 + group | Anti PL-12 + group | Anti EJ + group | Anti OJ + group |
|---|---|---|---|---|---|
| Global ex-novo triad findings (% of incomplete ASSD at the onset) | 302/486 (62) | 50/86 (58) | 24/79 (30) | 23/37 (62) | 7/17 (41) |
| p value | reference | 0.560 | <0.001 | 0.862 | 0.136 |




*Adapted from Cavagna L, et al. J Clin Med 2019:18;8. pii: E2013.*

# *Is the trend to progression independent to underlying ARS specificity?*

| | Anti Jo-1 + group | Anti PL-7 + group | Anti PL-12 + group | Anti EJ + group | Anti OJ + group |
|---|---|---|---|---|---|
| **Global ex-novo triad findings (% of incomplete ASSD at the onset)** | **302/486 (62)** | 50/86 (58) | 24/79 (30) | 23/37 (62) | 7/17 (41) |
| p value | **reference** | 0.560 | **<0.001** | 0.862 | 0.136 |

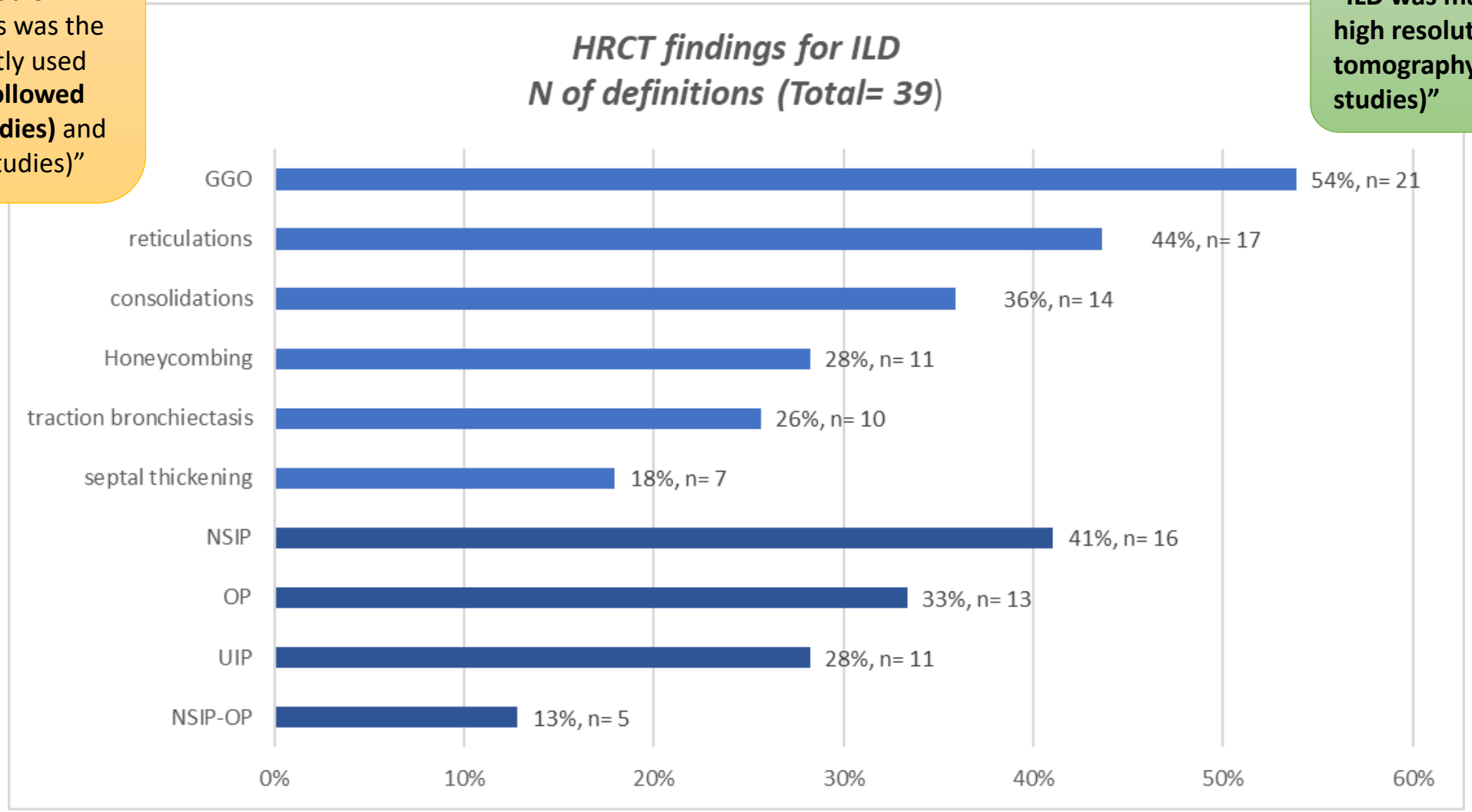



*Adapted from Cavagna L, et al. J Clin Med 2019:18;8. pii: E2013.*

# *What are the features of ASSD-ILD?*

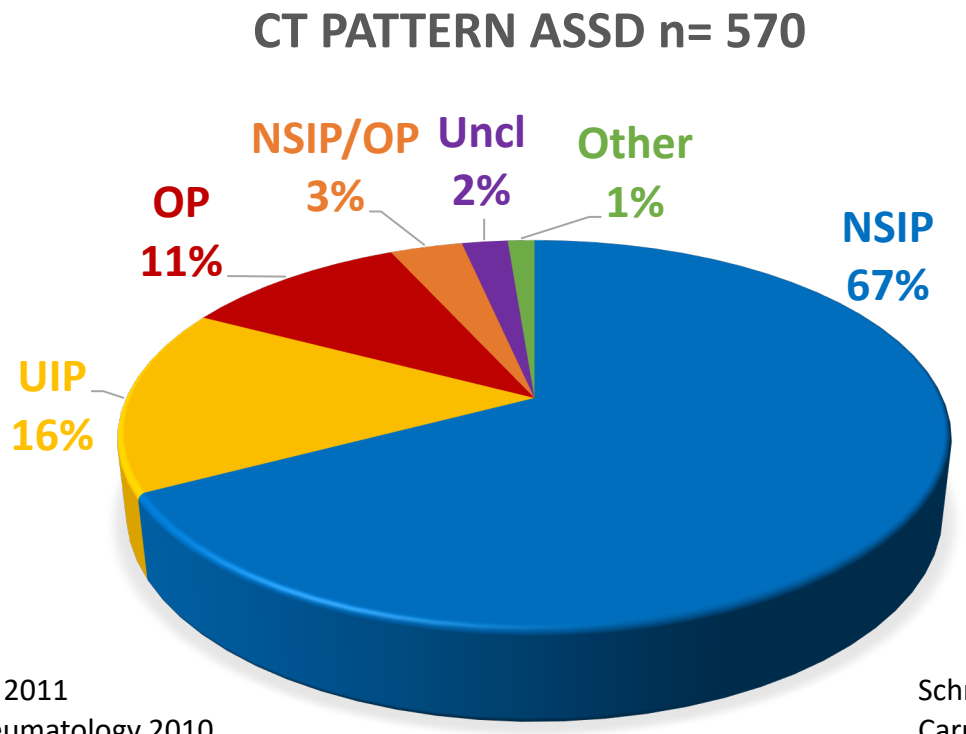
"Among the features of the clinical triad of ASSD, myositis was the most frequently used (64 studies) **followed by ILD (49 studies)** and arthritis (26 studies)"

**"ILD was mainly defined by high resolution computed tomography (HRCT) (39/49 studies)"**




Zanframundo G, et al. Clin Exp Rheumatol 2022, suppl mat

# *What are the features of ASSD-ILD?*

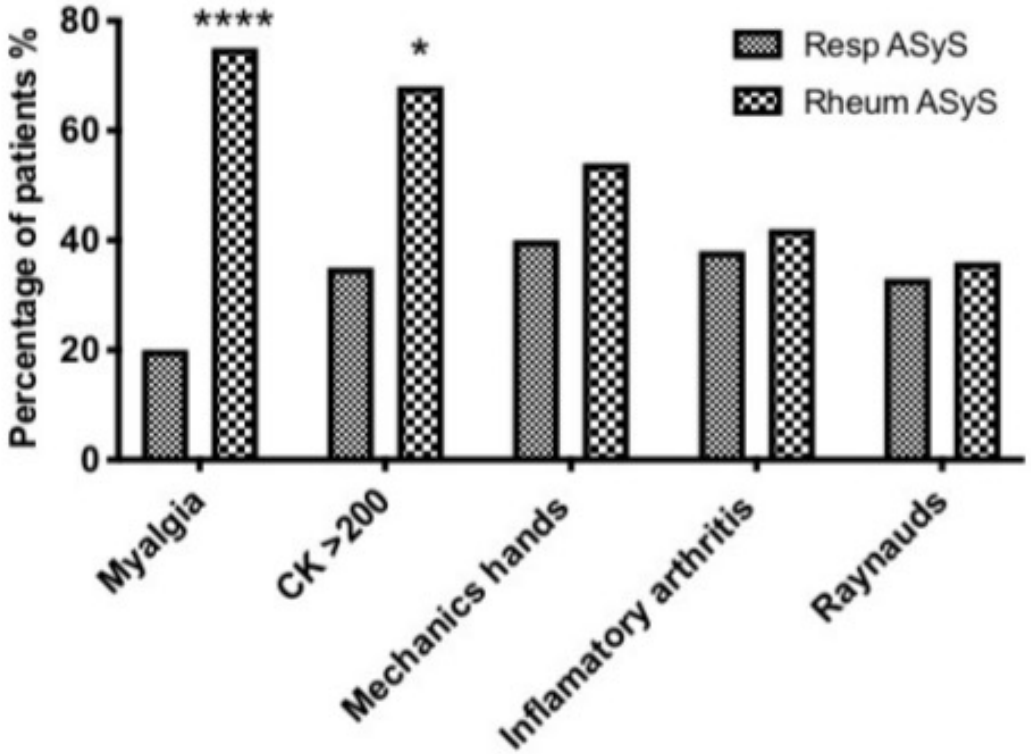



Hervier B et al, ERJ 2011
Hervier B et al, Rheumatology 2010
Lega et al, jrheum 2010
Shi et al, jrheum 2018
Yousem et al, Mod Pathol 2010
Yousem et al, Hum Pathol 2014
Kalluri et al, Chest 2009
Marie et al, Arthritis Care Res 2013
Sasano et al, BMC Pulmonary Medicine 2016
Marie et al, Presse Med. 2013
Schneider et al, Arch Pathol Lab Med. 2018

Schneider F, et al. J Clin Pathol 2014
Carrasco Cubero et al, Ann Rheum Dis 2018
Hervier et al, Autoimmun Rev 2012
Hervier et al, Autoimmun Rev 2012
Marie et al, Eur J Intern Med 2013
Fischer et al, Respir Med. 2009
Fischer et al, Respir Med. 2009
Stanciu et al, J Rheumatol 2012
Karadimitrakis S, et al. Eur J Radiol 2008
Zamora et al, Respir Med 2016

# *What are the ASSD-ILD features? vs IPF*

| Parameter | ASSD n=76 | IPF n=78 | P value |
|---|---|---|---|
| Age years (IQR) | 57 (47-65) | 77 (73-82) | <0,001 |
| Male n(%) | 33 (43%) | 52 (67%) | 0,006 |
| Ex smoker | 25 (33%) | 46 (59%) | 0,004 |
| ANA positivity | 16 (23%) | 26 (39%) | 0,038 |
| ANA Cytoplasmic | 29 (71%) | 0 | <0,001 |
| FVC actual (L) (IQR) | 2,53 (1,8-3,1) | 2,76 (2-3,2) | ns |
| FVC % predicted | 73 (63-84) | 87 (74-97) | 0,0002 |
| Definite UIP | 4 (5%) | 47 (60%) | - |
| Probable UIP | 0 | 26 (33%) | - |
| cNSIP | 14 (18%) | 0 | - |
| fNSIP | 24 (32%) | 0 | - |
| OP | 13 (17%) | 0 | - |
| NSIP/OP | 17 (22%) | 0 | - |

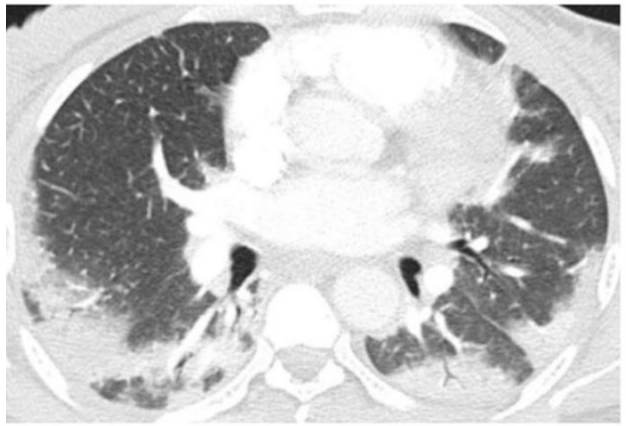



Adapted from Barratt SL, et al. BMJ Open Resp Res 2021

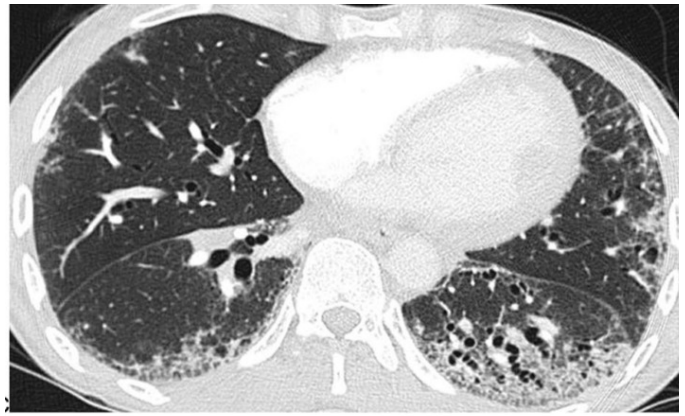
# *What are the ASSD-ILD features? vs other IIMs*

| Characteristic | Cluster 1 ($n=21$) | Cluster 2 ($n=39$) | Cluster 3 ($n=34$) | $p$ value |
|---|---|---|---|---|
| Consolidations (all types) | 20 (95.2) | 7 (17.9) | 13 (38.2) | <0.001* |
| Reticular pattern | 1 (4.8) | 15 (38.5) | 9 (26.5) | <0.001* |
| Cysts (all types) | 1 (4.8) | 0 | 34 (100) | <0.001* |
| ASyS autoAbs (anti-PL7, anti-PL12, or anti-Jo1) | 6 (28.6) | 22 (56.4) | 26 (76.5) | 0.002* |
| Anti-MDA5 | 12 (57.1) | 2 (5.1) | 2 (5.9) | 0.001* |
| Anti-SRP | 0 | 8 (20.5) | 5 (14.7) | 0.058 |
| MSA-negative or other | 3 (14.3) | 7 (17.9) | 1 (2.9) | 0.089 |

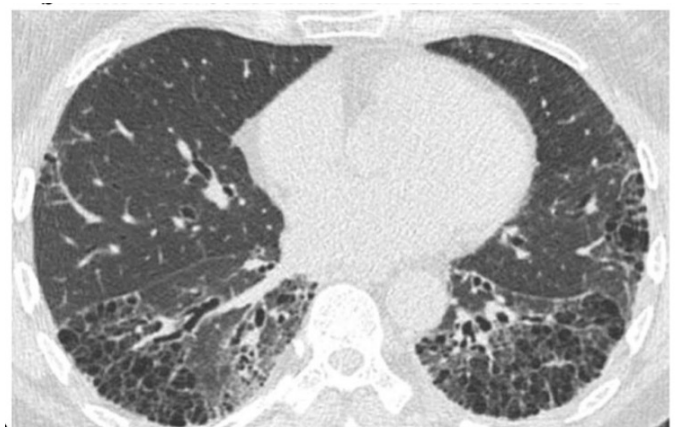
No differences in ARS positivity between cluster 2 and 3



Cluster1= consolidations (anti-MDA5)
IIM diagnosis delay= 940 days



Cluster 2= Reticular pattern (ASSD)
IIM diagnosis delay= 2009 days

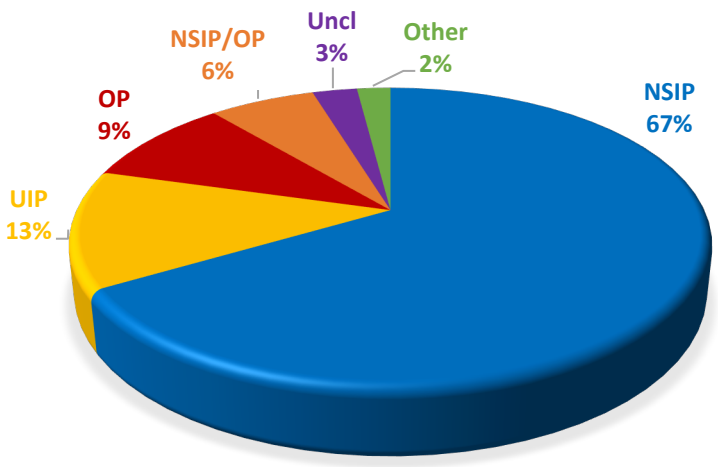


Cluster 3= microcysts (ASSD)
IIM diagnosis delay= 3964 days

Adapted from Barratt SL, et al. BMJ Open Resp Res 2021

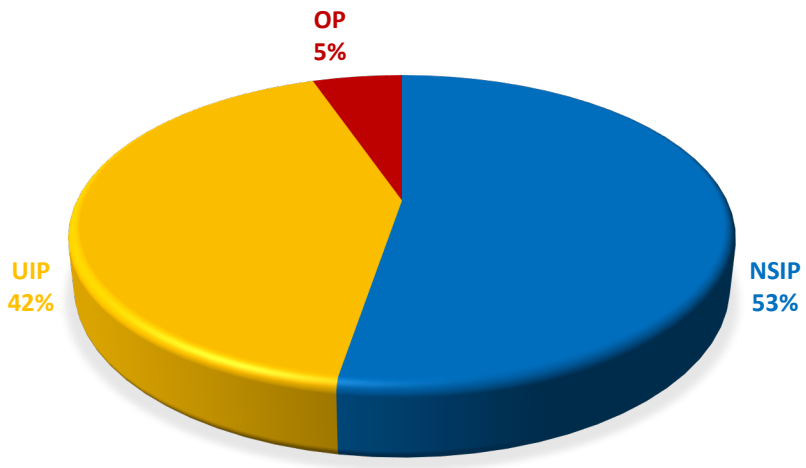
# *Does ILD pattern depend on ARS-specificity?*

## ANTI JO-1 (n= 299)



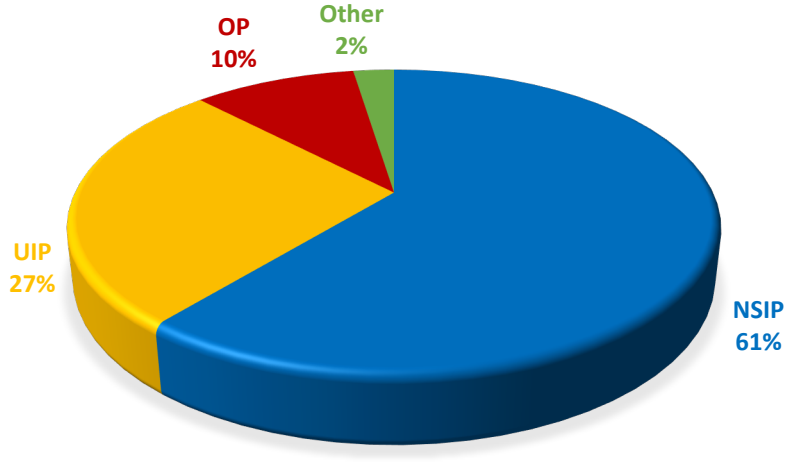

Yousem et al, Mod Pathol 2010
Marie et al, Arthritis Care Res 2013
Carrasco Cubero et al, Ann Rheum Dis 2018
Hervier et al, Autoimmun Rev 2012
Stanciu et al, J Rheumatol 2012
Karadimitrakis S, et al. Eur J Radiol 2008
Zamora et al, Respir Med 2016

## ANTI PL-12 (n= 57)



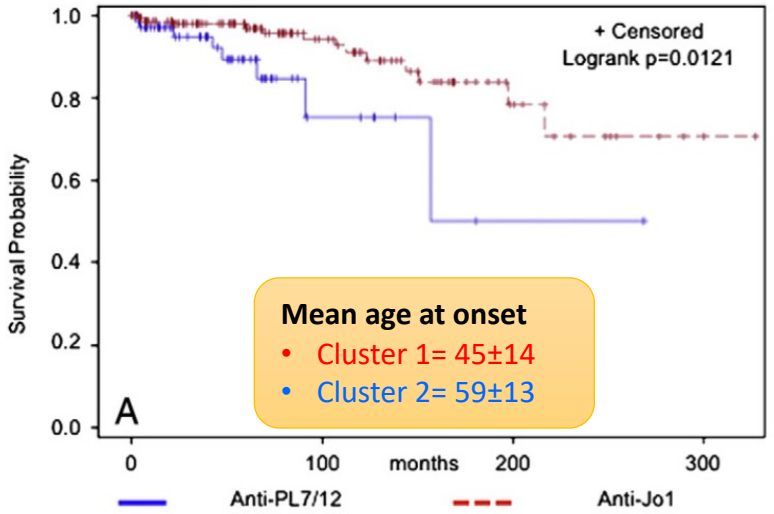

Hervier B et al, Rheumatology 2010
Kalluri et al, Chest 2009
Marie et al, Presse Med. 2013
Schneider et al, Arch Pathol Lab Med. 2018
Fischer et al, Respir Med. 2009

## ANTI PL-7 (n= 41)



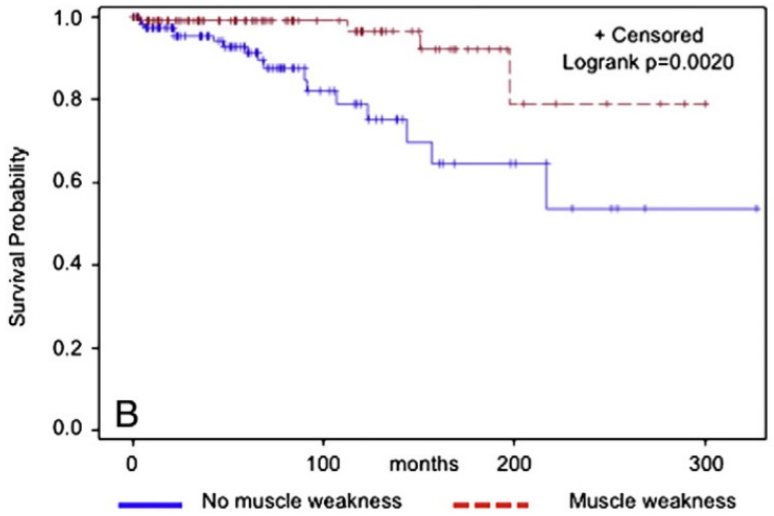

Hervier B et al, ERJ 2011
Yousem et al, Hum Pathol 2014
Marie et al, Eur J Intern Med 2013
Fischer et al, Respir Med. 2009

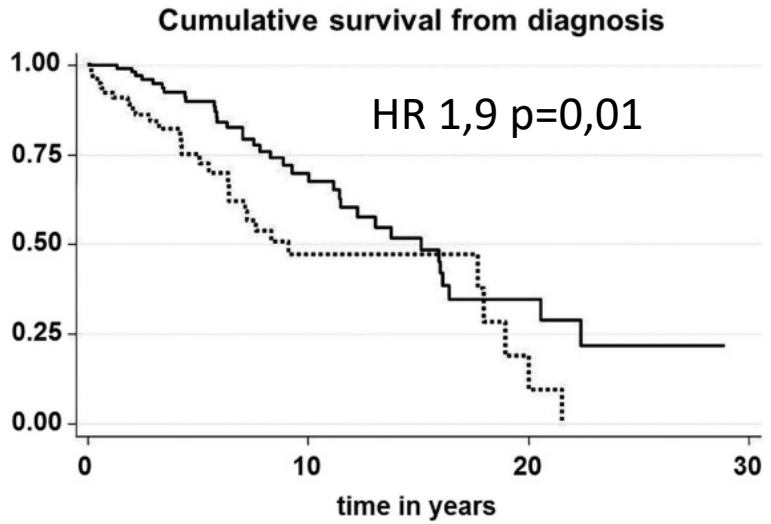
# *Is the prognosis influenced by underlying ARS positivity?*



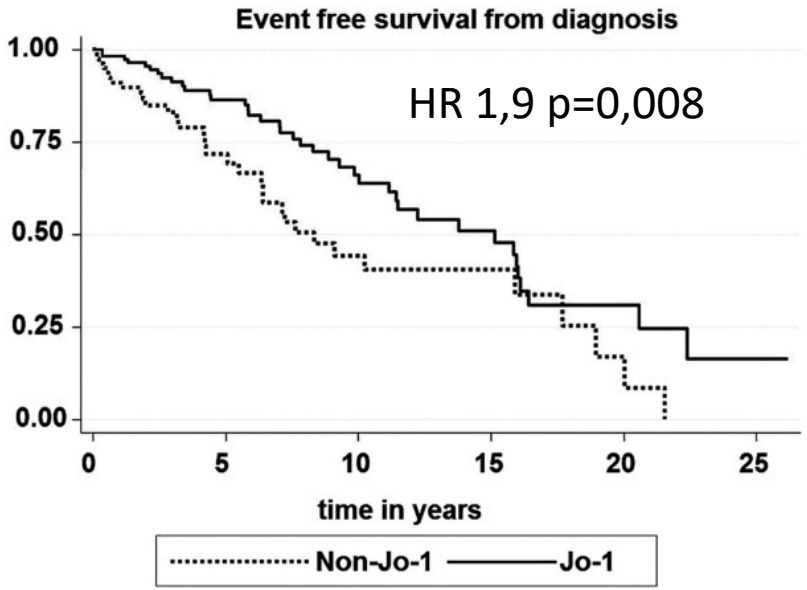

**Mean age at onset**

- Cluster 1= 45±14
- Cluster 2= 59±13




The 5- and 10-year unadjusted cumulative survival was 90% and 70% for Jo-1 patients, and 75% and 47% for non Jo-1 patients (p<0,005).

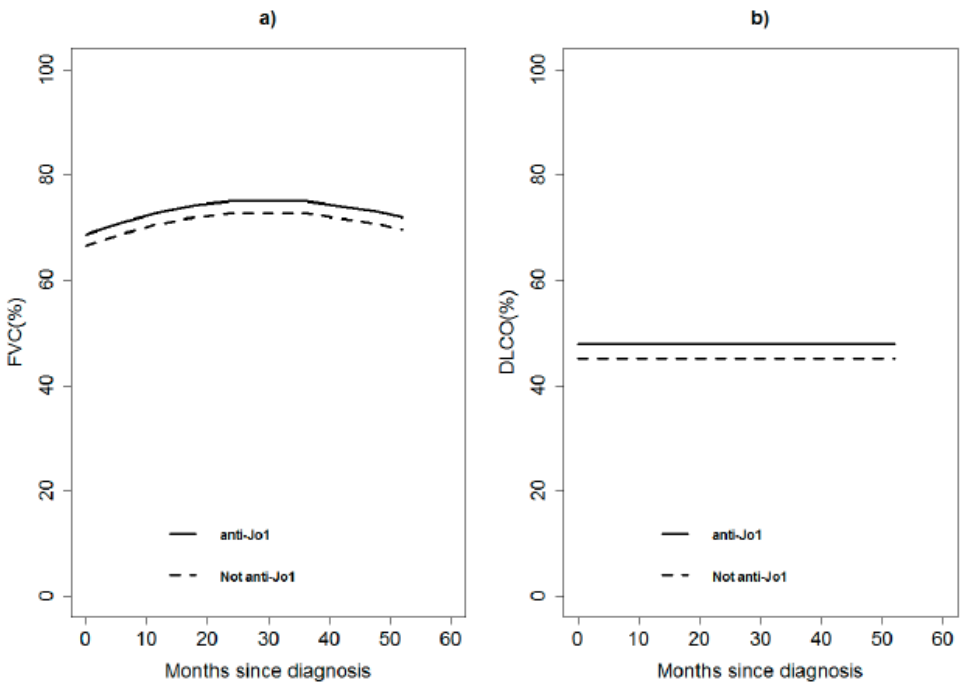


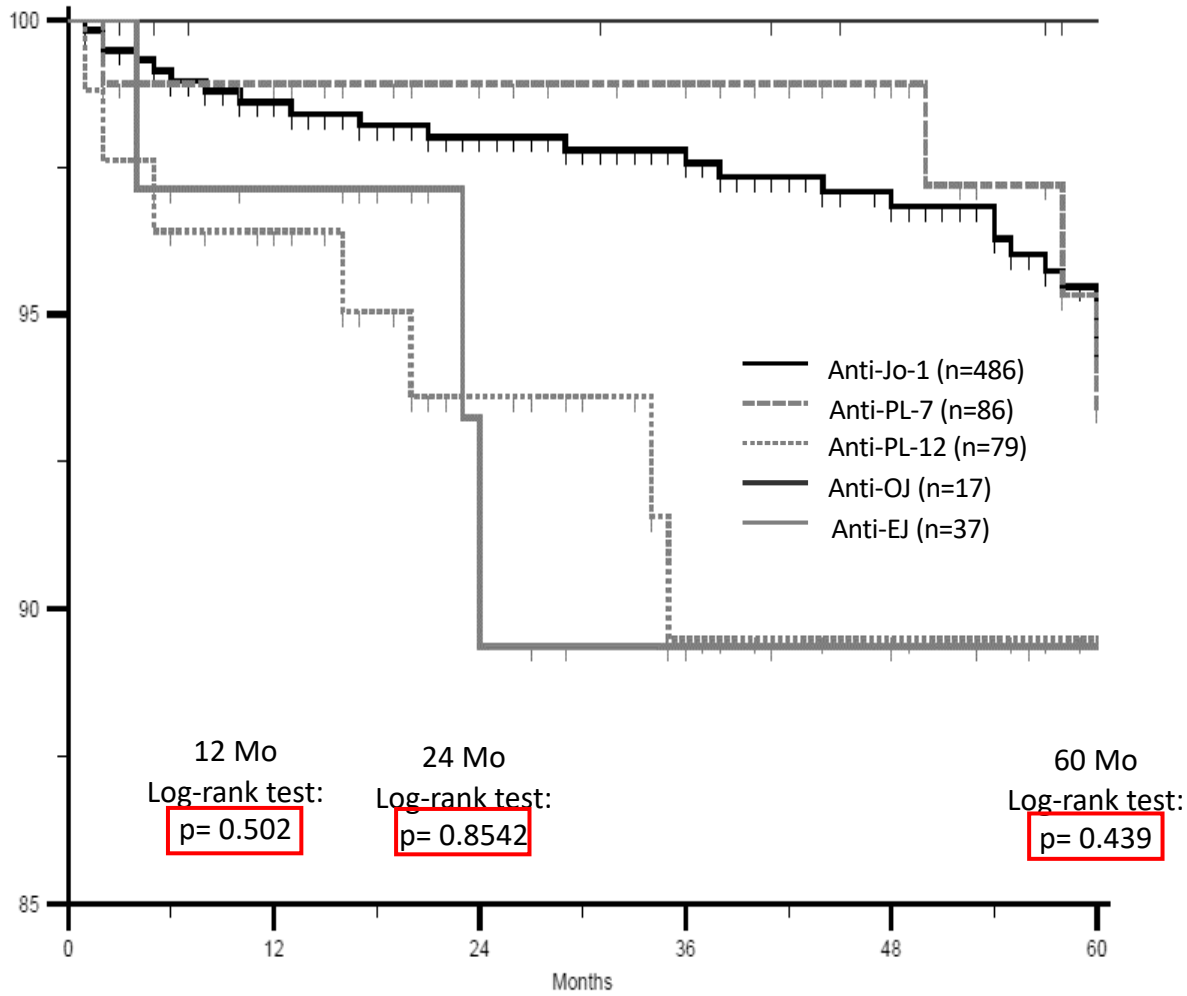

There was a significant (p<0,001) difference in the median time from the first CTD symptom until diagnosis (diagnostic delay) between Jo-1 (median 0,4 years) versus non-Jo-1 patients (median 1 year)

*Hervier B. et al. Autoimmunity Reviews 12 (2012)*

*Aggarwal et al, Ann Rheum Dis. 2014*

# *Is the prognosis influenced by underlying ARS positivity?*




*Dei G, et al. J Clin Med 2020*

*Cavagna L, et al. J Clin Med 2019:18;8. pii: E2013.*

# *Treatment*

# Therapy

- GCs are the mainstay of the treatment
- High frequency of relapse for GC alone
- Data for IS drugs based on observational studies (case series or small cohorts)
- Sub-analysis of the RIM trial: better muscular efficacy of RTX on ARS+ patients (IMACS)
- Patients with anti-Jo1 and anti-Ro52 antibodies show better response to RTX

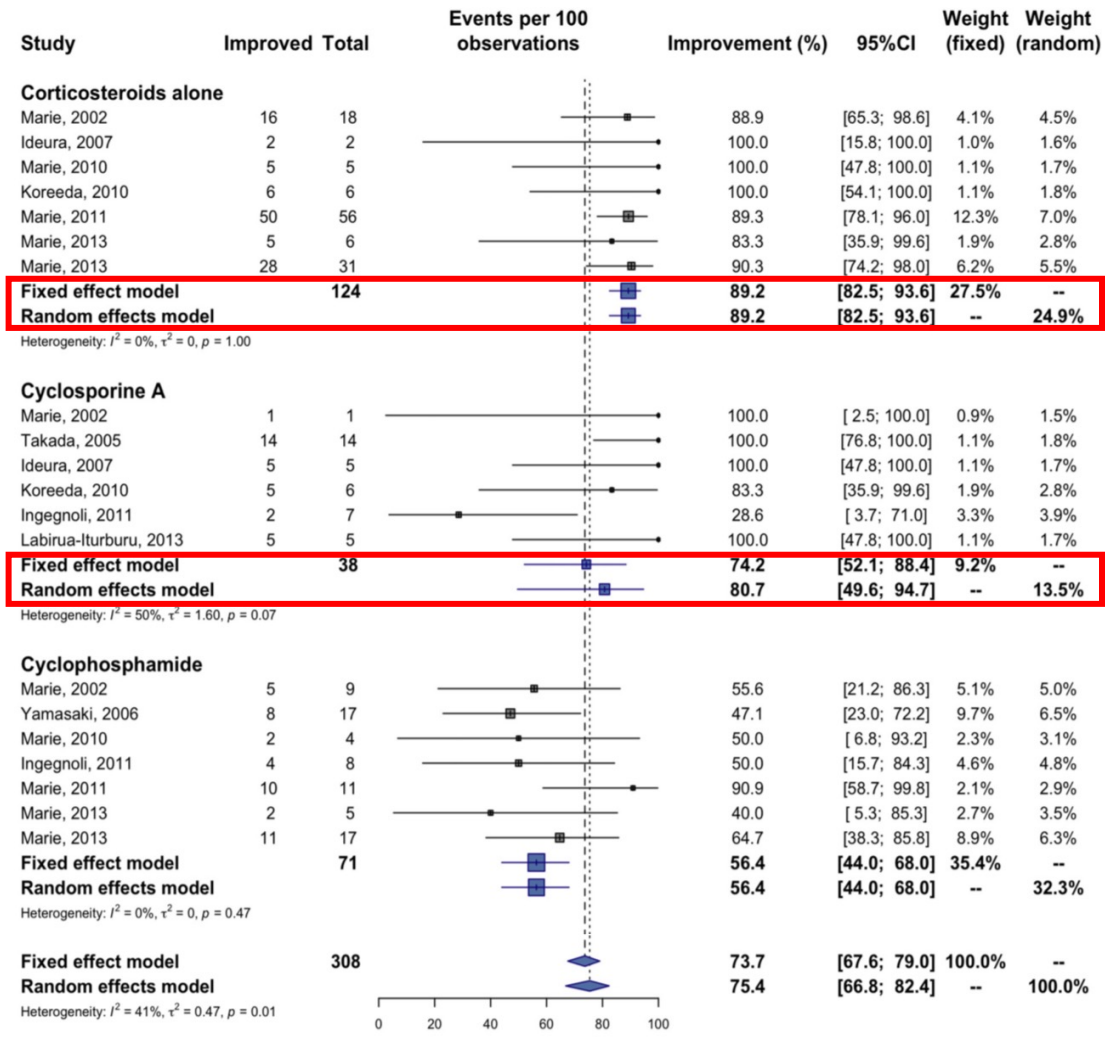
**Table 1. Available treatments and their area of effectiveness**

| | Myositis | Interstitial lung disease | Joints | Skin | Dosage |
|---|---|---|---|---|---|
| Corticosteroids | ◊ | ◊ | ◊ | ● | 1–2 mg/kg/day or I.V. bolus (1 g/day for 3 days) |
| Calcineurin inhibitors | ◊ | ◊ | ◊ | ●* | Cys 3 mg/kg/day; Tac initially 1 mg twice daily titrated until blood levels of 5–20 ng/ml |
| Cyclophosphamide | ◊ | ◊ | | ● | IV pulses 0.3–1.5 g/m2 or 10–15 mg/kg at weekly to monthly intervals for 6–12 months |
| Mycophenolate | ● | ◊ | | ● | 2–3 g/day |
| Rituximab | ◊ | ◊ | ◊ | ● | 1 g IV at day 0 and 14, then after 6 months |
| Methotrexate | ◊ | | § | | 7,5–25 mg/week |
| Azathioprine | ◊ | ● | | | 1–3 mg/Kg/day |
| Hydroxychloroquine | | | | ● | 200–400 mg/day |
| Intravenous Immunoglobulins | ◊ | ◊ | | ● | 2 g/Kg over 2 to 5 days repeated every 4–8 weeks accordingly to clinical response |

Legend.
not supporting data.
● currently used with data on polymyositis/dermatomyositis.
◊ currently used with data on ASSD.
* topical formulation
§ commonly used with data on other forms of arthritis (e.g., RA).

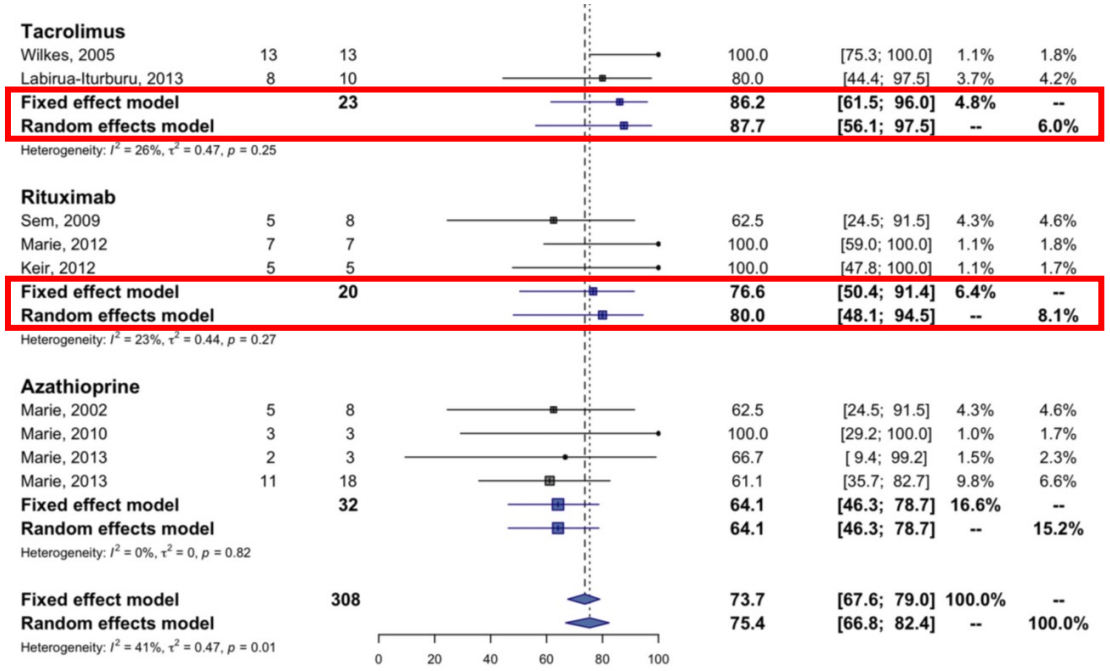
Aggarwal R et al, Arthritis Rheumatol 2014;66:740–9
Zanframundo G et al, Curr Treat Options in Rheum 2019
Bauhammer J et al, J Rheumatol. 2016

# *Treatment of idiopathic inflammatory myositis associated interstitial lung disease: A systematic review and meta-analysis*




27 studi
553 pazienti
- 40% Dermatomiositi
- 45% ASSD

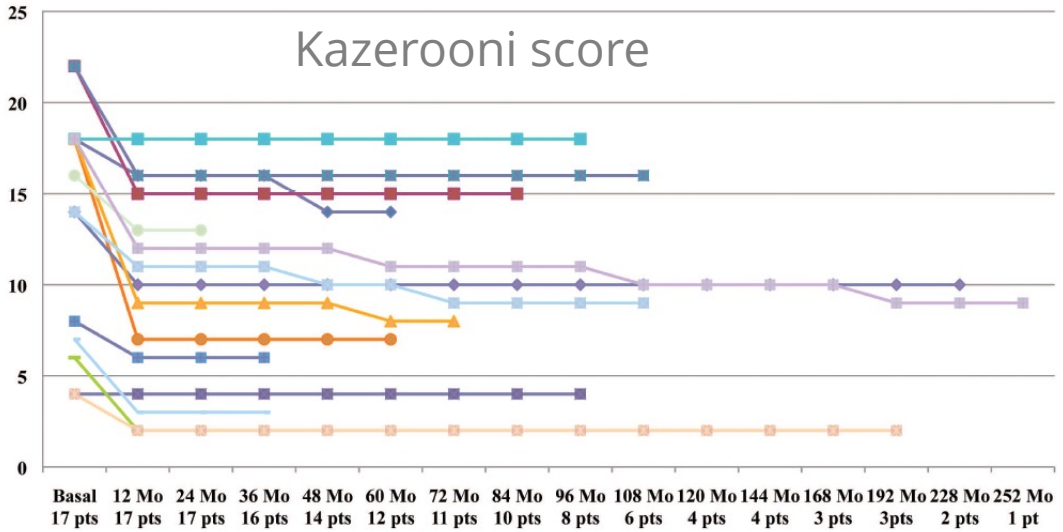
Overall improvement of C-ILD= 89%

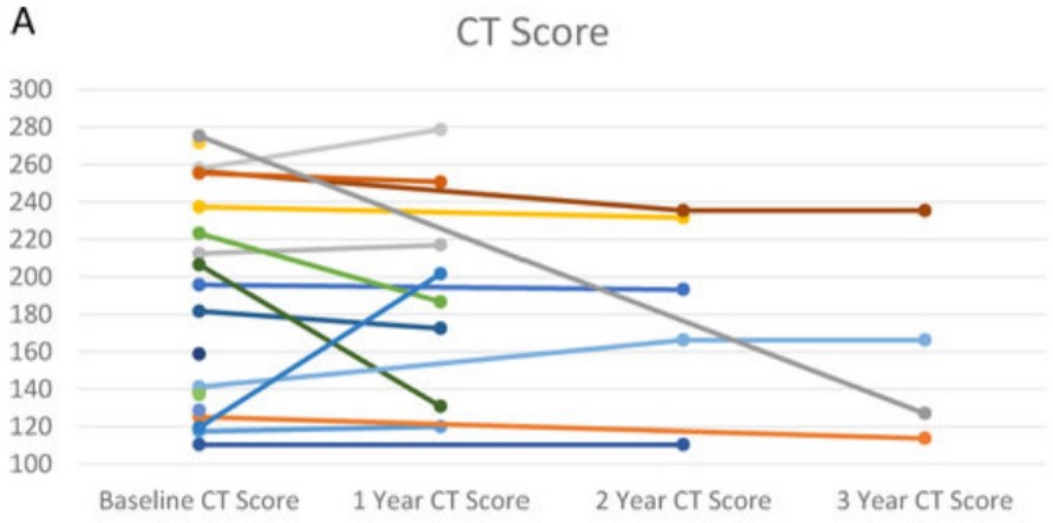



Barba T. et al, Autoimmunity Reviews 18 (2019) 113–122

# *Cyclosporine in Anti-Jo1* vs *Rituximab in ASSD*

## *n= 17* | *n= 25*



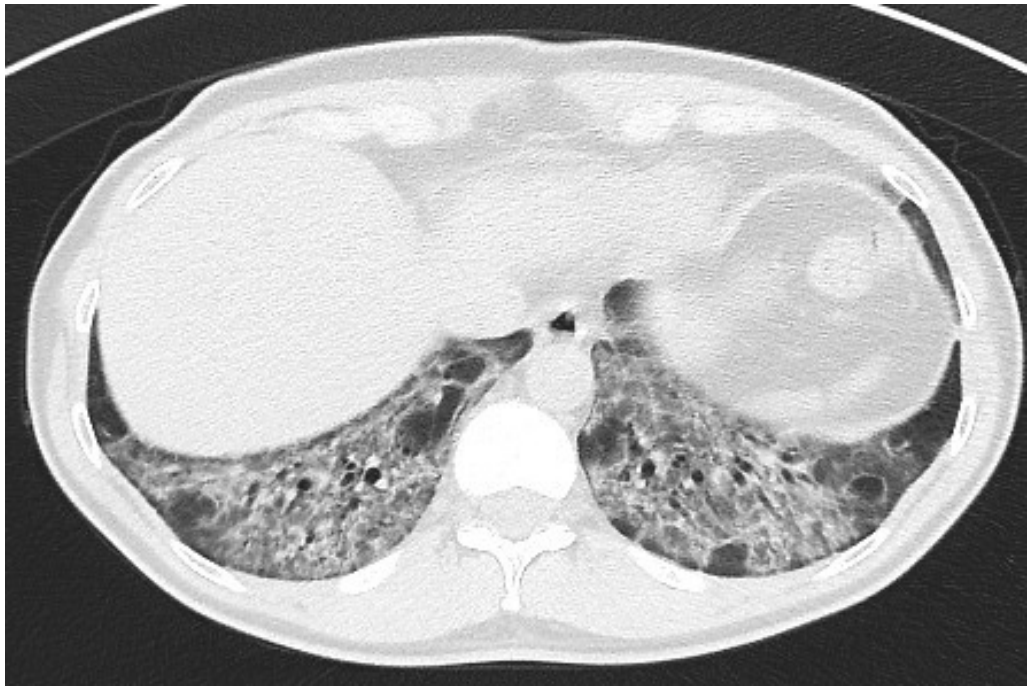

| | Basal | | 6 Mo. CYC | | 12 Mo. CYC | | 24 Mo. CYC | |
|---|---|---|---|---|---|---|---|---|
| | FVC | DLCO | FVC | DLCO | FVC | DLCO | FVC | DLCO |
| Mean | 65 | 55 | 71 | 60 | 75 | 63 | 76 | 63 |
| SD | 14 | 12 | 13 | 14 | 12 | 16 | 12 | 16 |
| Median | 60 | 60 | 70 | 65 | 75 | 66 | 78 | 68 |
| IQR | 56–70 | 50–62.75 | 61–80 | 55–68 | 67–85 | 57.25–72.25 | 70–87 | 57–72 |
| No. patients | 17 | | 17 | | 17 | | 17 | |

| | Baseline | 1 Year Follow-up | 2 Year Follow-up | 3 Year Follow-up |
|---|---|---|---|---|
| **FVC%** | 57 ± 17<br>n=22 | 60 ± 20<br>n=19 | 65 ± 22<br>n=12 | 82 ± 20<br>n=7 |
| **DLCO%** | 42 ± 17<br>n=19 | 36 ± 16<br>n=17 | 53 ± 26<br>n=9 | 70 ± 20<br>n=4 |

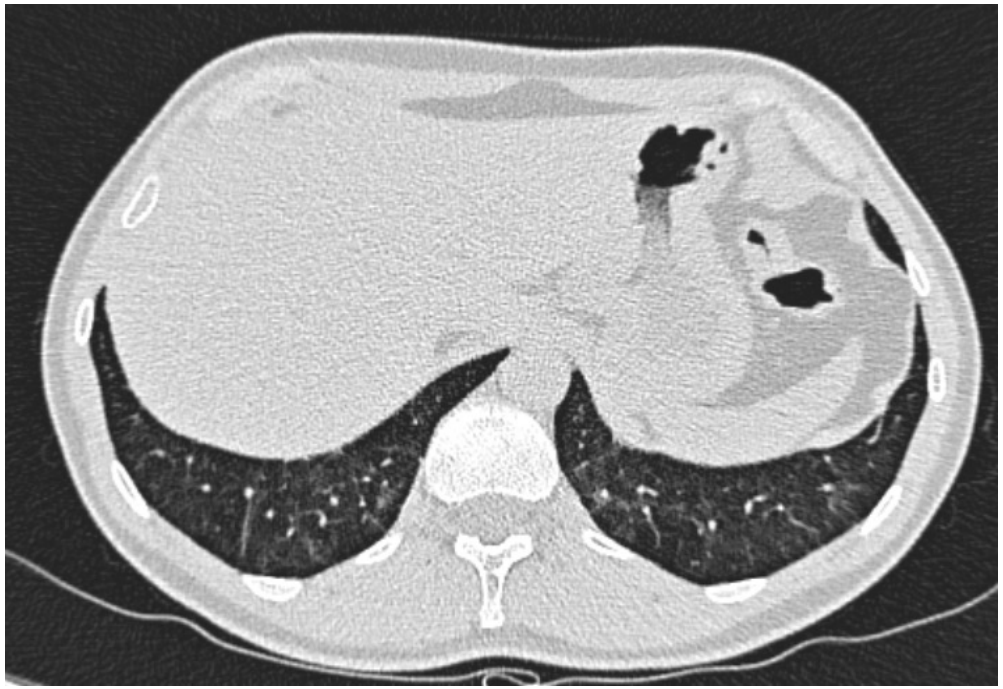
Cavagna L, et al. J Rheum 2013

Doyle T. et al, J Rheumatol. 2018

***Uomo, 49 anni***
***Esordio con dispnea, non artrite, non debolezza muscolare***
***ANA citoplasmatici, anti-Jo1+***



**12 MESI**



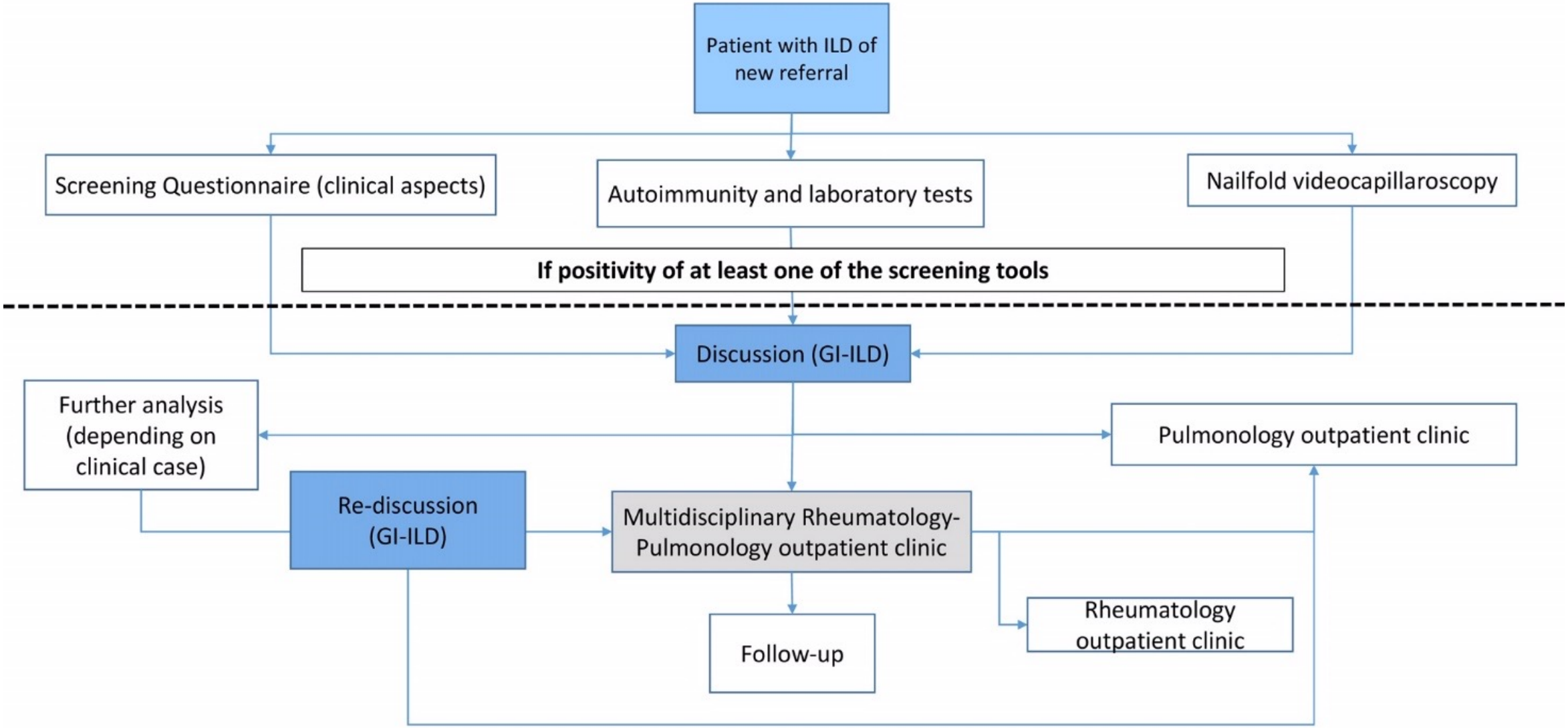
Ciclosporina 3 mg/Kg/die
Prednisone 25 mg/die a scalare

Ciclosporina 3 mg/Kg/die

# *The problem of (progressive) lung fibrosing disease*


*CTD-ILD outpatients clinic: 16 patients on nintedanib right now*

# *Pavia's ILD Multidisciplinary team*



# *Key points*

- ✓ Antisynthetase syndrome is to be considered a unique entity
- ✓ About 80% of ASSD will eventually develop ILD
- ✓ NSIP is the most common pattern at HRCT, but also UIP and OP have been described in ASSD
- ✓ Isolated triad finding onset is very common (arthritis -> anti-Jo1, myositis -> anti-PL7/OJ, ILD -> anti-PL12/EJ)
- ✓ A prompt diagnosis of ASSD may sensibly improve the prognosis

- ➢ Every patients presenting with ILD should be assessed for antisynthetase antibodies
  - ❑ Cytoplasmic ANA
  - ❑ Nailfold capillaroscopy
  - ❑ Anti-Ro52

# *CLASS (an EULAR/ACR funded) project*

## CLassification criteria for AntiSynthetase Syndrome

Principal Investigators:
Lorenzo Cavagna and Rohit Aggarwal

- Because ARS antibodied are not easily feasible worlwide
- Because we are not able to identify all ARS antibodies
- Because we do not know if an anti-Jo-1 positive patient with an isolated Raynaud's phenomenon could be diagnosed with ASSD
- Because some patients may have ARS without clinical manifestations of antisynthetase syndrome (eg, the 3% of SLE)
- etc, …….

UNIVERSITÀ DI PAVIA

# *The CTD team of Pavia*

European Reference Network

for rare or low prevalence complex diseases

**Network**
Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET)

**Member**
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Prof Lorenzo Cavagna

Dr.ssa Veronica Codullo

Dr. Giovanni Zanframundo

Dr.ssa Alessandra Milanesi

Dr. Fabio Brandolino

Dr. Lorenzo Bianchessi

Dr.ssa Eleonora Mauric

Dr.ssa Alice Bartoletti

Dr.ssa Carlotta Di Giorgi