

Rapidly progressive ILD

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Definition of RP-ILD

- RPILD was considered when worsening of radiologic interstitial changes with progressive dyspnea and hypoxemia within 1 month after the onset of respiratory symptoms appeared
- It was first described in 1990, based on a Japanese cohort with clinically amyopathic DM and RP-ILD
- Sato et al in 2005 discovered a novel Ab – anti 140kd polypeptide in CADM patients with RPILD

F Romero et al Semin Arthritis Rheum. 2020, Recommendations for the treatment of anti mda5 positive DM associated RPILD

Sato et al, Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheum. 2005

Definition of RP-ILD

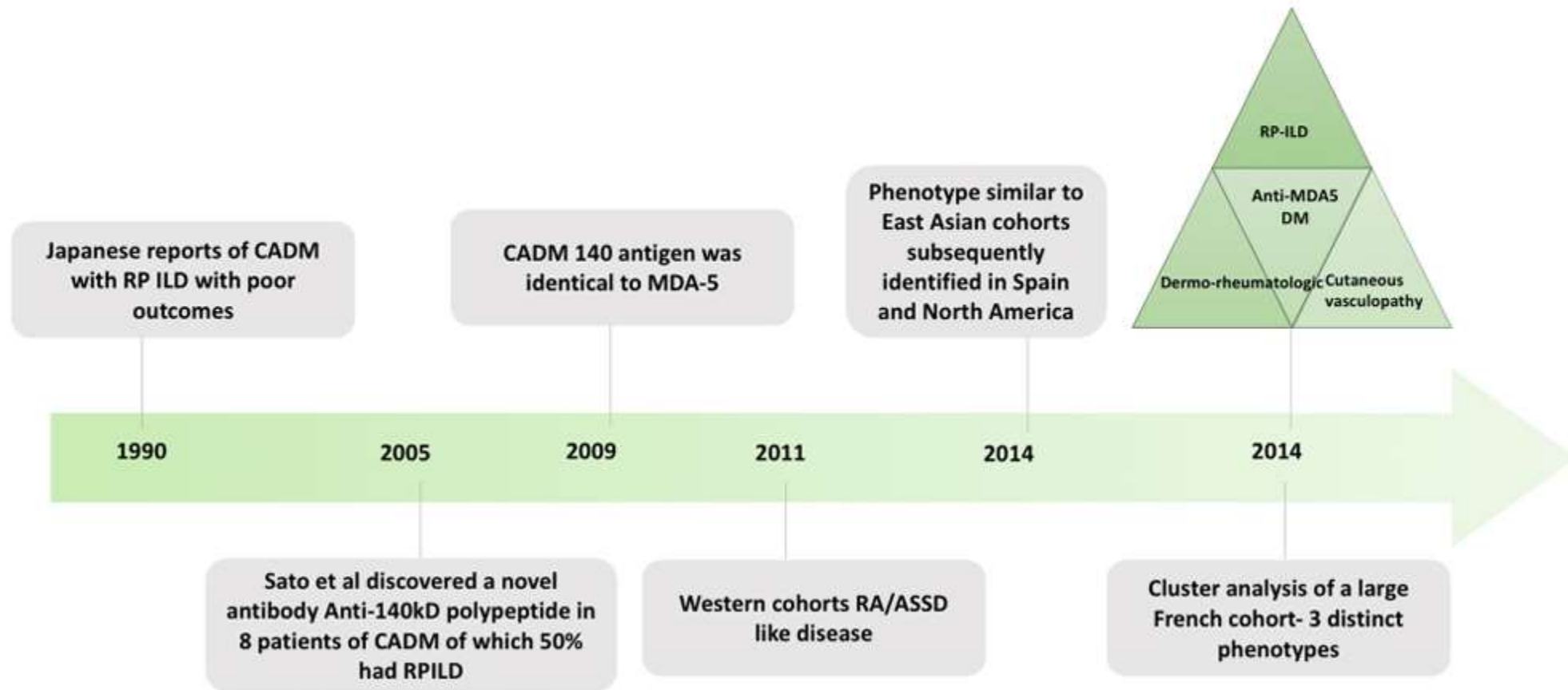
- RPILD - The acute and progressive worsening of dyspnoea onset within 1 month, with the presence of any of the following four conditions:
 1. Acute and progressive dyspnea requiring hospitalization or oxygen support
 2. Lung function decline: FVC decreases >10% or DLCO falls >15%
 3. HRCT shows interstitial abnormalities increasing by >20%
 4. ABG analysis suggests respiratory failure or oxygen partial pressure reduction >10 mmHg

Causes of rapidly progressive ILD

- Anti MDA5 associated
- Acute interstitial pneumonia
- Drug induced ILD
- Radiation induced ILD
- Acute HSP

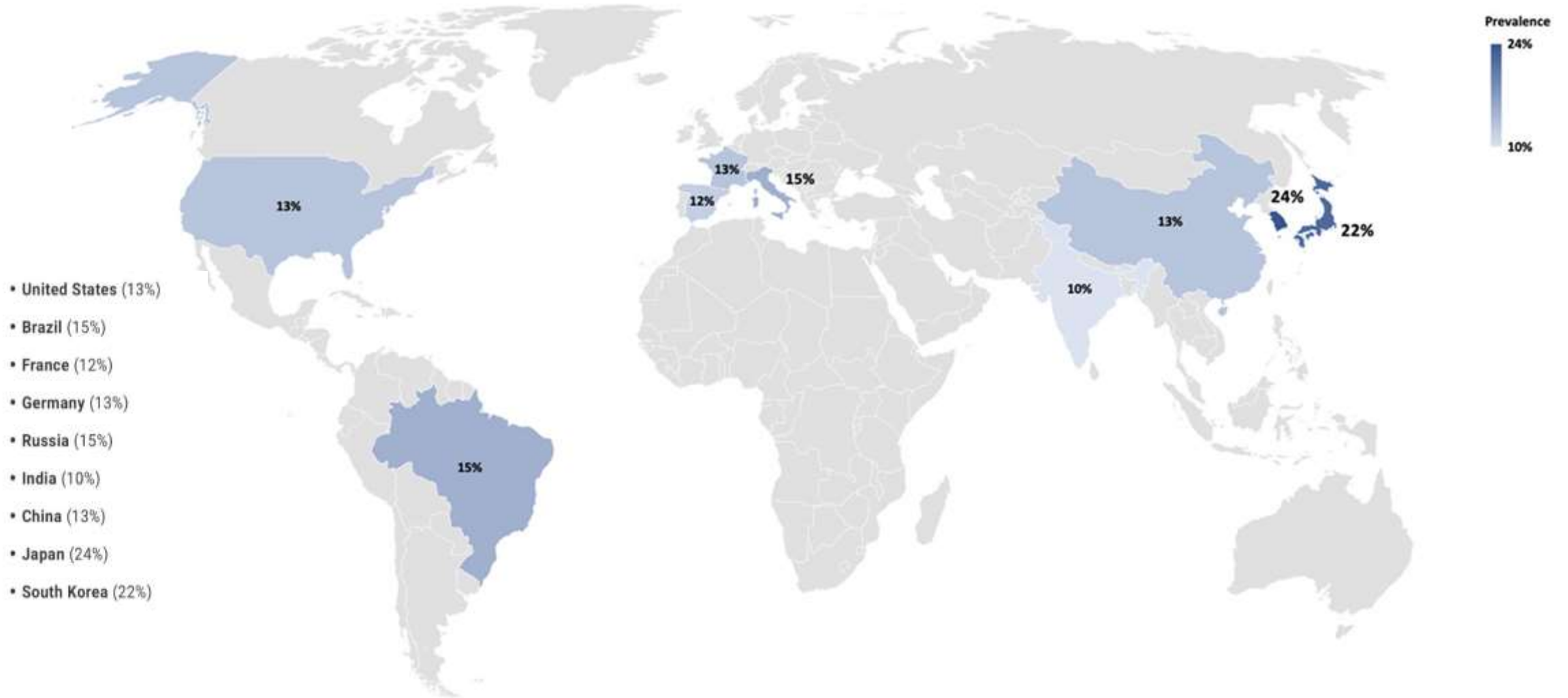
Anti MDA 5 associated ILD

Timeline



Pankti Mehta et al, Understanding and managing anti-MDA 5 dermatomyositis, including potential COVID-19 mimicry, Rheumatology International; 2021

Prevalence

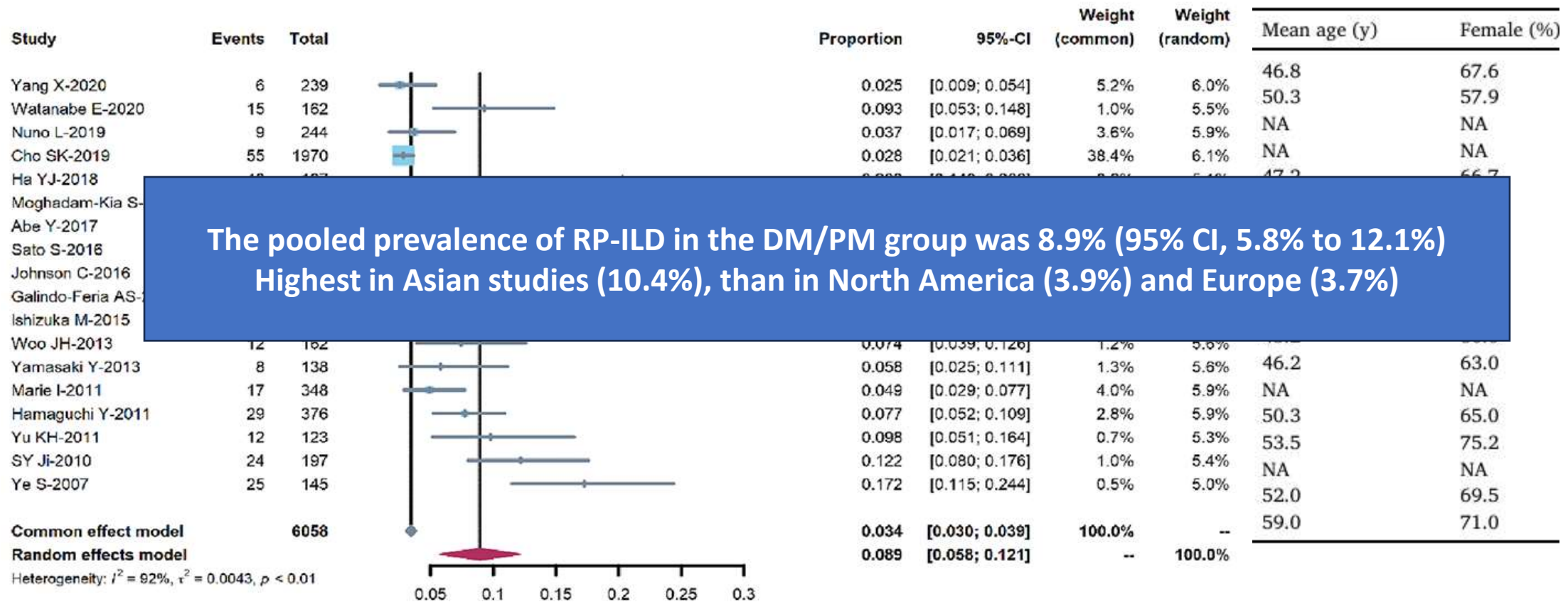


Sato S et al, Anti mda5 Ab: expanding the clinical spectrum in north American patients with dermatomyositis. J Rheumatol, 2017

Labradorr Horrillo et al, Anti-MDA5 antibodies in a large Mediterranean population of adults with dermatomyositis. J Immunol Res 2014

The prevalence and effects of treatments of rapidly progressive interstitial lung disease of dermatomyositis/polymyositis adults: A systematic review and meta-analysis

Hongli Wang^{a,b,c,1}, Jiyang Lv^{a,b,c,1}, Juan He^{a,b,c}, Wenqi Wu^{a,b,c}, Yuchao Zhong^{a,b,c},
Siyang Cao^d, Yueming Cai^{a,b,c,*}, Qingwen Wang^{a,b,c,*}

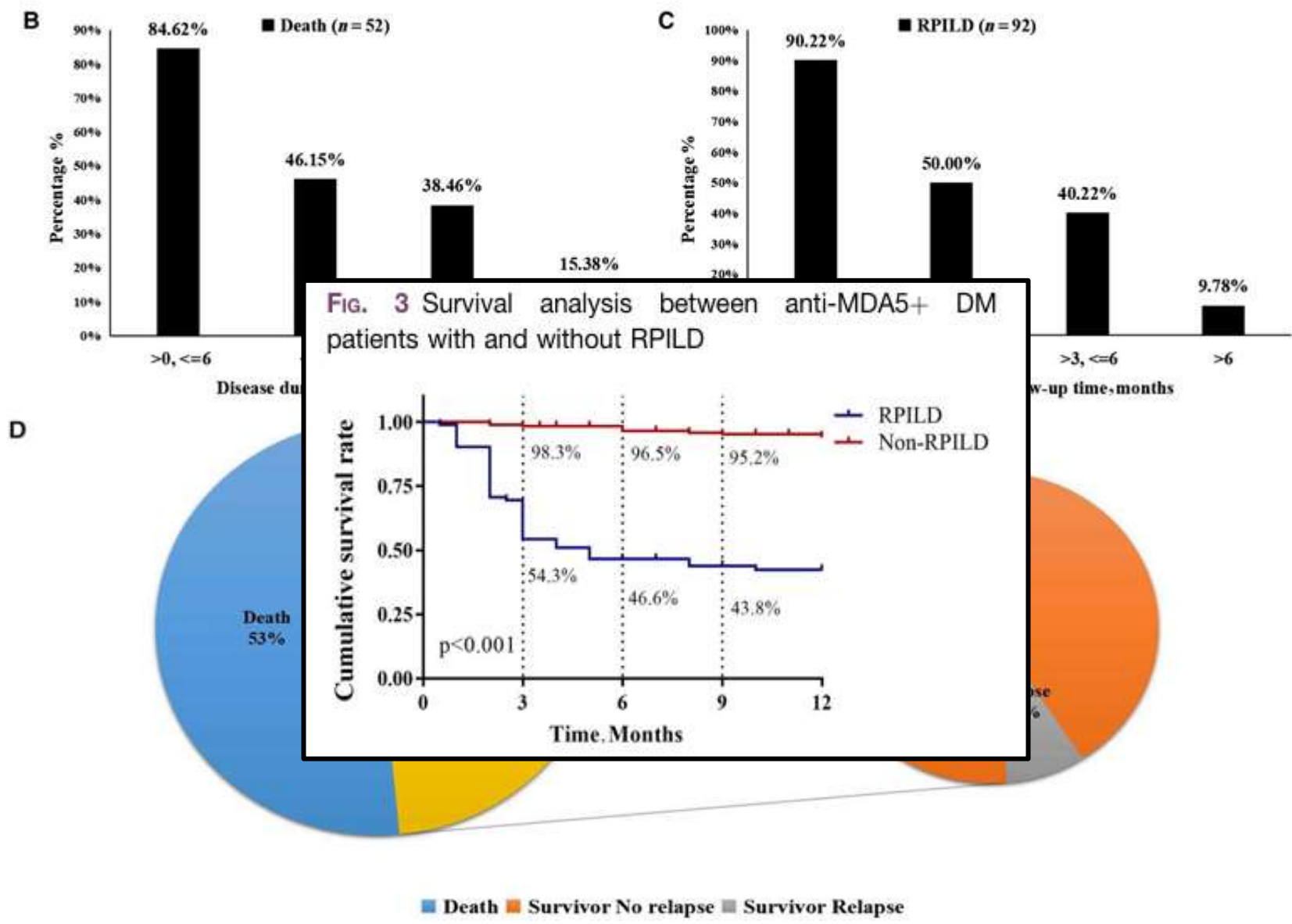


- RP-ILD has a high mortality rate ranging from 33% to 59.2% within the first 6 months after diagnosis
- One cohort study of 90 anti-MDA5-positive DM patients showed that 38.9% (35/90) developed RP-ILD and 24.4% (22/90) died within 6 months of diagnosis
- ILD associated with CADM (CADM-ILD) is often refractory and rapidly progressive, resulting in respiratory failure with a 6-month survival rate of 40.8–54.5 %

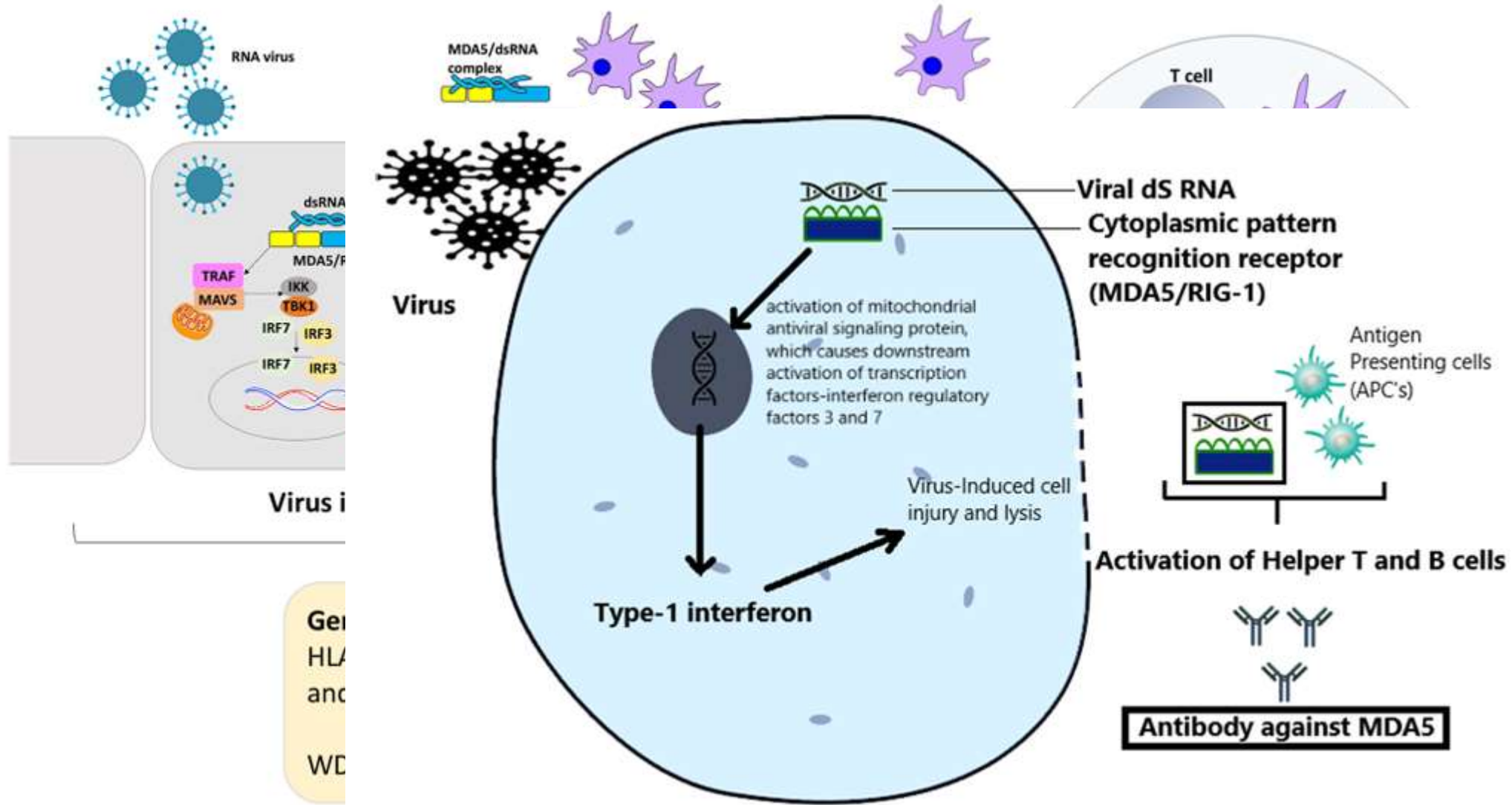
Time-dependent changes in RPILD and mortality risk in anti-MDA5+ DM patients: a cohort study of 272 cases in China

Hanxiao You ¹, Lei Wang¹, Jiajia Wang¹, Chengyin Lv¹, Lingxiao Xu¹,

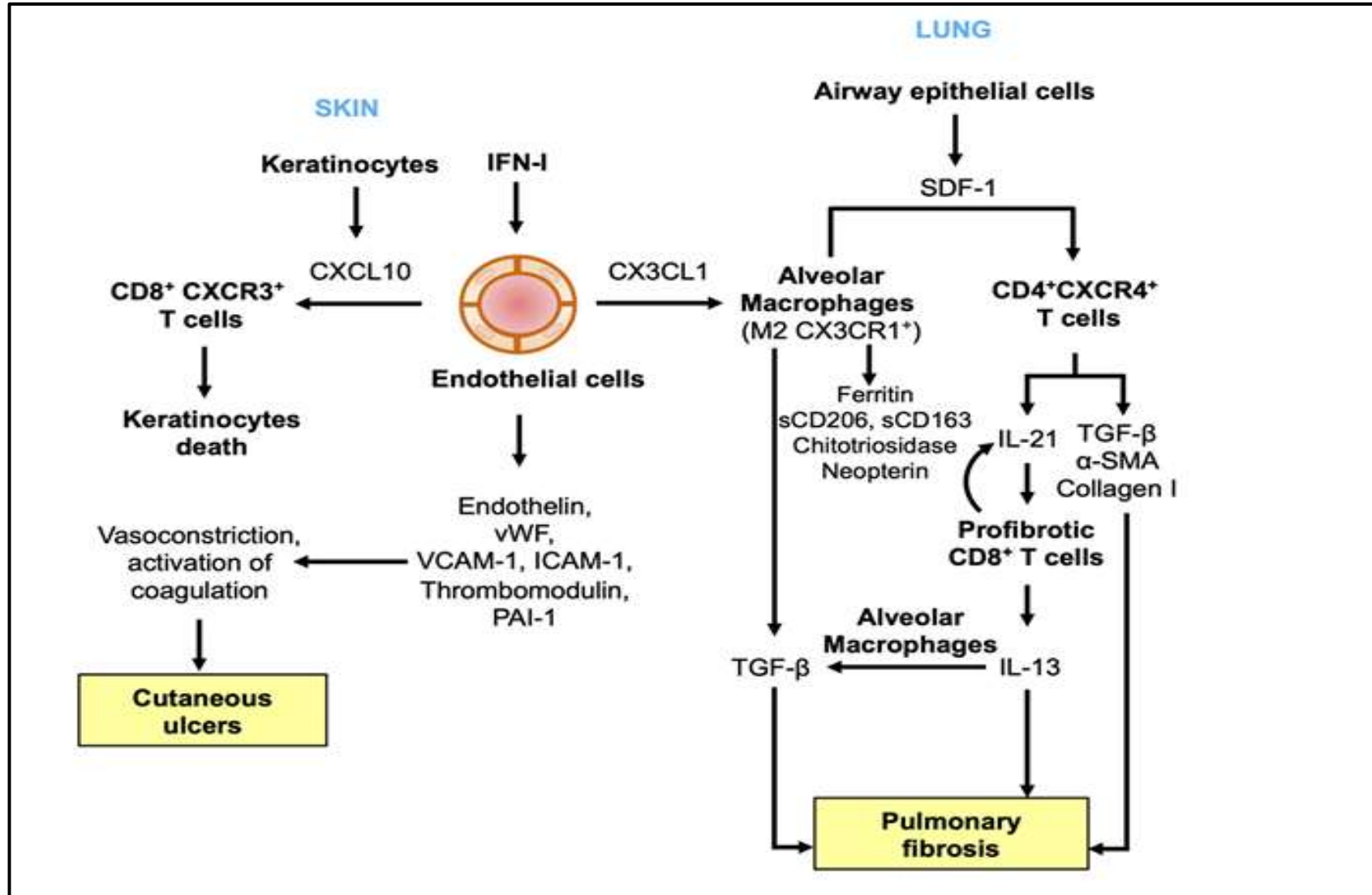
- Overall crude incidence of RPILD was 33.82% (92/272)
- The presence of RPILD in anti-MDA5 DM is associated with high mortality. The estimated prevalence of RPILD in anti-MDA5 DM is 38–71%
- 6-month all-cause mortality among these RPILD patients is as high as 40–60%
- Most RPILD and deaths occur at the early stages of anti-MDA5p DM



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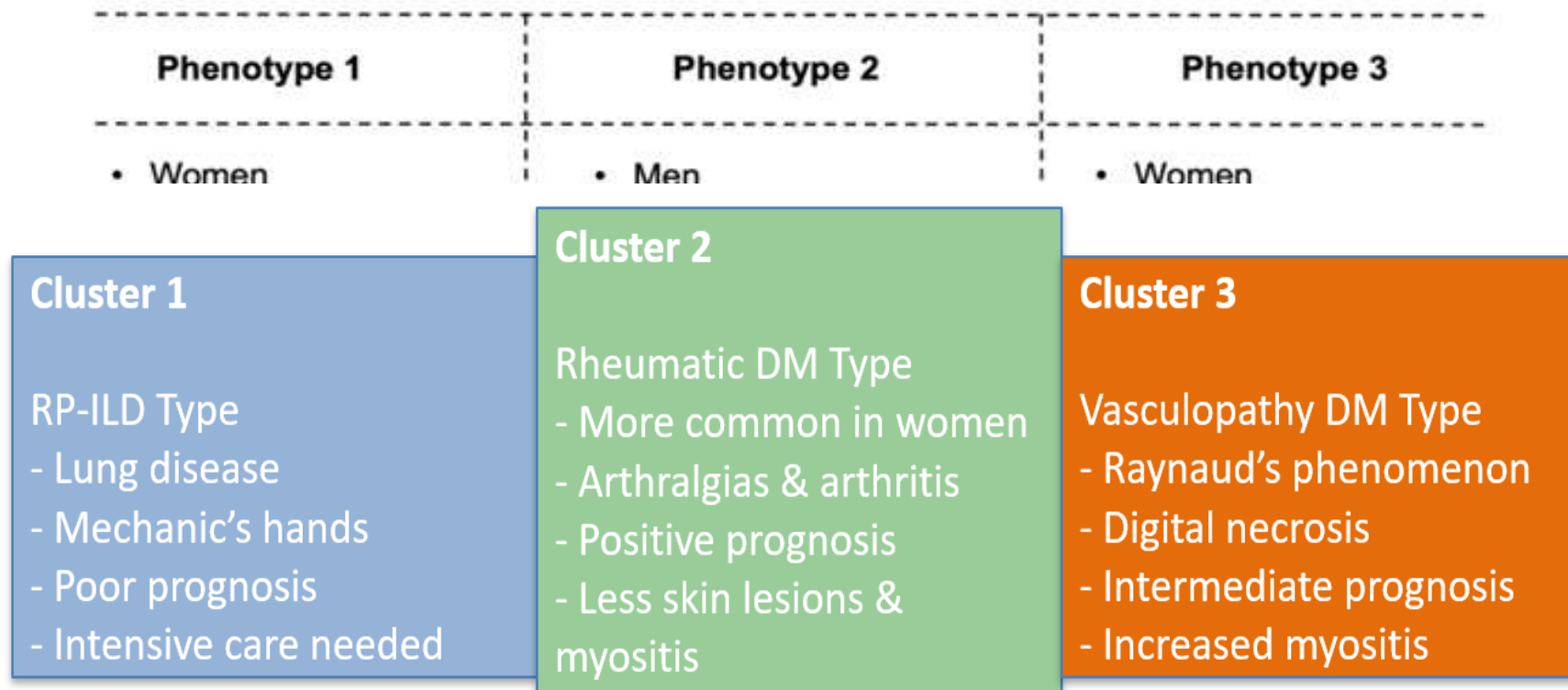
Gen
HLA
and
WD



Anais Nombel et al -Dermatomyositis With Anti MDA5 Antibodies: Bioclinical Features, Pathogenesis and Emerging Therapies, Frontiers in immunology 2021

Clinico-radiological presentation

Dermatomyositis with anti-MDA5 antibodies



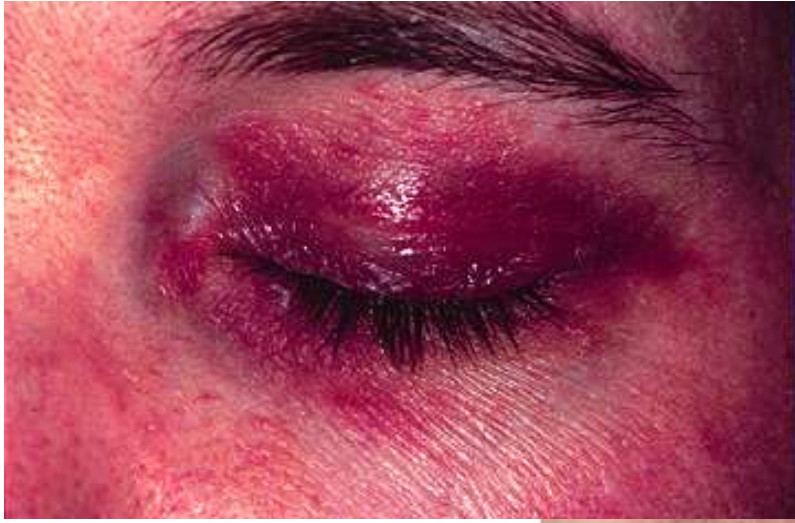




Figure 4. **Inverse Gottron's sign** unique to MDA-5 DM, inverse Gottron's sign presents as keratotic, palmar papules in the skin folds of the palms and fingers.

Variable	Total (n=272)	Non-RPILD (n=180)	RPILD (n=92)	P-value	Survival (n=197)	Death (n=62)	P-value
Age, mean	53.55 (12.55)	52.38 (12.82)	56.08 (11.58)	<0.001	51.86 (12.07)	58.63 (12.28)	<0.001
Gottrons papule	168 (61.76)	118 (65.56)	50 (54.35)	0.074	128 (64.97)	41 (50.00)	0.048
Heliotrope rash	159 (58.46)	113 (62.78)	46 (50.00)	0.043	128 (64.97)	41 (50.00)	0.048
V sign,	62 (22.79)	39 (21.67)	23 (25.00)	0.534	50 (25.38)	14 (22.58)	0.148
Shawl sign,	62 (22.79)	39 (21.67)	23 (25.00)	0.533	45 (22.84)	17 (27.42)	0.323
Mechanic's hands,	25 (9.19)	14 (7.78)	11 (11.96)	0.284	21 (10.66)	4 (6.45)	0.429
Arthritis	52 (19.12)	37 (20.56)	15 (16.30)	0.414	41 (20.81)	8 (12.90)	0.203

TABLE 3] Myositis-specific and Myositis-Associated Autoantibodies

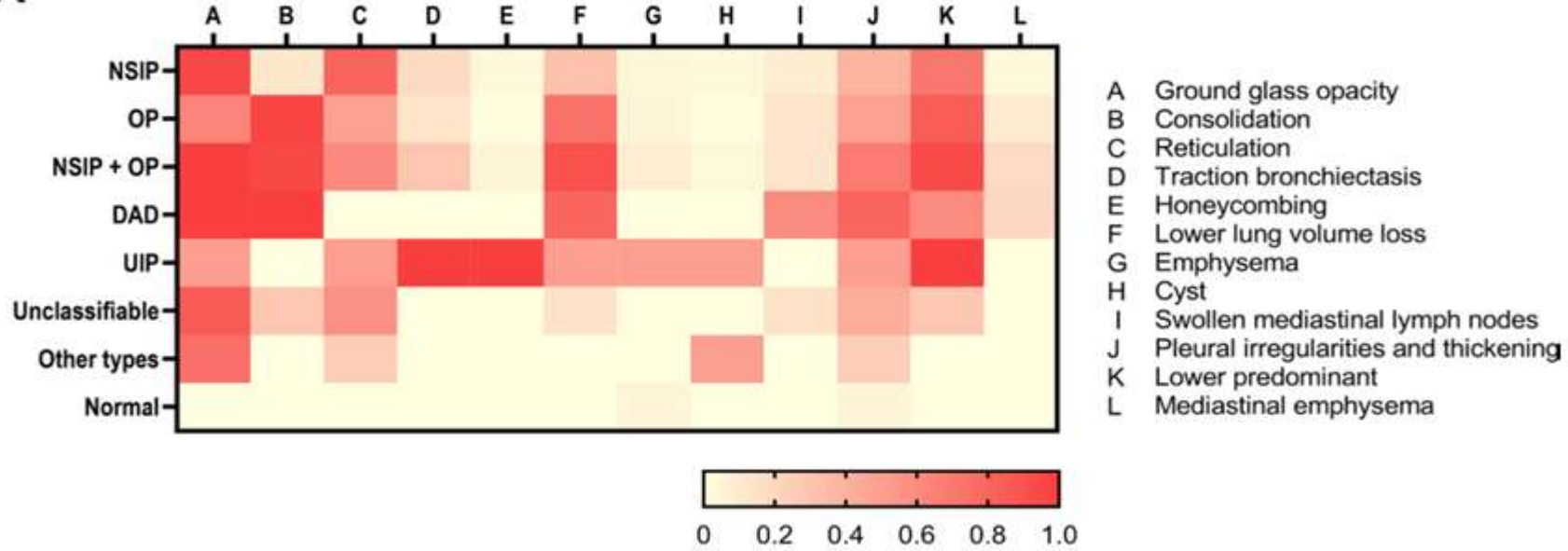
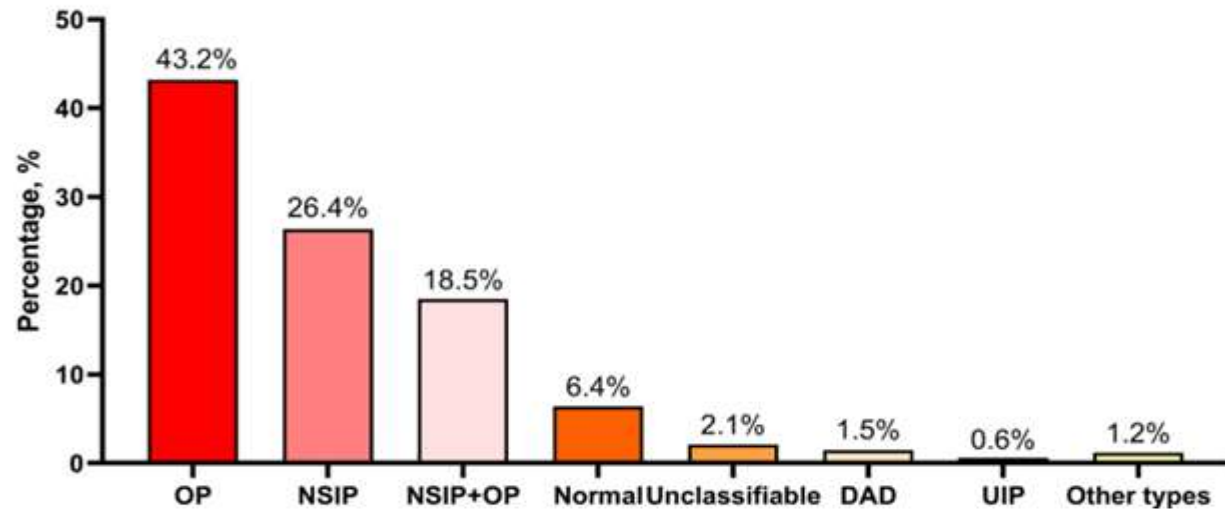
Antibody	Distinguishing Clinical Features
Myositis-specific antibodies	
Anti-synthetase autoantibodies: Jo-1, OJ, EJ, PL-7, PL-12 , Ks, Zo, Hu	Antisynthetase syndrome (mechanic's hands, myositis, fever, inflammatory arthritis, ILD, RP)
Signal recognition particle	Severe, necrotizing myositis
Mi-2	Classic cutaneous DM, mild myositis
MDA5/CADM-140	Vasculopathy, mucocutaneous ulceration, rapidly progressive ILD
TIF-1γ	DM, malignancy
NXP-2	DM, malignancy
Myositis-associated antibodies	
Anti-Ro (SSA)	
Anti-LA (SSB)	
Anti-Sm	
Anti-ribonucleoprotein	
Anti-Pm-Scl	Puffy fingers, calcinosis, RP, nail fold capillary distortion
Anti-Ku	

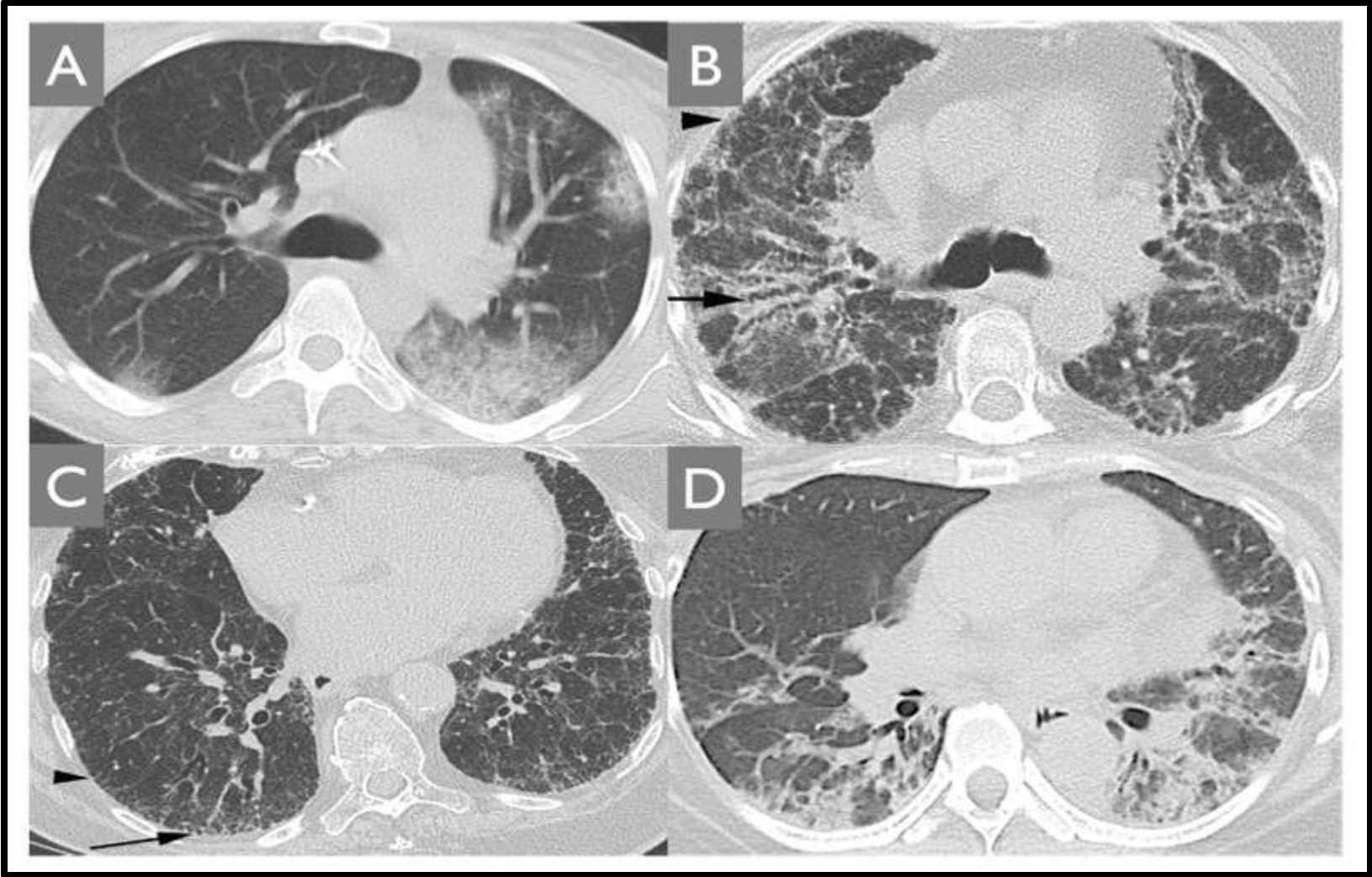
Clinical, radiological and pathological features of anti-MDA5 antibody-associated interstitial lung disease

Xixia Chen ¹, Wei Jiang,² Qiwen Jin,¹ Qinglin Peng ², Lu Zhang ²

Table 1 Characteristics of patients with anti-MDA5+DM

Variable	Total (N=329)	Clinical features at initial visit		Laboratory findings	
General characteristics		Heliotrope rash, n (%)		Creatine kinase, median (IQR), IU/L	
Age at initial visit, mean±SD, years	48.6±11.5	245 (74.5)		51.0 (25.0, 116.0)	
Female, n (%)	219 (66.6)	Gottron's sign, n (%)		Lymphocyte count, median (IQR), ×10 ⁹ /L	
Smoking history, n (%)	53 (16.1)	270 (82.1)		0.73 (0.50, 1.04)	
Malignancy, n (%)	12 (3.6)	Mechanic's hand, n (%)		Lactate dehydrogenase, median (IQR), IU/L	
Disease duration, median (IQR), months	3.5 (2.0, 7.0)	182 (55.3)		308.0 (254.8, 399.3)	
ILD, n (%)	308 (93.6)	Distal digital tip ulceration, n (%)		Ferritin*, median (IQR), ng/mL	
RPILD, n (%)	177 (53.8)	91 (27.7)		590.5 (256.2, 1169.9)	
Pulmonary infection, n (%)	216 (65.7)	V sign, n (%)		Anti-Ro-52 antibody-positive, n (%)	
		165 (50.2)		206 (62.6)	
		Shawl sign, n (%)			
		127 (38.6)			
		Myalgia, n (%)			
		141 (42.9)			
		Muscle weakness, n (%)			
		197 (59.9)			
		Fever, n (%)			
		166 (50.5)			

A**B**



Subpleural consolidation on HRCT, but showed extensive lymphocyte and plasma cell infiltration and preserved lung tissue structure on pathology, consistent with **cellular NSIP**

OP on HRCT, but showed focal OP superimposed on a background of **NSIP** pathologically

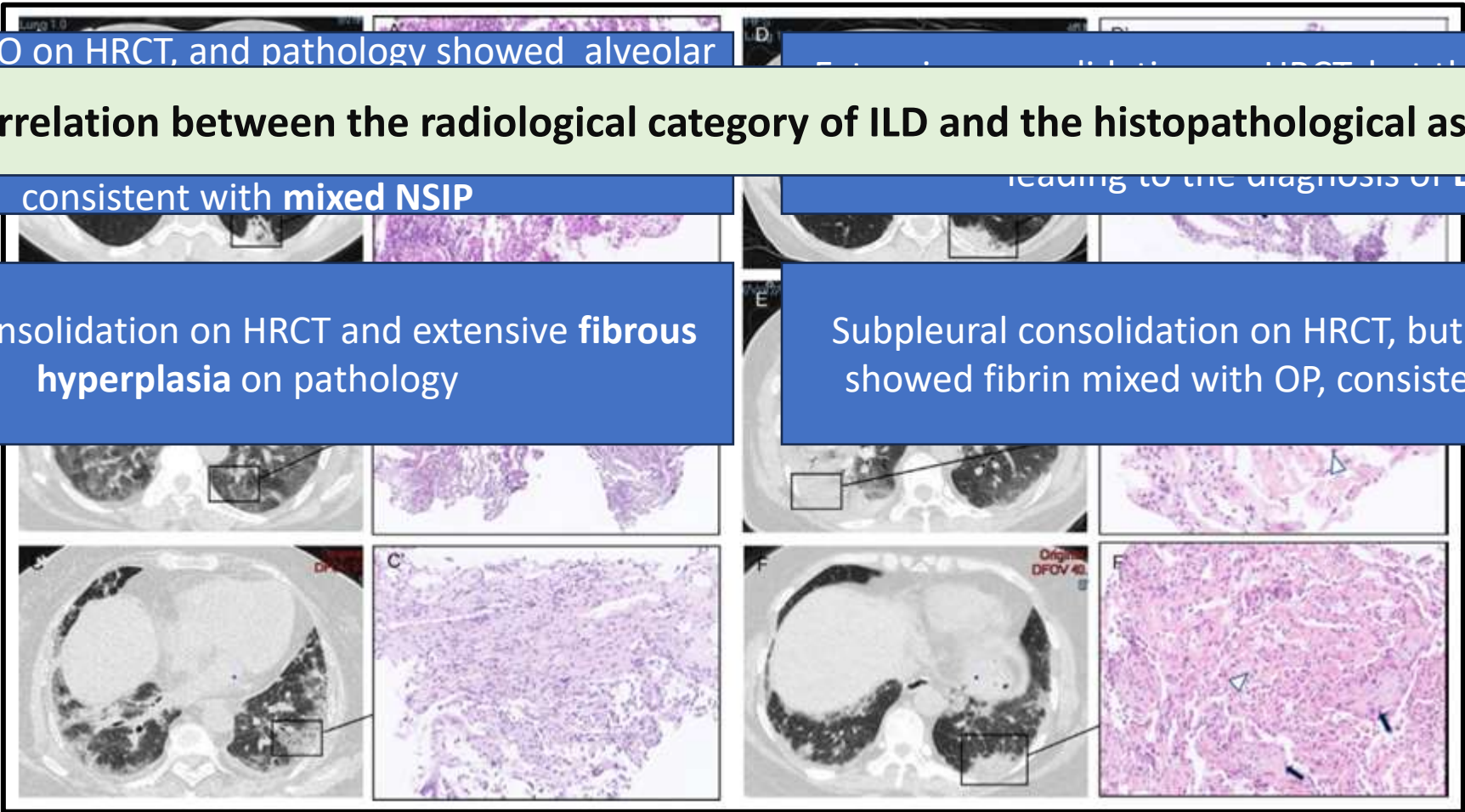
Extensive GGO on HRCT, and pathology showed alveolar thickening and hyperplasia, consistent with **mixed NSIP**

Extensive consolidation on HRCT, but pathology showed extensive alveolar thickening and hyperplasia, leading to the diagnosis of **DAD**

Poor correlation between the radiological category of ILD and the histopathological assessment

GGO and consolidation on HRCT and extensive **fibrous hyperplasia** on pathology

Subpleural consolidation on HRCT, but pathologically showed fibrin mixed with OP, consistent with **AFOP**



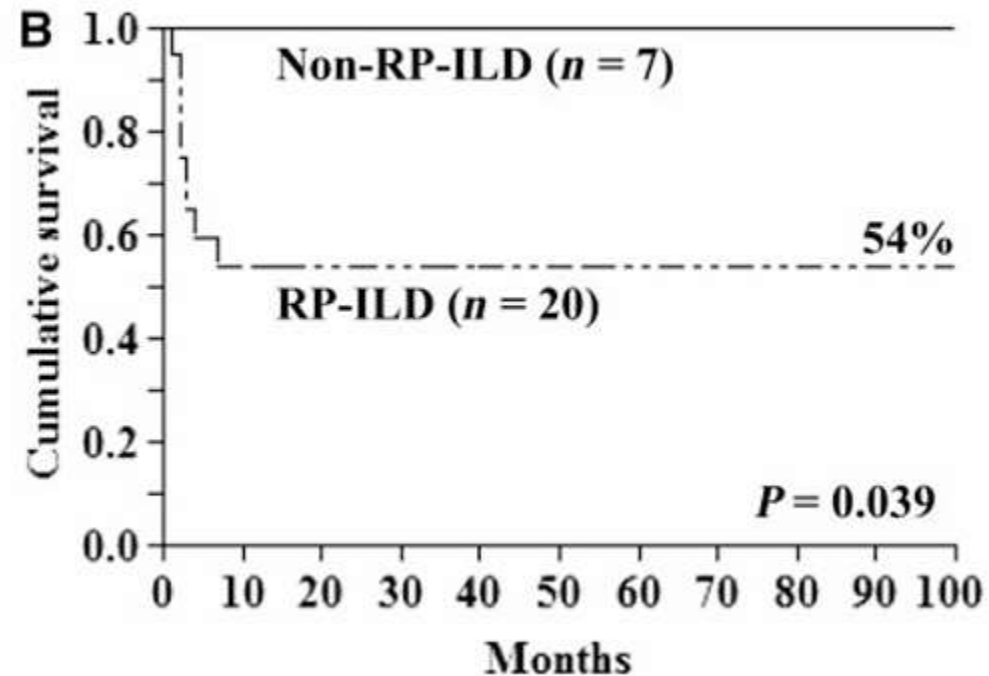
Analysis – (Did not specify RPILD and non RPILD group)

- 329 Anti mda 5 pts - 308(93.6%) – ILD, 177 (53.8%) – RPILD
- 13% (43/329) required mechanical ventilation
- Steroids received by >95% of patients, MPS pulse – 6% only
- ≥ 2 immunosuppressants – (91/329) 27.6%
- CNI – 65%, IVIG – 32%, JAKi – 9.1%, Cyc – 7.5%, MMF – 4.8%
- Mortality – 75/329 (22.79%)

Biomarkers

Biomarkers in RPILD

Variable	RP-ILD (-) (n = 7)	RP-ILD (+) (n = 20)	P
Age, years	35 (4)		0.21
Female, n (%)	6 (86)		0.3
Disease duration, weeks	8 (6-16)		
CADM, n (%)	6 (86)		
CK, IU/l	165 (84-27)		
LD, IU/l	472 (221-6)		
P/F ratio	448 (348-5)		0.79
AaDO ₂ , mmHg	4 (0-18)		0.31
%VC	82 (74-98)		
DLco, ml/min/mmHg	14.7 (12.5-)		
KL-6, U/ml (normal value ≤ 500)	346 (278-1)		
CRP, mg/dl	0.46 (0.02-1)		
Ferritin, ng/ml	186 (120-6)		0.3
IL-18, pg/ml (normal range 18-121)	550 (216-7)		
Anti-MDA5ab, U/ml	258.8 (217.1-376.1)	102.0 (0.0-310.0)	0.021
Fatal outcome, n (%)	0 (0)	9 (45)	0.036



Gono et al ; Anti-MDA5 antibody, ferritin and IL-18 are useful for the evaluation of response to treatment in ILD with anti-MDA5 DM, Rheumatology 2012

Variable	Alive (n=11)	Dead (n=9)	P
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D/Ferritin	360 (312-422)	310 (246-352)	0.02
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AaDO2 ≥ 32mmHg and ferritin ≥ 828 ng/ml at admission were poor prognostic factors in RP-ILD patients with anti-MDA5 ab-positive DM

Ferritin, ng/ml	409 (234-728)	1600 (835-1935)	0.017
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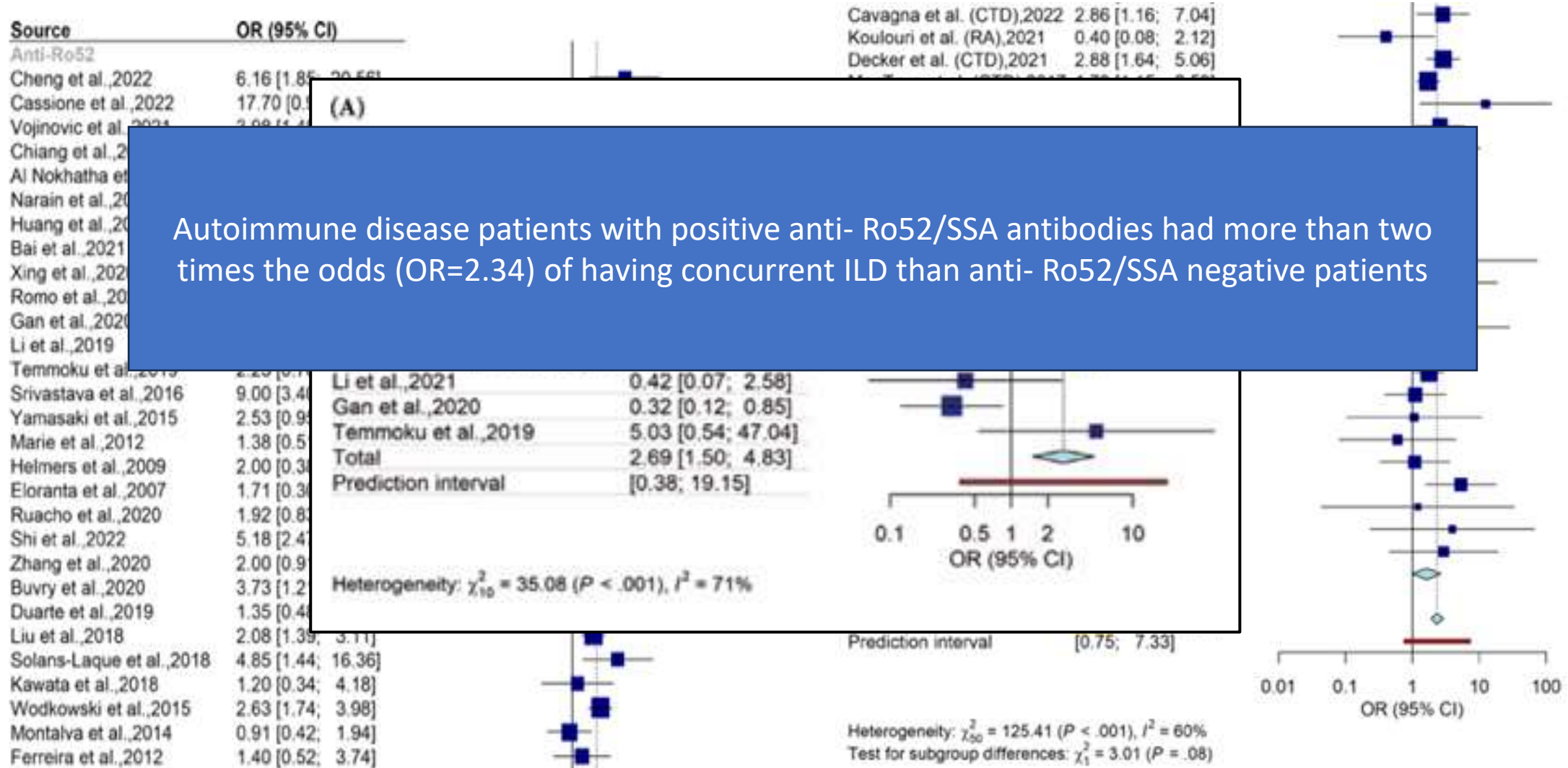


Increased serum level of IL-6 predicts

Variables	Total (n = 168)	Survival (n = 83)	Death (n = 85)	P-value	non-RP-ILD (n = 47)	RP-ILD (n = 121)	P-value
Gender (Male/Female)	72/96	31/52	41/44	0.154	14/33	58/63	0.033
Age on onset, years, mean (SD)	53.6 (10.4)	50.3 (11.2)	56.8 (8.5)	<0.001	49.4 (11.8)	55.2 (9.4)	0.001
Course of disease, months	2.0 (1.0, 4.0)	3.0 (1.0, 6.0)	1.0 (0.7, 3.0)	<0.001	5.0 (3.0, 12.0)	1.0 (1.0, 3.0)	<0.001
Lymphocytes ($\times 10^9/L$)	0.5 (0.4, 0.8)	0.8 (0.5, 1.1)	0.4 (0.3, 0.6)	<0.001	1.0 (0.7, 1.3)	0.5 (0.3, 0.6)	<0.001
Total T cells, cells/uL ^a	405 (232, 616)	549 (352, 829)	259 (170, 417)	<0.001	718 (529, 1071)	307 (194, 434)	<0.001
CD4+T cells, cells/uL ^a	232 (140, 380)	316 (190, 500)	192 (104, 264)	<0.001	452 (286, 661)	198 (116, 284)	<0.001
CD8+T cells, cells/uL ^a	123 (65, 204)	197 (120, 258)	79 (35, 126)	<0.001	224 (175, 315)	91 (53, 140)	<0.001
Total B cells, cells/uL ^b	84 (44, 227)	132 (51, 248)	74 (36, 174)	0.076	197 (77, 427)	75 (32, 191)	0.002
AST							0.001
ALT							0.070
γ -GT							0.001
CK (U/L)							0.067
CK-MB							0.20
Myoglobin	37 (21, 56)	24 (18, 27)	48 (25, 76)	<0.001	23 (18, 42)	45 (23, 71)	0.001
LDH (U/L)	385 (290, 542)	311 (253, 391)	474 (322, 645)	<0.001	283 (245, 347)	434 (345, 524)	<0.001
IL-2 (pg/mL)	0.94 (0.51, 1.60)	0.99 (0.61, 1.72)	0.87 (0.41, 1.52)	0.057	1.09 (0.55, 1.58)	0.89 (0.49, 1.61)	0.237
IL-4 (pg/mL)	1.31 (0.77, 2.07)	1.30 (0.85, 2.04)	1.33 (0.71, 2.09)	0.758	1.31 (0.98, 2.15)	1.32 (0.69, 2.06)	0.416
IL-6 (pg/mL)	13.41 (5.08, 25.27)	5.04 (3.20, 8.41)	20.30 (14.68, 50.68)	<0.001	4.29 (2.46, 5.79)	17.90 (11.36, 35.60)	<0.001
IL-10 (pg/mL)	4.32 (2.94, 5.93)	3.89 (2.53, 5.18)	4.83 (3.29, 8.21)	0.002	3.55 (2.21, 4.81)	4.77 (3.17, 7.34)	<0.001

Statistically lower lymphocyte count and CD4 and CD8 T cells
Significantly high LDH, IL-6, IL-10

Association of anti- Ro52 autoantibody with interstitial lung disease in autoimmune diseases: a systematic review and meta- analysis, Sepehr Nayebirad et al BMJ open 2023



Biomarkers

- Ferritin
- LDH
- IL-6
- Lymphocytes
- CRP
- Anti MDA-5

Variable	Total (n=272)	Non-RPILD (n=180)	RPILD (n=92)	P-value	Survival (n=197)	Death (n=62)	P-value
LDH, median	387 (172, 875)	362 (142, 750)	450 (193, 870)	<0.001	304 (135, 389.25)	487.5 (305, 1005.25)	<0.001
CRP, median	10.56 (1.5, 89.25)	7.5 (1.5, 30.9)	12.5 (3.7, 98.25)	0.003	7.45 (1.5, 29.25)	15.5 (6.5, 72.5)	<0.001
Ferritin, median	825.1 (224, 1500)	555.7 (208.2, 1186)	1339.85 (650, 1875.2)	<0.001	581.345 (264.55, 1235.775)	1500 (755.7, 2000)	<0.001
Anti-Ro52 positive	174 (69.89)	94 (62.42)	80 (86.96)	<0.001	126 (66.32)	48 (78.69)	0.148
Anti-MDA5 titre	148 (54.58)	90 (50.00)	58 (63.04)	0.003	104 (52.79)	44 (72.13)	0.004
RPILD	92 (33.82)	-	-	-	40 (20.3)	52 (85.25)	<0.001
Death	62 (22.79)	10 (5.56)	52 (56.52)	<0.001	-	-	-

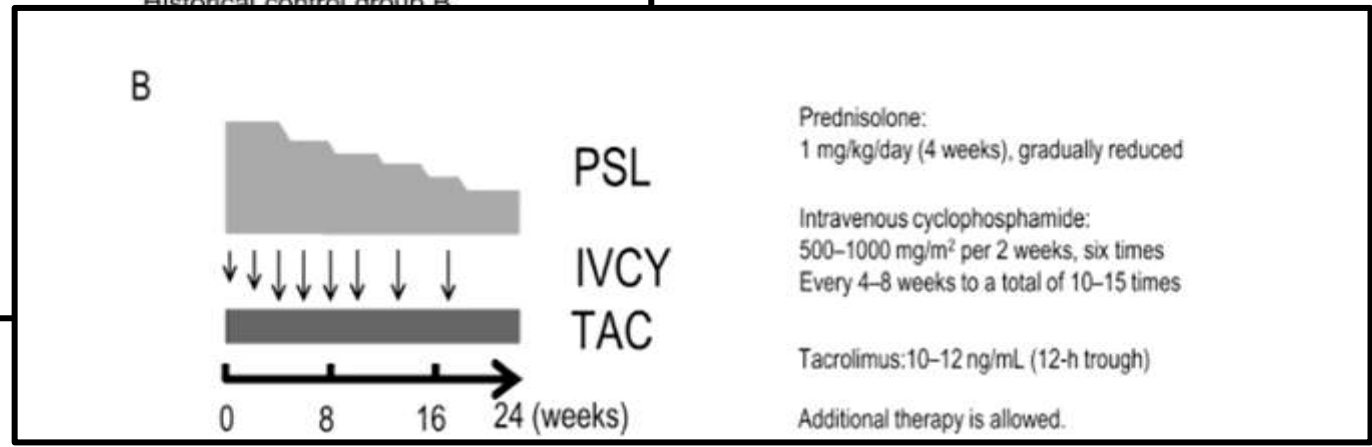
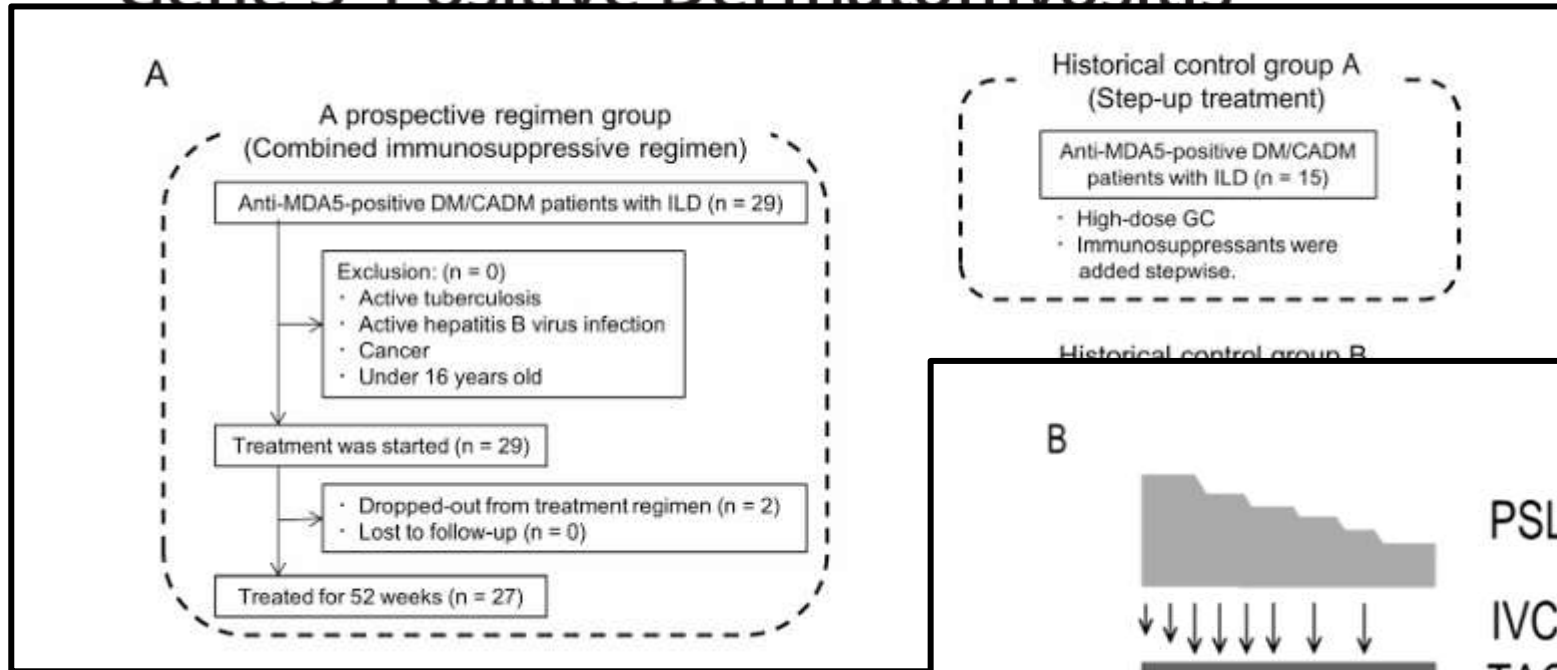
Management

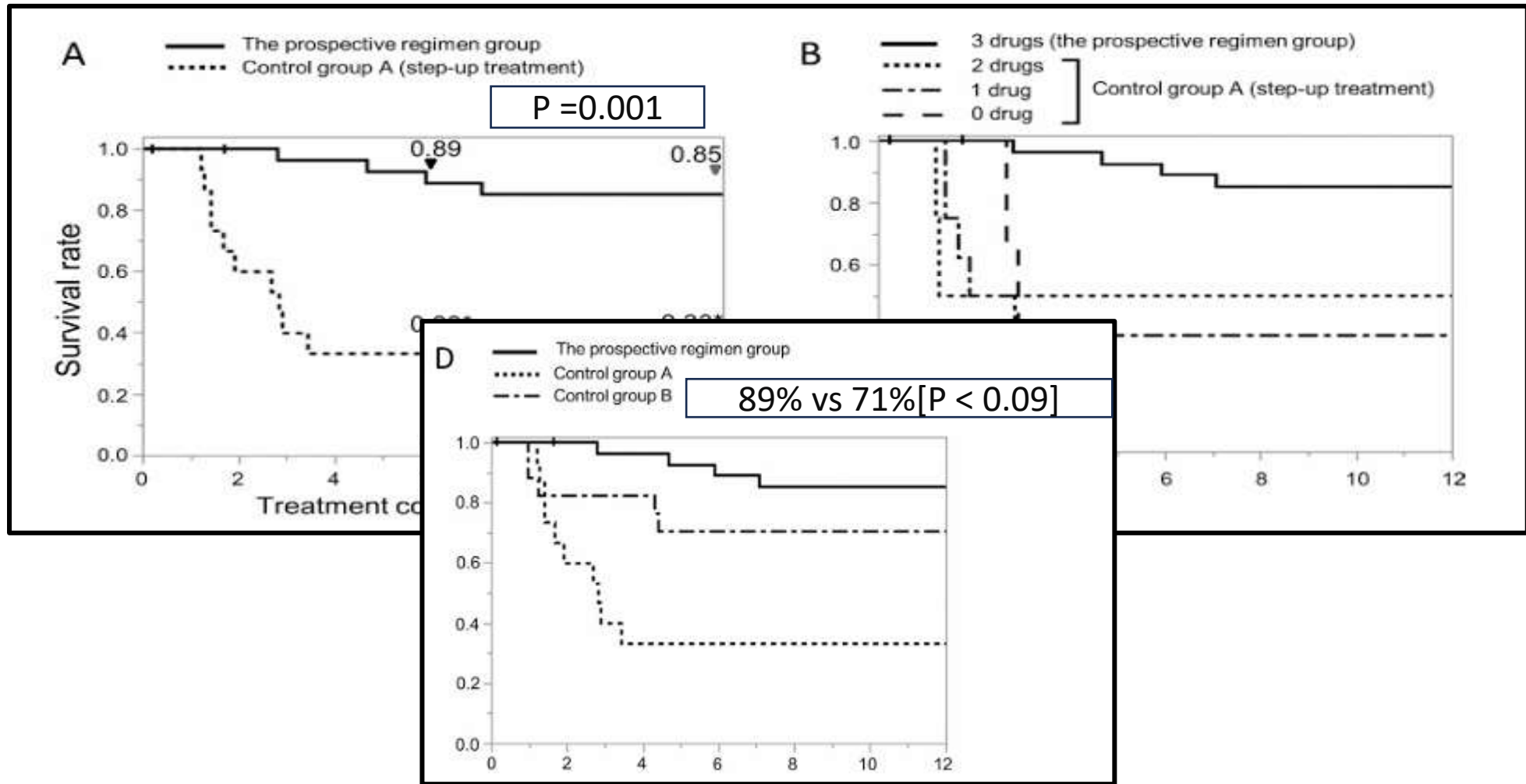
Commonly used Drug Dosage and Duration in MDA-5 DM Treatment

Medications	Dosage
Calcineurin inhibitors (Cyclosporine)	3-5 mg/kg/day (target trough 150-200 ng/mL)
Tacrolimus	0.075 mg/kg/day (target trough 5-10 ng/mL)
Glucocorticoids	IV methylprednisolone pulse (1000 mg for 3 days) or 0.75–1 mg/kg Prednisone for 4 weeks followed by taper (2–4 weeks)
Cyclophosphamide	300–1000 mg/m ² IV every 2-4 weeks (1-6 doses)
Rituximab	375 mg/m ² at 0 and 14 days or 100 mg weekly for 4 weeks
JAK inhibitors (Tofacitinib)	5 mg twice daily
Plasma Exchange	1–3 times/week for 3–15 weeks
IVIg	2 g/kg every 4 weeks
Antifibrotic Therapy (Pirfenidone)	Target dose 1800 mg/day (starting at 200 mg tid, increasing over 2 weeks)

Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis

Primary end point – 6 mo survival compared to historical control groups



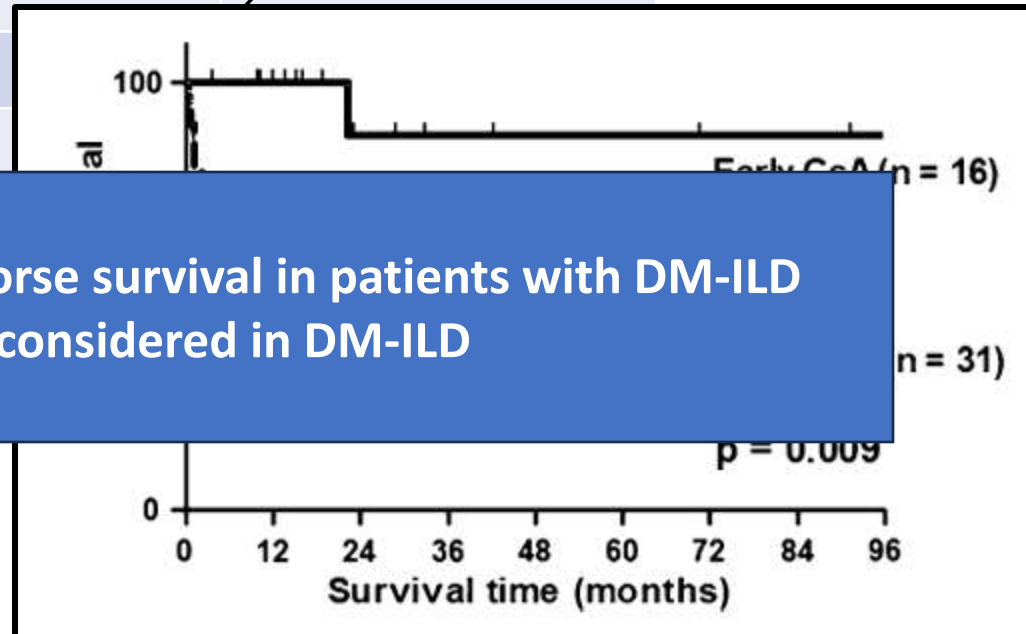


Survival benefit associated with early cyclosporine treatment for dermatomyositis-associated interstitial lung disease

Dong Jin Go^{1,2} · Jin Kyun Park^{1,2} · Eun Ha Kang³ · Hyun Mi Kwon¹ · Yun Jong Lee³ · Yeong Wook Song^{1,2} · Eun Bong Lee¹

	Early CsA treatment (n=16)	Delayed CsA treatment (n=31)	p value
Female	10 (62.5%)	25 (80.6%)	0.289
Age at ILD diagnosis (years)	49.9 ± 8.6	48 ± 10.2	0.560
Time between symptom onset and ILD diagnosis (months)	2.5 ± 2.9	3.3 ± 9	0.465
Time between ILD diagnosis and CsA treatment (months)	0.2 ± 0.4	3.2 ± 8.8	0.003
CsA dosage (mg/day)	167.2 ± 37.3	157.9 ± 77.5	0.663
Duration of CsA treatment (months)	16.7 ± 14.4	10.2 ± 21.8	0.350

Cause of death	Early CsA treatment (n=16)	Delayed CsA treatment (n=31)
Respiratory failure from ILD progression	0	6
Pneumonia after lung transplantation	1	3
Diffuse alveolar hemorrhage	0	1
Septic shock	0	2
Secondary tension pneumothorax	0	
Ventricular arrhythmia	0	



**Delay in CsA treatment is associated with a worse survival in patients with DM-ILD
Early CsA treatment should be considered in DM-ILD**

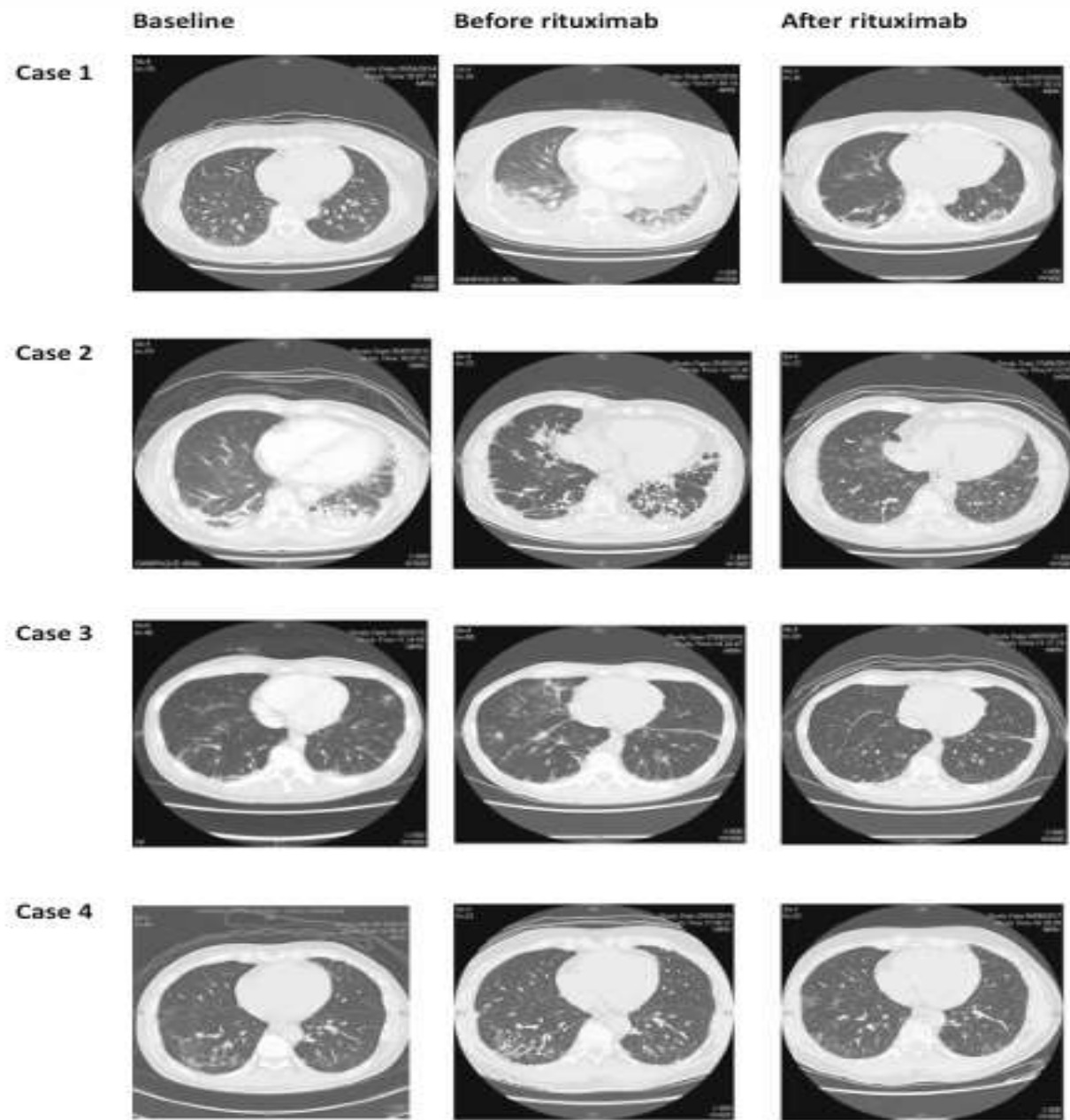
**Combination
therapy in RP-ILD**

Type of study	Patients (n) RPILD	Exitus
Gono T et al, 2012	n=20 12 (GC+CYC+CNI) 8 (GC+CYC or CNI)	9/20 (45%) 7/12 (58%) 2/8 (25%)
Hozumin et al, 2016	n=15 5 (GC+CYC+CNI) 10 (GC+CNI)	6/15 (40%) Not specified Not specified
Ikeda S et al, 2015	n=10 10 (GC+CYC+CNI)	6/10 (60%)
Max et al, 2016	n=7 7 (GC+CYC+CNI)	6/7 (85%)
Matsushita et al, 2017	n=11 11 (GC+CYC+CNI)	0/11 (0%)
Muro Y et al, 2013	n=17 6 (GC+CYC+CNI)	1/6 (16%) 3/11 (27%)
Nakashima et al, 2016	n=28 11 (GC+CYC or CNI) 14 (GC+CYC+CNI) 14 (Historical cohort)	71% survival rate in triple therapy vs 28.6% in step up therapy
Nara M et al, 2014	n=12 4 (GC+CYC+CNI) 8 (GC+CNI)	3/4 (75%) 3/8 (37%)

- Overall, published data are scarce and the level of evidence of the studies is weak
- Case reports with a total of 53 anti-MDA5 positive DM patients with RPILD
- In summary, from the analysis of the reported cases, 21 patients (40%) died, and 32 (60%) improved after immunosuppressive therapy

Rituximab in refractory RP-ILD

Case	Disease duration before RTX (mo)	Medications on top of PSL before RTX	Change of NYHA	Change of Lung Function	Ferritin	Side effects
49/F	18	MMF, CycA, CYP, IVIg	Class IV→II	FVC 39→67% predicted	NA/23	Vasculitic ulcer
50/M	4	MMF, CYP, and Tac	IV→II	76→105	NA/260	Chest infection
38/M	21	MMF, Tac, IVIg	III→II	94→121	2844/902	Chest infection
48/M	18	CycA	III→I	DLCO 54→72	NA/170	Nil



Ho So et al; clinical rheumatology 2018, Rituximab for refractory RP-ILD related to anti-MDA5 antibody-positive amyopathic dermatomyositis

Anti-melanoma differentiation-associated gene 5 (MDA5) antibody-positive dermatomyositis responds to rituximab therapy

Yongpeng Ge¹  · Shanshan Li¹ · Xiaolan Tian¹ · Linrong He¹ · Xin Lu¹ · Guochun Wang¹

Condition	n (%)
ILD	11/11 (100%)
Asymptomatic or mild ILD	3/11 (27%)
RP-ILD	8/11 (73%)
Ro-52 positivity	6/11 (55%)

- 7 received iv RTX (375 mg /m²) at 0 and 14 days

- 3 received iv RTX (100 mg) at 0, 7, 14, and 21 days

- 1 patient was treated with RTX (100 mg) at 0 and 7 days

Case No.	Age/Gender	Severity of ILD	Prior Treatment	Co-Intervention	Outcome
1	36/F	RP-ILD	Pred (12m), CTX (5m), CNI (5m), MMF (1m)	Pred, MMF, CNI	Lung CT improved, DLCO increased
2	50/M	RP-ILD	Pred (1m)	Pred, IVIG, CNI	Lung CT, DLCO improved,
3	2				n of ILD
4	4				and
5	3				
6	5				nary D
8	5				DLCO
9	28/M	Mild ILD	MP (3w), IVIG	Pred, CNI	Lung CT improved, DLCO increased
10	36/F	Mild ILD	MP (1m), CNI (1m), IVIG	Pred, CNI	Remission of ILD
11	39/M	RPILD	Pred (13m), MMF(7m), THD (1m) CTX (1w)	Pred	Initial improvement, LTFU

After RTX treatment, 2 patients (18%) with mild ILD showed complete remission, and 6 (55%) showed improvement in lung HRCT and/or lung function.

5/7 MDA5-DM patients (71%) with ILD responded to the conventional dose, and 3/4 (75%) patients' ILD showed improvement in the low dose group

Infection episodes occurred in four (57%) and one (25%) of the conventional-dose and low-dose group, respectively

Table 4 Literature review of 28 cases of anti-MDA5-positive DM with RP-ILD treated with rituximab

References	Age/sex/race	Previous therapy	RTX targeting lesion	Duration prior to RTX	Rx during or after RTX	Outcome
Berianu et al. ^a [25]	7 cases of ILD (4 NSIP, 2 with organizing pneumonia, one UIP)	Unknown	ILD	Unknown	Unknown	One died from RP-ILD. The other 6 stable
Patel et al. ^a [26]	55M African-American	GC, CYC	RP-ILD	Several months	GC, MMF, Tac	Died
Mohammed et al. ^a [27]	44M	None	RP-ILD	Several months	IV GC	Died
Alqatari et al. [28]	49F European	GC	RP-ILD	4 weeks	GC, CYC, IVIG, Tac	Died
So et al. [29]	49F Chinese	MMF, CsA, CYC	RP-ILD	18 months	GC	Improved
15 of the 28 patients responded to RTX						
Ogawa et al. [30]	48M Japanese	GC, CsA, CYC	RP-ILD and skin	125 days	GC, CsA	Improved
Oberg et al. ^a [31]	46M Japanese	Unknown	RP-ILD, necrotizing bronchitis and ulcerative skin lesion	Unknown	GC, CsA	Died
Sultan et al. ^a [32]	23F Hispanic	Unknown	RP-ILD	Unknown	GC, MMF, IVIG, VV-ECMO	Died
Koichi et al. [33]	71F Japanese	GC, Tac, CYC, PMX, IVIG	RP-ILD and skin	102 days	Tac GC	Improved
Tokunaga et al. [34]	71F Japanese	GC, Tac, CsA, CYC	RP-ILD	38 days	GC, CsA, MMF, Tac	Died
	69F Japanese	GC, CsA	RP-ILD	33 days	GC, CsA, IV CYC, Tocilizumab	Died
Watanabe et al. [35]	58F Japanese	GC, Tac, CYC	RP-ILD	3 months	GC, IV CYC, IVIG, PMX	Improved
Hershberger et al. ^a [36]	46F African-American	GC	RP-ILD	Several months	GC, MMF	Improved
Yokochi et al. ^a [37]	61 ^b Japanese	GC, CsA, CYC	RP-ILD	21 days	GC, CsA, CYC	Died
	71 ^b Japanese	GC, CsA, CYC	RP-ILD	51 days	GC, CsA, CYC	Died
	69 ^b Japanese	GC, CsA, CYC	RP-ILD	17 days	GC, CsA, CYC	Died
	75 ^b Japanese	GC, CsA, CYC	RP-ILD	21 days	GC, CsA, CYC	Died
Gil et al. [38]	55F Israelis	GC	RP-ILD	N/A	CYC, PLEX	Died
Clottu et al. [39]	68F European	GC, IVIG, CYC, MMF, CsA, Tac (topical), HCQ	Skin	2 year	N/A	Improved

Tocilizumab for refractory rapidly progressive interstitial lung disease

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, years	43	58	64	52	42	50
Sex	Male	Female	Male	Female	Male	Female
MSA/MAA	Anti-MDA5-Ab ⁺	Anti-MDA-Ab ⁺ , anti-Ro52-Ab ⁺	Anti-MDA5-Ab ⁺	Anti-MDA5-Ab ⁺	Anti-MDA5-Ab ⁺ , anti-Ro52-Ab ⁺	Anti-MDA5-Ab ⁺ , anti-Ro52-Ab ⁺
Initial treatment	Prednisone, CYC, TAC	MP, CYC, ciclosporin A	IVIg, MP, TAC, CYC	Ciclosporin A, MP, CYC	MP, CYC/TAC, IVIg	MP, TAC/CYC
Tocilizumab administration time since symptom onset, months	5	6	3	10	3	11
On admission Symptoms	Rash	Rash, muscle weakness	Rash, muscle weakness	Rash, swollen joints, weakness	Rash, fever	Rash
CK, U/l	105	397.4	66	26	46	16
LDH, U/l	351	286.6	313	296	546	522
Ferritin, $\mu\text{g/l}$	1825	471	1145	463	2046	1329
OI, mmHg	245.2	204.9	321.9	459.5	112.7	234
SpO ₂	92% with NC 2 l/min	99% with NC 5 l/min	98% with NC 2.5 l/min	98% with AA	93% with HFN 40 l/min	98 with NC 2 l/min
Response to tocilizumab (after discharge) SpO ₂	96% with NC 4 l/min	98% with NC 2 l/min	96% with AA	99% with AA	89% with VC FiO ₂ 80%	97% with AA
Ferritin, $\mu\text{g/l}$	641	113	446	106		902
Adverse events	CMV infection	-	-	-	Liver dysfunction	-
Duration of the combination therapy with tocilizumab	6 months	1 month	6 months	6 months		3 weeks
Latest treatment	Prednisone, CYC, TAC	Prednisone, TAC	MP, TAC	Prednisone, CYC	MP, CYC, TAC, tocilizumab	MP, CTX, tocilizumab
Prognosis	Alive	Alive	Alive	Alive	Treatment withdrawn	Alive

Role of IVIG in RPILD

Author(s)	Number of Patients	Prior Treatment	IVIG Start Time	Outcome
Wang et al. 2018	48 (31 IVIG, 17 non-IVIG)	GCs, immunosuppressants	Within 1 week of diagnosis	Lower mortality (22.6% vs. 52.9%)
Hamada-Ode et al. 2020	1	Methylprednisolone pulses	After 6 weeks of steroids	Improved respiratory function
Fujisawa et al. 2021	52 (13 IVIG, 39 control)	Pulse corticosteroids	Concurrent with steroids	Higher 90-day survival (76.9% vs. 38.5%)
Tsuji et al. 2018	4	High-dose steroids, immunosuppressants	After treatment failure	Improved lung function, infections noted

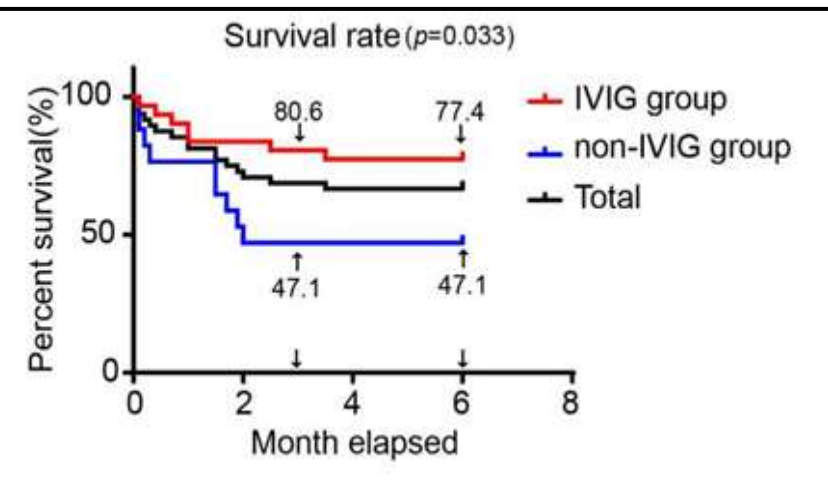
Intravenous immunoglobulin for interstitial lung diseases of anti-melanoma differentiation-associated gene 5-positive dermatomyositis

Li-Mei Wang ¹, Qi-Hua Yang, Lei Zhang ¹, Sheng-Yun Liu¹,
Pan-Pan Zhang ¹, Xin Zhang¹, Xiao-Jun Liu¹, Li-Shuai Han¹ and Tian-Fang Li¹

Retrospective observational study (2018-2020), 48 patients divided into IVIG and non-IVIG groups

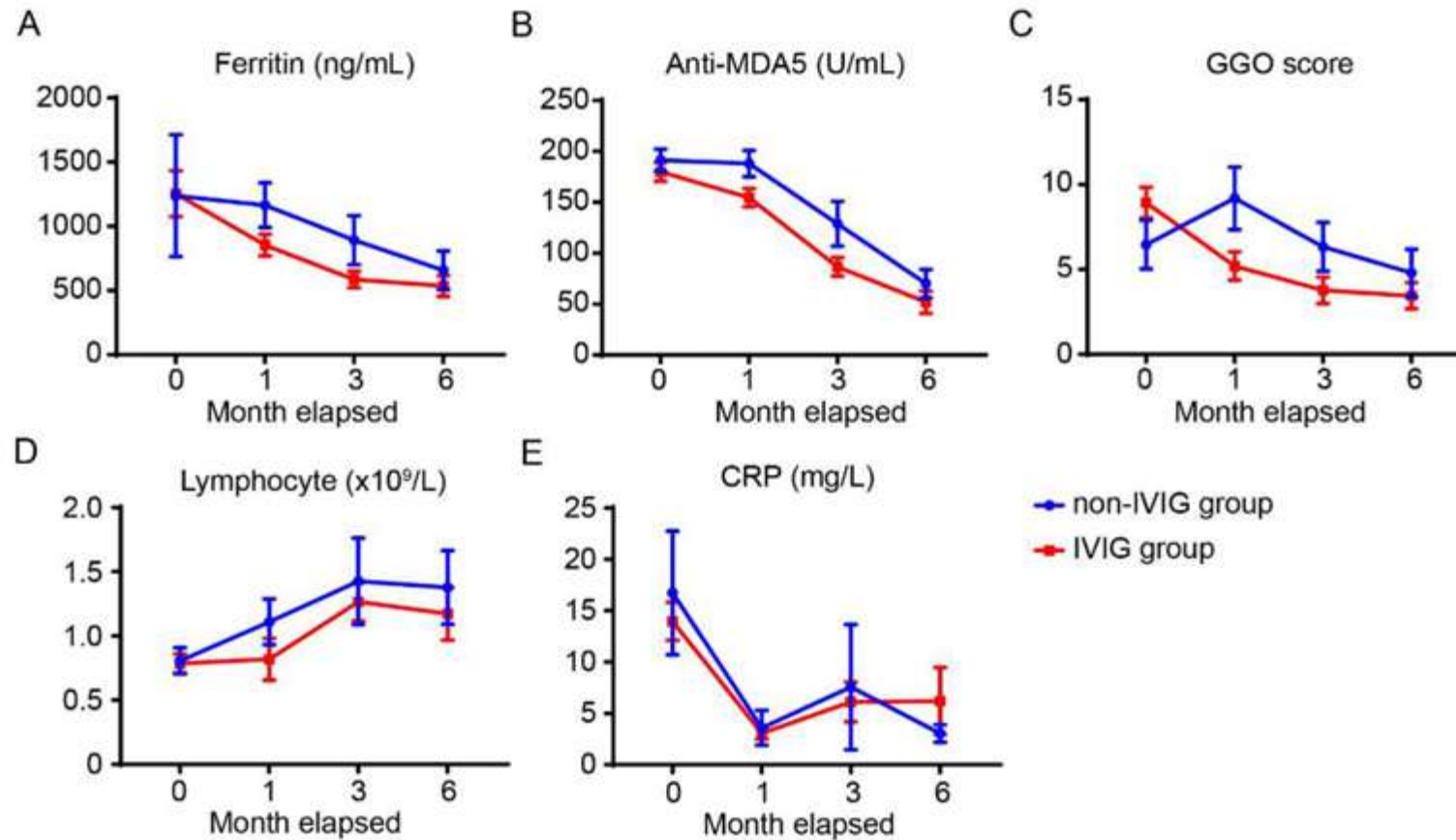
Studied efficacy of IVIG for MDA5 RPILD as the first-line

therapy in combination with other drugs



	IVIG used ($n = 31$)	IVIG no-used ($n = 17$)	<i>P</i>
Infection in 3 months, n (%)	8 (25.8)	3 (17.6)	0.776
Infection in 6 months, n (%)	8 (25.8)	3 (17.6)	0.776
Remission at 3 months, n (%)	22 (71.0)	7 (41.2)	0.044
Remission at 6 months, n (%)	20 (64.5)	8 (47.1)	0.241
GCs dosages at 3 months, mg/day	30 (22.5–55)	30 (20–50)	0.427
GCs dosages at 6 months, mg/day	15 (10–60)	20 (15–20)	0.800
<u>Mortality</u>			
Within 3 months, n (%)	6 (19.4)	9 (52.9)	0.016
Within 6 months, n (%)	7 (22.6)	9 (52.9)	0.033

Fig. 2 Changes of variables in each group



Role of Direct hemoperfusion with polymyxin B immobilized fibre treatment

Studies	No. of Patients	Outcome
Okabayashi et al	10	9/10 - died
Takada et al	13 2- PolyB Hemoperfusion	1/2 - died
Ichiyama et al	3	Significant improvement
Sasaki et al Silveira et al Teruya et al Turusava et al	4	Significant improvement

PLEX in RP-ILD

Study	Number of Patients	Intervention	Outcome (Numeric)
Shirakashi et al., Rheumatology 2020	13/38 – who progressed with immunosuppressive t/t	PLEX was done in 8/13	5/8 survived 62.5% survival with PE vs. 0% without
Abe et al., Rheumatology 2020	10/21 - refractory RP-ILD	6 patients received PE (PE group) and 4 did not (non-PE group)	100% 1-year survival with PE vs. 25% without

PLEX in RPILD

Successful treatment of anti-MDA5 antibody-positive refractory interstitial lung disease with plasma exchange therapy

Rheumatology 2020

Yoshiyuki Abe¹, Makio Kusaoi¹, Kurisu Tada¹, Ken Yamaji¹ and Naoto Tamura¹

Among 142 patients newly diagnosed with PM/DM or CADM, anti mda 5

Ab were detected in 28 pts, 21/28 were diagnosed as RPILD

10 were diagnosed with refractory RP-ILD and were positive for anti-

MDA5 antibodies

6 patients received PE (PE group) and 4 did not (non-PE group)

Variable	PE Group (n=6)	Non-PE Group (n=4)	P-value
LDH (IU/l)	355 (315-450)	436 (365-1247)	0.26
KL-6, median (IQR)	668 (548-1231)	940 (716-1176)	0.26
Ferritin (ng/dl)	857 (471-1322)	1740 (621-2365)	0.26
CRP (mg/dl)	2.1 (1.4-5.2)	0.6 (0.5-1.4)	0.04*
PaO2	72 (66-83)	71 (55-78)	0.48
FiO2	0.21 (0.21-0.34)	0.21 (0.21-0.21)	0.48
mPSL pulse therapy	5 (83)	4 (100)	1.00
Use of cyclosporin	3 (50)	2 (50)	1.00
Use of tacrolimus	3 (50)	2 (50)	1.00
IVIg	2 (50)	2 (50)	1.00
One-year survival	6 (100)	1 (25)	0.03*

Tofacitinib in RP-ILD

Study	Number of Patients & Characteristics	Intervention	Outcome
Kurasawa et al., Rheumatology, 2018	5 patients with anti-MDA5 Ab+ DM-ILD, refractory to triple therapy 15 historical control – to identify poor prognostic factors	Tofacitinib 10 mg/day in addition to triple therapy (GC, CSA, CYC)	3 survived, 2 died; improved survival rate vs historical controls
Chen et al., NEJM, 2019	18 patients with anti-MDA5+ ADM-ILD (FVC of 50% required) 32 historical controls	Tofacitinib 5 mg twice daily + glucocorticoids	100% survival at 6 months (18/18) vs. 78% in historical controls (25/32); (p=0.04) improved FVC, ferritin levels, and lung function

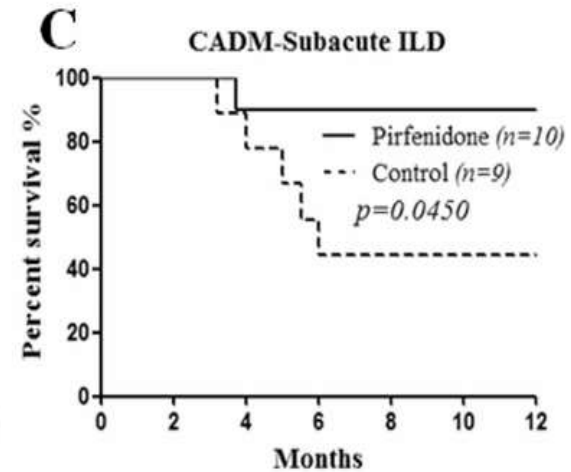
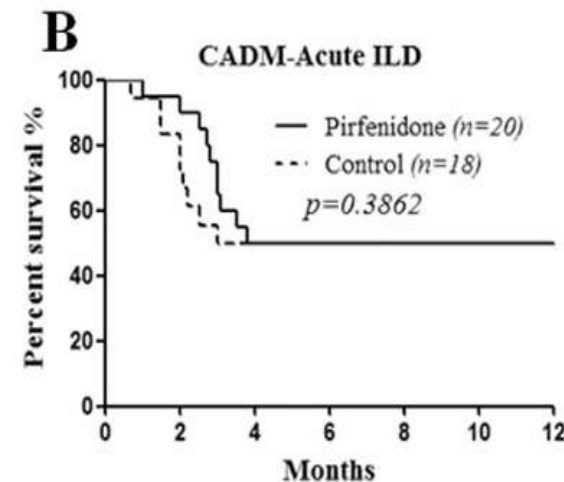
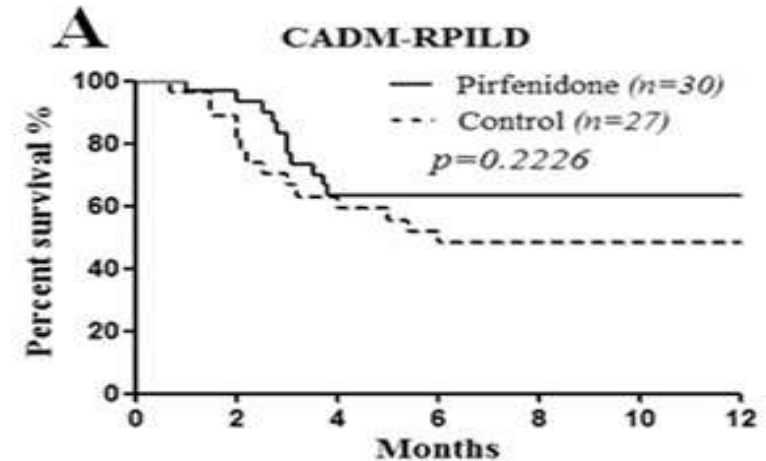
	Case 1	Case 2	Case 3	Case 4	Case 5
Age/sex	66/F	43/M	74/F	60/M	60/F
Diagnosis	ADM	DM	ADM	DM	ADM
Initial treatment	GC + CSA + IV CYC (triple therapy)	GC + CSA + IV CYC (triple therapy)	GC + CSA + IV CYC (triple therapy)	GC + CSA + IV CYC (triple therapy)	GC + CSA + IV CYC (triple therapy)
TOF administration	Day 13	Day 15	Day 5	Day 10	Day 7
Prognosis	Alive	Alive	Dead	Dead	Alive
Time of death	-	-	Day 55	Day 49	-
Cause of death	-	-	Hepatic failure after shock of unknown cause	Intramuscular bleeding, respiratory failure	-
			On admission		
Symptoms	Rash, malaise, arthralgia	Rash, malaise, arthralgia, fever	Rash, malaise, dyspnoea	Rash, malaise	Rash, malaise, cough
CK (IU/l) [59-248] ^a	69	3192	91	528	53
LDH (IU/l) [124-222]	430	558	409	462	384
Myoglobin (ng/ml) [<109]	62	258	ND	348	23
A-aDO ₂ (mm Hg)	50	24	44	39	31
KL-6 (U/ml) [105-401]	1190	261	913	661	370
Ferritin (ng/ml)[M: 12-301, F: 5-177]	1559	1461	1497	1994	1113
Number of lung fields with GGO/consolidation on admission	6	6	6	6	6
			Clinical course during treatment		
New GGO/consolidation during triple therapy	Y	Y	Y	Y	Y
Ferritin level (ng/ml) (maximum during treatment)	6813	4684	5367 ^b	4396	3986
Number of poor prognostic conditions ^c	3	3	3	3	3
Response to TOF					
Respiratory condition	Improved	Improved	Improved but worsened after respiratory infection and required mechanical ventilation	Gradually worsened	Improved
Ferritin levels	Decreased	Decreased	Decreased but increased after shock	Transiently decreased but gradually increased	Decreased
Adverse events	CMV reactivation, herpes zoster, bacterial respiratory infection, pneumomediastinum	CMV reactivation, herpes zoster, adenovirus cystitis, bacterial respiratory and urinary tract infection, fungal infection, lymphoproliferative disease	CMV reactivation, bacterial respiratory infection, pneumonia, sepsis, fungal infection, shock of unknown cause, hepatic failure	CMV reactivation, intramuscular bleeding, pneumomediastinum	CMV reactivation, herpes zoster, bacterial respiratory infection, pancytopenia
Duration of the combination therapy with TOF	7 months	14 weeks	4 weeks	6 weeks	18 weeks
Latest treatment	GC + TOF (24 months)	GC (19 months)	-	-	GC + CSA (10 months)

Pirfenidone in patients with rapidly progressive interstitial lung disease associated with clinically amyopathic dermatomyositis, Scientific Reports 2016

- Open-label, prospective study with matched retrospective controls
- 30 patients diagnosed with CADM-RPILD
- Treated with pirfenidone at a target dose of 1800 mg/d in addition to conventional treatment, such as a glucocorticoid and/or other immunosuppressants
- Matched patients without pirfenidone treatment (n = 27) were retrospectively selected as controls

Pirfenidone add-on group displayed a trend of lower mortality compared with the control group (36.7% vs 51.9%, $p = 0.2226$)

Subgroup analysis - the pirfenidone had no impact on the survival of acute ILD patients (<3 mo), vs subacute ILD ($n = 10$) had a significantly higher survival rate compared with the control subgroup ($n = 9$) (90% vs 44.4%, $p = 0.0450$)



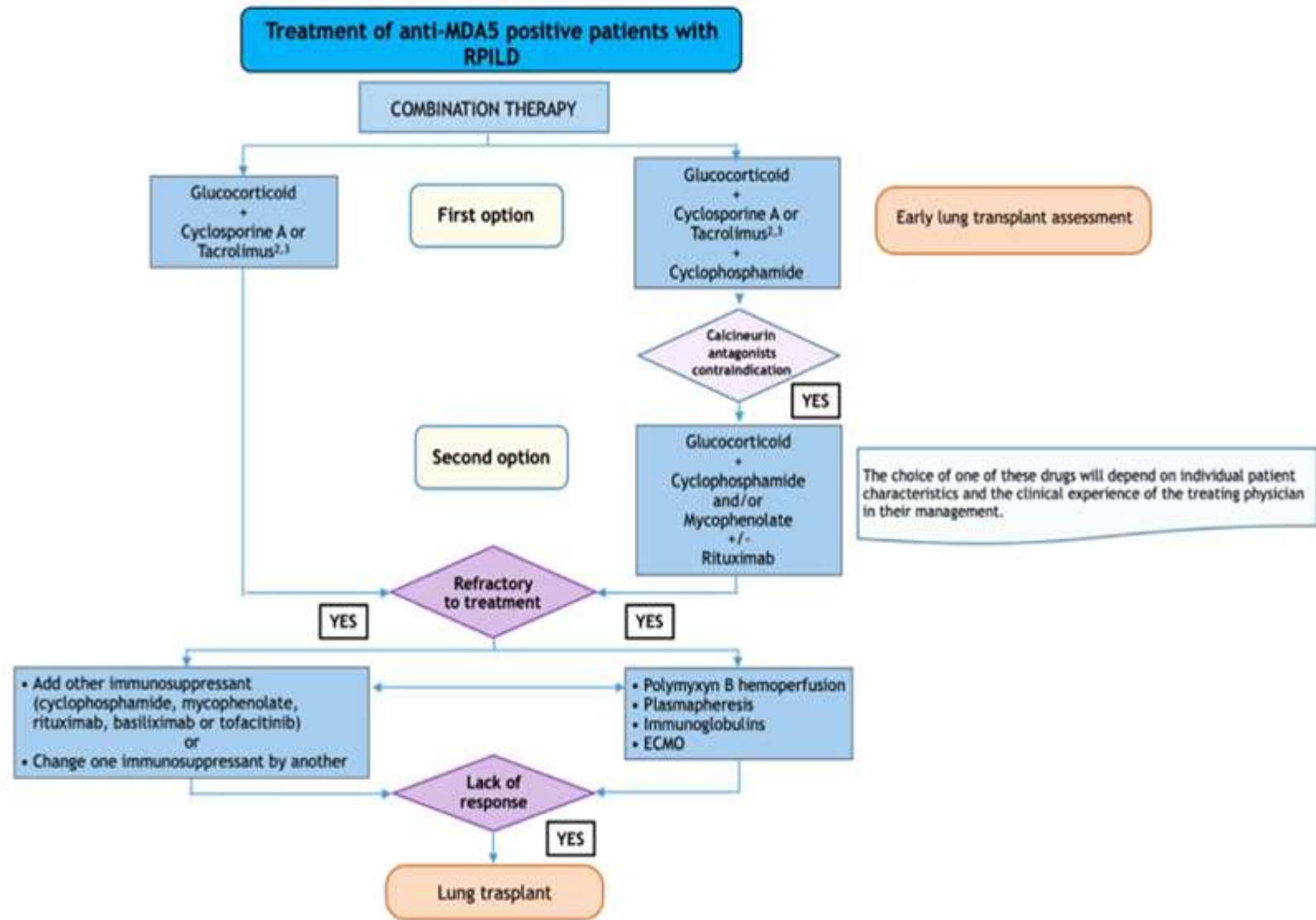
VV-ECMO IN RPILD

- Acts as a bridge to a most definitive solution like lung transplantation or while waiting for a response to the immunosuppressive drugs
- Scarce data on the efficacy of VV-ECMO in RPILD

Lung transplant in RPILD

- Lung transplantation emerges as a promising treatment, especially when initial immunosuppression fails
- There is a speculative notion that DM-ILD is triggered by factors like viral infections, causing a disruption in self-tolerance and prompting an autoimmune reaction
- According to this view, if a patient undergoes lung transplantation, the removal of the source of autoantigens would lead to the vanishing of the anti-MDA-5 Abs and the prevention of a recurrence of ILD symptoms

Study	Intervention	Outcome
Lian et al., Clin. Rheumatol., 2023	Lung transplantation in two cases of MDA-5 DM RP-ILD	One patient had successful rehabilitation; second patient succumbed to respiratory failure due to ILD flare in transplanted lungs
Zhang et al, Medicine 2025	One pt with RPILD VV ECMO was used as bridging therapy Double lung Tx	Successful outcome On F/up anti mda 5 titres – Negative
Kun Huang et al, Rheumatology International, 2019	8 RPILD (5/8 died) 3 received Lung Transplant ECMO was used as a bridge	3/8 survived with Lung transplant, 5 did not get Tx





Early referral for lung transplant

MDA-5 RP-ILD

Alternatives:
Rituximab, Plasma Exchange

"HIT IT HARD"

Triple Therapy

Early Combined Immunosuppressive Therapy:
High dose glucocorticoids+ CNI +/-CYC

MTX, TNFi, LEF, AZA are not recommended for induction.

Improvement

Disease Progression

ECMO as a Bridge

- Consider JAK inhibitor for refractory disease
- Consider IVIG for [redacted]
- Pirfenidone is useful in subacute MDA-5 ILD

Maintenance with CNI

Lung transplant +/- Plasma Exchange
(Consider Plasma Exchange Peri-transplant)

Acute interstitial pneumonia

- AIP is a term used for an idiopathic form of ALI characterized clinically by ARF with bilateral lung infiltrates and histologically by diffuse alveolar damage (DAD)
- AIP is distinguished from ARDS by the absence of a known cause of ARDS
- The first cases of AIP were described by Lois Hamman and Arnold Rich in 1935
- In 1986, Katzenstein and colleagues coined the term “acute interstitial pneumonia”
- Patients on autopsy had diffuse interstitial fibroblast proliferation—a finding that we get in organizing stage of DAD

Definition (Diagnostic Criteria)

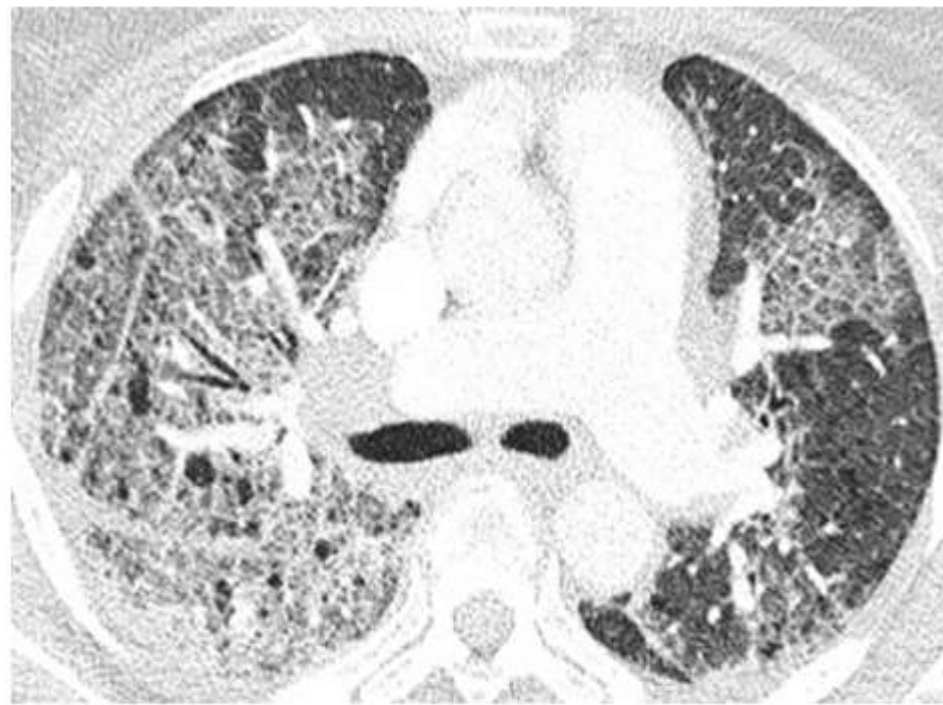
1. Acute onset of respiratory symptoms resulting in severe hypoxia and, in most cases, ARF
2. Bilateral lung infiltrates on radiographs
3. The absence of an identifiable etiology or predisposing condition despite adequate clinical investigation
4. Histological documentation of DAD

Radiology

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Evidence on AIP

Studies	Number of Patients	Causes of DAD That Were Excluded in the Study	Outcome
Katzenstein (1986)	8	Not specified	6 of 8 died; 2 survived (1 died at 6 months)
Olson (1990)	29	CTD, sepsis, infection, radiation, drugs, vasculitis, asbestos exposure, hairy cell leukemia	17 of 29 died; 12 survived, some for up to 2 years; no histology in survivors
Primack (1993)	9	Infections, including viral. Cases with underlying UIP/IPF and SLE were not excluded	8 of 9 died within 3 months of presentation
Ichikado (1997)	14	Not specified	All patients died within 2 weeks to 6 months
Vourlekis (2000)	13	Infections, cancer chemotherapy, collagen vascular diseases, AIDS, organ transplant, SIRS, toxic exposures	12 of 13 required MV; 4 died in hospital; 8 survived (hospital survival: 67%)

Quefatiqh (2003)	8	Dermatomyositis, infectious pneumonia/sepsis, cocaine, carmustine	7 of 8 survived to hospital discharge
Rice (2003)	6	Dermatomyositis, rheumatoid arthritis, Still disease, SLE	All patients died (this was an autopsy series)
Bonaccorsi (2003)	4	Infection, collagen vascular disease	3 of 4 died between 7 and 38 days
Suh (2006)	10	Infections, drugs, collagen vascular diseases, acute exacerbation of IPF	8 of 10 survived to hospital discharge; survivors were followed from 12 to 78 months; most were asymptomatic on follow-up
Parambil (2007)	12	Infections, noninfectious complications of transplantation, acute exacerbation of IPF, connective tissue diseases	6 of 12 died (50% hospital mortality)
Avnon (2009)	9	Cardiac disease, infections, autoimmune disease, malignancy	All patients died within 5–26 days of admission to intensive care unit (100% mortality)

- There is no proven effective therapy for AIP
- Virtually all patients require mechanical ventilation and supportive care
- Many patients are treated with high-dose iv corticosteroids, the use of which is based on reports of lower mortality in ARDS with such therapy

Early Intervention Can Improve Clinical Outcome of Acute Interstitial Pneumonia – Young et al 2006

- Studies 10 patients with AIP who presented with idiopathic ARDS and showed DAD on surgical lung biopsy
- Median duration of severe dyspnea of 9.5 days (2 to 34 days)
- All patients required mechanical ventilation – median duration – 9.5 days
- An aggressive diagnostic workup for respiratory infection, including BAL
- High-dose steroid pulse therapy was initiated on median hospital day 3.5 (1-8 days)

Patient/ Sex/Age, yr	Smoking Status	Fever	RR, breaths/ min	APACHE II Score	PaO ₂ /FIO ₂ at SLBs	Sx-Adm, d	Adm-MV, d	Adm-SLBx, d	Adm-Steroid, d	PEEP, cm H ₂ O	Vt/kg, mL	Outcome (F/U Duration)
1/F/68	NS	+	42	12	126.9	25	0	2	0	12	7.6	Died at 32 d
2/F/68	NS	-	32	9	93.3	21	5	7	7	10	8.9	Survived (75 mo)†
3/M/60	CS	+	32	13	287.3	2	1	3	1	8	7.7	Survived (78 mo)
4/M/70	ES	+	36	10	196.2	4	0	4	3	8	7.4	Survived (62 mo)
5/M/57	CS	+	36	18	147.0	4	1	6	8	16	6.4	Survived (60 mo)
6/M/38	CS											
7/M/63	CS											
8/F/70	CS											
9/F/73	NS											
10/M/51	CS											

Table 2—Initial Chest HRCT Scan Findings and Pathology of Patients With AIP*

Patient	Total Extent, %	GGO, %	Consolidation, %	Reticulation, %	Nodule, %	Pathology
1	80	50	30	—	—	Early proliferative phase with architectural distortion
2	60	40	20	—	—	Early proliferative phase with architectural distortion
3	90	80	10	—	—	Mixed exudative and proliferative phase with patchy distribution
4	80	55	25	—	—	Exudative phase with uniform distribution
5	95	65	30	—	—	Exudative phase with uniform distribution
6	90	65	20	—	5	Exudative phase with uniform distribution
7	70	50	20	—	—	Mixed exudative and proliferative phase with airway organization
8	50	30	20	—	—	Early proliferative phase with architectural distortion
9	95	85	—	10	—	Mixed exudative and proliferative phase with airway organization
10	45	25	20	—	—	Mixed exudative and proliferative phase with airway organization

Table 3—Clinical Data From Published Reports on AIP*

Study/Year	Patients, No.	Age, yr	Biopsy Type		Adm-LBx, d	Steroid Tx, %	Adm- Steroid	Mortality Rate, %
			SLBx	Autopsy				
Hamman and Rich ⁴ /1944	4	43	0	4	NA	NA	NA	100
Katzenstein et al ⁷ /1986	8	28	8	0	13	NA	NA	88
→ Olson et al ⁸ /1990	29	50	23	6	10	69	NA	59
Primack et al ⁹ /1993	9	65	5	4	NA	NA	NA	89
Ichikado et al ⁵ /1997	14	53	3	11	NA	NA	NA	100
Johkoh et al ⁶ /1999	36	61	11	25	NA	NA	NA	89
→ Vourelkis et al ¹⁰ /2000	13	54	13	0	13	90†	15	33‡
Ichikado et al ²¹ /2002	31	60	10	17	NA	100	NA	68
→ Quefatieh et al ¹² /2003	8	48	8	0	8	100	NA	13
→ This study	10	68	10	0	4	100	3	20

Our experience in last 1 year

Case	Intervention	Outcome
1. 64/F – Anti MDA 5 ++ Mi2 α ++, PL7+	MPS pulse 3 doses 1 dose of cyclophosphamide	VAP – Died
2. 24/F – Mi2 α +	High dose steroids	Secondary spontaneous PTX, VAP – Died
3. 53/F – Anti MDA 5 +++, Ro 52+ Had renaulds, skin rashes,	Triple therapy – MPS pulse + Cyclophosphamide + Tacrolimus	Developed cytopenias – severe neutropenis, VAP – Died

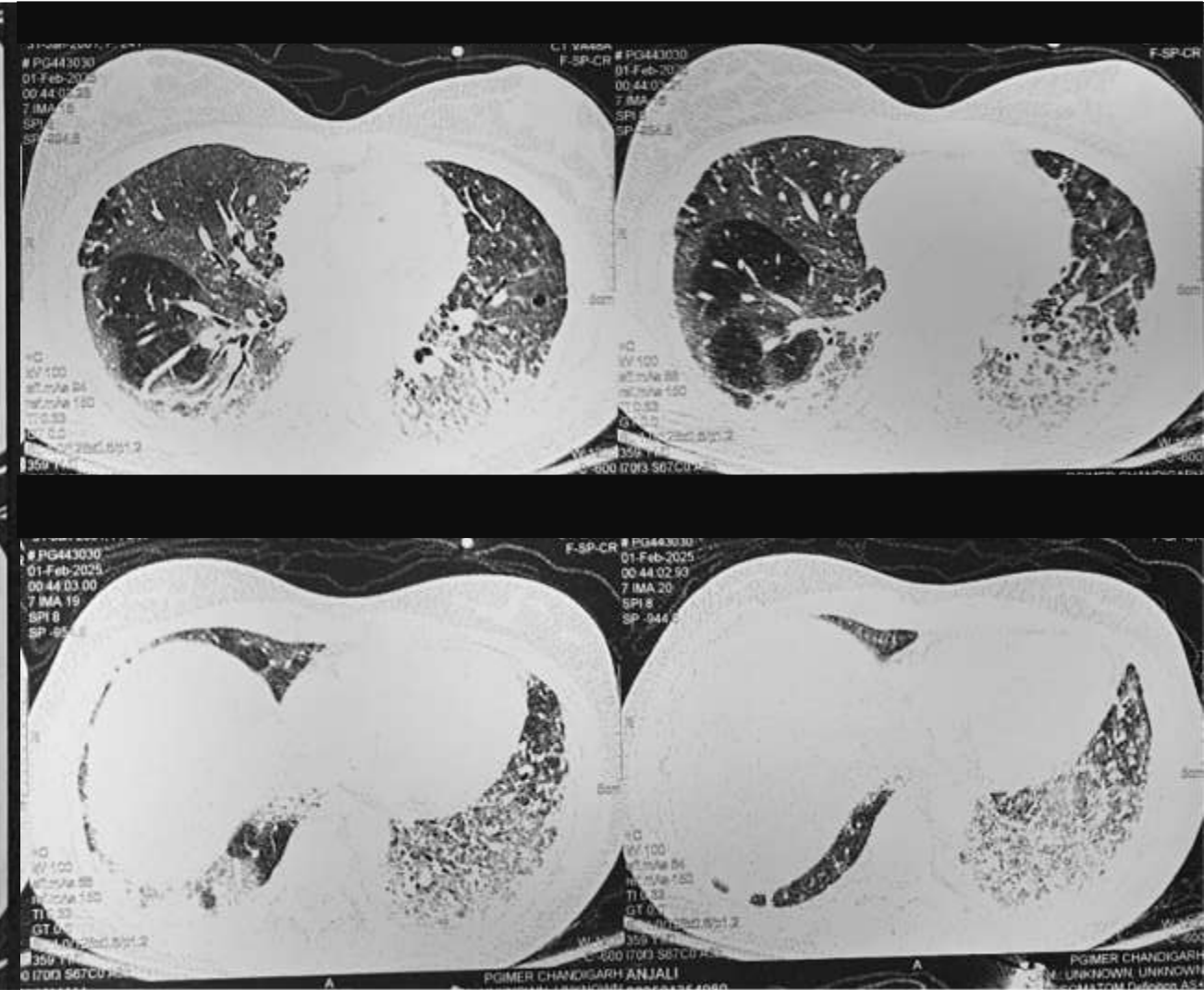
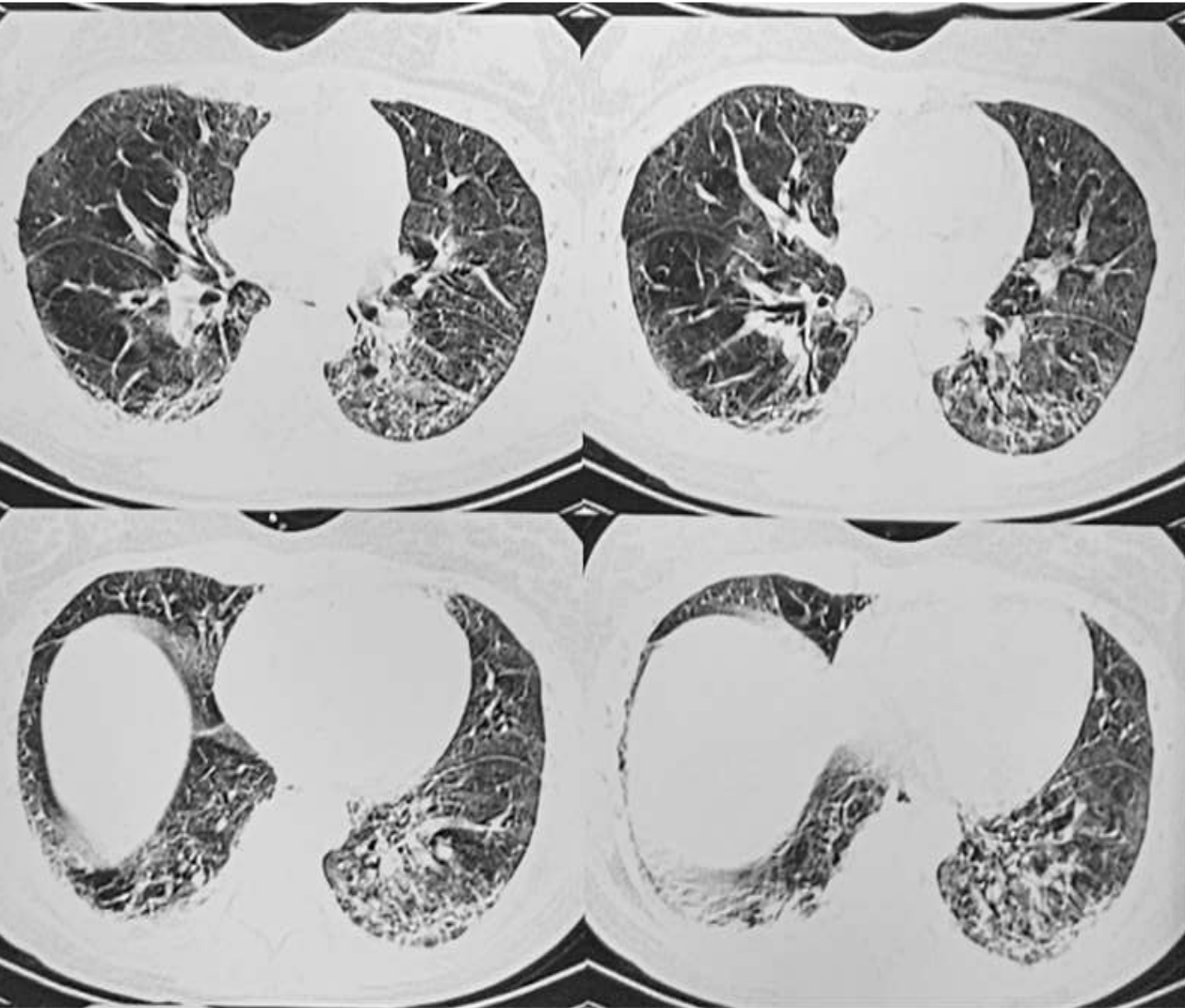
Biomarkers

	Case 1	Case 2	Case 3
Ferritin	2433	7413	1563
LDH	339	1577	1615
CRP	10.65	7.02	64
IL-6	-	-	17

CASE 2

25/1/25

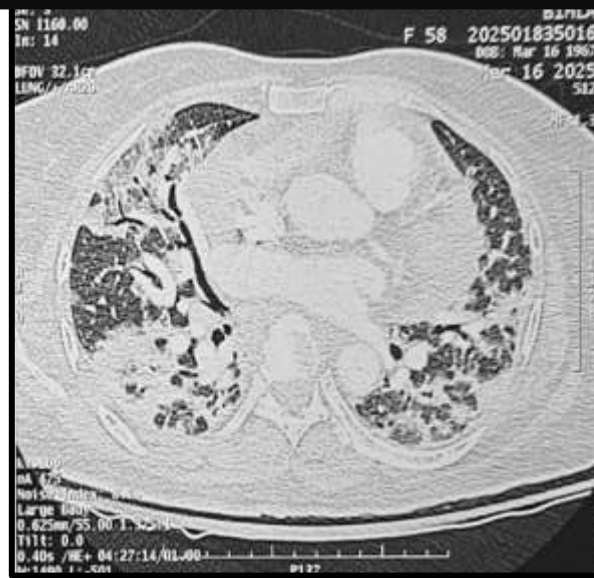
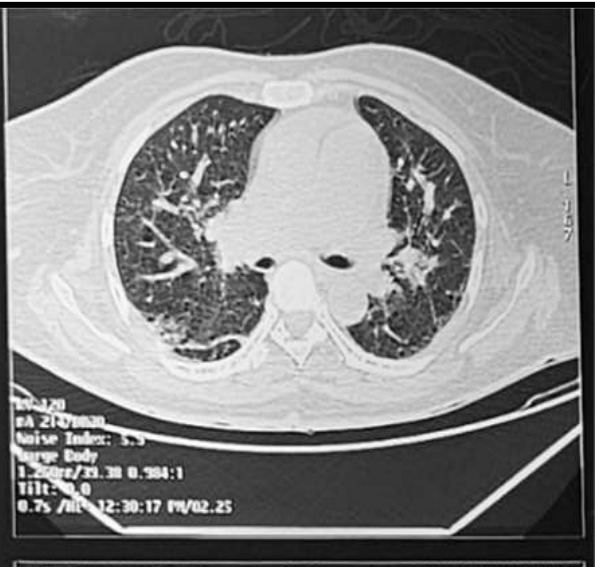
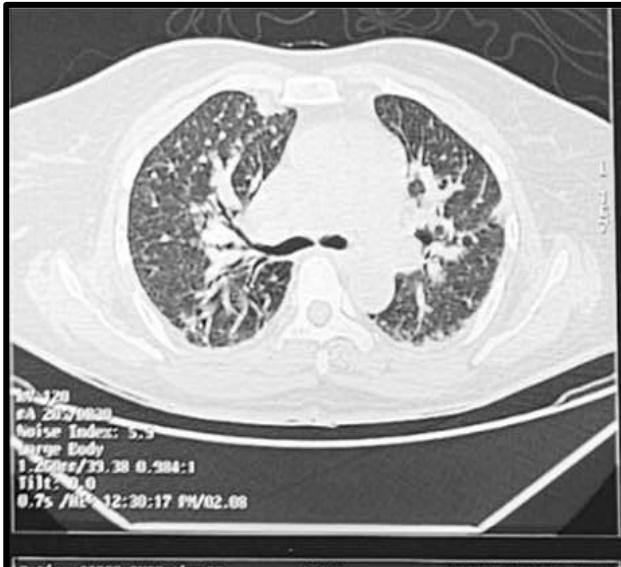
1/2/25



CASE 3

4/3/25

16/3/25



Suspected patient with rapidly progressive ILD

Rule out infection, drug induced, HSP
CTD w/up - myositis panel

Anti MDA-5 +

Send biomarkers

Combination therapy –
PSL+Cy+CNI (Alt – Ritux, IVIG,
PLEX)

Clinico-radiological response
along with biomarkers

Refractory cases – Tofacitinib, Rituximab,
Tocilizumab, Poly B hemoperfusion, PLEX,
IVIG

AIP

Supportive care with MV

High dose steroids/ MPS pulse
+/-

Thank you!