

Interstitial lung disease

Systemic sclerosis

Dr.Hoda Kavosi

Assistant professor of Rheumatology

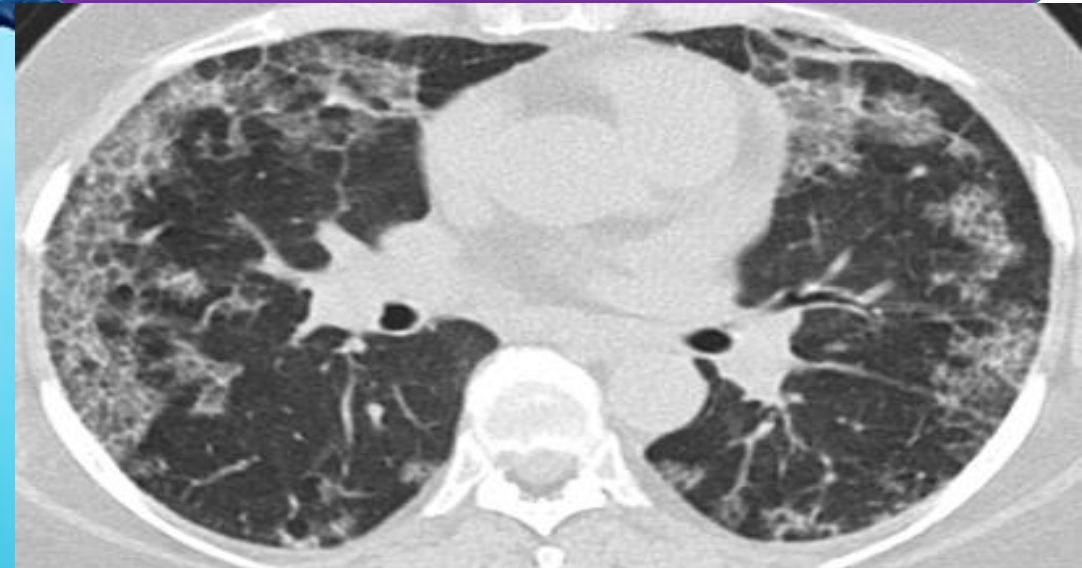
Rheumatology Research Center





55% SSC have ILD on HRCT on initial evaluation

Tyndall AJ, et al. a study from (EUSTAR) database. Ann Rheum Dis 2010



Comparison of the clinical phenotype of systemic sclerosis patients in Iran and France in two university centers

Journal of Scleroderma and
Related Disorders

1-11

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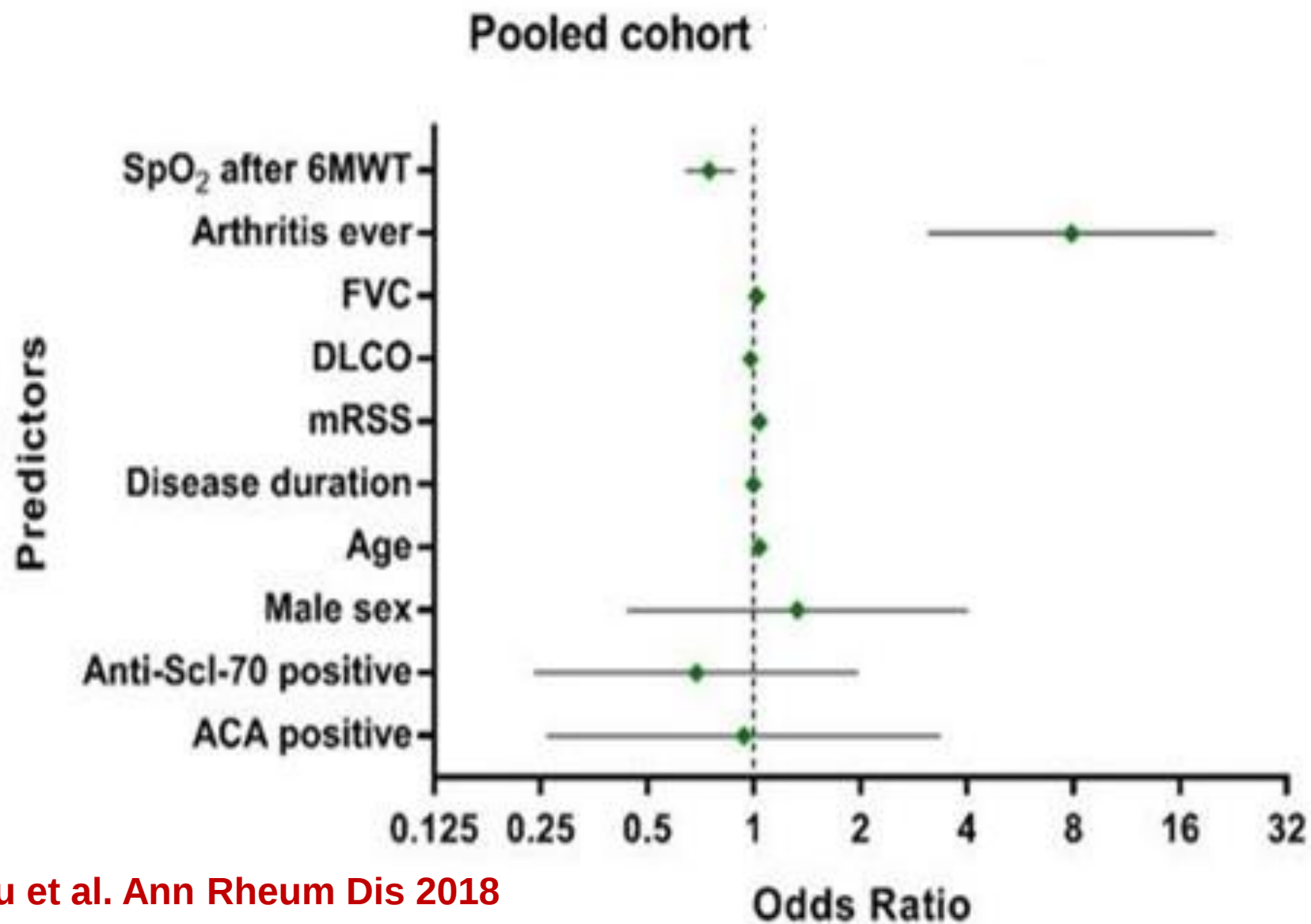
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Yannick Allanore¹, Farhad Gharibdoost², Ahmad Reza Jamshidi²,
Ali Javinani², Jérôme Avouac¹, Elnaz Rastkar², Sadid Hooshmandi²
and Hoda Kavosi² 

Table 2. Clinical and laboratory data of all Iranian and French patients.

Restrictive defect	15 (13.3)	31 (21.5)	53 (82.8)	14 (17.9)	<0.001	31.479 (13.498–73.411)
FVC (% predicted)	103 (93–118)	61 (42.4)	76 (67–90)	11 (14.1)	<0.001	–
ANA	247 (93.2)	3 (1.11)	151 (86.78)	26 (13)	0.049	0.478 (0.250–0.916)
ATA	84 (32.06)	6 (2.23)	107 (62.57)	29 (14.5)	<0.001	3.543 (2.365–5.307)
ACA	72 (27.27)	4 (1.49)	16 (10.38)	46 (23)	<0.001	0.309 (0.172–0.555)
ARA	8 (4.67)	97 (36.19)	2 (2)	100 (50)	0.391	0.416 (0.087–1.998)
Conduction block	27 (11.25)	28 (10.44)	38 (28.78)	68 (34)	<0.001	3.189 (1.840–5.526)
Arrhythmia	1 (1.92)	216 (80.59)	5 (3.81)	69 (34.5)	0.633	2.024 (0.231–17.752)
LVEF (%)	63.71 ± 4.48	95 (35.44)	56.04 ± 4.66	19 (9.5)	<0.001	–
ePAP (mm Hg)	32.52 ± 13.15	103 (38.43)	27.81 ± 9.81	27 (13.5)	<0.001	–
Pericardial effusion	16 (10.45)	115 (42.91)	4 (3.12)	72 (36)	0.000	0.276 (0.090–0.848)
Restrictive defect	54 (25.71)	58 (21.64)	127 (79.37)	40 (20)	<0.001	11.118 (6.795–18.191)
FVC (% predicted)	98 (84–113)	114 (42.53)	75 (60–87.75)	32 (16)	<0.001	–



Wanlong Wu et al. Ann Rheum Dis 2018

Anti EIF2B
(Eukaryotic Initiation Factor 2B)
ILD and diffuse SSC

2012 ACR/ARHP annual Meeting



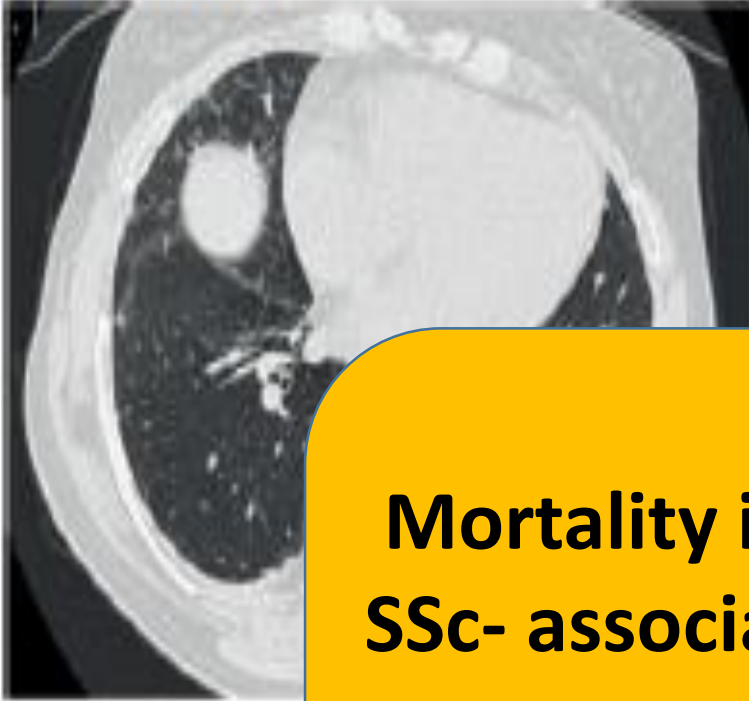
**PFT
BODYBOX**

DLCO

HRCT

CT appearance

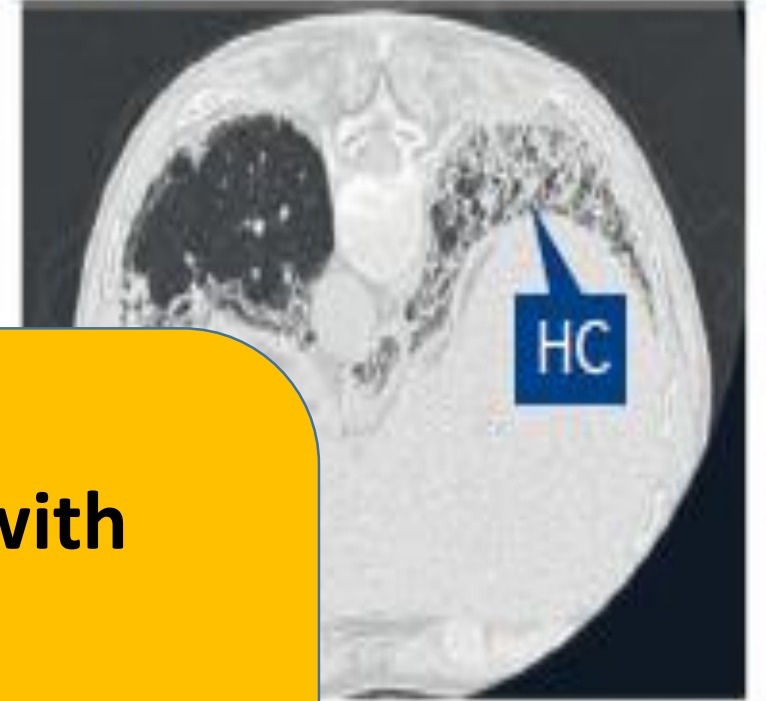
a NSIP mild



b NSIP extensive



c UIP

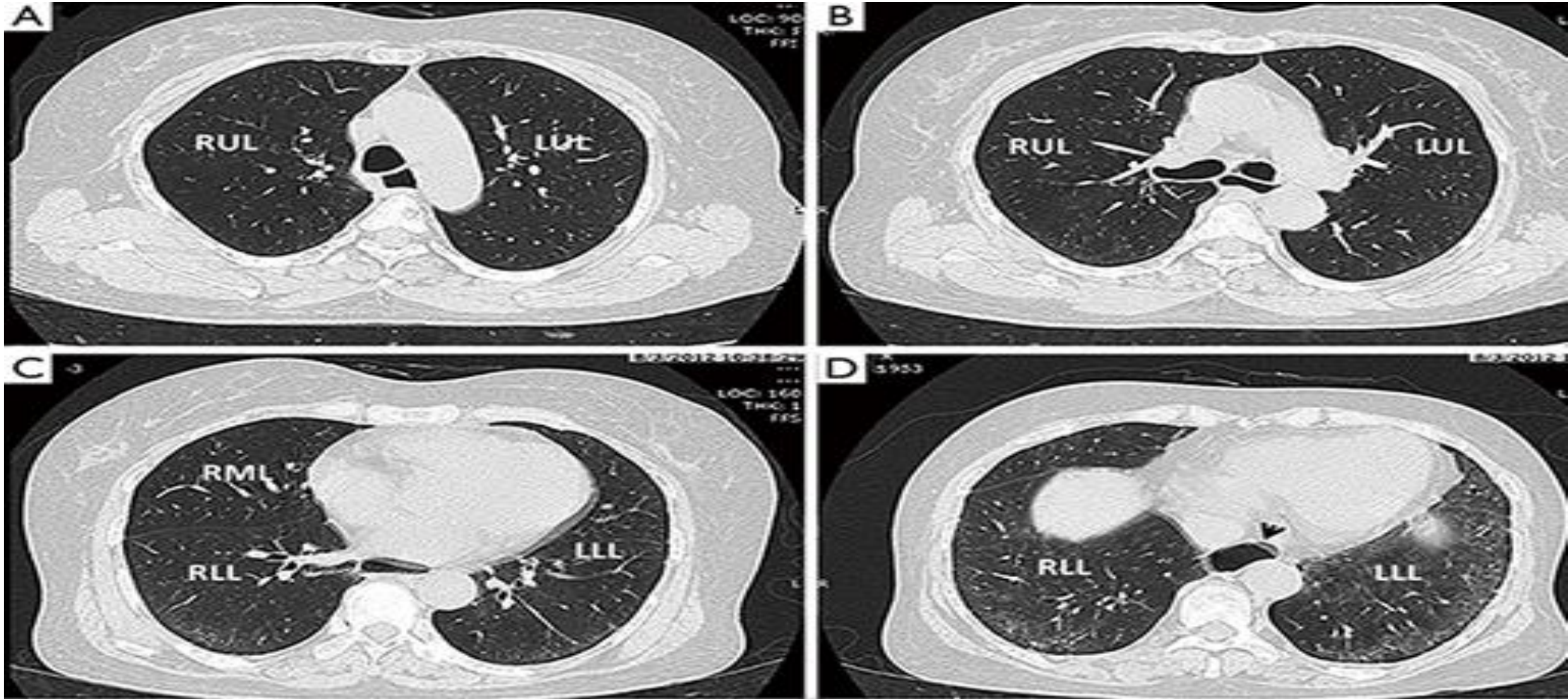


Mortality is similar for patients with SSc- associated ILD

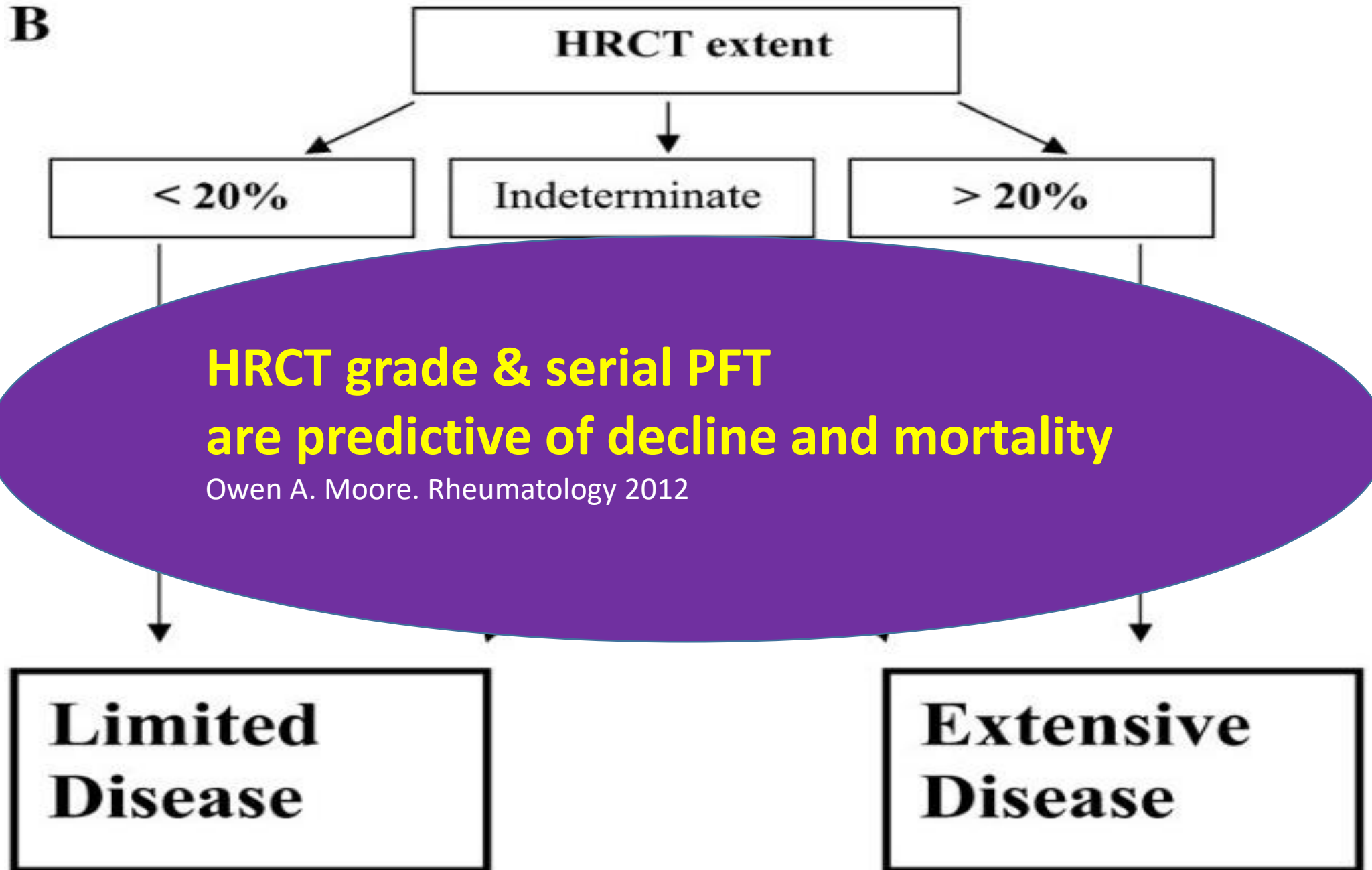
NSIP pattern = UIP pattern

Bouros, D. Am. J. Respir. Crit. Care Med 2002.

Staging HRCT



B



ILD progression and mortality

IL-6 predicted early disease progression

IL-6 values >767 pg·mL⁻¹ were predictive of risk of death within the first 30 months in patients with mild SSc-ILD

Prediction of mortality at 12 months

Drop in FVC of >10%

**Drop in FVC: 5–9% alongside a 15% fall in
DLCO**

- Khanna, D. *Arthritis Res. Ther.* 2015.

Treatment indication

- Ongoing disease progression based on PFT decline or radiographic deterioration need treatment **independent of disease extent**.
- Early disease, tendon friction rub, anti-topo I positivity and highIL6 levels may in future be considered when deciding whether or not to start an immunosuppressive therapy.

- **Susanna Cappeli,et al.Interstitial lung disease in systemic sclerosis: where do we stand?Eur Respir Rev 2015**

Example

- Patient 1:
- SSC duration 5 years
- FVC=67% stable in previous 2 years
- *Immunosuppression??*

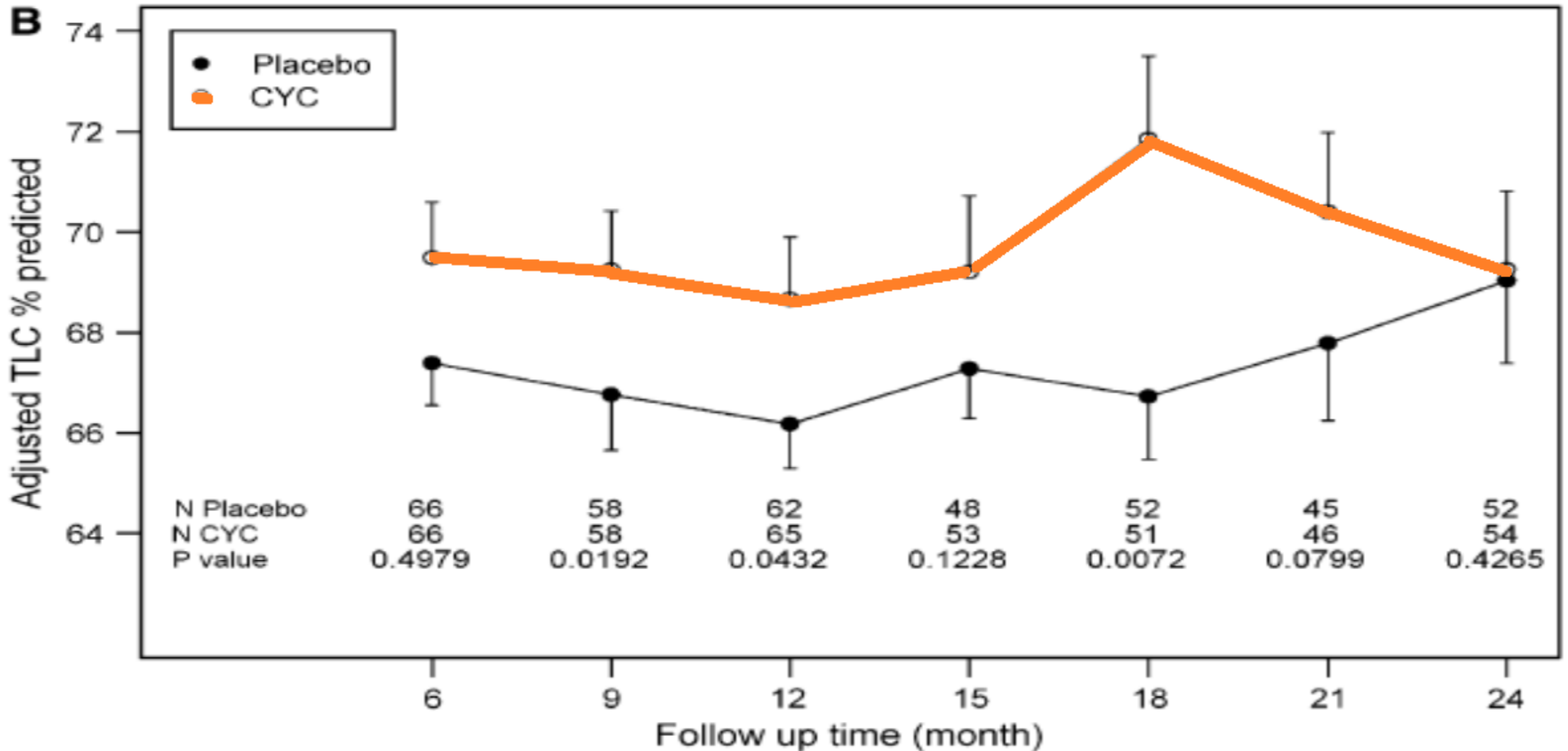


- Patient 2
- SSC duration 3 years
- FVC=80% and had 15% reduction in previous 3 years
- *Immunosuppression?*



TREATMENT

- Scleroderma Lung Study I (SLS I)

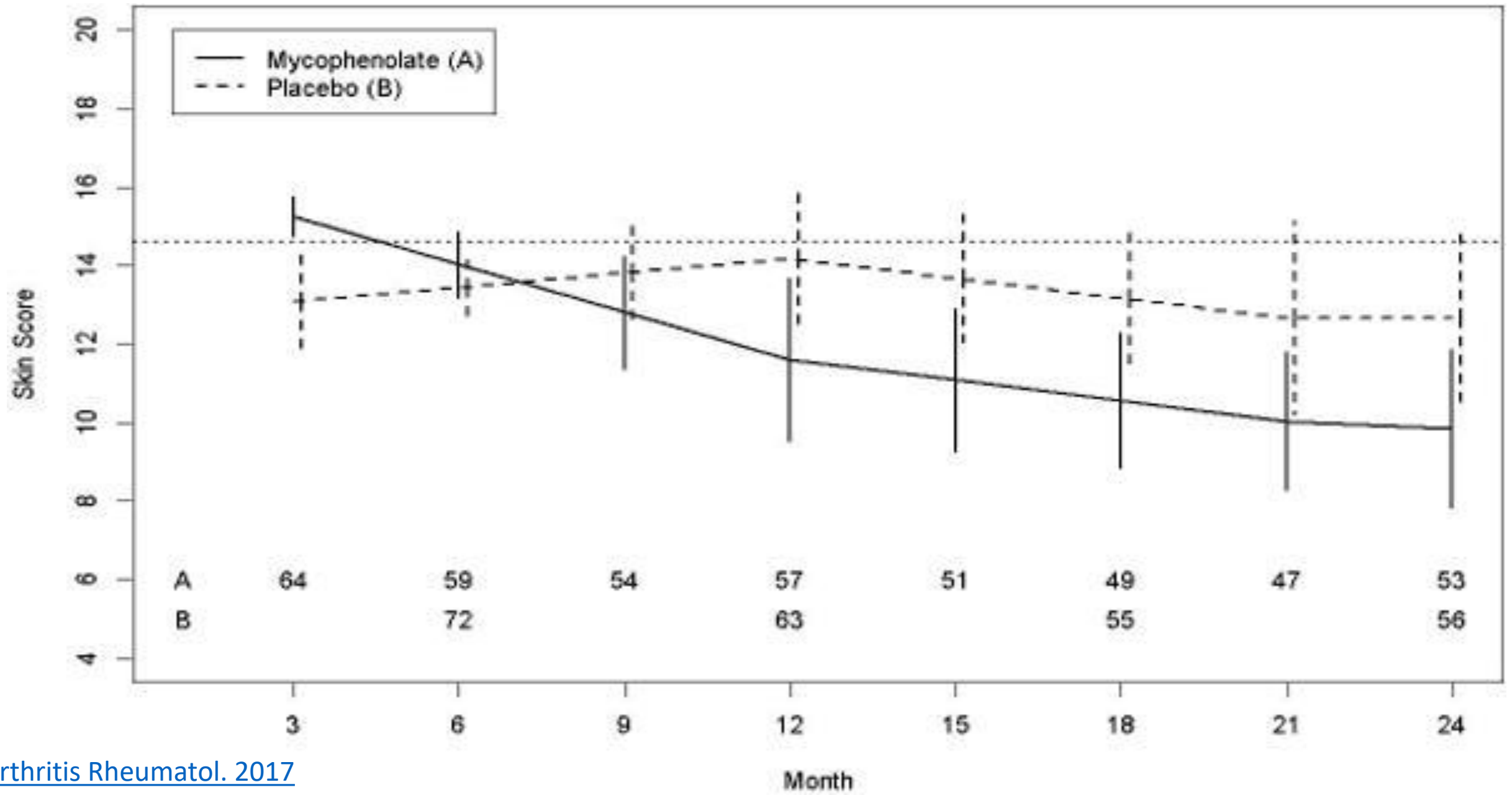


The Fibrosing Alveolitis in Scleroderma Trial (FAST)

The Fibrosing Alveolitis
n Scleroderma Trial
(FAST)

	Baseline		1-year followup		
	Treatment group (n = 22)	Placebo group (n = 23)	Treatment group (n = 19)	Placebo group (n = 18)	P†
Lung function, % predicted					
FVC	80.1 ± 10.3	81.0 ± 18.8	82.5 ± 11.3	78.0 ± 21.6	0.08
DLco _c	52.9 ± 11.5	55.0 ± 12.9	49.6 ± 10.7	51.8 ± 14.9	0.64
TLC	81.8 ± 10.1	76.8 ± 16.9	80.2 ± 9.8	74.4 ± 16.7	0.61
FEV ₁	79.6 ± 11.5	79.7 ± 19.1	81.3 ± 12.5	77.0 ± 21.3	0.16
Kco	71.3 ± 13.4	82.7 ± 19.1	71.5 ± 13.9	77.9 ± 23.3	0.32
Baseline HRCT‡					
Disease extent, mean (range) %	20 (6–40)	19 (5–40)	–	–	–
Ground-glass attenuation, mean (range) %	50 (15–91)	47 (0–95)	–	–	–
Improvement on serial HRCT, no (%)‡	–	–	6 (40)	3 (20)	0.39
Dyspnea score, mean (range)§	7.7 (2–14)	7.2 (0–18)	8.75 (0–14)	7.80 (2–14)	0.23

SLSII



Author	Duration of Therapy (months)	Mean baseline MRSS	Median baseline MRSS	MRSS at end of study	Level of significance
Stratton et al.[19]	12	28	NA	17	$p < 0.001$
Vanthuyne et al.[25]	12	20	NA	13	$p < 0.0001$ for all patients $p = 0.002$ for skin group
Nihtyanova et al.[27]	60	NA	26	11	NA
Le et al.[31]	12	24.4	NA	17.5	$p < 0.001$
Mendoza et al.[20]	Mean 18.2	24.56	NA	14.5	$p = 0.0004$
Derk et al.[21]	12	22.5	21.5	8.4	$p < 0.0001$
Koutroumpas et al. [29]	12	17.2	NA	17.7	$p = 0.55$

Effect of mycophenolate on pulmonary function.

	Therapy (months)	(% predicted)	study (% predicted)	significance	predicted)	(% predicted)	significance
Stratton et al.[19]	12	66	63	Not significant	87	88	Not significant
Vanthuyne et al. [25]	12	63	76	p = 0.0009	NA	NA	NA
Le et al.[31]	12	77.4	79.2	p = 0.336	79.4	80.7	p = 0.264
Mendoza et al. [20]	18.2	69	70.5	p = 0.45	NA	NA	NA
Cuomo et al.[36]	5	60	NA	NA	104	NA	NA
Saketkoo et al. [37]	3	30	NA	NA	80	NA	NA
Zamora et al.[28]	24	50	NA	p = 0.84	72	NA	p = 0.57
Gerbino et al.[26]	24	51	NA	p = 0.38	NA	NA	NA
Derk et al.[21]	12	71.2	74.3	Not significant	99.2	105	Not significant
Koutroumpas et al.[29]	12	80.7	86.7	p = 0.66	79.5	87.1	p = 0.04
Simeon-Aznar et	12	40	37	NA	64	64	NA

NA not available, DLCO diffusing capacity of carbon monoxide, FVC functional vital capacity, VC vital capacity, TLC total lung capacity

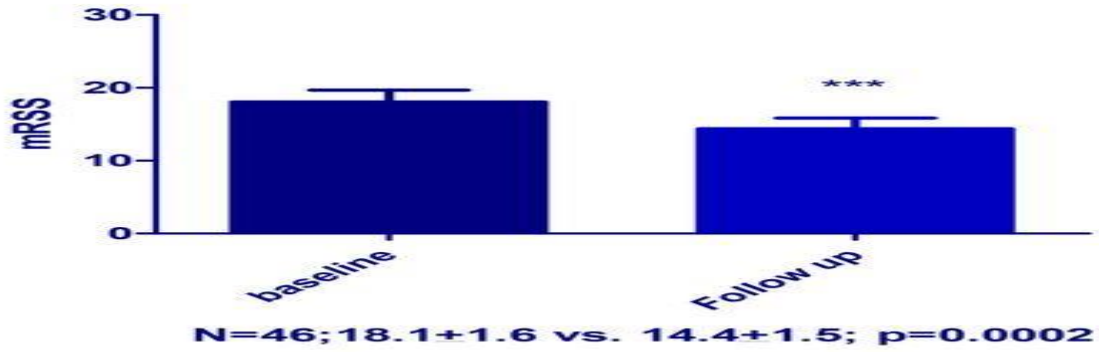


Most of patients unresponsive to
CYC also worsened under MMF

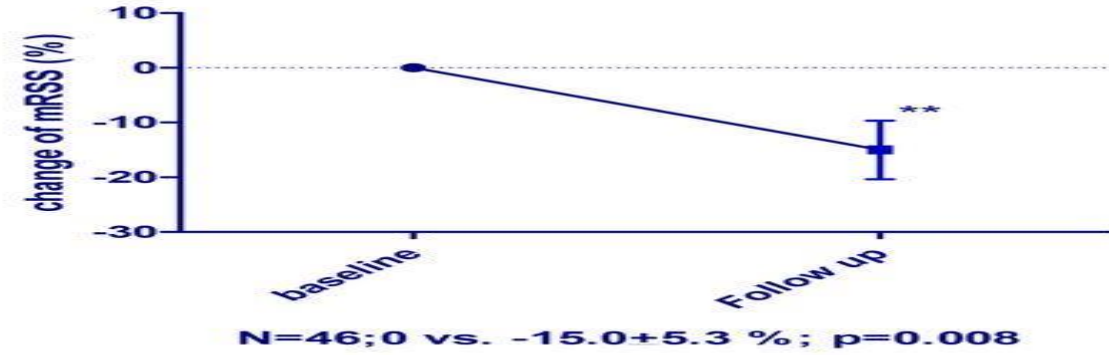
- Iudici M, et al. Low-dose pulse cyclophosphamide in (SSc-ILD): efficacy of maintenance immunosuppression in responders and non-responders. *Semin Arthritis Rheum* 2015

Rituximab

Whole Cohort

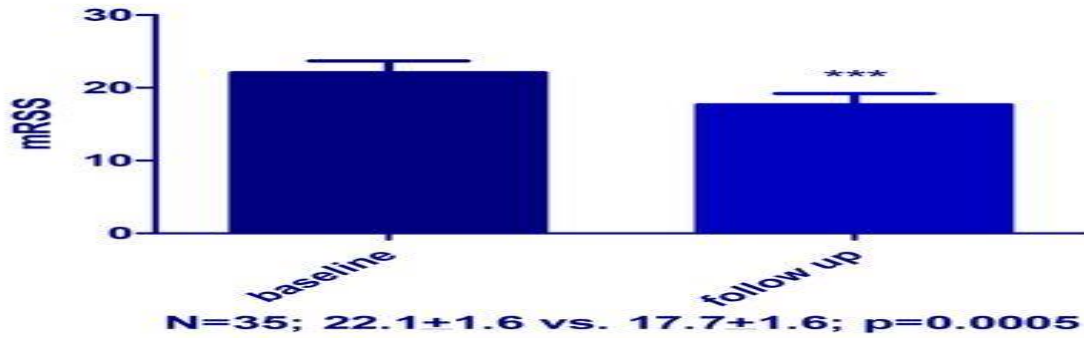


A

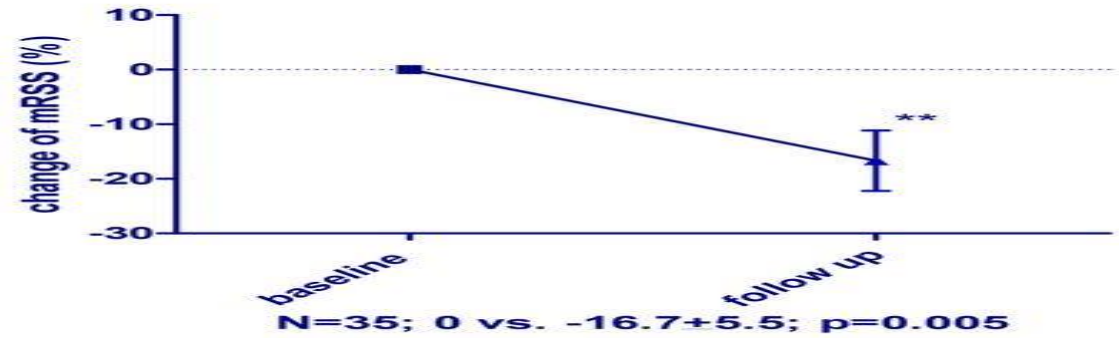


B

Diffuse SSc

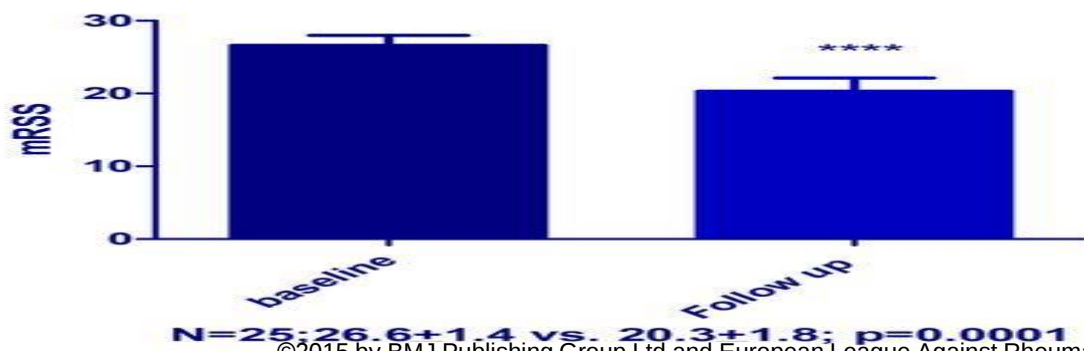


C

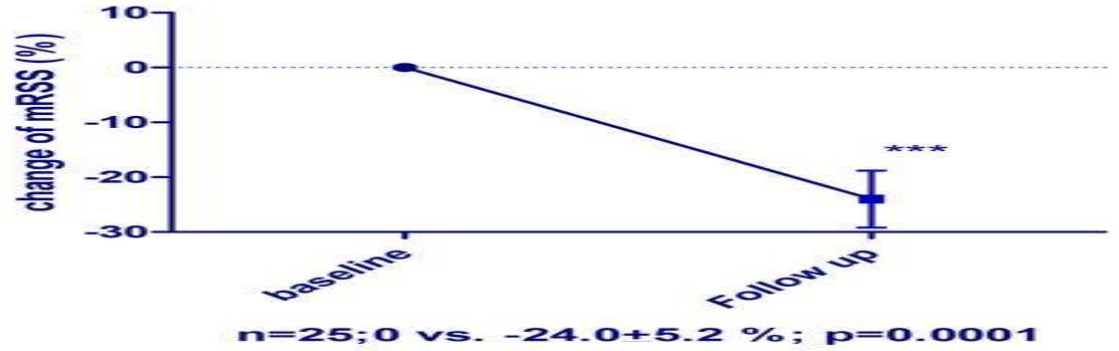


D

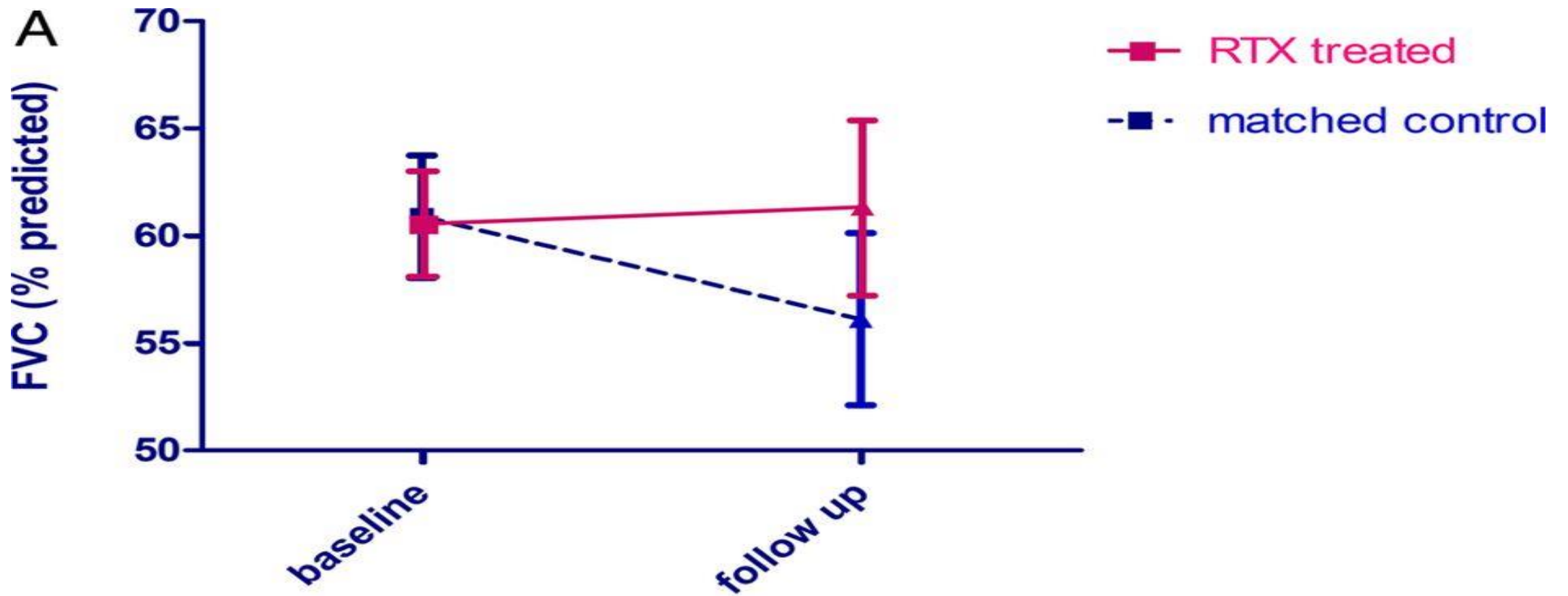
Severe diffuse SSc



E



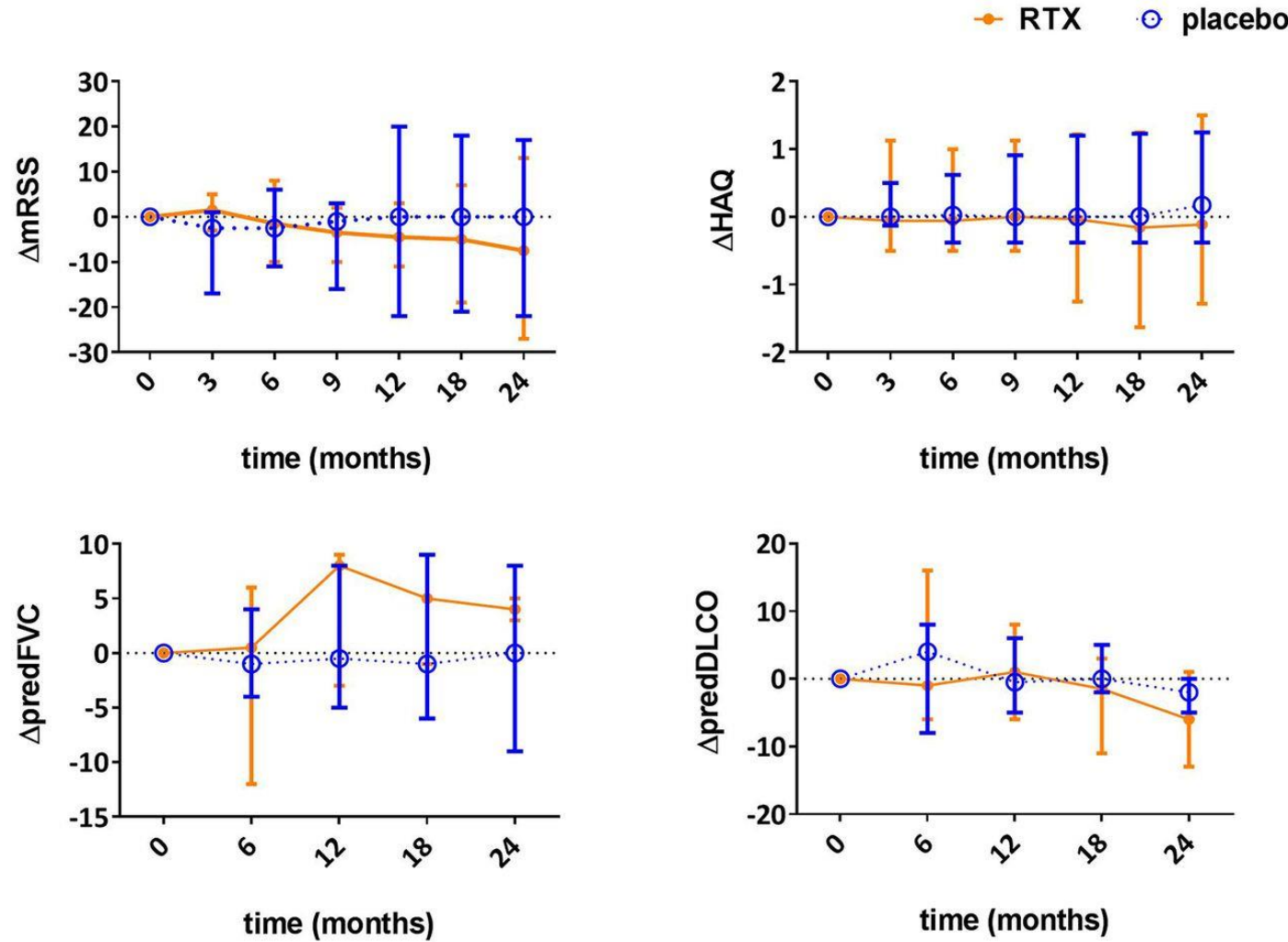
F



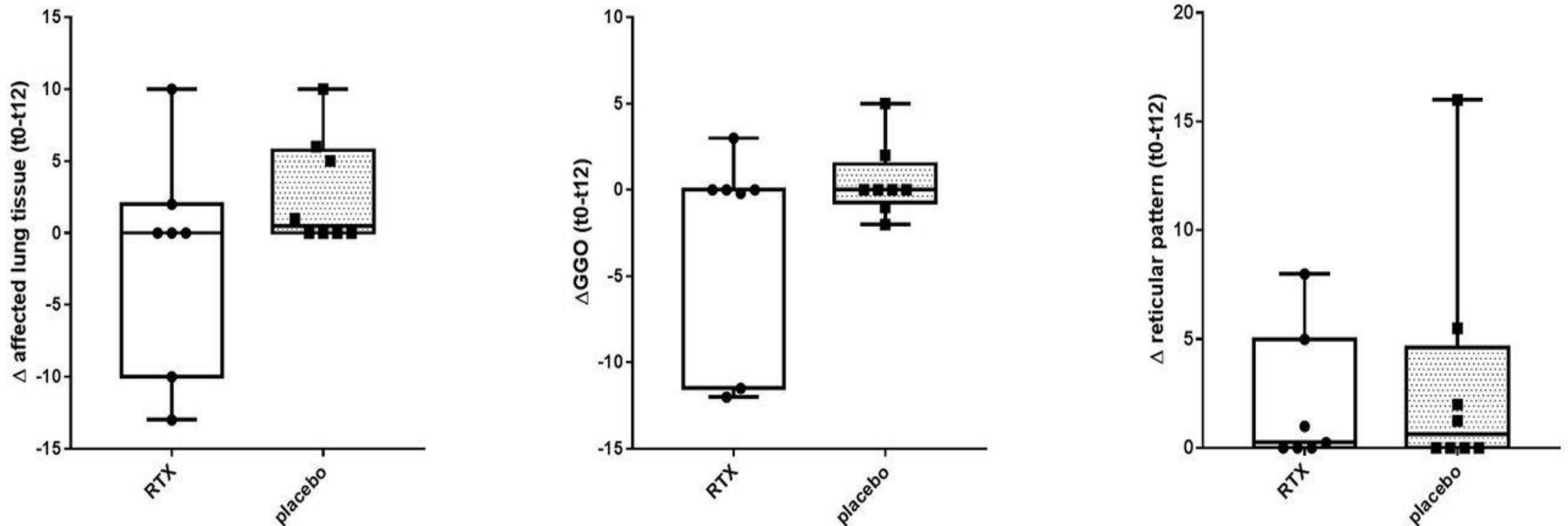
N=9; RTX (60.6±2.4 B vs. 61.3±4.1 FU; p=0.5) vs.
MC (60.9±2.8 B vs. 56.1±4.0 FU; p=0.02)

Jordan S, et al. Effects and safety of rituximab in systemic sclerosis: an analysis from the (EUSTAR) group. Ann Rheum Dis 2015

Change in modified Rodnan skin sore, forced vital capacity, diffusing capacity of the lung and HealthAssessment Questionnaire during 24-month follow-up in patients with systemic sclerosis treated with rituximab (RTX) or placebo



Change in mean extent of lung tissue and lung tissue with ground glass or reticular pattern involvement from baseline to 12 months follow-up in patients with systemic sclerosis. Vertical axis represent differences in Goh scores between baseline and 12 months for (from left to right): (1) mean extent of affected lung tissue, (2) GGO; mean extend of ground glass opacities, (3) mean extend of affected lung tissue with reticular pattern. At 12 months a non-significant trend in favour of rituximab was observed (mean change in lung involvement: -1.6% RTX group vs. +2.8% placebo group [p=0.28]).



Fresolimumab

MRSS	Baseline	15	26.9	24	8.6	22.5–31.2	
	Week 3	14	21	19	8.5	16.5–25.4	
	Week 7	14	20.6	18.5	9.2	15.8–25.4	
	Week 11	14	19.1	16.5	9.8	14.0–24.2	
	Week 17	12	18.3	13.5	11.2	12.0–24.6	
	Week 24	12	21.6	17.5	12.6	14.5–28.7	
Change	Week 3	14	–5.6	–6	3.8	–7.6 – –3.6	0.0002
	Week 7	14	–6.4	–5	6.4	–9.7 – –3.0	0.0032
	Week 11	14	–7.9	–6	6.1	–11.1 – –4.7	0.0005
	Week 17	12	–8.1	–9.5	6	–11.5 – –4.7	0.0024
	Week 24	12	–4.8	–5	7.2	–8.9 – –0.7	0.0508

Rice LM, et al. Fresolimumab treatment decreases biomarkers and improves clinical symptoms in systemic sclerosis patients. J Clin Invest 2015

Stem cell transplantation

- (ASSIST)/ (ASTIS) /(SCOT)
- HSCT was superior to cyclophosphamide therapy alone

Pirfenidone [19,20] NCT03221257	Antifibrotic and anti-inflammatory effects	ASCEND (IPF RCT), improved FVC and progression free survival in IPF; LOTUSS study for SSc-ILD
Nintedanib [18] NCT02597933	Inhibits receptor tyrosine kinases and nonreceptor tyrosine kinases	INPULSIS (IPF RCT), reduction in FVC decline; Phase III trial in progress in SSc-ILD
Tocilizumab [21]	mAb to IL-6 receptor	Phase II trial, trend towards improvement in mRSS at 48 weeks, trend towards slower decline in FVC
Rituximab [22,23]	mAb against CD20 on B-lymphocytes	Small randomized trials, less decline or improvement in FVC
Lysophosphatidic acid receptor antagonist, SAR100842 [24]	LPA ₁ receptor antagonist	Phase II trial, excellent safety profile
Autotaxin inhibitor (GLPG1690) [25]	Autotaxin inhibitor	Phase IIa trial in IPF, well tolerated
Fresolimumab [26]	mAb to TGF- β	Small open-label trial, improvement in mRSS and skin biomarkers
Haematopoietic stem cell transplant [27,28,29 [■]]	Lymphocyte ablation	ASSIST, improvement in FVC ASTIS, improved event-free and overall survival SCOT, improved event-free survival and less transplant-related mortality

Other treatment

- Management of GERD.
 - Prophylactic antibiotics in patients
 - Reporting frequent lower respiratory tract infections
 - Receiving long- term intensive immunosuppression
 - Vaccination for pneumococcal pneumonia, influenza and varicella
-
- Volkmann, E. R. Managing systemic sclerosis- related interstitial lung disease in the modern treatment era. *J. Scleroderma Relat. Disord.*(2017)

HRCT initial
After FVC reduction

Take home message

PFT
Bodybox
Dlco
HRCT
yearly

Maintenance
Cellcept
AZA
Rituximab

$FVC > 10\%$ decrease
 $DLCO > 15\%$
treatment

$FVC < 70$
HRCT GGO
First 5 years
treatment

Cellcept 2-3 gr
Rituximab

