Challenging topics in Rheumatoid Arthritis

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Για την σημερινή παρουσίαση δεν υπάρχει σύγκρουση συμφερόντων

Presentation outlines

- ❑ Tapering of cDMARDs / bDMARDs in RA patients on LDA /remission. What we know so far?
- ❑ Can we use LUS in our clinical practice for identifying asymptomatic RA-ILD patients ?
- ❑ D2T RA , how to identify patients at risk ? how to manage them promptly

Clinical case

- 55 years old male , 5 years history of Seropositive , CCP (+) RA
- Comorbidities : A.H, past smoking history, high BMI=35 Kg/m²
- Initially treated with Methotrexate 20 mg /week and soon after ETN 40 mg/week was added
- 12 months after ETN initiation had already LDA with DAS 28 CRP =2.9
- 2 years after diagnosis Methotrexate was stopped
- He was constantly on LDA with ETN monotherapy

Clinical case

- In the last assessment also in LDA
- Asking for ETN discontinuation
- After discussion we agreed to spacing ETN every 10 days
- In the next 6 months on LDA
- After that the ETN was fixed every 14 days
- In the next 12 months also LDA , but then he contacted us for probable relapse

Clinical case

- In the assessment MDA with mild elevation of CRP
- After discussion- reintroduction ETN every week
- 3 months after that again on LDA
- Agreement to stay in this dose regime

Main questions from patients

- ‘For how long do I have to take this treatment?’
- and once RA is well-controlled, ‘Can I stop my medication now that I am doing better?’

Main issues for Rheumatologists

- With a higher potential of achieving remission using advanced therapies like biologics and targeted synthetic DMARDs (bDMARD/ tsDMARDs), the focus is slowly shifting towards maintaining remission while balancing the long-term risks of immunosuppression.
- Rheumatologists were generally open to tapering (not stopping), though sometimes only when requested by their patients

1. Hazlewood GS, et al. Rheumatology 2022
2. Tarun Sharma et al. Rheumatology 2023

Guidelines

eular EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

11.	After glucocorticoids have been discontinued and a patient is in sustained remission, dose reduction of DMARDs (bDMARDs/tsDMARDs* and/or csDMARDs) may be considered.	1b	A	9.3±1.1	89

1. Tapering of DMARDs should only be started if a patient is in persistent stringent (ACR-EULAR) remission for at least 6 months, although more data may be needed to determine the lowest level of disease activity that provides a good prediction for maintenance of a good state. Finally, it was noted that tapering trials were very heterogeneous

2. Evidence has emerged indicating that there was no difference in clinical outcome when either a bDMARD or csDMARD was tapered first.

3. It had previously been suggested to start with a reduction of bDMARDs because of the costs involved. However, an economic analysis has revealed that the total costs of tapering csDMARDs first vs tapering anti-TNFs first did not differ.

1. Smolen JS, et al. Ann Rheum Dis 2023
2. van Mulligen E, et al. Ann Rheum Dis 2020

Guidelines

eular EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

11.	After glucocorticoids have been discontinued and a patient is in sustained remission, dose reduction of DMARDs (bDMARDs/tsDMARDs* and/or csDMARDs) may be considered.	1b	A	9.3±1.1	89

1. There is no preferred tapering sequence and this can be left to the discretion of patients and rheumatologists in a shared decision.
2. Either dose reduction or interval increase ('spacing') is preferred, but completely stopping may not be advisable.
3. Importantly, though, there is also compelling evidence that stopping bDMARDs and/or csDMARDs will ultimately lead to flares in most patients
4. Of note, most (though not all) patients who flare after dose reduction can be brought back into a good disease state after reintroduction of the original dose.

1. Smolen JS, et al. Ann Rheum Dis 2023
2. Emery P, et al.. Ann Rheum Dis 2015
3. Aguilar-Lozano L, et al. J Rheumatol 2013
4. Smolen JS, et al. Lancet 2013

Guidelines

AMERICAN COLLEGE of RHEUMATOLOGY

Table 5. Tapering disease-modifying antirheumatic drugs (DMARDs)*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
Continuation of all DMARDs at their current dose is **conditionally** recommended over a dose reduction of a DMARD.	Low	PICO 54.a	p. 381
Dose reduction is **conditionally** recommended over gradual discontinuation of a DMARD.	Low	PICO 52.C2 and PICO 53. C2	p. 351–5, p. 372–6
Gradual discontinuation is **conditionally** recommended over abrupt discontinuation of a DMARD.	Low	PICO 52.C1 and PICO 53.C1	p. 351, 372
Gradual discontinuation of sulfasalazine is **conditionally** recommended over gradual discontinuation of hydroxychloroquine for patients taking triple therapy who wish to discontinue a DMARD.	Very low	PICO 58	p. 400
Gradual discontinuation of methotrexate is **conditionally** recommended over gradual discontinuation of the bDMARD or tsDMARD for patients taking methotrexate plus a bDMARD or tsDMARD who wish to discontinue a DMARD.	Very low	PICO 59.C1	p. 401

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; bDMARD = biologic DMARD; tsDMARD = targeted synthetic DMARD.

Liana Fraenkel et al. Arthritis Care & Research Vol. 73, No. 7, July 2021

A real-world 2-year prospective study of medication tapering in patients with well-controlled rheumatoid arthritis within the rheumatoid arthritis medication tapering (RHEUMTAP) cohort

Mohamed Tageldin[1], Nicole Wilson[2], Yue Yin[3], Tarun S. Sharma [1,*]

The RHEUMTAP cohort included 131 patients that met eligibility criteria, of which 52 patients underwent a medication taper.

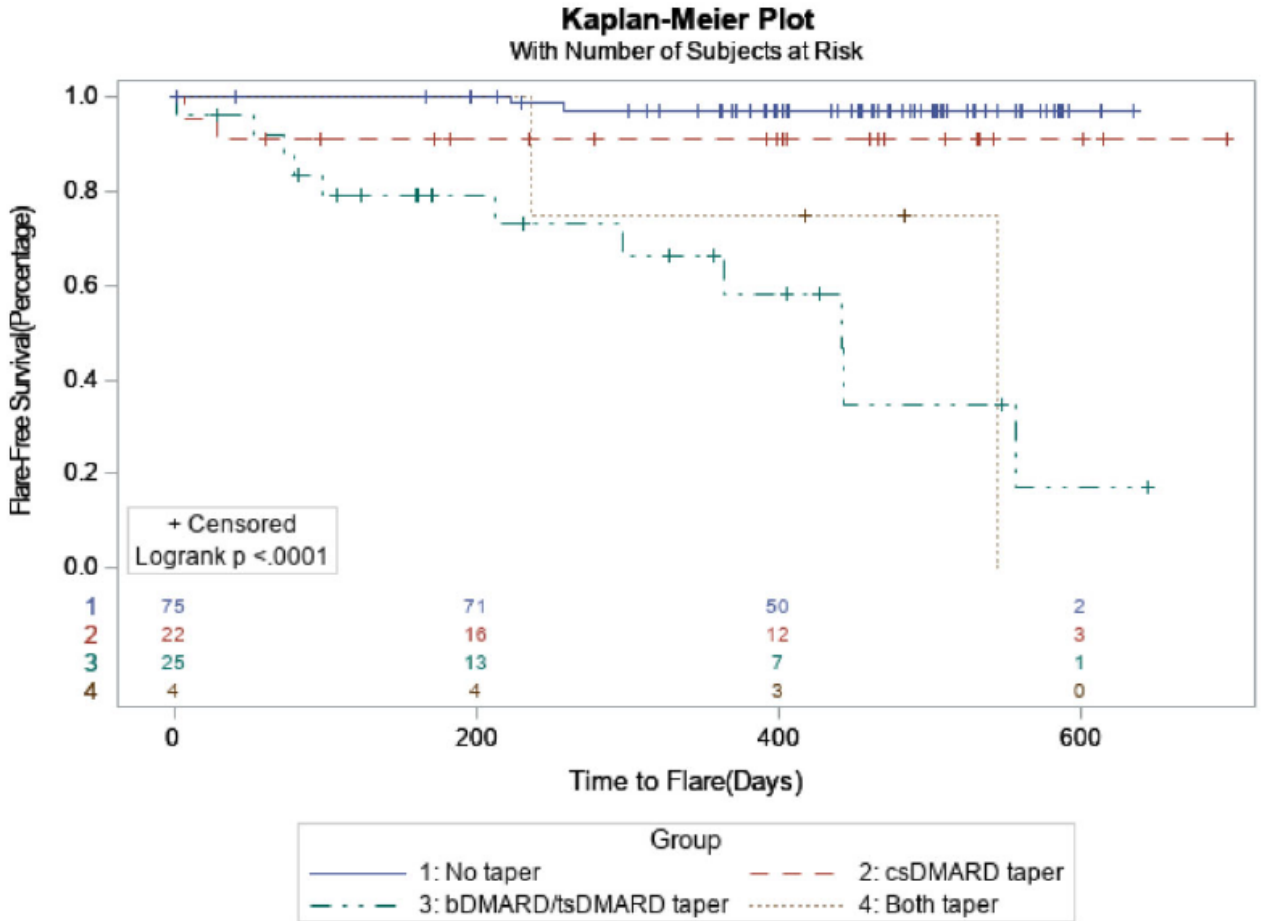


Figure 1. Kaplan–Meier flare-free survival curve. Survival analyses showing flare-free survival of patients with well-controlled rheumatoid arthritis in four groups: no-taper group, csDMARD taper, bDMARD/tsDMARD taper, and both csDMARD and bDMARD/tsDMARD taper. csDMARD: conventional synthetic DMARD; bDMARD/tsDMARD: biologic or targeted synthetic DMARD

Table 2. Proportion of flares after tapering in three taper groups compared with no-taper group

	All tapers/stops, HR (95% CI)	*P* value	Only tapers while on background therapy, HR (95% CI)	*P* value	Only stops, HR (95% CI)	*P* value
csDMARD taper *vs* no taper	5.32 (0.57–49.84)	0.1434	5.32 (0.57– 49.84)	0.1434	4.63 (0.38–57.04)	0.2315
bDMARD/tsDMARD taper *vs* no taper	31.43 (6.35–155.55)	<0.0001	29.09 (5.62–150.73)	<0.0001	28.66 (4.90–167.83)	0.0002
Both csDMARD and bDMARD/tsDMARD taper *vs* no taper	18.45 (2.55–133.37)	0.0039	18.45 (2.55–133.37)	0.0039	11.68 (1.00–136.56)	0.0501
csDMARD taper *vs* bDMARD/tsDMARD taper	0.09 (0.01–0.69)	0.0213	0.09 (0.01–0.80)	0.0304	0.10 (0.01–1.04)	0.0534

csDMARD: conventional synthetic DMARD; bDMARD/tsDMARD: biologic or targeted synthetic DMARD; HR: hazard ratio.

Rheumatology key messages

- Patients with stable RA who tapered/stopped their bDMARD/tsDMARD were at high risk of flare.
- Patients tapering only csDMARD had a lower risk of flare than patients tapering bDMARD/tsDMARD.
- All patients who flared regained remission within an average of 2.5 months.

Bertsias *et al. Arthritis Research & Therapy* (2022) 24:132
https://doi.org/10.1186/s13075-022-02826-6

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Rheumatoid arthritis patients initiating rituximab with low number of previous bDMARDs failures may effectively reduce rituximab dose and experience fewer serious adverse events than patients on full dose: a 5-year cohort study

Antonios Bertsias[1†], Nestor Avgoustidis[1†], Ioannis Papalopoulos[1], Argyro Repa[1], Nikolaos Kougkas[1], Eleni Kalogiannaki[1], Georgios Bertsias[1,2], Irini Flouri[1] and Prodromos Sidiropoulos[1,2*]

Results: Out of 361 patients / 81 patients (22.4%) entered LD in a median time of 24 months (95% CI 18–30 months).

- Seropositivity (OR 1.823)
- Less than 2 previous b-DMARDs failures (OR 1.259)
- DAS28 < 4.88 at 6 months (OR 2.329) predicted the odds of entering LD ($p < 0.05$ for all).
- During 60 months of follow-up, only 7.5% of patients on LD relapsed.

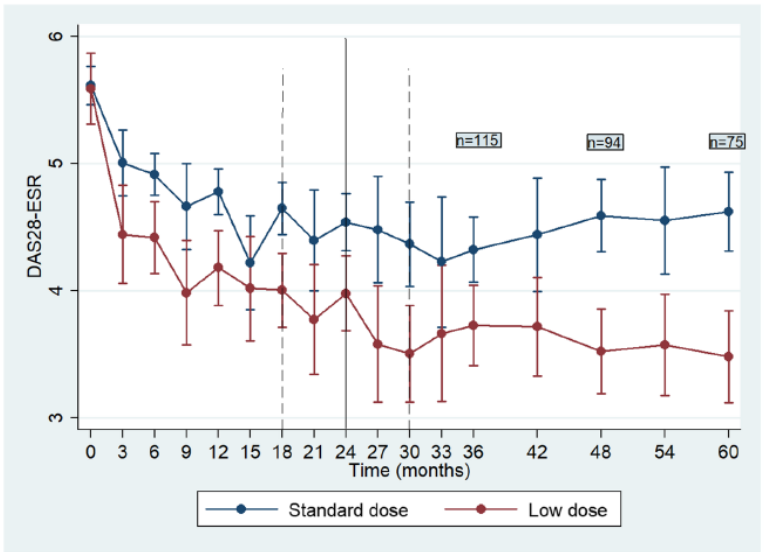


Fig. 1 Linear mixed model predictions of DAS28-ESR score according to rituximab dosing group

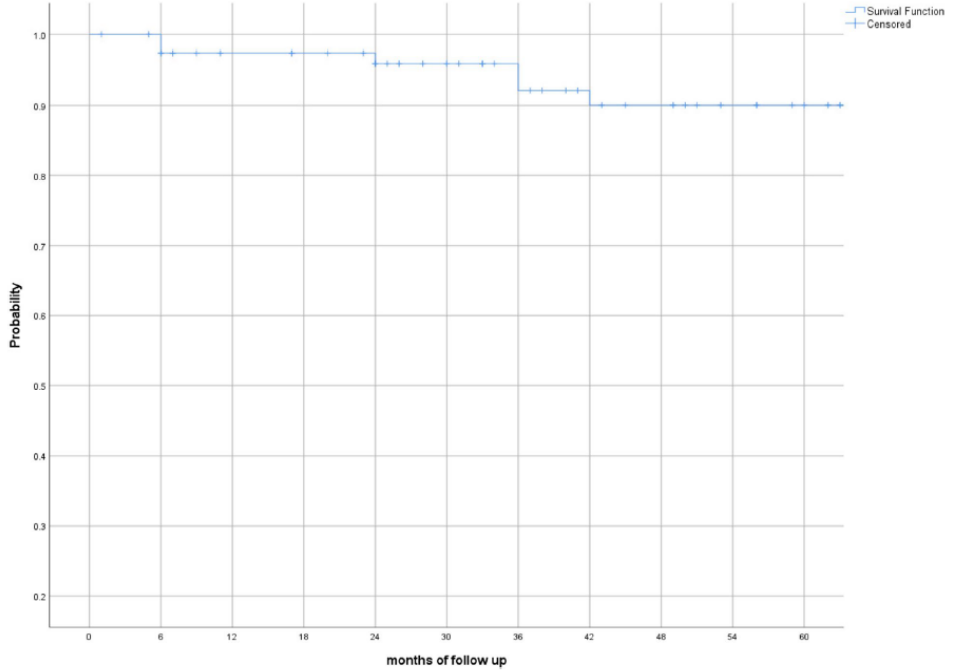


Fig. 2 Survival plot of flare probability within the low dose group

Table 5 Comparison of incidence rates of adverse events (events per 1000 person-years) for all patients and by dose group

	All patients	Standard dose	Low dose	*p* value
Total person-months of follow-up	12,111	4824	7287	
Number of adverse events (moderate and serious)	735	509	226	
Incidence rate for adverse events	5.07	5.82	3.90	< 0.0001
Number of serious adverse events	182	137	45	
Incidence rate of serious adverse events (grade IV–VI)	1.25	1.57	0.77	< 0.0001
Number of serious infections	103	75	28	
Incidence rate of serious infections	0.72	0.88	0.49	0.0026
Number of all hospitalizations	125	94	31	
Incidence rate for hospitalizations	0.86	1.08	0.53	0.0002
Number of incident cancer cases	12	8	4	
Incidence rate for cancer diagnosis	0.08	0.09	0.07	0.6719
Number of incident deaths	14	11	3	
Incidence rate for death	0.14	0.18	0.08	0.0994

Practical considerations

- Shared decision with patient
- Tapering of c/b/ts-DMARDs should only be started if a patient is in persistent stringent-deep (ACR-EULAR) remission for at least 6 months or even more.
- LDA is not acceptable state for tapering initiation
- Completely stopping is not advisable
- No clear evidence of which DMARD must be tapered first, but ACR suggest c-DMARD as b-DMARD was added later on when c-DMARD failed to lead on LDA/remission

Practical considerations

- Tapering should be conducted “slowly” and “carefully”, after having informed the patients of the risk of flares
- For c-DMARD gradually reduced the dose and then stopping
- For biologics mixed patterns of tapering are available, spacing or dose reduction
- The majority of patients on b-DMARD tapering will relapse .

Clinical case

- 62 years old female with history of Seropositive RA with high titers of RF & anti-CCP
- RF=252, anti-CCP= 1020
- Duration of RA = 4 years , no smoking history , A.H, Dyslipidemia
- On Methotrexate 20 mg/week , but on HDA , SJC=5, TJC=7, VAS=60, ESR:50 , DAS28(ESR): 5.69
- No symptoms from respiratory tract , no cough no exertional dyspnea
- From chest auscultation = subtle crackles in both lung bases , (-) Velcro

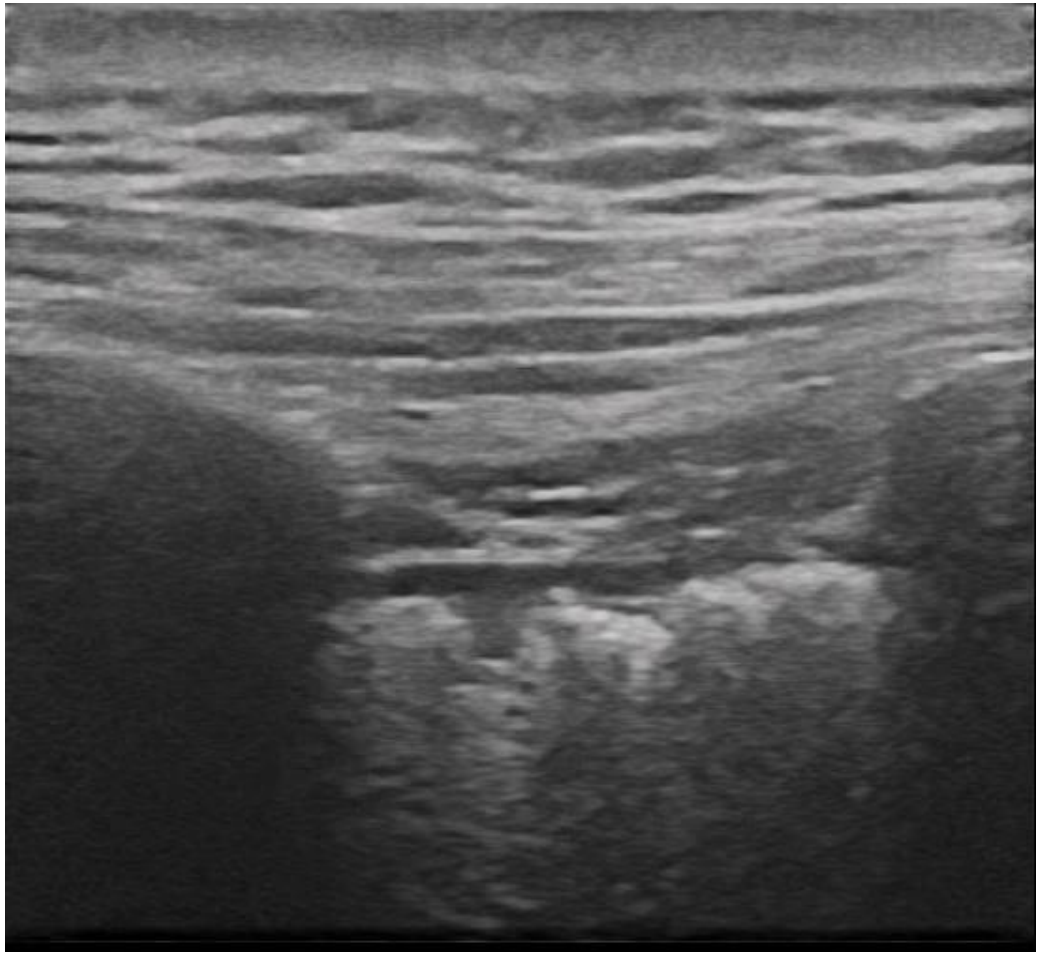
Which are the risk factors for RA-ILD in our patient ?

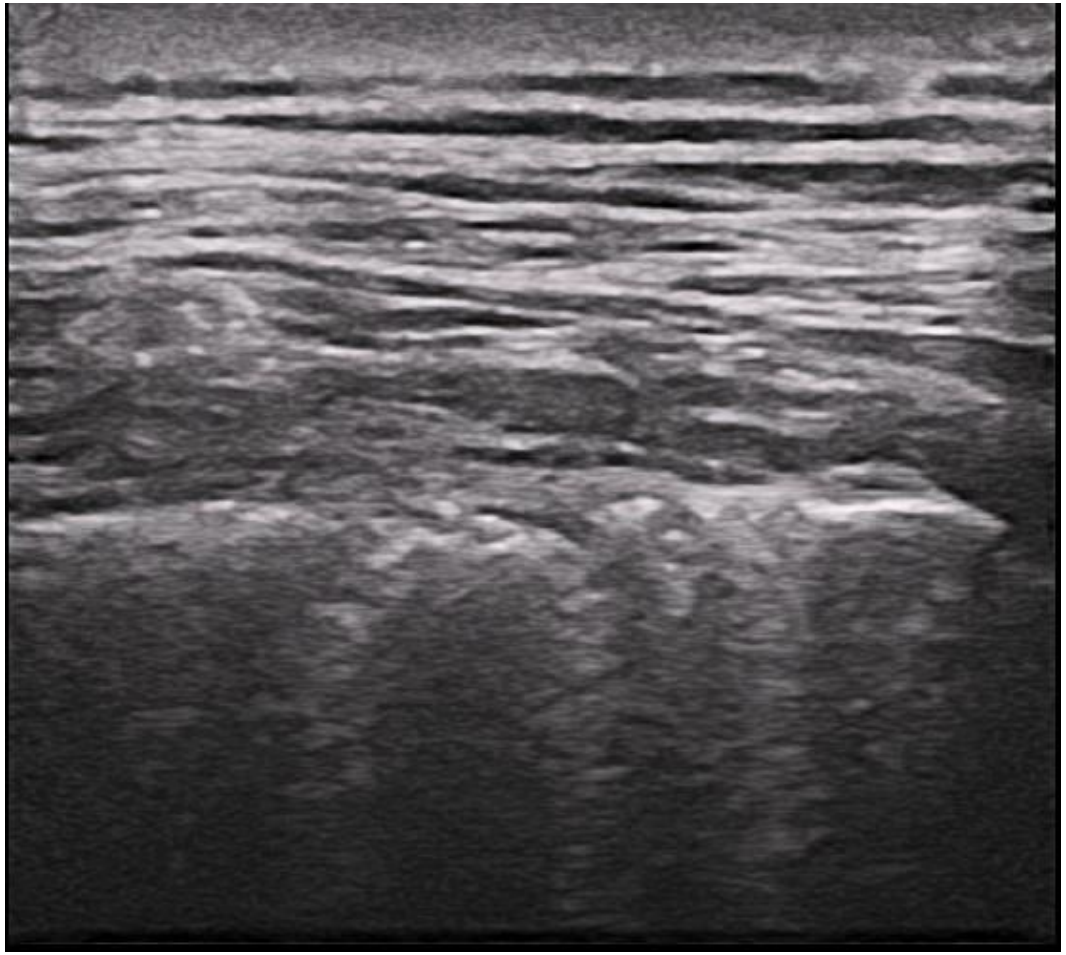
Risk Factor
Age ≥ 60 y[a]
Male sex
Past or current tobacco use[a]
RA duration ≥ 10 y[b]
Positive RF[a]
Positive anti-CCP antibodies[b]
DAS-28 ≥ 4.3[b]

Risk Factor
Age ≥ 60 y[a]
Male sex
Past or current tobacco use[a]
RA duration ≥ 10 y[b]
Positive RF[a]
Positive anti-CCP antibodies[b]
DAS-28 ≥ 4.3[b]

Otaola M et al. Chest. 2024 Dec 13:S0012-3692(24)05622-8.

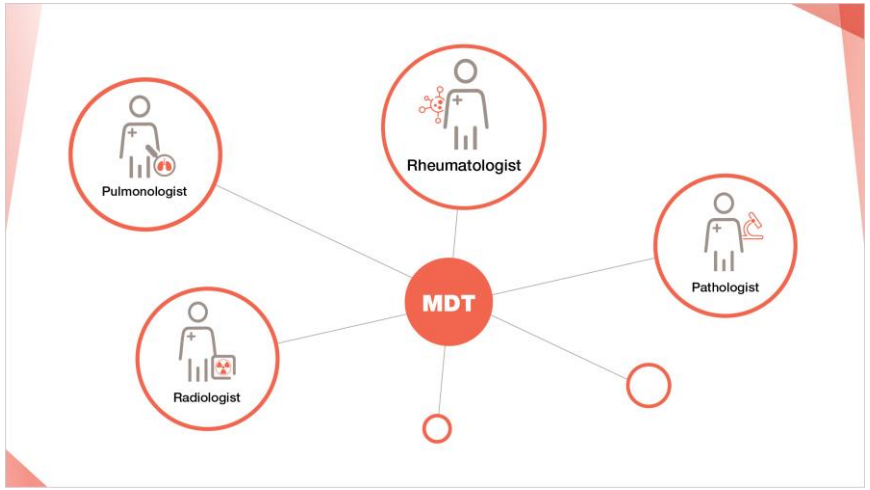
Irregular and fragmented pleural line . Linear probe , frequency 10 MHz





Clinical case

- HRCT confirm the diagnosis of RA-ILD with UIP pattern
- PFTs : FVC =88, DLCO=67
- After shared decision with patient add on ABT 125 mg /week and 2 months course of steroids
- Close monitoring for progression of ILD in cooperation with chest physicians



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Guideline Summary 2023

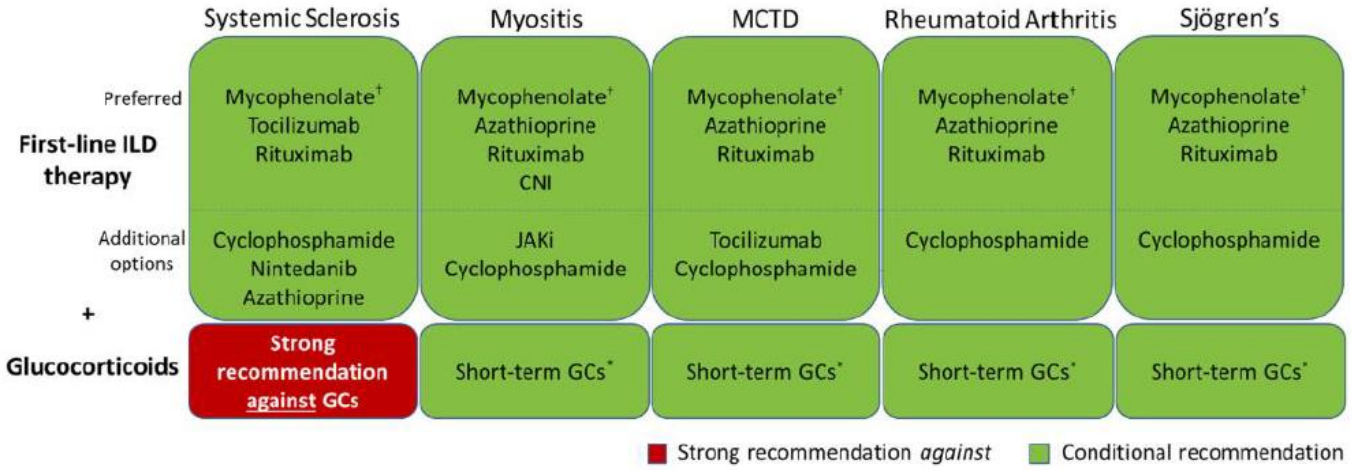
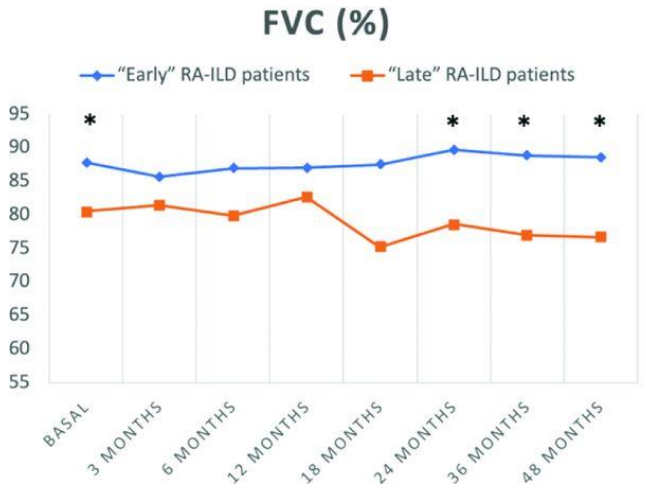


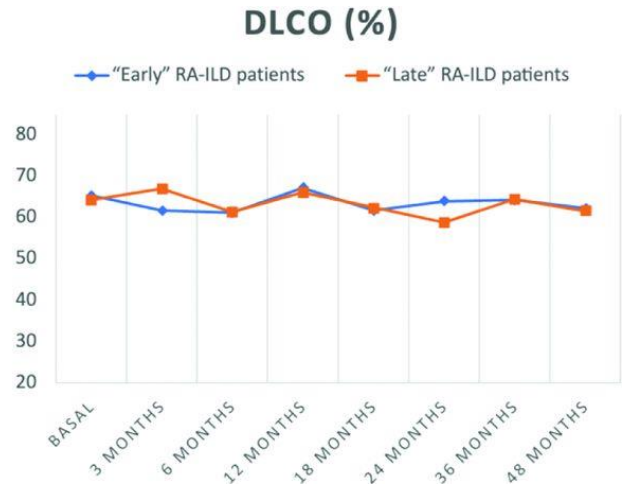
Figure 1: Initial treatment options for the treatment of interstitial lung disease associated with systemic autoimmune rheumatic diseases of interest.
* Decisions on GC dose and use of oral versus intravenous therapy depend on severity of disease. GCs should be used cautiously in patients with MCTD with a systemic sclerosis phenotype who may be at increased risk of renal crisis.
† Treatments are listed in order based on a hierarchy established by head-to-head votes, although the panel noted that decisions on which first-line therapy to use were dependent on specific situations and patient factors. In all diseases, mycophenolate was conditionally recommended over the other listed therapies. Therapies here are divided into "preferred" options and "additional options" based on the rank-order hierarchy.
MCTD = mixed connective tissue disease; GCs = glucocorticoids; CNI = calcineurin inhibitor; JAKi = janus kinase inhibitor

POS0689 WINDOW OF OPPORTUNITY IN THE TREATMENT OF RHEUMATOID ARTHRITIS-INTERSTITIAL LUNG DISEASE WITH ABATACEPT. NATIONAL MULTICENTER STUDY OF 526 PATIENTS

Results: A total of 216 patients were included in the "early" group and 165 patients in the "late" group

	All RA-ILD patients (n=526)	"Early" RA-ILD (n=216)	"Late" RA-ILD (n=165)	"Early" vs "Late" p
Age years mean±SD	66 ± 10	66 ± 9	66 ± 10	0.79
Women n (%)	292 (56)	98 (45)	91 (55)	0.91
Smoker ever, n (%)	280 (53)	117 (54)	85 (52)	0.61
ILD duration up to ABA, months, median [IQR]	9 (2-36)	2 (1-4)	52 (36-90)	**<0.001**
RF n (%); ACPA n (%)	459 (87); 451 (86)	187 (87); 185 (86)	146 (88); 140 (86)	0.58; 0.96
DAS28-ESR	4.44 ± 2.13	4.14 ± 1.55	4.43 ± 1.64	0.13
ILD pattern n (%)				
NIU	237 (46)	100 (47)	71 (44)	0.73
NINE	153 (29)	63 (30)	49 (30)	
FVC (% of the predicted) mean±SD	86 ± 22	88 ± 23	81 ± 19	**0.003**
DLCO (% of the predicted) mean±SD	66 ± 20	65 ± 19	64 ± 21	0.66
ABA monotherapy n (%)	232 (45)	101 (47)	73 (45)	0.56
ABA combined n (%)	282 (54)	112 (53)	90 (55)	
Prednisone at baseline, mg/day, median [IQR]	5 (5-10)	7.5 (5-10)	5 (5-10)	0.32
Previous immunosuppressive therapy n (%)				
MTX	394 (75)	172 (80)	118 (72)	0.05
Leflunomide	244 (46)	93 (43)	77 (47)	0.48
Sulfasalazine	72 (14)	27 (13)	23 (14)	0.66
Hydroxychloroquine	164 (31)	70 (33)	52 (32)	0.83
Anti-TNF drugs (IFX; ADA; ETA)	42 (8); 70 (13); 75 (14)	14 (6); 37 (17); 31 (14)	13 (8); 18 (11); 25 (15)	0.59; 0.08; 0.83
Rituximab	64 (12)	21 (10)	23 (14)	0.20
Tocilizumab	56 (10)	26 (12)	18 (11)	0.73





Conclusion: Treatment with ABA at any time of the course in the ILD seems to prevent interstitial lung progression. However, our results suggest that the same treatment (ABA) prescribed early in RA-ILD, may be preferable to preserve lung function ("window of opportunity").

https://doi.org/10.1136/annrheumdis-2024-eular.6222

ILD and Rheumatic Diseases

EUROPEAN RESPIRATORY REVIEW
REVIEW
G.M. JOY ET AL.

Prevalence, imaging patterns and risk factors of interstitial lung disease in connective tissue disease: a systematic review and meta-analysis

Greta M. Joy[1], Omri A. Arbiv[1], Carmen K. Wong[1], Stacey D. Lok[2], Nicola A. Adderley[3], Krzysztof M. Dobosz[1], Kerri A. Johannson[3] and Christopher J. Ryerson[1,4]

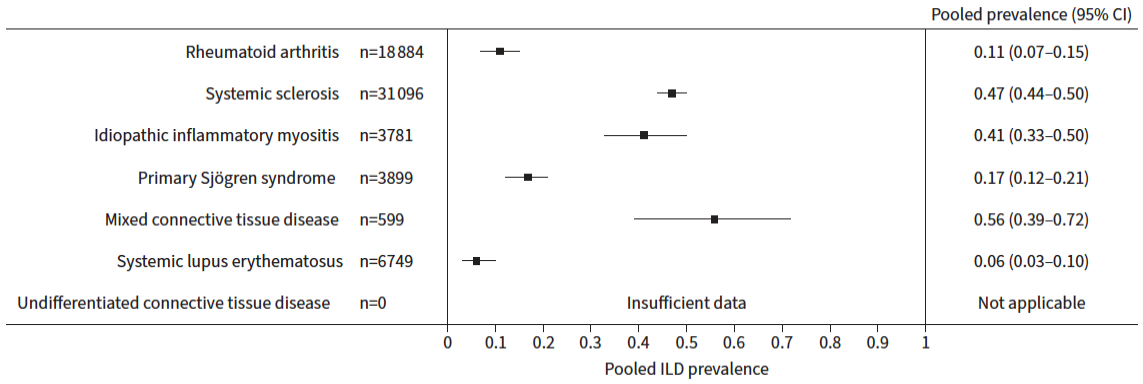
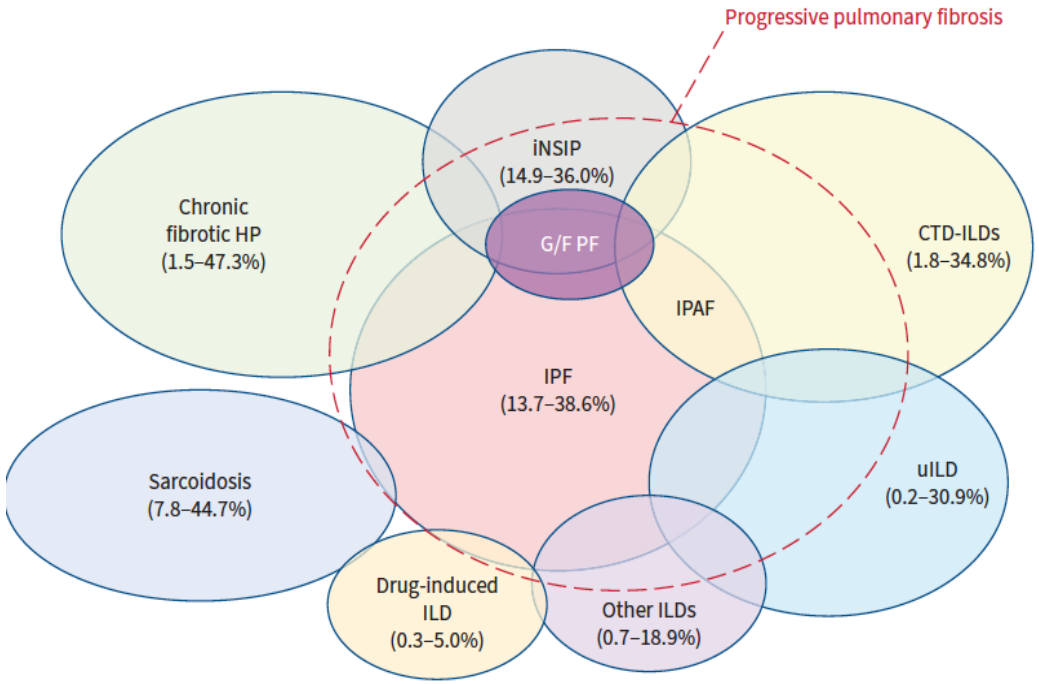


FIGURE 2 Pooled prevalence of interstitial lung disease (ILD) in patients with connective tissue disease.



Rajan SK, Cottin V, Dhar R, et al. Eur Respir J 2023

RA and ILD

ILD per se is associated:

- with poor prognosis and increased mortality
- it is currently considered the second cause of death in patients with RA after cardiovascular disease

need for early diagnosis

1. Robles-Pérez A , et al. Sci Rep 10.(2020)
2. Kakutani T, et al. Mod Rheumatol.(2019)

TABLE 2 Risk factors for the progression of non-idiopathic pulmonary fibrosis interstitial lung diseases (ILDs)

Risk factor	First author (year) [ref.]	Hazard ratio (95% CI)	p-value
General risk factors			
UIP	Flaherty (2019) [2]	1.53 (−0.68–3.74)	NA
BMI	Alakhras (2007) [19]	0.93 (0.89–0.97)	0.002
Oxygen desaturation during 6MWT[#]	Alfieri (2020) [20]	OR[¶] 8.7 (4.42–17.3)	NA
Disease			
Fibrotic hypersensitivity pneumonitis	Gimenez (2018) [21]		
Decline in FVC by ⩾10%	Gimenez (2018) [21]	4.13 (1.96–8.70)	0.005
Lower baseline FVC %	Gimenez (2018) [21]	1.03 (1.01–1.05)	0.003
Antigen identification	Gimenez (2018) [21]	0.18 (0.04–0.77)	0.021
MUC5B[+]/*TLD*[+] (gene variants)	Ley (2019) [22]	3.52 (1.87–6.62)	0.00009
Rheumatoid arthritis-ILD	Zamora-Legoff (2017) [9]		
UIP *versus* NSIP	Zamora-Legoff (2017) [9]	3.29 (1.28–8.41)	0.013
High levels of CCP antibody/anti-CCP2 titres[+]	Khan (2021) [23]	1.05 (1.01–1.10)	0.01
Smoking, 30 pack-years	Kronzer (2021) [24]	OR[¶] 6.06 (2.72–13.5)	NA
Fibrotic score on HRCT	Solomon (2016) [25]	1.02 (1.01–1.03)	0.0002
Extent of fibrosis on HRCT	Solomon (2016) [25]	1.12 (1.08–1.17)	<0.000006
Systemic sclerosis	Goh (2017) [26]		
Low baseline FVC <65% and low baseline D_{LCO} ⩽55%	Sánchez-Cano (2018) [27]; Hoffmann-Vold (2019) [28]	OR[¶] 1.02 (1.01–1.03)	<0.001
Decline in D_{LCO} >15%	Le Gouellec (2017) [29]	2.03 (1.25–3.29)	<0.005
Decline in K_{CO} >10%	Goh (2017) [26]	2.35 (1.40–3.95)	<0.001
Fibrotic score on HRCT	Ibrahim (2020) [30]	2.52 (1.16–5.49)	0.02
Extent of fibrosis on HRCT (HRCT extent 10–30% and FVC <70%)	Goh (2008) [31]	3.46 (2.19–5.46)	<0.0005

UIP: usual interstitial pneumonia; BMI: body mass index; 6MWT: 6-min walk test; NA: not available; FVC: forced vital capacity; NSIP: non-specific interstitial pneumonia; CCP: cyclic citrullinated peptide; HRCT: high-resolution computed tomography; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient of the lung for carbon monoxide. [#]: 6MWT correlates to some extent with D_{LCO} levels, but should not be strictly viewed as a surrogate marker [32]; [¶]: hazard ratio for the risk factor was not available in the literature; hence, odds ratio was considered; [+]: usefulness of assessing anti-citrullinated peptide antibody levels merits future research as this study was done only in women.

Rajan SK, Cottin V, Dhar R, et al. Eur Respir J 2023

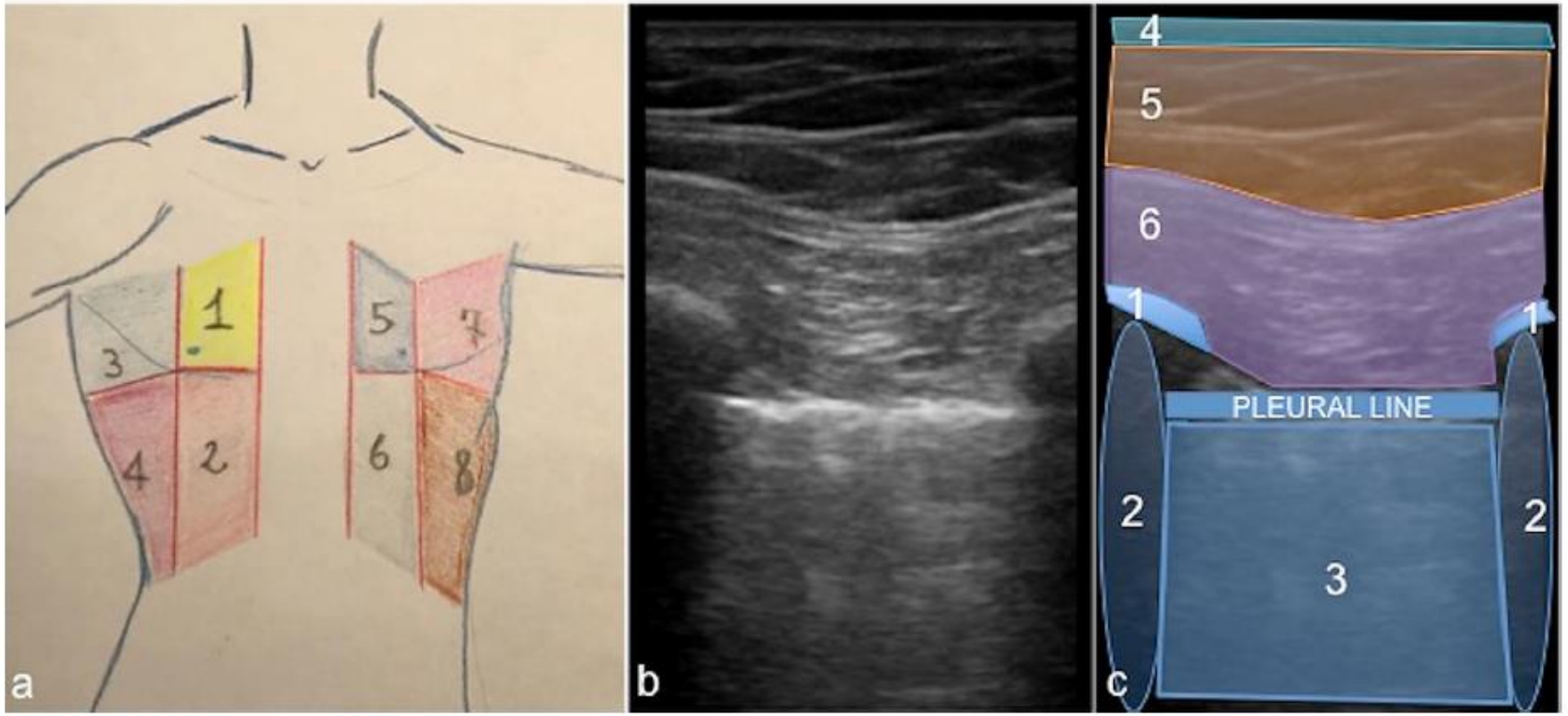


Fig. 1 Schematic representation of the chest ultrasound zone (**a**) and chest ultrasound examination performed with a high-frequency linear probe (15–7 MHz) (**b**, **c**). 8 zones of the chest—4 on each side (2 anterior and 2 lateral) (**a**): the anterior zones (1, 2, 5, 6) are delimited medially by the hemi-clavicular line and laterally by the anterior axillary line whereas the lateral ones (3, 4, 7, 8) are included between the anterior and posterior axillary lines. The sub-mammary line divides the upper and lower zones. Thoracic anatomy, longitudinal view acquired with linear probe (**b**), and schematic representation (**c**): there is a good anatomical definition of the pleural hyperechoic reflection (pleural line, **c**) between the two ribs (**c**, 1) and their shadow cone artifacts (**c**, 2). They outline an area of sub-pleural pulmonary artifacts (**c**, 3). The cutaneous (**c**, 4), subcutaneous (**c**, 5) and muscular planes (**c**, 6) are well represented

Marco Di Serafino et al. La radiologia medica (2020)

Normal signs

1. Pleural line
2. “Bat sign”
3. A - Lines
4. Lung sliding

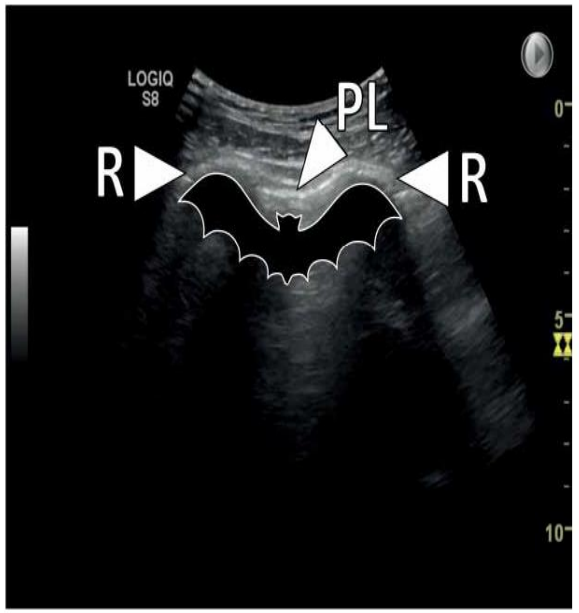
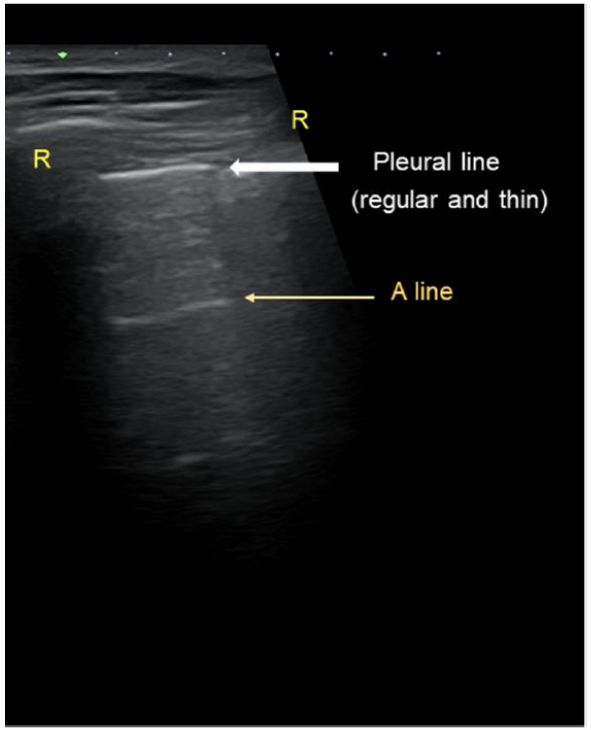


Figure 3. Identification of the “bat sign” is performed to identify the pleural line (PL) as being placed just below the two ribs (R). The ribs with posterior shadowing represent the bat’s wings and the pleural line represents the head of the bat.



Laursen CB, et al. Thoracic Ultrasound. ERS 2018
Vicente-Rabaneda EF , et al. Clinical Rheumatology (2021)

Abnormal signs:

Interstitial Syndrome

1. B - Lines
2. pleural line thickening
3. pleural line fragmentation/irregularity
4. sub-pleural nodules-consolidations

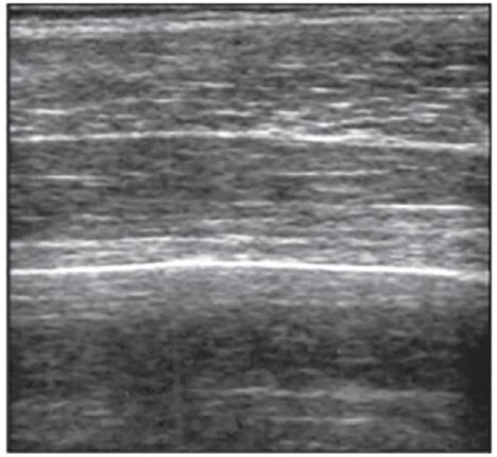


Fig. 2. LUS (linear scanner) from a healthy woman showing a normal, smooth echoic pleural line without any artifacts (42).

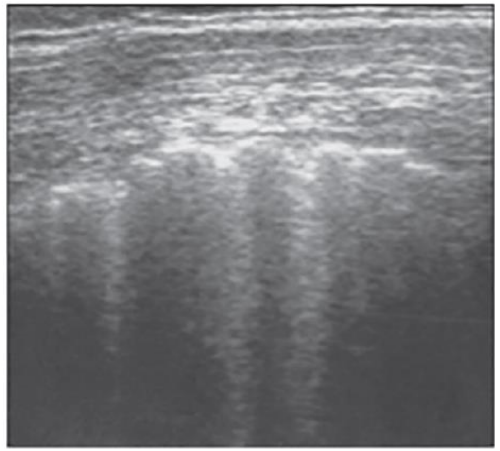
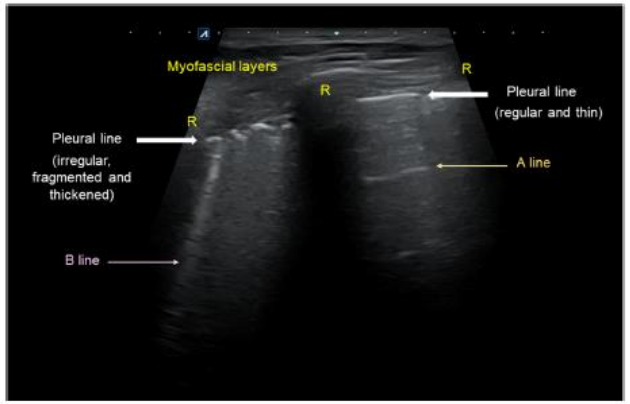


Fig. 3. LUS (linear scanner) from an ILD patient showing an irregular, fragmented and thickened pleural line and B-lines (42).

Fig. 2 LUS of interstitial lung disease This figure illustrates the characteristic LUS findings of a patient with an early interstitial lung disease in the lung intercostal space (LIS) on the left of the image: (a) irregular, fragmented, and thickened pleural line and (b) B line, which is the vertical laser beam-like artifact that arises from the pleural line and reaches the end of the screen, erasing A lines. The LIS on the right side of the image shows the typical normal LUS pattern with a thin regular pleural line and the horizontal artifacts called A lines. R, ribs



Esther F. Vicente-Rabaneda et al. Clinical Rheumatology (2021)

Lacedonia, D. et al. Diagnostics 2021
F. Ferro, A. Delle Sedie. Clin Exp Rheumatol 2018.

Clinical integration of the results is extremely important

B-lines due to cardiogenic pulmonary edema :

1. are usually bilateral
2. start appearing in the dependent zones
3. usually diffusing or recovering symmetrically.

B-lines due to pulmonary fibrosis generally:

1. start at the posterior lung basis
2. often associated with irregularity of the pleural line and subpleural small consolidations

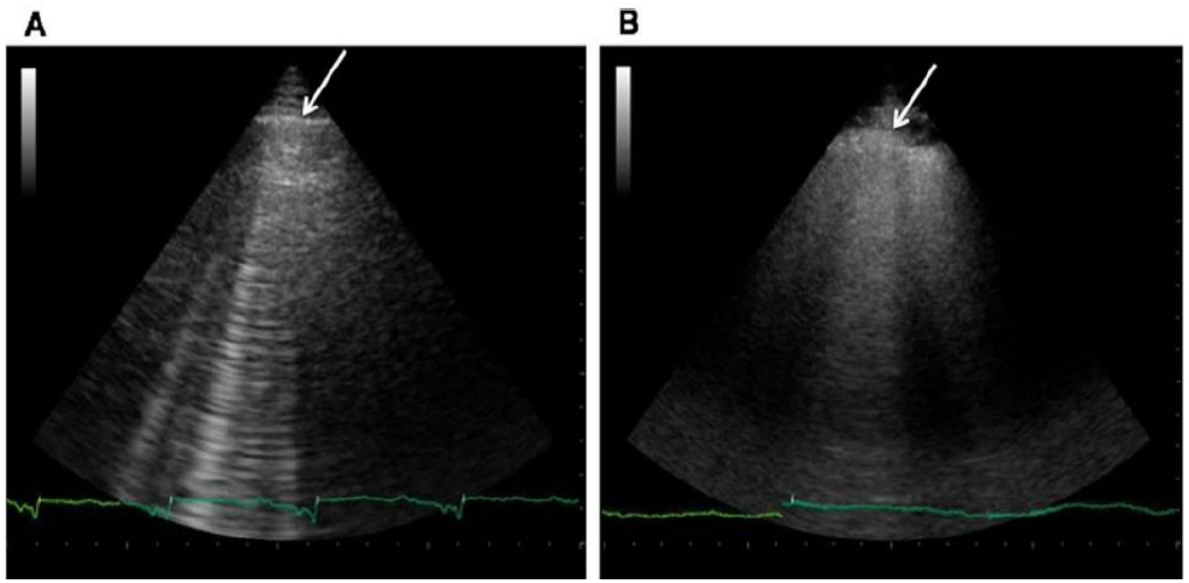


Figure 11 Multiple B-lines in cardiogenic pulmonary edema and lung fibrosis. A. Multiple B-lines in a patient with cardiogenic pulmonary edema: the arrow indicates a normal pleural line. **B.** Multiple B-lines in a patient with pulmonary fibrosis: the arrow indicates the abnormal pleural line, which looks irregular.

Gargani and Volpicelli *Cardiovascular Ultrasound* 2014,

Pleural irregularities

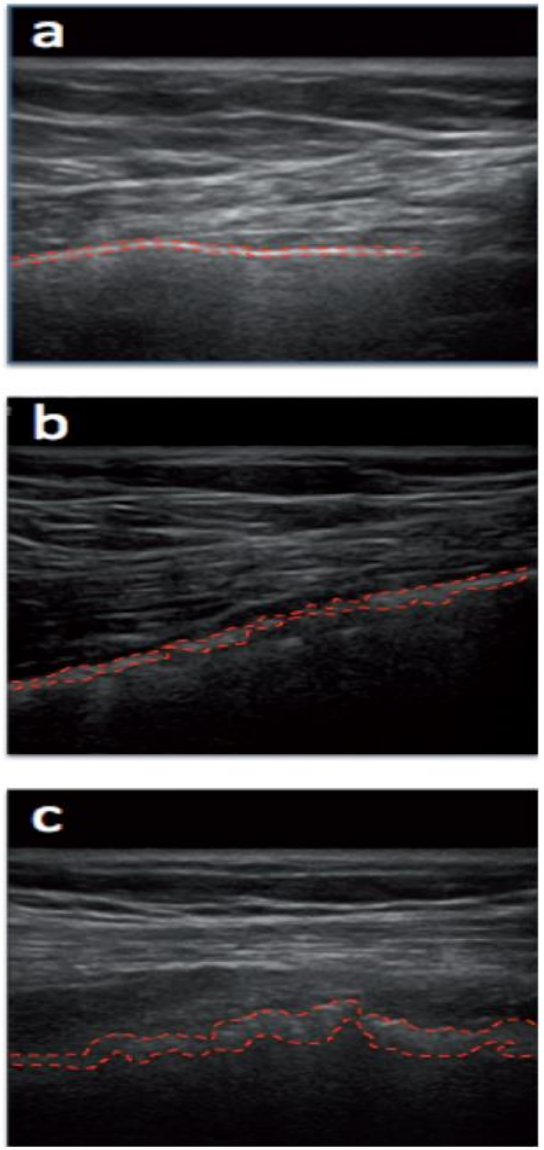
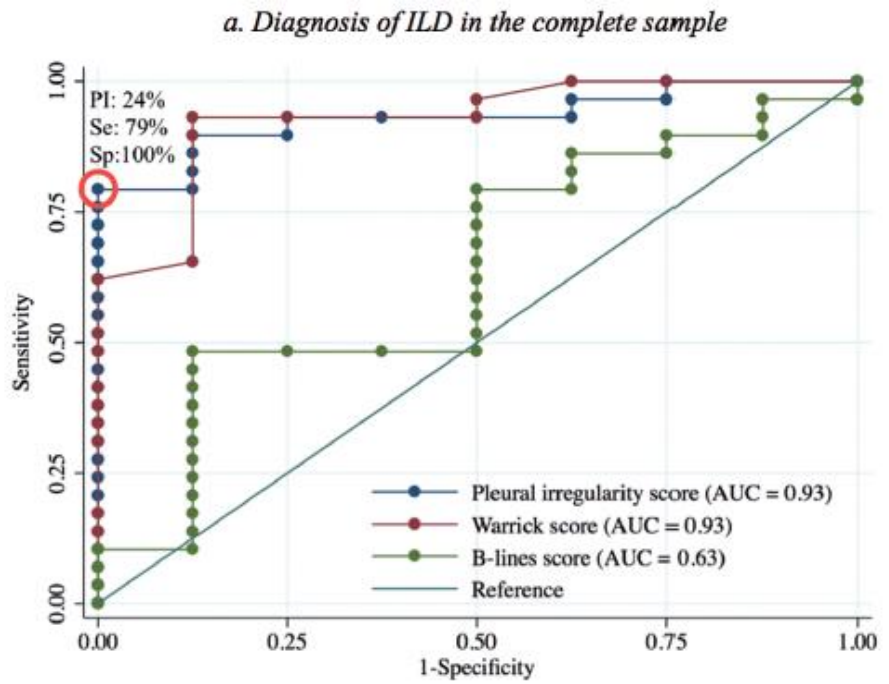


Fig. 1. Pleural line (contour marked with broken red line): (a) Normal. (b) Moderate pleural irregularity. (c) Severe pleural irregularity.



Performance of pleural irregularity as a diagnostic tool to detect ILD

Patients with ILD showed a significant higher PI score than those without it (35.3% *vs*. 6%; $p<0.001$). The AUC of the PI score for the diagnosis of ILD (AUC=0.93, 95% CI 0.85–1) was similar to that of the Warrick score (AUC=0.93, 95% CI 0.83–1) and significantly higher ($p=0.01$) than that of the B-line score (AUC=0.63, 95% CI 0.4–0.86)

Pleural irregularity in SSc and ASS ILD / I. Pinal-Fernandez et al. 2015

Proposed algorithm for RA-ILD detection

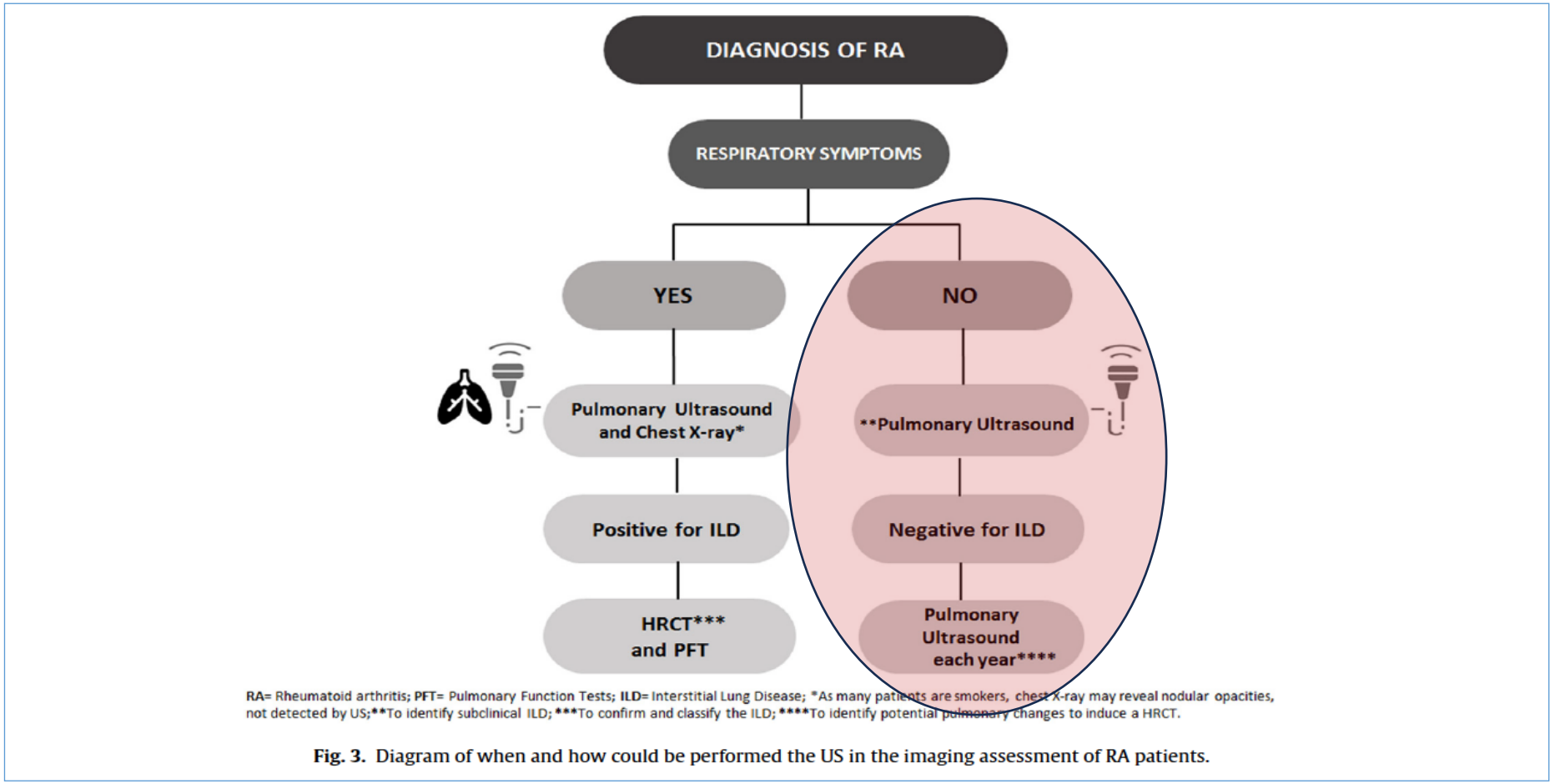


Fig. 3. Diagram of when and how could be performed the US in the imaging assessment of RA patients.

- The validation process of LUS in RA is more preliminary than in SSc, but current data suggest that B lines and pleural line alterations may be equally useful to diagnose and predict prognosis in RA-ILD patients

Marwin Gutierrez et al. Joint Bone Spine 2022

Esther F. Vicente-Rabaneda et al. Clinical Rheumatology (2021)

CHEST

Performance of Lung Ultrasound as a Screening Tool for Subclinical Rheumatoid Arthritis-Associated Interstitial Lung Disease

A Multicenter Study

Maria Otaola, MD; Eirini Vasarmidi, PhD; Sébastien Ottaviani, MD; Marwin Gutierrez, PhD; Marina Soledad Dalpiaz, MD; Adrian Gaser, MD; Pierre-Antoine Juge, PhD; Chiara Bertolazzi, MD; Nestor Avgoustidis, MD; Christos Skiadas, MD; Maricel Della Maggiora, MD; Paola Orausclio, MD; Alan Quintana-Rodriguez, MD; Marie-Pierre Debray, MD; Barbara Perez Cepas, MD; Emilce Schneeberger, MD; Prodromos Sidiropoulos, PhD; Nicolas Lloves Schenone, MD; Marcos Rosemffet, MD; Sebastian Marciano, MD; and Katerina Antoniou, PhD

TABLE 1] General Characteristics of Included Patients With RA (N = 203)

Variable	Result (N = 203)
Age, y[a]	63 (52-89)
Female sex	161 (79.3)
Past or current tobacco use[a]	97 (48)
Pack years[b]	15 (1-38.5)
RA duration, y[c]	7 (2-16)
Positive RF[a]	152 (75.3)
Positive anti-CCP antibodies[c]	138 (68.7)
DAS-28[c]	3.8 (2.6-4.8)
Erosive joint disease[d]	106 (57)
FVC, %[e]	89.5 (80.0-106.5)
DLCO, %[b]	84.0 (71.0-94.0)
ILD on HRCT imaging	53 (26.1)

Data are presented as median (interquartile range) or No. (%). Anti-CCP = anti-cyclic citrullinated peptide; DAS-28 = Disease Activity Score 28 Index; DLCO = diffusing capacity of the lungs for carbon monoxide; HRCT = high resolution CT; ILD = interstitial lung disease; RA = rheumatoid arthritis; RF = rheumatoid factor.
[a]Data are available for 202 patients.
[b]Data are available for 97 patients.
[c]Data are available for 201 patients.
[d]Data are available for 186 patients.
[e]Data are available for 152 patients.

TABLE 4] Performance of LUS and Pulmonary Function Tests as a Screening Tool for Interstitial Lung Disease in Asymptomatic Patients With Rheumatoid Arthritis

Variable	LUS (N = 203)	Spirometry (n = 152)	DLCO (n = 97)
Positive test result, No. (%)	72 (35.4)	36 (23.7)	41 (42.3)
Sensitivity (95% CI)	83 (70.2-91.9)	24.4 (12.9-39.5)	52 (31.3-72.2)
Specificity (95% CI)	81.2 (74.2-87.2)	76.6 (67.5-84.3)	61.1 (48.9-72.4)
NPV (95% CI)	93.1 (87.4-96.8)	70.7 (61.5-78.8)	78.6 (65.6-88.4)
PPV (95% CI)	61.1 (58.9-72.4)	30.6 (16.3-48.1)	31.7 (18.1-48.1)
AUROC (95% CI)	0.82 (0.76-0.88)	0.51 (0.43-0.58)	0.57 (0.45-0.68)

Data are presented as median (interquartile range). AUROC = area under receiver-operating characteristic curve; DLCO = diffusing capacity of the lungs for carbon monoxide; LUS = lung ultrasound; NPV = negative predictive value, PPV = positive predictive value.

Otaola M et al. Chest. 2024 Dec 13:S0012-3692(24)05622-8.

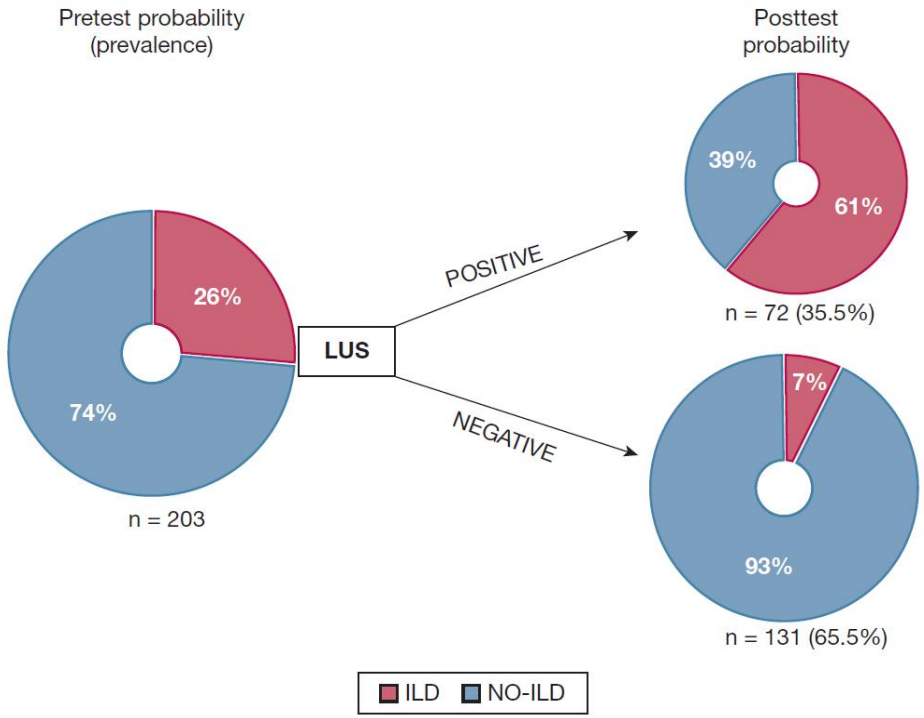


Figure 2 – *Pretest and posttest ILD probability based on LUS results. The pretest probability of not having ILD was 73.9%. In the 131 patients with a negative LUS, the posttest probability of not having ILD was 93%. The pretest probability of having ILD was 26.1%. Among the 72 patients with a positive LUS, the posttest probability was 61.1%. ILD = interstitial lung disease; LUS = lung ultrasound.*

Take-Home Points

Study Question: What is the diagnostic performance of lung ultrasound (LUS) for interstitial lung disease (ILD) screening in asymptomatic patients with rheumatoid arthritis?

Results: LUS showed a sensitivity of 83% and an negative predictive value of 93%, using high-resolution CT imaging as the gold standard for ILD diagnosis. This indicates that a negative LUS can effectively rule out ILD in 93 of 100 patients.

Interpretation: LUS is a low-cost, point-of-care tool with a high negative predictive value, and it is emerging as a valuable method for ruling out ILD in asymptomatic patients with rheumatoid arthritis.

Otaola M et al. Chest. 2024 Dec 13:S0012-3692(24)05622-8.

Standardization of interstitial lung disease assessment by ultrasound: results from a Delphi process and web-reliability exercise by the OMERACT ultrasound working group

Web-based intra- and inter-reader reliability exercise. Twenty-two out of 24 participants (92 %) involved

Table 1
Consensual definition of sonographic findings.

Finding	Definition	Level of agreement
Pleural line irregularity	a loss of regularity that may be associated with an increase in thickness (either focal, diffuse, linear, or nodular)	82.6 %
B-line	a vertical hyperechoic reverberation artifact that arises from the pleural line, extends to the bottom of the screen without fading, and moves synchronously with lung sliding	84.2 %

Table 2
Intra- and inter-reader reliability.

		Kappa value	CI
Intra-reader reliability	B-lines	0.72	0.67–0.78
	pleural line irregularity	0.75	0.69–0.81
Inter-reader reliability	B-lines	0.51	0.39–0.64
	pleural line irregularity	0.58	0.43–0.74

Conclusion
Consensus-based ultrasound definitions for B-lines and pleural line irregularity were obtained, with moderate to good reliability to detect these lesions using video-clips. The next step will be testing the reliability in patients with ILD linked to RMDs and to propose a consensual and standardized protocol to scan such patients.

Andrea Delle Sedie et al. Seminars in Arthritis and Rheumatism, Volume 65, **April 2024**

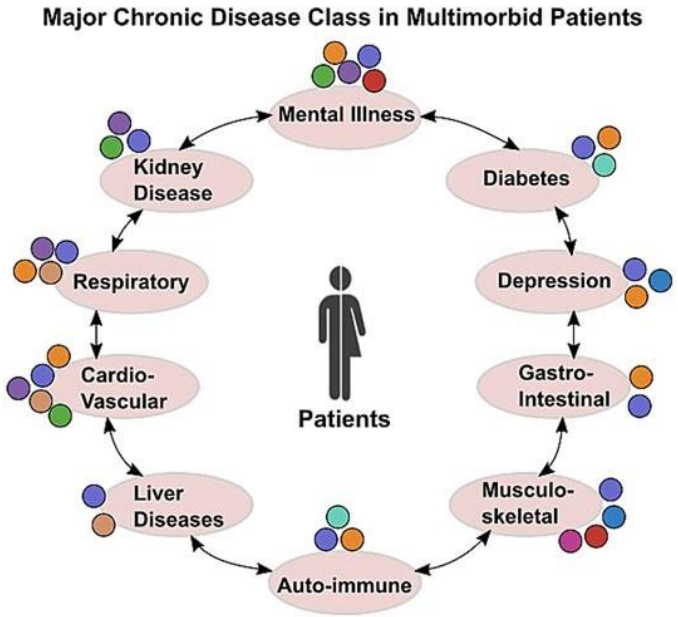
LUS -Future perspectives

- ✓ LUS can become extension of auscultation
- ✓ LUS can have a role as a screening tool for early ILD detection even in asymptomatic patients.
- ✓ Consider LUS every 12 months in asymptomatic seropositive patients especially –male sex /smokers/ older than 60
- ✓ More studies needing for evaluation of LUS as a potential tool for assessment of ILD progression and response to treatment

Clinical case

- 65 years old female , smoker with history of seropositive RA , RF(+), CCP(+)
- Initial diagnosis 15 years ago at the age of 50
- Medical history significant for :

1. A.H, CAD with PCI
2. Dyslipidaemia
3. Osteoporosis (-) fractures on Denosumab
4. Knee OA with significant pain
5. Fibromyalgia (side effects from Pregabalin+ amitriptyline)
6. Degenerative Spinal Disease
7. Depression without treatment



Clinical case

- Now on Rituximab 2 gr/6 months with Methotrexate 20 mg/week (SC)

- Previously treated with:

1. Adalimumab
2. Etanercept
3. Tocilizumab
4. Abatacept
5. Tofacitinib

- Reviewing medical notes patient had always VAS between 70-90 and number of TJC from 12-20 with 4 SJC while ESR was between 30-40 and CRP was normal in past 2 years.

Clinical case

- Multimorbid patient with RA, constantly in HDA with DAS28(ESR) : 5.3-6.7 across all treatment lines
- Do we need once again to change the treatment ?

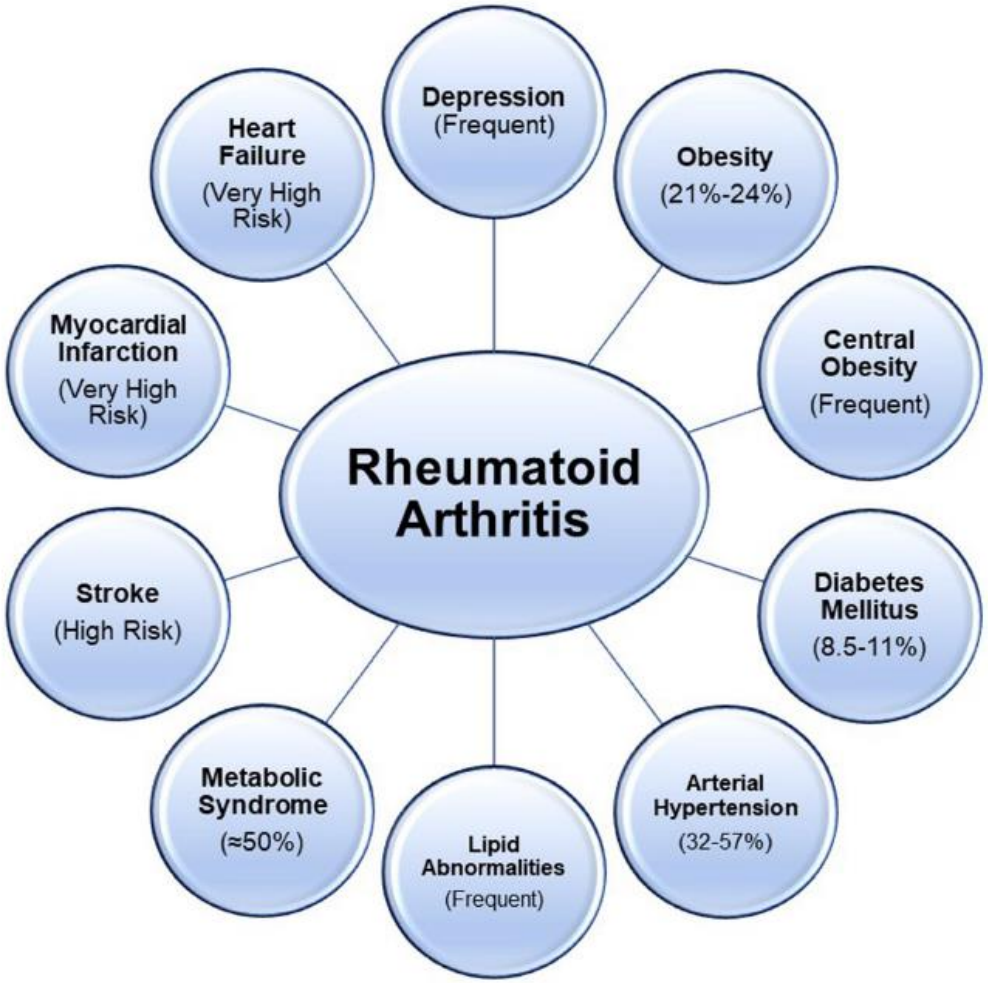


FIGURE 1
Cardiometabolic and other related conditions associated with Rheumatoid are represented. High risk refers to a hazard ratio greater than 1; very high risk refers to a hazard ratio greater than 2.

Corrao et al. 10.3389/fmed.2024.1421328

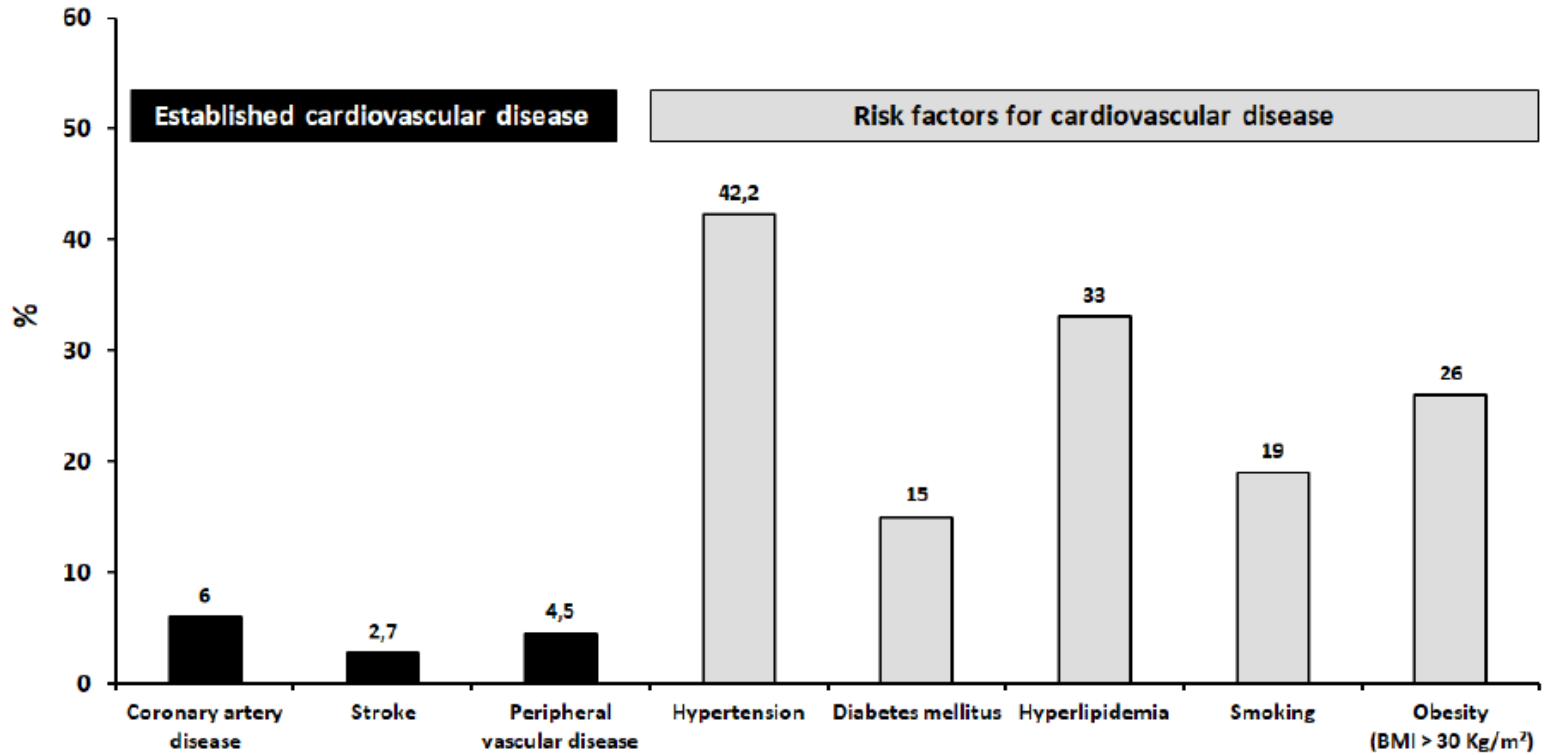


Figure 6. Prevalence of established cardiovascular disease and its risk factors.
The prevalence (%) of the established cardiovascular disease and its different risk factors in the whole RA cohort (n=2491) is shown.
BMI, body mass index.

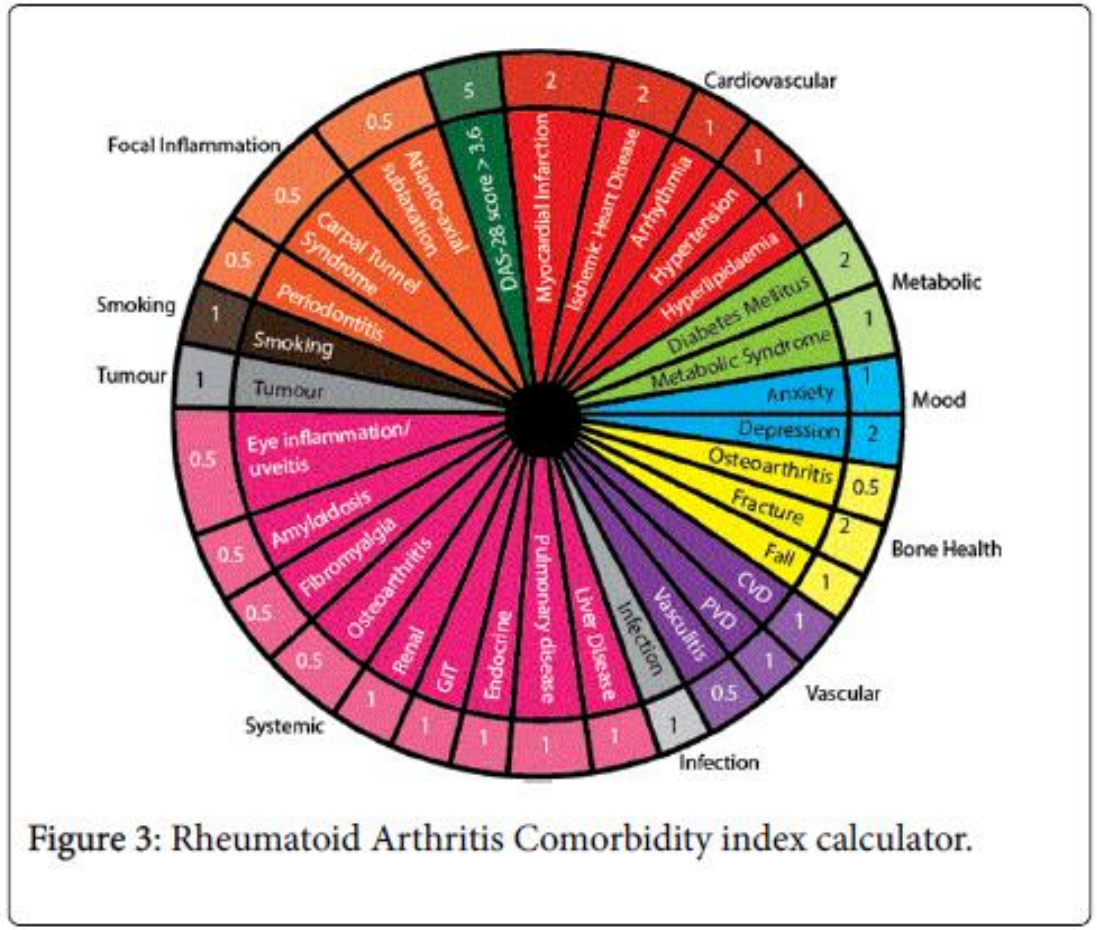


Figure 3: Rheumatoid Arthritis Comorbidity index calculator.

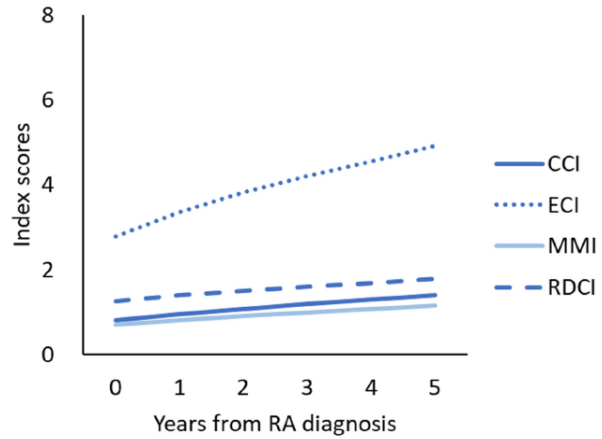


Figure 1. The mean scores of the comorbidity indexes according to the year of rheumatoid arthritis diagnosis. Abbreviations: Charlson Comorbidity Index (CCI), Elixhauser Comorbidity Index (ECI), Multimorbidity Index (MMI), Rheumatic Disease Comorbidity Index (RDCI), rheumatoid arthritis (RA).

Results: Comorbidities (18 conditions) were strongly associated with the 10-year death risk, and composed the RA-comorbidity index, include Cardiovascular (7 comorbidities), infection, osteoporotic fractures, falls risk, Depression/anxiety, functional status (HAQ >2), diabetes mellitus, steroid therapy >5 mg, DAS-28 >3.6), renal/liver/lung disease and tumors. Considering the comorbidities number, the comorbidities adjusted relative risk were employed as weights to develop a weighted index. Validation using ROC curve revealed AUC of 97%.

El Miedany Y et al., J Arthritis 2017, 6:3
DOI: 10.4172/2167-7921.1000244

Rheumatoid arthritis

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Patterns of comorbidities differentially affect long-term functional evolution and disease activity in patients with 'difficult to treat' rheumatoid arthritis

Antonios Bertsias,[1] Irini D Flouri ,[1] Argyro Repa,[1] Nestor Avgoustidis,[1] Eleni Kalogiannaki,[1] Sofia Pitsigavdaki,[1] George Bertsias ,[1,2] Prodromos Sidiropoulos [1,2]

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Several disease-related characteristics and comorbid diseases differentiate difficult to treat (D2T) patients from the rest of the rheumatoid arthritis population, while cross-sectional analysis revealed differences within the D2T group.

- ✓ 251 out of 1264 patients (19.9%) were identified as D2T.
- ✓ Predictors of patients becoming D2T.

1. Fibromyalgia
2. Osteoarthritis
3. DAS28 (ESR) scores at first (b/ts-DMARD) initiation
4. Failure to reduce DAS28-ESR scores within the first 6 months of b/ts-DMARD

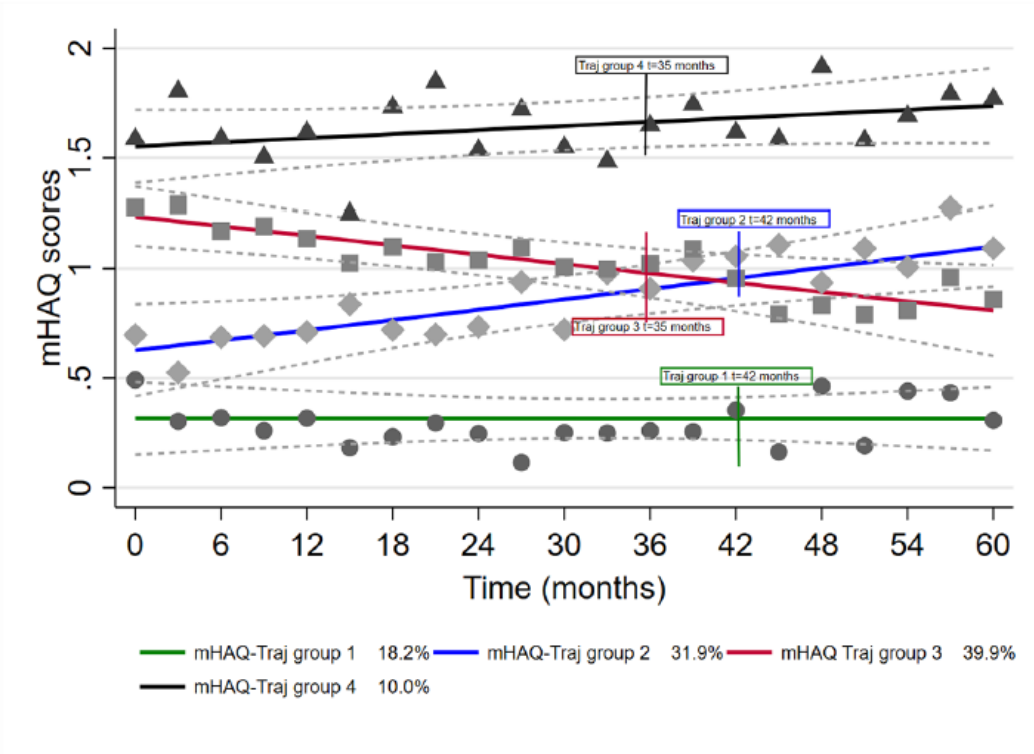


Figure 1 mHAQ latent-class trajectory analysis plots. Median time-to-characterisation as difficult to treat rheumatoid arthritis of each trajectory is given on the plots. mHAQ, modified Health Assessment Questionnaire.

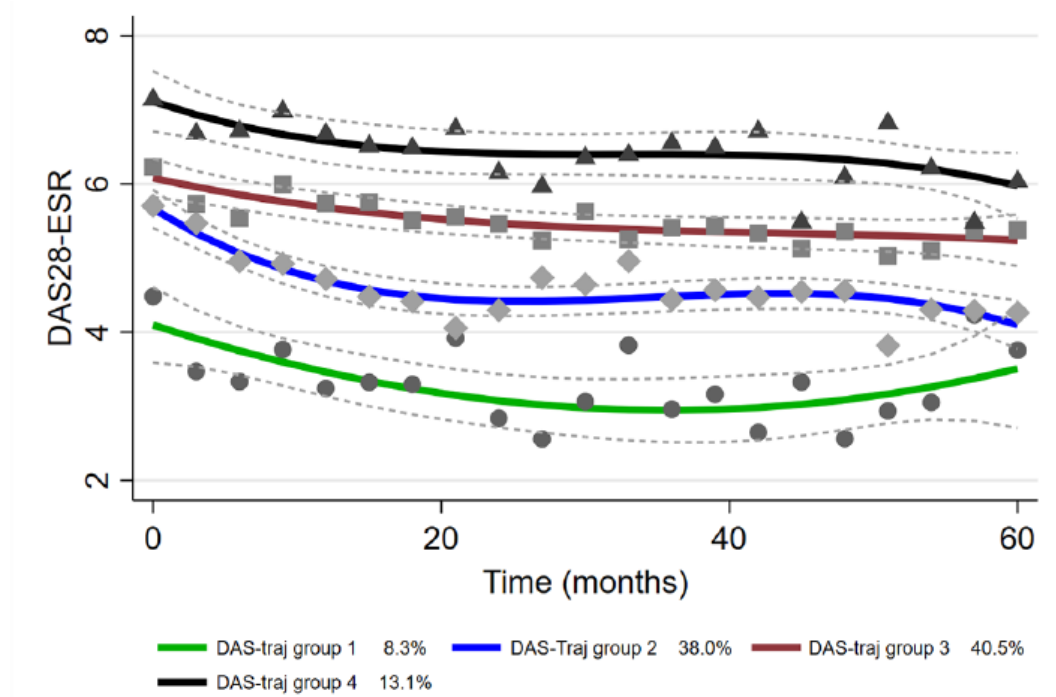


Figure 2 DAS28-ESR latent class trajectory analysis plot. DAS28-ESR, Disease Activity Index 28-erythrocyte sedimentation rate.

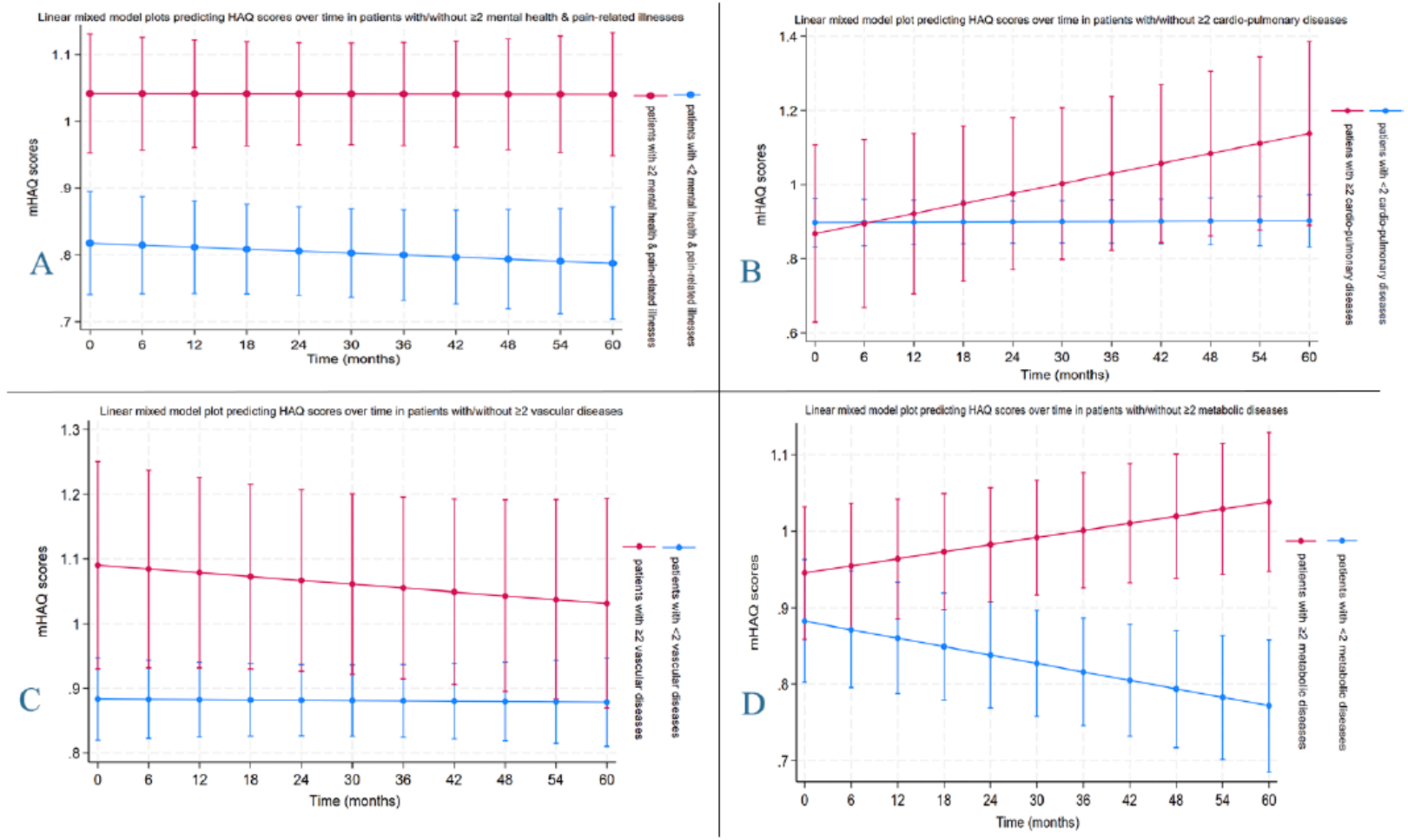


Figure 3 Linear mixed models plots of predicted mHAQ values over time using time and disease clusters membership as predictors. (A) Mental health and pain related (B) cardiopulmonary (C) vascular (D) metabolic. mHAQ, modified Health Assessment Questionnaire.

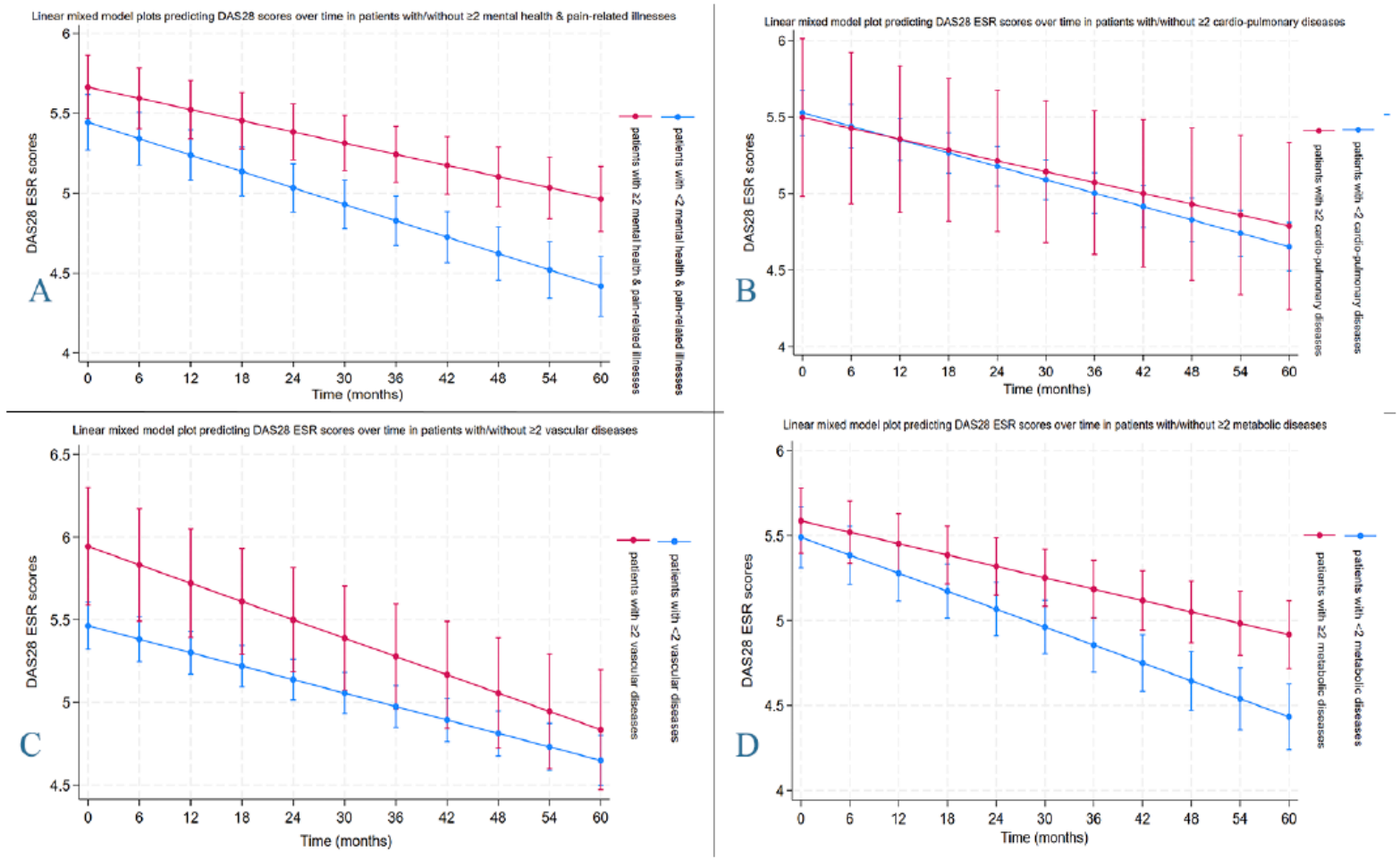


Figure 4 Linear mixed models plots of predicted DAS28-ESR values over time using time and disease clusters membership as predictors. (A) Mental health and pain related (B) cardiopulmonary (C) vascular (D) metabolic. DAS28-ESR, Disease Activity Index 28-erythrocyte sedimentation rate.

WHAT THIS STUDY ADDS

⇒ Our analysis of a prospectively followed cohort indicated that D2T represents a heterogeneous group in terms of long-term functional and disease activity evolution. Presence of mental-health/ pain-related illnesses as well as metabolic diseases significantly contribute to adverse outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Together with a better control of inflammatory burden, a special focus in the above comorbid diseases could possibly improve the outcome of these patients with major unmet-needs.

Bertsias A, *et al. RMD Open* 2024;**10**:e003808. doi:10.1136/rmdopen-2023-003808

Multimorbidity Patterns and Rheumatoid Arthritis Disease Outcomes: Findings From a Multicenter, Prospective Cohort

2,956 participants, of which 88.2% were male, 76.9% reported white race, and 79.3% had a smoking history.

SIGNIFICANCE & INNOVATIONS

- Most people with rheumatoid arthritis (RA) are multimorbid, experiencing multiple chronic conditions.
- Multimorbidity patterns are novel measures of multimorbidity occurring in people with RA, but their associations with RA-related outcomes are unknown.
- We characterized cross-sectional and longitudinal associations between different multimorbidity patterns with RA disease activity and functional status in a multicenter, prospective RA cohort.
- Mental health and substance abuse, chronic pain, and cardiovascular multimorbidity patterns are associated with increased RA disease activity and poorer functional status.

Sarah Dutt, et al. Arthritis Care and Research 2023

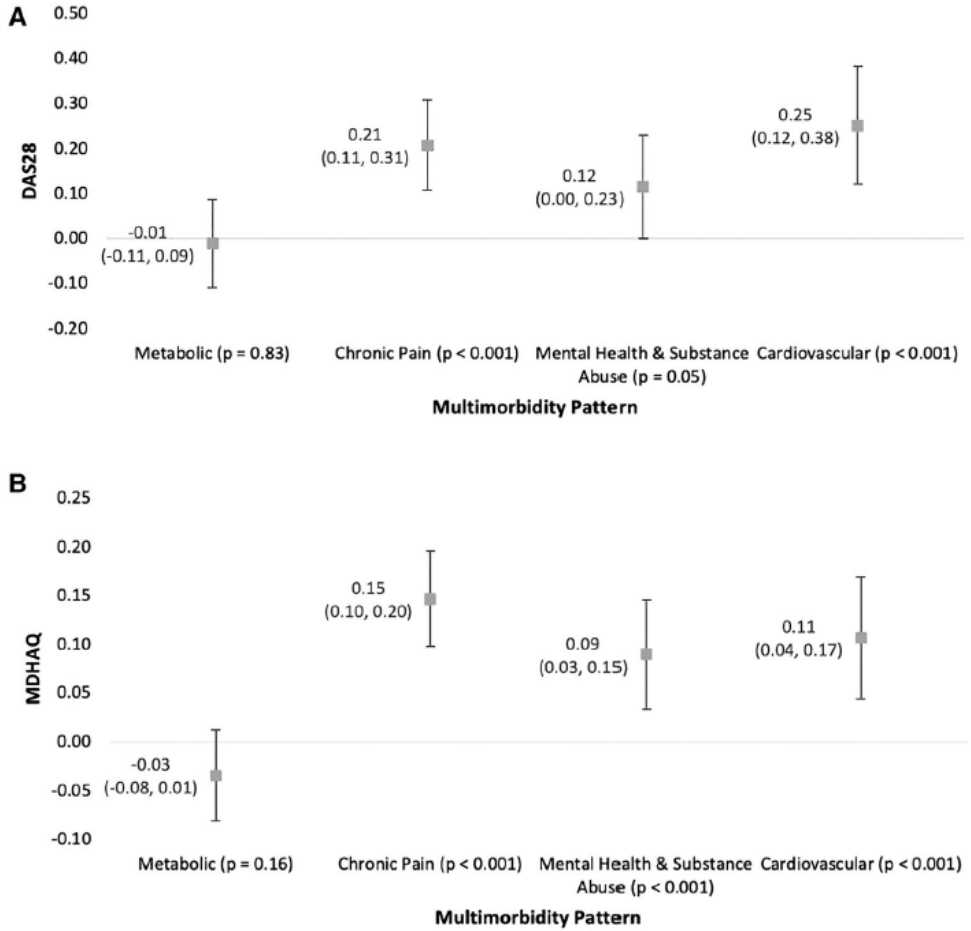


Figure 2. Associations of multimorbidity patterns with rheumatoid arthritis disease activity and functional status over follow-up. Longitudinal association of multimorbidity patterns with (A) disease activity (DAS28) and (B) functional status (MDHAQ) over follow-up (up to 5 years). Values are beta coefficients and 95% confidence intervals. Generalized estimating equations models adjusted for age, gender, education, smoking status, race, rheumatoid arthritis duration, rheumatoid factor or anti–cyclic citrullinated peptide seropositivity, conventional synthetic disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs, and prednisone. DAS28, Disease Activity Score in 28 joints; MDHAQ, Multidimensional Health Assessment Questionnaire.

Sarah Dutt, et al. Arthritis Care and Research 2023

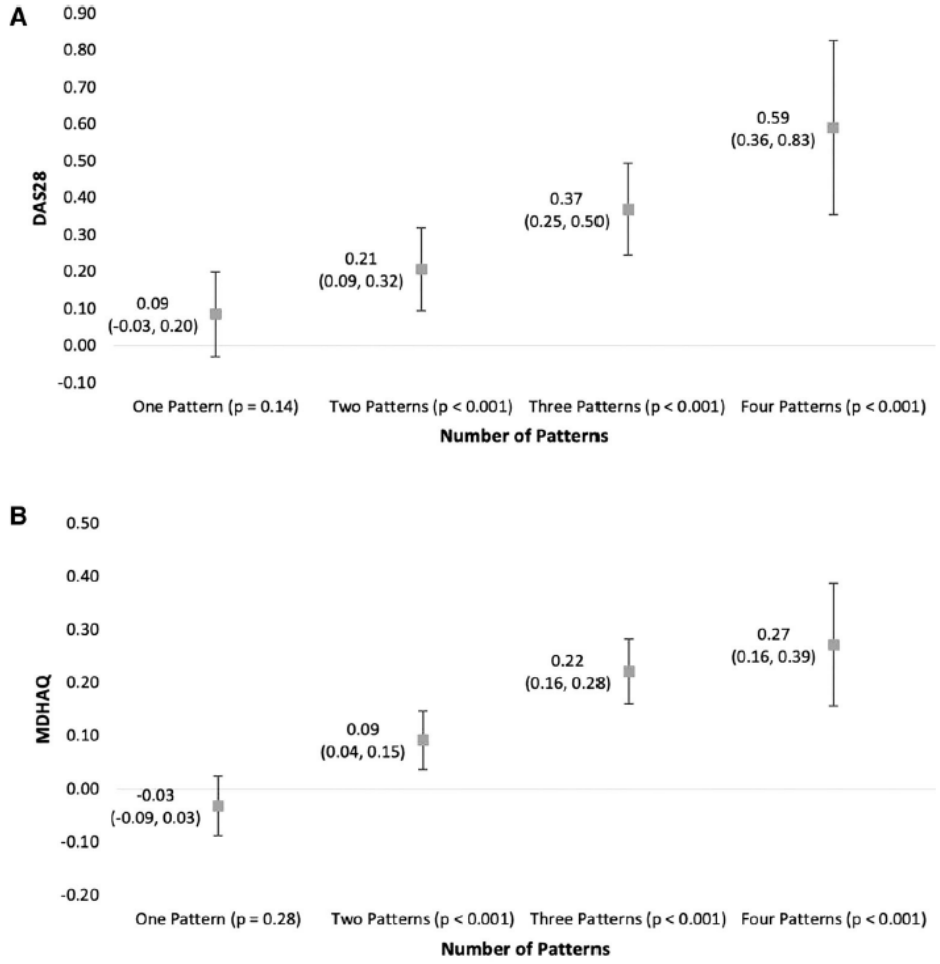


Figure 3. Associations of the number of multimorbidity patterns with rheumatoid arthritis disease activity and functional status over follow-up. Longitudinal association of the number of multimorbidity patterns present with (A) disease activity (DAS28) and (B) functional status (MDHAQ) over follow-up (up to 5 years). Values are beta coefficients and 95% confidence intervals. Generalized estimating equations models adjusted for age, gender, education, smoking status, race, rheumatoid arthritis duration, rheumatoid factor or anti–cyclic citrullinated peptide seropositivity, conventional synthetic disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs, and prednisone. The reference group were those with no multimorbidity patterns. DAS28, Disease Activity Score in 28 joints; MDHAQ, Multidimensional Health Assessment Questionnaire.

Conclusion. Mental health and substance abuse, chronic pain, and cardiovascular multimorbidity patterns are associated with increased RA disease activity and poorer functional status. Identifying and addressing these multimorbidity patterns may facilitate achieving RA treatment targets.

Sarah Dutt, et al. Arthritis Care and Research 2023

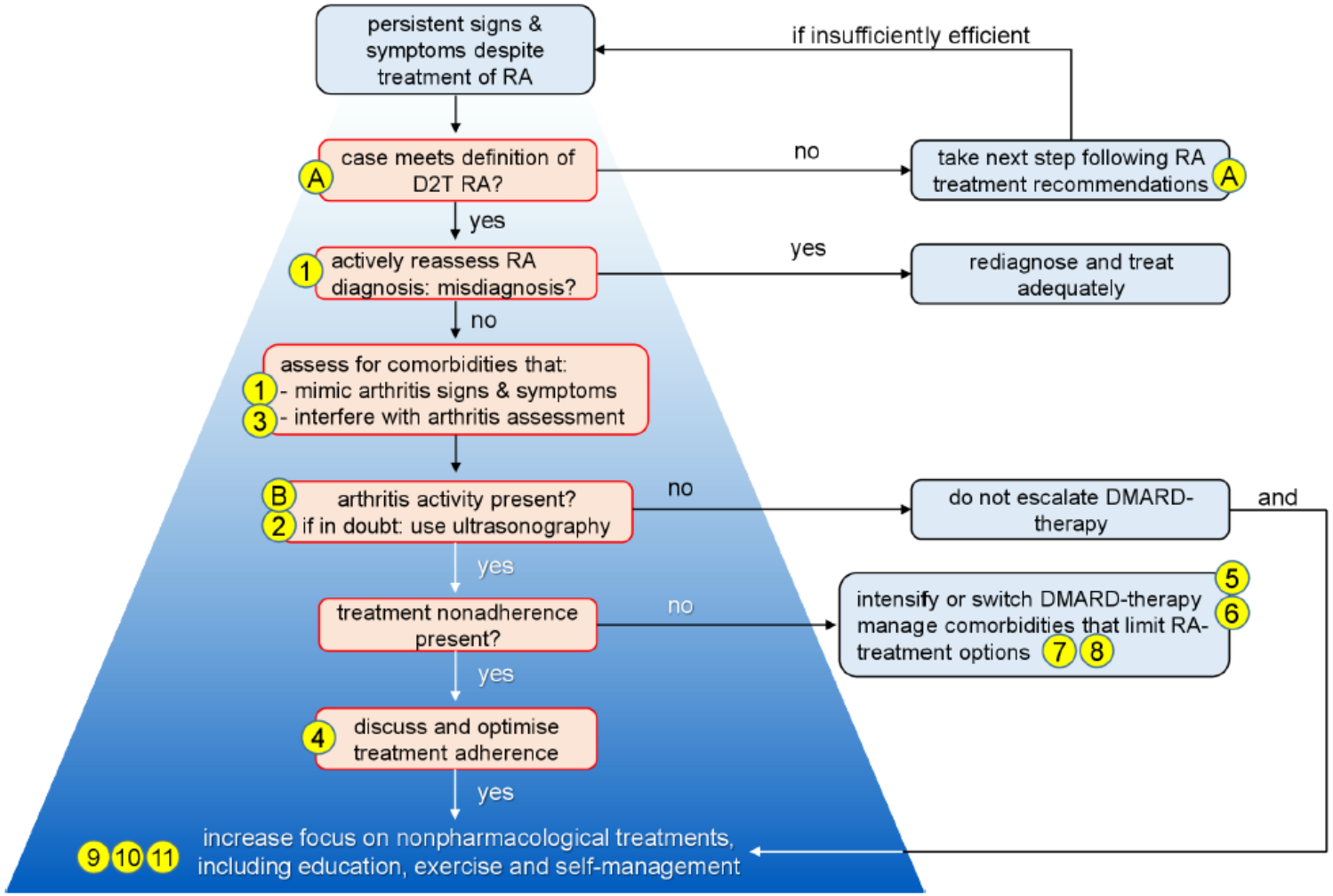


Figure 1 Algorithm based on the EULAR PtCs for the management of D2T RA. The pyramid background with increasing intensity of blue colour indicates non-pharmacological approaches and treatments, which are important throughout all phases of RA, but especially so if pharmacological treatment options are limited. The letters and numbers indicate the corresponding overarching principles and PtCs, respectively; see table 1. D2T, difficult-to-treat; DMARD, disease-modifying antirheumatic drug; EULAR, European Alliance of Associations for Rheumatology; PtCs, points to consider; RA, rheumatoid arthritis.

Box 1 Definition of D2T RA[17]

All three criteria need to be present in D2T RA:

1. Treatment according to EULAR recommendations and failure of ≥two b/tsDMARDs (with different mechanisms of action)† after failing csDMARD therapy (unless contraindicated).†
2. Signs suggestive of active/progressive disease, defined as ≥one of:
   a. At least moderate disease activity (according to validated composite measures including joint counts, for example, DAS28-ESR >3.2 or CDAI >10).
   b. Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other).
   c. Inability to taper glucocorticoid treatment (below 7.5 mg/day prednisone or equivalent).
   d. Rapid radiographic progression (with or without signs of active disease).‡
   e. Well-controlled disease according to above standards, but still having RA symptoms that are causing a reduction in quality of life.
3. The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient.

b/tsDMARDs, biological and targeted synthetic disease-modifying antirheumatic drugs; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; D2T, difficult-to-treat; DAS28-ESR, Disease Activity Score assessing 28 joints using erythrocyte sedimentation rate; RA, rheumatoid arthritis.
†Unless restricted by access to treatment due to socioeconomic factors.
†If csDMARD treatment is contraindicated, failure of ≥two b/tsDMARDs with different mechanisms of action is sufficient.
‡Rapid radiographic progression: change in van der Heijde-Modified Sharp Score ≥5 points in 1 year[184] or a similar progression in another validated scoring method.

What we did with patient

- We discussed about comorbidities and chronic pain and their impact to disease activity
- We performed MSK/US which confirms only chronic synovitis in the swollen joints without PD activity
- Advise for smoking cessation and referred her to appropriate outpatient clinic
- Initiate Duloxetine 30 mg/day and discuss for possible psychiatric assessment

- Referred patient to pain clinic
- As she has advanced knee OA discuss with patient the possibility for knee replacement
- We agreed to stay on the same treatment and review her in 4 months period of time

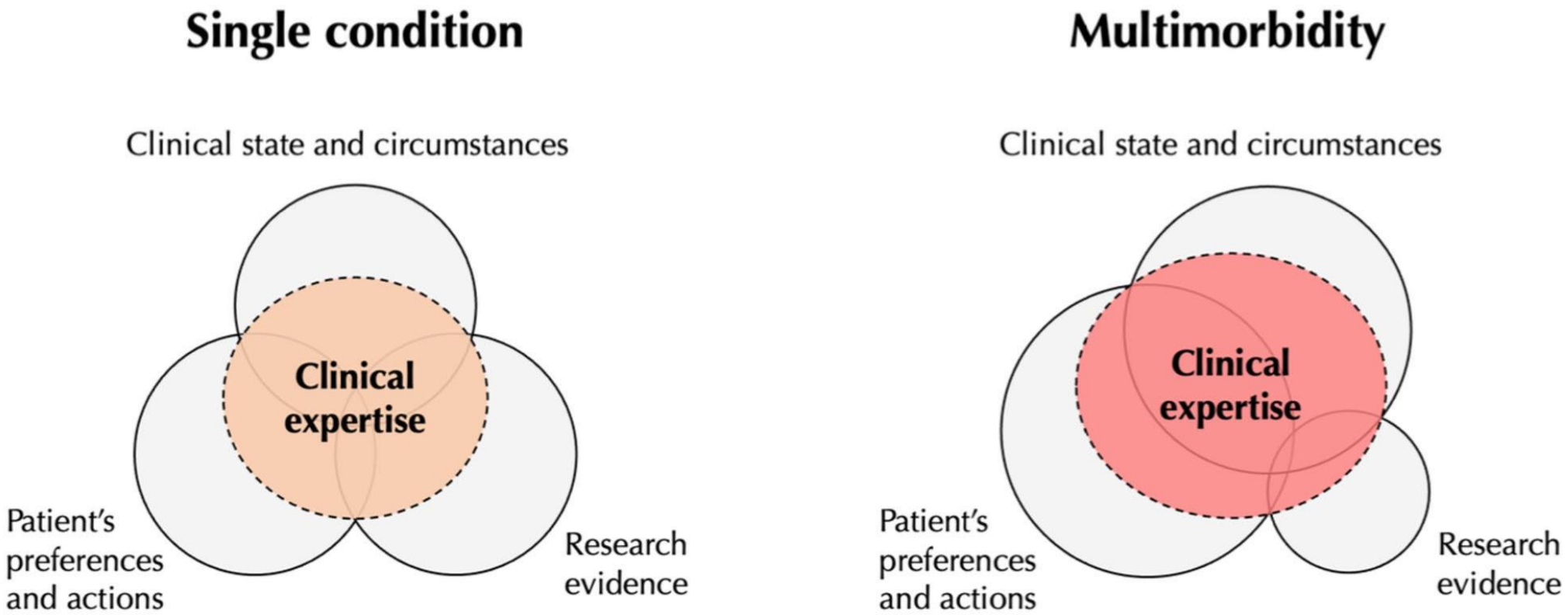


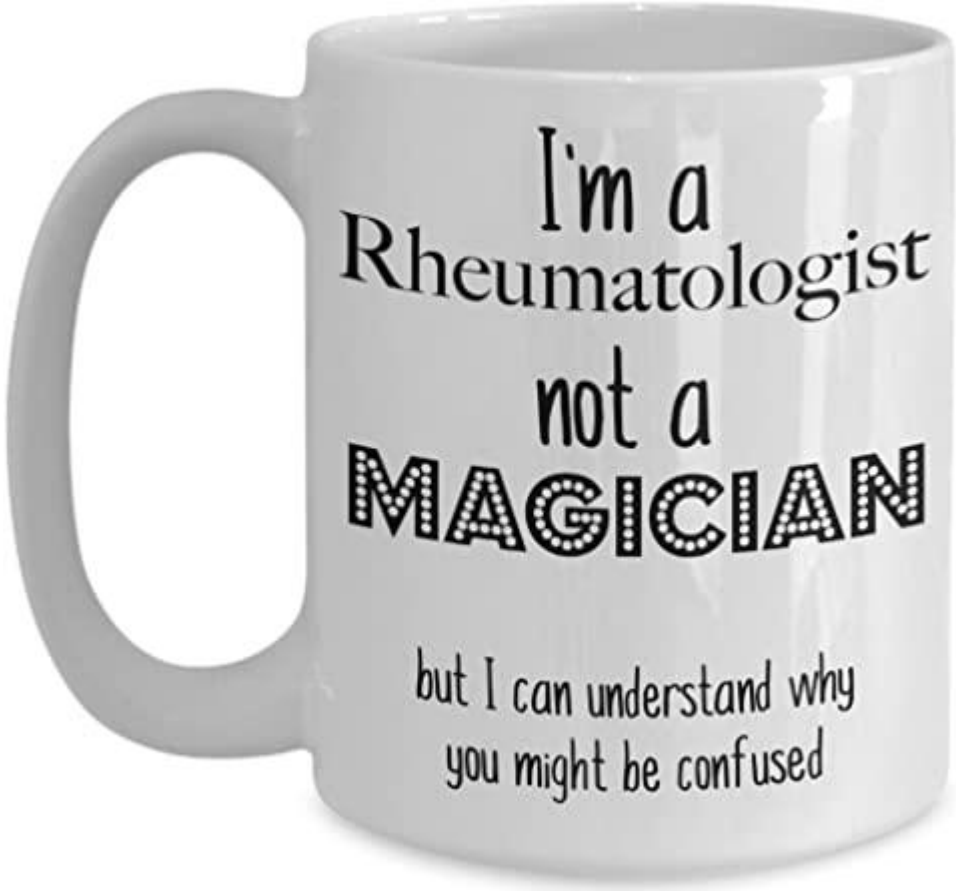
Figure 3. Clinical expertise is needed to a greater extend in multimorbidity compared to single condition situations.

Practical considerations

- Identify early patients with trend to be D2T
- Treat early and effectively comorbidities especially mental disorders and FM
- Don’t neglect to give appropriate advises for smoking cessation , BMI reduction and lifestyle modification
- Don’t forget cardiovascular comorbidities, vaccinations and osteoporosis treatment

Practical considerations

- Always check for extra-articular manifestations , especially ILD
- Before changing biologic re-assess patient adherence to treatment and don’t hesitate to use advance imaging (US) in order to confirm disease activity
- Explain patient the impact of OA, Degenerative Spinal Disease & FM in overall pain


I'm a
Rheumatologist
not a
MAGICIAN
but I can understand why
you might be confused


Thank You!
alt