

Atteinte pulmonaire dans la PR

Pr DIEUDE

Hôpital Bichat - Claude-Bernard

Rhumatologie en Occitanie,
groupe d'analyse et d'échange de pratiques
Du 24 Janvier 2024

RA-ILD

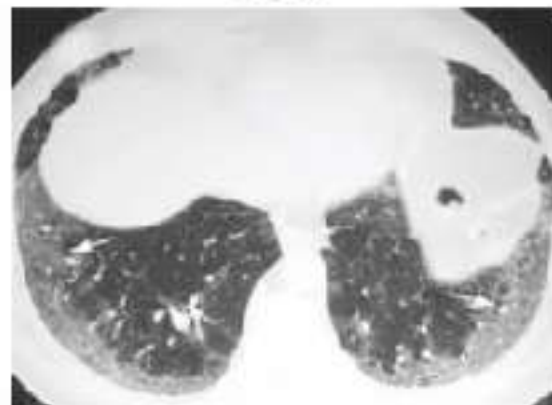
- Heterogeneity

- RA-ILD is **not a single entity**

OP



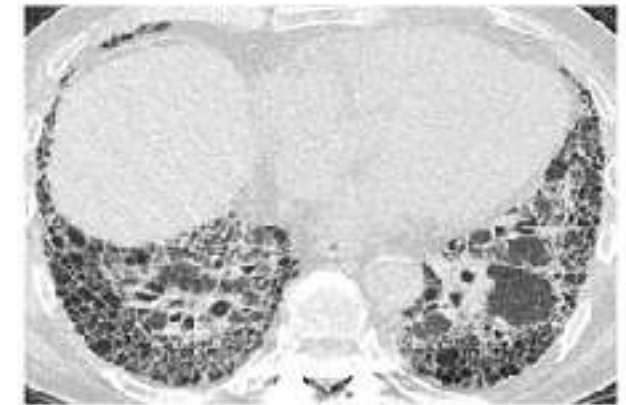
NSIP



f. NSIP



UIP



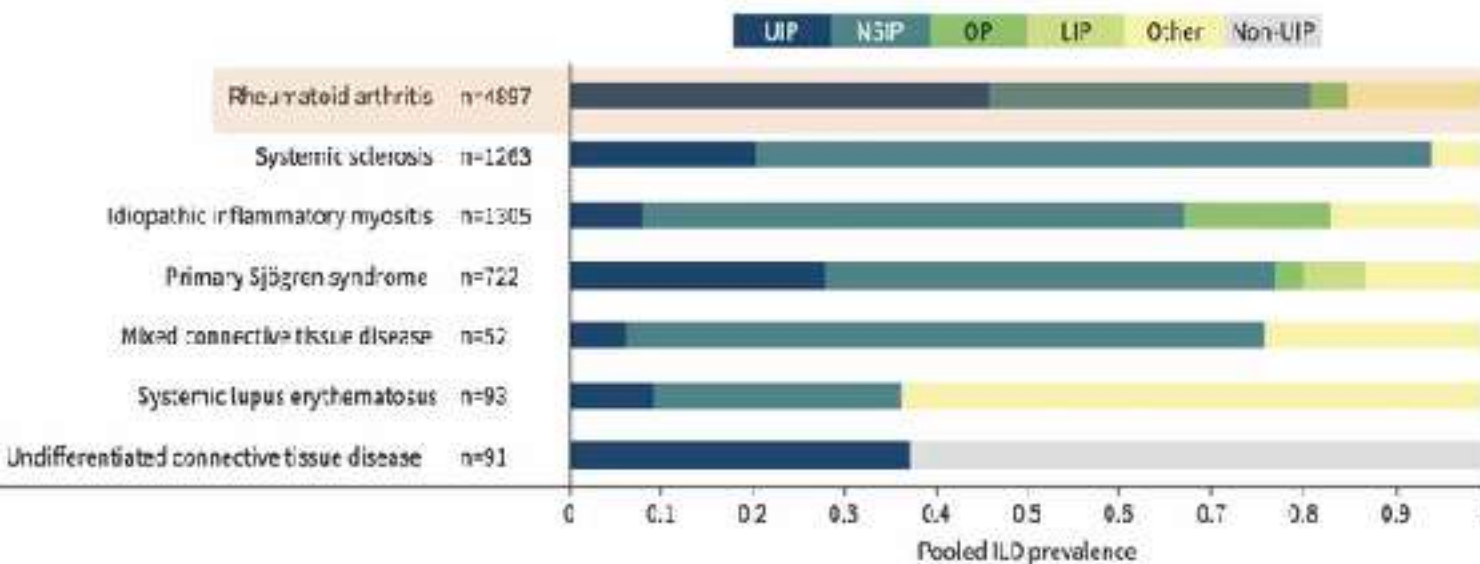
Inflammation

Fibrosis

RA-ILD

- High prevalence of UIP

- HRCT pattern: **UIP** ~ 50% >> other CTD-ILD



- Honeycombing
- Traction bronchiectasis
- Subpleural distribution
- Basal predominance

Diagnostic HRCT criteria for usual interstitial pneumonia (UIP) pattern - ATS/ERS/JRS/ALAT (2018)

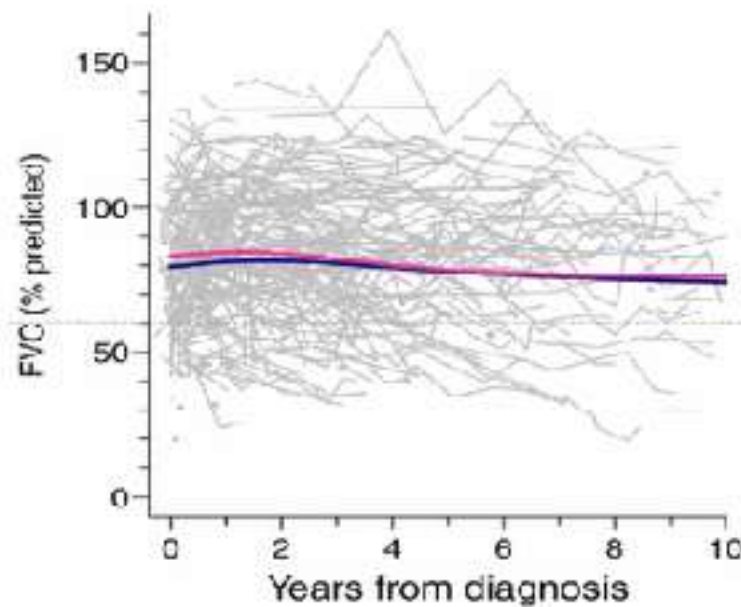
Bryson T, et al. *Semin Ultrasound CT MR* 2014 ; Demarville MK, et al. *Best Pract Res Clin Rheumatol* 2015; Spagnuolo R et al. *Arthritis Rheum* 2018; Jay GM et al. *Eur Respir Review* 2023.

RA-ILD

- **Potentially progressive**

- ~ **40 %** RA-ILD are **progressive** (HRCT extension and/or lung function decline)
- ILD trajectory **highly heterogenous**

261 patients with RA-ILD – Median follow up 3.5 years

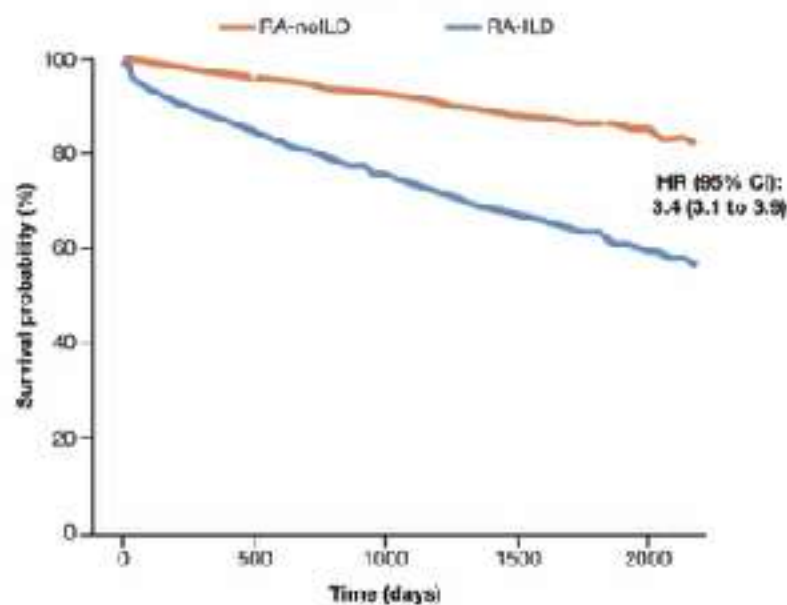


Juge PA et al. Semin Arthritis Rheum. 2021.

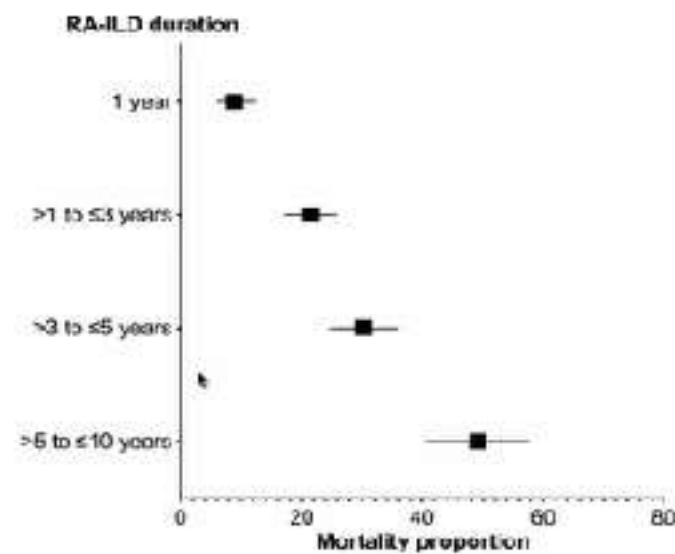
RA-ILD

Severe

French national claims database,
n= 4330 RA-ILD



Metaanalyse, 78 studies,
n= 5144 RA-ILD



Dannish national databases,
n= 679 RA-ILD

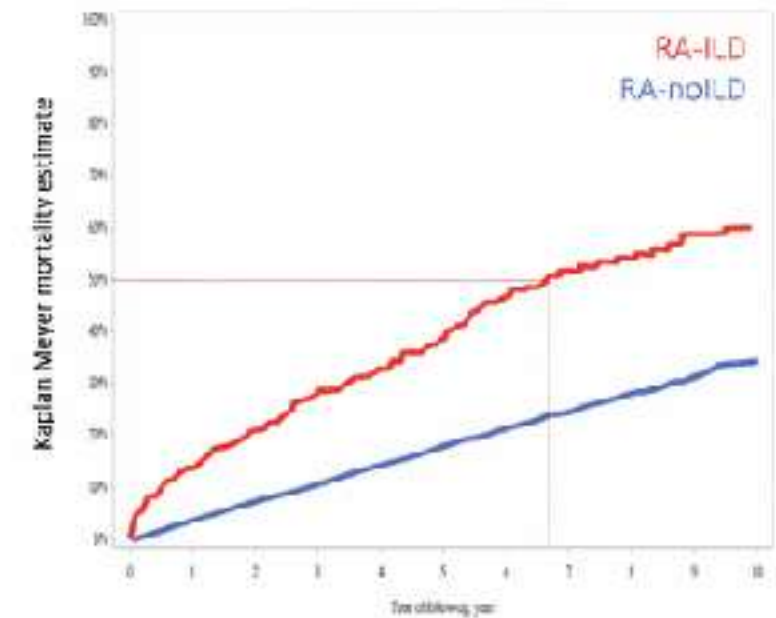


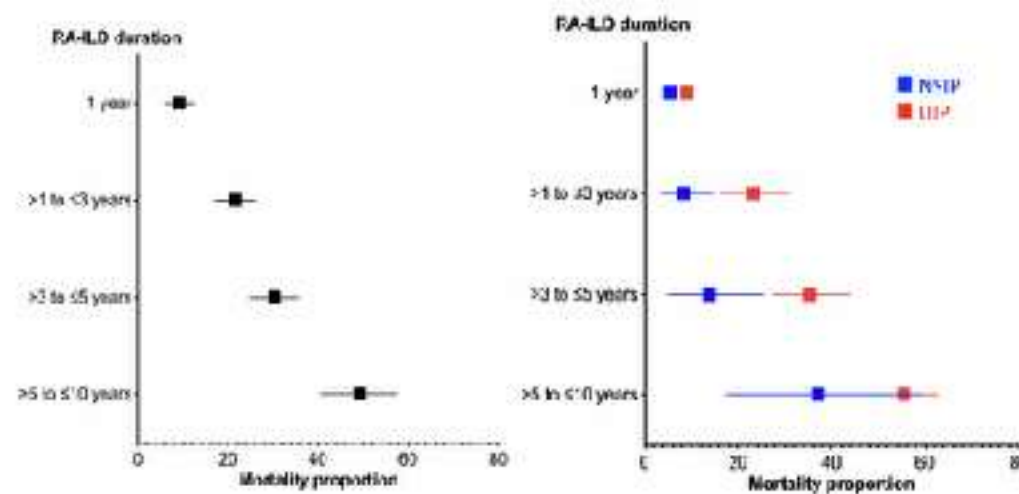
Figure 1 Survival in patients with RA-ILD versus RA-noILD in the matched population. ILD, interstitial lung disease; RA, rheumatoid arthritis; RA-ILD, RA with ILD; RA-noILD, RA without ILD.

Kim EJ et al, *Chest* 2009; Bongartz T. *Arthritis Rheum* 2010; Olson AL et al, *Am J Respir Crit Care Med* 2011; Solomon JJ et al, *Respir Med* 2013; Asayag D et al, *Respirology* 2014; Hyldgaard C et al, *Ann Rheum Dis* 2017; McDermott GC et al, *medRxiv* 2022; Fraquhar HJ et al, *Semin Arthritis Rheum*, 2023; Juge PA et al, *RMD Open* 2023.

RA-ILD

▪ Risk factors for mortality

▪ Male, UIP HRCT pattern, ILD > RA



Adapted from data of Fraaihaar HJ et al. Semin Arthritis Rheum. 2023

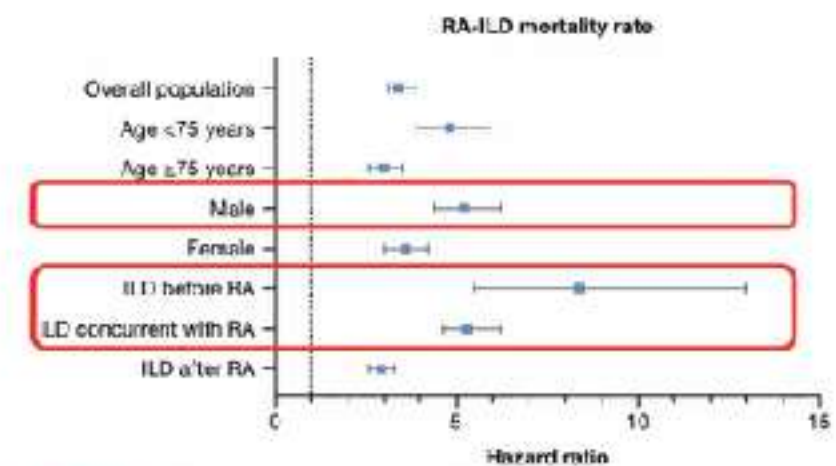


Figure 2 Forest plot showing HR for mortality in patients with RA-ILD compared with patients with RA-noILD. ILD, interstitial lung disease; RA, rheumatoid arthritis; RA-ILD, RA with ILD; RA-noILD, RA without ILD.

Kim EJ et al. Chest 2009; Bangartz T. Arthritis Rheum 2010; Olson AL et al. Am J Respir Crit Care Med 2011; Sokanion JJ et al. Respir Med 2013; Assayag D et al. Respirology 2014; Hylgaard C et al. Ann Rheum Dis 2017; Fraaihaar HJ et al. Semin Arthritis Rheum. 2023; Juge PA et al. RMD Open 2023

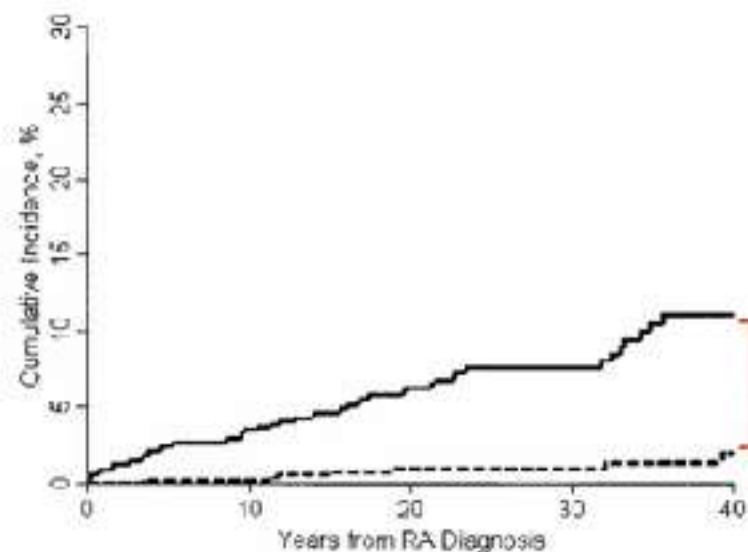


Natural history of RA-ILD

RA is risk factor for ILD

- Unknown
- **NOT a coincidental** occurrence of ILD in RA
- Incident RA-ILD increasing with **RA duration**

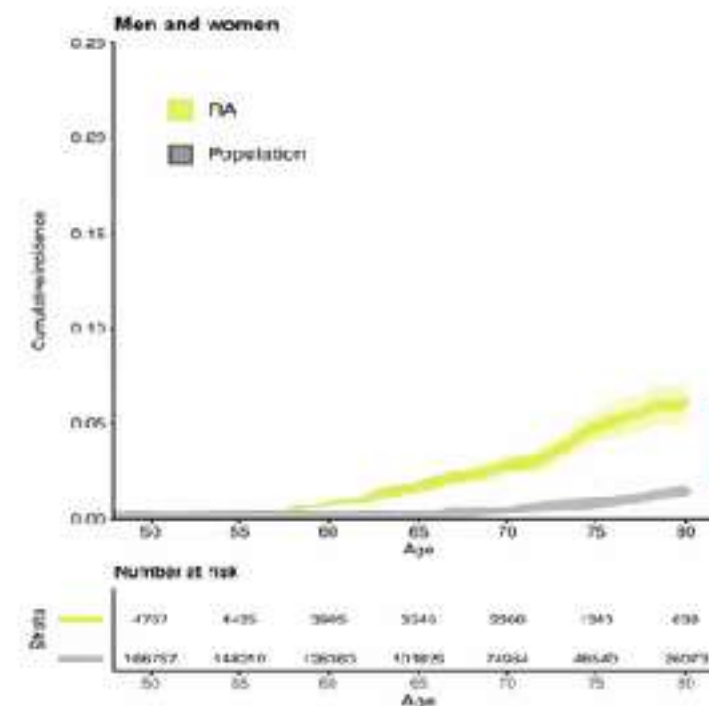
Population-based incidence cohort of RA (n= 582) & matched healthy control cohort (n= 603)



HR = 8.96 (4.02-19.94)

Figure 1. Incidence of interstitial lung disease in rheumatoid arthritis (RA) patients (solid line) and in control subjects (broken line).

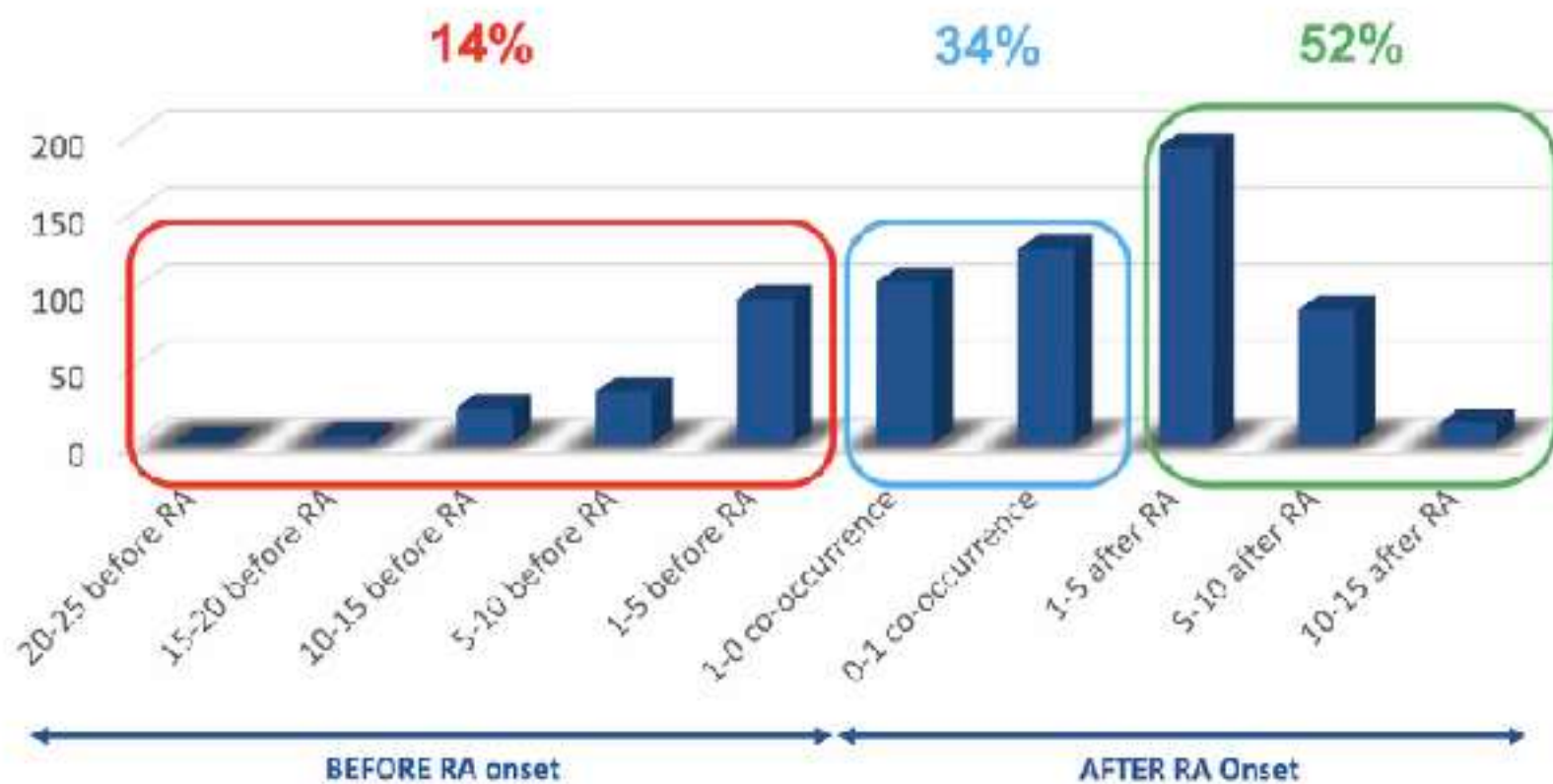
FinnGen : 293 972 individuals / 6869 patients with RA / 247 patients with RA-ILD



HR = 4.99 (4.20-5.94)

Natural history

- At least 1/3: ILD before or co-occurent of RA



Considerations for screening for RA-ILD

Screening vs diagnosis

- **HRCT** is the gold standard for **ILD diagnosis**
- **Diagnostic test** : **symptomatic** patients
- **Screening** : **asymptomatic high-risk** patients

DIAGNOSIS



Respiratory
symptoms +



HRCT



- Maybe invasive, expensive but necessary for diagnosis
- High specificity (true negative)
- Individuals with symptoms

SCREENING

Other detection
tools ?

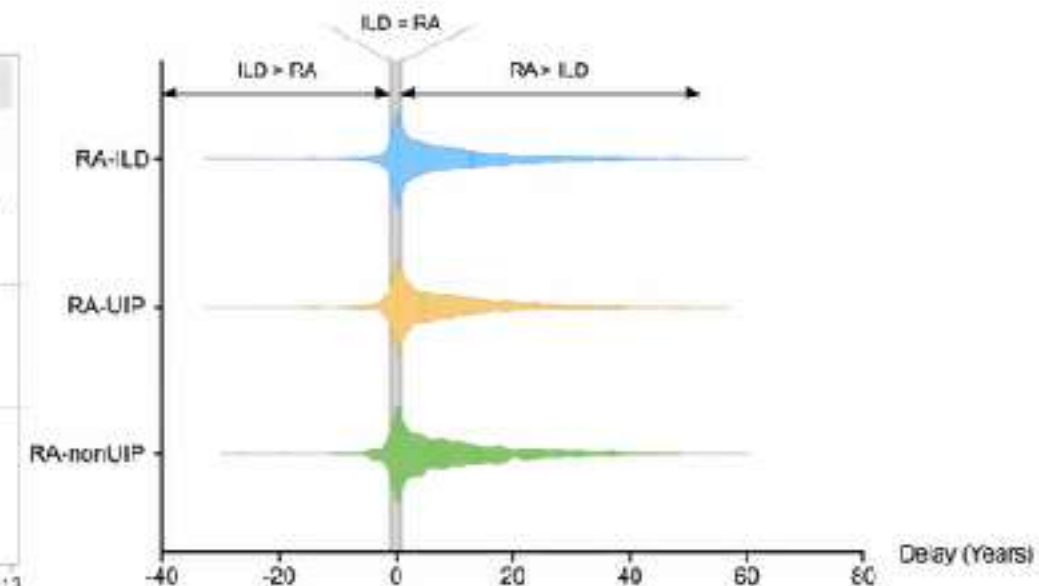
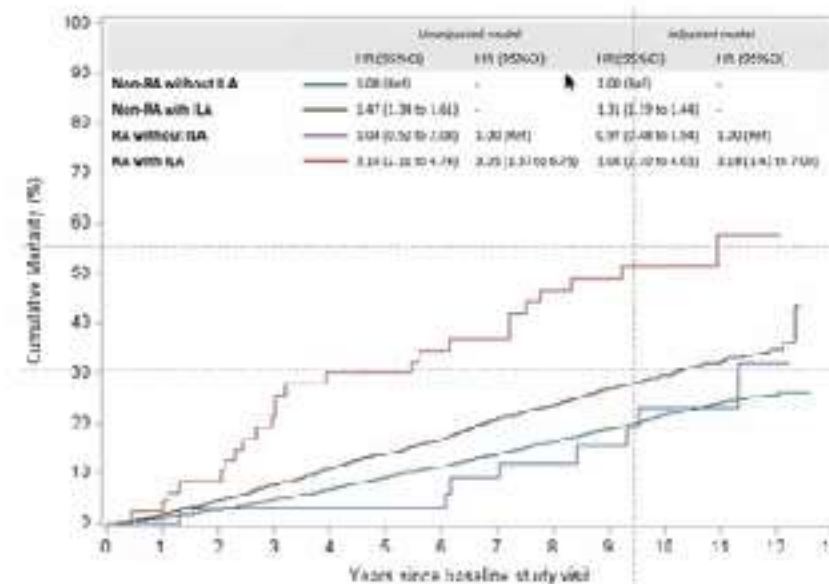
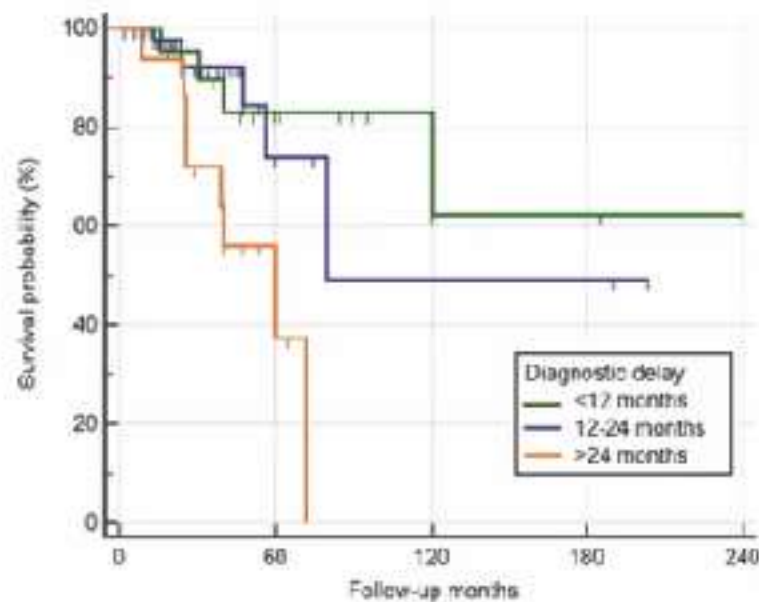


Respiratory
symptoms -

- Simple, acceptable to patients and staff
- High sensitivity not to miss potential disease
- Asymptomatic but at high-risk individuals

Indirect arguments for screening

- Diagnostic delay increased mortality
- Asymptomatic RA-ILD potentially severe
- $\sim 1/3$: ILD > RA



Screening for RA-ILD

- 5 conditions



1

Frequent & potentially severe

2

Identification of high-risk individuals

3

Specific treatment available

4

Evidence of treatment benefit

5

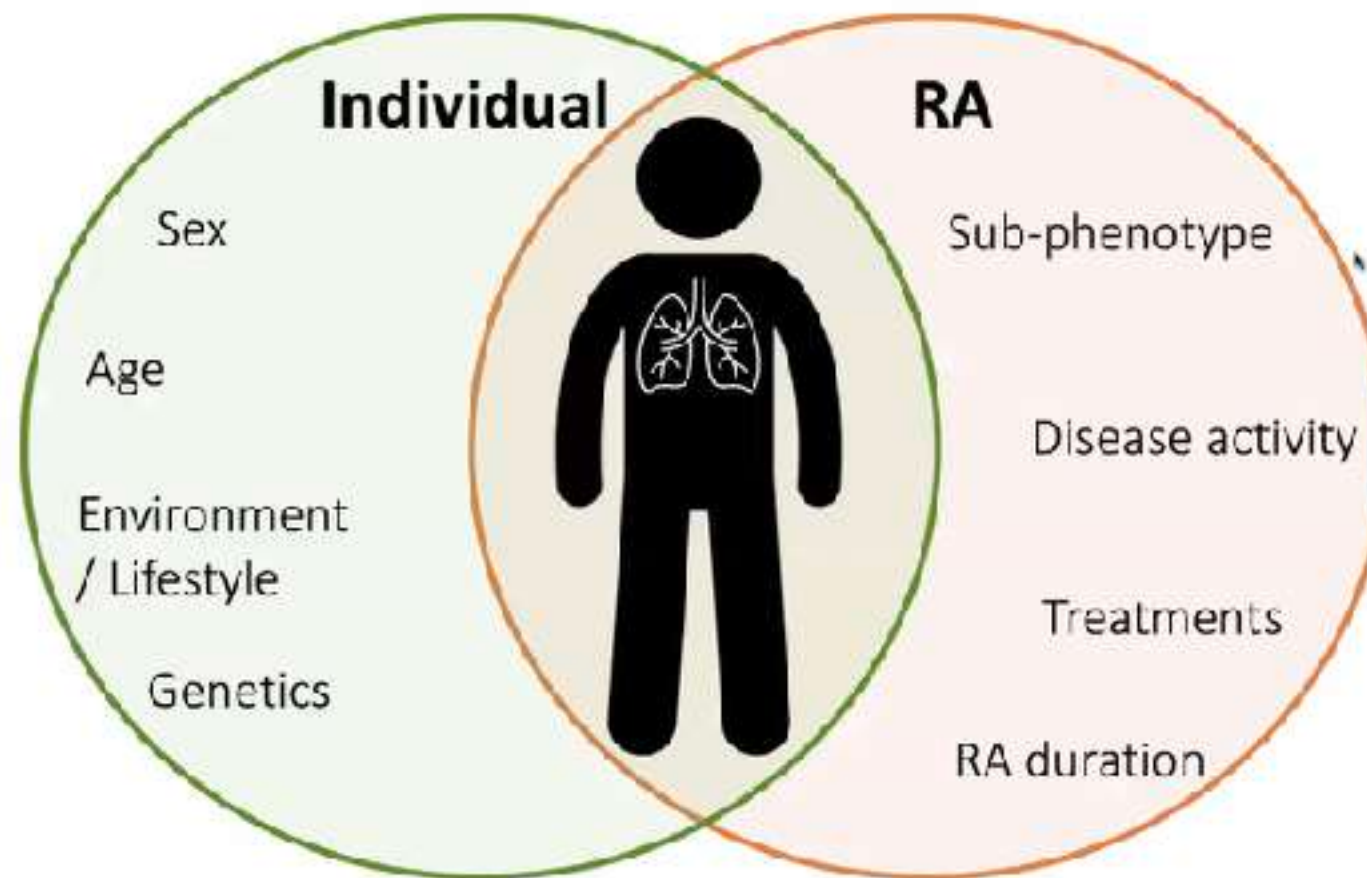
Known indication for treatment



**Which patients with RA
are at high-risk for ILD ?**

Main risk factors For RA-ILD

- Related to the individual
- Related to RA



Individual risk factors

- Older age at RA onset
- Male sex
- BMI ≥ 30

Case-control; 614 RA-ILD vs. 620 RA-noILD, all patients assessed by HRCT - Multi-ethnic

Table 1. Baseline Characteristics of Patients with Rheumatoid Arthritis (RA).^a

Characteristic	RA-ILD (N=620)	RA without ILD (N=614)	Crude P Value	Adjusted P Value [†]
Female sex — no./total no. (%)	345/565 (61.1)	446/540 (82.6)	8.12×10^{-15}	3.7×10^{-12}
Age at inclusion — yr	69.0 $\pm$ 10.3	60.4 $\pm$ 12.6	1.20×10^{-24}	1.3×10^{-21}
Age at onset of RA — yr	55.7 $\pm$ 14.5	45.7 $\pm$ 13.5	7.0×10^{-23}	5.6×10^{-14}

Nested case-control; 84 incident RA-ILD vs. 233 RA-noILD matched controls - (BRASS cohort)

Characteristic	OR Conditioned on Matching Factors ^a (95% CI)	Multivariable ^b OR (95% CI)
Education: Less than College	0.76 (0.46–1.26)	0.53 (0.30–0.95)
Body Mass Index, kg/m ²		
<20	0.98 (0.30–3.21)	1.00 (0.29,3.43)
20–<25	(ref)	(ref)
25–<30	1.35 (0.72–2.52)	1.56 (0.79,3.06)
≥ 30	2.05 (1.03–4.07)	2.42 (1.11,5.24)

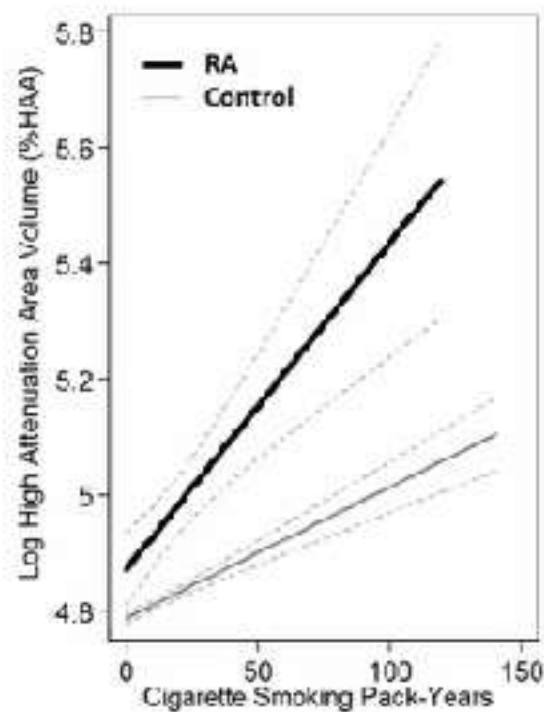
^aAll models were conditioned on matching factors (age, sex, RA duration, RF status, and time from study visit to index date). Bold values indicate statistical significance at $p < 0.05$.

^bAlso adjusting for anti-CCP, race/ethnicity, education (in BMI model), BMI (in education model), and smoking pack-years.

Individual risk factors

■ Smoking

- Higher contribution of smoking to the risk of ILD in RA vs controls



	Cigarette Pack-Years				Effect Estimate per 10 Pack-Yrs. (95% CI)	P Value
	0	1–10	11–20	>20		
ESCAPE RA						
No. of Subjects	67	23	17	58		
HAA Volume, cm ³	134 (±43)	148 (±44)	151 (±60)	176 (±68)	0.02% (0.001–0.04)	0.04
Controls						
No. of Subjects	2,119	601	344	742		
HAA Volume, cm ³	124 (±55)	128 (±20)	132 (±74)	139 (±61)	0.005% (0.001–0.009)	0.009

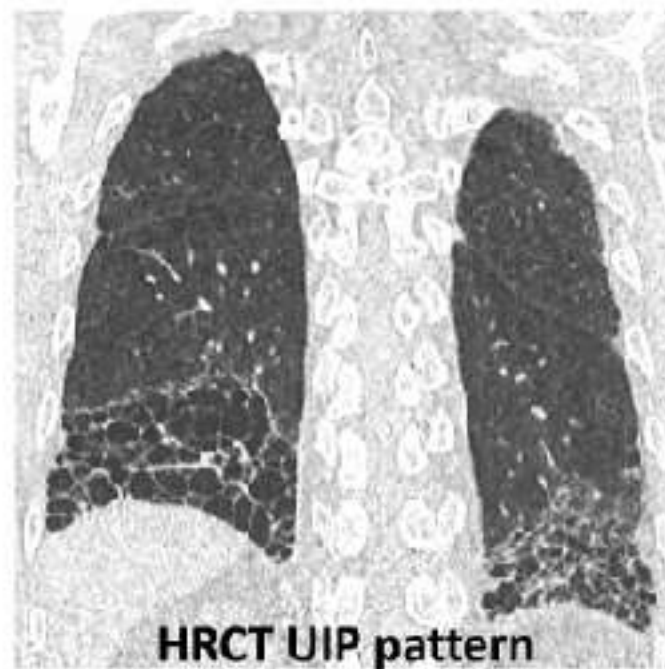
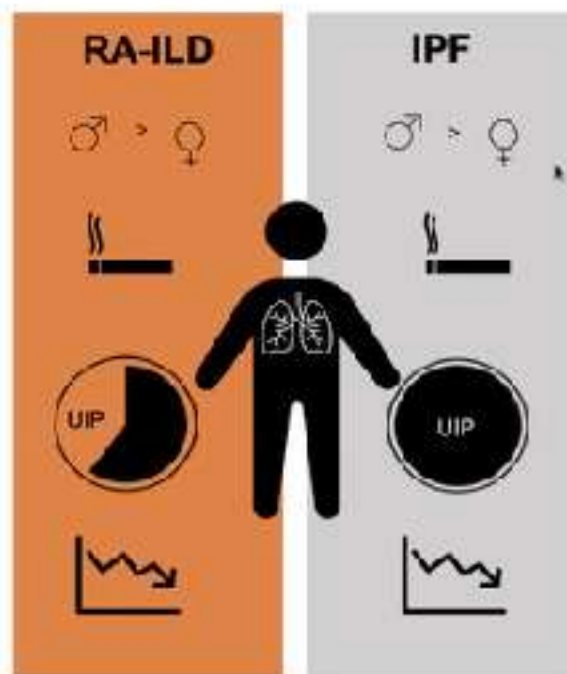
Secondary Analysis. The full multivariate model includes age, sex, race/ethnicity, smoking status, height, body mass index, hip circumference, waist circumference, total volume of imaged lung, and emphysema %.

doi:10.1371/journal.pone.0153024.t004

Individual risk factors

- High similarities between RA-ILD & IPF
- Notably, with RA-UIP

RA-ILD & IPF : shared genetic background ?

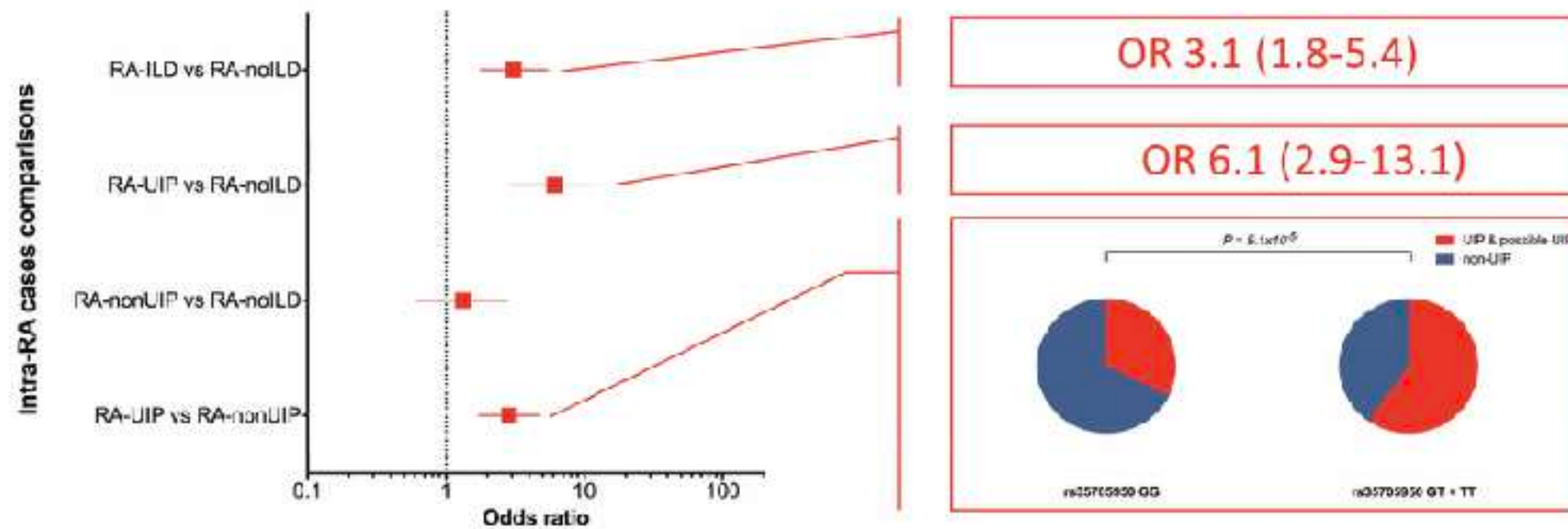


	RA-ILD	IPF
Male Sex	40% RA-ILD vs 20% RA-noILD	ratio 2:1
Age at ILD diagnosis	6 th decade	7 th decade
Smoking	OR ~ 3.8	OR ~ 2.5
UIP HRCT	40-60%	Required for diagnosis
Progressive	~ 50%	~ 90%
Mortality	Median survival 2.6 years (UIP)	Median survival 3.5 years

Individual risk factors

- ***MUC5B* rs35705950** shared risk factor with IPF
- Strongest RA-ILD genetic risk factor (OR >3)
- Association restricted to the UIP pattern

Suggest a common pathophysiology between IPF and RA-UIP

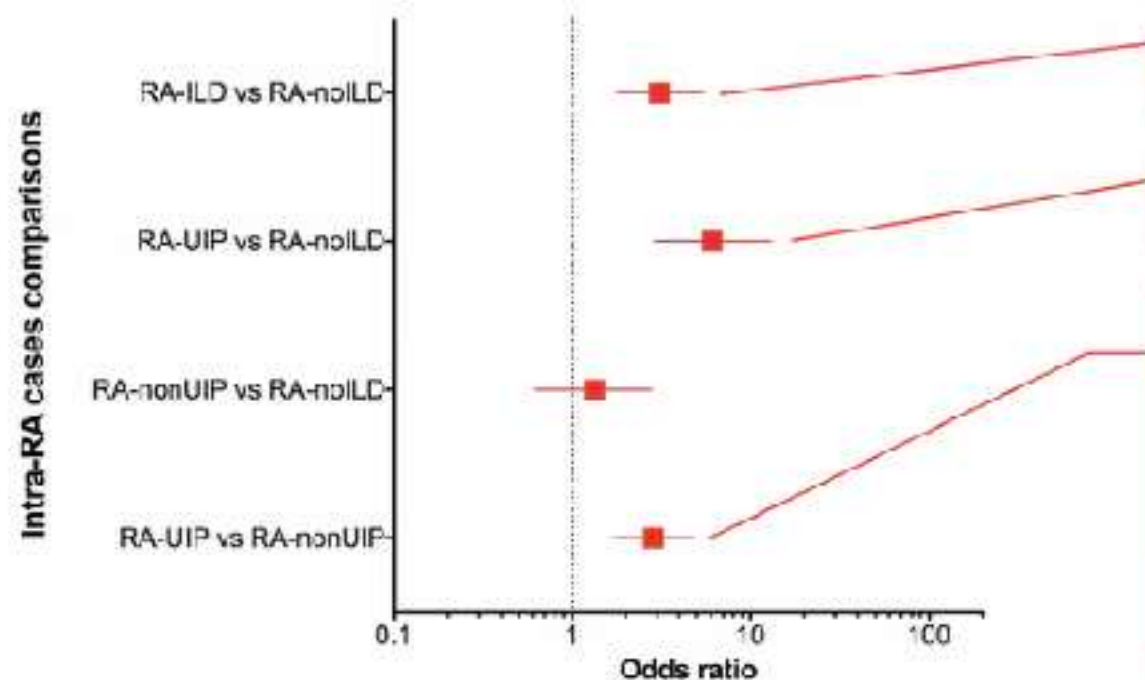


Juge PA et al. *N Engl J Med*. 2018.

Individual risk factors

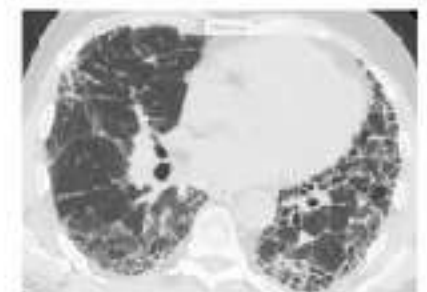
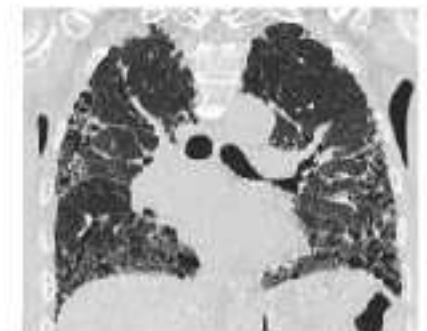
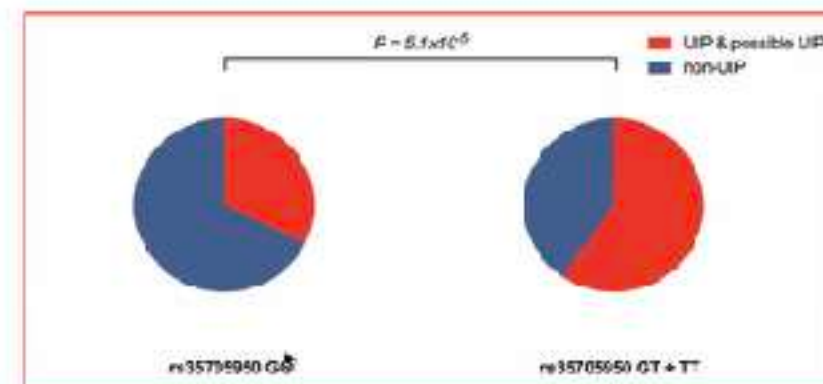
- ***MUC5B* rs35705950** shared risk factor with IPF
- **Strongest RA-ILD genetic risk factor (OR >3)**
- Association restricted to the UIP pattern

Suggest a common pathophysiology between IPF and RA-UIP



OR 3.1 (1.8-5.4)

OR 6.1 (2.9-13.1)



Individual risk factors

- Shared risk factors with IPF
- Independent replication required

SNP	Nearest gene	Minor allele frequency (%)						Genotypic association test			
		France		USA		Mexico		Crude		Adjusted**	
		RA-ILD n=118	RA-noILD n=105	RA-ILD n=99	RA-noILD n=68	RA-ILD n=55	RA-noILD n=69	Odds Ratio (95%CI)	P value	Odds Ratio (95%CI)	P value
rs6793295	LRR34	21.9	21.2	29.7	32.1	60.8	60.9	0.89 (0.68-1.15)	0.36	0.84 (0.55-1.25)	0.39
rs2609255	FAM13A	28.6	28.7	25.3	25.4	29.4	37.5	0.89 (0.67-1.16)	0.38	0.89 (0.52-1.29)	0.54
rs2736100	TERT	46.5	42.2	48.1	47.8	71.6	71.7	1.00 (0.79-1.27)	0.99	1.18 (0.84-1.67)	0.35
rs7887	EHMT2	42.3	38.6	36.7	42.5	58.8	72.5	0.82 (0.54-1.04)	0.10	0.91 (0.64-1.29)	0.59
rs2076795	DSP	50.0	50.0	44.3	46.3	31.0	34.0	1.01 (0.80-1.28)	0.94	1.03 (0.73-1.46)	0.85
rs4727443	Intergenic	35.2	46.0	41.8	35.8	50.0	53.7	0.83 (0.65-1.07)	0.15	0.76 (0.53-1.07)	0.11
rs11191865	OBFC1	49.5	46.8	38.0	55.4	37.3	43.4	0.81 (0.52-1.05)	0.11	1.13 (0.78-1.65)	0.52
rs35705950	MUC5B	32.6	12.9	28.8	11.0	16.4	3.6	3.63 (2.54-5.31)	7.31x10⁻¹³	3.00 (1.86-4.99)	1.15x10⁻⁰⁵
rs5743890	TOLLIP	21.5	14.2	16.7	15.1	10.0	4.5	1.61 (1.06-2.48)	0.03	2.13 (1.13-4.10)	0.02
rs111521887	TOLLIP	15.7	18.0	19.2	12.3	6.9	4.4	1.33 (0.89-1.98)	0.16	0.96 (0.55-1.69)	0.89
rs1278769	ATP11A	19.6	26.1	23.4	23.8	12.7	18.1	0.83 (0.61-1.12)	0.22	0.64 (0.41-0.99)	0.05
rs2034650	IVD	43.3	53.7	41.0	48.4	27.5	38.1	0.71 (0.54-0.95)	0.02	0.59 (0.38-0.89)	0.01
rs12610495	DPP9	31.4	33.0	32.9	31.1	19.6	12.5	1.14 (0.87-1.50)	0.33	1.19 (0.82-1.75)	0.37

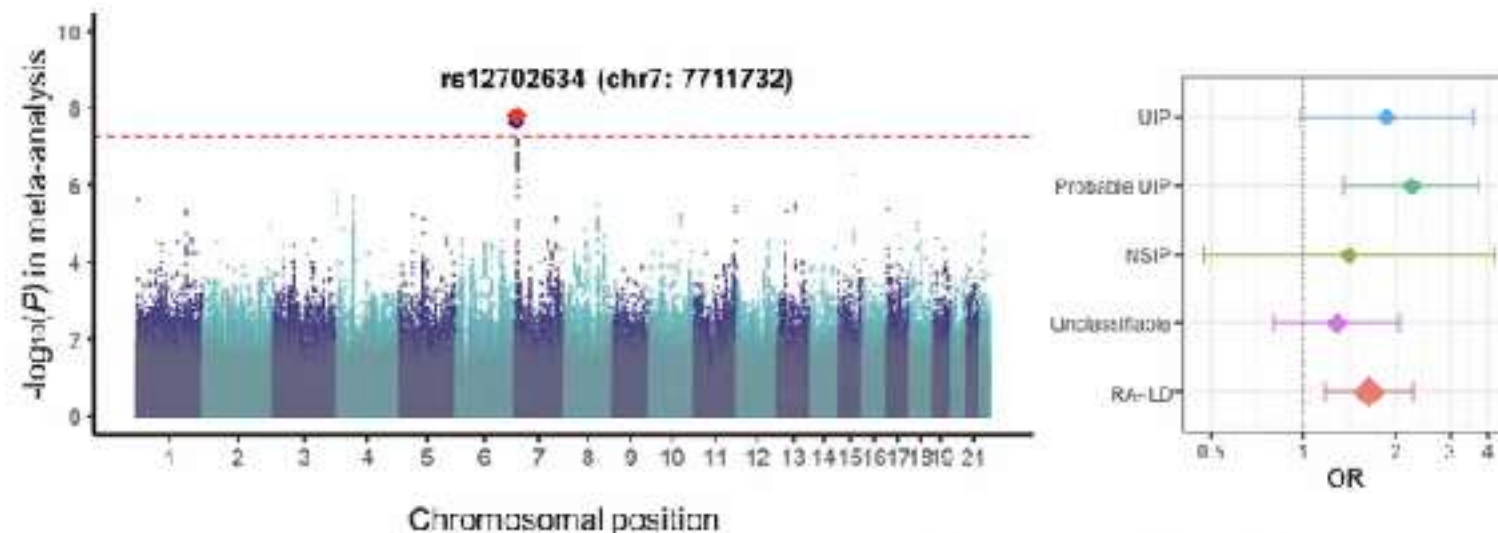
Juge PA et al. N Engl J Med. 2018.

Biomarkers of potential interest

▪ *RPA3-UMAD1* ?

- GWAS performed in the Japanese population
- *RPA3-UMAD1* rs12702634: OR 2.04 ; 95%CI (1.04-2.60), $P= 1.5 \times 10^{-8}$
- RPA3: potential role in telomerase activity

358 RA-ILD vs 4550 RA-noILD



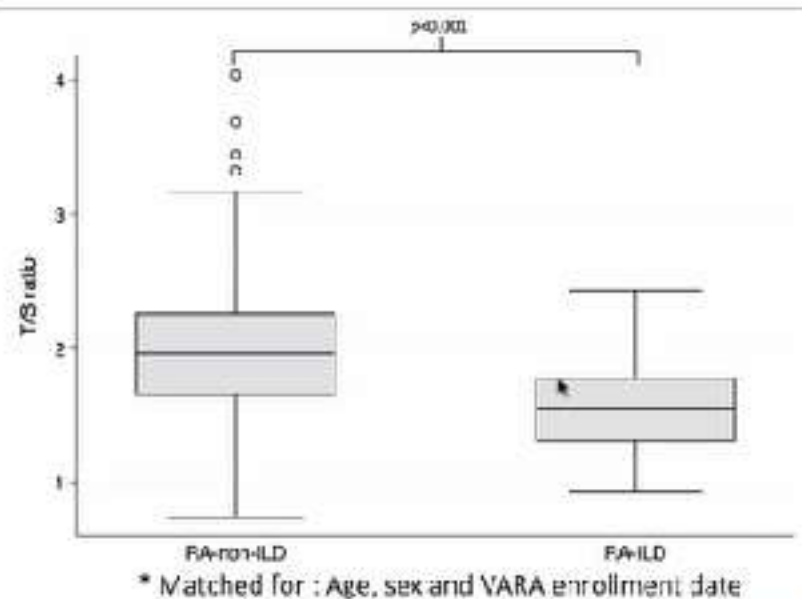
Shiroti Y et al. Ann Rheum Dis. 2020;

Biomarkers of potential interest

- Short TL length associated with prevalent RA-ILD
- Telomere related genes : excess of rare variants

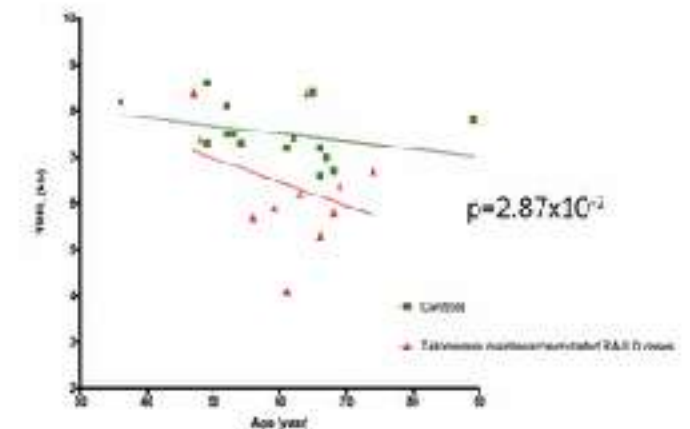
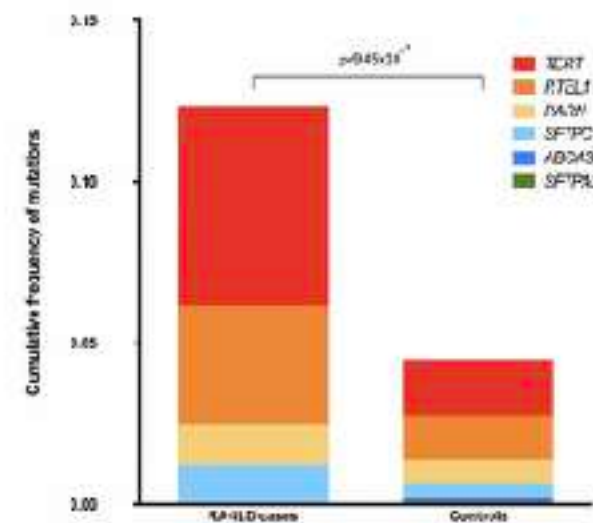
TL : 54 RA-ILD vs matched* RA-noILD
(cross-sectional study VARA cohort)

OR 6.60, 95% CI 1.78-24.51; $p = 0.005$



WES: 101 RA-ILD vs 1010 healthy controls

OR 3.17 95% CI 1.53–6.12; $p = 9.45 \times 10^{-4}$

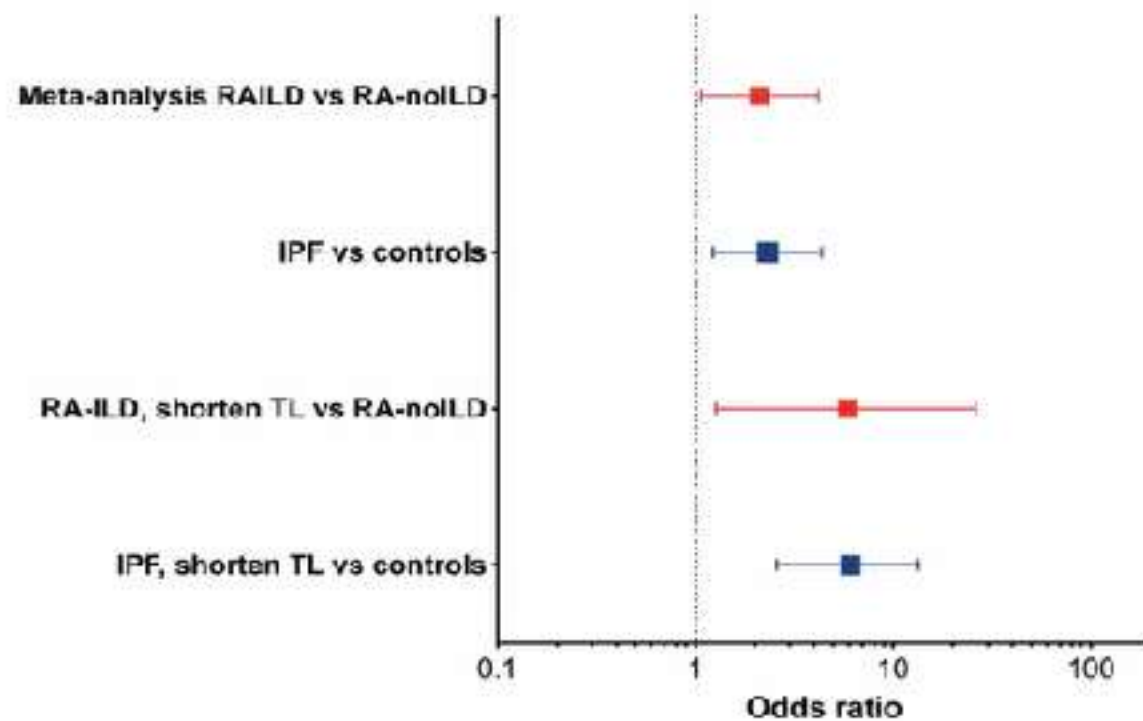


Juge PA et al. Eur Respir J. 2017; Natalini JG et al. Respir Med 2022.

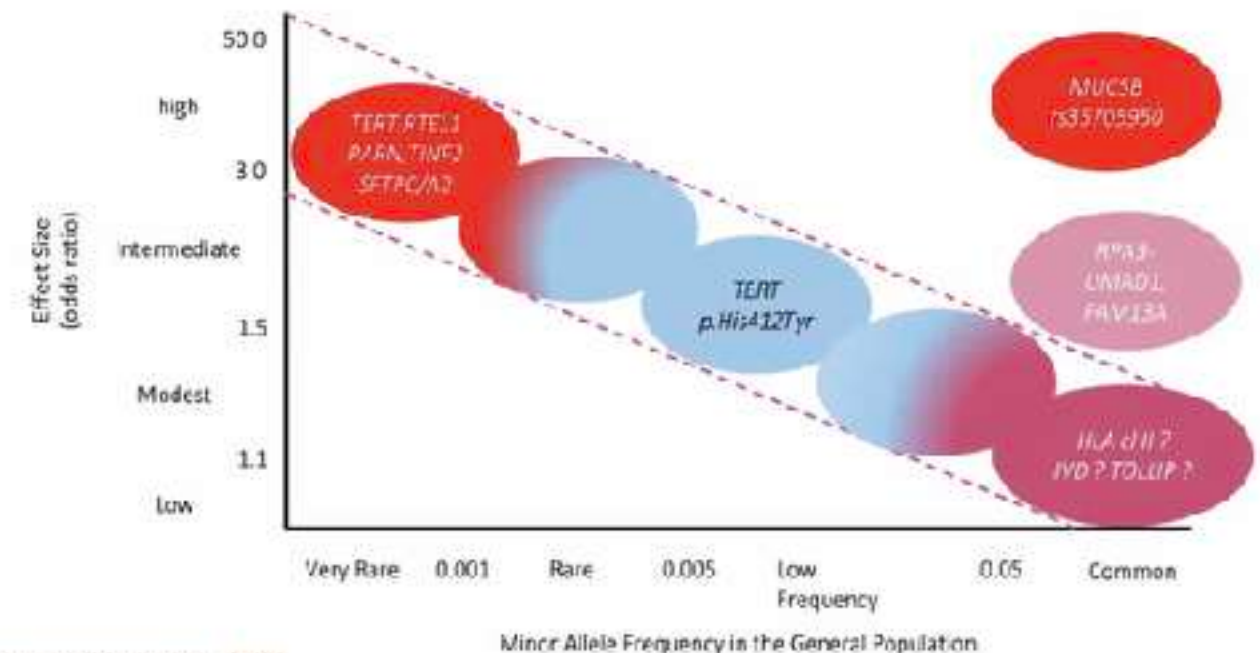
Biomarkers of potential interest

- Strong contribution of TRGs in RA-ILD risk
- Notably in patient with short TL (<10th percentile)
- Similar contribution in IPF risk

WES : 242 RA-ILD vs. 536 RA-noILD
1277 IPF vs. 1874 controls



Major contribution of TRGs & *MUC5B*



Juqz PA et al. ACR Convergence meeting San Diego, 2023

RA-related risk factors

- RA disease activity & RA duration (incident ILD)
- RF & ACPA + status : controversial...

Brigham RA Sequential Study (BRASS, 2003–2016): Prospective 1,419 patients with RA – 85 incident RA-ILD

4-level ordinal DAS28

	Remission (<2.6) HR (95% CI)	Low (2.6 to 3.2) HR (95% CI)	Moderate (>3.2 to 5.1) HR (95% CI)	High (>5.1) HR (95% CI)	P for trend
Cases/person – years	18/4,232	8/1,227	20/1,828	15/680	
Unadjusted	1.00 (Ref)	1.57 (0.68-3.62)	2.73 (1.44-5.17)	5.88 (2.92-11.82)	<0.001
Multivariable – adjusted ^a	1.00 (Ref)	1.41 (0.51-3.28)	2.08 (1.06-4.05)	3.48 (1.64-7.38)	0.001

^aPlus-minus values are means $\pm$ SD. ¹P values were adjusted for sex and country of origin, except where indicated.

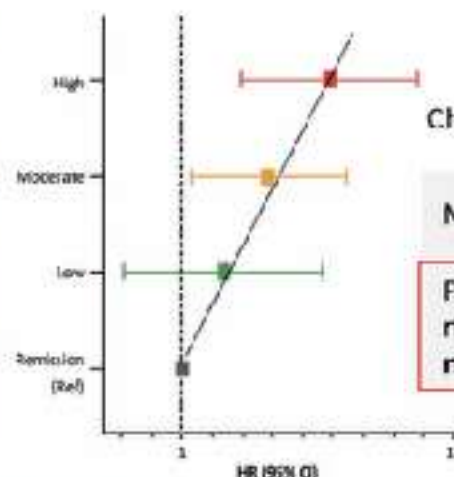
²The multivariable model was adjusted for age, sex, smoking pack-years, rheumatoid arthritis duration, and serologic status.

ACPA, anti-citrullinated peptide antibody; BRASS, Brigham RA Sequential Study; CI, confidence interval; HR, hazard ratio; CRP, c-reactive protein; DAS28, disease activity score-28; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; RF, rheumatoid factor.

Koduri G et al. *Rheumatology (Oxford)* 2010;49:1483–9; Kelly C et al. *Rheumatology (Oxford)* 2014;53:1676–82; Juge PA et al. *N Engl J Med* 2018;379:2209–19; Sparks JA et al. *Arthritis Rheumatol* 2019;71:1472–82.

Case-control; 614 RA-ILD vs 620 RA-noILD, all patients assessed by HRCT – Multi-ethnic

Baseline Characteristics of Patients with Rheumatoid Arthritis (RA)¹



Characteristic

Manifestations of RA

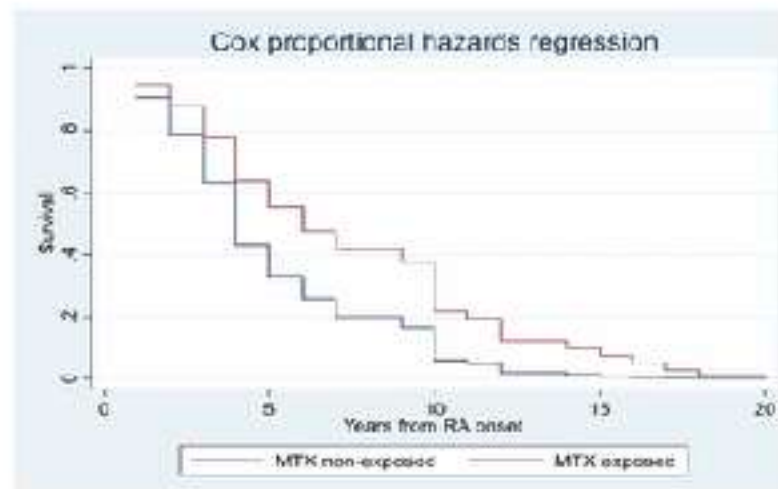
Positivity for ACPA or
rheumatoid factor —
no./total no. (%)

	RA-ILD (N=620)	RA without ILD (N=614)	Adjusted P Value ¹
Positivity for ACPA or rheumatoid factor — no./total no. (%)	449/506 (88.7)	446/468 (95.3)	0.72

Main RA-ILD risk factors

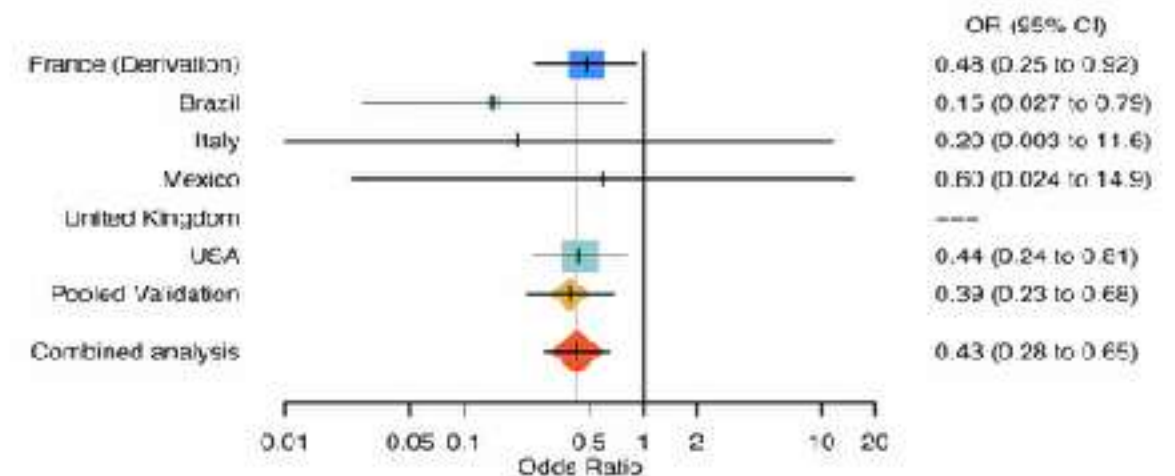
- MTX is **NOT** a risk factor
- ILD occurrence delayed in MTX users

**Cohort/analysis retrospective;
2721 RA/ 92 incident RA-ILD - UK**



OR 0.48, 95%CI [0.30-0.79], $P=0.004$

**Retrospective; 482 RA-ILD vs. 741 RA-noILD, all
patients assessed by HRCT - Multi-ethnic**

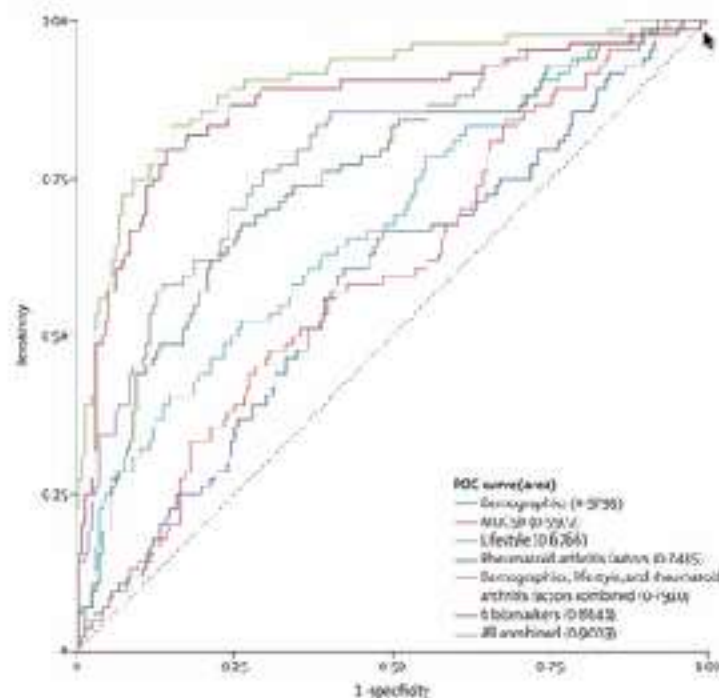


OR 0.43, 95%CI [0.28-0.65], $P=0.0006$
Independent of the HRCT pattern

Biomarkers of potential interest

- Fine-specificity ACPAS & anti-native proteins
- IgA isotypes (mucosal origins hypothesis of RA)
- Risk score to predict incident RA-ILD

Brigham RA Sequential Study (BRASS, 2003–2016): nested case-control study (84 incident RA-ILD vs 223 RA-noILD)



	Apparent AUC (95% CI)	Optimism	Optimism-corrected AUC (95% CI)
Demographic*	0.58 (0.51–0.65)	0.07	0.51 (0.45–0.57)
MUC5B promoter variant	0.60 (0.53–0.67)	0.05	0.55 (0.48–0.61)
Lifestyle†	0.68 (0.62–0.75)	0.04	0.64 (0.58–0.70)
Rheumatoid arthritis factors‡	0.74 (0.68–0.81)	0.06	0.68 (0.62–0.74)
Clinical factors§ combined	0.79 (0.73–0.85)	0.06	0.73 (0.67–0.78)
Established rheumatoid arthritis-associated ILD factors¶	0.80 (0.74–0.85)	0.07	0.73 (0.67–0.78)
Novel biomarkers (n=6)	0.86 (0.81–0.92)	0.03	0.84 (0.79–0.89)
All factors combined	0.90 (0.85–0.94)	0.06	0.84 (0.80–0.88)

Krause V et al. *Lancet Rheumatol* 2023.

Biomarkers of potential interest

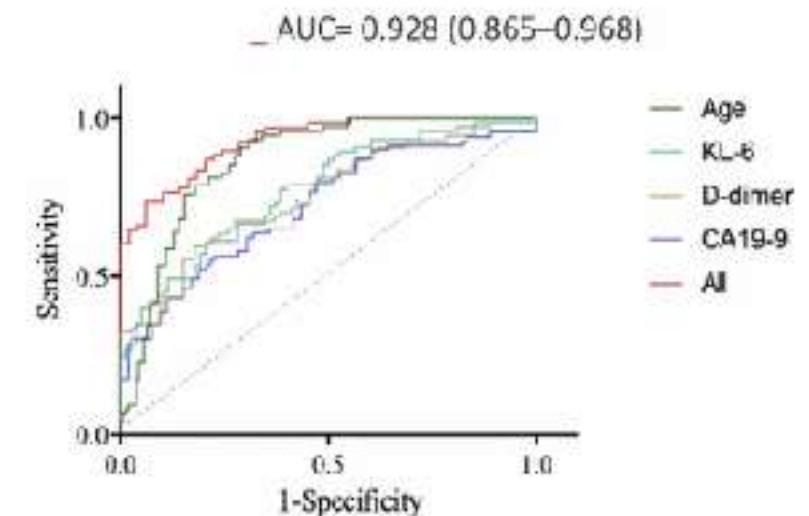
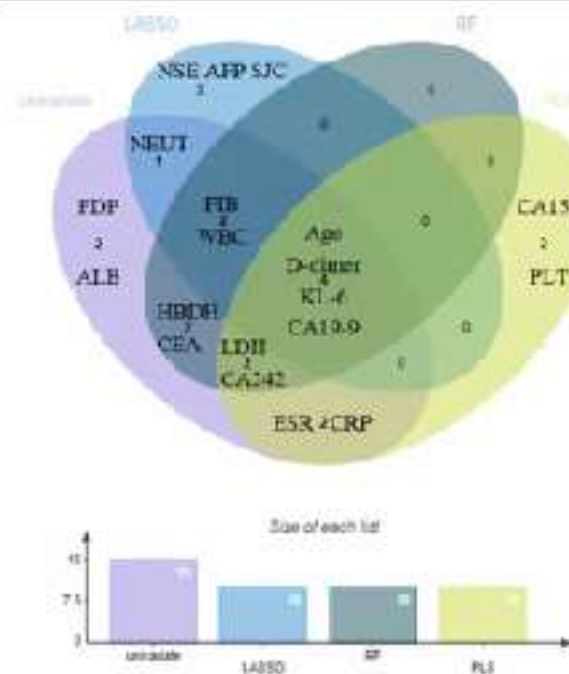
- KL-6, SP-D, D-dimer, CA 19-9, MMP 7, PARC, ...
- Mostly **unavailable** in current practice

Retrospective in BRASS & ACR cohorts , USA

Table 3. Biomarker Levels in a Spectrum of RA-ILD in BRASS and ACR cohorts

	BRASS Cohort			ACR Cohort			Combined Cohort		
	No RA- ILD (n = 29)	Subclinical RA-ILD (n = 29)	Clinically Evident RA-ILD (n = 17)	No RA- ILD (n = 22)	Subclinical RA-ILD (n = 18)	Clinically Evident RA-ILD (n = 21)	No RA- ILD (n = 51)	Subclinical RA-ILD (n = 47)	Clinically Evident RA-ILD (n = 28)
MMP7	5.7 ±2.5	9.1±3.3*	19.4± 3.2*	4.8 ± 2.1	10.0±5.4*	9.3±5.0*	5.3 ± 2.4	9.4±4.2*	9.8±4.3*
PARC	132 ±63	277±180±	160±72±	129 ±40	217±14*±	225± 157±	131 ±57	254±160±	200± 128±
SP-D	11.9 ±7.9	28.6± 12.0±	27.5± 29.7±	7.1 ± 3.1	18.4± 13.7±	31.2± 24.1±	8.8 ± 6.7	19.8± 12.6±	26.5± 24.0±

Restrospective case-control study (75 RA-ILD vs 78 RA-noILD) , China



Doyle T et al. AJRCCM 2014; Qin Y et al. Arthritis Res Ther 2022.