

Clinical and Serological Predictors of Interstitial Lung Disease in Rheumatoid Arthritis: Are Anti-Citrullinated Protein Antibodies Truly Relevant?

Martí Aguilar-Coll,^{1a} Javier Narváez,^{1a} Montserrat Roig-Kim,¹ Laia de Daniel Bisbe,¹ Pol Maymó-Paituvi,¹ Judith Palacios-Olid,¹ Joan Miquel Nolla¹

¹Department of Rheumatology, Bellvitge University Hospital, Bellvitge Biomedical Research Institute (IDIBELL), University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain; ^aMartí Aguilar-Coll and Javier Narváez equally contributed to this work.

OBJECTIVE

Evidence on which risk factors predict the development of ILD in patients with RA is scarce and of low scientific quality. This study examines whether several clinical and serological variables are associated with an increased risk of developing this complication.

METHODS

A retrospective study was performed in a cohort of patients with early RA (1987 ARA or 2010 ACR/EULAR criteria and symptom duration ≤ 12 months). All patients underwent ILD screening at diagnosis, which included targeted anamnesis for respiratory symptoms, chest auscultation for "velcro-like" crackles, CXR and PFTs with spirometry and DLCO. A thoracic HRCT was performed in case of symptoms, crackles or alterations in CXR or PFTs. Sex, age, smoking history, RF and ACPA variables were collected. Cumulative incidence curves (i.e. 1 minus Kaplan-Meier-estimated probability), Log-Rank test and a Cox regression model were applied to determine whether or not these variables are associated with an increased risk of ILD.

RESULTS

One hundred and eighty-eight RA patients without known ILD were included in the study. After a median follow-up time of 10.2 years (IQR 7.0-15.0), 30 new cases of ILD (16.0%) were diagnosed. The risk of developing lung involvement was higher among males and in patients aged ≥ 60 years (unadjusted Log-Rank p-value of 0.001 and 0.024, respectively) [table 1]. Cumulative incidence curves for these two variables are displayed in figures 1 and 2, respectively. In contrast, smoking, RF and ACPA showed no statistical differences, neither when tobacco dose or antibody titre were considered ($p > 0.05$ in all scenarios). The results of a Cox regression model including all five variables is shown in table 2. Male sex showed a HR of 3.62 (95% CI 1.44-9.15) for the development of ILD compared to females ($p = 0.006$). A 10-year increase in the age at the time of RA diagnosis entailed a risk 45% higher (1.03-2.04) for the development of this complication ($p = 0.034$). Smoking, RF and ACPA also failed to show significant results in the multivariate analysis ($p > 0.05$ in all three cases).

Table 1. Comparison of CI curves of each variable using Log-Rank test

	Log-Rank p-value
Male sex	0.001
Age (≥ 60 years)	0.024
Smoking	
Ever vs never smoker	0.164
1-20 vs 0 pack-years	0.249
>20 vs 0 pack-years	0.137
>20 vs 1-20 pack-years	0.923
Rheumatoid factor (RF)	
(+) vs (-)	0.728
(+) ≤ 3 times the ULN vs (-)	0.232
(+) >3 times the ULN vs (-)	0.511
(+) >3 times the ULN vs (+) ≤ 3 times the ULN	0.108
Anti-citrullinated protein antibodies (ACPA)	
(+) vs (-)	0.493
(+) ≤ 3 times the ULN vs (-)	0.352
(+) >3 times the ULN vs (-)	0.408
(+) >3 times the ULN vs (+) ≤ 3 times the ULN	0.265

Abbreviations: (+) = positive; (-) = negative; ULN = upper limit of normal

Table 2. Cox regression model including all five variables

	HR	95% CI	p-value
Male sex	3.62	1.44-9.15	0.006
Age (10-year increase)	1.45	1.03-2.04	0.034
Smoking	0.92	0.56-1.49	0.722
Rheumatoid factor (RF)	1.34	0.68-2.63	0.392
Anti-citrullinated protein antibodies (ACPA)	0.95	0.52-1.74	0.875

Abbreviations: HR = hazard ratio; 95% CI = 95% confidence interval

Figure 1. Cumulative incidence curve of ILD according to sex

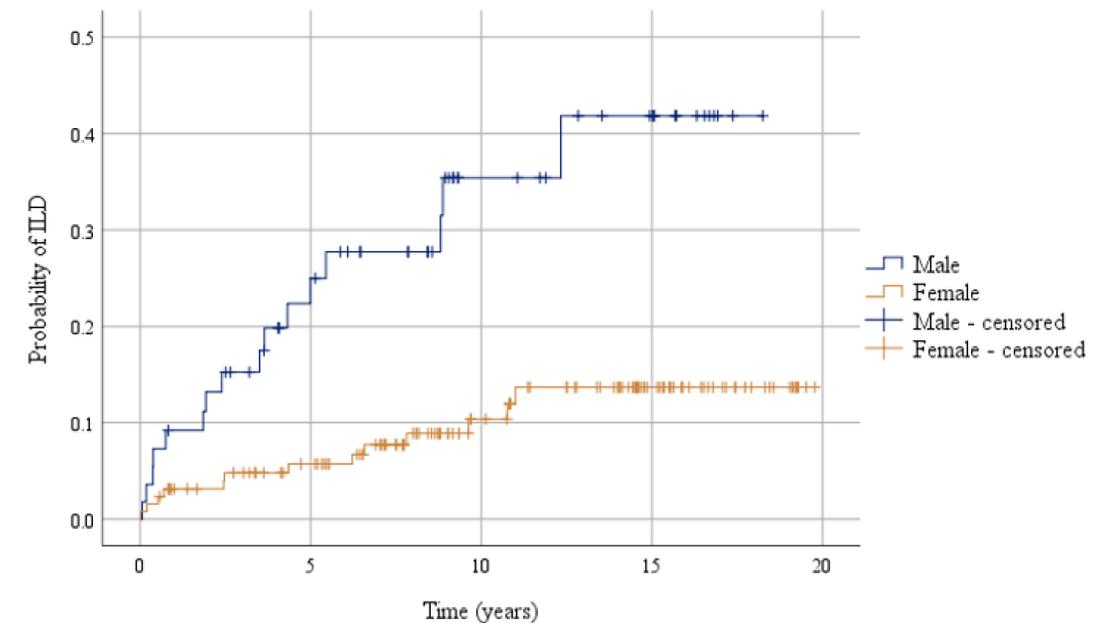
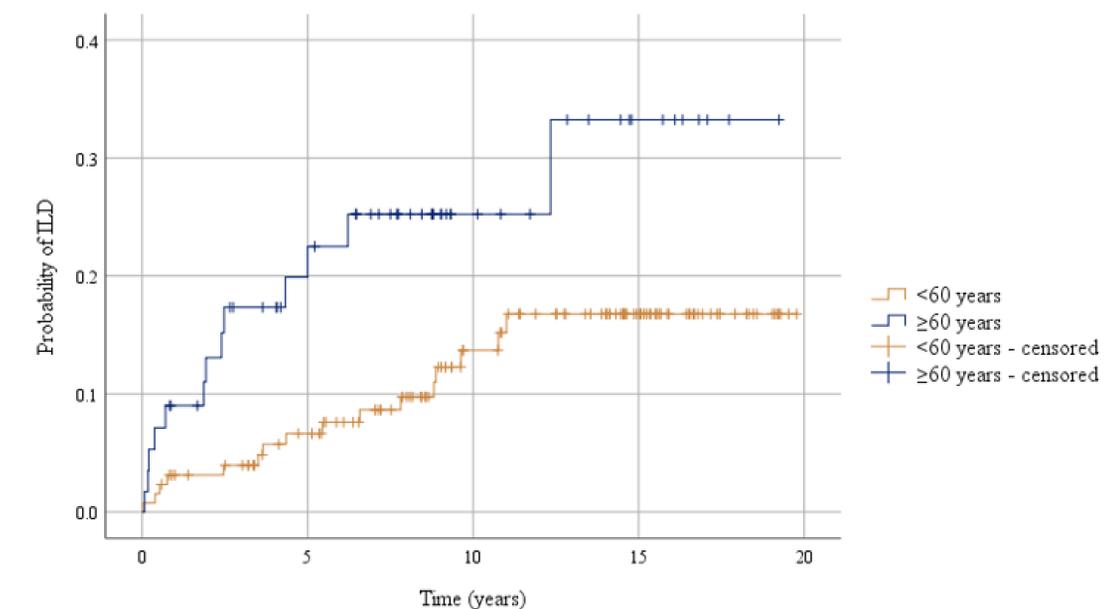


Figure 2. Cumulative incidence curve of ILD according to age at RA diagnosis



CONCLUSION

In accordance with published evidence, both male sex and older age at diagnosis are associated with a greater risk of developing ILD. However, the increased risk attributed to tobacco exposure and the presence of RF and/or ACPA, especially at high titres, has not been demonstrated in this study.