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The Influence of Sex on Prognosis of Patients With Idiopathic Pulmonary Fibrosis in a Retrospective Cohort☆

Influencia del género en el pronóstico de pacientes con fibrosis pulmonar idiopática en una cohorte retrospectiva

To the Editor,

Idiopathic pulmonary fibrosis (IPF) is a disease that occurs more often in men, with a reported male:female ratio of between 1.6:1 and 2:1.[1,2] Previous studies indicate that the course of IPF may be more benign in women, an observation which could be based on differences in gene expression.[3–5] Given that these studies were conducted prior to the publication of the current diagnostic criteria, and without taking into account the variable of autoantibodies, patients with diagnoses other than IPF might have been included. We believed, then, that a new study comparing the progress of these patients according to gender could provide valuable information.

For this reason, we decided to perform this retrospective cohort study in patients with a diagnosis of IPF (according to the 2011 ATS/ERS/JPS/ALAT)[6] seen in a multidisciplinary clinic specializing in interstitial lung diseases (ILD). Patients were recruited between March 2012 and July 2015. The main study outcome variable was time from date of diagnosis to date of all-cause death or lung transplantation. The main study exposure variable was sex. The following variables were analyzed to avoid potential confusion between sex and the outcome variable: age, smoking, time of dyspnea in months, the development of acute exacerbations (defined according to current international recommendations),[7] rheumatoid factor (RF) by nephelometry, and antinuclear antibodies (ANA) by indirect immunofluorescence. Other study variables included previous treatment with triple therapy (systemic corticosteroids, azathioprine, and N-acetylcisteine) before attending our clinic, and use of pirfenidone. Results were communicated according to the indications of the STROBE initiative.[8]

Time of death or transplantation was estimated using Kaplan–Meier methods. The rates of events between the sexes at 18 months were studied using survival estimators and 95% confidence intervals, and compared using the log rank test. A multivariate Cox model was applied, using sex as the first independent variable. Variables that were significant in the univariate analysis and those considered clinically relevant were included. Both crude and adjusted HR and their 95% CI were reported. A *P*-value of <.05 was considered statistically significant.

The study included 86 patients, of which 21 were women (24.4%). Mean (SD) age was 65.4 (9) years. When characteristics were compared by sex, the prevalence of smoking was higher among men (84.6% vs 59.1%, *P*<.01). No significant differences in age, baseline forced vital capacity (FVC%), time since onset of dyspnea, or percentage of patients with positive ANA or RF were found at diagnosis. No differences were observed in the time of administration or proportion of patients who received triple therapy prior to attending our clinic, nor in the percentage of patients who received pirfenidone or had an acute exacerbation. In the analysis of time to death or transplantation, overall all-cause mortality was 38.4% (33/86), 35.4% (23/65) in men, and 47.6% (10/21) in women. Median survival was 34.03 months in women and 36.06 months in men. Four patients received a lung transplant (3 men) and the indication for transplantation was established at the time of diagnosis. When survival at 18 months was compared by sex, no statistically significant differences were observed, with rates of 0.75 (95% CI, 0.61–0.85) in men and 0.71 (95% CI, 0.44–0.87) in women (*P* = .88). In the Cox univariate analysis (Table 1), treatment with pirfenidone was associated with longer survival, but this effect disappeared after adjusting for the remaining variables included. In the Cox multivariate analysis, the only variable that showed statistical significance was baseline FVC% (Table 1).

In our study, we found no significant differences when the survival of patients with IPF was compared by sex. Treatment with pirfenidone was significantly associated with better survival in the univariate analysis, but this effect disappeared in the multivariate analysis, although it maintained a trend toward statistical significance. This may be explained by the fact that patients who received pirfenidone had baseline FVC≥50% predicted value. Our study has some limitations. It is a retrospective study conducted in a single center. Moreover, with the exception of ANA and RF, other antibodies were not routinely analyzed. However, all patients were evaluated by the clinical immunology department, which ruled out the presence of an autoimmune disease by additional tests and determination of specific antibodies (e.g., citrullinated peptide antibodies or myospecific antibodies), when necessary.[9] Previous studies indicate that the female sex is associated with better survival in IPF, and was considered a factor for good prognosis in a score proposed by a group of researchers.[4,10] However, these studies were performed using the ATS/ERS criteria from the year 2000. A recent study showed that of 60 patients who met diagnostic criteria in the year 2000, only 46 met the current diagnostic criteria,[11] suggesting that approximately 25% of patients with IPF according to previous criteria could have had another IPD. This is of interest, given the differences in survival between IPF and other ILD.[12] Chronic hypersensitivity pneumonitis may be confused with IPF, which is relevant, since it has a more benign disease course.[11] Autoimmune diseases are more common in women[13] and may

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Table 1
Unadjusted and Adjusted HR for Time to Death or Transplantation in a Cohort of Patients with Idiopathic Pulmonary Fibrosis Between 2012 and 2015 (*N* = 86).

	Unadjusted HR (95% CI)	*P*-Value	Adjusted HR (95% CI)	*P*-Value
Sex	0.89 (0.42–1.89)	.78	1.08 (0.36–3.22)	.88
Age at diagnosis, years	0.99 (0.95–1.03)	.79	1.01 (0.96–1.07)	.48
Smoking habit	0.63 (0.29–1.32)	.22	1.15 (0.43–3.08)	.48
Baseline FVC%	0.96 (0.94–0.99)	.01	0.96 (0.92–0.99)	.01
Positive ANA or RF	0.87 (0.43–1.78)	.77	1.05 (0.44–2.48)	.90
Received pirfenidone	0.27 (0.10–0.73)	.01	0.37 (0.13–1.08)	.07
Received triple therapy	0.83 (0.36–1.9)	.66	0.52 (0.17–1.59)	.25

ANA: antinuclear antibody; FVC%: forced vital capacity as percentage; IPF: idiopathic pulmonary fibrosis; RF: rheumatoid factor; HR; hazard ratio; CI: confidence interval.

present a pattern of usual interstitial pneumonia indistinguishable from IPF,[14,15] and generally associated with better survival. We believe that including autoantibodies in a survival analysis according to sex in patients with IPF is of crucial importance. Our study has been the first to include this adjustment variable and to use current diagnostic criteria to analyze the relationship between sex and survival in patients with IPF. As the patients included in our study meet the current criteria of IPF, and were evaluated by a specialist multidisciplinary group, we believe that our results are valid and can be extrapolated to other populations. However, prospective studies are needed to confirm our results.

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Perceptions and Use of the e-Cigarette Among University Students☆

Percepciones y uso del cigarrillo electrónico en estudiantes universitarios

To the Editor,

The long-term effects of use of electronic cigarettes (e-cigarette) to control smoking has generated both debate and concern in the public health arena.[1] The prevalence of this device varies among the various European countries.[2] In general, however, it appears to be more widely used by individuals aged between 15 and 24 years,[3] and e-cigarette use is positively associated with being a student.[4] Nevertheless, little is known about the use of e-cigarettes and how they are perceived among young people in Spain. This study, then, was conducted in this setting, with the aim of determining the perceptions of university students of e-cigarettes and how they use these devices.

This was a cross-sectional study conducted in a reference population of undergraduate students enrolled in the 2015–2016 academic year in the Universidad de Almeria, with a calculated sample size of 373 students. Data were collected using a self-administered online questionnaire consisting of a total of 14 items ranging from sociodemographic variables, smoking habit, physical activity, and awareness, use and perception of the e-cigarette. For

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