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Clinical Characterization of patients with Idiopathic Pulmonary Fibrosis in a Tertiary Hospital of the City of Quito-Ecuador

Caracterización clínica de pacientes con fibrosis pulmonar idiopática en un hospital de tercer nivel en la ciudad de Quito-Ecuador

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ABSTRACT

Introduction: idiopathic pulmonary fibrosis is a progressive, fatal disease characterized by the findings of usual interstitial pneumonia in a high resolution tomography or lung biopsy, or in a multidisciplinary discussion, also discarding other etiologies such as connective tissue diseases or diseases associated with toxic exposure.
The objective of this work was to know the clinical characteristics, lung function and survival of the group of patients diagnosed with idiopathic pulmonary fibrosis who were evaluated at the Interstitial Lung Disease Clinic of the Hospital Carlos Andrade Marín.
Materials and methods: retrospective, cross-sectional, observational study. The study population consisted of patients diagnosed with idiopathic pulmonary fibrosis who had been treated at the Interstitial Lung Disease Clinic of the Hospital Carlos Andrade Marín between January, 2018 and February, 2020.
Results: 85.7% of the 35 patients with idiopathic pulmonary fibrosis included in the analysis were male. At the time of the diagnosis, the mean age was 69.7 years (SD [standard deviation]: 9.26, range: 38-87 years). 20% and 37.1% of patients showed dyspnea grade 3 and 4, respectively. 60% had smoking history.
45.7% of the diagnoses were made with a multidisciplinary clinical evaluation and high resolution computed axial tomography.
Conclusions: we have reported the largest cohort of patients with idiopathic pulmonary fibrosis in Ecuador; our results identified similar populations with other study groups where the high resolution computed tomography and multidisciplinary analysis are the most used methods for the diagnosis.

Key words: Idiopathic pulmonary fibrosis; Emphysema; Survival

RESUMEN

Introducción: la fibrosis pulmonar idiopática es una enfermedad progresiva y fatal caracterizada por el hallazgo de neumonía intersticial usual en tomografía de alta resolución o biopsia pulmonar, o en discusión multidisciplinar y el descarte de otras etiologías como enfermedades del tejido conectivo o exposicionales.

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En cuanto a los objetivos de este trabajo, consisten en conocer las características clínicas, la función pulmonar y la supervivencia del grupo de pacientes con diagnóstico de fibrosis pulmonar idiopática evaluados en la clínica de intersticiales del Hospital Carlos Andrade Marín.

Materiales y métodos: se trata de un estudio transversal, retrospectivo, observacional. La población de estudio la constituyeron los pacientes con diagnóstico de fibrosis pulmonar idiopática atendidos en la clínica de intersticiales del Hospital Carlos Andrade Marín entre enero del 2018 y febrero del 2020.

Resultados: de 35 pacientes con fibrosis pulmonar idiopática incluidos para el análisis, el 85,7 % fueron del sexo masculino. Al momento del diagnóstico, la edad promedio fue de 69,7 años (DE: 9,26, Rango: 38-87 años). El 20 % y 37,1 % presentaron disnea de grado 3 y grado 4, respectivamente. El 60 % presentaron antecedentes de tabaquismo.

El 45,7% de los diagnósticos se hicieron tanto con evaluación clínica multidisciplinaria y tomografía axial computarizada de alta resolución.

Conclusiones: hemos informado la mayor cohorte de fibrosis pulmonar idiopática en el Ecuador, nuestros resultados han identificado poblaciones similares con otros grupos de estudio en los que la tomografía computarizada de alta resolución y el análisis multidisciplinar son los métodos más utilizados en el diagnóstico.

Palabras clave: Fibrosis pulmonar idiopática; Enfisema; Sobrevida

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial disease of unknown origin and poor prognosis, which ranges between 2 and 5 years of survival from time of diagnosis. It is the most common form of diffuse interstitial lung disease (DILD), with a prevalence that oscillates between twelve cases for every 100,000 women and 20 cases for every 100,000 men.[1]

This disease has an insidious onset of symptoms, with non-specific symptoms characterized by progressive dyspnea, dry cough, Velcro-type tele-inspiratory crackles and acropachy.[1]

The diagnosis is based on the findings of usual interstitial pneumonia (UIP) in the high resolution computed tomography (HRCT) or lung biopsy, or in a multidisciplinary discussion, also discarding other etiologies, such as connective tissue diseases or diseases associated with toxic exposure. Treatment is based on antifibrotic agents, symptom management, and respiratory rehabilitation.[2, 3]

The first Latin American study reported 761 ill patients diagnosed with idiopathic pulmonary fibrosis, where Argentina and Mexico had the largest number of reported patients, 30.5% and 27.3%, respectively. 1.7% (n = 13) of the cases were from Ecuador.[4]

There are no DILD data in Ecuador, so the national epidemiologic characterization is complex. Taking this situation into account, the Hospital de Especialidad Carlos Andrade Marín has created a DILD Clinic of national reference, which was established in a multidisciplinary way, thus allowing for the optimization of diagnosis, treatment, and registration processes. Furthermore, access to antifibrotic treatment in the country is limited, on the one hand, due to the little availability in specialized care centers, and on the other hand, to the cost of these drugs. This situation has a negative impact on survival, as shown by Cottin.[5]

The objective of this work was to know the clinical characteristics, lung function and survival of the group of patients diagnosed with IPF who were evaluated at the Interstitial Lung Disease Clinic of the Hospital Carlos Andrade Marín.

MATERIALS AND METHODS

Retrospective, cross-sectional, observational study. The study population consisted of patients diagnosed with IPF who had been treated at the Interstitial Lung Disease Clinic of the Hospital Carlos Andrade Marín between January, 2018 and February, 2020.

Inclusion criteria comprised adult patients who met the diagnostic criteria of the 2012 and 2018 ATS/ERS/JRS/ALAT Guidelines for UIP, confirmed through tomography

or lung biopsy, in whom a secondary disease was discarded; also, the patients who had been analyzed by a multidisciplinary committee, with complete medical records were included. Exclusion criteria: pediatric patients, patients with other secondary interstitial diseases, or neoplasia, and those who didn't do the lung function tests.

Variables under evaluation: age, sex, tobacco use, gastroesophageal reflux disease, pulmonary emphysema, family history of pulmonary fibrosis, clinical characteristics (cough, grade of dyspnea, Velcro-type crackles, acropachy), respiratory functional characteristics, such as forced vital capacity (FVC) in liters and expressed as percentage of predictive value, diffusing capacity of the lungs for carbon monoxide (DLCO) as percentage of predictive value, six-minute walk test, diagnostic method (HRCT, lung biopsy or multidisciplinary discussion) and treatment.

In smokers, we calculated the smoke index according to the number of packs consumed per year. The Charlson index was used to describe comorbidities.[6]

Statistical analysis

The descriptive analysis of qualitative variables was carried out by calculating absolute and relative frequencies. The results of quantitative variables were expressed as mean values, since data distribution was normal according to the Kolmogórov-Smirnov test.

Factors taken into account for the analysis of survival were: sex, age, smoking history, diagnosis of pulmonary emphysema, Charlson index, grade of dyspnea, systolic pressure of pulmonary artery and treatment with disease modifiers. Survival was assessed in general and according to different factors with Kaplan-Meier models; and the Log Rank Mantel Cox test was used to establish differences between the survival gaps. The association of mortality with risk factors was calculated through Cox Regression, obtaining the hazard ratio values with their corresponding confidence intervals. A *p*-value of less than 0.05 was taken into account for statistical significance.

RESULTS

One patient was excluded from a total of 36 potentially eligible patients, due to incomplete lung function tests.

Table 1 shows the general characteristics of the participants. 85.7% were male. At the time of the diagnosis, the mean age was 69.7 years (SD: 9.26, range: 38-87 years). 20% and 37.1% of patients showed dyspnea grade 3 and 4, respectively. 60% had smoking history. The mean amount of packs/year among smokers was 9.1 (SD: 11.45). 45.7% died during the follow-up period.

With regard to clinical history, diagnosis and treatment, 22.9% and 8.6% were diagnosed with gastroesophageal reflux and pulmonary emphysema, respectively. 45.7% of the diagnoses were made both through multidisciplinary clinical evaluation and HRCT. 28.6% received treatment with disease-modifying drugs (17.1%, nintedanib and 11,4%, pirfenidone) (Table 2).

TABLE 1. Clinical and demographic characteristics of patients with idiopathic pulmonary fibrosis

Variable	n	%
Sex		
Male	30	85.7%
Female	5	14.3%
Age		
< 65 years	11	31.4%
> 65 years	24	68.6%
Dry cough		
Yes	34	97.1%
No	1	2.9%
Dyspnea (mMRC)		
Grade 1	5	14.3%
Grade 2	10	28.6%
Grade 3	7	20.0%
Grade 4	13	37.1%
Velcro-type crackles		
Yes	35	100.0%
No	0	0.0%
Acropachy		
Yes	18	51.4%
No	17	48.6%
Smoking		
Yes	21	60.0%
No	14	40.0%
State		
Alive	19	54.3%
Deceased	16	45.7%

mMRC: Modified Medical Research Council scale

Table 3 shows the physiological parameters evaluated in patients with IPF. The mean FVC obtained was 72.74% (range: 40 to 115), whereas the DLCO was 67.57% (range: 35-129). The mean distance travelled in the six-minute walk test was 447.23 m (SD: 85.60). The mean value of arterial oxygen pressure (mmHg) was 52-27 (SD: 13.72) with the height of Quito (2850 m). The mean value of the pulmonary artery systolic pressure was 42.44 mmHg (SD: 16.47).

Mean survival of analyzed patients was 57.24 months (95% CI: 45.07%-69.41%, SD: 6.21). When reaching 15 months of follow-up, around 15% (n = 5) of patients died. At 30 and 45 months, the cumulative mortality was 24% (n=8) and 36% (n=13). Until 65 months, the cumulative mortality reached 63% (n=22) (Figure 1).

Factors associated with survival are explained in Table 4. The diagnosis of pulmonary emphy-

TABLE 2. Clinical history, diagnosis and treatment of patients with idiopathic pulmonary fibrosis

Variable	n	%
Family history of pulmonary fibrosis		
Yes	8	22.9%
No	27	77.1%
Enfermedad por reflujo gastroesofágico		
Yes	8	22.9%
No	27	77.1%
Emphysema		
Yes	3	8.6%
No	32	91.4%
Charlson index		
< 3 points	18	51.4%
> 3 points	17	48.6%
Diagnostic method		
Biopsy	2	5.7%
Biopsy + multidisciplinary diagnosis	1	2.9%
Multidisciplinary diagnosis	16	45.7%
HRCT	16	45.7%
Treatment		
Expectant approach	26	71.4%
Nintedanib	6	17.1%
Pirfenidone	4	11.4%
Treatment withdrawal		
Yes	1	2.9%
No	34	97.1%

HRCT: high resolution computed tomography

TABLE 3. Physiological parameters of patients with idiopathic pulmonary fibrosis

Parameter	Mean (SD)	Range
FVC (liters)	2.52 (0.72)	(1.58-4.20)
FVC (%)	72.74 (18.17)	(40-115)
DLCO (%)	67.57 (21.14)	(35-129)
6-minute walk (meters)	447.23 (85.60)	(245-587)
Arterial oxygen pressure (mmHg)	52.27 (13.72)	(23-95)
Partial pressure of carbon dioxide (mmHg)	35.69 (11.55)	(28-93)
Pulmonary artery systolic pressure (mmHg)	42.44 (16.47)	(25-97)

FVC: forced vital capacity; DLCO: diffusing capacity of the lungs

sema was significantly associated with reduced survival time (HR: 4.210, 95% CI: 1.133-15.643, $p = 0.032$). Furthermore, patients older than 65 years (HR: 2.559, 95% CI: 0.779-8.409, $p = 0.122$), non-smokers (HR: 2.518 0.913-6.948, $p = 0.075$) with pulmonary hypertension (HR: 3.947, 95% CI: 0.926-16.832, $p = 0.063$) show clinically relevant mortality associations (Table 3).

The widest gaps in mean survival values according to the Kaplan-Meier analyses were observed in the following factors: age (< 65 years: 69.3 months versus > 65 years: 44.67), smoking (non-smokers: 45.44 months versus smokers: 71.77 months), diagnosis of emphysema (Yes: 29 months versus No: 60.87 months) and value of pulmonary artery systolic pressure (< 40 mmHg: 72.15 months versus

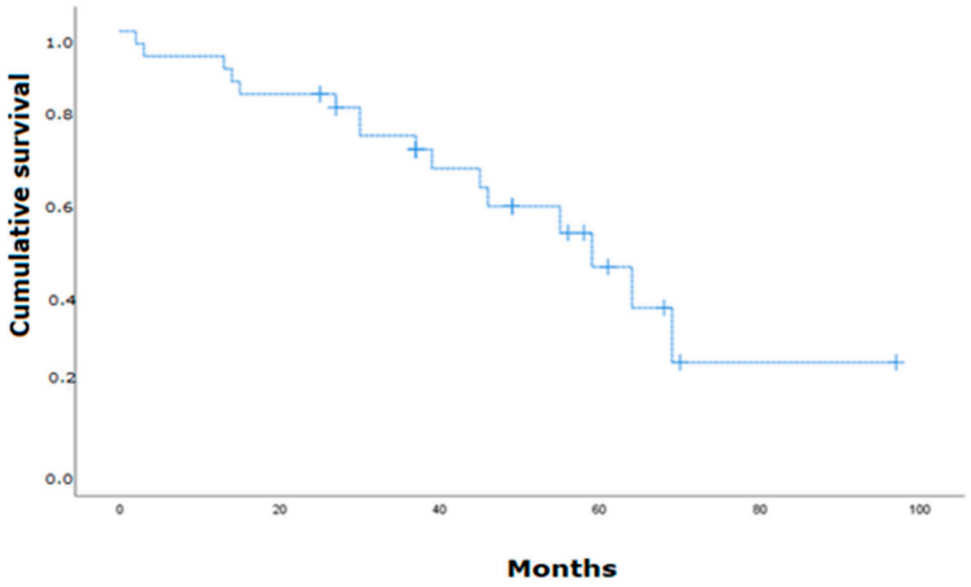

Figure 1. Kaplan-Meier survival model of patients with idiopathic pulmonary fibrosis

TABLE 4. Factors associated with mortality in patients with idiopathic pulmonary fibrosis

	Mean (SD)*	HR (95% CI) (p)	aHR (95% CI) (p)
Sex Female Male	 58.33 (7.89) 54.68 (6.38)	 Ref 2.664 (0.348-20.403) (0.346)	 Ref 2.664 (0.348-20.403) (0.346)
Age < 65 years > 65 years	 69.30 (8.85) 44.67 (4.87)	 Ref 2.559 (0.779-8.409) (0.122)	 Ref 3.649 (0.450-29.572) (0.225)
Smoking Yes No	 71.77 (8.85) 45.44 (4.87)	 Ref 2.518 (0.913-6.948) (0.075)	 Ref 4.547 (0.511-40.430) (0.174)
Dyspnea Grade 1-2 Grade 3-4	 64.23 (9.76) 49.23 (5.20)	 Ref 1.534 (0.542-4.346) (0.420)	 Ref 1.125 (0.188-6.744) (0.897)
Emphysema Yes No	 29.00 (13.65)** 60.87 (6.56)**	 4.210 (1.133-15.643) (0.032) Ref	 3.712 (0.918-10.717) (0.067) Ref
Pulmonary artery systolic pressure < 40 mmHg > 40 mmHg	 72.15 (9.48)** 33.14 (8.93)**	 Ref 3.947 (0.926-16.832) (0.063)	 Ref 6.493 (0.812-51.923) (0.078)
Treatment with disease modifiers Yes No	 56.02 (6.76) 52.49 (6.56)	 Ref 1.868 (0.531-6.575) (0.331)	 Ref 0.819 (0.096-6.998) (0.885)

*Survival expressed in months, **Log-Rank Mantel Cox ($p < 0.05$), aHR: Adjusted hazard ratio

> 40 mmHg: 33.14 months). Both the history of pulmonary emphysema and the value of the pulmonary artery systolic pressure showed statistical significance in the Log-Rank Mantel Cox Test ($p = 0.019$) and ($p = 0.046$), respectively.

DISCUSSION

The evaluation of this cohort of patients with IPF in a developing country such as Ecuador showed the common characteristics of this disease as regards its clinical and functional parameters and diagnostic methods.

The mean age at the time of the diagnosis was consistent with what is described in the literature, as well as the higher prevalence of men.[4, 5, 7]

According to the current ATS/ERS Guidelines, the lung biopsy is not necessary to establish the IPF diagnosis in patients with tomographic features that confirm UIP, they should even be avoided due to the significant risk of morbidity and mortality. Taking these reasoning and current guidelines into consideration, in this study we observe a reduction of only 3% in the number of lung biopsies. This percentage seems to be much lower than the one observed in other series.[8] In any case, as it has been informed in the literature in the past few years, there is a tendency to reduce the number of biopsies performed in patients with this disease, as reported by the Korean cohort analyzed by Sung Woo Moon.[9]

In the study of Wuyts, which analyzed 277 patients diagnosed with IPF, there was family history in 7% of patients, a low percentage compared to our research. It would be interesting in the long run to analyze this population genetically.[10]

The FVC was similar to PANTHER-NAC, higher than ASCEND, and lower than NPULSIS-1 and INPULSIS-2.[11-13] Furthermore, the DLCO expressed in percentage and other parameters of lung function, indicated less severe disease in our study group.[14]

Comorbid conditions are increasingly being observed among patients with DILD. Data suggest a higher prevalence of several comorbidities in patients with IPF compared to the general population. 48.6% of the study group has a Charlson index score of > 3, representing lower values in comparison to those of the Cottin study, which reports 47.3% with a Charlson index score of > 5. This could be partly explained by the younger age of our cohort of patients.[4] Pulmonary hypertension and pulmonary emphysema are associated with reduced survival time, as reported by the Mexican study of Mejía et al, with a HR for emphysema of 1.99 (1.12-3.53) $p = 0.018$, a PASP (pulmonary artery systolic pressure) of more than 75 mmHg, and HR of 1.88 (1.01-3.48) $p = 0.04$ for pulmonary hypertension.[15]

IPF is a disease with a high mortality rate. Thanks to the ATS/ERS guidelines, a diagnostic method has been standardized, thus allowing timely treatment. On the other hand, global epidemiological data have been obtained, with which significant breakthrough has been made in the research of this disease.

Basing on that information, it is time to establish in Ecuador the necessary measures to allow a better diagnostic/therapeutic approach for lung interstitial diseases and with that, the knowledge of the epidemiological impact they represent; to that end we propose a national record of patients with DILD and in turn, the creation of multidisciplinary committees for the purpose of directing treatment access in the long run.

CONCLUSION

We have reported the largest cohort of IPF patients in Ecuador. Our results have identified similar populations with other study groups where the HRCT and multidisciplinary analysis are the most used methods for the diagnosis. Comorbidities, such as pulmonary hypertension and emphysema show a reduction in survival time. Barely 29% of the population under evaluation received antifibrotic treatment, so, apart from providing information on the characterization, we are able to observe the natural course of the disease.

It is indispensable to have well-organized and unified records of IPF patients so as to obtain better results.

Conflicts of interest

The authors of this work declare there isn't any conflict of interest in relation to this publication.

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