

ORIGINAL ARTICLE

Asthma and Lower Airway Disease

Long-term outcomes in chronic hypersensitivity pneumonitis

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Abstract

Introduction: The objective of this study was to analyze mortality, possible predictors of long-term survival, and health-related quality of life of a large chronic hypersensitivity pneumonitis (CHP) patient sample.

Methods: Longitudinal study in patients diagnosed with CHP during 2004-2013, followed for at least 1 year. Patients remaining alive and consenting to participate had a follow-up visit during 2015, including a complete pulmonary function study and the EuroQol-5D and Beck Depression and Anxiety Inventories.

Results: Out of the 160 patients finally included, 87 remained alive. Seventy-three had died or underwent lung transplantation at the time of the study with a median survival of 7.0 (4.4-14.5) years. A Cox proportional risk model showed that factors associated with lower survival were as follows: increased age, a low percentage of lymphocytes in bronchoalveolar lavage (BAL), a decreased transfer factor of the lung for carbon monoxide (DLCO), presence of honeycomb in the high-resolution chest scan (HRCT), and the usual interstitial pneumonia (UIP) histologic pattern. At follow-up, all patients presented an EuroQol-5D score <0.8 and 21(50%) and 9(28.6%) subjects presented a probable anxiety and depressive syndrome, respectively.

Conclusion: CHP is a severe disease with a bad mid-term prognosis. Lymphocyte values in BAL and DLCO values at baseline, presence of honeycomb in HRCT, and UIP histologic pattern were found to be predictors of survival. Early accurate diagnosis of the disease is fundamental for prompt initiation of antigen avoidance.

KEYWORDS

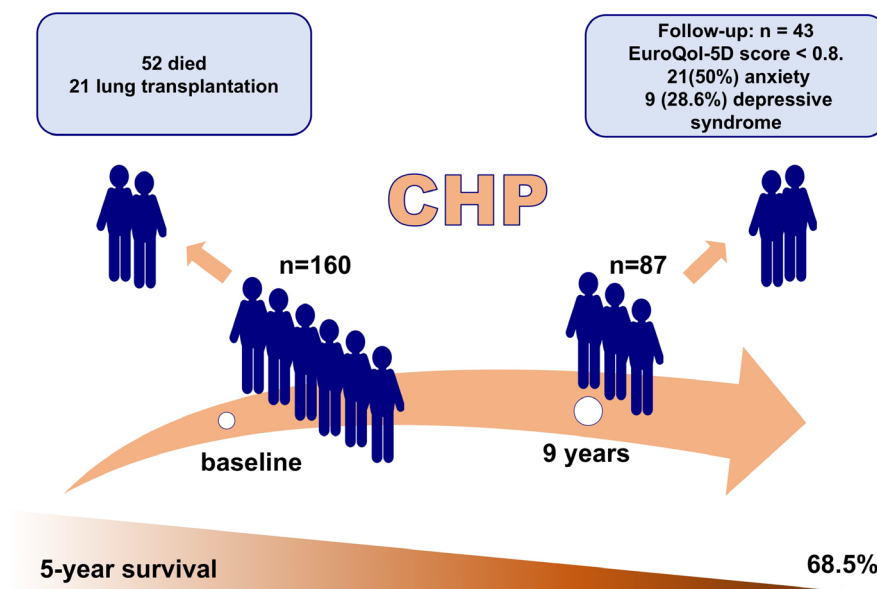
follow-up, hypersensitivity pneumonitis, lung fibrosis, lymphocytes, transfer factor of the lung for carbon monoxide

1 | INTRODUCTION

Hypersensitivity pneumonitis (HP) is a group of diseases characterized by bronchoalveolar inflammation which, in some genetically predisposed individuals, originates from the inhalation of some usually organic substances. The etiology is diverse with more than 100 causes currently known to produce the disease.¹

Hypersensitivity pneumonitis has classically been classified into 3 groups: acute, subacute, and chronic.² However, in the absence of clearly established criteria related to these three forms of the disease,

some authors currently consider HP to be classified into two clusters.³ Cluster differentiation is important since the evolution of the patients varies. Recently, in this same line, a differentiation between acute/inflammatory and chronic/fibrotic HP forms has been proposed.⁴ While avoidance of the causal antigen can lead to disease resolution in the acute or early forms of the disease,⁵ in the chronic forms, patients usually show a progressive loss of pulmonary function with the appearance of respiratory insufficiency conditioning patient survival.⁶ In these patients, survival rate varies from 4 to 11 years,^{7,8} and the extension of fibrosis in high-resolution computed tomography



GRAPHICAL ABSTRACT

Chronic hypersensitivity pneumonitis is a severe disease with a bad mid-term prognosis. Lymphocyte values in BAL and DLCO values at baseline, presence of honeycomb in HRCT, and UIP histologic pattern were found to be predictors of survival. At follow-up, all patients presented an EuroQol-5D score < 0.8 and a probable anxiety and depressive syndrome.

(HRCT)^{9,10} or histological lung biopsy findings^{11–13} has been described as predictive factors. However, limitations of the available studies include limited sample sizes, heterogeneous diagnostic criteria, and lack of highly useful HP diagnostic tools such as specific G immunoglobulins (IgG) or specific inhalation challenges (SICs).^{7–10}

Therefore, we aimed to evaluate the long-term outcomes of chronic HP (CHP) considering not only radiological and pathological parameters, but also clinical, immunological, and inflammatory characteristics in a large CHP patient sample. The objectives of this study were as follows: (a) to establish long-term survival among subjects with CHP; (b) to analyze the clinical, physiological, tomographic, and histologic findings as possible predictors of long-term survival; (c) to establish which factors influence greater loss of pulmonary function over time; and (d) to assess the repercussion of CHP on quality of life, dyspnea, anxiety, and depression.

2 | MATERIAL AND METHODS

2.1 | Patients and design

We performed a longitudinal study including all the patients referred to a university hospital with suspected HP and who were finally diagnosed with CHP from January 1, 2004, to December 31, 2013. Patients were invited to participate in a follow-up visit between August 1, 2015, and October 31, 2015. All the patients included had at least 1 year of follow-up since diagnosis. The study was approved by the local Ethics Committee, and all the subjects included gave informed consent prior to participation (PR (AG) 165/2016).

2.2 | Baseline data

In all the cases, the diagnosis of HP was established according to the Schuyler et al¹⁴ criteria. Medical history and ancillary tests were performed at baseline following standardized methodology: blood tests; specific IgG tests for birds and fungi; chest radiography; HRCT; respiratory function tests including spirometry, static lung volumes, and carbon monoxide transfer test (DLCO); bronchoscopy with bronchoalveolar lavage (BAL); and/or transbronchial biopsy or cryobiopsy after 2011 and SIC in some cases.

The intensity of exposure was quantified based on the total duration of exposure to the antigen source as reported in the clinical records. The modified criteria of Rodríguez de Castro et al¹⁵ were used to classify exposure into three categories: *mild* (including sporadic and short exposure), 1–6 hours per week; *moderate*, 6–18 hours per week; and *intense*, more than 18 hours per week. Subjects with a known cause of HP were recommended to avoid the offending antigen. Subjects with HP of unknown origin were equally instructed to avoid potential harmful exposures.

2.3 | Follow-up study

Information on dates of death or lung transplantation during follow-up was obtained from the clinical records. Patients still alive were contacted by telephone and were offered the possibility of reevaluation. Those accepting underwent a complete pulmonary function study including forced spirometry, static pulmonary volumes, and DLCO.¹⁶ They were also asked to complete the EuroQol-5D

	At risk patients n = 160
No of events (death or lung transplant)	73 (47.5)
Survival time (y), median (95%CI)	7.0 (4.4-14.5)

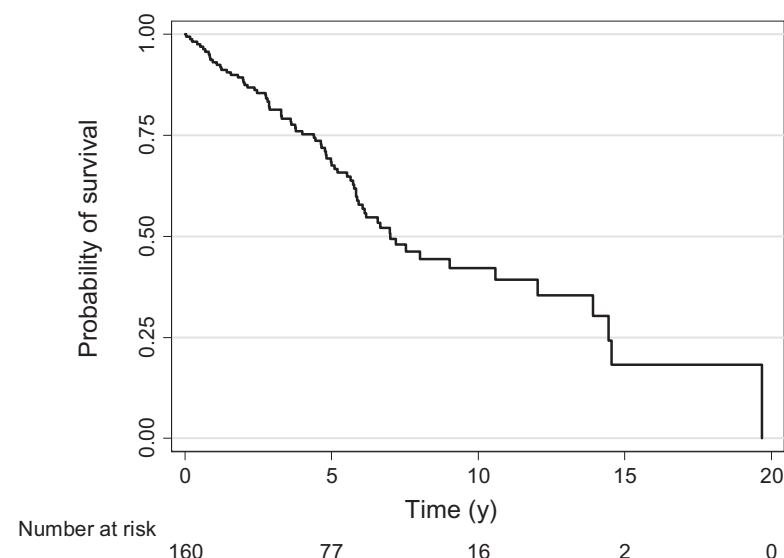


FIGURE 1 Kaplan-Meier plot of patients with chronic hypersensitivity pneumonitis

questionnaire¹⁷ and the Beck Depression¹⁸ and Beck Anxiety¹⁹ Inventories. Dyspnea was recorded according to Medical Research Council Scale (MRC).²⁰

2.4 | Statistical analysis

The data are expressed as absolute numbers and their corresponding percentages for qualitative variables, mean, and standard deviation for quantitative variables with a normal distribution and the median and 25th to 75th percentiles for quantitative variables with a non-normal distribution.

Comparison of the demographic and clinical variables was performed using the chi-square test for qualitative variables (or the Fisher exact test when one of the expected effects was less than 5) and Student's *t* test or Mann-Whitney *U* test for continuous variables, as appropriate. The annual rate of change for functional variables was calculated as the difference between the follow-up value minus the baseline value divided by follow-up time in each subject and described accordingly. Kaplan-Meier curves were built to estimate the overall survival. To identify the best predictive model of mortality, we performed a stepwise multivariate Cox regression with a backward elimination (entry threshold, $P < 0.05$; removal threshold, $P > 0.10$) fitted with all candidate variables that were significant predictors at the bivariate level. The final model was built keeping the most parsimonious model that still explains the data. To account for missing values, we used multiple imputation (20 times) through chained equations, replacing missing values by imputations drawn from the predictive distribution of each variable,²¹ before Cox models were built. Analyses were conducted using Stata 12.1 (StataCorp, College Station, TX, USA).

3 | RESULTS

A total of 179 CHP patients were initially evaluated. Of these, 19 were lost to follow-up. Of the 160 patients finally included, 52 died during follow-up and 21 underwent lung transplantation. The causes of death were as follows: underlying respiratory illness ($n = 28$), heart disease ($n = 3$), infectious disease ($n = 3$), cancer ($n = 1$), and not reported ($n = 17$). Out of the 87 patients that remained alive, they all were contacted and 43 attended the follow-up evaluation (Figure 1, Figure S1). Tables 1 and 2 show the baseline characteristics of the patients according to survival status at the time of diagnosis.

The median survival was 7.0 (4.4-14.5) years (Figure 1), and the 5-year survival was 68.5% (95% confidence interval [CI]: 60.1%-75.6%). Table 3 shows the influence of the variables included in the bivariate survival analysis on patient prognosis. The following characteristics at diagnosis were associated with a lower survival: older age, male gender, greater exposure to the causal agent, presence of crackling, higher levels of LDH, upper and middle lobe fibrosis or honeycomb in the radiologic pattern and usual interstitial pneumonia (UIP), or airway-centered fibrosis in the histological pattern. However, knowing the causal agent, a positive SIC, a higher percentage of lymphocytes in the BAL or higher forced vital capacity (FVC), total lung capacity or DLCO values, and peribronchiolar inflammation with poorly formed granulomas (PI-PFG) in the histological pattern were associated with a better prognosis. We found no significant differences with regard to smoking habit, the presence of acropachy, severe dyspnea (modified Medical Research Council [mMRC] score >2), and the number of neutrophils in the BAL (Table 3). In a stepwise multivariate Cox regression model, the variables showing a significant and independent association with survival were as follows: age, the percentage of lymphocytes in the

TABLE 1 Baseline clinical and demographic characteristics of the study population, according to survival status (n = 160)

	Total ^a n = 160	Alive n = 87	Dead/Lung transplant n = 73	P*
Sociodemographic and clinical data				
Age (years), mean (SD)	60.9 (12.9)	57.8 (14.3)	64.5 (9.9)	0.001
Sex (female), n (%)	93 (58.1)	59 (67.8)	34 (46.6)	0.007
Smoking habit, n (%)				
Smoker	15 (9.5)	9 (10.5)	6 (8.3)	0.841
Former smokers	54 (34.2)	28 (32.6)	26 (36.1)	
Nonsmoker	89 (56.3)	49 (56.9)	40 (55.6)	
Pack-years, median (p25-p75) [n = 69]	20 (10-40)	15 (10-22)	20 (15-40)	0.095
Crackles, n (%)	106 (68.4)	49 (56.9)	57 (82.6)	0.001
Nail clubbing, n (%)	33 (21.3)	11 (12.6)	22 (32.4)	0.003
Severe dyspnea (mMRC $\geq$ 2), n (%)	14 (8.8)	7 (8.1)	7 (9.7)	0.710
Occupational data				
Lifetime exposure (years), median (p25-p75)	10 (5-20)	10 (5-20)	10 (5-20)	0.999
Exposure intensity, n (%) [n = 142]				
Low	19 (13.4)	14 (17.7)	5 (7.9)	0.033
Moderate	81 (57.0)	48 (60.8)	33 (52.4)	
Intense	42 (29.6)	17 (21.5)	25 (39.7)	
Causal agent, n (%)				
Birds	72 (55.8)	44 (58.7)	28 (51.9)	0.346
Fungi	12 (9.3)	9 (12.0)	3 (5.6)	
Others	11 (8.5)	6 (8.0)	5 (9.2)	
Unknown	34 (26.4)	16 (21.3)	18 (33.3)	
Stopped exposition, n (%)	112 (95.7)	69 (97.2)	43 (93.5)	0.380
Treatment				
Oral corticosteroids, n (%)	130 (82.8)	65 (75.6)	65 (91.6)	0.008
Mycophenolate, n (%)	19 (12.1)	6 (7.0)	13 (18.3)	0.030
Azithromycin, n (%)	24 (15.3)	17 (19.8)	7 (9.9)	0.086

^aSome variables have missing values: 2 in age, 2 in smoking habits, 1 in pack/year, 1 in nail clubbing, 1 in mMRC: modified medical research council, 1 in lifetime exposure, 18 in intensity of exposure, 31 in causal agent, 12 in stopped exposition, 3 in oral corticosteroids, 3 in mycophenolate, and 3 in azithromycin.

*Alive vs Dead/lung transplant.

BAL, DLCO values, honeycomb radiologic pattern, and UIP histopathological pattern (Table 4).

3.1 | Follow-up visit

Table 5 shows the annual rate of change in the lung function parameters of the participants attending the reevaluation visit. Baseline FVC and DLCO values were the only variables associated with the annual rate of change in FVC (Spearman's $\rho = -0.4590$ $P = 0.002$ and -0.401 $P = 0.009$, respectively). Baseline DLCO and DLCO corrected by pulmonary volume (KCO) values were the only variables associated with the annual rate of change in DLCO (Spearman's $\rho = -0.458$ $P = 0.004$ and -0.512 $P = 0.001$, respectively). At the follow-up visit, all the patients had an EuroQoL-5D score below 0.8. Fifteen (34.9%) presented severe dyspnea (mMRC >2). Twenty-one

patients (50%) presented a probable anxiety syndrome and 9 (28.6%) a probable depressive syndrome (Table 5). Only dyspnea at follow-up (mMRC >2) was related to the quality of life score at follow-up. Female gender and dyspnea at follow-up (mMRC >2) were related to the anxiety score obtained at follow-up. Only the age at baseline was related to the depression score at follow-up. No other relationships were found. No differences were found on comparing the basal characteristics of the 44 who did not attend the control visit and those who were reevaluated (Table 1, Table S1).

4 | DISCUSSION

The results of the present study confirm the poor prognosis of patients with CHP, with a 5-year mortality of 31.5%. The DLCO,

TABLE 2 Baseline ancillary tests according to survival status (n = 160)

	Total ^a n = 160	Alive n = 87	Dead/Lung transplant n = 73	P*
Blood analysis				
Cell count, mean (SD)				
Neutrophils (%)	61.1 (12.4)	60.0 (13.3)	62.5 (11.2)	0.270
Lymphocytes (%)	26.5 (9.6)	27.6 (9.8)	25.3 (9.4)	0.152
LDH (IU/L), mean (SD)	430 (376-529)	409 (357-506)	488 (357-506)	0.003
ANA, mean (SD)	0.90 (1.13)	0.76 (0.98)	1.05 (1.28)	0.141
IgG to birds (+), n (%)	76 (49.4)	46 (54.8)	30 (42.9)	0.141
IgG to fungi (+), n (%)	66 (44.6)	39 (48.2)	27 (40.3)	0.339
Bronchoalveolar lavage [n = 133]				
Neutrophils (%), median (p25-p75)	6 (3-15)	8 (3-14)	4 (3-15)	0.446
Lymphocytes (%), median (p25-p75)	16 (9-31)	20 (10-40)	14 (7-22)	0.010
Macrophages (%), median (p25-p75)	72 (53-80)	65 (44-78)	75 (59-83)	0.015
Eosinophils (%), median (p25-p75)	2 (0-4)	1 (0-2)	2 (0-4)	0.130
Pulmonary function test				
FVC (% predicted), mean (SD)	68.5 (16.0)	72.1 (15.2)	64.0 (16.0)	0.001
FEV ₁ (% predicted), mean (SD)	77.0 (17.8)	80.4 (17.1)	72.8 (17.9)	0.007
RV (% predicted), mean (SD)	74.6 (29.2)	81.6 (30.9)	64.5 (23.3)	0.001
TLC (% predicted), mean (SD)	73.8 (18.4)	79.5 (19.5)	66.2 (13.6)	<0.001
DLCO (% predicted), mean (SD)	50.3 (17.2)	52.9 (17.2)	46.9 (16.8)	0.034
SIC (+) [n = 71], n (%)	37 (52.1)	28 (65.1)	9 (32.1)	0.008
Radiologic patterns ^b				
Upper and middle lobe fibrosis, n (%)	114 (80.9)	57 (73.1)	57 (90.5)	0.009
Peribronchovascular fibrosis, n (%)	120 (85.1)	62 (79.5)	58 (92.1)	0.037
Honeycomb, n (%)	54 (38.3)	16 (20.5)	38 (60.3)	<0.001
Mosaic pattern, n (%)	76 (53.9)	52 (66.7)	24 (38.1)	0.001
Air trapping, n (%)	77 (54.6)	50 (64.1)	27 (42.9)	0.012
Relative sparing in the bases, n (%)	61 (43.3)	39 (50.0)	22 (34.9)	0.072
Centrilobular nodules, n (%)	59 (41.8)	36 (46.2)	23 (36.5)	0.248
Lung biopsy ^b				
Histopathology patterns, n (%) [n = 139]				
Cellular NSIP	6 (4.3)	2 (2.5)	4 (6.5)	0.012
Fibrotic NSIP	7 (5.0)	4 (5.2)	3 (4.7)	
UIP	19 (13.7)	6 (7.8)	13 (21.0)	
PI-PFG	44 (31.7)	32 (41.6)	12 (19.4)	
Airway-centered fibrosis	15 (10.8)	5 (6.5)	10 (16.1)	
Unclassifiable	48 (34.5)	28 (36.4)	20 (32.3)	

ANA, antinuclear antibodies; DLCO, diffusing capacity of the lung carbon monoxide; FVC, forced vital capacity; FEV₁, forced expiratory capacity; IgG, immunoglobulin G; LDH, lactate dehydrogenase; NSIP, nonspecific interstitial pneumonia; PI-PFG, peribronchiolar inflammation with poorly formed granulomas; RV, residual volume; SIC, specific inhalation challenge; TLC, total lung capacity; UIP, usual interstitial pneumonia.

^aSome variable has missing values: 4 in leukocytes, 15 in neutrophils, 5 in lymphocytes, 25 in LDH, 25 in ANA, 6 in IgG to birds, 12 in IgG to fungi, and 19 in radiological patterns.

^bNot mutually exclusive.

*Alive vs Dead/lung transplant.

lymphocyte count in the BAL, honeycombing in the radiological pattern, and the histopathological UIP pattern were predictive factors of survival and similar to what occurs in other interstitial lung diseases (ILD), patients with CHP may present anxiety, depression, and

important impairment in their quality of life, mainly related to the presence of severe dyspnea.

Pérez Padilla et al⁷ reported a 5-year mortality of 29% in bird fancier's lung, beings lightly higher than the 27% reported by

TABLE 3 Cox proportional hazards model. Crude analyses (n = 160)

	Hazard ratio	95% CI	P
Age (years)	1.041	1.020-1.064	<0.001
Sex (male)	1.857	1.167-2.956	0.009
Smoking (current or former)	1.039	0.650-1.662	0.872
Lifetime exposure (years)	1.014	0.992-1.037	0.210
Intensity of exposure (intense)	2.097	1.251-3.517	0.005
Causal agent (known)	0.485	0.272-0.865	0.014
Stop exposition	1.168	0.273-5.003	0.834
Crackles	2.242	1.200-4.191	0.011
Nail clubbing	1.676	0.997-2.818	0.051
Severe dyspnea (mMRC>2)	1.572	0.716-3.452	0.260
Lymphocytes BAL (%)	0.973	0.956-0.991	0.004
Neutrophils BAL (%)	0.996	0.972-1.021	0.751
Macrophages BAL (%)	1.014	1.001-1.028	0.048
LDH (UI/L)	1.002	1.001-1.003	0.015
FVC (%predicted)	0.968	0.952-0.984	<0.001
TLC (%predicted)	0.971	0.957-0.985	<0.001
DLCO (%predicted)	0.975	0.959-0.990	0.002
Challenge test (positive)	0.311	0.139-0.696	0.004
Radiologic patterns (upper and middle lobe fibrosis)	2.952	1.269-6.866	0.012
Radiologic patterns (peribronchovascular fibrosis)	2.448	0.980-6.117	0.055
Radiologic patterns (honeycomb)	3.154	1.895-5.259	<0.001
Radiologic patterns (mosaic pattern)	0.620	0.371-1.036	0.068
Radiologic patterns (air trapping)	0.731	0.442-1.209	0.223
Radiologic patterns (relative sparing in the bases)	0.692	0.411-1.165	0.166
Radiologic patterns (centrilobular nodules)	0.905	0.540-1.518	0.706
Cellular NSIP	0.623	0.210-1.851	0.394
Fibrotic NSIP	0.853	0.266-2.732	0.789
UIP	3.266	1.741-6.129	<0.001
PI-PFG	0.431	0.224-0.828	0.012
Airway-centered fibrosis	2.257	1.134-4.492	0.020
Unclassifiable	0.905	0.529-1.548	0.716

BAL, bronchoalveolar lavage; DLCO, diffusing capacity of the lung carbon monoxide; FVC, forced vital capacity; LDH, lactate dehydrogenase; mMRC: modified medical research council; NSIP, nonspecific interstitial pneumonia; PI-PFG, peribronchiolar inflammation with poorly formed granulomas; TLC, total lung capacity; UIP, usual interstitial pneumonia.

Vourlekis et al²² in patients with subacute and CHP. Except for the underpowered study by Sahin et al⁸ who described a 5-year mortality of 61% among patients with CHP with fibrosis, the remaining studies as well as the present study have shown that despite the poor prognosis of patients with HP, the mortality rate is better than the 5-year mortality of 80% presented by patients with idiopathic

TABLE 4 Cox proportional hazards model. Variables independently related to risk of mortality or transplant during follow-up

	Hazard ratio ^a	95% CI	P
Age (years)	1.038	1.012-1.064	0.003
Lymphocytes in BAL (%)	0.973	0.955-0.991	0.003
DLCO (%predicted)	0.956	0.938-0.974	<0.001
Honeycomb (radiologic patterns)	1.745	1.060-2.873	0.029
UIP (histopathology)	2.260	1.195-4.273	0.012

BAL, bronchoalveolar lavage; DLCO, diffusing capacity of the lung carbon monoxide; TLC, total lung capacity; UIP, usual interstitial pneumonia.

^aHazard ratios were adjusted for gender and smoking status.

pulmonary fibrosis (IPF).²³ Indeed, this remains true even in many cases of CHP patients with the usual interstitial pneumonia pathological pattern.²⁴ Given the difference between CHP and IPF in terms of prognosis and also in the treatment approach (steroids vs antifibrotics), it seems fundamental to differentiate the two entities.^{4,25,26} In general, the diagnosis of HP requires proven or suspected exposure associated with exposure-related symptoms; proof of sensitization; and compatible chest radiography/HRCT abnormalities.¹⁴ However, CHP may represent a diagnostic dilemma,²⁶ particularly when the detailed clinical history does not reveal a temporal relationship between symptom onset and antigen exposure. In this context, SIC may be particularly useful in the diagnosis of HP as well as for differentiation from IPF.^{27,28}

Several authors have reported a clear relationship of survival in patients with CHP and pulmonary function at diagnosis and thus, with the initiation of treatment.^{9,29} Likewise, the present study shows that DLCO is a prognostic marker in these patients. Indeed, DLCO values at diagnosis are associated with higher survival. According to previous studies, survival in CHP patients is related to FVC, FEV₁/FVC, and DLCO values.^{9,12} The histological alterations in CHP are mainly in the form of UIP or nonspecific interstitial pneumonia (NSIP)³⁰ which substantially modify pulmonary distension and reduce the area of gas exchange. Therefore, it is logical to consider that DLCO determinations could predict these changes. Indeed, in similar processes such as IPF or connective tissue disease-associated ILD, which show a reduction in these parameters as occurs in CHP,^{31,32} there is increasing consensus to adding DLCO values not only for the diagnosis and management,³³ but also for evaluating response to new drugs in clinical trials.^{34,35} DLCO has recently been described as a predictive factor of survival in patients with IPF,³⁶ and Ley et al³⁷ have proposed an index combining gender, age, FVC, and DLCO as the best predictors of death in these patients. Indeed, except for FVC, these same parameters were found to be important independent variables for survival in patients with a possible UIP pattern independently of the UIP pattern itself.³⁸ In this context, it is important to note that age was also found to be associated with survival in the present study.

TABLE 5 Baseline and follow-up assessments, and annual rate of change of participants in the reevaluation visit (n = 43)

	Baseline	Follow-up	Annual rate of change ^a
Severe dyspnea (mMRC $\geq$ 2), n (%)	2 (4.7)	15 (34.9)	
Pulmonary function test, mean (SD)			
FVC (% pred)	73.3 (16.2)	69.5 (16.5)	-0.68 (-2.07 to 1.06)
FEV1 (% pred)	80.9 (18.4)	77.2 (18.7)	-0.50 (-2.67 to 0.75)
RV (% pred)	83.2 (34.6)	75.5 (31.6)	1.28 (-3.73 to 2.54)
TLC (% pred)	82.7 (18.5)	78.2 (20.6)	-0.24 (-1.96 to 0.71)
DLCO (% pred)	55.2 (20.4)	55.9 (20.4)	-0.32 (-1.77 to 1.92)
Quality of life (0-1), median (p25-p75)	-	0.74 (0.59-0.79)	-
HADS			
Anxiety, n (%)			
0-7	-	21 (50.0)	-
7-10	-	11 (26.2)	-
>10	-	10 (23.8)	-
HADS			
Depression, n (%)			
0-7	-	30 (71.4)	-
7-10	-	7 (16.7)	-
>10	-	5 (11.9)	-
Respiratory insufficiency, n (%)	-	4 (9.3)	-

DLCO, diffusing capacity of the lung carbon monoxide; FVC, forced vital capacity; FEV₁, forced expiratory capacity; HADS: Hospital Anxiety and Depression scale; mMRC, modified medical research council; RV, residual volume; TLC, total lung capacity.

Some variables have missing values: One in HADS Anxiety and 1 in HADS Depression.

^amedian (p25-p75).

A higher lymphocyte count in BAL was also related to a higher survival rate. Several studies have suggested that a high lymphocyte count in BAL is a finding that supports the diagnosis of this pathology, with a predominance of CD8 in the early stages and a predominance of CD4 in later phases.³⁹ Vourlekis et al²² argue that an exuberant lymphocytic inflammatory response may have a more acute onset and a greater probability of disease resolution and that BAL may therefore be an important predictive factor. In fact, some authors suggest that in patients with ILD, a higher lymphocyte count may predict a greater response to oral steroids.⁴⁰

Similarly to the findings observed by other authors, in this study, the presence of honeycomb in the HRCT and the UIP histological pattern were associated with a worse prognosis. In a prospective observational study of 190 patients with HP, Mooney et al⁹ showed that the extent of fibrosis in HRCT predicts higher mortality in these patients. Likewise, it has recently been shown that histological findings compatible with cellular NSIP and peribronchiolar inflammation with poorly formed granulomas have a better prognosis of transplant-free survival than the findings compatible with UIP, fibrotic NSIP, and airway-centered fibrosis.¹³ Our results corroborate those published in previous studies and confirm that the radiological pattern of honeycombing and the histological pattern of UIP are definitely predictors of higher mortality in these patients.

This paper describes the first cross-sectional study carried out to determine the current status of nondeceased or transplanted patients. The falls in both FVC and DLCO were related only to higher baseline levels; no other predictors were found. Indeed, it could be hypothesized that once CHP has been diagnosed, all patients should be treated regardless of their pulmonary function values.⁴¹ The usual practice in these patients is to recommend antigen avoidance and only to treat those who present symptoms or an alteration of pulmonary function.²⁵ The present study also analyzed, in this sample of patients, the repercussion of CHP on the quality of life, dyspnea, anxiety, and depression. Patients with CHP presented significant impairment in their quality of life consistent with findings in previous studies in patients with ILD.⁴² Lubin et al⁴³ described a series of 69 patients with CHP with worse quality of life indexes than those reported in patients with IPF, which could be explained, in part, by differences in gender, grade of dyspnea, and fatigue between these two groups. In our study, severe dyspnea (mMRC > II) was also associated with a worse quality of life similar to other reports.⁴⁴⁻⁴⁶ However, other variables such as the clinical characteristics, pulmonary function, or the probability of presenting anxiety or depression were not associated with a worse quality of life. Nonetheless, few studies are available on anxiety and depression in these patients. Only the recent study by Holland et al⁴⁷ in 124 patients with ILD, 12 of whom had HP, reported lower values than those observed in the present study.

This study has some limitations. The first is in relation to the analysis of the predictors of survival. The HRCT results were analyzed according to the most characteristic findings described in CHP without performing radiological quantification using a specific score.^{9,10} However, this same system of analysis in the HRCT has provided relevant findings in previous studies of CHP.²⁶ Another limitation is related to the follow-up study in that we were only able to reevaluate 43 of the 87 patients finally studied. Although no differences were observed between the 43 subjects that attended the follow-up visit compared to the 44 subjects that did not attend (Table 1, Table S1), this sample size may explain why no prognostic factors were found to predict the fall in the different spirometric variables, with the exception of an inverse relationship between FVC and DLCO and a greater reduction in these parameters. Finally, possibly the most updated recommendations for the diagnosis of CHP

are the ones recently published by Vasakova et al⁴. Due to the fact that this study is a retrospective series, we based the diagnosis of CHP on the criteria proposed by Schuyler et al¹⁴. Nevertheless, all patients met the criteria established by Vasakova et al⁴ and were agreed in the ILD multidisciplinary meeting.

In conclusion, the present findings demonstrate that CHP is a severe disease with a bad mid-term prognosis. The percentage of lymphocytes in the BAL, DLCO, presence of honeycomb in the HRCT, and UIP histological pattern were found to be predictors of survival. Early accurate diagnosis of the disease is fundamental for prompt initiation of antigenic avoidance. However, although it cannot be inferred directly from the results obtained in this study, it seems logical to think that the start of treatment with corticosteroids and/or immunosuppressive drugs in patients in whom clinical deterioration and pulmonary function are evident, probably needs to be evaluated in early stages. Likewise, early diagnosis and adequate treatment may prevent the appearance of severe dyspnea which was also found to be the main cause of loss of quality of life or the appearance of an anxiety/depressive syndrome.

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CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Figure 1. Flow chart of patient enrollment.

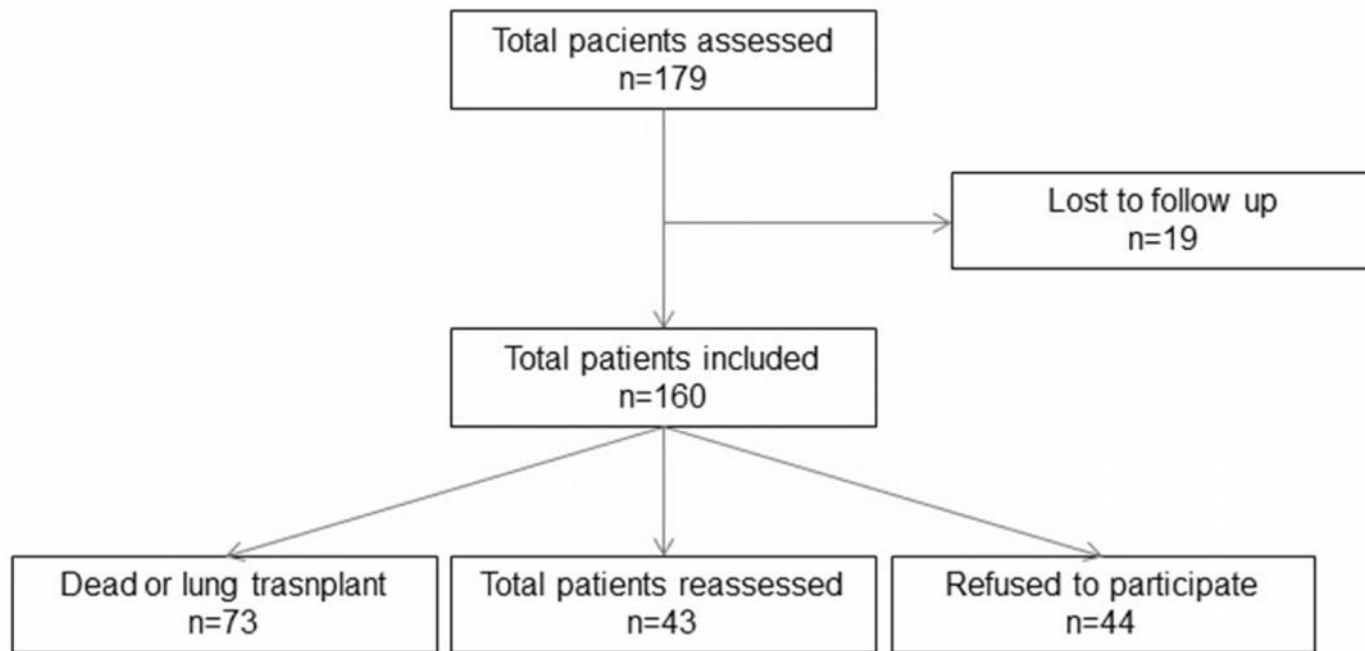


Table 1. Baseline ancillary tests in patient who were alive and could attend the follow-up visit and those who did not attend the follow-up visit (n=87).

	Alive n= 87	Attending follow- up visit n= 43	Not attending follow-up visit n=44	p#
Sociodemographic& clinical data				
Age (years), mean (SD)	57.8 (14.3)	56.6 (14.0)	59.3 (14.5)	0.382
Sex (female), mean (SD)	59 (67.8)	32 (74.4)	27 (61.4)	0.193
Smoking habit, n (%)				0.319
Smoker	9 (10.5)	6 (14.0)	3 (6.0)	
Former smokers	28 (32.6)	11 (25.5)	17 (39.5)	
Non-smoker	49 (56.9)	26 (60.5)	23 (53.5)	
Packet-years, [n=79] median (p25-p75)	15 (10-22)	15 (10-20)	18 (10-35)	0.747
Crackles, n (%)	49 (56.9)	25 (58.1)	24 (55.8)	0.828
Nail clubbing, n (%)	11 (12.6)	3 (6.9)	8 (18.2)	0.196
Severe Dyspnea (mMRC≥2), n (%)	7 (8.1)	2 (4.7)	5 (11.4)	0.434
Occupational data				
Lifetime exposure (years), median (p25-p75)	10 (5-20)	10 (5-15)	10 (5-20)	0.655
Intensity of exposure, n (%)				0.950
Low	14 (17.7)	7 (17.9)	7 (17.5)	
Moderate	48 (60.8)	23 (58.9)	25 (26.5)	
Intense	17 (21.5)	9 (23.1)	8 (20.0)	
Causal Agent, n (%) [n=75]				
Birds	44 (58.7)	21 (56.8)	23 (60.5)	0.980
Fungi	9 (12.0)	5 (13.5)	4 (10.5)	
Others	6 (8.0)	3 (8.1)	3 (7.9)	
Unknown	16 (21.3)	8 (21.6)	8 (21.1)	
Blood analysis				
Cell count, mean (SD)				
Neutrophils (%)	60.0 (13.3)	60.9 (10.6)	59.2 (15.6)	0.574
Lymphocytes (%)	27.6 (9.8)	27.5 (8.5)	27.7 (11.0)	0.938
LDH(IU/L), mean (SD)	409 (357-506)	411 (357-531)	407 (344-503)	0.568
IgG to birds (Positive), n (%)	46 (54.8)	23 (53.5)	23 (56.1)	0.810
IgG to fungi (Positive), n (%)	39 (48.2)	22 (56.7)	17 (42.5)	0.315
Bronchoalveolarlavage[n=70]				
Neutrophils (%),median (p25-p75)	8 (3-14)	8 (2-15)	8 (4-13)	0.720
Lymphocytes (%),median (p25-p75)	20 (10-40)	19 (7-39)	23 (11-46)	0.365
Macrophages (%),median (p25-p75)	65 (44-78)	67 (55-80)	64 (38-77)	0.358
Eosinophils (%),median (p25-p75)	1 (0-2)	1 (0-2)	1 (0-4)	0.620
Pulmonary function test				
FVC (% predicted), mean (SD)	72.1 (15.2)	73.3 (16.2)	71.0 (14.4)	0.502
FEV1 (% predicted), mean (SD)	80.4 (17.1)	80.9 (18.4)	79.9 (15.9)	0.780
RV (% predicted), mean (SD)	81.6 (30.9)	83.2 (34.6)	80.2 (27.5)	0.691
TLC (% predicted), mean (SD)	79.5 (19.5)	82.7 (18.5)	76.6 (20.0)	0.178
DLCO (% predicted), mean (SD)	52.9 (17.2)	55.2 (20.4)	50.8 (13.0)	0.240
Challenge test (Positive), n (%) [n=43]	28 (65.1)	16 (64.0)	12 (66.7)	0.856
Radiologic patterns^				
Upper and middle lobe fibrosis, n (%)	57 (73.1)	32 (74.4)	25 (71.4)	0.802
Peribronchovascular fibrosis, n (%)	62 (79.5)	36 (83.7)	26 (74.3)	0.400
Honeycomb, n (%)	16 (20.5)	10 (23.3)	6 (17.1)	0.581
Mosaic pattern, n (%)	52 (66.7)	26 (60.5)	26 (74.3)	0.233
Air trapping, n (%)	50 (64.1)	25 (58.1)	25 (71.4)	0.246
Relative sparing in the bases, n (%)	39 (50.0)	20 (46.5)	19 (54.3)	0.646

Centrilobular nodules, n (%)	36 (46.2)	20 (46.5)	16 (45.7)	0.944
Lung biopsy^				
Histopathology patterns, n (%) [n=77]				
Cellular NSIP	2 (2.5)	2 (5.2)	0 (0.0)	0.587
Fibrotic NSIP	4 (5.2)	1 (2.6)	3 (7.6)	
UIP	6 (7.8)	3 (7.9)	3 (7.)	
PI-PFG	32 (41.6)	18 (47.4)	14 (35.9)	
Airway-centered fibrosis	5 (6.5)	2 (5.3)	3 (7.6)	
Unclassifiable	28 (36.4)	12 (31.6)	16 (41.3)	

List of abbreviation: mMRC, modified medical research council, BAL, bronchoalveolar lavage; LDH, lactate dehydrogenase; FVC, forced vital capacity; FEV₁, forced expiratory capacity; RV, residual volume; TLC, total lung capacity; DLCO, diffusing capacity of the lung carbon monoxide. NSIP: Nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; PI-PFG: peribronchiolar inflammation with poorly formed granulomas. *Some variables have missing values: 1 in smoking habits, 8 in intensity of exposure, 12 in causal agent, 6 in IgG to birds and 6 in IgG to fungi, 9 in radiological patterns..# attending follow-up vs not attending follow-up. ^Not mutually exclusive