Identifying an Inciting Antigen Is Associated With Improved Survival in Patients With Chronic Hypersensitivity Pneumonitis

Evans R. Fernández Pérez, MD, FCCP; Jeffrey J. Swigris, DO, FCCP; Anna V. Forssén, MS; Olga Tourin, MD; Joshua J. Solomon, MD, FCCP; Tristan J. Huie, MD, FCCP; Amy L. Olson, MD, MSPH; and Kevin K. Brown, MD, FCCP

Background: The cornerstone of hypersensitivity pneumonitis (HP) management is having patients avoid the inciting antigen (IA). Often, despite an exhaustive search, an IA cannot be found. The objective of this study was to examine whether identifying the IA impacts survival in patients with chronic HP.

Methods: We used the Kaplan-Meier method to display, and the log-rank test to compare, survival curves of patients with well-characterized chronic HP stratified on identification of an IA exposure. A Cox proportional hazards (PH) model was used to identify independent predictors in time-to-death analysis.

Results: Of 142 patients, 67 (47%) had an identified IA, and 75 (53%) had an unidentified IA. Compared with survivors, patients who died ($n = 80$, 56%) were older, more likely to have smoked, had lower total lung capacity % predicted and FVC % predicted, had higher severity of dyspnea, were more likely to have pulmonary fibrosis, and were less likely to have an identifiable IA. In a Cox PH model, the inability to identify an IA (hazard ratio [HR], 1.76; 95% CI, 1.01-3.07), older age (HR, 1.04; 95% CI, 1.01-1.07), the presences of pulmonary fibrosis (HR, 2.43; 95% CI, 1.36-4.35), a lower FVC% (HR, 1.36; 95% CI, 1.10-1.68), and a history of smoking (HR, 2.01; 95% CI, 1.15-3.50) were independent predictors of shorter survival. After adjusting for mean age, presence of fibrosis, mean FVC%, mean diffusing capacity of the lung for carbon monoxide (%), and history of smoking, survival was longer for patients with an identified IA exposure than those with an unidentified IA exposure (median, 8.75 years vs 4.88 years; $P = .047$).

Conclusions: Among patients with chronic HP, when adjusting for a number of potentially influential predictors, including the presence of fibrosis, the inability to identify an IA was independently associated with shortened survival.

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Abbreviations: DLCO = diffusing capacity of the lung for carbon monoxide; HP = hypersensitivity pneumonitis; HRCT = high-resolution CT; IA = inciting antigen; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; SSDI = Social Security Death Index

Hypersensitivity pneumonitis (HP) is an interstitial lung disease (ILD) characterized pathologically by varying degrees of inflammation and/or fibrosis that result from the inhalation of an antigen to which a person has been previously sensitized. The clinical expression of HP can vary and includes acute, subacute, and chronic forms. Symptom onset that coincides with antigen exposure provides the first diagnostic clue; however, despite an exhaustive search, a recognizable, temporal relationship (between exposure and symptoms) is frequently absent, particu-

larly in patients who present with the chronic form of HP.

Chronic HP, characterized clinically by ventilatory restriction and, most commonly, upper-zone-predominant fibrosis on high-resolution CT (HRCT) scan, is irreversible and often progressive. It is believed that continued exposure to an inciting antigen (IA) perpetuates progression and the development of fibrosis in HP, but this belief hinges more on scientific rationale than systematic research. In this study, we hypothesized that among patients with histologic and

radiologic findings of chronic HP, those with an IA live longer than those without an IA.

MATERIALS AND METHODS

From our longitudinal ILD database, as described previously,¹ we identified 142 consecutive adult patients with clinical-radiologic-pathologic chronic HP evaluated in our multidisciplinary ILD and occupational medicine program between January 1, 1982, and January 1, 2008. Data from some of these patients were included in two previously published studies.^{1,2} We reviewed the complete medical records of included subjects and abstracted data pertaining to the following: demographics, smoking history (never or former smoker), dyspnea score,³ occupational and environmental history, pulmonary function, HRCT scan, histopathology, and treatment. All patients provided informed consent granting permission to record clinical data and review of medical records. The National Jewish Health institutional review board approved this study (protocol No. 1603).

Enrollment Criteria

The primary enrollment criterion for the current study was identification of an HP pattern in surgical lung biopsy specimens; this included a predominantly lymphocytic interstitial infiltrate (with poorly formed granulomas and/or organizing pneumonia) in a bronchiolocentric distribution and, for those with chronic HP, varying degrees of fibrosis. An expert pulmonary pathologist had previously reviewed all biopsies. In addition, other inclusion criteria included the following: (1) presence of compatible clinical features for > 1 year—at least two of the following five features: dyspnea, cough, chest tightness/wheezing, fatigue, and squeaks and/or crackles on auscultation; (2) abnormal pulmonary function tests (restriction, obstruction, or mixed pattern with decreased diffusing capacity of the lung for carbon monoxide [DLCO]); (3) compatible HRCT scan features, including centrilobular nodules, mosaic attenuation, reticular opacities, traction bronchiectasis, lobar volume loss, and honeycombing; (4) absence of an alternative diagnosis that could account for the pathologic findings (eg, infection based on fungal and mycobacterial smears and cultures of sputum); and (5) the presence of precipitating antibodies (was supportive but not required).

Definition of Fibrosis

HRCT scan features that defined fibrosis in our study were a predominantly upper-zone reticular pattern with or without hon-

eycombing, traction bronchiectasis, or upper lobe volume loss. Pathologic features that defined fibrosis included expansion of alveolar septae by mature collagen involving > 5% of the total lung field on a single slide or honeycomb fibrosis defined by the presence of subpleural cyst-like spaces lined by metaplastic epithelium and surrounded on at least three sides by dense interstitial fibrosis. Nonfibrotic HP was defined by a predominant pattern of centrilobular nodularity and ground-glass opacities without honeycombing or traction bronchiectasis on HRCT scan and by the absence of fibrosis histologically. HRCT scans were performed using standardized protocols and were available for every patient during initial evaluation.¹ The HRCT scans were reviewed in a blinded fashion by experienced thoracic radiologists. On lung biopsy, all specimens demonstrated concordant histopathologic findings. All patients with pulmonary fibrosis in surgical lung biopsy specimens also had a pattern of fibrosis on HRCT scan.

Identification of an IA Exposure

An antigen was considered to be the IA if it was a known cause of HP and exposure preceded the onset of symptoms. When an exposure was believed to be in the patient's home environment, we considered that exposure to be the IA only if it was confirmed by an industrial hygienist's report or the presence of serum precipitating antibodies. If the relevance of an antigen and environmental exposure could not be established, the exposure was classified as unknown.¹ Avoidance of the IA and abatement procedures were recommended for all patients. Abatement procedures included removal of the IA (if known) and extensive clean up and/or renovation of the exposure site, including drapery and carpet removal and air duct cleaning.

Statistical Analysis

Descriptive statistics are presented as mean and SD for normally distributed variables, median and interquartile range (IQR) for nonnormally distributed variables, or number (%) for categorical variables. Wilcoxon, Student *t*, χ^2 , and Fisher exact tests were used for univariate comparisons, as appropriate. We used the Kaplan-Meier method to display, and the log-rank test to compare, survival curves of patients stratified on identification of an IA. The date of surgical lung biopsy was accepted as the date of diagnosis. Survival period was calculated starting from the date of diagnosis until death. Vital status was ascertained on August 1, 2012 via query of the Social Security Death Index (SSDI). Subjects were censored on the date of query if their death was not found in the SSDI or if they underwent lung transplantation (*n* = 2).

A Cox proportional hazards (PH) model was used to identify independent predictors of survival for the cohort in time-to-death analysis. The PH assumption was examined with goodness-of-fit statistics and log (–log) plots. We first performed univariate analyses with each predictor. Variables with *P* values < .15 in univariate analyses were selected as candidates for the final model, taking into consideration collinearity. Collinearity was assessed visually with scatterplots and numerically with variance inflation factors and Pearson correlations.

The full model contained the following variables: fibrosis, IA exposure, the interaction between fibrosis and IA exposure, age, FVC % predicted, DLCO % predicted, smoking, sex, and dyspnea. Insignificant variables were backward eliminated with inclusion criteria of *P* value < .20. The backward eliminated model was compared with the full model using likelihood ratio test statistics. Median survival was defined as the time, *t*, at which the chance of surviving beyond *t* was 50%. All statistical testing was performed at the conventional two-tailed α level of 0.05. The statistical software R (version 2.15.2) (R Development Core Team) was used for all data analyses.

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Affiliations: From the Interstitial Lung Disease Program and Auto-immune Lung Center (Drs Fernández Pérez, Swigris, Solomon, Huie, Olson, and Brown), Division of Pulmonary and Critical Care Medicine, and the Department of Biostatistics and Bioinformatics (Ms Forssén), National Jewish Health, Denver, CO; and the Calgary Medical Center (Dr Tourin), Calgary, AB, Canada.

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Correspondence to: Evans R. Fernández Pérez, MD, FCCP, National Jewish Health, B'nai B'rith Bldg, Office #M322, 1400 Jackson St, Denver, CO 80206; e-mail: Fernandezevans@njhealth.org

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RESULTS

Of 142 subjects (mean age, 58 ± 12 years; 67 women), 67 (47%) had an IA, and 75 (53%) had no IA. The most common IAs were avian ($n = 24$, 41%) or mold ($n = 16$, 27%). Median follow-up for the cohort was 7.8 years. Table 1 displays the clinical characteristics of subjects stratified on survival. At diagnosis, compared with survivors, subjects who died were older, had lower total lung capacity % and DLCO%, had higher severity of dyspnea, were more likely to have fibrosis on HRCT scan and in surgical lung biopsy specimens, and were less likely to have an identifiable IA. There was a significant difference in the type of IA between survivors and nonsurvivors ($P = .04$).

With the cohort stratified on having an IA or not, there were no significant differences between subgroups in sex distribution, smoking, baseline pulmo-

nary function tests and dyspnea scores, treatment, or the presence of fibrosis (Table 2). Predictors of survival from univariate analyses are displayed in Table 3. Collinearity assessment revealed that the two highest pairwise correlations were between DLCO% and presence of fibrosis ($r = 0.39$, $P < .0001$), and DLCO% and FVC% ($r = 0.38$, $P < .0001$). Using survival times as the dependent variable, all variance inflation factors were ≤ 1.54 . Because of these findings, no covariates from the full model were removed for collinearity. Unidentified IA exposure had a large χ^2 statistic of 5.10 ($P = .0239$); however, the log(-log) plot for unidentified IA exposure did not indicate a strong violation of the PH assumption. All other variables met the PH assumption.

Among subjects with lung fibrosis, the median survival was 4.9 years, and among those without fibrosis,

Table 1—Clinical and Physiologic Characteristics of Patients With Chronic HP Who Did and Did Not Survive

Characteristics	All Patients (N = 142)	Survivors (n = 62)	Nonsurvivors (n = 80)	P Value
Median follow-up, y	7.8 (3.8-15.2)	12.7 (6.1-17.6)	5.9 (2.1-13.4)	< .01
Demographics				
Age, y	58 ± 12	54 ± 12	61 ± 12	< .01
Female sex	67 (47)	32 (52)	35 (44)	.35
Cigarette smoking status				
Former smoker ^a	72 (51)	27 (43)	45 (56)	.13
Smoking history, pack-y	27 ± 22	21 ± 19	31 ± 22	.05
Exposure				< .01
Identified IA	67 (47)	41 (66)	26 (32)	
Unidentified IA	75 (53)	21 (34)	54 (68)	
Type of exposure				.04
Pigeon breeders and bird fanciers	24 (17)	19 (31)	5 (6)	
Office/home mold	16 (11)	9 (14)	7 (9)	
Farmers and gardeners	4 (3)	1 (2)	3 (4)	
Hot tub users	6 (4)	4 (6)	2 (2)	
Farmers, veterinary work, and animal feed handlers	7 (5)	1 (2)	6 (7)	
Woodworker	3 (2)	1 (2)	2 (2)	
Auto mechanic	5 (3)	4 (6)	1 (1)	
Construction worker	1 (1)	0	1 (1)	
Plastic manufacturing plant worker	1 (1)	1 (2)	0	
Pulmonary function tests, % predicted				
TLC	82 ± 21	89 ± 21	77 ± 20	< .01
RV	117 ± 51	128 ± 46	109 ± 53	.01
FVC	64 ± 18	69 ± 18	60 ± 18	< .01
FEV ₁	68 ± 19	70 ± 18	66 ± 20	.14
FVC to FEV ₁ ratio	103 ± 17	97 ± 14	108 ± 19	< .01
DLCO	56 ± 19	58 ± 19	54 ± 19	.34
ATS dyspnea score ^b	9 ± 5	7 ± 4	10 ± 5	< .01
Medications during follow-up				
Prednisone	126 (89)	57 (92)	69 (86)	.28
Steroid-sparing drugs ^c	53 (37)	25 (40)	28 (35)	.51
HRCT scan and histopathologic pattern				< .01
Fibrotic	53 (37)	13 (21)	40 (50)	
Nonfibrotic	89 (63)	49 (79)	40 (50)	

Values are given as the median (25th-75th quartiles), mean $\pm$ SD, or No. (%). ATS = American Thoracic Society; DLCO = diffusing capacity of the lung for carbon monoxide; HP = hypersensitivity pneumonitis; HRCT = high-resolution CT; IA = inciting antigen; RV = residual volume; TLC = total lung capacity.

^aAt least 1 pack-y of smoking history who quit smoking at least 12 mo before presentation.

^bHigher score means more deterioration in severity of dyspnea.

^cAzathioprine, mycophenolate mofetil, cyclophosphamide.

Table 2—Clinical and Physiologic Characteristics in Patients With Chronic HP With and Without a Known Exposure

Characteristics	All Patients (N = 142)	Identified IA (n = 67)	Unidentified IA (n = 75)	P Value
Median follow-up, y	7.8 (3.8-15.2)	11.9 (6.1-16.9)	6.0 (2.3-13.6)	< .01
Demographics				
Age, y	58 ± 12	55 ± 13	60 ± 12	.01
Female sex	67 (47)	26 (38)	41 (54)	.46
Cigarette smoking status				
Former smoker ^a	72 (51)	27 (40)	45 (60)	.16
Smoking history, pack-y	27 ± 22	29 ± 22	26 ± 22	.52
Pulmonary function tests, % predicted				
TLC	82 ± 21	83 ± 21	81 ± 21	.50
RV	117 ± 51	114 ± 48	119 ± 53	.75
FVC	64 ± 18	66 ± 19	63 ± 18	.27
FEV ₁	68 ± 19	69 ± 20	67 ± 19	.36
FVC to FEV ₁ ratio	103 ± 17	102 ± 15	103 ± 19	.67
DLCO	56 ± 19	55 ± 20	56 ± 18	.71
ATS dyspnea score ^b	9 ± 5	8.3 ± 4.3	9.6 ± 5	.13
Medications during follow-up				
Prednisone	126 (89)	58 (86)	68 (90)	.71
Steroid-sparing drugs ^c	53 (37)	20 (29)	33 (44)	.45
HRCT scan and histopathologic pattern				.72
Fibrotic	53 (37)	24 (35)	29 (38)	
Nonfibrotic	89 (63)	43 (64)	46 (61)	

Values are given as the median (25th-75th quartiles), mean ± SD, and No. (%). See Table 1 legend for expansion of abbreviations.

^aAt least 1 pack-y of smoking history who quit smoking at least 12 mo before presentation.

^bHigher score means more deterioration in severity of dyspnea.

^cAzathioprine, mycophenolate mofetil, cyclophosphamide.

median survival was 16.9 years ($P < .01$) (Fig 1A). Survival was longer for subjects with an identified IA than for those with an unidentified IA (median, 18.2 years vs 9.3 years; $P < .01$) (Fig 1B). After adjusting for age, the presence of fibrosis, and cigarette smoking, median survival was longer for subjects with an identified IA than for those with an unidentified IA (median, 8.0 years vs 2.9 years) (Figs 1C, 1D, respectively).

In the final, backward-eliminated Cox PH model that included all potentially influential variables identified in the univariate analysis, independent predictors of lower survival included older age, former smoking, lower baseline FVC%, the presence of fibrosis, and unidentifiable IA (Table 4). The following variables

were backward eliminated from the full model: the interaction between pulmonary fibrosis and IA exposure, sex, and American Thoracic Society dyspnea score. The likelihood ratio test statistic for the full model compared with the backward-eliminated model was not significant, indicating that the reduced model was preferable.

When looking at the multivariable-adjusted (mean age, mean FVC%, mean DLCO%, the presence of smoking history) association between IA identification and survival for subjects with pulmonary fibrosis, median survival was longer for subjects with an identified IA than for those with an unidentified IA (median, 8.75 years vs 4.88 years; $P = .047$) (Fig 2).

Table 3—Univariate Analysis of Predictors of Survival

Variables	HR	95% CI	P Value
Patient age, y	1.05	1.03-1.07	< .01
Male sex	1.44	0.92-2.26	.11
Previous smoking	1.77	1.13-2.76	.01
Unidentifiable IA	2.25	1.40-3.64	< .01
DLCO, ^a %	1.25	1.10-1.42	< .01
FVC, ^b %	1.24	1.08-1.44	< .01
ATS dyspnea score	1.08	1.03-1.13	< .01
Pulmonary fibrosis	3.87	2.45-6.17	< .01

HR = hazard ratio. See Table 1 legend for expansion of other abbreviations.

^aPer 10% predicted FVC reduction.

^bPer 10% predicted DLCO reduction.

DISCUSSION

We identified 142 subjects with well-defined HP evaluated in our program between 1982 and 2008 and evaluated the effect of identifying an IA on prognosis. The main findings of this study were the following: (1) IAs were identified in only 47% of the cohort; (2) IAs were significantly more likely to be identified among survivors than among subjects who died; (3) avian antigens were the most commonly identified IA; (4) inability to identify an IA was a significant predictor of shortened survival, even after controlling for other important variables; and (5) older age, history

FIGURE 1. A, Survival time estimate of chronic hypersensitivity cohort based on the presence or absence of pulmonary fibrosis ($n = 142$, number of events = 80). Median survival time for those with pulmonary fibrosis was 4.9 y (95% CI, 2.9-7.5) and median survival time for those without pulmonary fibrosis was 16.9 y (95% CI, 14.9-22.5). B, Survival time estimate of chronic hypersensitivity pneumonitis (HP) cohort based on presence or absence of identified IA exposure ($n = 142$, number of events = 80). Median survival time for those with identified IA exposure was 18.2 y (95% CI, 14.4-not available [NA]*), and median survival time for those with unidentified IA exposure was 9.3 y (95% CI, 5.9-14.5). C, Survival time estimate of chronic HP cohort for those with identified IA exposure adjusted for mean age of 55 y, former cigarette smoking, and pulmonary fibrosis ($n = 67$, number of events = 27). Median survival times for nonfibrosis and nonsmoking (NA; 95% CI, 20.6-NA), nonfibrosis and smoking (20.6 y; 95% CI, 14.39-NA), fibrosis and nonsmoking (12.8 y; 95% CI, 8.0-NA), fibrosis and smoking (8.0 y; 95% CI, 6.1-NA). D, Survival time estimate of chronic HP cohort for those with unidentified IA exposure adjusted for mean age of 60 y, former cigarette smoking, and pulmonary fibrosis ($n = 75$, number of events = 53). Median survival times for nonfibrosis and nonsmoking (15.5 y; 95% CI, 12.9-NA), nonfibrosis and smoking (13.5 y; 95% CI, 9.10-20.5), fibrosis and nonsmoking (5.8 y; 95% CI, 2.64-13.9), fibrosis and smoking (2.9 y; 95% CI, 2.0-9.1). *Median or the 95% CI was not calculable because an insufficient number of subjects reached the event at the final time point for assessment. IA = inciting antigen.

of cigarette smoking, a lower FVC% at diagnosis, and especially the presence of pulmonary fibrosis were very poor prognostic markers. After adjusting for IA exposure, average age, and smoking status, subjects with fibrosis were 2.43 times more likely to die in follow-up than those without fibrosis.

Among patients with HP, determining the IA is believed to be essential, since this information is important for patient counseling and management.⁴ Although a thorough occupational, vocational, and environmental history should be performed, and an extensive

search for an IA should be undertaken, an important finding of this study is that an IA exposure was not identifiable in almost two-thirds of all patients.

In any patient with HP, great attempts are usually undertaken to identify an IA, since avoiding further exposure is believed to be paramount to their successful treatment. It is possible that failing to identify an IA perpetuates exposure that drives disease progression.⁵ Our results indirectly support the importance of antigen avoidance and the effect of abatement interventions. We presume that recommendations for

Table 4—Variables Included in the Final Cox Proportional Hazards Survival Model

Variables	HR	95% CI	P Value
Patient age, y	1.04	1.01-1.07	.005
Previous smoking	2.01	1.15-3.50	.014
Unidentifiable IA	1.76	1.01-3.07	.047
DLCO, ^a %	1.14	0.95-1.35	.153
FVC, ^b %	1.36	1.10-1.68	.004
Pulmonary fibrosis	2.43	1.36-4.35	.002

The following variables were backward eliminated from the full model: interaction between pulmonary fibrosis and IA exposure, sex, and ATS dyspnea score. See Table 1 and 3 legends for expansion of abbreviations.

^aPer 10% predicted FVC reduction.

^bPer 10% predicted DLCO reduction.

IA avoidance and abatement recommendations were followed, but we have no way of assessing the rigor with which that actually occurred. Intriguingly, in certain animal models, repeated antigen challenge results in waning inflammatory response rather than disease progression.^{6,7} Likewise, investigators have observed the same phenomenon among pigeon breeders and farmers who experienced no clinical deterioration despite continued IA exposure.⁸⁻¹⁰ We believe the contrasts in the literature^{11,12} reflect the complex pathogenesis of HP and that the HP phenotype that develops likely hinges on multiple factors, including the type of IA, extent of exposure, and, perhaps most

importantly, a person's unique, genetically determined response to the particular IA.^{13,14}

In contrast to our findings, three previous studies^{2,15,16} found no association between mortality rate and IA exposure in univariate analyses. One possible explanation for these conflicting results is that the effect of IA on chronic HP mortality may be small and require a large sample size to detect. The cohort in this study was larger than the three previous studies. Furthermore, in two of those studies,^{15,16} the relatively small number of outcome events did not allow for multivariate survival analysis. Also, one study differs from ours in that cases were solely selected on the basis of histopathologic findings that did not necessarily reflect fibrotic or chronic HP.¹⁵

Like other investigators, we observed that avian antigens were most common^{17,18} and that pulmonary fibrosis was a very important predictor of poor outcome. Gene expression patterns distinguish subjects with idiopathic pulmonary fibrosis (IPF) and subacute/chronic HP,¹⁹ but why some patients with chronic HP and not others develop fibrosis is unclear. Our data underscore the importance of seeking a better understanding of why certain people are susceptible to developing HP and among those who are, why a certain subgroup develops progressive fibrotic disease (in many despite the absence of continued exposure to the IA). One clue, corroborated by our data, is that as in patients with IPF, subjects with HP with pulmonary fibrosis tend to be older.²⁰

Several studies have shown that HP occurs less frequently in smokers than nonsmokers and that tobacco smoking is inversely associated with risk of granulomatous lung disease.²¹⁻²³ However, this might not be the case in the setting of fibrotic lung disease, and our data support the deleterious effects of cigarette smoking on disease prognosis. In IPF, severity-adjusted survival is longer in nonsmokers than in smokers (former and/or current).²⁴ To our knowledge, there is only one published study describing the effect of smoking on the clinical course of HP.²⁵ In that case-control study, current or former smokers among patients with farmer's lung disease had an insidious and chronic disease course, with a worse survival rate compared with nonsmokers.

The database of the ILD program at our institution includes >4,000 patients who are registered and followed prospectively. Methods to minimize bias that we implemented when using this database included the following: (1) outcome was ascertained with clinical status (eg, identified IA vs not, fibrosis vs not) concealed, (2) explicit case definitions were determined a priori, and (3) predictor variables were collected prospectively. However, as with other retrospective assessments of carefully collected data, our study has several potential shortcomings. Because of referral

FIGURE 2. Survival time estimate of chronic HP cohort for those with or without pulmonary fibrosis and with or without IA adjusted to former cigarette smoking, mean age of 58 y, mean FVC % predicted of 64%, and mean diffusing capacity of the lung for carbon monoxide % predicted of 55%. Median survival times for nonfibrosis and unidentified IA (11.8 y; 95% CI, 7.13-15.7), nonfibrosis and identified IA (14.5 y; 95% CI, 12.33-not available [NA]*), fibrosis and unidentified IA (4.88 y; 95% CI, 2.82-12.3), fibrosis and identified IA (8.75 y; 95% CI, 5.83-15.7). *Median or 95% CI was not calculable because an insufficient number of subjects reached the event at the final time point for assessment. See Figure 1 legend for expansion of abbreviation.

bias to our tertiary care center, our program likely evaluates and cares for a greater proportion of patients with fibrotic HP than most community practices; however, subjects in this cohort appear representative of the general population of patients with chronic HP.^{15,16,26} It is possible that some of the subjects without fibrosis had subacute HP. However, our cohort resembles subjects defined as having chronic HP by other investigators,²⁶ and our results do not extrapolate to those with acute HP. Differences in survival might be secondary to lead-time bias, since patients with HP with an identifiable IA were younger than those with an unknown exposure; however, after adjustment for age, the relationship between the presence or absence of IA and survival was significant, especially in former smokers with pulmonary fibrosis, arguing strongly against lead-time bias. Finally, other confounding variables potentially influencing survival, such as race/ethnicity and socioeconomic status, were not collected. Also, our cohort did not have information on the specific cause of death. Knowing the cause of death was desirable, but unobtainable, for this study and may have caused confounding in the results. An additional limitation of this study was the lag time of several months between the event of death and addition to the SSDI, which may have biased survival times slightly.

In conclusion, among patients with chronic HP evaluated at our center, the presence of lung fibrosis on HRCT scan and in surgical lung biopsy specimens was strongly associated with an increased rate of death. However, even after accounting for the presence of fibrosis, the inability to identify an IA was independently associated with shorter survival compared with when an IA was identified. These results suggest that in any patient with HP, clinicians should aggressively search for, identify, and remove the IA. All efforts to avoid potential sources of antigen exposure should be made even if that source has not been confirmed. Clinicians need reliable, validated, and more widely accessible methods for identification of IAs that cause HP and in distinguishing disease from ordinary past exposure.^{4,27} In addition, future studies of patients with HP, determinants of fibrosis, and the effectiveness of abatement procedures should be investigated.

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Dr Fernández Pérez: contributed to conception and design of the study, data collection and analysis, and drafting the manuscript for important intellectual content.

Dr Swigris: contributed to design of the study, data collection and analysis, and drafting the manuscript for important intellectual content.

Ms Forssén: contributed to data collection and analysis and drafting the manuscript for important intellectual content.

Dr Tourin: contributed to data collection and drafting of the manuscript for important intellectual content.

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