

# Clinical characteristics and outcomes of hypersensitivity pneumonitis: a population-based study in China

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## Abstract

**Backgrounds:** Hypersensitivity pneumonitis (HP) is an immune-mediated interstitial lung disease (ILD) that develops in response to the inhalation of various antigens. The clinical pathologies are very complex and undetermined. The clinical features and outcomes of HP have not been fully elucidated. The aim of this study was to analyze the incidence, clinical features, and outcomes of HP patients and construct a simple clinical model for diagnosing chronic HP (CHP).

**Methods:** The cohort study included 101 patients with HP admitted to the Nanjing Drum Tower Hospital from January 2009 to December 2017. The patients were categorized into acute HP (AHP,  $n = 72$ ) and CHP ( $n = 29$ ) groups according to the updated international criteria. The clinical, imaging, treatment, and follow-up data were retrospectively reviewed. All patients were followed up until December 31, 2017. Statistical analysis was performed, and a clinical scoring system for CHP was constructed by SPSS 20.0 software.

**Results:** The incidence of HP was 2.4% in ILD inpatients in our center. Patients in the CHP group were older ( $t = -2.212$ ,  $P = 0.029$ ), had more smokers ( $\chi^2 = 8.428$ ,  $P = 0.004$ ), and longer duration of symptoms ( $t = -4.852$ ,  $P < 0.001$ ) than those in the AHP group. Weight loss, crackles, digital clubbing, and cyanosis were more common in the CHP group than those in the AHP group ( $\chi^2 = 5.862$ ,  $P < 0.001$ ;  $\chi^2 = 8.997$ ,  $P = 0.003$ ;  $\chi^2 = 11.939$ ,  $P = 0.001$ ; and  $\chi^2 = 4.025$ ,  $P = 0.045$ , respectively). On chest high-resolution computed tomography (HRCT), reticular patterns, traction bronchiectasis, and accompanying honeycombing were more common in CHP cases than those in AHP cases ( $\chi^2 = 101.000$ ,  $P < 0.001$ ;  $\chi^2 = 32.048$ ,  $P < 0.001$ ; and  $\chi^2 = 36.568$ ,  $P < 0.001$ , respectively). The clinical scoring system for CHP was established based on the clinical variables (age [A], duration of symptoms [D], smoking history [S], unidentified exposure [U], and chest HRCT [C]; ADSUC) (area under the curve 0.935, 95% confidence interval: 0.883–0.987,  $P < 0.001$ ). Eleven patients (15.3%) in the AHP group developed CHP, and unidentified exposure was an independent risk factor for the progression of disease ( $P = 0.038$ ). The survival of patients with CHP, smoking history, unidentified antigens and fibrosis on Chest HRCT were significantly worse ( $P = 0.011$ ,  $P = 0.001$ ,  $P = 0.005$ , and  $P = 0.011$ , respectively) by Kaplan-Meier analysis. Cox multivariate regression analysis revealed that unidentified exposure and total lung volume (TLC pred%) were independent prognostic predictors for HP patients ( $P = 0.017$  and  $P = 0.017$ , respectively).

**Conclusions:** The clinical features and outcomes of the CHP patients differ from those of the AHP patients. ADSUC is a simple and feasible clinical model for CHP. Unidentified exposure is an independent risk factor for the progression of AHP to CHP. Unidentified exposure and a low baseline TLC pred% are independent predictors for survival in HP patients.

**Keywords:** Hypersensitivity pneumonitis; Chronic; Interstitial lung disease; Fibrosis

## Introduction

Hypersensitivity pneumonitis (HP), also called extrinsic allergic alveolitis, is a common form of interstitial lung disease (ILD) caused by repeated inhalation exposure to a variety of antigens. However, little is known about the epidemiology of the condition. Early studies estimating HP frequency are focused on the geographic distribution, patient occupation and concentration, and duration or frequency of exposure to the antigen as influencing

factors.<sup>[1,2]</sup> Recently, the reported incidence of occupational HP in the United Kingdom was one to two cases per million workers per year.<sup>[3]</sup> The 1-year cumulative incidence rate ranged from 1.28 to 1.94 per 100,000 persons in the United States, which is lower than the incidence of idiopathic pulmonary fibrosis (IPF; approximately 6.8–16.3 per 100,000 persons).<sup>[4,5]</sup>

A different perspective emerged from cohorts of patients investigated for new-onset ILDs wherein HP was part of

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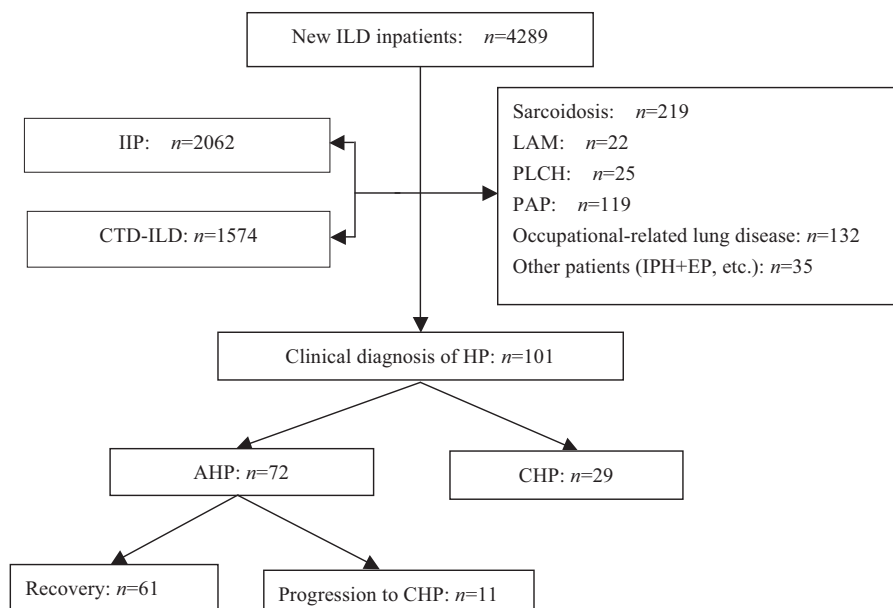
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**Figure 1:** Flow diagram of HP patients. AHP: Acute hypersensitivity pneumonitis; CHP: Chronic hypersensitivity pneumonitis; CTD: Connective tissue disease; EP: Eosinophilic pneumonia; HP: Hypersensitivity pneumonitis; IIP: Idiopathic interstitial pneumonia; ILD: Interstitial lung disease; IPH: Idiopathic pulmonary hemosiderosis; LAM: Lymphangioleiomyomatosis; PAP: Pulmonary alveolar proteinosis; PLCH: Pulmonary Langerhans cell histiocytosis.

the differential diagnosis. In this setting, the clinical diagnosis of HP was made by multidisciplinary discussion in nearly half of the patients with new-onset ILDs.<sup>[6]</sup>

Traditionally, HP is categorized into acute, subacute, and chronic forms, but this division appears to have little prognostic value.<sup>[7]</sup> From a practical standpoint, it is difficult to stratify patients into these three different patterns, particularly the subacute type of HP.<sup>[8]</sup> There is extensive overlap between the clinical phenotypes, particularly between the subacute and chronic forms. Confidently diagnosing chronic HP (CHP) is typically extremely challenging. More than 50% patients with CHP could not be identified inciting antigen.<sup>[9]</sup> Therefore, the differentiation of CHP from other fibrosing ILDs is quite difficult, particularly from IPF. Recently, international ILD experts proposed two main categories based on a clinical-radiologic correlation: acute/inflammatory HP (AHP) and chronic/fibrotic HP (CHP); the new criteria and classification will be very useful for pulmonologists when they are confronted with HP patients and can promote further studies in the future.<sup>[7]</sup>

However, there is little published data on HP, and most of the data are reported in a small series in China. The prevalence of farmer's lung disease among Chinese greenhouse farmers was 5.7%.<sup>[10]</sup> The most common exposures in HP patients were low molecular weight chemicals (42.7%) and animal proteins (37.5%).<sup>[11]</sup> However, the incidence, risk factors, clinical features, and outcomes of HP have not been fully elucidated. This retrospective cohort study included 101 cases of new-onset HP from Nanjing Drum Tower Hospital between January 2009 and December 2017. According to the updated international recommendations, the patients were categorized into AHP and CHP groups. In our study, we analyzed the incidence, clinical features, and outcomes of HP

patients in a single center and constructed a simple clinical model for diagnosing CHP.

## Methods

### Ethical approval

This study was approved by the Ethics Committee of Nanjing Drum Tower Hospital. This study was conducted in accordance with the principles set forth under the *Declaration of Helsinki* (1989; No. 2016-160-01). In addition, all participants provided written informed consent.

### Study population

As shown in Figure 1, this cohort study included 101 cases of new-onset HP from 4289 new ILD patients admitted to the Nanjing Drum Tower Hospital, Nanjing University Medical School, from January 2009 to December 2017. Patients with other patterns of ILD such as idiopathic interstitial pneumonitis, sarcoidosis, lymphangiomyomatosis, pulmonary Langerhans histiocytosis, pulmonary alveolar proteinosis, occupational-related lung disease, idiopathic pulmonary hemosiderosis, and eosinophilic pneumonia were excluded from our study. The clinical and follow-up data were retrospectively analyzed. All patients were followed up until December 31, 2017. The clinical and imaging findings were extracted from the medical records. Vital status information was obtained from medical records or telephone interviews at follow-up. The baseline characteristics were obtained upon admission to the hospital. All patients or their relatives signed an informed consent form.

HP was diagnosed according to the criteria proposed by Schuyler and Cormier.<sup>[12]</sup> The major criteria include the following items: (1) history of symptoms compatible with

HP; (2) evidence of exposure to the offending antigen in the patient history or through detection by serum or bronchoalveolar lavage (BAL) fluid antibodies; (3) changes that are characteristic of HP on chest high resolution computed tomography (HRCT; ground-glass opacities [GGOs], micronodules, honeycombing, linear opacities, air trapping); (4) demonstration of BAL fluid lymphocytosis, if BAL was performed; (5) demonstration of histologic changes consistent with HP, if a lung biopsy was performed, such as alveolitis, noncaseating granulomas, giant cells, foamy alveolar macrophages, or fibrosis; and (6) positive natural challenge that produces symptoms and objective abnormalities either through a controlled inhalational challenge or after reexposure to the offending environment. The minor criteria are as follows: (1) bibasilar rales; (2) decreased diffusion capacity; and (3) arterial hypoxemia, either at rest or with exercise. The diagnosis was confirmed if the patient fulfilled four of the major criteria and at least two of the minor criteria, and if other diseases with similar symptoms were ruled out (ie, sarcoidosis or IPF).

The patients in our study were categorized into the AHP group or CHP group based on their clinical, radiological, and pathological findings, as recently proposed by international experts.<sup>[7]</sup> The criteria for the AHP group are as follows: (1) symptom duration usually <6 months or <24 weeks duration if the symptoms were reversible; (2) typical HRCT image patterns including upper and midlobe predominant GGOs, poorly defined centrilobular nodules, mosaic attenuation, air trapping, or rare consolidation; and (3) pathological features including lymphoplasmacytic/mononuclear (macrophage) infiltration, airway-centered lymphocytic/peribronchiolar infiltrates, poorly/loosely formed granulomas, multinucleated giant cells, and cellular-like nonspecific interstitial pneumonia (NSIP).

The criteria for the CHP group are as follows: (1) symptom duration usually beyond 6 months or 24 weeks duration if the symptoms were potentially reversible to some extent, with a risk of progression; (2) typical HRCT image patterns including upper and midlobe predominant fibrosis, peribronchovascular fibrosis, honeycombing, mosaic attenuation, air trapping, centrilobular nodules, and relative sparing of the bases; and (3) pathological changes that manifested as usual interstitial pneumonia (UIP)-like pattern, fibrotic NSIP, airway-centered fibrosis, and nonclassifiable conditions. Histopathological signs of inflammatory HP could be present on the background of fibrosis. There were 72 patients (71%) in the AHP group and 29 patients (29%) in the CHP group. At the end of follow-up, 11 (15.3%) patients in the AHP group progressed to having CHP.

### HRCT scanning

#### Characteristics of HRCT

The imaging features of HP patients on chest HRCT showed GGOs, poorly defined centrilobular nodules, mosaic attenuation/air trapping (exhalation), reticulation, traction bronchiectasis, and honeycombing with upper lobe predominance.

### Fibrosis on chest HRCT

Fibrosis on chest imaging presented with predominantly upper-zone reticular patterns with or without honeycombing, traction bronchiectasis, or upper lobe volume loss.<sup>[9]</sup>

### Progression from AHP to CHP

The newly diagnosed AHP patients were followed up for more than 6 months, and the clinical symptoms did not improve. Changes of the fibrosis characteristics on HRCT were present. CHP was diagnosed according to the criteria proposed by Vasakova *et al.*<sup>[7]</sup>

### Constructing a clinical scoring system for CHP

The diagnostic value of small samples from transbronchial lung biopsy (TBLB) and BAL in unexplained causes of ILD is very limited, so surgical lung biopsy (SLB) is recommended when a diagnosis cannot be made by other methods.<sup>[13,14]</sup> The updated international classification of HP (AHP and CHP) was proposed according to the clinical, radiological and pathological changes.<sup>[7]</sup> In clinical practice, it is very difficult for clinical physicians to initially diagnose HP if the inciting antigen cannot be recognized or there is an absence of pathological evidence. To differentiate CHP from AHP at the initial diagnosis, we established a simple clinical scoring system according to the baseline clinical variables (age [A], duration of symptoms [D], smoking history [S], unidentified exposure [U], chest HRCT features [C]; ADSUC) without the need for pathology findings.

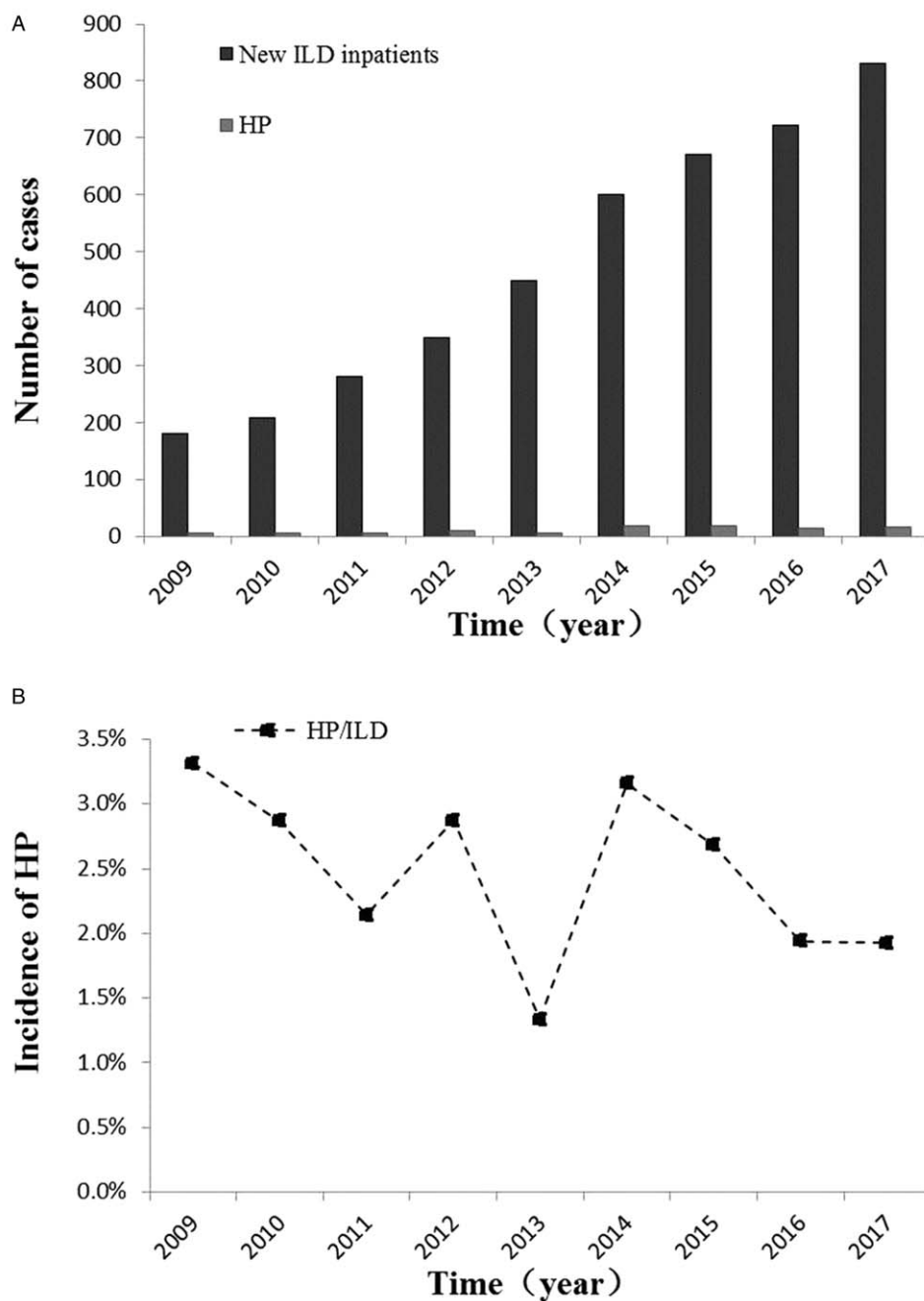
### Statistical analysis

Data are presented as the mean  $\pm$  standard deviation for continuous variables or percentages for categorical variables. The Mann-Whitney *U* test, Student *t*-test, chi-squared test, and Fisher exact tests were used for univariate comparisons, as appropriate. We constructed a scoring system that distinguishes between AHP and CHP by drawing a receiver operating characteristic (ROC) curve and analyzing the sensitivity and specificity of the area under the curve to evaluate its prediction effect. Logistic regression analysis was used to observe the risk factors affecting the progression of AHP to CHP. We used the Kaplan-Meier method to display the survival curve and the log-rank test to compare patients stratified by HP type. A Cox proportional hazards model analysis was utilized to detect independent predictors of survival. A  $P < 0.05$  was considered to represent statistical significance. Statistical analyses were performed by using IBM SPSS version 20 (SPSS, Inc., Chicago, IL, USA) and Prism version 5 (GraphPad, San Diego, CA, USA).

## Results

### Incidence

As shown in Figure 2, the incidence of HP in new ILD patients was 2.4% (101/4289) (range: 1.3%–3.3%).



**Figure 2:** Incidence of HP in new ILD inpatients. (A) The number of new HP and ILD inpatients per year. (B) The incidence of HP in new ILD inpatients per year. HP: Hypersensitivity pneumonitis; ILD: Interstitial lung disease.

### Baseline clinical characteristics

The baseline clinical features of HP patients are summarized in Table 1. Among the 101 patients, 54.5% (55) of the patients were females, the average age was  $53.6 \pm 12.4$  years, and 33.7% (34) of the patients had a smoking history. An exposure history was recognized in 72.3% (73) of the cases.

The patients in the CHP group were older ( $P = 0.029$ ) and were more likely to be smokers ( $P = 0.004$ ) than the AHP patients. Fevers were more common in the AHP group than in the CHP group ( $P = 0.046$ ), whereas weight loss,

lung crackles, digital clubbing, and cyanosis were more common in the CHP group than those in the AHP group ( $P < 0.001$ ,  $P = 0.003$ ,  $P = 0.001$ , and  $P = 0.045$ , respectively). On the chest HRCT, GGOs, centrilobular nodules, and air trapping/mosaic attenuation were more common in AHP patients than those in CHP patients ( $P = 0.037$ ,  $P < 0.001$ , and  $P = 0.006$ , respectively). However, reticular patterns, traction bronchiectasis, and accompanying honeycombing were more common in CHP patients than those in AHP patients ( $P < 0.001$ ,  $P < 0.001$ , and  $P < 0.001$ , respectively). Forced expiratory volume in one second (FEV1)/forced vital capacity (FVC)% was lower in the CHP group than that in the AHP group ( $P = 0.035$ ).

**Table 1: Baseline clinical features of the patients with HP.**

Variable	N	HP	AHP (n = 72)	CHP (n = 29)	t/ $\chi^2$	P
Demographic features						
Gender (M/F)	101	46/55	34/38	12/17	0.285*	0.594
Age (years)	101	53.6 ± 12.4	51.9 ± 12.1	57.8 ± 12.3	-2.212 <sup>†</sup>	0.029
Smoking history	101	34 (33.7)	18 (24.0)	16 (55.2)	8.428*	0.004
Exposure history	101	73 (72.3)	56 (77.8)	17 (58.6)	3.786*	0.052
Duration of symptoms (months)	101	6 (1-12)	2 (1-6)	12 (5-36)	-4.852 <sup>†</sup>	<0.001
Dyspnea	101	94 (93.1)	67 (93.1)	27 (93.1)	0.000*	0.993
Cough	101	93 (92.1)	65 (90.3)	28 (96.6)	1.116*	0.291
Sputum	101	72 (71.3)	50 (69.4)	22 (75.9)	0.416*	0.519
Chest pain	101	5 (5.0)	5 (6.9)	0	2.119*	0.146
Fever	101	36 (35.6)	30 (41.7)	6 (20.7)	3.966*	0.046
Weight loss	101	10 (9.9)	1 (1.4)	9 (31.0)	5.862*	<0.001
Crackles	101	46 (45.5)	26 (36.1)	20 (69.0)	8.997*	0.003
Digital clubbing	101	7 (6.9)	1 (1.4)	6 (20.7)	11.939*	0.001
Cyanosis	101	11 (10.9)	5 (6.9)	6 (20.7)	4.025*	0.045
Laboratory tests						
PaO <sub>2</sub> (mmHg)	84	73.5 ± 13.7	73.0 ± 12.2	74.1 ± 13.2	-0.384 <sup>†</sup>	0.702
WBC ( $\times 10^9$ )	101	6.8 ± 2.8	6.8 ± 2.9	6.7 ± 2.7	0.113 <sup>†</sup>	0.911
LDH (U/L)	101	227.5 ± 76.9	218.1 ± 71.3	250.9 ± 86.3	-1.971 <sup>†</sup>	0.051
CRP (mg/L)	101	3.3 (0.5-6.2)	2.7 (0.8-7.8)	3.5 (0.2-5.2)	0.764 <sup>†</sup>	0.812
ESR (mm/h)	94	25.7 ± 20.9	26.4 ± 23.4	24.1 ± 14.1	0.591 <sup>†</sup>	0.556
CD4/CD8	61	1.6 ± 0.9	1.6 ± 0.8	1.4 ± 1.1	0.648 <sup>†</sup>	0.522
PAH ( $\geq 40$ / $< 40$ mmHg)	72	13/59	7/41	6/18	1.210*	0.222
Pulmonary function tests						
FVC (L)	77	2.48 ± 0.73	2.57 ± 0.80	2.29 ± 0.49	1.826 <sup>†</sup>	0.072
FEV <sub>1</sub> /FVC (%)	77	83.76 ± 7.08	82.66 ± 7.27	86.35 ± 5.97	-2.144 <sup>†</sup>	0.035
TLC (% pred)	77	67.03 ± 17.47	68.64 ± 17.30	63.44 ± 17.70	1.189 <sup>†</sup>	0.238
DLCO (% pred)	75	55.27 ± 19.79	57.70 ± 21.34	50.02 ± 15.00	0.653 <sup>†</sup>	0.516
Chest HRCT						
GGOs	101	97 (96.0)	71 (98.6)	26 (89.7)	4.360*	0.037
Centrilobular nodules	101	80 (79.2)	68 (94.4)	12 (41.4)	35.348*	<0.001
Air trapping	101	66 (65.3)	53 (73.6)	13/(44.8)	7.564*	0.006
Reticular pattern	101	29 (28.7)	0	29 (100.0)	101.000*	<0.001
Traction bronchiectasis	101	20 (19.8)	4 (1.4)	16 (55.2)	32.048*	<0.001
Honeycombing	101	11 (10.9)	0	11 (37.9)	36.568*	<0.001
BALF	86	86 (85.1)	61 (84.7)	25 (86.2)	-	-
Macrophages (%)	86	41.2 ± 24.8	41.2 ± 25.8	41.4 ± 25.4	-0.030 <sup>†</sup>	0.976
Neutrophils (%)	86	10.0 (2.0-40.0)	6.0 (2.0-40.0)	28.0 (1.5-47.5)	-1.200 <sup>†</sup>	0.301
Eosinophils (%)	86	0	0	0	0.910 <sup>†</sup>	0.362
Lymphocytes (%)	86	20 (7-40)	21 (9-44)	15 (1-28)	-1.963 <sup>†</sup>	0.055
Lung biopsy	78	78 (77.2)	60 (83.3)	18 (62.1)		
Treatments after diagnosis						
Corticosteroids	84	84 (83.2)	56 (7.8)	28 (96.6)	5.205*	0.023
CTX	4	4 (4.0)	2 (2.8)	2 (6.9)	0.922*	0.337
AZA	1	1 (1.0)	1 (1.4)	0	0.407*	0.524
NAC	66	66 (65.3)	39 (54.2)	27 (93.1)	14.671*	<0.001
Survival state (survival/censored)	101	80/21	59/13	21/8		

Data were presented by *n*, *n* (%), the median (interquartile range) or mean ± standard deviation. \* Calculated using the chi-square test. <sup>†</sup> Calculated using Student *t* test. AHP: Acute hypersensitivity pneumonitis; AZA: Azathioprine; BALF: Bronchoalveolar lavage fluid; CHP: Chronic hypersensitivity pneumonitis; CRP: C reactive protein; CTX: Cyclophosphamide; DLCO: Carbon monoxide diffusing capacity; F: Female; FEV: Forced vital capacity; FEV1: Forced expiratory volume in one second; GGOs: Ground-glass opacities; HP: Hypersensitivity pneumonitis; HRCT: High-resolution computed tomography; LDH: Lactate dehydrogenase; M: Male; NAC: N-acetylcysteine; PAH: Pulmonary arterial hypertension; TLC: Total lung capacity; 1 mmHg = 0.133 kPa.

More CHP patients were treated with corticosteroids and N-acetylcysteine than AHP patients ( $P = 0.023$  and  $P < 0.001$ , respectively). There were no significant differences in the other clinical variables between the two groups.

### Constructing a scoring system for CHP

Based on the sample size of our cohort, the differences in baseline clinical characteristics between the AHP and CHP groups, and the published reports on CHP,<sup>[15]</sup> we



**Table 2: Clinical scoring system for CHP.**

Variable	Score
<b>A</b>	
Age	
≤55 years	0
>55 years	1
<b>D</b>	
Duration of symptoms	
≤6 months	0
>6 months	1
<b>S</b>	
Smoking history	
No	0
Yes	1
<b>U</b>	
Unidentified exposure	
No	0
Yes	1
<b>C</b>	
Reticular pattern	
No	0
Yes	1
Traction bronchiectasis	
No	0
Yes	1
Honeycombing	
No	0
Yes	1

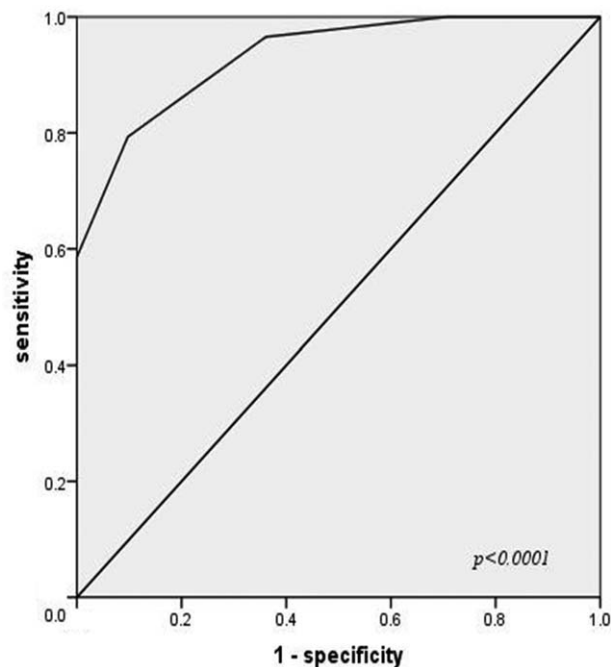
CHP: Chronic hypersensitivity pneumonitis; A: Age; C: Chest HRCT; D: Duration of symptoms; S: Smoking history; U: Unidentified exposure.

constructed a simple clinical scoring system for diagnosing CHP with the variables of age, duration of symptoms, smoking history, unidentified exposure, and HRCT features [Table 2].

ROC curve was calculated to compare the predictive value of the scoring system for CHP. The ROC curve is depicted in Figure 3. The area under the curve of the scoring system for diagnosing CHP was 0.935 (95% confidence interval, CI: 0.883–0.987,  $P < 0.0001$ ). The cut-off values and the diagnostic accuracy for predicting CHP are shown in Supplementary Table 1. When the score is  $\leq 2$  points, the negative predictive value is 92.9%, which can effectively exclude CHP, and when the score is  $\geq 4$  points, the positive predictive value is 100%, which can effectively diagnose CHP.

**Risk factors for the progression from AHP to CHP**

Among the 72 patients with AHP, 11 patients (15.3%) progressed to have CHP by the end of the follow-up period. The baseline clinical characteristics of the AHP patients were analyzed by univariate logistic analysis. The analysis showed that age and unidentified exposure to antigens were the risk factors for the progression from AHP into CHP. Multivariate logistic analysis showed that unidentified exposure was an independent risk factor for progressing into CHP for patients with AHP (odds ratio: 0.078, 95% CI: 0.007–0.864,  $P = 0.038$ ) [Table 3].



**Figure 3:** ROC curve of the scoring system for CHP. CHP: Chronic hypersensitivity pneumonitis; ROC: Receiver operating characteristic. The area under the curve of the scoring system for diagnosing CHP was 0.935 (95% confidence interval [CI]: 0.883–0.987,  $P < 0.0001$ ).

**Prognosis**

The Kaplan-Meier analysis showed that the survival of patients with CHP was significantly worse compared with that of patients with AHP ( $P = 0.011$ ) [Figure 4A]. The median survival time (MST) was 74.5 months in the CHP group, and the MST was 137.2 months in the AHP group. The survival was significantly better by log-rank tests in patients without a smoking history, without fibrosis on the chest HRCT, and with identified exposure than that in patients with a smoking history, fibrosis on chest HRCT, and unidentified exposure ( $P = 0.001$ ,  $P = 0.005$ , and  $P = 0.005$ , respectively) [Figure 4B–4D].

In the Cox univariate analysis, CHP, age, smoking history, unidentified exposure, TLC pred%, and fibrosis on HRCT were predictors for survival in all HP patients ( $P = 0.021$ ,  $P = 0.025$ ,  $P = 0.005$ ,  $P = 0.013$ ,  $P = 0.004$ , and  $P = 0.021$ , respectively) [Table 4]. However, unidentified exposure and TLC pred% were the independent risk factors for survival by Cox multivariate analysis (hazard ratio: 0.117, 95% CI: 0.02–0.681,  $P = 0.017$ , and hazard ratio: 0.965, 95% CI: 0.937–0.993,  $P = 0.017$ , respectively) [Table 4].

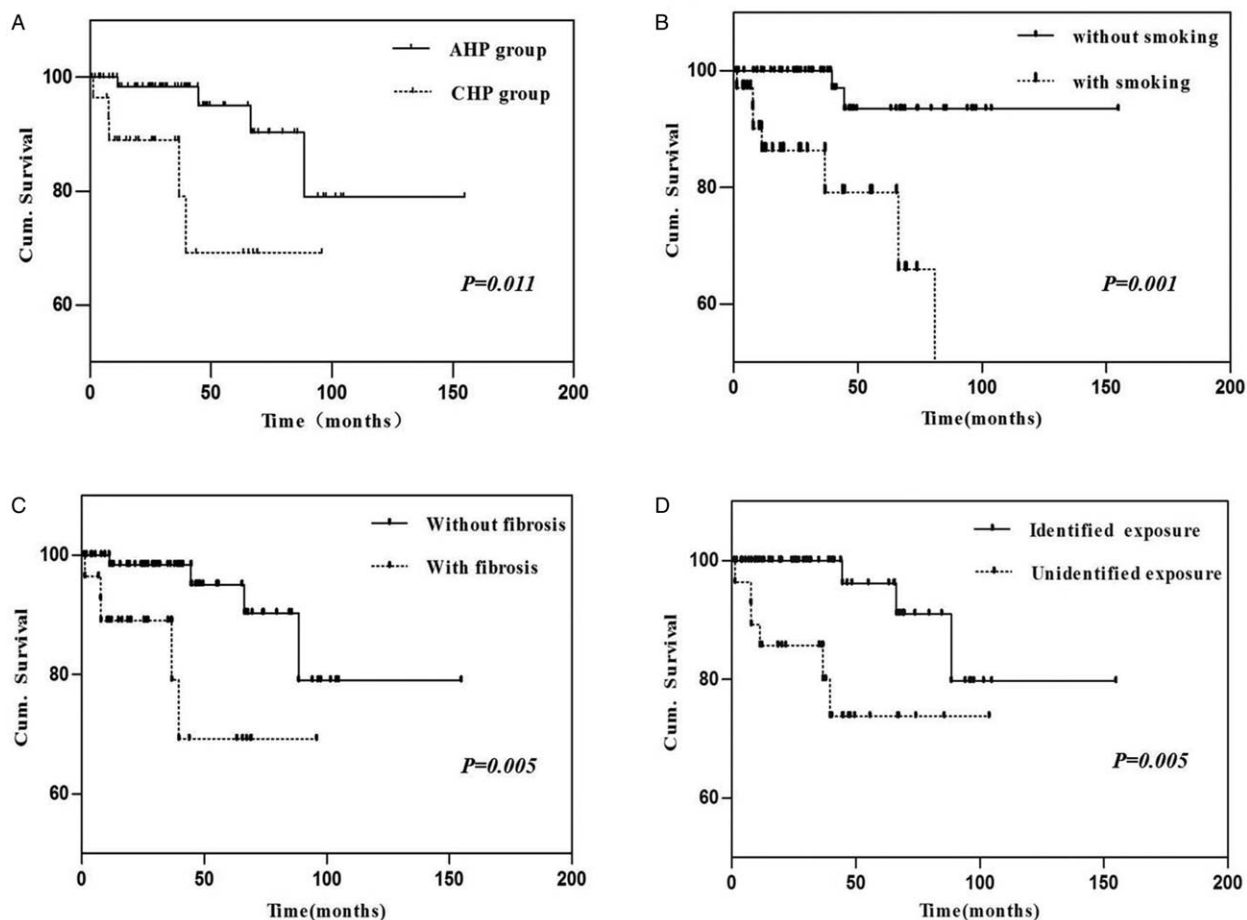
**Discussion**

This study demonstrated that the incidence of HP in ILD patients was 2.4% per year in our single center. The clinical features and outcomes of CHP patients differed from those of AHP patients. In total, 15.3% of AHP patients developed CHP because the offending exposure antigens could not be recognized. The unidentified

**Table 3: Logistic analysis of the risk factors for the progression from AHP to CHP.**

Clinical variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.058 (0.998–1.123)	0.047	1.044 (0.971–1.122)	0.250
Unidentified exposure	0.052 (0.010–0.277)	0.001	0.078 (0.007–0.864)	0.038

AHP: Acute hypersensitivity pneumonitis; CHP: Chronic hypersensitivity pneumonitis; CI: Confidence interval; OR: Odds ratio.



**Figure 4:** Survival of patients with HP. (A) Comparison of the survival between the AHP and CHP groups. (B) Comparison of the survival between patients with and without a smoking history. (C) Comparison of the survival between patients with and without fibrosis on chest HRCT. (D) Comparison of the survival of patients with identified and unidentified exposure. AHP: Acute hypersensitivity pneumonitis; CHP: Chronic hypersensitivity pneumonitis; HP: Hypersensitivity pneumonitis; HRCT: High-resolution computed tomography.

**Table 4: Risk factors for survival in all HP patients calculated by Cox regression models.**

Clinical variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
CHP	4.859 (1.275–18.524)	0.021	0.219 (0.031–1.554)	0.129
Age	1.072 (1.009–1.138)	0.025	1.004 (0.925–1.089)	0.928
Smoking history	9.522 (1.97–46.023)	0.005	4.155 (0.492–35.074)	0.191
Unidentified exposure	0.168 (0.041–0.692)	0.013	0.117 (0.020–0.681)	0.017
TLC pred%	0.957 (0.929–0.986)	0.004	0.965 (0.937–0.993)	0.017
Fibrosis on chest HRCT	4.859 (1.275–18.524)	0.021	0.982 (0.950–1.015)	0.293

CHP: Chronic hypersensitivity pneumonitis; CI: Confidence interval; HP: Hypersensitivity pneumonitis; HR: Hazard ratio; HRCT: High-resolution computed tomography.

exposure was an independent risk factor for the progression from AHP to CHP. ADSUC is a very useful and feasible way to differentiate CHP from AHP at the initial diagnosis. Unidentified exposure and a low baseline TLC pred% were independent predictors for survival in HP patients.

HP is very complex, and it is quite difficult to differentiate patients with CHP from IPF without clearly identified exposure and pathology.<sup>[16]</sup> The exact incidence and prevalence of HP are under debate because quite a few cases are misdiagnosed or go unrecognized.<sup>[16]</sup> According to data from registry study of ILDs in three European countries, HP accounts for 4% to 15% of all ILD cases.<sup>[17]</sup> The reported incidence of HP in a claims-based cohort analysis was approximately one to two per million people in the United States and United Kingdom.<sup>[3,4]</sup> In addition, the prevalence varies from country to country (even within the same country) owing to geographic, seasonal, and climatic factors.<sup>[18]</sup> In our study, HP accounted for 2.4% (1.3%–3.3%) of all ILD cases during the past 9 years, which is lower than that reported in the registry study and higher than that from large-scale national epidemiological studies.<sup>[1,17,19]</sup> The difference in the incidence rates between our report and other studies may be associated with the different diagnostic criteria and geographic and demographic factors.

HP was originally divided into acute, subacute, and chronic categories. This division is outdated.<sup>[9]</sup> From a practical standpoint, it is difficult to stratify patients into these three distinct groups, particularly into the subacute HP group.<sup>[8]</sup> Traditional subacute HP is particularly difficult to define because the features in this subset overlap with those of both the acute and chronic subtypes.<sup>[20]</sup> Thus, Vasakova *et al.*<sup>[7]</sup> proposed the new categories acute/inflammatory HP and chronic/fibrotic HP based on clinical-radiologic-pathologic findings. Following the new suggested classification, we divided our patients into AHP and CHP groups in our study. AHP is relatively easily recognized because the offending exposure antigens in most patients can be recognized. CHP is often unrecognized or misdiagnosed. Therefore, the exposure to a relevant antigen is a key component of clinical evaluation.

Fernández Pérez *et al.*<sup>[4]</sup> reported that the prevalence of HP increased with age, and old age and fibrosis were associated with high mortality rates.<sup>[21]</sup> Wheezing, a less common symptom of CHP, can be associated with airway hyperresponsiveness. CHP is the presence of inspiratory squeaks that are caused by coexisting bronchiolitis.<sup>[22]</sup> Digital clubbing and weight loss are very common in CHP. Our results were consistent with those of published reports that older age, a smoking history, unclear exposure to antigens, longer duration of symptoms, weight loss, crackles, digital clubbing, and cyanosis were more common in CHP patients than those in AHP patients.

The influence of smoking on HP patients is under debate in recent published reports. Warren<sup>[23]</sup> and Terho *et al.*<sup>[24]</sup> suggested that nonsmoking was significantly associated with HP, and AHP is more uncommon in current smokers than in nonsmokers with the same risk of exposure. Furuiye *et al.*<sup>[25]</sup> showed that cigarette smoke can decrease

inflammation and lymphocyte proliferation in AHP. In contrast, when HP occurs in smokers, the disease may develop a chronic clinical course with worse survival than that in nonsmokers since long-term exposure to cigarette smoke may enhance lung inflammation with fibrosis.<sup>[26]</sup> In our study, smoking was more common in CHP patients, and HP patients with a smoking history had a worse prognosis than those without a smoking history, which indicated that smoking may be associated with chronic fibrosis in HP.<sup>[26]</sup>

Chest HRCT is very useful and important tool for diagnosis in HP patients. It is possible to make a high-confidence HRCT-based diagnosis for HP (88%–92% accuracy and 44%–61% sensitivity), but the radiologic findings are often not specific and other granulomatous and fibrosing ILDs with predominately upper lobe distribution need to be considered.<sup>[7,27]</sup> When fibrotic HP is compared with IPF or NSIP, the CT features that indicate a diagnosis of HP are lobular air trapping, centrilobular GGOs, and the absence of lower lobe predominance.<sup>[27,28]</sup> The HRCT findings in CHP are those that indicate fibrosis, namely, reticulation and traction bronchiectasis with or without honeycomb changes and a predominately upper lobe distribution.

An increase in the total cell count with a remarkable elevation in the percentage of T lymphocytes in BAL, often over 50%, characterizes HP. This increase is unusual in other diseases generally considered in the differential diagnosis, such as IPF.<sup>[29,30]</sup> However, in patients with HP who are smokers or have chronic, fibrotic parenchymal abnormalities, the BAL lymphocyte count is low.<sup>[31]</sup> In agreement with the published reports,<sup>[31,32]</sup> the cytological analysis with BAL showed that the lymphocyte ratio was elevated in all HP patients, and the lymphocyte ratio in the AHP group was higher than that in the CHP group, although there was no significant difference in lymphocyte ratio between the two groups in our small cohort study.

SLB remains the gold standard to obtain lung histopathology and contributes substantially to the final diagnosis of HP, especially in chronic cases.<sup>[33]</sup> Transbronchial biopsy (TBB) appears to be of limited value in establishing a diagnosis of fibrotic HP. Approximately 11% to 25% of individuals were diagnosed with HP after TBB from the documented studies.<sup>[34–36]</sup> In the current study, 75 patients (74.3%) underwent TBLB and five patients underwent SLB. The diagnostic rate was approximately 30% based on the pathology from TBLB and 100% from that of SLB. The diagnosis of HP could be reached after a review of the clinical, chest imaging, and TBB data to ensure that they were in perfect agreement with the SLB data.<sup>[7,37]</sup>

Recently, international experts proposed the new diagnostic criteria and a novel classification of HP based on a combination of clinical experience and available evidence.<sup>[7]</sup> The proposed clinical criteria stratify patients into the following four diagnostic categories before obtaining lung biopsy material: (1) confident clinical diagnosis of HP; (2) probable HP; (3) possible HP; and (4) unlikely HP. The clinical diagnosis of HP based on the clinical features, imaging, and BAL data can be made with confidence, but a definite diagnosis of HP requires



histopathological confirmation. For patients who are unable or unwilling to be subjected to lung biopsy, a diagnosis of “probable or possible HP” may be reasonable if the combination of the provided clinical and radiologic evidence is highly suggestive of HP.<sup>[7]</sup> Johansson *et al.*<sup>[15]</sup> proposed a clinical prediction model based on the combination of compatible clinical features, exposure to birds and down, and typical HRCT features that predict the diagnosis of CHP without biopsy or BAL. This model looks very complex.<sup>[15]</sup> Our study did not include pathological findings and constructed a weight-free and clinically feasible scoring system to predict CHP. Our simple clinical scoring system based on clinical variables can easily differentiate CHP from AHP and has not been reported before. This scoring system is a clinically feasible, multidimensional diagnostic model for CHP that would allow for a highly specific diagnosis in the absence of SLB. However, a large-scale, multicenter, and prospective study is needed to further validate this scoring system as our study had a relatively small sample size and a difference in incidence rates when compared with other studies.

The first treatment intervention for HP is prompt and complete avoidance of further exposure to the inducer. Currently, corticosteroids are the mainstay of pharmacologic treatment. Although the general goal is to aim for the lowest possible dose and shortest duration, the dosage and duration of treatment have not been determined in any studies.<sup>[7,38]</sup> Corticosteroids may be indicated for acute symptomatic relief in patients with subacute progressive and chronic disease, but they do not appear to impact the long-term outcome.<sup>[38]</sup> In the current study, 83.2% of the patients were treated with systemic corticosteroids. More patients in the CHP group than those in the AHP group used corticosteroids, and the duration of treatment was longer in the CHP group than that in the AHP group, which is consistent with the results of the previous reports on the recommended drug therapy.<sup>[31]</sup> In patients with CHP, especially those with a progressive disease course, immunosuppressive agents such as mycophenolate mofetil and azathioprine may be considered.<sup>[39,40]</sup> In chronic progressive HP patients that do not respond to corticosteroids and/or immunosuppressant therapy, lung transplantation should be considered. Patients with HP have excellent medium-term survival and reduced risk for death after lung transplantation compared with patients with IPF.<sup>[41]</sup>

Morell *et al.*<sup>[34]</sup> reported that about half of the AHP patients with farmer’s lung had progressed to having CHP because two-thirds of the patients returned to their previous occupation of farming and cattle feeding. In this study, 15.3% of the patients with AHP progressed to having CHP. Unidentified and unavoidable antigen exposure after diagnosis was an independent risk factor for progression into CHP. Therefore, identification of the inciting antigen and further exposure avoidance are very important measures for HP management. To identify the suspected antigen, Vasakova *et al.*<sup>[7]</sup> proposed a standardized questionnaire to help recognize the source of the antigen.

The outcome of HP is highly variable and dependent on the type of initial clinical and radiological presentation and clinical patterns. AHP patients who are able to avoid

further antigen exposure tend to have mostly reversible symptoms. CHP patients may also experience partial recovery. The survival of CHP patients, even those with chronic progressive disease, appears to be better than that of IPF patients.<sup>[7,42]</sup> The risk factors for survival have been identified as old age, smoking, crackles, low baseline TLC and carbon monoxide diffusing capacity (DLCO), absence of lymphocytosis in BALF, presence of radiologic and/or histopathologic signs of fibrotic changes, and unidentified sources of exposure.<sup>[26,43,44]</sup> Our results showed that old age, smoking history, unidentified antigen exposure, low baseline TLC, and fibrosis on chest HRCT may be associated with poor prognosis in HP patients. Unidentified exposure and low baseline TLC were independent prognostic factors for HP, which is consistent with the results of the published reports.

The current study has limitations. First, it is a single-center, retrospective study with a small sample size, particularly for the CHP group. Second, the diagnoses of some patients were not confirmed by histopathologic evidence. Finally, the scoring system of this study was based on the clinical variables of the study population without weighting the factors, and the scoring system needs to be further improved through regression equations. A prospective, multicenter, and large sample cohort study in China would be useful to understand the incidence, clinical diagnosis accuracy, management, and prognosis of HP.

In summary, HP is a complex lung disease syndrome and a common form of ILD. The incidence of HP was 2.4% in ILD patients in our center from 2009 to 2017. Diagnosing CHP is a challenge, and the clinical scoring system, ADSUC, for CHP is simple and feasible. Unidentified exposure is an independent risk factor for the progression from AHP to CHP. Unidentified exposure and low baseline TLC pred% are independent predictors for survival in HP patients. Therefore, it is very important to identify the inciting antigen and avoid exposure to improve the prognosis of HP.

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### Conflicts of interest

None.

### References

1. Solaymani-Dodaran M, West J, Smith C, Hubbard R. Extrinsic allergic alveolitis: incidence and mortality in the general population. *QJM* 2007;100:233–237. doi: 10.1093/qjmed/hcm008.
2. Madsen D, Klock LE, Wenzel FJ, Robbins JL, Schmidt CD. The prevalence of farmer’s lung in an agricultural population. *Am Rev Respir Dis* 1976;113:171–174. doi: 10.1164/arrd.1976.113.2.171.
3. Barber CM, Wiggans RE, Carder M, Agius R. Epidemiology of occupational hypersensitivity pneumonitis; reports from the SWORD scheme in the UK from 1996 to 2015. *Occup Environ Med* 2017;74:528–530. doi: 10.1136/oemed-2016-103838.

4. Fernandez Perez ER, Kong AM, Raimundo K, Koelsch TL, Kulkarni R, Cole AL. Epidemiology of hypersensitivity pneumonitis among an insured population in the United States: a claims-based cohort analysis. *Ann Am Thorac Soc* 2018;15:460–469. doi: 10.1513/AnnalsATS.201704-288OC.
5. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824. doi: 10.1164/rccm.2009-040GL.
6. Singh S, Collins BF, Sharma BB, Joshi JM, Talwar D, Katiyar S, *et al.* Interstitial lung disease in India. Results of a prospective registry. *Am J Respir Crit Care Med* 2017;195:801–813. doi: 10.1164/rccm.201607-1484OC.
7. Vasakova M, Morell F, Walsh S, Leslie K, Raghu G. Hypersensitivity pneumonitis: perspectives in diagnosis and management. *Am J Respir Crit Care Med* 2017;196:680–689. doi: 10.1164/rccm.201611-2201PP.
8. Hanak V, Golbin JM, Ryu JH. Causes and presenting features in 85 consecutive patients with hypersensitivity pneumonitis. *Mayo Clin Proc* 2007;82:812–816. doi: 10.4065/82.7.812.
9. Fernández Pérez ER, Swigris JJ, Forssén AV, Tourin O, Solomon JJ, Huie TJ, *et al.* Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. *Chest* 2013;144:1644–1651. doi: 10.1378/chest.12-2685.
10. Liu S, Chen D, Fu S, Ren Y, Wang L, Zhang Y, *et al.* Prevalence and risk factors for farmer's lung in greenhouse farmers: an epidemiological study of 5,880 farmers from Northeast China. *Cell Biochem Biophys* 2015;71:1051–1057. doi: 10.1007/s12013-014-0308-7.
11. Jin BB, Xu WB, Peng M, Shi JH, Tian XL, Liu YJ, *et al.* Clinical characteristic analysis of 96 cases of hypersensitivity pneumonitis [in Chinese]. *Chin J Tuberc Respir Dis* 2013;36:83–87. doi: 10.3760/cma.j.issn.1001-0939.2013.02.003.
12. Schuyler M, Cormier Y. The diagnosis of hypersensitivity pneumonitis. *Chest* 1997;111:534–536. doi: 10.1378/chest.111.3.534.
13. Morell F, Villar A, Ojanguren I, Munoz X, Cruz MJ. Hypersensitivity pneumonitis: challenges in diagnosis and management, avoiding surgical lung biopsy. *Semin Respir Crit Care Med* 2016;37:395–405. doi: 10.1055/s-0036-1580692.
14. Mooney JJ, Koth LL. Surgical lung biopsy over bronchoalveolar lavage in chronic hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2014;189:371–372. doi: 10.1164/rccm.201309-1736LE.
15. Johannson KA, Elicker BM, Vittinghoff E, Assayag D, de Boer K, Golden JA, *et al.* A diagnostic model for chronic hypersensitivity pneumonitis. *Thorax* 2016;71:951–954. doi: 10.1136/thoraxjnl-2016-208286.
16. Morell F, Villar A, Montero MA, Munoz X, Colby TV, Pipvath S, *et al.* Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. *Lancet Respir Med* 2013;1:685–694. doi: 10.1016/S2213-2600(13)70191-7.
17. Thomeer MJ, Costabel U, Rizzato G, Poletti V, Demedts M. Comparison of registries of interstitial lung diseases in three European countries. *Eur Respir J Suppl* 2001;32:114s–118s. doi: 10.1016/S1010-7940(01)00915-0.
18. Grant IW, Blyth W, Wardrop VE, Gordon RM, Pearson JC, Mair A. Prevalence of farmer's lung in Scotland: a pilot survey. *Br Med J* 1972;1:530–534. doi: 10.1136/bmj.1.5799.530.
19. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824. doi: 10.1164/rccm.2009-040GL.
20. Lacasse Y, Selman M, Costabel U, Dalphin JC, Morell F, Erkinjuntti-Pekkanen R, *et al.* Classification of hypersensitivity pneumonitis: a hypothesis. *Int Arch Allergy Immunol* 2009;149:161–166. doi: 10.1159/000189200.
21. Lacasse Y, Selman M, Costabel U, Dalphin JC, Ando M, Morell F, *et al.* Clinical diagnosis of hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2003;168:952–958. doi: 10.1164/rccm.200301-137OC.
22. Costabel U, Bonella F, Guzman J. Chronic hypersensitivity pneumonitis. *Clin Chest Med* 2012;33:151–163. doi: 10.1016/j.ccm.2011.12.004.
23. Warren CP. Extrinsic allergic alveolitis: a disease commoner in non-smokers. *Thorax* 1977;32:567–569. doi: 10.1136/thx.32.5.567.
24. Terho EO, Husman K, Vohlonen I. Prevalence and incidence of chronic bronchitis and farmer's lung with respect to age, sex, atopy, and smoking. *Eur J Respir Dis Suppl* 1987;152:19–28. doi: 10.1378/chest.91.1.154-c.
25. Furuiye M, Miyake S, Miyazaki Y, Ohtani Y, Inase N, Umino T, *et al.* Effect of cigarette smoking on the development of murine chronic pigeon breeder's lung. The difference between a short-term and a long-term exposure. *J Med Dent Sci* 2007;54:87–95. doi: 10.11480/jmds.540112.
26. Churg A, Sin DD, Everett D, Brown K, Cool C. Pathologic patterns and survival in chronic hypersensitivity pneumonitis. *Am J Surg Pathol* 2009;33:1765–1770. doi: 10.1097/PAS.0b013e3181bb2538.
27. Silva CI, Muller NL, Lynch DA, Curran-Everett D, Brown KK, Lee KS, *et al.* Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. *Radiology* 2008;246:288–297. doi: 10.1148/radiol.2453061881.
28. Hirschmann JV, Pipavath SN, Godwin JD. Hypersensitivity pneumonitis: a historical, clinical, and radiologic review. *Radiographics* 2009;29:1921–1938. doi: 10.1148/rg.297095707.
29. Ohshimo S, Bonella F, Cui A, Beume M, Kohno N, Guzman J, *et al.* Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009;179:1043–1047. doi: 10.1164/rccm.200808-1313OC.
30. Meyer KC, Raghu G, Baughman RP, Brown KK, Costabel U, du Bois RM, *et al.* An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med* 2012;185:1004–1014. doi: 10.1164/rccm.201202-0320ST.
31. Selman M, Pardo A, King TE Jr. Hypersensitivity pneumonitis: insights in diagnosis and pathobiology. *Am J Respir Crit Care Med* 2012;186:314–324. doi: 10.1164/rccm.201203-0513CI.
32. Bronchoalveolar lavage constituents in healthy individuals, idiopathic pulmonary fibrosis, and selected comparison groups. The BAL Cooperative Group Steering Committee. *Am Rev Respir Dis* 1990;141 (5 Pt 2):S169–S202. doi: 10.1164/ajrccm/141.5\_Pt\_2.S169.
33. Myers JL. Hypersensitivity pneumonia: the role of lung biopsy in diagnosis and management. *Mod Pathol* 2012;25 (Suppl 1):S58–S67. doi: 10.1038/modpathol.2011.152.
34. Morell F, Roger A, Reyes L, Cruz MJ, Murio C, Munoz X. Bird fancier's lung: a series of 86 patients. *Medicine (Baltimore)* 2008;87:110–130. doi: 10.1097/MD.0b013e31816d1dda.
35. Lacasse Y, Fraser RS, Fournier M, Cormier Y. Diagnostic accuracy of transbronchial biopsy in acute farmer's lung disease. *Chest* 1997;112:1459–1465. doi: 10.18907/jjsre.8.4\_483.
36. Sheth JS, Belperio JA, Fishbein MC, Kazerooni EA, Lagstein A, Murray S, *et al.* Utility of transbronchial vs surgical lung biopsy in the diagnosis of suspected fibrotic interstitial lung disease. *Chest* 2017;151:389–399. doi: 10.1016/j.chest.2016.09.028.
37. Johannson KA, Marcoux VS, Ronksley PE, Ryerson CJ. Diagnostic yield and complications of transbronchial lung cryobiopsy for interstitial lung disease. A systematic review and metaanalysis. *Ann Am Thorac Soc* 2016;13:1828–1838. doi: 10.1513/AnnalsATS.201606-461SR.
38. Kokkarinen JJ, Tukiainen HO, Terho EO. Effect of corticosteroid treatment on the recovery of pulmonary function in farmer's lung. *Am Rev Respir Dis* 1992;145:3–5. doi: 10.1164/ajrccm/145.1.3.
39. Morisset J, Johannson KA, Vittinghoff E, Aravena C, Elicker BM, Jones KD, *et al.* Use of mycophenolate mofetil or azathioprine for the management of chronic hypersensitivity pneumonitis. *Chest* 2017;151:619–625. doi: 10.1016/j.chest.2016.10.029.
40. Adegunsoye A, Oldham JM, Fernandez Perez ER, Hamblin M, Patel N, Tener M, *et al.* Outcomes of immunosuppressive therapy in chronic hypersensitivity pneumonitis. *ERJ Open Res* 2017;3. pii: 00016-2017. doi: 10.1183/23120541.00016-2017.
41. Kern RM, Singer JP, Koth L, Mooney J, Golden J, Hays S, *et al.* Lung transplantation for hypersensitivity pneumonitis. *Chest* 2015;147:1558–1565. doi: 10.1378/chest.14-1543.
42. Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. *N Engl J Med* 2018;378:1811–1823. doi: 10.1056/NEJMra1705751.
43. Walsh SL, Sverzellati N, Devaraj A, Wells AU, Hansell DM. Chronic hypersensitivity pneumonitis: high resolution computed tomography patterns and pulmonary function indices as prognostic determinants. *Eur Radiol* 2012;22:1672–1679. doi: 10.1007/s00330-012-2427-0.
44. Walsh SL, Wells AU, Sverzellati N, Devaraj A, von der Thusen J, Yousem SA, *et al.* Relationship between fibroblastic foci profusion and high resolution CT morphology in fibrotic lung disease. *BMC Med* 2015;13:241. doi: 10.1186/s12916-015-0479-0.

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