



Predictors of survival in coexistent hypersensitivity pneumonitis with autoimmune features



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ABSTRACT

Background: Hypersensitivity pneumonitis (HP), an immune-mediated inflammatory interstitial lung disease (ILD), can result from exposure to several well-recognized antigens. Despite antigen avoidance, progressive pulmonary fibrosis and death can occur, suggesting that additional factors may contribute to disease activity. We hypothesized that the presence of autoimmunity might impact clinical course in patients with HP. In this study, we examined an HP cohort to identify those with HP and autoimmune features (HPAF), and determine its prevalence and outcomes.

Methods: The University of Chicago ILD registry was screened to identify patients with HP. Patients were characterized as HPAF if they had an autoimmune disease or features of autoimmunity, defined as the presence of specific connective tissue disease (CTD) symptoms and serologies. Demographics, clinical characteristics, and outcomes were compared between groups. Survival analysis was performed using Cox regression to identify predictors of transplant-free survival in this cohort.

Results: One hundred twenty patients with chronic, fibrotic HP were identified. Of these, 18/120 (15%) were characterized as HPAF. Compared to those without evidence of autoimmunity, patients with HPAF had a higher proportion of females (54% vs. 83%, respectively; $p = 0.02$) but were otherwise similar with regard to clinical characteristics. The presence of autoimmunity was an independent predictor of increased mortality (HR 4.45; 95% CI 1.43–13.88; $p = 0.01$) after multivariable adjustment.

Conclusions: Fifteen percent of patients with chronic, fibrotic HP displayed evidence of a concurrent defined autoimmune disease or autoimmune features suggestive of CTD. The presence of autoimmunity in patients with chronic, fibrotic HP may portend a poorer prognosis. Future studies are needed to validate these findings and determine the impact of immunosuppressive treatment.

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Interstitial lung disease (ILD) encompasses a heterogeneous group of diffuse parenchymal lung diseases often characterized by inflammation and scarring of the pulmonary parenchyma, resulting in significant morbidity and mortality [1]. While it is well-recognized that ILD can develop secondary to connective tissue disease (CTD), there is increasing awareness that features of autoimmunity are common among patients characterized as having

idiopathic interstitial pneumonia (IIP) [2], and that systematic evaluation of patients with IIP can reveal a previously unrecognized autoimmune process [3–6]. The clinical implications of autoimmune features in those with IIP who fail to meet established rheumatologic criteria remain unclear, but some studies suggest an improved prognosis [7,8].

Hypersensitivity pneumonitis (HP) is an ILD caused by a wide variety of small organic particles. These antigens include fungi, proteins from animals and insects and some chemical compounds [9]. As these antigens are ubiquitous, it remains unclear why only a small fraction of exposed individuals develop HP. One explanation may lie with abnormal T cell function, as individuals with HP do not suppress T-cell proliferation after exposure to known antigen when compared to healthy controls [10]. T cell dysregulation is also

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Abbreviation list

aCCP	anti-citrullinated protein antibody	HRCT	high-resolution computed tomography
ANA	antinuclear antibody	IIP	idiopathic interstitial pneumonia
ANCA	antineutrophil cytoplasmic antibody	ILD	interstitial lung disease
BMI	body mass index	IPF	idiopathic pulmonary fibrosis
CAD	coronary artery disease	IRB	institutional review board
CI	Confidence Interval	OR	odds ratio
C-reactive protein	CRP	PFT	pulmonary function testing
CTD	connective tissue disease	RA	rheumatoid arthritis
DLCO	diffusion capacity of the lung for carbon monoxide	RF	rheumatoid factor
FVC	forced vital capacity	SD	standard deviation
GER	gastroesophageal reflux	SLB	surgical lung biopsy
HLA	human leukocyte antigen	SLE	systemic lupus erythematosus
HP	Hypersensitivity pneumonitis	TLC	total lung capacity
HR	hazard ratio	UCTD	undifferentiated connective tissue disease
		UIP	usual interstitial pneumonia

common among individuals with several CTDs [11–13], and raises the question of whether autoimmune disease is more likely to be present among patients with HP.

In this study, we systematically assessed an HP cohort to identify patients with autoimmune features (HPAF), defined as the presence of documented autoimmune disease or contemporaneous autoimmune serologies and clinical features suggestive of an undifferentiated connective tissue disease (UCTD) [7]. We then characterized clinical features and outcomes among patients with HPAF and compared them to those HP patients without evidence of autoimmunity.

1. Materials and methods

1.1. Study population

This retrospective analysis was conducted at the University of Chicago with approval of our Institutional Review Board (IRB #14163A) and all patients provided informed consent. We identified consecutive patients aged ≥ 18 years who enrolled in the University of Chicago ILD registry, were diagnosed with HP based on multidisciplinary evaluation, and were seen in the ILD clinic between January 1, 2006 and February 28, 2015. (Fig. 1). Data was extracted using the electronic medical record. Variables collected included demographic data (age, race/ethnicity, gender), symptoms, co-morbid conditions (autoimmune disease, coronary artery disease, gastroesophageal reflux), history of tobacco use, use of chronic corticosteroid and immunosuppressive therapy, physical examination findings such as body mass index (BMI), crackles and clubbing, assessment of environmental antigen exposures (avian, mold, hot tub, unknown), laboratory data including serologies and C-reactive protein (CRP), serial PFTs including percent predicted total lung capacity (TLC), forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO), six minute walk test and histopathologic findings. An experienced pulmonary pathologist with expertise in ILD previously reviewed all surgical lung biopsies. Outcomes assessed included all-cause mortality, lung transplantation and $\geq 10\%$ decline in FVC. Outcomes were ascertained by review of medical records, telephone interviews and the Social Security Death Index.

1.2. Enrollment criteria

All patients in the University of Chicago ILD registry are assessed for exposure to antigens commonly associated with HP, regardless

of referring diagnosis. A diagnosis of HP was based on multidisciplinary evaluation of patients' clinical features, HRCT findings and surgical lung biopsy results by physicians with expertise in ILD. Patients were diagnosed with HP and were included in the current study if they met the following criteria:

(1) HRCT features compatible with HP: mosaic attenuation/air trapping, centrilobular nodules, reticulation, traction bronchiectasis, and honeycombing. (2) Surgical lung biopsy specimens, when obtained, demonstrated presence of a histologic pattern consistent with HP. This included lymphocytic predominant interstitial infiltrates, with/without poorly formed granulomas, distributed in a bronchiolocentric pattern. Histologic fibrosis was also noted when present. (3) Exclusion of an alternative etiology for these findings. The presence of antibodies to serum precipitins supported the diagnosis, but was not a requirement.

1.3. HRCT review and scoring

Features suggesting HP and pulmonary fibrosis, as defined by reticulation, traction bronchiectasis or honeycombing pattern, were recorded. All HRCTs were systematically reviewed and scored by a senior chest radiologist (S.M.) who was blinded to clinical phenotype. The mean extent of these morphological features was scored to the nearest 5% in all three zones of each lung as previously described [14,15] resulting in a semi-quantitative HRCT fibrosis score. These findings were graded on a scale of 1–4: 1 – normal attenuation; 2 – reticular abnormality; 3 – traction bronchiectasis; and 4 – honeycombing. Independent assessment was made for each of these four HRCT findings in three (upper, middle and lower) zones of each lung. The score for each zone was determined by multiplying the grading scale score by the percentage involvement for each zone. The average score of all six zones was calculated as the total score for each patient. Using this method, the highest score was 203 points and the lowest score was 100 points.

1.4. Autoimmune features

Patients were classified as HPAF if they had a documented diagnosis of autoimmune disease [16–19] including scleroderma, Sjogren's disease, idiopathic inflammatory myopathy (IIM), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and ulcerative colitis. Patients were also classified as HPAF if at least one specific CTD symptom and one serologic test suggestive of autoimmune disease were present, as previously proposed by Corte et al. [7]. Specific CTD symptoms included Raynaud's phenomenon,

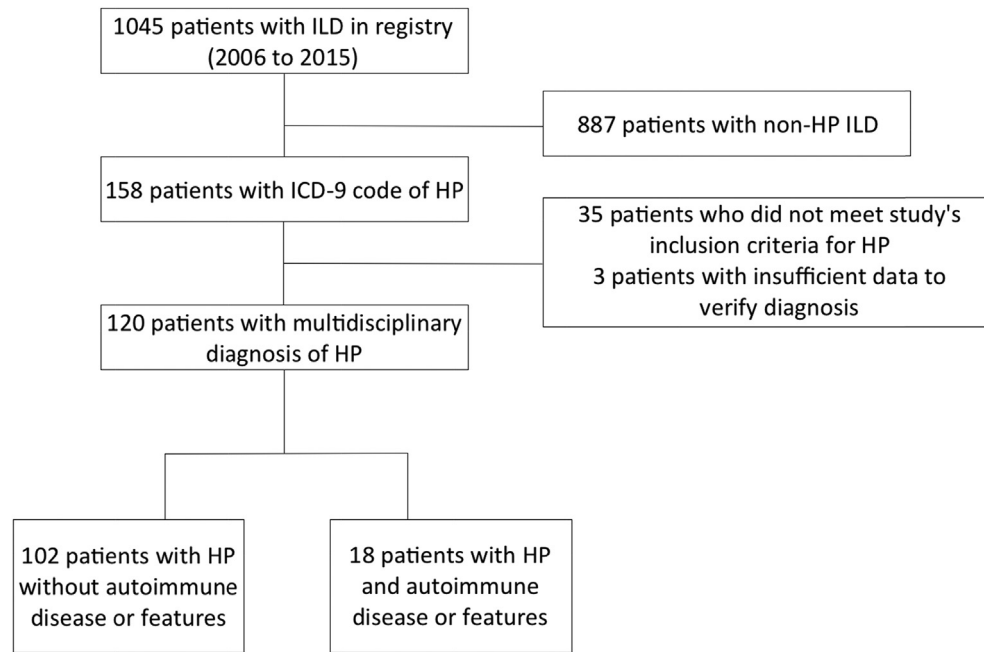


Fig. 1. Consort diagram.

arthralgias/joint swelling, morning stiffness, dry mouth/dry eyes and proximal muscle weakness. Positive autoimmune serologies were an anti-nuclear antibody (ANA) $\geq 1:320$, a rheumatoid factor (RF) $\geq 3x$ upper limit of normal, or a positive anti-neutrophil cytoplasmic antibody (ANCA), cyclic citrullinated peptide (aCCP); Jo1; dsDNA; ribonucleoprotein (anti-RNP); Scl-70; SS-A/Ro or SS-B/La. Patients were stratified based on HPAF status and further sub-stratified based on the presence of defined autoimmune disease.

1.5. Statistical analysis

Continuous variables were reported as means with standard deviation (SD) and compared using a two-tailed student's t-test. Categorical variables were reported as counts and percentages and compared using the Chi-square test or Fisher's exact test, as appropriate. A p-value of <0.05 was considered to be significant. Survival analysis was performed using univariate and multivariable Cox proportional hazards analysis along with the unadjusted log rank test and plotted using the Kaplan-Meier survival estimator. Transplant-free survival was defined as time from diagnosis to death or lung transplantation. Patients who were lost to follow-up were censored at that time. All data analysis was performed in Stata version 13.1 (Stata Corp; College Station, Texas).

2. Results

Of 1045 patients enrolled in our ILD registry, 158 had an ICD-9 diagnosis code of HP (Fig. 1). Of these 158, 38 were excluded due to an alternate ILD diagnosis or insufficient data to verify their diagnosis, leaving 120 patients with HP based on a multidisciplinary review of clinical data, radiographic and/or pathologic findings and a compatible exposure history. All 120 patients had chronic, fibrotic HP based on HRCT and/or SLB. Eighteen patients (15%) met criteria for HPAF. Of these patients, nine had a documented autoimmune disease (scleroderma, Sjogren's disease, IIM, SLE, RA, ulcerative colitis) and nine displayed features of autoimmunity (Table 1 and Supplemental Table 1).

Baseline demographics and clinical characteristics of the entire

cohort revealed that mean age at diagnosis of HP was 63 years (± 10 years); with a mean BMI of 32 (± 8) and a Caucasian (83%) and female predominance (58%). Comorbid clinical conditions included gastroesophageal reflux (59%) and coronary artery disease (21%). Fifty-eight percent had a prior smoking history and 72% required chronic systemic corticosteroid use for their ILD. On examination, most had crackles (85%) while a minority of patients had digital clubbing (24%). Exposure to avian antigens (47%) was the most common environmental exposure identified.

When comparing baseline characteristics between HPAF and HP patients without evidence of autoimmunity, HPAF had a higher proportion of females (83% vs. 54%, respectively; $p = 0.02$) and demonstrated less digital clubbing (6% vs. 28% $p = 0.045$) (Table 2). There were no differences between groups with regard to other demographic characteristics, antigen exposure, radiographic or histopathologic features, or pulmonary function testing (Tables 2 and 3). When comparing autoimmune serologies and clinical features between groups (Table 4), those meeting predefined criteria for HPAF had a higher prevalence of positive ANA, SS-A, anti-dsDNA, digital arthralgias, morning stiffness and dry eyes and dry mouth than patients with HP who did not meet these criteria.

During the study period, 28% of the entire HP cohort either died or underwent lung transplantation (Table 5 and Supplemental Fig. 1). Mean survival was 16.5 months (± 13.0 months) in HPAF compared to 29.7 months (± 21.5 months) ($p = 0.103$) in HP without

Table 1
Autoimmune disease or features in hypersensitivity pneumonitis.

Autoimmune disease or features	n (%)
Autoimmune disease ^a	9 (50.0)
Scleroderma	1 (5.6)
Sjogren's disease	2 (11.1)
Idiopathic inflammatory myopathy	1 (5.6)
Systemic lupus erythematosus	2 (11.1)
Rheumatoid arthritis	4 (22.2)
Ulcerative colitis	1 (5.6)
Autoimmune features	9 (50.0)

^a Some patients had more than one autoimmune disease.

Table 2
Baseline Characteristics in HP patients with and without autoimmune features.

Characteristics	HPAF (n = 18)	HP without AF (n = 102)	p-value
Age, mean (\pm SD)	62.2 (9.5)	62.7 (10.5)	0.858
Female gender, n (%)	15 (83.3)	55 (53.9)	0.020
Race/ethnicity			
Caucasian, n (%)	13 (72.2)	87 (85.3)	0.170
Hispanic, n (%)	1 (5.6)	9 (8.8)	1.000
African American, n (%)	2 (11.1)	5 (4.9)	0.282
Asian, n (%)	2 (11.1)	1 (0.98)	0.059
BMI, mean (\pm SD)	31.1 (8.2)	32.6 (8.0)	0.470
Ever smoker, n (%)	8 (44.4)	62 (60.8)	0.195
Chronic systemic corticosteroid use, n (%)	16 (61.5)	70 (74.5)	0.195
Other immunosuppressive therapy, n (%)	5 (27.8)	31 (30.4)	0.823
Antigen exposure			
Avian, n (%)	8 (44.4)	48 (47.1)	0.838
Mold, n (%)	6 (33.3)	29 (28.4)	0.673
Hot tub, n (%)	0 (0)	3 (2.9)	0.611
Unknown, n (%)	4 (22.2)	34 (33.3)	0.350
Gastroesophageal reflux, n (%)	13 (72.2)	58 (56.9)	0.222
Coronary artery disease, n (%)	4 (22.2)	21 (20.6)	0.875
Crackles, n (%)	15 (83.3)	87 (85.3)	0.830
Clubbing, n (%)	1 (5.6)	28 (27.5)	0.045

HP = Hypersensitivity Pneumonitis; HPAF = HP with Autoimmune features as defined in the text; AF = Autoimmune features.

Table 3
Assessment of lung function, HRCT and pathologic characteristics in HP.

Characteristics	HPAF (n = 18)	HP without AF (n = 102)	p-value
Pulmonary function tests			
TLC ^c (% predicted) (\pm SD)	72.9 (16.0)	72.3 (18.4)	0.889
FVC [®] (% predicted) (\pm SD)	63.7 (20.3)	65.1 (18.7)	0.773
DLCO (% predicted) (\pm SD)	55.1 (26.7)	54.3 (24.2)	0.906
Oxygen therapy, n (%)	7 (38.9)	61 (59.8)	0.099
6MWT distance (feet) (\pm SD)	1004.3 (424)	1120.0 (451)	0.328
HRCT features			
HRCT fibrosis score, mean (\pm SD)	123.3 (14.0)	124.0 (17.4)	0.862
Mosaic attenuation, n (%)	15 (83.3)	88 (86.3)	0.741
Centrilobular nodules, n (%)	11 (61.1)	40 (39.2)	0.083
Ground glass opacities, n (%)	17 (94.4)	97 (95.1)	0.631
Reticulation, n (%)	14 (77.8)	78 (76.5)	1.000
Traction bronchiectasis, n (%)	14 (77.8)	84 (82.4)	0.644
Honeycombing, n (%)	7 (38.9)	43 (42.2)	0.795
Absence of lower zone predominant fibrosis, n (%)	10 (55.6)	59 (57.8)	0.856
Histopathologic features			
Surgical lung biopsy obtained, n (%)	14 (77.8)	60 (58.8)	0.127
Poorly formed granulomas, n (%)	11 (78.6)	37 (61.7)	0.233
Lymphoplasmacytic infiltration/GC, n (%)	6 (42.9)	13 (21.7)	0.170
Honeycombing with UIP pattern, n (%)	7 (50.0)	28 (46.7)	0.822

HP = Hypersensitivity Pneumonitis; HPAF = Hypersensitivity Pneumonitis with Autoimmune features as defined in the text; AF = Autoimmune features; n = 112; [®]n = 114; 6MWT = 6 min walk test, n = 109; HRCT = High-resolution computerized tomography scan; GC = Germinal centers.

Table 4
Autoimmune serologic tests and clinical characteristics.

Characteristics	HPAF (n = 18)	HP without AF (n = 102)	p-value
Autoimmune serologic tests			
ANA \geq 1:320, n (%)	11 (61.1)	23 (22.5)	0.001
RF \geq 3x upper limit normal, n (%)	0 (0)	1 (1.0)	1.000
Anti-ENA RNP, n (%)	1 (5.5)	0 (0)	0.154
Anti-topoisomerase (Scl-70), n (%)	1 (5.5)	1 (1.0)	0.285
Anti-Ro (SS-A), n (%)	2 (11.1)	0 (0)	0.023
Anti-La (SS-B), n (%)	0 (0)	1 (1.0)	1.000
Anti-dsDNA, n (%)	3 (16.7)	1 (1.0)	0.011
Anti-CCP, n (%)	2 (11.1)	1 (1.0)	0.061
C-reactive protein ⁱ , mean (\pm SD)	13.6 (26.2)	9.9 (25.6)	0.575
Autoimmune clinical features			
Raynaud's phenomenon, n (%)	3 (16.7)	6 (5.9)	0.109
Arthralgias/multiple joint swelling, n (%)	6 (33.3)	3 (2.9)	<0.001
Morning stiffness, n (%)	6 (33.3)	3 (2.9)	<0.001
Dry mouth/dry eyes, n (%)	12 (66.7)	23 (22.5)	<0.001
Proximal muscle weakness, n (%)	2 (11.1)	2 (2.0)	0.106

HP = Hypersensitivity Pneumonitis; HPAF = Hypersensitivity Pneumonitis with Autoimmune features as defined in the text; AF = Autoimmune features.

Table 5
Outcomes in patients with HP.

Characteristics	HPAF (n = 18)	HP without AF (n = 102)	p-value
Deceased, n (%)	5 (27.8)	24 (23.5)	0.698
Mean survival period, months (\pm SD)	16.5 (13.0)	29.7 (21.5)	0.103
Transplanted, n (%)	1 (5.6)	4 (3.9)	0.749
Mean Time to transplant, months (\pm SD)	23.6 (0)	33.2 (28.4)	0.528
10% FVC decline ^a , n (%)	6 (50)	24 (30.4)	0.178
Mean Time to 10% FVC decline, months (\pm SD)	26.2 (16)	18.2 (18.2)	0.337

HP = Hypersensitivity Pneumonitis; HPAF = Hypersensitivity Pneumonitis with Autoimmune features as defined in the text; AF = Autoimmune features.

^a Follow up FVC available for 91 HP patients; 12 and 79, with and without autoimmune disease or features respectively.

autoimmune features. There were no statistically significant differences between groups with regard to number of deaths (28% vs 24%, respectively; $p = 0.698$) or lung transplantation (6% vs 4%, respectively; $p = 0.75$). The number of patients with a 10% or more decline in percentage predicted FVC did not differ (50% in HPAF vs 30% in HP without autoimmune features; $p = 0.178$) and the time to FVC decline was similar in both groups (26 ± 16 months vs 18 ± 18 months; $p = 0.337$).

The unadjusted comparison of HPAF to HP subjects without autoimmune features demonstrated no difference in survival between groups ($p = 0.59$) (Fig. 2). HPAF was sub-stratified based on the presence of defined autoimmune disease and no survival difference was detected ($p = 0.47$). However, when stratification of the entire HP cohort was performed by race/ethnicity, survival was greatest among non-Caucasian subjects ($p = 0.036$) (Fig. 3). Stratification of the entire HP cohort based on identification of an inciting antigen showed that antigen detection had no effect on prognosis (data not shown).

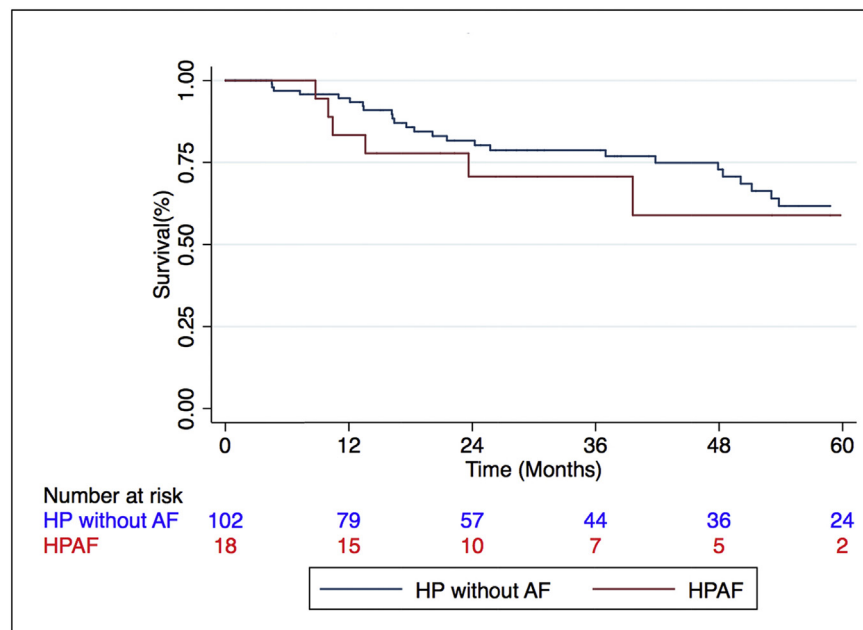
Unadjusted predictors of transplant-free survival included Caucasian race (HR 8.42; 95% CI 1.15–61.68; $p = 0.036$), BMI (HR 0.95; 95% CI 0.90–0.99; $p = 0.034$), presence of digital clubbing (HR 3.47; 95% CI 1.77–6.81; $p < 0.001$), HRCT fibrosis score (HR 1.04; 95% CI 1.02–1.05; $p < 0.001$) (Supplemental Fig. 2), and oxygen

therapy (HR 4.38; 95% CI 1.81–10.59; $p = 0.001$) (Table 6). After adjustment for age, gender, race, BMI, digital clubbing, oxygen therapy and disease severity (HRCT fibrosis score and percentage predicted FVC and DLCO), multivariable Cox regression analysis demonstrated HPAF to be an independent factor predicting mortality or lung transplantation (HR 4.45; 95% CI 1.43–13.88; $p = 0.01$). Predictors of transplant-free survival in multivariable Cox regression analysis also included non-Caucasian race (HR 9.33; 95% CI 1.14–76.30; $p = 0.037$) and HRCT fibrosis score (HR 1.02; 95% CI 1.00–1.04; $p = 0.045$).

3. Discussion

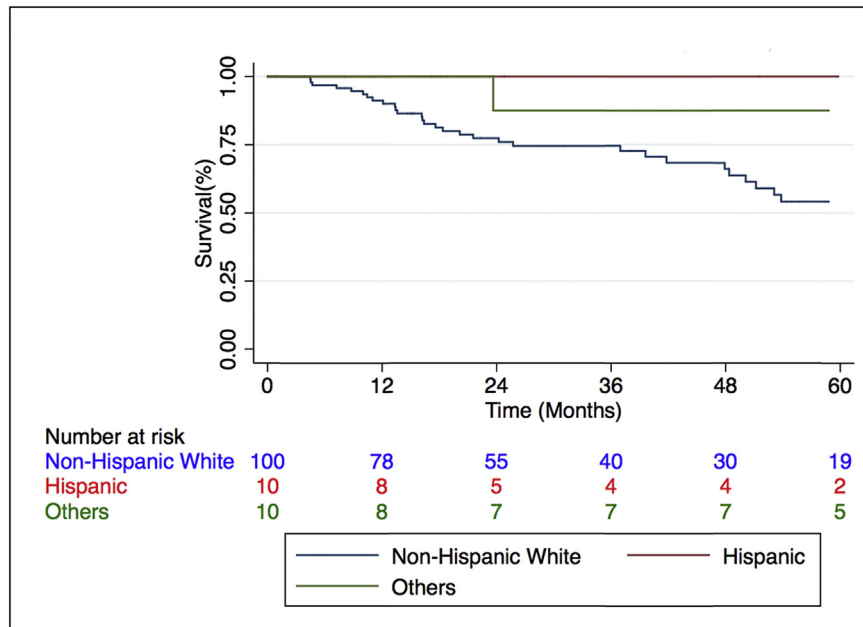
In this study, we showed that a significant minority of patients with HP displayed evidence of a concurrent defined autoimmune disease or autoimmune features suggestive of CTD. Patients with HPAF were predominantly female. We found that the presence of autoimmune disease or autoimmune features independently predicted worse outcomes for patients with HP after controlling for disease severity and radiographic extent of fibrosis. To our knowledge, this is the first study of autoimmunity in HP and identifies clinical factors associated with worse outcomes.

Predictors of survival in HP have previously been reported in the



Mean survival time in those with coexistent HP and autoimmune disease or features (HPAF) was 17.7 ± 12 months compared to 30.2 ± 22 months ($p = 0.59$) in those with HP alone. HP = Hypersensitivity pneumonitis. AF = autoimmune features.

Fig. 2. Survival among patients with HP stratified by HPAF status.



Caucasians with HP demonstrate a reduced survival time compared with non-Caucasians ($p=0.036$). HP = Hypersensitivity Pneumonitis.

Fig. 3. Survival among patients with HP stratified by race/ethnicity.

literature. Similar to Sansores et al., we found that digital clubbing was prevalent and predicted worse outcomes on univariate analysis [20]. Mooney et al. studied predictors of transplant-free survival in HP, and found that crackles, pulmonary function tests, and oxygen therapy were associated with outcome on univariate analysis [15]. While we confirmed a similar association between oxygen therapy and transplant-free survival in our entire cohort, we additionally found that a lower BMI was a poor prognostic marker. We also found that FVC and DLCO, key physiologic parameters of the ILD-GAP risk prediction model, were predictors of poor outcome. Lastly, like Mooney et al., we found that the HRCT fibrosis score independently predicted worse prognosis in our entire HP cohort [15].

To our knowledge, the role of race/ethnicity in predicting outcomes has not been previously studied in HP. In multivariable analysis, we found that Caucasian subjects were 9.33 times more likely to die or undergo a lung transplant during follow-up than non-Caucasian patients. These findings may support a genetic role as has been suggested in prior studies by others, in the

pathogenesis or disease course of HP but require validation [21,22].

This is the first systematic study to examine the presence of autoimmune diseases or specific CTD features in HP and their impact on patient outcomes. As might be expected given the higher prevalence of autoimmune diseases in women [23], our HPAF cohort was predominantly female. Although digital clubbing is commonly seen in HP [20], this was an uncommon finding in our HPAF patients. After controlling for disease severity as measured by pulmonary function tests and HRCT fibrosis score, we found that the presence of autoimmune disease or specific predefined autoimmune features remained a significant risk factor for poor outcomes.

The reasons underlying an association between autoimmunity and HP are unclear. Alteration of the pulmonary epithelium by inhaled environmental agents has been shown to promote post-translational modifications, which eventually alter respiratory mucosal proteins and results in the production of several citrullinated self-proteins [24]. This pathophysiologic process may explain the autoimmune phenomenon observed in our study in which

Table 6
Variables predicting survival in patients with HP.

Characteristic	Unadjusted (n = 120)			Adjusted ^a (n = 118)		
	HR	p-value	95% CI	HR	p-value	95% CI
Autoimmune disease or features (HPAF)	1.28	0.591	0.53–3.10	4.45	0.010	1.43–13.88
Age	1.02	0.184	0.99–1.06	1.00	0.893	0.95–1.05
Gender	1.09	0.798	0.55–2.17	1.73	0.151	0.82–3.65
Caucasian race	8.42	0.036	1.15–61.68	9.33	0.037	1.14–76.30
BMI	0.95	0.034	0.90–0.99	0.95	0.076	0.89–1.01
Digital clubbing	3.47	<0.001	1.77–6.81	1.34	0.469	0.60–2.99
HRCT fibrosis score	1.04	<0.001	1.02–1.05	1.02	0.045	1.00–1.04
FVC ^b (% predicted)	0.94	<0.001	0.92–0.97	0.97	0.059	0.94–1.00
DLCO (% predicted)	0.96	<0.001	0.95–0.98	0.99	0.489	0.97–1.01
Oxygen therapy	4.38	0.001	1.81–10.59	2.51	0.094	0.85–7.38

HP = Hypersensitivity Pneumonitis; HPAF = Hypersensitivity Pneumonitis with Autoimmune features as defined in the text.

^a Adjusted for all variables listed above; ^b n = 119.

almost half of those subjects with HP who did not meet our HPAF criteria had either a positive ANA or CTD symptoms. Perhaps like cigarette smokers [25,26] and coal workers who develop RA [27], silica-exposed individuals who develop RA and SLE [28–31], farmers at increased risk of primary systemic vasculitis [32] and the World Trade Center firefighters/rescue workers who developed diverse CTDs [33], inhaled environmental exposures may trigger autoimmune processes in genetically susceptible individuals.

Our study has several limitations. First, this is a retrospective study, although all data were prospectively acquired. Second, our cohort is drawn from a single tertiary referral center with expertise in ILD and these findings require external validation. Third, we recognize that beyond those patients with autoimmune disease, definitions of autoimmune features have varied in the literature [2,7,8]. We chose previously published and frequently cited criteria for autoimmune features that utilize more specific symptoms and serologies.

4. Conclusion

Our findings show that HP may coexist with autoimmune disease or features in the same patient and manifest as advanced ILD with increased mortality. Careful consideration should be given to the coexistence of both processes especially in female patients. Whether pre-existing autoimmunity delays recognition of HP and/or contributes to a more exuberant inflammatory response deserves further study. It is currently unknown if chronic environmental antigen exposure precipitates and/or exacerbates autoimmune disease. Recognition of autoimmunity in patients with HP may have an impact on subsequent ILD management and disease course.

Author contribution

Conception and design: AA, JO, SM, RV, MS. Data collection and interpretation: AA, JO, CD, SM, RV, MS. Data analysis and interpretation: AA, JO, RV, MS. Drafting the manuscript for important intellectual content: AA, JO, RV, MS.

Conflict of interest disclosures

Drs. Adegunsoye, Oldham, and Montner, along with Ms. Demchuk, have nothing to disclose. Dr. Vij has received funding from Genentech for the conduct of research in interstitial lung disease. Dr. Streck has institutional grants from the NIH, Bristol-Myers Squibb, Gilead, InterMune, and MedImmune for the conduct of clinical trials in IPF. She has received honoraria for serving on a Data Monitoring Committee for Boehringer Ingelheim and an advisory board for InterMune.

Guarantor

Adegunsoye is the guarantor of this paper and takes responsibility for the integrity of the work as a whole, from inception to published article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2016.03.012>.

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