Use of peripheral neutrophil to lymphocyte ratio and peripheral monocyte levels to predict survival in fibrotic hypersensitivity pneumonitis (fHP): a multicentre retrospective cohort study

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ABSTRACT

The factors determining disease course and survival in fibrotic hypersensitivity pneumonitis (fHP) have not been fully elucidated.

The aim of this study was to describe the characteristics of patients with fHP in a real-world cohort and investigate factors associated with worse outcomes. We aimed to explore the use of neutrophil to lymphocyte ratio (NLR) and peripheral blood monocyte levels in predicting mortality.

Methods A retrospective, multicentre, observational UK cohort study.

Results Patients with fHP were significantly younger than those with idiopathic pulmonary fibrosis (IPF) (median age fHP 73 vs IPF 75 years) and were much more likely to be woman (fHP 61% vs IPF 26%). In almost half of all fHP cases (49%, n=104/211), no causative antigen was identified from either the history or specific antigen testing. Overall, fHP was associated with a better survival than IPF, although median survival of both groups was poor (fHP 62 months vs IPF 52 months).

IPF survival in patients with a high NLR was significantly lower than those with a low NLR (44 vs 83 months). A monocyte count ≥ 0.95 K/uL also predicted significantly poorer outcomes for patients with IPF compared with <0.95 K/uL (33 vs 57 months). In contrast, NLR and monocyte count did not predict survival in the fHP cohort.

Conclusions Although fHP has a statistically lower mortality than IPF, absolute survival time of both conditions is poor. High baseline NLR and absolute monocyte counts predict worse survival in IPF but not in fHP, highlighting the potential for divergence in their pathogenic mechanisms.

INTRODUCTION

Hypersensitivity pneumonitis (HP) is an immune-mediated interstitial lung disease (ILD) caused by repeated exposure to environmental antigens, in a genetically

Key messages

- ▶ The aim of this study was to describe the characteristics of patients with fibrotic hypersensitivity pneumonitis (fHP) in a real-world cohort and investigate factors associated with worse outcomes. Specifically, we aimed to explore the use of routinely measured neutrophil to lymphocyte ratio (NLR) and peripheral blood monocyte levels in predicting mortality.
- ▶ High baseline NLR and absolute monocyte counts predict worse survival in IPF but not in fHP, highlighting the potential for divergence in the pathogenic mechanisms of these diseases.
- ▶ Although, fHP has a statistically lower mortality than IPF, absolute survival time of both conditions is poor. The lack of universally accepted diagnostic criteria presents a barrier to research in this area and needs urgently addressing.

susceptible individual. While HP has been traditionally classified according to the chronology of symptoms (acute, subacute or chronic),¹ this is generally considered as an outdated approach that does not enable accurate prognostic stratification. A more recent classification has been proposed that divides patients into two broad categories of acute/inflammatory HP or chronic/fibrotic HP (fHP), according to their clinical–radiological–pathological characteristics, with chronic forms displaying established fibrosis on high-resolution CT (HRCT) or histopathology where performed.²

While several diagnostic criteria for fHP have been proposed,³ multidisciplinary team

(MDT) consensus remains the current gold standard for diagnosis. Distinguishing fHP from other forms of ILD, particularly idiopathic pulmonary fibrosis (IPF) remains challenging, however,⁴ with poor inter-MDT agreement on fHP cases, potentially reflecting the lack of internationally agreed diagnostic criteria and disease heterogeneity in terms of presenting antigen (if identified) and radiological appearances.⁵

The disease course of fHP is also heterogeneous with increasing recognition of a subset of patients who develop a progressive fibrosing ILD phenotype of poorer prognosis that resembles IPF, but factors determining disease course and survival are yet to be fully elucidated.⁶ Routinely measured cellular biomarkers such as the polymorphonuclear leukocytes have been shown to predict survival in cohorts of IPF,^{7–9} but their value in predicting outcomes in other fibrotic lung diseases has not been established.

The aim of this study was to describe the characteristics of patients with fHP in a real-world cohort and investigate factors associated with worse outcomes. Specifically, we aimed to explore the use of routinely measured neutrophil to lymphocyte ratio (NLR) and peripheral blood monocyte levels in predicting mortality.

METHODS

Study design

This was a retrospective, multicentre observational cohort study undertaken across four secondary care institutions in the UK providing ILD services (three specialist centres: North Bristol NHS Trust, University Hospitals of Leicester NHS Trust and the Royal Devon & Exeter NHS Foundation Trust and one affiliate centre: Taunton and Somerset NHS Foundation Trust).

The study was approved by the Health Research Authority, UK (reference 19/HRA/1117).

Study subjects

Consecutive patients with a MDT consensus diagnosis of fHP, presenting to each study centre between January 2005 and December 2018, were included.

During data collection, the diagnosis of fHP was verified based on the clinical history and exposure to a potential causative antigen, alongside compatible HRCT findings (traction bronchiectasis and/or reticulation and/or honeycombing with bronchiolocentric, upper and middle lobe distribution of the abnormalities and/or mosaic pattern and/or ground glass centrilobular nodules), in keeping with an algorithm proposed by Morisset *et al*³ and recently published ATS/JRS/ALAT (American Thoracic Society/Japanese Respiratory Society/Latin American Thoracic Association) clinical practice guidance.¹⁰ Histological findings characteristic of fHP (chronic bronchiolocentric inflammation, poorly formed non-necrotizing granulomas, giant cells, airway centred interstitial fibrosis and absence

of alternative diagnosis) and bronchoalveolar lavage lymphocyte percentage were taken into account where available.

Consecutive patients with an MDT consensus diagnosis of IPF, in accordance with ATS/ERS/JRS/ALAT guidelines,^{11 12} presenting to these same centres within the defined time frame were also included as a comparator cohort. All case diagnoses were verified by the study team at each centre.

Outcome measures

The primary outcome was mortality. Data on patient demographics, environmental and occupational exposures and diagnostic tests (including serological tests, broncho-alveolar differential cell count, lung physiology and histology) were collated where available. The NLR and peripheral monocyte counts at the point of diagnosis were noted. Patients with fHP and IPF were stratified according to a high or low NLR (taking 2.19 as the upper limit of normal according to Azab *et al*⁹ and peripheral monocyte count (cut-offs ≥ 0.95 or < 0.95 were used, according to Scott *et al*).⁷ Gender-Age-Physiology (GAP) scores were calculated.¹³

Statistical analysis

Categorical variables were presented as counts with percentages. All continuous data were parametric and, therefore, presented as mean with SE. Unpaired t test was used for comparison of two groups, with or without Welch correction dependent on the variance of data. Fisher's exact test or χ^2 testing was used for comparison of categorical data.

For the primary analysis, Kaplan Meier curves were generated to assess survival, censored to 12 July 2019. Univariate and multivariate Cox proportional hazards modelling were performed to explore the relationship between baseline characteristics and mortality. The factors used in the multivariable model were decided *a priori* and included male gender, age, stratified monocytes, stratified NLR and baseline lung physiology. For all tests, a p value < 0.05 was considered statistically significant. Data were analysed using Prism V.8.0 (Graphpad software, San Diego) and OriginPro 2020b (OriginLab, USA) for logistic regression analysis.

RESULTS

Baseline demographics of fHP and IPF patients

A total of 281 patients with fHP and 603 patients with IPF were identified across the four UK centres. Table 1 demonstrates baseline demographic data (and associated n number, indicating where data were missing/unavailable). Patients with fHP were statistically more likely to be woman (fHP 61% vs IPF 26%), and younger than patients with IPF (median age fHP 73 vs IPF 75 years). Patients with fHP and IPF were rarely current smokers. Former and never smokers were evenly split across the

Table 1 Baseline demographics of patients with fibrotic HP and IPF

Baseline demographic	Fibrotic HP (n=281)	IPF (n=603)	P value
Gender (M: F)	M 41%: F 61%, n=281	M 74%: F 26%, n=603	<0.0001*
Age (in years)	73 (65–80), n=252	75 (70–80), n=580	0.0013
Smoking status n, (%)			
Unknown	121	212	0.0015*
Ex-smoker	74 (46%)	246 (63%)	
Current	4, (3%)	8, (2%)	
Never	82 (51%)	137 (35%)	
FEV1 actual (L)	1.76 (1.33–2.19), n=220	2.14 (1.71–2.49), n=335	<0.0001
FEV1 % predicted	80 (66–96), n=198	85 (74–97), n=340	0.0166
FVC actual (L)	2.19 (1.62–2.75), n=218	2.64 (2.18–3.18), n=337	<0.0001
FVC % predicted	79 (65–94), n=198	81 (68–95), n=386	0.2673
TLCO (L)	3.77 (2.89–5.09), n=168	3.75 (2.93–4.77), n=258	0.4556
TLCO (% predicted)	50 (43–64), n=163	49 (39–60), n=286	0.0296
GAP stage			
I	62%	18%	<0.0001*
II	35%	68%	
III	3%	14%	
Peripheral monocyte K/uL	0.60 (0.45–0.77), n=227	0.70 (0.54–0.82), n=530	<0.0001
NLR	2.92 (2.08–4.50), n=226	2.78 (2.06–4.08), n=530	0.2441
CRP	4 (2–11), n=147	4 (2–8), n=220	0.4171

All values presented as median with IQR, analysed with Mann Whitney U, unless otherwise stated. $p < 0.05$ was considered statistically significant.

*Fisher's exact test.

%, percentage; CRP, C reactive protein; F, female; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; IPF, idiopathic pulmonary fibrosis; L, litres; M, male; n, number; NLR, neutrophil to lymphocyte ratio; TLCO, transfer factor for carbon monoxide.

cohort patient with fHP, while approximately two-thirds of patients with IPF were ex-smokers ($n=246$, 63%). Lung physiology suggested that both populations had mild to moderate restriction. Patients with fHP presented with a lower GAP stage compared with patients with IPF (GAP stage I fHP 62% vs IPF 18%).

Baseline NLR did not differ significantly between patients with fHP and IPF, but the peripheral monocyte count was statistically lower for patients with fHP compared with patients with IPF (median monocyte count fHP 0.6 K/uL, $n=227$ vs IPF 0.7 K/uL, $n=523$).

Antigen exposure fHP

The causative agents of cases of fHP are presented in figure 1. In almost half of all cases (49%, $n=104/211$), no causative antigen was identified from either the history or specific antigen testing. In fHP cases attributable to a known antigen (45%, $n=96$), the most common causes were birds ($n=31$, 32% of those with known antigen) or avian exposure in bedding/pillows ($n=16$) and domestic mould exposure ($n=21$), including one case of confirmed *purpureocillium lilacinum* overgrowth in a brass musical instrument. Drug causes included nitrofurantoin ($n=2$), methotrexate ($n=2$), leflunomide ($n=1$),

hydroxycarbamide ($n=1$) and statins ($n=2$) (in one case the drug was not specified). Occupational exposures included sandblasting ($n=1$), woodworking ($n=2$), metal working fluid exposure ($n=3$), cotton dust exposure through working in an industrial laundry ($n=1$), a sugar cane worker exposed to bagasse and a rubber-melting

Figure 1 Causative agent of fibrotic hypersensitivity pneumonitis (fHP) grouped by source ($n=211$). Information on the potential causative agent of fHP was available in 211 patients. In almost half of these, a causative antigen could not be identified (49%, $n=104/211$). Avian proteins (birds $n=31$, feather bedding/duvet $n=16$) and mould exposure ($n=21$) were the the most common identified antigens.

Diagnosis	fHP	IPF
Number of deaths	83	218
Median survival (months)	62	52

Figure 2 Kaplan-Meier survival curves of idiopathic pulmonary fibrosis (IPF) and fibrotic hypersensitivity pneumonitis (fHP) cohorts. There was a statistically significant higher mortality in patients with IPF compared with fHP (median survival fHP 62 vs IPF 52 months, $p=0.033$, HR by logrank test HR 0.73, (95% CI 0.58 to 0.92).

plant worker exposed to aromatic hydrocarbons ($n=1$). In one patient, the causative antigen was attributed to exposure from living within a ‘cob-house’—an organic building material typically made from straw, soil, water and sometimes lime (‘other’). Causative agents described were not always mutually exclusive, with nine patients having two potential exposures, and one patient, three potential exposures. The identified cause of fHP was not specified in the case notes of 13 patients.

In patients in whom exposure to birds was considered the causative antigen and underwent serum-specific avian IgG antibody testing, only 25% (6/24) tested positive.

Survival correlations

There were 83 fHP and 218 IPF deaths during the study period. Overall, fHP was associated with a statistically significantly better survival than IPF (HR¹⁴ 0.70, 95% CI 0.56 to 0.89; fHP $n=279$, IPF $n=594$) although median survival of both groups was poor (fHP 62 months vs IPF 52 months) (figure 2).

Patients were stratified according to their baseline NLR, using an upper limit of normal of 2.19.⁹ The survival of patients with IPF with a high NLR was significantly lower than in those with a low NLR (median survival 44 vs 83 months; HR 2.1, 95% CI 1.54 to 2.81, $p<0.0001$, $n=520$). In contrast, NLR did not predict survival in the fHP cohort ($n=225$; figure 3).

Similarly, a monocyte count ≥ 0.95 K/uL predicted significantly poorer outcome for patients with IPF

Figure 3 Kaplan-Meier survival curves of patients Idiopathic pulmonary fibrosis (IPF) and fibrotic hypersensitivity pneumonitis (fHP) stratified according to baseline neutrophil to lymphocyte ratio (NLR): (A) fHP, (B) IPF and baseline peripheral monocyte: (C) fHP (D) IPF. The survival of IPF patients with a high NLR was significantly lower than in those with a low NLR (median survival 83 vs 44 months, $p<0.0001$, $n=520$). In contrast, NLR did not predict survival in the fHP cohort. A monocyte count ≥ 0.95 K/uL predicted significantly poorer outcome for patients with IPF compared with those with a monocyte count of <0.95 K/uL (median survival 33 vs 57 months, $p=0.0003$, $n=520$) but did not predict survival in the fHP cohort.

compared with those with a monocyte count of <0.95 K/uL (median survival 33 vs 57 months; HR 1.9, 95% CI 1.2 to 3.0, $p=0.0003$, $n=520$) but did not predict survival in the fHP cohort ($n=226$; figure 3).

In the Cox univariable analysis, older age, lower forced vital capacity % predicted and lower transfer factor for carbon monoxide (TLCO) % predicted at baseline were associated with increased mortality in the fHP cohort. Specifically, identification of causative antigen or a baseline BAL lymphocyte count of $>20\%$ did not significantly impact on survival. By Cox multivariable analysis, older age and lower TLCO % predicted were the only variables independently associated with an increased risk of mortality in fHP (table 2).

DISCUSSION

In this multicentre retrospective observational study, we examined the clinical characteristics of patients with fHP, using IPF as a comparator cohort. Patients with fHP were significantly younger than those with IPF and were more likely to be woman, in accordance with existing published cohorts.¹⁵ Statistically, the survival of patients with fHP was also significantly better than those with IPF,^{2 16} although the median survival was still strikingly poor; only 5.2 years following diagnosis.

In keeping with the findings of others,^{15 17 18} older age and lower baseline TLCO independently predicted worse survival in our fHP cohort. Other factors, such

Table 2 Survival modelling in fHP

Covariate	Univariate analysis			Multivariate analysis		
	HR (95% CI)	P value	N	HR (95% CI)	P value	N
Age	1.05 (1.03 to 1.08)	<0.0001	251	1.04 (1.01 to 1.08)	0.0091	156
Gender	0.73 (0.30 to 1.17)	0.1591	279	0.79 (0.14 to 1.45)	0.4851	156
Stratified monocytes	1.45 (0.67 to 2.24)	0.3508	226	0.85 (−0.15 to 1.85)	0.7519	156
Stratified NLR	1.44 (0.89 to 1.99)	0.2584	225	1.46 (0.76 to 2.17)	0.2878	156
FVC % predicted	0.98 (0.97 to 1.00)	0.0107	198	0.99 (0.95 to 1.02)	0.4272	156
FEV1 % predicted	0.99 (0.98 to 1.00)	0.086	198	1.01 (0.97 to 1.04)	0.6428	156
TLCO % predicted	0.97 (0.95 to 0.99)	0.0014	162	0.97 (0.94 to 1.00)	0.0358	156

In multivariate analysis, younger age and higher baseline TLCO showed better survival rates.

%, percentage; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; n, number; NLR, neutrophil to lymphocyte ratio; P value, statistical significance; TLCO, transfer factor for carbon monoxide.

as a history of pulmonary hypertension, diabetes and diastolic dysfunction have also been associated with worse survival in fHP, although unlike in IPF, a clear association between the frequency of comorbidities and survival has not been established.¹⁹ We recognise that the mean age of this cohort is older than some other published cohorts of HP.^{20–21} There are several plausible explanations for this. First, three of the hospital centres described in this cohort are located in the South West of England, which has markedly higher proportions of people in the 75–84 and 85 and over age groups than all other regions in the UK and is largely rural.²² Furthermore, the prevalence of HP is considered to be highest among older individuals and may vary with regional disparities in occupational and environmental exposures.¹⁸ Finally, this cohort describes patients with fHP which are more likely to be older than those patients with non-fHP.²³

Several studies have investigated the potential role of serum and BAL epithelial and extracellular proteins in predicting all-cause mortality and disease progression in HP, predominantly in relation to bird-related HP.^{24–27} Interpretation is limited by their small sample size and lack of validation in prospective cohort studies. Peripheral monocyte and neutrophil counts have both been shown to predict mortality in IPF.^{7, 8, 28} Monocytes have been implicated in the pathogenesis of pulmonary fibrosis; monocyte-derived populations of alveolar macrophages have a profibrotic gene expression very different to that of tissue-resident alveolar macrophages, while genetic deletion of monocyte-derived alveolar macrophages, after their recruitment to the lung, ameliorates lung fibrosis in a murine model of bleomycin-induced fibrosis.²⁹ Our findings provide independent validation of the use of absolute peripheral monocyte threshold of $\geq 0.95 \text{ K/uL}$ as a marker of increased mortality in IPF, as defined by Scott *et al*,⁷ while on the contrary, this threshold was not a predictor of mortality in fHP.

Similarly, in our cohort, a high NLR was also associated with increased mortality in IPF, but not in the fHP cohort. Neutrophils have also been implicated in the pathogenesis of lung fibrosis³⁰; neutrophil-elastase promotes

fibroblast proliferation and myofibroblast differentiation in vitro and in vivo,³¹ while increased bronchoalveolar lavage fluid (BALF) and lung tissue polymorphonuclear leucocytes have been demonstrated in human studies.³² Consistent with our findings, Scott *et al* showed that a high neutrophil count predicted death in IPF, but in contrast, also in other fibrotic diseases such as systemic sclerosis and myelofibrosis.⁷ Recent work has also highlighted potential differences in BALF NLR between patients with IPF and fHP, with significantly higher NLRs in the BALF of patients with IPF compared with those with fHP (mean $\pm$ SD NLR, 2.1 ± 3.8 IPF vs 1.6 ± 3.1 fHP).³³ Preliminary assessment of BALF as a prognostic marker in ILD corresponded with serum NLR findings, with an inverse correlation between BALF NLR and lung function parameters.³³ Together these findings suggest divergence in cellular pathways between fHP and IPF. Further prospective studies are required to understand these differences and may help to maximise the benefit of therapies aimed at progressive fibrotic phenotypes.

In this study, we chose to use the GAP stage as a descriptive tool to portray the disease severity of the HP and IPF cohorts at presentation. The composite physiology index (CPI) is an alternative validated mortality prediction tool in IPF.³⁴ Each model has advantages and disadvantages, for example, GAP considers clinical data such as age, gender, known to be independent risk factors for IPF, while CPI takes into consideration HRCT appearances. In a retrospective study of 832 patients with IPF, both CPI and GAP stage predicted disease progression according to Cox proportional hazard modelling, with no significant difference in the predictive value of CPI and GAP stage at 1, 2 and 3-year mortality.³⁵ To our knowledge, neither have been formally validated in HP.

We acknowledge the limitations of this study. First, the majority of patients included in this study were diagnosed at a time when there were no universally accepted criteria for the diagnostic criteria of fHP. Various classifications of HP have been proposed over several decades, but agreement among experts regarding disease definition, diagnostic criteria and diagnostic approach has been

notably lacking. This has been a major challenge for clinicians for disease diagnosis but has also been a significant barrier to research. We used an adapted version of an algorithm proposed by others^{2 10 36} and this potentially limits the comparison of results with other studies that have used different criteria. The more recently proposed consensus clinical practice guideline¹⁰ will hopefully help drive research in this disease.

Furthermore, we were unable to determine the effect of different treatments, such as antifibrotic medications in IPF or corticosteroids/immunomodulatory therapies on survival of these cohorts. We also acknowledge the limitations inherent to retrospective studies, including those of missing data and the potential for selection bias; however, our data provide rationale warranting the investigation of simple blood cell counts in future prospective studies. Finally, we recognise that single white blood cell measures in peripheral blood may also be influenced by many short-term factors and evaluation of trends may be superior. Despite this, a clear signal was observed to suggest that peripheral counts provide a marker of increased mortality in IPF. While we accept that the original aim of the study was to examine fHP, the large comparator cohort of IPF patients is a particular strength of this study and enables independent validation of these prognostic markers that may be useful for future research.

In conclusion, although fHP has a statistically lower mortality than IPF, absolute survival times of both conditions are poor. High baseline NLR and absolute monocyte counts predict worse survival in IPF but not in fHP, highlighting the potential for divergence in the pathogenic mechanisms of these diseases. The lack of universally accepted diagnostic criteria is a significant barrier to research in fHP and needs addressing urgently.

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