EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Bronchoalveolar Lavage Fluid Lymphocytosis in Chronic Hypersensitivity Pneumonitis: A Systematic Review and Meta-Analysis

Nicola Adderley, Christopher J. Humphreys, Hayley Barnes, Brett Ley, Zahra A. Premji, Kerri A. Johannson

Please cite this article as: Adderley N, Humphreys CJ, Barnes H, *et al*. Bronchoalveolar Lavage Fluid Lymphocytosis in Chronic Hypersensitivity Pneumonitis: A Systematic Review and Meta-Analysis. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.00206-2020).

Bronchoalveolar Lavage Fluid Lymphocytosis in Chronic Hypersensitivity Pneumonitis: A Systematic Review and Meta-Analysis

Nicola Adderley[1], Christopher J. Humphreys[2], Hayley Barnes[3,4], Brett Ley[4], Zahra A. Premji[5], Kerri A. Johannson[2,6]

Affiliations: [1]Faculty of Medicine & [2]Department of Medicine, University of Calgary, Calgary AB, Canada; [3]Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Melbourne, Australia; [4]Department of Medicine, University of California, San Francisco, San Francisco CA, USA; Departments of [5]Libraries and Cultural Resources & [6]Community Health Sciences, University of Calgary, Calgary AB, Canada.

Corresponding Author: Dr. Kerri A. Johannson, 4448 Front Street S.E., Calgary AB T3M-1M4 Canada; Email: kerri.johannson@ahs.ca; Phone: (403) 956-2435.

Keywords: Interstitial lung disease; Clinical epidemiology; Occupational health; Extrinsic allergic alveolitis

Take Home Message: BAL fluid lymphocyte % is higher in patients with #CHP compared to #IPF #IIP and #CTD-ILD, but available studies are limited to fully address this question. #AdvancesinILD

ABSTRACT

Background

The role of bronchoalveolar lavage fluid (BAL) lymphocyte% to diagnose chronic hypersensitivity pneumonitis (CHP) is unclear. We conducted a systematic review and meta-analysis of BAL lymphocyte% in the diagnosis of CHP.

Methods

We searched Medline, Embase and Cochrane library from inception to August 2019. Individual patient data were obtained to test performance characteristics of BAL lymphocyte% at different thresholds. Random-effects models were used for pooled estimates, with comparisons made between CHP and non-CHP interstitial lung diseases (ILD).

Results

Fifty-three studies were included in the systematic review and 42 in the meta-analysis. The pooled estimate for BAL lymphocyte% was 42.8% (95%CI 37.7-47.8, I^2=95.3%) in CHP, 10.0% (95%CI 6.9-13.1, I^2=91.2%) in idiopathic pulmonary fibrosis (IPF), 23.1% (95% CI 3.0-43.2, I^2=85.2%) in non-IPF idiopathic interstitial pneumonia (IIP), 23.4% (95%CI 11.0-35.9, I^2=45.7%) in connective-tissue disease ILD (CTD-ILD), and 31.2% (95% CI 17.6-44.8, I^2=95.2%) in sarcoidosis. Results differed between CHP and IPF (p<0.0001), non-IPF IIP (p=0.0309), and CTD-ILD (p=0.0824), but not between sarcoidosis (p=0.0966). Using individual patient data from eight studies, lymphocyte% threshold >20% provided sensitivity of 68.1% and specificity of 64.8% for CHP. Higher thresholds provided lower sensitivity with higher specificity. Older age and ever having smoked were associated with lower lymphocyte% in CHP.

Conclusions

BAL lymphocyte% is higher in CHP compared to IPF and other IIP, with higher thresholds providing improved specificity at the cost of sensitivity. However, parent studies are at risk of incorporation bias, and prospective studies should evaluate the additive discriminate value of BAL lymphocyte% to accurately diagnose CHP.

INTRODUCTION

Hypersensitivity pneumonitis (HP) is an inflammatory and/or fibrotic immune-mediated interstitial lung disease (ILD) caused by sensitization to an inciting antigen. In its chronic form, HP is characterized by an insidious progressive course, which obscures the link between causative antigen and disease. Chronic HP (CHP) shares overlapping clinical and radiological features with other ILDs,(1) and the absence of consensus diagnostic criteria further complicates establishing a diagnosis. Differentiating CHP from non-CHP ILDs (e.g. idiopathic pulmonary fibrosis [IPF], idiopathic non-specific interstitial pneumonia [NSIP]) can be challenging, but is critical for disease management and prognostication.(2, 3) The gold standard for diagnosis of CHP involves multidisciplinary team discussion and integration of radiological, clinical, and pathological data.(4)

Bronchoalveolar lavage (BAL) fluid analysis is proposed as an informative tool in the diagnostic evaluation of patients with HP and CHP.(5) Increased cellularity with lymphocytosis is associated with HP, with the range of lymphocyte counts believed to reflect the degree of alveolitis.(6, 7) However, there is a paucity of robust evidence supporting the role of alveolar lymphocytosis in diagnosing CHP.(8) In a study of antigen-determinate HP patients, the mean lymphocyte percentage (%) was elevated in all forms of disease but was lower in CHP compared to the acute or subacute forms.(9) Radiographic fibrosis is associated with lower BAL lymphocyte % in ILD,(10) and in advanced fibrotic HP with a histological pattern resembling usual interstitial pneumonia, BAL lymphocytosis may be less pronounced.(11) In a recent Delphi study, more than 75% of ILD experts rated BAL lymphocytosis >40% as ‘important’ or ‘very important’ for the diagnosis of CHP.(4) No consensus was met on the importance of BAL lymphocytosis 30-39%, and findings of 20-30% were deemed uninformative. These findings underscore the need for research to identify an optimal threshold for BAL lymphocytosis in the diagnosis of CHP.

BAL lymphocytosis may be influenced by several variables, including the presence and extent of fibrosis, timing relative to antigen exposure, smoking status, and procedural technique for BAL collection(5). In addition, the presence of BAL lymphocytosis may not differentiate between other histologic entities also characterized by lymphocytic inflammation, particularly NSIP or cryptogenic organizing pneumonia.(12) International guidelines exist to guide the BAL fluid collection procedure, yet there remains heterogeneity in the collection, processing and analysis, with the potential for misclassification.(13, 14) BAL lymphocyte subset analysis (ie. CD4:CD8 ratio) was historically thought to be helpful in establishing diagnoses of specific ILD, but recent data suggest it is not informative in CHP and testing is not routinely recommended in ILD.(5)

The role of BAL lymphocytosis in establishing a diagnosis of CHP remains unclear. The aim of this systematic review and meta-analysis was to describe BAL lymphocyte % in CHP and compare these findings to non-CHP ILDs. We further sought to test the performance characteristics of BAL lymphocyte % at different thresholds to accurately differentiate CHP from other non-CHP ILDs.

METHODS

Search Strategy and Selection Criteria

We performed a systematic review and meta-analysis following Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.(15) The protocol was registered in the PROSPERO database (CRD42019122236). Searches of MEDLINE, Cochrane Central Register of Clinical Trials, and Embase were conducted from database inception to August 2019. The search strategy design was supported by an academic research librarian (ZP) and included both text words and controlled vocabulary, with details presented in **Table S1**. The search strategy was intentionally broad to capture articles likely to report BAL cellular analysis in CHP and other ILDs, even if BAL results were only presented to characterize the study populations. No language, study design, or publication

status restrictions were imposed on the initial search. Electronic database searches were supplemented with manual review of bibliographies and searches of conference proceedings from the American Thoracic Society and the European Respiratory Society's International Scientific Conferences from inception through August 2019.

Two authors (NA, CH) independently screened and reviewed articles, with discrepancies resolved by consensus and/or review by a third author (KJ). Studies were eligible for inclusion if they met the following criteria: (1) original research; (2) patients with a diagnosis of CHP (ie. those in which the authors described the cohort as patients with 'chronic' or 'fibrotic' HP, and/or if HP cohort data described the presence of radiological and/or histological fibrosis); (3) reported BAL lymphocyte percentages; (4) did not include paediatric patients (<18 years old); (5) full text available in English or French. In the event of multiple publications with overlapping study periods, we included only the study with the largest number of participants to prevent double counting of the patient cohorts.

Data Extraction and Quality Assessment

Two authors (NA, CH) extracted data independently and in duplicate using a standardized protocol and reporting forms. Data collected included details of study design, population characteristics, BAL lymphocyte %, BAL CD4:CD8 ratio, antigen determinate status (known or unknown) and specific antigen (if known), forced vital capacity (FVC) % predicted, diffusion capacity of the lung for carbon monoxide (DLCO) % predicted, and the definition of chronicity applied in the study. We contacted the corresponding authors of articles that reported summary statistics of BAL findings in CHP compared to other non-CHP ILDs and requested anonymized individual patient data (IPD). The variables requested for IPD were similar to those described above and were pooled as a single cohort. Assessment for risk of bias of individual studies was undertaken using the standard Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool.(16)

Statistical Analysis

We calculated pooled estimates using the DerSimonian and Laird random-effects models to assess the frequency and distribution of BAL lymphocytosis in CHP.(17) Data were graphically displayed using forest plots. Pooled lymphocyte % estimates for CHP were compared to the pooled estimates for specific diagnostic categories using the student's unpaired t-test. Where reported, healthy controls or acute/subacute HP patients were excluded from the aggregate analyses. As a sensitivity analysis, we calculated a pooled estimate from the subset of studies that defined CHP according to the presence of fibrosis on chest imaging and/or histopathology. Heterogeneity between studies was assessed using the I^2 statistic to quantify the percentage of variation attributable to between-study differences.(18) We also conducted a sensitivity analysis of the CHP pooled lymphocyte % estimate using the inverse variance heterogeneity model. Similar methods were used to evaluate the CD4:CD8 ratio in CHP, comparing to other non-CHP ILDs. IPD from contributing studies was pooled and treated as a single cohort to test the performance characteristics of lymphocyte thresholds to identify patients with CHP from non-CHP ILD, and specifically to differentiate from non-IPF idiopathic interstitial pneumonia (IIP)/IPF. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of BAL lymphocyte % were calculated at thresholds of >20%, >30%, >40%, and >50%. The optimal cut-point of all pooled IPD was calculated using Youden's index.(19) Linear regression was used to identify variables associated with BAL lymphocytosis in univariate analysis, then using multivariate analysis with pre-specified covariates including age, sex, smoking history, individual study, FVC% and DLCO%. Funnel plots were used to assess for publication bias.

RESULTS

Study Selection and Individual Patient Data

The systematic review yielded 2500 unique references. After abstract and title screening, 390 articles underwent full text review, with 53 meeting criteria for inclusion in the systematic review

and 42 included in the meta-analysis (**Figure 1**). We contacted, or attempted to contact the corresponding authors of 23 studies that reported BAL findings in CHP and at least one non-CHP ILD comparator population to request IPD. IPD was obtained from eight unique studies.

Characteristics of included studies

Articles included in the systematic review included 23 retrospective and 30 prospective studies (**Table S2**). Studies originated from 16 countries, with 16 studies originating from Japan. Thirty studies reported data from patients with CHP only, and 23 included comparator populations of non-CHP ILD. IPF was the non-CHP ILD population most frequently reported, followed by sarcoidosis. Surgical lung biopsy or HRCT findings of pulmonary fibrosis were used to define HP as chronic in 35 studies, while other methods of defining CHP were varied and are summarized in **Table S3**. Twenty-one studies reported BAL CD4:CD8 ratio in a usable format, with a total of 315 CHP and 85 non-CHP ILD patients. IPD from eight studies was obtained, yielding a total cohort of 716 patients, with 188 CHP and 528 non-CHP ILD (229 IPF, 126 non-IPF idiopathic interstitial pneumonia [IIP], 105 connective tissue disease associated ILD [CTD-ILD] and 68 sarcoidosis) (**Table 1**). Most studies were of low quality to address the question of how BAL lymphocytosis informs the diagnosis of CHP (**Table S4**), with serious risk of incorporation bias, in that BAL lymphocyte % was used as part of the diagnostic evaluation. Visual assessment of funnel plots demonstrates asymmetry, suggesting publication bias in the parent studies addressing BAL lymphocytosis in CHP (**Figure S1**).

Table 1: Cohort Characteristics for the Individual Patient Data

	CHP (n=188)	Non-CHP ILD (n=528)
Age, years mean (SD)	60.3 (12.9)	58.5 (13.1)
Sex, male (%)	81 (43.1)	284 (54.8)
Never smoker, n (%)	66 (49.6)	101 (48.3)
Former smoker, n (%)	61 (45.9)	79 (37.8)
Current smoker, n (%)	6 (4.5)	29 (13.9)
FVC % predicted, mean (SD)	68.1 (19.6) n=172	73.1 (20.7) n=513

DLCO % predicted, mean (SD)	52.1 (18.9) n=158	59.2 (22.0) n=435
BAL lymphocyte %, mean (SD)	35.4 (24.2)	19.8 (19)
BAL lymphocyte & median (IQR)	32.5 (13.6, 53.5)	13 (6, 28)
Antigen known	168 (89)	--
Antigen unknown	10 (5.3)	--
Antigen not reported	10 (5.3)	--
Idiopathic pulmonary fibrosis, n (%)	--	229 (43.4)
Idiopathic interstitial pneumonia*, n (%)	--	126 (23.9)
Connective-tissue disease associated ILD, n (%)	--	105 (19.9)
Sarcoidosis, n (%)	--	68 (12.9)

Abbreviations: CHP=chronic hypersensitivity pneumonitis; ILD=interstitial lung disease; FVC=forced vital capacity; DLCO=diffusion capacity of the lung for carbon monoxide; BAL=bronchoalveolar lavage; SD=standard deviation, IQR=interquartile range. *non-IPF

BAL lymphocytosis in CHP vs. non-CHP ILDs

BAL lymphocyte data was extracted from a total of 42 studies with 52 unique entries, given that some studies reported CHP data by specific phenotypes or radiological patterns. The pooled estimate for BAL lymphocyte % in CHP was 42.8% (95% CI 37.7, 47.8, I^2 = 95.3%) (**Figure 2**). The pooled estimate for BAL lymphocyte % in IPF was calculated from 11 studies at 10.0% (95% CI 6.9, 13.1, I^2=91.2%), for non-IPF IIP calculated from five studies at 23.1% (95% CI -3.0, 43.2, I^2=85.2%), for CTD-ILD calculated from three studies at 23.4% (95%CI 11.0-35.9, I^2=45.7%), and for sarcoidosis calculated from nine studies at 31.2% (95% CI 17.6, 44.8, I^2=95.2%) (**Figure 3A-D**). The I^2 values suggest high heterogeneity for the CHP, IPF, non-IPF IIP, and sarcoidosis estimates. The BAL lymphocyte % differed between CHP and IPF (p<0.0001), and CHP and non-IPF IIP (p=0.0309), but not CHP and sarcoidosis (p<0.0966). Although the number of studies was small, we identified a numerical difference between CHP and CTD-ILD (p=0.0824). The sensitivity analysis using 26 studies

that defined CHP based on radiographic and/or histologic fibrosis provided a similar pooled estimate for CHP lymphocyte % at 43.9% (95% CI 37.4, 50.4, I^2=95.3%). Results were similar for the CHP pooled estimate using the inverse variance heterogeneity model (**Figure S2**).

CD4: CD8 for CHP vs other ILDs

BAL CD4:CD8 ratio data was extracted from a total of 21 studies for CHP, with a pooled estimate of 1.6 (95% CI 1.1, 2.1, I^2=89.3%) (**Figure 4**). The pooled estimate for IPF was estimated from 4 studies at 1.6 (95% CI 0.6, 2.5, I^2=90.9%), and for sarcoidosis from 5 studies at 4.6 (95% CI 1.9, 7.3, I^2=87.0%). Again, the I^2 values suggest high heterogeneity for CHP, IPF and sarcoidosis estimates. The CD4:CD8 ratio did not differ between CHP and IPF (p=0.9053) but differed between CHP and sarcoidosis (p=0.0007). No CD4:CD8 data were reported for CTD-ILD.

Performance characteristics of lymphocyte thresholds

The IPD data from eight studies was pooled and analysed as a single cohort to calculate the performance characteristics of BAL lymphocytosis at four different thresholds **(Table 2)**. A comparison of studies providing IPD to those not providing IPD is presented in the supplement (**Table S5**). A threshold of >20% yielded a sensitivity of 68.1% and specificity of 64.8% to identify CHP from non-CHP ILD. A threshold of >30% yielded a sensitivity of 54.8% and specificity of 78.9% to identify CHP from non-CHP ILD. A threshold of >40% yielded a sensitivity of 43.1% and specificity of 85.5% to identify CHP from non-CHP ILD. A threshold of >50% yielded a sensitivity of 30.7% and a specificity of 92.4% to identify CHP from non-CHP ILD. The PPV increased and the NPV decreased with increasing thresholds. The thresholds that maximized sensitivity and specificity were 20% and 50%, respectively, and as expected increasing specificity lowered the sensitivity and vice versa. The BAL lymphocytosis value that concurrently optimized sensitivity (66.5%) and specificity (65.9%) was

21.3%. In comparison to findings from the pooled non-CHP population, BAL lymphocyte % differentiated patients with CHP from those with non-IPF IIP/IPF more accurately with higher specificity, and PPV (**Table 3**), The value that optimized sensitivity (70.7%) and specificity (67.6%) was similar at 21%.

Table 2: Performance characteristics at lymphocyte % thresholds to identify CHP from non-CHP ILD

Threshold	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
20%	68.1% (60.9-74.7)	64.8% (60.5-68.9)	40.8% (37.2-44.5)	85.1% (82.1-87.6)
30%	54.8% (47.4-62.0)	78.9% (75.3-82.2)	46.6% (41.6-51.7)	82.9% (80.4-85.1)
40%	43.1% (35.9-50.5)	85.5% (82.2-88.4)	51.6% (45.0-58.14)	80.7% (78.7-82.7)
50%	30.7% (24.3-37.8)	92.4% (89.8-94.5)	59.6% (50.6-68.0)	78.4% (76.8-80.1)

Abbreviations: CHP=chronic hypersensitivity pneumonitis; ILD=interstitial lung disease; CI=confidence interval; PPV=positive predictive value; NPV=negative predictive value.

Table 3: Performance characteristics at lymphocyte % thresholds to identify CHP from IPF/IIP

Threshold	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
20%	68.1% (60.9-74.7)	72.7% (67.7-77.3)	56.9% (52.0-61.6)	81.1% (77.6-84.3)
30%	54.8% (47.4-62.0)	84.0% (79.8-87.6)	64.4% (58.0-70.3)	77.9% (74.9-80.6)
40%	43.1% (35.9-50.5)	90.3% (86.8-93.2)	70.4% (62.5-77.3)	74.8% (72.3-77.2)
50%	30.9% (24.4-38.0)	95.1% (92.3-97.2)	77.6% (67.6-85.3)	71.6% (69.6-73.6)

Abbreviations: CHP=chronic hypersensitivity pneumonitis; IIP=idiopathic interstitial pneumonia; IPF=idiopathic pulmonary fibrosis; CI=confidence interval; PPV=positive predictive value; NPV=negative predictive value.

In univariate analyses, older age, male sex, and ever having smoked were associated with lower lymphocyte % in patients with CHP (**Table 4**). In pre-specified multivariate analysis, age (β=-0.32,

95% CI -0.58, -0.06, p=0.016) and ever having smoked (β=-11.3 95% CI -19.9, -2.6, p=0.011) were associated with lower lymphocyte % in patients with CHP. In multivariate analysis, we did not identify an association between lung function measures and BAL lymphocyte %, although these may not accurately reflect fibrosis extent or disease severity in this cohort. Of 169 CHP patients with an implicated antigen exposure, 126 (75%) were reportedly bird fanciers while the remaining 43 (25%) patients had diverse other exposures. We did not identify an association between antigen type and BAL lymphocyte %, comparing bird fanciers to other exposures.

Table 4: Variables associated with lymphocyte % in chronic hypersensitivity pneumonitis

Variable	Univariate analysis		Multivariate analysis		
	β coefficient (95% CI)	p-value	Covariates	β coefficient (95% CI)	p-value
Age	-0.42 (-0.68, -0.15)	0.002	Smoking, study	-0.32 (-0.58, -0.06)	0.016
Sex	-12.9 (-19.7, -6.07)	<0.0001	Smoking, study	-5.8 (-14.0, 2.5)	0.168
Smoking	-16.0 (-22.9, -9.1)	<0.0001	Age, sex, study	-11.3 (-19.9, -2.6)	0.011
FVC %	-0.3 (-0.48, -0.12)	0.001	Age, sex, smoking, study	-0.11 (-0.3, 0.09)	0.297
DLCO %	-0.1 (-0.3, 0.1)	0.306	Age, sex, smoking, study	-0.02 (-0.21, 0.17)	0.869

Abbreviations: β=beta; CI=confidence interval; FVC=forced vital capacity; DLCO=diffusion capacity of the lung for carbon monoxide.

DISCUSSION

BAL fluid lymphocyte % is higher in patients with CHP compared to other non-CHP ILDs, most notably IPF and non-IPF IIP. However; there is high heterogeneity across studies and given that almost all studies used BAL fluid cellular analysis findings as part of the CHP diagnostic evaluation,

there exists a high potential for incorporation bias, which would be expected to inflate test characteristics. Higher thresholds provide greater specificity for CHP at a cost of lower sensitivity, with a threshold of 21% optimizing both sensitivity and specificity. However, because BAL is often used as an intermediate diagnostic step to determine if definitive diagnosis by surgical lung biopsy is needed, higher BAL lymphocyte % thresholds, providing higher specificity, may be more clinically useful. Older age and ever having smoked were associated with lower BAL lymphocyte % in CHP. Unfortunately, the data do not inform the impact of other clinical variables on BAL lymphocyte % in a patient with suspected CHP.

CHP can be challenging to diagnose, largely due to the historical lack of widely accepted consensus criteria. The role of BAL lymphocyte % to establish a diagnosis of CHP has remained controversial, with its use largely carried over from clinical experience with acute (non-fibrotic) HP.(4, 20, 21) The most recent international IPF guideline conditionally recommended BAL in patients with suspected IPF and a non-diagnostic high-resolution computed tomography (HRCT) pattern, though a meta-analysis of eight studies reported therein found no difference in BAL lymphocyte % between IPF and CHP.(22) Notably, the HP BAL lymphocytosis data used in this analysis was drawn from only two studies, both excluded from our analysis due to patients not having 'chronic' or 'fibrotic' HP, or the full text being unavailable in English or French.(23, 24) Clinicians and patients must consider the risk-benefit ratio of diagnostic tests, and the anticipated yield of clinically relevant information. Our findings highlight that no studies have robustly tested the additive discriminative value of BAL lymphocytosis in differentiating CHP from other forms of fibrotic ILD. The identification of a threshold that provides best sensitivity and specificity suggests that such a value could be tested prospectively to determine the performance of BAL cellular analysis as a diagnostic test in CHP. However; given the limitations of the data, this number should not as of yet be considered a diagnostic test, either to rule in or rule out CHP.

The pooled estimates for BAL lymphocyte % show high heterogeneity and, based on the characteristics of the studies, we could not perform robust subset analyses to explain the differences between studies. Data suggest that the extent of pulmonary fibrosis, the type of antigen and time since last exposure will influence the degree of alveolar inflammation in HP, with lower lymphocyte % in CHP relative to acute HP.(11, 25, 26) In our IPD analysis, older age and a history of smoking were associated with lower lymphocyte %, with smoking status known to influence BAL cellular analyses.(5) Neither FVC% or DLCO% were associated with degree of lymphocytosis, although these may not be accurate surrogates of fibrosis. The lack of granular data on antigen type and time since exposure limited our ability to evaluate associations with lymphocytosis, and this is an area in need of further study. The CD4:CD8 ratio was found to be lower in CHP than in sarcoidosis, but with high between-study variability. The CD4:CD8 ratio is known to be influenced by exposure, smoking and disease severity, and this test has largely fallen out of favour in clinical practice.(5, 27)

This study has important limitations. Despite the breadth of our literature search, relevant references may have been missed. We specifically focused on chronic/fibrotic HP, therefore these findings cannot be extrapolated to acute/non-fibrotic forms of HP. Given the heterogeneity in diagnostic criteria for CHP across studies, we cannot determine the validity of the CHP diagnoses. We tried to address this through the sensitivity analysis that demonstrated consistent findings. Data from the parent studies did not permit assessment of BAL technique and quality, or the potential impact of treatment on BAL cellular analysis. The data did not allow stratification of patients based on degree of fibrosis or presence of other HRCT morphologic features (e.g. air-trapping, centrilobular nodules, and ground glass opacities), which may impact the test performance characteristics. Further, our data did not allow for strong characterization of antigen exposure, a variable that likely influences the degree of alveolitis. Most importantly, the validity of our findings is limited by the

quality of the parent studies, the majority of which are subject to incorporation bias. Despite these limitations, our study has several important strengths. We identified studies with an intentionally broad search strategy and created a large cohort using individual patient data. To the best of our knowledge, the current study provides the most comprehensive assessment of this clinically meaningful question in this patient population to date.

CONCLUSIONS

BAL lymphocyte % is higher in CHP compared to non-CHP forms of ILD, with older age and ever smoking associated with lower lymphocyte %. Higher thresholds of lymphocyte % provide greater specificity at a cost of sensitivity. Further work is needed to inform the role of BAL in the absence of incorporation bias, by testing the discriminative performance of lymphocyte % in established diagnostic prediction models. Finally, a deeper understanding of the relationships between antigen exposure, host factors and alveolar lymphocytosis will guide the use of BAL in the diagnostic evaluation of CHP.

ACKNOWLEDGEMENTS

Competing Interests: KAJ reports reports personal fees and other from Boehringer-Ingelheim, personal fees and other from Hoffman La Roche Ltd, personal fees and other from Theravance, personal fees and other from Blade Therapeutics, grants from Chest Foundation, grants from University of Calgary School of Medicine, grants from Pulmonary Fibrosis Society of Calgary, grants from UCB Biopharma SPRL, outside the submitted work. NA, CJH, HB, BL, and ZAP have nothing to disclose.

Funding: No funding to disclose.

Data sharing statement: Data from the systematic review and meta-analysis are available upon reasonable request made to the corresponding author. Individual patient data may be available from the corresponding authors of the cited studies.

Patient consent for publication: Not required.

ICMJE Contributorship Statement: NA and KJ conceived of the study, all authors contributed to the study design and protocol development, HB and KJ conducted the statistical analyses, NA and KJ drafted the manuscript, all authors contributed to, critically appraised, and approved the final version of the manuscript.

REFERENCES

1. Johannson K, Ryerson CJ. Making an accurate diagnosis of chronic hypersensitivity pneumonitis. *Can Respir J* 2014; 21: 371-370.
2. Morell F, Villar A, Montero MA, Munoz X, Colby TV, Pipvath S, Cruz MJ, Raghu G. Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. *Lancet Respir Med* 2013; 1: 685-694.
3. Kern RM, Singer JP, Koth L, Mooney J, Golden J, Hays S, Greenland J, Wolters P, Ghio E, Jones KD, Leard L, Kukreja J, Blanc PD. Lung transplantation for hypersensitivity pneumonitis. *Chest* 2015; 147: 1558-1565.
4. Morisset J, Johannson KA, Jones KD, Wolters PJ, Collard HR, Walsh SLF, Ley B. Identification of Diagnostic Criteria for Chronic Hypersensitivity Pneumonitis: An International Modified Delphi Survey. *Am J Respir Crit Care Med* 2017.
5. Meyer KC, Raghu G, Baughman RP, Brown KK, Costabel U, du Bois RM, Drent M, Haslam PL, Kim DS, Nagai S, Rottoli P, Saltini C, Selman M, Strange C, Wood B. 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.
6. Pardo A, Barrios R, Gaxiola M, Segura-Valdez L, Carrillo G, Estrada A, Mejia M, Selman M. Increase of lung neutrophils in hypersensitivity pneumonitis is associated with lung fibrosis. *Am J Respir Crit Care Med* 2000; 161: 1698-1704.
7. Ohtani Y, Hisauchi K, Sumi Y, Miyashita Y, Sawada M, Miyake S, Yoshizawa Y. Sequential changes in bronchoalveolar lavage cells and cytokines in a patient progressing from acute to chronic bird Fancier's lung disease. *Intern Med* 1999; 38: 896-899.
8. Lacasse Y, Selman M, Costabel U, Dalphin JC, Ando M, Morell F, Erkinjuntti-Pekkanen R, Muller N, Colby TV, Schuyler M, Cormier Y. Clinical diagnosis of hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2003; 168: 952-958.
9. 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.
10. Espoladore LM, Gregorio BB, Lima MS, de Pereira CA, Soares MR, Coletta EN. Cytological analysis of bronchoalveolar lavage in patients with interstitial lung diseases and the relation of cytological analysis to fibrosis in high-resolution computed tomography. *Anal Quant Cytopathol Histpathol* 2014; 36: 206-212.
11. Ohtani Y, Saiki S, Kitaichi M, Usui Y, Inase N, Costabel U, Yoshizawa Y. Chronic bird fancier's lung: histopathological and clinical correlation. An application of the 2002 ATS/ERS consensus classification of the idiopathic interstitial pneumonias. *Thorax* 2005; 60: 665-671.
12. Ohshimo S, Bonella F, Cui A, Beume M, Kohno N, Guzman J, Costabel U. Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009; 179: 1043-1047.
13. Barss L, Fraser KL, Kelly MM, Johannson KA. Impact of processing technique on bronchoalveolar lavage cellular analysis. *Eur Respir J* 2018; 51.
14. Bollmann B-A, Seeliger B, Drick N, Welte T, Gottlieb JT, Greer M. Cellular analysis in bronchoalveolar lavage: inherent limitations of current standard procedure. *European Respiratory Journal* 2017; 49.
15. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama* 2000; 283: 2008-2012.
16. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; 155: 529-536.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177-188.

18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539-1558.
19. López-Ratón M, Rodríguez-Álvarez MX, Cadarso-Suárez C, Gude-Sampedro F. OptimalCutpoints: An R Package for Selecting Optimal Cutpoints in Diagnostic Tests. *2014* 2014; 61: 36.
20. Mooney JJ, Collard HR. COUNTERPOINT: Should BAL Be Routinely Performed in the Diagnostic Evaluation of Idiopathic Pulmonary Fibrosis? No. *Chest* 2017; 152: 919-922.
21. Wells AU, Kokosi MA. POINT: Should BAL Be Routinely Performed in the Diagnostic Evaluation of Idiopathic Pulmonary Fibrosis? Yes. *Chest* 2017; 152: 917-919.
22. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F, Flaherty KR, Wells A, Martinez FJ, Azuma A, Bice TJ, Bouros D, Brown KK, Collard HR, Duggal A, Galvin L, Inoue Y, Jenkins RG, Johkoh T, Kazerooni EA, Kitaichi M, Knight SL, Mansour G, Nicholson AG, Pipavath SNJ, Buendia-Roldan I, Selman M, Travis WD, Walsh S, Wilson KC. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med* 2018; 198: e44-e68.
23. Lee W, Chung WS, Hong KS, Huh J. Clinical usefulness of bronchoalveolar lavage cellular analysis and lymphocyte subsets in diffuse interstitial lung diseases. *Ann Lab Med* 2015; 35: 220-225.
24. Schildge J, Frank J, Klar B. [The Role of Bronchoalveolar Lavage in the Diagnosis of Idiopathic Pulmonary Fibrosis: An Investigation of the Relevance of the Protein Content]. *Pneumologie* 2016; 70: 435-441.
25. Gaxiola M, Buendia-Roldan I, Mejia M, Carrillo G, Estrada A, Navarro MC, Rojas-Serrano J, Selman M. Morphologic diversity of chronic pigeon breeder's disease: clinical features and survival. *Respir Med* 2011; 105: 608-614.
26. Drent M, Wagenaar S, van Velzen-Blad H, Mulder PG, Hoogsteden HC, van den Bosch JM. Relationship between plasma cell levels and profile of bronchoalveolar lavage fluid in patients with subacute extrinsic allergic alveolitis. *Thorax* 1993; 48: 835-839.
27. Barrera L, Mendoza F, Zuniga J, Estrada A, Zamora AC, Melendro EI, Ramirez R, Pardo A, Selman M. Functional diversity of T-cell subpopulations in subacute and chronic hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2008; 177: 44-55.

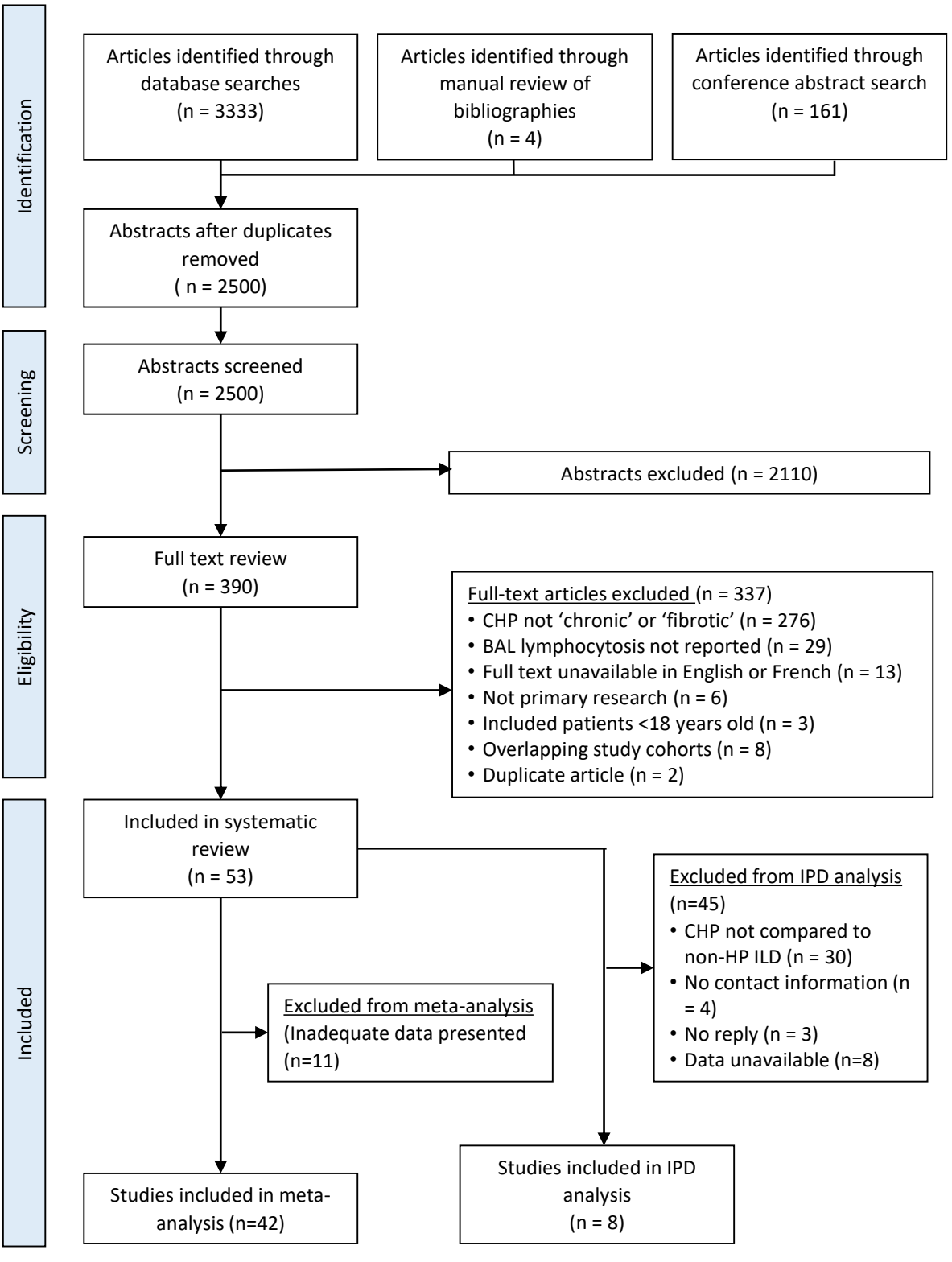
Figure Legend

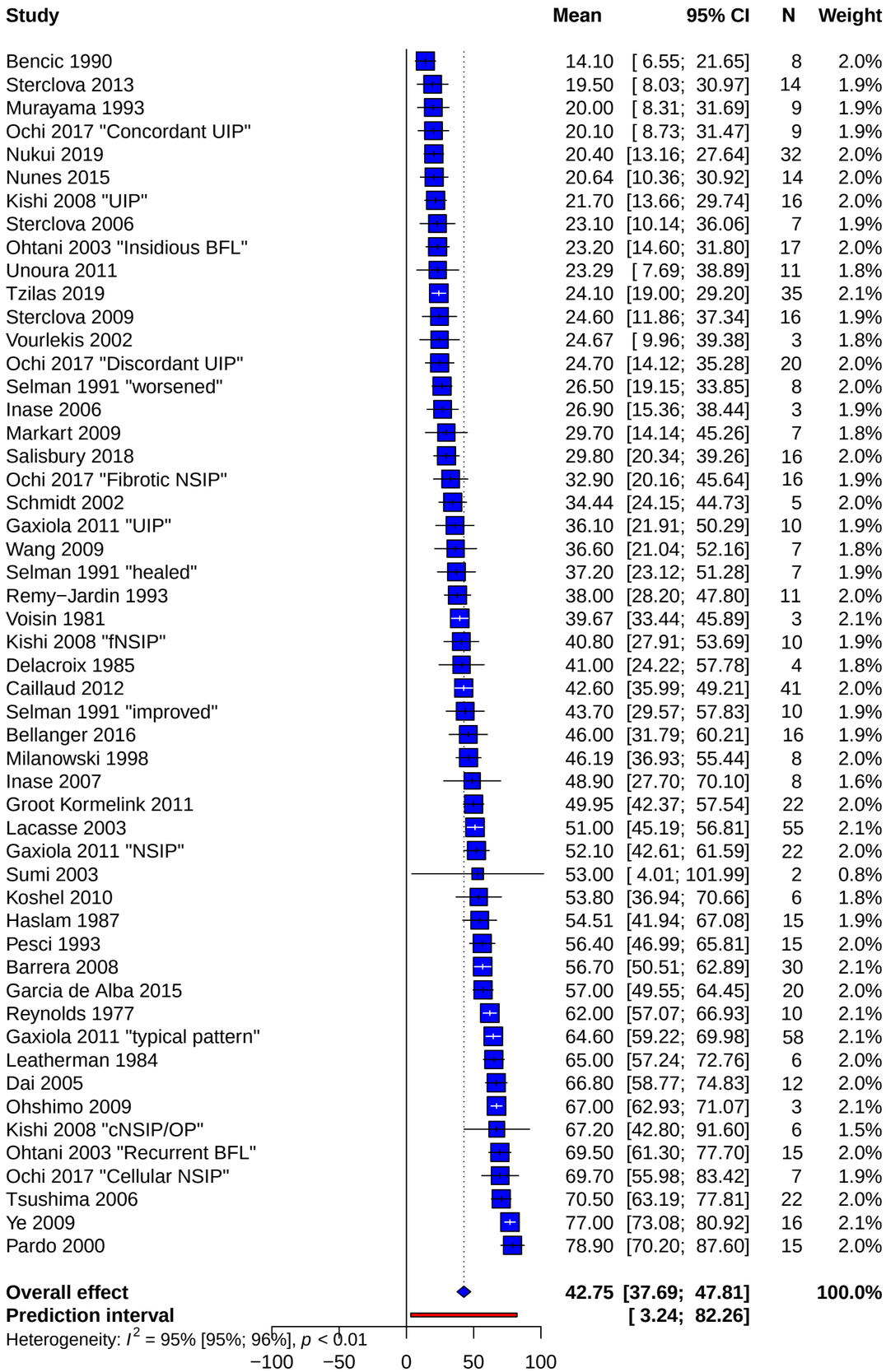
Figure 1: Flow diagram of included studies based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols.

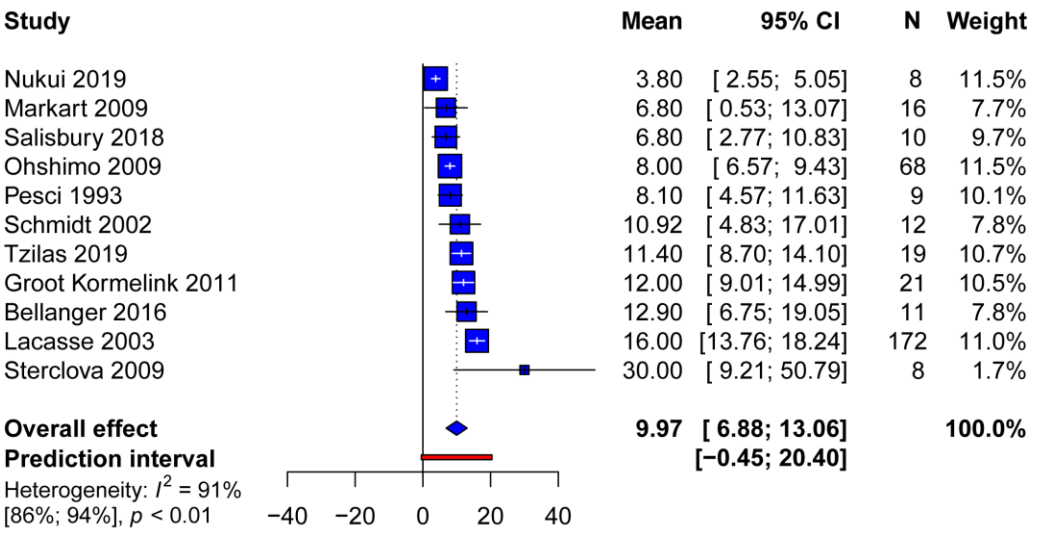
Figure 2: Pooled estimate for bronchoalveolar lavage lymphocyte % in chronic hypersensitivity pneumonitis.

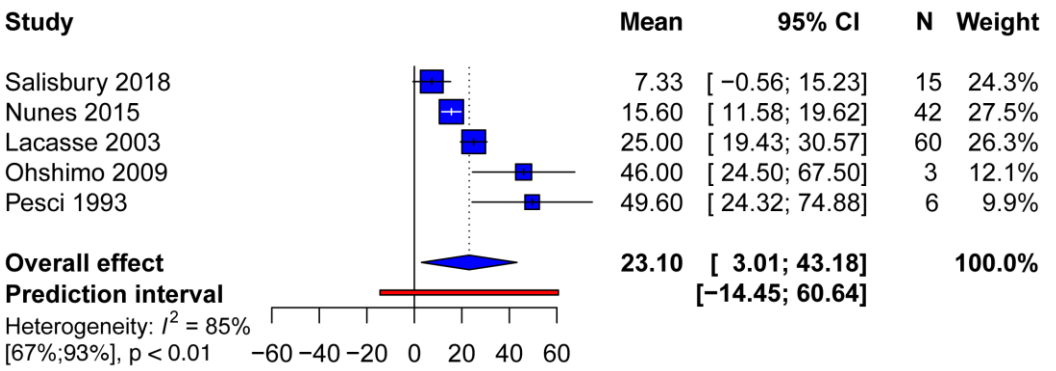
Figure 3 A-D: Pooled estimates for bronchoalveolar lavage lymphocyte % in A) idiopathic pulmonary fibrosis (IPF), B) non-IPF idiopathic interstitial pneumonia, C) connective-tissue disease related interstitial lung disease, D) sarcoidosis.

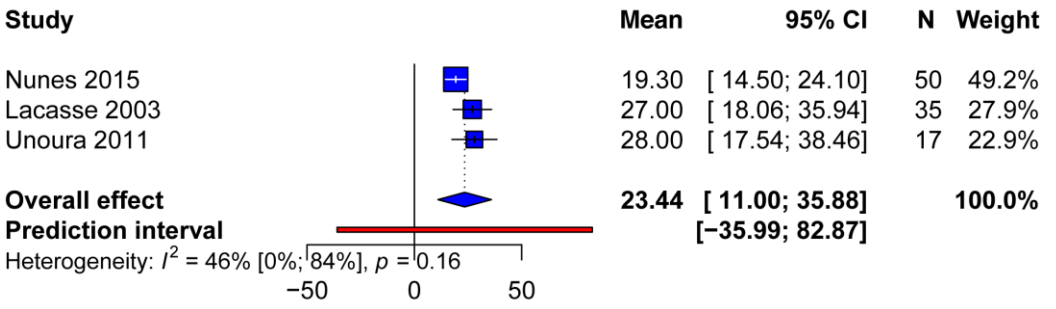
Figure 4: Pooled estimate for bronchoalveolar lavage CD4:CD8 ratio in chronic hypersensitivity pneumonitis.

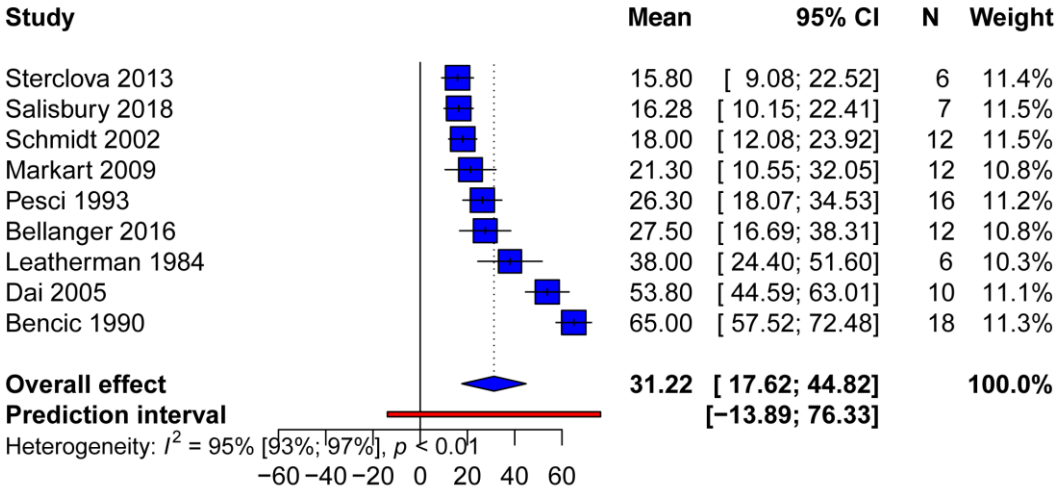

Identification
Articles identified through database searches (n = 3333)
Articles identified through manual review of bibliographies (n = 4)
Articles identified through conference abstract search (n = 161)
Abstracts after duplicates removed (n = 2500)
Screening
Abstracts screened (n = 2500)
Abstracts excluded (n = 2110)
Eligibility
Full text review (n = 390)
Full-text articles excluded (n = 337)
• CHP not 'chronic' or 'fibrotic' (n = 276)
• BAL lymphocytosis not reported (n = 29)
• Full text unavailable in English or French (n = 13)
• Not primary research (n = 6)
• Included patients <18 years old (n = 3)
• Overlapping study cohorts (n = 8)
• Duplicate article (n = 2)
Included
Included in systematic review (n = 53)
Excluded from IPD analysis (n=45)
• CHP not compared to non-HP ILD (n = 30)
• No contact information (n = 4)
• No reply (n = 3)
• Data unavailable (n=8)
Excluded from meta-analysis (Inadequate data presented (n=11)
Studies included in meta-analysis (n=42)
Studies included in IPD analysis (n = 8)

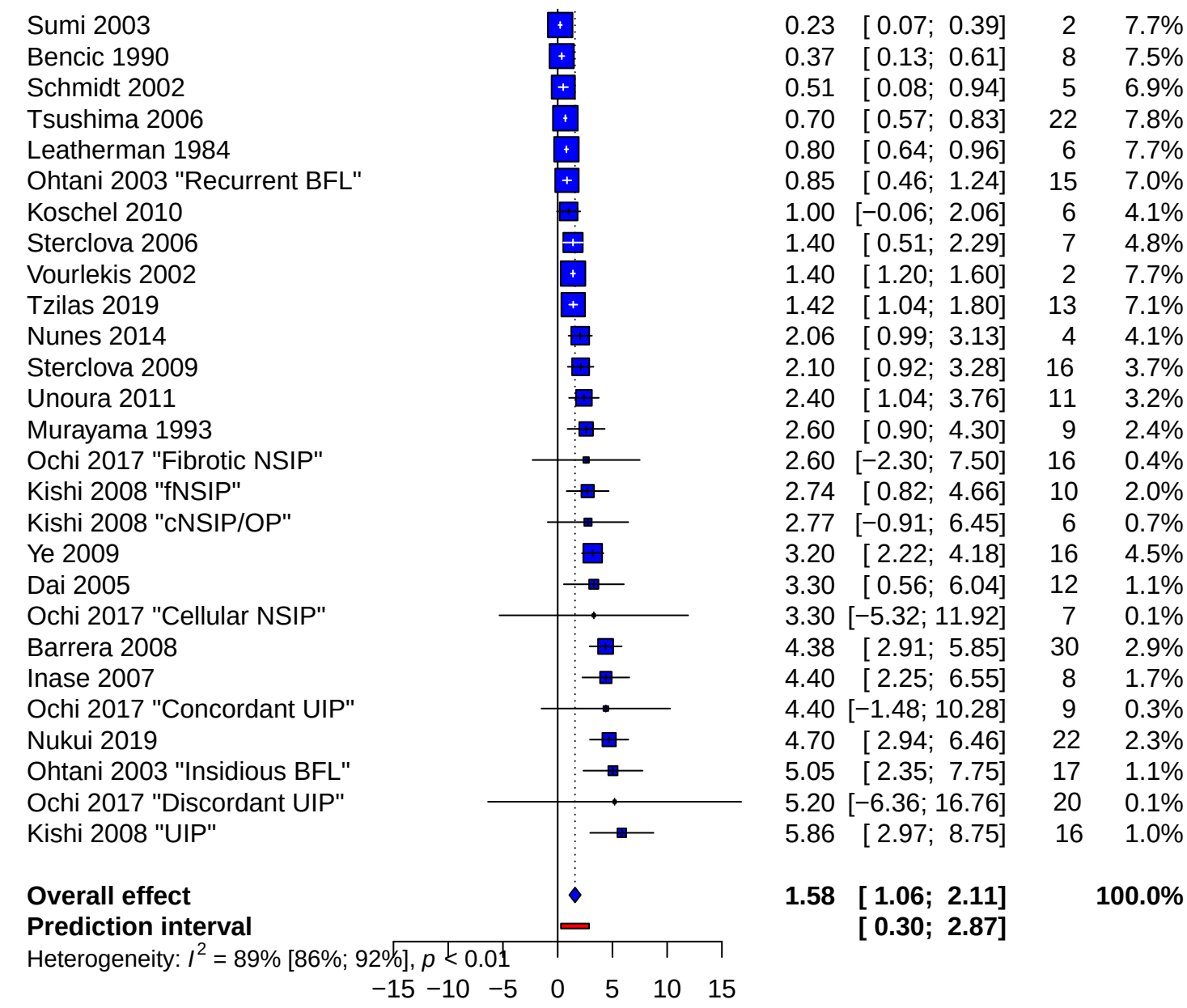

Study
Mean
95% CI
N
Weight
Bencic 1990 14.10 [6.55; 21.65] 8 2.0%
Sterclova 2013 19.50 [8.03; 30.97] 14 1.9%
Murayama 1993 20.00 [8.31; 31.69] 9 1.9%
Ochi 2017 "Concordant UIP" 20.10 [8.73; 31.47] 9 1.9%
Nukui 2019 20.40 [13.16; 27.64] 32 2.0%
Nunes 2015 20.64 [10.36; 30.92] 14 2.0%
Kishi 2008 "UIP" 21.70 [13.66; 29.74] 16 2.0%
Sterclova 2006 23.10 [10.14; 36.06] 7 1.9%
Ohtani 2003 "Insidious BFL" 23.20 [14.60; 31.80] 17 2.0%
Unoura 2011 23.29 [7.69; 38.89] 11 1.8%
Tzilas 2019 24.10 [19.00; 29.20] 35 2.1%
Sterclova 2009 24.60 [11.86; 37.34] 16 1.9%
Vourlekis 2002 24.67 [9.96; 39.38] 3 1.8%
Ochi 2017 "Discordant UIP" 24.70 [14.12; 35.28] 20 2.0%
Selman 1991 "worsened" 26.50 [19.15; 33.85] 8 2.0%
Inase 2006 26.90 [15.36; 38.44] 3 1.9%
Markart 2009 29.70 [14.14; 45.26] 7 1.8%
Salisbury 2018 29.80 [20.34; 39.26] 16 2.0%
Ochi 2017 "Fibrotic NSIP" 32.90 [20.16; 45.64] 16 1.9%
Schmidt 2002 34.44 [24.15; 44.73] 5 2.0%
Gaxiola 2011 "UIP" 36.10 [21.91; 50.29] 10 1.9%
Wang 2009 36.60 [21.04; 52.16] 7 1.8%
Selman 1991 "healed" 37.20 [23.12; 51.28] 7 1.9%
Remy−Jardin 1993 38.00 [28.20; 47.80] 11 2.0%
Voisin 1981 39.67 [33.44; 45.89] 3 2.1%
Kishi 2008 "fNSIP" 40.80 [27.91; 53.69] 10 1.9%
Delacroix 1985 41.00 [24.22; 57.78] 4 1.8%
Caillaud 2012 42.60 [35.99; 49.21] 41 2.0%
Selman 1991 "improved" 43.70 [29.57; 57.83] 10 1.9%
Bellanger 2016 46.00 [31.79; 60.21] 16 1.9%
Milanowski 1998 46.19 [36.93; 55.44] 8 2.0%
Inase 2007 48.90 [27.70; 70.10] 8 1.6%
Groot Kormelink 2011 49.95 [42.37; 57.54] 22 2.0%
Lacasse 2003 51.00 [45.19; 56.81] 55 2.1%
Gaxiola 2011 "NSIP" 52.10 [42.61; 61.59] 22 2.0%
Sumi 2003 53.00 [4.01; 101.99] 2 0.8%
Koshel 2010 53.80 [36.94; 70.66] 6 1.8%
Haslam 1987 54.51 [41.94; 67.08] 15 1.9%
Pesci 1993 56.40 [46.99; 65.81] 15 2.0%
Barrera 2008 56.70 [50.51; 62.89] 30 2.1%
Garcia de Alba 2015 57.00 [49.55; 64.45] 20 2.0%
Reynolds 1977 62.00 [57.07; 66.93] 10 2.1%
Gaxiola 2011 "typical pattern" 64.60 [59.22; 69.98] 58 2.1%
Leatherman 1984 65.00 [57.24; 72.76] 6 2.0%
Dai 2005 66.80 [58.77; 74.83] 12 2.0%
Ohshimo 2009 67.00 [62.93; 71.07] 3 2.1%
Kishi 2008 "cNSIP/OP" 67.20 [42.80; 91.60] 6 1.5%
Ohtani 2003 "Recurrent BFL" 69.50 [61.30; 77.70] 15 2.0%
Ochi 2017 "Cellular NSIP" 69.70 [55.98; 83.42] 7 1.9%
Tsushima 2006 70.50 [63.19; 77.81] 22 2.0%
Ye 2009 77.00 [73.08; 80.92] 16 2.1%
Pardo 2000 78.90 [70.20; 87.60] 15 2.0%
Overall effect 42.75 [37.69; 47.81] 100.0%
Prediction interval [3.24; 82.26]
Heterogeneity: I^2 = 95% [95%; 96%], p < 0.01
−100
−50
0
50
100


Study
Mean
95% CI
N
Weight
Nukui 2019 3.80 [2.55; 5.05] 8 11.5%
Markart 2009 6.80 [0.53; 13.07] 16 7.7%
Salisbury 2018 6.80 [2.77; 10.83] 10 9.7%
Ohshimo 2009 8.00 [6.57; 9.43] 68 11.5%
Pesci 1993 8.10 [4.57; 11.63] 9 10.1%
Schmidt 2002 10.92 [4.83; 17.01] 12 7.8%
Tzilas 2019 11.40 [8.70; 14.10] 19 10.7%
Groot Kormelink 2011 12.00 [9.01; 14.99] 21 10.5%
Bellanger 2016 12.90 [6.75; 19.05] 11 7.8%
Lacasse 2003 16.00 [13.76; 18.24] 172 11.0%
Sterclova 2009 30.00 [9.21; 50.79] 8 1.7%
Overall effect 9.97 [6.88; 13.06] 100.0%
Prediction interval [−0.45; 20.40]
Heterogeneity: I^2 = 91% [86%; 94%], p < 0.01
−40 −20 0 20 40


Study
Mean
95% CI
N
Weight
Salisbury 2018 7.33 [−0.56; 15.23] 15 24.3%
Nunes 2015 15.60 [11.58; 19.62] 42 27.5%
Lacasse 2003 25.00 [19.43; 30.57] 60 26.3%
Ohshimo 2009 46.00 [24.50; 67.50] 3 12.1%
Pesci 1993 49.60 [24.32; 74.88] 6 9.9%
Overall effect 23.10 [3.01; 43.18] 100.0%
Prediction interval [−14.45; 60.64]
Heterogeneity: I^2 = 85% [67%;93%], p < 0.01
−60 −40 −20 0 20 40 60


Study
Mean
95% CI
N
Weight
Nunes 2015 19.30 [14.50; 24.10] 50 49.2%
Lacasse 2003 27.00 [18.06; 35.94] 35 27.9%
Unoura 2011 28.00 [17.54; 38.46] 17 22.9%
Overall effect 23.44 [11.00; 35.88] 100.0%
Prediction interval [−35.99; 82.87]
Heterogeneity: I^2 = 46% [0%; 84%], p = 0.16
−50 0 50


Study
Mean
95% CI
N
Weight
Sterclova 2013 15.80 [9.08; 22.52] 6 11.4%
Salisbury 2018 16.28 [10.15; 22.41] 7 11.5%
Schmidt 2002 18.00 [12.08; 23.92] 12 11.5%
Markart 2009 21.30 [10.55; 32.05] 12 10.8%
Pesci 1993 26.30 [18.07; 34.53] 16 11.2%
Bellanger 2016 27.50 [16.69; 38.31] 12 10.8%
Leatherman 1984 38.00 [24.40; 51.60] 6 10.3%
Dai 2005 53.80 [44.59; 63.01] 10 11.1%
Bencic 1990 65.00 [57.52; 72.48] 18 11.3%
Overall effect 31.22 [17.62; 44.82] 100.0%
Prediction interval [−13.89; 76.33]
Heterogeneity: I^2 = 95% [93%; 97%], p < 0.01
−60 −40 −20 0 20 40 60


Study
Mean
95% CI
N
Weight
Sumi 2003 0.23 [0.07; 0.39] 2 7.7%
Bencic 1990 0.37 [0.13; 0.61] 8 7.5%
Schmidt 2002 0.51 [0.08; 0.94] 5 6.9%
Tsushima 2006 0.70 [0.57; 0.83] 22 7.8%
Leatherman 1984 0.80 [0.64; 0.96] 6 7.7%
Ohtani 2003 "Recurrent BFL" 0.85 [0.46; 1.24] 15 7.0%
Koschel 2010 1.00 [−0.06; 2.06] 6 4.1%
Sterclova 2006 1.40 [0.51; 2.29] 7 4.8%
Vourlekis 2002 1.40 [1.20; 1.60] 2 7.7%
Tzilas 2019 1.42 [1.04; 1.80] 13 7.1%
Nunes 2014 2.06 [0.99; 3.13] 4 4.1%
Sterclova 2009 2.10 [0.92; 3.28] 16 3.7%
Unoura 2011 2.40 [1.04; 3.76] 11 3.2%
Murayama 1993 2.60 [0.90; 4.30] 9 2.4%
Ochi 2017 "Fibrotic NSIP" 2.60 [−2.30; 7.50] 16 0.4%
Kishi 2008 "fNSIP" 2.74 [0.82; 4.66] 10 2.0%
Kishi 2008 "cNSIP/OP" 2.77 [−0.91; 6.45] 6 0.7%
Ye 2009 3.20 [2.22; 4.18] 16 4.5%
Dai 2005 3.30 [0.56; 6.04] 12 1.1%
Ochi 2017 "Cellular NSIP" 3.30 [−5.32; 11.92] 7 0.1%
Barrera 2008 4.38 [2.91; 5.85] 30 2.9%
Inase 2007 4.40 [2.25; 6.55] 8 1.7%
Ochi 2017 "Concordant UIP" 4.40 [−1.48; 10.28] 9 0.3%
Nukui 2019 4.70 [2.94; 6.46] 22 2.3%
Ohtani 2003 "Insidious BFL" 5.05 [2.35; 7.75] 17 1.1%
Ochi 2017 "Discordant UIP" 5.20 [−6.36; 16.76] 20 0.1%
Kishi 2008 "UIP" 5.86 [2.97; 8.75] 16 1.0%
Overall effect 1.58 [1.06; 2.11] 100.0%
Prediction interval [0.30; 2.87]
Heterogeneity: I^2 = 89% [86%; 92%], p < 0.01
−15 −10 −5 0 5 10 15

Bronchoalveolar Lavage Fluid Lymphocytosis in Chronic Hypersensitivity Pneumonitis: A Systematic Review and Meta-Analysis

Nicola Adderley, Christopher J. Humphreys, Hayley Barnes, Brett Ley, Zahra A. Premji, Kerri A. Johannson

Supplementary Material

Table S1: Search Strategy

Medline: Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to August 01, 2019

#	Searches	Results
1	exp Bronchoalveolar Lavage/	27125
2	((bronchoalveolar or bronchioalveolar) adj2 lavage*).tw,kf.	28781
3	(bronchopulmonary adj2 lavage*).tw,kf.	212
4	(bronchial adj2 lavage*).tw,kf.	1346
5	(lung adj2 (lavage* or washing)).tw,kf.	2938
6	(pulmonary adj2 (lavage* or washing)).tw,kf.	531
7	((bronchoalveolar or bronchioalveolar) adj2 fluid*).tw,kf.	14029
8	1 or 2 or 3 or 4 or 5 or 6 or 7	41761
9	alveolitis, extrinsic allergic/ or bird fancier's lung/ or farmer's lung/ or silo filler's disease/ or trichosporonosis/	4169
10	((allergic or hypersensitiv*) adj1 (alveoliti* or pneumoni*)).tw,kf.	3356
11	(Bird adj (Fancier* or breeder* or raiser*) adj (Lung* or disease*)).tw,kf.	206
12	"Pigeon Breeder* Lung*".tw,kf.	63
13	((Farmer* or fancier* or forber* or peasant*) adj (Lung* or asthma or disease)).tw,kf.	958
14	"Silo Filler* Disease".tw,kf.	45
15	"feather duvet lung*".tw,kf.	6
16	(worker* adj lung*).tw,kf.	143
17	"hot tub lung?".tw,kf.	47
18	(plasterer* adj lung*).tw,kf.	1
19	"Cheese-washer* lung*".tw,kf.	1
20	(Furrier* adj lung*).tw,kf.	2
21	Trichosporonos*.tw,kf.	184
22	suberosis.tw,kf.	31
23	stipatosis.tw,kf.	5
24	espartosis.tw,kf.	4
25	bagassosis.tw,kf.	68
26	(ventilation adj pneumoniti*).tw,kf.	2
27	sequoiosis.tw,kf.	2
28	Respiratory Hypersensitivity/	9416
29	limit 28 to yr="1860 - 1980"	2555
30	(respiratory adj hypersensitivit*).tw,kf.	340
31	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 29 or 30	8189
32	8 and 31	1028

Table S2: Study Characteristics

Author (country, year of publication)	Study design	CHP patients	Mean age of CHP patients (SD)	CHP male/female	Mean CHP BAL lymphocyte % (SD)	Mean CD4:CD8 (SD)	FVC (mean, SD)	Comparator populations (n)
Studies included in meta-analysis (n=42)								
Barrera et al.[1] (Mexico, 2008)	P	30	50.3 (8.1)	2/28	56.7 (17.3)	4.4 (4.1)	59.6 (17.9)	-
**Bellanger et al.[2] (France, 2016)	P	16	58.7 (13.5)	11/5	46 (29)	-	-	IPF (11) Sarcoidosis (12)
**Bencic et al.[3] (Yugoslavia, 1990)	P	8	-	3/5	14.1 (10.9)	0.4 (0.4)	-	Sarcoidosis (29)
Caillaud et al.[4] (France, 2012)	P	41	-	-	42.6 (21.6)	-	-	-
**Dai et al.[5] (Germany, 2005)	P	12	55 (2 SEM)	4/8	66.8 (4.1 SEM)	3.3 (1.4 SEM)	66 (7 SEM)	Sarcoidosis (10)
**Delacroix et al.[6] (Belgium, 1985)	P	4	64	2/2	41	-	-	IPF (1) Sarcoidosis (17) CTD-ILD (1)
Garcia de Alba et al.[7] (Mexico, 2015)	P	20	54 (16)	2/18	57 (17)	-	62 (17)	-
Gaxiola et al.[8] (Mexico, 2011)	P	Typical pattern: 58 NSIP:22 UIP: 10	-	-	Typical pattern: 64.6 (20.9) NSIP: 52.1 (22.7) UIP: 36.1 (22.9)	-	54.5 (17)	-
#Groot Kormelink et al.[9] (Netherlands, 2011)	P	22	52 (12)	4/18	50 (19)	-	61 (16)	IPF (21)
Haslam et al.[10] (United Kingdom, 1987)	P	15	45.4 (13.1)	8/7	54.5 (24.8)	-	74.1 (17.1)	-
Inase et al.[11] (Japan, 2006)	R	3	71.3 (3.8)	2/1	30 (10)	9.4 (7.6)	81.3 (24.8)	-
Inase et al.[12] (Japan, 2007)	R	8	-	-	48.9 (30.6)	4.4 (3.1)	-	-
Kishi et al.[13] (Japan, 2008)	R	UIP: 16 fNSIP: 10 cNSIP/OP: 6	UIP: 62.4 (7.3) fNSIP: 58.6 (9.8)	23/17	UIP: 21.7 (16.4) fNSIP: 40.8 (20.8)	UIP: 5.9 (5.9) fNSIP: 2.7 (3.1) cNSIP/OP: 2.8	UIP: 77.5 (25.6) fNSIP: 75.9 (18)	-

			cNSIP/OP: 57.1 (10.7)		cNSIP/OP: 67.2 (30.5)	(4.6)	cNSIP/OP: 91.1 (27.8)	
Koschel et al.[14] (Germany, 2010)	R	6	59.5 (10.3)	0/6	53.8 (21.1)	1 (1.3)	74.5 (13.9)	-
#Lacasse et al.[15] (Canada, 2003)	P	55	55 (11.5)	8/47	51 (21.6)	-	61 (21.2)	IPF (172) Sarcoidosis (51) CTD-ILD (35) IIP (60)
**Leatherman et al.[16] (USA, 1984)	P	6	-	-	65 (4 SEM)	0.8 (0.2)	72 (8 SE)	Sarcoidosis (6)
**Markart et al.[17] (Germany, 2009)	P	7	54.9 (6.3 SEM)	4/3	29.7 (8 SEM)	-	68.5 (7.9 SEM)	IPF (16) Sarcoidosis (12)
Milanowski et al.[18] (Poland, 1998)	P	8	-	-	46.2 (13.4)	-	-	-
Murayama et al.[19] (Japan, 1993)	P	9	61.1 (12.3)	-	20 (17.9)	2.6 (2.6)	78.1 (22.4)	-
#Nukui et al.[20] (Japan, 2019)	P	32	-	-	20.4 (20.9)	4.7 (4.2)	76.7 (15.7)	IPF (8)
#Nunes et al.[21] (France, 2015)	R	14	-	-	20.6 (19.7)	-	59 (14.3)	CTD-ILD (50) IIP (42)
Ochi et al.[22] (Japan, 2017)	R	Cellular NSIP: 7 Fibrotic NSIP: 16 Discordant NSIP: 20 Concordant NSIP: 9	Cellular NSIP: 55.4 (3.7 SE) Fibrotic NSIP: 61.3 (2.9 SE) Discordant NSIP: 56.6 (3.4 SE) Concordant NSIP: 60.7 (3.6 SE)	29/23	Cellular NSIP: 69.7 (11 SE) Fibrotic NSIP: 32.9 (6.5 SE) Discordant NSIP: 24.7 (5.4 SE) Concordant NSIP: 20.1 (5.8 SE)	Cellular NSIP: 3.3 (4.4 SE) Fibrotic NSIP: 2.6 (2.5 SE) Discordant NSIP: 5.2 (5.9 SE) Concordant NSIP: 4.4 (3 SE)	Cellular NSIP: 80.2 (7.6 SE) Fibrotic NSIP: 77.1 (4.2 SE) Discordant NSIP: 69.3 (4.7 SE) Concordant NSIP: 63.9 (7.6 SE)	-
&Ohshimo et al.[23] (Germany, 2009)	R	3	74 (8.9)	3/0	67 (3.6)	-	-	IPF (68) IIP (3)
Ohtani et al.[24] (Japan, 2003)	R	32 Recurrent: 15 Insiduous: 17	Recurrent: 57.1 (2.4 SEM) Insiduous: 64.3 (1.9 SEM)	18/14	Recurrent: 69.5 (4.2 SEM) Insiduous: 23.2 (4.4 SEM)	Recurrent: 0.9 (0.2 SEM) - Insiduous: 5.1 (1.	Recurrent: 73.5 (6.3 SEM) - Insidu	-

						4 SEM)	ous: 74.8 (5.3 SEM)	
Pardo et al.[25] (Mexico, 2000)	P	15	37 (9)	3/12	78.9 (17.2)	-	65 (14)	-
**Pesci et al.[26] (Italy, 1993)	P	15	45.8 (8.2 SE)	10/5	56.4 (4.8)	-	84.7 (59-117 RANGE)	IPF (9) Sarcoidosis (16) IIP (6) Other (3)
Remy-Jardin et al.[27] (France, 1993)	P	11	-	-	38 (5 SEM)	-	77 (4.3 SEM)	-
**Reynolds et al.[28] (USA, 1977)	P	7	54 (8.6)	3/4	62	-	82.1 (6.4 SEM)	IPF (19)
#Salisbury et al.[29] (USA, 2018)	R	16	-	-	19 (16)	-	61.6 (18.2)	IPF (10) Sarcoidosis (7) IIP (15) Other (4)
**Schmidt et al.[30] (Germany, 2002)	P	5	53.5 (5.6 SE)	1/4	34.4 (5.3 SEM)	0.5 (0.2 SE)	62 (4.7 SE)	IPF (12) Sarcoidosis (12)
Selman et al.[31] (Mexico, 1991)	P	Healed: 7 Improved: 10 Worsened: 8	37.4 (10.6)	7/18	Healed: 37.2 (19) Improved: 43.7 (22.8) Worsened: 26.5 (10.6)	-	59.3 (16.7)	-
**Sterclova et al.[32] (Czech Republic, 2009)	P	16		3/13	24.6 (6.6 SEM)	2.1 (0.6 SEM)	72.2 (4.7 SEM)	- IPF (8)
**Sterclova et al.[33] (Czech Republic, 2013)	P	14	59 (11)	7/7	19.5 (21.9)	-	79.8 (17.8)	Sarcoidosis (6)
Sterclova et al.[34] (Czech Republic,	R	7	67 (13.3)	2/5	23.1 (17.5)	1.4 (1.2)	-	

2006)								
Sumi et al.[35] (Japan, 2003)	P	2	-	2/0	53 (35.4)	0.23 (0.1)	66.7 (15.4)	-
Tsushima et al.[36] (Japan, 2006)	P	22	57.1	1/21	70.5 (17.5)	0.7 (0.3)	87.1 (20)	-
#Tzilas et al.[37] (Greece, 2019)	R	35	69.7 (9.3)	25/10	24.1 (15.4)		78.1 (18.9)	IPF (19)
#Unoura et al.[38] (Japan, 2011)	P	9	*69 (58-79)	7/2	*14.9 (0-81)	-		Sarcoidosis (10) CTD-ILD (17)
Voisin et al.[39] (France, 1981)	P	3	-	-	39.7 (5.5)	-	80.7 (21.2)	-
Vourlekis et al.[40] (USA, 2002)	R	3	-	0/4	24.7 (13)	1.4 (0.1)	-	- -
Wang et al.[41] (China, 2009)	R	7	-	-	36.6 (21)	-	-	-
						-		
Ye et al.[42] (Germany, 2009)	P	16	62 (3 SE)	12/4	77 (2 SE)	3.2 (0.5 SE)	62 (5 SE)	-
Studies not included in meta-analysis (n=11)								
Adams et al.[43] (USA, 2018)	R	39	-	-	*19 (11-41)	-	-	-
**Chockalingam et al.[44] (India, 2016)	P	16	53.2	13/3	*39 (26-55)	-	-	IPF (8) Sarcoidosis (3) CTD-ILD (9) Other (8)
**Masuo et al.[45] (Japan, 2016)	R	44	-	-	*13.3	*3	62.7	-
Miyazaki et al.[46] (Japan, 2013)	R	AE: 11 NAE: 37	-	-	AE: *20.5 (5-62.2) NAE: *26 (2-86)	AE: *2.2 (0.5-19.5) NAE: *2.1 (0.2-15.8)	AE: *68.6 (38.7-114) NAE: *80.7 (37.6-130.9)	-
Okamoto et al.[47] (Japan, 2013)	P	222	*64 (57-70.5)	120/102	*24.5 (9.8-64.8)	*2 (1-3.8)	*76.7 (59.8-87.7)	-
Okamoto et al.[48] (Japan, 2013)	R	Familial: 20 Non-Familial: 94	Familial: *57.5 Non-Familial: *64	77/37	Familial: *9.7 Non-Familial: *14.6	Familial: *1.8 Non-Familial: *2.4	-	-
Ojanguren et al.[49] (Spain, 2019)	P	133	-	-	*16	-	68.5 (16)	-

**Suhara et al.[50] (Japan, 2015)	R	35	*64	23/12	*19.6	*2.6	*80	Other chronic IP (42)
Vergnon et al.[51] (France, 1983)	P	8	51.6	6/2	24	-	-	-
[**]Willems et al.[52] (Belgium, 2013)	P	11	*57	6/5	*28		*73	IPF (11)
Yoshizawa et al.[53] (Japan, 1999)	P	24	-	-	46.3	1.7	67.4	-

- *median (range)
- [#]study from which IPD was obtained; [**]study from which IPD could not be obtained; [&]study from which IPD was obtained from figures, but full data set could not be obtained
- P, prospective; R, retrospective; SD, standard deviation; SE, standard error; SEM, standard error of the mean; BAL, bronchoalveolar lavage; CD4:CD8, ratio of CD4 to CD8 cells in BAL fluid ; IPF, idiopathic pulmonary fibrosis; IIP, interstitial idiopathic pneumonias (non-specific interstitial pneumonia, lymphoid interstitial pneumonia, cryptogenic organizing pneumonia, respiratory bronchiolitis ILD, desquamative interstitial pneumonia, pleuroparenchymal fibroelastosis, acute fibrinous and organizing pneumonia, acute interstitial pneumonia; other (silicosis, pulmonary langerhans cell histiocytosis, amyloidosis, eosinophilic pneumonia, vasculitidites; AE, acute exacerbation; NAE, non-acute exacerbation; CTD-ILD, connective tissue disease ILD.

Table S3: Definitions of Chronic Hypersensitivity Pneumonitis

Author	Antigen status	CHP antigens (n)	HP criteria	CHP Definition
Adams et al.[43] 2018	Mixed	Bird (55) Feather (44)		Fibrosis on HRCT
Barrera et al.[1] 2008	-	-	Lung histology compatible with HP and fulfilment of the following: (1) pigeon's exposure preceding disease, and positive serum antibodies against avian antigens; shortness of breath with partial improvement upon avoidance of the avian antigen exposure; (3) clinical, radiological, and functional features of an ILD; (4) >40% of lymphocytes in BAL	>24 months of symptoms before diagnosis; HRCT showing nodules, ground glass, irregular linear opacities, lobar volume loss, +/- cystic lesions; biopsy (22 patients) with >20% fibrotic infiltrate
Bellanger et al.[2] 2016	Identified	Bird (1) Domestic exposure (6) Hay (9)		Clinical course, insidious onset, history of antigen exposure, radiological evidence of fibrosis on HRCT
Bencic et al.[3] 1990	-	-	-	Radiography, functional parameter assessment, transbronchial biopsy, total T-lymphocyte count in BAL, and T-lymphocyte subpopulation count in monoclonal antibodies
Caillaud et al.[4] 2012	Mixed	-	Fulfilment of all main criteria and $\geq$2 additional criteria: Main criteria: (1) exposure to antigen evidenced by history, microbiological investigations of the environment OR positive precipitin antibodies; (2) symptoms compatible with HP; (3) chest radiographs showing infiltration suggestive of HP which was confirmed by HRCT Additional criteria: (1) basal crepitants audible on auscultation of lungs; (2) decreased TLco; (3) arterial oxygen saturation decreased at rest or during exercise; (4) restrictive ventilatory defect in spirometry; (5) histological changes compatible with HP in a biopsy specimen from the lung; (6) positive respiratory provocation test).	Insidious onset over a period of months, with increasing cough and exertional dyspnea
Chockalingam et al.[44] 2016	Unidentified	-	-	Fibrosis on HRCT

Dai et al.[5] 2005	Identified	Bird (11) Hay (1)	History of exposure to organic antigens, clinical signs and symptoms consistent with HP, radiological features and/or functional abnormalities characteristic of ILD, BAL with lymphocytes >40%	No definition given. HP described as "chronic" by authors.
Delacroix et al.[6] 1985	Identified	Bird (2) Hay (2)		Septal fibrosis with cellular infiltration, typical clinical history of chronic intermittent respiratory and systemic symptoms related to the home environment or work environment
Garcia de Alba et al.[7] 2015	Identified	Bird (20)		≥4 criteria in addition to lung histology: (1) history of exposure to birds and the presence of antibodies to avian antigen measured by ELISA; (2) compatible clinical history with more than 6 months of symptoms; (3) HRCT showing bronchiolocentric centrilobular nodules, ground-glass opacity, and reticular images indicative of fibrosis in at least 20% of the lungs; (4) BAL with ≥ 40% lymphocytes (5) lung biopsy with morphologic features of HP
Gaxiola et al.[8] 2011	Identified	Bird (110)		Chronic bird-fancier's lung: (1) relevant exposure to birds preceding respiratory symptoms; (2) strong positive specific antibodies against avian antigens measured by ELISA; (3) clinical and functional features of ILD; (4) HRCT showing either ground glass attenuation with areas of lobular air trapping and/or poorly defined centrilobular nodules; (5) presence of some poorly formed granuloma or multinucleated giant cells in lung tissue obtained through surgical lung biopsy
Groot Kormelink et al.[9] 2011	Identified	Bird (22)		Chronic bird-fancier's lung: (1) history of pigeon exposure and positive serum antibodies against avian antigens; (2) clinical, radiological, and functional features of an ILD with ≥ 6 months of symptoms; (3) >30% lymphocytes in BAL fluid; (4) lung histology compatible with HP
Haslam et al.[10] 1987	Identified	Bird (10) Hay (3) Fungi/mould (2)	All had histories of exposure to organic dusts and exposure-related respiratory symptoms. In addition to the tabulated details, specific precipitating antibodies to antigens of the dusts were present or had previously been detected in the serum of all patients.	No definition given. Patients had "chronic changes."
Inase et al.[11] 2006	Identified	Bird (7)	History of contact with a feather duvet, antibodies against avian antigens or lymphocyte proliferation induced by avian antigens, reproduction of HP-related symptoms by an environmental or inhalation provocation test	Evidence of pulmonary fibrosis on pathologic examination OR honeycombing on HRCT; progressive deterioration of a restrictive impairment of pulmonary function throughout 1 year OR ≥ 6 months of HP-related symptoms
Inase et al.[12]	Identified	Trichospor		Chronic summer-type HP: (1) living in the home with a hot and humid environment during the

2007		on sp. (14)		summer season; (2) clinical improvement after withdrawal from the suspected environment and/or a positive environmental challenge test; (3) antibodies against Trichosporon sp and/or lymphocyte proliferation induced by Trichosporon sp related antigen; (4) evidence of pulmonary fibrosis on a pathological examination or on HRCT; (5) more than 6 months' duration of HP-related symptoms
Kishi et al.[13] 2008	Identified	Bird (40)		Chronic bird-fancier's lung: (1) history of avian contact; (2) antibodies and/or lymphocyte proliferation to avian antigen; (3) reproduction of symptoms of HP by environmental provocation or laboratory-controlled inhalation of avian antigen; (4) evidence of pulmonary fibrosis with or without granulomas on histological analysis OR (5) honeycombing on HRCT; (6) progressive deterioration of a restrictive impairment on pulmonary function for 1 year OR (7) respiratory symptoms related to HP for more than 6 months
Koschel et al.[14] 2010	Identified	Bird (13)	≥6 criteria needed to define bird-fancier's lung: (1) a definite history of using feather duvets and/or pillows; (2) recurrent episodes of symptoms compatible with HP; (3) elevated/positive specific IgG antigens to goose or duck feathers; (4) inspiratory crackles on physical examination; (5) findings compatible with HP on chest radiograph or HRCT scan; (6) decreased diffusing capacity and/or arterial hypoxemia, either at rest or during exercise; (7) lymphocytic alveolitis in BAL fluid; (8) pulmonary histological changes compatible with HP; (9) positive inhalation challenge; (10) positive avoidance test	Fibrosis on HRCT
Lacasse et al.[15] 2003	Identified	Bird (48) Hay (3) Summer-type (1) Fungi/mold (1) Humidifier lung (2)	BAL lymphocytosis (≥30% for non and ex-smokers and ≥20% for current smokers) and bilateral ground glass or poorly defined centrilobular nodular opacities on HRCT. If the investigators were not confident in a final diagnosis of HP or non-HP with this this data, the investigators performed additional investigations at their own discretion (BAL fluid cytology or culture, transbronchial or endobronchial biopsy, or mediastinoscopy). Patients underwent surgical lung biopsy when the HRCT, the BAL, and other diagnostic procedures failed to yield a diagnosis.	Fibrosis on HRCT (personal communication)

Leatherman et al.[16] 1984	Identified	Bird (2) Hay (4)		All patients had gradually progressive dyspnea on slight to moderate exertion and ongoing exposure to etiologic antigens
Markart et al.[17] 2009	-		Evidence of exposure to appropriate antigen by history, investigation of the environment, serum precipitin test, and/or BAL fluid antibody, BAL fluid lymphocytosis , and positive "natural challenge" or by controlled inhalational challenge	Permanent impairment of lung function and presence of fibrosis on HRCT scans, traction bronchiectasis, and/or honeycombing
Masuo et al.[45] 2016	Mixed	Bird (60)	History of avian antigen exposure, findings on high-resolution computed tomography, lung biopsy findings, or results of immunological examinations with the lymphocyte proliferation test or specific antibodies to avian antigens	Positive inhalation-provocation test
Milanowski et al.[18] 1998	Identified	Hay (14)	History and antigen provocation	Chronicity stated in patients based on their clinical picture, BAL analysis, and allergological tests.
Miyazaki et al.[46] 2013	Identified	Bird (56)		Chronic bird-fancier's lung: (1) history of avian contact; (2) antibodies and/or lymphocyte proliferation against avian antigens; (3) reproduction of symptoms of HP by an environmental provocation or a laboratory-controlled inhalation of an avian antigens; (4) progressive deterioration of a restrictive impairment on pulmonary function for at least 1 year; (5) respiratory symptoms related to HP for at least 6 months; (6) evidence of pulmonary fibrosis with or without granulomas on histopathological analysis OR (7) honeycombing on HRCT
Murayama et al.[19] 1993	Mixed	Bird (5) Summer-type HP (5) Isocyanate (1) Unknown (6)	Diagnosis of HP was based on history, clinical evaluation, and radiologic patterns, including provocation tests or home challenge tests	Fibrosis on transbronchial lung biopsy and HRCT
Nukui et al.[20] 2019	Identified	Bird (63)		≥3 or more of the following (including 5, either 2 or 3, and either 1 or 6): (1) Reproduction of symptoms of HP by an environmental provocation or laboratory-controlled inhalation of the causative antigen; (2) evidence of pulmonary fibrosis with or without granulomas; (3) honeycombing on computed tomography scans; (4) progressive deterioration of a restrictive impairment on pulmonary function over 1 year; (5) over 6 months duration of respiratory symptoms related to HP; or (6) antibodies and/or lymphocyte proliferation to the presumptive

				antigen.
Nunes et al.[21] 2015	Identified	Bird (12) Hay (1) Textile/organic dust (1) Fungi/mould(1)		History of exposure to an inhaled antigen known to cause CHP and either confirmatory serum precipitins or a lymphocytic BAL
Ochi et al.[22] 2017	Identified	Bird (52)		≥3 or more of the following (including 5, either 2 or 3, and either 1 or 6): (1) reproduction of symptoms of HP by an environmental provocation or laboratory-controlled inhalation of the causative antigen; (2) evidence of pulmonary fibrosis with or without granulomas; (3) honeycombing on computed tomography scans; (4) progressive deterioration of a restrictive impairment on pulmonary function over 1 year; (5) over 6 months duration of respiratory symptoms related to HP; or (6) antibodies and/or lymphocyte proliferation to the presumptive antigen.
Ohshimo et al.[23] 2009	Identified	Bird (1) Humidifier lung (1) Hay (1)	The diagnosis of patients initially diagnosed with IPF was refined by histories of exposure to relevant environmental antigens, positive serum precipitins, and a favourable clinical course after avoidance of antigens and the administration of corticosteroids.	*Fibrosis on HRCT
Ohtani et al.[24] 2003	Identified	Bird (32)		Chronic bird fancier's lung: (1) history of avian contact; (2) antibodies and/or lymphocyte proliferation to avian antigen; (3) reproduction of symptoms of HP by an environmental provocation or laboratory-controlled inhalation of avian antigen; (4) evidence of pulmonary fibrosis with or without granulomas on histopathologic analysis OR (5) honeycombing on HRCT; (7) progressive deterioration of a restrictive impairment on pulmonary function throughout 1 year OR (8) more than 6 months' duration of respiratory symptoms related to HP
Ojanguren et al.[49] 2019	Mixed	Bird (72) Fungi (12) Others (11) Unknown (34)		≥4 major criteria (symptoms compatible with HP, evidence of exposure to antigen by history or detection in serum and/or BAL fluid antibody, findings compatible with HP on chest radiograph or HRCT, BAL fluid lymphocytosis, pulmonary histologic changes compatible with HP, positive "natural challenge") and ≥2 minor criteria (bibasilar rales, decreased DLCO, arterial hypoxemia).

Okamoto et al.[47] 2013	Mixed	Bird (134) Summer-type HP (33) Home-related HP (25) Isocyanate (3) Farmer's (4) Other (4) Unknown (19)		Clinical improvement after withdrawal from the suspected environment and/or reproduction of symptoms by an environmental provocation nor laboratory-controlled inhalation of a causative antigen and/or antibodies or lymphocyte proliferation to the presumptive antigen, evidence of pulmonary fibrosis on a pathological examination or on HRCT, and respiratory symptoms related to HP for 6 months or longer
Okamoto et al.[48] 2013	Identified	Bird (114)	≥3 of: (1) recurrence of HP symptoms triggered by an environmental stimulus or laboratory-controlled inhalation of the antigen; (2) antibodies and/or lymphocyte proliferation to the antigen; (3) evidence of pulmonary fibrosis with or without granulomas; (4) honeycombing evident on CT scans; (5) progressive deterioration of a restrictive impairment in pulmonary function over the course of 1 year; (6) persistence of respiratory symptoms associated with HP for more than 6 months	*Fibrosis on HRCT
Pardo et al.[25] 2000	Identified	Bird (15)	Pigeon-breeder's disease: (1) pigeon's exposure preceding disease, and positive serum antibodies against avian antigens; (2) shortness of breath with partial improvement upon avoidance of the avian antigen exposure; (3) clinical, radiological, and functional features of an ILD; (4) >40% of lymphocytes in BAL fluid; (5) lung histology compatible with HP	*Fibrosis on lung biopsy
Pesci et al.[26] 1993	Identified	Hay (15)	Farmer's lung disease: (1) history of exposure to mouldy hay; (2) clinical and radiological features and/or functional pattern of interstitial lung disease; (3) evidence of antibodies against Micropolyspora faeni	Fibrosis on lung biopsy
Remy-Jardin et al.[27] 1993	Identified	Bird (24)	Confirmation of HP was obtained with a combination of a typical clinical history, physical examination findings, and positive results of a serum precipitin test	*Fibrosis on HRCT

Reynolds et al.[28] 1977	Mixed		No explicit criteria for HP. The authors describe 7 patients initially diagnosed with IPF, "but the episodic nature of the respiratory symptoms, serological studies, or histopathology of the lung biopsy suggested that they had a form of hypersensitivity pneumonitis"	No definition given. HP described as "chronic" by authors.
Salisbury et al.[29] 2018	Mixed	Bird (17) Textile/organic dust (1) Other (20)	Supporting evidence sufficient for HP diagnosis verification including classic findings on surgical lung biopsy, or at least two of: (1) BAL lymphocytosis >20%; (2) consistent findings on transbronchial or surgical lung biopsy (any of loose non-necrotizing granulomas, giant cells, mononuclear inflammatory interstitial or peribronchiolar infiltrate); (3) a plausible exposure history	Fibrosis on lung biopsy
Schmidt et al.[30] 2002	Identified	Bird (4) Hay (1)	Proof of hypersensitivity response to an inhaled antigen, precipitating antibodies against offending antigen, patchy interstitial infiltrations in CXR or HRCT, elevated BALF counts with decreased CD4-to-CD8 ratio	No definition given. Patients included in study described as having "chronic ILDs."
Selman et al.[31] 1991	Identified	Bird (25)	Bird fancier's lung: (1) a close exposure to pigeons with a relationship between avian antigen exposure and disease onset; (2) progressive dyspnea, bilateral roentgenographic shadowing without hilar adenopathy, predominantly restrictive functional impairment and hypozxmia at rest which usually worsened with exercise; (3) specific serum and BAL precipitating antibodies to avian antigens determined by enzyme-linked immunosorbent assay and morphologic findings consistent with the diagnosis of HP	No definition given. HP described as "chronic" by authors.
Sterclova et al.[34] 2006	Identified	Bird (2) Hay (2) Textile/organic dust (2) Metallic (1)	No criteria listed. Patients underwent BAL with cytological and cytometric examination of BAL fluid, HRCT of the chest, serum concentrations of IgG, and exposure to a known offending antigen at the time of diagnosis.	HRCT interstitial score used to define disease chronicity
Sterclova et al.[32] 2009	-			History of exposure to suspect antigen, symptoms, physical findings, radiographic abnormalities, pulmonary function, immunological tests, and BAL results. Lung biopsy required when the diagnosis was not

				definite (2 patients)
Sterclova et al.[33] 2013	Not described			+/- history of exposure to inhalation antigen; crackles; decreased DLCO; +/- BAL fluid lymphocytosis; BAL fluid CD4/CD8 (increased, decreased, or normal); HRCT showing centrilobular nodules, GGO, mosaic perfusion, condensations, interstitial septa thickening, honeycombing; histology showing granuloma, organizing pneumonia, usual interstitial pneumonia, non-specific interstitial pneumonia, desquamative interstitial pneumonia
Suhara et al.[50] 2015	Identified	Bird (35)		$\geq$ 3 or more of the following (including 5, either 2 or 3, and either 1 or 6): (1) reproduction of symptoms of HP by an environmental provocation or laboratory-controlled inhalation of the causative antigen; (2) evidence of pulmonary fibrosis with or without granulomas; (3) honeycombing on computed tomography scans; (4) progressive deterioration of a restrictive impairment on pulmonary function over 1 year; (5) over 6 months duration of respiratory symptoms related to HP; or (6) antibodies and/or lymphocyte proliferation to the presumptive antigen. Chronic cases underwent surgical lung biopsy and tested positive on the inhalation challenge test for diagnostic confirmation.
Sumi et al.[35] 2003	Identified	Di-isocyanate (3)	Di-isocyanate-induced HP: reproduction of acute symptoms after environmental exposure in the workplace, consistent levels of IgG antibody to diisocyanate-human serum antibody (HSA) and BAL fluid, IgA antibodies only in BAL fluid, BAL lymphocytosis with a low ratio of CD4 to CD8, proliferation of peripheral blood to antigen, BAL lymphocyte responsiveness to diisocyanate-HSA and histological findings compatible with HP	Fibrosis on transbronchial lung biopsy
Tsushima et al.[36] 2006	Identified	Fungi/mould (22)	Clinical features, laboratory findings, histological examination of tissues obtained by transbronchial lung biopsy, lymphocyte stimulation test and precipitating antibody due to Bunashimeji spores, characteristic findings on HRCT, and typical BAL findings	*Fibrosis on HRCT
Tzilas et al.[37] 2019				Presence of an inciting antigen, compatible HRCT imaging, BALF lymphocytosis and new information during dynamic follow up of the patients (identification of a previously

				unrecognized inciting antigen)
Unoura et al.[38] 2011	Identified	Home-related (9)		≥ 3 of the following (including 5, either 2 or 3, and either 1 or 6): (1) reproduction of symptoms of HP by an environmental provocation or laboratory-controlled inhalation of the causative antigen; (2) evidence of pulmonary fibrosis with or without granulomas; (3) honeycombing on computed tomography scans; (4) progressive deterioration of a restrictive impairment on pulmonary function over 1 year; (5) over 6 months duration of respiratory symptoms related to HP; or (6) antibodies and/or lymphocyte proliferation to the presumptive antigen
Vergnon et al.[51] 1983	Identified	Bird (3) Isocyanate (1) Other (4)		No definition given. HP described as "chronic" by authors.
Voisin et al.[39] 1981	Identified	Bird (3)	Clinical, radiological, and biological features of bird-fancier's lung	No definition given. HP described as "chronic" by authors.
Vourlekis et al.[40] 2002		Bird (3) Fungi/mould (1)	Clinical evidence of ILD and characteristic chest radiography, exposure to antigen known to cause HP and either confirmatory serum precipitins or a lymphocytic BAL	Fibrosis on biopsy
Wang et al.[41] 2009	Mixed		Criteria 1-5 required for diagnosis without recourse to BAL and lung biopsy. At least one of 6 or 7 required if criteria 1 or 2 not fulfilled: (1) known exposure; (2) recurrent episodes of symptoms after exposure and improvement with contact avoidance; (3) recurrent or chronic respiratory symptoms such as cough and dyspnea; (4) serological tests for antinuclear antibodies, anti-double-stranded DNA antibody, anti-extractable nuclear antigen antibodies, antineutrophil cytoplasmic autoantibodies, and angiotensin-converting enzyme were negative; (5) radiological evidence of diffuse lung diseases; (6) bronchoalveolar lavage fluid revealed lymphocytosis (≥30% for non-smokers and ex-smokers or ≥20% for current smokers; (7) lung biopsy specimen showing bronchiolocentric, chronic interstitial pneumonitis with non-necrotizing granulomas	Respiratory symptoms or evidence of lung disease lasting for more than 4 months

Willems et al.[52] 2013	-			Clinical course and insidious onset over a period of months, history of antigen exposure, radiological, and/or histopathological data. Presence of fibrosis in radiological data.
Ye et al.[42] 2009	Identified	Bird (10) Humidifier lung (1) Fungi/mould (5)	HP diagnosed based on the following criteria: (1) history of exposure to organic antigens; (2) clinical signs and symptoms consistent with HP; (3) radiologic features and/or functional abnormalities characteristic of interstitial lung disease; (4) evidence of serum precipitins against 1 or more organic antigens; (5) BAL fluid with increased lymphocytes	Characterized by insidious loss of exercise tolerance associated with dyspnea, dry cough, and weigh loss. HRCT showed widespread and dominant ground glass densities, with some reticulation and minor or no honeycombing.
Yoshizawa et al.[53] 1999	Identified	Summer-type (10) Home-related (5) Bird (7) Isocyanate (5) Hay (4) Other (5)		≥3 of the following (including 5, either 2 or 3, and either 1 or 6): (1) reproduction of symptoms of HP by an environmental provocation or laboratory-controlled inhalation of the causative antigen; (2) evidence of pulmonary fibrosis with or without granulomas; (3) honeycombing on computed tomography scans; (4) progressive deterioration of a restrictive impairment on pulmonary function over 1 year; (5) over 6 months duration of respiratory symptoms related to HP; or (6) antibodies and/or lymphocyte proliferation to the presumptive antigen

Table S4: Quality Assessment of Included Studies Using the Quadas-2 Tool[54]

	Risk of Bias				Applicability concerns		
Study	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Adams et al.[43] 2018	L	H	H	U	L	L	L
Barrera et al.[1] 2008	U	H	L	L	L	L	L
Bellanger et al.[2] 2016	L	H	L	U	L	L	L
Bencic et al.[3] 1990	U	H	H	L	L	L	H
Caillaud et al.[4] 2012	L	H	U	L	L	L	H
Chockalingam et al.[44] 2016	U	H	H	U	L	L	H
Dai et al.[5] 2005	L	H	H	L	H	L	H
Delacroix et al.[6] 1985	U	H	L	U	L	L	L
Garcia de Alba et al.[7] 2015	U	U	H	L	L	L	L
Gaxiola et al.[8] 2011	U	H	U	L	L	L	L
Groot Kormelink et al.[9] 2011	U	H	H	U	U	L	H
Haslam et al.[10] 1987	U	U	U	U	H	L	H
Inase et al.[11] 2006	U	U	U	U	L	L	L
Inase et al.[12] 2007	U	U	U	U	L	L	L
Kishi et al.[13] 2008	U	U	U	L	L	L	L

Koschel et al.[14] 2010	U	H	H	L	L	L	L
Lacasse et al.[15] 2003	L	H	H	L	L	L	L
Leatherman et al.[16] 1984	U	H	U	U	H	L	H
Markart et al.[17] 2009	L	H	H	L	L	L	L
Masuo et al.[45] 2016	U	H	H	L	U	L	H
Milanowski et al.[18] 1998	U	H	U	U	H	L	H
Miyazaki et al.[46] 2013	L	U	U	U	L	L	L
Murayama et al.[19] 1993	U	H	H	U	L	L	L
Nukui et al.[20] 2019	L	H	L	L	L	L	L
Nunes et al.[21] 2015	L	H	H	L	U	L	H
Ochi et al.[22] 2017	L	U	U	L	L	L	L
Ojanguren et al.[49] 2019	L	H	H	U	U	L	H
Ohshimo et al.[23] 2009	L	H	L	L	L	L	L
Ohtani et al.[24] 2003	L	U	L	L	L	L	L
Okamoto et al.[47] 2013	U	H	U	L	L	L	L
Okamoto et al.[48] 2013	L	U	U	U	L	L	L
Pardo et al.[25] 2000	U	H	H	L	L	L	L
Pesci et al.[26] 1993	U	U	U	L	L	L	L

Remy-Jardin et al.[27] 1993	L	U	U	U	L	L	L
Reynolds et al.[28] 1977	U	U	U	U	U	L	H
Salisbury et al.[29] 2018	L	H	H	L	L	L	L
Schmidt et al.[30] 2002	U	U	U	U	U	L	U
Selman et al.[31] 1991	U	L	U	L	H	L	H
Sterclova et al.[34] 2006	L	H	L	L	L	L	L
Sterclova et al.[32] 2009	U	H	H	U	L	L	U
Sterclova et al.[33] 2013	U	H	H	L	L	L	L
Suhara et al.[50] 2015	L	U	U	U	L	L	L
Sumi et al.[35] 2003	U	H	H	L	L	L	L
Tsushima et al.[36] 2006	L	H	H	L	L	L	L
Tzilas et al.[37] 2019	L	H	H	L	L	L	L
Unoura et al.[38] 2011	L	U	U	L	L	L	L
Vergnon et al.[51] 1983	U	U	H	L	H	L	H
Voisin et al.[39] 1981	U	H	U	U	H	L	H
Vourlekis et al.[40] 2002	L	H	H	L	L	L	L
Wang et al.[41] 2009	L	H	H	L	H	L	H
Willems et al.[52] 2013	L	H	H	L	L	L	L

Ye et al.[42] 2009	L	H	H	L	L	L	L
Yoshizawa et al.[53] 1999	U	L	L	L	L	L	L

Abbreviations: H=high; L=low; U=unclear.

Table S5: Characteristics of Studies Providing or Not Providing Individual Patient Data

	Provided IPD, mean (SD)	**No IPD, mean (SD)**
Number of studies	8	15
Number of patients	232	373
Year range	2003-2019	1977-2019
Age (years)	60.2 (12.4)	58.2 (78.3)[1]
Male Sex (%)	95 (41%)	134 (36%)
Smoking (current/ex/never/NR)	7/85/70/55	19/70/168/40
BAL lymphocyte %	35.4 (24.2)	40.4 (66.3)[2]
FVC (% pred) (SD)	66.6 (19.8)	70.9 (109)[3]

IPD=individual patient data; NR = not reported; BAL=bronchoalveolar lavage, FVC=forced vital capacity

1. Based on 10 studies that provided mean age
2. Based on 10 studies that provided mean lymphocyte %
3. Based on 10 studies that provided mean FVC % predicted

Figure S1: Funnel Plot Assessment of Studies on Bronchoalveolar Lavage Lymphocyte % in Chronic Hypersensitivity Pneumonitis

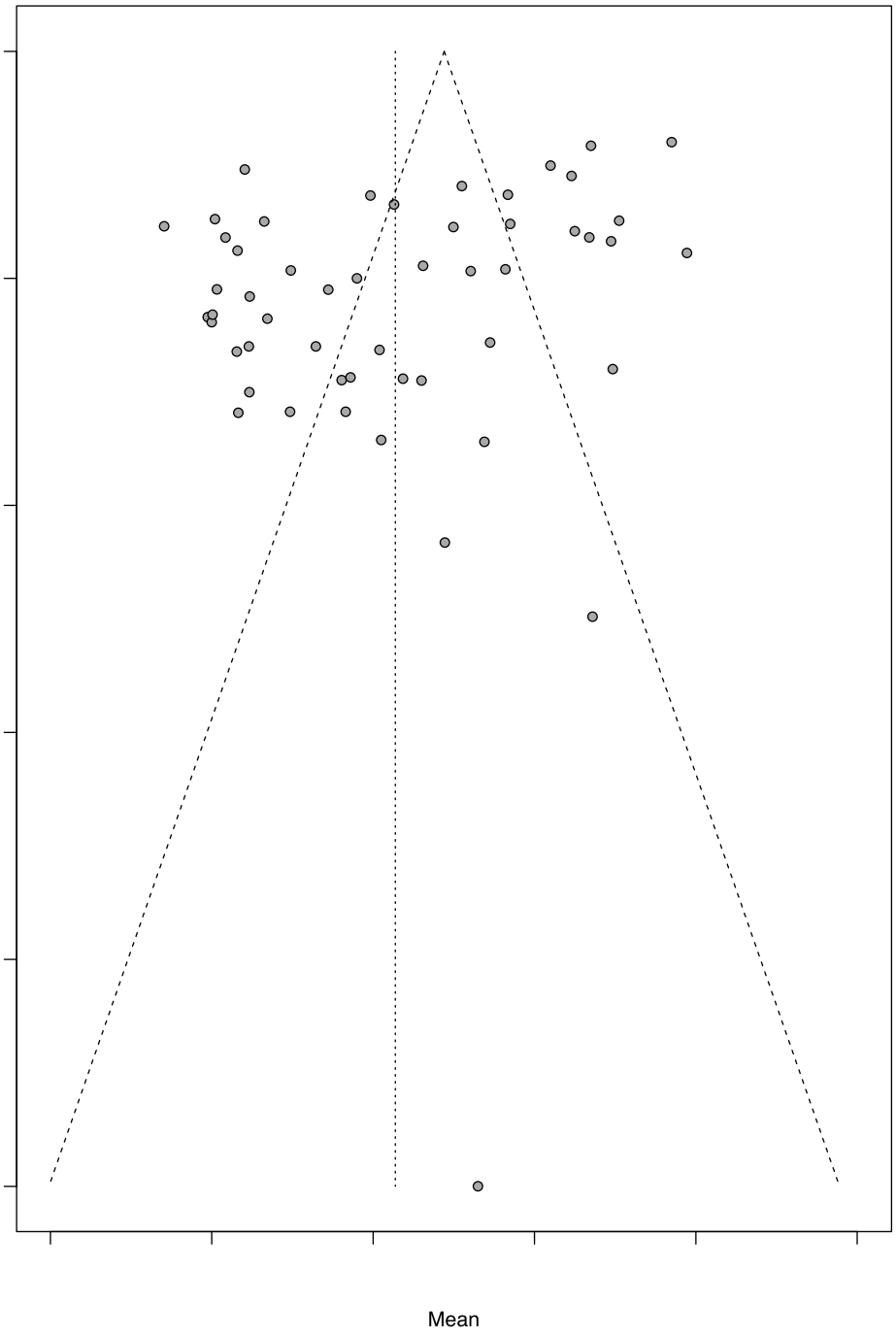
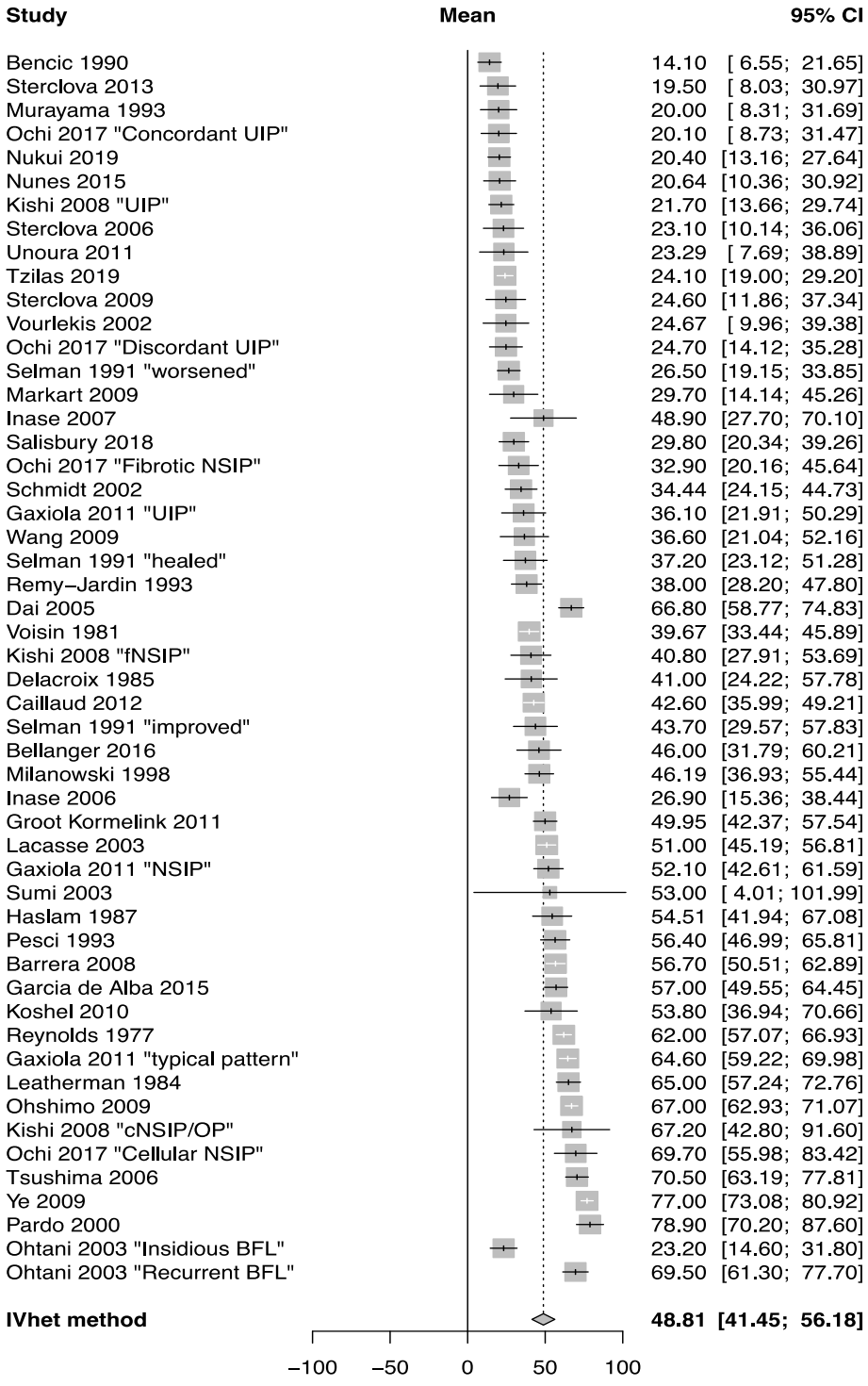


Figure S2: Forest plot of Bronchoalveolar Lavage Lymphocyte % in Chronic Hypersensitivity Pneumonitis, using inverse variance heterogeneity model



References

1. Barrera LM, Felipe; Zuniga, Joaquin; Estrada, Andrea; Zamora, Ana C.; Melendro, Emma I.; Ramirez, Remedios; Pardo, Annie; Selman, Moises. Functional diversity of T-cell subpopulations in subacute and chronic hypersensitivity pneumonitis. *American journal of respiratory and critical care medicine* 2008;177(1):44-55.
2. Bellanger A-PG-H, Houssein; Gondoin, Anne; Pallandre, Jean-Rene; Vacheyrou, Mallory; Valot, Benoit; Soumagne, Thibaud; Reboux, Gabriel; Dalphin, Jean-Charles; Millon, Laurence. Positive fungal quantitative PCR and Th17 cytokine detection in bronchoalveolar lavage fluids: Complementary biomarkers of hypersensitivity pneumonitis? *Journal of immunological methods* 2016;434:61-5. doi: https://dx.doi.org/10.1016/j.jim.2016.04.008
3. Bencic DB, D.; Cucevic, I.; Boranic, M.; Miculinic, N. The role of T-lymphocyte subpopulation in bronchoalveolar lavage in pulmonary parenchyma diseases. *Sarcoidosis* 1990;7(2):106-9.
4. Caillaud DMV, Jean M.; Madroszyk, Anne; Melloni, Boris M.; Murris, Marlene; Dalphin, Jean C.; French Group of Environmental Immunoallergic Bronchopulmonary, Diseases. Bronchoalveolar lavage in hypersensitivity pneumonitis: a series of 139 patients. *Inflammation & allergy drug targets* 2012;11(1):15-9.
5. Dai HG, Josune; Chen, Baomin; Costabel, Ulrich. Production of soluble tumor necrosis factor receptors and tumor necrosis factor-alpha by alveolar macrophages in sarcoidosis and extrinsic allergic alveolitis. *Chest* 2005;127(1):251-6.
6. Delacroix DLM, F. X.; Francis, C.; Sibille, Y. Alpha-2-macroglobulin, monomeric and polymeric immunoglobulin A, and immunoglobulin M in bronchoalveolar lavage. *The American review of respiratory disease* 1985;132(4):829-35.
7. Garcia de Alba CB-R, Ivette; Salgado, Alfonso; Becerril, Carina; Ramirez, Remedios; Gonzalez, Yolanda; Checa, Marco; Navarro, Carmen; Ruiz, Victor; Pardo, Annie; Selman, Moises. Fibrocytes contribute to inflammation and fibrosis in chronic hypersensitivity pneumonitis through paracrine effects. *American journal of respiratory and critical care medicine* 2015;191(4):427-36. doi: https://dx.doi.org/10.1164/rccm.201407-1334OC
8. Gaxiola MB-R, Ivette; Mejia, Mayra; Carrillo, Guillermo; Estrada, Andrea; Navarro, Mary Carmen; Rojas-Serrano, Jorge; Selman, Moises. Morphologic diversity of chronic pigeon breeder's disease: clinical features and survival. *Respiratory medicine* 2011;105(4):608-14. doi: https://dx.doi.org/10.1016/j.rmed.2010.11.026
9. Groot Kormelink TP, Annie; Knipping, Karen; Buendia-Roldan, Ivette; Garcia-de-Alba, Carolina; Blokhuis, Bart R.; Selman, Moises; Redegeld, Frank A. Immunoglobulin free light chains are increased in hypersensitivity pneumonitis and idiopathic pulmonary fibrosis. *PloS one* 2011;6(9):e25392. doi: https://dx.doi.org/10.1371/journal.pone.0025392
10. Haslam PLD, A.; Butchers, P.; Primett, Z. S.; Newman-Taylor, A.; Turner-Warwick, M. Mast cells, atypical lymphocytes, and neutrophils in bronchoalveolar lavage in extrinsic allergic alveolitis. Comparison with other interstitial lung diseases. *The American review of respiratory disease* 1987;135(1):35-47.
11. Inase N, Ohtani Y, Sumi Y, et al. A clinical study of hypersensitivity pneumonitis presumably caused by feather duvets. *Ann Allergy Asthma Immunol* 2006;96(1):98-104. doi: 10.1016/s1081-1206(10)61047-2 [published Online First: 2006/01/31]
12. Inase NO, Yoshio; Usui, Yutaka; Miyazaki, Yasunari; Takemura, Tamiko; Yoshizawa, Yasuyuki. Chronic summer-type hypersensitivity pneumonitis: clinical similarities to idiopathic pulmonary fibrosis. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG* 2007;24(2):141-7.

13. Kishi MM, Y.; Jinta, T.; Furusawa, H.; Ohtani, Y.; Inase, N.; Yoshizawa, Y. Pathogenesis of cBFL in common with IPF? Correlation of IP-10/TARC ratio with histological patterns. *Thorax* 2008;63(9):810-6. doi: https://dx.doi.org/10.1136/thx.2007.086074
14. Koschel DW, Horst; Renck, Thomas; Muller-Wening, Dietrich; Hoffken, Gert. Presenting features of feather duvet lung. *International archives of allergy and immunology* 2010;152(3):264-70. doi: https://dx.doi.org/10.1159/000283036
15. Lacasse YS, Moises; Costabel, Ulrich; Dalphin, Jean-Charles; Ando, Masayuki; Morell, Ferran; Erkinjuntti-Pekkanen, Riitta; Muller, Nestor; Colby, Thomas V.; Schuyler, Mark; Cormier, Yvon; H. P. Study Group. Clinical diagnosis of hypersensitivity pneumonitis. *American journal of respiratory and critical care medicine* 2003;168(8):952-8.
16. Leatherman JWM, A. F.; Schwartz, B. A.; Hoidal, J. R. Lung T cells in hypersensitivity pneumonitis. *Annals of internal medicine* 1984;100(3):390-2.
17. Markart PL, Thomas; Korfei, Martina; Schmidt, Reinhold; Wygrecka, Malgorzata; Mahavadi, Poornima; Mayer, Konstantin; Wilhelm, Jochen; Seeger, Werner; Guenther, Andreas; Ruppert, Clemens. Alveolar oxidative stress is associated with elevated levels of nonenzymatic low-molecular-weight antioxidants in patients with different forms of chronic fibrosing interstitial lung diseases. *Antioxidants & redox signaling* 2009;11(2):227-40. doi: https://dx.doi.org/10.1089/ARS.2008.2105
18. Milanowski JD, J.; Potoczna, H.; Kus, L.; Urbanowicz, B. Allergic alveolitis among agricultural workers in eastern Poland: a study of twenty cases. *Annals of agricultural and environmental medicine : AAEM* 1998;5(1):31-43.
19. Murayama JY, Y.; Ohtsuka, M.; Hasegawa, S. Lung fibrosis in hypersensitivity pneumonitis. Association with CD4+ but not CD8+ cell dominant alveolitis and insidious onset. *Chest* 1993;104(1):38-43.
20. Nukui Y, Miyazaki Y, Masuo M, et al. Periostin as a predictor of prognosis in chronic bird-related hypersensitivity pneumonitis. *Allergology international : official journal of the Japanese Society of Allergology* 2019;68(3):363-69. doi: https://dx.doi.org/10.1016/j.alit.2019.02.007
21. Nunes HS, K.; Piver, D.; Magois, E.; Feuillet, S.; Uzunhan, Y.; Carton, Z.; Tazi, A.; Levy, P.; Brillet, P. Y.; Nicholson, A. G.; Kambouchner, M.; Valeyre, D. Nonspecific interstitial pneumonia: Survival is influenced by the underlying cause. *European Respiratory Journal* 2015;45(3):746-55. doi: http://dx.doi.org/10.1183/09031936.00148613
22. Ochi JO, Yoshio; Takemura, Tamiko; Akashi, Takumi; Tateishi, Tomoya; Miyazaki, Yasunari; Inase, Naohiko; Yoshizawa, Yasuyuki. Histological variability and consequences in chronic bird-related hypersensitivity pneumonitis. *Respirology (Carlton, Vic)* 2017;22(7):1350-56. doi: https://dx.doi.org/10.1111/resp.13070
23. Ohshimo SB, Francesco; Cui, Ai; Beume, Martin; Kohno, Nobuoki; Guzman, Josune; Costabel, Ulrich. Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine* 2009;179(11):1043-7. doi: https://dx.doi.org/10.1164/rccm.200808-1313OC
24. Ohtani YS, Shigeki; Sumi, Yuki; Inase, Naohiko; Miyake, Shuji; Costabel, Ulrich; Yoshizawa, Yasuyuki. Clinical features of recurrent and insidious chronic bird fancier's lung. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* 2003;90(6):604-10.
25. Pardo AB, R.; Gaxiola, M.; Segura-Valdez, L.; Carrillo, G.; Estrada, A.; Mejia, M.; Selman, M. Increase of lung neutrophils in hypersensitivity pneumonitis is associated with lung fibrosis. *American journal of respiratory and critical care medicine* 2000;161(5):1698-704.
26. Pesci AB, G.; Gabrielli, M.; Olivieri, D. Mast cells in fibrotic lung disorders. *Chest* 1993;103(4):989-96.

27. Remy-Jardin MR, J.; Wallaert, B.; Muller, N. L. Subacute and chronic bird breeder hypersensitivity pneumonitis: sequential evaluation with CT and correlation with lung function tests and bronchoalveolar lavage. *Radiology* 1993;189(1):111-8.
28. Reynolds HYF, J. D.; Kazmierowski, J. A.; Roberts, W. C.; Frank, M. M.; Crystal, R. G. Analysis of cellular and protein content of broncho alveolar lavage fluid from patients with idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis. *Journal of Clinical Investigation* 1977;59(1):165-75.
29. Salisbury ML, Gross BH, Chughtai A, et al. Development and validation of a radiological diagnosis model for hypersensitivity pneumonitis. *European Respiratory Journal* 2018;52(2):1800443. doi: http://dx.doi.org/10.1183/13993003.00443-2018
30. Schmidt RM, U.; Markart, P.; Grimminger, F.; Velcovsky, H. G.; Morr, H.; Seeger, W.; Gunther, A. Altered fatty acid composition of lung surfactant phospholipids in interstitial lung disease. *American journal of physiology Lung cellular and molecular physiology* 2002;283(5):L1079-85.
31. Selman MP, A.; Barquin, N.; Sansores, R.; Ramirez, R.; Ramos, C.; Montano, M.; Stricklin, G. Collagenase and collagenase inhibitors in bronchoalveolar lavage fluids. *Chest* 1991;100(1):151-5.
32. Sterclova MV, Martina; Pavlicek, Jan; Metlicka, Monika; Krasna, Eliska; Striz, Ilja. Chemokine receptors in a regulation of interstitial lung fibrosis and inflammation. *Experimental lung research* 2009;35(6):514-23.
33. Sterclova MM, Radoslav; Mandakova, Petra; Skibova, Jelena; Vasakova, Martina. Role of interleukin 4 and its receptor in clinical presentation of chronic extrinsic allergic alveolitis: a pilot study. *Multidisciplinary respiratory medicine* 2013;8(1):35. doi: https://dx.doi.org/10.1186/2049-6958-8-35
34. Sterclova MV, M.; Dutka, J.; Kalanin, J. Extrinsic allergic alveolitis: comparative study of the bronchoalveolar lavage profiles and radiological presentation. *Postgraduate medical journal* 2006;82(971):598-601.
35. Sumi YK, Min; Miyazaki, Yasunari; Ohtani, Yoshio; Miyake, Shuji; Yoshizawa, Yasuyuki. Cytokine mRNA expression in isocyanate-induced hypersensitivity pneumonitis. *Respiration; international review of thoracic diseases* 2003;70(3):284-91.
36. Tsushima KF, Shino; Yoshikawa, Sumiko; Yasuo, Masanori; Yamazaki, Yoshitaka; Koizumi, Tomonobu; Fujimoto, Keisaku; Kubo, Keishi. Therapeutic effects for hypersensitivity pneumonitis induced by Japanese mushroom (Bunashimeji). *American journal of industrial medicine* 2006;49(10):826-35.
37. Tzilas V, Tzouvelekis A, Bouros E, et al. Diagnostic value of BAL lymphocytosis in patients with indeterminate for UIP imaging pattern. 2019:1901144. doi: 10.1183/13993003.01144-2019 %J European Respiratory Journal
38. Unoura KM, Yasunari; Sumi, Yuki; Tamaoka, Meiyo; Sugita, Takashi; Inase, Naohiko. Identification of fungal DNA in BALF from patients with home-related hypersensitivity pneumonitis. *Respiratory medicine* 2011;105(11):1696-703. doi: https://dx.doi.org/10.1016/j.rmed.2011.07.009
39. Voisin CT, A. B.; Lahoute, C.; Robin, H.; Lebas, J.; Aerts, C. Bird fancier's lung: Studies of broncho-alveolar lavage and correlations with inhalation provocation tests. *Lung* 1981;159(1):17-22.
40. Vourlekis JSS, M. I.; Cool, C. D.; Tuder, R. M.; King Jr, T. E.; Brown, K. K. Nonspecific interstitial pneumonitis as the sole histologic expression of hypersensitivity pneumonitis. *American Journal of Medicine* 2002;112(6):490-93. doi: http://dx.doi.org/10.1016/S0002-9343%2802%2901046-X
41. Wang PX, Zuo-jun; Xu, Wen-bing; Shi, Ju-hong; Tian, Xin-lun; Feng, Rui-e; Zhu, Yuan-jue. Clinical features and prognosis in 21 patients with extrinsic allergic alveolitis. *Chinese medical sciences journal = Chung-kuo i hsueh k'o hsueh tsa chih* 2009;24(4):202-7.
42. Ye QN, Shinobu; Sarria, Rafael; Costabel, Ulrich; Guzman, Josune. Interleukin 12, interleukin 18, and tumor necrosis factor alpha release by alveolar macrophages: acute and chronic hypersensitivity

pneumonitis. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* 2009;102(2):149-54. doi: https://dx.doi.org/10.1016/S1081-1206(10)60246-3
43. Adams TNN, Chad A.; Batra, Kiran; Abu-Hijleh, Muhanned; Barbera, Tyonn; Torrealba, Jose; Glazer, Craig S. Utility of Bronchoalveolar Lavage and Transbronchial Biopsy in Patients with Hypersensitivity Pneumonitis. *Lung* 2018 doi: https://dx.doi.org/10.1007/s00408-018-0139-1
44. Chockalingam AD, Ranganathan; Jagadeesan, Madhavan. Bronchoalveolar lavage cellular analyses in conjunction with high-resolution computed tomography imaging as a diagnostic intervention for patients with suspected interstitial lung disease. *Lung India : official organ of Indian Chest Society* 2016;33(3):287-91. doi: https://dx.doi.org/10.4103/0970-2113.180806
45. Masuo M, Miyazaki Y, Suhara K, et al. Factors associated with positive inhalation provocation test results in subjects suspected of having chronic bird-related hypersensitivity pneumonitis. *Respiratory Investigation* 2016;54(6):454-61. doi: http://dx.doi.org/10.1016/j.resinv.2016.05.002
46. Miyazaki YU, Koji; Tateishi, Tomoya; Akashi, Takumi; Takemura, Tamiko; Tomita, Makoto; Inase, Naohiko; Yoshizawa, Yasuyuki. Higher serum CCL17 may be a promising predictor of acute exacerbations in chronic hypersensitivity pneumonitis. *Respiratory research* 2013;14:57. doi: https://dx.doi.org/10.1186/1465-9921-14-57
47. Okamoto TM, Yasunari; Ogura, Takashi; Chida, Kingo; Kohno, Nobuoki; Kohno, Shigeru; Taniguchi, Hiroyuki; Akagawa, Shinobu; Mochizuki, Yoshiro; Yamauchi, Kohei; Takahashi, Hiroki; Johkoh, Takeshi; Homma, Sakae; Kishi, Kazuma; Ikushima, Soichiro; Konno, Satoshi; Mishima, Michiaki; Ohta, Ken; Nishioka, Yasuhiko; Yoshimura, Nobuyuki; Munakata, Mitsuru; Watanabe, Kentaro; Miyashita, Yoshihiro; Inase, Naohiko. Nationwide epidemiological survey of chronic hypersensitivity pneumonitis in Japan. *Respiratory investigation* 2013;51(3):191-9. doi: https://dx.doi.org/10.1016/j.resinv.2013.03.004
48. Okamoto TM, Yasunari; Tomita, Makoto; Tamaoka, Meiyo; Inase, Naohiko. A familial history of pulmonary fibrosis in patients with chronic hypersensitivity pneumonitis. *Respiration; international review of thoracic diseases* 2013;85(5):384-90. doi: https://dx.doi.org/10.1159/000338123
49. Ojanguren I, Morell F, Ramon M-A, et al. Long-term outcomes in chronic hypersensitivity pneumonitis. *Allergy* 2019;74(5):944-52. doi: https://dx.doi.org/10.1111/all.13692
50. Suhara KM, Yasunari; Okamoto, Tsukasa; Yasui, Makito; Tsuchiya, Kimitake; Inase, Naohiko. Utility of immunological tests for bird-related hypersensitivity pneumonitis. *Respiratory investigation* 2015;53(1):13-21. doi: https://dx.doi.org/10.1016/j.resinv.2014.08.001
51. Vergnon JMB, N.; Pacheco, Y.; Perrin-Fayolle, M. [Angiotensin converting enzyme at different stages of extrinsic allergic alveolitis. Serum and alveolar study]. *L'enzyme de conversion de l'angiotensine au cours des differents stades des alveolites allergiques extrinseques Etude serique et alveolaire* 1983;19(5):439-45.
52. Willems SV, Stijn E.; Vanaudenaerde, Bart M.; Wynants, Marijke; Dooms, Christophe; Yserbyt, Jonas; Somers, Jana; Verbeken, Eric K.; Verleden, Geert M.; Wuyts, Wim A. Multiplex protein profiling of bronchoalveolar lavage in idiopathic pulmonary fibrosis and hypersensitivity pneumonitis. *Annals of thoracic medicine* 2013;8(1):38-45. doi: https://dx.doi.org/10.4103/1817-1737.105718
53. Yoshizawa YO, Y.; Hayakawa, H.; Sato, A.; Suga, M.; Ando, M. Chronic hypersensitivity pneumonitis in Japan: a nationwide epidemiologic survey. *The Journal of allergy and clinical immunology* 1999;103(2 Pt 1):315-20.
54. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of internal medicine* 2011;155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009 [published Online First: 2011/10/19]