Original Article

Diagnostic accuracy of specific IgG antibodies for bird fancier's lung: a systematic review and meta-analysis

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Background: Serologic assays for specific immunoglobulin G (IgG) antibodies are available for diagnosing the condition of bird fancier's lung, however, their usefulness is controversial. This systematic review was aimed at investigating the diagnostic accuracy of specific IgG antibodies used for avian antigens.

Methods: Medline, Embase, the Cochrane Library, the International Clinical Trials Registry Platform, and the Web of Science were searched for studies performed to evaluate the diagnostic accuracy of the Ouchterlony method, enzyme-linked immunosorbent assays (ELISAs), electrosyneresis, and ImmunoCAP assays for diagnosing bird fancier's lung. Nine articles were included in the meta-analysis. The pooled sensitivity and specificity were summarized using a bivariate mixed-effects model, and a hierarchical summary receiver operating characteristic curve was rendered to determine the diagnostic accuracy of the antibodies.

Results: The pooled sensitivities and specificities of each specific IgG antibody were 82.9% (95% confidence interval, 71.1–90.5%) and 93.0% (95% confidence interval, 74.4–98.4%) for the Ouchterlony method, 92.5% (95% confidence interval, 71.3–98.4%) and 90.8% (95% confidence interval, 72.1–97.4%) for ELISAs, 90.0% (95% confidence interval, 55.5–99.7%) and 84.6% (95% confidence interval, 73.5–92.4%) for the electrosyneresis method, and 43.5% (95% confidence interval, 35.3–52.1%) and 100% (95% confidence interval, 0–100%) for ImmunoCAP assays. The overall quality of the collective evidence was low, primarily due to the high risk of bias, indirectness, and imprecision of the included studies.

Conclusions: The Ouchterlony method demonstrated high specificity, the ELISA method showed high sensitivity, and the diagnostic utilities of electrosyneresis and ImmunoCAP assay testing remain unclear.

Keywords: Interstitial lung disease; meta-analysis; hypersensitivity pneumonitis; bird fancier's lung (BFL)

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Introduction

Bird fancier's lung (BFL), a type of hypersensitivity pneumonitis (HP), is a complex syndrome caused by lung inflammation in response to avian proteins inhaled from avian droppings, serum, and feathers (1). The prevalence of BFL is reported to be 20 to 20,000 per 100,000 at-risk persons (2). Further, the incidence of HP mortality, including that from BFL, has increased recently (3). The diagnosis of BFL is made in patients with a history of avian exposure using a combination of serologic assays, radiological and pathological findings, and an antigen-avoidance trial (4).

In particular, serological assays target specific anti-avian

immunoglobulin G (IgG) antibodies using various methods, such as the Ouchterlony double-immunodiffusion, enzyme-linked immunosorbent assay (ELISA), electrosyneresis, and ImmunoCAP methods (5). Although IgG-specific serologic assays are considered critical for accurately diagnosing BFL, their diagnostic accuracies remain controversial (6-9). Indeed, a recent survey demonstrated that 40% of healthy bird breeders tested positive for anti-avian antibodies using available serologic assays, which raises questions about the validity of such tests for diagnostic purposes (10). In this systematic review, the diagnostic value of specific IgG serologic assays in the diagnosis of BFL was assessed.

Methods

Data sources and searches

The following electronic bibliographic databases were searched: Medline, Embase, the Cochrane Library, and the International Clinical Trials Registry Platform. The search strategy included terms relating to or describing BFL (i.e., BFL, bird breeder's lung, avian HP, feather duvet lung, bird-related HP, budgerigar fancier's lung, and pigeon breeder's lung) and serologic assays for IgG antibodies (precipitation reaction, Ouchterlony method, electrosyneresis method, ELISA, and ImmunoCAP assay; *Figure S1*). There were no restrictions concerning language, the publication year, or the type of publication. In addition, the references of the included publications were searched, and the Web of Science citation search function was used to identify additional articles. This systematic review was completed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (*Table S1*). The protocol was preregistered in the International Prospective Register of Systematic Reviews (CRD42019122441). We used data from previous published articles in which the investigators state they obtained informed consent from the patients. Thus, no ethical approval was needed for our systematic review.

Study selection

Firstly, the title and abstracts of potential articles were independently screened by two pulmonologists, A Shiroshita and Y Tanaka, using the inclusion criteria. Secondly, the full manuscripts of the included articles were obtained and assessed by the same two independent reviewers, irrespective of whether the obtained articles were included. The inclusion criteria were as follows: prospective or retrospective cohort studies, or case-control studies assessing the sensitivity and specificity of serologic assays for anti-avian IgG antibodies (Ouchterlony method, ELISA, electrosyneresis method, and ImmunoCAP assay) among patients with suspected BFL. If there was a disagreement between the two reviewers with regard to a publication's inclusion, it was solved by discussion or consultation with another pulmonologist (K Nakashima).

Data extraction and study quality

The following data were extracted: author, publication type, publication year, countries where the studies were performed, information on study participants, analytical methods used with the antibodies, BFL subtype (acute or chronic), setting where the studies were performed (private or university hospital), BFL diagnostic criteria, and antibody test results (true positive, true negative, false positive, and false negative). The methodological quality of the included articles was evaluated by two pulmonologists, A Shiroshita and Y Tanaka, using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (11). If there were discrepancies between the assessments by the two reviewers, then they were resolved by discussion or consultation with another pulmonologist (K Nakashima).

Data analysis

Data were collected regarding the sensitivity and specificity (including the 95% confidence interval) of each BFL serologic assay. To assess for pooled sensitivity and specificity, a bivariate random-effects model was used, and a hierarchical summary receiver operating characteristic (HSROC) curve was rendered to synthesize information on the diagnostic accuracy of the antibody-based tests. To assess the overall quality of the evidence, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used with independent review, as mentioned above. Although subgroup analysis targeting unhealthy people and those with acute versus chronic BFL was planned in the protocol, information on the sensitivity and specificity of patients without healthy controls was lacking; thus, the subgroup analysis was not feasible.

All analyses were completed using Diagnostic Test Accuracy Meta-Analysis software, version 1.21 (12) and RevMan software, version 5.3 (Copenhagen: The Nordic

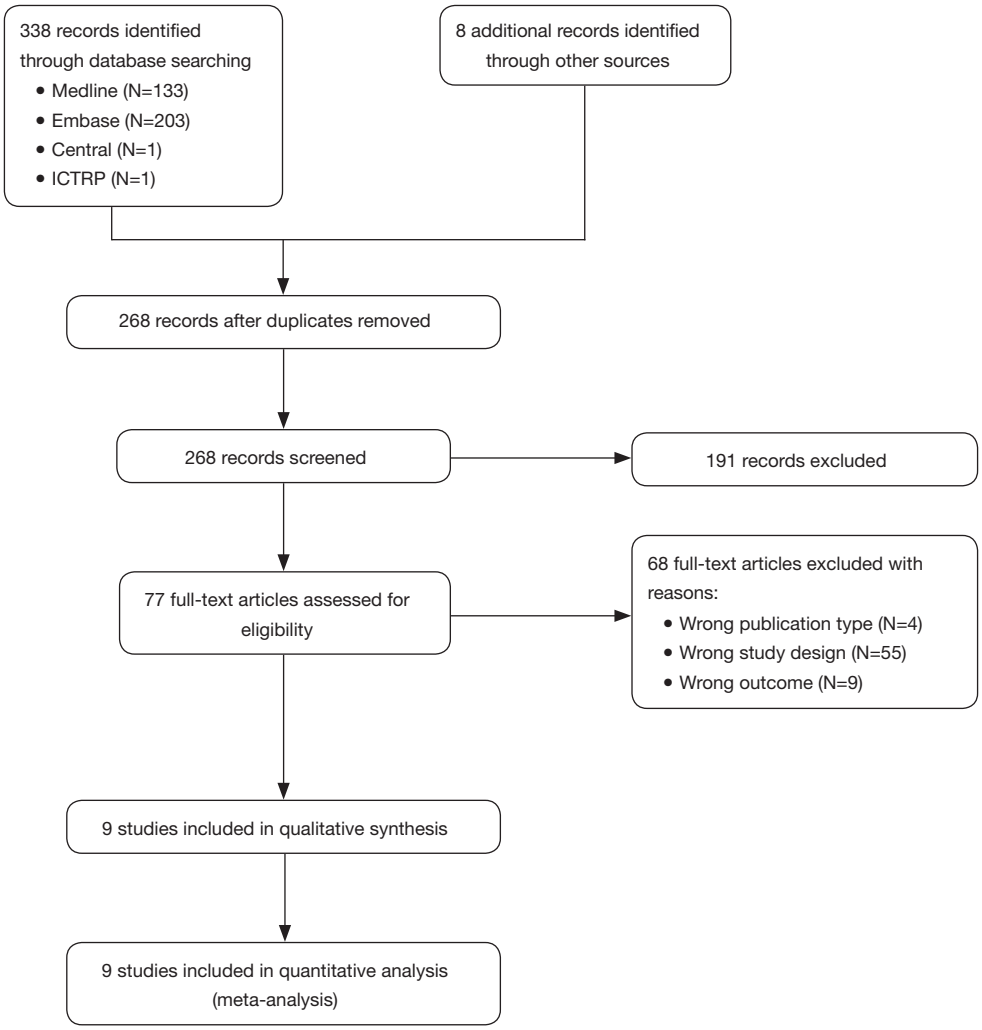

Figure 1 PRISMA flow diagram.

Cochrane Centre, The Cochrane Collaboration).

Results

Search results and study characteristics

A total of 346 citations were identified up to January 21, 2019. Of these, 78 duplicate articles were removed, and the titles and abstracts of 268 articles were screened. Thus, 77 full-text manuscripts were acquired, of which four articles were excluded due to publication type (three case series and one review article), 55 articles were excluded due to the study design, and nine articles were excluded due to outcome measures. Finally, nine articles were included in this meta-analysis (*Figure 1*) (13-21). The study characteristics are summarized in *Table 1* and *Table S2*. Notably, insufficient data pertaining to the study setting or BFL subtype were available to perform subgroup analysis of these parameters. Further, participant characteristics varied largely across the included studies.

Study quality

The risk of bias and the applicability of each antibody were evaluated using QUADAS-2 (*Figure 2*). Of note, almost all of the included studies demonstrated a low applicability risk and were associated with a high or uncertain risk of bias. Further, the studies were unclear regarding the processes used to diagnose BFL, lacked index test cut-offs, and did not prespecify diagnostic reference standards or indicate

Table 1 Characteristics of the included studies

First author	Year	Number of participants	Study design	Region	Study setting	Study participants	Index test (antigen)	Male	Female	Mean or median age (SD or 1–3 IQR)
Inase (13)	2011	165	Case-control	Japan	University hospital	BFL, CTD-ILD, normal people	ImmunoCAP assay (pigeon serum, feather, and feces)	NA	NA	NA
	2011	166	Case-control	Japan	University hospital	BFL, CTD-ILD, normal people	ImmunoCAP assay (budgerigar serum, feather, and feces)	NA	NA	NA
Cordero (14)	2000	31	Case-control	Mexico	NA	Interstitial lung disease with positive IgM for avian serum antigen	Ouchterlony method (avian serum)	7	24	47.2 (13.4)
Suhara (15)	2015	135	Retrospective cohort	Japan	University hospital	HP, other interstitial lung diseases	ELISA (pigeon feces)	71	64	NA
Simpson (16)	1992	150	Case-control	United Kingdom	NA	BFL, asthma, ABPA, asbestosis, bronchiectasis, mycetoma, healthy control	ELISA (pigeon feces)	44	6	45.7 [14–69]
	1992	150	Case-control	United Kingdom	NA	BFL, asthma, ABPA, asbestosis, bronchiectasis, mycetoma, healthy controls	Ouchterlony method (pigeon feces)	44	6	45.7 [14–69]
Rouzet (17)	2017	193	Case-control	France, Belgium	University hospital	People exposed to birds	ELISA (pigeon dropping extract)	10	15	65.5 [42–80]
	2017	55	Case-control	France, Belgium	University hospital	People exposed to birds	ELISA (Immunoglobulin lambda-like polypeptide-1)	10	15	65.5 [42–80]
	2017	55	Case-control	France, Belgium	University hospital	People exposed to birds	ELISA (proproteinase E)	10	15	65.5 [42–80]
Sandoval (18)	1990	146	Prospective cohort	Mexico	NA	Diffuse interstitial lung disease	ELISA (pigeon serum)	NA	NA	NA
Fraux (19)	1971	160	Case-control	United Kingdom, Switzerland, Canada	NA	Healthy people who had no contact with budgerigars	Ouchterlony method (budgerigar serum)	NA	NA	NA
						Healthy people with budgerigars				
						Patients with respiratory disease and budgerigars				

Table 1 (*continued*)

Table 1 (*continued*)

First author	Year	Number of participants	Study design	Region	Study setting	Study participants	Index test (antigen)	Male	Female	Mean or median age (SD or 1–3 IQR)
	1971	75	Case-control	United Kingdom, Switzerland, Canada	NA	Healthy people who had no contact with budgerigars Healthy people who had budgerigars Patients with respiratory disease and who had budgerigars	Electrosyneresis method (budgerigar serum)	NA	NA	NA
Pelikan (20)	1983	18	Retrospective cohort	The Netherlands	NA	People exposed to pigeons or pigeon excretion, and who had bronchial symptoms	Ouchterlony method (pigeon serum)	9	9	28.6 (14.5)
	1983	18	Retrospective cohort	The Netherlands	NA	People exposed to pigeons or pigeon excretion, and who had bronchial symptoms	Ouchterlony method (pigeon feces)	9	9	28.6 (14.5)
Rodrigo (21)	2000	28	Case-control	Spain	NA	HP asymptomatic fanciers	ELISA (pigeon serum)	14	14	NA
	2000	28	Case-control	Spain	NA	HP asymptomatic fanciers	ELISA (bloom extract)	14	14	NA

ABPA, allergic bronchopulmonary aspergillosis; BFL, bird fancier's lung; CTD-ILD, connective tissue disease-associated interstitial lung disease; HP, hypersensitivity pneumonitis; SD, standard deviation; IQR, interquartile range; NA, not available.

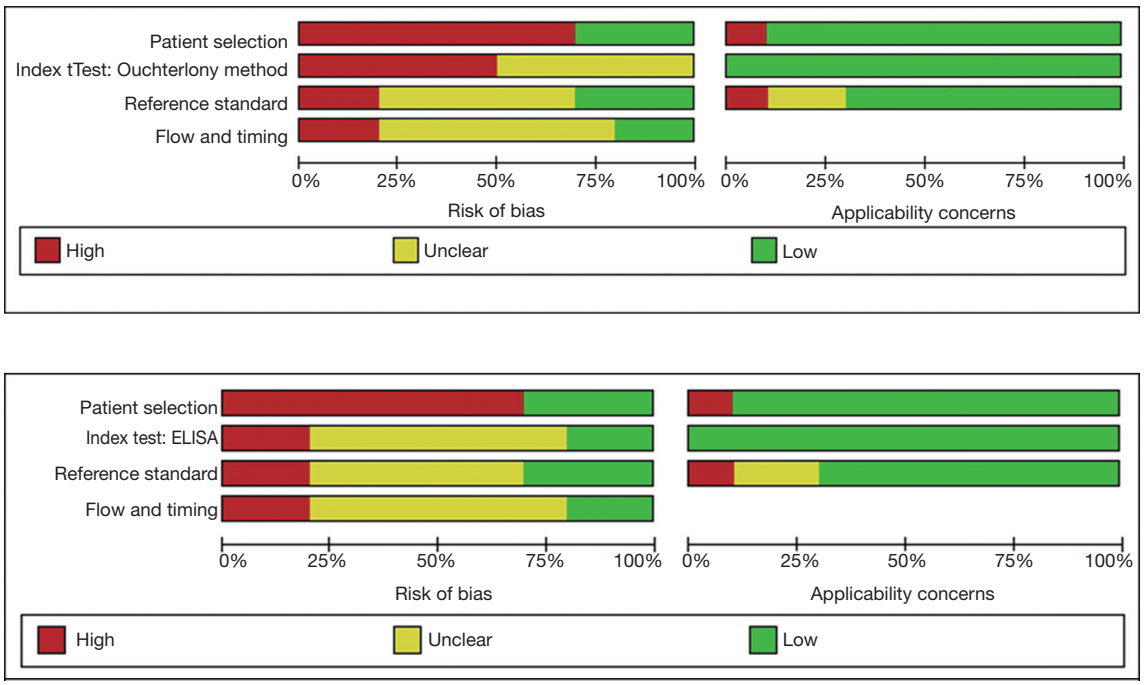

Figure 2 Methodological evaluation of the Ouchterlony and ELISA methods using QUADAS-2. ELISA, enzyme-linked immunosorbent assay; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2.

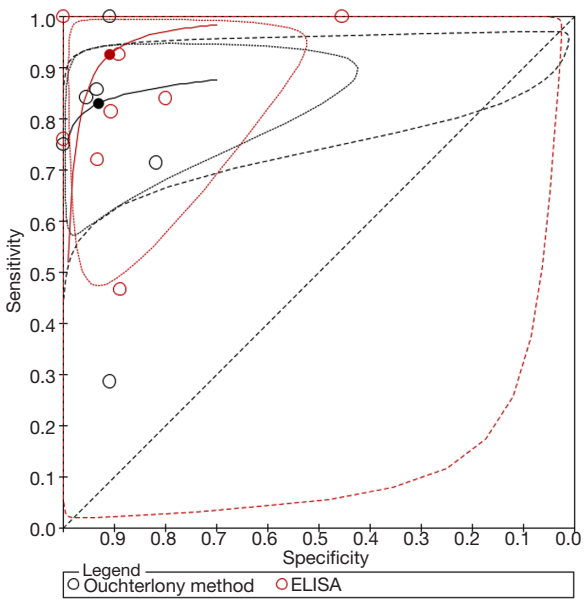

Figure 3 Hierarchical summary of receiver operating characteristics curves of the Ouchterlony and ELISA methods for diagnosing bird fancier's lung. The bivariate summary estimates (solid ellipses), with the corresponding 95% prediction ellipses (outer dotted lines) and 95% confidence ellipses (inner dashed lines). ELISA, enzyme-linked immunosorbent assay.

whether physicians made a diagnosis without knowledge of an index test. Moreover, most of the studies lacked information on the workflow and timing of diagnostic testing and had a high risk of bias.

Diagnostic accuracy of IgG antibodies

The pooled sensitivity and specificity of each specific IgG antibody was calculated using a bivariate mixed-effect model. Accordingly, the respective sensitivity and specificity of each method were as follows: Ouchterlony method, 82.9% (95% confidence interval, 71.1–90.5%) and 93.0% (95% confidence interval, 74.4–98.4%); ELISA method, 92.5% (95% confidence interval, 71.3–98.4%) and 90.8% (95% confidence interval, 72.1–97.4%); electrosyneresis method, 90.0% (95% confidence interval, 55.5–99.7%) and 84.6% (95% confidence interval, 73.5–92.4%); ImmunoCAP assay 43.5% (95% confidence interval, 35.3–52.1%) and 100% (95% confidence interval, 0–100%). Further, the diagnostic accuracy of the Ouchterlony and ELISA methods were visually evaluated using rendered HSROC curves (*Figure 3*), which demonstrated that the 95% prediction region was imprecise, as the Ouchterlony method had a higher sensitivity and the ELISA method had

Table 2 Findings with the Ouchterlony method using the Grading of Recommendations, Assessment, Development and Evaluation approach

Outcome	No. studies (no. patients)	Study design	Factors that may decrease the certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 80%	Pre-test probability of 40%	Pre-test probability of 10%	
True positive	10 studies [1,608]	Cohort & case-control studies	Very serious[†]	Not serious	Serious[‡]	Serious[§]	None	232 to 688	116 to 344	29 to 86	Very low
False negative								112 to 568	56 to 284	14 to 71	
True negative	10 studies [1,608]	Cohort & case-control studies	Very serious[†]	Not serious	Not serious	Serious[¶]	None	164 to 200	492 to 600	738 to 900	Very low
False positive								0 to 36	0 to 108	0 to 162	

[†], most of the included studies were designed as case-control studies. In most of the included studies, it was unclear whether antibody-based testing was done before diagnosis of BFL, or whether interpretation of the test results was done without knowledge of the results of other test results; [‡], the study participants and study settings were different between the included studies; [§], In the studies by Cordero *et al.* (14) and Pelikan *et al.* (20), the 95% confidence interval of sensitivity crossed 50%; [¶], in the study by Pelikan *et al.* (20), the 95% confidence interval of specificity crossed 50%. CoE, certainty of evidence; BFL, bird fancier's lung.

a higher specificity.

Subgroup analysis was performed using a bivariate mixed-effect model according to the type of BFL (acute or chronic); only two studies and three types of index tests (one ELISA and two ImmunoCAP assay) were included in this analysis. As such, both the sensitivity and specificity were higher in acute relative to chronic BFL (sensitivity 100% versus 98.0%, specificity 89.3% versus 55.1%, respectively).

Finally, the overall quality of evidence was assessed for the Ouchterlony and ELISA methods, using the GRADE approach (*Tables 2,3*).

Conclusions

In this systematic review, the sensitivity and specificity were estimated for four specific-IgG serologic assays used in diagnosing BFL because accurate antigen detection is crucial for treating this disease (22). Accordingly, the sensitivity and specificity of the methods were ranked as follows: sensitivity, ELISA > electrosyneresis method > Ouchterlony method > ImmunoCAP; specificity, ImmunoCAP method > electrosyneresis method > Ouchterlony method > ELISA. However, the overall quality of evidence was low due to a high risk of bias, indirectness, and imprecision associated with the included studies. Moreover, as the number of publications describing the use of electrosyneresis and ImmunoCAP assays was limited, the assessment of the diagnostic accuracy of these tests lacks precision. Thus, this analysis focused on comparing the Ouchterlony and ELISA methods.

According to this analysis, the Ouchterlony method of diagnosing BFL was associated with high specificity, suggesting that this method is a useful diagnostic tool in cases where physicians suspect BFL based on exposure history and radiological evidence of interstitial pneumonia. Further, the use of the Ouchterlony method may decrease unnecessary antigen avoidance, which is a first-line treatment strategy for BFL. Indeed, removing all bird, or bird-related items (such as feather bedding) is recommended, although some patients require a complete change of environment as the antigen can remain in the environment even after cleanup (23). Antigen avoidance can be emotionally and financially challenging to patients; thus, using a diagnostic method with high specificity may decrease the rate of false positives and the associated stress to patients and their families.

However, the Ouchterlony method is associated with disadvantages, including the fact that it is a qualitative

Table 3 Summary of findings by ELISA using the Grading of Recommendations, Assessment, Development and Evaluation approach

Outcome	No. studies (no. patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 10%	Pre-test probability of 40%	Pre-test probability of 80%	
True positive	5 studies [680]	Cohort & case-control studies	Very serious[†]	Not serious	Very serious[‡]	Serious[§]	None	77 to 100	308 to 400	616 to 800	Very low
False negative								0 to 23	0 to 92	0 to 184	
True negative	5 studies [680]	Cohort & case-control studies	Very serious[†]	Not serious	Very serious	Serious[¶]	None	414 to 900	276 to 600	92 to 200	Very low
False positive								0 to 486	0 to 324	0 to 108	

[†], most of the included studies were designed as case-control studies. In most of the included studies, it was unclear whether antibody-based testing was done before diagnosis of BFL, or whether interpretation of the test results was done without knowledge of the results of other test results; [‡], the study participants and study settings were different between the included studies; [§], in the study by Rouzet *et al.* (17), the 95% confidence interval of sensitivity crossed 50%; [¶], in the study by Rodrigo *et al.* (21), the 95% confidence interval of specificity crossed 50%. CoE, certainty of evidence; BFL, bird fancier's lung.

method that is both time consuming and technically challenging. Thus, it is associated with poor reproducibility. Additionally, relatively large quantities of antigens are required to visualize a precipitating line (24). Unfortunately, information was not available regarding whether the method was performed by trained laboratory staff with standardized procedures. Future studies should include detailed workflows, including staff qualifications, to address this issue.

In contrast, the sensitivity of ELISA testing was higher than that of the Ouchterlony method, suggesting that ELISA may be a useful screening tool when BFL is suspected. The greater sensitivity may be explained by the consideration that ELISAs do not depend on visualization of a precipitate line, whereas the Ouchterlony method does. Further, ELISA testing is relatively fast and simple (25). Based on the publications included in this review, ELISA is also used more frequently for diagnosing BFL than the Ouchterlony method. In particular, Suhara *et al.* used ELISA for diagnosing acute and chronic BFL (15). As such, the researchers determined that the test exhibited higher sensitivity and specificity in diagnosing acute BFL, relative to chronic BFL. In acute BFL, humoral immunity is believed to dominate the immune response, while cell-mediated immunity dominates in chronic BFL (26). Thus, ELISA may be a more useful screening tool for acute rather than for chronic BFL.

Unfortunately, only a limited number of studies have utilized the electrosyneresis (n=1) or ImmunoCAP assay (n=1) methods for diagnosing BFL, which is likely due to the fact that these are relatively new antibody-based detection methods. However, according to this analysis, the electrosyneresis method had high sensitivity and specificity, whereas the ImmunoCAP assay had low sensitivity and high specificity. Notably, other investigators have suggested that the electrosyneresis method could be expected to support the diagnosis of HP caused by mold antigens as well (27), which was not accounted for by the single electrosyneresis publication included in this systematic review (19). For the ImmunoCAP assay, the only study included in this review was conducted in Japan (15). Concerning the high risk of bias in these tests, interpretation without knowledge of other test results will be needed for future cohort studies.

This systematic review has several limitations. Firstly, the number of included studies was small, and the heterogeneity was high. This contributed to unstable prediction regions for both the Ouchterlony and ELISA methods, suggesting that the mean observed sensitivity and specificity may change following the publication of additional studies

in the future. Secondly, most of the studies had a high risk of bias because they were designed as case-control studies, and the processes used for BFL diagnosis were not described in detail. Moving forward, future studies should be completed as prospective cohort studies with larger sample sizes. It is also important to note that the antigenic component of the avian protein is currently unknown (23) and that identification of the antigenic peptide will likely be associated with a significant increase in diagnostic accuracy.

According to this systematic review and meta-analysis, the Ouchterlony method for BFL diagnosis is likely associated with high specificity, whereas the ELISA method likely has high sensitivity. Unfortunately, the diagnostic value of the electrosyneresis method and ImmunoCAP assay could not be accurately assessed at this moment.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Medline via Ovid	
1. Bird fancier's lung	exp Bird Fancier's Lung/OR (bird fancier adj3 lung?).tw. OR (lung?, bird fancier's).tw. OR (bird breeder*).tw. OR (lung?, bird breeder's).tw. OR (pneumonitis adj3 avian hypersensitivity).tw. OR (avian hypersensitivity pneumoni*).tw. OR (budgerigar fancier*).tw. OR (lung?, pigeon breeder's).tw. OR (pigeon breeder*).tw. OR (feather duvet lung?).tw. OR (bird-related hypersensitivity pneumonitis).tw.
2. Serologic assay for IgG antibodies	Exp immunoassay/OR (immunoassay).tw. OR (immunoassay?).tw. OR (immunochemical technique?).tw. OR (antibody testing?).tw. OR (serum antibody detection?).tw. OR (serum assay?).tw. OR (IgG).tw. OR (immunoglobulin G).tw. OR (enzyme-linked immunosorbent assay).tw. OR (enzyme immunoassay).tw. OR (enzyme?linked immunosorbent assay).tw. OR (ELISA).tw. OR (precipitation reaction?).tw. OR (serum precipitins*).tw. OR (immunoprecipitation technique?).tw. OR (precipitating antibod*).tw. OR (double adj6 diffusion).tw. OR (Ouchterlony).tw. OR (electrosyneresis).tw. OR (ImmunoCAP).tw.
Final search 1 AND 2	
Embase via Embase.com	
1. Bird fancier's lung	bird breeder lung/exp OR (bird fancier NEAR/3 lung):ab,ti OR (lung, bird fancier):ab,ti OR (bird breeder*):ab,ti OR (avian hypersensitivity pneumoni*):ab,ti OR (budgerigar fancier*):ab,ti OR (lung, pigeon breeder):ab,ti OR (pigeon breeder*):ab,ti OR (feather duvet lung):ab,ti OR (bird-related hypersensitivity pneumonitis):ab,ti
2. Serologic assay for IgG antibodies	immunoassay/exp OR (immunoassay*):ab,ti OR (immunochemical technique*):ab,ti OR (antibody testing*):ab,ti OR (serum antibody detection):ab,ti OR (serum assay*):ab,ti OR (IgG):ab,ti OR (immunoglobulin G):ab,ti OR (enzyme linked immunosorbent assay):ab,ti OR (enzyme immunoassay):ab,ti OR (enzyme-linked immunosorbent assay):ab,ti OR (ELISA):ab,ti OR (precipitation reaction*):ab,ti OR (serum precipitins*):ab,ti OR (immunoprecipitation technique*):ab,ti OR (precipitating antibod*):ab,ti OR (double immunodiffusion):ab,ti OR (Ouchterlony):ab,ti OR (electrosyneresis):ab,ti OR (ImmunoCAP):ab,ti
Final search 1 AND 2	
The Cochrane Library	
Bird fancier's lung	[bird fancier's lung] explode all trees OR (bird fancier NEAR/3 lung?):ti,ab,kw OR (lung?, bird fancier's):ti,ab,kw OR (bird breeder*):ti,ab,kw OR (lung?, bird breeder's):ti,ab,kw
Serologic assay for IgG antibodies	[immunoassay] explode all trees OR (immunoassay):ti,ab,kw OR (immunoassay?):ti,ab,kw OR (immunochemical technique?):ti,ab,kw OR (antibody testing?):ti,ab,kw OR (serum antibody detection?):ti,ab,kw OR (serum assay?):ti,ab,kw OR (IgG):ti,ab,kw OR (immunoglobulin G):ti,ab,kw OR (enzyme-linked immunosorbent assay):ti,ab,kw OR (enzyme immunoassay):ti,ab,kw OR (enzyme?linked immunosorbent assay):ti,ab,kw OR (ELISA):ti,ab,kw OR (precipitation reaction?):ti,ab,kw OR (serum precipitins*):ti,ab,kw OR immunoprecipitation technique?:ti,ab,kw OR (precipitating antibod*):ti,ab,kw OR (double NEAR/6 diffusion):ti,ab,kw OR (Ouchterlony):ti,ab,kw OR (ImmunoCAP):ti,ab,kw
Final search 1 AND 2	
International Clinical Trials Registry Platform	
Final search (bird-related hypersensitivity pneumonitis)	

Figure S1 The strategy used for searching publications related to bird fancier's lung and serologic assays for IgG antibodies.

Table S1 The preferred reporting Items for systematic review and meta-analyses guidelines

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
Title/abstract			
Title	1	Identify the report as a systematic review (+/– meta-analysis) of DTA studies	1
Abstract	2	Abstract: see PRISMA-DTA for abstracts	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	1–2
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design)	1–2
Objectives	4	Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s)	1–2
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	2
Eligibility criteria	6	Specify study characteristics (participants, setting, index test(s), reference standard(s), target condition(s), and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	2
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated	2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	2
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target condition(s), index test(s), reference standard(s) and other characteristics (e.g., study design, clinical setting)	2
Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question	2
Diagnostic accuracy measures	13	State the principal diagnostic accuracy measure(s) reported (e.g., sensitivity, specificity) and state the unit of assessment (e.g., per-patient, per-lesion)	2
Synthesis of results	14	Describe methods of handling data, combining results of studies and describing variability between studies. This could include, but is not limited to: (I) handling of multiple definitions of target condition; (II) handling of multiple thresholds of test positivity; (III) handling multiple index test readers; (IV) handling of indeterminate test results; (V) grouping and comparing tests; (VI) handling of different reference standards	2
Meta-analysis	D2	Report the statistical methods used for meta-analyses, if performed	2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	2
Results			
Study selection	17	Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram	3
Study characteristics	18	For each included study provide citations and present key characteristics including: (I) participant characteristics (presentation, prior testing); (II) clinical setting; (III) study design; (IV) target condition definition; (V) index test; (VI) reference standard; (VII) sample size; (VIII) funding sources	3–5
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study	3,6
Results of individual studies	20	For each analysis in each study (e.g., unique combination of index test, reference standard, and positivity threshold) report 2×2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot	6
Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals	6–7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events)	7
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence	7–8
Limitations	25	Discuss limitations from included studies (e.g., risk of bias and concerns regarding applicability) and from the review process (e.g., incomplete retrieval of identified research)	8–9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g., the intended use and clinical role of the index test)	9
Funding			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders	9

TP, true positive; FP, false positive; FN, false negative; TN, true negative; DTA, diagnostic test accuracy.

Table S2 Detailed information about index test and reference standard in included studies

Study ID	Index test (antigen)	Cut-off	Reference standard
Inase *et al.* (13)	ImmunoCAP (pigeon serum, feather, and feces antigens)	34.2 μg/mL for acute bird-related HP, 35.9 μg/mL for chronic bird-related HP	Acute bird-related HP: (I) history of bird exposure; (II) fine crackle; (III) elevated lymphocytes in BALF; (IV) centrilobular nodule or ground grass opacities; (V) positive antigen-avoidance test
			Chronic bird-related hypersensitivity pneumonitis: (I) history of bird exposure; (II) fine crackle; (III) elevated lymphocytes in BALF; (IV) pathological findings of surgical biopsy is chronic HP; (V) restrictive pulmonary dysfunction which had progressed for over 1 year or related symptoms lasting more than 6 months; (VI) positive pigeon feces-inhalation test or symptom improvement by antigen avoidance
	ImmunoCAP assay (budgerigar serum, feather, and feces antigens)	20.0 μg/mL for acute bird-related HP, 13.4 μg/mL for chronic bird-related HP	Acute bird-related HP: (I) history of bird exposure; (II) fine crackle; (III) elevated lymphocytes in BALF; (IV) centrilobular nodule or ground grass opacities; (V) positive antigen-avoidance test
			Chronic bird-related HP: (I) history of bird exposure; (II) fine crackle; (III) elevated lymphocytes in BALF; (IV) pathological findings of surgical biopsy is chronic HP; (V) restrictive pulmonary dysfunction which had progressed for over 1 year or related symptoms lasting more than 6 months; (VI) positive pigeon feces-inhalation test or symptom improvement by antigen avoidance
Martínez-Cordero *et al.* (14)	Ouchterlony method (avian serum antigens)	One or more precipitation arcs	Clinical, immunological, functional, and histopathological criteria and by X-ray abnormalities compatible with pigeon breeder's disease after analysis of clinical records
Suhara *et al.* (15)	ELISA (pigeon feces antigens)	0.364 for acute bird-related HP versus acute summer-type HP	The diagnosis of acute and chronic bird-related HP was based on clinical, radiological, and histological criteria
		0.376 for choric bird-related HP (unknown unit)	
Simpson *et al.* (16)	ELISA (pigeon feces antigens)	An optical density of 0.082 (3 standard deviations)	History of exposure to pigeons and clinical symptoms such as fever, cough, and breathlessness, suggestive of pigeon breeder's disease
	Ouchterlony method (pigeon feces antigens)	One or more precipitation arcs	History of exposure to pigeons and clinical symptoms such as fever, cough, and breathlessness, suggestive of pigeon breeder's disease
Rouzet *et al.* (17)	ELISA (pigeon dropping extract)	0.489 (unknown unit)	(I) exposure to offending antigens; (II) symptoms and HRCT compatible with HP and basal crepitant rales; (III) elevated lymphocytes in BALF; (IV) decreased DLCO for carbon monoxide during exercise
	ELISA (immunoglobulin lambda-like polypeptide-1)	0.196 (unknown unit)	(I) exposure to offending antigens; (II) symptoms and HRCT compatible with HP and basal crepitant rales; (III) elevated lymphocytes in BALF; (IV) decreased DLCO during exercise
	ELISA (proproteinase E)	0.435 (unknown unit)	(I) exposure to offending antigens; (II) symptoms and HRCT compatible with HP and basal crepitant rales; (III) elevated lymphocytes in BALF; (IV) decreased DLCO during exercise
Sandoval *et al.* (18)	ELISA (pigeon serum antigens)	0.55 optical density units	Not described
Faux *et al.* (19)	Ouchterlony method (budgerigar serum antigens)	Not described	Patients who had budgerigars and clinical symptoms of dyspnea without wheezing, crepitant rales, micronodular infiltration of the lungs and (in some cases) evidence suggestive of pulmonary fibrosis in X-rays, and pulmonary function tests showing a restrictive ventilatory defect with impaired gas transfer
	Electrosyneresis method (budgerigar serum antigens)	Not described	Patients who had budgerigars and clinical symptoms of dyspnea without wheezing, crepitant rales, micronodular infiltration of the lungs and (in some cases) evidence suggestive of pulmonary fibrosis in X-rays, and pulmonary function tests showing a restrictive ventilatory defect with impaired gas transfer
Pelikan *et al.* (20)	Ouchterlony method (pigeon serum antigens)	Two or more precipitation arcs	Positive for bronchial-challenge test with pigeon feces, among bronchial patient complaints
	Ouchterlony method (pigeon feces antigens)	Two or more precipitation arcs	Positive for bronchial-challenge test with pigeon feces, among bronchial patient complaints
Rodrigo *et al.* (21)	ELISA (pigeon serum antigens)	367 (unknown unit)	Patients who had positive precipitated antibodies (by the countercurrent-immunoelectrophoresis method) and had a positive inhalation test or a lung biopsy with changes typical of extrinsic allergic alveolitis
	ELISA (bloom extract antigens)	953 (unknown unit)	Patients who had positive precipitated antibodies (by the countercurrent-immunoelectrophoresis method) and had a positive inhalation test or a lung biopsy with changes typical of extrinsic allergic alveolitis

BALF, bronchoalveolar lavage fluid; DLCO, diffusing capacity of lung; ELISA, enzyme-linked immunosorbent assay; HP, hypersensitivity pneumonitis; HRCT, high resolution computed tomography.