Diagnostic Performance of Bronchoalveolar Lavage Fluid CD4/CD8 Ratio for Sarcoidosis: A Meta-analysis

Yongchun Shen 1, Caishuang Pang 1, Yanqiu Wu, Diandian Li, Chun Wan, Zenglin Liao, Ting Yang, Lei Chen *, Fuqiang Wen *

Department of Respiratory and Critical Care Medicine, West China Hospital of Sichuan University and Division of Pulmonary Diseases, State Key Laboratory of Biotherapy of China, Chengdu 610041, China

ABSTRACT

Background: The usefulness of bronchoalveolar lavage fluid (BALF) CD4/CD8 ratio for diagnosing sarcoidosis has been reported in many studies with variable results. Therefore, we performed a meta-analysis to estimate the overall diagnostic accuracy of BALF CD4/CD8 ratio based on the bulk of published evidence.

Methods: Studies published prior to June 2015 and indexed in PubMed, OVID, Web of Science, Scopus and other databases were evaluated for inclusion. Data on sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were pooled from included studies. Summary receiver operating characteristic (SROC) curves were used to summarize overall test performance. Deeks’s funnel plot was used to detect publication bias.

Results: Sixteen publications with 1885 subjects met our inclusion criteria and were included in this meta-analysis. Summary estimates of the diagnostic performance of the BALF CD4/CD8 ratio were as follows: sensitivity, 0.70 (95%CI 0.64–0.75); specificity, 0.83 (95%CI 0.76–0.86); PLR, 4.04 (95%CI 3.13–5.20); NLR, 0.36 (95%CI 0.30–0.44); and DOR, 11.17 (95%CI 7.31–17.07). The area under the SROC curve was 0.84 (95%CI 0.81–0.87). There was no evidence of publication bias.

Conclusion: Measuring the BALF CD4/CD8 ratio may assist in the diagnosis of sarcoidosis when interpreted in parallel with other diagnostic factors.

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2. Methods

This study was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews, as well as the Meta-analysis Statement and methods recommended by the Cochrane Diagnostic Test Accuracy Working Group (Leeﬂang et al., 2008). Institutional review board approval was not required for this retrospective meta-analysis.

2.1. Search Strategy

PubMed, OVID, Web of Science, Scopus, Wanfang, Weipu and CNKI databases were searched for original articles that examined the diagnostic performance of BALF CD4/CD8 for sarcoidosis and that were published up to October 2015. In PubMed, the search string was “(Bronchoalveolar lavage OR Bronchoalveolar lavage fluid OR BAL OR BALF) AND sarcoidosis) AND CD4/CD8 ratio”. In OVID, references in EMBASE from 1974 to June 2015 and in Medline from 1946 to October 2015 were searched using the following string: “Bronchoalveolar lavage OR “Bronchoalveolar lavage fluid” OR “BAL” OR “BALF” AND “CD4/CD8 ratio” AND “sarcoidosis” AND “sensitivity OR speciﬁcity OR accuracy”. Search results were limited to human and clinical trials. In Wanfang, Weipu and CNKI databases, the following search string was used: “Bronchoalveolar lavage ﬂuid” AND “sarcoidosis” AND “CD4/CD8 ratio”. The “remove duplicates” function was applied during searches in OVID and the Chinese databases. Additional articles were also searched using the “related articles” function in PubMed. References within identiﬁed articles were searched manually to find more articles.

2.2. Selection of Publications

We screened titles and abstracts of identiﬁed publications, and those studies that could not be immediately excluded were retrieved as full text. Publications were included in our meta-analysis if they fulﬁlled the following criteria: (1) they used BALF CD4/CD8 ratio for diagnosing sarcoidosis; (2) they reported sufﬁcient data to calculate true positive (TP), false positive (FP), false negative (FN), and true negative (TN) of the BALF CD4/CD8 ratio for diagnosing sarcoidosis; and (3) they constituted original research published in English or Chinese. To avoid selection bias, we excluded studies involving fewer than 20 subjects. Conference abstracts, reviews, editorials, and case reports were also excluded.

2.3. Data Extraction and Quality Assessment

Two reviewers (YCS and CSP) independently judged the eligibility of publications and extracted the following data: ﬁrst author, year of publication, country, number of cases and controls, diagnostic standard, sample, method, cut-off values, TP, FP, FN, TN, and study design. Discrepancies in data extraction were resolved by consensus. Efforts were made to contact authors when information was not reported in the article. For studies in which several different cut-off values were tested, only the data associated with the best diagnostic performance was included in this meta-analysis.

The methodological quality of each study was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 (Whiting et al., 2011). This tool consists of four domains: patient selection, index test, reference standard, as well as ﬂow and timing. Risk of bias was assessed in four domains, the ﬁrst three of which concern applicability.

2.4. Statistical analysis

Standard methods recommended for diagnostic accuracy meta-analysis were used (Devillé et al., 2002; Nguyen et al., 2015). We analyzed the test accuracy of each study by calculating sensitivity, speciﬁcity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), together with the corresponding 95% CIs. Summary receiver operating characteristic (SROC) curves and the area under the curve (AUC) were also calculated (Moses et al., 1993). Heterogeneity between studies was evaluated using the χ2 test and Fisher’s exact tests. If signiﬁcant heterogeneity existed among studies, meta-regression analysis was performed using covariates reported in most included studies: cut-off values, sample size (<100 subjects vs. ≥100 subjects), study design (prospective vs. retrospective), publication year (before 2005 vs. after 2005), sampling method (consecutive vs. not reported), risk of bias (low vs. high), income in study country (high vs. low or middle, based on World Bank ranking of national economies), and ethnicity (Asian vs. Caucasian). Sensitivity analysis was conducted by subgroups based on the meta-regression results.

Deeks’s funnel plot was used to detect publication bias (Deeks et al., 2005). Post-test probability (PTP) was calculated using the overall prevalence of 20% with Fagan nomograms. Three statistical software programs were used in this meta-analysis: STATA 12.0 (Stata Corp., College Station, TX), Meta-Disc 1.4 (XI, Cochrane Colloquium, Barcelona, Spain), and RevMan 5.2 (Cochrane Collaboration, Oxford, UK). All statistical tests were two-sided, and P<0.05 was considered statistically signiﬁcant.

2.5. Role of the Funding Source

The funders had no role in the study design, collection, analysis or interpretation of the data, or writing of the report. All authors had access to the raw data. The corresponding author had full access to all the data and assumed responsibility for submitting for publication.

3. Results

3.1. Characteristics and Quality of the Included Studies

Fig. 1 outlines the study selection, which led to the inclusion of 16 publications in this meta-analysis (Lee et al., 2015; Suchankova et al., 2013; von Bartheld et al., 2013; Hylgaard et al., 2012; De Smet et al., 2010; Korosec et al., 2010; Danila et al., 2009a; Yao et al., 2008; Heron et al., 2008; Fireman et al., 2006; Smith et al., 2006a; Greco et al., 2005; Marruchella and Tondini, 2002; Fireman et al., 1999; He et al., 1994; Winterbauer et al., 1993). In the studies by Heron et al, BALF CD4/CD8 ratio was analyzed in an analysis cohort and a validation cohort; each was treated as an independent study in our meta-analysis (Heron et al., 2008). Consequently, 17 studies were meta-analyzed, 12 of which were prospective and 5 retrospective.

The mean sample size of eligible studies was 111 (range 30–503), involving 999 patients with sarcoidosis and 886 non-sarcoidosis controls. In all studies, BALF samples were analyzed using flow cytometry. One of the 17 studies blinded diagnosis of patients (von Bartheld et al., 2013), while the others did not report blinding. In 10 studies (nine publications) (Hylgaard et al., 2012; De Smet et al., 2010; Korosec et al., 2010; Yao et al., 2008; Heron et al., 2008; Greco et al., 2005; Marruchella and Tondini, 2002; Fireman et al., 1999; He et al., 1994), all patients in the case group had biopsy-confirmed sarcoidosis. In seven studies (Lee et al., 2015; Suchankova et al., 2013; von Bartheld et al., 2013; Danila et al., 2009a; Fireman et al., 2006; Smith et al., 2006a; Winterbauer et al., 1993), sarcoidosis was diagnosed based on the combination of clinical, radiological and pathological evidence: diagnosis was based on biopsy showing non-caseating granulomas, after exclusion of other known causes of granulomatosis. Two studies were done in middle-income countries; the others, in high-income countries.
Key characteristics of included studies are shown in Table 1. Patient demographic information is listed in Supplementary Table 1.

The methodological quality of each study was assessed using QUADAS-2. When a criterion was fulfilled, an answer of Yes was given, Unclear if a criterion was unclear or not reported, and No if a criterion was not achieved. The quality of studies was generally good (Fig. 2), but three studies were judged to have a high risk of bias in the patient selection domain (Hyldgaard et al., 2012; Yao et al., 2008; Greco et al., 2005). Two of these studies also showed high risk of bias related to flow and timing (Hyldgaard et al., 2012; Yao et al., 2008).

### Table 1
Summary of studies included in the meta-analysis.

| Author/year [ref] | Country  | Ethnicity | Cases/controls | Method | Cut-off value | TP  | FP  | FN  | TN  | Study design | Sampling method | Risk of bias | Income |
|-------------------|----------|-----------|----------------|--------|---------------|-----|-----|-----|-----|--------------|----------------|-------------|--------|
| Lee et al. (2015) | South Korea | Asian | 12/57 | FCM | 2.16 | 11 | 9 | 1 | 48 | P | Consecutive | Low | High |
| Suchankova et al. (2013) | Slovakia | Caucasian | 36/27 | FCM | 3.5 | 18 | 1 | 8 | 26 | P | Consecutive | Low | High |
| von Bartheld et al. (2013) | Netherlands | Caucasian | 136/13 | FCM | 3.5 | 73 | 1 | 63 | 12 | P | Consecutive | Low | High |
| Hyldgaard et al. (2012) | Denmark | Caucasian | 19/83 | FCM | 3.8 | 13 | 22 | 6 | 61 | P | Consecutive | Low | High |
| De Smet et al. (2010) | Belgium | Caucasian | 36/117 | FCM | 2.62 | 24 | 21 | 12 | 96 | R | Consecutive | Low | High |
| Korosec et al. (2010) | Slovenia | Caucasian | 47/8 | FCM | 3.3 | 33 | 14 | 7 | 70 | P | Consecutive | Low | High |
| Danila et al. (2009a) | Lithuania | Caucasian | 318/185 | FCM | 3.5 | 254 | 18 | 64 | 167 | P | Consecutive | Low | High |
| Yao et al., (2008) | China | Asian | 41/10 | FCM | 4 | 28 | 3 | 13 | 7 | R | Consecutive | High | Middle |
| Heron et al., (2008) | Netherlands | Caucasian | 56/63 | FCM | 3 | 38 | 17 | 18 | 46 | P | Unknown | Low | High |
| Heron et al. (2008) | Netherlands | Caucasian | 26/13 | FCM | 3 | 16 | 2 | 10 | 11 | P | Unknown | Low | High |
| Fireman et al. (2006) | Israel | Caucasian | 67/53 | FCM | 2.5 | 51 | 15 | 16 | 38 | R | Unknown | Low | High |
| Smith et al. (2006a) | USA | Caucasian | 14/12 | FCM | 2.3 | 10 | 2 | 4 | 10 | P | Unknown | Low | High |
| Greco et al. (2005) | Italy | Caucasian | 88/76 | FCM | 3.5 | 48 | 18 | 40 | 58 | R | Consecutive | High | High |
| Marruchella and Tondini (2002) | Italy | Caucasian | 51/38 | FCM | 3.5 | 30 | 5 | 21 | 33 | R | Consecutive | Low | High |
| Fireman et al. (1999) | Israel | Caucasian | 14/16 | FCM | 2.5 | 14 | 3 | 0 | 13 | P | Unknown | Low | High |
| He et al., (1994) | China | Asian | 21/14 | FCM | 3.5 | 18 | 0 | 3 | 14 | P | Consecutive | Low | Middle |
| Winterbauer et al. (1993) | USA | Caucasian | 27/101 | FCM | 4 | 29 | 17 | 7 | 84 | P | Consecutive | Low | High |

BALF = bronchoalveolar lavage fluid; FCM = flow cytometry; FN = false negative; FP = false positive; P = prospective; R = retrospective; TN = true negative; TP = true positive.
3.2. Diagnostic Accuracy

Fig. 3 shows individual study data and provides the Forest plots of sensitivity and specificity for using the BALF CD4/CD8 ratio to diagnose sarcoidosis. Table 2 shows summary estimates of diagnostic performance. Sensitivity ranged from 0.54 to 1.00, and pooled sensitivity was 0.70 (95%CI, 0.64–0.75). Specificity ranged from 0.70 to 1.00, and pooled specificity was 0.83 (95% CI, 0.78–0.86). Pooled PLR and NLR were 4.04 (95%CI, 3.13–5.20) and 0.36 (95%CI, 0.30–0.44), respectively. DOR was 11.17 (95%CI, 7.31–17.07), and the AUC was 0.84 (95%CI, 0.81–0.87) (Fig. 4).

3.3. Meta-regression Analysis

Chi-squared values for pooled diagnostic performance parameters were high: sensitivity, 58.53; specificity, 31.83; PLR, 33.98; NLR, 50.55; and DOR, 1.5 × 108 (all P < 0.05). This indicates significant heterogeneity among the included studies (Table 2). In order to identify possible reasons for this heterogeneity, meta-regression was conducted to assess the effect of study quality on the relative DOR (RDOR) of BALF CD4/CD8 ratio for diagnosis of sarcoidosis. The characteristics of these covariates are listed in Table 1. Diagnostic accuracy was not significantly affected by sample size (P = 0.24), publication year (P = 0.34), sampling method (P = 0.56), income (P = 0.93), or cut-off value (P = 0.57). Ethnicity (Asian vs. Caucasian) did not significantly affect RDOR (P = 0.93) Two factors may affect the diagnostic accuracy: study design (P = 0.048) and risk of bias (P = 0.03). The meta-regression results are shown in detail in Table 3.

Based on these meta-regression results, we performed sensitivity analysis by stratifying study participants based on study design and risk of bias. These two analyses suggested that prospective studies and high-quality studies (with low risk of bias) reported much better diagnostic performance than retrospective studies or studies with high or uncertain risk of bias (Table 2).

3.4. Publication Bias Evaluation

Deeks’s funnel plot asymmetry test was used to assess likelihood of publication bias in the final set of studies. The slope coefficient was associated with P = 0.75, and the shape of the funnel plot of the pooled DOR of the CD4/CD8 ratio was not obviously asymmetrical (Fig. 5).

4. Discussion

Numerous studies have focused on the potential value of BALF CD4/CD8 ratio for diagnosis of sarcoidosis. This is based on the fact that CD4+ T cells interacting with antigen-presenting cells appear to trigger formation of sarcoid granulomas and help maintain them (Iannuzzi et al., 2007; Baughman et al., 2003). In addition, activated alveolar

![Fig. 2. Quality assessment of individual studies in terms of risk of bias and applicability concerns based on the Quality Assessment of Diagnostic Accuracy Studies-2.](Image)

![Fig. 3. Forest plot of the summary sensitivity and specificity of BALF CD4/CD8 ratio for the diagnosis of sarcoidosis. The sensitivity/specificity of each study is represented as a circle, and the 95%CI is shown as a horizontal line running through the circle. TP = true positive. FP = false positive. FN = false negative. TN = true negative. BALF = bronchoalveolar lavage fluid.](Image)
macrophages and CD4+ T cells participate in the influx of mononuclear cells into the alveoli that often precedes sarcoid granuloma formation in the lung (Baughman et al., 2011; Jones, 2002). Diagnostic studies have reported highly variable sensitivity and specificity when using the CD4/CD8 ratio, prompting us to perform what we believe to be the first meta-analysis to assess the available evidence on the diagnostic usefulness of this ratio in sarcoidosis.

The pooled results indicate relatively low diagnostic sensitivity of 0.70, and specificity of 0.83, suggesting a relatively high rate of missed diagnoses (30%) and misdiagnoses (17%), Likelihood ratios >10 and <0.1 are considered as strong indicators to rule in or rule out a diagnosis, respectively (Deeks and Altman, 2004). In the present meta-analysis, PLR was 4.04 and NLR was 0.36, suggesting relatively low ability to discriminate sarcoidosis from non-sarcoidosis, although the AUC in SROC analysis was relatively high (0.84). While it appears the BALF CD4/CD8 ratio is not robust enough on its own to diagnose sarcoidosis, PLR was 4.04 and NLR was 0.36, suggesting relatively low ability to discriminate sarcoidosis from non-sarcoidosis, although the AUC in SROC analysis was relatively high (0.84). While it appears the BALF CD4/CD8 ratio is not robust enough on its own to diagnose sarcoidosis, it may be a helpful ancillary tool that, when interpreted together with other diagnostic factors, can improve sarcoidosis diagnosis.

QUADAS-2 was used to assess methodological quality of the studies included in our meta-analysis. QUADAS-2 provides more detailed and rigorous assessment than the earlier QUADAS, such as in the explanation of indeterminate results. Although this instrument can be used to assign quality scores (Whiting et al., 2003), it is fundamentally a qualitative tool, which we used to characterize risk of bias along four domains as low, high, or unclear. This analysis suggested quality differences among the included studies, and meta-regression suggested that study quality may have affected the reported diagnostic performance of the BALF CD4/CD8 ratio. In addition, diagnostic performance of the BALF CD4/CD8 ratio was variable even among studies at low risk of bias. These findings highlight the need for better-designed diagnostic studies, particularly prospective studies and studies with low risk of bias. These studies should carefully address the issue of variability of the BALF CD4/CD8 ratio as a diagnostic tool.

The studies included in this meta-analysis varied in their cut-off values for the CD4/CD8 ratio, which usually fell between 2 and 4. No international standards exist about what cut-off value to use, and this value is likely to vary with clinical context, depending on country, ethnicity, examination equipment, disease severity, and history of corticosteroid treatment. Our meta-regression of cut-off values suggests that different cut-off values did not substantially affect the diagnostic accuracy of the BALF CD4/CD8 ratio (P = 0.57, Table 2). This contrasts

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**Table 2**

Summary of overall analysis and sensitivity analysis based on study design and risk of bias.

| Study design | Number of studies | Sensitivity (95%CI) | Specificity (95%CI) | Heterogeneity (I²) | Risk of bias (QUADAS-2) |
|--------------|------------------|--------------------|--------------------|-------------------|------------------------|
| Prospective  | 12               | 0.70 (0.64–0.75)   | 0.83 (0.78–0.86)   | 31.83 (0.01)      | Low (3)                |
| Retrospective| 5                | 0.64 (0.58–0.70)   | 0.84 (0.81–0.87)   | 17.07 (0.001)     | Low (3)                |

**Table 3**

Meta-regression of the diagnostic accuracy of BALF CD4/CD8 ratio.

| Covariate | No. of studies | Coefficient | RDOR (95%CI) | P     |
|-----------|----------------|-------------|--------------|-------|
| Sample size |     |             |              |       |
| ≥ 100    | 8              | −0.61       | 0.54 (0.19–1.58) | 0.24  |
| <100     | 9              |             |              |       |
| Study design |     |             |              |       |
| Prospective | 12         | −0.91       | 0.40 (0.16–0.99) | 0.048 |
| Retrospective | 5          |             |              |       |
| Publication year |     |             |              |       |
| After 2005 | 13           | −0.59       | 0.55 (0.15–2.02) | 0.34  |
| Before 2005 | 4            |             |              |       |
| Sampling method |     |             |              |       |
| Consecutive | 12           | 0.34        | 1.41 (0.42–4.75) | 0.56  |
| Unknown   | 5              |             |              |       |
| Risk of Bias |     |             |              |       |
| Low       | 14             | 1.14        | 3.12 (1.12–8.7) | 0.03  |
| High      | 3              |             |              |       |
| Income    |     |             |              |       |
| High      | 15             | 0.08        | 1.08 (0.15–7.68) | 0.93  |
| Low/middle| 2              |             |              |       |
| Cut-off value |     |             |              |       |
| 3–4       | 13             | −0.35       | 0.70 (0.19–2.59) | 0.57  |
| <3 or >4  | 4              |             |              |       |
| Ethnicity |     |             |              |       |
| Asian     | 2              | 0.08        | 1.08 (0.15–7.68) | 0.93  |
| Caucasian | 15             |             |              |       |
with previous studies showing that a CD4/CD8 ratio ≥ 3.5 strongly suggests sarcoidosis, but is not specific enough on its own to diagnose the disease (Marruchella and Tondini, 2002; Costabel et al., 2010). Further work should aim to identify the cut-off value that provides optimal diagnostic accuracy, and researchers should be open to the possibility that different cut-offs are needed for different types of patients or clinical contexts. In addition, all included studies utilized flow cytometry to determine the BALF CD4/CD8 ratio based on a protocol developed for peripheral blood samples. Several studies have reported that flow cytometric typing of lymphocytes from BALF correlates well with results from conventional immunocytochemistry (Brandt et al., 1996; Ma et al., 2001; Smith et al., 2006b; Szpechcinski et al., 2011), though the results may depend on combinations of antibodies and gating strategies. Therefore future studies are needed to optimize these parameters for typing lymphocytes in BALF.

There are several factors that should be addressed which may influence the BALF CD4/CD8 ratio. One factor is smoking, which is associated with higher total cell number, higher proportions of CD8 + lymphocytes and CD4 + cells, and lower CD4+ /CD8+ ratio in BALF (Hoser et al., 1999). Numbers of CD4+ and CD8+ cells in BALF are also affected in smokers with comorbidities such as chronic obstructive pulmonary disease (Forslund et al., 2014). Several studies included in this meta-analysis reported smoking history, while its effect on BALF CD4/CD8 ratio remains unclear (Korosec et al., 2010; Fireman et al., 2006). Future studies should examine the potential impact of smoking on BALF cell numbers and proportions, and thereby on the potential diagnostic usefulness of the BALF CD4/CD8 ratio. Another factor was the stage of sarcoidosis. As pulmonary sarcoidosis advances from stage I to stage III, the number of CD8+ cells increases and the number of CD4+ cells decreases, leading to a decrease in the CD4/CD8 ratio (Danila et al., 2008). Indeed, previous work has shown that the diagnostic sensitivity of the BALF CD4/CD8 ratio decreases with increasing stage of sarcoidosis (Danila et al., 2009a); on the other hand, the ratio may be less clinically useful in stage I disease, for which clinical and radiographic features on their own show high diagnostic reliability. A third factor that should be addressed is the recovery rate of BALF, which has been reported to range widely from 23.3% to 91.3% (Fireman et al., 2006; Winterbauer et al., 1993). Most studies included in our meta-analysis did not report the recovery rate, which may bias diagnostic accuracy. A fourth factor was whether or not participants were on corticosteroid treatment, which can modify lymphocyte proportions in BALF and thereby the BALF CD4/CD8 ratio (Danila et al., 2009b). Indeed, some studies suggest that this ratio shows lower diagnostic sensitivity in patients on such treatment (Danila et al., 2009a; He et al., 1994). None of the patients in nine studies (eight publications) received corticosteroids (Suchankova et al., 2013; De Smet et al., 2010; Korosec et al., 2010; Yao et al., 2008; Heron et al., 2008; Fireman et al., 2006; Fireman et al., 1999; Winterbauer et al., 1993), while the other studies did not report corticosteroid status (Lee et al., 2015; von Bartheld et al., 2013; Hyldgaard et al., 2012; Smith et al., 2006a; Greco et al., 2005; Marruchella and Tondini, 2002). Future studies should take into account possible confounding by smoking status, recovery rate, and corticosteroid treatment when assessing the diagnostic performance of BALF CD4/CD8 ratio. Studies should also look systematically at whether the ratio is more clinically useful for advanced stages of the disease, where clinical and radiographic features on their own can be less informative.

The findings of this meta-analysis should be interpreted with caution because of several limitations. First, we excluded conference abstracts, reviews, editorials, case reports and articles not written in English or Chinese, which may bias our results. In addition, we omitted unpublished studies and studies not indexed in our set of databases. Nevertheless, our funnel plots suggested no significant risk of publication bias. Second, there may have been misclassification bias. The diagnosis of sarcoidosis in the case group was biopsy-confirmed in only 12 studies (11 publications); in the remaining five studies (Lee et al., 2015; Suchankova et al., 2013; Danila et al., 2009a; Fireman et al., 2006; Smith et al., 2006a), sarcoidosis was diagnosed based on the combination of clinical, radiological, pathological and follow-up observation. Some cases lacked histological evidence of non-caseating granulomas. Third, most studies in our meta-analysis did not report blinding, which increases the risk of analytical bias. Future diagnostic studies should avoid these methodological problems. Future studies should also examine the cost-effectiveness of determining BALF lymphocyte ratios relative to more invasive biopsy, as well as compare the ratio with endobronchial ultrasound transbronchial needle aspiration, which has been shown to be a safe and effective diagnostic procedure (Costabel et al., 2010; Agarwal et al., 2012).

In conclusion, our meta-analysis provides the most comprehensive evidence to date that the determination of the BALF CD4/CD8 ratio can aid in the diagnosis of sarcoidosis, with an elevated ratio associated with greater likelihood of disease in patients who present a typical clinical/radiological picture of the disease. However, the ratio is not specific or selective enough to use on its own; rather, it must always be combined with other established diagnostic factors and tests.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebiom.2016.04.024.

Author Contributions

Y.C.S. and C.S.P. conceived the project, performed the systematic review and meta-analysis, and drafted and revised the manuscript. These authors also take full responsibility for the integrity of the data and the accuracy of the data analysis. Y.Q.W., C.W. and D.D.L. contributed to the systematic review and helped draft the manuscript. Z.L.L., T.Y. and L.C. contributed to data acquisition and analysis. F.Q.W. drafted and revised the manuscript. These authors also take full responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

All authors have read the journal’s policy on disclosure of potential conflicts of interest and have none to declare.

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