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Research Paper

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

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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 0.78–0.86); 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.

1. Introduction

Sarcoidosis, a chronic inflammatory disorder of unknown cause, is the most frequently observed interstitial lung disease of unknown origin in Europe (Baughman and Grutters, 2015). It usually affects the lung and lymphatic system, but its clinical features are varied and non-specific, and it shows variable radiographic presentation, all of which makes accurate diagnosis a challenge. Typically, sarcoidosis is diagnosed when clinical and/or radiographic findings are supported by histological evidence of non-caseating granulomatous inflammation, and when other causes of granulomas and local reactions can be reasonably excluded (Iannuzzi et al., 2007; Costabel et al., 2008; Am J Respir Crit Care Med, 1999). Another problem with diagnosing sarcoidosis is that, unless patients show typical manifestations of Löfgren syndrome, biopsy is recommended, making diagnosis invasive (Iannuzzi et al., 2007; Costabel et al., 2008; Am J Respir Crit Care Med, 1999). As a result, investigators continue to search for reliable, less invasive methods to diagnose sarcoidosis.

Growing evidence points to the possibility of analyzing the bronchoalveolar lavage fluid (BALF) to aid in diagnosis. In sarcoidosis, T_H1 hyperimmune response to an unknown agent causes CD4+ T lymphocytes to accumulate in affected tissues and leads to the formation of non-caseating granulomas (Baughman et al., 2003). As a result, many patients with sarcoidosis show elevated lymphocytosis and CD4/CD8 ratio in BALF, and this elevated ratio has been associated with a diagnosis of sarcoidosis (Baughman et al., 2003; Costabel, 1997). Indeed, clinicians may opt not to perform diagnostic biopsy in patients who present both a clinical picture typical of sarcoidosis and an elevated BALF CD4/CD8 ratio (Kvale, 2003; Kantrow et al., 1997). Several studies have suggested that the BALF CD4/CD8 ratio can supplement the results of other tests when diagnosing sarcoidosis (Wells and Hirani, 2008; Chretien et al., 1985; Stoller et al., 1987).

However, whether the BALF CD4/CD8 ratio can reliably perform as a diagnostic tool remains controversial. The ratio shows high variability (Kantrow et al., 1997), and studies of its diagnostic performance suggest variable sensitivity and specificity. To gain a clearer picture of the

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diagnostic usefulness of this ratio, we performed a meta-analysis to summarize its overall diagnostic performance based on the available literature.

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 χ^2 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; Hyldgaard 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) (Hyldgaard 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.