Efficacy and safety of convex probe EBUS-TBNA in sarcoidosis: A systematic review and meta-analysis

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TBNA;
Meta-analysis

Summary
Background and aim: Real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive technique for diagnosis of mediastinal lymphadenopathy. Although most studies have reported the utility of EBUS-TBNA in malignancy, its use has been extended to benign conditions including sarcoidosis. Herein, we perform a systematic review and meta-analysis of studies reporting the diagnostic yield and safety of EBUS-TBNA in sarcoidosis.

Methods: We searched the PubMed and Embase databases for relevant studies published from 2004 to 2011, and included studies that have reported the diagnostic yield of EBUS-TBNA in sarcoidosis. The quality of studies was assessed using the QualSyst tool. We calculated the proportions with 95% confidence interval (CI) to assess the diagnostic yield of EBUS-TBNA in sarcoidosis and then pooled the results using a random effects model. Heterogeneity was assessed using the $I^2$ and Cochran-Q tests while publication bias was assessed using both graphical and statistical methods.

Results: Our search yielded 15 studies (553 patients of sarcoidosis). The diagnostic yield of EBUS-TBNA ranged from 54 to 93% with the pooled diagnostic accuracy being 79% (95% CI, 71–86%) by the random effects model. The yield was not statistically different in studies employing on-site cytological evaluation (80.1%) vs. those without (81.3%). However, the diagnostic yield was significantly higher in prospective studies (83.9%) vs. the retrospective studies (74.3%). Only five minor complications were reported in 553 patients. There was evidence of heterogeneity and publication bias.

Conclusions: EBUS-TBNA is a safe and efficacious procedure in the diagnosis of sarcoidosis, and should be routinely employed wherever available.

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Introduction

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology that commonly presents with bilateral hilar adenopathy, pulmonary infiltrates, ocular and skin lesions. The diagnosis is established in presence of compatible clinicoradiographic findings and histologic evidence of noncaseating epithelioid cell granulomas after exclusion of other known causes for granulomatous inflammation. As the lung and mediastinal lymph nodes are most often affected in sarcoidosis, bronchoscopic techniques are often employed for demonstration of noncaseating granulomas. Bronchoscopic lung biopsy (BLB), endobronchial biopsy (EBB) and transbronchial needle aspiration (TBNA) are currently the most commonly used methods for demonstration of granuloma in sarcoidosis. Endobronchial ultrasound-guided TBNA (EBUS-TBNA) is a minimally invasive technique for sampling the hilar/mediastinal lymph nodes, and can improve the diagnostic yield by direct visualization of lymph node beyond the tracheobronchial wall thereby allowing real-time sampling of the lymph nodes.

Krasnik et al. first reported the utility of convex probe EBUS-TBNA in sampling mediastinal nodes in 2003. With time, the diagnostic yield of EBUS-TBNA has been further enhanced by rapid on-site cytological evaluation (ROSE), increasing the number of lymph nodes sampled, increase in the number of aspirates taken per node, and use of a larger bore 21G needle. Although EBUS-TBNA was primarily intended for minimally invasive staging of bronchogenic carcinoma, its use has been extended in diagnosis of lymphoma and benign conditions like tuberculosis and sarcoidosis. Several systematic reviews and meta-analyses have reported the diagnostic performance of EBUS-TBNA but most of these reviews have primarily focused on patients with malignancy.

Sarcoidosis is a common pulmonary disorder worldwide. Demonstration of noncaseating granulomas and exclusion of other causes of granulomatous inflammation is essential particularly in countries with high prevalence of tuberculosis. We had previously reported the diagnostic yield of BLB and the additive yield of EBB in patients with sarcoidosis. We have also recently reported the diagnostic yield of TBNA in patients with mediastinal lymphadenopathy of diverse etiologies including sarcoidosis. In this study, we perform a systematic review and meta-analysis to define the diagnostic efficacy and safety of convex probe EBUS-TBNA in patients with sarcoidosis.

Material and methods

Search strategy

We first searched the literature for available systematic review that had reported the diagnostic efficacy of EBUS-TBNA in sarcoidosis. No systematic reviews were found. All the authors independently searched two computer databases PubMed and Embase for relevant studies published from 2004 to 2011 describing the diagnostic value of EBUS-TBNA in patients with sarcoidosis using the following search terms: (“ebus” OR “ebus tbna” OR “tbna” OR “endobronchial ultrasound” OR “endobronchial ultrasonography” OR “endobronchial ultrasound-guided” OR “endoscopic ultrasound” OR “transbronchial needle aspiration”) AND sarcoidosis; and, (“ebus” OR “endobronchial ultrasound” OR “endobronchial ultrasonography” OR “endobronchial ultrasound-guided” OR “endoscopic ultrasound”) AND (“tbna” OR “transbronchial needle aspiration”). We reviewed the reference lists of primary studies, reviews, and editorials. In addition, we reviewed our personal files. We excluded the following studies: (a) abstracts, editorials, reviews and case reports; (b) studies describing diagnostic accuracy of TBNA or endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) or radial probe EBUS-TBNA in sarcoidosis; (c) studies describing EBUS-TBNA in ≤10 patients with sarcoidosis; (d) studies in which the denominator i.e. number of patients with final diagnosis of sarcoidosis (granulomas on EBUS-TBNA or demonstration of granulomas from any site by any methodology and a clinical picture deemed by the investigator to be compatible with sarcoidosis) was not reported. The criteria for conclusive diagnosis by EBUS-TBNA in sarcoidosis was lymph node aspirates showing epithelioid, noncaseating granulomas without necrosis OR epithelioid and giant cells AND absence of identifiable malignancy, lymphoma, or infection (i.e. tuberculosis or fungal disease).

Initial review of studies

The initial database created from the electronic searches was compiled and all duplicate citations were eliminated. Two reviewers (RA and AS) screened these citations, without blinding, by title and abstract review to capture the relevant studies. Any disagreement was resolved by discussion between the authors. This database was then screened again to include only primary articles, and the full text of each citation was obtained and reviewed. Studies were eligible for inclusion if they reported the diagnostic yield of convex probe EBUS-TBNA in patients with clinical suspicion of sarcoidosis.

Data abstraction

Data was recorded on a standard data extraction form. The following items were extracted: (a) publication details (title; authors; and other citation details) including the geographic location of the study; (b) type of study (prospective or retrospective); (c) stage of sarcoidosis and lymph node size on CT chest; (d) type of sedation used, diameter of EBUS-TBNA needle, stations sampled, size of lymph node on EBUS, number of lymph node aspirated and/ or passes made through EBUS, availability of on-site cytology; (e) diagnostic yield of EBUS-TBNA in sarcoidosis wherein the numerator was the diagnosis of sarcoidosis with EBUS-TBNA, and the denominator was number of patients with confirmed sarcoidosis; and, (f) complications associated with the procedure.

Assessment of study quality

The quality and validity of each article included in this meta-analysis was assessed using the QualSyst tool for qualitative studies. This tool consists of 10 questions with
score from 0 to 2 with the maximum total score being 20. Each study was independently evaluated by two authors (RA, AS) for the stated criteria. Weighted Cohen’s kappa (κ) co-efficient was used to determine the inter-observer agreement for selection of studies.

**Statistical analysis**

The statistical software package (StatsDirect, version 2.7.8 for MS Windows; StatsDirect Ltd; Cheshire, UK [http://www.statsdirect.com]) was used to perform all the statistical analysis.

**Determination of the pooled effect**

We calculated the diagnostic yield of EBUS-TBNA by calculating proportion with 95% confidence intervals (CI) for each study and then pooled the data to derive a pooled proportion with 95% CI. For the purpose of proportion meta-analysis, the proportions were first turned into a quantity (the Freeman-Tukey variant of the arcsine square root transformed proportion) suitable for the random effects summary. The pooled proportion was calculated as the back-transform of the weighted mean of the transformed proportions, using DerSimonian weights for the random effects model in the presence of significant heterogeneity.

**Assessment of heterogeneity**

The impact of heterogeneity on the pooled estimates of the outcome was assessed using the Cochran Q statistic and I² test (measures the extent of inconsistency among the results of the studies). An I² value ≥50% indicates significant heterogeneity. As the Cochran Q test has a low sensitivity for detecting heterogeneity, a p value <0.1 was considered to be significant for the presence of statistical heterogeneity.

**Sensitivity/subgroup analysis**

We planned sensitivity analysis a priori by using subgroup analysis of prospective vs. retrospective studies due to the limitations associated with retrospective studies, and the occurrence of errors associated with the retrieval of information retrospectively from databases. A subgroup analysis was also planned by partitioning the studies based on the utilization of ROSE for histological diagnosis.

**Assessment of publication bias**

The presence of publication bias was evaluated using the Begg’s funnel plot, which is a measure of the proportion (in the X-axis) against the standard error of the proportion (in the Y-axis). Each open circle represents an individual study in the meta-analysis. The line in the center indicates the pooled proportion and the other two lines indicate the 95% CI. The proportion estimates from smaller studies are expected to be scattered above and below the summary estimate, producing a triangular or funnel shape, if there is no publication bias.

Publication bias was also investigated using three statistical tests: (a.) Egger test: detects asymmetry of the funnel plot; (b.) Harbord’s test: similar to Egger’s test but uses a modified linear regression method; and, (c.) Begg and Mazumdar’s test: tests the interdependence of variance and effect size using a rank correlation method.

An Institutional review board clearance was not required for this study as this was a meta-analysis of published studies.

**Results**

Our initial database search retrieved a total of 504 citations (Fig. 1) of which 15 studies finally met our inclusion criteria. Of these, nine studies were prospective and six were retrospective (Table 1). These 15 studies were published from across the globe and included 553 confirmed patients of sarcoidosis. Eight studies included stage I and II patients of sarcoidosis, two studies included all stages of sarcoidosis while the stage was not reported in five studies (Table 1). The procedure was performed under conscious sedation without any artificial airway in 12 studies (Table 2). Two studies used conscious sedation with either endotracheal tube or laryngeal mask while one study used general anesthesia with laryngeal mask. Majority of the studies had sampled the paratracheal, subcarinal, hilar and interlobar nodes, and all the studies had used the 22G dedicated EBUS-TBNA needle.

The lymph node size on CT and EBUS, the number of lymph nodes aspirated and the number of aspirates per patient is shown in Table 2. Five studies employed additional rapid on-site cytology and use of different cytological techniques for diagnosis. The quality of studies was generally good (Table 3) with the median (IQR) score being 18 (18–19). The inter-observer agreement for scoring the quality of studies was good. (Cohen’s κ = 0.78).

The diagnostic yield of EBUS-TBNA in sarcoidosis ranged from 54 to 93% with the pooled accuracy being 79% (95% CI, 71–86%) by the random effects model (Fig. 2). The yield was not statistically different (p = 0.66) in studies employing on-site cytological evaluation (165/206; 80.1%) vs. those without (282/347; 81.3%). The diagnostic yield was higher in prospective studies (314/374; 83.9%) compared to retrospective studies (133/179; 74.3%), and this difference was statistically significant (p = 0.006). Only five minor complications (minimal pneumothorax, minor bleeding, airway edema/hypoxemia [n = 2], prolonged cough) were reported in 532 patients.

There was clinical heterogeneity reflected in the nature of the study (prospective vs. retrospective), inclusion of patients with various stages, variation in the number of passes or lymph nodes sampled, utilization of on-site cytology and use of different cytological techniques (Tables 1 and 2). There was also significant statistical heterogeneity (I² 79.7; [95% CI, 65.9–86.3%]; Cochran Q statistic 69.03, p < 0.0001). There was evidence of publication bias on some (Egger: bias = −3.22, p < 0.0008) but not all statistical tests (Begg-Mazumdar: Kendall’s tau = −0.371, p = 0.05; Harbord-Egger: bias = −2.89, p = 0.19).
Sensitivity analysis

A subgroup analysis was performed and only prospective studies were included after which there was no significant change in heterogeneity ($I^2$ 84%; Cochran Q statistic 50.1 ($p < 0.0001$)) or publication bias (Egger: bias = -3.01, $p < 0.02$; Begg-Mazumdar: Kendall's tau = -0.33, $p = 0.18$; Harbord-Egger: bias = -2.81, $p = 0.38$). Similarly there was no change in heterogeneity ($I^2$ 79.4%; Cochran Q statistic 19.4 ($p = 0.0007$)) and publication bias (Egger: bias = -5.46, $p = 0.01$; Begg-Mazumdar: Kendall's tau = -1, $p < 0.0001$; Harbord-Egger: bias = -13.56, $p = 0.03$) after inclusion of studies employing ROSE.

Discussion

The result of this meta-analysis suggests an excellent overall diagnostic yield (79%) of EBUS-TBNA in sarcoidosis suggesting that this technique should be routinely
employed in diagnosis of sarcoidosis wherever available. The analysis includes good quality studies involving more than 550 confirmed predominantly stage I and II patients of sarcoidosis. The lower paratracheal and subcarinal lymph nodes (stations 4 and 7) were the most frequently accessed with a very low rate of complications.

The diagnosis of sarcoidosis is incomplete without the demonstration of noncaseating granuloma.1 Serum angiotensin converting enzyme levels are often elevated in sarcoidosis, but are non-specific as several common conditions like tuberculosis and diabetes mellitus also show similar elevation.39,40 Gallium-67 scan findings of panda or

| Table 1 | Demographic characteristics of patients in studies reporting the performance of EBUS-TBNA in sarcoidosis. |
|-----------------|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Author (year)   | Geographic locale | Type of study | Age (in years) | Patients included | Stage of sarcoidosis |
| Garwood (2007)  | USA | Prospective | 19–79 (range) | 48 | 0–4 |
| Oki (2007)     | Japan | Prospective | 27–73 (range) | 14 | 1,2 |
| Wong (2007)   | Germany, Japan | Prospective | 45 (mean) | 61 | 1,2 |
| Szlubowski (2008) | Poland | Retrospective | NA | 21 | NA |
| Nakajima (2009) | Japan | Retrospective | 48.2 (median) | 32 | 1,2 |
| Tremblay (2009) | Canada | Prospective | 39.5 (mean) | 24 | 1,2 |
| Eckardt (2010) | Denmark | Retrospective | 53 (median) | 43 | 1,2 |
| Kim (2010) | Korea | Prospective | 45.1 (mean) | 25 | 1,2 |
| Tian (2010) | China | Prospective | 52.3 (mean, all patients) | 16 | NA |
| Tournoy (2010) | Belgium | Prospective | 43 (median, all patients) | 54 | 0–4 |
| Cetinkaya (2011) | Turkey | Prospective | 50.2 (mean, all patients) | 105 | NA |
| Delattre (2011) | France | Retrospective | 21–79 (range) | 18 | NA |
| Jernlas (2011) | Sweden | Retrospective | 63 (mean, all patients) | 28 | NA |
| Nakajima (2009) | Japan | Retrospective | 7.3 (mean) | 51 in 38 patients | 3 passes per node |
| Tremblay (2009) | NA | Conscious sedation | As appropriate | NA | 4 (majority) |
| Eckardt (2010) | NA | GA via LMA | 2,3,4,7,10,11 | NA | 2 per node |
| Kim (2010) | NA | Conscious sedation | 4,7,10,11 | NA | 2 per node |
| Tian (2010) | NA | Conscious sedation | 2,3,4,7,10,11 | NA | 2 per node |
| Tournoy (2010) | NA | Conscious sedation | 4,7,10,11 | NA | 2 per node |
| Cetinkaya (2011) | NA | Conscious sedation | 2,4,7,10 | NA | 2.6 per node |
| Delattre (2011) | NA | Conscious sedation | As appropriate | NA | 3 per node |
| Jernlas (2011) | NA | Conscious sedation | 4,7,10 | NA | 4 per node |
| Navani (2011) | NA | Conscious sedation | 4,7 | NA | Yes |
| Plit (2011) | NA | Conscious sedation | 4,7 | 61 in 40 patients | 1–3 per node |

CT = computed tomography.  
GA = general anesthesia.  
LMA = laryngeal mask airway.  
NA = not available.

Table 2 | Details of the EBUS-TBNA procedure in various studies reporting the performance of EBUS-TBNA in sarcoidosis. |
<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Author (year)</td>
<td>Node size on CT (mm)</td>
<td>Sedation</td>
<td>Stations examined</td>
<td>Node size on EBUS (mm)</td>
<td>Number of lymph nodes</td>
</tr>
<tr>
<td>Garwood (2007)</td>
<td>&gt;10 mm</td>
<td>Conscious sedation</td>
<td>4,7,10,11</td>
<td>4–40 (median 16)</td>
<td>NA</td>
</tr>
<tr>
<td>Oki (2007)</td>
<td>&gt;10 mm</td>
<td>Conscious sedation</td>
<td>4,7,10,11</td>
<td>11–38</td>
<td>23 in 14 patients</td>
</tr>
<tr>
<td>Wong (2007)</td>
<td>&gt;10 mm</td>
<td>Conscious sedation</td>
<td>2,4,7,10,11</td>
<td>7–37</td>
<td>77 in 64 patients</td>
</tr>
<tr>
<td>Szlubowski (2008)</td>
<td>&gt;10 mm</td>
<td>Conscious sedation</td>
<td>2,3,4,7,10,11</td>
<td>7–42 (total)</td>
<td>30 in 21 patients</td>
</tr>
<tr>
<td>Nakajima (2009)</td>
<td>&gt;10 mm</td>
<td>Conscious sedation</td>
<td>4,7,10</td>
<td>7.3–30</td>
<td>51 in 38</td>
</tr>
<tr>
<td>Tremblay (2009)</td>
<td>&gt;10 mm</td>
<td>Conscious sedation</td>
<td>As appropriate</td>
<td>NA</td>
<td>4 (mean)</td>
</tr>
<tr>
<td>Eckardt (2010)</td>
<td>NA</td>
<td>GA via LMA</td>
<td>2,3,4,7,10,11</td>
<td>NA</td>
<td>2 per node</td>
</tr>
<tr>
<td>Kim (2010)</td>
<td>NA</td>
<td>Conscious sedation</td>
<td>4,7,10,11</td>
<td>5–40</td>
<td>50 in 25</td>
</tr>
<tr>
<td>Tian (2010)</td>
<td>NA</td>
<td>Conscious sedation</td>
<td>2,3,4,7,10,11</td>
<td>NA</td>
<td>2 per node</td>
</tr>
<tr>
<td>Tournoy (2010)</td>
<td>NA</td>
<td>Conscious sedation</td>
<td>4,7,10,11</td>
<td>NA</td>
<td>2 per node</td>
</tr>
<tr>
<td>Cetinkaya (2011)</td>
<td>NA</td>
<td>Conscious sedation</td>
<td>2,4,7,10</td>
<td>NA</td>
<td>2.6 per node</td>
</tr>
<tr>
<td>Delattre (2011)</td>
<td>NA</td>
<td>Conscious sedation</td>
<td>As appropriate</td>
<td>NA</td>
<td>3 per node</td>
</tr>
<tr>
<td>Jernlas (2011)</td>
<td>NA</td>
<td>Conscious sedation</td>
<td>4,7,10</td>
<td>NA</td>
<td>4 per node</td>
</tr>
<tr>
<td>Navani (2011)</td>
<td>NA</td>
<td>Conscious sedation</td>
<td>4,7</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Plit (2011)</td>
<td>NA</td>
<td>Conscious sedation</td>
<td>4,7</td>
<td>61 in 40 patients</td>
<td>1–3 per node</td>
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</table>
lambda sign can support the diagnosis but are seen only in limited patients and cannot replace histology. Over the last two decades, bronchoscopic techniques are most often used to confirm the diagnosis of sarcoidosis. The bronchoalveolar lavage fluid lymphocyte marker specifically the CD4/CD8 ratio (>3.5) has been used as an adjunct to support the diagnosis of sarcoidosis. Although a high CD4/CD8 ratio supports the diagnosis of sarcoidosis, its distribution is variable and is not a substitute for histology. BLB is the most commonly performed procedure in establishing a diagnosis of sarcoidosis. However, the yield of BLB depends not only on the experience of operator but also on the stage of sarcoidosis (higher in stage II than I), and the number of biopsies obtained (optimal at 8–10). The diagnostic yield of BLB ranges between 40 and 90%, and carries a risk of pneumothorax (2%) and hemoptysis (5%). EBB can add to the diagnostic yield of BLB especially if the mucosa appears abnormal, although 30% of normal appearing mucosa can also show evidence of granuloma on histology. Conventional TBNA alone has a variable success ranging from 42 to 76%, with a higher yield in stage I disease. However, the steep learning curve and variable yield has lured few pulmonologists to adopt TBNA as a routine procedure. Combination of modalities such as conventional TBNA, EBB and TBLB can increase the yield to 70–90%, but is often associated with an increase in duration of procedure and complications. EUS-FNA has shown promise in diagnosis of sarcoidosis with studies reporting sensitivity of 89–100% and specificity of 94–96%. The limitations of EUS-FNA include inability to perform additional procedures like BLB or EBB at the same time and difficulty in accessing paratracheal, hilar and interlobar (stations 2, 4, 10, 11) especially on the right side given the fact that these are the nodes that are usually enlarged in sarcoidosis.

Mediastinoscopy is currently the ‘gold’ standard for sampling mediastinal lymph nodes. However, the procedure is not routinely available at all centers, and is associated with major morbidity/mortality ranging from 1.4 to 2.3% depending on the experience of the operator. The diagnostic yield ranges between 82 and 97% for undiagnosed mediastinal adenopathy, with the major caveat being that not all mediastinal nodes can be accessed with this technique. Mediastinoscopy however is the final resort if all other techniques fail. There is scarce evidence regarding computed tomography (CT)-guided transthoracic needle aspiration (TTNA) and/or biopsy of the mediastinal nodes for diagnosis of sarcoidosis. Moreover, there is a high risk of complications especially pneumothorax with CT-guided TTNA. Klein et al. recently reported their 10 year single center experience in 41 patients of sarcoidosis. The diagnostic yield was 78% with cytology and 96% with core biopsy, however they also reported pneumothorax in 22% of patients.

Most studies included in this meta-analysis have reported a diagnostic yield around 80% for EBUS-TBNA in sarcoidosis. According to the results of this study, the diagnostic yield of EBUS-TBNA surpasses every other bronchoscopic investigation in isolation. Moreover, combining EBUS-TBNA with BLB and EBB would significantly add to the diagnostic yield, and would be able to achieve a diagnosis in majority of the cases. Of the
studies reporting a lower yield, Jernlas et al. and Tian et al. have attributed their results to learning curve, diversity of diagnosis and referral bias.32,36 Eckardt et al. and Tournoy et al. included only patients who remained undiagnosed despite usual bronchoscopic interventions and thus a subset of patients where the granuloma load was likely to have been less than usual.30,33 Nakajima et al. reported a diagnostic yield on 91.4% however they had used the presence of epithelioid cells alone as criteria for diagnosis of sarcoid in 10 of the 32 cases thereby decreasing their actual yield to 69%.28

Finally, the meta-analysis has certain limitations. There was presence of significant clinical and statistical heterogeneity in the studies evaluated although we used the random effects model for minimizing the effects of heterogeneity.18 We also performed a sensitivity analyses to investigate the cause of heterogeneity by including only studies of prospective nature and those employing ROSE. The sensitivity analysis did not explain the statistical heterogeneity suggesting that other factors contributed to heterogeneity. The meta-analysis included studies from various centers with operators having differing levels of expertise in performing EBUS-TBNA which we believe is the prime contributor of heterogeneity in this analysis. Heterogeneity is the presence of variability among studies included in a systematic review and can be broadly classified as clinical heterogeneity (variability in the participants, interventions, and outcomes) or methodological heterogeneity (variations in trial design and quality) or statistical heterogeneity (variability in the treatment effects being evaluated in different trials). In fact, one can argue that in a meta-analysis heterogeneity is inevitable whether or not statistical tests detect them or not. The strength of this meta-analysis is the sample size (almost 550 patients with sarcoidosis), detailed extraction of data from

Figure 2  Diagnostic yield of EBUS-TBNA in patients with sarcoidosis (random effects model). The yield in individual studies is represented by a square (percentage) through which runs a horizontal line (95% confidence interval). The diamond at the bottom represents the pooled prevalence from the studies (79% [95% CI, 71–86%]).

Figure 3  Funnel plot comparing proportion vs. the standard error of proportion. Open circles represent trials included in the meta-analysis. The line in the center indicates the summary proportion. The other lines represent the 95% confidence intervals. Asymmetry about the pooled line is consistent with the presence of publication bias.
individual studies and the robust statistical methods applied in the analysis. Future studies on EBUS-TBNA in sarcoidosis should employ a uniform methodology with regard to the number of lymph nodes aspirated (at least two lymph node stations), the number of passes per lymph node (at least two passes per lymph node) and the use of consistent liquid-based cytology protocol.

Conclusions

In conclusion, the result of this study suggests a high diagnostic yield and safety of EBUS-TBNA in sarcoidosis, indicating that EBUS-TBNA should be routinely employed in the diagnosis of sarcoidosis wherever available.

Author contributions

RA — systematic review, meta-analysis, drafted and revised the manuscript
AS — systematic review, drafted and revised the manuscript
ANA — systematic review, drafted and revised the manuscript
DG — conceived the article, systematic review, drafted and revised the manuscript
DG — guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article

Conflict of interest statement

All authors do not have any conflict of interest.

Financial disclosure

None.

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