Endobronchial Ultrasound-guided Transbronchial Needle Aspiration versus Standard Bronchoscopic Modalities for Diagnosis of Sarcoidosis: A Meta-analysis

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Abstract

Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is an effective technique used to precisely detect enlarged mediastinal lymph nodes. The efficacy of EBUS-TBNA versus standard modalities for the diagnosis of sarcoidosis remains to be elucidated. In this meta-analysis, we compared the efficacies of these methods.

Methods: We searched PubMed, Embase, The Cochrane Library, Wanfang, Cpvip, CNKI, and the bibliographies of the relevant references. We analyzed the data obtained with Revman 5.2 (Nordic Cochrane Center, Copenhagen, Denmark) and Stata 12.0 software (Stata Corporation, College Station, TX, USA). The Mantel-Haenszel method was used to calculate the pooled odds ratio (*OR*) and 95% confidence intervals (*CIs*).

Results: Sixteen studies with a total of 1823 participants met the inclusion criteria, and data were extracted regarding the diagnostic yield of each approach. The *ORs* for EBUS-TBNA versus transbronchial lung biopsy (TBLB) for the diagnosis of sarcoidosis ranged from 0.26 to 126.58, and the pooled *OR* was 5.89 (95% *CI*, 2.20–15.79, $P = 0.0004$). These findings indicated that EBUS-TBNA provided a much higher diagnostic yield than TBLB. The pooled *OR* for EBUS-TBNA + TBLB + endobronchial biopsy (EBB) versus TBNA + TBLB + EBB was 1.54 (95% *CI*, 0.61–3.93, $P = 0.36$), implying that there was no significant difference between their diagnostic yields. However, clinical heterogeneity was reflected in the nature of the studies and in the operative variables.

Conclusions: The results of this meta-analysis suggest that EBUS-TBNA + TBLB + EBB could be used for the diagnosis of sarcoidosis, if available. At medical centers without EBUS-TBNA, TBNA + TBLB + EBB could be used instead.

Key words: Bronchoscopy; Diagnostic Yield; Endobronchial Ultrasound-guided Transbronchial Needle Aspiration; Meta-analysis; Sarcoidosis

Introduction

Sarcoidosis is a granulomatous disease.[1] Its diagnosis is sometimes based on histological features.[2] Bronchoscopy is the most commonly used diagnostic method for this disease. The diagnostic yields of transbronchial needle aspiration (TBNA) and TBNA + transbronchial lung biopsy (TBLB) are 62% and 83%, respectively.[3] Endobronchial ultrasound-guided TBNA (EBUS-TBNA) is a new technique used for the diagnosis of patients with sarcoidosis.[4] The authors have reported that the diagnostic yield of this technique is 79% (95% confidence interval [*CI*], 71–86%).[5] The first case involving the use of EBUS-TBNA to sample mediastinal nodes was reported in 2003.[6] In this study, we performed a meta-analysis to compare the diagnostic yields of EBUS-TBNA and standard bronchoscopy to help guide the diagnosis of sarcoidosis.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.184458

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Received: 01-03-2016 **Edited by:** Peng Lyu

How to cite this article: Hu LX, Chen RX, Huang H, Shao C, Wang P, Liu YZ, Xu ZJ. Endobronchial Ultrasound-guided Transbronchial Needle Aspiration versus Standard Bronchoscopic Modalities for Diagnosis of Sarcoidosis: A Meta-analysis. Chin Med J 2016;129:1607-15.

Methods

Data collection

We first searched PubMed, Embase, and The Cochrane Library for systematic reviews reporting the diagnostic yield of EBUS-TBNA versus standard bronchoscopy for sarcoidosis. No systematic reviews were found. Next, two authors independently searched PubMed, Embase, The Cochrane Library, Wanfang, Cqvip, and CNKI using the following search terms: sarcoidosis AND ("endobronchial ultrasound-guided transbronchial needle aspiration" AND "transbronchial needle aspiration") OR ("endobronchial ultrasound-guided transbronchial needle aspiration" AND "endobronchial biopsy") OR ("endobronchial ultrasound-guided transbronchial needle aspiration" AND "transbronchial lung biopsy") OR (ultrasound AND biopsy) OR bronchoscopy OR "endoscopic ultrasound-guided fine needle aspiration" OR endosonography. We retrieved all related studies, and the references were hand-checked for other relevant publications.

Study selection

The initial database created from the electronic search was screened by two reviewers without blinding. Disagreements were resolved via discussion between the reviewers. Studies were included if they met the following criteria: (1) evaluation of the diagnostic yield of EBUS-TBNA versus standard bronchoscopy for sarcoidosis; (2) use of a retrospective, prospective, or randomized controlled trial (RCT) study design; (3) use of a sample size of >20; and (4) availability of absolute numbers or the potential to derive them from the data reported in the primary studies. Studies were excluded for the following reasons: they (1) did not use EBUS-TBNA or standard bronchoscopy to diagnose sarcoidosis, (2) were reviews or abstracts, or (3) contained insufficient or duplicate data.

Data extraction and quality assessment

Two investigators independently extracted data from the primary studies. Data were recorded on a standard data extraction form. The absolute diagnostic yields of the different biopsy methods were extracted from the selected articles. Two authors independently assessed the quality of each included study using the risk of bias tool in Review Manager 5.2 software (Nordic Cochrane Center, Copenhagen, Denmark). This tool consists of a series of questions with possible responses of "low risk," "high risk," or "unclear" and is used to assess study bias. Specifically, we considered the biases of surgical-related characteristics, including the major lymph node stations sampled, the sizes of lymph nodes sampled by TBNA, the number of lymph nodes sampled by TBNA, the number of passes made using TBNA, the sample number for TBLB, the locations of TBLB, and the sample number for endobronchial biopsy (EBB). We defined a provision of the above items to be low risk and others to be unclear. Any disagreements were resolved by reaching a consensus or by arbitration.

Statistical analysis

All statistical analyses were performed using Review Manager 5.2 statistical software and Stata 12.0 statistical software (Stata Corporation, College Station, TX, USA). We extracted the dichotomous data from the data presented in each primary study for each sarcoidosis diagnosis. We compared the diagnostic yields of the EBUS-TBNA and standard bronchoscopic modalities by calculating the odds ratios (*ORs*) and 95% *CIs* for each study and then pooling the data using the random-effect or fixed-effect model to calculate a pooled efficacy and *CI*. We assessed the influence of statistical heterogeneity on the pooled estimates of the individual results using the I^2 test. An I^2 value of ≥50% indicated significant heterogeneity. A value of $P < 0.05$ was considered significant for the Chi-square test of heterogeneity. We performed sensitivity analysis in which a subgroup analyses of the retrospective studies versus nonretrospective studies (including RCT and prospective studies). Sensitivity analysis was also conducted in which the studies were grouped based on whether rapid on-site evaluation (ROSE) had been performed. The presence of publication bias was evaluated by generation of a funnel plot, in which the *OR* was plotted. We also assessed publication bias via Begg's test and Egger's linear regression test using Stata 12.0.

Results

Study characteristics

We collected 1178 records from PubMed, Embase, and The Cochrane Library and 113 records from Wanfang, Cpvip, and CNKI. We excluded 231 duplicates from the initial 1291 records. Screening of the titles, abstracts, publication types, and full texts of the remaining 1060 records resulted in the identification of 28 qualifying studies. Finally, we obtained 16 studies for the systematic review and meta-analysis.[4,7-21] The process of identifying eligible studies is summarized in Figure 1. A total of 1823 participants in the 16 studies had a confirmed diagnosis of sarcoidosis. The main information from the 16 articles is summarized in Supplementary Table 1. Among these studies, seven were retrospective,[4,10,14,18-21] five were RCTs,[7,8,13,15,17], and four were prospective.[9,12,11,16] The participants were from Japan, Africa, Australia, Korea, China, India, America, Canada, and Poland. The ages of the participants were homogeneous. Among all of the studies, 11 included patients with Stage I or II sarcoidosis,[4,8-15,17,18] four included those with Stage I, II, or III,[7,19-21] and only one study included those with Stage I, II, III, or IV.[16] Among all of the studies, 11 used a 22-gauge needle to perform EBUS-TBNA,[4,7-14,17,18] and two studies used a 21-gauge needle.[15,16] Most of the biopsied nodes were larger than 10 mm. The majority of the studies biopsied lymph node stations 4 and 7. Only five studies used ROSE.[4,7,9,10,19] Study quality was generally good [Supplementary Figure 1].

Meta-analysis results

We analyzed the different procedures utilized for sarcoidosis diagnosis. One analysis included a sufficient number of studies to perform subgroup analyses on the different sarcoidosis stages, study designs, and protocols. The

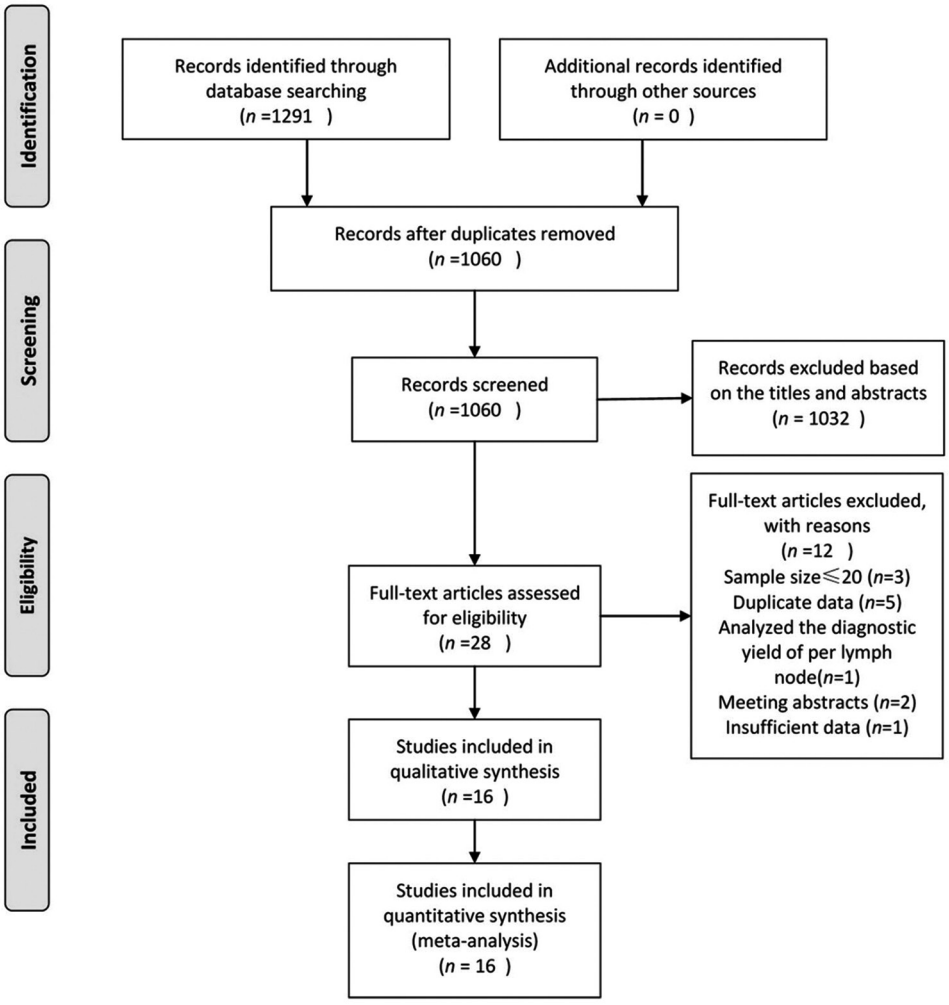

Figure 1: Flow diagram of individual studies screening. A preferred reporting items for meta-analyses flow diagram detailed the search, identification, and screening.

funnel plot and results of Begg's test and Egger's test of publication bias are presented in the supporting information section [Supplementary Figure 2].

Endobronchial ultrasound-guided transbronchial needle aspiration versus transbronchial lung biopsy

The random-effect model was used in this analysis ($P < 0.00001$, $I^2 = 93\%$). The diagnostic yields of EBUS-TBNA and TBLB were 83.1% and 38.1%, respectively. The *OR* for EBUS-TBNA versus TBLB for the diagnosis of sarcoidosis ranged from 0.26 to 126.58, and the pooled *OR* was 5.89 (95% *CI*, 2.20–15.79, $P = 0.0004$) [Figure 2]. These results indicated that EBUS-TBNA had a much higher diagnostic yield than TBLB.

Seven studies were included in the analysis of the use of EBUS-TBNA versus TBLB for diagnosis of Stage I and II sarcoidosis. The pooled *ORs* for Stages I and II were 16.99 (95% *CI*, 4.93–58.58, $P < 0.00001$) [Supplementary Figure 3a] and 6.56 (95% *CI*, 4.31–9.98, $P < 0.00001$) [Supplementary Figure 3b], respectively, indicating that EBUS-TBNA was more effective than TBLB for diagnosis of both stages (especially Stage I).

Endobronchial ultrasound-guided transbronchial needle aspiration versus transbronchial lung biopsy + endobronchial biopsy

Six articles were included in the meta-analysis of EBUS-TBNA versus TBLB + EBB. High heterogeneity ($P < 0.00001$, $I^2 = 92\%$) was detected among these studies. The pooled *OR* for EBUS-TBNA versus TBLB + EBB was 2.07 (95% *CI*, 0.68–6.37, $P = 0.20$) [Figure 3]. Thus, the diagnostic yield of EBUS-TBNA was not significantly better than that of TBLB + EBB.

Only two studies were included in the analysis of the use of EBUS-TBNA versus TBLB + EBB for the diagnosis of Stage I and II sarcoidosis. The pooled *ORs* for Stages I and II were 21.25 (95% *CI*, 2.43–185.88, $P = 0.006$) [Supplementary Figure 4a] and 5.55 (95% *CI*, 0.19–161.62, $P = 0.32$) [Supplementary Figure 4b], respectively, indicating that EBUS-TBNA was more effective than TBLB + EBB for the diagnosis of Stage I sarcoidosis only.

Endobronchial ultrasound-guided transbronchial needle aspiration versus conventional transbronchial needle aspiration

Seven articles included in this meta-analysis showed no

significant heterogeneity ($P = 0.73$, $I^2 = 0$). The diagnostic yields of EBUS-TBNA and conventional transbronchial needle aspiration (cTBNA) were 79.9% and 51.6%, respectively. The pooled *OR* for EBUS-TBNA versus cTBNA was 3.22 (95% *CI*, 2.09–4.96, $P < 0.00001$) [Figure 4]. Therefore, EBUS-TBNA was more effective than cTBNA for the diagnosis of sarcoidosis.

Endobronchial ultrasound-guided transbronchial needle aspiration versus + transbronchial lung biopsy + endobronchial biopsy

Five articles were included in this meta-analysis. The diagnostic yields of EBUS-TBNA and EBUS-TBNA + TBLB + EBB were 82.7% and 89.7%, respectively. The pooled *OR* for the two groups was 0.55 (95% *CI*, 0.39–0.78, $P = 0.0007$) [Figure 5a]. Therefore, EBUS-TBNA + TBLB + EBB were more effective than EBUS-TBNA for the diagnosis of sarcoidosis.

Endobronchial ultrasound-guided transbronchial needle aspiration versus transbronchial needle aspiration + transbronchial lung biopsy + endobronchial biopsy

Only two studies were included in this analysis. These studies showed no significant heterogeneity ($P = 0.21$, $I^2 = 37\%$). We concluded that TBNA + TBLB + EBB had much greater efficacy than EBUS-TBNA for the diagnosis of sarcoidosis, with an *OR* of 0.34 (95% *CI*, 0.17–0.68, $P = 0.002$) [Figure 5b].

Endobronchial ultrasound-guided transbronchial needle aspiration + transbronchial lung biopsy + endobronchial biopsy versus transbronchial lung biopsy + endobronchial biopsy

Three articles were included in this meta-analysis. The pooled *OR* of EBUS-TBNA + TBLB + EBB versus TBLB + EBB was 5.91 (95% *CI*, 1.72–20.37, $P = 0.005$) [Figure 5c]. Thus,

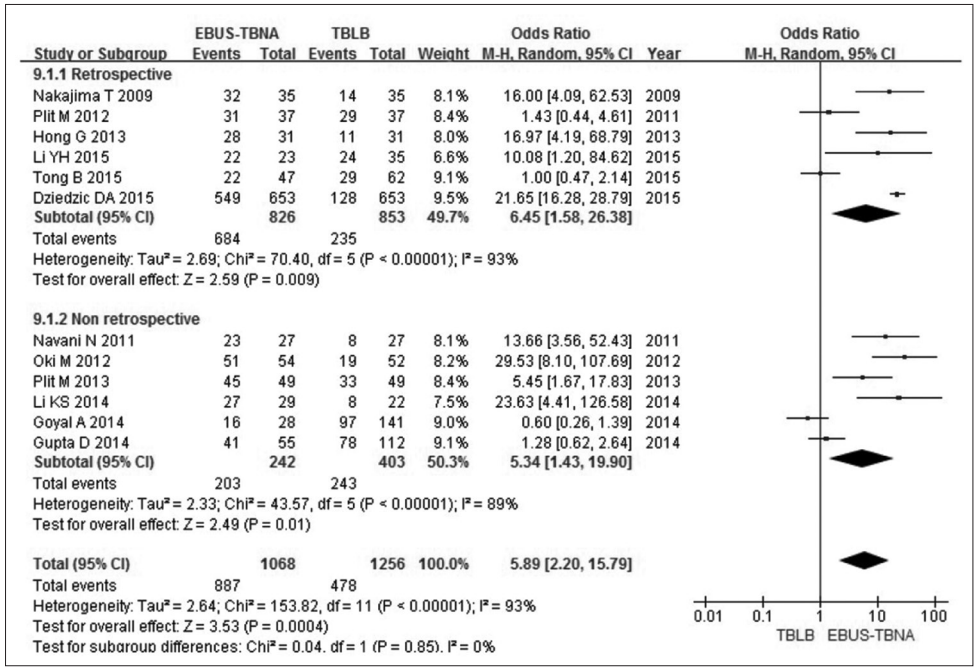

Figure 2: Forest plots of the EBUS-TBNA versus TBLB for sarcoidosis diagnosis. The *OR* for each individual study is represented by a square with a horizontal line (95% *CI*). The diamonds represents the pooled *OR* of the studies. Twelve trials were analyzed for the pooled overall diagnostic yield. EBUS-TBNA had a much higher diagnostic yield than TBLB. The *ORs* showed no significant differences between the retrospective and nonretrospective studies. *CI*: Confidence interval; EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; TBLB: Transbronchial lung biopsy; *OR:* Odds ratio.

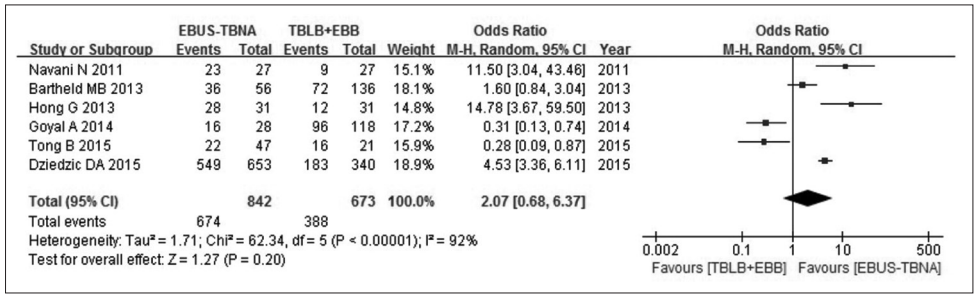

Figure 3: Forest plot of EBUS-TBNA versus TBLB + EBB for the diagnosis of sarcoidosis. Six trials were analyzed for the pooled overall diagnostic yield. The diagnostic yield of EBUS-TBNA was not significantly better than TBLB + EBB. *CI*: Confidence interval; EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; TBLB: Transbronchial lung biopsy; EBB: Endobronchial biopsy.

the diagnostic yield of EBUS-TBNA + TBLB + EBB was significantly higher than that of TBLB + EBB.

Endobronchial ultrasound-guided transbronchial needle aspiration + transbronchial lung biopsy + endobronchial biopsy versus transbronchial needle aspiration + transbronchial lung biopsy + endobronchial biopsy

The pooled *OR* for EBUS-TBNA + TBLB + EBB versus TBNA + TBLB + EBB was 1.54 (95% *CI*, 0.61–3.93, $P = 0.36$) [Figure 5d]. The diagnostic yields of EBUS-TBNA + TBLB + EBB and TBNA + TBLB + EBB were 90.9% and 86.2%, respectively. Thus, EBUS-TBNA + TBLB + EBB had a higher diagnostic yield than TBNA + TBLB + EBB. However, this difference was not significant.

Complications

Not all of the studies clearly mentioned complication rates. The following results were obtained using the available data. A total of 15 patients experienced pneumothorax after TBLB,[7,9,11-16] among whom at least two patients needed drainage.[7,9] In addition, eight patients experienced bleeding after TBLB,[7,9,11,13] among whom at least four lost over 50ml of blood.[7,9] One patient developed a severe cough,[11] and four developed minor bleeding after EBUS-TBNA,[13,15] however, the exact quantities of blood loss were not specified. Further, seven patients experienced minor bleeding after cTBNA, but no exact quantities of blood loss were reported.[8,13,15]

Heterogeneity analysis results

Clinical heterogeneity was reflected in the nature of each study, and significant statistical heterogeneity was also detected ($I^2 = 93\%$). After excluding the studies by Plit *et al*., Goyal *et al*., Gupta *et al*., and Tong *et al.*, the heterogeneity was not significant ($I^2 = 0$, $P = 0.52$) [Supplementary Figure 3c].[10,15,16,20] In addition, we performed subgroup analyses of the following comparisons: ROSE versus No-ROSE and retrospective versus nonretrospective. The results revealed the presence of significant heterogeneity in both the ROSE ($I^2 = 72\%$, $P = 0.03$) and No-ROSE subgroups ($I^2 = 95\%$, $P < 0.00001$) [Supplementary Figure 3d]. In subgroup analysis between the retrospective and nonretrospective studies, the *OR*s did not significantly differ ($P = 0.85$) [Figure 2]. Significant heterogeneity was detected in both the retrospective and nonretrospective groups ($I^2 = 93\%$, $P < 0.00001$; and $I^2 = 89\%$, $P < 0.00001$, respectively). Therefore, the heterogeneity was not solely attributed to the study design.

Publication bias

The funnel plot was slightly asymmetric [Supplementary Figure 2]. However, Begg's and Egger's tests did not demonstrate significant publication bias ($P = 0.304$ and $P = 0.223$, respectively). Therefore, our meta-analysis did not reveal evidence of significant publication bias.

Discussion

The results of this meta-analysis indicated that EBUS-TBNA had an excellent diagnostic yield for sarcoidosis, especially when combined with TBLB and (or) EBB. Therefore, EBUS-TBNA should be performed for the diagnosis of sarcoidosis if it is available. However, no significant difference in diagnostic yield was observed between the EBUS-TBNA + TBLB + EBB and TBNA + TBLB + EBB, although there was a trend toward a higher yield in EBUS-TBNA + TBLB + EBB. Thus, further study must be performed to obtain definitive conclusions. As demonstrated in Table 1, the absolute diagnostic yield of EBUS-TBNA + TBLB + EBB ranged from 86.4% to 100%, while that of TBNA + TBLB + EBB ranged from 85.5% to 92.9%. Therefore, if EBUS-TBNA is not available, particularly in developing countries, then clinicians should perform a standard bronchoscopy. This suggestion had been previously provided by Mondoni *et al.*[22] EBUS-TBNA was found to be more effective than TBLB for the diagnosis of Stage I and II sarcoidosis (especially Stage I). Further, EBUS-TBNA was more effective than TBLB + EBB for the diagnosis of Stage I sarcoidosis only. As most of the studies only included patients with Stage I or II sarcoidosis, and the sample sizes of patients in Stage III or IV were very small, so it is difficult to draw conclusions regarding Stage III and IV sarcoidosis. The ROSE technique guarantees that samples are handled and processed in the best way.[23] However, no difference was observed between the ROSE and No-ROSE subgroups. These findings might indicate that all patients should undergo EBUS-TBNA + TBLB + EBB, even if ROSE is available.

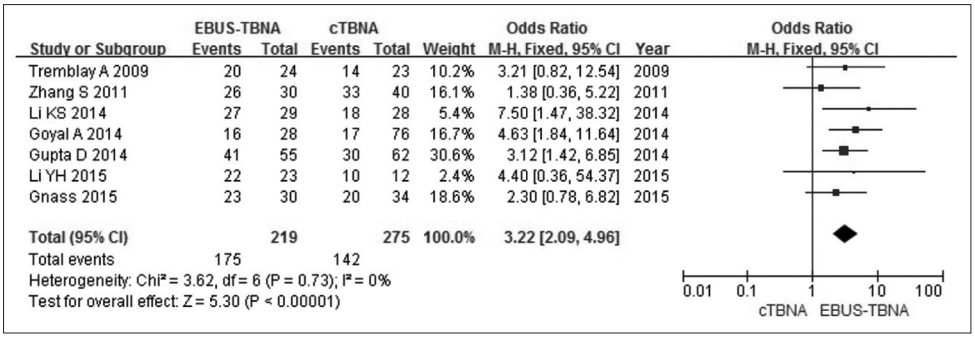

Figure 4: Forest plot of EBUS-TBNA versus cTBNA for the diagnosis of sarcoidosis. Seven trials were analyzed for the overall pooled diagnostic yield. EBUS-TBNA is better than cTBNA for the diagnosis of sarcoidosis. *CI*: Confidence Interval; EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; cTBNA: Conventional transbronchial needle aspiration.

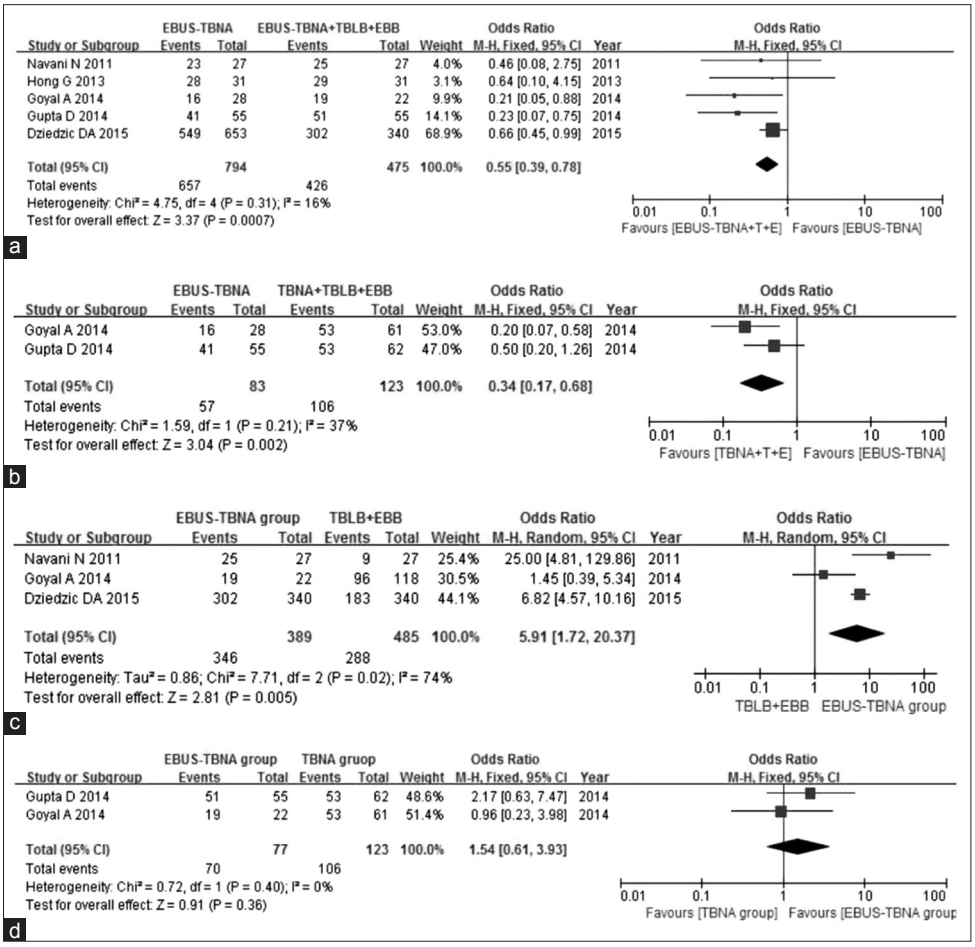

Figure 5: Forest plot of (a) EBUS-TBNA versus EBUS-TBNA + TBLB + EBB.EBUS-TBNA + TBLB + EBB was better than EBUS-TBNA for the diagnosis of sarcoidosis. (b) EBUS-TBNA versus TBNA + TBLB + EBB. TBNA + TBLB + EBB was much better than EBUS-TBNA (c) EBUS-TBNA + TBLB + EBB versus TBLB + EBB. The diagnostic yield of EBUS-TBNA + TBLB + EBB was significantly better than TBLB + EBB. (d) EBUS-TBNA + TBLB + EBB versus TBNA + TBLB + EBB. EBUS-TBNA + TBLB + EBB had a higher diagnostic yield than TBNA + TBLB + EBB. However, there was no significant difference. EBUS-TBNA group: EBUS-TBNA + TBLB + EBB, TBNA group: TBNA + TBLB + EBB. *CI*: Confidence interval; EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; TBLB: Transbronchial lung biopsy; EBB: Endobronchial biopsy.

However, the sample size is too small to definitively make this conclusion.

Not all of the studies clearly mentioned patient complications. According to the available data, we have concluded that the complication rate is higher for TBLB than for (EBUS)-TBNA.

Although not all cases require a pathological diagnosis, it is necessary to identify a noncaseating granuloma and to exclude common infections that might cause granulomatous inflammation, such as tuberculosis in epidemic countries.[2] Lymphocyte markers in bronchoalveolar lavage fluid (BALF) with a CD4/CD8 ratio of >4 support the diagnosis of sarcoidosis.[24] However, more than half of biopsy-proven cases have a ratio of <4.[25] Therefore, BALF examination cannot completely replace pathological examination. Although the serum angiotensin-converting enzyme level is elevated in sarcoidosis patients, the specificity of this marker is very low.[26] A finding of the panda or lambda sign on a gallium-67 scan also supports the diagnosis of sarcoidosis; however, these signs are only observed in a limited number of patients. Therefore, gallium-67 scanning cannot replace histological examination.[27] Endoscopic ultrasound (EUS)-fine needle aspiration (FNA) can also be used to diagnose sarcoidosis. However, unlike EBUS-TBNA or TBNA, additional procedures cannot be performed following EUS-FNA. It is also difficult to access the paratracheal, hilar, and interlobar nodes using EUS-FNA, especially on the right side, which is where these nodes are typically enlarged in sarcoidosis patients.[28]

As we all know, the tissues obtained by bronchoscopy are very small, and surgical lung biopsy provides large tissue samples. It cannot be denied that large tissue samples acquired by surgical lung biopsy can allow doctors to make more definite diagnosis. However, the procedure is performed in the operating room under general anesthesia and it has been associated with significant morbidity, including prolonged air leakage, prolonged hospital admission, and mortality.[29]

Table 1: The absolute diagnostic yield of the different modalities among the different studies

Studies	Study design	Number of patients, *n*	EBUS-TBNA (%)	TBNA (%)	TBLB (%)	EBB (%)	TBLB + EBB (%)	EBUS-TBNA group (%)	TBNA group (%)
Nakajima *et al*., 2009[4]	Retrospective	35	91.4	–	40	–	–	–	–
Tremblay *et al*., 2009[8]	RCT	50	83.3	60.9	–	–	–	–	–
Navani *et al*., 2011[12]	Prospective	27	85	–	29.6	11.1	33.3	92.6	–
Zhang *et al*., 2011[19]	Retrospective	50	86.7	82.5	–	–	66.7	–	–
Oki *et al*., 2012[11]	Prospective	54	94	–	37	–	–	–	–
Plit *et al*., 2012[10]	Retrospective	37	84	–	78	27.0	–	100	–
von Bartheld *et al*., 2013[7]	RCT	192	66	–	–	–	53	–	–
Hong *et al*., 2013[14]	Retrospective	31	90.0	–	35.0	6.0	39.0	94.0	–
Plit *et al*., 2013[9]	Prospective	49	91.8	–	67.3	28.6	–	–	–
Gupta *et al*., 2014[15]	RCT	117	74.5	48.4	69.6	36.3	–	92.7	85.5
Goyal *et al*., 2014[16]	Prospective	151	57.1	22.4	68.7	49.6	81.4	86.4	86.9
Li and Jiang, 2014[13]	RCT	57	93.0	64	36.4	5	–	–	92.9
Dziedzic *et al*., 2015[18]	Retrospective	653	84.0	–	43.9	29.7	54.0	89.0	–
Gnass *et al*., 2015[17]	RCT	64	76.7	58.8	–	–	–	–	–
Li *et al*., 2015[21]	Retrospective	56	95.7	83.3	68.6	31.3	–	–	–
Tong *et al*., 2015[20]	Retrospective	200	72.7	–	46.7	80.4	76.2	–	–

EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; TBNA: Transbronchial needle aspiration; TBLB: Transbronchial lung biopsy; EBB: Endobronchial biopsy; EBUS-TBNA group: EBUS-TBNA + TBLB + EBB; TBNA-group: TBNA + TBLB + EBB; RCT: Randomized controlled trial; –: No data; %: Diagnostic yield of sarcoidosis.

The diagnosis of sarcoidosis requires specific clinical findings, histological demonstration of noncaseating granulomas, and exclusion of other diseases with similar histological or clinical findings.[30] Although some patients do not need to be biopsied, for example, those with a pulmonary impairment that is too severe to undergo biopsy and those with classic Lofgren's syndrome, bronchoscopy is the recommended procedure in most cases. At our center, most patients suspected to have sarcoidosis undergo bronchoscopy. However, the diagnostic yield of this procedure depends largely on the surgeon's experience.[30] In this meta-analysis, we have summarized the needle gauges used, node sizes sampled, numbers of lymph nodes sampled by TBNA, numbers of needle passes made, and sample number for TBLB, sample number for EBB, etc., which might have influenced the sizes of the tissues acquired [Supplementary Table 1]. However, no articles included in this meta-analysis provided detailed information on accurate tissue sizes.

Furthermore, one article discussed sample sizes on lung biopsy that evaluated the diagnostic yields of cryo-TBLB and flexible forceps biopsy. The authors found that cryo-TBLB resulted in a very high diagnostic yield, and this result may have been attributed to the large sample size studied.[29] In this meta-analysis, although no data were analyzed regarding the sizes of tissues acquired, approximately ten specimens were obtained by TBLB in the Plit *et al*.[10] 2012 study, which may have led to the high diagnostic yield observed for this procedure. In one of the included articles, the authors compared the diagnostic yields of EBUS-TBNA performed with a 22-gauge needle and TBNA performed with a standard 19-gauge needle in patients with mediastinal adenopathy and clinical suspicion of sarcoidosis. The total numbers of passes per patient were similar, and the diagnostic yield of EBUS-guided TBNA was superior to that of TBNA using a standard 19-gauge needle.[8] Thus, slightly increasing the sample size might not increase the diagnostic yield for sarcoidosis, and proper needle guidance might be more important. These findings are in agreement with those of our meta-analysis. In general, the diagnostic yield was increased for EBUS-TBNA. Nearly, 87% of sarcoidosis patients with isolated mediastinal lymphadenopathy were spared from a surgical lung biopsy. Further, TBLB yielded granulomas in an additional 8–16% of patients when performed in conjunction with EBUS-TBNA. EBB may also be useful, especially in patients with visible mucosal abnormalities, but it does not appear to increase the sensitivity of bronchoscopy sufficiently to warrant routine use when combined with EBUS-TBNA.[31] According to the experience acquired and research performed at our center, the combination of these three methods (EBUS-TBNA + TBLB + EBB) in real clinical practice achieves higher accuracy in patients with a limited number of bronchial mucosal lesions, and EBB may be more suitable for patients with increased bronchial mucosal lesions.[20]

Finally, this meta-analysis has limitations due to the presence of significant clinical and statistical heterogeneity. RCTs are well known to produce the best clinical research evidence. However, only five RCTs were included in this meta-analysis; therefore, subgroup analysis could not be performed. This lack of RCTs might be due to limited application of bronchoscopy for the diagnosis of pulmonary sarcoidosis. Notably, the design of RCTs should be based on a sufficient amount of data, including results from prospective and retrospective studies and systemic reviews. If possible, clinicians should carry out more RCTs in the future. Further, there are limitations for diagnosing pulmonary sarcoidosis by bronchoscopy for several reasons. First, different medical centers have different medical device levels. Second,

different doctors might have different surgical skill. In this meta-analysis, we conducted sensitivity analyses in which subgroup analyses were conducted to investigate the causes of this heterogeneity. The Plit *et al*. 2012[10], Gupta *et al*. 2014[15], Goyal *et al*. 2014[16], and Tong *et al*. 2015[20] studies contributed to part of this heterogeneity, probably because of differing operative skills of the surgeons, differences in the populations studied or another factor. In the Plit *et al*.[10] 2012 study, approximately, ten specimens were obtained via TBLB, which could have led to the high diagnostic yield determined for this procedure. The Gupta *et al.* 2014[15] and Goyal *et al.* 2014[16] studies were performed at the same medical center, and EBUS-TBNA was first introduced to the center at the time of this study. Moreover, the size of lymph nodes sampled by TBNA, the numbers of lymph nodes sampled by TBNA, the number of passes made using TBNA, the major stations sampled, the sample number for TBLB, the locations of TBLB, whether fluoroscopy was performed, and the sample number for EBB were not uniform across studies. Further, the sample sizes of some of the meta-analysis groups were too small, which resulted in the reduced power of this meta-analysis. In addition, data on confounding factors, such as age and gender, were mostly unavailable and could not be corrected by performing meta-regression analysis. Those confounding effects might have influenced the results. Therefore, the conclusions are not convincing.

Some of the challenges experienced in this study were due to the fact that the diagnosis of sarcoidosis is extremely difficult, even with pathological analysis of surgical biopsy tissue. In addition, the diagnosis of sarcoidosis changes over the time. Because EBUS-TBNA is a relatively new technology used for the diagnosis of sarcoidosis, a very limited number of trials have been performed particularly on Asian populations. Therefore, we examined all relevant published studies regardless of date published or level of research. Sarcoidosis is diagnosed by excluding other nodular disorders, such as tuberculosis and lymphoma, and there is no gold standard for its diagnosis. In this meta-analysis, all of the patients were diagnosed based on clinical/radiological findings and were followed up for at least 6 months. We intended to analyze the data included in the articles to evaluate the application of different methods for the diagnosis of Stage I and II pulmonary sarcoidosis; unfortunately, we could not obtain additional information from these articles. Therefore, we could not analyze other clinical characteristics associated with bronchoscopy examination. It cannot be denied that the combined use of EBUS-TBNA + TBLB + EBB would be more expensive; however, the rate of misdiagnosis would also be much lower; thus, we believe that their combined use is very important for the diagnosis and subsequent effective treatment of this disease. We agree that these data are truly necessary, and the economic factors should be taken into consideration in the future.

In conclusion, EBUS-TBNA + TBLB + EBB should be utilized for the diagnosis of sarcoidosis if it is available. At medical centers without EBUS-TBNA, TBNA + TBLB + EBB can be used instead. All surgeons should obtain as much experience with performing these procedures as possible to achieve a high diagnostic yield and low complication rate. It appears that more studies are necessary to determine whether EBUS-TBNA + TBLB + EBB produce the same or a higher diagnostic yield than routine bronchoscopy and whether it reduces the complication rate.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

Acknowledgment

We thank Dr. Li KS and Tong B for giving us the unavailable papers online.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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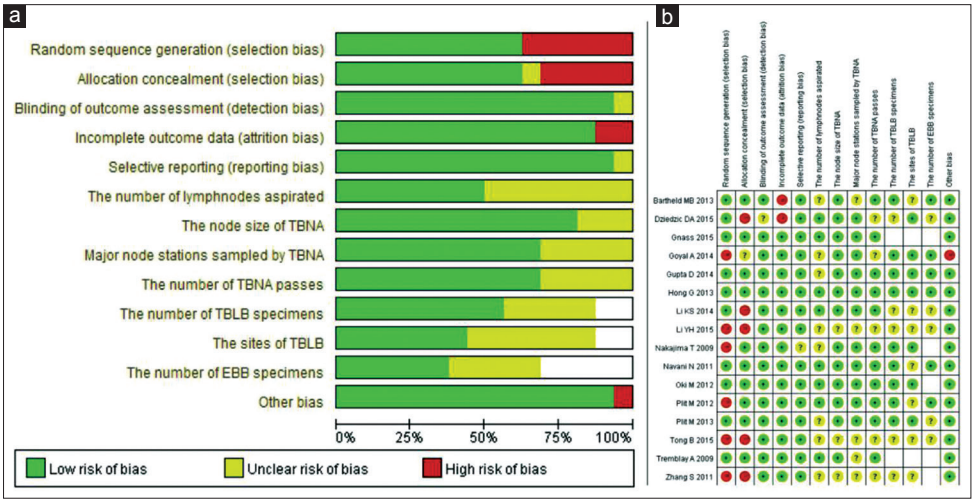
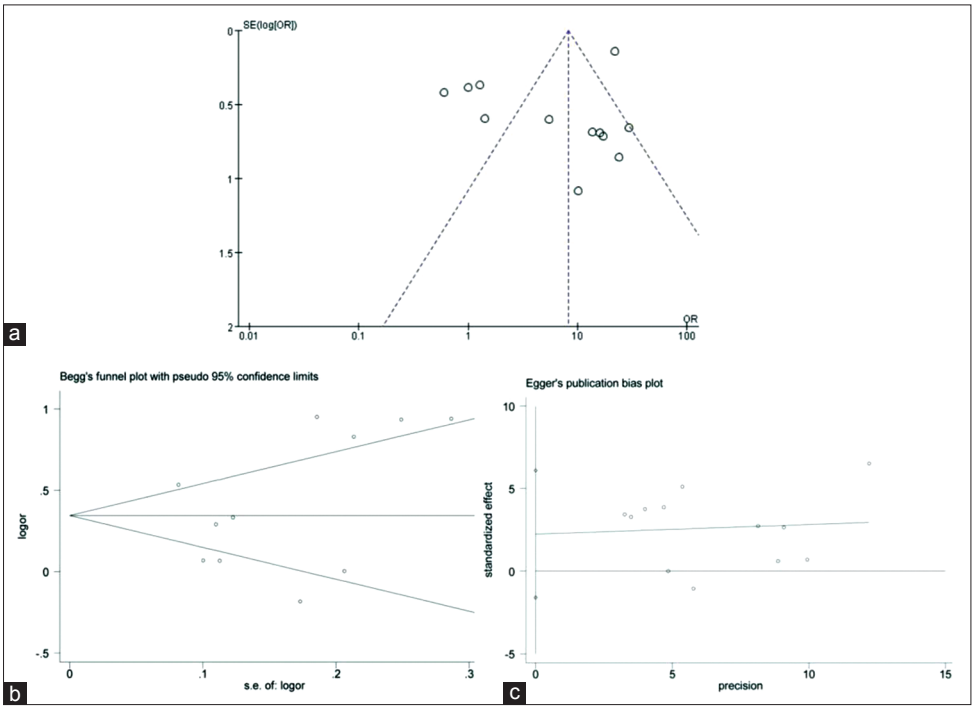
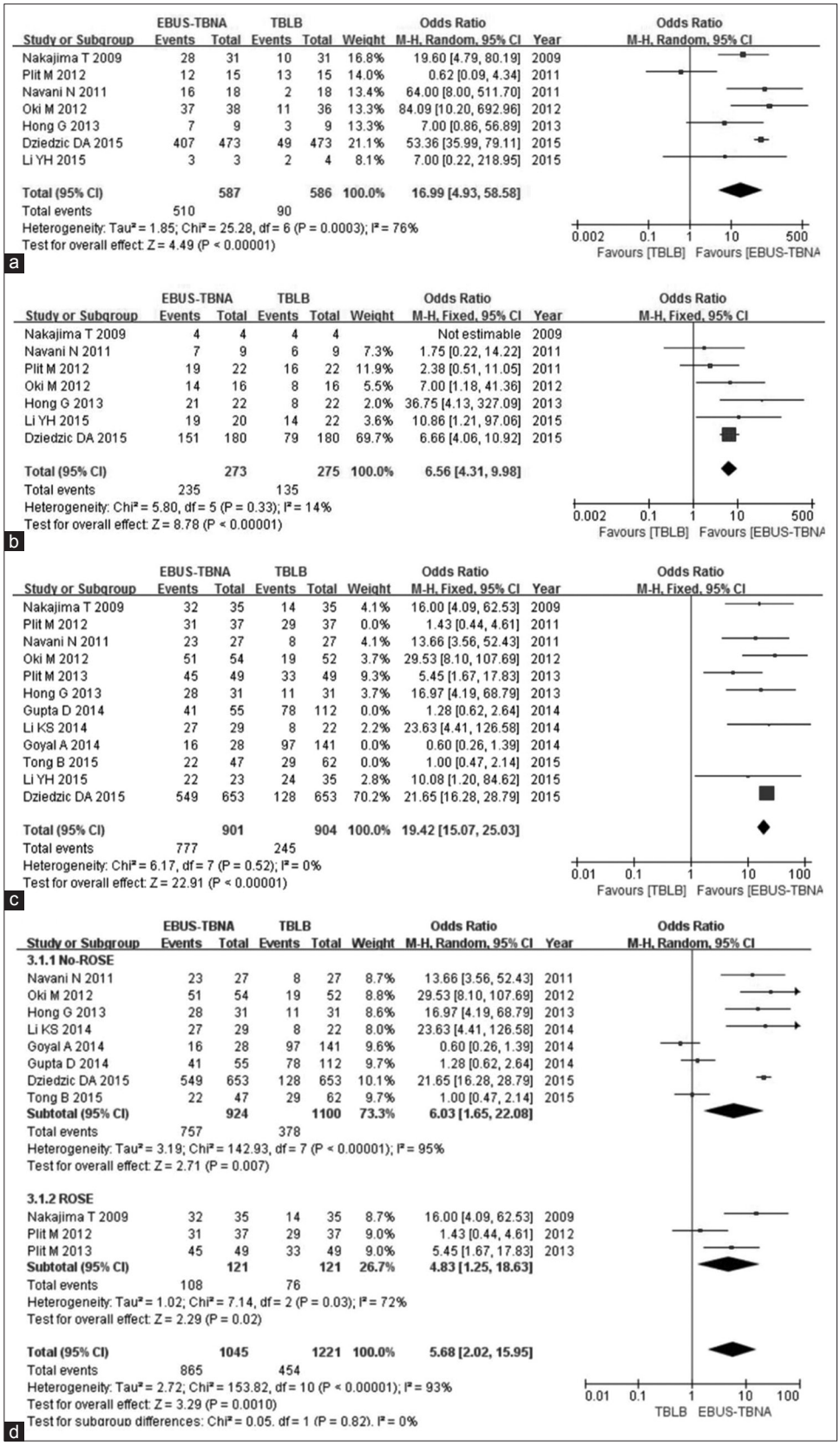


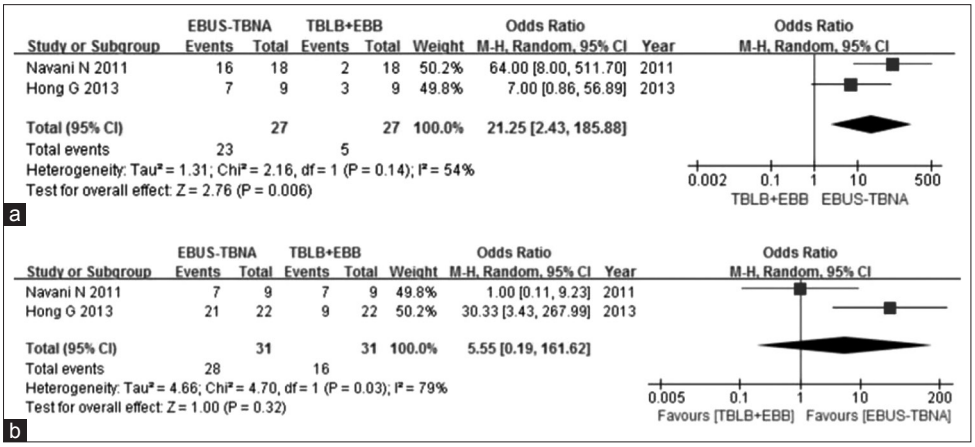
Supplementary Figure 1: Risk of bias of the 16 included studies. (a) Risk of bias graph of the 16 included studies. (b) Risk of bias summary. The blank parts represent the studies that did not perform TBLB or EBB. The quality of studies was generally good. TBNA: Transbronchial needle aspiration; TBLB: Transbronchial lung biopsy; EBB: Endobronchial biopsy.



Supplementary Figure 2: The graphs of assessment of publication bias. (a) The open circles represent the studies included in this meta-analysis. The line in the center indicates the summary *OR*. The funnel plot was slightly asymmetric. (b) Begg's test of publication bias ($P = 0.304$). (c) Egger's test of publication bias $P = 0.223$. There was no evidence for a significant publication bias in our meta-analysis. SE: Standard error; *CI*: Confidence interval; *OR:* odds ratio.



Supplementary Figure 3: Forest plot of EBUS-TBNA versus TBLB for the diagnosis of sarcoidosis. (a) Stage I. The pooled *OR* for stage I was 16.99 (95% *CI*, 4.93–58.58, $P < 0.00001$); (b) Stage II. The pooled *OR* for stage II was 6.56 (95% *CI*, 4.31–9.98, $P < 0.00001$). EBUS-TBNA was better than TBLB for both stages (especially Stage I). (c) Except the Plit 2012, Goyal 2014, Gupta 2014, and Tong 2015 studies. After excluding the study by Plit, Goyal, Gupta and Tong *et al.*, the heterogeneity was not significant. (d) ROSE and No-ROSE subgroups. The heterogeneity in the ROSE group was significant, and it is the same with No-ROSE subgroup. *CI*: Confidence interval; *OR:* Odds ratio; ROSE: Rapid on-site evaluation; EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; TBLB: Transbronchial lung biopsy.



Supplementary Figure 4: Forest plot of EBUS-TBNA versus TBLB + EBB for the diagnosis of sarcoidosis. (a) EBUS-TBNA versus TBLB + EBB for the diagnosis of Stage I sarcoidosis. (b) EBUS-TBNA versus TBLB + EBB for the diagnosis of Stage II sarcoidosis. EBUS-TBNA was better than TBLB + EBB only for Stage I sarcoidosis. *CI*: Confidence interval; EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; TBLB: Transbronchial lung biopsy; EBB: Endobronchial biopsy.

Supplementary Table 1: Demographic characteristics of patients

Studies	Patients' geographic features	Study design	Age (years), mean (± SD) or mean (range)	Number of patients, *n*	Stage	Needle gauge	Node size (mm), mean (± SD), or mean (range)	Major lymph node stations sampled	Number of lymph nodes sampled by TBNA, *n* or range	Number of passes made using TBNA, *n*, or range	Sample number of TBLB, *n*, or range	Locations of TBLB	Fluroscopy	Sample number of EBB, *n*	ROSE	Mean duration (min), mean (± SD), or mean (range)
Nakajima *et al.*, 2009[4]	Japan	Retrospective	48.2 (23–77)	35	I, II	22	>10	4 right, 7	–	≤3	≥3	Lesion region or right upper lobe	Yes	NA	Yes	–
Tremblay *et al.*, 2009[8]	Canada	RCT	TBNA: 40.8 EBUS-TBNA: 39.5	50	I, II	TBNA: 19 EBUS-TBNA: 22	TBNA: 17.9 EBUS-TBNA: 16.5	–	TBNA: 2.2 EBUS-TBNA: 4.0	3–5	NA	NA	NA	NA	No	TBNA: 34 EBUS-TBNA: 44.2
Navani *et al.*, 2011[12]	African or Caribbean, Asian, and Caucasian	Prospective	19–68	27	I, II	22	>10	4 right, 7 or 10 right	1–2	≥4	4–6	–	No	≥4	No	EBUS-TBNA: 22 TBLB + EBB: 25 EBUS-TBNA group: 46
Zhang *et al.*, 2011[19]	China	Retrospective	48.8	50	I, II, III	–	–	–	–	–	–	–	–	–	Yes	–
Oki *et al.*, 2012[11]	Japan	Prospective	49.4 (18–74)	54	I, II	22	>10	4 right, 7	2	2	5	Lesion region or middle and lower lobes	-	NA	No	–
Plit *et al.*, 2012[10]	Australia	Restropective	42 (20–69)	37	I, II	22	16 (8–36)	4 right, 7	1–2	5	8–12	–	–	4	Yes	–
Von Bartheld *et al.*, 2013[7]	America	RCT	Bronchoscopy: 41 Endosonography: 45	192	I, II, III	22	20.6 (± 7.1)	–	–	≥4	≥4	–	Partly	≥4	Optinal	TBLB + EBB: 20 (7–37) Endosonography: 29 (7–60)
Hong *et al.*, 2013[14]	Korea	Retrospective	46 (21–72)	31	I, II	22	>10	4 right, 7	2 (1–3)	3 (1–5)	≥5	Lesion region or right lower lobe	-	≥3	No	–
Plit *et al.*, 2013[9]	Australia	Prospective	47 (± 12.2)	49	I, II	22	16 (8–42)	7, 4 right	According to ROSE	Average: 4	8–10	Middle and lower lobes	Yes	4	Yes	EBUS-TBNA + TBLB + EBB: 49.2 (± 11.5) EBUS-TBNA: 20
Gupta *et al.*, 2014[15]	India	RCT	43.4 (18–68)	117	I, II	21	>10	4 right, 7	–	≥3	≥4	Lesion region or right lower lobe	No	≥4	No	EBUS-TBNA group: 33.5 (± 5.6) TBNA group: 22.9 (± 3.9)
Goyal *et al.*, 2014[16]	India	Prospective	43.3 (18–68)	151	I–IV	21	>10	4 right, 7	–	–	≥4	Lesion region or right lower lobe	No	≥4	No	–
Li and Jiang 2014[13]	China	RCT	TBNA: 38.8 (± 9.6) EBUS-TBNA: 39.2 (± 8.4)	57	I, II	22	>10	4,7	2	2	–	–	–	–	No	–
Dziedzic *et al.*, 2015[18]	Poland	Retrospective	42 (19–63)	653	I, II	22	>10	4, 7	1.6	–	–	Lesion region	–	–	No	–

Contd...

Supplementary Table 1: Contd...

Studies	Patients' geographic features	Study design	Age (years), mean (± SD) or mean (range)	Number of patients, *n*	Stage	Needle gauge	Node size (mm), mean (± SD), or mean (range)	Major lymph node stations sampled	Number of lymph nodes sampled by TBNA, *n* or range	Number of passes made using TBNA, *n*, or range	Sample number of TBLB, *n*, or range	Locations of TBLB	Fluroscopy	Sample number of EBB, *n*	ROSE	Mean duration (min), mean (± SD), or mean (range)
Gnass *et al*., 2015[17]	Poland	RCT	TBNA: 44.3 (± 14.2) EBUS-TBNA: 42.9 (± 11.6)	64	I, II	21 or 22	>10	4 right, 7, 10 right	1–3	3–5	NA	NA	NA	NA	No	–
Li *et al*., 2015[21]	China	Retrospective	44.3 (± 1.4)	56	I, II, III	–	–	–	–	–	–	–	–	–	–	–
Tong *et al*., 2015[20]	China	Retrospective	48 (± 10)	200	I, II, III	–	–	–	–	–	–	–	–	–	No	–

Details of the EBUS-TBNA procedure in studies reporting the performance of the EBUS-TBNA for sarcoidosis patients. RCT: Randomized controlled trial; SD: Standard deviation; TBNA: Transbronchial needle aspiration; TBLB: Transbronchial lung biopsy; EBB: Endobronchial biopsy; ROSE: Rapid on-site evaluation; EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; EBUS-TBNA group: EBUS-TBNA + TBLB + EBB; TBNA group: TBNA + TBLB + EBB; –: No data; NA: No association.