



# Comparison between closed pleural biopsy and medical thoracoscopy for the diagnosis of undiagnosed exudative pleural effusions: a systematic review and meta-analysis

Yuqing Wei<sup>1,2#</sup>, Kaikai Shen<sup>3#</sup>, Tangfeng Lv<sup>2</sup>, Hongbing Liu<sup>2</sup>, Zimu Wang<sup>2</sup>, Juan Wu<sup>4</sup>, He Zhang<sup>1</sup>, Sara Colella<sup>5</sup>, Fu-Zong Wu<sup>6,7</sup>, Michael T. Milano<sup>8</sup>, Ping Zhan<sup>2</sup>, Yong Song<sup>2</sup>, Zhiwei Lu<sup>1</sup>; written on behalf of AME Lung Cancer Collaborative Group

<sup>1</sup>Department of Respiratory Medicine, Yijishan Hospital of Wannan Medical College, Wuhu 241000, China; <sup>2</sup>Department of Respiratory Medicine, Jinling Hospital, Nanjing University School of Medicine, Nanjing 210002, China; <sup>3</sup>Department of Critical Care Medicine, Yijishan Hospital of Wannan Medical College, Wuhu 241000, China; <sup>4</sup>Department of Pathology and Pathophysiology, Wannan Medical College, Wuhu 241002, China; <sup>5</sup>“UOC Pneumologia,” “C. e G. Mazzini” Hospital, Ascoli Piceno, Italy; <sup>6</sup>Department of Radiology, Kaohsiung Veterans General Hospital, Kaohsiung; <sup>7</sup>Faculty of Medicine, School of Medicine, Institute of Clinical Medicine, National Yang Ming University, Taipei; <sup>8</sup>Department of Radiation Oncology, University of Rochester Medical Center, Rochester, NY, USA

**Contributions:** (I) Conception and design: Y Wei, H Liu, P Zhan, Y Song; (II) Administrative support: K Shen, T Lv, Z Lu, Z Wang, J Wu, H Zhang; (III) Provision of study materials or patients: Y Wei, K Shen; (IV) Collection and assembly of data: Y Wei, K Shen; (V) Data analysis and interpretation: Y Wei, K Shen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

<sup>#</sup>These authors contributed equally to this work.

**Correspondence to:** Zhiwei Lu. Department of Respiratory Medicine, Yijishan Hospital of Wannan Medical College, Wuhu 241000, China.

Email: sduzhiwei@sina.com; Yong Song; Ping Zhan. Department of Respiratory Medicine, Jinling Hospital, Nanjing University School of Medicine, 305 East Zhongshan Road, Nanjing 210002, China. Email: yong\_song6310@yahoo.com; zhanping207@163.com.

**Background:** Exudative pleural effusion (EPE) is a common diagnostic challenge. The utility of medical thoracoscopy (MT) and closed pleural biopsy (CPB) to aid in the diagnosis of EPE has been reported in many published studies. Herein, we perform a systematic review and meta-analysis to compare the diagnostic yield and safety of CPB and MT in EPE.

**Methods:** Four databases were searched for studies reporting the diagnostic yield of CPB and MT for EPE. The quality of the included studies was evaluated according to the quality assessment of diagnostic accuracy studies (QUADAS) tool. The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and complication risks were compared between the two groups.

**Results:** Ten studies dealing with CPB and twenty-three studies dealing with MT for the diagnosis of EPE were included in this meta-analysis. Pooled sensitivity, specificity, PLR, NLR and DOR of CPB group was 77%, 99%, 32.55, 0.22, 165.71, respectively, while pooled sensitivity, specificity, PLR, NLR and DOR of MT group was 93%, 100%, 10.82, 0.08, 162.81, respectively. The area under the summary receiver operating characteristic (SROC) curve of CPB and MT were both 0.97. The ability of CPB to diagnose non-malignant diseases was like MT (69% *vs.* 68%), while the ability was lower than that of MT to diagnose malignant diseases (72% *vs.* 92%). The pooled diagnostic accuracy of CPB and MT for mesothelioma was 26% (95% CI, 14–38%) and 42% (95% CI, 22–62%) ( $P < 0.001$ ), respectively. The rate of complications with CPB was lower than that reported for MT.

**Conclusions:** CPB is a relatively accurate tool with a lower complication rate compared to MT in the diagnosis of EPE, especially in diagnosing non-malignant diseases. We confirm the utility of MT in the diagnostic workup of malignancy (especially mesothelioma); however, in selected cases, CPB could be used as the first diagnostic approach with a favorable safety profile.

**Keywords:** Closed pleural biopsy (CPB); medical thoracoscopy (MT); exudative pleural effusion (EPE); diagnosis; meta-analysis

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## Introduction

Pleural effusion, referring to the abnormal accumulation of fluid in the pleural cavity, is potentially caused due to several reasons. For example, malignancies (either primitive or secondary pleural tumors), infections like tuberculosis or pneumonia, systemic conditions like in the case of congestive heart failure, renal failure, and connective tissue disorders, exposure to drugs and pulmonary embolism (1). When a unilateral pleural effusion is detected, an extensive investigation with non-invasive and invasive procedures must manage the patient correctly (2). At least 15–20 percent of all pleural effusions are still undiagnosed despite extensive clinical work (3). The simplest and least invasive way to establish the diagnosis of undiagnosed exudative pleural effusion (EPE) is thoracentesis with pleural fluid cytology and microbiological analysis, but this procedure has a high rate of false-negative results, with a sensitivity of around 60% (range, 40–87%) thus especially in patients with a high suspicion of neoplastic or infectious disease further exams have to be considered (4).

Thus, the next step in undiagnosed EPE is to obtain pleural tissue samples for pathological and microbiological examination. Currently, there are two ways to obtain tissue samples of the pleura, closed pleural biopsy (CPB) or medical thoracoscopy (MT). CPB was firstly described in 1955 by De Francis and co-workers (5,6) and it consists of taking a transthoracic biopsy of the pleura and a diagnostic accuracy of slightly less than 60% if the procedure is performed blindly, but this percentage rises if the pleural biopsy is taken image-guided (ultrasound- and CT scan-guided) (7). It can be performed in an outpatient setting, but limitations of the procedure are that multiple biopsies could not be done and abnormalities in the apical or diaphragmatic region are difficult to be biopsied; complications of CPB are a pain, pneumothorax, vasovagal reaction, haemothorax, hematoma, and transient fever. MT

has its roots in the early 1900s: with this technique, most of the pleural cavity can be overseen, allowing pleural biopsy under direct visualization and also therapeutic interventions such as talc pleurodesis. MT has a diagnostic yield ranging from 91% to 95% for malignant pleural effusions (MPE) and 100% for tuberculous pleural effusions (TPE) (8), so it is currently considered as the gold standard (9). However, because of the prohibitive cost, need for specialized equipment, and the need for specialized training of physicians and medical staff, thoracoscopy is not widely available in community health centers.

At present, many published studies have described the diagnostic utility of CPB and MT, but with some inconsistent results that make it difficult to draw firm conclusions. Therefore, in order to increase statistical power and reduce uncertainty, we performed a systematic review of CPB and MT in patients with EPE and compared the overall diagnostic yield and safety of CPB and MT in the diagnosis of EPE using a meta-analytic approach.

## Methods

### *Search strategy*

The literature search was independently conducted by two investigators (Y Wei and K Shen) who searched four databases (PubMed, Web of Science, Cochrane Library and Embase) for studies that described the diagnostic value and safety of CPB or MT, and also searched for references of the included studies to identify other relevant studies. The following terms were used in the literature search: “closed pleural biopsy”, “CPB”, “medical thoracoscopy”, “MT”, “exudative pleural effusion”, “EPE”, “indeterminate pleural effusion”, “undiagnosed exudative pleural effusion”, “pleural biopsy”, “pleuroscope”, “thoracoscope”, “diagnostic accuracy”, “sensitivity and specificity”. Literature citations within selected studies were also searched to find other

potentially relevant studies. The search included studies published from January 2000 to July 2018.

### *Eligibility criteria*

Studies that met the following criteria were included: (I) prospective or retrospective studies that enrolled at least 20 consecutive patients; (II) studies providing the diagnostic yield and complications of CPB and/or MT for the diagnosis of indeterminate pleural effusion; (III) full text available in the English language; (IV) when the results of the same study were reported in different articles, only the latest and complete data were included in this meta-analysis; (V) the search was focused on researches that had been conducted in humans. The following type of studies was excluded: (I) conference abstracts, review articles, case report and letters to journal editors; (II) studies describing CPB and/or MT in <20 patients; and (III) studies that did not provide sufficient data for statistical analysis. Two reviewers (Y Wei and K Shen) independently assessed the eligibility of enrolled study. Any disagreement was resolved by discussion between the reviewers.

### *Literature review and data extraction*

Study retrieval were conducted by two independent reviewers, and disagreements were resolved by consensus. First, a review of the title and abstract was initially conducted to identify potentially relevant articles, then the eligibility by reading the full text of the potentially relevant articles was evaluated; lastly, we also searched for references of the included articles to identify other relevant studies. Two authors (Y Wei and K Shen) independently extracted the data into a standard data extraction form. The extracted items included publication details such as authors, year of publication, and country where the study was conducted, type of study (prospective or retrospective), number of enrolled patients, inclusion criteria, true positive (TP), false positive (FP), true negative (TN), false negative (FN) from each study and complications.

### *Assessment of study quality*

The quality assessment of diagnostic accuracy studies

(QUADAS) tool was used (10). The QUADAS test can result in a maximum score of 14, in which a score of 1 is given when a criterion is fulfilled, 0 if a criterion is unclear, and -1 if the criterion is not achieved. Two reviewers (Y Wei and K Shen), working independently, assessed the quality of selected papers according to empirical evidence, expert opinion, and formal consensus (11).

### *Statistical analysis*

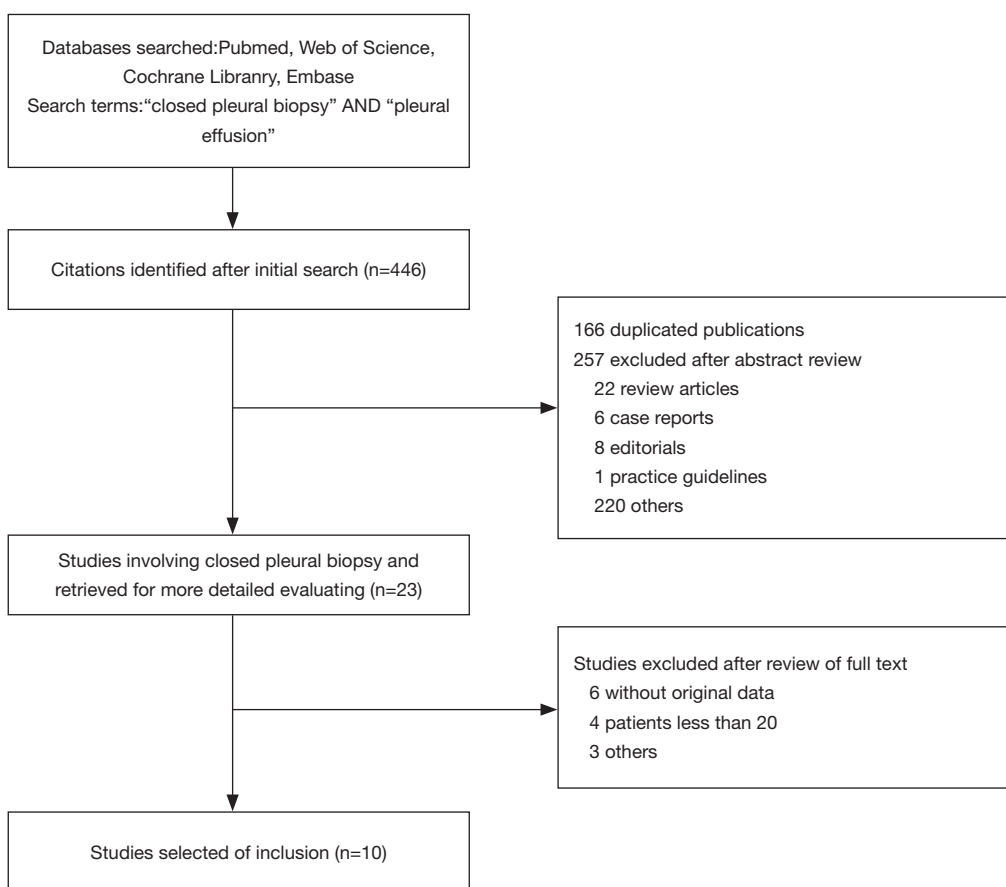
Statistical software packages Meta-Disc (Version 1.4, XI Cochrane Colloquium; Barcelona, Spain) and STATA version 12.0 software (Stata Corporation College Station, TX, USA) were used to perform the statistical analysis.

### *Determination of the pooled effect*

Meta-analysis was done by calculating the sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR; PLR/NLR) for each study. The sensitivity, specificity, PLR, and NLR were pooled using the DerSimonian-Laird random-effects model, while DOR was pooled using the fixed effects model to derive a pooled estimate with 95% confidence intervals (CI). What would be considered a good diagnostic test would have a PLR >10 and NLR <0.1. Also, a summary receiver operating characteristic curve (SROC) was constructed using the random effects model. The area under the curve (AUC) was computed by the numeric integration of the curve equation by the trapezoidal method. A perfect test will have values of AUC close to 1 while poor test has AUC close to 0.5.

### *Assessment of Heterogeneity and estimation of publication bias*

Heterogeneity for the individual outcomes was assessed by using the  $I^2$  test, which measures the extent of inconsistency among the results of the studies. An  $I^2$  value of  $\geq 50\%$  indicates significant heterogeneity. Heterogeneity was also assessed by using the Cochran Q statistic. A P value <0.1 was significant. A fixed-effect model (FEM) was used in the analyses for which no significant heterogeneity was found among different studies; otherwise, the random



**Figure 1** Search and selection flow diagram of studies on closed pleural biopsy.

effects model (REM) was applied. Funnel plots and the Deek test were used to investigate the potential presence of publication bias.

## Results

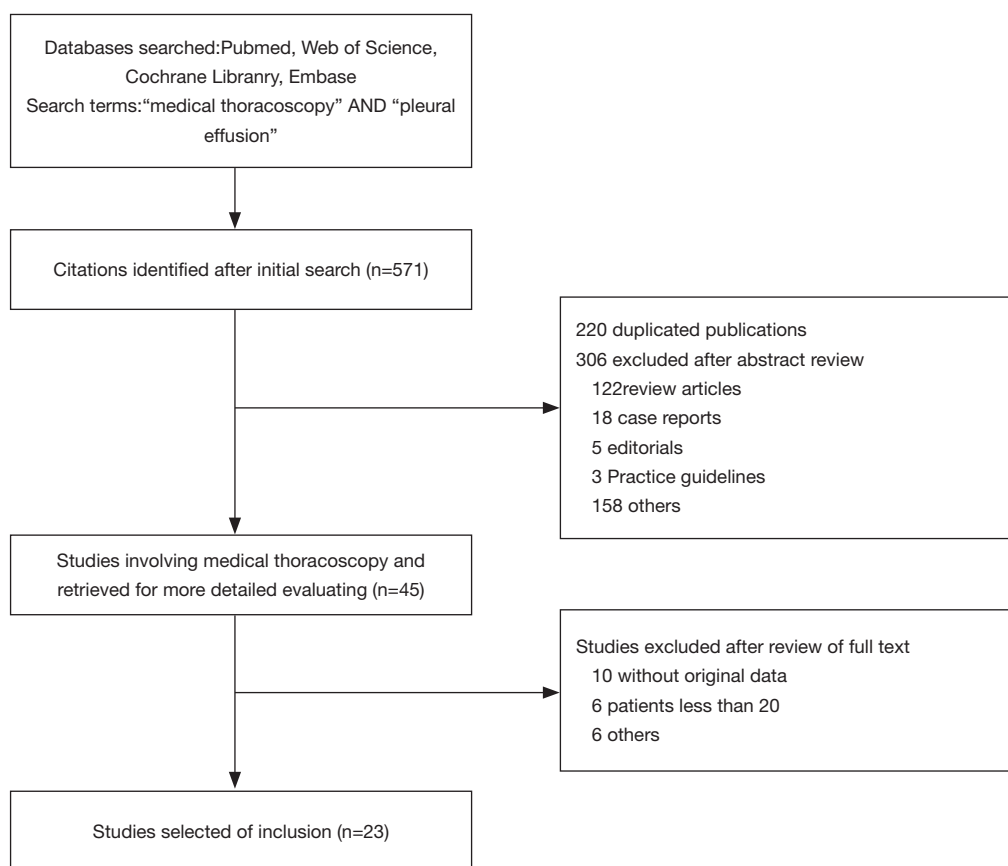
### *Study Selection and characteristics of included studies*

The search and selection flow diagram of studies on CPB and MT are shown in *Figures 1* and *2*, respectively. For CPB, our initial database search yielded a total of 446 citations (*Figure 1*) from which 10 studies on CPB ultimately met our inclusion criteria and were selected for meta-analysis (2,7,12-19); for MT, our initial database search yielded a total of 571 citations (*Figure 2*) from which 23 studies on MT ultimately met our inclusion criteria and were selected for meta-analysis (1,8,20-40). *Tables 1* and *2* show the basic features of the studies selected for analysis as well as their QUADAS scores. Among the 10 CPB

publications on CPB, 4 studies are retrospective, and 6 are perspective (included one randomized controlled trial). Nine studies were conducted at single centers, and one study was multicentric. Among the 23 published studies on MT, 12 studies are retrospective, and 11 are perspective (included two randomized controlled trials). Eighteen studies were conducted at single centers, and five studies were multicentric.

### *Diagnostic accuracy of studies dealing with CPB and MT*

Ten studies (1,747 subjects) described the diagnostic yield of CPB in patients with an EPE. The sensitivity in the diagnosis of undetermined EPE ranged from 57% to 97% (*Figure 3A*), with the pooled sensitivity being 77% (95% CI, 75–80%). The pooled specificity of the procedure was 99% (*Figure S1A*). Twenty-three studies (1,783 subjects) described the diagnostic yield of MT in patients with an EPE and *Figure 3B* depicted the forest plot of sensitivity



**Figure 2** Search and selection flow diagram of studies on medical thoracoscopy.

and showed a pooled sensitivity of 93% (95% CI, 91–94%). The forest plot for specificity was shown in *Figure S1B*. All the included studies yielded the pooled specificity of MT was 100%. The pooled positive and negative LR of CPB were 32.55 (95% CI, 17.42–60.82) and 0.22 (95% CI, 0.16–0.31) respectively (*Figure S2A,S2B*), while *Figure S2C,S2D* illustrated the forest plots of positive and negative LR of MT, pooled positive and negative LR (95% CI) were 10.82 (5.65–20.72) and 0.08 (0.05–0.15), respectively. The diagnostic odds ratio (*Figure S3A*) of CPB was 165.71 (95% CI, 85.14–322.54) and the pooled diagnostic odds ratio (95% CI) of MT was 162.81 (68.41–387.44) (*Figure S3B*). Both the area under the SROC curve were 0.97 (*Figure S4A,S4B*).

### Subgroup analysis

Separate subgroup analyses were conducted in subjects with malignant diseases and non-malignant diseases (tuberculosis, infections and so on), after excluding

those studies that do not report the diagnostic accuracy in malignant and non-malignant diseases. The resulted pooled diagnostic accuracy of CPB and MT for non-malignant diseases were 69% (95% CI, 51–88%) and 68% (95% CI, 48–87%) (*Figure 4A*), respectively, whereas the pooled diagnostic accuracy of CPB and MT for malignant diseases were 72% (95% CI, 62–82%) and 92% (95% CI, 88–95%), respectively (*Figure 4B*). The ability of CPB to diagnose non-malignant diseases was similar to MT, while the ability was lower than that of MT to diagnose malignant diseases. In addition, another subgroup analysis showed that the pooled diagnostic accuracy of CPB and MT for mesothelioma was 26% (95% CI, 14–38%) and 42% (95% CI, 22–62%) ( $P<0.001$ ), respectively (*Figure 4C*).

### Heterogeneity and publication bias

Because of significant statistical heterogeneity for the

**Table 1** Characteristics of included studies on closed pleural biopsy

Author [year]	Country/region	Number of centres	Type of study	No. of patients	Inclusion criteria	Q score	TP	FP	FN	TN	No. of complications
Nusair <i>et al.</i> [2002]	Israel	Unicentric	Retrospective	44	Patients with an exudative pleural effusion with no accompanying pleural or subpleural thickening or mass	5	13	0	10	19	3
Al-Shimemeri <i>et al.</i> [2003]	Saudi Arabia	Unicentric	Retrospective	110	Patients with an exudative pleural effusion	6	54	0	32	24	4
Maskell <i>et al.</i> [2003]	UK	Unicentric	RCT	25	Patients with cytologically negative suspected malignant pleural effusions	7	15	0	9	1	1
Botana-Rial <i>et al.</i> [2013]	Spain	Unicentric	Prospective	67	Patients with an exudative pleural effusion	4	48	0	6	13	1
Jakubec <i>et al.</i> [2014]	Olomouc	Unicentric	Prospective	222	Patients with pleural effusion and cytologic examination of pleural fluid was negative	7	99	0	58	65	22
Devkota <i>et al.</i> [2014]	Nepal	Unicentric	Prospective	47	Patients with an exudative pleural effusion	6	28	0	3	16	–
Maturu <i>et al.</i> [2015]	India	Unicentric	Retrospective	84	Patients with exudative pleural effusions and remain undiagnosed after thoracentesis	7	63	0	13	8	7
Báez-Saldaña <i>et al.</i> [2017]	México	Unicentric	Prospective	863	Diagnosing malignancy in patients with pleural effusion	5	450	5	137	271	38
Zuberi <i>et al.</i> [2016]	Pakistan	Multicentric	Prospective	94	Patients with an exudative pleural effusion	7	74	0	2	20	–
Rajawat <i>et al.</i> [2017]	India	Unicentric	Retrospective	191	Patients with exudative lymphocytic pleural effusion	4	123	0	13	55	–

TP, true positive; FP, false positive; FN, false negative; TN, true negative; RCT, randomized controlled trial.

outcomes (sensitivity, NLR), a random effects model was used. No significant statistical heterogeneity for other outcomes (specificity, PLR, DOR) and using a fixed effects model was found. There was no publication bias either on visual inspection of the funnel plot (*Figure S5A*) or on statistical tests for studies describing CPB ( $P=0.74$ ). The funnel plots of publication bias for studies describing MT show some asymmetry, and the evaluation of publication bias showed that the Deek test was significant ( $P=0.00$ )

and (*Figure S5B*).

### Complication rates

The main shortcoming of MT for the undiagnosed EPE was safety. The complication rate of MT in the diagnosis of pleural effusions of undetermined etiology ranged from 2–30% with the pooled rate being 8% (95% CI, 6–11%), which was significantly higher ( $P<0.001$ ) than that of CPB



**Table 2** Characteristics of included studies on medical thoracoscopy

Author [year]	Country	Number of centres	Type of study	No. of patients	Inclusion criteria	Q score	TP	FP	FN	TN	No. of complications
Lee <i>et al.</i> [2007]	USA	Unicentric	Prospective	51	Patients with indeterminate pleural effusions	6	49	0	2	0	13
Munavvar <i>et al.</i> [2007]	UK	Unicentric	Prospective	55	Pleural effusions undiagnosed after thoracentesis	6	49	0	5	1	0
Wang <i>et al.</i> [2008]	China	Unicentric	Retrospective	27	Patients with undiagnosed pleural effusions	6	24	0	2	1	4
Ng <i>et al.</i> [2008]	Malaysia	Unicentric	Retrospective	22	Patients with undiagnosed pleural effusions	8	14	0	2	6	4
Sasada <i>et al.</i> [2009]	Japan	Unicentric	Prospective	20	Pleural effusions undiagnosed after one thoracentesis and pleural biopsy	6	12	0	8	0	0
Xie <i>et al.</i> [2009]	China	Unicentric	Retrospective	30	Pleural effusions undiagnosed after thoracentesis	5	30	0	0	0	0
Ishida <i>et al.</i> [2009]	Japan	Unicentric	Prospective	45	Pleural effusions undiagnosed after thoracentesis	5	44	0	1	0	1
Kannan <i>et al.</i> [2009]	Malaysia	Multicentric	Prospective	61	Pleural effusions undiagnosed after thoracentesis	6	55	0	6	0	1
Mohan <i>et al.</i> [2010]	UK	Unicentric	Retrospective	160	Pleural effusions undiagnosed after thoracentesis	5	143	0	13	4	6
Huang <i>et al.</i> [2011]	China	Unicentric	Retrospective	47	Patients with pleural effusion and thickening of unknown etiology	7	44	0	0	3	5
Davies <i>et al.</i> [2010]	UK	Unicentric	Retrospective	142	Patients who underwent medical thoracoscopy	7	98	0	5	39	/
Metintas <i>et al.</i> [2010]	Turkey	Unicentric	RCT	51	patients with exudative Pleural effusion that could not be diagnosed by cytologic analysis	9	40	0	2	9	25
Khan <i>et al.</i> [2012]	UK	Multicentric	Retrospective	66	Patients with unilateral exudative pleural effusions	8	62	0	4	0	8
Prabhu <i>et al.</i> [2012]	India	Multicentric	Prospective	68	Pleural effusions undiagnosed after thoracentesis	5	65	0	2	1	4
Rozman <i>et al.</i> [2013]	Slovenia	Unicentric	Prospective	41	Pleural effusions undiagnosed after less invasive means	7	40	0	1	0	4

Table 2 (continued)

Table 2 (continued)

Author [year]	Country	Number of centres	Type of study	No. of patients	Inclusion criteria	Q score	TP	FP	FN	TN	No. of complications
Dhooia <i>et al.</i> [2014]	India	Unicentric	RCT	82	Patients with undiagnosed exudative pleural effusions	7	50	0	21	11	25
Willendrup <i>et al.</i> [2014]	Denmark	Multicentric	Retrospective	56	Patients with unexplained exudative pleural effusion	9	44	0	11	1	2
Gao <i>et al.</i> [2014]	China	Multicentric	Retrospective	215	Patients with undiagnosed exudative pleural effusion	6	190	0	2	23	16
Kiani <i>et al.</i> [2015]	Iran	Unicentric	Prospective	300	Patients with undiagnosed pleural effusions	6	261	0	4	35	11
Verma <i>et al.</i> [2015]	Singapore	Unicentric	Retrospective	41	Patients with symptomatic pleural effusions	9	36	0	2	3	6
Nattusamy <i>et al.</i> [2015]	India	Unicentric	Retrospective	48	Patients with undiagnosed pleural effusions	8	32	0	3	13	11
Patil <i>et al.</i> [2016]	India	Unicentric	Prospective	129	Patients with undiagnosed exudative pleural effusions using rigid thoracoscope	7	110	0	16	3	17
Kim <i>et al.</i> [2017]	Korea	Unicentric	Retrospective	26	Patients who had undergone MT	8	19	0	2	5	1

TP, true positive; FP, false positive; FN, false negative; TN, true negative; RCT, randomized controlled trial; MT, medical thoracoscopy.

ranged from 1–10% with the pooled rate being 5% (95% CI, 3–7%) (Figure S6). The most common complication of CPB was pneumothorax, while as for MT, the most common complications were subcutaneous emphysema and fever.

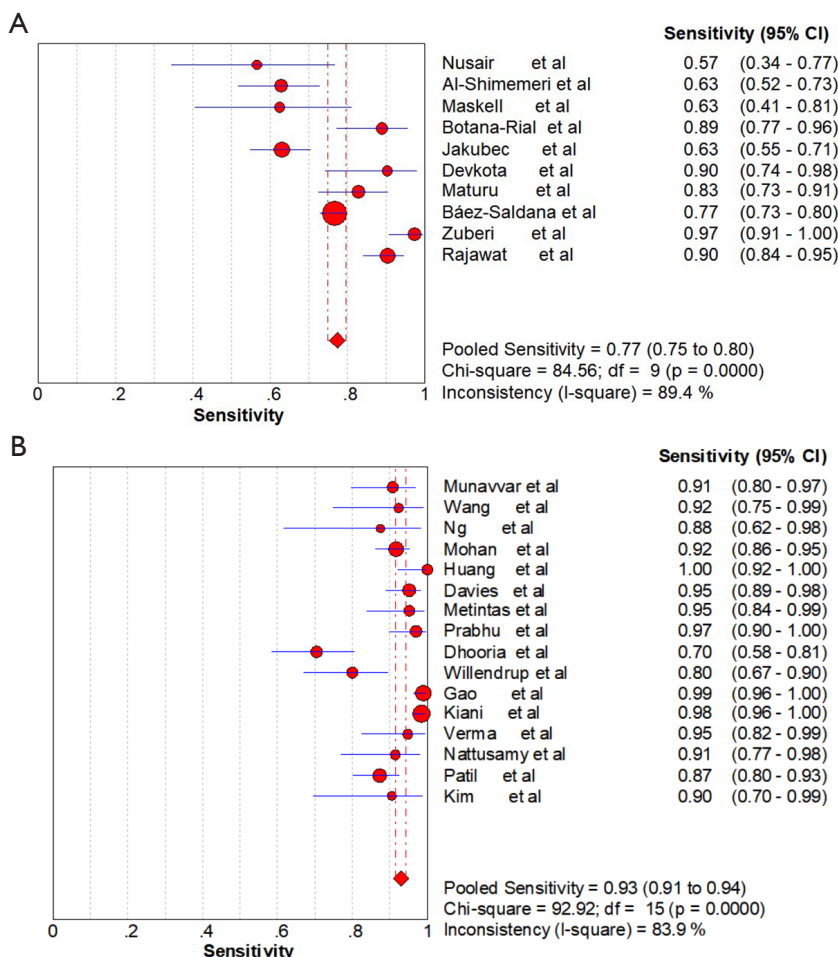
## Discussion

In this meta-analysis, we compared the overall diagnostic efficacy and safety of CPB and MT in EPE from previously published studies. The results of this meta-analysis (10 studies, 1,747 patients with undiagnosed EPE) suggested that CPB was a relatively accurate tool with pooled sensitivity (77%) and an excellent specificity (99%) in patients with undetermined EPE; the sensitivity was lower than the pooled (23 studies, 1,783 patients) sensitivity of MT (93%). Although the diagnostic accuracy of CPB was not superior to that of MT, the major advantage of CPB over MT was its safety. Our meta-analysis proved that lower pooled complication rates with CPB (5%) compared to MT (8%). Furthermore, in subgroup analysis, the ability of CPB to diagnose non-malignant diseases was like MT (69% vs. 68%), while the ability was lower than that of MT to diagnose malignant diseases (72% vs. 92%). Another

subgroup analysis showed that the pooled diagnostic accuracy of CPB and MT for mesothelioma was 26% (95% CI, 14–38%) and 42% (95% CI, 22–62%) ( $P < 0.001$ ), respectively.

Since the early 19th century, thoracentesis (with biochemical, cytological, and microbiological analysis of pleural fluid) has been the standard initial intervention to determine the cause of pleural effusion (41). However, thoracentesis is often non-diagnostic, with the diagnostic yield of pleural fluid cytology varying widely in the published literature, ranging from 40% to 90%. Therefore, to allow for proper treatment of the effusion, other approaches must be considered for those patients with non-diagnostic pleural effusion. In 1955, Defrancis *et al.* first proposed the use of CPB (without the need for surgery) for the diagnosis of pleural effusion (5). Its gained widespread use for more than 5 decades is due to its ease of operation, low cost, excellent patient tolerance, within a brief period of hospital stay, and low morbidity and mortality. Maturu *et al.* showed that CPB could establish the diagnosis in 71 (84.5%) patients with EPE (16), and Zuberi *et al.* reported the overall specific diagnostic yield of CPB is 78.7% (18). However, after the availability of thoracoscopy, the use of CPB for the diagnosis of cytology negative malignant



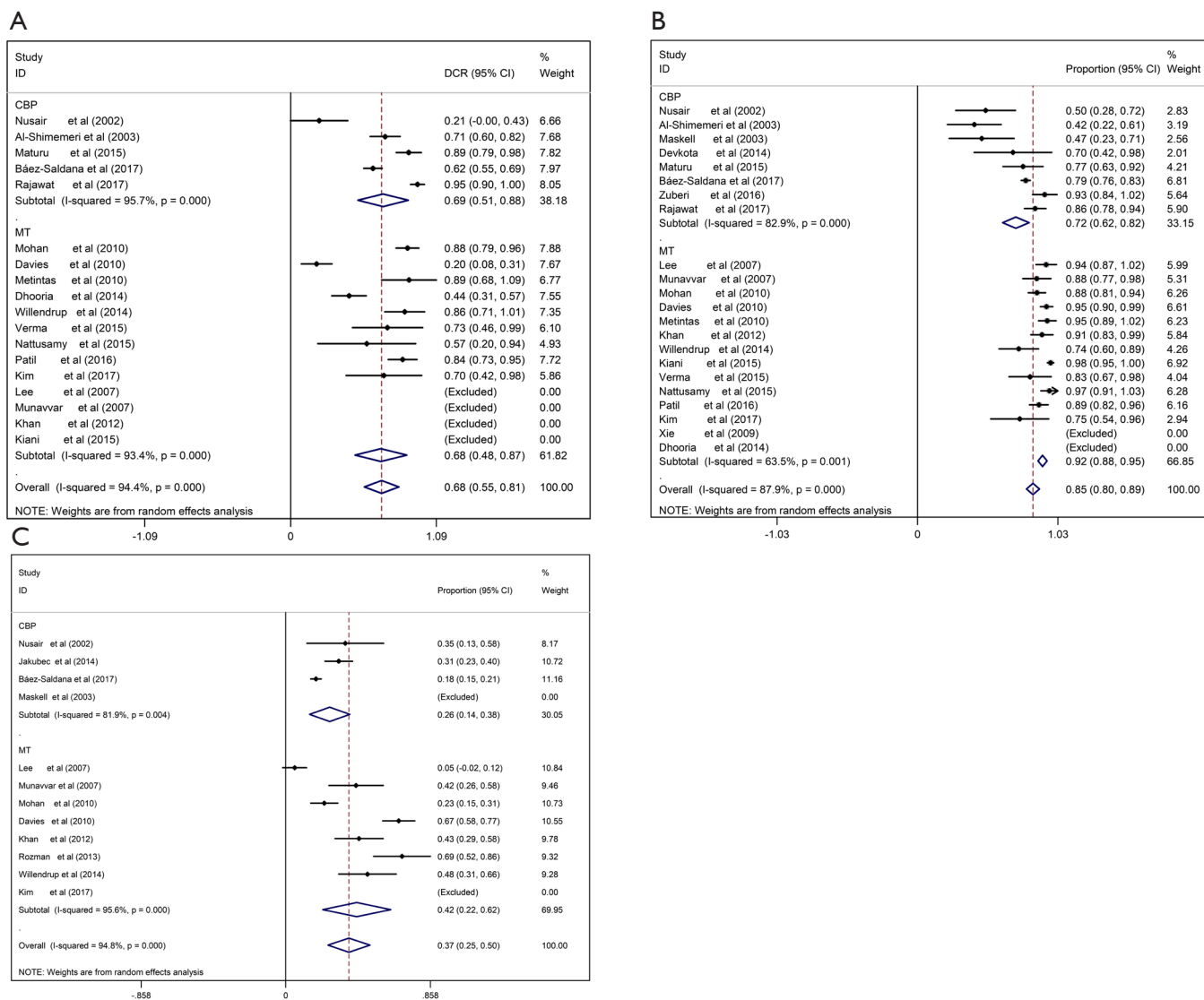


**Figure 3** Forest plot of sensitivity analysis. (A) Forest plot of the pooled sensitivity analysis of CPB in undiagnosed exudative pleural effusions. (B) Forest plot of the pooled sensitivity analysis of MT in undiagnosed exudative pleural effusions. CPB, closed pleural biopsy; MT, medical thoracoscopy.

pleural effusion has constantly been decreasing, especially in the developed world. To use MT in the diagnosis of EPE has been widely accepted, as it allows the operator to visualize any pleural abnormalities directly. The 2010 British Thoracic Society (BTS) guidelines recommended MT as the optimal choice for patients with EPE where a diagnostic pleural aspiration is inconclusive, malignancy is suspected, and Abrams needle biopsy has diagnostic value only in areas with a high incidence of tuberculosis (4). However, the advantages of MT must be weighed against the costs of performing such procedure in terms of training, equipment, and skilled operators as well as the need for chest tube drainage after the procedure, which further increases the hospital stay as well as the healthcare cost. There is a large gap between what is recommended and

what is available, not only in China but also in most of the developing world (19).

The reported sensitivity of CPB for the diagnosis of malignant pleural effusion is 48–56%, which is lower than that of cytological examination, thoracoscopy remains the gold standard for the diagnosis of MPE (4). Our study also showed that the ability of MT to diagnose malignant diseases was significantly higher than that of CBP. CPB for mesothelioma is typically low diagnostic accuracy in clinical practice. Attanoos *et al.* (42) evaluated the diagnostic accuracy of closed and open pleural biopsies in diagnosing malignant pleural mesothelioma, they found that definitive diagnostic accuracy of CPB for mesothelioma was low (16%), while open pleural biopsy produced the highest diagnostic accuracy (100% sensitivity, 95% specificity);



**Figure 4** Forest plot of subgroup analysis. (A) Forest plot of the pooled diagnostic accuracy of CPB and MT for non-malignant diseases. (B) Forest plot of the pooled diagnostic accuracy of CPB and MT for malignant diseases. (C) Forest plot of the pooled diagnostic accuracy of CPB and MT for mesothelioma. CPB, closed pleural biopsy; MT, medical thoracoscopy.

McLaughlin *et al.* indicated that a role for CPB in patients with suspected malignant pleural mesothelioma as it correctly identified 44% of unselected cases (43). Our subgroup analysis showed that the pooled diagnostic accuracy of CPB was lower than MT for mesothelioma (26% *vs.* 42%).

Nevertheless, some studies have suggested that image guided CPB can achieve a diagnostic yield like thoracoscopy. Koegelenberg *et al.* evaluated the value of ultrasound-guided CPB in patients with undiagnosed EPE

and they found that ultrasound-guided biopsy increased the combined yield for all diagnoses from 48.0% to 90.0% ( $P < 0.001$ ), for malignancy from 31.0% to 89.7% ( $P < 0.001$ ) and for tuberculosis from 77.8% to 88.9% ( $P = 0.688$ ) (44). Botana-Rial *et al.* analyzed patients who underwent CPB with thoracic ultrasound guidance, performed by an experienced pulmonologist, and they concluded that the diagnostic yields of CPB using thoracic ultrasound for tuberculous pleural effusion and MPE were 89.5% and 77.4%, respectively (14). Ultrasound provides detailed

information on the extent of the pleural effusion, enables the clinician to select an optimal biopsy site, allows biopsies to be performed in the lower thoracic parietal pleura, and detects other specific pleural abnormalities, which improve the diagnostic yield of biopsy and minimizes potential complications to the most extent. Otherwise, Management of Malignant Pleural Effusions (An Official ATS/STS/STR Clinical Practice Guideline) was published in July 2018, the new guideline recommended that ultrasound imaging be used to guide pleural interventions in patients with known or suspected MPE, the panel agreed that ultrasound guidance has no significant harms associated with its usage, and has an important benefit of reducing pneumothorax rates (45). Ultrasound-assisted CPB has a high diagnostic yield and is safe and can be considered as a first-line diagnostic tool in undiagnosed pleural effusion.

Our meta-analysis has several limitations. Firstly, differences in study design, in enrolled sample size, in patient's baseline disease status limit the interpretation of the pooled data. Whether the characteristics of enrolled study subjects are fully representative of patients receiving CPB or MT in clinical practice may limit the accuracy and safety of this quantitative analysis. Secondly, some factors influencing the performance of CPB and MT, including the experience of the operator, the number of biopsies obtained, and the type of thoracoscopy (rigid or semi-rigid), further exploration is needed. Finally, studies were limited to those published in English, which may result in potential language bias.

## Conclusions

In summary, our systematic review and meta-analysis confirm the values of CPB and MT in the diagnosis of EPE. CPB could be considered a first diagnostic approach or could be the procedure of choice in case of abnormalities at the CT scan or chest ultrasound. MT is paramount to exclude malignancy (especially mesothelioma) or infections, allowing direct visualization of the pleural cavity and therapeutic pleurodesis at the same time.

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## Footnote

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

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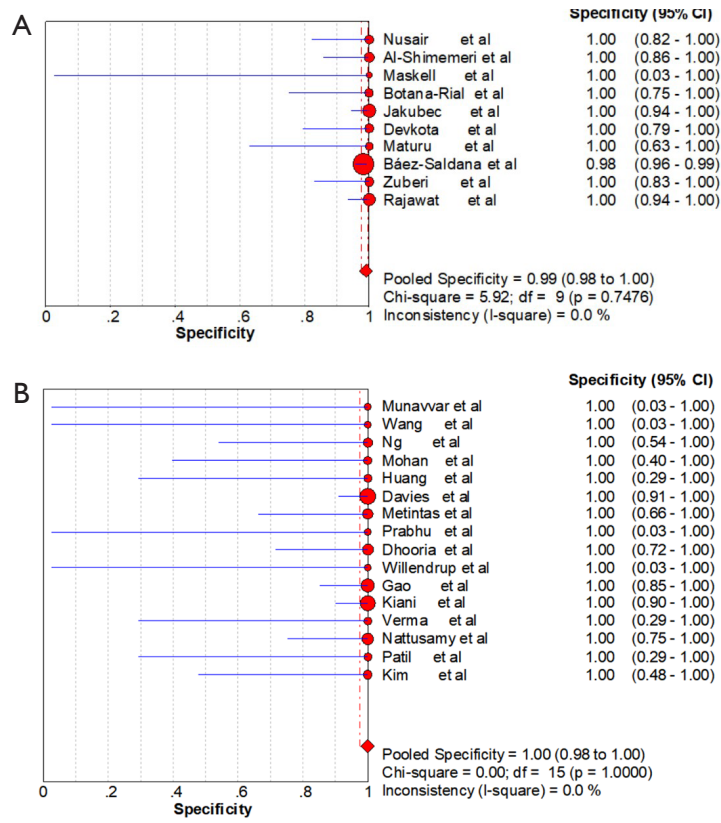
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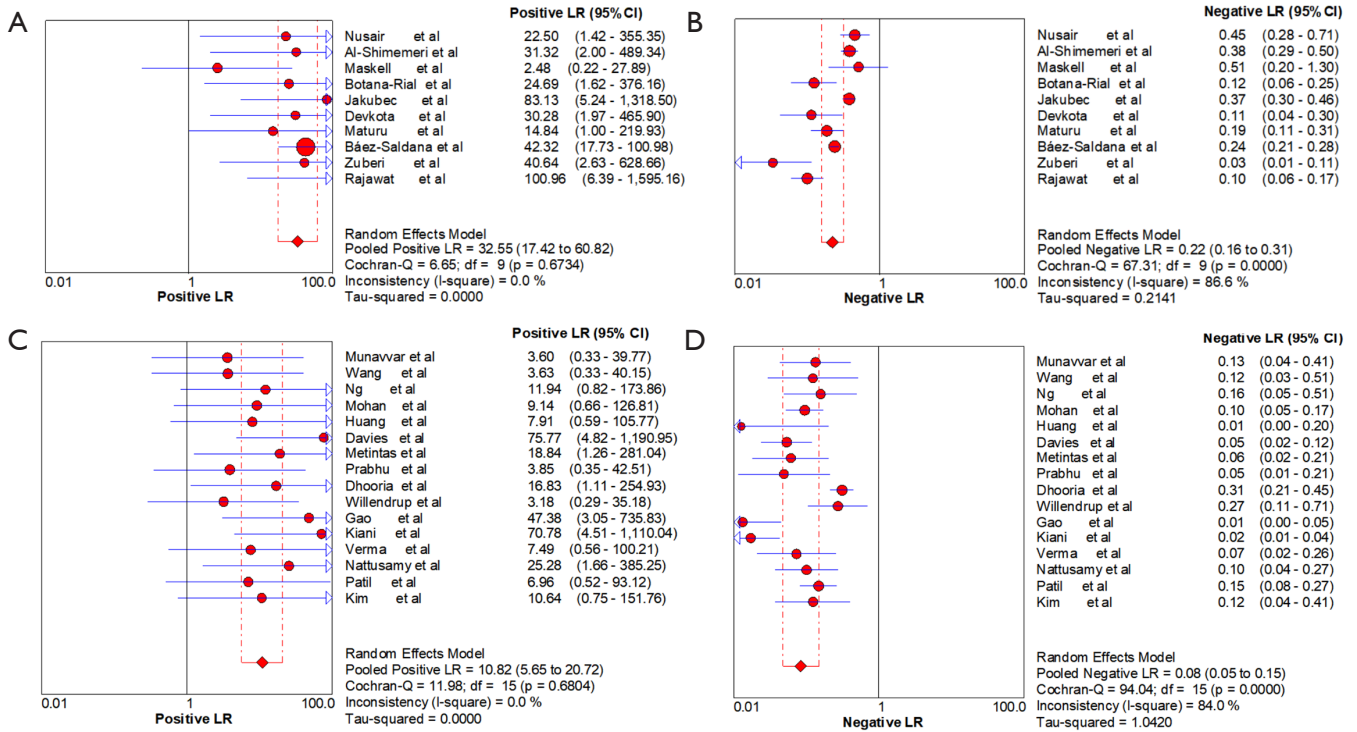
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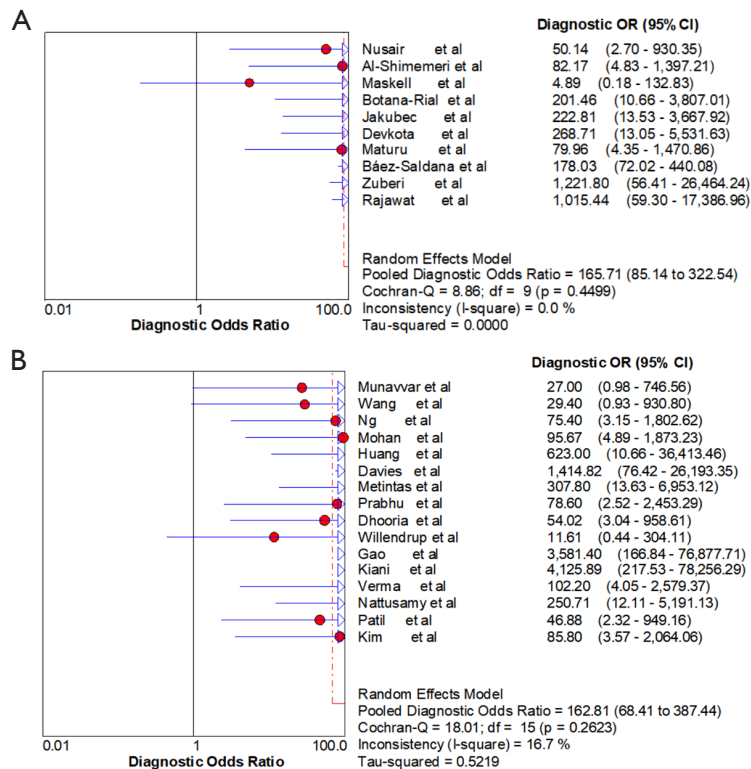


**Figure S1** Forest plot of specificity analysis. (A) Forest plot of the pooled specificity analysis of CPB in undiagnosed exudative pleural effusions. (B) Forest plot of the pooled specificity analysis of MT in undiagnosed exudative pleural effusions. CPB, closed pleural biopsy; MT, medical thoracoscopy.

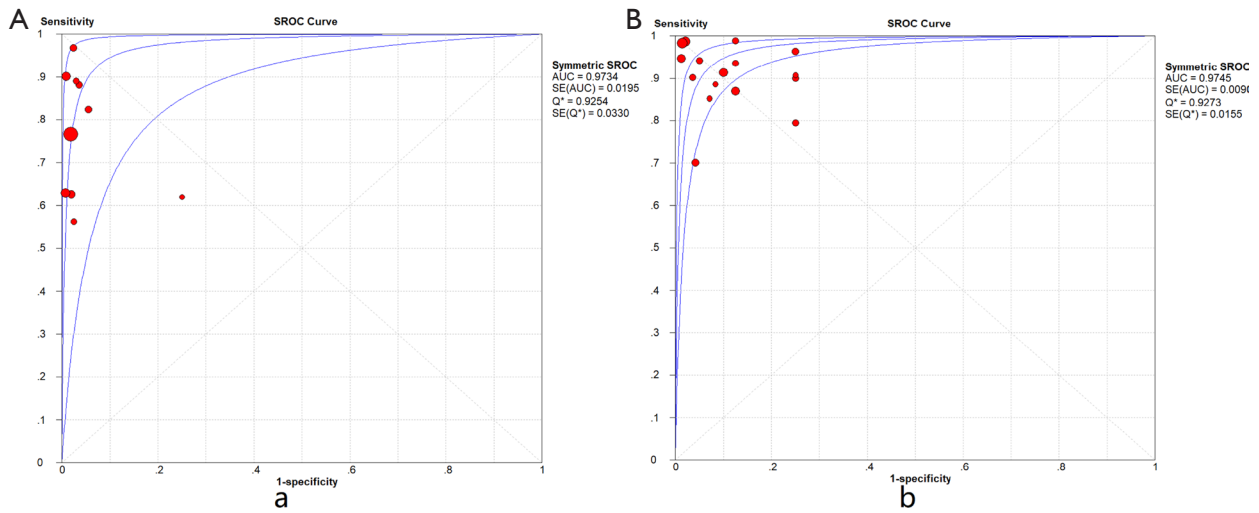




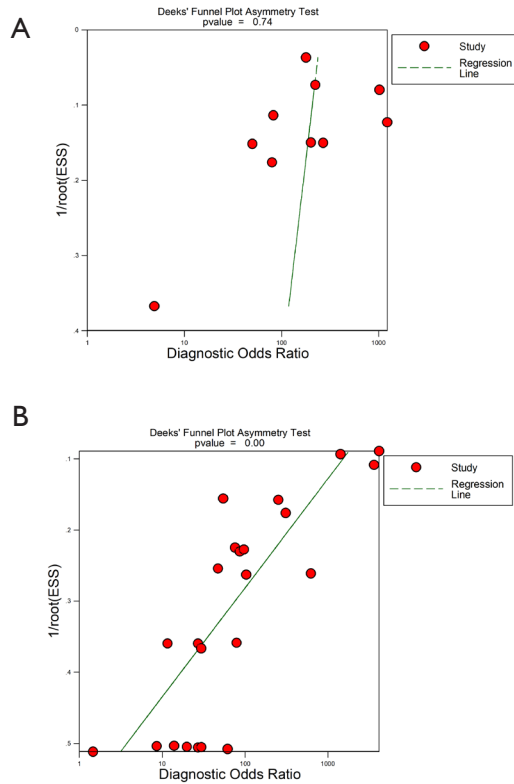
**Figure S2** Forest plot of positive and negative likelihood ratios. (A,B) Forest plot of the pooled positive and negative likelihood ratios of CPB in undiagnosed exudative pleural effusions. (C,D) Forest plot of the pooled positive and negative likelihood ratios of MT in undiagnosed exudative pleural effusions. CPB, closed pleural biopsy; MT, medical thoracoscopy.



**Figure S3** Forest plot of diagnostic odds ratio. (A) Forest plot of the pooled diagnostic odds ratio of CPB in undiagnosed exudative pleural effusions. (B) Forest plot of the pooled diagnostic odds ratio of MT in undiagnosed exudative pleural effusions. CPB, closed pleural biopsy; MT, medical thoracoscopy.



**Figure S4** Summary receiver operating characteristics plot. (A) Summary receiver operating characteristic (SROC) curve of CPB in undiagnosed exudative pleural effusions. (B) SROC curve of MT in undiagnosed exudative pleural effusions. CPB, closed pleural biopsy; MT, medical thoracoscopy.



**Figure S5** Funnel graph for the assessment of potential publication bias. (A) Funnel graph for the assessment of potential publication bias of CPB. (B) Funnel graph for the assessment of potential publication bias of MT. CPB, closed pleural biopsy; MT, medical thoracoscopy.

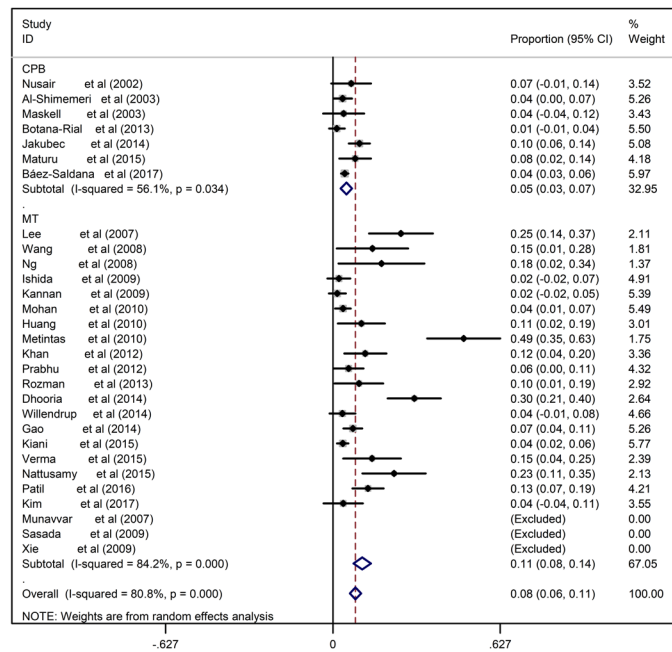


Figure S6 Forest plot of the pooled complication rates of CPB and MT. CPB, closed pleural biopsy; MT, medical thoracoscopy.