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Diagnostic Yield and Safety of Image-Guided Pleural Biopsy: A Systematic Review and Meta-Analysis

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Keywords
Ultrasound-guided biopsy · Computed tomography-guided biopsy · Mesothelioma · Pleural diseases · Meta-analysis

Abstract
Background: Diagnostic yield (DY) and safety of computed tomography (CT)- and thoracic ultrasound (TUS)-guided biopsies in the diagnosis of pleural lesions have been investigated in a number of studies, but no synthesis of data from the literature has ever been performed. ***Objectives:*** We aimed to provide the first systematic review and meta-analysis on the DY and safety of CT- versus TUS-guided biopsy in the diagnosis of pleural lesions. ***Method:*** We searched MEDLINE and EMBASE for all studies reporting outcomes of interest published up to April 2018. Two authors reviewed all titles/abstracts and retrieved selected full text to identify studies according to predefined selection criteria. Summary estimates were derived using the random-effects model. Cumulative meta-analysis assessed the influence of increasing adoption of the procedures over time. ***Results:*** Thirty original studies were included in the present review; the number of studies on TUS-guided biopsy was almost three-fold higher than those on CT-guided biopsy. The pooled DYs of the 2 procedures were overall excellent and differed <10%, being 84% for TUS-guided biopsy and 93% for CT-guided biopsy. Safety profiles were reassuring for both the techniques, being 7 and 3% for CT- and TUS-guided biopsy, respectively. DY of ultrasound technique significantly improved over time, while no time effect was observed for CT-guided biopsy. ***Conclusions:*** Data show that CT- and TUS-guided biopsies in the diagnosis of pleural lesions are both excellent procedures, without meaningful differences in DYs and safety. Considering that TUS is non-ionizing and easily performed at the bedside, it should be the preferred approach in presence of adequate skills.

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Introduction

Pleural diseases, affecting >300 people per 100,000 each year, include a wide spectrum of malignant and benign conditions, with varying prognosis and treatment options [1, 2]. Although pleural fluid examination and imaging provide essential information, the final characterization of disease relies, in most cases, on histologic findings obtained through pleural biopsy. Available options for tissue sampling are closed needle biopsy (either Abram's needle or cutting needle biopsy) with or without image guidance, and medical thoracoscopy, the latter currently considered as the gold standard [3]. However, medical thoracoscopy is not always feasible, and major contraindications include advanced comorbidities and challenging anatomical conditions (e.g., heavily loculated pleural fluid and non-sliding lung on thoracic ultrasound [TUS]) [4–7].

The technique of closed pleural biopsy is long established, and in recent years, technological progress has led to the increasing adoption of different image-guided techniques. Computed tomography (CT) is the most common imaging system employed in the radiological setting, as it provides accurate information about anatomical structures as well as information on needle position within the pleural target. However, CT-guided biopsy is not a real-time procedure, does not allow monitoring of potential needle displacement during respiratory activity, and requires expensive and time consuming scanning time in the context of already busy radiology departments [1].

The growing and widespread access to TUS in daily practice over the past decades has transformed the pulmonologist's role in pleural disease management. Its current use ranges from basic evaluation of pleural/pulmonary features to guidance for advanced interventional procedures in both the diagnostic and therapeutic fields. Compared to CT-guided biopsy, TUS-guided sampling offers the advantage of being non-ionizing, quicker, easily available at patient's bedside, and real time, allowing a direct vision of the needle without the need for breath-hold manoeuvres [8, 9].

Accuracy and safety of CT- and TUS-guided biopsies in the diagnostic work-up of pleural lesions have been investigated in a number of studies worldwide, with heterogeneous results, and limited data are available on a direct comparison between the 2 techniques [1]. The aims of this study were to provide the first systematic review and meta-analysis on the diagnostic yield (DY) and safety of CT- versus TUS-guided biopsy in the diagnosis of pleural lesions as well as to identify the main predictors of successful outcomes.

Methods

A systematic review of the literature was performed according to guidelines developed by the Meta-analysis Of Observational Studies in Epidemiology group [8]. We searched MEDLINE and EMBASE for all original articles on DY and safety of CT- and TUS-guided biopsy in the diagnostic work-up of pleural lesions published up to April 2018, using a combination of free text and MeSH/Emtree terms related to pleural diseases and bioptic techniques (see online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000511626). The electronic search was supplemented by hand searching the bibliography of relevant articles [10].

The following criteria were used for inclusion:

1. Studies reporting data on DY and/or safety of CT-guided biopsy for diagnosis of pleural lesions, including effusion, masses, nodules, and thickening.
2. Studies reporting data on DY and/or safety of TUS-guided biopsy for diagnosis of pleural lesions, including effusion, masses, nodules, and thickening.
3. Studies reporting data on comparison between DYs and/or safety of CT- and TUS-guided biopsies.

Exclusion criteria were:

1. Studies reporting data on DY and safety of CT- and TUS-guided biopsies for the diagnosis of both pleural and peripheral lung lesions, without providing separate results for pleural and parenchymal abnormalities.
2. Studies reporting data on DY and safety of CT- and TUS-guided biopsies in <20 patients.
3. Non-English full text.

Study Screening and Ascertainment of Eligibility

Two independent authors (F.M. and D.M.) reviewed all titles/abstracts and retrieved detailed full text of potentially relevant articles. Disagreements were resolved by discussion. When multiple reports were available on the same cohort of patients, we included the most recent or informative one.

The 2 reviewers independently retrieved information on country, study design, number of subjects, study population, procedural aspects, and main outcomes (DY, sensitivity, specificity, accuracy, and safety). The measure of interest for DY and safety analyses was the proportion of events. Adverse events were further classified into major and minor complications according to severity. Major complications (decided pre hoc) included procedure-related death, pneumothorax requiring chest drainage, haemorrhage requiring blood transfusions or embolization, haemoptysis, bleeding from biopsy site requiring intervention, and haemodynamic shock. Minor complications were pneumothorax not requiring chest drainage, vasovagal reaction, wound infection and bleeding from biopsy site not requiring intervention.

Risk of Bias Assessment

We assessed the studies for methodological quality using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [9]. This consists of 2 sections aimed to assess risk of bias and applicability concerns using predefined key domains (patient selection, index test, reference standard, flow and timing of patients' selection of the index tests and reference standard). Patient selection, index test, and reference standard

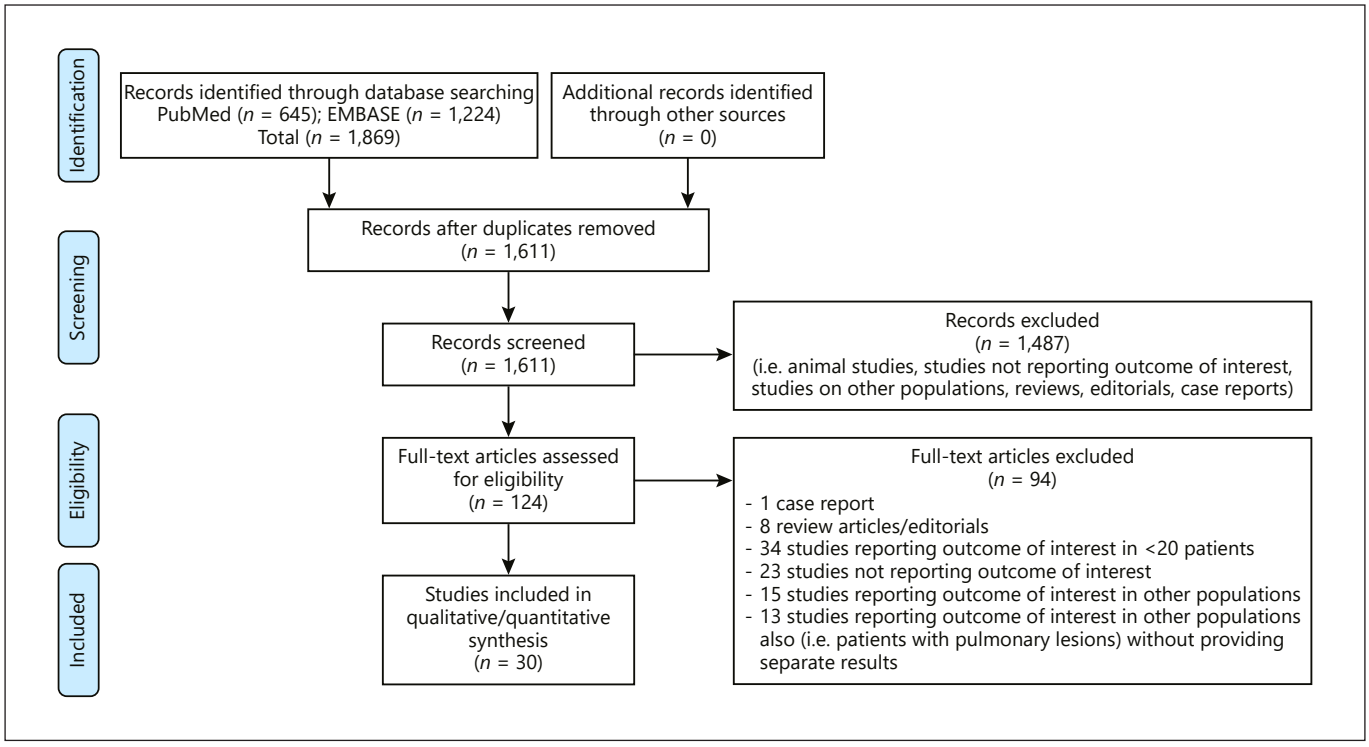

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Fig. 1. Flow chart of study selection.

are examined concerning risk of bias and applicability concerns, while flow and timing of patient selection addresses risk of bias only. Each domain is rated as "low," "high," or "unclear" for both risk of bias and concerns about applicability. If a study is judged as "low" on all domains relating to bias or applicability, then it receives an overall judgement of "low risk of bias" or "low concern regarding applicability." If a study is judged "high" or "unclear" in 1 or more domains, then it may be judged "at risk of bias" or as having "concerns regarding applicability" [11].

In order to obtain pooled estimates, we performed meta-analyses of untransformed proportions using the random-effects model with the DerSimonian and Laird [12] estimator of the variance component and generated the corresponding forest plots. Both the individual study-specific and the pooled 95% confidence interval (CI) were computed through the Clopper-Pearson "exact" method. Heterogeneity among studies was assessed using the χ^2 test, defining a significant heterogeneity as a p value <0.10, while inconsistency was quantified using the I^2 statistic. Cumulative meta-analysis was conducted to assess the influence of increasing adoption of the procedures over time. Further sensitivity analyses were performed to explore selected, predefined predictors of successful outcomes as follows: study design (retrospective/prospective) and underlying disease (malignancy/tuberculosis). Publication bias risk was evaluated by visual inspection of funnel plot and through the Egger's test for asymmetry. All analyses have been carried out with the "metafor" package version 2.0-0.

Results

Search Results

After removing duplicates between MEDLINE and EMBASE, the systematic review identified 1,611 references (shown in Fig. 1). The initial screening based on title/abstracts led to the exclusion of 1,487 papers, due to non-relevance (i.e., case reports, review articles, and animal studies), and the remaining 124 articles were retrieved for detailed full-text evaluation. Thirty original studies were included in the present review, and the main characteristics are presented in Table 1. Twenty-one studies were focused on DY and/or safety of TUS-guided biopsy, 6 on outcomes of CT-guided biopsy, and 3 provided data for both techniques.

Diagnostic Yield

The summary estimate of DY of TUS-guided biopsy is shown in Figure 2. The overall DY, derived from 24 studies including 1,887 patients, was 0.84 (95% CI 0.80–0.87), and a significant heterogeneity among studies was detected (I^2 80%, $p < 0.01$). The pooled DY of CT-guided biopsy, retrieved from 9 investigations including 396 patients, was 0.93 (95% CI 0.89–0.96) with a significant heterogeneity among studies (I^2 60%, $p < 0.01$; shown in

Table 1. Characteristics of included studies [13–42]

Study	Country	Study design	Cases, *n*	Study population	Index test	Type of needle	Technique of biopsy	Real-time biopsy	Operator	Outcomes of study	Notes
Chang et al. [16]	Taiwan	Retrosp	25	Pe	TUS	16 G	ns	Yes	ns	Comparison of US-guided biopsy versus blind Abrams DY	
Hsu et al. [17]	Taiwan	Prosp	36	Pe, Pm	TUS	16, 21 G	Needle guide	Yes	ns	DY	
Heilo et al. [18]	Norway	Retrosp	70	ns	TUS	14, 18 G	Needle guide, free-hand	Yes	ns	DY and safety	
Diacon et al. [19]	South Africa	Prosp	39	Pm	TUS	14 G	Free-hand	No	Pulmonologist	DY, SE, Sp, safety	
Koegelenberg et al. [20]	South Africa	RCT	89	Pe	TUS	Abrams, 14 G	ns	No	Pulmonologist	Comparison of TUS-guided Abrams versus Tru-Cut biopsy (DY, safety)	High suspicion TB
Lee et al. [21]	UK	Prosp	30	Pe	TUS	ns	ns	Yes	Pulmonologist	DY, SE, Sp	
Kamel and Kaffas [22]	Egypt	Retrosp	25	Pe	TUS	18 G	Free-hand	Yes	Pulmonologist	DY, SE	Malignant PE
Abd El-Zaher et al. [23]	Egypt	RCT	50	Pe, Pt	TUS	Abrams, 14 G	Free-hand	No	Pulmonologist	DY, safety	High suspicion TB
Botana-Rial et al. [24]	Spain	Prosp	114	Pe, Pt	TUS	Abrams	Free-hand	No	Pulmonologist	DY, safety	Malignant PE
Mohamed et al. [25]	Egypt	RCT	20	Pe	TUS	14 G, 18 G	ns	No	Pulmonologist	Comparison of TUS-guided biopsy versus thoracoscopy (DY, SE, safety)	
Agmy et al. [26]	Egypt	Prosp	96	Pe	TUS	Abrams	ns	ns	ns	SE	Forceps biopsy
Bahr et al. [27]	Egypt	Retrosp	30	Pe, Pm	TUS	ns	ns	Yes	Pulmonologist	DY, SE, Sp, accuracy, safety	
Botana Rial et al. [28]	Spain	Retrosp	127	Pe	TUS	ns	ns	No	Pulmonologist	DY	
Hallifax et al. [29]	UK	Retrosp	50	Pe, Pt, Pn, Pm	TUS	18 G	Free-hand	Yes	Pulmonologist	DY, SE, Sp	
Imran et al. [30]	Singapore	Retrosp	36	ns	TUS	Abrams	ns	Yes	Pulmonologist	DY	All TB pts
Mohamed et al. [31]	Egypt	RCT	20	Pe	TUS	Abrams	Free-hand	Yes	ns	SE	
Koegelenberg et al. [32]	South Africa	Prosp	100	Pe, Pt, Pn, Pm	TUS	Abrams, 14 G, 22 G	Free- hand	No	Pulmonologist	DY, safety	
Abdella et al. [33]	Egypt	RCT	20	Pe, Pt, Pn, Pm	TUS	14 G, 16 G	Needle guide	Yes	ns	Comparison of US-guided biopsy versus thoracoscopy (DY, safety)	
Sitt et al. [34]	Hong Kong	Retrosp	111	Pe, Pt, Pm	TUS	18 G	Free-hand	Yes	Radiologist	DY, safety	
Wang et al. [35]	China	Prosp	172	Pe	TUS	16 G	Free-hand	Yes	Pulmonologist	Dy, SE, Sp, accuracy, safety	
Sobhy et al. [36]	Egypt	Retrosp	32	Pe	TUS	14 G	ns	No	Pulmonologist	Comparison US-guided biopsy versus thoracoscopy (DY, SE, accuracy, safety)	
Metintas et al. [37]	Turkey	Retrosp	30	Pe, Pt, Pn, Pm	CT	8 G, 11 G	ns	na	ns	DY, safety	
Scott et al. [38]	UK	Prosp	42	Pt	CT	18 G	ns	na	Radiologist	DY, SE, Sp	
Maskell et al. [39]	UK	RCT	23	Pe, Pt	CT	18 G	Free-hand	na	Radiologist	DY, SE, Sp, safety	
Metintas et al. [40]	Turkey	RCT	48	Pe	CT	Abrams	Free-hand	na	Pulmonologist	Comparison CT-guided Abrams biopsy versus thoracoscopy (SE, safety)	
Cao et al. [41]	China	Retrosp	90	Pe, Pt	CT	18 G	ns	na	Radiologist	DY, SE, Sp, accuracy safety	
Lim et al. [42]	Korea	Retrosp	36	Pn, Pm	CT	18 G, 20 G	Needle guide	na	ns	DY, SE, Sp, accuracy, safety	
Metintas et al. [13]	Turkey	RCT	150	Pe, Pt, Pn	TUS, CT	16 G (US) Abrams (CT)	Free-hand	Yes*	Radiologist (both CT and TUS)	Comparison CT-guided Abrams' needle versus TUS-guided biopsy (DY, SE, safety)	
Sivakumar et al. [15]	UK	Retrosp	92	Pe, Pt, Pn, Pm	TUS, CT	Abrams	ns	No*	CT: radiologist TUS: ns	Comparison TUS-guided Abrams' needle versus CT-guided biopsy (DY, SE, Sp)	
Ahmed et al. [14]	Egypt	RCT	40	Pe	TUS, CT	18 G	ns	ns	ns	DY, safety	

CT, computed tomography; DY, diagnostic yield; G, gauge; ns, not specified; na, not applicable; Pe, pleural effusion; Pm, pleural mass; Pn, pleural nodule; Prosp, prospective; Pt, pleural thickening; RCT, randomized controlled trial; Retrosp, retrospective; SE, sensitivity; Sp, specificity; TUS, thoracic ultrasound. * Data refer to US-biopsy patient.

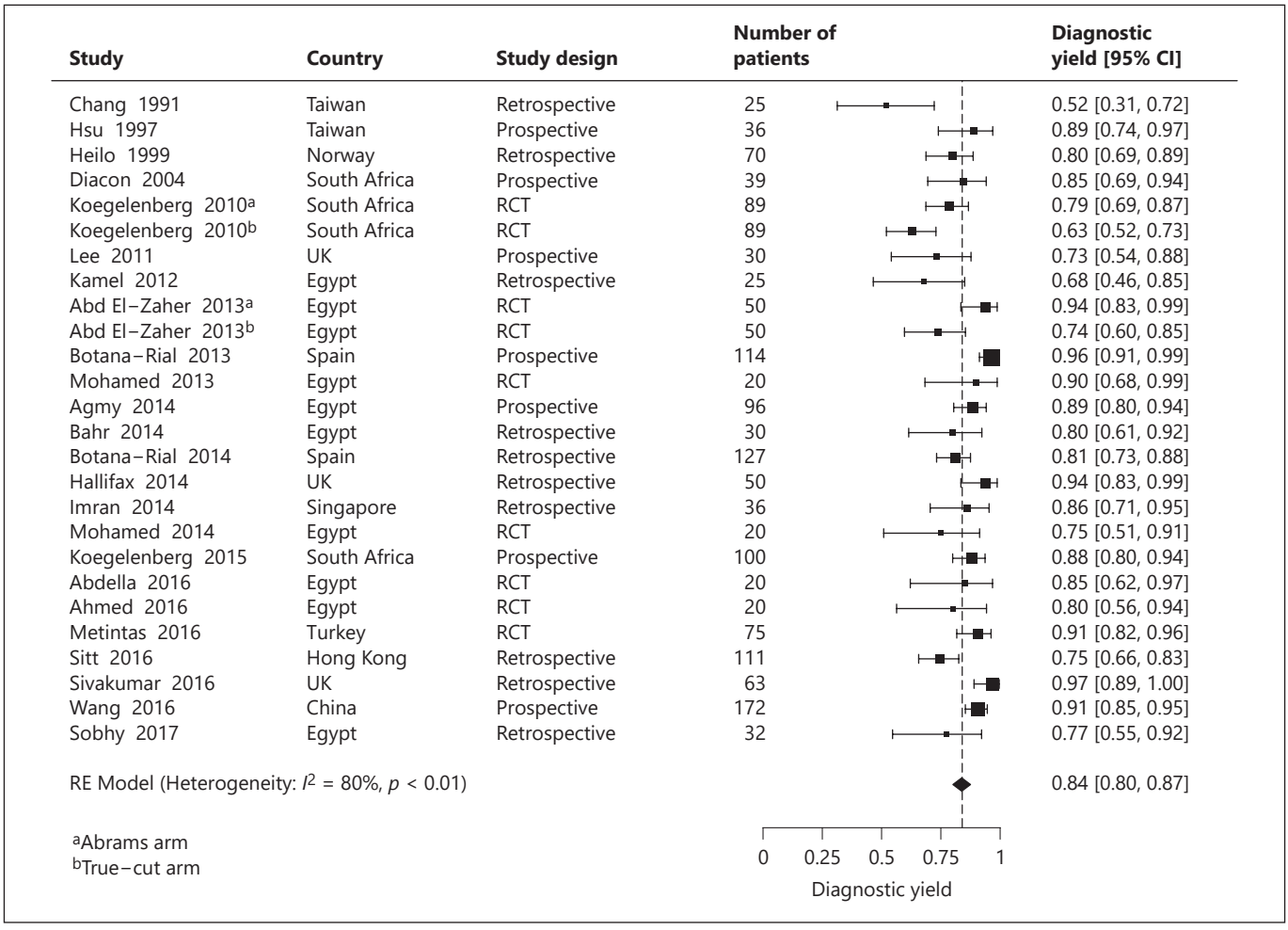

Fig. 2. DY of TUS-guided pleural biopsy. DY, diagnostic yield; TUS, thoracic ultrasound.

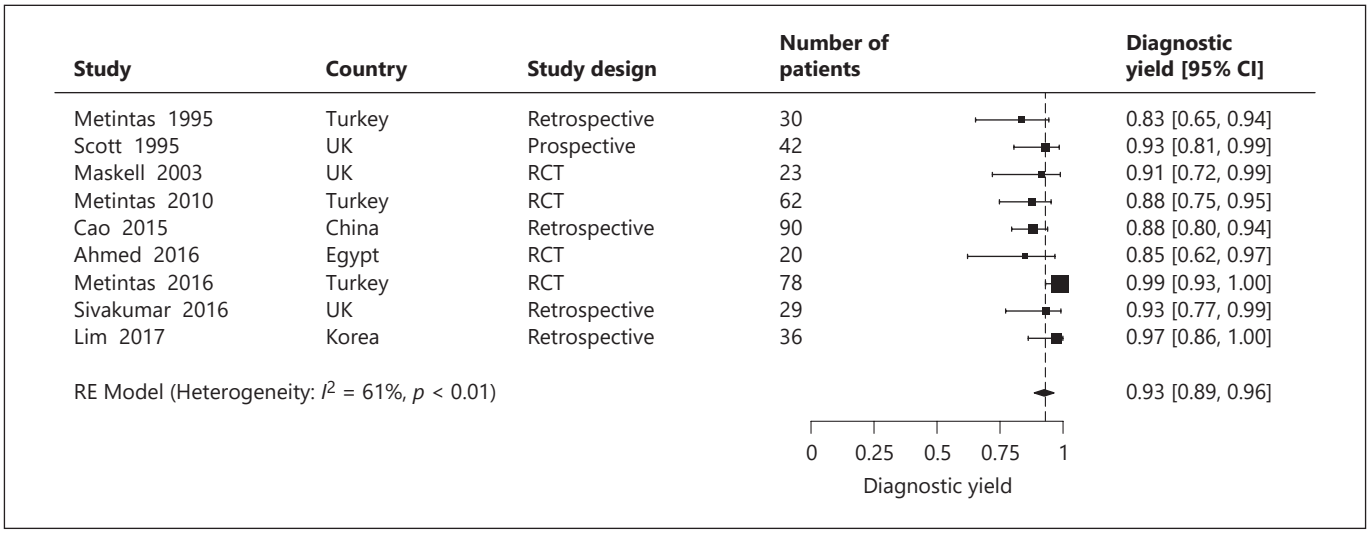

Fig. 3. DY of CT-guided pleural biopsy. DY, diagnostic yield; CT, computed tomography.

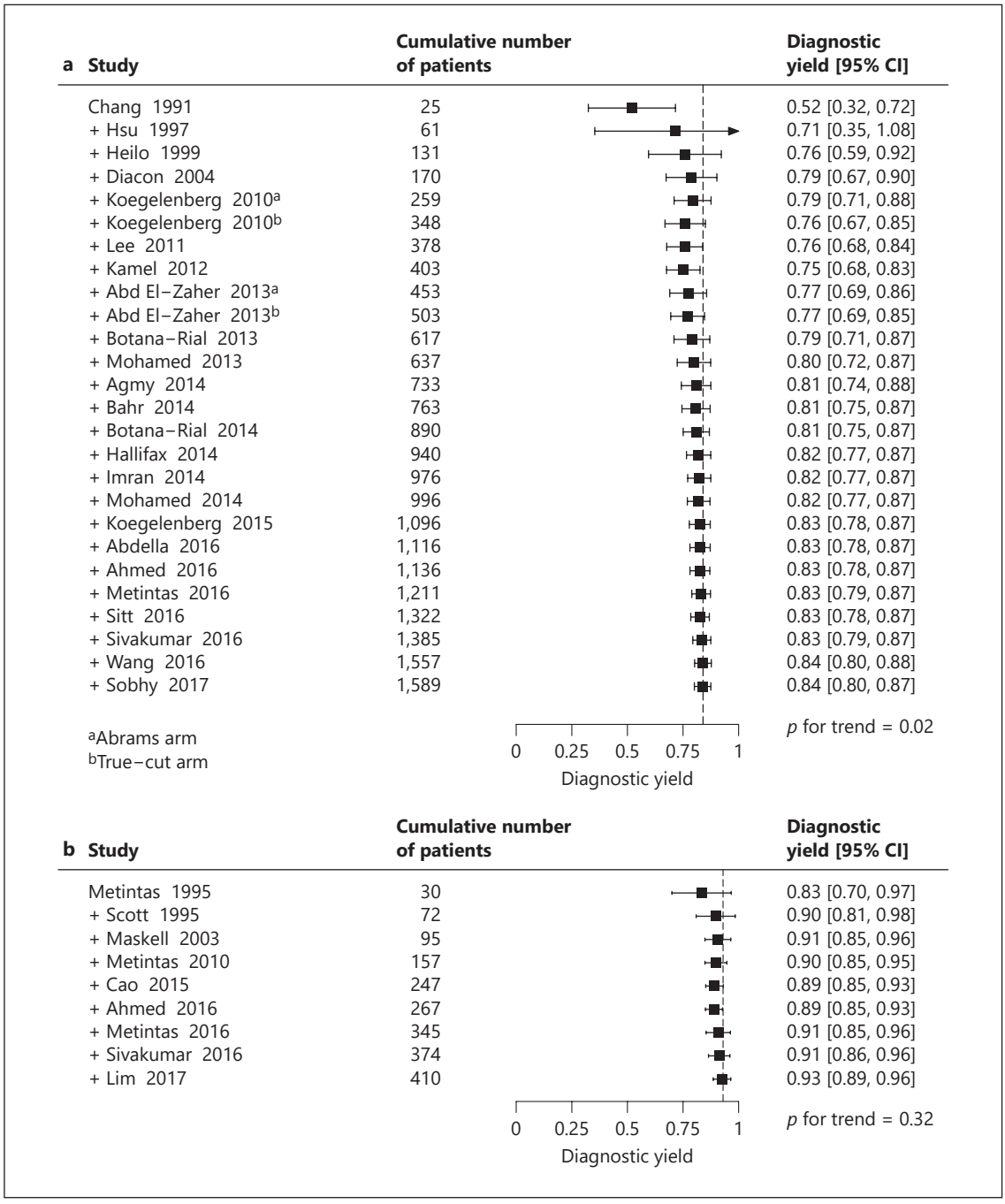

Fig. 4. Cumulative meta-analyses for TUS- (**a**) and CT-guided biopsy (**b**). DY, diagnostic yield; TUS, thoracic ultrasound; CT, computed tomography.

Fig. 3). The cumulative meta-analyses, shown in Figure 4, demonstrated a significant increase of DY for TUS-guided biopsy over the last 3 decades ($p = 0.02$), while DY of CT-guided biopsy seemed not to be significantly influenced by time effect ($p = 0.32$).

With reference to sensitivity analyses, the pooled DY by study design did not substantially differ from the overall estimate but was higher for prospective studies compared to retrospective studies for both techniques. Pooled DYs of TUS-guided biopsy were 0.85 (CI 95% 0.81–0.90) for pro-

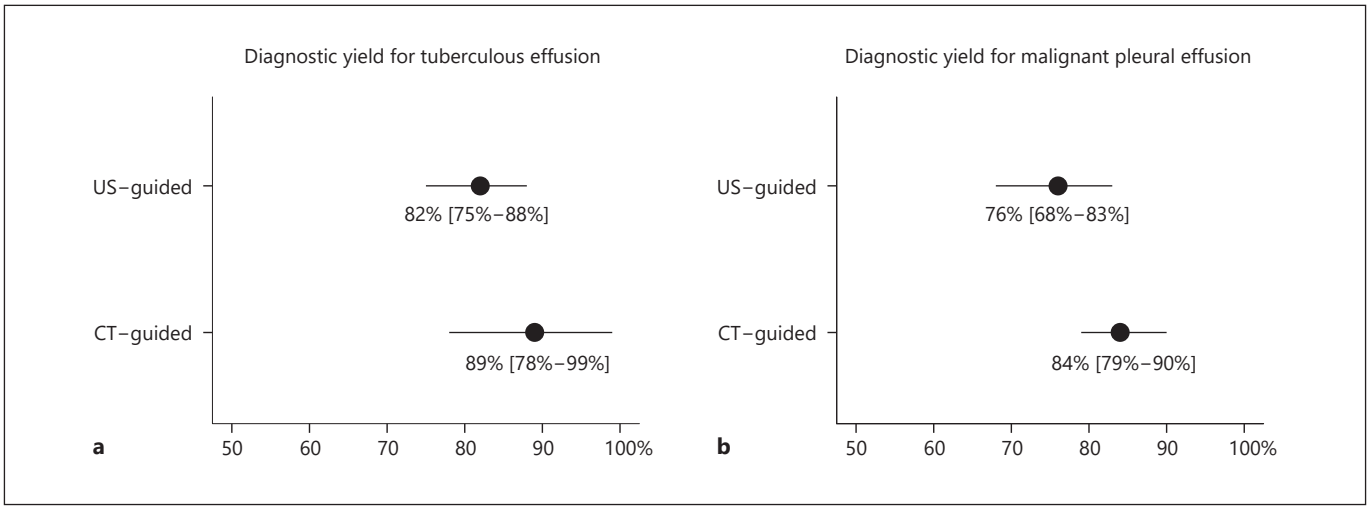

Fig. 5. DY of TUS- and CT-guided biopsy for (**a**) tuberculous and (**b**) malignant effusion. DY, diagnostic yield; TUS, thoracic ultrasound; CT, computed tomography.

spective studies (n = 14) and 0.81 (CI 95% 0.74–0.88) for retrospective studies (n = 10). The summary DYs of CT-guided biopsy were 0.93 (CI 95% 0.87–0.99) for prospective studies (n = 5) and 0.92 (CI 95% 0.86–0.98) for studies retrospective (n = 4). For TUS-guided biopsy, subgroup analyses on DY according to the underlying pathological condition were provided in 11 studies for tuberculosis and 17 for malignancy. For CT-guided biopsy, these were reflected in 3 studies for tuberculosis and 6 for malignancy. Pooled estimates overall showed a better performance for both the procedures in patients finally diagnosed with tuberculosis (TUS-guided DY 0.82, 95% CI 0.75–0.88; CT-guided biopsy DY 0.89, 95% CI 0.78–0.99) compared to those with malignancy (TUS-guided DY 0.76, 95% CI 0.68–0.83; CT-guided biopsy DY 0.84, 95% CI 0.79–0.90). As graphically displayed in Figure 5, DYs according to disease did not significantly differ between the 2 techniques, with overlapping CIs in both subgroup analyses.

Safety/Complications

Data on complications were retrieved from 18 studies including 1,342 patients for TUS-guided biopsy and in 7 studies including 361 subjects for CT-guided biopsy (shown in Fig. 6). The overall proportion of adverse events was 3% (0.03; 95% CI 0.02–0.04) for TUS-guided biopsy and 7% (0.07; 95% CI 0.03–0.12) for CT-guided biopsy. Subgroup analyses according to severity showed an overall probability of developing major complications of 1% (0.01; 95% CI 0.00–0.01) for TUS-guided biopsy and 2% (0.02; 95% CI 0.01–0.04) for CT-guided biopsy. The proportion of minor complications was 2% (0.02; 95% CI 0.01–0.03) for TUS-guided biopsy and 5% (0.05; 95% CI, 0.02–0.08) for CT-guided biopsy. No procedure-related deaths were reported.

Quality Assessment and Publication Bias

The application of QUADAS-2 tool revealed overall low methodological quality. Online suppl. Figure 1 (online suppl. material) presents the judgements on risk of bias and concerns about applicability (A) for each domain, and the final summarized proportion of studies deemed as "low" or "high" risk of bias and having "low" or "high" concerns regard applicability to the review question (B). Overall, only 1 study was judged at "low risk of bias" and eleven as having "low concerns about applicability" and none of these met both conditions. The main reasons for "high risk of bias" judgements were concerns related to patient selection and the lack of a systematic reference standard. Some asymmetry in contour-enhanced funnel plots was evident for both TUS- and CT-guided techniques (shown in Online suppl. Fig. 2, 3 – Online suppl. material), as also shown by Egger's test results ($p < 0.01$).

Discussion

Accuracy and safety of CT- and TUS-guided biopsy in the diagnostic work-up of pleural lesions have been investigated in a number of studies worldwide, reporting het-

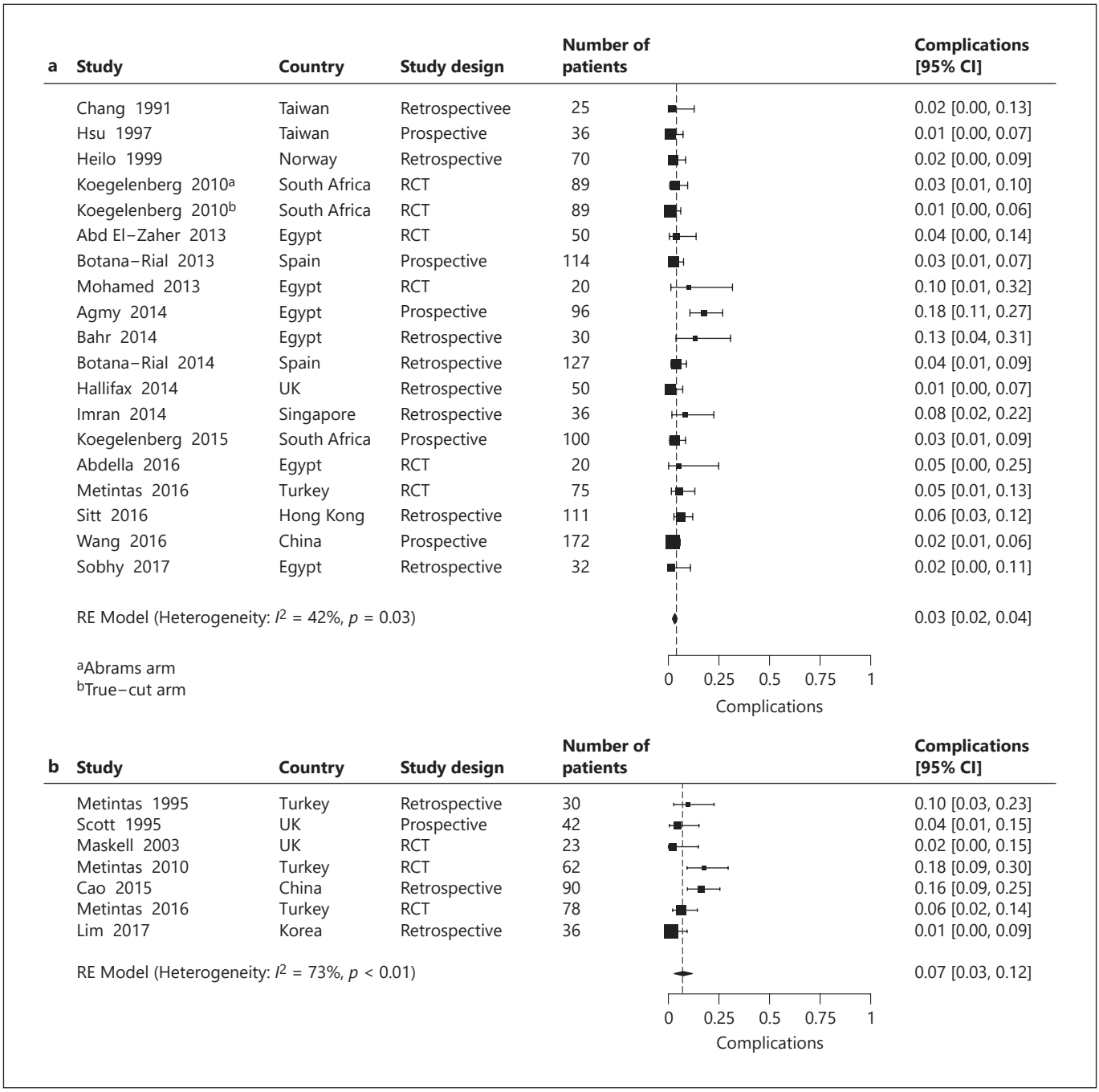

Fig. 6. Overall proportions of complications for TUS-guided pleural biopsy (**a**) and CT-guided pleural biopsy (**b**). TUS, thoracic ultrasound; CT, computed tomography.

erogeneous and conflicting results. Different factors may influence procedural outcomes, including underlying pathology, extent of disease, number of samples taken, size of needle, and operator experience. To date, no synthesis of studies from the literature has ever been performed and predictors of a successful procedure have not been assessed. However, insights on these aspects could be extremely helpful in daily practice for choosing the technique with the best risk-benefit profile according to the specific clinical context.

This systematic review and meta-analysis provides the first synthesis of data from the literature on diagnostic performance and safety profile of TUS- and CT-guided biopsy in the diagnostic work-up of pleural lesions. We have also explored the role of potential predictors of procedural outcomes, including intrinsic, non-modifiable factors, such as prevalence and type of underlying pathologic condition, as well as methodological aspects related to technical issues in performing procedures.

The pooled DYs of the 2 procedures were overall excellent, being 84% for TUS-guided biopsy and 93% for CT-guided biopsy. Although relatives CIs did not overlap, a difference of <10% is perceived as not clinically significant, especially balancing a slightly lower diagnostic performance with advantages, such as being non-ionizing, quicker, and easily available at the bedside.

The summary of data on safety profiles was reassuring for both the techniques although the probability of developing complications was slightly, but not significantly, higher for CT-guided biopsy compared to TUS-guided biopsy (respectively 7 and 3%).

Results according to potential predictors of successful outcomes showed that the DY of TUS techniques significantly improved over time ($p = 0.02$), suggesting a role of increasing operator skills due to the growing adoption of this technology in pulmonology practice, while no time effect was observed for CT-guided biopsy ($p = 0.32$). The increasing access and clinician confidence in the TUS-guided approach are also suggested by the higher number of studies published on diagnostic performance of TUS-guided biopsy compared to those related to the CT-guided technique. Indeed, the weight of the literature in terms of patient numbers is much in favour of TUS-guided biopsy, with the number of studies included in the present review almost three times higher than those with CT-guided biopsy and the number of patients approximately 5 times higher.

As expected, sensitivity analyses exploring the role of underlying pathologic conditions in diagnostic outcomes showed an overall higher DY in malignancy compared to tuberculosis for both the techniques. Of note, the difference in DY between the TUS- and CT-guided approaches was not statistically significant, as shown by the overlap of relative CIs, but this may be related to sample size overall.

A comparison of risk-benefit profiles of TUS- and CT-guided procedures was assessed in 3 studies only, which differed in terms of methodology, sample size, and findings [13–15]. A significant superiority of the CT- over the US-guided approach was documented in 1 study, performed by Metintas et al. [13], while no substantial difference was reported by Sivakumar et al. [15] and by Ahmed et al. [14] In the RCT by Metintas et al. [13] including 150 patients, the sensitivity values of CT-guided Abrams' needle biopsy and of TUS-guided cutting needle biopsy were, respectively, 82.4 and 66.7% ($p = 0.029$) although an adequate sampling was achieved in more than 90% of cases with both the techniques (respectively, 98.7 and 90.7%; p not significant) [13]. However, some sources of potential bias should be considered when interpreting the results. Both procedures were performed by a radiologist, without specifying years of experience with the 2 techniques, and US biopsies were not "real time" and different sampling techniques were used in the 2 arms (Abrams' needle for CT and "Tru-Cut" needle for TUS). In the retrospective study by Sivakumar et al. [15], Abrams' needle was employed for TUS-guided biopsy and cutting needle for CT-guided technique and no significant difference was documented in diagnostic performance (sensitivity, respectively, 71 and 75%) [15]. However, a potential selection bias due to the retrospective nature of the study as well as the use of different needles may have affected the reliability of this study's findings. Lastly, in the prospective study by Ahmed et al. [14], patients were assigned in a randomized fashion to TUS-guided biopsy (cutting needle), CT-guided biopsy (cutting needle), or thoracoscopy. The sensitivities were, respectively, 80, 85, and 92.5% (p 0.45) although the limited sample size (20 patients in each arm) should be taken into account [14].

Strengths of the current study include a systematic and extensive search of the available literature, and the large number of included studies and patients, which lends precision to the results. The concordance of most results among studies is reassuring in terms of reliability and validity of information obtained. However, there are several potential limitations. First, there was baseline heterogeneity among studies in terms of design, size of sample and outcome measure assessed (using patient or lesions as unit of analysis), various cytopathologic criteria for classification of specimens and different definition of test performance, as "diagnostic yield," "accuracy," or "sensitivity." Some investigations were not primarily designed as diagnostic studies but reported experiences from routine clinical practice. It is likely that the poor methodological quality of studies, as reported by QUADAS-2 results, affects the validity of our findings. With reference to selection bias, some studies did not state if there was a consecutive enrolment and some others made inappropriate exclusions (i.e., patients with pleural lesions other

than thickening). Most investigations enrolled patients with suspected/known selected clinical diagnoses, leading to an overestimation of sensitivity, since the probability to obtain a positive result is closely related to the prevalence of the underlying condition. Several confounding factors could have affected the performance and interpretation of index test as the guided procedures were often performed within the same study by different operators with different needle types, sizes, and number of passes. Another relevant limitation is represented by the poor and heterogenic application of reference standard test. Finally, a significant publication bias risk was found for both the techniques, and thus the pooled DYs may be the result of an overestimation of real-world outcomes.

Synthesis of data overall shows excellent DYs and reassuring safety profiles in the diagnosis of pleural lesions for both CT-guided biopsy and TUS-guided biopsy, in absence of meaningful differences between the 2 procedures.

The DY of the ultrasound approach significantly improved over time, and considering that ultrasound offers the advantages of being non-ionizing and easily performed by pulmonologists at the bedside or in the endoscopy room, in the presence of adequate skills and sources, TUS-guided biopsy should be the preferred, initial approach.

Statement of Ethics

Not applicable.

Conflict of Interest Statement

Prof. N.M. Rahman has received academic grant funding from Esaote UK and G.E Healthcare. Prof. M. Bonifazi has received personal speaking fees from Roche and Boehringer Ingelheim. The remaining authors (F.M., M.R., L.C., C.D., M.G., E.B, D.M., L.Z., and S.G.) have no conflict of interests.

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Author Contributions

All authors contributed to the following activities: study design, data collection and analysis, and manuscript writing/review. All authors approved final version of manuscript and agreed to be 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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