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Thoracic ultrasound for malignant pleural effusion: A systematic review and meta–analysis

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Summary:

This systematic review showed that thoracic ultrasound cannot rule out malignant pleural effusion. Pleural nodularity could be a ruling-in test for performing repeated thoracentesis or other invasive procedures when malignant pleural effusion is suspected.

Abstract

This systematic review aimed to evaluate the diagnostic accuracy of thoracic ultrasound in malignant pleural effusion.

Articles published until December 2019 in MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and the International Clinical Trials Registry Platform were screened by two authors independently to extract data and evaluate the risks of bias and applicability using the modified Quality Assessment of Diagnostic Accuracy Studies-2 tool. We described the forest plots of each thoracic ultrasound finding. We estimated the pooled sensitivity and specificity of pleural nodularity using the bivariate random-effects model.

We included seven articles and found that each thoracic ultrasound finding had low sensitivity. The pooled specificity of pleural nodularity was 96.9% (95% confidence interval, 93.2%–98.6%).

In conclusion, thoracic ultrasound is not useful in ruling out malignant pleural effusion. Physicians can proceed rigorously to repeat thoracentesis or other invasive procedures when pleural nodularity is detected.

Introduction

Malignant pleural effusion (MPE) is a common malignancy complication [1]. Since patients with MPE usually have poor prognoses, a prompt diagnosis is crucial to allow patients to start optimal treatment as early as possible [2]. A diagnostic thoracentesis is the first step in detecting MPE; however, the initial cytological evaluation only has a sensitivity of approximately 50%–70% [1]. If the initial thoracentesis fails to provide a definite diagnosis, pulmonologists or radiologists have to either repeat it or choose another invasive procedure, such as image-guided biopsy or thoracoscopy [3].

Ultrasound is a non-invasive and inexpensive tool; therefore, it is increasingly used by physicians[4]. Its other advantages include lack of radiation exposure and easy personal training because of easy bedside accessibility [5].

The international guidelines recommended ultrasound guidance when performing diagnostic thoracentesis to reduce the risk of complications [6,7]. Many recent, studies have explored the utility of morphological findings of transthoracic ultrasound (TUS) as a tool for detecting MPE [8-14]. However, these studies had a small sample size and were conducted at a single centre; hence, the diagnostic accuracy of TUS remains unclear. Our systematic review aimed to evaluate the diagnostic accuracy of TUS both as a triage test and an add-on test in patients with suspected MPE.

Material and methods

The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (CRD42020162846). Our systematic review is based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) for

Diagnostic Test Accuracy (Supplementary Table S1). Informed consent from study participants was waived because of the study design. We performed a comprehensive search of MEDLINE, Embase, the Cochrane Library, and the International Clinical Trials Registry Platform for publications until December 25, 2019, without any limitations on the language or publication status. Our search terms were based on TUS (index test); MPE (target condition); and specific morphological findings of TUS including pleural thickening, hepatic metastases, pleural nodules, diaphragmatic thickening, diaphragmatic nodules, solitary pulmonary lesions, and swirling (Supplementary Table S2). We reviewed all the reference lists of the included articles and searched the citations with Web of Science to search for additional relevant articles.

Two authors (AS and SN) independently screened the title and abstracts of the listed articles and subsequently reviewed the complete text of potential articles. The inclusion criteria were prospective or retrospective observational studies, case-control studies, or case series that assessed the sensitivity and specificity of morphological findings of TUS for MPE. We carefully confirmed that all included studies reported obtaining informed consent from each study participant and protocol approval by an ethics committee or institutional review board. The exclusion criteria were (i) case reports, review articles, or articles that used animal models; and (ii) studies that used ultrasound on lesions other than those in the lung (e.g., abdominal ultrasound). We extracted the following details of the included articles: study design, participants, index tests, reference standards, and diagnostic accuracy.

AS and SN independently evaluated the risk of bias and concerns of applicability of the included articles using the modified Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [14]. During the entire review

process, disagreements between the two authors were resolved through discussions and consultations with another pulmonologist, YT. Forest plots were created to illustrate the diagnostic accuracy of each index test in each study. Generally, there are 4 types of TUS findings in patients with MPE: (1) gross macroscopic findings, including echogenicity and swirling sign; (2) pleural thickness, in which different thresholds may be used; (3) nodularity of parietal or visceral pleura, or the diaphragm; and (4) other findings, such as parenchymal lesions and hepatic metastases. Although we planned to estimate the pooled sensitivity and specificity for each type of finding using a bivariate random-effects model, we expected that the sensitivity and specificity of each TUS finding might vary widely. Therefore, we visually checked the heterogeneity for each finding on the forest plots, moreover, we only calculated the pooled sensitivity and specificity for findings lacking apparent heterogeneity. In addition, we described the hierarchical summary receiver operating characteristic (HSROC) curve for these findings. The overall quality of evidence of pleural nodularity was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [15].

For statistical analysis, we used R 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) to generate forest plots; STATA 15 (STATA Corp. College Station, TX, USA) to calculate the pooled sensitivity and specificity; and RevMan v5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to summarise the risk of bias and applicability, and create the HSROC curve.

Results

Figure 1 illustrates the study selection process. After removing duplicates, we screened 504 articles and included seven studies after applying the exclusion criteria [8-13,16]. Table 1 summarises the characteristics of the included articles. The included articles assessed 840 patients. All the included articles were prospective studies. Experienced radiologists or pulmonologists performed TUS at a university hospital or tertiary care centre (Table 2). Regardless of the follow-up periods, pathological results, including cytology or other biopsy results, were used as a reference standard.

Supplementary Figure S1 and S2 summarise the quality of each study using the modified QUADAS-2 tool. Regarding the risk of bias, the reference standard domain was labelled as unclear because we could not ascertain whether the pathologists were blinded in all the articles. In one article by Faheem, the risk of bias in the index test domain was high since the ultrasound operators were unblinded [10].

Figures 2 and 3 illustrate the forest plots of sensitivity and specificity according to each index test. The gross macroscopic findings were assessed and echogenicity—a specific sign of MPE—demonstrated a wide range of sensitivity and specificity. Parietal thickness was evaluated using different cut-off values—3 mm vs. 10 mm. Pleural thickness assessment demonstrated low sensitivity and varying specificity. Although only two studies used a cut-off value of 10 mm, they revealed high specificity. We did not calculate the pooled sensitivity and specificity of either echogenicity or parietal pleural thickness given the heterogeneity of the results. Nodularity was assessed in the parietal pleura, visceral pleura, or diaphragm. The pooled sensitivity and specificity of nodularity was 42.5% (95% confidence interval [CI], 25.3%–61.6%) and 96.9% (95% CI, 93.2%–98.6%), respectively, using the bivariate random effect model. Additionally, the HSROC revealed high specificity (Supplemental Figure S3). Finally, we evaluated

the overall quality of evidence of pleural nodularity using the GRADE approach, which showed a moderate certainty of evidence (Table 3).

Discussion

This systematic review revealed that each macroscopic finding on TUS demonstrated low sensitivity and a wide range of specificity. It demonstrated high specificity and moderate overall quality of evidence for pleural nodularity, including the parietal and somatic pleural nodules and diaphragmatic nodules.

Since pleural nodularity had a high specificity and positive predictive value, it can be used as an add-on test for ruling-in MPE. Cytopathologic evaluations, such as cytology or cell blocks, can contribute to a definite diagnosis. However, one-time thoracentesis demonstrated low sensitivity [7]. In case chest physicians or radiologists detect pleural nodules during TUS, the pre-test probability of MPE may be increased and repeat thoracentesis or other invasive procedures can be justified. However, physicians should keep in mind that biopsy in pleural or other sites could guide the treatment more precisely based on specific histologic subtypes and molecular patterns.

Contrary to pleural nodularity, other index tests demonstrated low specificity, and therefore cannot be used as add-on tests. In the current systematic review, we evaluated the diagnostic accuracy of each morphological finding on TUS. Future studies should combine assessments of each of these findings [13]. Qureshi et al. [13] calculated the sensitivity and specificity of combining nodularity, pleural thickening > 1 cm, and hepatic metastasis. Thy found that this combination demonstrated extremely high specificity compared with contrast-enhanced computed tomography (sensitivity 73%, specificity 100%). We could not identify any other articles that reported the

overall diagnostic yield. Currently, physicians cannot use any other single morphological pattern except pleural nodularity for ruling-in MPE.

TUS cannot be used as a triage test for ruling out MPE among patients with pleural effusion who are suspected to have malignancy. The result is plausible because thoracentesis is a relatively easy and safe procedure; therefore, it only has a few contraindications, such as the presence of small pleural effusion or inability to maintain the position [17]. When MPE is suspected, it is reasonable to proceed to histopathological tests, such as thoracentesis or thoracoscopy.

This systematic review has several limitations. First, in each article, experienced radiologists or pulmonologists performed TUS in university hospitals. TUS is operator-dependent and a relatively new module. Physicians and ultrasound practitioners require further education and experience to popularise the use of TUS. There is a need for future studies in primary or secondary care settings. Second, five of the seven studies were conducted in Europe, which is not an endemic region for tuberculosis. Pleural tuberculosis—among the most common forms of extrapulmonary tuberculosis—can be visualised as pleural nodules on computed tomography [18]. There are concerns regarding the applicability of pleural nodularity in patients in tuberculosis endemic areas. Third, we could not assess publication bias and heterogeneity using statistical methods. Currently there is no valid method to test for publication bias; further, the methodology of meta–analyses for diagnostic accuracy comprises a substantial risk of bias.

In conclusion, the morphological findings of thoracic ultrasound were not useful as a ruling-out test. Nevertheless, pleural nodularity on ultrasound could motivate us to proceed with repeat thoracentesis or other invasive procedures when MPE is suspected.

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Conflict of interest: There are no conflicts of interest to declare.

Data availability: The data that support the findings of this study are available from the request.

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Figure legends

Figure 1: PRISMA flow diagram

Figure 2: Forest plot of the sensitivity for each ultrasound finding in malignant pleural effusion

Figure 3: Forest plot of the specificity of each ultrasound finding in malignant pleural effusion

Tables

Table 1: Characteristics of the included studies

First author	Year	Number of participants	Mean age (SD)	Male (%)	Prevalence of MPE (%)	Study design	Country	Study setting
Yang[16]	1992	320	54 (16)	59	35	Prospective cohort	China	University hospital
Lomas[11]	1993	86	58	64	34	Prospective cohort	United Kingdom	University hospital
Marcun[12]	2009	40	58	67	23	Prospective cohort	Slovenia	University hospital
Qureshi[13]	2009	52	63	67	60	Prospective cohort	United Kingdom	Tertiary care centre
Bugalho[9]	2014	133	67 (16)	46	50	Prospective cohort	Portugal	University hospital
Asciak[8]	2018	140	Not described	Not described	45	Prospective cohort	United Kingdom	University hospital

Faheem[10]	2019	69	50 (16)	42	33	Prospective cohort	Egypt	University hospital

SD: standard deviation, MPE: malignant pleural effusion

Table 2: Detailed information about thoracic ultrasound

Study	Machine	Probe	Operators and interpreters	Position
Yang et al.[16]	Aloka SSD 630, SSD 650, Aloka, Tokyo; Toshiba 1OOA, Toshiba, Tokyo	3.5-, 5.0-, and 7.5-MHz linear and convex transducers.	One of three sonographers performed the ultrasound. The images were recorded on Polaroid film (Polaroid, Cambridge, MA, USA) and were interpreted by the other two sonographers.	Sitting or supine
Lomas et al.[11]	An Aloka SSD-650 or Siemens Sonoline	3.5 MHz transducers	One of the three radiologists performed the ultrasound.	Sitting
Marcun et al.[12]	ATL HDI 5000CV	Phase array P4-2 convex transducer.	An experienced pulmonologist conducted ultrasound and the images were stored on hard disc for further evaluation.	Sitting or supine
Qureshi et al.[13]	A single Esaote Technos MPX 25	A 3–5-MHz curvilinear probe +/- 8–15 MHz linear probe (to visualise the pleura and chest wall in greater detail).	An experienced radiologist performed the ultrasound and the images were stored as anonymised data. Consultant radiologists separately reviewed them.	Upright or lateral decubitus
Bugalho et al.[9]	ACUSON X300 (Siemens, Germany)	A 2- to 5-MHz convex-array probe +/- a	Pulmonologists with at least 5 years of thoracic ultrasound experience (average of 450 exams/year) conducted ultrasound	Sitting or supine (or

		5–10-MHz linear-array transducer (to see details of the thoracic wall and parietal pleura)	and the images were stored as 10–20-second digital video clips. At least three other ultrasound operators reviewed them.	lateral decubitus)
Asciak et al.[8]	Hitachi Avius	The abdomen pre-set	The ultrasound reporters held a minimum of Royal College of Radiologists level 1 accreditation, and at least two sonographers performed the pre-procedure ultrasound scan and agreed on the described echogenic qualities of the fluid.	Not described
Faheem[10]	GE logiq P6 pro	Convex array (3–5 MHz) & linear array (4–11 MHz)	Not described	Supine, prone, lateral, or sitting

Table 3: Findings with the pleural nodularity via thoracic ultrasound using the Grading of Recommendations, Assessment, Development and Evaluation approach.

Question: Should pleural nodularity via thoracic ultrasound be used in diagnosing malignant pleural effusion in patients with pleural effusion who are suspected to have malignancy?

Sensitivity	0.42 (95% CI: 0.25 to 0.62)
Specificity	0.97 (95% CI: 0.93 to 0.99)

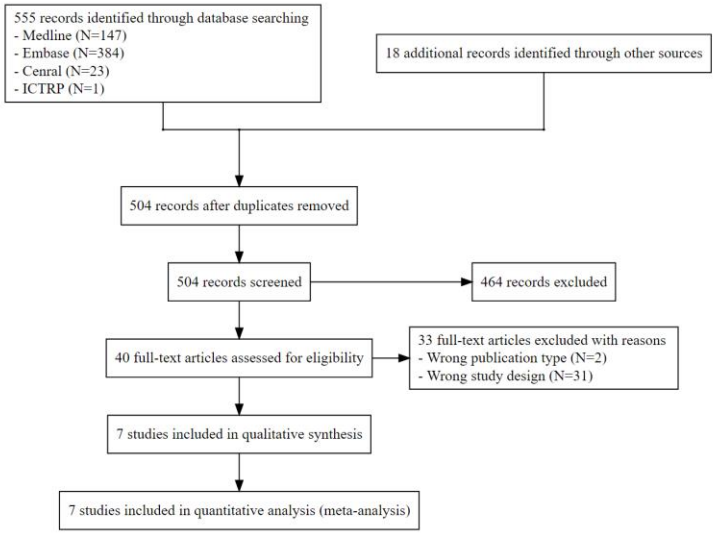
Prevalence	10%	20%	40%

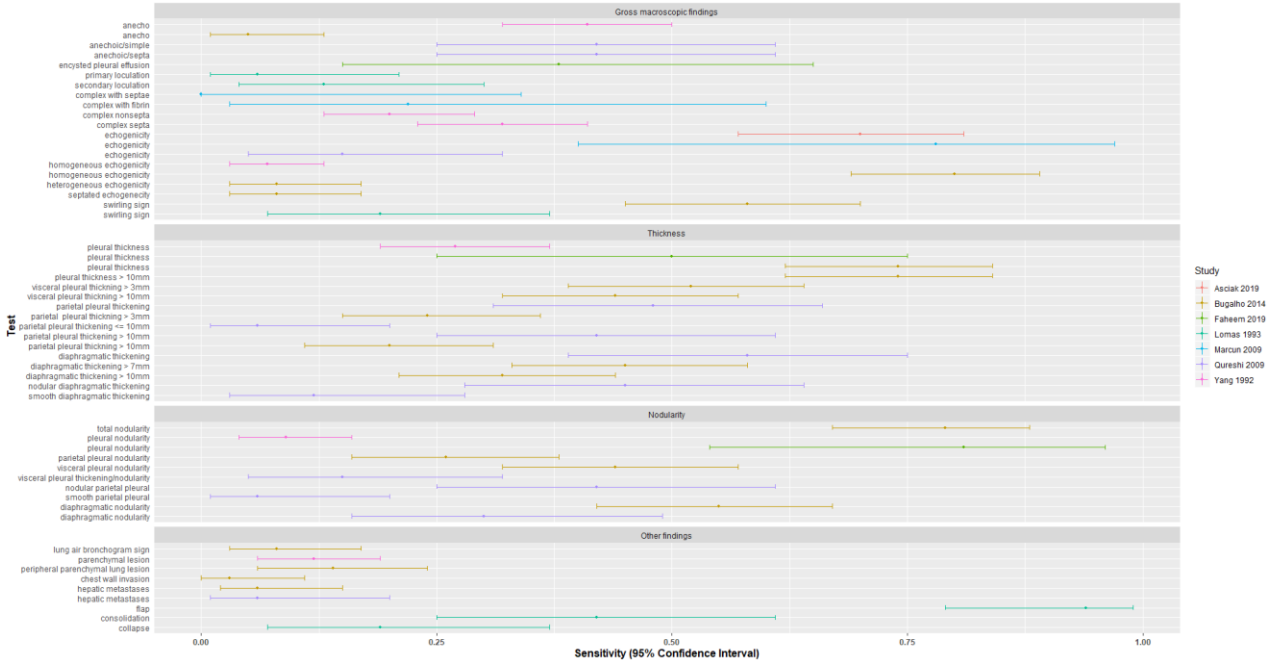
Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 10%	pre-test probability of 20%	pre-test probability of 40%	
True positives (patients with MPE)	4 studies 459 patients	cohort & case-control type studies	serious [a]	not serious	not serious	not serious	none	43 (25–62)	85 (51–123)	170 (101–246)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having MPE)								57 (38–75)	115 (77–149)	230 (154–299)	
True negatives (patients without MPE)	4 studies 545 patients	cohort & case-control type studies	serious [a]	not serious	not serious	not serious	none	872 (839–887)	775 (746–789)	581 (559–592)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having MPE)								28 (13–61)	25 (11–54)	19 (8–41)	

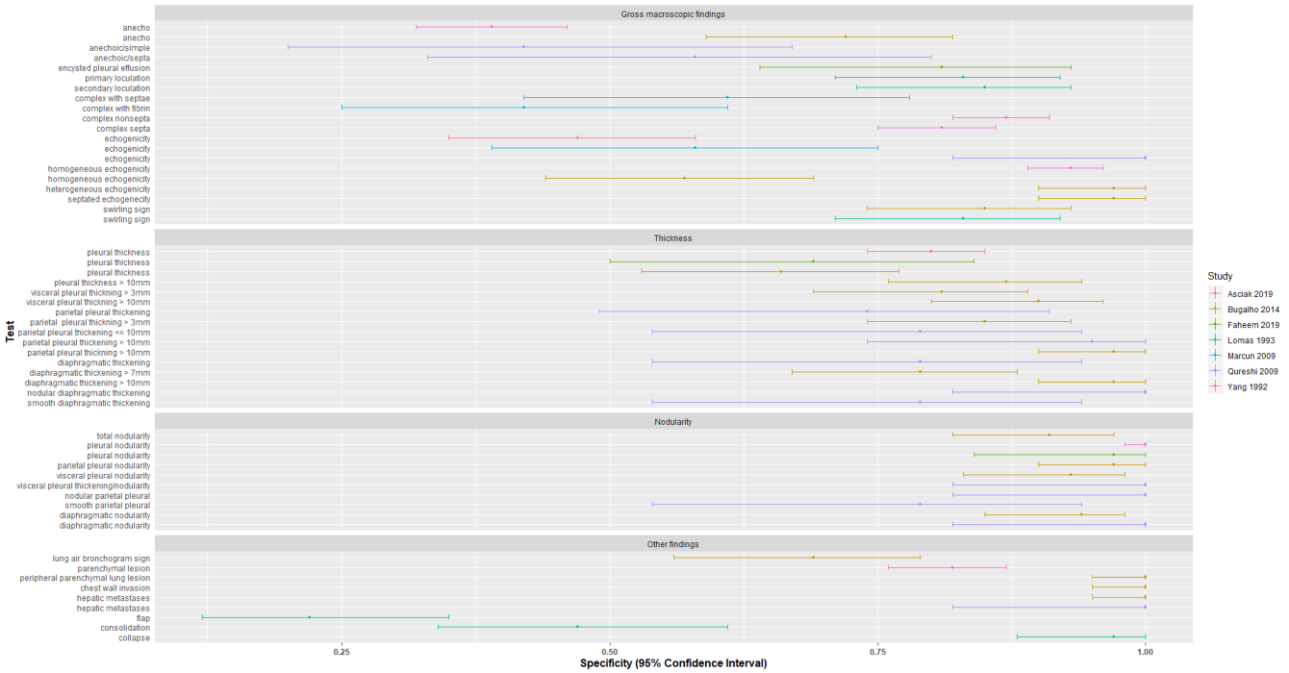
MPE, malignant pleural effusion; CoE, certainty of evidence

Explanations

a. In all the included studies, it was unclear whether the pathologists were aware of the patients' backgrounds or other test results, including thoracic ultrasound. In some studies, the ultrasound operators were aware of the patients' background information before performing the thoracic ultrasound scan.


555 records identified through database searching
- Medline (N=147)
- Embase (N=384)
- Cenral (N=23)
- ICTRP (N=1)
18 additional records identified through other sources
504 records after duplicates removed
504 records screened
464 records excluded
40 full-text articles assessed for eligibility
33 full-text articles excluded with reasons
- Wrong publication type (N=2)
- Wrong study design (N=31)
7 studies included in qualitative synthesis
7 studies included in quantitative analysis (meta-analysis)


Gross macroscopic findings
anecho
anecho
anechoic/simple
anechoic/septa
encysted pleural effusion
primary loculation
secondary loculation
complex with septae
complex with fibrin
complex nonsepta
complex septa
echogenicity
echogenicity
echogenicity
homogeneous echogenicity
homogeneous echogenicity
heterogeneous echogenicity
septated echogenecity
swirling sign
swirling sign
Thickness
pleural thickness
pleural thickness
pleural thickness
pleural thickness > 10mm
visceral pleural thickning > 3mm
visceral pleural thickning > 10mm
parietal pleural thickening
parietal pleural thickning > 3mm
parietal pleural thickening <= 10mm
parietal pleural thickening > 10mm
parietal pleural thickning > 10mm
diaphragmatic thickening
diaphragmatic thickening > 7mm
diaphragmatic thickening > 10mm
nodular diaphragmatic thickening
smooth diaphragmatic thickening
Nodularity
total nodularity
pleural nodularity
pleural nodularity
parietal pleural nodularity
visceral pleural nodularity
visceral pleural thickeninghodularity
nodular parietal pleural
smooth parietal pleural
diaphragmatic nodularity
diaphragmatic nodularity
Other findings
lung air bronchogram sign
parenchymal lesion
peripheral parenchymal lung lesion
chest wall invasion
hepatic metastases
hepatic metastases
flap
consolidation
collapse
Test
0.00
0.25
0.50
0.75
1.00
Sensitivity (95% Confidence Interval)
Study
Asciak 2019
Bugalho 2014
Faheem 2019
Lomas 1993
Marcun 2009
Qureshi 2009
Yang 1992


Gross macroscopic findings
anecho
anecho
anechoic/simple
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encysted pleural effusion
primary loculation
secondary loculation
complex with septae
complex with fibrin
complex nonsepta
complex septa
echogenicity
echogenicity
echogenicity
homogeneous echogenicity
homogeneous echogenicity
heterogeneous echogenicity
septated echogenecity
swirling sign
swirling sign
Thickness
pleural thickness
pleural thickness
pleural thickness
pleural thickness > 10mm
visceral pleural thickning > 3mm
visceral pleural thickning > 10mm
parietal pleural thickening
parietal pleural thickning > 3mm
parietal pleural thickening <= 10mm
parietal pleural thickening > 10mm
parietal pleural thickning > 10mm
diaphragmatic thickening
diaphragmatic thickening > 7mm
diaphragmatic thickening > 10mm
nodular diaphragmatic thickening
smooth diaphragmatic thickening
Nodularity
total nodularity
pleural nodularity
pleural nodularity
parietal pleural nodularity
visceral pleural nodularity
visceral pleural thickening/nodularity
nodular parietal pleural
smooth parietal pleural
diaphragmatic nodularity
diaphragmatic nodularity
Other findings
lung air bronchogram sign
parenchymal lesion
peripheral parenchymal lung lesion
chest wall invasion
hepatic metastases
hepatic metastases
flap
consolidation
collapse
Test
0.25
0.50
0.75
1.00
Specificity (95% Confidence Interval)
Study
Asciak 2019
Bugalho 2014
Faheem 2019
Lomas 1993
Marcun 2009
Qureshi 2009
Yang 1992

Supplementary Material

Utility of thoracic ultrasound in detecting malignant pleural effusion: A systematic review and meta–analysis

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Figure S1: Methodological evaluation of thoracic ultrasound using the modified Quality Assessment of Diagnostic Accuracy Studies-2 tool

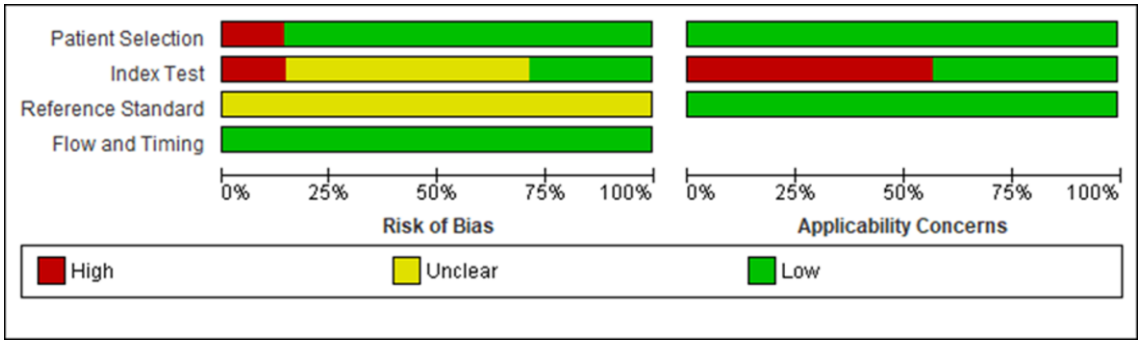

Figure S2: Assessment of risk of bias and applicability for each domain in the included studies

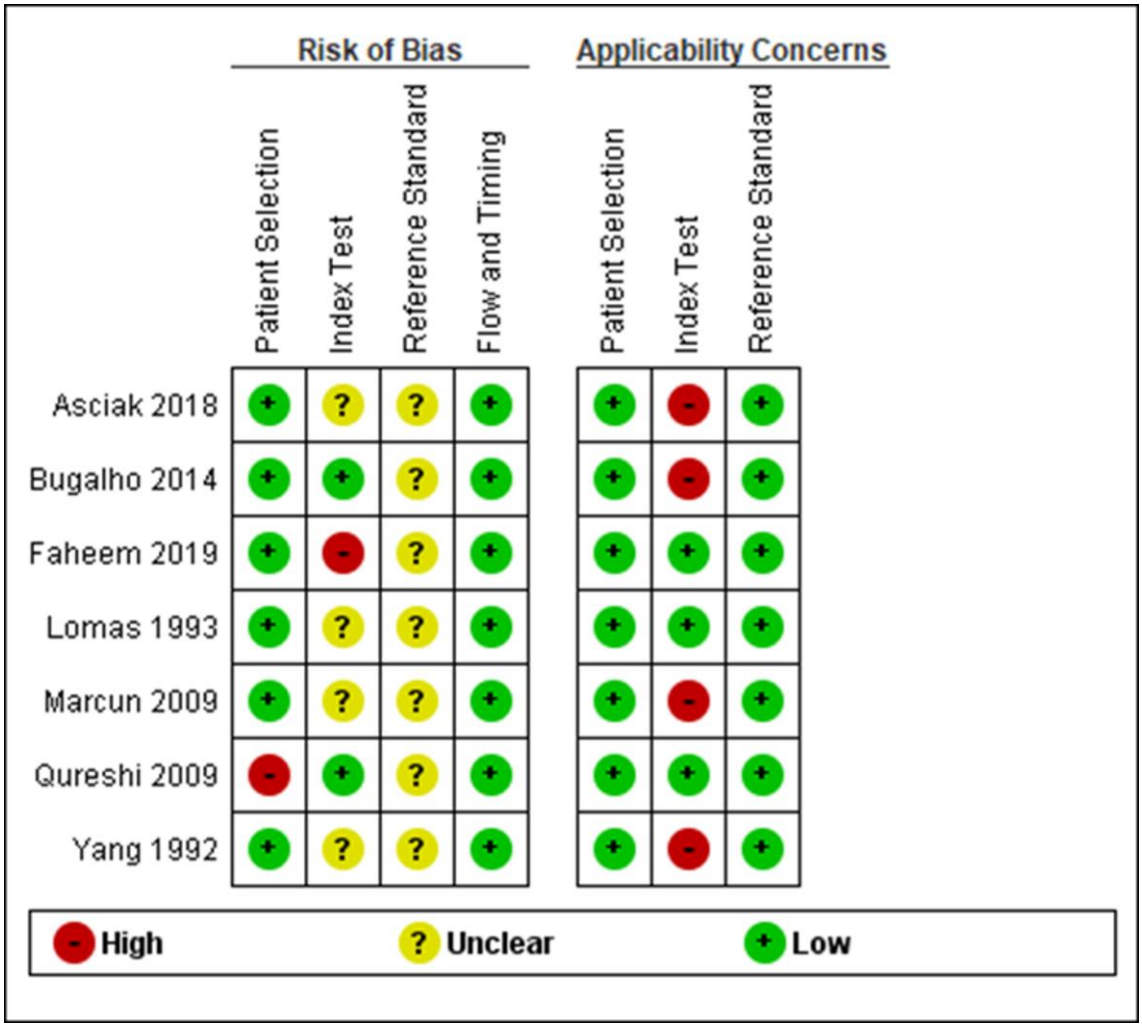

Figure S3: The hierarchical summary of receiver operating characteristics curve of pleural nodularity via thoracic ultrasound

The hierarchical summary of receiver operating characteristics curve of pleural nodularity revealed low sensitivity and high specificity.

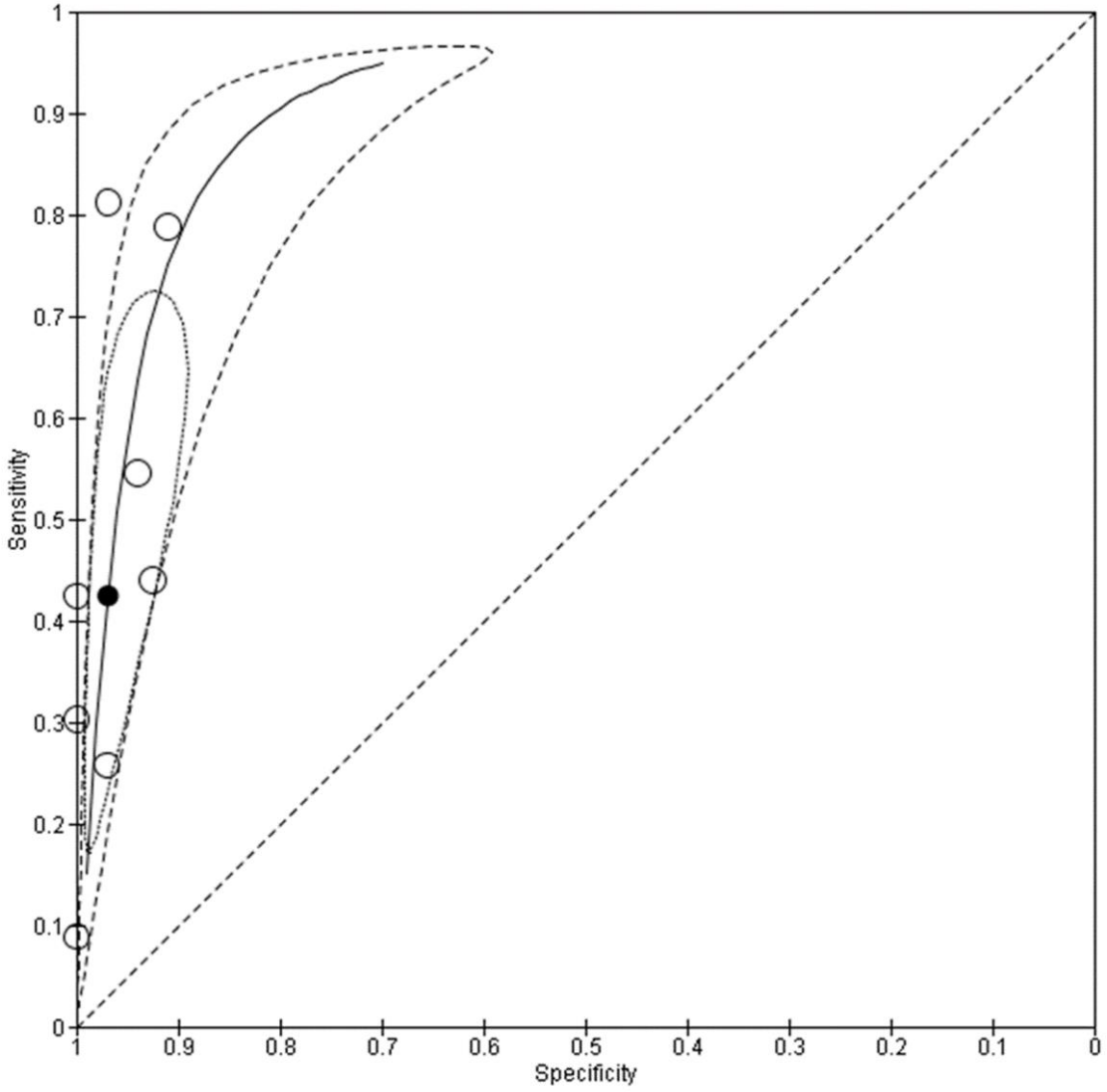

Table S1: The Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
TITLE / ABSTRACT			
Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.	1
Abstract	2	Abstract: See PRISMA-DTA for abstracts.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design).	3
Objectives	4	Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (participants, setting, index test(s), reference standard(s), target condition(s), and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated.	Page 4 of the main text, and page 8 of the

			supplemental information
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target condition(s), index test(s), reference standard(s) and other characteristics (e.g. study design, clinical setting).	4
Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.	5
Diagnostic accuracy measures	13	State the principal diagnostic accuracy measure(s) reported (e.g. sensitivity, specificity) and state the unit of assessment (e.g. per-patient, per-lesion).	5
Synthesis of results	14	Describe methods of handling data, combining results of studies and describing variability between studies. This could include but is not limited to: a) handling of multiple definitions of target condition. b) handling of multiple thresholds of test positivity, c) handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests, f) handling of different reference standards	5

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
Meta-analysis	D2	Report the statistical methods used for meta-analyses, if performed.	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	

RESULTS			
Study selection	17	Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each included study provide citations and present key characteristics including: a) participant characteristics (presentation, prior testing), b) clinical setting, c) study design, d) target condition definition, e) index test, f) reference standard, g) sample size, h) funding sources	14-17
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study.	7
Results of individual studies	20	For each analysis in each study (e.g. unique combination of index test, reference standard, and positivity threshold) report 2x2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot.	6-7
Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.	6-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence.	7
Limitations	25	Discuss limitations from included studies (e.g. risk of bias and concerns regarding applicability) and from the review process (e.g. incomplete retrieval of identified research).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g. the intended use and clinical role of the index test).	7-8
FUNDING			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders.	9

Table S2: The search strategy for publications related to thoracic ultrasound and malignant pleural effusion

Medline via Ovid	
1. Ultrasound	Exp (Ultrasonography) / OR ((chest or lung* or thora* or pulm*) adj4 (sonogra* or ultrasound* or ((chest or lung* or thora* or pulm*) adj4 (sonogra* or ultrasound* or ultrasonic* or ultrasonogra* or ultra-sound* or ultra-sonic* or ultra-sonogra*)).tw.
2. Malignant pleural effusion	Exp (Pleural Effusion, Malignant)/dg OR Exp (Pleural Neoplasms)/dg OR (MPE).tw. OR (malignant).tw. OR (malignancy).tw.
3. Ultrasound findings	(pleural thickening?).tw. OR（hepatic metastas*).tw. OR (pleural nodule?).tw. OR (diaphragm thickening?).tw. OR (diaphragm nodule?).tw. OR (solitary pulmonary lesion).tw. OR (swirling).tw.
Final search 1 AND 2 AND 3	
Embase via Embase.com	
1. Ultrasound	((Ultrasound)/exp AND (diagnosis/lnk)) OR ((chest or lung* or thora* or pulm*) NEAR4 (sonogra* or ultrasound* or ((chest or lung* or thora* or pulm*) NEAR4 (sonogra* or ultrasound* or ultrasonic* or ultrasonogra* or ultra-sound* or ultra-sonic* or ultra-sonogra*)):ab,ti
2. Malignant pleural effusion	((Malignant pleural effusion/exp AND (diagnosis/lnk)) OR (MPE):ab,ti OR (malignant):ab,ti OR (malignancy):ab,ti
3. Ultrasound findings	(pleural thickening?):ab,ti OR（hepatic metastas*):ab,ti OR (pleural nodule?):ab,ti OR (diaphragm thickening?):ab,ti OR (diaphragm nodule?):ab,ti OR (solitary pulmonary lesion):ab,ti OR (swirling):ab,ti
Final search 1 AND 2 AND 3	
The Cochrane Library	
1. Ultrasound	[Ultrasonography] explode all trees OR ((chest or lung* or thora* or pulm*) NEAR/4 (sonogra* or ultrasound* or ((chest or lung* or thora* or pulm*) NEAR/4 (sonogra* or ultrasound* or ultrasonic* or ultrasonogra* or ultra-sound* or ultra-sonic* or ultra-sonogra*)):ti,ab,kw
2. Malignant pleural effusion	[Pleural Effusion, Malignant] explode all trees OR [Pleural Neoplasms] explode all trees OR (MPE):ti,ab,kw OR (malignant):ti,ab,kw OR (malignancy):ti,ab,kw

3. Ultrasound findings	(pleural thickening?):ti,ab,kw OR（hepatic metastas*):ti,ab,kw OR (pleural nodule?):ti,ab,kw OR (diaphragm thickening?):ti,ab,kw OR (diaphragm nodule?):ti,ab,kw OR (solitary pulmonary lesion):ti,ab,kw OR (swirling):ti,ab,kw
Final search 1 AND 2 AND 3	
International Clinical Trials Registry Platform	
Final search (malignant pleural effusion) AND ((ultrasound) OR (ultrasonography))	