Online Appendix B5 BTS Guideline for Pleural Disease

Section B Investigation of the undiagnosed pleural effusion

Question B5 Evidence Review and Protocol

B5 What is the diagnostic accuracy of serum biomarkers when diagnosing adult patients with unilateral pleural effusion?

Contents

Question Evidence Review

B5 What is the diagnostic accuracy of serum biomarkers when diagnosing adult patients with unilateral pleural effusion?

Background

Unilateral pleural effusion may result from a variety of conditions, including malignant, inflammatory, infectious and cardiovascular illnesses. Serum biomarkers that directly reflect underlying pathophysiology have the potential to shorten diagnostic pathways, either by obviating the need for invasive pleural investigations or by directing interventions such as tissue biopsy or fluid drainage. To address this review, it was necessary to define the disease states that are of clinical interest in adults presenting with unilateral effusion and to define a relevant gold standard for each (Table B5a), as the index tests reviewed varied with target disease.

Table D5a: Unilateral pleural effusion disease states and corresponding gold standards

Disease State	Gold Standard
Secondary pleural malignancy	Malignant fluid cytology or pleural biopsy, or malignant pleural nodules/thickening and confirmed extra-pleural primary cancer
Heart failure	Clinical composite including reduced left ventricular ejection fraction on echocardiography +/- MRI
Complex parapneumonic effusion (CPE) or empyema	Clinical composite including evidence of infection plus purulent fluid, positive culture or Gram's stain, fluid pH <7.2
Tuberculous pleural effusion (TPE)	Clinical composite, including definite TPE (AAFB in pleural tissue or fluid culture, or sputum AAFB plus effusion) and probable TB (granulomatous histology or lymphocytic fluid, effusion resolved after TB therapy and other causes excluded
Autoimmune pleuritis	Clinical compositive based on all available data

Outcomes

Diagnostic accuracy of serum biomarkers for diagnosing unilateral pleural effusion

Evidence Review

The initial literature review identified 43 studies, of which 9 were deemed relevant.[1-9] Prospective and retrospective studies were included.

1. Secondary pleural malignancy

Two studies reported on four serum biomarkers and the study results are summarised in Table B5b.

Table B5b: Secondary pleural malignancy serum biomarker study summary

Study	Patients	Marker	Cut-Point	Sensitivity	Specificity
Botana Rial 2011[1]	100	CRP	35.5mg/L	0.71	0.56
Wagner 2007[2]	85	CYFRA 21-1	3.12 ng/ml	0.71	0.93
		CEA	3.35 ng/ml	0.57	0.93
		CA15-3	30.86 ng/ml	0.49	0.93

CA15-3 – cancer antigen 15-3; CEA – carcinoembryonic antigen; CRP – C-reactive protein; CYFRA 21-1 – fragment of cytokeratin 19

Mesothelioma studies were excluded from this guideline as this has previously been covered in the BTS Guideline for the Investigation and management of pleural mesothelioma 2018.[10]

2. Tuberculous pleural effusion (TPE)

Two studies tested multiple markers in a mixture of blood and pleural fluid (including T-spot, tuberculosis (TB) antibody and adenosine deaminase (ADA)) in populations with high TB prevalence. Only data regarding serum measurements were extracted and related to two different markers (T-spot and TB antibody, Table B5c).

Table B5c: Tuberculous pleural effusion biomarker study summary

Study	Marker	TPE Prevalence	Sensitivity [95% CI]	Specificity [95% CI]
He 2015[3]	T-spot	41%	0.93 [0.83, 0.97]	0.69 [0.58, 0.78]
Huo 2019[4]	TB antibody	68%	0.48 [0.35, 0.61]	0.76 [0.55, 0.89]

TPE – tuberculous pleural effusion; CI – confidence intervals

3. Heart failure

Four prospective studies evaluated N-terminal pro-brain natriuretic peptide (NT-proBNP) as a diagnostic serum biomarker for diagnosing heart failure in unilateral pleural effusion patients. Each study used a different cut-point to define a positive index test result (Table B5d) and meta-analysis of the corresponding data resulted in a pooled sensitivity of 0.90 [0.84, 0.94] and pooled specificity of 0.88 [0.71, 0.96] [95% confidence intervals] (Figure B5a).

Table B5d: Heart failure N-terminal pro hormone BNP (NT-proBNP) cut-point per study

Study	Cut-point
Kolditz 2006[6]	4000 ng/L
Bayram 2009[7]	925 ng/L
Valdes 2011[8]	1409 pg/ml
Bintcliffe 2016[5]	1500 pg/ml

4. Pleural infection (complex parapneumonic effusion (CPPE) or empyema)

No studies directly reported on the diagnostic accuracy of serum biomarkers to diagnose complex parapneumonic effusion (CPE), or empyema in unilateral effusion patients, with reference to the corresponding gold standard detailed in Table B5a. One prospective study reported that serum procalcitonin, at a cut-point of 0.085 ng/L, had a sensitivity and specificity of 0.69 and 0.80 respectively for identifying pleural infection, but no information was provided on how correct patient diagnoses were achieved.[9]

5. Autoimmune pleuritis

There were no studies that reported on the diagnostic accuracy of serum biomarkers to diagnose autoimmune pleuritis in unilateral pleural effusion patients.

Evidence Statements

Serum N-terminal pro hormone pro-brain natriuretic peptide (NT-proBNP) provides high sensitivity and specificity for diagnosing heart failure in unilateral pleural effusion patients (**Low**)

There is insufficient evidence to support the use of serum biomarkers to diagnose secondary pleural malignancy, pleural infection, tuberculous pleural effusion or autoimmune pleuritis in unilateral pleural effusion patients

Recommendation

- Serum N-terminal pro hormone BNP (NT-proBNP) should be considered to support a diagnosis of heart failure in patients with unilateral pleural effusion suspected of having heart failure (**Conditional**)

Good Practice Points

- ✓ Serum biomarkers should not currently be used to diagnose secondary pleural malignancy, pleural infection or autoimmune pleuritis
- ✓ Serum biomarkers should not routinely be used to diagnose tuberculous pleural effusion, but may be considered in high prevalence areas
- ✓ Serum biomarkers, including N-terminal pro hormone pro-brain natriuretic peptide (NT-proBNP), should not be used in isolation for diagnosing unilateral pleural effusion as multiple conditions may co-exist

Research Recommendations

- Further research is needed to investigate the diagnostic accuracy of serum biomarkers to diagnose pleural malignancy, pleural infection or autoimmune pleuritis
- Further research is needed to prospectively validate a consistent diagnostic cut-point for serum N-terminal pro hormone BNP (NT-proBNP) in the diagnosis of heart failure
- Further research is needed to prospectively validate serum T-spot testing in the diagnosis of tuberculous pleural effusion, which should include areas of lower TB prevalence

Meta-analyses

Diagnostic accuracy table contents and summary receiver operating characteristic (SROC) curve legend

Table contents

Pooled sensitivity [95% confidence intervals]

Pooled specificity [95% confidence intervals]

Likelihood ratio of a positive test result (LR+) [95% confidence intervals]

Likelihood ratio of a negative test result (LR-) [95% confidence intervals]

Diagnostic odds ratio (DOR, an indicator of the likelihood of a positive test result) [95% confidence intervals]

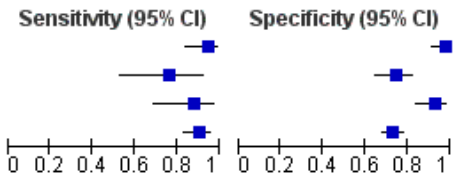
Summary receiver operating characteristic (SROC) curve legend

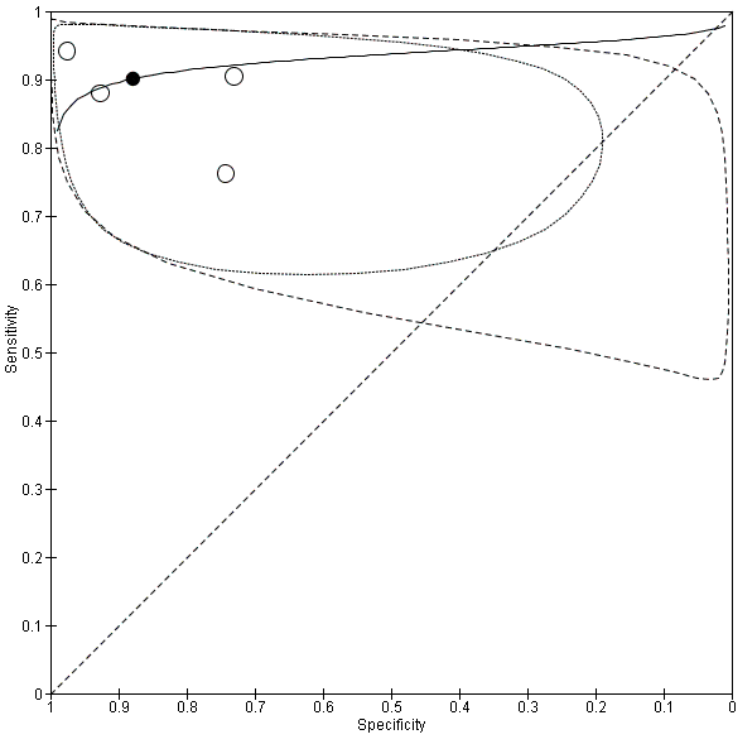
——	SROC
○	Study estimate
●	Summary point
·····	95% confidence region
- - -	95% prediction region

3. Heart failure

Figure B5a NT-proBNP (N-terminal pro hormone BNP)

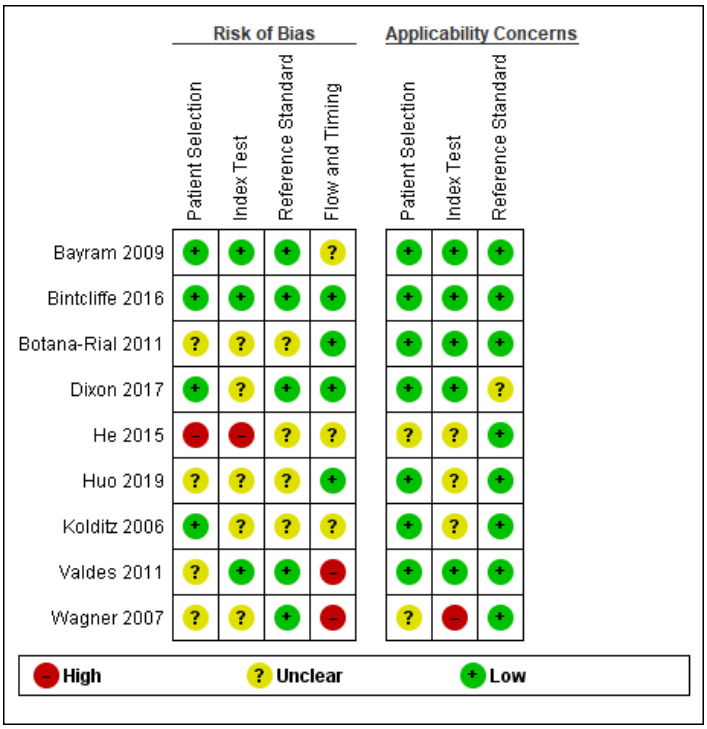
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bayram 2009	48	2	3	80	0.94 [0.84, 0.99]	0.98 [0.91, 1.00]
Bintcliffe 2016	16	27	5	78	0.76 [0.53, 0.92]	0.74 [0.65, 0.82]
Kolditz 2006	22	5	3	63	0.88 [0.69, 0.97]	0.93 [0.84, 0.98]
Valdes 2011	85	82	9	222	0.90 [0.83, 0.96]	0.73 [0.68, 0.78]





Pooled Sensitivity	0.901	[0.839, 0.941]
Pooled Specificity	0.879	[0.709, 0.956]
LR+	7.440	[0.108, 14.772]
LR-	0.113	[0.048, 0.117]
DOR	66.091	[-27.915, 160.096]

Risk of bias summary



GRADE analysis

3. Heart failure

NT-proBNP (N-terminal pro hormone BNP)

What is the diagnostic accuracy of serum biomarkers when diagnosing adult patients with unilateral pleural effusion?

Patient or population: Adults aged 18+ with unilateral pleural effusion

New test: NT-proBNP (N-terminal pro hormone BNP)

Pooled sensitivity: 0.90 (95% CI: 0.84 to 0.94) | **Pooled specificity**: 0.88 (95% CI: 0.71 to 0.96)

Test result	Number of results per 1,000 patients tested (95% CI) **Prevalence 51%*** Typically seen in	Number of participants (studies)	Certainty of the Evidence (GRADE)
True positives	**460** (428 to 480)	191 (4)	⨁⨁◯◯ **LOW** [a,b]
False negatives	**50** (30 to 82)		
True negatives	**431** (347 to 468)	559 (4)	⨁⨁◯◯ **LOW** [a,b]
False positives	**59** (22 to 143)		

CI: Confidence interval

Explanations

a. Some risk of bias across studies
b. Some inconsistency across sensitivity and specificities

Recommendation Table

Question Details

POPULATION:	Adults (18+) with unilateral pleural effusion
INDEX TESTS:	Serum biomarkers
GOLD STANDARD:	Clinico-pathology
OUTCOME:	Diagnostic accuracy of serum biomarkers for diagnosing unilateral pleural effusion

3. Heart failure

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	**Accurate**	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
☐	☐	☐	☒	☐

CONCLUSIONS

Recommendation

Pleural fluid cytology should be used as an initial diagnostic test in patients with suspected secondary pleural malignancy, accepting that a negative cytology should lead to consideration of further investigation

Pleural fluid biomarkers should not be used for diagnosing secondary pleural malignancy

Justification

Serum N-terminal pro hormone pro-brain natriuretic peptide (NT-proBNP) provides high sensitivity and specificity for diagnosing heart failure in unilateral pleural effusion patients (**Low**)

Subgroup considerations

All data were considered as subgroups

Research priorities

Further research is needed to prospectively validate a consistent diagnostic cut-point for serum N-terminal pro hormone BNP (NT-proBNP) in the diagnosis of heart failure

References

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10. Woolhouse I, Bishop L, Darlison L, et al. British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma. *Thorax.* 2018;73(Suppl 1):i1-i30.

Question Protocol

Field	Content
Review Question	What is the diagnostic accuracy of serum biomarkers when diagnosing unilateral pleural effusion in adults?
Type of review question	Diagnostic accuracy
Objective of the review	The use of a range of serum biomarkers in specific diagnoses
Eligibility criteria – population / disease / condition / issue / domain	Adults with unilateral pleural effusion 18+
Eligibility criteria – index test(s)	Serum biomarkers (ADA Mesothelin NT BNP CRP Pro-calcitonin Tumour markers Autoantibodies TB IGra tests)
Eligibility criteria – gold standard	Clinico-pathology
Outcomes and prioritisation	Diagnostic accuracy
Eligibility criteria – study design	RCTs Prospective comparative studies Case series of >100 patients
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but **DO NOT** use in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	ADA Mesothelin NT BNP

	CRP Pro-calcitonin Tumour markers Autoantibodies TB IGra tests
Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus
Data management (software)	RevMan5 — Meta-analysis data input. Evidence review/considered judgement. Storing Guideline text, tables, figures, etc. MetaDTA — Data meta-analyses Gradepro — Quality of evidence assessment / Recommendations
Information sources – databases and dates	MEDLINE, Embase, PubMED, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews 1966 - present
Methods for assessing bias at outcome / study level	RevMan5 diagnostic accuracy full review template (based on QUADAS2) (follow instructions in '*BTS Guideline Process Handbook - Diagnostic Accuracy*')
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for forest plots, summary ROC plot MetaDTA to combine studies (pooled specificity, sensitivity, likelihood ratios, diagnostic odds ratio and confidence intervals) and calculate RevMan parameters for summary ROC plot (follow instructions in '*BTS Guideline Process Handbook - Diagnostic Accuracy*')
Meta-bias assessment – publication bias, selective reporting bias	GRADEpro — Diagnostic accuracy quality of evidence assessment for each index test (follow instructions in '*BTS Guideline Process Handbook - Diagnostic Accuracy*')
Rationale / context – what is known	Specific tests are known to have diagnostic meaning in pleural disease – e.g. serum ADA and BNP in the diagnosis of TB and heart failure