Diagnostic value of carcinoembryonic antigen in malignant pleural effusion: a meta-analysis

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CRD summary
This review concluded that pleural carcinoembryonic antigen may be useful for confirming malignant pleural effusion and differentiating between malignant pleural mesothelioma and metastatic lung cancer. The lack of reporting of the reference standards used and the inclusion of many small and poor- or moderate-quality studies mean that this conclusion should be treated with caution.

Authors' objectives
To determine the accuracy of pleural carcinoembryonic antigen in the early diagnosis of malignant pleural effusion.

Searching
MEDLINE, EMBASE, The Cochrane Library and Web of Science were searched without language restrictions to October 2006; search terms were reported. References of identified articles were also scanned. Only English-language studies were included. Conference abstracts were excluded.

Study selection
Studies that assessed the accuracy of pleural carcinoembryonic antigen for the diagnosis of malignant pleural effusion were eligible for inclusion if at least 10 pleural effusion specimens were assessed and where measures of sensitivity and specificity could be extracted or calculated. Most of the studies used radioimmunoassay or enzyme immunoassays to measure antigen levels. Cut-offs varied considerably across studies, from 3ng/mL to 50ng/mL (5ng/mL to 40ng/mL for radioimmunoassay; 3ng/mL to 15ng/mL enzyme immunoassays). Reference standards were not reported.

Two independent reviewers selected studies for the review; disagreements were resolved by consensus.

Assessment of study quality
Study quality was assessed using the STARD statement (maximum score 25) and QUADAS (maximum score 14); the number of reviewers who performed the quality assessment was not reported.

Data extraction
Data for a 2x2 table of test performance was extracted for each study, from which sensitivity, specificity, positive and negative likelihood ratios (LR+/-) and the diagnostic odds ratio (DOR), along with 95% confidence intervals (CI), were calculated. Where multiple publications were identified, data were used from the best quality study.

It appeared that two reviewers performed the data extraction.

Methods of synthesis
Summary estimates of sensitivity, specificity, positive and negative likelihood ratios and DOR, along with 95% CI, were calculated using a random-effects model. Heterogeneity was assessed using X² and Fisher's exact test. Summary receiver operating characteristic (sROC) curves were produced using the Moses and Littenberg model and area under the curve was calculated. Separate curves were produced for weighted and unweighted analyses; variable on which studies were weighted was not reported. Separate analysis were made for the differential diagnosis of lung cancer and malignant mesothelioma. Meta-regression was undertaken with study quality scores included as covariates. Publication bias was assessed using funnel plots and the Egger test.

Results of the review
Forty-five studies met the inclusion criteria (n=2,834 with malignant pleural effusion and 3,251 without). STARD scores ranged from 8 to 16 out of 25. QUADAS scores ranged from 5 to 13 out of 14. Sample sizes varied from 25 to 654. There was evidence of publication bias for both the evaluation for the diagnosis of malignant pleural effusion and
the differential diagnoses due to metastatic lung cancer and mesothelioma. Statistically significant heterogeneity was observed for all analyses.

The overall pooled estimates for pleural carcinoembryonic antigen for the diagnosis of malignant pleural effusion (45 studies) were 54% for sensitivity (95% CI 52% to 55%; range 27% to 82%), 94% for specificity (95% CI 93% to 95%; range 77% to 100%), 9.52 for LR+ (95% CI 6.97 to 13.01), 0.49 for LR- (95% CI 0.44 to 0.54) and 22.5 for the DOR (95% CI 15.6 to 32.5). The area under the curve was 0.77 (standard error 0.05) when studies were unweighted and 0.75 when studies were weighted.

The pooled estimates of sensitivity were 60% (95% CI 55% to 65%; range 38% to 88%) for malignant pleural effusion due to metastatic lung cancer when carcinoembryonic antigen concentration exceeded the cut off values and 97% (95% CI 93% to 99%; range 73% to 100%) for malignant pleural mesothelioma when carcinoembryonic antigen concentration was below the cut-off values (11 studies). The area under the curve for differential diagnosis was 0.86 (standard error 0.12) when studies were unweighted and 0.85 when studies were weighted.

The meta-regression indicated that study quality did not impact on accuracy.

**Authors’ conclusions**
The measurement of pleural carcinoembryonic antigen is likely to be a useful diagnostic tool for confirming malignant pleural effusion. It is also helpful in the differential diagnosis between malignant pleural mesothelioma and metastatic lung cancer.

**CRD commentary**
The authors addressed a clear research question, however, the inclusion criteria were poorly defined and any specification of the reference standard used was absent. Several relevant sources were searched, but only English language publications were utilised. Evidence for publication bias was observed. Two independent reviewers selected studies for the review; it was unclear whether similar measures were taken to reduce error and bias during data extraction and the assessment of study quality. Many of the included studies were small and achieved poor or moderate quality scores. Reporting of study details was minimal. There was no information regarding the reference standard used in the included studies, and the lack of reporting of results for each criteria of the quality assessment meant that the appropriateness of the tests used to confirm diagnosis (and hence the reliability of the diagnostic outcomes) could not be assessed. Although the results of the analysis showed that a person with malignant pleural effusion was nearly 10 times more likely to have a positive test than a person who did not have the disease, the low sensitivity was due to a high false negative rate. Therefore, a large proportion of patients who had the disease would receive a negative test. All of the analyses were subject to statistically significant heterogeneity, and the reliability of the pooled estimates of sensitivity and specificity is uncertain. Given the limitations of the review and the included studies, the conclusion should be treated with some caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that given the similarity of the diagnostic accuracy of carcinoembryonic antigen (low sensitivity and high specificity) to more conventional tests, it may not be useful in practice. They added that the results of pleural carcinoembryonic antigen assays should be interpreted in parallel with clinical findings and the results of conventional tests.

**Research:** The authors did not state any implications for research.

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Not stated.

**Bibliographic details**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.