Diagnostic utility of pleural fluid carcinoembryonic antigen and CYFRA 21-1 in patients with pleural effusion: a systematic review and meta-analysis


CRD summary
The authors concluded that both carcinoembryonic antigen and CYFRA 21-1 had good performance in the differential diagnosis of pleural effusion. CYFRA 21-1 did not offer an advantage over carcinoembryonic antigen. In light of the poor reporting of the review methods, uncertain quality of included studies and the presence of heterogeneity between studies, the authors' conclusions should be treated with caution.

Authors' objectives
To assess and compare the diagnostic value of pleural fluid carcinoembryonic antigen (CEA) and CYFRA 21-1 (cytokeratin fragment 19) in differential diagnosis of pleural effusions.

Searching
PubMed, Cancerlit, EMBASE, The Cochrane Library, China Bio-Medicine Database and China National Knowledge Infrastructure were searched from 1996 to 2007 for published articles in English or Chinese. Search terms were reported. The bibliographies of identified articles were hand searched.

Study selection
Studies that compared the diagnostic performance of pleural fluid carcinoembryonic antigen or CYFRA 21-1 using commercially available assays with a standard reference test (cytological examination, biopsy or histological proven malignancy) in patients with benign or malignant pleural effusions were eligible for inclusion. Eligible studies had to report sensitivity and specificity values or data that enabled the calculation of sensitivity and specificity. Studies were excluded from the review if they were of a healthy population or where the definition of malignant pleural effusion was inconsistent with the inclusion criteria.

Prospective and retrospective studies of carcinoembryonic antigen and CYFRA 21-1 using radioimmunoassay (RIA), electrochemiluminescent immunoassay (ECLIA), enzyme-linked immunosorbent assay (ELISA), immunoradiometric assay (IRMA), chemiluminescence immunoassay (CLIA) and microparticle enzyme immunoassay (MEIA) were included for review. The cutoff point for CYFRA 21-1 ranged from 3.3ng/mL to 175ng/mL. The cutoff point for carcinoembryonic antigen ranged from 3ng/mL to 50ng/mL. The percentage of patients with malignancy in the included studies ranged from 31.4% to 68%. Included studies were from a wide range of countries.

Two reviewers independently selected the articles for review. Disagreements were resolved by consensus.

Assessment of study quality
Methodological quality was assessed using items selected from QUADAS (Quality Assessment of Diagnostic Accuracy Studies) that assessed patient collection, study design, blinding, assay method, study size and cut off point.

The authors did not state how the validity assessment was performed.

Data extraction
Data were extracted on the number of true positive, true negative, false positive and false negative outcomes for each study and were used to calculate specificity and sensitivity with 95% confidence intervals (CI).

The authors stated neither how the data were extracted for the review nor how many reviewers performed the data extraction.

Methods of synthesis
Pooled sensitivity and specificity with 95% CI were calculated using the DerSimonian and Laird Method. Forest plots were used to depict the sensitivity and specificity of each study. Heterogeneity was assessed using the X² test; possible
sources of heterogeneity were explored by applying a metaregression using the Littenberg and Moses linear model weighted by the inverse of the variance. Diagnostic odds ratio was used as the accuracy measure. The Spearman correlation was used to determine the relationship between sensitivity and specificity and to identify a possible threshold effect. A summary operator receiving curve (SROC) was drawn using Moses' linear model and the area under the curve (AUC) was calculated. The difference between the area under the curve of CYFRA-21-1 and carcinoembryonic antigen was tested using the z-test.

Results of the review
Nineteen studies (3,228 patients) were included in the review: seven prospective (1,276 patients); three retrospective (497 patients); and nine with unspecified study design. Twelve studies reported blinding.

Carcinoembryonic antigen (15 studies): Carcinoembryonic antigen had a pooled sensitivity of 45.9% (95% CI: 43.2 to 48.5) and a pooled specificity of 97.0% (95% CI: 96.0% to 97.8%). The sensitivity of carcinoembryonic antigen in individual studies ranged from 28.8% to 82.4% and the specificity for individual studies ranged from 76.7% to 100%. The Spearman correlation of the logit of sensitivity and the logit of 1-sensitivity was 0.268, which suggested a threshold effect. The area under the curve was 0.7691.

CYFRA-21-1 (12 studies): CYFRA 21-1 had a pooled sensitivity of 47.3% (95% CI: 44.0% to 50.6%) and a pooled specificity of 91.8% (95%: 89.5% to 93.7%). The sensitivity of individual studies ranged from 21.8% to 90.9% and the specificity of individual studies ranged from 7.7% to 100%. The Spearman correlation of the logit of sensitivity and the logit of 1-sensitivity was 0.644, which suggesting a threshold effect. The area under the curve was 0.8213.

There was no significant difference between the area under the curve of carcinoembryonic antigen and the area under the curve of CYFRA 21-1 (p>0.05). There was evidence of significant statistical heterogeneity for both specificity and sensitivity of carcinoembryonic antigen and CYFRA 21-1 (\(\chi^2\) ranged from 71.53 to 152.10, \(p=0.000\)). In metaregression analyses, the different assays used accounted for the greatest source of heterogeneity (diagnostic odds ratio 2.60 for carcinoembryonic antigen and diagnostic odds ratio 2.32 for CYFRA 21-1).

Authors’ conclusions
Both carcinoembryonic antigen and CYFRA 21-1 had good performance in the differential diagnosis of pleural effusion. CYFRA 21-1 did not offer an advantage over carcinoembryonic antigen.

CRD commentary
The review question was clearly stated and the inclusion criteria for patients and outcomes were well defined. The inclusion criteria for study design were not specified and were only implicit in the review question for the intervention. Several relevant databases were searched. Restricting the search to published articles in Chinese or English meant that publication and language biases could not be ruled out. Appropriate measures were taken in the study selection process to minimise reviewer error and bias. It was unclear whether similar steps were taken in the data extraction or validity assessment process, therefore, reviewer error and bias could not be ruled out. A validity assessment was carried out, but insufficient information was provided on the outcome of this to determine the quality of included studies and the authors’ did not appear to have used the validity assessment to inform the results. Given the presence of clinical heterogeneity between included studies and the presence of significant statistical heterogeneity, the results may have been better treated with a narrative synthesis. In light of the uncertain quality of included studies and the presence of heterogeneity between studies, the authors’ conclusions should be treated with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research was needed on the use of a combination of tumour markers in pleural fluid to aid differential diagnosis.

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