Diagnostic value of N-terminal pro-brain natriuretic peptide for pleural effusion due to heart failure: a meta-analysis

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CRD summary
This review concluded that N-terminal pro-brain natriuretic peptide levels in pleural fluid showed a high diagnostic accuracy and may help accurately differentiate cardiac from non-cardiac conditions in patients with pleural effusion. Given the limitations of the included studies and the statistical analyses employed, and the potential for missed studies, the authors’ conclusions should be treated with some caution.

Authors’ objectives
To establish the overall diagnostic accuracy of pleural N-terminal pro-brain natriuretic peptide for identifying pleural effusion due to heart failure.

Searching
PubMed, EMBASE, Web of Science, and the Cochrane Library were searched from inception to September 2009; search terms were reported. References of identified articles were searched manually. Only studies published in English were included.

Study selection
Eligible studies were those that reported both the sensitivity and specificity of N-terminal pro-brain natriuretic peptide for the diagnosis of pleural effusion.

In included studies, electrochemiluminescence was the most common method for determining N-terminal pro-brain natriuretic peptide concentrations. The cut-off for a positive test varied widely across studies, ranging from 599pg/mL to 4,000pg/mL. The reference standard for the diagnosis of cardiac effusion was made in all studies included in the meta-analysis based on clinical findings supported by chest radiographs or echocardiogram, and response to diuretic therapy.

Two reviewers independently selected studies; disagreements were resolved by consensus.

Assessment of study quality
Study quality was assessed using QUADAS (Quality Assessment of Diagnostic Accuracy Studies, maximum score 14), the STARD statement (Standards for Reporting of Diagnostic Accuracy, maximum score 25), and criteria relating to study design (cross-sectional or case-control design; prospective or retrospective data collection), patient selection (consecutive or random), and blinding of the interpreters of the reference standard results.

Two reviewers independently assessed study quality; disagreements were resolved by consensus.

Data extraction
Data were extracted to produce 2x2 tables of test performance, from which sensitivity, specificity, positive and negative likelihood ratios, and the diagnostic odd ratio, with 95% confidence intervals (CI), were calculated. Authors were contacted to obtain additional data where necessary.

Two reviewers independently extracted data; disagreements were resolved by consensus.

Methods of synthesis
Studies were combined using summary receiver operating characteristic curves; the Moses-Shapiro-Littenberg model was employed. An estimate of joint sensitivity and specificity and the area under the curve were calculated. Pooled
estimates of diagnostic accuracy outcomes were calculated using a fixed-effects model; a random-effects model was used as a sensitivity analysis. The $X^2$ and Fisher's exact tests were used to assess statistically heterogeneity across studies. Publication bias was investigated using funnel plots and the Egger test.

**Results of the review**

Eight studies met the inclusion criteria (n=907 patients; range 28 to 240); 369 patients had cardiac effusions and 538 had non-cardiac effusions. STARD scores ranged from 13 to 19; QUADAS scores ranged from 8 to 12. All studies recruited patients consecutively or randomly (six prospectively and two retrospectively). Two studies were cross-sectional in design. Six studies reported blinding the interpreters of the reference standard.

Across studies, diagnostic sensitivity of pleural N-terminal pro-brain natriuretic peptide ranged from 0.91 to 1.00 (pooled 0.95, 95% CI 0.92 to 0.97); diagnostic specificity ranged from 0.88 to 1.00 (pooled 0.94, 95% CI 0.92 to 0.96). The pooled positive likelihood ratio was 14.12 (95% CI 10.23 to 19.51), the pooled negative likelihood ratio was 0.06 (95% CI 0.04 to 0.09), and the pooled diagnostic odds ratio was 213.87 (95% CI 122.50 to 373.40). Only the analysis of specificity was considered to show statistically significant heterogeneity (the authors used p<0.05).

From the summary receiver operating characteristic curve, joint sensitivity and specificity was 0.94 (standard error 0.009) and the area under the curve was 0.98 (standard error 0.005). Evidence for publication bias was observed.

**Authors' conclusions**

N-terminal pro-brain natriuretic peptide levels in pleural fluid showed a high diagnostic accuracy and may help accurately differentiate cardiac from non-cardiac conditions in patients presenting with pleural effusion.

**CRD commentary**

The review addressed a clear research question supported by appropriate inclusion criteria. Several relevant sources were searched. However, only English language studies were included, a diagnostic filter was used during the electronic searches, and unpublished studies were not specifically sought. Therefore, studies may have been missed. Each stage of the review process was conducted in duplicate, reducing the potential for error and bias.

Study quality was assessed using appropriate criteria, although only summary results were reported, which made it difficult to determine the methodological limitations of individual studies. Insufficient study details were provided to allow any judgment on different aspects of study quality. The use of p=0.05 for the assessment of heterogeneity meant that this was likely to have been underestimated. The methods used to synthesise the data had their limitations, which made the reliability of the pooled results uncertain; more robust methods were available. In addition, several studies were small, and it was clear from the summary QUADAS scores that there were methodological limitations.

Given the limitations of the included studies, the unknown nature of the methodological biases to which the included studies were subject, the limitations of the statistical analyses employed, and the potential for missed studies, the authors' conclusions should be treated with some caution.

**Implications of the review for practice and research**

The authors did not state implications for practice or research.

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