Diagnostic value of tests that discriminate between exudative and transudative pleural effusions

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Authors' objectives
To determine the diagnostic accuracy and appropriate cut-off values for pleural fluid (PF) tests in order to distinguish between exudative and transudative pleural effusions.

Searching
MEDLINE was searched for articles published since 1976. Additional articles were identified by reviewing the bibliographies of retrieved articles, review articles and pulmonary textbooks. Only published, English language articles were included.

Study selection
Study designs of evaluations included in the review
No inclusion criteria relating to the study design were specified.

Specific interventions included in the review
Studies evaluating PF tests were eligible for inclusion. The included studies evaluated the following tests: PF protein (P-PF), PF to serum P ratio (P-R), PF to serum bilirubin ratio (BILI-R), lactate dehydrogenase (LDH)-PF, PF to serum LDH ratio (LDH-R), PF cholesterol (C-PF), PF to serum cholesterol ratio (C-R), and PF to serum albumin gradient (A-G). The presence of exudative pleural effusion was defined as a positive test; PF tests are a screening method to identify patients with exudative pleural effusions who require additional investigations.

Reference standard test against which the new test was compared
The included studies were required to report a reference standard for diagnosis. Details of the reference standards used in the included studies were not reported. No study completely defined explicit, objective criteria for determining the presence of the underlying disease. The presence of exudative pleural effusion was defined as positive.

Participants included in the review
No inclusion criteria relating to the study population were specified. The included studies were of hospitalised patients undergoing thoracentesis for pleural effusions.

Outcomes assessed in the review
Studies were included if the original data (individual PF test results) were available from the investigators, or could be extracted from published articles, and sufficient information was available to ascribe test results to individual patients. The following measures of diagnostic accuracy were calculated for each PF test and reported in the review: sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, diagnostic odds ratio, and area under the receiver operating characteristic (ROC) curve.

How were decisions on the relevance of primary studies made?
Two authors independently examined the studies for eligibility. Any disagreements were reviewed independently by a third author and the majority decision was accepted.

Assessment of study quality
Study quality was assessed using the following criteria: adequate description of the use of an appropriate reference standard; independence of observations (blinding); uniform application of the reference standard (avoidance of verification bias); generalisability; cohort assembly; and description of the index test(s). Each component was scored as present, absent, or incomplete. Two authors independently assessed study quality. Any disagreements were reviewed independently by a third author and the majority decision was accepted.
Data extraction
The principal investigators of the retrieved articles were asked to participate in the meta-analysis by providing their original data. The results of PF tests and the underlying diagnoses (for transudates and exudates) of study participants were extracted.

Methods of synthesis
How were the studies combined?
ROC curves were generated for each of the PF tests using all available data. These were used to derive optimal cut-off points, selected to maximise sensitivity for the detection of exudative pleural effusions (the goal of screening). For LDH-PF the cut-off point was derived as a fraction of the upper limits of normal to control for variation in assay techniques between laboratories. Diagnostic accuracy outcome measures and their 95% confidence intervals (CIs) were calculated for each PF test using the cut-off values derived.

The area under the ROC curve, calculated with a trapezoidal method, was the main measure used to compare diagnostic accuracies between tests; a non-overlapping 95% CI indicated a significant difference in diagnostic accuracy at the P less than 0.05 level.

For parallel combinations of tests, where an 'or' rule (any test positive = positive) is used to increase sensitivity, Pearson product-moment correlations were used to determine the strength of linear relationships between the tests. The tests were defined as correlated and possibly unsuitable for parallel combination if the correlation was greater than 0.75. Diagnostic accuracy outcome measures were calculated for parallel testing strategies in paired and triplet combinations. Comparisons between strategies were made as described above.

How were differences between studies investigated?
No method for investigating sources of heterogeneity was described. Differences in the methodological quality of the primary studies were discussed in the text.

Results of the review
Seven studies, containing one or more PF test results from a total of 1,448 patients, were included. Seventy-four percent of the effusions were exudates and 26% were transudates. Three studies were excluded because the original data were no longer available from the investigators and the test results could not be extracted from the published report.

Except for BILI-R, which was significantly less accurate, the PF tests evaluated had similar diagnostic accuracies by ROC analysis. The derived cut-off values differed from those previously reported for LDH-PF (>0.45 upper limits of normal) and C-PF (>45 mg/dL). Parallel test combinations (paired and triplet) tended to have higher diagnostic accuracy than individual tests. However, no clearly superior test combination could be identified (the 95% CIs overlapped).

The analysis was limited by a high likelihood of bias in the primary studies.

Authors’ conclusions
Several strategies exist for clinicians utilising PF tests to classify pleural effusions as transudates or exudates. However, there is no clear optimal strategy and further, better designed studies are required.

CRD commentary
The review addressed a clear research question using defined inclusion criteria. The search strategy was very limited and was restricted to studies published in English; this might have resulted in the loss of relevant data. The review methodology was well described and included measures to avoid the introduction of bias. The methodological quality of the primary studies was assessed and their limitations were discussed. The data collection and analysis were appropriate, and the analyses were clearly described and justified. A more detailed description of the primary study populations...
would have been useful and might have enabled some assessment of the likely effects of heterogeneity on the meta-
analysis. The authors' conclusions were appropriately cautious, given the limitations outlined.

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

Practice: The authors stated that clinicians can select one of several diagnostic strategies for identifying exudates. Light's criteria have excellent discriminative properties, but the cut-off value for LDH-PF of >0.45 of the upper limit of the laboratory's normal LDH should be used. LDH-PF can be removed from Light's criteria because it is correlated with LDH-R and so does not significantly enhance discriminative properties. Alternatively, clinicians can avoid blood tests without sacrificing accuracy by using test combinations that include only PF assays. The combinations of LDH-PF/C-PF and P-PF/LDH-PF/C-PF have similar accuracies to Light's criteria.

Research: The authors stated that future investigations with large data sets and improved methodological quality would be beneficial. Particular attention should be paid to the importance of an a priori definition of an explicit, independent reference standard that unequivocally establishes the presence or absence of disease (exudates).

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