Non-invasive diagnostic assessment tools for the detection of liver fibrosis in patients with suspected alcohol-related liver disease: a systematic review and economic evaluation

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CRD summary
This review concluded that no conclusion could be drawn on the most cost-effective non-invasive test for liver fibrosis in patients with symptoms of alcoholic liver disease, until further data were available. Despite concerns over the potential for error and bias in the review process, the authors’ conclusions are suitably cautious and reliable.

Authors’ objectives
To evaluate the diagnostic accuracy and clinical utility of four non-invasive tests for liver fibrosis in patients with symptoms of alcoholic liver disease (ALD).

Searching
MEDLINE, EMBASE, The Cochrane Library, CINAHL, Web of Knowledge and Science Citation Index were searched, without language restrictions, for articles from database inception to January 2010. The search strategies were reported. Bibliographies of retrieved papers and previous systematic reviews were searched, and experts in alcoholic liver disease were contacted.

Study selection
Studies evaluating any of four non-invasive tests for the identification of liver fibrosis, in patients with suspected fibrosis due to alcohol consumption, were eligible for inclusion. The four tests were the Enhanced Liver Fibrosis (ELF) test; FibroTest; FibroMAX; and FibroScan. The eligible reference standards were liver biopsy for liver fibrosis, hepatic venous pressure gradient measurement for portal hypertension, and upper gastrointestinal endoscopy for oesophageal varices. The primary outcome measure was the accuracy of identifying significant fibrosis, defined as a METAVIR stage of F2 to F4. Studies providing the best level of evidence were included, with priority given to controlled studies.

Most of the included studies were conducted in France and were cross-sectional in design. The populations varied considerably in their alcohol consumption, stage of liver disease, and reason for testing. Most of the included studies used biopsy as the reference standard.

Study selection was conducted by one reviewer.

Assessment of study quality
Study quality was assessed by one reviewer, using a modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. The criteria for incorporation bias and clinical review bias were omitted, and the study’s independence from the manufacturer was added.

Data extraction
Data were extracted to construct 2x2 tables of test performance, from which the sensitivity, specificity and positive and negative predictive values, with 95% confidence intervals, were calculated. If any cell contained zero, 0.5 was added to all cells.

Data extraction was conducted by one reviewer, with no independent checking.

Methods of synthesis
Studies were combined in a narrative synthesis. Differences between them were discussed in the text, and the study characteristics were tabulated.

Results of the review
Fourteen studies (reported in 17 articles) met the inclusion criteria; at least 1,321 patients were assessed. Few studies recruited a representative patient spectrum. Several studies were open to progression bias, and about half were unclear...
on whether they blinded interpreters of the reference standard or index test; where blinding was stated, this was often for one or other test, but not both. The number of results that could not be interpreted or were intermediate, in each study, was generally poorly reported. No study evaluated the ELF test and none evaluated FibroMAX. No study reported the impact of the tests on patient management or clinical outcomes.

**European Liver Fibrosis Test:** One study evaluated this test, which was almost the same as the ELF test. Compared with liver biopsy, in patients with chronic liver disease. Using a threshold of 0.431, sensitivity was 93% and specificity was 100% for differentiating between moderate or severe fibrosis and mild or no fibrosis, in 64 patients with alcoholic liver disease. The accuracy was worse for cirrhosis.

**FibroTest:** Five studies were found. Using a threshold of 0.30, the sensitivity was 84% and the specificity was 66% for differentiating between moderate or severe fibrosis and mild or no fibrosis. A threshold of 0.70 could distinguish cirrhosis with a sensitivity of 91% and a specificity of 87% (one study). Smaller studies suggested that a threshold of 0.58 had a sensitivity of 93% and a specificity of 87% for distinguishing between patients with and without clinically significant portal hypertension. A threshold of 0.85 could distinguish between those with and without grade 2 oesophageal varices, with a sensitivity of 89% and a specificity of 50%.

**FibroScan:** Six studies were found. Compared with liver biopsy, in patients with known or suspected alcoholic liver disease, for differentiation between patients with and without fibrosis, moderate or severe fibrosis, or severe fibrosis, the sensitivity was between 80% and 87% and the specificity was between 80.5% and 90.5%. The test seemed to distinguish between patients with and without portal hypertension, and with less success between patients with and without large oesophageal varices. There were no long-term data on survival or other clinical outcomes.

**Adverse events:** The tests appeared to be safe; adverse events included pain and bruising; vasovagal reactions and potentially disabling nerve injuries were occasionally reported. Liver biopsy was associated with a high level of morbidity and occasional mortality. No contraindications were specified that could cause harm, but some operational contraindications could restrict the tests’ practical utility.

**Cost information**
A mathematical model was constructed to estimate the incremental costs and quality-adjusted life-years (QALYs) for each test scenario, compared with liver biopsy. Thirty-six scenarios were assessed for each non-invasive test. No conclusive estimate of the cost per QALY for each test could be provided. There were scenarios in which each of the tests was more cost-effective than biopsying all patients and, other scenarios in which each test was less cost-effective than biopsying all patients.

**Authors’ conclusions**
There was some unreliable evidence that the tests could identify fibrosis and cirrhosis. No conclusion could be drawn on the most cost-effective test, until further data were available.

**CRD commentary**
The review addressed a clear question, with reproducible inclusion criteria. Several relevant sources were searched, with attempts to reduce the potential for language and publication bias. Diagnostic filters were used in the search strategy, therefore some studies could have been missed. The review process was conducted by one reviewer, increasing the potential for error and bias. Study quality was assessed, using appropriate criteria, and the results were reported in full. The decision to combine the studies in a narrative synthesis seems to have been appropriate.

Despite the concerns over the potential for error and bias during the review process, the authors’ conclusions are suitably cautious and reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that they could not make any recommendations for changes, due to the lack of a conclusion on the cost-effectiveness of the tests.

**Research:** The authors stated that many parameters for their model required better data. The most important one was the sensitivity and specificity of each non-invasive liver test, compared with biopsy, at validated and pre-selected cut-off thresholds. Others were the influence of potential confounding variables, such as current drinking behaviour and the
degree of hepatic inflammation, on the performance of the tests; the likelihood, and size, of decreases in abstinence rates with a diagnosis of significant alcoholic liver disease, by diagnostic test; and the incidental gains in QALYs that may be associated with biopsy.

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