Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review

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CRD summary
This review concluded that many blood tests were moderately useful for identifying clinically significant fibrosis or cirrhosis in hepatitis C virus-infected patients. Despite some limitations of the review and available evidence, the authors’ conclusions were suitably cautious, and the limitations of the evidence for some of the tests were acknowledged.

Authors’ objectives
To evaluate the diagnostic accuracy of blood tests to identify fibrosis or cirrhosis in patients with hepatitis C virus (HCV) infection.

Searching
MEDLINE, EMBASE, The Cochrane Library, Scopus and PsycINFO were searched to January 2013 for studies in English; the search strategy was reported. The reference lists of retrieved articles were also searched. Abstracts were excluded.

Study selection
Studies that compared the accuracy of blood tests with that of liver biopsy for diagnosing fibrosis or cirrhosis in patients infected with HCV were eligible for inclusion. Studies conducted in post-transplant patients, patients co-infected with HIV or hepatitis B, patients who received haemodialysis, and/or children, were excluded from the review. The inclusion/exclusion criteria varied considerably across studies, as did the tests used, and the cutoffs used to identify clinically significant fibrosis and cirrhosis.

Two reviewers independently selected studies for the review.

Assessment of study quality
Quality was assessed in terms of patient spectrum, appropriateness of the reference standard, differential verification bias, reporting of uninterpretable/unobtainable results, incorporation bias, the use of predefined test cutoff thresholds, and where appropriate, the use of an independent validation sample. The Downs and Black, QUADAS and US Preventive Services Task Force tools were cited. The strength of evidence was determined based on the quality, consistency, directness and precision of the results.

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

Data extraction
One reviewer extracted data in order to construct 2x2 tables of test performance, from which sensitivity and specificity were calculated. Data extraction was checked by a second reviewer. Where a summary receiver operating characteristic (SROC) curve was presented, the area under the curve (AUC) was extracted. The cutoffs of interest were clinically significant fibrosis and cirrhosis (definitions provided).

Methods of synthesis
Studies were not formally combined in a meta-analysis; median sensitivity, specificity and AUC with associated ranges were reported. Positive and negative likelihood ratios (LR+/-) based on the median sensitivities and specificities were calculated, and reported with their associated ranges. Study details and results were summarised in tables. Studies that directly compared two or more blood tests in the same population were synthesised separately. A range of sensitivity analyses were conducted by excluding prespecified types of studies from the calculation of the median.

Results of the review
After screening, 172 studies met the inclusion criteria (over 60,000 patients; range 25 to 5,257). Fifteen studies were
considered good quality, five poor quality, and 152 fair quality; 73 studies did not blind interpreters of the liver biopsy and 93 did not clearly describe enrolment of a consecutive or random sample.

Fifteen tests were evaluated for accuracy to detect clinically significant fibrosis. Across the tests, the median sensitivities ranged from 22% (FibroTest; range 20% to 50%; five studies) to 94% (FibroIndex; range 62% to 97%; three studies), specificity from 38% (FibroTest; range 27% to 56%; six studies) to 98% (Pohl Index; range 76% to 100%; three studies), and AUC from 0.52 (Pohl Index; range 0.52 to 0.53; three studies) to 0.86 (FIBROSpect II; range 0.77 to 0.90; seven studies).

Fifteen tests were evaluated for accuracy to detect cirrhosis: Across the tests, the median sensitivities ranged from 17% (Bonacini Index; range 15% to 34%; three studies) to 98% (Forns Index; one study), specificity from 27% (Forns Index; one study) to 98% (Pohl Index; range 90% to 99%; four studies), and AUC from 0.65 (Pohl Index; range 0.64 to 0.66; three studies) to 0.91 (Fibrometer; range 0.89 to 0.94; five studies).

APRI and FibroTest were compared directly with a range of other tests (68 studies). The median differences in the AUCs were generally minimal, although there were three exceptions: APRI had an AUC 0.17 higher than the AST-ALT ratio and the Pohl Index for detecting fibrosis; APRI had an AUC 0.19 higher than the AST-ALT ratio for detecting cirrhosis. The differences in AUC ranged from -0.06 (range -0.07 to -0.02; eight studies) to 0.19 (range -0.18 to 0.23; 11 studies). Further results were presented.

Authors’ conclusions
Many blood tests were moderately useful for identifying clinically significant fibrosis or cirrhosis in HCV-infected patients; accuracy was greater for identifying cirrhosis than less advanced fibrosis.

CRD commentary
The review addressed a clear, though broad, question which was supported by reproducible inclusion criteria. The search for published studies was comprehensive. However, only studies published in English were included, diagnostic filters were used during the electronic searches, and unpublished studies were not sought. Therefore, studies may have been missed.

A large number of studies were included in the review, but some tests were evaluated in just one or two of the studies. Each stage of the review was conducted in duplicate, which reduced the risk of error and bias. Appropriate criteria were used to assess study quality, but some areas of potential bias were not assessed. A large proportion of studies were subject to bias. Though the review included very heterogeneous studies, it did appear that several tests had substantial numbers of studies providing data for sensitivity and specificity, so it was unclear why a statistical model was not used to derive summary estimates of sensitivity and specificity with 95% predictive regions that could maintain the intra-study relationship between these measures. The presentation of medians and ranges was of limited value and the calculation of likelihood ratios from these medians was questionable.

Despite some limitations of the review and available evidence, the authors’ conclusions were suitably cautious, and limitations of the evidence for some of the tests were acknowledged.

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

Research: The authors stated that studies that evaluated the virologic and clinical outcomes of antiviral treatment in HCV-infected patients who have not had liver biopsy were needed to further define optimum work-up strategies.

Funding
Agency for Healthcare Research and Quality.

Bibliographic details

PubMedID
Other publications of related interest

Correction: Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection. Annals of Internal Medicine 2013; 159(4): 308.

Indexing Status
Subject indexing assigned by NLM

MeSH
Aspartate Aminotransferases /blood; Disease Progression; Hematologic Tests; Hepatitis C, Chronic /complications; Humans; Liver Cirrhosis /blood /diagnosis; Liver Function Tests; Platelet Count

AccessionNumber
12013030770

Date bibliographic record published
05/06/2013

Date abstract record published
11/06/2013

Record Status
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.