Does this patient with liver disease have cirrhosis?


CRD summary
This generally well-conducted review concluded that various clinical and laboratory test findings increased the likelihood of detecting cirrhosis; combinations of laboratory findings were most useful for excluding the diagnosis. The conclusions reflect the evidence presented, but the associations with cirrhosis for many of the tests were not sufficiently strong to confidently conclude presence or absence of disease.

Authors' objectives
To identify simple clinical indicators that can exclude or detect cirrhosis in adults with known or suspected liver disease.

Searching
MEDLINE and EMBASE were searched for peer-reviewed papers from inception to December 2011. Search terms were reported in an on-line appendix. There were no language restrictions. Reference lists of retrieved studies, review articles and textbooks were searched.

Study selection
Studies that evaluated the reliability and diagnostic accuracy of at least one component of the clinical examination and routine investigations (medical history, physical examination, routine laboratory tests and scoring models that used these components) for detecting cirrhosis in adults (18 years or over) with known or suspected liver disease of any aetiology were eligible for inclusion. Prediction models had to be validated at a specific cut-off value in more than one study. Cirrhosis had to be confirmed by histological examination of liver tissue using published classification schemes. Complicated specialised serum marker formulas that were not routinely available, diagnostic imaging studies and studies in patients with previous liver transplant were excluded.

Studies were published between 1962 and 2011. The most common cause of liver disease was hepatitis C (overall prevalence 19%). Most studies included patients with chronically abnormal serum transaminases. Overall prevalence of cirrhosis was 24% (range 2% to 72%). Reported mean age ranged from 33 to 59 years. The proportion of males ranged from 13% to 100%.

Two authors independently selection studies for the review; disagreements were resolved through discussion or by a third reviewer.

Assessment of study quality
Study quality was assessed by two independent reviewers who used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. Only studies that met GRADE levels of 1 to 3 were included in the review. Disagreements were resolved through discussion or by a third reviewer.

Data extraction
Data were extracted by two independent reviewers in order to construct 2x2 tables of test performance from which sensitivity, specificity and positive/negative likelihood ratios (LR+/−) with 95% confidence intervals (CI) were calculated. Disagreements were resolved through discussion or by a third reviewer.

Methods of synthesis
Summary estimates with 95% confidence intervals were calculated using a univariate random-effects model where three studies assessed the same outcome or (where possible) a bivariate random-effects model where four or more studies were available. Heterogeneity was assessed using $I^2$. A positive likelihood ratio more than 4.0 and a negative likelihood ratio of less than 0.4 were used as thresholds to identify the most useful positive and pertinent negative findings. Subgroup analyses were conducted to investigate the impact of study quality and the aetiology of the liver disease on prevalence.
Results of the review

Eighty-eight studies met the inclusion and quality criteria and these studies included 19,415 participants (figure calculated from the table) (range 35 to 1,252). Forty-one of the 86 diagnostic accuracy studies were retrospective. Twenty-six studies were GRADE level 1, nine were GRADE level 2 and 51 were GRADE level 3.

The physician's overall clinical impression of cirrhosis was associated with a positive likelihood ratio of 4.8 (95% CI 2.5 to 7.2, I²=57%; seven studies). Clinical signs and symptoms considered useful for identifying liver disease were: presence of diabetes (LR+ 2.8, 95% CI 1.5 to 4.0, I²=66%; eight studies), distended abdominal veins (LR+ 11, 95% CI 2.7 to 44, I²=78%; four studies), encephalopathy (LR+ 10, 95% CI 1.5 to 77, I²=74%; five studies), ascites (LR+ 7.2, 95% CI 2.9 to 12, I²=46%; 11 studies), spider nevi (LR+ 4.3, 95% CI 2.4 to 6.2, I²=78%; 13 studies), lack of a firm liver (LR- 0.37, 95% CI 0.31 to 0.43; I²=0%; four studies) and hepatomegaly (LR- 0.37, 95% CI 0.24 to 0.51; I²=81%; 10 studies). Peripheral oedema, jaundice, splenomegaly and a firm liver may also have had some diagnostic utility.

Presence of thrombocytopenia was considered the most useful laboratory investigation. A platelet count threshold of less than 160x103/μL had the highest diagnostic accuracy and precision (LR+ 6.3, 95% CI 4.3 to 8.3, I²=90% and LR- 0.29, 95% CI 0.20 to 0.39, I²=81%; 19 studies). Other laboratory tests with diagnostic utility included prolonged prothrombin time/international normalised ratio (LR+ 5.0, 95% CI 3.2 to 6.9, I²=82%; 12 studies) and a serum albumin less than 3.5g/dL (LR+ 4.4, 95% CI 1.5 to 7.3, I²=57%; eight studies).

Results for a wide range of other signs, symptoms, tests and scoring indices, and results of subgroup analyses on prevalence data were reported.

Authors' conclusions

For identifying cirrhosis, presence of a variety of clinical findings or abnormalities in a combination of simple laboratory tests that reflect the underlying pathophysiology increase its likelihood. To exclude cirrhosis, combinations of normal laboratory findings are most useful.

CRD commentary

The review addressed a clear review question supported by well-defined inclusion criteria. Relevant sources were searched, but the search was restricted to the published literature and publication could not be ruled out. Each stage of the review was conducted in duplicate. Study quality was assessed using appropriate criteria and the results were taken into account in the analysis. Most of the studies included in the review were retrospective and GRADE Level 3.

Methods of synthesis were appropriate, although several meta-analyses were subject to substantial heterogeneity and this was not fully investigated. The authors chose cut-offs for diagnostic utility (LR+ of 4 and LR- of 0.4) that were lower than the cut-offs used typically (LR+ >10 and LR- <0.2). Positive likelihood ratios were below 5.0 for most variables considered to have diagnostic utility. This limited the ability to conclude that there was a significantly increased probability of having the disease. The negative likelihood ratio was less than 0.2 for only a single test (Lok index probability ≥0.2). This limited the ability to rule out the disease. The populations in the included studies may not have fully reflected those seen in clinical practice; the authors acknowledged that generalisability of the results to patients with persistently normal enzymes, physical findings in the absence of suspected liver disease and acute liver injury was uncertain.

This was a generally well-conducted review and the conclusions reflect the evidence presented, but the associations with cirrhosis for many of the tests were not sufficiently strong to confidently conclude the presence or absence of disease.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that future research should target constructing and validating clinical algorithms that combine elements of the history, physical examination, laboratory tests, non-invasive markers and medical imaging. Prospective clinical trials were required to investigate whether patients received clinical benefit from biopsies driven by the overall clinical impression compared with those obtained once a prediction model exceeded a defined threshold.

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