

Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Udell JA. et al. (2012) Does this patient with liver disease have cirrhosis? <i>JAMA</i> , 307(8):832-842			
Date of Review:	April 4, 2015			
Reviewer(s):	Christine Hu			
Part A				
Category:	Basic Science <input type="checkbox"/> Clinical Science <input type="checkbox"/> Public Health/Epidemiology <input type="checkbox"/> Social Science <input type="checkbox"/> Programmatic Review <input checked="" type="checkbox"/>			
Best Practice/Intervention:	Focus: Hepatitis C <input type="checkbox"/> Hepatitis C/HIV <input type="checkbox"/> Other: cirrhosis _____ Level: Group <input checked="" type="checkbox"/> Individual <input type="checkbox"/> Other: _____ Target Population: <u>patients with liver disease or suspected liver disease</u> Setting: Health care setting/Clinic <input checked="" type="checkbox"/> Home <input type="checkbox"/> Other: _____ Country of Origin: <u>United States</u> Language: English <input checked="" type="checkbox"/> French <input type="checkbox"/> Other: _____			
Part B				
	YES	NO	N/A	COMMENTS
<i>Is the best practice/intervention a meta-analysis or primary research?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Meta-analysis; systematic review to identify useful symptoms, signs, and routine laboratory investigations for detecting cirrhosis in patients with liver disease or suspected liver disease.
<i>Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Data was not used for decision-making
<i>Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Limitation of meta-analysis: - Majority of patients included in the study have chronically abnormal serum transaminases

				possibly due to lack of utility of blood tests for ALT and bilirubin. - Results may not be generalizable to patients with persistently normal enzyme levels
<i>Are the best practices/methodology/results described applicable in developed countries?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Similar analysis can be done using the same inclusion criteria.
	YES	NO	N/A	COMMENTS
<i>Are the best practices/methodology/results described applicable in developing countries?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>The research study/tool/data dictionary is easily accessed/available electronically</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Journal subscription required for download at http://jama.jamanetwork.com/
<i>Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? Please go to Comments section</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>How is the research study/tool funded? Please got to Comments section</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The study was funded by a Canadian Association of Gastroenterology-Axcan Pharma Inc Resident Research Grant awarded to Dr Wang.
<i>Is the best practice/intervention dependent on external funds?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Other relevant criteria:</i> _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
<i>Are these data regularly collected?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Searched literature published from 1966 to December 2011 in MEDLINE, and from 1974 to December 2011 in EMBASE

<i>Are these data regularly collected at and/or below a national level?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Are these data collected manually or electronically?</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Electronically: searched Medline and EMBASE
RESEARCH REPORTS				
<i>Has this research been published in a juried journal?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>JAMA</i>
<i>Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Utilize existing data: 86 articles included in meta-analysis

Does This Patient With Liver Disease Have Cirrhosis?

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CLINICAL SCENARIOS

Case 1

A 50-year-old man is referred for evaluation of fatigue, weakness, and abdominal swelling that has been present for 3 months. He has no other symptoms, and his medical history is unremarkable. Physical examination reveals palmar erythema, 5 spider nevi on his chest wall, moderate amount of ascites, multiple distended abdominal wall veins draining away from the umbilicus, and peripheral edema. Laboratory tests show a platelet count of $90 \times 10^3/\mu\text{L}$, aspartate aminotransferase (AST) of 85 U/L (upper limit of normal [ULN], 30 U/L), alanine aminotransferase (ALT) of 35 U/L (ULN, 30 U/L), prothrombin international normalized ratio (INR) of 1.6, and an albumin level of 2.5 g/dL.

Case 2

A 50-year-old woman with hepatitis C virus infection diagnosed 1 year ago is referred for consideration of therapy. She has a history of diabetes mellitus

Context Among adult patients with liver disease, the ability to identify those most likely to have cirrhosis noninvasively is challenging.

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

Data Sources We searched MEDLINE and EMBASE (1966 to December 2011) and reference lists from retrieved articles, previous reviews, and physical examination textbooks.

Study Selection We retained 86 studies of adequate quality that evaluated the accuracy of clinical findings for identifying histologically proven cirrhosis.

Data Extraction Two authors independently abstracted data (sensitivity, specificity, and likelihood ratios [LRs]) and assessed methodological quality. Random-effects meta-analyses were used to calculate summary LRs across studies.

Results Among the 86 studies, 19 533 patients were included in this meta-analysis, among whom 4725 had biopsy-proven cirrhosis (prevalence rate, 24%; 95% CI, 20%-28%). Many physical examination and simple laboratory tests increase the likelihood of cirrhosis, though the presence of ascites (LR, 7.2; 95% CI, 2.9-12), a platelet count $<160 \times 10^3/\mu\text{L}$ (LR, 6.3; 95% CI, 4.3-8.3), spider nevi (LR, 4.3; 95% CI 2.4-6.2), or a combination of simple laboratory tests with the Bonacini cirrhosis discriminant score >7 (LR, 9.4; 95% CI, 2.6-37) are the most frequently studied, reliable, and informative results. For lowering the likelihood of cirrhosis, the most useful findings are a Lok index <0.2 (a score created from the platelet count, serum aspartate aminotransferase and alanine aminotransferase, and prothrombin international normalized ratio; LR, 0.09; 95% CI, 0.03-0.31); a platelet count $\geq 160 \times 10^3/\mu\text{L}$ (LR, 0.29; 95% CI, 0.20-0.39); or the absence of hepatomegaly (LR, 0.37; 95% CI, 0.24-0.51). The overall impression of the clinician was not as informative as the individual findings or laboratory combinations.

Conclusions For identifying cirrhosis, the 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.

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but is otherwise healthy with no symptoms. Physical examination reveals 5 spider nevi on her chest wall but no other abnormalities. Blood tests show a platelet count of $210 \times 10^3/\mu\text{L}$, AST of 89 U/L, ALT of 82 U/L, normal INR, and a normal albumin level.

mation of regenerative nodules.¹ In the United States, cirrhosis is the 10th leading cause of death overall,² with mortality rates of approximately 9.3 per 100 000 persons.³ Compared with patients with less severe histological injury (eg, precirrhotic stages of fibro-

WHY IS THIS QUESTION IMPORTANT?

Cirrhosis, the pathologic end result of many types of chronic liver injury, is characterized histologically by extensive fibrosis in association with the for-

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See also Patient Page.

 CME available online at www.jamaarchivescme.com and questions on p 868.

sis), patients with cirrhosis are at higher risk of morbidity and mortality.⁴⁻⁸ Patients with cirrhosis may need endoscopic screening and therapy for gastroesophageal varices,⁹ screening for hepatocellular carcinoma,¹⁰ prompt recognition, and therapy for hepatic encephalopathy and spontaneous bacterial peritonitis^{11,12} and consideration for liver transplant.¹³

Patients with chronic liver disease are often first identified by abnormal liver enzyme (aminotransferases [also known as transaminases]) or function test results (prothrombin time /INR [PT/INR], bilirubin, and albumin). The prevalence of serum aminotransferase elevation in the United States is approximately 7.9%,² and approximately 10% to 17% of patients with unexplained aminotransferase elevation have previously unsuspected cirrhosis.^{2,14} Liver biopsy is the best tool to stage liver disease and diagnose cirrhosis¹⁵; however, it is costly (estimated at US \$1000 per liver biopsy),¹⁶ associated with potential morbidity including excessive bleeding,¹⁷ and has a small risk of mortality (up to 0.5%).^{18,19} Moreover, there are inherent errors associated with the use of a liver biopsy, including sampling error, with discordant results when sampling each lobe of the liver in up to a third of cases in some cohorts, and interobserver variability in the estimation of fibrosis.^{20,21}

Clinicians need to be able to accurately and efficiently recognize cirrhosis non-invasively due to the high prevalence of abnormal liver tests, significant cost and consequences associated with cirrhosis, questionable feasibility, and potential complications of performing liver biopsies on a large group of patients and potential influence on treatment modalities that need adjustment in the presence of cirrhosis.^{2,9,22} Therefore, the purpose of this review is to identify useful symptoms, signs, and routine laboratory investigations for detecting cirrhosis in patients with known or suspected liver disease.

PATHOPHYSIOLOGY OF CIRRHOSIS AND ITS MANIFESTATIONS

Clinical features of cirrhosis result from morphologic alterations that disturb he-

Figure 1. Spider Nevi Lesions on the Upper Chest



patic function.¹ Palmar erythema, spider nevi, gynecomastia, decreased body hair, and testicular atrophy are thought to result from decreased hepatic metabolism and clearance of androstenedione, allowing increased peripheral conversion to estrogen.²³ Loss of functioning hepatocellular mass leads to jaundice and hypoalbuminemia.²⁴ Thrombocytopenia may result from hypersplenism or direct bone marrow suppression. Liver production of coagulation factors I, II, V, VII, IX, and X is reduced in chronic liver disease. Factors II, VII, IX, and X are further reduced by vitamin K deficiency due to cholestasis.²⁵ Prothrombin time can be selectively elevated because factor VII is the first factor to be depleted in cirrhosis due to its short half-life.²⁶ Gastroesophageal varices and splenomegaly are sequelae of portal hypertension, which is defined as an increase in portal venous pressure gradient above 10 mm Hg.²⁷ Edema, ascites, and hepatic encephalopathy result from both hepatocellular insufficiency and portal hypertension.²⁸⁻³⁰

HOW TO ELICIT SYMPTOMS AND SIGNS

Appropriate methods for obtaining a history and performing a physical examination of the liver³¹ and spleen,³² along with the detection of ascites³³ and clubbing³⁴ have been described in previous Rational Clinical Examination publications.

Jaundice is a yellow discoloration resulting from tissue deposition of biliary pigments. It is best detected by examining the sclera under natural light or examining the mucous membranes below the tongue.³⁵ The presence of

scleral icterus can usually be appreciated when the bilirubin level is above 2.5 to 3 mg/dL (to convert to micromoles per liter, multiply by 17.104).³⁵

White nails (Terry nails) describe a silver-white pallor of the proximal nail bed that sometimes obscures the nail lunula.^{36,37} As severity of the sign progresses, the entire nail plate can be colored white with only a narrow 0.5- to 3-mm normal pink-colored distal band.^{36,37} The thumb and index finger are most commonly involved.³⁷ Palmar erythema refers to an intense reddening involving the thenar and hypothenar eminences sparing the center of the palm.³⁸ The color blanches on pressure and returns rapidly on release. When a glass slide is pressed onto the palm, it can flush with each arterial pulse.³⁹

Gynecomastia is the enlargement of the male breast. It is important to distinguish true breast tissue enlargement from adipose tissue enlargement (lipomastia). True breast glandular tissue is often palpable, especially around the areola, and is firmer and contains cordlike features that are distinct from the softer texture of adipose tissue.⁴⁰

Spider nevi are arterial lesions consisting of a central arteriole with numerous small radiating vessels that resemble a spider's legs (FIGURE 1).⁴¹ Pressure on the central arteriole causes blanching of the entire lesion, which fills from the center outward. Occasionally, central pulsation can be seen or felt, an effect that is enhanced by gentle pressure over the central arteriole with a glass slide. Spider nevi are usually found in the vascular territory

of the superior vena cava.^{41,42} Although no specific cutoff is pathologic, more than 2 or 3 spider nevi is likely to be abnormal.⁴³ Similarly, facial telangiectasia refer to dilated superficial capillary blood vessels on the cheeks, nose, forehead, and neck.⁴⁴

When prominent or distended abdominal wall veins are seen, the direction of blood flow should be determined both cranial and caudal to the umbilicus (FIGURE 2). To determine the direction of flow, a finger is used to occlude the vein, and a second finger is used to empty the blood below the occluding finger. The second finger is then removed. If the vein refills, then the direction of flow is toward the occluding finger. If the vein does not refill, the process is repeated but with the occluding finger being removed to confirm blood flow toward the second finger.⁴³ In portal hypertension, the direction of blood flow is away from the umbilicus. This is differentiated from inferior vena caval obstruction, in which the collateral veins (above and below the umbilicus) all flow cranial toward the superior vena cava; while in superior vena caval obstruction, the collateral veins all flow caudal toward

the inferior vena cava.⁴³ The important pathophysiologic distinction emphasizes why this maneuver should be repeated both cranial and caudal to the umbilicus for it to be of practical use.

The severity of hepatic encephalopathy ranges from an altered sleep pattern to coma.²⁹ Asterixis is a typical feature and is characterized by sudden brief lapses of voluntary sustained muscle contraction and is not present at rest.⁴⁵ It is best elicited by having the patient extend the arms and dorsiflex the wrist, with fingers extended and abducted, and with eyes closed for 30 seconds or more.⁴⁵ Sudden involuntary flexion-extension movements of the wrist and metacarpophalangeal joints, often accompanied by lateral movements of the fingers, followed by rapid correction to the original position is a positive finding.⁴⁵

METHODS

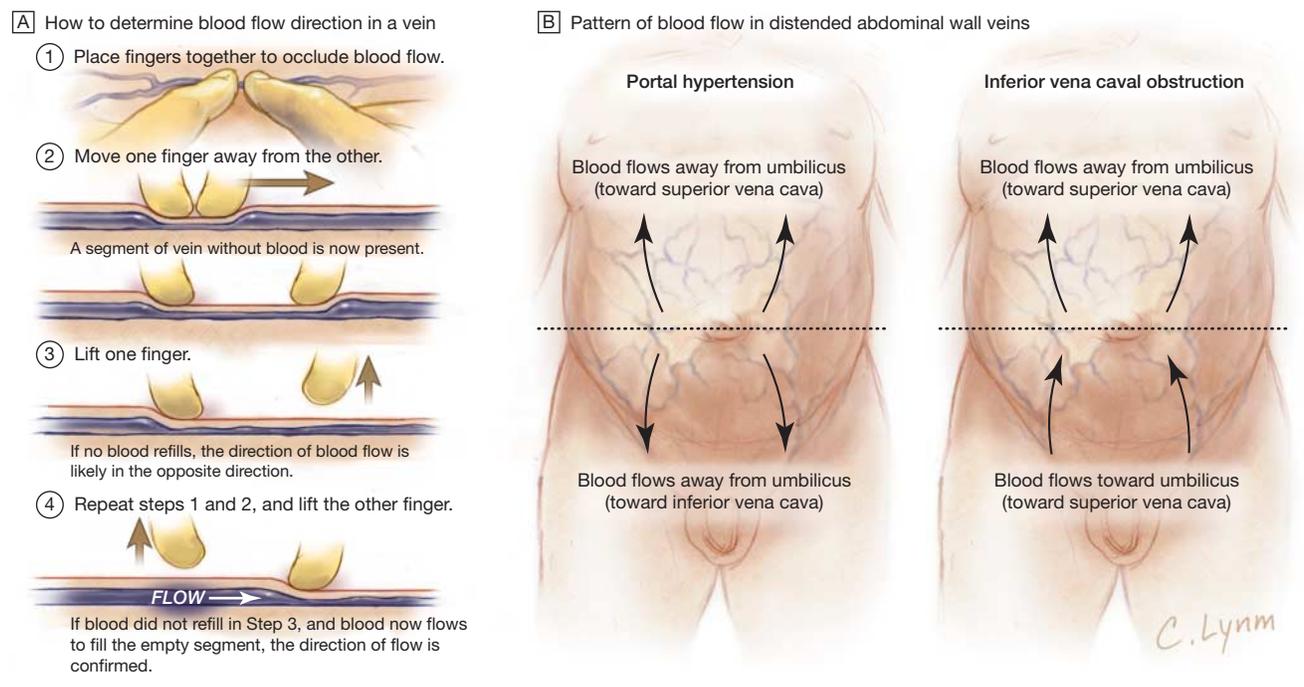
Search Strategy and Study Selection

We searched MEDLINE (from 1966 to December 2011) and EMBASE (from 1974 to December 2011) for articles on the reliability and diagnostic accuracy of components of the clinical examination

and routine investigations for detecting cirrhosis in patients with liver disease. Our strategy was deliberately broad to minimize the possibility of overlooking relevant articles. The search was conducted using a similar strategy developed for the Rational Clinical Examination series (eMethods available at <http://www.jama.com>).⁴⁶ We included studies that evaluated the reliability or likelihood ratios (LRs) of some element of the medical history, physical examination, or routine laboratory tests (defined a priori as complete blood cell count, electrolytes, urea, creatinine, AST, ALT, alkaline phosphatase, γ -glutamyl transpeptidase, PT/INR, bilirubin, albumin, glucose, cholesterol, and triglyceride levels for detecting cirrhosis in adult patients with known or suspected liver disease of any etiology. These commonly ordered laboratory tests must be interpreted within the clinical context to assess whether the patient might have cirrhosis.

Studies of scoring models were included, provided the items comprising the scoring system were derived only from the medical history, physical examination, and routine laboratory tests

Figure 2. Direction of Blood Flow in Distended Abdominal Wall Veins



(as set out above). In these studies, only data from the validation cohort (and not derivation cohort) were used. In articles in which a specific cutoff value for a prediction model was not validated in more than 1 study, we did not include the result because it could not be meta-analyzed. Complicated specialized serum marker formulas not routinely available and diagnostic imaging, including elastography, were beyond the scope of this review.⁴⁷ We required that studies include a histological examination of liver tissue using published classification schemes as the reference standard for the diagnosis of cirrhosis.^{48,49}

We excluded studies that (1) enrolled patients younger than 18 years or those with previous liver transplant; (2) did not use histology as the gold standard for the diagnosis of cirrhosis; (3) had no clinical examination performed or reported; (4) only used medical imaging to detect cirrhosis; (5) used specialized serum markers,⁵⁰ radio-labeled breath tests of hepatic function, protein chips, or artificial neural networks to detect cirrhosis; (6) derived scoring models from these specialized tests to detect cirrhosis; (7) were population based (eg, included patients not suspected to have, or without known, liver disease); or (8) were review articles with no original data. Abstracts from conference proceedings

were also excluded due to the wide variation in design, lack of peer review, and inability to review study quality.

Two authors (J.A.U. and C.S.W.) screened the titles and abstracts of the computerized search to identify all potentially relevant articles and assessed their quality based on the grading scheme used in the series⁵¹ (see eMethods for further details available at <http://www.jama.com>).

Statistical Methods

For reliability studies, we report the percent agreement, κ statistic, or both for each variable. We used mixed effects for prevalence and comparison of prevalence across groups (Comprehensive Meta-Analysis version 2, Biostat Inc).⁵² Published raw data were used to construct 2×2 contingency tables for each clinical variable. When multiple publications from the same group were found, the studies were carefully reviewed to ensure no data were analyzed in duplicate. From these 2×2 tables we confirmed the sensitivity, specificity, and diagnostic accuracy of the findings expressed as LRs. When the finding was evaluated in only 1 study, we report the point estimate and its confidence interval, the range for findings evaluated in only 2 studies, and univariate random-effects summary measures for findings evalu-

ated in only 3 studies.⁵² We attempted to fit bivariate random-effects summary measures for findings evaluated in 4 or more studies.^{53,54} When a bivariate solution did not converge, we used the univariate random-effect summary estimates. Only studies of sufficient quality (levels 1 to 3) were considered for the quantitative analysis. Heterogeneity was described with the I^2 parameter and associated P value for findings evaluated in 3 or more studies. Thresholds of a positive LR of more than 4.0 and a negative LR of less than 0.4 were empirically selected to focus clinicians on the most useful positive and pertinent negative findings related to liver cirrhosis.

RESULTS

Search Results

Of 6188 citations, 5727 were excluded after review of their titles and abstracts, leaving 461 studies. These remaining studies were reviewed in detail and a total of 91 met eligibility criteria (88 accuracy studies and 3 reliability studies of the clinical examination for cirrhosis; see eFigure). Of the 88 accuracy studies meeting inclusion criteria, 86 were included in the meta-analysis.⁵⁵⁻¹³⁴ Because 2 studies were graded as level 4, they were not included in the evidence tables (eTable 1).^{135,136}

Table 1. Summary Measures for the Diagnostic Accuracy of the Medical History for Detecting Cirrhosis

Finding	Source	No. of Studies	Total No. of Patients	Patients With Cirrhosis	Sensitivity	Specificity	Positive LR (95% CI)	I^2 , %	P Value	Negative LR (95% CI)	I^2 , %	P Value
Past history												
Diabetes mellitus ^a	56, 66, 84, 87, 92, 104, 110, 115	8	1518	379	0.34	0.88	2.8 (1.5-4.0)	66	.005	0.75 (0.58-0.91)	59	.02
Minor nose or gum bleeding	110	1	277	150	0.25	0.84	1.6 (0.99-2.6)			0.89 (0.79-1.0)		
Alcohol use	55, 58, 59, 62, 63, 70, 92, 94, 110, 116	10	2457	703	0.47	0.66	1.5 (1.0-2.0)	46	.05	0.76 (0.52-1.0)	67	.001
Upper GI tract bleed	59, 94	2	340	72	0.22-0.65	0.07-0.84	0.70-1.4			0.92-4.9		
Symptoms												
Fatigue ^b	59, 62, 63	3	438	69	0.63	0.51	1.3 (1.1-1.6)	0	.71	0.80 (0.53-1.2)	35	.21
Weakness	86, 110	2	377	205	0.40-0.80	0.31-0.64	1.1-1.2			0.64-0.94		
Pruritus	58, 59	2	364	79	0.14-0.23	0.65-0.93	0.69-2.0			0.92-1.2		
Anorexia	58, 59	2	364	79	0.37-0.43	0.23-0.68	0.56-1.2			0.93-2.5		

Abbreviations: Blank cell, not applicable because the finding comes from only 1 or 2 studies; GI, gastrointestinal; LR, likelihood ratio.

^aBivariate random-effects summary measures.

^bUnivariate random-effects summary measures.

Prevalence of Cirrhosis

All the studies included patients with known or suspected liver disease (eTable 1 available at <http://www.jama.com>). The summary prevalence of cirrhosis was 24% (95% CI, 20%-28%; n=86 studies; n=4725 patients with biopsy-documented cirrhosis). There was no significant difference in prevalence across study quality levels ($P=.26$; eTable 2). Once the underlying etiology of liver disease is known, the cause-specific prevalence should be used for estimating the pretest probability of cirrhosis because of heterogeneity across etiology ($P<.001$; range of prevalence grouped by etiology, 9%-39%). The most frequently studied liver disease was hepatitis C (summary prevalence 19% [15%-23%; n=43

studies]). Despite the narrow confidence interval around prevalence of cirrhosis in hepatitis C, statistical heterogeneity ($I^2=95%$, $P<.001$) suggests that sociodemographic and clinical factors within study populations might affect the prevalence.^{113,137}

Reliability of the Clinical Examination

Precision of the examination for a firm liver edge, splenomegaly, and ascites is considered good (the interobserver agreement κ statistic ranges from 0.50-0.75), whereas it is only fair for clubbing ($\kappa=0.36-0.45$).³¹⁻³⁴ Three additional studies were identified that reported the reliability of the clinical examination for cirrhosis. Spider nevi, facial telangiectasia, jaundice, and pal-

mar erythema had good interobserver agreement (eTable 3).^{80,138,139}

Accuracy of the History and Physical Examination

Risk Factors and Symptoms. Diabetes increases the likelihood of cirrhosis (LR, 2.8; 95% CI, 1.5-4.0), whereas the absence of diabetes has almost no effect (LR, 0.75; 95% CI, 0.58-0.91). A history of alcohol use was not useful. Despite variability in defining alcohol use across 10 studies, the results were consistent with relatively narrow confidence intervals (95% CI, 1.0-2.0). All other historical features and symptoms had LR confidence intervals that included 1 for both the positive and negative LRs (TABLE 1 and TABLE 2).

Table 2. Summary Measures for the Diagnostic Accuracy of the Physical Examination for Detecting Cirrhosis

Finding	Source	No. of Studies	Total No. of Patients	No. of Patients With Cirrhosis	Sensitivity	Specificity	Positive LR (95% CI)	I^2 , %	P Value	Negative LR (95% CI)	I^2 , %	P Value
Terry nails	59, 80	2	912	130	0.43-0.44	0.97-0.98	16-22			0.57-0.58		
Gynecomastia	59, 80	2	912	130	0.18-0.58	0.97-0.98	5.8-35			0.43-0.84		
Distended abdominal veins ^a	58, 59, 80, 86	4	1208	215	0.31	0.98	11 (2.7-44)	78	.003	0.72 (0.57-0.91)	83	.001
Encephalopathy ^b	59, 60, 82, 83, 95	5	622	160	0.16	0.98	10 (1.5-77)	74	.004	0.86 (0.76-0.95)	50	.09
Decreased body hair ^a	58, 59, 80	3	973	160	0.36	0.97	9.0 (6.4-13)	0	.78	0.65 (0.51-0.84)	76	.02
Ascites ^b	57-61, 79, 82, 83, 86, 94, 95	11	1198	450	0.35	0.95	7.2 (2.9-12)	46	.05	0.69 (0.59-0.78)	65	.001
Facial telangiectasia	59, 80	2	912	130	0.73-0.82	0.88-0.92	5.9-10			0.20-0.31		
Testicular atrophy	59	1	303	49	0.18	0.97	5.8 (2.4-14)			0.84 (0.74-0.96)		
Palmar erythema ^b	55, 58, 59, 63, 80, 83, 86	7	1795	536	0.46	0.91	5.0 (0.80-9.1)	94	<.001	0.59 (0.39-0.79)	90	<.001
Spider nevi ^a	55, 57-60, 62-64, 79, 82, 83, 86, 106	13	1821	694	0.46	0.89	4.3 (2.4-6.2)	78	<.001	0.61 (0.54-0.68)	31	.14
Jaundice ^a	57, 59, 61, 79, 80	5	1425	312	0.28	0.93	3.8 (2.0-7.2)	73	.005	0.82 (0.77-0.88)	0	.53
Splenomegaly ^b	55, 57, 58, 60-62, 64, 79, 82-84, 86, 110	13	1707	819	0.34	0.90	3.5 (1.8-5.2)	73	<.001	0.74 (0.61-0.86)	81	<.001
Firm liver ^a	55, 62, 102, 110	4	849	461	0.73	0.81	3.3 (2.3-4.7)	57	.07	0.37 (0.31-0.43)	0	.46
Peripheral edema ^a	57, 59, 86	3	455	131	0.37	0.90	3.0 (1.9-4.8)	0	.45	0.71 (0.56-0.91)	62	.07
Hepatomegaly ^b	55, 57-59, 62, 64, 79, 82, 86, 110	10	1558	674	0.74	0.69	2.4 (1.2-3.6)	89	<.001	0.37 (0.24-0.51)	81	<.001
Obesity ^a	84, 104, 115	3	241	41	0.64	0.52	1.3 (1.1-1.6)	0	.77	0.76 (0.49-1.2)	0	.45

Abbreviations: Blank cell, not applicable because the finding comes from only 1 or 2 studies; LR, likelihood ratio.

^aUnivariate random-effects summary measures because data did not converge on a bivariate solution.

^bBivariate random-effects summary measures.

Signs. The presence of distended abdominal veins (LR, 11; 95% CI, 2.7-44; Figure 2); encephalopathy (LR, 10; 95% CI, 1.5-77), ascites (LR, 7.2; 95% CI, 2.9-12), and spider nevi (LR, 4.3; 95% CI, 2.4-6.2) were the most frequently studied findings with positive LRs of more than 4.0. Of these, ascites ($I^2=46%$) and spider nevi ($I^2=78%$) may be the most reliable because they had the narrowest confidence intervals. The presence of peripheral edema, jaundice, splenomegaly, and a firm liver were reported in at least 3 studies, and they had positive LRs of 3.0 to 4.0 with confidence intervals that did not cross unity.

The absence of findings was not as efficient for lowering the likelihood of cirrhosis among patients with liver disease. The lack of a firm liver (LR, 0.37; 95% CI, 0.31-0.43; $I^2=0%$) or hepatomegaly (LR, 0.37; 95% CI, 0.24-0.51; $I^2=81%$) were the only findings evaluated in more than 3 studies that had a negative LR of less than 0.40.

Accuracy of Routine Laboratory Investigations

The presence of thrombocytopenia was the single most useful laboratory investigation and performed similarly to the presence of ascites for identifying cirrhosis. A platelet count threshold of

less than $160 \times 10^3/\mu\text{L}$ had the highest diagnostic accuracy with narrow confidence intervals despite statistical heterogeneity (positive LR, 6.3; 95% CI, 4.3-8.3; negative LR, 0.29; 95% CI 0.20-0.39). A prolonged prothrombin time or INR (LR, 5.0; 95% CI, 3.2-6.9), or a serum albumin less than 3.5 g/dL (LR, 4.4; 95% CI, 1.5-7.3) were the other findings evaluated in several studies with a summary positive LR of more than 4.0 (TABLE 3). An increased ALT or bilirubin was not useful because their confidence intervals included unity. No other single laboratory finding had a negative LR that was substantially lower (range of negative LR, 0.28-1.3) than

Table 3. Summary Measures for the Diagnostic Accuracy of Routine Laboratory Investigations for Detecting Cirrhosis

Finding	Source	No. of Studies	Total No. of Patients	No. of Patients With Cirrhosis	Sensitivity	Specificity	Positive LR (95% CI)	I^2 , %	P Value	Negative LR (95% CI)	I^2 , %	P Value
Thrombocytopenia, platelet count, $\times 10^3/\mu\text{L}$												
<110 ^a	55, 60, 61, 85, 112, 113, 140	7	2533	1137	0.50	0.95	9.8 (2.6-17)	87	<.001	0.53 (0.35-0.71)	90	<.001
<160 ^a	62, 65, 81, 96-99, 105-107, 110, 113, 115, 117, 119, 124, 126, 141	19	6670	1394	0.74	0.88	6.3 (4.3-8.3)	90	<.001	0.29 (0.20-0.39)	81	<.001
<200 ^a	66, 67, 72, 78, 84, 113	6	2154	697	0.80	0.72	2.9 (1.7-4.1)	95	<.001	0.28 (0.07-0.48)	86	<.001
Prolonged PT/INR ^a	55, 60-63, 76-78, 81, 113, 117, 124	12	3418	1392	0.48	0.90	5.0 (3.2-6.9)	82	<.001	0.57 (0.39-0.75)	95	<.001
Albumin <3.5 g/dL ^a	55, 58, 60, 62, 81, 86, 103, 108	8	961	499	0.45	0.90	4.4 (1.5-7.3)	57	.02	0.61 (0.41-0.81)	79	<.001
AST>2 \times ULN	72	1	179	20	0.65	0.80	3.2 (2.1-5.0)			0.44 (0.24-0.80)		
GGT >300 U/L	86	1	100	55	0.49	0.82	2.8 (1.4-5.5)			0.62 (0.46-0.83)		
Bilirubin >1.2 mg/dL ^a	58, 62, 81, 86, 140	5	486	166	0.43	0.84	2.7 (0.85-7.9)	89	.001	0.69 (0.35-1.1)	83	<.001
WBC <4 $\times 10^3/\mu\text{L}$	62, 81, 86	3	268	115	0.25	0.90	2.5 (0.72-8.7)	41	.18	0.90 (0.83-0.98)	0	.80
AST>ULN ^b	56, 66, 103, 106, 108	5	605	184	0.78	0.62	2.1 (1.2-3.6)	91	<.001	0.38 (0.21-0.67)	67	.02
Hb <13 g/dL	60, 62, 81	3	269	99	0.45	0.80	1.9 (1.3-2.7)	0	.58	0.80 (0.62-1.0)	48	.15
ALT>ULN ^a	56, 71, 103, 108, 122, 128	6	1296	184	0.88	0.23	1.1 (0.99-1.3)	48	.08	0.54 (0.17-0.91)	46	.10
ALT>2 \times ULN	61	1	213	113	0.53	0.35	0.82 (0.65-1.0)			1.3 (0.96-1.9)		

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; blank cell, not applicable because the finding comes from only 1 or 2 studies; GGT, γ -glutamyl transpeptidase; Hb, hemoglobin; LR, likelihood ratio; PT/INR, prothrombin time/international normalized ratio; ULN, upper limit of normal; WBC, white blood cell.

SI conversion factor: To convert bilirubin from mg/dL to $\mu\text{mol/L}$, multiply by 17.104.

^aBivariate random-effects summary measures.

^bUnivariate random-effects summary measures because data did not converge on a bivariate solution.

the platelet count at a threshold of $160 \times 10^3/\mu\text{L}$.

Accuracy of Overall Clinical Impression and Combination Scoring Indices

The physician's overall clinical impression of cirrhosis was associated with a high positive LR (4.8; 95% CI, 2.5-7.2), whereas the impression that cir-

rhosis was absent decreased the likelihood by half (negative LR, 0.52; 95% CI, 0.33-0.71; TABLE 4).

No scoring indices that met eligibility included historical factors, symptoms, or signs together. The AST:ALT ratio (AAR) and the AST:platelet ratio index (APRI, FIGURE 3) have been the most extensively studied indices and are the easiest to calculate. An AST:ALT ra-

tio higher than 1 increases the likelihood of cirrhosis (LR, 4.6; 95% CI, 2.6-6.5) as does an APRI higher than 2 (LR, 4.6, 95% CI, 3.2-6.0). The Bonacini cirrhosis discriminant score (CDS) combines the ALT:AST ratio with the platelet count and INR into a discriminant function with possible total values between 0 and 11; higher values increase the likelihood of cirrhosis.⁹³ A

Table 4. Summary Measures for the Diagnostic Accuracy of the Overall Clinical Impression and Combination Indices or Models for Detecting Cirrhosis

Finding	Source	No. of Studies	Total No. of Patients	No. of Patients With Cirrhosis	Sensitivity	Specificity	Positive LR (95% CI)	<i>P</i>	<i>P</i> Value	Negative LR (95% CI)	<i>P</i>	<i>P</i> Value
Overall clinical impression	58, 62, 63, 86, 88, 101, 109	7	1061	223	0.54	0.89	4.8 (2.5-7.2)	57	.03	0.52 (0.33-0.71)	55	.04
Bonacini CDS ^a												
>8 ^b	63, 93, 117, 123, 132	5	613	113	0.25	0.98	13 (2.4-72)	75	.003	0.77 (0.57-0.90)	70	.01
>7 ^b	93, 96, 109, 117, 123, 132	6	906	170	0.39	0.96	9.4 (2.6-37)	53	.06	0.65 (0.44-0.82)	63	.018
>3 ^c	64, 96, 109, 117, 132	5	756	136	0.90	0.32	1.4 (1.2-1.6)	87	<.001	0.30 (0.18-0.50)	0	.66
Lok index ^a												
Probability $\geq 0.5^c$	98, 113, 124, 132	4	807	151	0.48	0.87	5.0 (1.6-16)	95	<.001	0.60 (0.52-0.69)	0	.51
Probability $\geq 0.2^b$	98, 113, 124, 141	4	907	157	0.94	0.61	2.4 (1.7-3.6)	90	.001	0.09 (0.03-0.31)	52	.10
AST:ALT > 1 ^b	73-75, 89, 91, 93, 96, 98-100, 105, 107, 111, 113, 117, 118, 120, 123, 124, 127, 131, 140	23	5998	1443	0.48	0.90	4.6 (2.6-6.5)	83	<.001	0.58 (0.49-0.68)	86	<.001
APRI ^a												
>2 ^b	70, 96, 98-100, 116, 117, 120, 121, 123-126, 128, 131	15	4052	589	0.44	0.90	4.6 (3.2-6.0)	73	<.001	0.62 (0.51-0.73)	79	<.001
>1 ^b	68, 70, 72, 96, 98, 100, 116, 117, 123, 124, 126-128, 142	14	2762	517	0.76	0.72	2.7 (2.3-3.2)	72	<.001	0.33 (0.23-0.43)	62	.001
GUCI index $\geq 1.0^d$	72, 131	2	289	42	0.23-0.80	0.78-0.91	2.5-3.6			0.26-0.85		
FIB-4 index ^e												
≥ 3.25	123, 126	2	375	69	0.28-0.40	0.88-0.91	2.2-4.3			0.66-0.83		
$\geq 1.9^e$	142, 143	2	317	52	0.69-0.74	0.75-0.89	2.8-6.5			0.29-0.41		

Abbreviations: APRI, AST:platelet ratio index; AST:ALT, aspartate aminotransferase:alanine aminotransferase ratio; blank cells, not applicable because the finding comes from only 1 or 2 studies; CDS, cirrhosis discriminant score; GUCI, Göteborg University Cirrhosis Index; LR, likelihood ratio.

^aSee Figure 3.

^bBivariate random effects summary measures.

^cUnivariate random effects summary measures because data did not converge on a bivariate solution.

^dThe GUCI index is a normalized multivariate logistic regression model= $\text{AST}:\text{AST}_{\text{ULN}} \times \text{INR} \times 100 / \text{platelet count} [\times 10^3/\mu\text{L}]$; higher values increase the likelihood of cirrhosis and lower values decrease the likelihood of cirrhosis.⁷²

^eFIB-4 index= $\text{Age} \times \text{AST} / \text{platelet count} [\times 10^3/\mu\text{L}] \times \text{ALT}_{\%}$; higher values increase the likelihood of cirrhosis and lower values decrease the likelihood of cirrhosis.¹⁴⁴

Bonacini CDS higher than 7 was the most frequently studied threshold (LR, 9.4; 95% CI, 2.6-37).

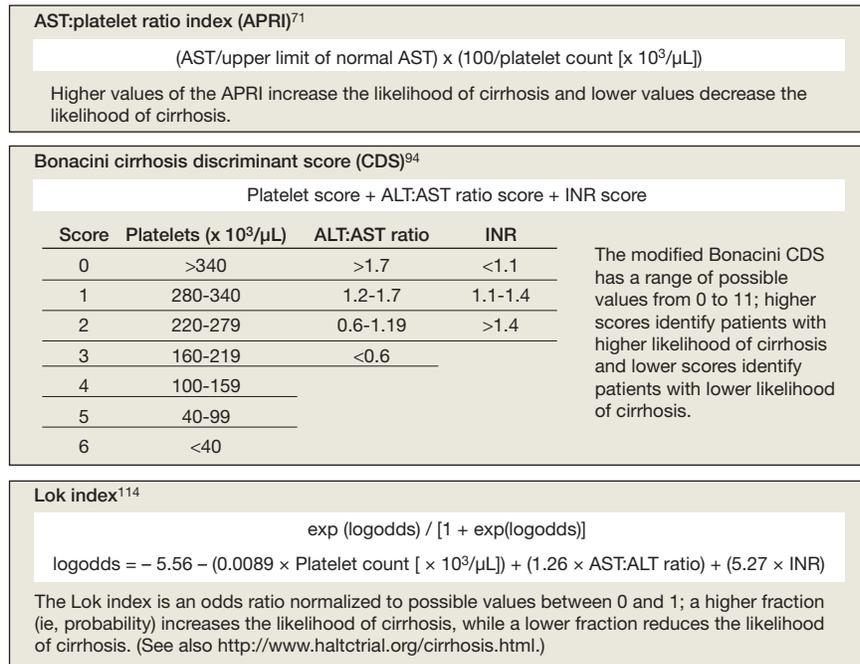
A Bonacini CDS of less than 3 makes cirrhosis less likely (negative LR, 0.30; 95% CI, 0.18-0.50). The Lok index, originally derived from the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial cohort,¹¹³ is an odds ratio normalized to probabilities between 0 and 1 that uses the same factors as the Bonacini CDS but estimates the probability of cirrhosis through a logistic model (Figure 3).¹¹³ An index less than 0.2 (which represents a probability of <20%) reduces the likelihood of cirrhosis (LR, 0.09; 95% CI, 0.03-0.31).

LIMITATIONS

Our data are derived from studies of patients who were referred for known or suspected chronic liver disease who underwent biopsy. The majority of studies included patients with chronically abnormal serum transaminases, perhaps accounting for the lack of utility of blood tests for ALT and bilirubin. Therefore, these results may not be generalizable to patients with persistently normal enzymes, those with physical findings in the absence of suspected liver disease, and those with acute liver injury. For physical examination findings that appear useful, we could not assess their independence, so we do not know if they retain their importance or are amplified when present in combination. However, the physician's overall clinical impression, which would have taken into account all the findings, performed better than some individual findings and not as well as others.

All of our candidate findings evaluated in 4 or more studies fit a bivariate random-effect solution, whereas findings evaluated less frequently were conservatively derived using univariate random-effects measures. However, many of the summary prevalence rates and likelihood ratios had significant heterogeneity, suggesting differences among results based on study characteristics. A potential explanation for this finding is there are true differences in the under-

Figure 3. Definition of the Aspartate Aminotransferase:Platelet Ratio Index, Bonacini Cirrhosis Discriminant Score, and Lok Index



AST indicates aspartate transaminase; ALT, alanine aminotransferase; INR, international normalized prothrombin ratio.

lying prevalence of cirrhosis across studies influencing the utility of diagnostic findings. More likely, detected heterogeneity may be a result of including studies conducted over the prior half-century, during which time potential differences in cirrhosis prevalence and risk factors, referral bias for a liver biopsy, and accuracy of pathology sampling may have occurred. Nevertheless, we found many LRs with robust magnitude and narrow confidence intervals that may aid in diagnostic decision making in the appropriate context.

There are inherent errors associated with the use of a liver biopsy as a gold standard including selection bias, sampling error, estimation of fibrosis, and inter-observer variability.²⁰ A biopsy specimen only samples an estimated 1/50 000th of the entire liver mass, which can result in an underestimation of the prevalence of cirrhosis. We did not include studies in which the outcome was advanced fibrosis because that definition would have been highly variable across studies. Despite the liver biopsy

being an imperfect test, it remains the primary tool and reference standard for staging liver fibrosis.^{20,145}

SCENARIO RESOLUTION

Case 1

Using the results from Tables 1 to 4, the patient has many features that raise the suspicion of cirrhosis, such as palmar erythema (LR, 5.0), spider nevi (LR, 4.3), ascites (LR, 7.2), distended abdominal veins (LR, 11), peripheral edema (LR, 3.0), thrombocytopenia (LR, 9.8), AST greater than 2 times ULN (LR, 3.2), elevated PT/INR (LR, 5.0), hypoalbuminemia (LR, 4.4), an AAR of 2.4 (LR, 4.6), an APRI of 3.1 (LR, 4.6), and Bonacini CDS of 10 (LR, 13). His complaints of fatigue and weakness do not contribute to the diagnosis but contextualize his duration of symptoms. Three months of symptoms suggest the abnormal serum transaminase results may be chronic and allows one to approximate a pretest probability of liver cirrhosis of 24% (95% CI, 20%-28%; eTable 2). Since the patient has ascites, the absence of hepato-

megaly or a firm liver (2 features that have good negative LRs for decreasing the suspicion of cirrhosis) cannot be assessed. The overall constellation of signs and laboratory tests are so suggestive that a liver biopsy is not required to confirm cirrhosis.

Case 2

This patient has a prior history of hepatitis C virus infection, which allows one to approximate a pretest probability of liver cirrhosis of 19% (95% CI, 15%-23%; eTable 2). Using the results from Tables 1 to 4, the absence of a firm liver (LR, 0.37), and hepatomegaly (LR, 0.37) on physical examination suggest the absence of cirrhosis. In addition, her platelet count is higher than $200 \times 10^3/\mu\text{L}$ (LR, 0.28), she has a normal PT/INR (LR, 0.57), and her albumin level is higher than 3.5 g/dL (LR, 0.61). Unfortunately, she also has some features that raise suspicion for cirrhosis, specifically a history of diabetes mellitus (LR, 2.8), spider nevi (LR, 4.3), and an AAR of 1.1 (LR, 4.6). She has a Bonacini CDS of 5 (LR, 1.4), Göteborg University Cirrhosis Index (GUCI) index of 1.4 (LR, 2.5-3.6), APRI of 1.4 (LR, 2.7), Lok index of 0.31 (LR, 2.4), and FIB-4 index of 2.3 (LR, 2.8-6.5). Given the diagnostic uncertainty, she may require a liver biopsy to assess for histological evidence of cirrhosis.

COMMENT

Our results expand on and update a previous review of the accuracy of physical signs for detecting cirrhosis.¹⁴⁶ For increasing the likelihood of cirrhosis, the best (ie, reported in multiple studies, robust LRs, narrow CIs) findings in each category were history of diabetes, ascites on physical examination, and a platelet count of less than $160 \times 10^3/\mu\text{L}$ on routine laboratory investigations. For decreasing the likelihood of cirrhosis, the best findings were absence of hepatomegaly or a firm liver on physical examination, and a platelet count of more than $160 \times 10^3/\mu\text{L}$ on routine laboratory investigations. In general, individual features were more powerful for identifying the presence

of cirrhosis rather than its absence. The history of alcohol use is a notable exception in not being useful, most likely because its use in the general population is common while the proportion that develops liver cirrhosis is very low.

The overall clinical impression of the clinician incorporating history, physical examination, and laboratory tests was also valuable. However, scoring indices such as the Bonacini CDS and Lok prediction models that combine simple laboratory tests, such as the platelet count, AST:ALT ratio, and INR may prove more useful than individual findings or unstructured clinical judgment, especially for identifying patients without cirrhosis. Constructing and validating clinical algorithms that combine elements of the history, physical examination, laboratory tests, non-invasive markers,⁴⁷ and medical imaging to improve diagnostic sensitivity and specificity is ongoing and should continue to be a target for future research. Prospective clinical trials are required to know whether patients receive clinical benefit from biopsies driven by the overall clinical impression vs those obtained once a prediction model exceeds a defined threshold.

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