Screening for Hepatitis C Virus Infection in Adults

Appendixes

Appendix A. Exact Search Strategy

The following databases have been searched for relevant information:

Database Searches: Hepatitis C: Screening/Diagnosis, Treatment, and Pregnancy

Name	Date Limits	Platform Provider
Medline	2002 to February Week 3 2011	OvidSP
Embase	2002-2011	Embase (Elsevier)
Cochrane Library: CDSR, DARE, CCRCT	2002-2011	Cochrane Library
Clinical Trials.gov	2002-2011	
Drugs@FDA	2002-2011	
Health Canada Drug Products Database	2002-2011	
European Public Assessment Reports (European Medicine Agency)	2002-2011	
Scopus	2002-2011	Scopus
PsycINFO	2002 to February Week 4 2011	OvidSP

Hand Search of Journals & Supplements - Topic-Specific Search Terms

Concept	Controlled Vocabulary	Keywords
Hepatitis C	Hepatitis C/ Hepatitis C, Chronic/ Hepacivirus/ OR	hcv.mp hepacivirus$.mp
Screening	Exp Mass screening/ Population surveillance/ Sentinel Surveillance/ Seroepidemiologic Studies/	((public$ or communit$ or universal$ or widespread or open$ or unrestricted or group$ or adult$) adj3 (screen$ OR test$ or surveillance)) (antibod$ ADJ3 (test$ or screen$ or surveillance))
Diagnosis	Hepatitis C/di, pa, ra, us Immunoenzyme Techniques/ Enzyme-Linked Immunosorbent Assay/ Immunoblotting/ Polymerase Chain Reaction/ Reverse Transcriptase Polymerase Chain Reaction/ Liver function tests/ (liver/ AND biopsy/) Breath Tests/ Diagnostic Imaging/ Magnetic Resonance Imaging/ EXP Tomography, X-ray Computed/ Alanine Transaminase/ "sensitivity and specificity"/	ELISA EIA recombinant immunoblot assay RIBA PCR RT-PCR transcription-mediated amplification TMA Branched-chain DNA bDNA radioimmunoblot assay HCV-RNA (liver$ ADJ3 biops$) Fibrosis non-invasive

	Limit of Detection/ ROC Curve/ Diagnostic errors/ False Negative Reactions/ False Positive Reactions/ Hepatitis C Antibodies/ Antibodies, viral/	blood test$ blood marker$ breath$ test$ transient elastography Fibrometer FibroTest Hepascore MRI alanine aminotransferase ALT misdiagnos$ CT-scan Ultrasound HCV Antibodies anti hcv anti-hcv
Treatment	Antiviral agents/ Interferons/ Interferon-alpha/ Interferon Alfa-2a/ Interferon Alpha-2b/ Exp Polyethylene Glycols/ Ribavirin/ Exp Protease Inhibitors/	Interferon$ interferon alpha-2a interferon alpha-2b IFNalpha2a IFNalpha2b interferon alpha 2a interferon alpha 2b pegasys Peg-intron peginterferon alpha-2a peginterferon alpha-2b peginterferon alpha 2a peginterferon alpha 2b pegylated interferon$ IFN$ PEG IFN$ Ribavirin RBV protease inhibitor$ polymerase inhibit$ HCV protease$ Telaprevir boceprevir
Harms - treatment	AE.fs MO.fs PO.fs TO.fs CT.fs AE=adverse effects CT=contraindications MO=mortality PO=poisoning TO=toxicity	Unsafe Safety harm$ complication$ poison$ risk$ side-effect$ side effect$ (undesirable ADJ1 effect$) (treatment ADJ1 emergent) tolerab$ toxic$ adrs (adverse ADJ2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)) (undesirable ADJ1 effect$) (treatment ADJ1 emergent) tolerab$ toxic$ adrs (adverse ADJ2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))

Harms - screening	AE.fs CT.fs AE=adverse effects CT=contraindications	Unsafe Safety Harm Harm complication$ risk$ side-effect$ (undesirable ADJ1 effect$) (treatment ADJ1 emergent) tolerab$ adrs (adverse ADJ2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)) Anxiety anxious$ label$ impact$
Pregnancy	Pregnancy/ Pregnancy Complications, Infectious/ Pregnancy Complications/ Exp Delivery, Obstetric/ Maternal Exposure/ Fetus/ Infant, Newborn/ Infant/ Prenatal Diagnosis/ Neonatal Screening/ Prenatal Care/ Infectious Disease Transmission, Vertical/ Milk, Human/ Breast Feeding/ Postpartum Period/	gravid$ pregnan$ prenatal perinatal antenatal parturiency partuition gestat$ childbirth child birth reproduct$ birth$ childbearing child-bearing
High Risk Groups	Substance-abuse, Intravenous/ Needle Sharing/ Opioid-Related Disorders/ Unsafe Sex/ Sexual Behavior/ HIV/ HIV Infections/	high risk high-risk drug$ abuse$
Counseling Immunizations	Counseling/ Sex Counseling/ Health Education/ Patient Education as Topic/ Psychotherapy/ Behavior Therapy/ Cognitive Therapy/ Immunization/ Immunotherapy/ Psychotherapy, Brief/ Socioenvironmental Therapy/	

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1947 to June Week 2 2011,

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations June 17, 2011

Date Searched: 06/20/2011

1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C.mp. or hepacivirus$.mp. or HCV.mp.	54983
2	Mass Screening/ or Population Surveillance/ or Sentinel Surveillance/ or Seroepidemiologic Studies/ or Prenatal Diagnosis/ or Neonatal Screening/ or Infectious Disease Transmission, Vertical/ or Disease Transmission, Infectious/ or tm.fs. or transmi$.ti,ab. or ((public$ or communit$ or universal$ or widespread or open$ or unrestricted or group$ or adult$ or adolescen$ or antibod$) adj3 (screen$ or test$ or surveillance)).ti,ab.	555260
3	Pregnancy/ or Pregnancy Complications, Infectious/ or Pregnancy Complications/ or exp Delivery, Obstetric/ or Maternal-Fetal Exchange/ or Fetal Monitoring/ or Labor, Induced/ or Fetus/ or Infant, Newborn/ or Infant/ or Prenatal Care/ or Milk, Human/ or Breast Feeding/ or Postpartum Period/ or exp cesarean section/ or exp obstetric labor/ or amniocentesis/ or chorionic villi/	1401109
4	1 and 2 and 3	1247
5	remove duplicates from 4	1234

Medline Update Search

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to October Week 3 2011,

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 31, 2011

Date Searched: 10/31/2011

1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C.mp. or hepacivirus$.mp. or HCV.mp.	58120
2	Mass Screening/ or Population Surveillance/ or Sentinel Surveillance/ or Seroepidemiologic Studies/ or Prenatal Diagnosis/ or Neonatal Screening/ or Infectious Disease Transmission, Vertical/ or Disease Transmission, Infectious/ or tm.fs. or transmi$.ti,ab. or ((public$ or communit$ or universal$ or widespread or open$ or unrestricted or group$ or adult$ or adolescen$ or antibod$) adj3 (screen$ or test$ or surveillance)).ti,ab.	576254
3	Pregnancy/ or Pregnancy Complications, Infectious/ or Pregnancy Complications/ or exp Delivery, Obstetric/ or Maternal-Fetal Exchange/ or Fetal Monitoring/ or Labor, Induced/ or Fetus/ or Infant, Newborn/ or Infant/ or Prenatal Care/ or Milk, Human/ or Breast Feeding/ or Postpartum Period/ or exp cesarean section/ or exp obstetric labor/ or amniocentesis/ or chorionic villi/	1436320

4	1 and 2 and 3	1291
5	remove duplicates from 4	1250

Appendix B. Hepatitis C Screening: Inclusion Criteria by Key Question

	Inclusion Criteria
All Key Questions	
Populations	Asymptomatic adults and pregnant women without known liver function test abnormalities
Settings	For screening studies, primary care, or other settings generalizable to primary care (e.g., family planning clinics, school-based health clinics), other settings in which screening is commonly performed (e.g., emergency room or urgent care). Focus on studies conducted in the U.S. and other developed countries.
Study designs	Randomized controlled trials and cohort studies (all KQ's), studies of diagnostic accuracy (KQ 2b, 4a), before-after studies (KQ's 3, 4b, 5, 6a, 6b, 6c, and 7), and cross sectional studies (KQ's 2a, 2b, 6b)
Screening	KQ 1a. Does screening for hepatitis C virus (HCV) infection in non pregnant adults without known abnormal liver function tests reduce mortality and morbidity due to HCV infection, affect quality of life, or reduce incidence of HCV infection? KQ 1b. Does screening for HCV infection during pregnancy reduce vertical transmission of HCV or improve mortality or morbidity for the mother or child? KQ 2a. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes? KQ 2b. What is the sensitivity and number needed to screen to identify one case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection? KQ 3. What are the harms associated with screening for HCV infection, including adverse effects such as anxiety, labeling, and impact on relationships?
Interventions	HCV antibody testing
Outcomes	KQs 1a, 1b, and 2: Intermediate outcomes: sustained virological response rates, histological improvements, behavioral changes to improve health outcomes, and reduce HCV transmission. Clinical outcomes: mortality due to HCV infection, morbidity due to HCV infection including hepatic cirrhosis, hepato-cellular carcinoma, rate of liver transplantation, and quality of life. KQ 1b: Mother-to-child transmission rates of HC. KQ 3: Anxiety; labeling; partner discord, abuse, or violence.
Comparisons	KQs 1a, 1b, and 3: HCV screening vs. no screening. KQ 2: Comparisons of different screening strategies.
Workup	KQ 4a. What is the comparative effectiveness and comparative diagnostic accuracy of various tests and strategies for the workup to guide treatment decisions in patients who are HCV positive? KQ 4b. What proportion of patients with screen-detected HCV infection receives treatment? KQ 5. What are the harms associated with the workup for guiding treatment decisions?
Populations	KQ 4b and 5: Persons with screen-detected HCV infection.
Interventions	KQ 4a and 5: Liver biopsy, laboratory tests, imaging tests.
Comparisons	KQ 4a and 5: Comparisons of different workup strategies and different tests to diagnose fibrosis or cirrhosis.
Outcomes	KQ 4a: Diagnostic accuracy, clinical outcomes (see KQs 1a, 1b, and 2). KQ 4b: Proportion who receives treatment. KQ 5: Bleeding, infection, other complications

Interventions	KQ 6a. How effective is counseling or immunizations of patients with HCV infection at improving health outcomes or reducing the spread of HCV? KQ 6b. Does becoming aware of positive HCV infection status decrease high risk behaviors? KQ 6c. How effective is counseling or immunizations of patients with HCV infection at improving intermediate outcomes, including change in high risk behaviors? KQ 7. Do any interventions decrease or increase the vertical transmission of HCV during delivery or in the perinatal period?
Populations	KQ 6a, 6b, 7: Persons with chronic HCV infection
Interventions	KQ 6a and 6b: Counseling on risky behaviors or alcohol use and immunizations for HAV and HBV infection. KQ 7: Labor management or delivery practices and breast feeding.
Comparisons	KQ 6a and 6b: Counseling or immunizations vs. no intervention. KQ 7: Comparisons of different labor and delivery practices; breast feeding vs. no breast feeding.
Outcomes	KQ 6a, 6b: See KQs 1a, 1b, and 2. KQ 7: See KQ 1b.

Appendix C. Included Studies List

KQ 1a & b:

Cullen W, Stanley J, Langton D, et al. Hepatitis C infection among injecting drug users in general practice: A cluster randomised controlled trial of clinical guidelines' implementation. British Journal of General Practice. 2006;56(532):848-56.

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KQ 2a &b:

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Zuniga IA, Chen JJ, Lane DS, et al. Analysis of a hepatitis C screening programme for US veterans. Epidemiology & Infection2006. p. 249-57.

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KQ 3:

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KQ 4a

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Boeker KH, Haberkorn CI, Michels D, et al. Diagnostic potential of circulating TIMP-1 and MMP-2 as markers of liver fibrosis in patients with chronic hepatitis C. Clin Chim Acta. 2002;316(1-2):71-81.

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Al Knawy B, Shiffman M. Percutaneous liver biopsy in clinical practice. Liver Int. 2007;27(9):1166-73.

KQ 6b:

Fabris P, Tositti G, Giordani MT, et al. Assessing patients' understanding of hepatitis C virus infection and its impact on their lifestyle. Alimentary Pharmacology & Therapeutics: Blackwell Publishing Ltd; 2006. p. 1161-70.

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Latka MH, Hagan H, Kapadia F, et al. A randomized intervention trial to reduce the lending of used injection equipment among injection drug users infected with hepatitis C. Am J Public Health. 2008;98:853-61.

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Ceci O, Margiotta M, Marello F, et al. High rate of spontaneous viral clearance in a cohort of vertically infected hepatitis C virus infants: What lies behind? [4]. Journal of Hepatology2001. p. 687-8.

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Pipan C, Amici S, Astori G, et al. Vertical transmission of hepatitis C virus in low-risk pregnant women. European Journal of Clinical Microbiology & Infectious Diseases1996. p. 116-20.

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Appendix D. Excluded Studies List

KQ 1 – 6c:

Afdhal, N. H. and D. Nunes (2004). "Evaluation of liver fibrosis: a concise review." Am J Gastro 99(6): 1160-1174. ***No Original Data***

Al-Faleh, F. Z., A. Aljumah, et al. (2000). "Treatment of chronic hepatitis C genotype IV with interferon-ribavirin combination in Saudi Arabia: a multicentre study." Journal of Viral Hepatitis 7(4): 287-291. ***Wrong Outcomes***

Alice Unah, L. (2009). "When liver stiffness is not so straight forward and Fibroscan not so simple." J Gastroenterol Hepatol 24(6): 934-936.***No Original Data***

Andrade, R. J., M. D. Garcia-Escano, et al. (2000). "Effects of interferon-beta on plasma lipid and lipoprotein composition and post-heparin lipase activities in patients with chronic hepatitis C." Alimentary Pharmacology & Therapeutics 14(7): 929-935. ***Wrong Population***

Anonymous (2004). "Screening for Hepatitis C Virus Infection in Adults: Recommendation Statement." Annals of Internal Medicine 140(6): 462-464. ***No Original Data***

Anonymous (2008). Should you screen for hepatitis C in patients at risk? Journal of Family Practice. 57: 303. ***Not Relevant***

Barbaro, G., G. Di Lorenzo, et al. (1996). "Hepatic glutathione deficiency in chronic hepatitis C: quantitative evaluation in patients who are HIV positive and HIV negative and correlations with plasmatic and lymphocytic concentrations and with the activity of the liver disease." American Journal of Gastroenterology 91(12): 2569-2573. ***Wrong Population***

Bedossa, P. and F. Carrat (2009). "Liver biopsy: the best, not the gold standard." Journal of Hepatology 50(1): 1-3.***No Original Data***

Bini, E. J., N. Bräu, et al. (2005). "Prospective multicenter study of eligibility for antiviral therapy among 4,084 U.S. veterans with chronic hepatitis C virus infection." Am J Gastroenterol 100(8): 1772-1779. ***Wrong Population***

Bonkovsky, H. L. and J. M. Woolley (2000). "Outcomes research in chronic viral hepatitis C: effects of interferon therapy." Canadian Journal of Gastroenterology 14(Suppl B): 21B-29B. ***Wrong Intervention***

Bravo, A. A., S. G. Sheth, et al. (2001). "Liver Biopsy." N Engl J Med 344(7): 495-500 ***Background***
Burt, R. D., H. Thiede, et al. (2009). Serosorting for hepatitis C status in the sharing of injection equipment among Seattle area injection drug users. Drug and Alcohol Dependence. 105: 215-220. ***Wrong Population***

Cales, P., F. Oberti, et al. (2005). A novel panel of blood markers to assess the degree of liver fibrosis. Hepatology. 42: 1373 - 1381. ***Wrong Population***

Calès, P., J. Boursier, et al. (2008). Evaluation and improvement of a reliable diagnosis of cirrhosis by blood tests. Gastroenterologie Clinique et Biologique. 32: 1050-1060. ***No Original Data***

Castera, L., X. Forns, et al. (2008). "Non-invasive evaluation of liver fibrosis using transient elastography." J Hepatol 48(5): 835-847. ***Wrong Intervention***

Cheung, K. J., L. Libbrecht, et al. (2010). Galectin-3-binding protein: a serological and histological assessment in accordance with hepatitis C-related liver fibrosis. European Journal of Gastroenterology & Hepatology. 22: 1066-1073 1010.1097/MEG.1060b1013e328337d328602. ***Wrong Outcomes***

Crofts, N., D. Jolley, et al. (1997). Epidemiology of hepatitis C virus infection among injecting drug users in Australia. Journal of Epidemiology and Community Health. 51: 692-697.***Wrong Outcomes***

Croquet, V., E. Vuillemin, et al. (2002). Prothrombin index is an indirect marker of severe liver fibrosis. European Journal of Gastroenterology & Hepatology. 14: 1133-1141. ***Wrong Population***

Davis, G. L., M. J. Alter, et al. (2009). Aging of the Hepatitis C Virus-Infected Persons in the United States: A Multiple Cohort Model of HCV Prevalence and Disease Progression. Gastroenterology. ***Background***

de Lédinghen, V., B. Le Bail, et al. (2007). Liver Stiffness Measurement in Children Using FibroScan: Feasibility Study and Comparison With Fibrotest, Aspartate Transaminase to Platelets Ratio Index, and Liver Biopsy. Journal of Pediatric Gastroenterology and Nutrition. 45: 443-450 410.1097/MPG.1090b1013e31812e31856ff. ***Wrong Population***

de Lédinghen, V., C. Douvin, et al. (2006). "Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/hepatitis C virus-coinfected patients." J Acquir Immune Defic Syndr 41(2): 175-179. ***Wrong Intervention***

Di Bisceglie, A. M., J. H. Hoofnagle, et al. (1993). "Changes in hepatitis C virus antigen in liver with antiviral therapy." Gastroenterology 105(3): 858-862. ***Wrong Population***

Follett, E. A., B. C. Dow, et al. (1991). "HCV confirmatory testing of blood donors." Lancet 338(8773): 1024. ***Wrong Intervention***

Foucher, J., E. Chanteloup, et al. (2006). Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut. 55: 403-408. ***Wrong Intervention***

Fried, M. W. (2001). "Pegylated interferon in combination with ribavirin: efficacy and safety results from a phase III randomized actively controlled multicenter study [abstract]." Gastroenterology 120(Suppl): A-55. ***Animal Study***

Ganne-Carrié, N., M. Ziol, et al. (2006). "Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases." Hepatology 44(6): 1511-1517. ***Wrong Intervention***
Gebo, K., H. Herlong, et al. (2002). "Role of liver biopsy in management of chronic hepatitis C: A systematic review." Hepatology 36: S161 - S172. ***Wrong Study Design***

Giannini, E., S. Caglieris, et al. (2001). "Serum pro-collagen III peptide levels are related to lobular necrosis in untreated patients with chronic hepatitis C." European Journal of Gastroenterology & Hepatology 13(2): 137-141. ***Wrong Population***

Goldstein, N. S., D. E. Blue, et al. (1999). "Serum alpha-fetoprotein levels in patients with chronic hepatitis C. Relationships with serum alanine aminotransferase values, histologic activity index, and hepatocyte MIB-1 scores." American Journal of Clinical Pathology 111(6): 811-816. ***Wrong Population***

Hagan, H., J. Campbell, et al. (2006). Self-reported hepatitis C virus antibody status and risk behavior in young injectors. Public Health Reports. 121: 710-719. ***Not Relevant***

Hahn, J. A., D. Wylie, et al. (2009). Potential impact of vaccination on the hepatitis C virus epidemic in injection drug users. Epidemics. 1: 47-57. ***Wrong Study Design***

Halfon, P., M. Munteanu, et al. (2008). "FibroTest-ActiTest as a non-invasive marker of liver fibrosis." Gastroenterologie Clinique et Biologique 32(6, Supplement 1): 22-39. ***Wrong Study Design***

Harris, M. (2010). Pleasure and Guilt: Alcohol Use and Hepatitis C. Qualitative Health Research. ***Wrong Study Design***

Hayashi, J., N. Furusyo, et al. (2000). "A relationship between the evolution of hepatitis C virus variants, liver damage, and hepatocellular carcinoma in patients with hepatitis C viremia." Journal of Infectious Diseases 181(5): 1523-1527. ***Wrong Population***

Hoffmann, R. M., M. C. Jung, et al. (1998). "Sarcoidosis associated with interferon-alpha therapy for chronic hepatitis C." Journal of Hepatology 28(6): 1058-1063. ***Wrong Outcomes***

Kramer, J. R., F. Kanwal, et al. (2010). "Importance of Patient, Provider, and Facility Predictors of Hepatitis C Virus Treatment in Veterans: A National Study." Am J Gastroenterol. ***Wrong Population***

Larcos, G., H. Sorokopud, et al. (1998). "Sonographic screening for hepatocellular carcinoma in patients with chronic hepatitis or cirrhosis: an evaluation." AJR American Journal of Roentgenology 171(2): 433-435. ***Wrong Population***

Leroy, V. (2008). "Other non-invasive markers of liver fibrosis." Clin Res Hepatol Gastroenterol 32(6 Suppl 1): 52-57. ***No Original Data***

Lin, Z.-H., Y.-N. Xin, et al. (2011). "Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: An updated meta-analysis." Hepatology 53(3): 726-736. ***Wrong Study Design***

Lorenzo-Zúñiga, V., R. Bartolí, et al. (2007). Serum Concentrations of Insulin-Like Growth Factor-I (IGF-I) as a Marker of Liver Fibrosis in Patients With Chronic Hepatitis C. Digestive Diseases and Sciences, Springer Netherlands. 52: 3245-3250. ***Wrong Outcomes***

Lucidarme, D., J. Foucher, et al. (2008). "Factors of accuracy of transient elastography (fibroscan) for the diagnosis of liver fibrosis in chronic hepatitis C." Hepatology 49(4): 1083-1089. ***Wrong Intervention***

Lurie, Y., D.-A. Landau, et al. (2007). Medex Test, a Novel Modality for Liver Disease Diagnosis: A Pilot Study. Journal of Clinical Gastroenterology. ***Wrong Population***

Maor, Y., P. CalÈS, et al. (2007). Improving estimation of liver fibrosis using combination and newer noninvasive biomarker scoring systems in hepatitis C-infected haemophilia patients. Haemophilia, Blackwell Publishing Ltd. 13: 722-729. ***Wrong Population***

Martinez, S. M., G. Crespo, et al. (2011). "Noninvasive assessment of liver fibrosis." Hepatology 53(1): 325-335. ***Wrong Study Design***

Mehta, S. H., B. Lau, et al. (2009). Exceeding the limits of liver histology markers. Journal of Hepatology. 50: 36-41. ***Wrong Outcomes***

Moyer, L. A., E. E. Mast, et al. (1999). "Hepatitis C: Part II. Prevention counseling and medical evaluation." American Family Physician 59(2): 349-354, 357. ***Wrong Intervention***

Myers, R., Y. Benhamou, et al. (2003). Serum biochemical markers accurately predict liver fibrosis in HIV and hepatitis C virus-coinfected patients. AIDS. 17: 1 - 5. ***Wrong Population***

Nalpas, B., V. Thiers, et al. (1992). Hepatitis C viremia and anti-HCV antibodies in alcoholics. Journal of Hepatology. 14: 381-384. ***Wrong Outcomes***

Narasimhan, G., T. N. Sargios, et al. (2006). Treatment rates in patients with chronic hepatitis C after liver biopsy. Journal of Viral Hepatitis, Blackwell Publishing Ltd. 13: 783-786. ***Wrong Population***

Ngo, Y., M. Munteanu, et al. (2006). A Prospective Analysis of the Prognostic Value of Biomarkers (FibroTest) in Patients with Chronic Hepatitis C. Clin Chem. 52: 1887-1896. ***No Original Data***

Nguyen, D. and J. A. Talwalkar (2011). Noninvasive assessment of liver fibrosis. Hepatology, Wiley Subscription Services, Inc., A Wiley Company. 53: 2107-2110. ***No Original Data***

Parkes, J., I. N. Guha, et al. (2006). "Performance of serum marker panels for liver fibrosis in chronic hepatitis C." Journal of Hepatology 44(3): 462-474. ***Wrong Study Design***

Paul V, H. (1996). Strategies for prevention of viral hepatitis in the United States. International Hepatology Communications. 5: 3-9. ***No Original Data***

Peters, L. and J. K. Rockstroh (2010). Biomarkers of fibrosis and impaired liver function in chronic hepatitis C: how well do they predict clinical outcomes? Current Opinion in HIV and AIDS. 5: 517-523 510. ***Wrong Outcomes***

Poynard, T., F. Imbert-Bismut, et al. (2004). Overview of the diagnostic value of biochemical markers of liver fibrosis (FibroTest, HCV-Fibrosure) and necrosis (ActiTest) in patients with chronic hepatitis C. Comp Hepatol. 3: 8. ***Wrong Study Design***

Poynard, T., M. Munteanu, et al. (2004). Prospective Analysis of Discordant Results between Biochemical Markers and Biopsy in Patients with Chronic Hepatitis C. Clin Chem. 50: 1344-1355. ***Wrong Outcomes***

Poynard, T., R. Morra, et al. (2007). "Meta-analyses of FibroTest diagnostic value in chronic liver disease." BMC Gastroenterology 7(1): 40. ***Wrong Study Design***

Proude, E. (2009). Alcohol Reduction for People with Hepatitis C Discipline of Addiction Medicine: 1-16. ***No Original Data***

Rifai, M. A., J. K. Moles, et al. (2006). Hepatitis C screening and treatment outcomes in patients with substance use/dependence disorders. Psychosomatics. 47: 112-121. ***Wrong Population***

Rockey, D. C. and D. M. Bissell (2006). "Noninvasive measures of liver fibrosis." Hepatol 43(2 Suppl 1): S113-S120. ***No Original Data***

Rodger, A. J., J. A. Thomson, et al. (1999). "Assessment of long-term outcomes of hepatitis C virus infection in a cohort of patients with acute hepatitis in 1971-1975: results of a pilot study." Journal of Gastroenterology & Hepatology 14(3): 269-273. ***Background***

Rosenberg, W. M. C., M. Voelker, et al. (2004). Serum markers detect the presence of liver fibrosis: A cohort study. Gastroenterology. 127: 1704-1713. ***Wrong Population***

Rosenberg, W., Voelker M, Thiel R et al (2008). "Other non-invasive markers of liver fibrosis." Clin Res Hepatol Gastroenterol 32(6 Suppl 1): 52-57. ***No Original Data***

Saito H, T. S., Nakamoto N, Kitamura K, Horikawa H, Kurita S, Saito Y, Iwai H, and I. H. (2004). "Efficacy of non-invasive elastometry on staging of hepatic fibrosis." Hepatol Res. 29(2): 97-103. ***Wrong Intervention***

Sandrin, L., B. Fourquet, et al. (2003). "Transient elastography: a new noninvasive method for assessment of hepatic fibrosis." Ultrasound Med Biol 29(12): 1705-1713. ***No Original Data***

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Schöniger-Hekele, M. and C. Müller (2006). The Combined Elevation of Tumor Markers CA 19-9 and CA 125 in Liver Disease Patients Is Highly Specific for Severe Liver Fibrosis. Digestive Diseases and Sciences, Springer Netherlands. 51: 338-345. ***Wrong Population***

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KQ 7:

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Wahl, M., S. Hermodsson, et al. (1994). Prevalence of antibodies against hepatitis B and C virus among pregnant women and female blood donors in Sweden. Serodiagnosis and Immunotherapy in Infectious Disease. 6: 127-129. ***Background***

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Zein, N. N. (1997). Vertical transmission of hepatitis C: To screen or not to screen. Journal of Pediatrics. 130: 859-861. ***Background***

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Zuccotti, G. V., M. L. Ribero, et al. (1995). Effect of hepatitis C genotype on mother-to-infant transmission of virus. UNITED STATES, Pediatric Department, University of Milan, Italy. 127: 278-280. ***Not Relevant***

Appendix E. Quality Assessment Methods

Individual studies were rated as "good," "fair" or "poor" as defined below[1]:

For Controlled Trials:
Each criterion was give an assessment of yes, no, or unclear.

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
    - Randomization reported, but method not stated
    - Not clear or not reported
    - Not randomized
2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization (randomization performed without knowledge of patient characteristics).
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Sealed opaque envelopes
    - Inferior approaches to concealment of randomization:
        - Use of alternation, case record numbers, birth dates or week days
        - Open random numbers lists
        - Serially numbered non- opaque envelopes
        - Not clear or not reported
3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors and/or data analysts blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient kept unaware of the treatment received?
8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?
9. Did the study maintain comparable groups?
10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to followup or overall high loss to followup?

For Cohort Studies:
Each criterion was give an assessment of yes, no, or unclear.

1. Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?

2. Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?
3. Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?
4. Were outcome assessors and/or data analysts blinded to treatment?
5. Did the article report attrition?
6. Did the study perform appropriate statistical analyses on potential confounders?
7. Is there important differential loss to followup or overall high loss to followup?
8. Were outcomes pre-specified and defined, and ascertained using accurate methods?

For Case-control Studies

Each criterion was given an assessment of yes, no, or unclear.

1. Did the study attempt to enroll all (or a random sample of) cases using pre-defined criteria?
2. Were the controls derived from the same population as the cases, and would they have been selected as cases if the outcome was present?
3. Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?
4. Did the study report the proportion of cases and controls who met inclusion criteria that were analyzed?
5. Did the study use accurate methods for identifying outcomes?
6. Did the study use accurate methods for ascertaining exposures and potential confounders?
7. Did the study perform appropriate statistical analyses on potential confounders?

For Studies of Diagnostic Accuracy

Each criterion was given an assessment of yes, no, or unclear.

1. Did the study evaluate a representative spectrum of patients?
2. Did the study enroll a random or consecutive sample of patients meeting pre-defined criteria?
3. Did the study evaluate a credible reference standard?
4. Did the study apply the reference standard to all patients, or to a random sample?
5. Did the study apply the same reference standard to all patients?
6. Was the reference standard interpreted independently from the test under evaluation?
7. If a threshold was used, was it pre-specified?

Appendix E References:

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Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377-84.

Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Ann Intern Med. 2011;155(8):529-36.

Appendix F. Overall Strength of Evidence Tables

Key Question	Number of studies	Risk of Bias (High, Moderate or Low)	Consistency (No serious inconsistency Serious, inconsistency, Very serious inconsistency)	Directness (Direct or indirect)	Precision (No serious imprecision, Serious imprecision, Very serious imprecision)	Number of subjects	Strength of Evidence
1a. Does screening for hepatitis C virus (HCV) infection in non pregnant adults without known abnormal liver function tests reduce mortality and morbidity due to HCV infection, affect quality of life, or reduce incidence of HCV infection?	**No studies**	No studies	No studies	No studies	No studies	No studies	Insufficient
1b.Does screening for HCV infection during pregnancy reduce vertical transmission of HCV or improve mortality or morbidity for the mother or child?	**No studies**	No studies	No studies	No studies	No studies	No studies	Insufficient
2a.What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?	**No studies**	No studies	No studies	No studies	No studies	No studies	Insufficient

Key Question	Number of studies	Risk of Bias (High, Moderate or Low)	Consistency (No serious inconsistency Serious, inconsistency, Very serious inconsistency)	Directness (Direct or indirect)	Precision (No serious imprecision, Serious imprecision, Very serious imprecision)	Number of subjects	Strength of Evidence
2b.What is the sensitivity and number needed to screen to identify one case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection?	**5 studies (4 cross-sectional, one case-control)**	High	No serious inconsistency	Direct	No serious imprecision	8044	Low
3.What are the harms associated with screening for HCV infection, including adverse effects such as anxiety, labeling, and impact on relationships?	**4 (1 cross-sectional, 3 intervention series)**	High	Unable to assess (assessed different outcomes)	Direct	Very serious imprecision	254	Insufficient
4a. What is the comparative effectiveness and comparative diagnostic accuracy of various tests and strategies for the work-up to guide treatment decisions in patients who are HCV positive?[a]							

Key Question	Number of studies	Risk of Bias (High, Moderate or Low)	Consistency (No serious inconsistency Serious, inconsistency, Very serious inconsistency)	Directness (Direct or indirect)	Precision (No serious imprecision, Serious imprecision, Very serious imprecision)	Number of subjects	Strength of Evidence
Clinical outcomes	**1 cohort study**	Moderate	Unable to assess (one study)	Direct	Very serious imprecision	156	Insufficient
Diagnostic accuracy: Platelet counts vs. liver biopsy	**12 studies of diagnostic accuracy**	Moderate	Serious inconsistency	Direct	Very serious imprecision	719 (AUROC for fibrosis) and 194 (AUROC for cirrhosis)	Low
Diagnostic accuracy: Age-platelet index vs. liver biopsy	**6 studies of diagnostic accuracy**	Moderate	No serious inconsistency	Direct	Serious imprecision	1121 (AUROC for fibrosis) and 1113 (AUROC for cirrhosis)	Moderate
Diagnostic accuracy: Aspartate transaminase -platelet ratio index (APRI) vs. liver biopsy	**43 studies of diagnostic accuracy**	Moderate	No serious inconsistency	Direct	No serious imprecision	9282 (AUROC for fibrosis) and 9135 (AUROC for cirrhosis)	High
Diagnostic accuracy: Aspartate transaminase -alanine transaminase ratio (AST/ALT ratio, or AAR) vs. liver biopsy	**24 studies of diagnostic accuracy**	Moderate	No serious inconsistency	Direct	No serious imprecision	1794 (AUROC for fibrosis) and 1741 (AUROC for cirrhosis)	High
Diagnostic accuracy: Cirrhosis Discriminant Score (CDS, also Bonacini Index) vs. liver biopsy	**7 studies of diagnostic accuracy**	Moderate	No serious inconsistency	Direct	Serious imprecision	963 (AUROC for fibrosis) and 1815 (AUROC for cirrhosis)	Moderate

Key Question	Number of studies	Risk of Bias (High, Moderate or Low)	Consistency (No serious inconsistency Serious, inconsistency, Very serious inconsistency)	Directness (Direct or indirect)	Precision (No serious imprecision, Serious imprecision, Very serious imprecision)	Number of subjects	Strength of Evidence
Diagnostic accuracy: Enhanced Liver Fibrosis Index (ELF) or Simplified Enhanced Liver Fibrosis Index (Simplified ELF) vs. liver biopsy	**5 studies of diagnostic accuracy**	Moderate	No serious inconsistency	Direct	Serious imprecision	781 (AUROC for fibrosis) and 754 (AUROC for cirrhosis)	Moderate
Diagnostic accuracy: FIB-4 vs. liver biopsy	**7 studies of diagnostic accuracy**	Moderate	No serious inconsistency (two studies)	Direct	Serious imprecision	1187 (AUROC for severe fibrosis)	Low
Diagnostic accuracy: Fibrometer vs. liver biopsy	**5 studies of diagnostic accuracy**	Moderate	No serious inconsistency	Direct	Serious imprecision	729 (AUROC for fibrosis) and 2237 (AUROC for cirrhosis)	Moderate
Diagnostic accuracy: Fibrotest vs. liver biopsy	**19 studies of diagnostic accuracy**	Moderate	No serious inconsistency	Direct	No serious imprecision	4345 (AUROC for fibrosis) and 3192 (AUROC for cirrhosis)	High
Diagnostic accuracy: Forns' Index vs. liver biopsy	**10 studies of diagnostic accuracy**	Moderate	No serious inconsistency	Direct	No serious imprecision	1800 (AUROC for fibrosis) and 507 (AUROC for cirrhosis)	High
Diagnostic accuracy: Hepascore vs. liver biopsy	**9 studies of diagnostic accuracy**	Moderate	No serious inconsistency	Direct	No serious imprecision	3787 (AUROC for fibrosis) and 3437 (AUROC for cirrhosis)	High
Diagnostic accuracy: Lok Index vs. liver biopsy	**6 studies of diagnostic accuracy**	Moderate	No serious inconsistency	Direct	Serious imprecision	2333 (AUROC for cirrhosis)	Moderate

Key Question	Number of studies	Risk of Bias (High, Moderate or Low)	Consistency (No serious inconsistency Serious, inconsistency, Very serious inconsistency)	Directness (Direct or indirect)	Precision (No serious imprecision, Serious imprecision, Very serious imprecision)	Number of subjects	Strength of Evidence
Diagnostic accuracy: Pohl Index vs. liver biopsy	**10 studies of diagnostic accuracy**	Moderate	No serious inconsistency (two studies)	Direct	Very serious imprecision	490 (AUROC for fibrosis) and 718 (AUROC for fibrosis)	Low
APRI vs. Fibrotest	**11 studies of diagnostic accuracy**	Moderate	No serious inconsistency	Direct	Serious imprecision	2542 (excluding overlapping populations)	Moderate
AST/ALT ratio vs. other indices	**11 studies of diagnostic accuracy**	Moderate	No serious inconsistency	Direct	Serious imprecision	1987	Moderate
4b.What proportion of patients with screen-detected HCV infection receives treatment?	**3 intervention series**	Moderate	No serious inconsistency	Direct	Serious imprecision	18580	Moderate
5. What are the harms associated with the work-up for guiding treatment decisions?	**6 intervention series (1 of patients specifically undergoing liver biopsy for evaluation of HCV infection)**	Moderate	No serious inconsistency	Direct	No serious imprecision	88,587	Moderate
6a. How effective is counseling or immunizations of patients with HCV infection at improving health outcomes or reducing the spread of HCV?	**1 randomized controlled trial**	Moderate	Unable to assess (one study)	Direct	Very serious imprecision	137	Insufficient

Key Question	Number of studies	Risk of Bias (High, Moderate or Low)	Consistency (No serious inconsistency Serious, inconsistency, Very serious inconsistency)	Directness (Direct or indirect)	Precision (No serious imprecision, Serious imprecision, Very serious imprecision)	Number of subjects	Strength of Evidence
6b.Does becoming aware of positive HCV infection status decrease high risk behaviors?	**7 (2 prospective before-after studies, 3 retrospective post-intervention series, 2 cross-sectional studies)**	Moderate	Serious inconsistancy	Direct	Serious imprecision	1660	Low
6c.How effective is counseling or immunizations of patients with HCV infection at improving intermediate outcomes, including change in high risk behaviors?	**3 (2 RCTs, 1 before-after study)**	Moderate	No serious inconsistency	Direct	Very serious imprecision	1316	Insufficient
7. Do any interventions decrease or increase the vertical transmission of HCV during delivery or in the perinatal period?							
Elective cesarean vs. vaginal delivery	**4 cohort studies**	Moderate	Serious inconsistancy	Direct	Very serious imprecision	2089	Low
Any cesarean vs. vaginal delivery	**11 cohort studies**	Moderate	No serious inconsistency	Direct	Very serious imprecision	2332	Moderate
Internal fetal monitoring vs. no internal fetal monitoring	**3 cohort studies**	Moderate	Serious inconsistancy	Direct	Very serious imprecision	928	Insufficient

Key Question	Number of studies	Risk of Bias (High, Moderate or Low)	Consistency (No serious inconsistency Serious, inconsistency, Very serious inconsistency)	Directness (Direct or indirect)	Precision (No serious imprecision, Serious imprecision, Very serious imprecision)	Number of subjects	Strength of Evidence
Prolonged rupture of membranes vs. less prolonged rupture of membranes	**2 cohort studies**	Moderate	No serious inconsistency	Direct	Very serious imprecision	245	Low
Breastfeeding vs. no breastfeeding	**15 cohort studies**	Moderate	No serious inconsistency	Direct	No serious imprecision	4137	Moderate

[a] Not all studies of diagnostic accuracy reported the area under the receiver operating curve (AUROC). Sensitivity and specificity at different cutoffs are summarized in the Results.

Screening for Hepatitis C Virus Infection in Adults

Appendixes

Appendix G. Evidence Tables and Quality Ratings

Evidence Table 1: Key Question 2b. Screening Strategies

Author, year Country Risk of bias	Eligibility	Sample size	Baseline characteristics	Screening strategy	HCV prevalence	Results	Funding source	Comments
Gunn, 2003 USA Moderate	STD clinic attendees in San Diego offered HCV screening as part of routine care	3,367	Age ≥30 years: 4.6% Female: Not reported Self-reported intravenous drug use: 5.7%	A: All screened for HCV infection B: HCV screening only those who self-reported ever injecting drugs C: HCV screening only those who self-reported ever injecting drugs or had blood transfusions before 1992 D: HCV screening only those who self-reported ever injecting drugs, blood transfusion before 1992, or sex partner was an injection drug user E: HCV screening only those who self-reported or were identified by clinic staff as ever injecting drugs, blood transfusion before 1992, or sex partner was an injection drug user F: HCV screening only those who self-reported or were identified by clinic staff as ever injecting drugs, blood transfusion before 1992, sex partner was an injection drug user, or bacterial sexually transmitted disease G: HCV screening only those who self-reported or were identified by clinic staff as ever injecting drugs, blood transfusion before 1992, sex partner was an injection drug user, bacterial sexually transmitted disease, or age ≥30 years	4.9%	**A vs. B vs. C vs. D vs. E vs. F vs. G** Proportion screened: 100% (3356/3356) vs. 6% (193/3356) vs. 8% (253/3356) vs. 10% (347/3356) vs. 12% (413/3356) vs. 34% (1145/3356) vs. 63% (2127/3356) Sensitivity: 100% (165/165) vs. vs. 60% (99/165) vs. 64% (105/165) vs. 67% (110/165) vs. 70% (116/165) vs. 81% (134/165) vs. 97% (160/165) Number needed to screen to identify one case of HCV infection: 20 vs. 1.9 vs. 2.4 vs. 3.2 vs. 3.6 vs. 8.5 vs. 13	Centers for Disease Control and Prevention	Proportion screened, and number needed to screen calculated from prevalence and sensitivity/specificity provided in the article.

Author, year Country Risk of bias	Eligibility	Sample size	Baseline characteristics	Screening strategy	HCV prevalence	Results	Funding source	Comments
McGinn, 2008 USA Moderate	Patients attending an adult primary care clinic in New York for a scheduled visit with their primary care provider or for an unscheduled visit for an urgent problem, age >18 years, language English or Spanish	1,000	Age: Mean 50 years Female: 73% Non-white: 90%	A: HCV screening patients based on positive findings in 5 domains (medical, exposure, social, work, and personal history) B: HCV screening patients based on positive findings in 3 domains (medical, exposure, and social history)	8.3% (2.5% newly diagnosed)	**A vs. B** AUROC: 0.73 (0.68-0.79) vs. 0.77 (0.71-0.80) Based on 3-domain risk assessment instrument, screening of all patients vs. those with ≥1 vs. ≥2 vs. 3 positive domains Proportion screened: 100% (1000/1000) vs. 71% (709/1000) vs. 23% (228/1000) vs. 0.5% (56/1000) Sensitivity: 100% (83/83) vs. 91% (76/83) vs. 65% (54/83) vs. 34% (28/83) Number needed to screen to identify one case of HCV infection: 12 vs. 9.3 vs. 4.2 vs. 2.0	None reported	Proportion screened, and number needed to screen calculated from prevalence and sensitivity/specificity provided in the article.
Nguyen, 2005 USA High	Age 18 to 60; able to complete English-language survey; patients with known HCV infection receiving care in gastroenterology clinic and patients receiving care in general internal medicine clinic with no apparent clinical liver disease, no history of previous HCV testing	429 (222 known HCV-positive, 207 unknown HCV status)	Born 1940-1949: 20% Born 1950-1959: 38% Back 1960-1969: 18% Female: 58% Non-white: 37% Reports seeing use of injecting drugs: 34%	A: Screen all B: At least 1 risk factor, based on 7-item instrument (self-report history of sex with a prostitute, history of exposure to potentially infected blood during transfusion, rejection as a blood donor, refused life insurance, witnessing use of injecting drugs, sexual intercourse with an injecting drug user, self-report of HBV infection) C: At least 2 risk factors D: At least 3 risk factors E: Four or more risk factors	Not applicable (case-control design)	**A vs. B vs. C vs. D vs. E** Proportion screened: 100% (429/429) vs. 78% (335/429) vs. 48% (207/429) vs. 28% (118/429) vs. 13% (56/429) Sensitivity: 100% (225/225) vs. 94% (212/225) vs. 79% (178/225) vs. 51% (115/225) vs. 24% (55/225) Number needed to screen to identify one case of HCV infection: 1.9 vs. 1.6 vs. 1.2 vs. 1.0 vs. 1.0	Schering-Plough Corp	Estimated positive predictive value for 1.0% HCV prevalence population ≥0 risk factors: 1.0% ≥1 risk factor: 1.6% ≥2 risk factors: 5.3% ≥3 risk factors: 25% ≥4 risk factors: 33%

Author, year Country Risk of bias	Eligibility	Sample size	Baseline characteristics	Screening strategy	HCV prevalence	Results	Funding source	Comments
Zuniga, 2006 USA Moderate	Patients with one or more risk factors for HCV infection in primary care outpatient departments in New York	5400 (2263 tested for HCV infection and with confirmatory PCR testing)	Age 40-54 years: 31% White: 78% Female: 3.9% Vietnam era veteran: 50% Blood transfusion prior to 1992: 17% Any intravenous drug use: 4.5% Unexplained liver disease: 3.2% Abnormal liver function tests: 9.1%	A: HCV screening for any of 11 positive risk factors (Vietnam era veteran, multiple sexual contacts, tattoo/body piercing, intemperate alcohol use, blood transfusion prior to 1992, intranasal cocaine use, blood exposure (mucous membranes), abnormal liver function tests, injection drug use (past or present), unexplained liver disease, hemodialysis B: HCV screening for any of 5 positive risk factors (Vietnam era veteran, tattoo/body piercing, blood transfusion prior to 1992, abnormal liver function tests, injection drug use) C: HCV screening only those with self-reported injection drug use (past or present)	4.6%	**A vs. B vs. C** Proportion screened: 100% (2263/2263) vs. 78% (1776/2263) vs. 3% (68/2263)* Sensitivity: 100% (103/103) vs. 97% (100/103) vs. 41% (42/103) Number needed to screen to identify one case of HCV infection: 22 vs. 18 vs. 1.6	Funding source not stated, declared no conflicts of interest	*Study reports 3% of subjects screened if screening targeted only to injection drug users, but elsewhere in article reports 4.5% prevalence of injection drug use

Author, year Country Risk of bias	Eligibility	Sample size	Baseline characteristics	Screening strategy	HCV prevalence	Results	Funding source	Comments
Zuure, 2010 Netherlands Moderate	Patients screened for HCV in a sexually transmitted disease clinics in the Netherlands	985	Not reported	A: Screen all B: HCV screening for at least 1 risk factor, based on 20-item questionnaire (injection drug use, born in HCV-endemic country, blood transfusion prior to 1992, HCV-infected bother, mother is/was injection drug user, living with HCV-infected individual, living with injection drug user, needle exposure to high-risk person, needle exposure in HCV-endemic country, hemophilia patient, hemodialysis patient, organ recipient, received blood products in medium/high risk country, exposure of healthcare workers to blood/tissue in medium/high risk country, surgical/dental procedure in medium/high risk country, ritual intervention (circumcision, scarification) in medium/high risk country, tattoo in medium/high risk country, body-piercing in medium/high risk country, HIV-positive status, non-injection drug use ≥3 times/week for ≥3 months)	1%	**A vs. B** Proportion screened: 100% (985/985) vs. 14% (140/985) Sensitivity: 100% (98/98) vs. 90% (9/10) Number needed to screen to identify one case of HCV infection: 10 vs. 14	Netherlands organization for health research and development	Questionnaire developed in a population with high prevalence of previously diagnosed self-reported HCV infection (48%), remainder self-reported as negative or unknown HCV status (results not reported here)

Abbreviations: AUROC = Area Under Receiver Operator Characteristic; HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; PCR = Polymerase Chain Reaction; STD = Sexually Transmitted Disease.

Evidence Table 2: Key Question 2b. Screening Strategies Quality Rating/Risk of Bias

Study, year	(1) Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	(2) Did the study evaluate a representative spectrum?	(3) Did the study report the proportion of eligible patients who met inclusion criteria who underwent screening?	(4) Was there a high rate of non-screening among eligible patients?	(5) Did the study describe methods for ascertaining risk factors?	(6) Did the study prospectively compare different pre-defined screening strategies?	Overall risk of bias
Gunn, 2003	Yes	Yes	No	Unclear	Yes (questionnaire)	No	Moderate
McGinn, 2008	Yes	Yes	Yes	Yes (67%)	Yes (risk factor assessment questionnaire)	No	Moderate
Nguyen, 2005	Unclear	No (case-control design)	No	Yes (76%)	Yes (questionnaire)	No	High
Zuniga, 2006	Yes	Yes	Yes	Yes (58%)	Yes (screening questionnaire)	No	Moderate
Zuure,, 2010	Unclear	Yes	No	Unclear	Yes (screening questionnaire)	No	Moderate

Evidence Table 3: Key Question 4a. Biopsy Outcomes

Author, year Country	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Baseline characteristics	Intervention	Duration of followup	Results	Funding source	Risk of bias
Andriulli, 2004 Italy	Patients referred for evaluation for elevated liver enzymes and markers of HCV infection, scheduled for treatment with interferon and ribavirin but refused pretreatment liver biopsy; matched controls who underwent biopsy prior to treatment	Previously treated with antiviral therapies, hepatitis B surface antigen positive, required biopsy for suspicion of malignancy, decompensated cirrhosis, referred for transplant evaluation	Number screened and eligible not reported 78 cases and 78 matched controls	Reports no differences across groups, results reported for whole sample Age: 49 years Female: 41% Genotype 1: 53% No liver biopsy vs. liver biopsy Cirrhosis: 24% vs. 17%	A: No liver biopsy prior to interferon + ribavirin B: Liver biopsy prior to interferon + ribavirin	72 weeks (48 weeks treatment and 24 weeks follow-up for SVR)	A vs. B End-of-treatment response: 53% (41/78) vs. 58% (45/78) (p=0.63) SVR: 41% (32/78) vs. 44% (34/78) (p=0.87) Withdrawal due to adverse events: 10% (8/78) vs. 6.4% (5/78)	Not reported	Moderate

Abbreviations: HCV, hepatitis C virus; SVR, sustained virological response.

Evidence Table 4: Key Question 4a. Biopsy Quality Rating/Risk of Bias

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?	Were outcome assessors and/or data analysts blinded to treatment?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to follow-up or overall high loss to followup?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Risk of bias
Andriulli, 2004	Yes	Yes	Yes	Unclear	Yes	No	No	Yes	Moderate

Evidence Table 5: Key Question 4a. Diagnostic Accuracy

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Adams, 2005	Hepascore (bilirubin, g-glutamyltransferase, hyaluronic acid, a-2 macroglobulin, age, and sex) Fibrotest	Prospective	Derivation and validation samples reported separately	Australia	117 (derivation sample) 104 (validation sample)	Fibrosis (METAVIR F2-F4): 44% (derivation sample) and 57% (validation sample) Cirrhosis (METAVIR F4): 6% and 16%	Hepascore: Cutoff ≥0.5 (range 0.0-1.0) for fibrosis; ≥0.84 for cirrhosis	No for derivation sample, yes for validation sample	All ≥5 portal tracts; median 9 portal tracts and 13 mm	Derivation vs. validation sample Age: 40 vs. 41 years Female: 32% vs. 27% Genotype 1: 61% vs. 48% All treatment-naïve	Not stated	Predictive values not reported
Alsatie, 2007	5-item predictive index (DM, platelet count, INR, bilirubin, AST)	Retrospective	Derivation and validation samples reported separately	USA	190 (derivation sample) 94 (validation sample)	Fibrosis (METAVIR F2-F4): 41% Cirrhosis (METAVIR F4): 17%)	5-item predictive index: Cutoffs ranged from 0 to 4	No for derivation sample, yes for validation sample	All ≥15 mm	Reported for derivation and validation samples together Age: 45 years Female: 40% Genotype 1: 50% All treatment-naïve	Not stated	Yes
Anderson, 2000	AST/ALT ratio	Retrospective	No	Canada	133	Fibrosis or cirrhosis (method unclear): 82% Cirrhosis (method unclear): 46%	AST/ALT ratio ≥1	Yes	Not reported	Age: 46 years Female: 30% Genotype 1: Not reported All had elevated ALT 18% on treatment	6/139 excluded for unavailable liver biopsy	Yes
Becker, 2009	HepascoreAPRIFIB-4	Unclear	No	USA	391	Fibrosis (METAVIR F2-F4): 50%Cirrhosis (METAVIR F4): 19%	Hepascore >0.2, >0.55, or ≥0.8APRI >0.5 or >1.5FIB-4 ≥1.45 or >3.2.5	Yes for APRI and FIB-4, no for Hepascore	All ≥10 mm or ≥8 portal tracts; median 16 mm, 11% <10 mm	Age: 50 yearsFemale: 30%Genotype 1: 75%None treated at time of biopsy	Not stated	Yes
Bejarano, 2009	Sabadell NIHCED index	Prospective	No	Spain	321	Severe fibrosis (Knodell 3-4): 59% (no patients had Knodell 2) Cirrhosis (Knodell 4): 20%	Sabadell NIHCED index >6	No	Mean 11.6 mm and 12.2 portal tracts	Age: 48 years Female: 44% Genotype 1: Not reported	Not stated	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Berg, 2004	APRI	Retrospective	No	Germany	484	Fibrosis (Scheuer F2-F4): 52% Cirrhosis (Scheuer F4): 13%	APRI: Cutoffs ranged from >0.50 to >2.0	Yes	Not reported	Age: 46 years Female: 44% Genotype 1: Not reported All treatment-naïve	Not stated	Yes
Boeker, 2002	TIMP-1MMP-2Hyaluronic acidASTALTAlkaline phosphataseGGTAlbumin	Unclear	No	Germany	78	Fibrosis (Ishak, grades not reported): 46% (27/59, excluding patient with cirrhosis)Cirrhosis (Ishak, grades not reported): 24% (19/78)	TIMP-1 (Biotrak) >950 mcg/lTIMP-1 (Quantikine) >85 mcg/lMMP-2 (Biotrak) >1500 mcg/lMMP-2 (Quantikine) >320 mcg/lHyaluronic acid >30 mcg/lAST >18 U/lALT >22 U/lAlkaline phosphatase >190 U/lGGT >28 U/lAlbumin <37 g/l	Unclear	Not reported	Age: Not reportedFemale: Not reportedGenotype 1: Not reported	Not stated	Predictive values not reported
Bonacini, 1997	Cirrhosis discriminant score (platelet count, AST/ALT ratio, prothrombin index, ascities, spider angiomata)AST/ALT ratio	Retrospective	Yes	USA	79	Fibrosis: Not reportedSevere fibrosis (Knodell F3-F4): 35%Cirrhosis: Not reported	Cirrhosis discriminant score ≥7 or ≥8AST/ALT ratio	No (for cirrhosis discriminant score)	Not reported	Age: Not reportedFemale: Not reportedGenotype 1: Not reportedNo histologic evidence of alcoholic liver disease	Not stated	Predictive values not reported

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Borroni, 2006	AST/ALT ratio Cirrhosis Discriminant Score APRI Pohl's Index Age-platelet index	Retrospective	No	Italy	228	Severe fibrosis (Knodell F3-F4): 49% Cirrhosis (Knodell F4): 13%)	AST/ALT ratio ≥1 Cirrhosis Discriminant Score >2 or >7 APRI ≥2 Pohl's Index positive Age-platelet index ≥6 Combinations of APRI and age-platelet index: cutoffs not reported	No	All ≥6 portal fields	Age: 42 years Female: 27% Genotype 1: 47% All elevated transaminases All treatment-naïve	4 with <6 portal tracts excluded from analysis	Yes
Bourliere, 2008	HepascoreFibrotest	Prospective	No	France	467	Fibrosis (METAVIR F2-F4): 49%Cirrhosis (METAVIR F4): 7.5%	Hepascore ≥0.5 and ≥0.84 or not reportedFibrotest: Not reported	Unclear	Mean 20 mm and median 9 portal tracts; 59% ≥15 mm and ≥5 portal tracts	Age: 47 yearsFemale: 41%Genotype 1: Not reported	Not stated	Yes
Bourliere, 2006	Fibrotest APRI Forn's Index	Unclear	No	France	235	Fibrosis (METAVIR F2-F4): 42% Cirrhosis (METAVIR F4): 6.8%	Fibrotest >0.1 or ≥0.6 APRI >0.5 to >2 Forn's Index: ≥4.21 or >6.9	Yes	Mean 20 mm and median 9 portal tracts; 59% ≥15 mm and ≥5 portal tracts	Age: 46 years Female: 45% Genotype 1: Not reported	Not stated	Yes
Boursier, 2011	FibroMeter	Unclear	No	France	349 (derivation sample) 380 (validation sample)	Derivation vs. validation sample Fibrosis (METAVIR F2-F4): 68% vs. 49% Cirrhosis (METAVIR F4): 12% vs. 18%	Not reported	No	94% ≥15 mm and ≥8 portal tracts	Derivation vs. validation sample Age: 52 vs. 51 years Female: 40% vs. 38% Genotype 1: Not reported	Not stated	Predictive values not reported

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Boursier, 2009	FibroMeterFibrotestHepascoreAPRIModified Fibrotest	Retrospective	No, except for modified Fibrotest	France	1056	Fibrosis (METAVIR F2-F4): 52%Cirrhosis (METAVIR F4): 11%	FibroMeter >0.628, >0.830, or >0.979Fibrotest >0.448, >0.631, >0.660, or >0.862Hepascore >0.497, >0.801, >0.904, or >0.999APRI >0.581, >0.652, >1.159, or >2.532Modified Fibrometer >0.089 or >0.442	No	Not reported	Mean age: 46 yearsFemale: 40%Genotype 1: Not reported	Not stated	Yes
Burton, 2011	APRI	Retrospective	No	USA	268 (142 black, 117 white)	Fibrosis (Batt-Ludwig 2-4): 49%Cirrhosis (Batt-Ludwig 4): 16%	APRI: Cutoffs ranged from >0.50 to >1.0	No	Not reported	Age: 52 yearsFemale: 4.5%Genotype 1: 81%All treatment-naïve	Not stated	Yes
Cales, 2008	FibroMeter Fibrotest Hepascore APRI FIB-4	Retrospective	No	France	1056	Fibrosis (METAVIR F2-F4): 52% Cirrhosis (METAVIR F4): 11%	FibroMeter >0.419 Fibrotest >0.435 Hepascore >0.465 APRI >0.548 FIB-4 >1.116	No	Not reported	Mean age: 46 years Female: 40% Genotype 1: Not reported No antiviral treatment in last 6 months	Not stated	Yes
Castera, 2010	SAFE algorithm (based on APRI and Fibrotest)	Prospective	No (for SAFE algorithm)	France	302	Fibrosis (METAVIR F2-F4): 76% Cirrhosis (METAVIR F4): 25%	APRI: Algorithm based on scores ≤0.5, 0.5-1.5, or >1.5 Fibrotest (for patients with APRI 0.5-1.5): >0.48	Yes	All ≥10 mm and ≥6 portal tracts; mean 20 mm and 15 portal tracts	Age: 52 years Female: 43% Genotype 1: Not reported All elevated ALT	12 insufficient liver tissue	Yes
Castera, 2009	AST/ALT ratioAPRIProthrombin indexPlatelet countFibrotest Lok Index	Prospective	No	France	298	Fibrosis (METAVIR F2-F4): 74%Cirrhosis (METAVIR F4): 23%	Platelet count: <150Fibrotest: ≥0.75Prothrombin index: ≤85%AST/ALT ratio: ≥1APRI: ≥1.0 or 2.0Lok Index: ≥0.2 or ≥0.5	Yes	All ≥10 mm and ≥6 portal tracts; mean 20 mm and 15 portal tracts	Age: 52 yearsFemale: 43%Genotype 1: Not reported	Not reported	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Castera, 2005	APRI Fibrotest	Prospective	No	France	193	Fibrosis (METAVIR F2-F4): 74% Cirrhosis (METAVIR F4): 25%	Only AUROC reported	Only AUROC reported	Median 17 mm, median 2 fragments	Age: 51 years Female: 43% Genotype 1: Not reported	Not reported	Unable to construct 2 x 2 table
Cheong, 2011	Significant Fibrosis Index (haptoglobin, a2MG, TIMP1, MMP2, GGT) Zeng Index APRI Forn's Index FIB-4 ELF index	Prospective	Yes (for Significant Fibrosis Index)	Korea	HCV infected: 79 (derivation sample) and 27 (validation sample)	Derivation and validation samples, respectively (includes persons with HCV and HBV infection) Fibrosis (METAVIR F2-F4): 79% and 77% Cirrhosis (METAVIR F4): 13% and 28%	Significant Fibrosis Index >2.2 or >3.3	No (for Significant Fibrosis Index)	Mean 12.6 mm and mean 13.2 portal tracts; 71% had ≥11 portal tracts	Derivation vs. validation samples (includes persons with HCV and HBV infection) Age: 42 vs. 42 years Female: 31% vs. 35% Genotype 1: Not reported No antiviral treatment in last 6 months	Not reported	Sensitivity, specificity, and predictive values not reported for HCV subgroup
Cheung, 2011	Fibrosis-protein Index (a-2 macroglobulin and hemopexin)APRI	Unclear	Yes (for Fibrosis-protein Index)	Belgium	62 (derivation sample)73 (validation sample)	Derivation and validation samples, respectivelyFibrosis (METAVIR F2-F4): 50% and 71%Cirrhosis (METAVIR F4): 26% and 14%	Fibrosis-protein Index: >3.53 and >4.78APRI: >0.5 or >1.0	No (for Fibrosis-protein Index), yes for APRI	Median 1.6-2.0 cm and >8 portal tracts	Derivation vs. validation samplesAge: 50 vs. 50 yearsFemale: 48% vs/ 53%Genotype 1 or 4: 69% vs. 71%All treatment-naïve	Not reported	Yes for Fibrosis-protein Index, not reported for APRI

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Cheung, 2008	Platelet count Normalized AST/ALT ratio Pohl score APRI Lok Index	Prospective	No	USA	490	Fibrosis (Batt-Ludwig 2-4): 66% Cirrhosis (Batt-Ludwig 4): 14%	Platelet count: <100 or <150 Normalized AST/ALT ratio: ≥1 Pohl score: Positive (platelet count <150 and AST/ALT ratio ≥1) APRI: ≥0.5, ≥1.0, ≥1.5, or ≥2.0 Lok Index: >0.2 or >0.5	Yes	Not reported	Age: 49 years Female: 2% Genotype 1: Not reported	Not reported	Yes, except for AST/ALT ratio for severe fibrosis
Chrysanthos, 2006	APRI	Unclear	No	Greece	284	Fibrosis (Ishak score ≥3): 51%Cirrhosis (Ishak score 5 or 6): 20%	APRI: >0.50 or >1.50 for fibrosis, >1.00 or >2.00 for cirrhosis	Yes	All >1.5 cm	Age: 49 yearsFemale: 49%Genotype 1: Not reportedNo antiviral treatment last 6 months	14 patients out of entire (HCV + HCV) sample of 489 patients had inadequate biopsy specimen	Yes
Cobbold, 2010	APRI ELF Index Hepatic transit time	Prospective	No	UK	67	Fibrosis (Ishak ≥3): 55% Cirrhosis (Ishak 5 or 6): 21%	APRI >0.66 or >0.92 ELF Index >8.75 or >9.4 Hepatic Transit Time >8.0 or >10.25	No	All ≥10 mm, mean 24 mm	Age: 50 years Female: 34% Genotype 1: Not reported No current antiviral treatment Excluded if >20 g alcohol/day	3 had inadequate biopsy specimen	Some inconsistency
Colletta, 2005	Fibrotest	Unclear	No	Italy	40	Fibrosis (METAVIR F2-F4): 35% Cirrhosis (METAVIR F4): 0%	Fibrotest: ≥0.31	Yes	Mean 20 mm, 7 portal tracts	Age: 44 years Female: 45% Genotype 1: 30% All had ALT ≤1.2 times the upper limit of the reference range and Ishak score ≤2 All treatment-naïve	Not stated	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Cross, 2010	King's Score	Unclear	No	UK	187	Fibrosis (Ishak ≥3): 48%Cirrhosis (Ishak 5 or 6): 27%	King's Score: >9.87 or >24.3	No	All ≥10 mm or >10 portal tracts; mean 15 mm	Age: 49 yearsFemale: 41%Genotype 1: 42%Patients with high alcohol consumption excludedAll treatment-naïve	Not reported	Yes
Cross, 2009	King's Score (age, AST, INR, platelets), AST/ALT ratio AST APRI Age-platelet index Cirrhosis Discriminant Score FIB-4 index Pohl index (AAR≥1 and platelets <150)	Retrospective	Yes, measures of diagnostic accuracy similar for derivation and validation samples, diagnostic accuracy reported for derivation sample	UK	602 (derivation sample) 105 (validation sample)	Derivation vs. validations amples, respectively Fibrosis (Ishak ≥3): 45% vs. 48% Cirrhosis (Ishak 5 or 6): 22% vs. 14%	King's Score: >12.3 or 16.7 AST: >62 or >64.5 Age-platelet index: >3.5 or >5 APRI: >0.53 or >0.75 Platelets: <187 or <149 FIB-4: >0.34 or 0.41	No	All >10 mm and >10 portal tracts	Derivation vs. validation samples Age: median 43 vs. 43 years Female: 35% vs. 30% Genotype 1: 55% vs. not reported Heavy alcohol excluded (>60 g/day men, >40 g/day women) All treatment-naïve	12 insufficient liver tissue	Yes
Ehsan, 2008	Age-platelet indexLok IndexCirrhosis discriminant scoreGoteborg University Cirrhosis IndexAPRIPohl IndexAST/ALT ratio	Unclear	No	Egypt	116	Fibrosis: Not reportedCirrhosis (Ishak 5-6): 30%	Age-platelet index >5Lok Index >0.6Cirrhosis discriminant score >7Goteborg University Cirrhosis Index >1.5APRI >1.5Pohl Index positiveAST/ALT ratio >1.5	No	Mean 12 mm	Age: 39 yearsFemale: 16%Genotype 1: Not reportedNo alcoholSchistosomiasis: 46%All treatment-naïve	Not reported	No
El-Gindy, 2003	MMP-2 TIMP-1	Unclear	No	Egypt	41	Fibrosis (Ishak 1-6): 71% Cirrhosis (Ishak 5-6):34%	MMP-2 >400 ng/ml TIMP-1 >195 ng/ml AST >34 IU/L ALT >44 IU/L Albumin <3.5 g/100 ml	No	Not reported	Age: 48 years Female: 41% Genotype 1: Not reported No habitual alcohol All treatment-naïve	Not reported	Predictive values not reported; some sensitivities and specificities don't match reported data

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
El-Shorbagy, 2004	7-item predictive index (platelet count, MMP-9, portal vein diameter, spleen diameter, ALT, AST, viral load)	Unclear	Yes	Egypt	109	Fibrosis (G2S2 or G3S3): 80% Cirrhosis (G3S3): 18%	7-item predictive index >3 or ≥6	No	Not reported	Age: 46 years Female: 29% Genotype 1: Not reported	Not reported	Yes
Fabris, 2008	APRIAST/ALT ratioAge-platelet indexCirrhosis Discriminant ScoreForn's IndexFibro Index	Retrospective	No	Italy	167	Fibrosis (METAVIR F2-F4): 41%Cirrhosis (METAVIR F4): 11%	Fibroindex >1.6Not reported for other tests	Unclear	Average 19 mm and median 7 portal tracts	Age: 49 yearsFemale: 50%Genotype 1 + 4: 50%1/4 reported significant alcohol useAll treatment-naïve	Unclear	Yes for Fibro Index (Sensitivity, specificity, and predictive values not reported for other tests)
Fontana, 2008	HALT-C model (platelet count, TIMP-1, hyaluronic acid) Lok Index APRI Cirrhosis Discriminant Score	Unclear	Yes (for HALT-C model)	USA	513	Fibrosis (Ishak score ≥3): 93% Cirrhosis (Ishak 5 or 6): 38% (study excluded patients with Ishak 0 or 1)	HALT-C model at cutoffs from <0.1 to >0.9	No	Mean 1.84 cm	Age: 49 years Female: 29% Genotype 1: Not reported All previously failed treatment, all had Ishak 3 fibrosis within the last year	2/515	Yes
Forns, 2002	Forns Index (age, GGT, cholesterol, platelet count)	Unclear	Derivation and validation samples reported separately	Spain	351 (derivation sample)125 (validation sample)	Derivation vs. validation samplesFibrosis (Scheuer F2-F4): 24% vs. 26%Cirrhosis (Scheuer F4): 6.0% vs. 3.2%	Forns Index <4.21 and >6.9	Yes (for validation sample)	All ≥6 portal tracts	Derivation vs. validation samplesAge: 39 vs. 38 yearsFemale: 36% vs. 36%Genotype 1: 86% vs. 84%All had elevated ALTExcluded regular alcohol >30 g/dayAll treatment-naïve	Unclear	Yes
Gabrielli, 1997	Laminin P1 PIIIP	Unclear	No	Italy	99	Fibrosis (Scheuer F2-F4): Not reported Cirrhosis (Scheuer F4): 16%	Laminin P1 range from 1.4 to 2.4 U/ml PIIIP range from 0.6 to 1.6 U/ml	No	≥5 portal tracts and ≥5 terminal hepatic veins	Age: 50 years Female: 36% Genotype 1: Not reported All had histologically proven chronic hepatitis	Unclear	Unable to construct 2 x 2 table

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Giannini, 2006	AST/ALT ratioPlatelet count	Retrospective	No	Italy and USA	409	Fibrosis (Ishak ≥3 in Italian sample, METAVIR F2-F4 in US sample): 43%	AST/ALT >0.66Platelet count <163,000	No	Not reported	Age: 47 (Italy) and 43 (USA) yearsFemale: 27% and 36%Genotype 1: Not reportedExcludes >40 g alcohol/dayAll treatment-naïve	Unclear	Yes
Giannini, 2003a	AST/ALT ratio Platelet count AST/ALT ratio and platelet count (Pohl Index variant)	Retrospective	Yes (for platelet count and combination of AST/ALT ratio and platelet)	Italy	252	Fibrosis (Scheuer F2-F4 or clinical signs of portal hypertension): 55% Cirrhosis (Scheuer F4 or clinical signs of portal hypertension): 36%	AST/ALT ratio ≥1 Platelet count <130,000	Yes for AST/ALT ratio, no for platelet count	Not reported	Age: 48 years Female: 26% Genotype 1: 57%	Unclear	Yes
Giannini, 2003b	AST/ALT ratio APRI	Retrospective	No	Italy	239	Fibrosis (criteria not reported): 54% Cirrhosis (criteria not reported): 27%	AST/ALT ratio ≥1 APRI cutoffs not reported	Yes for AST/ALT ratio, unclear for APRI	Not reported	Age: 47 years Female: 28% Genotype 1: Not reported	Unclear	Predictive values not reported
Gomes da Silva, 2008	APRI	Retrospective	No	Brazil	50	Fibrosis (METAVIR F2-F4): 56%Cirrhosis (METAVIR F4): 26%	APRI >0.50 to >2.00	Yes (reported best cutoffs and pre-defined cutoffs)	Not reported	Age: 50 yearsFemale: 32%Genotype 1: 54%All treatment-naïve	Not stated	Yes (slight discrepancies)
Guechot, 2010	Hepascore (with automated hyaluronic acid assay)	Prospective	No	France	512	Fibrosis (METAVIR F2-F4): 48% Cirrhosis (METVIR F4): 15%	Hepascore ≥0.25, >0.5, >0.6, >0.75, or >0.84	No	Mean 25 mm, >25 mm in 49%	Age: Median 50 years Female: 40% Genotype 1: Not reported All treatment-naïve	42 excluded due to insufficient liver tissue	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Guechot, 1996	PIIIP Hyaluronic acid	Unclear	No	France	326	Severe fibrosis (Knodell F3-F4): 34% Cirrhosis (Knodell F4): 16%	PIIIP >0.80 or >1.00 U/ml Hyaluronic acid >85 or >100 mcg/l	No	Not reported	Age: 44 years Female: 45% Genotype 1: Not reported All elevated ALT All treatment-naïve	Unclear	Predictive values not reported
Guechot, 1994	PIIIPHyaluronic acid	Unclear	No	France	58	Fibrosis (Knodell F1-3): 76%Cirrhosis (Knodell F3): 17%	PIIIP >0.80 U/mlHyaluronic acid >90 mg/l	No	Not reported	Age: Mean not reported (range 25-68 years)Female: 29%Genotype 1: Not reported	Unclear	Yes
Halfon, 2007	Fibrotest APRI Fibrometer Hepascore	Retrospective	No	France	356	Fibrosis (METAVIR F2-F4): 41% Cirrhosis (METAVIR F4): 4%	FibroMeter >0.57 or >0.88 Fibrotest >0.44 or >0.56 Hepascore >0.32 or >0.61 APRI >0.39 or >0.83	Unclear	All >15 mm	Age: 45 years Female: 47% Genotype 1: Not reported No antiviral treatment in last 6 months	Not reported	Yes
Halfon, 2006	Fibrotest	Prospective	No	France	504	Fibrosis (METAVIR F2-F4): 46% Cirrhosis (METAVIR F4): 5.8%	Fibrotest cutoffs ranged from 0.10 to 0.80	No	Median 15 mm and 9 portal tracts; 55% ≥15 mm and ≥5 portal tracts	Age: 45 years Female: 46% Genotype 1: Not reported	15	Yes
Halfon, 2005	Hyaluronic acid	Prospective	Derivation and validation samples reported separately	France	151 (derivation sample)254 (validation sample)	Derivation vs. validation samplesFibrosis (METAVIR F2-F4): 48% vs. 46%Cirrhosis (METAVIR F4): 7% vs. 5%	Hyaluronic acid ≥16 to >237	Yes (for validation sample)	Biopsy ≥25 mm	Derivation vs. validation samples: 51 vs. 47 yearsFemale: 54% vs. 52%Genotype 1: Not reported	Not reported	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Hsieh, 2009	FibroQ (age, AST, PT, platelets, ALT) AAR APRI	Retrospective	Yes (for FibroQ)	Taiwan	140 (113 HCV, 9 HCV/HBV, 18 HBV)	Fibrosis (METAVIR F2-F4): 83% Cirrhosis (METAVIR F4): 4.3%	FibroQ >1.6 or >2.6 APRI >0.54 to >1 AAR >0.5 to >2.0	No for FibroQ and for some analyses of AAR and APRI	Not reported	Age: 53 years Female: 35% Genotype 1: Not reported No alcohol >20 g/day 6% HBV/HCV coinfected and 13% HBV infected without HCV infection All treatment-naïve	Not stated	Yes
Iacobellis, 2005a	Platelet count, ultrasonographic parameters	Retrospective	Yes, for combined findings	Italy	1143	Fibrosis (Scheuer F2-F4): 57%Cirrhosis (Scheuer F4): 7.2%	Platelet count <140Spleen >120 mmNodular liver presentPortal vein >12 mm	Yes	All ≥5 portal tracts	Age: 53 yearsFemale: 43%Genotype 1: Not reportedAll elevated aminotransferasesAll treatment-naïve	109 (lacking ultrasound parameters)	No, for platelet count <140
Iacobellis, 2005b	AST/ALT ratioPlatelet countGlobulin/albumin ratioCombinations of the aboveAPRIForns' Index	Retrospective	Yes, for combined tests	Italy	1252	Fibrosis (Scheuer F3 or F4): 19%Cirrhosis (Scheuer F4): 6.2%	AST/ALT ratio ≥1Platelet count <140,000 or <150,000Globulin/albumin ratio >1Combinations of the aboveAPRI >1.5 or >2Forns' Index >6.9	Yes	All ≥5 portal tracts	Age: 54 yearsFemale: 43%Genotype 1: Not reportedAll elevated aminotransferasesAll treatment-naïve	Unclear	No
Imbert-Bismut, 2001; Thabut, 2003; Le Calvez, 2004	Fibrotest (original 6-marker version)APRI	Prospective	Derivation and validation samples reported separately	France	205 (derivation sample)134 (validation sample)	Derivation vs. validation sampleFibrosis (METAVIR F2-F4): 38% vs. 45%Cirrhosis (METAVIR F4): 10% vs. 16%	Fibrotest cutoffs ranged from 0.10 to 0.90	No	All ≥10 mm	Derivation vs. validation sampleAge: 47 vs. 48 yearsFemale: 47% vs. 34%Genotype 1: Not reported	38/377 (10%) of derivation + validation samples did not have stageable fibrosis (30) or had missing biomarkers (8)	Yes
Imperiale, 2000	AST/ALT ratio	Retrospective	No	USA	177	Fibrosis: Not reported Cirrhosis (Hytiroglou 4): 23%	AST/ALT ratio ≥1	Yes	Not reported	Age: 42 years Female: 37% Genotype 1: Not reported	Not stated	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Islam, 2005	Normalized ASTPlatelet countAPRIGoteborg University Cirrhosis Index (GUCI) (AST x PT-INR x 100/platelet count)	Retrospective	Yes (for GUCI)	Sweden	179	Fibrosis (Ishak ≥3): 41%Cirrhosis (Ishak 5 or 6): 11%	Normalized AST/ALT ratio >2.0Platelet count <190APRI >1.0GUCI >1.0	No	≥10 mm and ≥4 portal tracts	Age: 44 yearsFemale: 44%Genotype 1: Not reported	Not reported	Yes
Jazia, 2009	AST/ALT ratio APRI Platelet count	Retrospective	No	Tunisia	35	Fibrosis (METAVIR F2-F4): 77% Cirrhosis (METAVIR F4): Not reported	APRI >0.72 AST/ALT ratio and platelet count: Cutoffs not reported	No	Not reported	Age: 49 years Female: 69% Genotype 1: 46% All treatment-naïve	Not reported	No
Kaul, 2002	4-item predictive model (seg, AST, platelet count, spider nevi)	Retrospective	Derivation and validation samples reported separately	USA	264 (derivation sample) 102 (validation sample)	Fibrosis (Scheuer F2-F4): Not reported Cirrhosis (Scheuer F4): 33% (derivation sample) vs. 16% (validation sample)	Not reported (reports only AUROC)	4-item predictive model: Only AUROC reported	Not reported	Derivation vs. validation samples Age: 45 vs. not reported Female: 39% vs. not reported Genotype 1: Not reported All in derivation sample had elevated AST or ALT	Not reported	Measures of diagnostic accuracy not reported
Khan, 2008	APRI	Unclear	No	Pakistan	120	Fibrosis (METAVIR F2-F4): 54%Cirrhosis (METAVIR F4): 8%	APRI >0.5 to >1.75	No	Not reported	Age: 37 yearsFemale: 30%Genotype 1: Not reportedAll treatment-naïve	Unclear	Yes
Khokhar, 2003	Pohl Index	Retrospective	Yes	Pakistan	266	Fibrosis (METAVIR F2-F4): 80% Cirrhosis (METAVIR F4): 56%	Pohl Index positive	No	Not reported	Age: 45 years Female: 44% Genotype 1: Not reported No alcohol use	Unclear	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Koda, 2007	Fibro Index (platelet count, AST, GGT) Forn's Index APRI	Unclear	Derivation and validation samples reported separately	Japan	240 (derivation sample) 162 (validation sample)	Derivation vs. validation sample Fibrosis (METAVIR F2-F3): 51% vs. 50% (excluding F4) Cirrhosis (F4): 0% vs. 0% (excluded from primary analyses; 26% in secondary analysis of validation sample)	Fibro Index >1.25 or ≥2.25 APRI >0.36 or ≥0.85 Forns Index >4.5 or ≥8.7	Yes (for validation sample)	Mean 18 mm, all ≥10 mm	Age: 54 years Female: 40% Genotype 1: Not reported No alcohol >10 g/day All treatment-naïve	Unclear	Yes
Lackner, 2005 and Lackner, 2006	AST/ALT ratioCirrhosis Discriminant ScoreAge-platelet IndexPohl IndexAPRIPlatelet countLok Index	Unclear	No	Austria	194	Fibrosis (Ishak score ≥3): 50%Cirrhosis (Ishak score 5 or 6): 16%	AST/ALT ratio ≥1.0Cirrhosis Discriminant Score ≥8Age-platelet index ≥6Pohl Index positiveAPRI ≥0.5 to ≥2.0Platelet count <130,000 or <150,000Lok Index ≥0.20	Yes	All ≥6 portal tracts	Age: 48 yearsFemale: 43%Genotype 1: 84%No alcohol >20 g/dayAll treatment-naïve	17	Yes
Leroy, 2008	FibroMeterFibrotestHepascoreAPRI	Retrospective	No	France	825	Fibrosis (METAVIR F2-F4): 48%Cirrhosis (METAVIR F4): 11%	Not reported	Unclear	55% >20 mm; 84% >15 mm	Age: 44 yearsFemale: 40%Genotype 1: Not reportedNo alcohol >30 g/dayNo antiviral treatment in last 6 months	441/1266 excluded due to missing data	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Leroy, 2007	MP3FibroMeterFibrotestHepascoreForn's IndexAPRI	Unclear	No	France	180	Fibrosis (METAVIR F2-F4): 51%Cirrhosis (METAVIR F4): 14%	MP3: ranged from >0.20 to >0.50FibroMeter: No cutoff assessed (only estimated AUROC)Fibrotest: ranged from >0.22 to >0.59Hepascore: >0.50 or >0.84Forn's Index: >4.20 or >6.90APRI: ranged from >0.50 to >2.0	Yes	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	Age: 44 yearsFemale: 38%Genotype 1: 61%No alcohol >30 g/dayAll treatment-naïve	Not reported	Yes
Leroy, 2004	Hyaluronic acidPIIIPMP3 score (MMP-1 and PIIIP)	Unclear	Yes	France	188	Fibrosis (METAVIR F2-F4): 45%Cirrhosis (METAVIR F4): 7.4%	MP3 cutoffs ranged from >0.20 to >0.50PIIIP >5 or >6 ng/mlHyaluronic acid >35 ng/ml or >80 g/mlTIMP-1 >1300 ng/ml	No	Not reported	Age: 43 yearsFemale: 36%Genotype 1: 51%All treatment-naïve	Stage of fibrosis not determined in 6 patients	No
Liu, 2006	APRI Age-platelet index AST/ALT ratio Splenic artery pulsatility index	Unclear	No	Taiwan	79	Fibrosis (METAVIR F2-F4): 27% Cirrhosis (METAVIR F4): 0%	APRI >0.40, >0.50, or >1.50 Age-platelet index >4.00 or >6.00 AST/ALT ratio >0.60 or >1.00 Splenic artery pulsatility index >0.85 or >1.05	Unclear	Mean 19 mm length and 1.4 mm diameter	Age: 43 years Female: 65% Genotype 1: 61% All had normal ALT All treatment-naïve	Not stated	Yes
Lo Iacono, 1998	Soluble ICAM-1 Solube VCAM-1 PIIIP	Unclear	No	Italy	52	Fibrosis (Scheuer F2-F4): Not reported Cirrhosis (Scheuer F4): 21%	sICAM-1 >520 ng/ml sVCAM-1 >1208 ng/ml PIIIP >10.57 mcg/ml	No	Not reported	Age: 41 years Female: 37% Genotype 1: 73%	Not reported	Predictive values not reported

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Lok, 2005	Lok Index (platelet count, AST/ALT ratio, and INR)	Prospective	Derivation and validation samples reported separately	USA	783 (derivation sample)358 (internal validation sample)265 (external validation sample)	Derivation vs. internal validation vs. external validation samplesFibrosis (Ishak score ≥3): 100% vs. 100% vs. 48%Cirrhosis (Ishak score 5 or 6): 39% vs. 34% vs. 15%	Lok Index: Ranged from 0.10 to 0.90Platelet count ≤150,000INR >1AST/ALT ratio >1	Yes (for validation sample)	65% ≥ 1.5 cm, 14% >2.5 cm	Derivation vs. internal validation vs. external validation samplesAge: 50 vs. 50 vs. 47 yearsFemale: 28% vs. 27% vs. 36%Genotype 1: 90% vs. 87% vs. 74%All patients in derivation and internal validation samples had failed interferon plus ribavirin therapyAll Ishak ≥3	4 subjects excluded from derivation and internal validation samples due to biopsies too small; 5 subjects excluded from validation sample for missing INR	Yes
Luo, 2002	AST/ALT ratioGlobulin/albumin ratioPlatelet countAST/ALT ratio + globulin/albumin ratioAST/ALT ratio + platelet countGlobulin/albumin ratio + platelet count	Unclear	Yes (for combined tests)	Taiwan	103	Fibrosis (Scheuer F2-F4): 48%Cirrhosis (Scheuer F4): 21%	AST/ALT ratio ≥1Globulin/albumin ratio ≥1Platelet count ≤140,000AST/ALT ratio ≥1 + globulin/albumin ratio ≥1AST/ALT ratio ≥1 + platelet count <140,000Globulin/albumin ratio ≥1 + platelet count ≤140,000	Unclear	All >5 portal tracts	Age: 52 yearsFemale: 31%Genotype 1: Not reportedAll elevated ALTNo alcohol >60 g/day	Not reported (8 excluded for incomplete data)	Yes
Martinez, 2011	Forn's Index APRI Simplified ELF index (PIIIP, HA, and TIMP-1, without age) FIB-4	Unclear	Yes (for modified ELF)	Spain	340	Fibrosis (METAVIR F2-F4): 67% Cirrhosis (METAVIR F4): 36%	Forn's Index >4.2 or >6.9 APRI >0.5, >1, >1.5, or >2 Simplified ELF index >-0.45, >0.06, >1.07, or >1.73 FIB-4 >1.45 or >3.25	Yes, except for modified ELF	Mean 15 mm, 72% >15 mm	Age: 48 years Female: 36% Genotype 1: 74%	Not reported	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
McHutchison, 2000	Hyaluronic acid	Prospective	No	USA	486	Fibrosis (Knodell 1-3): 76%Cirrhosis (Knodell 3): 17%	Hyaluronic acid range from >60 to >100 mcg/l	No	≥1 cm and at least 3 portal tracts	Age: Median 41 yearsFemale: 27%Genotype 1: not reportedExcluded those with history of alcoholism	486/821 enrollees had adequate liver biopsy	Yes
Metwally, 2007	3-item predictive index (platelet count, AST, albumin)	Prospective	No (diagnostic accuracy only reported for validation sample)	USA	137 (validation sample)	Severe fibrosis (METAVIR F3-F4): 23% Cirrhosis (METAVIR F4): Not reported	3-item predictive index: Cutoffs ranged from 1 to 7	No	Not reported	Demographics not reported for validation sample All treatment-naïve	Not reported	Yes
Murawaki, 2001a	Type-IV collagen Platelet count	Unclear	No	Japan	165	Fibrosis (Desmet F2-F3): 47% Cirrhosis (Desmet F4): 0% (excluded)	Type-IV collagen >110 or >130 ng/ml Platelet count: <140,000 or <160,000	No	Not reported	Age: 53 years Female: 33% Genotype 1: Not reported All had elevated ALT All treatment-naïve	Not reported	Yes
Murawaki, 2001b	7S fragment of type IV collagen (PIVNP)PIIIPHyaluronic acidMMP-2TIMP-1ALT	Unclear	No	Japan	169	Fibrosis (Desmet F2-F3): 48%Cirrhosis (Desmet F4): 0% (excluded)	PIVNP >6.0 or >6.5 ng/mlPIIIP >0.80 or >0.90 ng/mlHyaluronic acid >50 or >70 ng/mlMMP-2 >550 or >575 ng/mlTIMP1 >160 or >170 ng/mlALT >80 IU/l	No	Not reported	Age: 53 yearsFemale: 34%Genotype 1: Not reportedAll had elevated ALTAll treatment-naïve	Not reported	Yes
Myers, 2003	Fibrotest7-item index (Fibrotest items plus PT and platelet count)	Unclear	No	France	323	Fibrosis (METAVIR F2-F4): 41%Cirrhosis (METAVIR F4): 13%	Fibrotest: >0.20 and >0.70Platelet count: <150,000Prothrombin time: <80% and 100%Age-platelet Index: >2.0 and >7.0	No	All ≥10 mm	Age: 47 yearsFemale: 42%Genotype 1: Not reportedAll treatment-naïve	Fibrosis not stage able in 30/422; biochemical markers missing in 24/422	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Myers, 2002	Fibrotest Historical index (age at infection and biopsy, sex, and alcohol consumption)	Unclear	Yes (for historical index and revised historical index)	France	211	Fibrosis (METAVIR F2-F4): 40% Cirrhosis (METAVIR F4): 9%	Fibrotest: >0.20 and >0.80 Historical index: >0.20 and >0.60	No	All ≥10 mm	Age: Median 42 years Female: 44% Genotype 1: Not reported All treatment-naïve	Fibrosis not stage able in 30/422; biochemical markers missing in 24/422	Yes
Obrador, 2006	Sabadell NIHCED (non-invasive hepatitis C related cirrhosis early detection) index (age ≥60 years, platelet count ≤100, AST/ALT index ≥1, PT ≥1.1, right hepatic lobe atrophy, splenomegaly, caudate lobe hypertrophy)	Unclear	Derivation and validation samples reported separately	Spain	170 (derivation sample)162 (validation sample)	Derivation vs. validation sampleFibrosis: Not reportedCirrhosis (Knodell F4): 28% and 12%	Sabadell NIHCED index ≥22	No for derivation sample, yes for validation sample	Mean 11.6 mm, 12.2 portal tracts	Derivation vs. validation samplesMean age: 52 vs. 45 yearsFemale: 44% vs. 44%Genotype 1: Not reportedAll elevated liver enzymes	Not reported	Yes
Paggi, 2008	APRI Liver surface nodularity	Unclear	No	Italy	430	Fibrosis (METAVIR F2-F4): 70% Cirrhosis (METAVIR F4): 37%	APRI >1 or >2 Liver surface nodularity present	Yes	Median 4.1 cm	Age: Median 43 years Female: 45% Genotype 1 or 4: 55% All elevated liver enzymes	Not reported	Predictive values not reported
Parise, 2006	Hyaluronic acid APRI GGT AST/ALT ratio	Prospective	No	Brazil	206	Fibrosis (Batt-Ludwig F2-F4): 42% Cirrhosis (Batt- Ludwig F4): 21%	Hyaluronic acid ≥34.2 or ≥78.6 APRI ≥0.70 or >1.5 GGT ≥1.5xULN or ≥2xULN AST/ALT ≥0.8 or >1	No	Not reported	Age: 47 years Female: 44% Genotype 1: 61% Excluded men with >40 g/day and women with >20 g/day alcohol	Not reported	Predictive values not reported
Park, 2000 and 2005	AST/ALT ratio	Retrospective	No	Australia	153	Fibrosis: Not reportedCirrhosis (Scheuer F4): 20%	AST/ALT ratio ≥1	Yes	Not reported	Age: 47 yearsFemale: 36%Genotype 1: Not reportedAll treatment-naïve	Not reported	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Parkes, 2011	Simplified Enhanced Liver Fibrosis index (ELF) (TIMP-1, hyaluronic acid, PIIIP)	Retrospective and prospective (3 cohorts)	Results for HCV patients only reported for validation sample	UK	347	Fibrosis (METAVIR F2-F4 or Ishak ≥3): 51% Cirrhosis (F4 or Ishak 5-6): 14%	Simplified ELF: >9.13 to >10.90	No	Not reported	Age: Median 42 to 45 years (3 cohorts) Female: Not reported Genotype 1: Not reported All treatment-naïve	Not stated	Yes
Patel, 2009	Fibrotest (Fibrosure) FibroSpect II APRI Forn's Index FIB-4	Unclear	No	France, Germany, Canada	95	Fibrosis (METAVIR F2-F4): 95% Cirrhosis: Not reported	Fibrotest ≥0.48 FibroSpect II >0.36 APRI >0.5 or ≥1.5 Forn's Index >4.21 or >6.9 FIB-4 >1.45 or >3.25	Yes	Mean 18 mm	Age: 46 years Female: 40% Genotype 1: Not reported All treatment-naïve	Not stated	Yes
Patel, 2004	FibroSpect II (TIMP-1, alpha-2-macroglobulin, hyaluronic acid)	Retrospective	Derivation and validation samples reported separately	USA and France	294 (derivation sample)402 (validation sample)	Fibrosis (METAVIR F2-F4): 0.52 (both samples)Cirrhosis (METAVIR F4): 18% (derivation sample) and 16% (validation sample)	FibroSpect II: >0.36	No for derivation sample, yes for validation sample	Biopsy ≥10 mm and at least 5 portal tracts	Derivation vs. validation samplesAge: 45 vs. 46 yearsFemale: 31% vs. 35%Genotype 1: Not reportedAll alcohol <10 g/day	Not stated	Yes
Plevris, 2000	Hyaluronic acid	Prospective	No	UK	69 (hepatitis C subgroup)	Fibrosis: Not reported Cirrhosis (Knodell F4): 22%	Hyaluronic acid >100 to >300 mcg/l	No	Not reported	Age: Not reported Female: Not reported Genotype 1: Not reported All treatment-naïve	Not stated	Predictive values not reported
Pohl, 2001	AST/ALT ratio Pohl Index (AST/ALT ratio and platelet count)	Retrospective	Yes	USA	153 (excludes patients with history of alcohol abuse)	Fibrosis (METAVIR F2-F4): 35% Cirrhosis (METAVIR F4): 13%	AST/ALT ratio ≥1 Pohl Index positive (AST/ALT ratio ≥1 and platelet count <150,000)	No (for Pohl Index)	Not reported	Age: 46 years Female: 48% Genotype 1: 49% No history of alcohol abuse	Not stated	Some inconsistency

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Poynard, 2003	Fibrotest	Retrospective	No	Europe, Canada, Argentina, and USA	352	Fibrosis (METAVIR F2-F4): 38%Cirrhosis (METAVIR F4): 8.5%	Fibrotest: No cutoffs reported, only AUROC reported	No	Not reported	Age: 45 yearsFemale: 36%Genotype 2 or 3: 27%All patients had elevated ALTAll treatment-naïve	Not stated, 352/1530 randomized patients included	Predictive values not reported
Poynard, 2002	Fibrotest Hyaluronic acid	Retrospective	No	France	165	F3 fibrosis (Knodell F3): 33% Cirrhosis (Knodell F4): 0%	Fibrotest: No cutoffs reported, only AUROC reported	No	Not reported	Age: 41 years Female: 40% Genotype 1: Not reported All patients had ALT >1.5 x upper limit of normal No chronic alcohol use All treatment-naïve	Not stated, 165/244 randomized patients included	Predictive values not reported
Pradat, 2002	ALT	Unclear	No	Europe	864	Fibrosis (METAVIR F2-F4): 71% Cirrhosis (METAVIR F4): 7.5%	ALT > upper limit or normal or > 2.25 upper limit of normal	Yes (for upper limit of normal), no for >2.25 upper limit of normal	Not reported	Age: Not reported Female: Not reported Genotype: Not reported	Not stated	Yes
Reedy, 1998	AST/ALT ratio	Retrospective	No	USA	71	Fibrosis: Not reportedCirrhosis (Knodell F4): 32%	AST/ALT ratio ≥1	Yes	Not reported	Age: 44 yearsFemale: 31%Genotype 1: Not reportedNo history of significant alcohol	Not stated	Yes
Renou, 2001	Platelet count	Unclear	No	France	104	Fibrosis (METAVIR F2-F4): 45% Cirrhosis (F4): 13%	Platelet count <140,000	No	Not reported	Age: Not reported Female: Not reported Genotype 1: Not reported All had elevated ALT All treatment-naïve	Not stated	Predictive values not reported
Romera, 2006	Forn's Index APRI Fibrosis Probability Index (Sud or Sydney Index)	Retrospective	No	Spain	131	Fibrosis (Scheuer F2-F4): 47% Cirrhosis (Scheuer F4): 17%	Forn's Index ≥4.2 APRI ≥0.5 Fibrosis Probability Index ≥0.2	Yes	Mean 10 portal tracts	Age: 40 years Female: 40% Genotype 1: 43% All treatment-naïve	Not stated	Sensitivity and specificity not provided, calculated from predictive values

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Rosenberg, 2004	European Liver Fibrosis test (age, hyaluronic acid, amino-terminal propeptide of type III collagen, and TIMP-1)	Prospective	No (diagnostic accuracy for HCV subgroup only reported on validation sample)	Europe	Number of HCV patients in validation sample (n=521) not reported	Not reported	ELF cutoffs ranged from >0.063 to >0.564	No	>12 mm and >5 portal tracts	Age: Not reported Female: Not reported Genotype 1: Not reported All abnormal liver function tests for >6 months	Not reported	Unable to construct 2 x 2 table
Rossi, 2003	Fibrotesta-2 macroglobulin Apolipoprotein A1BilirubinGG THaptoglobin	Unclear	No	Australia	125	Fibrosis (METAVIR F2-F4): 38%Cirrhosis (METAVIR F4): 7.2%	Cutoffs ranged from <0.1 to >0.6	Yes for Fibrotest; unclear for individual tests	Not reported	Age: 40 yearsFemale: 34%Genotype 1: Not reported	Not reported	Yes for Fibrotest (predictive values not reported for individual tests)
Saadeh, 2001	Cirrhosis discriminant score	Retrospective	No	USA	111	Fibrosis: Not reported Cirrhosis (Knodell F4): 31%	Cirrhosis discriminant score >3 or >7	No	Not reported	Age: 44 years Female: 25% Genotype 1: Not reported All had elevated ALT	Not reported; results reported for 111/126	Predictive values not reported
Saitou, 2005	Type IV collagen PIIIP Hyaluronic acid YKL-40	Unclear	No	Japan	109	Fibrosis (METAVIR F2-F4): 71% Cirrhosis (METAVIR F4): 28%	Type IV collagen >5.75 or >6.55 ng/ml PIIIP >0.835 or >0.995 U/ml Hyaluronic acid >75.7 or >183.5 ng/ml YKL-40 >186.4 or >284.8 ng/ml	No	Not reported	Age: 54 years Female: 43% Genotype 1: Not reported	Not reported	No
Schneider, 2006	APRIPortal venous flow	Prospective	No	Germany	83	Fibrosis (Ishak 3-6): 57%Cirrhosis (Ishak 5 or 6): 23%	APRI >0.7 or >1.0Portal venous flow <12.5 cm/s	No	Not reported	Age: 48 yearsFemale: 51%Genotype 1: 84%	Not reported	Predictive values not reported

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Schneider, 2005	Portal venous flow Portal venous undulations Hepatic venous flow pattern Longitudinal spleen size Transverse spleen size	Prospective	No	Germany	119	Fibrosis: Not reported Cirrhosis (Ishak 5 or 6): 14%	Portal venous flow: <14.5 cm/s Portal venous undulations: Reduced Hepatic venous flow pattern: Mono- or biphasic Longitudinal spleen size: Not reported Transverse spleen size: >5 cm	No for spleen size and portal venous flow	Not reported	Age: median 45 years Female: 45% Genotype 1: 77%	Not reported	Yes for portal venous undulations, predictive values not reported for other tests
Sebastiani, 2009	APRISAFE fibrosis algorithmSAFE cirrhosis algorithm	Retrospective	No	Europe	2035	Fibrosis (METAVIR F2-F4): 46%Cirrhosis (METAVIR F4): 9.4%	APRI >0.5, >1.0, >1.5, or >2.0SAFE fibrosis algorithm positiveSAFE cirrhosis algorithm positive	Yes	Mean 18 mm and mean 10.6 portal tracts	Age: 47 yearsFemale: 44%Genotype 1: 68%All treatment-naïve	Not reported	Yes
Sebastiani, 2008	Fibrotest AST/ALT ratio Forn's Index Fibroindex APRI	Unclear	No	Italy	244 (80 normal ALT, 164 elevated ALT)	Fibrosis: (METAVIR F2-F4): 60% Cirrhosis (METAVIR F4): 9.8%	Fibrotest >0.49 AST/ALT ratio >1 Forn's Index >4.2 or >6.9 Fibroindex >1.25 or >2.25 APRI >0.5 or >1.5	Yes	All ≥15 mm and ≥7 portal tracts	Age: 48 years Female: 45% Genotype 1: 57%	Not reported	No
Sebastiani, 2006	FibrotestAPRI	Unclear	No	Italy	190	Fibrosis (METAVIR F2-F4): 59%Cirrhosis (F4): 15%	Fibrotest: F2 and F4 cutoffAPRI >2.0	Yes for APRI, unclear for Fibrotest	All ≥1.5 cm and ≥7 portal tracts	Age: 49Female: 44%Genotype 1: 63%No alcohol >20 g/day	Not reported	Some inconsistency
Sheth, 1998	AST/ALT ratio	Retrospective	No	USA	139	Fibrosis: Not reported Cirrhosis (Hytiroglou F4): 34%	AST/ALT ratio ≥1	Yes	Not reported	Age: 44 years Female: 33% Genotype 1: Not reported All had elevated ALT	Not reported	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Silva, 2004	GGT	Retrospective	No	Brazil	201	Severe fibrosis (Desmet 3 or 4): 28% Cirrhosis (Desmet 4): 16%	GGT >1x upper limit of normal	Yes	Not reported	Age: 40 years Female: 29% Genotype 1: Not reported No alcohol >20 g/day All treatment-naïve	Not reported	Predictive values not reported
Snyder, 2006	APRI	Retrospective and prospective	No	USA	339 (retrospective sample)151 (prospective sample)174+176	Fibrosis (Batt-Ludwig F2-F4): 49% (retrospective sample) and 52% (prospective sample)Cirrhosis (Batt-Ludwig F4): 1.8% and 17%	APRI: Cutoffs ranged from ≥0.30 to ≥1.50	No	Not reported	Retrospective vs. prospective samplesAge: 44 vs. 48 yearsFemale: 28% vs. 30%Genotype 1: 76% vs. 74%No antiviral treatment within 1 year	60 patients in retrospective sample didn't have screening test labs, 5 patients in prospective sample unable to obtain biopsy sample	Yes
Sud, 2004	Fibrosis probability index	Prospective	Derivation and validation samples reported separately	Australia	170 (derivation sample)126 (validation sample)	Fibrosis (Scheuer F2-F4): 49% (derivation sample) and 59% (validation sample)Cirrhosis (Scheuer F4): 6% and 13%	Cutoffs ranged from ≥0.2 to ≥0.8	No for derivation sample, yes for validation sample	Not reported	Data reported for derivation sample onlyAge: 41 yearsFemale: 35%Genotype 1: Not reported	Not reported	Yes
Testa, 2006	Body mass index Platelet-spleen diameter ratio APRI Fibrosis model 1 (BMI, APRI, PLT/SPD)	Unclear	Yes (for fibrosis models)	Italy	75	Fibrosis (Ishak ≥3): 49% Cirrhosis (Ishak 5 or 6): 12%	ABT >8.1 BMI >25 Platelet-spleen diameter ratio <1750 APRI >0.864 Fibrosis model 1 >1.589	No	All ≥15 mm; mean 24 mm	Age: 50 years Female: 32% Genotype 1b: 43% All elevated transaminases No alcohol abuse	5/80 had inadequate sample size on liver biopsy	Predictive values not reported
Trocme, 2006	PIIIP/MMP-1 index	Retrospective	No	France	79	Fibrosis (METAVIR F2-F4): 66% Cirrhosis (METAVIR F4): 8.9%	PIIIP/MMP-1 index ≥0.20 or >0.50	Unclear	Not reported	Age: 46 years Female: 43% Genotype 1: 62% All elevated ALT All treatment-naïve	Not stated	Diagnostic accuracy not reported

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Vallet-Pichard, 2007	FIB-4	Retrospective	No	France	847	Fibrosis (METAVIR F2-F4): 36%Cirrhosis (METAVIR F4): 7.2%	FIB-4 ≥1.45 or >3.25	Yes	Not reported	Age: 44 yearsFemale: 46%Genotype 1: Not reported	Not stated	Yes
Verbaan, 1997	Procollagen III propeptide (PIIIP) Type-IV collagen	Retrospective	No	Sweden	98	Fibrosis: Not reported Cirrhosis (Scheuer F4): 11%	PIIIP >1.11 U/ml Type-IV collagen >250 ng/ml	No	Not reported	Age: 46 years Female: 34% Genotype 1: Not reported All treatment-naïve	Not stated	Predictive values not reported
Wai, 2003	Aspartate aminotransferase to platelet ratio index (APRI)	Retrospective	Yes, measures of diagnostic accuracy similar for derivation and validation samples, diagnostic accuracy reported for combined sample	USA	270 (derivation + validation sample)	Fibrosis (Ishak ≥3): 48% Cirrhosis (Ishak 5 or 6): 15%	Cutoffs ranged from >0.50 to >2.00	No (derivation sample)	Not reported	Age: 48 years Female: 36% Genotype 1: 74% All treatment-naïve	20 (4 insufficient liver tissue, 16 incomplete data on CBC and/or liver panel)	Yes
Walsh, 2000	Type-IV collagen Serum laminin ALT	Unclear	No	UK	37	Advanced liver disease (Ishak score ≥3 and HAI ≥6): Not reported	Type IV collagen >148 ng/ml Serum laminin >1.26 U/ml ALT cutoff not reported	Unclear	Not reported	Age: Not reported Female: 32% Genotype 1: Not reported Excludes excess alcohol intake	Not stated	Predictive values not reported
Walsh, 1999a	PIIIPALT	Unclear	No	UK	30	Advanced liver disease (Ishak score ≥3 and HAI ≥6): Not reported	PIIIP (Col 1-3 and Col 1 peptide assay) >0.8 U/mlPIIIP (Col 1-3 peptide) >4.2 mg/lALT >55 IU/l	Unclear	Not reported	Age: Not reportedFemale: 36%Genotype 1: Not reported	Not stated	Predictive values not reported

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive screening exam	Cutoffs pre-defined	Biopsy quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Walsh, 1999b	TIMP-1 TIMP-2 MMP-2 ALT	Unclear	No	UK	43 (TIMP-1 and ALT) 30 (TIMP-2 and MMP-2)	Advanced liver disease (Ishak score ≥3 and HAI ≥6): Not reported	TIMP-1 >500 ng/ml TIMP-2 >102 ng/ml MMP-2 >860 ng/ml ALT >60 IU/l	Unclear	Not reported	Age: Not reported Female: 33% Genotype 1: Not reported	4/43 biopsies insufficient tissue	Predictive values not reported
Williams, 1988	AST/ALT ratio	Unclear	No	USA	44 (non-A, non-B hepatitis subgroup)	Fibrosis: Not reported Cirrhosis (Hoofnagle criteria): 25%	AST/ALT ratio >1.0	Yes	Not reported	Age: 51 years Female: Not reported Genotype 1: Not reported All elevated aminotransferases All treatment-naïve	Not stated	Predictive values not reported
Wilson, 2006	Fibrotest (Fibrosure) APRI ALT AST	Prospective	No	USA	119	Ishak 3-4 fibrosis: 9.2% Cirrhosis (Ishak 5-6): 0% (excluded)	Fibrotest ≥0.31 or >0.48 APRI ≥0.5 or >1.5 ALT >upper limit of normal AST >upper limit of normal	Unclear	Not reported	Age: 42 years Female: 18% Genotype 1: 97%	Not stated	Yes
Wong, 1998	Hyaluronic acidALTa-glutathione-S transferase (GST)	Unclear	No	UK	130	Fibrosis (modified Ishak 3-5 [max 5]): 34%Cirrhosis (modified Ishak 5): 8.5%	Hyaluronic acid: cutoff not reportedALT: cutoff not reportedGST: cutoff not reported	Unclear	Not reported	Age: median 37 yearsFemale: 28%Genotype 1: not reportedExcludes excess alcohol useAll treatment-naïve	Not stated	Predictive values not reported
Zaman, 2007	FibroSpect II	Prospective	No	USA	108	Fibrosis (METAVIR F2-F4): 36% Cirrhosis (METAVIR F4): 2%	FibroSpect II ≥42	Yes	All >15 mm and >5 portal tracts	Age: 44 years Female: 35% Genotype 1: Not reported Alcohol-associated liver disease: 15%	Not stated	Yes

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Adams, 2005	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hepascore ≥0.5: 0.67 (34/51) and 0.63 (37/59) Advanced fibrosis (METAVIR F3-F4) Hepascore ≥0.5: 0.95 (21/22) and 0.88 (21/214) Cirrhosis (METAVIR F4) Hepascore ≥0.84: 0.71 (5/7) and 0.71 (12/17)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hepascore ≥0.5: 0.92 (61/66) and 0.89 (40/45) Advanced fibrosis (METAVIR F3-F4) Hepascore ≥0.5: 0.81 (77/95) and 0.74 (59/80) Cirrhosis (METAVIR F4) Hepascore ≥0.84: 0.84 (92/110) and 0.89 (77/87)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hepascore ≥0.5: 0.87 (34/39) and 0.88 (37/42) Advanced fibrosis (METAVIR F3-F4) Hepascore ≥0.5: 0.54 (21/39) and 0.50 (21/42) Cirrhosis (METAVIR F4) Hepascore ≥0.84: 0.22 (5/23) and 0.55 (12/22)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hepascore ≥0.5: 0.78 (61/78) and 0.65 (40/62) Advanced fibrosis (METAVIR F3-F4) Hepascore ≥0.5: 0.99 (77/78) and 0.95 (59/62) Cirrhosis (METAVIR F4) Hepascore ≥0.84: 0.98 (92/94) and 0.94 (77/82)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hepascore: 0.85 (0.78-0.93) and 0.82 (0.74-0.90) Fibrotest: 0.79 (0.71-0.88) and not reported Advanced fibrosis (METAVIR F3-F4) Hepascore: 0.96 (0.92-1.0) and 0.90 (0.84-0.97) Fibrotest: 0.91 (0.83-0.98) and not reported Cirrhosis (METAVIR F4) Hepascore: 0.94 (0.92-1.0) and 0.89 (0.80-0.98) Fibrotest: 0.97 (0.92-1.0) and not reported	Sir Charles Gairdner Hospital Research Fund	Moderate	
Alsatie, 2007	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) 5-item predictive index score ≥1: 0.88 (53/60) and 0.85 (22/26); ≥4: 0.38 (23/60) and 0.56 (9/26)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) 5-item predictive index score ≥1: 0.53 (69/130) and 0.49 (33/68); ≥4: 0.98 (128/130) and 0.99 (67/68)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) 5-item predictive index score ≥1: 0.46 (53/114) and 0.39 (22/57); ≥4: 0.92 (23/25) and 0.90 (9/10)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) 5-item predictive index score ≥1: 0.91 (69/76) and 0.89 (33/37); ≥4: 0.78 (128/165) and 0.80 (67/84)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) 5-item predictive index: 0.79 and 0.75 (CI's not reported)	National Institutes of Health K24 Grant	Moderate	
Anderson, 2000	Cirrhosis (method unclear) AST/ALT ratio ≥1: 0.31 (19/61)	Cirrhosis (method unclear) AST/ALT ratio ≥1: 0.99 (71/72)	Cirrhosis (method unclear) AST/ALT ratio ≥1: 0.95 (19/20)	Cirrhosis (method unclear) AST/ALT ratio ≥1: 0.67 (71/113)	Not reported	Not reported	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Becker, 2009	Fibrosis (METAVIR F2-F4)Hepascore ≥0.55: 0.82 (161/196)Severe fibrosis (METAVIR F3-F4)Hepascore >0.2: 0.99 (138/139); ≥0.8: 0.67 (93/139)APRI >0.5: 0.77 (107/139); >1.5: 0.27 (38/139)FIB-4 ≥1.45: 0.73 (101/139); >3.25: 0.30 (42/139)	Fibrosis (METAVIR F2-F4)Hepascore ≥0.55: 0.65 (127/195)Severe fibrosis (METAVIR F3-F4)Hepascore >0.2: 0.23 (58/252); ≥0.8: 0.77 (194/252)APRI >0.5: 0.60 (152/252); >1.5: 0.97 (245/252)FIB-4 ≥1.45: 0.67 (169/252); >3.25: 0.98 (248/252)	Fibrosis (METAVIR F2-F4)Hepascore ≥0.55: 0.70 (161/229)Severe fibrosis (METAVIR F3-F4)Hepascore >0.2: 0.42 (138/332); ≥0.8: 0.62 (93/151)APRI >0.5: 0.52 (107/207); >1.5: 0.84 (38/45)FIB-4 ≥1.45: 0.55 (101/184); >3.25: 0.91 (42/46)	Fibrosis (METAVIR F2-F4)Hepascore ≥0.55: 0.78 (127/162)Severe fibrosis (METAVIR F3-F4)Hepascore >0.2: 0.98 (58/59); ≥0.8: 0.81 (194/240)APRI >0.5: 0.83 (152/184); >1.5: 0.71 (245/346)FIB-4 ≥1.45: 0.82 (169/207); >3.25: 0.72 (248/345)	Fibrosis (METAVIR F2-F4)Hepascore: 0.81 (CI not reported)Severe fibrosis (METAVIR F3-F4)Hepascore: 0.83 (CI not reported)APRI: Not reportedFIB-4: Not reportedCirrhosis (METAVIR F4)Hepascore: 0.88 (CI not reported)	Quest Diagnostics	Moderate	AUROC for Hepascore and fibrosis similar when biopsies <10 mm included (0.81) and excluded (0.82).Excluding patients with single hepascore component elevation resulted in better diagnostic accuracy.PPV for fibrosis increased from 0.62 for hepascore ≥0.8 alone to 0.91 with hepascore ≥0.8 followed by FIB>3.25 and to 0.82 for hepascore ≥0.8 followed by APRI >1.5
Bejarano, 2009	Severe fibrosis (Knodell 3-4) Sabadell NIHCED index >6: 0.72 (137/190)	Severe fibrosis (Knodell 3-4) Sabadell NIHCED index >6: 0.75 (98/131)	Severe fibrosis (Knodell 3-4) Sabadell NIHCED index >6: 0.81 (137/170)	Severe fibrosis (Knodell 3-4) Sabadell NIHCED index >6: 0.64 (98/151)	Severe fibrosis (Knodell 3-4) Sabadell NIHCED index: 0.79 (0.74-0.84)	Corporacio Parc Taulf, Instituto de Salud Carlos III	Moderate	Same population as Obrador, 2006
Berg, 2004	Fibrosis (Scheuer F2-F4) APRI >0.50: 0.82 (207/253) APRI >1.50: 0.37 (93/253) Cirrhosis (Scheuer F4) APRI >1.0: 0.76 (47/62) APRI >2.0: 0.48 (30/62)	Fibrosis (Scheuer F2-F4) APRI >0.50: 0.53 (122/231) APRI >1.50: 0.93 (215/231) Cirrhosis (Scheuer F4) APRI >1.0: 0.74 (310/422) APRI >2.0: 0.89 (377/422)	Fibrosis (Scheuer F2-F4) APRI >0.50: 0.66 (207/316) APRI >1.50: 0.85 (93/109) Cirrhosis (Scheuer F4) APRI >1.0: 0.30 (47/159) APRI >2.0: 0.40 (30/75)	Fibrosis (Scheuer F2-F4) APRI >0.50: 0.73 (122/168) APRI >1.50: 0.57 (215/375) Cirrhosis (Scheuer F4) APRI >1.0: 0.95 (310/325) APRI >2.0: 0.92 (377/409)	Not reported	German BMBF Network of Competence for Viral Hepatitis (Hep Net)	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Boeker, 2002	Fibrosis (Ishak, grades not reported)TIMP-1 (Biotrak) >950 mcg/l: 0.52 (14/27)TIMP-1 (Quantikine) >85 mcg/l: 0.67 (18/27)MMP-2 (Biotrak) >1500 mcg/l: 0.07 (2/27)MMP-2 (Quantikine) >320 mcg/l: 0.07 (2/27)Hyaluronic acid >30 mcg/l: 0.48 (13/27)AST >18 U/l: 0.78 (21/27)ALT >22 U/l: 0.96 (26/27)Alkaline phosphatase >190 U/l: 0.22 (6/27)GGT >28 U/l: 0.67 (18/27) [0.65*]Albumin <37 g/l: 0.26 (7/27) [0.27*]Cirrhosis (Ishak, grades not reported)TIMP-1 (Biotrak) >950 mcg/l: 1.0 (19/19)TIMP-1 (Quantikine) >85 mcg/l: 1.0 (19/19)MMP-2 (Biotrak) >1500 mcg/l: 0.74 (14/19)MMP-2 (Quantikine) >320 mcg/l: 0.84 (16/19) [0.84*]Hyaluronic acid >30 mcg/l: 0.89 (17/19) [0.90*]AST >18 U/l: 0.79 (15/19) [0.81*]ALT >22 U/l: 0.89 (17/19) [0.88*]Alkaline phosphatase >190 U/l: 0.47 (9/19)GGT >28 U/l: 0.74 (14/19) [0.73*]Albumin <37 g/l: 0.74 (14/19) [0.73*]	Fibrosis (Ishak, grades not reported)TIMP-1 (Biotrak) >950 mcg/l: 0.88 (28/32)TIMP-1 (Quantikine) >85 mcg/l: 0.69 (22/32) [0.68*]MMP-2 (Biotrak) >1500 mcg/l: 1.0 (32/32)MMP-2 (Quantikine) >320 mcg/l: 0.97 (31/32)Hyaluronic acid >30 mcg/l: 0.84 (27/32)AST >18 U/l: 0.41 (13/32) [0.40*]ALT >22 U/l: 0.16 (5/32)Alkaline phosphatase >190 U/l: 0.84 (27/32)GGT >28 U/l: 0.53 (17/32)Albumin <37 g/l: 0.91 (29/32) [0.90*]Cirrhosis (Ishak, grades not reported)TIMP-1 (Biotrak) >950 mcg/l: 0.75 (44/59)TIMP-1 (Quantikine) >85 mcg/l: 0.56 (33/59)MMP-2 (Biotrak) >1500 mcg/l: 1.0 (59/59)MMP-2 (Quantikine) >320 mcg/l: 0.97 (57/59) [0.96*]Hyaluronic acid >30 mcg/l: 0.73 (43/59)AST >18 U/l: 0.59 (35/59) [0.60*]ALT >22 U/l: 0.10 (6/59) [0.11*]Alkaline phosphatase >190 U/l: 0.85 (50/59) [0.85*]GGT >28 U/l: 0.47 (28/59)Albumin <37 g/l: 0.86 (51/59)	Fibrosis (Ishak, grades not reported)TIMP-1 (Biotrak) >950 mcg/l: 0.78 (14/18)TIMP-1 (Quantikine) >85 mcg/l: 0.64 (18/28)MMP-2 (Biotrak) >1500 mcg/l: 1.0 (2/2)MMP-2 (Quantikine) >320 mcg/l: 0.67 (2/3)Hyaluronic acid >30 mcg/l: 0.72 (13/18)AST >18 U/l: 0.52 (21/40)ALT >22 U/l: 0.49 (26/53)Alkaline phosphatase >190 U/l: 0.55 (6/11)GGT >28 U/l: 0.55 (18/33)Albumin <37 g/l: 0.70 (7/10)Cirrhosis (Ishak, grades not reported)TIMP-1 (Biotrak) >950 mcg/l: 0.56 (19/34)TIMP-1 (Quantikine) >85 mcg/l: 0.42 (19/45)MMP-2 (Biotrak) >1500 mcg/l: 1.0 (14/14)MMP-2 (Quantikine) >320 mcg/l: 0.89 (16/18)Hyaluronic acid >30 mcg/l: 0.52 (17/33)AST >18 U/l: 0.38 (15/39)ALT >22 U/l: 0.24 (17/70)Alkaline phosphatase >190 U/l: 0.50 (9/18)GGT >28 U/l: 0.31 (14/45)Albumin <37 g/l: 0.64 (14/22)	Fibrosis (Ishak, grades not reported)TIMP-1 (Biotrak) >950 mcg/l: 0.68 (28/41)TIMP-1 (Quantikine) >85 mcg/l: 0.71 (22/31)MMP-2 (Biotrak) >1500 mcg/l: 0.56 (32/57)MMP-2 (Quantikine) >320 mcg/l: 0.55 (31/56)Hyaluronic acid >30 mcg/l: 0.66 (27/41)AST >18 U/l: 0.68 (13/19)ALT >22 U/l: 0.83 (5/6)Alkaline phosphatase >190 U/l: 0.56 (27/48)GGT >28 U/l: 0.65 (17/26)Albumin <37 g/l: 0.59 (29/49)Cirrhosis (Ishak, grades not reported)TIMP-1 (Biotrak) >950 mcg/l: 1.0 (44/44)TIMP-1 (Quantikine) >85 mcg/l: 1.0 (33/33)MMP-2 (Biotrak) >1500 mcg/l: 0.92 (59/64)MMP-2 (Quantikine) >320 mcg/l: 0.95 (57/60)Hyaluronic acid >30 mcg/l: 0.96 (43/45)AST >18 U/l: 0.90 (35/39)ALT >22 U/l: 0.75 (6/8)Alkaline phosphatase >190 U/l: 0.83 (50/60)GGT >28 U/l: 0.85 (28/33)Albumin <37 g/l: 0.91 (51/56)	Not reported	Gesselschaft der Freunde der MHH	High	Excluded patients with cirrhosis from fibrosis analyses; appeared to use case-control design for cirrhosis analysis
Bonacini, 1997	(Knodell F3-F4)Cirrhosis discriminant score ≥7: 0.86 (24/28); ≥8: 0.46 (13/28)AST/ALT ratio >1: 0.83 (23/28)	(Knodell F3-F4)Cirrhosis discriminant score ≥7: 0.84 (43/51); ≥8: 0.98 (50/51)AST/ALT ratio >1: 0.75 (38/51)	(Knodell F3-F4)Cirrhosis discriminant score ≥7: 0.75 (24/32); ≥8: 0.93 (13/14)AST/ALT ratio >1: 0.64 (23/36)	(Knodell F3-F4)Cirrhosis discriminant score ≥7: 0.91 (43/47); ≥8: 0.77 (50/65)AST/ALT ratio >1: 0.88 (38/43)	Not reported	Not stated	Moderate	Study reports 77 enrolled but diagnostic results presented for 79; 22% HIV-positive

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Borroni, 2006	Cirrhosis (Knodell F4) AST/ALT ratio ≥1: 0.30 (9/30) Cirrhosis Discriminant Score >2: 1.0 (30/30); >7: 0.17 (5/30) APRI >1: 0.77 (23/30); ≥2: 0.43 (13/30) Pohl's Index positive: 0.27 (8/30) Age-platelet index ≥6: 0.67 (20/30) Combination A (APRI and age-platelet index) (cutoff not reported): 0.37 (11/30) Combination B (APRI and age-platelet index) (cutoff not reported): 0.73 (22/30)	Cirrhosis (Knodell F4) AST/ALT ratio ≥1: 0.97 (192/198) Cirrhosis Discriminant Score >2: 0.22 (43/198); >7: 1.0 (198/198) APRI >1: 0.83 (164/198); ≥2: 0.94 (186/198) Pohl's Index positive: 0.99 (196/198) Age-platelet index ≥6: 0.87 (172/198) Combination A (APRI and age-platelet index) (cutoff not reported): 0.98 (194/198) Combination B (APRI and age-platelet index) (cutoff not reported): 0.83 (164/198)	Cirrhosis (Knodell F4) AST/ALT ratio ≥1: 0.60 (9/15) [0.57*] Cirrhosis Discriminant Score >2: 0.16 (30/185); >7: 1.0 (5/5) APRI >1: 0.40 (23/57); ≥2: 0.52 (13/25) [0.54*] Pohl's Index positive: 0.80 (8/10) Age-platelet index ≥6: 0.43 (20/46) [0.46*] Combination A (APRI and age-platelet index) (cutoff not reported): 0.73 (11/15) [0.79*] Combination B (APRI and age-platelet index) (cutoff not reported): 0.39 (22/56)	Cirrhosis (Knodell F4) AST/ALT ratio ≥1: 0.90 (192/213) Cirrhosis Discriminant Score >2: 1.0 (43/43); >7: 0.89 (198/223) APRI >1: 0.96 (164/171); ≥2: 0.92 (186/203) Pohl's Index positive: 0.90 (196/218) Age-platelet index ≥6: 0.95 (172/182) Combination A (APRI and age-platelet index) (cutoff not reported): 0.91 (194/213) Combination B (APRI and age-platelet index) (cutoff not reported): 0.95 (164/172)	Cirrhosis (Knodell F4) AST/ALT ratio: 0.76 (0.68-0.84) Cirrhosis Discriminant Score : 0.83 (0.75-0.92) APRI: 0.86 (0.79-0.93) Pohl's Index: Not reported Age-platelet index: 0.88 (0.82-0.94) Combinations A and B (APRI and age-platelet index): Not reported	No external funding	Moderate	
Bourliere, 2008	Cutoffs unclear except as notedFibrosis (METAVIR F2-F4)Hepascore: 0.55 (134/231); ≥0.5: 0.63 (146/231)Fibrotest: 0.62 (143/231)Severe fibrosis (METAVIR F3-F4)Hepascore: 0.69 (90/130)Fibrotest: 0.69 (90/130)Cirrhosis (METAVIR F4)Hepascore: 0.86 (30/35); ≥0.84: 0.71 (25/35)Fibrotest: 0.91 (32/35)	Cutoffs unclear except as notedFibrosis (METAVIR F2-F4)Hepascore: 0.86 (203/236); ≥0.5: 0.86 (203/236)Fibrotest: 0.86 (203/236)Severe fibrosis (METAVIR F3-F4)Hepascore: 0.87 (293/337)Fibrotest: 0.86 (290/337)Cirrhosis (METAVIR F4)Hepascore: 0.83 (359/432); ≥0.84: 0.88 (380/432)Fibrotest: 0.75 (324/432)	Cutoffs unclear except as notedFibrosis (METAVIR F2-F4)Hepascore: 0.80 (134/167) [0.82*]; ≥0.5: 0.82 (146/179)Fibrotest: 0.81 (143/176)Severe fibrosis (METAVIR F3-F4)Hepascore: 0.67 (90/134)Fibrotest: 0.66 (90/137) [0.65*]Cirrhosis (METAVIR F4)Hepascore: 0.29 (30/103); ≥0.84: 0.32 (25/77) [0.33*]Fibrotest: 0.23 (32/140)	Cutoffs unclear except as notedFibrosis (METAVIR F2-F4)Hepascore: 0.68 (203/300) [0.69*]; ≥0.5: 0.70 (203/288)Fibrotest: 0.70 (203/291) [0.67*]Severe fibrosis (METAVIR F3-F4)Hepascore: 0.88 (293/333)Fibrotest: 0.88 (290/330)Cirrhosis (METAVIR F4)Hepascore: 0.99 (359/364); ≥0.84: 0.97 (380/390)Fibrotest: 0.99 (324/327)	Fibrosis (METAVIR F2-F4)Hepascore: 0.82 (0.79-0.86)Fibrotest: 0.83 (0.79-0.86)Severe fibrosis (METAVIR F3-F4)Hepascore: 0.84 (0.80-0.87)Fibrotest: 0.84 (0.80-0.87)Cirrhosis (METAVIR F4)Hepascore: 0.90 (0.87-0.93)Fibrotest: 0.89 (0.86-0.93)	Reports no financial support or competing interests	Moderate	Population overlaps with Halfon 2006 and Halfon 2007 and Bourliere 2006. Diagnostic accuracy of Hepascore at defined cutoffs doesn't match tables comparing Hepascore and Fibrotest (with undefined cutoffs). Study evaluated a number of algorithms but didn't report diagnostic accuracy of them.

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Bourliere, 2006	Fibrosis (METAVIR F2-F4) Fibrotest >0.1: 0.97 (96/99); ≥0.6: 0.55 (54/99) APRI >0.5: 0.70 (69/99); ≥1.5: 0.22 (22/99) Forn's Index ≥4.21: 0.90 (79/99); >6.9: 0.30 (30/99) Cirrhosis (METAVIR F4) APRI >1.0: 0.69 (11/16); >2: 0.38 (6/16)	Fibrosis (METAVIR F2-F4) Fibrotest >0.1: 0.20 (27/136); ≥0.6: 0.90 (122/136) APRI >0.5: 0.55 (75/136); ≥1.5: 0.95 (129/136) Forn's Index ≥4.21: 0.54 (73/136); >6.9: 0.96 (130/136) Cirrhosis (METAVIR F4) APRI >1.0: 0.82 (180/219); >2: 0.96 (210/219)	Fibrosis (METAVIR F2-F4) Fibrotest >0.1: 0.45 (96/215) [0.47*]; ≥0.6: 0.79 (54/68) APRI >0.5: 0.53 (69/130); ≥1.5: 0.76 (22/29) Forn's Index ≥4.21: 0.56 (79/142); >6.9: 0.83 (30/36) Cirrhosis (METAVIR F4) APRI >1.0: 0.22 (11/50); >2: 0.40 (6/15)	Fibrosis (METAVIR F2-F4) Fibrotest >0.1: 0.590(27/30); ≥0.6: 0.73 (122/167) APRI >0.5: 0.71 (75/105); ≥1.5: 0.63 (129/206) Forn's Index ≥4.21: 0.78 (73/93) [0.79*]; >6.9: 0.65 (130/199) Cirrhosis (METAVIR F4) APRI >1.0: 0.97 (180/185); >2: 0.95 (210/220) [0.96*]	Fibrosis (METAVIR F2-F4) Fibrotest: 0.81 (0.76-0.86) APRI: 0.71 (0.67-0.79) Forn's Index: 0.76 (0.70-0.82) Cirrhosis (METAVIR F4) APRI: 0.81 (0.76-0.86)	Not stated	Moderate	Population (Fibropaca) overlaps with Halfon 2006 and Halfon 2007 and Bourliere 2008. Study evaluated an algorithm but didn't report diagnostic accuracy.
Boursier, 2011	Not reported	Not reported	Not reported	Not reported	Fibrosis (derivation and validation samples, respectively) FibroMeter: 0.81 (0.78-0.83) and 0.84 (0.82-0.86)	French National Agency for Research on AIDS and Viral Hepatitis	Moderate	FIBROSTAR study database

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Boursier, 2009	Severe Fibrosis (METAVIR F3-F4)Fibrometer >0.628: 0.84 (221/264); >0.830: 0.60 (158/264)Fibrotest >0.448: 0.84 (223/264); >0.631: 0.67 (176/264)Hepascore >0.497: 0.82 (217/264); >0.904: 0.48 (127/264)APRI >0.581: 0.78 (205/264); >1.159: 0.51 (134/264)Cirrhosis (METAVIR F4)Fibrometer >0.628: 0.96 (111/116); >0.979: 0.36 (41/116)Fibrotest >0.660: 0.82 (96/116); >0.862: 0.42 (49/116)Hepascore >0.801: 0.80 (93/116); >0.999: 0.38 (45/116)APRI >0.652: 0.85 (98/116); >2.532: 0.27 (32/116)Modified Fibrometer >0.089: 0.87 (101/116); >0.442: 0.55 (64/116)	Severe Fibrosis (METAVIR F3-F4)Fibrometer >0.628: 0.79 (629/792); >0.830: 0.91 (722/792)Fibrotest >0.448: 0.71 (563/792); >0.631: 0.84 (664/792)Hepascore >0.497: 0.71 (560/792); >0.904: 0.93 (737/792)APRI >0.581: 0.75 (591/792); >1.159: 0.92 (726/792)Cirrhosis (METAVIR F4)Fibrometer >0.628: 0.71 (668/940); >0.979: 0.98 (921/940)Fibrotest >0.660: 0.77 (726/940); >0.862: 0.96 (898/940)Hepascore >0.801: 0.82 (776/940); >0.999: 0.98 (926/940)APRI >0.652: 0.72 (672/940); >2.532: 0.98 (918/940)Modified Fibrometer >0.089: 0.81 (761/940); >0.442: 0.98 (920/940)	Severe Fibrosis (METAVIR F3-F4)Fibrometer >0.628: 0.58 (221/384); >0.830: 0.69 (158/228) [0.70*]Fibrotest >0.448: 0.49 (223/452); >0.631: 0.58 (176/304) [0.57*]Hepascore >0.497: 0.48 (217/449); >0.904: 0.70 (127/182)APRI >0.581: 0.50 (205/406); >1.159: 0.67 (134/200)Cirrhosis (METAVIR F4)Fibrometer >0.628: 0.29 (111/383) [0.30*]; >0.979: 0.68 (41/60) [0.70*]Fibrotest >0.660: 0.31 (96/310) [0.29*]; >0.862: 0.54 (49/91) [0.52*]Hepascore >0.801: 0.36 (93/257) [0.37*]; >0.999: 0.76 (45/59)APRI >0.652: 0.27 (98/366); >2.532: 0.59 (32/54) [0.62*]Modified Fibrometer >0.089: 0.36 (101/280) [0.37*]; >0.442: 0.76 (64/84) [0.77*]	Severe Fibrosis (METAVIR F3-F4)Fibrometer >0.628: 0.94 (629/672 [0.93*]); >0.830: 0.87 (722/828)Fibrotest >0.448: 0.93 (563/604) [0.94*]; >0.631: 0.88 (664/752) [0.89*]Hepascore >0.497: 0.92 (560/607); >0.904: 0.84 (737/874)APRI >0.581: 0.91 (591/650); >1.159: 0.85 (726/856)Cirrhosis (METAVIR F4)Fibrometer >0.628: 0.99 (668/673); >0.979: 0.92 (921/996)Fibrotest >0.660: 0.97 (726/746) [0.98*]; >0.862: 0.93 (898/965) [0.94*]Hepascore >0.801: 0.97 (776/799); >0.999: 0.93 (926/997)APRI >0.652: 0.97 (672/690); >2.532: 0.92 (918/1002)Modified Fibrometer >0.089: 0.98 (761/776); >0.442: 0.95 (920/972) [0.94*]	Severe Fibrosis (METAVIR F3-F4)Fibrometer: 0.88 (0.86-0.91)Fibrotest: 0.84 (0.81-0.86)Hepascore: 0.83 (0.81-0.86)APRI: 0.82 (0.79-0.85)Cirrhosis (METAVIR F4)Fibrometer: 0.91 (0.88-0.93)Fibrotest: 0.88 (0.86-0.91)Hepascore: 0.90 (0.87-0.92)APRI: 0.84 (0.80-0.88)Modified Fibrometer: 0.92 (CI not reported)	French Department of Health	Moderate	Same population as Cales, 2008 (which included Cales 2005 (excluded b/c it evaluated patients with HBV and HCV infection), Halfon 2007, and Leroy 2007)

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Burton, 2011	Whole sample, black subjects, and white subjects, respectivelyFibrosis (Batt-Ludwig 2-4)APRI >0.60: 0.70 (92/131), 0.65 (38/58), 0.75 (52/69)Severe fibrosis (Batt-Ludwig 3-4)APRI >0.99: 0.65 (47/72), 0.62 (18/29), 0.70 (29/41)Cirrhosis (Batt-Ludwig 4)APRI >1.0: 0.74 (33/44), 0.60 (9/15), 0.85 (24/28)	Whole sample, black subjects, and white subjects, respectivelyFibrosis (Batt-Ludwig 2-4)APRI >0.60: 0.72 (99/137), 0.75 (63/84), 0.68 (33/48)Severe fibrosis (Batt-Ludwig 3-4)APRI >0.99: 0.82 (161/196), 0.86 (97/113), 0.75 (57/76)Cirrhosis (Batt-Ludwig 4)APRI >1.0: 0.78 (175/224), 0.81 (103/127), 0.73 (65/89)	Whole sample, black subjects, and white subjects, respectivelyFibrosis (Batt-Ludwig 2-4)APRI >0.60: 0.71 (92/130) [0.72*], 0.67 (38/57) [0.68*], 0.78 (52/67) Severe fibrosis (Batt-Ludwig 3-4)APRI >0.99: 0.57 (47/82), 0.53 (18/34) [0.55*], 0.60 (29/48) [0.61*]Cirrhosis (Batt-Ludwig 4)APRI >1.0: 0.40 (33/82), 0.27 (9/33), 0.50 (24/48)	Whole sample, black subjects, and white subjects, respectivelyFibrosis (Batt-Ludwig 2-4)APRI >0.60: 0.72 (99/138) [0.73*], 0.76 (63/83 [0.77*], 0.66 (33/50)Severe fibrosis (Batt-Ludwig 3-4)APRI >0.99: 0.87 (161/186), 0.90 (97/108), 0.83 (57/69)Cirrhosis (Batt-Ludwig 4)APRI >1.0: 0.94 (175/186), 0.94 (103/109) [0.95*], 0.94 (65/69)	Black and white samples, respectively (not reported for whole sample)Fibrosis (Batt-Ludwig 2-4) APRI: 0.70 (0.60-0.80) and 0.76 (0.66-0.76)Severe fibrosis (Batt-Ludwig 3-4)APRI: 0.77 (0.65-0.89) and 0.76 (0.66-0.86)Cirrhosis (Batt-Ludwig 4)APRI: 0.75 (0.59-0.91) and 0.82 (0.74-0.90)	South Central VA Healthcare Network	Moderate	
Cales, 2008	Fibrosis (METAVIR F2-F4) FibroMeter >0.419: 0.80 (439/549) Fibrotest >0.435: 0.68 (372/549) Hepascore >0.46: 0.66 (363/549) APRI >0.55: 0.62 (343/549) FIB-4 >1.116: 0.74 (406/549)	Fibrosis (METAVIR F2-F4) FibroMeter >0.419: 0.76 (385/507) Fibrotest >0.435: 0.82 (415/507) Hepascore >0.46: 0.79 (401/507) APRI >0.55: 0.84 (423/507) FIB-4 >1.116: 0.72 (365/507)	Fibrosis (METAVIR F2-F4) FibroMeter >0.419: 0.78 (439/561) Fibrotest >0.435: 0.80 (372/464) Hepascore >0.46: 0.77 (363/469) [0.78*] APRI >0.55: 0.80 (343/427) FIB-4 >1.116: 0.74 (406/548)	Fibrosis (METAVIR F2-F4) FibroMeter >0.419: 0.78 (385/495) Fibrotest >0.435: 0.70 (415/592) Hepascore >0.46: 0.68 (401/587) APRI >0.55: 0.67 (423/629) FIB-4 >1.116: 0.72 (365/508)	Fibrosis (METAVIR F2-F4) FibroMeter: 0.85 Fibrotest: 0.81 Hepascore: 0.78 APRI: 0.79 FIB-4: 0.80	French Department of Health	Moderate	Same population as Boursier, 2009 (which included Cales 2005 (excluded b/c it evaluated patients with HBV and HCV infection), Halfon 2007, and Leroy 2007)
Castera, 2010	Fibrosis (METAVIR F2-F4) SAFE algorithm: 1.0 (230/230) Cirrhosis (METAVIR F4) SAFE algorithm: 0.86 (64/74)	Fibrosis (METAVIR F2-F4) SAFE algorithm: 0.87 (63/72) Cirrhosis (METAVIR F4) SAFE algorithm: 0.90 (205/228)	Fibrosis (METAVIR F2-F4) SAFE algorithm: 0.96 (230/239) Cirrhosis (METAVIR F4) SAFE algorithm: 0.74 (64/87) [0.78*]	Fibrosis (METAVIR F2-F4) SAFE algorithm: 1.0 (63/63) Cirrhosis (METAVIR F4) SAFE algorithm: 0.95 (205/215) [0.94*]	Fibrosis (METAVIR F2-F4) SAFE algorithm: 0.94 (0.90-0.98) Cirrhosis (METAVIR F4) SAFE algorithm: 0.87 (0.84-0.90)	Authors report no funding from industry or conflicts of interests	Moderate	Same population as Castera 2009 and incorporates population from Castera 2005
Castera, 2009	Cirrhosis (METAVIR F4)Platelet count <150: 0.41 (29/70)Fibrotest ≥0.75: 0.56 (39/70)Prothrombin index ≤85%: 0.36 (25/70)AST/ALT ratio ≥1: 0.31 (22/70)APRI ≥1.0: 0.64 (45/70); ≥2.0: 0.30 (21/70)Lok Index ≥0.2: 0.86 (60/70); ≥0.5: 0.40 (28/70)	Cirrhosis (METAVIR F4)Platelet count <150: 0.94 (214/228)Fibrotest ≥0.86: 0.55 (197/228)Prothrombin index ≤85%: 0.90 (205/228)AST/ALT ratio ≥1: 0.89 (203/228)APRI ≥1.0: 0.82 (186/228) [0.81*]; ≥2.0: 0.94 (215/228)Lok Index ≥0.2: 0.46 (105/228); ≥0.5: 0.94 (215/228)	Cirrhosis (METAVIR F4)Platelet count <150: 0.67 (29/43)Fibrotest ≥0.75: 0.56 (39/70) [0.55*]Prothrombin index ≤85%: 0.52 (25/48)AST/ALT ratio ≥1: 0.47 (22/47)APRI ≥1.0: 0.52 (45/87); ≥2.0: 0.62 (21/34)Lok Index ≥0.2: 0.33 (60/183) [0.32*]; ≥0.5: 0.68 (28/41)	Cirrhosis (METAVIR F4)Platelet count <150: 0.84 (214/255)Fibrotest ≥0.86: 0.86 (197/228)Prothrombin index ≤85%: 0.82 (205/250)AST/ALT ratio ≥1: 0.81 (203/251)APRI ≥1.0: 0.88 (186/211); ≥2.0: 0.81 (215/264)Lok Index ≥0.2: 0.91 (105/115); ≥0.5: 0.84 (215/257)	Cirrhosis (METAVIR F4)Platelet count: 0.79 (0.72-0.85)Fibrotest: 0.82 (0.73-0.86)Prothrombin index: 0.73 (0.66-0.80)AST/ALT ratio: 0.61 (0.53-0.70)APRI: 0.80 (0.74-0.86)Lok Index: 0.80 (0.73-0.86)	No funding from manufacturers of tests evaluated in study	Low	Same population as Castera 2010 and incorporates population from Castera 2005

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Castera, 2005	Not reported	Not reported	Not reported	Not reported	Fibrosis (METAVIR F2-F4) APRI: 0.78 (0.70-0.85) Fibrotest: 0.85 (0.78-0.90) Severe fibrosis (METAVIR F3-F4) APRI: 0.84 (0.78-0.89) Fibrotest: 0.90 (0.85-0.94)	Not stated	Low	Same population incorporated in Castera 2009 and 2010
Cheong, 2011	Not reported for HCV subgroup	Not reported for HCV subgroup	Not reported for HCV subgroup	Not reported for HCV subgroup	Validation sample only Fibrosis (METAVIR F2-F4) Significant Fibrosis Index: 0.80 (0.70-0.90) Zeng Index: 0.80 (0.70-0.90) APRI: 0.82 (0.72-0.92) Forn's Index: 0.80 (0.70-0.90) FIB-4: 0.80 (0.70-0.90) ELF index: 0.72 (0.60-0.84)	Ministry for Health, Welfare and Family Affairs, Republic of Korea	Moderate	
Cheung, 2011	Fibrosis (METAVIR F2-F4)Fibrosis-protein index >3.53: 0.81 (75/93) [0.80-0.83*]APRI >0.5: Not reportedSevere fibrosis (METAVIR F3-F4)Fibrosis-protein Index >4.78: 0.79 (33/42) [0.74-0.89*]APRI: Not reportedCirrhosis (METAVIR F4)Fibrosis-protein index >5.31: 0.75 (21/28) [0.80-0.81*]APRI >1.0: Not reported	Reported only as rangesFibrosis (METAVIR F2-F4)Fibrosis-protein Index >3.53: 0.71 (30/42) [0.62-0.79*]APRI >0.5: Not reportedSevere fibrosis (METAVIR F3-F4)Fibrosis-protein Index >4.78: 0.78 (73/93) [0.71-0.87*]APRI: Not reportedCirrhosis (METAVIR F4)Fibrosis-protein Index >5.31: 0.81 (84/104) [0.73-0.94*]APRI >1.0: Not reported	Reported for derivation and validation samples combinedFibrosis (METAVIR F2-F4)Fibrosis-protein Index >3.53: 0.86 (75/87)APRI >0.5: 0.89Severe fibrosis (METAVIR F3-F4)Fibrosis-protein Index >4.78: 0.62 (33/53) [0.51-0.61*]APRI: Not reportedCirrhosis (METAVIR F4)Fibrosis-protein Index >5.31: 0.51 (21/41) [0.51-0.61*]APRI >1.0: 0.62	Reported for derivation and validation samples combinedFibrosis (METAVIR F2-F4)Fibrosis-protein Index >3.53: 0.62 (30/48)APRI >0.5: 0.50Severe fibrosis (METAVIR F3-F4)Fibrosis-protein Index >4.78: 0.89 (73/82) [0.90-0.95*]Cirrhosis (METAVIR F4)Fibrosis-protein Index >5.31: 0.92 (84/91) [0.90-0.95*]APRI >1.0: 0.94	Validation sample onlyFibrosis (METAVIR F2-F4)Fibrosis-protein Index: 0.82 (0.73-0.92)APRI: 0.72 (0.60-0.85)Severe fibrosis (METAVIR F3-F4)Fibrosis-protein Index: 0.92 (0.86-0.99)APRI: 0.87 (0.75-0.98)Cirrhosis (METAVIR F4)Fibrosis-protein Index: 0.88 (0.77-0.98)APRI: 0.92 (0.84-1.0)	Declared no financial disclosures or conflicts of interest	Moderate	Reported PPV's and NPV's unclear for Fibrosis-protein Index and severe fibrosis or cirrhosis and inconsistent with data from 2 x 2 table constructed from Figure 4; also total sample size went down from 135 to 132 based on Figure 4.

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Cheung, 2008	Fibrosis (Batt-Ludwig 2-4) Platelet count <100: 0.05 (15/323), <150: 0.28 (89/323) AST/ALT ratio ≥1.0: 0.20 (65/323) Pohl score positive: 0.07 (21/323) APRI Severe fibrosis (Batt-Ludwig 3 or 4) Platelet count <100: 0.08 (14/187); <150: 0.39 (72/187) [0.38*] AST/ALT ratio ≥1.0: 0.19 (40/210) [0.21*] Pohl score positive: 0.09 (17/187) APRI Lok Index ≥0.2: 0.93 (174/187); >0.5: 0.51 (95/187)	Fibrosis (Batt-Ludwig 2-4) Platelet count <100: 0.99 (166/167), <150: 0.92 (153/167) AST/ALT ratio ≥1.0: 0.82 (137/167) Pohl score positive: 0.98 (164/167) APRI Severe fibrosis (Batt-Ludwig 3 or 4) Platelet count <100: 0.99 (301/303); <150: 0.90 (272/303) AST/ALT ratio ≥1.0: 0.97 (248/255) [0.82*] Pohl score positive: 0.98 (296/303) APRI Lok Index ≥0.2: 0.31 (94/303); >0.5: 0.83 (252/303)	Fibrosis (Batt-Ludwig 2-4) Platelet count <100: 0.94 (15/16), <150: 0.86 (89/103) AST/ALT ratio ≥1.0: 0.68 (65/95) Pohl score positive: 0.88 (21/24) APRI Severe fibrosis (Batt-Ludwig 3 or 4) Platelet count <100: 0.88 (14/16); <150: 0.70 (72/103) AST/ALT ratio ≥1.0: 0.85 (40/47) [0.42*] Pohl score positive: 0.71 (17/24) APRI Lok Index ≥0.2: 0.45 (174/383); >0.5: 0.65 (95/146)	Fibrosis (Batt-Ludwig 2-4) Platelet count <100: 0.35 (166/474), <150: 0.40 (153/387) AST/ALT ratio ≥1.0: 0.35 (137/395) Pohl score positive: 0.35 (164/466) APRI Severe fibrosis (Batt-Ludwig 3 or 4) Platelet count <100: 0.64 (301/474); <150: 0.70 (272/387) AST/ALT ratio ≥1.0: 0.59 (248/418) [0.63*] Pohl score positive: 0.64 (296/466) APRI Lok Index ≥0.2: 0.88 (94/107); >0.5: 0.73 (252/344)	Fibrosis (Batt-Ludwig 2-4) Platelet count: 0.60 (0.56-0.63) for <150; 0.52 (0.51-0.53) for <100 AST/ALT ratio: 0.54 (0.48-0.59) Pohl score: 0.52 (0.51-0.54) APRI: 0.69 (0.64-0.74) Severe fibrosis (Batt-Ludwig 3 or 4) Platelet count: 0.64 (0.60-0.68) for <150; 0.53 (0.52-0.55) for <100 AST/ALT ratio: 0.52 (0.47-0.58) Pohl score: 0.53 (0.51-0.56) APRI: 0.76 (0.71-0.81) Lok Index: 0.69 (0.64-0.74)	Schering Plough Corporation and VA National Hepatitis C Program	Moderate	Sensitivities/specificities for increasing APRI values inconsistent with expected trends.
Chrysanthos, 2006	Fibrosis (Ishak ≥3)APRI >0.50: 0.79 (115/146); >1.50: 0.30 (44/146)Cirrhosis (Ishak 5 or 6)APRI >1.00: 0.60 (35/58); >2.00: 0.38 (22/58)	Fibrosis (Ishak ≥3)APRI >0.50: 0.46 (64/138); >1.50: 0.88 (122/138)Cirrhosis (Ishak 5 or 6)APRI >1.00: 0.72 (162/226); >2.00: 0.91 (206/226)	Fibrosis (Ishak ≥3)APRI >0.50: 0.61 (115/189); >1.50: 0.73 (44/60)Cirrhosis (Ishak 5 or 6)APRI >1.00: 0.35 (35/99); >2.00: 0.52 (22/42)	Fibrosis (Ishak ≥3)APRI >0.50: 0.67 (64/95); >1.50: 0.54 (122/224)Cirrhosis (Ishak 5 or 6)APRI >1.00: 0.88 (162/185); >2.00: 0.85 (206/242)	Not reported for HCV subgroup	Funding source not reported, no conflicts of interest declared	Low	AUROC's for APRI entire sample (HBV + HCV): 0.65 for fibrosis and 0.70 for cirrhosis (CI's not reported)
Cobbold, 2010	Fibrosis (Ishak 3-6) APRI >0.66: 0.83 (31/37) [0.84*] ELF Index >8.75: 0.84 (31/37) Hepatic transit time >8.0: 0.53 (20/37) [0.54*] Cirrhosis (Ishak 5-6) APRI >0.92: 0.86 (12/14) ELF Index >8.75: 0.93 (13/14) Hepatic transit time >8.0: 0.71 (10/14)	Fibrosis (Ishak 3-6) APRI >0.66: 0.78 (23/30) [0.77*] ELF Index >8.75: 0.70 (21/30) Hepatic transit time >8.0: 0.73 (22/30) Cirrhosis (Ishak 5-6) APRI >0.92: 0.77 (41/53) ELF Index >8.75: 0.79 (42/53) Hepatic transit time >8.0: 0.91 (48/53)	Fibrosis (Ishak 3-6) APRI >0.66: 0.82 (31/38) [0.76*] ELF Index >8.75: 0.78 (31/40) Hepatic transit time >8.0: 0.71 (20/28) [0.62*] Cirrhosis (Ishak 5-6) APRI >0.92: 0.50 (12/24) ELF Index >8.75: 0.54 (13/24) Hepatic transit time >8.0: 0.67 (10/15)	Fibrosis (Ishak 3-6) APRI >0.66: 0.79 (23/29) [0.85*] ELF Index >8.75: 0.78 (21/27) Hepatic transit time >8.0: 0.56 (22/39) [0.66*] Cirrhosis (Ishak 5-6) APRI >0.92: 0.95 (41/43) ELF Index >8.75: 0.98 (42/43) Hepatic transit time >8.0: 0.92 (48/52)	Fibrosis (Ishak 3-6) APRI: 0.83 (0.73-0.93) ELF Index: 0.82 (0.73-0.92) Hepatic transit time: 0.71 (0.59-0.84) Cirrhosis (Ishak 5-6) APRI: 0.86 (0.75-0.97) ELF Index: 0.91 (0.82-1.0) Hepatic transit time: 0.83 (0.69-0.97)	Pfizer UK Ltd., Sandwich, United Kingdom National Institute of Health Research, British Medical Research Council	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Colletta, 2005	Fibrosis (METAVIR F2-F4) Fibrotest ≥0.31: 0.64 (9/14)	Fibrosis (METAVIR F2-F4) Fibrotest ≥0.31: 0.31 (8/26)	Fibrosis (METAVIR F2-F4) Fibrotest ≥0.31: 0.33 (9/27)	Fibrosis (METAVIR F2-F4) Fibrotest ≥0.31: 0.62 (8/13)	Not reported	University of Eastern Piedmont and MIUR	Moderate	
Cross, 2010	Fibrosis (Ishak ≥3)King's Score >9.87: 0.84 (75/89)Cirrhosis (Ishak 5 or 6)King's Score >24.3: 0.74 (37/50)	Fibrosis (Ishak ≥3)King's Score >9.87: 0.70 (69/98)Cirrhosis (Ishak 5 or 6)King's Score >24.3: 0.90 (123/137)	Fibrosis (Ishak ≥3)King's Score >9.87: 0.72 (75/104) [0.74*]Cirrhosis (Ishak 5 or 6)King's Score >24.3: 0.73 (37/51) [0.70*]	Fibrosis (Ishak ≥3)King's Score >9.87: 0.83 (69/83) [0.80*]Cirrhosis (Ishak 5 or 6)King's Score >24.3: 0.90 (123/136) [0.91*]	Whole sample, normal AST, elevated AST, liver biopsy <15 mm, liver biopsy >15 mm, respectivelyFibrosis (Ishak ≥3)King's Score: 0.89 (CI not reported), 0.83 (0.68-0.99), 0.79 (0.69-0.89), 0.84 (0.70-0.98), 0.83 (0.72-0.93)Cirrhosis (Ishak 5 or 6)King's Score: 0.88 (0.82-0.94), 0.96 (0.91-1.0), 0.78 (0.67-0.88), 0.94 (0.87-1.0), 0.82 (0.71-0.90)	Not reported	Moderate	Different population from Cross, 2009

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Cross, 2009	Derivation sample only Fibrosis (Ishak ≥3) King's Score ≥12.3: 0.70 (190/271) FIB-4 score >0.34: 0.62 (168/271) Age-platelet index >3.5: 0.70 (190/271) APRI >0.53: 0.69 (187/271) Platelets <187: 0.64 (173/271) AST >62: 0.60 (163/271) Cirrhosis (Ishak 5 or 6) King's Score ≥16.7: 0.86 (114/132) FIB-4 score >0.41: 0.83 (110/132) Age-platelet index >5: 0.80 (106/132) APRI >0.75: 0.84 (111/132) Platelets <149: 0.72 (95/132) AST >64.5: 0.77 (102/132)	Derivation sample only Fibrosis (Ishak ≥3) King's Score ≥12.3: 0.85 (281/331) FIB-4 score >0.34: 0.79 (261/331) Age-platelet index >3.5: 0.74 (245/331) APRI >0.53: 0.77 (255/331) Platelets <187: 0.74 (245/331) AST >62: 0.81 (268/331) Cirrhosis (Ishak 5 or 6) King's Score ≥16.7: 0.80 (376/470) FIB-4 score >0.41: 0.78 (367/470) Age-platelet index >5: 0.89 (418/470) APRI >0.75: 0.78 (367/470) Platelets <149: 0.91 (428/470) AST >64.5: 0.75 (352/470)	Derivation sample only Fibrosis (Ishak ≥3) King's Score ≥12.3: 0.79 (190/240) [0.81*] FIB-4 score >0.34: 0.71 (168/238) Age-platelet index >3.5: 0.69 (190/276) [0.70*] APRI >0.53: 0.71 (187/263) [0.75*] Platelets <187: 0.67 (173/259) [0.68*] AST >62: 0.72 (163/226) [0.73*] Cirrhosis (Ishak 5 or 6) King's Score ≥16.7: 0.55 (114/208) [0.56*] FIB-4 score >0.41: 0.52 (110/213) [0.41*] Age-platelet index >5: 0.67 (106/158) APRI >0.75: 0.52 (111/214) [0.53*] Platelets <149: 0.69 (95/137) AST >64.5: 0.46 (102/220) [0.47*]	Derivation sample only Fibrosis (Ishak ≥3) King's Score ≥12.3: 0.78 (281/362) [0.77*] FIB-4 score >0.34: 0.72 (261/364) Age-platelet index >3.5: 0.75 (245/326) [0.74*] APRI >0.53: 0.75 (255/339) Platelets <187: 0.71 (245/343) AST >62: 0.71 (268/376) Cirrhosis (Ishak 5 or 6) King's Score ≥16.7: 0.95 (376/394) [0.96*] FIB-4 score >0.41: 0.94 (367/389) [0.96*] Age-platelet index >5: 0.94 (418/444) APRI >0.75: 0.95 (367/388) [0.94*] Platelets <149: 0.92 (428/465) AST >64.5: 0.92 (352/382)	Derivation and validation samples, respectively Fibrosis (Ishak ≥3) King's Score: 0.79 (0.75-0.83) and 0.89 (0.81-0.96) FIB-4: 0.76 (0.68-0.83) and NR AST: 0.68 (0.62-0.74) and NR 1/platelets: 0.66 (0.60-0.72) and NR AST/ALT ratio: 0.58 (0.51-0.64) and NR Age-platelet index: 0.77 (0.73-0.81) and NR Cirrhosis Discriminant Score: 0.67 (0.62-0.72) and NR APRI: 0.76 (0.72-0.80) and NR Pohl Index: 0.53 (0.46-0.59) and NR Cirrhosis (Ishak 5 or 6) King's Score: 0.91 (0.89-0.94) and 0.94 (0.87-1.0) FIB-4: 0.87 (0.82-0.91) and NR AST: 0.79 (0.74-0.83) and NR 1/platelets: 0.88 (0.85-0.91) and NR AST/ALT ratio: 0.68 (0.60-0.75) and NR Age-platelet index: 0.90 (0.86-0.93) and NR Cirrhosis Discriminant Score: 0.74 (0.68-0.81) and NR APRI: 0.88 (0.85-0.92) and NR Pohl Index: 0.64 (0.55-0.73) and NR	Funding source not reported, no conflicts of interest declared	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Ehsan, 2008	Cirrhosis (Ishak 5-6)Age-platelet index >5: 0.72 (25/35)Lok Index >0.6: 0.79 (28/35)Cirrhosis discriminant score >7: 0.48 (17/35)Goteborg University Cirrhosis Index >1.5: 0.74 (26/35)APRI >1.5: 0.66 (23/35)Pohl Index positive: 0.34 (12/35)AST/ALT ratio >1.5: 0.44 (15/35)	Cirrhosis (Ishak 5-6)Age-platelet index >5: 0.93 (75/81)Lok Index >0.6: 0.88 (71/81)Cirrhosis discriminant score >7: 0.99 (80/81)Goteborg University Cirrhosis Index >1.5: 0.89 (72/81)APRI >1.5: 0.94 (76/81)Pohl Index positive: 0.99 (80/81)AST/ALT ratio >1.5: 0.91 (74/81)	Cirrhosis (Ishak 5-6)Age-platelet index >5: 0.81 (25/31) [0.91*]Lok Index >0.6: 0.74 (28/38) [0.87*]Cirrhosis discriminant score >7: 0.94 (17/18) [0.98*]Goteborg University Cirrhosis Index >1.5: 0.74 (26/35) [0.87*]APRI >1.5: 0.82 (23/28) [0.92*]Pohl Index positive: 0.92 (12/13)AST/ALT ratio >1.5: 0.68 (15/22) [0.83*]	Cirrhosis (Ishak 5-6)Age-platelet index >5: 0.88 (75/85) [0.77*]Lok Index >0.6: 0.91 (71/78) [0.80*]Cirrhosis discriminant score >7: 0.82 (80/98) [0.66*]Goteborg University Cirrhosis Index >1.5: 0.89 (72/81) [0.77*]APRI >1.5: 0.86 (76/88) [0.74*]Pohl Index positive: 0.78 (80/103) [0.60*]AST/ALT ratio >1.5: 0.79 (74/94) [0.72*]	Cirrhosis (Ishak 5-6)Age-platelet index: 0.91 (CI not reported)Lok Index: 0.88 (CI not reported)Cirrhosis discriminant score: 0.87 (CI not reported)Goteborg University Cirrhosis Index: 0.86 (CI not reported)APRI: 0.86 (CI not reported)Pohl Index: 0.66 (CI not reported)AST/ALT ratio: 0.65 (CI not reported)	Not stated, reported no competing interests	High	
El-Gindy, 2003	Fibrosis (Ishak 1-4 vs. Ishak 0) MMP-2 >400 ng/ml: 0.07 (1/15) TIMP-1 >195 ng/ml: 0.67 (10/15) AST >34 IU/L: 0.80 (12/15) [0.78*] ALT >44 IU/L: 0.93 (14/15) [0.96*] Albumin <3.5 g/100 ml: 0.27 (4/13) Cirrhosis (Ishak 5-6) MMP-2 >400 ng/ml: 0.86 (12/14) [0.83*] TIMP-1 >195 ng/ml: 1.0 (14/14) AST >34 IU/L: 0.79 (11/14) [0.81*] ALT >44 IU/L: 0.86 (12/14) [0.88*] Albumin <3.5 g/100 ml: 0.71 (10/14) [0.73*]	Fibrosis (Ishak 1-4 vs. Ishak 0) MMP-2 >400 ng/ml: 0.92 (11/12) [0.97*] TIMP-1 >195 ng/ml: 0.67 (8/12) [0.69*] AST >34 IU/L: 0.42 (5/12) [0.40*] ALT >44 IU/L: 0.17 (2/12) [0.16*] Albumin <3.5 g/100 ml: 0.92 (11/12) [0.90*] Cirrhosis (Ishak 5-6) MMP-2 >400 ng/ml: 0.96 (26/27) TIMP-1 >195 ng/ml: 0.74 (20/27) [0.75*] AST >34 IU/L: 0.59 (16/27) [0.60*] ALT >44 IU/L: 0.11 (3/27) Albumin <3.5 g/100 ml: 0.85 (23/27) [0.86*]	Fibrosis (Ishak 1-4 vs. Ishak 0) MMP-2 >400 ng/ml: 0.50 (1/2) TIMP-1 >195 ng/ml: 0.71 (10/14) AST >34 IU/L: 0.63 (12/19) ALT >44 IU/L: 0.58 (14/24) Albumin <3.5 g/100 ml: 0.80 (4/5) Cirrhosis (Ishak 5-6) MMP-2 >400 ng/ml: 0.92 (12/13) TIMP-1 >195 ng/ml: 0.67 (14/21) AST >34 IU/L: 0.50 (11/22) ALT >44 IU/L: 0.33 (12/36) Albumin <3.5 g/100 ml: 0.71 (10/14)	Fibrosis (Ishak 1-4 vs. Ishak 0) MMP-2 >400 ng/ml: 0.44 (11/25) TIMP-1 >195 ng/ml: 0.62 (8/13) AST >34 IU/L: 0.62 (5/8) ALT >44 IU/L: 0.67 (2/3) Albumin <3.5 g/100 ml: 0.55 (11/20) Cirrhosis (Ishak 5-6) MMP-2 >400 ng/ml: 0.93 (26/28) TIMP-1 >195 ng/ml: 1.0 (20/20) AST >34 IU/L: 0.84 (16/19) ALT >44 IU/L: 0.60 (3/5) Albumin <3.5 g/100 ml: 0.85 (23/27)	Fibrosis (Ishak 1-4 vs. Ishak 0) MMP-2: 0.57 (0.49-0.65) TIMP-1 >195 ng/ml: 0.71 (0.64-0.78) AST: NR ALT: NR Albumin: NR Cirrhosis (Ishak 5-6) MMP-2 >400 ng/ml: 0.97 (0.95-0.99) TIMP-1 >195 ng/ml: 0.89 (0.85-0.93) AST: NR ALT: NR Albumin: NR	Not stated	Moderate	
El-Shorbagy, 2004	Fibrosis (G2S2 or G3S3) 7-item predictive index >3: 0.80 (70/87) Cirrhosis (G3S3) 7-item predictive index ≥6: 0.80 (16/20)	Fibrosis (G2S2 or G3S3) 7-item predictive index >3: 0.82 (18/22) Cirrhosis (G3S3) 7-item predictive index ≥6: 0.97 (86/89)	Fibrosis (G2S2 or G3S3) 7-item predictive index >3: 0.95 (70/74) Cirrhosis (G3S3) 7-item predictive index ≥6: 0.84 (16/19)	Fibrosis (G2S2 or G3S3) 7-item predictive index >3: 0.51 (18/35) Cirrhosis (G3S3) 7-item predictive index ≥6: 0.96 (86/90)	Not reported	Not stated	High	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Fabris, 2008	Fibrosis (METAVIR F2-F4)Fibro Index >1.6: 0.54 (37/69)Cirrhosis (METAVIR F4)Fibro Index >1.6: 0.90 (17/19)	Fibrosis (METAVIR F2-F4)Fibro Index >1.6: 0.82 (80/98)Cirrhosis (METAVIR F4)Fibro Index >1.6: 0.74 (110/148)	Fibrosis (METAVIR F2-F4)Fibro Index >1.6: 0.67 (37/55)Cirrhosis (METAVIR F4)Fibro Index >1.6: 0.31 (17/55)	Fibrosis (METAVIR F2-F4)Fibro Index >1.6: 0.71 (80/112)Cirrhosis (METAVIR F4)Fibro Index >1.6: 0.98 (110/112)	Fibrosis (METAVIR F2-F4)Fibro Index: 0.71 (0.63-0.77)Age-platelet index: 0.64 (0.56-0.72)AST/ALT ratio: 0.59 (0.51-0.66)APRI: 0.72 (0.64-0.79)Cirrhosis Discriminant Score: 0.64 (0.56-0.71)Forn's Index: 0.70 (0.62-0.76)Cirrhosis (METAVIR F4)Fibro Index: 0.86 (0.80-0.91)Age-platelet index: 0.67 (0.59-0.74)AST/ALT ratio: 0.66 (0.58-0.73)APRI: 0.86 (0.79-0.90)Cirrhosis Discriminant Score: 0.71 (0.64-0.78)Forn's Index: 0.86 (0.80-0.91)	Not stated	Moderate	
Fontana, 2008	Cirrhosis (Ishak 5-6) HALT-C model ≥0.2: 0.88 (156/177); ≥0.5: 0.47 (84/177)	Cirrhosis (Ishak 5-6) HALT-C model ≥0.2: 0.45 (132/294); ≥0.5: 0.92 (270/294)	Cirrhosis (Ishak 5-6) HALT-C model ≥0.2: 0.49 (156/318); ≥0.5: 0.78 (84/108)	Cirrhosis (Ishak 5-6) HALT-C model ≥0.2: 0.86 (132/153); ≥0.5: 0.74 (270/363)	Cirrhosis (Ishak 5 or 6) HALT-C model: 0.81 (0.77-0.85) Lok Index: 0.79 (0.74-0.83) APRI: 0.73 (0.69-0.78) Cirrhosis Discriminant Score: 0.70 (0.66-0.75)	NIDDKD, NIAID, NCI, NIH, Hoffman-La Roche Inc	Moderate	HALT-C cohort also evaluated in Lok, 2005
Forns, 2002	Derivation and validation samples, respectivelyFibrosis (Scheuer F2-F4)Forns Index >4.2: 0.94 (80/85) and 0.94 (31/33); >6.9: 0.44 (37/85) and 0.30 (10/33)	Derivation and validation samples, respectivelyFibrosis (Scheuer F2-F4)Forns Index >4.2: 0.45 (120/266) and 0.51 (47/92); >6.9: 0.96 (256/266) and 0.95 (87/92)	Derivation and validation samples, respectivelyFibrosis (Scheuer F2-F4)Forns Index >4.2: 0.35 (80/226) and 0.41 (31/76); >6.9: 0.79 (37/47) and 0.67 (10/15)	Derivation and validation samples, respectivelyFibrosis (Scheuer F2-F4)Forns Index >4.2: 0.96 (120/135) and 0.96 (47/49); >6.9: 0.84 (256/304) and 0.79 (87/11)	Derivation and validation samples, respectivelyFibrosis (Scheuer F2-F4)Forns Index: 0.86 and 0.81 (CI's not reported)	Not stated	Low	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Gabrielli, 1997	Severe fibrosis (Scheuer F3-F4) Laminin P1 >1.4: 0.79, >2.0: 0.48; >2.4: 0.31 PIIIP >0.6: 0.93, >1.0: 0.34, >1.6: 0.03	Severe fibrosis (Scheuer F3-F4) Laminin P1 >1.4: 0.40; >2.0: 0.88; >2.4: 0.96 PIIIP >0.6: 0.13, >1.0: 0.94; >1.6: 0.98	Severe fibrosis (Scheuer F3-F4) Laminin P1 >1.4: 0.35, >2.0: 0.63; >2.4: 0.88 PIIIP >0.6: 0.30, >1.0: 0.71, >1.6: 0.47	Severe fibrosis (Scheuer F3-F4) Laminin P1 >1.4: 0.82; >2.0: 0.81; >2.4: 0.77 PIIIP >0.6: 0.82, >1.0: 0.78; >1.6: 0.71	Not reported	Ministero dell'Universita e della Ricerca Scientifica, Italy	Moderate	
Giannini, 2006	Fibrosis (Ishak 3-6 or METAVIR F2-F4)AST/ALT >0.66: 0.74 (129/175)Platelet count <163: 0.62 (108/175)	Fibrosis (Ishak 3-6 or METAVIR F2-F4)AST/ALT >0.66: 0.65 (152/234)Platelet count <163: 0.81 (189/234)	Fibrosis (Ishak 3-6 or METAVIR F2-F4)AST/ALT >0.66: 0.61 (129/211)Platelet count <163: 0.71 (108/153)	Fibrosis (Ishak 3-6 or METAVIR F2-F4)AST/ALT >0.66: 0.77 (152/198)Platelet count <163: 0.74 (189/256)	Not reported	Not stated	Moderate	
Giannini, 2003a	Cirrhosis (Scheuer F4 or clinical signs of portal hypertension) AST/ALT ratio ≥1: 0.78 (70/90) Platelet count <130,000: 0.91 (82/90) AST/ALT ratio ≥1 or platelet count <130,000: 0.97 (87/90) AST/ALT ratio ≥1 and platelet count <130,000: 0.72 (65/90)	Cirrhosis (Scheuer F4 or clinical signs of portal hypertension) AST/ALT ratio ≥1: 0.97 (157/162) Platelet count <130,000: 0.88 (143/162) AST/ALT ratio ≥1 or platelet count <130,000: 0.86 (140/162) AST/ALT ratio ≥1 and platelet count <130,000: 0.99 (160/162)	Cirrhosis (Scheuer F4 or clinical signs of portal hypertension) AST/ALT ratio ≥1: 0.93 (70/75) Platelet count <130,000: 0.81 (82/101) AST/ALT ratio ≥1 or platelet count <130,000: 0.80 (87/109) AST/ALT ratio ≥1 and platelet count <130,000: 0.97 (65/67)	Cirrhosis (Scheuer F4 or clinical signs of portal hypertension) AST/ALT ratio ≥1: 0.89 (157/177) Platelet count <130,000: 0.95 (143/151) AST/ALT ratio ≥1 or platelet count <130,000: 0.98 (140/143) AST/ALT ratio ≥1 and platelet count <130,000: 0.86 (160/185)	Not reported	Not stated	Moderate	
Giannini, 2003b	Not reported	Not reported	Fibrosis (criteria not reported) AST/ALT ratio ≥1: 0.89 (n/N not reported) APRI: Not reported	Not reported	Fibrosis (criteria not reported) AST/ALT ratio: 0.82 (CI not reported) APRI: 0.77 (CI not reported) Cirrhosis (criteria not reported) AST/ALT ratio: 0.91 (CI not reported) APRI: 0.81 (CI not reported)	Not stated	Moderate	Substantial overlap with population evaluated in Giannini 2003a (199 of 239 subjects were included in Giannini 2003a)
Gomes da Silva, 2008	Fibrosis (METAVIR F2-F4)APRI >0.50: 0.93 (26/28); >0.93: 0.93 (26/28); >1.50: 0.50 (14/28) [0.46*]Cirrhosis (METAVIR F4)APRI >1.00: 0.92 (12/13); >1.73: 0.77 (10/13); >2.00: 0.54 (7/13) [0.46*]	Fibrosis (METAVIR F2-F4)APRI >0.50: 0.45 (10/22); >0.93: 0.96 (21/22); >1.50: 1.0 (22/22) Cirrhosis (METAVIR F4)APRI >1.00: 0.70 (26/37) [0.73*]; >1.73: 0.97 (36/37); >2.00: 0.97 (36/37)	Fibrosis (METAVIR F2-F4)APRI >0.50: 0.68 (26/38) [0.70*]; >0.93: 0.96 (26/27); >1.50: 1.0 (14/14)Cirrhosis (METAVIR F4)APRI >1.00: 0.52 (12/23) [0.54*]; >1.73: 0.91 (10/11); >2.00: 0.88 (7/8) [0.86*]	Fibrosis (METAVIR F2-F4)APRI >0.50: 0.83 (10/12) [0.85*]; >0.93: 0.91 (21/23); >1.50: 0.61 (22/36) [0.60*] Cirrhosis (METAVIR F4)APRI >1.00: 0.96 (26/27); >1.73: 0.92 (36/39); >2.00: 0.86 (36/42) [0.84*]	Fibrosis (METAVIR F2-F4)APRI: 0.92 (0.83-1.0)Cirrhosis (METAVIR F4)APRI: 0.92 (0.85-1.0)	Not stated	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Guechot, 2010	Fibrosis (METAVIR F2-F4) Hepascore ≥0.25: 0.47 (117/247); >0.5: 0.77 (190/247) Severe fibrosis (METAVIR F3-F4) Hepascore >0.6: 0.80 (124/155) Cirrhosis (METAVIR F4) Hepascore >0.75: 0.86 (65/76); >0.84: 0.72 (55/76) [0.73*]	Fibrosis (METAVIR F2-F4) Hepascore ≥0.25: 0.95 (252/265); >0.5: 0.70 (186/265) Severe fibrosis (METAVIR F3-F4) Hepascore >0.6: 0.70 (250/357) Cirrhosis (METAVIR F4) Hepascore >0.75: 0.74 (323/436); >0.84: 0.81 (353/436)	Fibrosis (METAVIR F2-F4) Hepascore ≥0.25: 0.90 (117/130); >0.5: 0.71 (190/269) Severe fibrosis (METAVIR F3-F4) Hepascore >0.6: 0.54 (124/231) Cirrhosis (METAVIR F4) Hepascore >0.75: 0.37 (65/178); >0.84: 0.40 (55/138) [0.41*]	Fibrosis (METAVIR F2-F4) Hepascore ≥0.25: 0.66 (252/382); >0.5: 0.77 (186/243) Severe fibrosis (METAVIR F3-F4) Hepascore >0.6: 0.90 (250/281) Cirrhosis (METAVIR F4) Hepascore >0.75: 0.97 (323/334); >0.84: 0.94 (353/374)	Fibrosis (F2-F4) Hepascore: 0.81 (0.78-0.85) Severe fibrosis (F3-F4) Hepascore: 0.92 (0.78-0.86) Cirrhosis (F4) Hepascore: 0.88 (0.84-0.91)	French de National Agency for Research on AIDS and Viral Hepatitis (ANRS), Societe Francaise de Biologie Clinique, Association pour l'Etude du Foie	Moderate	
Guechot, 1996	Severe fibrosis (Knodell F3-F4) PIIIP >0.80 U/ml: 0.70 (77/110) Hyaluronic acid >85 mcg/l: 0.65 (71/110) [0.64*] Cirrhosis (Knodell F4) PIIIP >1.00 U/ml: 0.60 (32/53) Hyaluronic acid >110 mcg/l: 0.79 (42/53)	Severe fibrosis (Knodell F3-F4) PIIIP >0.80 U/ml: 0.63 (137/216) Hyaluronic acid >85 mcg/l: 0.91 (197/216) Cirrhosis (Knodell F4) PIIIP >1.00 U/ml: 0.74 (202/273) Hyaluronic acid >110 mcg/l: 0.89 (244/273)	Severe fibrosis (Knodell F3-F4) PIIIP >0.80 U/ml: 0.49 (77/156) Hyaluronic acid >85 mcg/l: 0.79 (71/90) Cirrhosis (Knodell F4) PIIIP >1.00 U/ml: 0.31 (32/103) Hyaluronic acid >110 mcg/l: 0.59 (42/71)	Severe fibrosis (Knodell F3-F4) PIIIP >0.80 U/ml: 0.81 (137/170) Hyaluronic acid >85 mcg/l: 0.83 (197/236) Cirrhosis (Knodell F4) PIIIP >1.00 U/ml: 0.91 (202/223) Hyaluronic acid >110 mcg/l: 0.96 (244/255)	Severe fibrosis (Knodell F3-F4) PIIIP: 0.69 (CI not reported) Hyaluronic acid: 0.86 Cirrhosis (Knodell F4) PIIIP: 0.73 (CI not reported) Hyaluronic acid: 0.92 (CI not reported)	Not stated	Moderate	Degree of overlap with Guechot 1994 unclear.
Guechot, 1994	Severe fibrosis (Knodell F2 or F3)PIIIP >0.80 U/ml: 0.40 (8/20)Hyaluronic acid >85 mg/l: 0.55 (11/20)	Severe fibrosis (Knodell F2 or F3)PIIIP >0.80 U/ml: 0.66 (25/38)Hyaluronic acid >85 mg/l: 0.92 (35/38)	Severe fibrosis (Knodell F2 or F3)PIIIP >0.80 U/ml: 0.38 (8/21)Hyaluronic acid >85 mg/l: 0.79 (11/14)	Severe fibrosis (Knodell F2 or F3)PIIIP >0.80 U/ml: 0.68 (25/37)Hyaluronic acid >85 mg/l: 0.80 (35/44)	Not reported	Not stated	Moderate	Degree of overlap with Guechot 1996 unclear. Cirrhosis defined as Knodell F3 (?old system).

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Halfon, 2007	Fibrosis (METAVIR F2-F4) FibroMeter >0.57: 0.64 (93/146) Fibrotest >0.44: 0.67 (98/146) Hepascore >0.32: 0.77 (112/146) APRI >0.39: 0.77 (112/146) Severe fibrosis (METAVIR F3-F4) FibroMeter >0.67: 0.82 (42/51) Fibrotest >0.45: 0.84 (43/51) Hepascore >0.53: 0.78 (40/51) APRI >0.58: 0.75 (38/51) Cirrhosis (METAVIR F4) FibroMeter >0.88: 0.92 (12/13) Fibrotest >0.56: 0.85 (11/13) Hepascore >0.61 : 0.92 (12/13) APRI >0.39: 1.0 (13/13)	Fibrosis (METAVIR F2-F4) FibroMeter >0.57: 0.81 (170/210) Fibrotest >0.44: 0.80 (168/210) Hepascore >0.32: 0.63 (132/210) APRI >0.39: 0.66 (139/210) Severe fibrosis (METAVIR F3-F4) FibroMeter >0.67: 0.76 (232/305) Fibrotest >0.45: 0.69 (210/305) Hepascore >0.53: 0.72 (220/305) APRI >0.58: 0.76 (232/305) Cirrhosis (METAVIR F4) FibroMeter >0.88: 0.87 (298/343) Fibrotest >0.56: 0.74 (254/343) Hepascore >0.61 : 0.72 (247/343) APRI >0.39: 0.83 (285/343)	Fibrosis (METAVIR F2-F4) FibroMeter >0.57: 0.70 (93/133) Fibrotest >0.44: 0.70 (98/140) Hepascore >0.32: 0.59 (112/190) APRI >0.39: 0.61 (112/183) Severe fibrosis (METAVIR F3-F4) FibroMeter >0.67: 0.37 (42/115) Fibrotest >0.45: 0.31 (43/138) Hepascore >0.53: 0.32 (40/125) APRI >0.58: 0.34 (38/111) Cirrhosis (METAVIR F4) FibroMeter >0.88: 0.21 (12/57) Fibrotest >0.56: 0.11 (11/100) Hepascore >0.61 : 0.11 (12/108) APRI >0.39: 0.18 (13/71)	Fibrosis (METAVIR F2-F4) FibroMeter >0.57: 0.76 (170/233) [0.77*] Fibrotest >0.44: 0.78 (168/216) Hepascore >0.32: 0.80 (132/166) APRI >0.39: 0.80 (139/173) Severe fibrosis (METAVIR F3-F4) FibroMeter >0.67: 0.96 (232/241) Fibrotest >0.45: 0.96 (210/218) Hepascore >0.53: 0.95 (220/231) APRI >0.58: 0.95 (232/245) Cirrhosis (METAVIR F4) FibroMeter >0.88: 1.0 (298/299) Fibrotest >0.56: 0.99 (254/256) Hepascore >0.61 : 1.0 (247/248) APRI >0.39: 1.0 (285/285)	Fibrosis (METAVIR F2-F4) FibroMeter: 0.78 (0.73-0.82) Fibrotest: 0.79 (0.75-0.83) Hepascore: 0.76 (0.71-0.80) APRI: 0.76 (0.72-0.81) Severe fibrosis (METAVIR F3-F4) FibroMeter: 0.84 (0.80-0.88) Fibrotest: 0.81 (0.77-0.85) Hepascore: 0.81 (0.76-0.85) APRI: 0.81 (0.76-0.85) Cirrhosis (METAVIR F4) FibroMeter: 0.94 (0.91-0.96) Fibrotest: 0.86 (0.82-0.89) Hepascore: 0.89 (0.86-0.92) APRI: 0.92 (0.88-0.94)	Not stated	Moderate	Some overlap in patient populations between Halfon 2006 and Halfon 2007
Halfon, 2006	Fibrosis (METAVIR F2-F4) Fibrotest >0.10: 0.97 (223/230); >0.36: 0.73 (168/230); >0.80: 0.20 (46/230) Severe fibrosis (METAVIR F3 or F4) Fibrotest >0.10: 0.99 (119/120); >0.44: 0.76 (91/120); >0.80: 0.29 (35/120)	Fibrosis (METAVIR F2-F4) Fibrotest >0.10: 0.27 (74/274); >0.36: 0.72 (197/274); >0.80: 0.98 (269/274) Severe fibrosis (METAVIR F3 or F4) Fibrotest >0.10: 0.21 (81/384); >0.44: 0.70 (269/384); >0.80: 0.97 (372/384)	Fibrosis (METAVIR F2-F4) Fibrotest >0.10: 0.53 (223/423); >0.36: 0.69 (168/245); >0.80: 0.90 (46/51) Severe fibrosis (METAVIR F3-F4) Fibrotest >0.10: 0.28 (119/422); >0.44: 0.44 (91/206); >0.80: 0.73 (35/47) [0.74*]	Fibrosis (METAVIR F2-F4) Fibrotest >0.10: 0.91 (74/81); >0.36: 0.76 (197/259); >0.80: 0.59 (269/453) Severe fibrosis (METAVIR F3-F4) Fibrotest >0.10: 0.99 (81/82); >0.44: 0.90 (269/298); >0.80: 0.81 (372/457)	Fibrosis (METAVIR F2-F4) Fibrotest: 0.79 (0.75-0.82) Severe fibrosis (METAVIR F3-F4) Fibrotest: 0.80 (0.76-0.83)	Not stated	Moderate	Some overlap in patient populations between Halfon 2006 and Halfon 2007

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Halfon, 2005	Derivation and validation samples, respectivelyFibrosis (METAVIR F2-F4)Hyaluronic acid ≥16 mcg/l: 0.96 (69/72) and 0.91 (107/118); >121 mcg/l: 0.18 (13/72) and 0.14 (16/118)Advanced fibrosis (METAVIR F3-F4)Hyaluronic acid >25 mcg/l: 0.92 (36/39) and 0.78 (47/60); >160 mcg/l: 0.26 (10/39) and 0.22 (13/60)Cirrhosis (METAVIR F4)Hyaluronic acid >50 mcg/l: 0.92 (11/12) and 1.0 (13/13); >237 mcg/l: Not reported and 0.31 (4/13)	Derivation and validation samples, respectivelyFibrosis (METAVIR F2-F4)Hyaluronic acid ≥16 mcg/l: 0.19 (15/79) and 0.36 (49/136); >121 mcg/l: 0.97 (77/79) and 0.99 (135/136)Advanced fibrosis (METAVIR F3-F4)Hyaluronic acid >25 mcg/l: 0.54 (61/112) and 0.53 (103/194); >160 mcg/l: 0.99 (111/112) and 1.0 (194/194)Cirrhosis (METAVIR F4)Hyaluronic acid >50 mcg/l: 0.72 (100/139) and 0.79 (190/241); >237 mcg/l: Not reported and 0.99 (239/241)	Derivation and validation samples, respectivelyFibrosis (METAVIR F2-F4)Hyaluronic acid ≥16 mcg/l: 0.52 (69/133) and 0.55 (107/194); >121 mcg/l: 0.87 (13/15) and 0.94 (16/17)Advanced fibrosis (METAVIR F3-F4)Hyaluronic acid >25 mcg/l: 0.41 (36/87) and 0.34 (47/138); >160 mcg/l: 0.91 (10/11) and 1.0 (13/13)Cirrhosis (METAVIR F4)Hyaluronic acid >50 mcg/l: 0.22 (11/50) and 0.20 (13/64); >237 mcg/l: 0.71 (n/N not reported) and 0.67 (4/6)	Derivation and validation samples, respectivelyFibrosis (METAVIR F2-F4)Hyaluronic acid ≥16 mcg/l: 0.83 (15/18) and 0.82 (49/60); >121 mcg/l: 0.57 (77/136) and 0.57 (135/237)Advanced fibrosis (METAVIR F3-F4)Hyaluronic acid >25 mcg/l: 0.95 (61/64) and 0.89 (103/116); >160 mcg/l: 0.79 (111/140) and 0.80 (194/241)Cirrhosis (METAVIR F4)Hyaluronic acid >50 mcg/l: 0.99 (100/101) and 1.0 (190/190); >237 mcg/l: Not reported and 0.96 (239/248)	Derivation and validation samples, respectivelyFibrosis (METAVIR F2-F4)Hyaluronic acid: 0.75 (0.72-0.78) and 0.73 (0.70-0.76)Advanced fibrosis (METAVIR F3-F4)Hyaluronic acid: 0.82 (0.80-0.84) and 0.77 (0.73-0.81)Cirrhosis (METAVIR F4)Hyaluronic acid: 0.89 (0.86-0.92) and 0.97 (0.93-1.0)	Not stated	Moderate	Overlap with Halfon 2006 and 2007?
Hsieh, 2009	Fibrosis (METAVIR F2-F4) FibroQ >1.6: 0.79 (92/116) AAR >0.54: 0.77 (89/116); >1: 0.10 (12/116) APRI >0.5: 0.97 (113/116); >1.2: 0.66 (77/116); >1.5: 0.54 (63/116) Cirrhosis (METAVIR F4) FibroQ >2.6: 1.0 (6/6) AAR >0.75: 0.83 (5/6); >1.0: 0.33 (2/6) APRI >1.0: 1.0 (6/6); >1.5: 0.83 (5/6); >2.0: 0.50 (3/6)	Fibrosis (METAVIR F2-F4) FibroQ >1.6: 0.71 (17/24) AAR >0.54: 0.63 (15/24); >1: 1.0 (24/24) APRI >0.5: 0.13 (3/24); >1.2: 0.50 (12/24); >1.5: 0.58 (14/24) Cirrhosis (METAVIR F4) FibroQ >2.6: 0.65 (87/134) AAR >0.75: 0.67 (90/134); >1.0: 0.92 (123/134) APRI >1.0: 0.30 (40/134); >1.5: 0.50 (67/134); >2.0: 0.65 (87/134)	Fibrosis (METAVIR F2-F4) FibroQ >1.6: 0.93 (92/99) AAR >0.54: 0.91 (89/98); >1: 1.0 (12/12) APRI >0.5: 0.84 (113/134); >1.2: 0.87 (77/89); >1.5: 0.86 (63/73) Cirrhosis (METAVIR F4) FibroQ >2.6: 0.12 (6/51) AAR >0.75: 0.10 (5/49); >1.0: 0.15 (2/13) APRI >1.0: 0.06 (6/100); >1.5: 0.07 (5/72); >2.0: 0.06 (3/50)	Fibrosis (METAVIR F2-F4) FibroQ >1.6: 0.41 (17/41) AAR >0.54: 0.36 (15/42); >1: 0.19 (24/128) APRI >0.5: 0.50 (3/6); >1.2: 0.24 (12/51); >1.5: 0.21 (14/67) Cirrhosis (METAVIR F4) FibroQ >2.6: 1.0 (87/87) AAR >0.75: 0.99 (90/91); >1.0: 0.97 (123/127) APRI >1.0: 1.0 (40/40); >1.5: 0.99 (67/68); >2.0: 0.97 (87/90)	Fibrosis (METAVIR F2-F4) FibroQ: 0.78 (0.69-0.88) AAR: 0.73 (0.62-0.85) APRI: 0.63 (0.52-0.74) Cirrhosis (METAVIR F4) FibroQ: 0.79 (0.68-0.90) AAR: 0.78 (0.60-0.97) APRI: 0.63 (0.51-0.76)	Not stated	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Iacobellis, 2005a	Fibrosis (Scheuer F2-F4)Platelet count <140: 0.51 (330/648)Spleen >120 mm: 0.16 (104/648)Nodular liver present: 0.16 (104/648)Portal vein >12 mm: 0.07 (45/648)Spleen >120 mm or platelets <140: 0.33 (214/648)Nodular liver or platelets <140: 0.33 (214/648)Portal vein >12 mm or platelets <140: 0.31 (201/648)Cirrhosis (Scheuer F4)Platelet count <140: 0.82 (67/82)Spleen >120 mm: 0.40 (33/82)Nodular liver present: 0.46 (38/82)Portal vein >12 mm: 0.19 (15/82)Spleen >120 mm or platelets <140: 0.85 (70/82)Nodular liver or platelets <140: 0.90 (74/82)Portal vein >12 mm or platelets <140: 0.83 (68/82)	Fibrosis (Scheuer F2-F4)Platelet count <140: 0.90 (446/495)Spleen >120 mm: 0.96 (475/495)Nodular liver present: 0.97 (480/495)Portal vein >12 mm: 1.0 (494/495)Spleen >120 mm or platelets <140: 0.92 (455/495)Nodular liver or platelets <140: 0.93 (460/495)Portal vein >12 mm or platelets <140: 0.95 (470/495)Cirrhosis (Scheuer F4)Platelet count <140: 0.87 (923/1061)Spleen >120 mm: 0.91 (966/1061)Nodular liver present: 0.93 (987/1061)Portal vein >12 mm: 0.97 (1029/1061)Spleen >120 mm or platelets <140: 0.82 (870/1061)Nodular liver or platelets <140: 0.83 (881/1061)Portal vein >12 mm or platelets <140: 0.85 (902/1061)	Fibrosis (Scheuer F2-F4)Platelet count <140: 0.87 (330/379)[0.96*]Spleen >120 mm: 0.84 (104/124) [0.85*]Nodular liver present: 0.87 (104/119)Portal vein >12 mm: 0.98 (45/46)Spleen >120 mm or platelets <140: 0.84 (214/254) [0.85*]Nodular liver or platelets <140: 0.86 (214/249)Portal vein >12 mm or platelets <140: 0.89 (201/226) [0.90*]Cirrhosis (Scheuer F4)Platelet count <140: 0.33 (67/205) [0.32*]Spleen >120 mm: 0.26 (33/128)Nodular liver present: 0.34 (38/112) [0.33*]Portal vein >12 mm: 0.32 (15/47) [0.35*]Spleen >120 mm or platelets <140: 0.27 (70/261)Nodular liver or platelets <140: 0.33 (74/254) [0.30*]Portal vein >12 mm or platelets <140: 0.30 (68/227) [0.31*]	Fibrosis (Scheuer F2-F4)Platelet count <140: 0.58 (446/764) [0.29*]Spleen >120 mm: 0.47 (475/1019)Nodular liver present: 0.47 (480/1024)Portal vein >12 mm: 0.45 (494/1097)Spleen >120 mm or platelets <140: 0.51 (460/894) [0.52*]Nodular liver or platelets <140: 0.51 (460/894)Portal vein >12 mm or platelets <140: 0.51 (470/917)Cirrhosis (Scheuer F4)Platelet count <140: 0.98 (923/938)Spleen >120 mm: 0.95 (966/1015)Nodular liver present: 0.96 (987/1031)Portal vein >12 mm: 0.94 (1029/1096)Spleen >120 mm or platelets <140: 0.99 (870/882) [0.98*]Nodular liver or platelets <140: 0.99 (881/889)Portal vein >12 mm or platelets <140: 0.98 (902/916)	Not reported	States no external funding	Moderate	Same population as Iacobellis 2005b. Unclear if positive combinations of tests based on both tests positive or either test positive

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Iacobellis, 2005b	Significant fibrosis (Scheuer F3 or F4)AST/ALT ratio ≥1: 0.26 (63/243)Platelet count <140,000: 0.71 (172/243)Globulin/albumin ratio >1: 0.31 (74/243)Platelets and G/A: 0.29 (70/243)Platelets and AST/ALT: 0.19 (47/243)G/A and AST/ALT: 0.11 (27/243)Platelets and G/A and AST/ALT: 0.09 (22/243)AST/ALT and platelets: 0.20 (48/243)APRI >1.5: 0.60 (145/243)Forns' Index >6.9: 0.79 (193/243)Cirrhosis (Scheuer F4)AST/ALT ratio ≥1: 0.32 (25/78)Platelet count <140,000: 0.86 (67/78)Globulin/albumin ratio >1: 0.38 (30/78)Platelets and G/A: 0.34 (27/78)Platelets and AST/ALT: 0.29 (23/78)G/A and AST/ALT: 0.20 (15/78)Platelets and G/A and AST/ALT: 0.17 (13/78)AST/ALT and platelets: 0.03 (2/78)APRI >2: 0.66 (51/78)	Significant fibrosis (Scheuer F3 or F4)AST/ALT ratio ≥1: 0.88 (883/1009)Platelet count <140,000: 0.86 (873/1009)Globulin/albumin ratio >1: 0.85 (858/1009)Platelets and G/A: 0.84 (850/1009)Platelets and AST/ALT: 0.84 (845/1009)G/A and AST/ALT: 0.82 (829/1009)Platelets and G/A and AST/ALT: 0.82 (827/1009)AST/ALT and platelets: 0.84 (845/1009)APRI >1.5: 0.88 (891/1009)Forns' Index >6.9: 0.86 (871/1009)Cirrhosis (Scheuer F4)AST/ALT ratio ≥1: 0.87 (1020/1174)Platelet count <140,000: 0.87 (1018/1174)Globulin/albumin ratio >1: 0.96 (1125/1174)Platelets and G/A: 0.96 (1125/1174)Platelets and AST/ALT: 0.95 (1120/1174)G/A and AST/ALT: 0.95 (1114/1174)Platelets and G/A and AST/ALT: 0.95 (1113/1174)AST/ALT and platelets: 0.96 (1129/1174)APRI >2: 0.90 (1054/1174)	Significant fibrosis (Scheuer F3 or F4)AST/ALT ratio ≥1: 0.33 (63/189)Platelet count <140,000: 0.56 (172/308) [0.77*]Globulin/albumin ratio >1: 0.33 (74/225) [0.58]Platelets and G/A: 0.31 (70/229) [0.91*]Platelets and AST/ALT: 0.22 (47/211) [0.82*]G/A and AST/ALT: 0.13 (27/207) [0.64*]Platelets and G/A and AST/ALT: 0.11 (22/204) [0.88*]AST/ALT and platelets: 0.23 (48/212) [0.74*]APRI >1.5: 0.55 (145/263)Forns' Index >6.9: 0.58 (193/331)Cirrhosis (Scheuer F4)AST/ALT ratio ≥1: 0.14 (25/179)Platelet count <140,000: 0.30 (67/223) [0.29*]Globulin/albumin ratio >1: 0.38 (30/79) [0.23*]Platelets and G/A: 0.36 (27/76) [0.44*]Platelets and AST/ALT: 0.30 (23/77) [0.39*]G/A and AST/ALT: 0.20 (15/75) [0.36*]Platelets and G/A and AST/ALT: 0.18 (13/74) [0.50*]AST/ALT and platelets: 0.04 (2/47) [0.34*]APRI >2: 0.30 (51/171)	Significant fibrosis (Scheuer F3 or F4)AST/ALT ratio ≥1: 0.83 (883/1065)Platelet count <140,000: 0.92 (873/944) [0.93*]Globulin/albumin ratio >1: 0.83 (858/1028) [0.95*]Platelets and G/A: 0.83 (850/1023) [0.995*]Platelets and AST/ALT: 0.81 (845/1041) [0.99*]G/A and AST/ALT: 0.79 (829/1045) [0.98*]Platelets and G/A and AST/ALT: 0.79 (827/1048) [0.997*]AST/ALT and platelets: 0.81 (845/1040) [0.98*]APRI >1.5: 0.90 (891/989)Forns' Index >6.9: 0.95 (871/921)Cirrhosis (Scheuer F4)AST/ALT ratio ≥1: 0.95 (1020/1073)Platelet count <140,000: 0.99 (1018/1029) [0.87*]Globulin/albumin ratio >1: 0.96 (1125/1173) [0.91*]Platelets and G/A: 0.96 (1125/1176) [0.97*]Platelets and AST/ALT: 0.95 (1120/1175) [0.97*]G/A and AST/ALT: 0.95 (1114/1177) [0.98*]Platelets and G/A and AST/ALT: 0.94 (1113/1178) [0.99*]AST/ALT and platelets: 0.94 (1129/1205) [0.96*]APRI >2: 0.98 (1054/1081) [0.98*]	Not reported	Not reported	Moderate	Same population as Iacobellis 2005a

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Imbert-Bismut, 2001; Thabut, 2003; Le Calvez, 2004	Fibrosis (METAVIR F2-F4) (validation sample only)Fibrotest (original 6-marker version) >0.20: 0.92 (55/60); >0.50: 0.75 (45/60); >0.80: 0.38 (23/60)	Fibrosis (METAVIR F2-F4) (validation sample only)Fibrotest (original 6-marker version) >0.20: 0.46 (34/74); >0.50: 0.85 (63/74); >0.80: 0.97 (72/74)	Derivation and validation samples, respectivelyFibrosis (METAVIR F2-F4)Fibrotest (original 6-marker version) >0.20: 0.89 (106/119) [0.90*] and 0.58 (55/95); >0.50: NR and 0.80 (45/56); >0.80: NR and 0.92 (23/25)	Derivation and validation samples, respectivelyFibrosis (METAVIR F2-F4)Fibrotest (original 6-marker version) >0.20: NR and 0.87 (34/39); >0.50: NR and 0.81 (63/78) [0.80*]; >0.80: 0.90 (45/50) and 0.66 (72/109) [0.62*]	Derivation and validation samples, respectivelyFibrosis (METAVIR F2-F4)Fibrotest (original 6-marker version): 0.84 (SD 0.43) and 0.87 (SD 0.34)Fibrotest (original 5-marker version): 0.83 (SD 0.43) and 0.85 (SD 0.34)	Association pour la Recherche sur le Cancer	Moderate	Original study deriving the Fibrotest; included 6 (rather than 5) markers (alpha-2 globulin removed for the 5-item Fibrotest).Le Calvez 2004 reported an AUROC of 0.74 for APRI vs. 0.83 for Fibrotest in a sample of 323 patients from this population; sensitivities/specificities not reported. Thabut 2003 reported an AUROC of 0.78 (0.75-0.81) for Forn's Index and 0.84 (0.82-0.86) for Fibrotest for F2-F4 fibrosis/
Imperiale, 2000	Whole sample, excluding patients with normal AST and ALT, and excluding patients with heavy alcohol use, respectively Cirrhosis (Hytiroglou 4) AAR ≥1: 0.56 (23/41), 0.56 (23/41) and 0.52 (15/29)	Whole sample, excluding patients with normal AST and ALT, and excluding patients with heavy alcohol use, respectively Cirrhosis (Hytiroglou 4) AAR ≥1: 0.90 (123/136), 0.94 (117/124) and 0.91 (116/128)	Whole sample, excluding patients with normal AST and ALT, and excluding patients with heavy alcohol use, respectively Cirrhosis (Hytiroglou 4) AAR ≥1: 0.64 (23/36), 0.77 (23/30) [0.74*] and 0.56 (15/27)	Whole sample, excluding patients with normal AST and ALT, and excluding patients with heavy alcohol use, respectively Cirrhosis (Hytiroglou 4) AAR ≥1: 0.87 (123/141), 0.87 (117/135) and 0.89 (116/130)	Not reported	Not stated	Moderate	
Islam, 2005	Cirrhosis (Ishak 5 or 6)Normalized AST/ALT ratio >2.0: 0.67 (13/20)Platelet count <190,000: 0.80 (16/20)APRI >1.0: 0.78 (16/20)GUCI >1.0: 0.80 (16/20)	Cirrhosis (Ishak 5 or 6)Normalized AST/ALT ratio >2.0: 0.80 (127/159)Platelet count <190,000: 0.77 (122/159)APRI >1.0: 0.75 (119/159)GUCI >1.0: 0.78 (124/159)	Cirrhosis (Ishak 5 or 6)Normalized AST >2.0: 0.29 (13/45) [0.30*]Platelet count <190,000: 0.30 (16/53)APRI >1.0: 0.29 (16/56) [0.30*]GUCI >1.0: 0.31 (16/51)	Cirrhosis (Ishak 5 or 6)Normalized AST/ALT ratio >2.0: 0.95 (127/134)Platelet count <190,000: 0.97 (122/126)APRI >1.0: 0.97 (119/123) [0.96*]GUCI >1.0: 0.97 (124/128)	Fibrosis (Ishak ≥3)Normalized AST/ALT ratio: Not reportedPlatelet count: Not reportedAPRI: 0.71 (CI not reported)GUCI: 0.72 (CI not reported)Cirrhosis (Ishak 5 or 6)Normalized AST/ALT ratio: Not reportedPlatelet count: Not reportedAPRI: 0.83 (CI not reported)GUCI: 0.85 (CI not reported)	Not stated	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Jazia, 2009	Fibrosis (METAVIR F2-F4) APRI >0.72: 0.93 (25/27) AST/ALT ratio: Not reported Platelet count: Not reported	Fibrosis (METAVIR F2-F4) APRI >0.72: 0.58 (5/8) AST/ALT ratio: Not reported Platelet count: Not reported	Fibrosis (METAVIR F2-F4) APRI >0.72: 0.83 (25/28) [0.87*] AST/ALT ratio: Not reported Platelet count: Not reported	Fibrosis (METAVIR F2-F4) APRI >0.72: 0.71 (5/7) [0.60*] AST/ALT ratio: Not reported Platelet count: Not reported	Fibrosis (METAVIR F2-F4) APRI: 0.91 (CI not reported) AST/ALT ratio: 0.68 (CI not reported) Platelet count: 0.38 (CI not reported)	Not stated	Moderate	
Kaul, 2002	Not reported	Not reported	Not reported	Not reported	Derivation and validation samples, respectively Cirrhosis (Scheuer F4) 4-item predictive model: 0.94 (0.91-0.97) and 0.93 (CI not reported)	Not stated	Moderate	
Khan, 2008	Fibrosis (METAVIR F2-F4)APRI >0.5: 0.83 (53/64); >1.5: 0.41 (26/64)Severe fibrosis (METAVIR F3-F4)APRI >0.90: 0.87 (26/30) [0.90*]; >1.75: 0.57 (17/30) [0.56*]	Fibrosis (METAVIR F2-F4)APRI >0.5: 0.57 (32/56); >1.5: 0.95 (53/56)Severe fibrosis (METAVIR F3-F4)APRI >0.90: 0.70 (63/90); >1.75: 0.94 (85/90)	Fibrosis (METAVIR F2-F4)APRI >0.5: 0.69 (53/77) [0.72*]; >1.5: 0.90 (26/29)Severe fibrosis (METAVIR F3-F4)APRI >0.90: 0.49 (26/53); >1.75: 0.77 (17/22) [0.78*]	Fibrosis (METAVIR F2-F4)APRI >0.5: 0.74 (32/43) [0.78*]; >1.5: 0.58 (53/91)Severe fibrosis (METAVIR F3-F4)APRI >0.90: 0.94 (63/67) [0.95*]; >1.75: 0.87 (85/98) [0.86*]	Fibrosis (METAVIR F2-F4)APRI: Not reportedCirrhosis (METAVIR F3-F4)APRI: 0.87 (0.79-0.94)	Not stated	Moderate	
Khokhar, 2003	Severe fibrosis (METAVIR F3-F4) AST/ALT ratio >1 and platelet count <150,000: 0.86 (134/157)	Severe fibrosis (METAVIR F3-F4) AST/ALT ratio >1 and platelet count <150,000: 0.90 (98/109)	Severe fibrosis (METAVIR F3-F4) AST/ALT ratio >1 and platelet count <150,000: 0.92 (134/145)	Severe fibrosis (METAVIR F3-F4) AST/ALT ratio >1 and platelet count <150,000: 0.81 (98/121)	Not reported	Not stated	Moderate	Reports different diagnostic test accuracy for diagnosis of F0-F2 compared to diagnosis of F3-F4 though they should be evaluating the same thing.

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Koda, 2007	Derivation vs. validation samples, respectively F2 or F3 fibrosis (METAVIR) Fibro Index >1.25: 0.94 (116/123) and 0.97 (58/60); ≥2.25: 0.36 (44/123) and 0.30 (18/60) Forn's Index >4.5: 0.98 (120/123) and 0.93 (56/60); ≥8.7: 0.24 (30/123) and 0.22 (13/60) APRI >0.36: 0.95 (117/123) and 0.98 (59/60); ≥1.85: 0.34 (42/123) and 0.32 (19/60)	Derivation vs. validation samples, respectively F2 or F3 fibrosis (METAVIR) Fibro Index >1.25: 0.40 (70/117) and 0.40 (24/60); ≥2.25: 0.97 (114/117) and 0.97 (58/60) Forn's Index >4.5: 0.26 (30/117) and 0.25 (15/60); ≥8.7: 0.97 (113/117) and 0.98 (59/60) APRI >0.36: 0.26 (31/117) and 0.32 (19/60); ≥0.85: 0.96 (112/117) and 0.92 (55/60)	Derivation vs. validation samples, respectively F2 or F3 fibrosis (METAVIR) Fibro Index >1.25: 0.62 (116/186) and 0.62 (58/94); ≥2.25: 0.94 (44/47) and 0.90 (18/20) Forn's Index >4.5: 0.58 (120/207) and 0.55 (56/101); ≥8.7: 0.88 (30/34) and 0.93 (13/14) APRI >0.36: 0.58 (117/203) and 0.59 (59/100); ≥1.85: 0.89 (42/47) and 0.79 (19/24)	Derivation vs. validation samples, respectively F2 or F3 fibrosis (METAVIR) Fibro Index >1.25: 0.87 (47/54) and 0.92 (24/26); ≥2.25: 0.59 (114/193) and 0.58 (58/100) Forn's Index >4.5: 0.91 (30/33) and 0.79 (15/19); ≥8.7: 0.55 (113/206) and 0.56 (59/106) APRI >0.36: 0.84 (31/37) and 0.95 (19/20); ≥1.85: 0.58 (112/193) and 0.57 (55/96)	Derivation sample, derivation sample (normal ALT only, n=73), validation sample (excluding F4), validation sample (with F4), and validation sample (normal ALT only, n=39), respectively F2-3 or F2-4 fibrosis (METAVIR) Fibro Index: 0.83 (0.78-0.88), 0.77 (0.65-0.89), 0.83 (0.75-0.90), 0.86 (0.81-0.92), and 0.86 (0.74-0.98) Forns Index: 0.79 (0.73-0.84), 0.74 (0.62-0.86), 0.78 (0.70-0.86), 0.84 (0.77-0.90), and 0.81 (0.67-0.96) APRI: 0.79 (0.74-0.85), 0.72 (0.60-0.84), 0.78 (0.69-0.86), 0.82 (0.76-0.88), and 0.88 (0.76-1.0) F3 or F3-4 fibrosis (METAVIR) Fibroindex: 0.81 (0.76-0.87), 0.76 (0.58-0.95), 0.81 (0.73-0.89), 0.85 (0.79-0.91) and 0.93 (0.85-1.0) Forn's Index: 0.77 (0.70-0.83), 0.74 (0.55-0.92), 0.76 (0.68-0.85), 0.83 (0.77-0.89), and 0.90 (0.79-1.0) APRI: 0.80 (0.74-0.86), 0.64 (0.44-0.84), 0.77 (0.69-0.86), 0.81 (0.74-0.88), and 0.92 (0.82-1.0)	Not stated	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Lackner, 2005 and Lackner, 2006	Fibrosis (Ishak 3-6)Platelet count <130,000: 0.30 (29/97); <150,000: 0.42 (41/97)APRI ≥0.5: 0.88 (85/97); ≥1.5: 0.44 (43/97)Age-platelet index ≥6: 0.51 (49/97)Severe fibrosis (Ishak 4-6)Cirrhosis Discriminant Score ≥8: 0.10 (5/50)Pohl Index positive: 0.18 (9/50)Cirrhosis (Ishak 5-6)Platelet count <130,000: 0.53 (17/32); <150,000: 0.78 (25/32) [0.77*]APRI ≥1.0: 0.93 (30/32); ≥2.0: 0.55 (18/32)AST/ALT ratio ≥1: 0.36 (12/32)Lok Index ≥0.20: 1.0 (32/32); ≥0.50: 0.44 (14/32)	Fibrosis (Ishak 3-6)Platelet count <130,000: 1.0 (97/97); <150,000: 0.97 (94/97)APRI ≥0.5: 0.44 (43/97); ≥1.5: 0.96 (93/97)Age-platelet index ≥6: 0.93 (90/97)Severe fibrosis (Ishak 4-6)Cirrhosis Discriminant Score ≥8: 1.0 (144/144)Pohl Index positive: 0.98 (141/144)Cirrhosis (Ishak 5-6)Platelet count <130,000: 0.93 (151/162); <150,000: 0.88 (143/162)APRI ≥1.0: 0.70 (113/162); ≥2.0: 0.93 (151/162)AST/ALT ratio ≥1: 0.90 (146/162)Lok Index ≥0.20: 0.58 (94/162); ≥0.50: 0.94 (152/162)	Fibrosis (Ishak 3-6)Platelet count <130,000: 1.0 (29/29); <150,000: 0.93 (41/44)APRI ≥0.5: 0.61 (85/139) [0.60*]; ≥1.5: 0.91 (43/47)Age-platelet index ≥6: 0.88 (49/56)Severe fibrosis (Ishak 4-6)Cirrhosis Discriminant Score ≥8: 1.0 (5/5)Pohl Index positive: 0.75 (9/12) [0.73*]Cirrhosis (Ishak 5-6)Platelet count <130,000: 0.61 (17/28) [0.59*]; <150,000: 0.57 (25/44) [0.56*]APRI ≥1.0: 0.38 (30/79); ≥2.0: 0.62 (18/29)AST/ALT ratio ≥1: 0.43 (12/28) [0.41*]Lok Index ≥0.20: 0.32 (32/100) [0.30*]; ≥0.50: 0.58 (14/24)	Fibrosis (Ishak 3-6)Platelet count <130,000: 0.59 (97/165); <150,000: 0.63 (94/150)APRI ≥0.5: 0.78 (43/55) [0.80*]; ≥1.5: 0.63 (93/147) [0.64*]Age-platelet index ≥6: 0.64 (90/140) [0.66*]Severe fibrosis (Ishak 4-6)Cirrhosis Discriminant Score ≥8: 0.76 (144/189) [0.77*]Pohl Index positive: 0.77 (141/182)Cirrhosis (Ishak 5-6)Platelet count <130,000: 0.91 (151/166); <150,000: 0.95 (143/150)APRI ≥1.0: 0.98 (113/115); ≥2.0: 0.92 (151/165)AST/ALT ratio ≥1: 0.88 (146/166) [0.87*]Lok Index ≥0.20: 1.0 (94/94); ≥0.50: 0.89 (152/170) [0.90*]	Fibrosis (Ishak 3-6)Platelet count: 0.71 (0.64-0.79)APRI: 0.80 (0.73-0.86)Age-platelet index: 0.74 (0.67-0.81)AST/ALT ratio: 0.57 (0.48-0.65)Cirrhosis Discriminant Score: 0.71 (0.63-0.79)Cirrhosis (Ishak 5-6)Platelet count: 0.89 (0.83-0.94)APRI: 0.90 (0.85-0.95)Age-platelet index: 0.91 (0.87-0.96)AST/ALT ratio: 0.73 (0.63-0.83)Cirrhosis Discriminant Score: 0.91 (0.85-0.96)	Not stated, though reports no conflicts of interest to report	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Leroy, 2008	Fibrosis (METAVIR F2-F4)FibroMeter (unclear cutoff): 0.75 (301/400)Fibrotest (unclear cutoff): 0.58 (231/400)Hepascore (unclear cutoff): 0.64 (254/400)APRI (unclear cutoff): 0.39 (155/400)	Fibrosis (METAVIR F2-F4)FibroMeter (unclear cutoff): 0.78 (332/425)Fibrotest (unclear cutoff): 0.85 (363/425)Hepascore (unclear cutoff): 0.80 (341/425)APRI (unclear cutoff): 0.95 (404/425)	Fibrosis (METAVIR F2-F4)FibroMeter (unclear cutoff): 0.76 (301/394)Fibrotest (unclear cutoff): 0.79 (231/293)Hepascore (unclear cutoff): 0.75 (254/338)APRI (unclear cutoff): 0.88 (155/176)	Fibrosis (METAVIR F2-F4)FibroMeter (unclear cutoff): 0.77 (332/431)Fibrotest (unclear cutoff): 0.68 (363/532)Hepascore (unclear cutoff): 0.70 (341/487)APRI (unclear cutoff): 0.62 (404/649)	Fibrosis (METAVIR F2-F4)FibroMeter: 0.84 (0.81-0.87)Fibrotest: 0.80 (0.77-0.83)Hepascore: 0.78 (0.75-0.81)APRI: 0.79 (0.76-0.82)Severe fibrosis (METAVIR F3-F4)FibroMeter: 0.89 (0.87-0.92)Fibrotest: 0.85 (0.82-0.88)Hepascore: 0.84 (0.81-0.87)APRI: 0.84 (0.80-0.87)Cirrhosis (METAVIR F4)FibroMeter: 0.93 (0.90-0.95)Fibrotest: 0.89 (0.86-0.92)Hepascore: 0.89 (0.86-0.93)APRI: 0.86 (0.82-0.90)	French Department of Health	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Leroy, 2007	Fibrosis (METAVIR F2-F4)MP3 >0.20: 0.96 (87/91); >0.30: 0.82 (75/91); >0.40: 0.44 (40/91); >0.50: 0.19 (17/91)APRI >0.50: 0.92 (83/91); >1.0: 0.80 (72/91); >1.5: 0.72 (66/91); >2.0: 0.58 (53/91)Forn's Index >4.2: 0.88 (80/91); >6.9: 0.42 (38/91)Fibrotest >0.22: 0.89 (81/91); >0.32: 0.76 (69/91); >0.59: 0.45 (41/91)Hepascore >0.50: 0.54 (49/91); >0.84: 0.33 (30/91)Severe fibrosis (METAVIR F3-F4)MP3 >0.20: 1.0 (51/51); >0.30: 0.92 (47/51); >0.40: 0.61 (31/51); >0.50: 0.31 (16/51)APRI >0.50: 0.94 (48/51); >1.00: 0.89 (45/51); >1.50: 0.87 (44/51); >2.00: 0.74 (38/51)Forn's Index >4.2: 0.92 (47/51); >6.9: 0.54 (28/51)Fibrotest >0.22: 0.94 (48/51); >0.32: 0.90 (46/51); >0.59: 0.67 (34/51)Hepascore >0.50: 0.76 (39/51); >0.84: 0.47 (24/51)	Fibrosis (METAVIR F2-F4)MP3 >0.20: 0.24 (21/89); >0.30: 0.73 (65/89); >0.40: 0.96 (85/89); >0.50: 0.99 (88/89)APRI >0.50: 0.27 (24/89); >1.0: 0.63 (56/89); >1.5: 0.88 (78/89); >2.0: 0.94 (84/89)Forn's Index >4.2: 0.42 (38/89); >6.9: 0.93 (83/89)Fibrotest >0.22: 0.53 (47/89); >0.32: 0.74 (66/89); >0.59: 0.90 (80/89)Hepascore >0.50: 0.84 (75/89); >0.84: 0.92 (82/89) Severe fibrosis (METAVIR F3-F4)MP3 >0.20: .20 (26/129); >0.30: 0.59 (76/129); >0.40: 0.90 (116/129); >0.50: 0.98 (127/129)APRI >0.50: 0.22 (28/129); >1.00: 0.54 (69/129); >1.50: 0.75 (96/129); >2.00: 0.84 (108/129)Forn's Index >4.2: 0.34 (44/129); >6.9: 0.87 (112/129)Fibrotest >0.22: 0.42 (54/129); >0.32: 0.64 (83/129); >0.59: 0.88 (114/129)Hepascore >0.50: 0.81 (105/129); >0.84: 0.90 (116/129)	Fibrosis (METAVIR F2-F4)MP3 >0.20: 0.56 (87/155); >0.30: 0.76 (75/99); >0.40: 0.91 (40/44); >0.50: 0.94 (17/18)APRI >0.50: 0.56 (83/148); >1.0: 0.69 (72/105); >1.5: 0.86 (66/77); >2.0: 0.91 (53/58)Forn's Index >4.2: 0.61 (80/131); >6.9: 0.86 (38/44)Fibrotest >0.22: 0.66 (81/123); >0.32: 0.75 (69/92); >0.59: 0.82 (41/50)Hepascore >0.50: 0.78 (49/63); >0.84: 0.81 (30/37) Severe fibrosis (METAVIR F3-F4)MP3 >0.20: 0.33 (51/154); >0.30: 0.47 (47/100) [0.48*]; >0.40: 0.70 (31/44); >0.50: 0.89 (16/18)APRI >0.50: 0.32 (48/149); >1.00: 0.43 (45/105); >1.50: 0.57 (44/77); >2.00: 0.64 (38/59)Forn's Index >4.2: 0.36 (47/132) [0.35*]; >6.9: 0.62 (28/45)Fibrotest >0.22: 0.39 (48/123); >0.32: 0.50 (46/92); >0.59: 0.69 (34/49) [0.68*]Hepascore >0.50: 0.62 (39/63); >0.84: 0.65 (24/37)	Fibrosis (METAVIR F2-F4)MP3 >0.20: 0.84 (21/25); >0.30: 0.80 (65/81); >0.40: 0.62 (85/136); >0.50: 0.54 (88/162)APRI >0.50: 0.75 (24/32); >1.0: 0.75 (56/75); >1.5: 0.76 (78/103); >2.0: 0.69 (84/122)Forn's Index >4.2: 0.78 (38/49); >6.9: 0.61 (83/136)Fibrotest >0.22: 0.82 (47/57); >0.32: 0.75 (66/88); >0.59: 0.62 (80/130)Hepascore >0.50: 0.64 (75/117); >0.84: 0.57 (82/143)Severe fibrosis (METAVIR F3-F4)MP3 >0.20: 1.0 (26/26); >0.30: 0.95 (76/80); >0.40: 0.85 (116/136); >0.50: 0.78 (127/162)APRI >0.50: 0.90 (28/31); >1.00: 0.92 (69/75) [0.93*]; >1.50: 0.93 (96/103) [0.94*]; >2.00: 0.89 (108/121) [0.92*]Forn's Index >4.2: 0.92 (44/48) [0.91*]; >6.9: 0.83 (112/135)Fibrotest >0.22: 0.95 (54/57); >0.32: 0.94 (83/88); >0.59: 0.87 (114/131)Hepascore >0.50: 0.90 (105/117); >0.84: 0.81 (116/143)	Whole sample and excluding patients with biopsy <15 mm or <7 portal tracts (n=161)Fibrosis (METAVIR F2-F4)MP3: 0.84 (0.78-0.90) and 0.83 (CI not reported)APRI: 0.81 (0.74-0.88) and 0.80 (CI not reported)Forn's Index: 0.78 (0.71-0.85) and 0.78 (CI not reported)Fibrotest: 0.84 (0.79-0.90) and 0.83 (CI not reported)Hepascore: 0.79 (0.72-0.85) and 0.78 (CI not reported)Fibrometer: 0.86 (0.80-0.91) and 0.85 (CI not reported)Severe fibrosis (METAVIR F3-F4)MP3: 0.88 (0.82-0.93) and 0.89 (CI not reported)APRI: 0.82 (0.74-0.90) and 0.81 (CI not reported)Forn's Index: 0.78 (0.71-0.87) and 0.80 (CI not reported)Fibrotest: 0.87 (0.81-0.93) and 0.86 (CI not reported)Hepascore: 0.85 (0.80-0.92) and 0.85 (CI not reported)Fibrometer: 0.91 (0.86-0.96) and 0.90 (CI not reported)	Direction de la Recherche Clinique, CHU de Grenoble, France	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Leroy, 2004	Fibrosis (METAVIR F2-F4)MP3 score >0.20: 0.91 (76/84); >0.30: 0.65 (55/84); >0.40: 0.35 (29/84); >0.50: 0.17 (14/84)PIIIP >6 ng/ml: 0.47 (39/84)Hyaluronic acid >8 g/ml: 0.43 (36/84)TIMP-1: Not reportedSevere fibrosis (METAVIR F3-F4)MP3 score >0.20: 0.94 (34/36); >0.30: 0.85 (31/36); >0.40: 0.58 (21/36); >0.50: 0.26 (9/36)PIIIP >5 ng/ml: 0.92 (33/36)Hyaluronic acid >36 ng/ml: 0.86 (31/36)TIMP-1 >1300 ng/ml: 0.75 (27/36)	Fibrosis (METAVIR F2-F4)MP3 score >0.20: 0.35 (36/104); >0.30: 0.85 (88/104); >0.40: 0.96 (100/104); >0.50: 0.99 (103/104)PIIIP >6 ng/ml: 0.93 (95/104)Hyaluronic acid >8 g/ml: 0.90 (94/104)TIMP-1: Not reportedSevere fibrosis (METAVIR F3-F4)MP3 score >0.20: 0.28 (43/152); >0.30: 0.74 (112/152); >0.40: 0.92 (140/152); >0.50: 0.97 (147/152)PIIIP >5 ng/ml: 0.76 (116/152)Hyaluronic acid >36 ng/ml: 0.70 (106/152)TIMP-1 >1300 ng/ml: 0.70 (106/152)	Fibrosis (METAVIR F2-F4)MP3 score >0.20: 0.53 (76/144); >0.30: 0.77 (55/71) [0.76*]; >0.40: 0.88 (29/33) [0.91*]; >0.50: 0.93 (14/15) [1.0*]PIIIP >6 ng/ml: 0.85 (39/46)Hyaluronic acid >8 g/ml: 0.78 (36/46)TIMP-1: Not reportedSevere fibrosis (METAVIR F3-F4)MP3 score >0.20: 0.24 (34/143); >0.30: 0.44 (31/71) [0.43*]; >0.40: 0.64 (21/33) [0.66*]; >0.50: 0.64 (9/14) [0.77*]PIIIP >5 ng/ml: 0.48 (33/69)Hyaluronic acid >36 ng/ml: 0.40 (31/77)TIMP-1 >1300 ng/ml: 0.37 (27/73)	Fibrosis (METAVIR F2-F4)MP3 score >0.20: 0.82 (36/44) [0.88*]; >0.30: 0.75 (88/117); >0.40: 0.65 (100/155); >0.50: 0.60 (103/173)PIIIP >6 ng/ml: 0.68 (95/140)Hyaluronic acid >8 g/ml: 0.66 (94/142)TIMP-1: Not reportedSevere fibrosis (METAVIR F3-F4)MP3 score >0.20: 0.96 (43/45) [0.95*]; >0.30: 0.96 (112/117) [0.95*]; >0.40: 0.90 (140/155) [0.91*]; >0.50: 0.85 (147/173)PIIIP >5 ng/ml: 0.97 (116/119)Hyaluronic acid >36 ng/ml: 0.95 (106/111)TIMP-1 >1300 ng/ml: 0.92 (106/115)	Fibrosis (METAVIR F2-F4)MP3 score: 0.82 (CI's not provided)PIIIP: 0.77 (CI's not provided)Hyaluronic acid: 0.74 (CI's not provided)Severe fibrosis (METAVIR F3-F4)MP3 score: 0.88 (CI's not provided)PIIIP: 0.88 (CI's not provided)Hyaluronic acid: 0.82 (CI's not provided)	DRRC, CHU de Grenoble	Moderate	
Liu, 2006	Fibrosis (METAVIR F2-F4) APRI >0.40: 0.48 (10/21); >0.50: 0.29 (6/21); >1.5: 0.0 (0/21) Age-platelet index: >4.00: 0.52 (11/21); >6.00: 0.19 (4/21) AST/ALT ratio >0.60: 0.86 (18/21); >1.00: 0.45 (10/21) Splenic artery pulsatility index >0.85: 0.98 (20/21); >1.05: 0.67 (14/21)	Fibrosis (METAVIR F2-F4) APRI >0.40: 0.75 (44/58); >0.50: 0.94 (55/58); >1.5: 1.0 (58/58) Age-platelet index: >4.00: 0.77 (45/58); >6.00: 0.86 (50/58) AST/ALT ratio >0.60: 0.05 (3/58); >1.00: 0.62 (36/58) Splenic artery pulsatility index >0.85: 0.39 (23/58); >1.05: 0.90 (52/58)	Fibrosis (METAVIR F2-F4) APRI >0.40: 0.41 (10/24); >0.50: 0.67 (6/9) [0.63*]; >1.5: 0.0 (0/0) Age-platelet index: >4.00: 0.46 (11/24) [0.45*]; >6.00: 0.33 (4/12) [0.34*] AST/ALT ratio >0.60: 0.25 (18/73); >1.00: 0.31 (10/32) [0.30*] Splenic artery pulsatility index >0.85: 0.36 (20/55) [0.37*]; >1.05: 0.70 (14/20)	Fibrosis (METAVIR F2-F4) APRI >0.40: 0.80 (44/55); >0.50: 0.79 (55/70) [0.78*]; >1.5: 0.73 (58/79) [1.0*] Age-platelet index: >4.00: 0.82 (45/55); >6.00: 0.75 (50/67) AST/ALT ratio >0.60: 0.50 (3/6); >1.00: 0.77 (36/47) [0.76*] Splenic artery pulsatility index >0.85: 0.96 (23/24) [0.98*]; >1.05: 0.88 (52/59)	Fibrosis (METAVIR F2-F4) APRI: 0.67 (0.54-0.81) Age-platelet index: 0.64 (0.51-0.77) AST/ALT ratio: 0.50 (0.35-0.66) Splenic artery pulsatility index: 0.86 (0.78-0.95)	National Taiwan University Hospital, National Science Council, Department of Health, Executive Yuan, Taiwan	Moderate	
Lo Iacono, 1998	Severe fibrosis (Scheuer F3 or F4) sICAM-1 >520 ng/ml: 0.64 sVCAM-1 >1208 ng/ml: 1.00 PIIIP >10.57 mcg/ml: 0.89	Severe fibrosis (Scheuer F3 or F4) sICAM-1 >520 ng/ml: 0.56 sVCAM-1 >1208 ng/ml: 0.85 PIIIP >10.57 mcg/ml: 0.52	NR	NR	Severe fibrosis (Scheuer F3 or F4) sICAM-1: 0.75 (CI not reported) sVCAM-1 >1208 ng/ml: 0.96 (CI not reported) PIIIP >10.57 mcg/ml: 0.73 (CI not reported)	INSALUD and Comunidad Autonoma de Madrid	Moderate	Unable to generate 2x2 table

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Lok, 2005	Derivation and external validation samples, respectivelyCirrhosis (Ishak 5-6)Lok Index ≥0.2: 0.92 (284/309) and 0.98 (39/40); ≥0.5: 0.54 (167/309) and 0.53 (21/40)?Sample (n=403)Platelet count <150,000: 0.76 (146/191)AST/ALT ratio >1: 0.41 (79/191)INR >1: 0.79 (150/191)	Derivation and external validation samples, respectivelyCirrhosis (Ishak 5-6)Lok Index ≥0.2: 0.30 (142/474) and 0.53 (119/225); ≥0.5: 0.85 (403/474) and 0.95 (213/225)?Sample (n=403)Platelet count <150,000: 0.71 (150/212)AST/ALT ratio >1: 0.80 (169/212)INR >1: 0.74 (157/212)	Derivation and external validation samples, respectivelyCirrhosis (Ishak 5-6)Lok Index ≥0.2: 0.46 (284/616) and 0.27 (39/145); ≥0.5: 0.70 (167/238) and 0.64 (21/33)?Sample (n=403)Platelet count <150,000: 0.70 (146/208)AST/ALT ratio >1: 0.65 (79/122)INR >1: 0.73 (150/205)	Derivation and external validation samples, respectivelyCirrhosis (Ishak 5-6)Lok Index ≥0.2: 0.85 (142/167) [0.86*]and 0.99 (119/120); ≥0.5: 0.74 (403/545) and 0.92 (213/232)?Sample (n=403)Platelet count <150,000: 0.77 (150/195)AST/ALT ratio >1: 0.60 (169/281)INR >1: 0.79 (157/198)	Derivation, internal validation, external validation, fragmented biopsies, nonfragmented biopsies, biopsy <1.5 cm, biopsy 1.5-2.5 cm, and biopsy >2.5 cm (biopsy subgroups from derivation + internal validation samples) samples, respectivelyCirrhosis (Ishak 5-6)Lok Index: 0.78 (0.74-0.81), 0.81 (0.75-0.86), and 0.91 (0.84-0.97), 0.72 (0.66-0.78), 0.80 (0.76-0.83), 0.77 (0.72-0.82), 0.80 (0.76-0.84), and 0.79 (0.70-0.88)Platelet count: 0.73 (0.69-0.77), 0.78 (0.72-0.84), not reported, 0.68 (0.61-0.74), 0.75 (0.71-0.79), 0.74 (0.68-0.79), 0.75 (0.70-0.79), and 0.76 (0.66-0.84)AST/ALT ratio: 0.66 (0.62-0.70), 0.64 (0.57-0.71), not reported, 0.60 (0.53-0.66), 0.67 (0.63-0.71), 0.64 (0.58-0.70), 0.66 (0.61-0.71), and 0.64 (0.54-0.76)APRI: 0.70 (0.66-0.75), 0.79 (0.74-0.85), not reported, 0.70 (0.64-0.76), 0.73 (0.69-0.77), 0.74 (0.68-0.79), 0.74 (0.70-0.79), and 0.67 (0.57-0.78)	National Institute of Diabetes and Digestive and Kidney Diseases, and other federal agencies	Moderate	HALT-C cohort also evaluated in Fontana, 2008. External validation sample is the same population evaluated in Wai, 2003.

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Luo, 2002	Cirrhosis (Scheuer F4)AST/ALT ratio ≥1: 0.39 (9/23)Globulin/albumin ratio ≥1: 0.43 (10/23)Platelet count ≤140,000: 0.83 (19/23)AST/ALT ratio ≥1 + globulin/albumin ratio ≥1: 0.39 (9/23)AST/ALT ratio ≥1 + platelet count <140,000: 0.26 (6/23)Globulin/albumin ratio ≥1 + platelet count ≤140,000: 0.39 (9/23)	Cirrhosis (Scheuer F4)AST/ALT ratio ≥1: 0.92 (81/88)Globulin/albumin ratio ≥1: 0.98 (86/88)Platelet count ≤140,000: 0.85 (75/88)AST/ALT ratio ≥1 + globulin/albumin ratio ≥1: 1.0 (88/88)AST/ALT ratio ≥1 + platelet count <140,000: 0.98 (86/88)Globulin/albumin ratio ≥1 + platelet count ≤140,000: 1.0 (88/88)	Cirrhosis (Scheuer F4)AST/ALT ratio ≥1: 0.56 (9/16)Globulin/albumin ratio ≥1: 0.83 (10/12)Platelet count ≤140,000: 0.59 (19/32)AST/ALT ratio ≥1 + globulin/albumin ratio ≥1: 1.0 (9/9)AST/ALT ratio ≥1 + platelet count <140,000: 0.75 (6/8)Globulin/albumin ratio ≥1 + platelet count ≤140,000: 1.0 (9/9)	Cirrhosis (Scheuer F4)AST/ALT ratio ≥1: 0.85 (81/95)Globulin/albumin ratio ≥1: 0.87 (86/99)Platelet count ≤140,000: 0.95 (75/79)AST/ALT ratio ≥1 + globulin/albumin ratio ≥1: 0.86 (88/102)AST/ALT ratio ≥1 + platelet count <140,000: 0.83 (86/103)Globulin/albumin ratio ≥1 + platelet count ≤140,000: 0.86 (88/102)	Not reported	Taipei Veterans General Hospital	Moderate	
Martinez, 2011	Fibrosis (METAVIR F2-F4) Forn's Index >4.2: 0.89 (204/229); >6.9: 0.44 (101/229) APRI >0.5: 0.91 (209/229); >1.5: 0.47 (107/220) Simplified ELF index >-0.45: 0.90 (207/229); >1.07: 0.47 (108/229) Severe fibrosis (METAVIR F3-F4) FIB-4 >1.45: 0.92 (142/155); >3.25: 0.54 (83/155) Cirrhosis (METAVIR F4) APRI >1: 0.82 (102/124); >2: 0.49 (61/124) Simplified ELF index >0.06: 0.90 (111/124); >1.73: 0.52 (65/124)	Fibrosis (METAVIR F2-F4) Forn's Index >4.2: 0.58 (64/111); >6.9: 0.93 (103/111) APRI >0.5: 0.50 (56/111) [0.51*]; >1.5: 0.93 (103/111) Simplified ELF index >-0.45: 0.52 (58/111); >1.07: 0.90 (100/111) Severe fibrosis (METAVIR F3-F4) FIB-4 >1.45: 0.64 (118/185); >3.25: 0.91 (168/185) Cirrhosis (METAVIR F4) APRI >1: 0.74 (159/216); >2: 0.91 (196/216) Simplified ELF index >0.06: 0.53 (114/216); >1.73: 0.90 (195/216)	Fibrosis (METAVIR F2-F4) Forn's Index >4.2: 0.81 (204/251); >6.9: 0.93 (101/109) APRI >0.5: 0.79 (209/264); >1.5: 0.93 (107/115) Simplified ELF index >-0.45: 0.80 (207/260); >1.07: 0.91 (108/119) Severe fibrosis (METAVIR F3-F4) FIB-4 >1.45: 0.68 (142/209) [0.74*]; >3.25: 0.83 (83/100) Cirrhosis (METAVIR F4) APRI >1: 0.64 (102/159); >2: 0.75 (61/81) Simplified ELF index >0.06: 0.52 (111/213); >1.73: 0.76 (65/86)	Fibrosis (METAVIR F2-F4) Forn's Index >4.2: 0.72 (64/89); >6.9: 0.45 (103/231) APRI >0.5: 0.74 (56/76); >1.5: 0.46 (103/225) Simplified ELF index >-0.45: 0.73 (58/80); >1.07: 0.45 (100/221) Severe fibrosis (METAVIR F3-F4) FIB-4 >1.45: 0.90 (118/131); >3.25: 0.70 (168/240) [0.77*] Cirrhosis (METAVIR F4) APRI >1: 0.88 (159/181); >2: 0.76 (196/259) Simplified ELF index >0.06: 0.90 (114/127); >1.73: 0.77 (195/254)	Fibrosis (METAVIR F2-F4) Forn's Index: 0.83 (0.78-0.87) APRI: 0.83 (0.79-0.88) FIB-4: 0.85 (0.81-0.89) Simplified ELF index : 0.81 (0.76-0.86) Severe fibrosis (METAVIR F3-F4) Forn's Index: 0.85 (0.81-0.89) APRI: 0.86 (0.82-0.90) FIB-4: 0.87 (0.83-0.91) Simplified ELF index : 0.83 (0.79-0.87) Cirrhosis (METAVIR F4) Forn's Index: 0.87 (0.83-0.91) APRI: 0.86 (0.82-0.90) FIB-4: 0.89 (0.85-0.92) Simplified ELF index: 0.82 (0.78-0.87)	Instituto de Salud Carlos III, Direccion General de Investigacion Cientifica y Tecnica	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
McHutchison, 2000	Severe fibrosis (Knodell 3 or 4)Hyaluronic acid >60 mcg/l: 0.88 (123/139); >80 mcg/l: 0.83 (115/139); >100 mcg/l: 0.76 (105/139); >110 mcg/l: 0.73 (101/139)Cirrhosis (Knodell 4)Hyaluronic acid >60 mcg/l: 0.98 (78/80); >80 mcg/l: 0.93 (74/80); >100 mcg/l: 0.89 (71/80); >110 mcg/l: 0.88 (70/80)	Severe fibrosis (Knodell 3 or 4)Hyaluronic acid >60 mcg/l: 0.59 (206/347); >80 mcg/l: 0.72 (250/347); >100 mcg/l: 0.82 (284/347); >110 mcg/l: 0.83 (288/347)Cirrhosis (Knodell 4)Hyaluronic acid >60 mcg/l: 0.54 (220/406); >80 mcg/l: 0.66 (268/406); >100 mcg/l: 0.76 (309/406); >110 mcg/l: 0.78 (316/406)	Severe fibrosis (Knodell 3 or 4)Hyaluronic acid >60 mcg/l: 0.47 (123/264); >80 mcg/l: 0.54 (115/212); >100 mcg/l: 0.63 (105/168); >110 mcg/l: 0.63 (101/160)Cirrhosis (Knodell 4)Hyaluronic acid >60 mcg/l: 0.30 (78/264); >80 mcg/l: 0.35 (74/212); >100 mcg/l: 0.42 (71/168); >110 mcg/l: 0.44 (70/160)	Severe fibrosis (Knodell 3 or 4)Hyaluronic acid >60 mcg/l: 0.93 (206/222); >80 mcg/l: 0.91 (250/274); >100 mcg/l: 0.89 (284/318); >110 mcg/l: 0.88 (288/326)Cirrhosis (Knodell 4)Hyaluronic acid >60 mcg/l: 0.99 (220/222); >80 mcg/l: 0.98 (268/274); >100 mcg/l: 0.97 (309/318); >110 mcg/l: 0.97 (316/326)	Not reported	Not reported	Moderate	
Metwally, 2007	Severe fibrosis (METAVIR F3-F4) 3-item predictive index ≥2: 0.88 (28/32) [0.87*]; ≥4: 0.47 (15/32)	Severe fibrosis (METAVIR F3-F4) 3-item predictive index ≥2: 0.69 (72/105); ≥4: 0.99 (104/105)	Severe fibrosis (METAVIR F3-F4) 3-item predictive index ≥2: 0.46 (28/61); ≥4: 0.94 (15/16)	Severe fibrosis (METAVIR F3-F4) 3-item predictive index ≥2: 0.95 (72/76); ≥4: 0.86 (104/121)	Severe fibrosis (METAVIR F3-F4) 3-item predictive index: 0.88 (CI not reported)	Not reported	Moderate	
Murawaki, 2001a	F2 or F3 fibrosis (Desmet) Type-IV collagen >110: 0.77 (60/78) Platelet count <160,000: 0.68 (53/78) Type-IV collagen >110 and platelet count <160,000: 0.53 (41/78) Type IV collagen >110 or platelet count <160,000: 0.91 (71/78) F3 fibrosis (Desmet) Type-IV collagen >130: 0.66 (25/38) Platelet count <140,000: 0.68 (26/38) Type-IV collagen >130 and platelet count <140,000: 0.47 (18/38) Type-IV collagen >130 or platelet count <140,000: 0.87 (33/38)	F2 or F3 fibrosis (Desmet) Type-IV collagen >110: 0.74 (64/87) [0.73*] Platelet count <160,000: 0.71 (62/87) Type-IV collagen >110 and platelet count <160,000: 0.93 (81/87) Type IV collagen >110 or platelet count <160,000: 0.52 (45/87) F3 fibrosis (Desmet) Type-IV collagen >130: 0.75 (95/127) Platelet count <140,000: 0.74 (94/127) Type-IV collagen >130 and platelet count <140,000: 0.89 (113/127) Type-IV collagen >130 or platelet count <140,000: 0.49 (62/127)	F2 or F3 fibrosis (Desmet) Type-IV collagen >110: 0.72 (60/83) Platelet count <160,000: 0.68 (53/78) Type-IV collagen >110 and platelet count <160,000: 0.87 (41/47) Type IV collagen >110 or platelet count <160,000: 0.63 (71/113) F3 fibrosis (Desmet) Type-IV collagen >130: 0.44 (25/57) Platelet count <140,000: 0.44 (26/59) Type-IV collagen >130 and platelet count <140,000: 0.56 (18/32) Type-IV collagen >130 or platelet count <140,000: 0.34 (33/98) [0.40*]	F2 or F3 fibrosis (Desmet) Type-IV collagen >110: 0.78 (64/82) Platelet count <160,000: 0.71 (62/87) Type-IV collagen >110 and platelet count <160,000: 0.69 (81/118) Type IV collagen >110 or platelet count <160,000: 0.87 (45/52) [0.86*] F3 fibrosis (Desmet) Type-IV collagen >130: 0.88 (95/108) Platelet count <140,000: 0.89 (94/106) Type-IV collagen >130 and platelet count <140,000: 0.85 (113/133) Type-IV collagen >130 or platelet count <140,000: 0.93 (62/67) [0.94*]	Not reported	Viral Hepatitis Research Foundation of Japan	Moderate	Excluded patients with cirrhosis. Sample appears to overlap with Murawaki 2001b.

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Murawaki, 2001b	F2 or F3 fibrosis (Desmet)PIVNP >6.0: 0.70 (57/81)PIIIP >0.80: 0.74 (60/81)Hyaluronic acid >50 ng/ml: 0.75 (61/81)MMP-2 >550 ng/ml: 0.75 (61/81)TIMP-1 >160 ng/ml: 0.79 (64/81)ALT >80 IU/l: 0.60 (49/81)Hyaluronic acid >50 ng/ml and MMP-2 >550 ng/ml: 0.60 (49/81) [0.61*]Hyaluronic acid >50 ng/ml or MMP-2 >550 ng/ml: 0.86 (70/81)F3 fibrosis (Desmet)PIVNP >6.5: 0.63 (25/40)PIIIP >0.90: 0.65 (26/40) [0.64*]Hyaluronic acid >70 ng/ml: 0.50 (20/40)MMP-2 >575 ng/ml: 0.68 (27/40)TIMP-1 >170 ng/ml: 0.82 (33/40) [0.83*]	F2 or F3 fibrosis (Desmet)PIVNP >6.0: 0.73 (64/88)PIIIP >0.80: 0.52 (46/88)Hyaluronic acid >50 ng/ml: 0.80 (70/88)MMP-2 >550 ng/ml: 0.70 (62/88)TIMP-1 >160 ng/ml: 0.56 (49/88)ALT >80 IU/l: 0.66 (58/88)Hyaluronic acid >50 ng/ml and MMP-2 >550 ng/ml: 0.84 (74/88)Hyaluronic acid >50 ng/ml or MMP-2 >550 ng/ml: 0.60 (53/88)F3 fibrosis (Desmet)PIVNP >6.5: 0.73 (94/129)PIIIP >0.90: 0.59 (76/129)Hyaluronic acid >70 ng/ml: 0.79 (102/129)MMP-2 >575 ng/ml: 0.69 (89/129)TIMP-1 >170 ng/ml: 0.54 (70/129)	F2 or F3 fibrosis (Desmet)PIVNP >6.0: 0.70 (57/81) [0.71*]PIIIP >0.80: 0.59 (60/102) [0.60*]Hyaluronic acid >50 ng/ml: 0.77 (61/79)MMP-2 >550 ng/ml: 0.70 (61/87) [0.72*]TIMP-1 >160 ng/ml: 0.62 (64/103) [0.63*]ALT >80 IU/l: 0.62 (49/79)Hyaluronic acid >50 ng/ml and MMP-2 >550 ng/ml: 0.78 (49/63) [0.80*]Hyaluronic acid >50 ng/ml or MMP-2 >550 ng/ml: 0.67 (70/105) [0.69*]F3 fibrosis (Desmet)PIVNP >6.5: 0.42 (25/60) [0.41*]PIIIP >0.90: 0.33 (26/79)Hyaluronic acid >70 ng/ml: 0.43 (20/47) [0.42*]MMP-2 >575 ng/ml: 0.40 (27/67) [0.44*]TIMP-1 >170 ng/ml: 0.36 (33/92) [0.34*]	F2 or F3 fibrosis (Desmet)PIVNP >6.0: 0.73 (64/88) [0.72*]PIIIP >0.80: 0.69 (46/67) [0.68*]Hyaluronic acid >50 ng/ml: 0.78 (70/90)MMP-2 >550 ng/ml: 0.76 (62/82) [0.73*]TIMP-1 >160 ng/ml: 0.74 (49/66) [0.73*]ALT >80 IU/l: 0.64 (58/90) [0.65*]Hyaluronic acid >50 ng/ml and MMP-2 >550 ng/ml: 0.70 (74/106) [0.68*]Hyaluronic acid >50 ng/ml or MMP-2 >550 ng/ml: 0.83 (53/64) [0.81*]F3 fibrosis (Desmet)PIVNP >6.5: 0.86 (94/109) [0.87*]PIIIP >0.90: 0.84 (76/90)Hyaluronic acid >70 ng/ml: 0.84 (102/122)MMP-2 >575 ng/ml: 0.87 (89/102) [0.85*]TIMP-1 >170 ng/ml: 0.91 (70/77)	Not reported	Ministry of Education, Science, and Culture of Japan and Viral Hepatitis Research Foundation of Japan	Moderate	Excluded patients with cirrhosis. Sample appears to overlap with Murawaki 2001a.

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Myers, 2003	Fibrosis (METAVIR F2-F4)Fibrotest >0.20: 0.88 (115/131); >0.70: 0.50 (66/131)Platelet count <150,000: 0.34 (45/131)Prothrombin time <80% predicted: 0.15 (20/131); 100% predicted: Not reportedAge-platelet index >2.0 or >7.0: Not reportedSevere fibrosis (METAVIR F4)Fibrotest >0.70: Not reported; >0.80: Not reported	Fibrosis (METAVIR F2-F4)Fibrotest >0.20: 0.56 (107/192); >0.70: 0.95 (183/192)Platelet count <150,000: 0.89 (170/192)Prothrombin time <80% predicted: 0.96 (185/192); 100% predicted: Not reportedAge-platelet index >2.0 or >7.0: Not reportedSevere fibrosis (METAVIR F3-F4)Fibrotest >0.70: Not reported; >0.80: Not reported	Fibrosis (METAVIR F2-F4)Fibrotest >0.20: 0.58 (115/200); >0.70: 0.88 (66/75)Platelet count <150,000: 0.67 (45/67)Prothrombin time <80% predicted: 0.74 (20/27); 100% predicted: Not reportedAge-platelet index >2.0: Not reported; >7.0: 0.69 (n/N not available)Severe fibrosis (METAVIR F3-F4)Fibrotest >0.70: Not reported; >0.80: 0.73 (n/N not available)	Fibrosis (METAVIR F2-F4)Fibrotest >0.20: 0.87 (107/123); >0.70: 0.74 (183/248)Platelet count <150,000: 0.66 (170/256)Prothrombin time <80% predicted: 0.62 (185/296); 100% predicted: 0.71 (n/N not available)Age-platelet index >2.0: 0.69; >7.0: 0.86 (n/N's not available)Severe fibrosis (METAVIR F3-F4)Fibrotest >0.70: 0.93 (n/N not available); >0.80: Not reported	Fibrosis (METAVIR F2-F4)Fibrotest: 0.84 (0.82-0.86)7-item index: 0.84 (0.82-0.86)Platelet count: 0.67 (0.64-0.70)Prothrombin time: 0.66 (0.63-0.69)Age-platelet index: 0.72 (0.69-0.75)Severe fibrosis (METAVIR F3-F4)Fibrotest: 0.92 (0.90-0.94)7-item index: 0.94 (0.92-0.96)Platelet count: 0.74 (0.70-0.78)Prothrombin time: 0.76 (0.72-0.80)Age-platelet index: 0.81 (0.78-0.84)	Canadian Association for the Study of the Liver, Schering Canada, Royal College of Physicians and Surgeons of Canada, and Association Pour la Recherche sur les Maladies Hepatiques Viroles	Moderate	Same population as Myers, 2002
Myers, 2002	Fibrosis (METAVIR F2-F4) Fibrotest >0.20: 0.88 (74/84); >0.80: 0.25 (21/84) Historical index >0.20: 0.94 (79/84); >0.60: 0.24 (20/84)	Fibrosis (METAVIR F2-F4) Fibrotest >0.20: 0.53 (67/127); >0.80: 0.93 (118/127) Historical index >0.20: 0.21 (27/127); >0.60: 0.91 (116/127)	Fibrosis (METAVIR F2-F4) Fibrotest >0.20: 0.55 (74/134); >0.80: 0.70 (21/30) Historical index >0.20: 0.44 (79/179); >0.60: 0.65 (20/31)	Fibrosis (METAVIR F2-F4) Fibrotest >0.20: 0.87 (67/77); >0.80: 0.65 (118/181) Historical index >0.20: 0.84 (27/32); >0.60: 0.64 (116/180)	Fibrosis (METAVIR F2-F4) Fibrotest: 0.80 (0.76-0.83) Historical index: 0.71 (0.67-0.75) Severe fibrosis (METAVIR F3-F4) Fibrotest: 0.92 (0.89-0.95) Historical index: 0.76 (0.71-0.81)	Canadian association for the Study of the Liver, Schering Canada, Royal College of Physicians and Surgeons of Canada, and Association Pour la Recherche sur les Maladies Hepatiques Viroles	Moderate	Same population as Myers, 2003
Obrador, 2006	Derivation and validation samples, respectivelyCirrhosis (Knodell F4)Sabadell NIHCED index ≥22: 0.89 (42/47) and 0.80 (16/20)	Derivation and validation samples, respectivelyCirrhosis (Knodell F4)Sabadell NIHCED index ≥22: 0.83 (102/123) and 0.96 (136/142)	Derivation and validation samples, respectivelyCirrhosis (Knodell F4)Sabadell NIHCED index ≥22: 0.67 (42/63) and 0.73 (16/22)	Derivation and validation samples, respectivelyCirrhosis (Knodell F4)Sabadell NIHCED index ≥22: 0.95 (102/107) and 0.97 (136/140)	Derivation and validation samples, respectivelyCirrhosis (Knodell F4)Sabadell NIHCED index: 0.91 (0.86-0.96) and not reported	Funding sources not stated, no conflicts of interest declared	Moderate	Same population as Bejarano, 2009.

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Paggi, 2008	Severe fibrosis (METAVIR F3-F4) APRI >1: 0.79 (127/160); >2: 0.36 (58/160) Liver surface nodularity present: 0.72 (116/160) [0.73*]	Severe fibrosis (METAVIR F3-F4) APRI >1: 0.70 (189/270); >2: 0.92 (249/270) Liver surface nodularity present: 0.90 (243/270)	Severe fibrosis (METAVIR F3-F4) APRI >1: 0.61 (127/208); >2: 0.73 (58/79) Liver surface nodularity present: 0.81 (116/143)	Severe fibrosis (METAVIR F3-F4) APRI >1: 0.85 (189/222); >2: 0.71 (249/351) Liver surface nodularity present: 0.85 (243/287)	Severe fibrosis (METAVIR F3-F4) APRI: Not reported Liver surface nodularity: Not reported Sequential APRI and liver surface nodularity: 0.81 (0.76-0.85) Sequential FIB-4 and liver surface nodularity: 0.83 (0.79-0.87)	Declared no financial disclosures or conflicts of interest	Moderate	
Parise, 2006	Fibrosis (Batt-Ludwig F2-F4) Hyaluronic acid ≥34.2: 0.85 (73/86) APRI ≥0.70: 0.85 (73/86) GGT ≥1.5xULN: 0.77 (66/86) [0.76*] AST/ALT ratio ≥0.8: 0.52 (45/86) Cirrhosis (Batt-Ludwig F4) Hyaluronic acid ≥78.6: 0.91 (40/44) APRI >1.5: 0.73 (32/44) GGT ≥2xULN: 0.61 (27/44) AST/ALT ratio >1: 0.36 (16/44)	Fibrosis (Batt-Ludwig F2-F4) Hyaluronic acid ≥34.2: 0.71 (85/120) APRI ≥0.70: 0.66 (79/120) GGT ≥1.5xULN: 0.55 (66/120) AST/ALT ratio ≥0.8: 0.61 (73/120) Cirrhosis (Batt-Ludwig F4) Hyaluronic acid ≥78.6: 0.81 (132/162) [0.82*] APRI >1.5: 0.81 (131/162) GGT ≥2xULN: 0.58 (94/162) AST/ALT ratio >1: 0.82 (133/162)	Fibrosis (Batt-Ludwig F2-F4) Hyaluronic acid ≥34.2: 0.68 (73/108) APRI ≥0.70: 0.64 (73/114) GGT ≥1.5xULN: 0.55 (66/120) AST/ALT ratio ≥0.8: 0.49 (45/92) Cirrhosis (Batt-Ludwig F4) Hyaluronic acid ≥78.6: 0.57 (40/70) APRI >1.5: 0.51 (32/63) GGT ≥2xULN: 0.28 (27/95) AST/ALT ratio >1: 0.36 (16/45)	Fibrosis (Batt-Ludwig F2-F4) Hyaluronic acid ≥34.2: 0.87 (85/98) APRI ≥0.70: 0.86 (79/92) GGT ≥1.5xULN: 0.77 (66/86) AST/ALT ratio ≥0.8: 0.64 (73/114) Cirrhosis (Batt-Ludwig F4) Hyaluronic acid ≥78.6: 0.97 (132/136) APRI >1.5: 0.92 (131/143) GGT ≥2xULN: 0.85 (94/111) AST/ALT ratio >1: 0.83 (133/161)	Fibrosis (Batt-Ludwig F2-F4) Hyaluronic acid: 0.88 (0.83-0.93) APRI: 0.82 (0.77-0.88) GGT: 0.70 (0.63-0.78) AST/ALT ratio: 0.59 (0.51-0.67) Cirrhosis (Batt-Ludwig F4) Hyaluronic acid: 0.91 (0.87-0.95) APRI: 0.84 (0.77-0.90) GGT: 0.67 (0.59-0.75) AST/ALT ratio: 0.65 (0.56-0.75)	FAPESP	Moderate	
Park, 2000 and 2005	Cirrhosis (Scheuer F4)AST/ALT ratio ≥1: 0.47 (14/30)	Cirrhosis (Scheuer F4)AST/ALT ratio ≥1: 0.96 (118/123)	Cirrhosis (Scheuer F4)AST/ALT ratio ≥1: 0.74 (14/19)	Cirrhosis (Scheuer F4)AST/ALT ratio ≥1: 0.88 (118/134)	Fibrosis (Scheuer F2-F4)AST/ ALT ratio: 0.71 (0.62-0.79)Cirrhosis (Scheuer F4)AST/ALT ratio: 0.85 (0.77-0.93)	Not stated	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Parkes, 2011	Severe fibrosis (METAVIR F3-F4 or Ishak 4-6) Simplified ELF >9.39: 0.90 (100/111); >10.22: 0.70 (78/111); >10.90: 0.54 (60/111)	Severe fibrosis (METAVIR F3-F4 or Ishak 4-6) Simplified ELF >9.39: 0.55 (130/236); >10.22: 0.85 (201/236); >10.90: 0.95 (224/236)	Severe fibrosis (METAVIR F3-F4 or Ishak 4-6) Simplified ELF >9.39: 0.49 (100/206) [0.48*]; >10.22: 0.69 (78/113) [0.68*]; >10.90: 0.83 (60/72) [0.82*]	Severe fibrosis (METAVIR F3-F4 or Ishak 4-6) Simplified ELF >9.39: 0.92 (130/141); >10.22: 0.86 (201/234); >10.90: 0.81 (224/275)	Reported separately for 3 validation cohorts Fibrosis (METAVIR F2-F4 or Ishak 3-6) Simplified ELF: 0.74 (0.63-0.84), 0.83 (0.76-0.89), 0.87 (0.80-0.95) Severe fibrosis (METAVIR F3-F4 of Ishak 4-6) Simplified ELF: 0.84 (0.74-0.94), 0.86 (0.80-0.92), 0.89 (0.83-0.96) Cirrhosis (METAVIR F4 or Ishak 5-6) Simplified ELF: 0.90 (0.81-0.98), 0.87 (0.81-0.93), 0.89 (0.82-0.96)	Funding sources not stated, some authors disclosed interests and stocks in companies that conduct ELF assays	Moderate	Simplified version of original ELF evaluated in Rosenberg 2004.
Patel, 2009	Whole sample and excluding biopsies <15 mm, respectively (subgroup analysis only reported for Fibrosure and FibroSpect II) Fibrosis (METAVIR F2-F4) Fibrotest ≥0.48: 1.0 (18/18) and 1.0 (12/12) FibroSpect II >0.36: 0.95 (21/22) and 1.0 (15/15) APRI >0.5: 0.95 (21/22); ≥1.5: 0.41 (9/22) Forn's Index >4.21: 0.91 (20/22); 0.50 (11/22) FIB-4 >1.45: 0.86 (12/14); >3.25: 0.43 (6/14)	Whole sample and excluding biopsies <15 mm, respectively (subgroup analysis only reported for Fibrosure and FibroSpect II) Fibrosis (METAVIR F2-F4) Fibrotest ≥0.48: 0.61 (40/66) and 0.66 (21/32) FibroSpect II >0.36: 0.66 (48/73) and 0.73 (27/37) APRI >0.5: 0.64 (46/72); ≥1.5: 0.99 (71/72) Forn's Index >4.21: 0.53 (38/72); 0.93 (67/72) FIB-4 >1.45: 0.68 (54/80); >3.25: 0.96 (77/80)	Whole sample and excluding biopsies <15 mm, respectively (subgroup analysis only reported for Fibrosure and FibroSpect II) Fibrosis (METAVIR F2-F4) Fibrotest ≥0.48: 0.41 (18/44) and 0.52 (12/23) FibroSpect II >0.36: 0.46 (21/46) and 0.60 (15/25) APRI >0.5: 0.45 (21/47); ≥1.5: 0.90 (9/10) Forn's Index >4.21: 0.37 (20/54); 0.69 (11/16) FIB-4 >1.45: 0.32 (12/38); >3.25: 0.67 (6/9)	Whole sample and excluding biopsies <15 mm, respectively (subgroup analysis only reported for Fibrosure and FibroSpect II) Fibrosis (METAVIR F2-F4) Fibrotest ≥0.48: 1.0 (40/40) and 1.0 (21/21) FibroSpect II >0.36: 0.98 (48/49) and 1.0 (27/27) APRI >0.5: 0.98 (46/47); ≥1.5: 0.85 (71/84) Forn's Index >4.21: 0.95 (38/40); 0.86 (67/78) FIB-4 >1.45: 0.96 (54/56) [0.95*]; >3.25: 0.91 (77/85)	Whole sample and excluding biopsies <15 mm, respectively Fibrosis (METAVIR F2-F4) Fibrotest: 0.89 (0.81-0.97) and 0.89 (0.79-0.99) FibroSpect II: 0.90 (0.84-0.96) and 0.94 (0.88-1.0) APRI: Not reported Forn's Index: Not reported FIB-4: Not reported	Human Genome Sciences and Novartis	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Patel, 2004	Fibrosis (derivation and validation samples, respectively)FibroSpect II >0.36: 0.83 (123/149) and 0.77 (160/208)	Derivation and validation samples, respectivelyFibrosis (METAVIR F2-F4)FibroSpect II >0.36: 0.66 (96/145) and 0.73 (144/194)	Derivation and validation samples, respectivelyFibrosis (METAVIR F2-F4)FibroSpect II >0.36: 0.72 (123/172) and 0.76 (160/210)	Derivation and validation samples, respectivelyFibrosis (METAVIR F2-F4)FibroSpect II >0.36: 0.79 (96/122) and 0.75 (144/192)	Derivation and validation samples, respectivelyFibrosis (METAVIR F2-F4)FibroSpect II: and 0.82 (confidence interval not reported)(For the following markers, AUROC evaluated for sample of 194 patients)Hyaluronic acid: 0.82 (0.76-0.78)TIMP-1: 0.77 (0.71-0.85)Laminin: 0.52 (0.44-0.61)PIIIP: 0.78 (0.72-0.84)Type IV-7S collagen: 0.73 (0.66-0.80)YKL-40: 0.70 (0.62-0.77)Alpha2-macroglobulin: 0.72 (0.65-0.79)	Scripps Clinic	Moderate	
Plevris, 2000	Cirrhosis (Knodell F4) Hyaluronic acid >100 mcg/l: 0.73 (11/15) [0.72*]; >200 and >300 mcg/l: not reported	Cirrhosis (Knodell F4) Hyaluronic acid >100 mcg/l: 0.93 (50/54); >200: 0.98 (53/54); >300 mcg/l: 1.0 (54/54)	Cirrhosis (Knodell F4) Hyaluronic acid >100 mcg/l: 0.73 (11/15); >200 and >300 mcg/l: not reported	Cirrhosis (Knodell F4) Hyaluronic acid >100 mcg/l: 0.93 (50/54); >200 and >300 mcg/l: not reported	Not reported	Not reported	Moderate	
Pohl, 2001	Fibrosis (METAVIR F2-F4) AST/ALT ≥1: 0.35 (19/54) Pohl Index positive: 0.60 (32/54) Severe fibrosis (METAVIR F4) AST/ALT ≥1: 0.47 (17/36) Pohl Index positive: 0.42 (15/36) [0.41*]	Fibrosis (METAVIR F2-F4) AST/ALT ≥1: 0.77 (76/99) Pohl Index positive: 0.76 (74/99) [0.75*] Severe fibrosis (METAVIR F3 or F4) AST/ALT ≥1: 0.81 (95/117) [0.82*] Pohl Index positive: 0.99 (116/117)	Fibrosis (METAVIR F2-F4) AST/ALT ≥1: 0.45 (19/42) Pohl Index positive: 0.56 (32/57) [0.60*] Severe fibrosis (METAVIR F3 or F4) AST/ALT ≥1: 0.44 (17/39) [0.43*] Pohl Index positive: 0.94 (15/16) [0.93*]	Fibrosis (METAVIR F2-F4) AST/ALT ≥1: 0.68 (76/111) Pohl Index positive: 0.78 (74/95) [0.67*] Severe fibrosis (METAVIR F3 or F4) AST/ALT ≥1: 0.83 (95/114) [0.84*] Pohl Index positive: 0.85 (116/137)	Not reported	Not reported	Moderate	Analyses excluded 54 patients with history of alcohol abuse due to no correlation between AST/ALT ratio and fibrosis stage
Poynard, 2003	Not reported	Not reported	Not reported	Not reported	Fibrosis (METAVIR F2-F4)Fibrotest: 0.73 (0.70-0.76)Severe fibrosis (METAVIR F3-F4)Fibrotest: 0.73 (0.69-0.77)	Schering Plough Research Institute and Associatiogn pour la Recherche sur les Maladies Hepatiques Virales	Moderate	Evaluated patients enrolled in a randomized trial of antiviral therapy

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Poynard, 2002	Not reported	Not reported	Not reported	Not reported	F3 fibrosis (Knodell) Fibrotest: 0.74 (0.71-0.77) Hyaluronic acid: 0.65 (0.62-0.68)	Direction Regionale de la Recherche Clinique and Association pour la Recherche sur le Cancer	Moderate	Evaluated patients enrolled in a randomized trial of antiviral therapy
Pradat, 2002	Fibrosis (METAVIR F2-F4) ALT >ULN: 0.99 (603/612) Greater than METAVIR A1F1 ALT >2.25 ULN: 0.72 Severe fibrosis (METAVIR F3-F4) ALT >ULN: 1.0 (200/201) Cirrhosis (METAVIR F4) ALT >ULN: 0.98 (64/65)	Fibrosis (METAVIR F2-F4) ALT >ULN: 0.23 (57/252) Greater than METAVIR A1F1 ALT >2.25 ULN: 0.74 Severe fibrosis (METAVIR F3-F4) ALT >ULN: 0.10 (65/663) Cirrhosis (METAVIR F4) ALT >ULN: 0.08 (65/799)	Fibrosis (METAVIR F2-F4) ALT >ULN: 0.76 (603/798) Greater than METAVIR A1F1 ALT >2.25 ULN: NR Severe fibrosis (METAVIR F3-F4) ALT >ULN: 0.25 (200/798) Cirrhosis (METAVIR F4) ALT >ULN: 0.08 (64/798)	Fibrosis (METAVIR F2-F4) ALT >ULN: 0.86 (57/66) Greater than METAVIR A1F1 ALT >2.25 ULN: NR Severe fibrosis (METAVIR F3-F4) ALT >ULN: 0.98 (65/66) Cirrhosis (METAVIR F4) ALT >ULN: 0.98 (65/66)	Greater than METAVIR A1F1 ALT: 0.82 (CI not reported)	Schering-Plough International	Moderate	
Reedy, 1998	Cirrhosis (Knodell F4)AST/ALT ratio ≥1: 0.43 (10/23) [0.44*]	Cirrhosis (Knodell F4)AST/ALT ratio ≥1: 0.94 (45/48)	Cirrhosis (Knodell F4)AST/ALT ratio ≥1: 0.77 (10/13)	Cirrhosis (Knodell F4)AST/ALT ratio ≥1: 0.78 (45/58)	Not reported	Hoffman LaRoche, Inc. and Schering-Plough Corporation	Moderate	Study reports 77 patients evaluated but diagnostic data only presented for 71
Renou, 2001	Fibrosis (METAVIR F2-F4) Platelet count <140,000: 0.30 (14/33) Severe fibrosis (METAVIR F3-F4) Platelet count <140,000: 0.47 (14/30) Cirrhosis (METAVIR F4) Platelet count <140,000: 0.93 (13/14)	Fibrosis (METAVIR F2-F4) Platelet count <140,000: 1.0 (57/57) Severe fibrosis (METAVIR F3-F4) Platelet count <140,000: 1.0 (74/74) Cirrhosis (METAVIR F4) Platelet count <140,000: 0.99 (89/90)	Fibrosis (METAVIR F2-F4) Platelet count <140,000: 1.0 (14/14) Severe fibrosis (METAVIR F3-F4) Platelet count <140,000: 1.0 (14/14) Cirrhosis (METAVIR F4) Platelet count <140,000: 0.93 (13/14)	Fibrosis (METAVIR F2-F4) Platelet count <140,000: 1.0 (57/57) Severe fibrosis (METAVIR F3-F4) Platelet count <140,000: 1.0 (74/74) Cirrhosis (METAVIR F4) Platelet count <140,000: 0.99 (89/90)	Not reported	Not reported	Moderate	?Overlap with Halfon?

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Romera, 2006	Fibrosis (Scheuer F2-F4) Forn's Index ≥4.2: 0.79 (49/62) APRI ≥0.5: 0.81 (50/62) Fibrosis Probability Index ≥0.2: 0.77 (48/62)	Fibrosis (Scheuer F2-F4) Forn's Index ≥4.2: 0.48 (33/69) APRI ≥0.5: 0.36 (25/69) Fibrosis Probability Index ≥0.2: 0.58 (40/69)	Fibrosis (Scheuer F2-F4) Forn's Index ≥4.2: 0.58 (49/85) APRI ≥0.5: 0.53 (50/94) Fibrosis Probability Index ≥0.2: 0.62 (48/77)	Fibrosis (Scheuer F2-F4) Forn's Index ≥4.2: 0.72 (33/46) APRI ≥0.5: 0.68 (25/37) Fibrosis Probability Index ≥0.2: 0.74 (40/54)	Fibrosis (Scheuer F2-F4) Forn's Index: 0.71 (CI not reported) APRI: 0.70 (CI not reported) Fibrosis Probability Index: 0.80 (CI not reported)	Consejeria de Innovacion,Junta de Analucia, Spain	Moderate	
Rosenberg, 2004	Severe fibrosis (Scheuer F3-F4) ELF >0.063: 0.95; >0.190: 0.63; >0.564: 0.30	Severe fibrosis (Scheuer F3-F4) ELF >0.063: 0.29; >0.190: 0.80; >0.564: 0.99	Severe fibrosis (Scheuer F3-F4) ELF >0.063: 0.28; >0.190: 0.48; >0.564: 0.90	Severe fibrosis (Scheuer F3-F4) ELF >0.063: 0.95; >0.190: 0.88; >0.564: 0.83	Severe fibrosis (Scheuer F3-F4) ELF: 0.77 (0.70-0.85)	Not stated	Moderate	
Rossi, 2003	Fibrosis (METAVIR F2-F4)Fibrotest >0.10: 0.92 (44/48); >0.30: 0.75 (36/48); >0.60: 0.42 (20/48); >0.80: 0.22 (11/48)a-2 macroglobulin >2.52 g/L: 0.75 (36/48)Apolipoprotein A1 >1.41 g/L: 0.26 (12/48)Bilirubin >10 mmol/L: 0.61 (29/48)GGT >45 U/L: 0.57 (27/48)Haptoglobin >0.56 g/L: 0.21 (10/48)	Fibrosis (METAVIR F2-F4)Fibrotest >0.10: 0.29 (22/77); >0.30: 0.61 (47/77); >0.60: 0.94 (72/77); >0.80: 0.96 (74/77)a-2 macroglobulin >2.52 g/L: 0.67 (52/77)Apolipoprotein A1 >1.41 g/L: 0.50 (38/77)Bilirubin >10 mmol/L: 0.53 (41/77)GGT >45 U/L: 0.55 (42/77)Haptoglobin >0.56 g/L: 0.79 (61/77)	Fibrosis (METAVIR F2-F4)Fibrotest >0.10: 0.44 (44/99) [0.45*]; >0.30: 0.55 (36/66) [0.54*]; >0.60: 0.80 (20/25) [0.78*]; >0.80: 0.79 (11/14)a-2 macroglobulin >2.52 g/L: 0.43 (36/61)Apolipoprotein A1 >1.41 g/L: 0.24 (12/51)Bilirubin >10 mmol/L: 0.45 (29/65)GGT >45 U/L: 0.39 (27/62)Haptoglobin >0.56 g/L: 0.38 (10/26)	Fibrosis (METAVIR F2-F4)Fibrotest >0.10: 0.85 (22/26); >0.30: 0.80 (47/59); >0.60: 0.72 (72/100); >0.80: 0.67 (74/111) [0.66*]a-2 macroglobulin >2.52 g/L: 0.81 (52/64)Apolipoprotein A1 >1.41 g/L: 0.51 (38/74)Bilirubin >10 mmol/L: 0.68 (41/60)GGT >45 U/L: 0.67 (42/63)Haptoglobin >0.56 g/L: 0.62 (61/99)	Fibrosis (METAVIR F2-F4)Fibrotest: 0.74 (0.64-0.84)	Sir Charles Gairdner Hospital Research Fund	Moderate	
Saadeh, 2001	Cirrhosis (Knodell F4) Cirrhosis discriminant score >3: 0.85 (29/34); >7: 0.15 (5/34)	Cirrhosis (Knodell F4) Cirrhosis discriminant score >3: 0.58 (45/77); >7: 1.0 (77/77)	Cirrhosis (Knodell F4) Cirrhosis discriminant score >3: 0.48 (29/61); >7: 1.0 (5/5)	Cirrhosis (Knodell F4) Cirrhosis discriminant score >3: 0.90 (45/50); >7: 0.73 (77/106)	Cirrhosis (Knodell F4) Cirrhosis discriminant score: 0.80	Not stated	Moderate	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Saitou, 2005	Fibrosis (METAVIR F2-F4) Type IV collagen >5.75: 0.65 (50/77) PIIIP >0.835: 0.78 (60/77) Hyaluronic acid >75.7: 0.75 (58/77) YKL-40 >186.4: 0.78 (60/77) Cirrhosis (METAVIR F4) Type IV collagen >6.55: 0.60 (18/30) PIIIP >0.995: 0.77 (23/30) Hyaluronic acid >183.5: 0.80 (24/30) YKL-40 >284.8: 0.80 (24/30)	Fibrosis (METAVIR F2-F4) Type IV collagen >5.75: 0.69 (22/32) PIIIP >0.835: 0.75 (24/32) Hyaluronic acid >75.7: 0.81 (26/32) YKL-40 >186.4: 0.81 (26/32) Cirrhosis (METAVIR F4) Type IV collagen >6.55: 0.61 (48/79) PIIIP >0.995: 0.66 (52/79) Hyaluronic acid >183.5: 0.80 (63/79) YKL-40 >284.8: 0.71 (56/79)	Fibrosis (METAVIR F2-F4) Type IV collagen >5.75: 0.83 (50/60) [0.67*] PIIIP >0.835: 0.88 (60/68) [0.76*] Hyaluronic acid >75.7: 0.91 (58/64) [0.79*] YKL-40 >186.4: 0.91 (60/66) [0.80*] Cirrhosis (METAVIR F4) Type IV collagen >6.55: 0.37 (18/49) [0.61*] PIIIP >0.995: 0.46 (23/50) [0.69*] Hyaluronic acid >183.5: 0.60 (24/40) [0.80*] YKL-40 >284.8: 0.51 (24/47) [0.73*]	Fibrosis (METAVIR F2-F4) Type IV collagen >5.75: 0.45 (22/49) [0.66*] PIIIP >0.835: 0.59 (24/41) [0.77*] Hyaluronic acid >75.7: 0.58 (26/45) [0.76*] YKL-40 >186.4: 0.60 (26/43) [0.79*] Cirrhosis (METAVIR F4) Type IV collagen >6.55: 0.80 (48/60) [0.60*] PIIIP >0.995: 0.88 (52/59) [0.67*] Hyaluronic acid >183.5: 0.91 (63/69) [0.80*] YKL-40 >284.8: 0.90 (56/62) [0.78*]	Fibrosis (F2-F4) Type IV collagen: 0.74 (CI not reported) PIIIP: 0.75 (CI not reported) Hyaluronic acid: 0.80 (CI not reported) YKL-40: 0.81 (CI not reported) Cirrhosis (F4) Type IV collagen: 0.60 (CI not reported) PIIIP: 0.79 (CI not reported) Hyaluronic acid: 0.85 (CI not reported) YKL-40: 0.80 (CI not reported)	Not stated	High	
Schneider, 2006	Fibrosis (Ishak 3-6)APRI >0.7: 0.81 (38/47)Cirrhosis (Ishak 5-6)APRI >1.0: 0.79 (15/19) [0.77*]Portal venous flow <12.5 cm/s: 0.89 (17/19) [0.88*]	Fibrosis (Ishak 3-6)APRI >0.7: 0.65 (23/36)Cirrhosis (Ishak 5-6)APRI >1.0: 0.63 (40/64)Portal venous flow <12.5 cm/s: 0.66 (42/64) [0.65*]	Fibrosis (Ishak 3-6)APRI >0.7: 0.75 (38/51)Cirrhosis (Ishak 5-6)APRI >1.0: 0.38 (15/39)Portal venous flow <12.5 cm/s: 0.44 (17/39)	Fibrosis (Ishak 3-6)APRI >0.7: 0.72 (23/32)Cirrhosis (Ishak 5-6)APRI >1.0: 0.91 (40/44)Portal venous flow <12.5 cm/s: 0.95 (42/44)	Fibrosis (Ishak 3-6)APRI: 0.75 (CI not reported)Portal venous flow: Not reportedCirrhosis (Ishak 5-6)APRI: 0.71 (CI not reported)Portal venous flow: 0.80 (CI not reported)	Not stated	Moderate	Degree of population overlap with Schneider 2005 unclear
Schneider, 2005	Cirrhosis (Ishak 5-6) Portal venous flow <14.5 cm/s: 0.74 (13/17) Portal venous undulations reduced: 0.76 (13/17) Hepatic venous flow pattern mono- or biphasic: 0.31 (5/17) Longitudinal spleen size (cutoff not reported): 0.78 (13/17) Transverse spleen size >5 cm: 0.86 (15/17)	Cirrhosis (Ishak 5-6) Portal venous flow <14.5 cm/s: 0.53 (54/102) Portal venous undulations reduced: 1.0 (102/102) Hepatic venous flow pattern mono- or biphasic: 0.47 (48/102) Longitudinal spleen size (cutoff not reported): 0.53 (54/102) Transverse spleen size >5 cm: 0.35 (36/102)	Cirrhosis (Ishak 5-6) Portal venous flow <14.5 cm/s: 0.21 (13/61) Portal venous undulations reduced: 1.0 (13/13) Hepatic venous flow pattern mono- or biphasic: 0.08 (5/59) Longitudinal spleen size (cutoff not reported): 0.21 (13/61) Transverse spleen size >5 cm: 0.19 (15/81)	Cirrhosis (Ishak 5-6) Portal venous flow <14.5 cm/s: 0.93 (54/58) Portal venous undulations reduced: 0.96 (102/106) Hepatic venous flow pattern mono- or biphasic: 0.80 (48/60) Longitudinal spleen size (cutoff not reported): 0.93 (54/58) Transverse spleen size >5 cm: 0.95 (36/38)	Not reported	Not stated	Moderate	Degree of population overlap with Schneider 2006 unclear

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Sebastiani, 2009	Fibrosis (METAVIR F2-F4)APRI >0.5: 0.67 (625/931); >1.5: 0.27 (255/931)SAFE fibrosis algorithm positive (whole sample, excluding F4 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 1.0 (931/931), 1.0 (740/740), 1.0, and 1.0Cirrhosis (METAVIR F4)APRI >1.0: 0.78 (149/191); >2.0: 0.47 (90/191)SAFE cirrhosis algorithm positive (whole sample, excluding F0 and F1 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 0.90 (173/191), 0.53 (100/191), 0.84, and 0.96	Fibrosis (METAVIR F2-F4)APRI >0.5: 0.73 (810/1104); >1.5: 0.96 (1064/1104)SAFE fibrosis algorithm positive (whole sample, excluding F4 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 0.77 (850/1104), 0.82 (905/1104), 0.80, and 0.79Cirrhosis (METAVIR F4)APRI >1.0: 0.84 (1542/1844); >2.0: 0.94 (1743/1844)SAFE cirrhosis algorithm positive (whole sample, excluding F0 and F1 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 0.93 (1709/1844), 0.92 (683/740), 0.91, and 0.92	Fibrosis (METAVIR F2-F4)APRI >0.5: 0.68 (625/919); >1.5: 0.86 (255/295)SAFE fibrosis algorithm positive (whole sample, excluding F4 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 0.79 (740/939) [0.84*], 1.0 (905/905), 0.83, and 0.85Cirrhosis (METAVIR F4)APRI >1.0: 0.33 (149/451); >2.0: 0.47 (90/191)SAFE cirrhosis algorithm positive (whole sample, excluding F0 and F1 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 0.56 (173/308), 0.64 (100/157) [0.60*], 0.53, and 0.56	Fibrosis (METAVIR F2-F4)APRI >0.5: 0.73 (810/1116); >1.5: 0.61 (1064/1740) [0.38*]SAFE fibrosis algorithm positive (whole sample, excluding F4 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 1.0 (850/850), 1.0 (905/905), 1.0, and 1.0Cirrhosis (METAVIR F4)APRI >1.0: 0.97 (1542/1584); >2.0: 0.95 (1743/1844)SAFE cirrhosis algorithm positive (whole sample, excluding F0 and F1 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 0.99 (1709/1727), 0.88 (683/774) [0.90*], 0.98, and 1.0	Fibrosis (METAVIR F2-F4)APRI >0.5: 0.70 (0.65-0.75); >1.5: 0.62 (0.59-0.65)SAFE fibrosis algorithm positive (whole sample, excluding F4 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively): 0.89 (0.87-0.90), 0.90 (0.87-0.93), 0.90 (0.88-0.93), 0.89 (0.87-0.92)Cirrhosis (METAVIR F4)APRI >1.0: 0.80 (0.77-0.83); >2.0: 0.71 (0.69-0.73)SAFE cirrhosis algorithm positive (whole sample, excluding F0 and F1 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively): 0.92 (0.89-0.94), 0.77 (0.73-0.81), 0.88 (0.83-0.93), 0.94 (0.91-0.97)	Not stated, though reports no conflicts of interest to report	Moderate	Population overlaps with Sebastiani 2008 and 2006 and appears to overlap with Halfon, Castera. Not clear how positive and negative results with SAFE algorithms defined and samples used to estimate diagnostic accuracy; unclear why different AUROC's reported for APRI based on cutoff values; unclear why specificity changes when excluding F4 patients from the SAFE fibrosis algorithm analysis

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Sebastiani, 2008	Whole sample, normal ALT, and elevated ALT, respectively Fibrosis (METAVIR F2-F4) Fibroindex >1.25: 0.62 (91/147), 0.41 (13/32), 0.68 (78/115); >2.25: 0.17 (25/147), 0.09 (3/32) [0.10*], 0.19 (22/115) APRI >0.5: 0.70 (103/147), 0.36 (12/32), 0.79 (91/115); >1.5: 0.24 (35/147), 0.14 (4/32), 0.27 (31/115) Fibrotest >0.49: 0.78 (115/147), 0.66 (21/32) [0.67*], 0.82 (94/115) AAR >1: 0.37 (54/147), 0.13 (4/32) [0.12*], 0.43 (50/115) Forns' Index >4.2: 0.79 (116/147), 0.56 (18/32) [0.57*], 0.85 (98/115); >6.9: 0.18 (27/147), 0.06 (2/32) [0.05*], 0.22 (25/115) [0.21*]	Whole sample, normal ALT, and elevated ALT, respectively Fibrosis (METAVIR F2-F4) Fibroindex >1.25: 0.48 (46/97), 0.77 (37/48), 0.18 (9/49) [0.19*]; >2.25: 1.0 (97/97), 1.0 (48/48), 1.0 (49/49) APRI >0.5: 0.74 (72/97), 0.91 (44/48), 0.57 (28/49); >1.5: 1.0 (97/97), 1.0 (48/48), 1.0 (49/49) Fibrotest >0.49: 0.78 (76/97), 0.85 (41/48), 0.71 (35/49) [0.72*] AAR >1: 0.73 (71/97), 0.88 (42/48), 0.59 (29/49) [0.58*], Forns' Index >4.2: 0.58 (56/97),0.67 (32/48), 0.49 (24/49); >6.9: 0.99 (96/97), 0.98 (48/49), 1.0 (48/48)	Whole sample, normal ALT, and elevated ALT, respectively Fibrosis (METAVIR F2-F4) Fibroindex >1.25: 0.65 (91/140), 0.54 (13/24) [0.75*], 0.66 (78/118) [0.84*]; >2.25: 1.0 (25/25), 1.0 (3/3), 1.0 (22/22) APRI >0.5: 0.80 (103/128), 0.75 (12/16) [0.90*], 0.81 (91/112); >1.5: 1.0 (35/35), 1.0 (4/4), 1.0 (31/31) Fibrotest >0.49: 0.85 (115/136), 0.75 (21/28) [0.88*], 0.87 (94/108) AAR >1: 0.68 (54/80), 0.40 (4/10) [0.70*], 0.71 (50/70) [0.67*] Forns' Index >4.2: 0.74 (116/157), 0.53 (18/34) [0.75*], 0.80 (98/123) [0.79*]; >6.9: 0.96 (27/28), 1.0 (2/2), 0.96 (25/26)	Whole sample, normal ALT, and elevated ALT, respectively Fibrosis (METAVIR F2-F4) Fibroindex >1.25: 0.45 (46/102), 0.66 (37/56) [0.43*], 0.20 (9/46) [0.47*]; >2.25: 0.44 (97/219), 0.62 (48/77) [0.39*], 0.35 (49/142) [0.33*] APRI >0.5: 0.62 (72/116), 0.69 (44/64) [0.42*], 0.54 (28/52); >1.5: 0.46 (97/209), 0.63 (48/76) [0.57*], 0.37 (49/133) [0.36*] Fibrotest >0.49: 0.70 (76/108), 0.79 (41/52) [0.61*], 0.63 (35/56) [0.64*] AAR >1: 0.43 (71/164), 0.60 (42/70) [0.30*]; 0.31 (29/94) [0.35*] Forns' Index >4.2: 0.64 (56/87), 0.70 (32/46) [0.47*], 0.59 (24/41) [0.58*]; >6.9: 0.44 (96/216), 0.62 (48/78) [0.38*], 0.35 (48/138)	Normal ALT and elevated ALT, respectively (AUROC not reported for whole sample) Fibrosis (METAVIR F2-F4) Fibroindex: 0.58 (0.43-0.73) and 0.74 (0.63-0.85) APRI: 0.69 (0.54-0.85) and 0.75 (0.65-0.85) Fibrotest: 0.70 (0.59-0.81) and 0.79 (0.74-0.84) AAR: 0.51 (0.40-0.62) and 0.54 (0.48-0.60) Forns' Index: 0.60 (0.50-0.71) and 0.76 (0.71-0.81)	Not stated	Moderate	Population substantially overlaps with Sebastiani 2006
Sebastiani, 2006	Elevated ALT and normal ALT subgroups, respectively [n/N not reported]Fibrosis (METAVIR F2-F4) Fibrotest F2 cutoff: 0.65 and 0.58Forn's Index >4.2: 0.80 and 0.79; >6.9: 0.24 and 0.12APRI >0.5: 0.84 and 0.79; >1.5: 0.30 and 0.27Cirrhosis (METAVIR F4) (whole sample)APRI >2.0: 0.38 (11/29)Fibrotest (cutoff not reported): 0.48 (14/29) [0.50*]	Elevated ALT and normal ALT subgroups, respectively [n/N not reported]Fibrosis (METAVIR F2-F4) Fibrotest F2 cutoff: 0.81 and 0.91Forn's Index >4.2: 0.61 and 0.82; >6.9: 0.77 and 1.0APRI >0.5: 0.77 and 0.95; >1.5: 0.94 and 1.0Cirrhosis (METAVIR F4) (whole sample)APRI >2.0: 0.87 (140/161)Fibrotest (cutoff not reported): 0.93 (150/161)	Elevated ALT and normal ALT subgroups, respectively [n/N not reported]Fibrosis (METAVIR F2-F4) Fibrotest F2 cutoff: 0.80 and 0.78Forn's Index >4.2: 0.78 and 0.85; >6.9: 0.95 and 1.0APRI >0.5: 0.87 and 0.96; >1.5: 0.96 and 1.0Cirrhosis (METAVIR F4) (whole sample)APRI >2.0: 0.34 (11/32)Fibrotest (cutoff not reported): 0.56 (14/25)	Elevated ALT and normal ALT subgroups, respectively [n/N not reported]Fibrosis (METAVIR F2-F4) Fibrotest F2 cutoff: 0.67 and 0.81Forn's Index >4.2: 0.64 and 0.75; >6.9: 0.51 and 0.52APRI >0.5: 0.72 and 0.72; >1.5: 0.53 and 0.57Cirrhosis (METAVIR F4) (whole sample)APRI >2.0: 0.89 (140/158)Fibrotest (cutoff not reported): 0.91 (150/165)	Elevated ALT and normal ALT subgroups, respectively [n/N not reported]Fibrosis (METAVIR F2-F4) Fibrotest F2 cutoff: 0.81 (0.72-0.91) and 0.71 (0.49-0.92)Forn's Index: 0.79 (0.68-0.90) and 0.58 (0.43-0.73)APRI: 0.69 (0.54-0.85) and 0.77 (0.63-0.91)Cirrhosis (METAVIR F4) (whole sample)APRI: 0.61 (0.49-0.73)Fibrotest: 0.71 (0.60-0.82)	Not stated	Moderate	Population substantially overlaps with Sebastiani 2008

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Sheth, 1998	Cirrhosis (Hytiroglou F4) AST/ALT ratio ≥1: 0.53 (25/47)	Cirrhosis (Hytiroglou F4) AST/ALT ratio ≥1: 1.0 (92/92)	Cirrhosis (Hytiroglou F4) AST/ALT ratio ≥1: 1.0 (25/25)	Cirrhosis (Hytiroglou F4) AST/ALT ratio ≥1: 0.81 (92/114)	Not reported	Not stated	Moderate	
Silva, 2004	Severe fibrosis (Desmet 3 or 4) GGT >1x upper limit of normal: 0.63 (40/63)	Severe fibrosis (Desmet 3 or 4) GGT >1x upper limit of normal: 0.59 (82/138)	Severe fibrosis (Desmet 3 or 4) GGT >1x upper limit of normal: 0.42 (40/96)	Severe fibrosis (Desmet 3 or 4) GGT >1x upper limit of normal: 0.78 (82/105)	Not reported	Not stated	Moderate	
Snyder, 2006	Fibrosis (Batt-Ludwig F2-F4) (retrospective and prospective samples, respectively)APRI >0.50: 0.84 (147/176) [0.83*] and 0.87 (68/78); ≥1.0: Not reported and 0.65 (51/78); ≥1.2: 0.39 (69/107) [0.41*] and not reported; ≥1.5: 0.30 (52/176) [0.31*] and 0.45 (35/78) [0.44*]Severe fibrosis (Batt-Ludwig F3-F4) (retrospective and prospective samples, respectively)APRI >0.50: 0.94 (62/66) and 0.96 (47/49); >0.70: 0.79 (52/66) and 0.88 (43/49); ≥1.20: 0.50 (33/66) and 0.71 (35/49) [0.73*]Cirrhosis (Batt-Ludwig F4) (prospective sample)APRI ≥2.0: 0.50 (13/26)AST/ALT ≥1.0: 0.42 (11/26)	Fibrosis (Batt-Ludwig F2-F4) (retrospective and prospective samples, respectively)APRI >0.50: 0.55 (95/174) [0.54*] and 0.62 (45/72); ≥1.0: Not reported and 0.92 (66/72); ≥1.2: 0.90 (157/174) and not reported; ≥1.5: 0.97 (168/174) [0.96*] and 0.94 (68/72)Severe fibrosis (Batt-Ludwig F3-F4) (retrospective and prospective samples, respectively)APRI >0.50: 0.43 (117/273) and 0.48 (49/102); >0.70: 0.62 (169/273) and 0.64 (65/102) [0.63*]; ≥1.20: 0.81 (220/273) and 0.82 (84/102)Cirrhosis (Batt-Ludwig F4) (prospective sample)APRI ≥2.0: 0.94 (118/125)AST/ALT ≥1.0: 0.87 (109/125)	Fibrosis (Batt-Ludwig F2-F4) (retrospective and prospective samples, respectively)APRI >0.50: 0.65 (147/226) and 0.72 (68/95); ≥1.0: Not reported and 0.89 (51/57) [0.90*]; ≥1.2: 0.80 (69/86) [0.78*] and not reported; ≥1.5: 0.90 (52/58) and 0.90 (35/39)Severe fibrosis (Batt-Ludwig F3-F4) (retrospective and prospective samples, respectively)APRI >0.50: 0.28 (62/218) and 0.47 (47/100); >0.70: 0.33 (52/104) and 0.54 (43/80); ≥1.20: 0.38 (33/86) and 0.66 (35/53)Cirrhosis (Batt-Ludwig F3-F4) (prospective sample)APRI ≥2.0: 0.65 (13/20)AST/ALT ≥1.0: 0.41 (11/27)	Fibrosis (Batt-Ludwig F2-F4) (retrospective and prospective samples, respectively)APRI >0.50: 0.77 (95/124) and 0.82 (45/55); ≥1.0: Not reported and 0.71 (66/93); ≥1.2: 0.59 (157/264) and not reported; ≥1.5: 0.58 (168/292) and 0.61 (68/111)Severe fibrosis (Batt-Ludwig F3-F4) (retrospective and prospective samples, respectively)APRI >0.50: 0.97 (117/121) and 0.96 (49/51); >0.70: 0.92 (169/183) and 0.92 (65/71); ≥1.20: 0.87 (220/253) and 0.86 (84/98)Cirrhosis (Batt-Ludwig F4) (prospective sample)APRI ≥2.0: 0.90 (118/131)AST/ALT ≥1.0: 0.88 (109/124)	Fibrosis (retrospective and prospective samples, respectively)APRI: 0.79 (0.74-0.83) and 0.89 (0.82-0.93)AST/ALT: 0.52 (0.47-0.57) and 0.62 (0.54-0.69)Severe fibrosis and cirrhosis: Not reported	National Institutes of Health	Moderate	Data presented for 350 patients in retrospective sample, but only 339 reported as enrolled

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Sud, 2004	Derivation and validation samples, respectivelyFibrosis (Scheuer F2-F4)Fibrosis probability index ≥0.2: 0.96 (80/83) and 0.85 (63/74); ≥0.8: 0.45 (37/83) and 0.42 (31/74)	Derivation and validation samples, respectivelyFibrosis (Scheuer F2-F4)Fibrosis probability index ≥0.2: 0.44 (38/87) and 0.48 (25/52); ≥0.8: 0.94 (82/87) and 0.98 (51/52)	Derivation and validation samples, respectivelyFibrosis (Scheuer F2-F4)Fibrosis probability index ≥0.2: 0.62 (80/129) and 0.70 (63/90); ≥0.8: 0.88 (37/42) and 0.97 (31/32)	Derivation and validation samples, respectivelyFibrosis (Scheuer F2-F4)Fibrosis probability index ≥0.2: 0.93 (38/41) and 0.69 (25/36); ≥0.8: 0.64 (82/128) and 0.54 (51/94)	Derivation and validation samples, respectivelyFibrosis (Scheuer F2-F4)Fibrosis probability index: 0.84 and 0.77 (confidence intervals not reported)	National Institutes of Health, the Centre for Clinical Research Excellence award, the Australian National Health and Medical Research Council, and the Robert W. Storr Bequest	Moderate	
Testa, 2006	Fibrosis (Ishak ≥3) BMI >25: 0.62 (23/37) Platelet-spleen diameter ratio <1750: 0.78 (29/37) APRI >0.864: 0.70 (11/37) Fibrosis model 1 >0.801: 0.81 (30/37)	Fibrosis (Ishak ≥3) BMI >25: 0.84 (32/38) Platelet-spleen diameter ratio <1750: 0.79 (30/38) APRI >0.864: 0.79 (30/38) Fibrosis model 1 >0.801: 0.71 (27/38)	Fibrosis (Ishak ≥3) BMI >25: 0.79 (23/29) Platelet-spleen diameter ratio <1750: 0.78 (29/37) APRI >0.864: 0.58 (11/19) Fibrosis model 1 >0.801: 0.73 (30/41)	Fibrosis (Ishak ≥3) BMI >25: 0.70 (32/46) Platelet-spleen diameter ratio <1750: 0.79 (30/38) APRI >0.864: 0.54 (30/56) Fibrosis model 1 >0.801: 0.79 (27/34)	Fibrosis (Ishak ≥3) BMI: 0.73 (0.61-0.82) Platelet-spleen diameter ratio: 0.74 (0.63-0.84) APRI: 0.72 (0.60-0.82) Fibrosis model 1: 0.80 (0.69-0.88)	Funded in part by Ministero dell'universita e della Ricerca Scientifica e Tecnologica and by Fondazione Aurelia Castagnino ONLUSS	Moderate	
Trocme, 2006	Fibrosis Not reported	Fibrosis Not reported	Fibrosis Not reported	Fibrosis Not reported	Fibrosis PIIIP/MMP-1 index: 0.77 (CI not reported)	DRRC, CHU de Grenoble	Moderate	
Vallet-Pichard, 2007	Severe fibrosis (METAVIR F3-F4)FIB-4 ≥1.45: 0.74 (108/146); >3.25: 0.38 (55/146)	Severe fibrosis (METAVIR F3-F4)FIB-4 ≥1.45: 0.80 (562/701); >3.25: 0.98 (688/701)	Severe fibrosis (METAVIR F3-F4)FIB-4 ≥1.45: 0.44 (108/247); >3.25: 0.81 (55/68) [0.82*]	Severe fibrosis (METAVIR F3-F4)FIB-4 ≥1.45: 0.94 (562/600) [0.95*]; >3.25: 0.88 (688/779)	Severe fibrosis (METAVIR F3-F4)FIB-4: 0.85 (0.82-0.89)	Not stated	Moderate	
Verbaan, 1997	Cirrhosis (Scheuer F4) PIIIP >1.11 U/ml: 0.82 (9/11) [0.78*] Type-IV collagen >250 ng/ml: 0.91 (10/11) [0.87*]	Cirrhosis (Scheuer F4) PIIIP >1.11 U/ml: 0.56 (49/87) Type-IV collagen >250 ng/ml: 0.75 (65/87)	Cirrhosis (Scheuer F4) PIIIP >1.11 U/ml: 0.19 (9/47) Type-IV collagen >250 ng/ml: 0.31 (10/32)	Cirrhosis (Scheuer F4) PIIIP >1.11 U/ml: 0.96 (49/51) Type-IV collagen >250 ng/ml: 0.98 (65/66)	Not reported	Not stated	Moderate	Unable to construct 2 x 2 table
Wai, 2003	Fibrosis (Ishak 3-6) APRI >0.50: 0.91 (83/91); >1.50: 0.41 (37/91) Cirrhosis (Ishak 5 or 6) APRI >1.00: 0.89 (25/28); >2.00: 0.57 (16/28)	Fibrosis (Ishak 3-6) APRI >0.50: 0.47 (47/101); >1.50: 0.95 (96/101) Cirrhosis (Ishak 5 or 6) APRI >1.00: 0.75 (41/164); >2.00: 0.93 (152/164)	Fibrosis (Ishak 3-6) APRI >0.50: 0.61 (83/137); >1.50: 0.88 (37/42) Cirrhosis (Ishak 5 or 6) APRI >1.00: 0.38 (25/66); >2.00: 0.57 (16/28)	Fibrosis (Ishak 3-6) APRI >0.50: 0.86 (47/55); >1.50: 0.64 (96/150) Cirrhosis (Ishak 5 or 6) APRI >1.00: 0.98 (123/126); >2.00: 0.93 (152/164)	Fibrosis (Ishak 3-6) APRI: 0.83 (0.78-0.88) Cirrhosis (Ishak 5 or 6) APRI: 0.90 (0.86-0.94)	Singapore HMDP Fellowship and National Institutes of Health	Low	Derivation and validation sets, results not reported separately but estimates were similar between groups.

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Walsh, 2000	Advanced liver disease (Ishak ≥3 and HAI ≥6) Type IV collagen >148 ng/ml: 0.73 Serum laminin >1.26 U/ml: 0.80	Advanced liver disease (Ishak ≥3 and HAI ≥6) Type IV collagen >148 ng/ml: 0.85 Serum laminin >1.26 U/ml: 0.83	Not reported	Not reported	Advanced liver disease (Ishak ≥3 and HAI ≥6) Type IV collagen: 0.83 (0.69-0.97) Serum laminin: 0.82 (0.66-0.98) ALT: 0.54 (0.34-0.74)	Sanofi Winthrop Foundation and Peel Medical Research Trust	Moderate	Can't create 2 x 2 table (no prevalence of advanced liver disease given). May be same population as Walsh 1999a and 1999b.
Walsh, 1999a	Advanced liver disease (Ishak ≥3 and HAI ≥6)PIIIP (Col 1-3 and Col 1 assay) >0.8 U/ml: 0.50PIIIP (Col 1-3 assay) >4.2 mg/l: 0.85ALT >55 IU/l: 0.71	Advanced liver disease (Ishak ≥3 and HAI ≥6)PIIIP (Col 1-3 and Col 1 assay) >0.8 U/ml: 0.88PIIIP (Col 1-3 assay) >4.2 mg/l: 0.38ALT >55 IU/l: 0.44	Not reported	Not reported	Advanced liver disease (Ishak ≥3 and HAI ≥6)PIIIP (Col 1-3 and Col 1 assay): 0.76 (0.58-0.94)PIIIP (Col 1-3 assay): 0.67 (0.57-0.87)ALT: 0.51 (0.39-0.63)	Sanofi Winthrop Foundation and Peel Medical Research Trust	Moderate	Can't create 2 x 2 table (no prevalence of advanced liver disease given). Appears to be same population as Walsh 1999b, and may be same population as Walsh 2001.
Walsh, 1999b	Advanced liver disease (Ishak ≥3 and HAI ≥6) TIMP-1 >500 ng/ml: 0.94 TIMP-2 >102 ng/ml: 0.85 MMP-2 >860 ng/ml: 0.69 ALT >60 IU/l: 0.67	Advanced liver disease (Ishak ≥3 and HAI ≥6) TIMP-1 >500 ng/ml: 0.57 TIMP-2 >102 ng/ml: 0.47 MMP-2 >860 ng/ml: 0.59 ALT >60 IU/l: 0.52	Not reported	Not reported	Advanced liver disease (Ishak ≥3 and HAI ≥6) TIMP-1: 0.73 (0.57-0.89) TIMP-2: 0.73 (0.55-0.91) MMP-2: 0.67 (0.47-0.87) ALT: 0.59 (0.41-0.77)	Sanofi Winthrop Foundation and Peel Medical Research Trust	Moderate	Can't create 2 x 2 table (no prevalence of advanced liver disease given). Appears to be same population as Walsh 1999a, and may be same population as Walsh 2001.
Williams, 1988	Cirrhosis (Hoofnagle criteria) AST/ALT ratio >1.0: 0.27 (3/11)	Cirrhosis (Hoofnagle criteria) AST/ALT ratio >1.0: 0.94 (31/33)	Cirrhosis (Hoofnagle criteria) AST/ALT ratio >1.0: 0.60 (3/5)	Cirrhosis (Hoofnagle criteria) AST/ALT ratio >1.0: 0.79 (31/39)	Not reported	Not stated	Moderate	Non-A, non-B hepatitis based on history of parenteral drug abuse or exposure to blood products, elevation in serum aminotransferases for at least 6 months, absence of hepatitis B surface antigen, absence of other known cause for liver disease, and compatible hepatic histology

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Risk of bias	Notes
Wilson, 2006	Ishak 3-4 fibrosis Fibrotest ≥0.31: 0.89; >0.48: 0.56 (n/N unclear) APRI ≥0.5: 0.73 (8/11); >1.5: 0.18 (2/11) ALT >upper limit of normal: 0.73 (8/11) AST >upper limit of normal: 0.82 (9/11)	Ishak 3-4 fibrosis Fibrotest ≥0.31: 0.49; >0.48: 0.65 (n/N unclear) APRI ≥0.5: 0.59 (63/108) [0.58*]; >1.5: 0.94 (102/108) ALT >upper limit of normal: 0.73 (79/108) AST >upper limit of normal: 0.64 (69/108)	Ishak 3-4 fibrosis Fibrotest ≥0.31: 0.13 (n/N unclear); >0.48: 0.14 (5/37) [0.12*] APRI ≥0.5: 0.15 (8/53); >1.5: 0.25 (2/8) ALT >upper limit of normal: 0.22 (8/37) AST >upper limit of normal: 0.19 (9/48)	Ishak 3-4 fibrosis Fibrotest ≥0.31: 0.98 (52/53); >0.48: 0.94 APRI ≥0.5: 0.95 (63/66); >1.5: 0.92 (102/111) ALT >upper limit of normal: 0.96 (79/82) AST >upper limit of normal: 0.97 (69/71)	Fibrosis (Ishak 3-4) Fibrotest: 0.74 (CI not reported) APRI: 0.70 (CI not reported) ALT >upper limit of normal: Not reported AST >upper limit of normal: Not reported	US Public Health Service	Moderate	Excludes patients with Ishak 5-6 fibrosis; all injection drug users
Wong, 1998	Severe fibrosis (modified Ishak 4-5 [max 5])Hyaluronic acid (cutoff not described): 0.86 (18/21)ALT (cutoff not described): 0.76 (16/21)GST (cutoff not described): 0.48 (10/21)	Severe fibrosis (modified Ishak 4-5 [max 5])Hyaluronic acid (cutoff not described): 0.88 (96/109)ALT (cutoff not described): 0.48 (52/109)GST (cutoff not described): 0.39 (43/109)	Severe fibrosis (modified Ishak 4-5 [max 5])Hyaluronic acid (cutoff not described): 0.58 (18/31)ALT (cutoff not described): 0.22 (16/73)GST (cutoff not described): 0.13 (10/76)	Severe fibrosis (modified Ishak 4-5 [max 5])Hyaluronic acid (cutoff not described): 0.97 (96/99)ALT (cutoff not described): 0.91 (52/57)GST (cutoff not described): 0.80 (43/54)	Not reported	Not stated	Moderate	
Zaman, 2007	Fibrosis (METAVIR F2-F4) FibroSpect II ≥42: 0.72 (28/39) Severe fibrosis (METAVIR F3-F4) FibroSpect II ≥42: 0.82 (11/14)	Fibrosis (METAVIR F2-F4) FibroSpect II ≥42: 0.74 (51/69) Severe fibrosis (METAVIR F3-F4) FibroSpect II ≥42: 0.63 (59/94)	Fibrosis (METAVIR F2-F4) FibroSpect II ≥42: 0.61 (28/46) Severe fibrosis (METAVIR F3-F4) FibroSpect II ≥42: 0.24 (11/46) [0.20*]	Fibrosis (METAVIR F2-F4) FibroSpect II ≥42: 0.82 (51/62) Severe fibrosis (METAVIR F3-F4) FibroSpect II ≥42: 0.95 (59/62) [0.97*]	Fibrosis (METAVIR F2-F4) FibroSpect II: 0.83 (CI not reported) Severe fibrosis (METAVIR F3-F4) FibroSpect II: Not reported	Not stated	Moderate	

Abbreviations: HCV, hepatitis C virus; SVR, sustained virological response.

Evidence Table 6: Key Question 4a. Quality Rating/Risk of Bias

Study, year	Representative spectrum	Random or consecutive sample	Test cutoffs predefined	Credible reference standard	Attempted to apply reference standard to all patients, or a random subset	Same reference standard applied to all patients	Reference standard interpreted independently from test under evaluation	Risk of bias
Adams, 2005	Yes	Unclear	Yes (for validation sample)	Yes	Yes	Yes	Yes	Moderate
Alsatie, 2007	Yes	Unclear	Yes (for validation sample)	Yes	Yes	Yes	Unclear	Moderate
Anderson, 2000	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Moderate
Becker, 2009	Yes	Unclear	Unclear (for Hepascore)	Yes	Yes	Yes	Yes	Moderate
Bejarano, 2009	No (no grade 2 fibrosis)	Yes	No	Yes	Yes	Yes	Yes	Moderate
Berg, 2004	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Moderate
Boeker, 2002	No (case-control design)	Unclear	Unclear	Yes	Yes	Yes	Unclear	High
Bonacini, 1997	Yes	Unclear	No (for Cirrhosis Discriminant Score)	Yes	Yes	Yes	Yes	Moderate
Borroni, 2006	Yes	Yes	No	Yes	Yes	Yes	Yes	Moderate
Bourliere, 2006	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Moderate
Bourliere, 2008	Yes	Yes	No	Yes	Yes	Yes	Unclear	Moderate
Boursier, 2009	Yes	Unclear	No	Yes	Yes	Yes	Yes	Moderate
Boursier, 2011	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Moderate
Burton, 2011	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Moderate
Cales, 2008	Yes	Unclear	No	Yes	Yes	Yes	Yes	Moderate
Castera, 2005	Yes	Yes	Only AUROC reported	Yes	Yes	Yes	Yes	Moderate
Castera, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Castera, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Cheong, 2011	Yes	Yes	No (for Significant Fibrosis Index)	Yes	Yes	Yes	Yes	Moderate
Cheung, 2008	Yes	No	Yes	Yes	Yes	Yes	Unclear	Moderate
Cheung, 2011	Yes	Unclear	No (for Fibrosis-protein Index)	Yes	Yes	Yes	Unclear	Moderate

Study, year	Representative spectrum	Random or consecutive sample	Test cutoffs predefined	Credible reference standard	Attempted to apply reference standard to all patients, or a random subset	Same reference standard applied to all patients	Reference standard interpreted independently from test under evaluation	Risk of bias
Chrysanthos, 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Cobbold, 2009	Yes	Unclear	No	Yes	Yes	Yes	Yes	Moderate
Colletta, 2005	Yes	Yes	Yes (for Fibrotest)	Yes	Yes	Yes	Yes	Moderate
Cross, 2007	Yes	Yes	No	Yes	Yes	Yes	Yes	Moderate
Cross, 2009	Yes	Yes	No	Yes	Yes	Yes	Yes	Moderate
Ehsan, 2008	Yes	Unclear	No	Yes	Yes	Yes	Unclear	High
El-Gindy, 2003	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Moderate
El-Shorbagy, 2004	Yes	Unclear	No	Unclear	Yes	Yes	Unclear	High
Fabris, 2008	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Moderate
Fontana, 2008	Yes	Yes	No	Yes	Yes	Yes	Unclear	Moderate
Forns, 2002	Yes	Yes	Yes (for validation sample)	Yes	Yes	Yes	Yes	Low
Gabrielli, 1997	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Moderate
Giannini, 2003a	Yes	Unclear	Yes (for AST/ALT ratio)	Yes	Yes	Yes	Yes	Moderate
Giannini, 2003b	Yes	Unclear	Yes (for AST/ALT ratio)	Yes	Yes	Yes	Unclear	Moderate
Giannini, 2006	Yes	Unclear	No	Yes	Yes	Yes	Yes	Moderate
Gomes da Silva, 2008	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Moderate
Guechot, 1994	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Moderate
Guechot, 1996	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Moderate
Guechot, 2010	Yes	Unclear	No	Yes	Yes	Yes	Yes	Moderate
Halfon, 2005	Yes	Unclear	Yes (for validation sample)	Yes	Yes	Yes	Unclear	Moderate
Halfon, 2006	Yes	Yes	No	Yes	Yes	Yes	Unclear	Moderate
Halfon, 2007	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Moderate
Hsieh, 2009	Yes	Yes	No	Yes	Yes	Yes	Unclear	Moderate
Iacobellis, 2005a	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Moderate
Iacobellis, 2005b	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Moderate

Study, year	Representative spectrum	Random or consecutive sample	Test cutoffs predefined	Credible reference standard	Attempted to apply reference standard to all patients, or a random subset	Same reference standard applied to all patients	Reference standard interpreted independently from test under evaluation	Risk of bias
Imbert-Bismut, 2001	Yes	Yes	No	Yes	Yes	Yes	Yes	Moderate
Imperiale, 2000	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Moderate
Islam, 2005	Yes	Unclear	No	Yes	Yes	Yes	Yes	Moderate
Jazia, 2009	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Moderate
Kaul, 2002	Yes	Unclear (for validation sample)	No (only AUROC reported)	Yes	Yes	Yes	Yes	Moderate
Khan, 2008	Yes	Unclear	No	Yes	Yes	Yes	Yes	Moderate
Khokhar, 2003	Yes	Unclear	No	Yes	YEs	Yes	Yes	Moderate
Koda, 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Lackner, 2005 and 2006	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Moderate
Leroy, 2004	Yes	Yes	No	Yes	Yes	Yes	Yes	Moderate
Leroy, 2007	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Moderate
Leroy, 2008	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Moderate
Liu, 2006	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Moderate
Lo Iacono, 1998	Yes	Yes	No	Yes	Yes	Yes	Unclear	Moderate
Lok, 2005	No	Yes	Yes	Yes	Yes	Yes	Unclear	Moderate
Luo, 2002	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Moderate
Martinez, 2011	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Moderate
McHutchison, 2000	No (no grade 2 fibrosis)	Unclear	Yes	Yes	Yes	Yes	Yes	Moderate
Metwally, 2007	Yes	Yes	No	Yes	Yes	Yes	Yes	Moderate
Murawaki, 2001a	Yes (except no F4)	Unclear	No	Yes	Yes	Yes	Yes	Moderate
Murawaki, 2001b	Yes (except no F4)	Unclear	No	Yes	Yes	Yes	Unclear	Moderate
Myers, 2002	Yes	Yes	No	Yes	Yes	Yes	Yes	Moderate
Myers, 2003	Yes	Yes	No	Yes	Yes	Yes	Yes	Moderate
Myers, 2003	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Moderate
Obrador, 2006	Yes	Yes	Yes (for derivation sample)	Yes	Yes	Yes	Yes	Moderate
Paggi, 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Parise, 2006	Yes	Yes	No	Yes	Yes	Yes	Yes	Moderate

Study, year	Representative spectrum	Random or consecutive sample	Test cutoffs predefined	Credible reference standard	Attempted to apply reference standard to all patients, or a random subset	Same reference standard applied to all patients	Reference standard interpreted independently from test under evaluation	Risk of bias
Park, 2000	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Moderate
Parkes, 2011	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Moderate
Patel, 2004	Yes	No	Yes (for validation sample)	Yes	Yes	Yes	Yes	Moderate
Patel, 2009	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Moderate
Plevris, 2000	Yes	Unclear	No	Yes	Yes	Yes	Yes	Moderate
Pohl, 2001	Yes	Yes	No (for Pohl Index)	Yes	Yes	Yes	Yes	Moderate
Poynard, 2002	Yes	No	No	Yes	Yes	Yes	Unclear	Moderate
Poynard, 2003	Yes	No	No	Yes	Yes	Yes	Unclear	Moderate
Pradat, 2002	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Moderate
Reedy, 1998	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Moderate
Renou, 2001	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Moderate
Romera, 2006	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Moderate
Rosenberg, 2005	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Moderate
Rossi, 2003	Yes	Yes	Yes (for Fibrotest)	Yes	Yes	Yes	Yes	Moderate
Saadeh, 2001	Yes	Yes	No	Yes	Yes	Yes	Unclear	Moderate
Saitou, 2005	Yes	Unclear	No	Yes	No	No	Unclear	High
Schneider, 2005	Yes	Yes	No (for portal venous flow and spleen size)	Yes	Yes	Yes	Unclear	Moderate
Schneider, 2006	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Moderate
Sebastiani, 2006	Yes	Yes	Yes/unclear (APRI/Fibrotest)	Yes	Yes	Yes	Yes	Moderate
Sebastiani, 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Sebastiani, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Moderate
Sene, 2006	Yes	Yes	No	Yes	Yes	Yes	Unclear	Moderate
Sheth, 1998	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Silva, 2004	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Moderate
Snyder, 2006	Yes	Unclear	No	Yes	Yes	Yes	Unclear (for retrospective sample)	Moderate

Study, year	Representative spectrum	Random or consecutive sample	Test cutoffs predefined	Credible reference standard	Attempted to apply reference standard to all patients, or a random subset	Same reference standard applied to all patients	Reference standard interpreted independently from test under evaluation	Risk of bias
Sud, 2004	Yes	Yes	Yes (for validation sample)	Yes	Yes	Yes	Unclear	Moderate
Testa, 2006	Yes	Unclear	No	Yes	Yes	Yes	Yes	Moderate
Trocme, 2006	Yes (except no F0)	No	Unclear	Yes	Yes	Yes	Yes	Moderate
Vallet-Pichard, 2007	Yes	No	Yes	Yes	Yes	Yes	Unclear	Moderate
Varaut, 2005	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Moderate
Wai, 2003	Yes	Yes	Yes (for validation sample)	Yes	Yes	Yes	Unclear	Low
Walsh, 1999a	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Moderate
Walsh, 1999b	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Moderate
Walsh, 2001	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Moderate
Williams, 1988	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Moderate
Wilson, 2006	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Moderate
Wong, 1998	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Moderate
Zaman, 2007	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Moderate

Abbreviations: APRI = aspartate aminotransferase (AST) to platelets ratio; AST/ALT = aspartate aminotransferase–alanine aminotransferase; AUROC = area under the receiver operating. characteristic.

Evidence Table 7: Key Question 4b. Proportion of Screened Patients who were Treated

Author, year Country	Study Type	Study population Timeframe	Criteria for antiviral treatment eligibility	Liver biopsy	Number screened	Number HCV antibody positive	Proportion HCV antibody positive who were viremic	Proportion viremic who received treatment	Proportion viremic classified as eligible for treatment	Reasons for ineligibility: % (n)	Proportion classified as eligible for treatment who received treatment
Groom, 2008 USA	Retrospective intervention series	Veterans affairs patients who tested positive for anti-HCV antibody by risk-based screening from January 2000 to December 2001 (Minneapolis)	Based on VA hepatitis C treatment guidelines and 1997 NIH consensus document	61% of 382 viremic patients evaluated in hepatitis clinic had liver biopsy performed	12485	681	76% (520/681)	24% (124/520)	Not reported	Not reported	Not reported

Author, year Country	Study Type	Study population Timeframe	Criteria for antiviral treatment eligibility	Liver biopsy	Number screened	Number HCV antibody positive	Proportion HCV antibody positive who were viremic	Proportion viremic who received treatment	Proportion viremic classified as eligible for treatment	Reasons for ineligibility: % (n)	Proportion classified as eligible for treatment who received treatment
Lindenburg et al, 2010 The Netherlands	Prospective intervention series	Active and former drug users who tested positive for anti-HCV antibody from January 2005 to April 2007	Decompensated liver cirrhosis Cardiac failure Autoimmune disease No stable housing (Psychiatric illness, active drug and alcohol use not considered exclusion criteria if they did not interfere with scheduled visits and considered stable by managing physician)	Yes, for patients with genotype 1 or 4, however could refuse (not part of protocol for other genotypes)	449	267	64% (134/208, HIV-negative) 63% (84/134) completed further screening	33% (44/134)	71% (60/84)	Medical, social, or psychiatric contraindication: 33% (n=8) Genotype 1 or 4 with less than moderate fibrosis on liver biopsy (treatment postponed): 67% (n=16)	73% (44/60)
Mallette et al, 2008 USA	Retrospective intervention series	Veterans Affairs patients who tested positive for anti-HCV antibody by risk-based screening from July 2000 to June 2001 (Providence)	Not described	Not specified, however biopsy results reported for 32% (39/122)	5646	260 newly diagnosed	58% (122/211)	15% (18/122)	57% (70/122)	Ongoing substance or alcohol abuse: 24% (n=29) Major medical contraindication: 7.4% (n=9) Severe psychiatric disease: 6.6% (n=8) Refused further evaluation: 4.9% (n=6)	26% (18/70)

Abbreviations: HCV, hepatitis C virus

Evidence Table 8: Key Questions 6a and 6c: Counseling RCTs

Author, year Country Study name Risk of bias	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Baseline characteristics	Intervention program	Duration of follow-up	Results	Funding source
Groessl, 2011 USA (VA San Diego Healthcare System) Moderate	US military veterans ≥ 18 years of age with a confirmed diagnosis of chronic HCV, receiving care at VA Sand Diego Health Care system and willing to participate in a 6 weekly sessions of 2.5 hours in length.	Ongoing or scheduled to receive antiviral therapy, outside of geographic region, fatal co-morbid condition (life expentancy < 6 months), or receiving treatment for another life-threatening illness.	NR/327/137/132 (ITT)	Mean age: 54.6 years [Groups (A vs. B) signficantly different in age 56.4 vs. 53.0 years; p=0.003] 5% Female 59% Non-hispanic white 24% African American 10% Hispanics Marital status: 79% divorsed, separated or never married	A: Information only: Educational booklet and handouts B: Self-management program (SMP): 6 weekly workshops based on self-management and cognitive-behavioral principles, each 2-2.5 hours	6 weeks (end of program)	Information only vs. self-management program (p-value): 1) HCV knowledge change: 1.3 vs. 3.4 (p<0.0001) 2) HCV self-efficacy change: -0.09 vs. 0.75 (p= 0.01) 3) Energy change: 0.15 vs. 0.05 (p=0.46) 4) CES-D change: 1.0 vs. -0.7 (p=0.93) 5) Health distress change: 1.0 vs. -0.07 (p=0.06) 6) QWB change: 0.01 vs. 0.04 (p=0.26) 7) Global health status change (VAS 0-100): -0.4 vs. 5.5 (0.11) 8) SF-36 results (change in scores): a) Physical function: -3.6 vs. 3.3 (p=0.06) b) General health: 1.8 vs. 1.1 (p=0.2) c) Body pain: 7.8 vs. 0.9 (p=0.07) d) PCS: 0.5 vs. 1.7 (p=0.4) e) MCS: -0.5 vs. 0.6 (p=0.6) 9) HQLQ results (change in scores) a) Health distress (covariate=age): -3.3 vs. 3.6 (p=0.1) b) Postive well-being: 1.3 vs. 0.5 (p=0.8) c) HCV-specific limitations: 2.0 vs. -0.2 (p=0.6) d) HCV-specific health distress (covariate=age): -2.7 vs. 0.3 (p=0.5)	VA HSR&D Grant

Author, year Country Study name Risk of bias	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Baseline characteristics	Intervention program	Duration of follow-up	Results	Funding source
Latka, 2008USAThe Study to Reduce Intravenous Exposures (STRIVE)Moderate	Aged 18 to 35 years, used injection drugs within 6 months, plans to live in area for 12 months, documented HCV-antibody positive and HIV-antibody negative serostatus, able to provide sample for liver function and HCV RNA testing, able to complete assessments and group sessions in English (recruited from a largerstudy of HIV- and HCV-negative injection drug users)	Not stated	640/Not reported/418 (222 to behavioral intervention, 196 to control)/261 at 3 months	Age: 27 vs. 26 yearsFemale: 24% vs. 24%Non-white: 43% vs. 43%Aware of positive HCV status >6 months: 55% vs. 46%Injecting at least once daily: 70% vs. 68%	A: Peer mentoring intervention: 6 sessions x hours, twice weekly, trained participants to be peer mentors for safer injection practices (hypothesized to reduce risky behaviors in the participants as well); content delivered via various methods including demonstrations, games, discussions, and videosB: Video discussion: 6 sessions x 2 hours, twice weekly	6 months	Peer mentoring intervention vs. video discussionCombined distributive risk (how often lent used syringe, shared drug preparation equipment, divided drugs with syringe used by onself): 44% vs. 59% at 3 months, p=0.02, AOR 0.46 (95% CI 0.27 to 0.79); 37% vs. 53% at 6 months, p=0.007, AOR 0.51 (95% CI 0.31-0.83)Frequency of lending used syringe to other: No differences at 3 months or 6 months (unadjusted)Frequency of preparing drugs with a syringe previously used by onself: No differences at 3 months or 6 months (unadjusted)Frequency of sharing drug preparation equipment with or before someone else: 41% vs. 55%, at 3 months, p=0.03, AOR 0.47 (95% CI 0.27-0.82); 35% vs. 23% at 6 months, p=0.03, AOR 0.55 (95% CI 0.33-0.92)Refrained from injection drug use: 24% vs. 9.6% at 3 months, p=0.002, AOR 3.6 (95% CI 1.6-7.8); 34% vs. 23% at 6 months, p=0.03, AOR 1.6 (95% CI 0.96-2.7)Refrained from lending syringe because of HCV-positive status: 69% vs. 69% at 3 months, p=0.98, AOR 1.3 (95% CI 0.65-2.7); 67% vs. 60% at 6 months, p=0.39, AOR 1.5 (95% CI 0.74-3.0)	National Institute on Drug Abuse (NIDA)

Author, year Country Study name Risk of bias	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Baseline characteristics	Intervention program	Duration of follow-up	Results	Funding source
Zule et al 2009USAModerate	At least 18 years of age, self-reported IDU in previous 30 days, visible tracks or positive urine speciman for heroin, cocaine, or methamphetamine, no formal substance abuse treatment in previous 30 days and current residence in area of study.	Not stated	861/855/847/625Note: 1286 (of 1786) met preliminary eligibility criteria	Mean age: 41.2 years, 9.3 SD66% African American27% Non-hispanic whilte7% Other27% Female55% HCV positiveRisk Behaviors (in past 30 days):70% used alcohol 17% shared syringe 23% shared cooker, cotton or rinse water27% > 1 sexual partner57% unprotected at last sexual intercourse	A. Motivational intervention: 6 sessions including 2 cue-card sessions presented by powerpoint. First session included 20 slides adapted from NIDA; 2nd session included 24 slides (number depended on test results) and additional sessions focused increasing motivation to change, deloping a plan for change, reviewing progress and reaffirming committments to change.B. Educational intervention: 6 sessions with first 2 session based on cue cards from the NIDA and followed up with 4 additional sessions with videos of 1 hour in length. Topics included hepatitis A, B, C; indirect screening practices; and addiction.Note: participants screened for HCV and given results during the study.	12 months	Motivational intervention vs. educational education, HCV positive participants: OR (95% CI)Alcohol use (in past 30 days):1) 6 months follow-up: 0.65 (0.44, 0.94)) 2) 12 months follow-up: 0.94 (0.64-1.38) Other results not straified by those HCV positive	NIDA and NIH

Evidence Table 9: Key Questions 6a and 6c: Counseling RCTs Quality Rating/Risk of Bias

Author, Year	Random-ization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat (ITT) analysis	Risk of bias
Groessl, 2011	Yes	Unclear	No (age, % homeless)	Yes	No	No	No	Yes	No	Yes	Moderate
Latka, 2008	No (mixed method depending on group size)	Unclear	Yes	Yes	No	No	No	No	Yes	No	Moderate
Zule, 2009	Unclear	Unclear	No (alcohol use)	Yes	No	No	No	Yes	Yes	No	Moderate

Evidence Table 10: Key Question 7 Pregnancy Intervention Observational Studies

Author, year Country Study Name Risk of bias	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population (i.e. age, race)	Genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Ceci, 2001 Italy **Moderate**	Prospective cohort study	Presence of anti-HCV antibodies beyond 18 months or HCV-positive on two separate tests	HCV maternal risk factors (exposure to blood products and IVDU), HCV viral load, HCV genotype, gestational age, mode of delivery, birth weight	24 months	HCV-positive, HIV-negative women	HIV-positive	2447/ 78/ 78/ 78	**age (n=78)** median (range): 30 (21-42) ***characteristics of HCV-RNA positive mothers (n=60)** **HCV risk factors** **a**bsent: 25 (42%) blood transfusion: 14 (23%) IVDU: 20 (33%) blood transf&IVDU: 1 (2%) **mode of delivery** vaginal: 43 (72%) cesarean: 17 (28%) **gestational age** <36 weeks: 9 (15%) >=36 weeks: 51 (85%) **birth weight** <2500g: 14 (23%) >=2500g: 46 (77%)	**mother HCV-RNA status (n=78)** positive: 60 (77%) negative: 18 (23%) ***characteristics of HCV-RNA positive mothers (n=60)** **maternal viral load** $<0.2X10^6$: 9 (15%) $>0.2X10^6$: 51 (85%) **genotypes** 1a: 9 (15%) 1b: 25 (42%) 2a: 20 (33%) 3: 6 (10%)	**overall transmission (n=78)** 2 consecutive positive tests: 8 (10%) 24 month follow up: 2 (3%) *not adjusted	NR

Author, year Country Study Name Risk of bias	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population (i.e. age, race)	Genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Conte, 2000 Italy **High**	Prospective cohort study	Newborns of anti-HCV positive mothers were tested at birth (on cord blood samples) and infants underwent determination of AST, ALT, anti-HCV and HCV/RNA after 4, 8, 12, and 18 months	NR	First month of pregnancy through 18 months after birth	Anti-HCV positive pregnant women between 1/95 and 12/98 attending Ob/Gyn unit of local Ospedale Maggiore (living in area of about 20 km around Bergamo in northern Italy)	NR	15,250/370/370/370	**mean maternal age (n=370):** 30.9 (± 5.2) **mode of delivery (n=370)** vaginal: 259 (71%) cesarean: 106 (29%)	**HCV/RNA+ (n=370):** 266 (72%) **HCV genotype (n=370):** 1a: 51 (19%) 1b: 82 (31%) 2: 64 (24%) 3a: 53 (20%) 4: 5 (2%) indeterminate: 11 (4%) **HIV positive (n=370):** 15 (4%) **past or current IVDU (heroin only) (n=370):** 118 (32%) **past blood transfusions (n=370):** 68 (18.4%)	**HCV/RNA+** at birth (n=366): 18 (4.9%) 4 months (n=167): 8 (4.8%) 8 months (n=161): 8 (5%) 12 months (n=155): 8 (5.1%)	NR

Author, year Country Study Name Risk of bias	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population (i.e. age, race)	Genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
European Pediatric Hepatitis C Virus Network, 2001 (Pembrey) Italy, Spain, Germany, Ireland, Scotland, Belgium, Sweden **Low**	Multicenter prospective cohort study	infected: antibody positive beyond 18 months and/or had at least two positive PCR tests (on 2 separate occasions) indeterminate: born more than 18 months before data collection, antibody positive before 18 months of age, and either 1) no PCR performed, 2) no positive PCR result, or 3) only a single PCR result	mode of delivery, breastfeeding, HIV status, maternal age at delivery	at least until 18 months of age	Mother HCV positive at or before delivery or baby identified as HCV positive within 1 month of delivery & maternal infection confirmed Children born on or after Jan 1 1992 (when 2nd generation tests widely used) and at least 18 months at last laboratory assessment (or born more than 18 months before data collection and no longer in follow up)	Children with a history of blood transfusion	1655 mother-child pairs/1474 children/1474/1474 (916 HIV-)	**maternal age (n=1311)** <20: 219 (17%) 20-25: 563 (43%) 30-39: 495 (38%) >=40: 34 (3%) **gestational age (n=1248)** <36 weeks: 105 (8%) >=36 weeks: 1143 (92%) **low birth weight (<2500g) (n=1362)** yes: 523 (38%) no: 839 (62%) **fetal scalp monitors (n=724)** yes: 93 (13%) no: 631 (87%) **mode of delivery (n=1400)** cesarean: 382 (27%) vaginal: 1018 (73%) **breastfeeding (n=1424)** breastfed: 351 (25%) not breastfed: 1073 (75%) **other infections in pregnancy (n=996)** yes: 90 (9%) no: 906 (91%)	**maternal HIV infection (n=1419)** yes: 503 (35%) no: 916 (65%) **maternal IV drug use (n=1384)** during this pregnancy: 362 (26%) yes, but not during pregnancy: 455 (33%) never: 567 (41%) **maternal history of hepatitis (n=1038)** yes: 421 (41%) no: 617 (59%)	**overall transmission (n=1474)** 136 (9.2%) *not adjusted	NR

Author, year Country Study Name Risk of bias	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population (i.e. age, race)	Genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
European Pediatric Hep C Virus Network, 2005 (Tovo) Italy, Spain, Germany, Ireland, UK, Norway, Sweden **Low**	Multicenter prospective cohort study	Children considered infected if they had >=2 positive HCV RNA PCR test results and/or were anti-HCV antibody positive after 18 months. Children considered uninfected if they had <2 positive HCV RNA PCR test results and <=2 negative HCV RNA PCR rest results and/or were anti-HCV antibody negative after 18 months.	To account for differences between centers in the HCV RNA PCR assays used to determine infection, and to allow for center-associated unobserved differences in background characteristics, the authors incorporated a random effect in the multivariable models at the center level	Children received clinical examinations at birth, 6 weeks, and 3, 6, 9, 12, 18, and 24 months; and thereafter every 6 months if infected or every year if uninfected	HCV infected mothers and their singleton infants or first-born infants from multiple pregnancies with confirmed HCV infection status.	Second-born twins and second- and third-born triplets were excluded. Mother-infant pairs with infants of indeterminate infection status were excluded.	1787/ 1479/ 1479/ 1220 (1034 HIV-)	**age (n=1205)** mean (SD): 31.7 (5.17) median (range): 32 (17.1-45.1) **mode of delivery (n=1455)** vaginal: 764 (52.5%) emergency CS: 160 (11%) elective CS: 480 (33%) CS (unspecified): 51 (3.5%) **infant feeding type (n=1357)** breast-fed: 452 (32.7%) formula fed: 930 (67.3%) **sex of child (n=1470)** male: 802 (54.6%) female: 668 (45.4%) **gestational age (n=1382)** <=34 weeks: 97 (7%) 35-36 weeks: 122 (8.8%) >=37 weeks: 1163 (84.2%)	**maternal HIV status (n=1391)** positive: 208 (15%) negative: 1183 (85%) **child HIV status (n=1435)** positive: 10 (0.7%) negative: 1397 (97.4%) indeterminate: 28 (1.9%) **IV drug use (n=1162)** history: 448 (38.6%) no history: 714 (61.4%)		

Author, year Country Study Name Risk of bias	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population (i.e. age, race)	Genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Garland, 1998 Australia **High**	Prospective cohort study	Infants tested at 3, 6 and 12 months for HCV antibodies. Testing included detection of antibody to HCV, and genotyping for presence of 1a, 2a, 2b, 3 a, 4 & 6 HCV genotypes.	NR/Unclear: Collected data on age, parity, type of delivery, time of rupture, drug use, scalp electrodes and breastfeeding but did not indicate if adjustment for confounding was analyzed.	Three years; follow-up included seropositive women, their newborns & siblings of the newborns.	Women with a history of illicit IV drug use, seen in the Chemical Dependency Unit (CDU) of the Royal Women's Hospital and subject to routine screening for HCV. Women with positive anti-HCV test results.	NR	NR/ 84/ 83/ 83 women, 91 newborns & 16 siblings of newborns	**age of mother:** NR age of infant: NR (n=91) age of sibling: NR (n=16) **race:** NR **mode of delivery:** vaginal (n=83): 74%	**genotype:** NR **HCV viral load:** NR **HIV infection:** None **IV drug use:** n=83 (100%)	3/91 (3%)	NR

Author, year Country Study Name Risk of bias	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population (i.e. age, race)	Genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Gibb, 2001 Ireland, UK **Moderate**	Prospective cohort study	Positive result for HCV antibody within 90 days of birth	adjusted for HIV status, breastfeeding, and mode of delivery	24 months	Mother known to be HCV infected during pregnancy or if child had positive result for HCV antibody within 90 days of birth	UK children born before 1996	499/ 441/ 441/ 441	**age (n=441)** mean (SD): 27 (6) **race (n=441)** white: 413 (94%) non-white: 28 (6%) **breastfeeding (n=414)** yes: 59 (14%) no: 355 (86%) **mode of delivery (n=424)** vaginal: 339 (80%) emergency cesarean: 54 (13%) elective cesarean: 31 (7%)	**maternal HIV status (n=441)** infected: 22 (5%) uninfected: 328 (74%) unknown: 91 (21%) **IV drug use (n=441)** history: 343 (78%) no history: 98 (22%)	**overall (n=441)** 6.7% (4.1-10.2) unadjusted	NR
LaTorre, 1998 Italy **High**	Prospective cohort study	Babies were tested for ALT levels, anti-HCV antibodies by ELISA III and RIBA II and HCV-RNA by RT-PCR. Babies who retained anti-HCV antibodies through 12 months were considered infected	none	Blood test and clinical evaluation of infants within days after birth and then every 4 months for 2 years	Mothers who tested anti-HCV positive before delivery and were HIV negative	Mothers who tested negative for HCV or positive for HIV	5025/ 5000/ 80/ 80	**mode of delivery (n=80)** vaginal: 66 (82.5%) *52/66 were HCV-RNA positive cesarean: 14 (17.5%) **breastfeeding (n=80)** Yes: 24 (30%) *including 10 HCV-RNA positive and 14 HCV-RNA negative women	**mother HCV-RNA positive (n=80)** 56 (70%) **HCV viral load (n=19)** ALT increase>40 U/L: 18 (32.5%) **IV drug use (n=80):** 34 (43%) **blood transfusion (n=80):** 10 (12%)	**overall transmission (n=80)** 2/80 (2.5%)	NR

Author, year Country Study Name Risk of bias	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population (i.e. age, race)	Genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Lin, 1995 Republic of China **High**	Prospective cohort study	Detection of HCV antibodies (serum); detection of HCV RNA in infants tested at 1, 3, 6, 9 or 12 months of age	NR	Up to 12 months	HCV infected mothers	NR	NR 40/ 15/+3 healthy controls 15	NR	**Genotype:** NR **HCV viral load:** (n=15) RNA titers 10^2 to 2.5 x 10^8copies/mL **HIV infection:** None **IV drug use:** NR	0/15 (0%)	NR

Author, year Country Study Name Risk of bias	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population (i.e. age, race)	Genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Mast, 2005 US (Houston & Honolulu) **Low**	Prospective cohort study	Infant serum collected at birth and 8 well-child visits. Testing included detection of antibody to HCV, detection of HCV RNA (qualitative and quantitative), and genotyping.	Variables with p<.1 from the univariate analysis and maternal demographic characteristics included in multivariate analysis	Infants born to HCV+ mothers followed from birth to >=12 months, HCV-infected infants followed annually until age 5	Women presenting for prenatal care (and in Houston, those who didn't receive prenatal care who presented for delivery at 2 county hospitals) were offered testing. Women with positive anti-HCV test results were invited to enroll (those with indeterminate status were invited to enroll until HCV status was confirmed).	Mothers with serum testing as RIBA indeterminate and HCV RNA negative were excluded from the analysis.	75,909/ 567/ 332/ 242 women & 244 infants	**age (n=242)** <20: 7 (2.9%) 20-29: 103 (42.6%) 30-39: 120 (49.6%) >=40: 12 (4.9%) **race (n=242)** White: 79 (32.6%) Black: 77 (31.8%) Hispanic: 49 (20.3%)	**mother HCV RNA+ (n=242)** at enrollment or delivery: 194 (79.5%) both: 179 (77.2%) delivery: 5 (2.2%) enrollment: 4 (1.7%) **maternal HIV status (n=242):** positive: 11 (4.5%) **HIV&HCV RNA+ (n=242):** 7 (2.9%) **maternal IVDU (n=242):** 126 (52.3%) **geometric mean HCV RNA level at delivery (n=194)** HCV/HIV+: $1.48*10^7$ HIV-: $2.38*10^6$ **HCV genotype of mother (n=116)** Genotype 1a: 76 (66%) Genotype 1b: 16 (14%) Genotype 2b: 10 (9%) Genotype 3a: 13 (11%) Genotype 4a: 1 (.01%)	9/244(3.7%)	NR

Author, year Country Study Name Risk of bias	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population (i.e. age, race)	Genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
McMenamin, 2008Ireland**High**	Retrospective cohort study	Positive neonatal results for HCV antibody after 1 month of age	None	Infant HCV RNA samples tested at median of 6 weeks after delivery, mean 12.5 weeks (range 4-166 weeks)	Mothers who tested positive for HCV antibody antenatally and delivered a liveborn infant, HCV positive mothers identified through the National Virus Reference Laboratory	Mothers who tested negative for HCV antenatally or mothers who tested positive for HCV antenatally and miscarried or had a stillbirth	26,390/559/559/441	**age (n=559)**median (range): 26 (16-44)**mode of delivery (n=559)**vaginal delivery: 443 (79%)emergency cesarean: 72 (13%)planned pre labor cesarean: 44 (8%)**gestation (n=559)**median (range): 39 (28-42)**intrapartum procedures (n=559)**intrapartum fetal blood sample: 1 (.002%)fetal scalp electrode: 23 (4%)	**maternal HIV status (n=559)**positive: 18 (3%)**maternal HBV status (n=559)**positive: 3 (0.5%)**maternal HCV RNA status (n=559)**positive: 295 (53%)negative: 166 (30%)missing: 98 (17%)	**overall transmission (n=441)** 18/441 (4.1%)	NR

Author, year Country Study Name Risk of bias	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population (i.e. age, race)	Genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Moriya, 1995 Japan **High**	2 prospective cohort studies, additional pediatric chart review	Infants testing positive for antibody to HCV	NR	12 months, up to 24 months	Infants born to mothers who were HCV RNA positive	NR	16714/ 163/ 100 mothers/ 84 mothers, 87 infants	NR	Genotype:(cases only, n=4 mother/child pairs) Type 111/2a: n=2 Type 11/1b: n=2 HCV viral load: NR HIV infection: None IV drug use: NR	2/87 (2.3%) ("during follow-up period")	NR
Okamoto et al, 2000 Japan (Tottori University & Medical Center) **High**	Prospective cohort study	Positive test for HCV RNA by RT-PCR analysis with high titers of HCV RNA within 3 months of age. Serum samples of the children born to Ab1 mothers were tested for anti-HCV antibody, HCV RNA, and liver function approximately every 3 months during the first year and biannually thereafter.	NR	Minimum follow-up period was 6 months	Pregnant women were screened for anti-HCV antibody in Tottori Prefecture, Japan. None of the mothers had risk factors for HIV infection	NR	21791/NR Eligible/NR Enrolled/ followed 84 children (unclear how many women were enrolled)	**Mode of delivery (n=84)** vaginal: 56 (66%) Cesarean: 28 (33%)	68 Ab+/ 50 RNA+/ 21 High viral load ((≥ 2.5 x 106 copies/mL) *these categories are not mutually exclusive	7/84 (8%)	NR

Author, year Country Study Name Risk of bias	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population (i.e. age, race)	Genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Pipan, 1996 Italy **High**	Prospective cohort	HCV/RNA detection in children over a period of 12 months	none	Every three months for one year	Anti-HCV positive pregnant women, no history of Hepatitis B, no apparent source of HCV exposure	History of Hepatitis B, apparent source of HCV exposure	1338/36/25/25	**mean age at delivery** (n=25): 26.4 (19-35)	**HCV/RNA+** (n=25): 18 (72%)	**infant HCV/RNA+ at birth** (n=25): 0 (0%) **infant HCV/RNA+ at 12 months** (n=25): 0 (0%)	NR
Resti et al, 1998 Italy Moderate	Prospective cohort study	Children were considered infected when hepatitis C virus RNA was detected or when anti-bodies to the virus persisted beyond age 2 years or reappeared after having disappeared. Alanine aminotransferase concentrations were defined as raised if they were higher than twice the upper limit of normal	Study data suggests that there may be a higher risk of vertical transmission in mothers with a higher viral titre, but the results were not significant. IV drug users were not excluded from analysis, but authors suggest inclusion of these mothers did not significantly impact findings	Median follow up in the 403 children who completed the study was 28 (24-38) months	19 centres participated in the study Women (and their babies) with confirmed hepatitis C antibodies but negative for HIV1	History of blood product transfusions or IV drug use was carefully investigated by face to face interviews with experienced pediatricians using standardized questionnaires, but these individuals were not excluded	NR/442/403/ 403 & 403 infants (275 RNA+ mothers)	**RNA+/HIV- mothers (n=275)** **mode of delivery** Vaginal: 213 (77%) Caesarean: 62 (23%) **breastfeeding** Yes: 87 (32%) No: 188 (68%)	**maternal IVDU (n=275)** 111 (80%)	13/275 (4.7%)	NR

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Spencer, 1997 Australia **High**	prospective cohort study	Presence of HCV RNA in serum collected from infant anytime during follow up.	Potential maternal risk factors assessed: duration/type of drug use, alcohol, smoking, past HBV infection, age	At least 6 months, up to 6 years when possible	HCV positive and HCV negative pregnant women, IVDU on methadone maintenance program and their infants	NR	NR/ NR/ 131/ 125 anti-HCV+, 63 HCV RNA+	**maternal age (mean)** 30 years anti-HCV+: 125/131 (95%) HCV RNA+: 63/125 (62.4%)	**Genotype** Transmitting mothers: Type 1a: 5 (83.3%) Type 3a: 1 (16.7%) Non-transmitting mothers: Type 1: 1 (1.6%) Type 1a: 36 (57.1%) Type 1b: 4 (6.3%) Type 2a: 1 (1.6%) Type 2b: 2 (3.2%) Type 3a: 18 (28.6%) Untypeable: 1 (1.6%) **HCV viral load:** NR **HIV infection:** None (0%) **IV drug use:** 131 (100%)	6/63 (9.5%) (at 18 months)	NR

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Syriopoulou, 2005 Greece **High**	Prospective cohort study	HCV/RNA+ more than 2 times after 3 months and/or anti-HCV+ after 18 months	univariate analysis of IVDU, mother's age, mode of delivery, genotype, type of feeding (but no multivariate analysis)	Every three months until 1 year of age, then every 6 months	anti-HCV positive pregnant women	NR	NR/86/86/86 mother-child pairs	**mean age at delivery** (SD): 29.6 (+/- 3 yrs) **mode of delivery (n=86)** vaginal: 53 (62%) cesarean: 33 (38%)	**HCV genotype (n=54)** 3a: 23 (42%) 1a: 10 (19%) 1b: 7 (13%) 1a/1b: 6 (11%) 2a/2c: 6 (11%) 4c/4d: 2 (4%) **HCV/RNA+ at or near delivery (n=86):** 56 (65%) **HIV+ (n=86):** 1 (1%) **IVDU (n=86)** during pregnancy: 2 (2%) before pregnancy: 6 (7%)	**overall transmission (n=86):** 2 (2.3%)	NR

Author, year Country Study Name Risk of bias	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population (i.e. age, race)	Genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Tajiri et al, 2001 Japan (seven hospitals in the Osaka metropolitan area) **High**	Prospective cohort study	Babies were tested for serum alanine aminotransferase (ALT) activity, anti-HCV antibodies and HCV RNA at 0, 3, 6, 9, 12 months and every year thereafter. Babies with repeated positive HCV RNA tests were considered infected.	NR	All infants were followed 9 to 61 months	Pregnant women who tested positive for anti-HCV antibodies	NR	16800/154/141/114	**maternal route of transmission (n=141)** mother-to-child: 9/141 (6%) blood transfusion: 31/141 (22%) Accidental needle stick injury: 3/141 (2%) HCV carriers in their families: 11/141 (8%) Other/unidentified: 87/141 (62%) **mode of delivery (n=114)** vaginal: 90 (21%) cesarean: 24 (79%)	No history of drug use or tattooing was present. 73 tested for HIV, all were negative. 68 not tested because HIV infection is not endemic in Japan including the areas studied (adult rate of infection, 0.01%) Genotype NR HCV Viral Load: High: 46 Low: 27	9/114 (7.8%)	NR

Author, year Country Study Name Risk of bias	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population (i.e. age, race)	Genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Tanzi, 1997 Italy **Moderate**	Prospective cohort study	presence of antibodies for one or more HCV antigens at birth, 3, 6, 10, and 18 months	none	18 months	Women admitted to the Maternity Clinic of University of Parma from January to December 1993, those who tested positive for antibodies were invited to submit their children for period checks	NR	1347/1347/1347/1347	NR	**mother anti-HCV+ (n=1347)** 31 (2.3%) **mother HCV-RNA+ (n=1347)** 18 (1.3%) **mother HIV+ (n=1347)** 4 (.27%)	**overall transmission (n=32)** **infant HCV/RNA+** at birth: 2 (6%) at 3, 6, 10, 18 months: 0 (0%) **infant anti-HCV+** at birth: 32 (100%) at 18 months: 0 (0%)	NR

Author, year Country Study Name Risk of bias	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population (i.e. age, race)	Genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Zanetti et al, 1998 (Intervirology) Italy A prospective Study on Mother-to-Infant Transmission of Hepatitis C virus Zanetti et al, 1999 (Journal of Hepatology) Italy Mother-to-infant transmission of hepatitis C virus High	Prospective cohort study	Detection of HCV-RNA, persistence of anti-HCV beyond 18 months of age or ex novo production of antibody were assumed to represent evidence of infection	NR	For babies born to HCV seropositive mothers, peripheral blood sampling, laboratory and clinical evaluations were scheduled at birth, about every 3 months during the 1st year of life and then every 6 months.	Infants born to HCV-infected mothers, including mothers with history of IV drug use who were screened for HIV antibodies.	NR	40000+/482/291/ 291 & 291 infants	NR	(HCV+ vs. HCV+/HIV+ Maternal infection: 251/291 vs. 40/291 All mothers coinfected with HIV were IV drug users and 10 (25%) had been diagnosed with chronic hepatitis The HCV genotypes of infected babies matched those of their mothers (n=17): Genotype 3a - 6/17 Genotype 1a - 4/17 Genotype 2a - 3/17 Genotype 1b - 2/17 Genotype 4a - 1/17 Genotype 4c/4d - 1/17	HCV+: 17/291 (5.8%) HCV+/HIV+: 3/17 (17.6%)	NR

Author, year Country Study Name Risk of bias	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Subgroup analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
Ceci, 2001 Italy **Moderate**	NR	NR	no association (data NR)	NR	transmission from women with no known risk of infection was significantly lower (RR=0.17%, 0.04-0.73%; P=0.0063)	NR	NR	NR	NR	**by maternal blood transfusion (n=38)** **2+ positive tests vs. 0 positive tests** 3/8 (37.5%) vs. 2/30 (6.7%), p<0.05 **by maternal viremia (n=38)** **2+ positive tests vs. 0 positive tests** 6.90 +/- 5.87 x 10^6 vs. 3.93 +/- 2.94 x 10^6	
Conte, 2000 Italy **High**	NR	NR	**cesarean vs. vaginal (n=365)** 1/106 (1%) vs. 7/259 (2.7%) *RR: .245 (.275- 49.463)	**breast vs. formula (n=370)** 2/90 (2%) vs. 6/280 (2%) *RR: 1.02 (.305-3.45)	NR	NR	NR	NR	NR		

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European Pediatric Hepatitis C Virus Network, 2001 (Pembrey) Italy, Spain, Germany, Ireland, Scotland, Belgium, Sweden **Low**	**fetal scalp monitoring during delivery (yes vs. no) (n=724)** 11/93 (11.8%) vs. 58/631 (9.2%) OR=1.33 (95% CI 0.63-2.74) *not adjusted	NR	**cesarean vs. vaginal (n=1400)** 28/382 (7.3%) vs. 101/1018 (9.9%) OR: .739 (.467-1.163) *type of cesarean (CS) or vaginal delivery elective CS: 20/192 (10.4%) emergency CS: 7/115 (6.1%) unspecified CS: 1/75 (1.3%) vaginal, spontaneous: 81/825 (9.8%) vaginal, instrumented: 12/79 (15.2%) vaginal, unspecified: 8/114 (7%) **HIV- mothers (n=884)** **cesarean vs. vaginal** 15/218 (6.9%) vs. 39/666 (5.9%) OR 1.17 (0.59-2.31, p=.66) *adjusted for breastfeeding status, maternal age at delivery, and center category *info on type of CS or vaginal delivery NR for HIV-	**breast vs. formula (n=1424)** 29/351 (8.3%) vs. 102/1073 (9.5%) **HIV- mothers** **breast vs. formula (n=887)** 21/319 (6.6%) vs. 36/568 (6.3%) OR 1.07 (0.57-2.02, p=0.83) *adjusted for mode of delivery, maternal age at delivery **HIV+ mothers** **breast vs. formula (n=497)** 5/13 (38.5%) vs. 64/484 (13.2%) OR 6.41 (1.25-32.94), p=0.03 *adjusted for mode of delivery, maternal age at delivery	**mother HIV positive vs. negative (n=1419)** 70/503 (13.9%) vs. 60/916 (6.6%), OR 2.31 (1.58-3.37) **no maternal drug use ever vs. not during pregnancy vs. during pregnancy (n=1384)** 43/567 (7.6%) vs. 49/455 (10.8%) vs. 33/362 (9.1%), OR=0.82 (.50-1.35) vs. OR=1.20 (.74-1.97) **maternal history of hepatitis (yes vs. no) (n=1038)** 50/421 (11.9%) vs. 55/617 (8.9%), OR=1.38 (0.90-2.10) **other infections during pregnancy (yes vs. no) (n=996)** 7/90 (7.8%) vs. 84/906 (9.3%), OR=0.83 (0.38-1.81) *not adjusted	**<36 weeks gestational age vs. >36 weeks (n=1248)** 7/105 (6.7%) vs. 109/1143 (9.5%), OR 0.68 (0.26-1.50) **birth weight <2500g vs. >2500 g (n=1362)** 49/523 (9.4%) vs. 109/1143 (9.5%), OR 1.05 (0.71-1.56)	NR	NR	European Commission DG XII Biomed 2 Programme		

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European Pediatric Hep C Virus Network, 2005 (Tovo) Italy, Spain, Germany, Ireland, UK, Norway, Sweden **Low**			**elective cesarean vs. emergency cesarean or vaginal delivery (n=1220)** OR 1.66 (1.00-2.74) unadjusted, p=.05 OR 1.46 (0.86-2.48) adjusted, p=.16 **HIV- mothers elective vs. emergency cesarean or vaginal delivery (n=1034)** 1.57 (0.88-2.83) unadjusted, p=.13 1.59 (0.88-2.86) adjusted, p=.13 *adjusted for sex, mode of delivery, prematurity, and infant feeding type	**breast vs. formula (n=1220)** OR 0.74 (0.42-1.31) unadjusted, p=.30 OR .88 (0.48-1.61) adjusted, p=.68 **HIV- mothers breast vs. formula (n=1034)** OR 0.88 (0.48-1.61) unadjusted, p=.68 OR 0.92 (0.50-1.70) adjusted, p=.60	**mother HIV positive vs. negative (n=1220)** OR 1.89 (1.05-3.40) unadjusted, p=.03 OR 1.82 (0.94-3.52) adjusted, p=.06	**female vs. male (n=1220)** OR 2.12 (1.27-3.56) unadjusted, p=.004 OR 2.07 (1.23-3.48) adjusted, p=.006 **premature vs. term (n=1220)** OR 0.54 (0.23-1.26) unadjusted, p=.15 OR 0.45 (0.19-1.08) adjusted, p=.07 **HIV- mothers female vs. male (n=1034)** OR 1.79 (1.00-3.22) unadjusted, p=.05 OR 1.80 (1.00-3.24) adjusted, p=.07 **HIV- mothers premature vs. term (n=1034)** OR 0.83 (0.32-2.13) unadjusted, p=.69 0.83 (0.32-2.15) adjusted, p=.80	NR	NR	European Commission; Regione Piemonte, Italy; UK Medical Research Council		

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Garland, 1998 Australia **High**	NR	NR	**vaginal vs. cesarean (n=83)** 3/61 (4.9%) vs. 0/22 (0%)	Viral RNA detected in breast milk: 0/18 (0%)	NR	NR	Sibling HCV RNA+: 1/16 (6%)	NR	NR	NW	
Gibb, 2001 Ireland, UK **Moderate**	NR	NR	**elective cesarean vs. emergency cesarean vs. vaginal (n=424)** 0% (0-7.4) vs. 5.9% (1.0-17.8) vs. 7.7% (4.5-11.9) OR elective cesarean 0 (95% CI 0-0.86) vs. OR emergency cesarean 0.84 (95% CI 0.12-3.63) vs. *adjusted for HIV status and breastfeeding **elective cesarean vs. vaginal/emergency cesarean (n=424)** 0% (0-7.4) vs. 7.4% (4.5-11.3) OR 0 (0-0.87) *adjusted for HIV status and breastfeeding	**breast vs. formula (n=414)** 7.7% (2.2-17.8) vs. 6.7% (3.7-10.6) OR 1.52 (0.35-5.12) *adjusted for HIV status and mode of delivery	**HIV positive vs. negative (n=441)** 18.6% (5.8-38.6) vs. 6.4% (3.5-10.3) OR= 3.8 (0.92-13.2) *adjusted for breastfeeding and HIV status	NR	NR	NR	UK Department of Health	NR	

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LaTorre, 1998 Italy **High**	NR	NR	**vaginal vs. cesarean (n=80)** 1/66 (1.5%) vs. 1/14 (7%)	**breastfed vs. formula fed (n=80)** 0/24 (0%) vs. 2/56 (3.6%) *none of the HCV-RNA positive mothers breastfed	**by maternal HCV RNA status (n=80)** mother positive: 2/56 (3.6%) mother negative: 0/24 (0%) *not adjusted	NR	NR	NR	not specified, research and testing took place at Careggi Hospital, University of Florence		
Lin, 1995 Republic of China **High**	NR	NR	NR	Breast feeding transmission rate: (n=11 breast fed) None (0%)	IVDU during pregnancy: 1/12 (8.3%) infants HCV+	NR	NR	NR	National Science Council, Yuan, China	NW	

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Mast, 2005 US (Houston & Honolulu) **Low**	*** results are for HCV RNA+/HIV- mothers (n=181)** **internal vs. external** 3/16 (18.8%) vs. 4/165 (2.4%), RR 7.7 (1.9-31.6), p=.02 **internal fetal monitoring** *adjusted OR, 6.7 (1.1-35.9)	*** results are for HCV RNA+/HIV- mothers (n=182)** **rupture of membranes before onset of labor yes vs. no** 4/45 (8.9%) vs. 3/137 (2.2%), RR 4.1 (0.9-17.5), p=.06 **Duration of membrane rupture** <1 vs. 1-5 vs. 6-12 vs. >=13 0/53 vs. 1/59 (1.7%) vs. 4/40 (10%) vs. 2/30 (6.7%), p=.02 **membrane rupture >6 hrs** OR, 9.3 (1.5-179.7) *adjusted	*** results are for HCV RNA+/HIV- mothers (n=181)** **elective cesarean vs. emergency cesarean vs. vaginal delivery** 0/12 (0%) vs. 1/18 (5.5%) vs. 6/151 (4%), elective cesarean RR undefined, emergency cesarean RR 1.4 (0.2-1.1), p=.55 **elective cesarean vs. emergency cesarean/vaginal** 0/12 vs. 7/169 (4%), RR 1.1 (0.07-19)	*** results are for HCV RNA+/HIV- mothers (n=182)** **breast vs. formula** 2/62 (3.2%) vs. 5/120 (4.2%), RR 0.8 (0.2-3.9), p=1.0	**maternal HCV/RNA status at delivery** positive vs. negative 9/190 (4.6%) vs. 0/54, RR undefined ***remaining results are for HCV/RNA+ mothers (n=190)** **maternal HIV status** positive vs. negative 2/8 (25%) vs. 7/182 (3.8%), RR 6.5 (1.6-26.4) **maternal HCV RNA level, genome copies/mL** $<=10^6$ vs. $>10^6$, $<10^7$ vs. $>=10^7$ 1/61 (1.6%) vs. 2/87 (2.3%) vs. 4/34 (11.8%), p=.03 **maternal age at delivery, years** >=30 vs. <30 5/100(5) vs. 2/81(2.5), RR 2.0(0.4-10.2), p=0.46 **(results continued in last 2 columns)**	***results for infants born to HCV/RNA+ mothers (n=190)** **sex** male vs. female 2/85 (2.3%) vs. 5/96 (5.2%), RR 0.45 (0.09-2.27), p=.45 **gestational age** <37 vs. >=37 0/27 vs. 7/155 (4.5%), RR undefined, p=.6 **birth weight** <2500g vs. >=2500g 1/22 (4.6%) vs. 6/160 (3.8%), RR 1.2 (0.2-9.6), p=1 **Apgar score at 5 min** <=8 vs. >8 0/21 vs. 7/161 (4.4%), RR undefined, p=1	NR	NR	Centers for Disease Control	**prior pregnancies** >4 vs. <=4 2/73 vs. 5/109, RR 0.6(0.1-3.0) **ALT level at delivery, U/L** >35 vs. <=35 3/45(6.7) vs. 4/137, RR 2.3(0.5-9.8) **duration of membrane rupture** <1 vs. 1-5 vs. 6-12 vs. >=13 0/53(0) vs. 1/59(1.7) vs. 4/40(10) vs. 2/30(6.7), (p=.02) adjusted OR for membrane rupture >6h, 9.3(1.5-179.7) **duration of labor, h** <=6 vs. 7-12 vs. >=13 2/84(2.4) vs. 4/48(8.3) vs. 1/44(2.3), (p=.78)	**cigarette smoking during** pregnancy yes vs. no 1/99(1) vs. 6/83(7.23), RR 0.14(0.02-1.1) **alcohol intake during pregnancy** yes vs. no 1/42(2.4) vs. 6/140(4.3), RR 0.6(0.1-4.5) **history of IVDU** yes vs. no 1/94(1.1) vs. 6/88(6.8), RR 0.2 (0.02-1.27) **amniotic fluid** clear (ref) vs. meconium vs. bloody 2/129(1.6) vs. 4/40(10) vs. 1/10(10), RR 6.5(1.2-33.9) RR 6.5 (0.6-65.2)

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McMenamin, 2008Ireland**High**	**fetal scalp electrode (n=23)**infant HCV RNA+: 0/11 (0%)infant not tested: 12	NR	**elective cesarean vs. emergency cesarean or vaginal delivery (n=441):** 1/33 (3%, 95% CI 0% - 8%) vs. 17/408 (4.2%, 95% CI 2.3%-6.2%) p=NS*not adjusted*same results if limited to HIV-mothers**elective cesarean vs. emergency cesarean or vaginal delivery HCV-RNA+ women (n=295)**5.3% vs. 7.2%p=NS*not adjusted*authors didn't provide raw numbers	NR	**HCV RNA positive vs. negative vs. unknown (n=441)**positive vs. negative vs. unknown: 18/255 (7.1%, 95% CI 6.3%-7.9%, p<.05) vs. 0/17 (0%, p<.05) vs. 0/69 (0%)*not adjusted**HIV positive vs. negative (n=441)** 1/17 (5.9%, 95% CI 0%-17.2%, p=NS)vs. 17/418 (4.1%, 95% CI 2.2%-6.0%, p=NS)mother status unknown: 0/6 (0%)	NR	NR	NR	not specified, retrospective review of data from National Maternity Hospital and Rotunda Hospital		
Moriya, 1995 Japan **High**	NR	NR	NR	Breast feeding transmission rate (n=74): 5/6 infected received breast milk (83%%) vs. 54/68 uninfected (79%) *RR: 1.03 (.397-1.79)	NR	NR	NR	NR	Ministry of Health & Welfare, Japan	NW	

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Okamoto et al, 2000 Japan (Tottori University & Medical Center) **High**	NR	NR	**vaginal vs. cesarean** **HCV+ mothers** 7/50 (14%) vs. 0/28 (0%), p=.045 **RNA+ mothers** 7/41 (17%) vs. 0/18 (0%), p=089 **high Viral Load mothers** (>2.5x106 copies/mL): 7/16 (44%) vs. 0/10 (0%), p=.023	The sample size was too small to test the effect of breast-feeding.	History of blood transfusion, history of clinical hepatitis NS, data NR	HCV-RNA+ titers of vaginally delivered infants born to RNA+ mothers: Mothers (Geometric average, 95% CI): Infectious: 5, (7.0, 2.4–20.0) vs. Noninfectious: 31, (1.5, 0.9–2.3), p<.001 Children (Geometric average, 95% CI): Infected: 7, (8.0, 3.8–16.7) vs. Uninfected: 34, (1.4 0.9–2.2), p<.001	NR	Research on Children and Families of the Ministry of Welfare of Japan	NR		
Pipan, 1996 Italy **High**	NR	NR	NR	**breast vs. formula (n=25)** 0/6 (0%) vs. 0/19 (0%)	NR	NR	NR	NR	MURST grant and the FVG Branch of Italian League against Virus Disease		

Author, year Country Study Name Risk of bias	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Subgroup analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
Resti et al, 1998 Italy Moderate	NR	NR	**vaginal vs. cesarean (n=275)** 9/213 (4%) vs. 4/62 (6%), RR 0.65 (0.21-2.05), p=0.498	**breast vs. formula (n=275)** 6/87(7%) vs. 7/188(4%), RR = 1.85 (0.64 to 5.35), p=0.358. 3/6 infected breast fed children had hepatitis C virus RNA detected on the day of birth	Transmission from women with no known risk of infection was significantly lower (RR=0.17%, 0.04-0.73%; P=0.0063) **IVDU during pregnancy** 1/12 (8.3%) infants HCV+ **HCV viral load** No significant difference (z=0.380; P=0.704) in RNA load between mothers who transmitted the virus and those who did not (3.8 (0.02 to 56)×105 RNA copies/ml v 2.4 (0.01 to 92.7)×105 RNA copies/ml)	6 babies had hepatitis C virus RNA immediately after birth. The transmission rate was higher in 20 recipients of blood transfusions (RR=10%, 95% CI 3-17%)	NR	NR	Partially supported by grant 394/A from Regione Toscana, III Programma Ricerca Sanitaria and by a grant from Ministero della Ricerca Scientifica	NR	

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Spencer, 1997 Australia **High**	NR	**viremic mothers (mean hours ± SD) (n=63)** transmitted vs. not transmitted: 28±10 vs. 16±4, p=.03	**viremic mothers, cesarean (n=63) transmitted vs. not transmitted** 1/6 (14%) vs. 6/56 (9%), p=.5 **cesarean vs. vaginal** 1/7 (14%) vs. 5/55 (9%)	**viremic mothers breastfeeding (n=63)** transmitted vs. not transmitted 2/6 (33%) vs. 31/57 (54%) p=0.4 **breast fed vs. formula fed** 2/33 (6%) vs. 4/30 (13%) viral RNA detected in breast milk: (n= 38) 0%	viremic mothers transmitting vs. non-transmitting **viral load at delivery** 8.9x105 vs. 3.9x105, p=0.04 **drug use, mean years** 8.8±1.4 vs. 10±0.8, p=0.7 **past HBV infection** 4/6 (66%) vs. 34/55 (62%), p<0.9 **heroin use during pregnancy** 2/2 (100%) vs. 38/45 (84%), p<0.9	**Birth weight (mean g)** 2698 (transmitted n=6) vs. 3020 (no transmission n=57) p= 0.4 **Gestational Age** transmitting vs. non-transmitting: 37±0.9 weeks vs. 39±0.3 weeks, p=0.3	NR	NR	NR	NW	

Author, year Country Study Name Risk of bias	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Subgroup analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
Syriopoulou, 2005 Greece **High**	NR	NR	**vaginal vs. cesarean (n=56)** 2/39 (5%) vs. 0/17 (0%), p=0.34	**breast vs. formula (n=56)** 0/15 (0%) vs. 2/41 (5%), p=0.38	**HCV/RNA+ vs. HCV/RNA- (n=86)** 2/56 (3.6%) vs. 0/30 (0%) **HIV+ vs. HIV- (n=56)** 1/2 (50%) vs. 1/54 (2%) (p<.001) **IVDU use during pregnancy, yes vs. no (n=56)** 2/3 (67%) *1 mother was HIV+ vs. 0/54 (0%) (p<.001) **IVDU ever, yes vs. no (n=56)** 2/8 (25%) vs. 0/48 (0%) (p<.001)	NR	NR	NR	NR		
Tajiri et al, 2001 Japan (seven hospitals in the Osaka metropolitan area) **High**	NR	NR	**vaginal vs. cesarean (n=114)** 8/90 (8.8%) vs. 1/24 (4.2%), p = 0.396 *RR: 2.04 (.284 - 43.42)	**breast vs. formula (n=114)** 9/98 (9.2%) vs. 0/16, p=0.243	Maternal HCV Viremia: positive: 9/81 vs. negative: 0/33, p=.040 Maternal viral load: High: 8/46 vs. Low: 0/27, p=0.019	NR	NR	NR	NR		

Author, year Country Study Name Risk of bias	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Subgroup analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
Tanzi, 1997 Italy **Moderate**	NR	NR	NR	HCV RNA+ mothers (n=18) 12/18 HCV/RNA+ mothers breastfed, none infected at 3 month follow-up	NR	NR	NR	NR	NR		
Zanetti et al, 1998 (Intervirology) Italy A prospective Study on Mother-to-Infant Transmission of Hepatitis C virus Zanetti et al, 1999 (Journal of Hepatology) Italy Mother-to-infant transmission of hepatitis C virus High	NR	NR	**vaginal vs. cesarean (HCV+)** 7/193 (3.6%) vs. 1/58 (1.7%), p = 0.7 **(HCV+/HIV+)** 0/4(0%) vs. 9/36(25%), p = 0.5	**HIV- mothers breast vs. formula (n=251)** 3/127 (2.4%) vs. 5/124 (4.0%), p = 0.5 **HIV+ mothers breast vs. formula (n= 40)** 0 vs. 9/40 (22.5%)	Transmission by History of IVDU: HCV+: Yes: 3/67 (4.5%) vs. No: 5/184 (2.7%), p=0.4 HCV+/HIV+: Yes: 9/40 (22.5%) vs. No: 0 Transmission by History of Chronic Liver Disease or elevated ALT: HCV+: Yes: 3/85 (3.5%) vs. No: 5/166 (3%), p=1 HCV+/HIV+: Yes: 4/10 (40%) vs. No: 5/30 (16.7%), p=0.2	NR	NR	NR	NR		

Abbreviations: HCV, hepatitis C virus; SVR, sustained virological response.

Evidence Table 11: Key Question 7 Pregnancy Intervention Observational Studies Quality Rating/Risk of Bias

Author, Year	(1) Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	(2) Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	(3) Did the study maintain comparable groups through the study period?	(4) Did the study use accurate methods for ascertaining exposures and potential confounders?	(5) Were outcome assessors and/or data analysts blinded to the exposure being studied?	(6) Did the article report attrition?	(7) Is there important differential loss to follow-up or overall high loss to follow-up?	(8) Did the study perform appropriate statistical analyses on potential confounders?	(9) Were outcomes pre-specified and defined, and ascertained using accurate methods?	Risk of bias (high, moderate, low)
Ceci, 2001	Yes	Unclear	Unclear	Yes	No	Yes	Unclear	Yes	Yes	Moderate
Conte, 2000	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Yes	High
European Paediatric Hepatitis C Virus Network, 2001 (Pembrey)	Yes	Yes	Yes	Yes	Unclear	No	No	Yes	Yes	Low
European Paediatric Hepatitis C Virus Network, 2005 (Tovo)	Yes	Yes	Yes	Yes	Unclear	No	No	Yes	Yes	Low
Garland, 1998	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	No	Yes	High
Gibb, 2000	Unclear	Unclear	Unclear	Yes	No	No	No	Yes	Yes	Moderate

LaTorre, 1998	Yes	Unclear	Unclear	Yes	Unclear	No	Unclear	No	Unclear	High
Lin, 1995	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Unclear	No	Yes	High
Mast, 2005	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Low
McMenamin, 2008	Yes	Yes	Unclear	Yes	Unclear	Yes	No	Yes	No	High
Moriya, 1995	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes	High
Okamoto, 2000	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear	High
Pipan, 1996	Yes	Unclear	Unclear	Yes	Yes	No	No	No	Yes	High
Resti et al, 1998	Yes	Yes	Yes	Unclear	Unclear	Yes	No	No	Yes	Moderate
Spencer, 1997	Unclear	Unclear	Unclear	No	Unclear	Yes	Yes	No	Yes	High
Syriopoulou, 1998	Unclear	Unclear	Unclear	No	Unclear	No	No	No	Yes	High
Tajiri, 2001	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear	High
Tanzi, 1997	Yes	Unclear	Unclear	Yes	Unclear	No	Unclear	No	Yes	High
Zanetti et al, 1998; Zanetti et al, 1999	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	Yes	High