Noninvasive Methods to Assess Liver Disease in Patients With Hepatitis B or C

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The prognosis and management of patients with chronic viral hepatitis B and C depend on the amount and progression of liver fibrosis and the risk for cirrhosis. Liver biopsy, traditionally considered to be the reference standard for staging of fibrosis, has been challenged over the past decade by the development of noninvasive methodologies. These methods rely on distinct but complementary approaches: a biologic approach, which quantifies serum levels of biomarkers of fibrosis, and a physical approach, which measures liver stiffness by ultrasound or magnetic resonance elastography. Noninvasive methods were initially studied and validated in patients with chronic hepatitis C but are now used increasingly for patients with hepatitis B, reducing the need for liver biopsy analysis. We review the advantages and limitations of the noninvasive methods used to manage patients with chronic viral hepatitis B or C infection.

Keywords: Diagnostic Test; Virology; Treatment; Therapy.

It is important to assess liver disease in patients with viral hepatitis B or C, not only to determine prognosis but to identify patients who require antiviral therapy.[1–5] Liver biopsy has traditionally been the standard for evaluation of tissue damage, including fibrosis.[6] Histologic staging of liver fibrosis is a combinatorial assessment of amount of fibrosis and architectural disorganization using the Ishak[7] and METAVIR[8] semiquantitative scoring systems. The clinically relevant end points are detection of significant fibrosis (METAVIR, F ≥2 or Ishak, ≥3), which indicates that patients with hepatitis B or C should receive antiviral treatment, and detection of cirrhosis (METAVIR, F4 or Ishak, 5–6), which indicates that patients should be monitored for complications related to portal hypertension and hepatocellular carcinoma (HCC).[1,5]

Liver biopsy analysis has several limitations. It is an invasive procedure that is prone to sampling errors and to intra- and interobserver variation.[9,10] Recent American Association for the Study of Liver Diseases guidelines recommended a biopsy of at least 2–3 cm in length, obtained with a 16-gauge needle, that contains more than 11 complete portal tracts for adequate staging and grading of diffuse parenchymal disease.[11] However, in clinical practice, few percutaneous needle biopsies meet these criteria.

These limitations, as well as powerful virologic tools for determining genotypes and viral load and new antiviral drugs, have rapidly reduced the use of liver biopsy in management of patients with viral hepatitis. The development of noninvasive methods to assess liver fibrosis over the past decade has advanced the practice of hepatology.[12] Apart from assessing liver fibrosis, these noninvasive methods could be used in deciding whether to treat a patient or defer antiviral treatment, in monitoring patients' response to treatment and progression of disease, and in determining prognosis. We review methods for noninvasive evaluation of liver fibrosis and discuss their advantages and limitations in managing patients with viral hepatitis B or C.

Methodologies

The performance of a noninvasive diagnostic method is evaluated by calculation of the area under the receiver operator characteristic curve (AUROC), taking liver biopsy as the reference standard. However, biopsy analysis is an imperfect reference standard: taking into account a range of accuracies of the biopsy, even in the

Table 1. Currently Available Noninvasive Methods to Assess Liver Disease in Patients With Hepatitis B or C

Serum biomarkers
HCV
Fibrotest (Biopredictive, Paris, France) patented formula combining α-2-macroglobulin, γGT, apolipoprotein A1, haptoglobin, total bilirubin, age, and gender
Forn index $= 7.811 - 3.131 \times \ln(\text{platelet count}) + 0.781 \times \ln(\text{GGT}) + 3.467 \times \ln(\text{age}) - 0.014 \times (\text{cholesterol})$
AST to platelet ratio (APRI) $= \text{AST}\ (/\text{ULN})/\text{platelet}\ (10^9/\text{L}) \times 100$
FibroSpectII (Promotheus Laboratory Inc, San Diego, CA) patented formula combining α-2-macroglobulin, hyaluronate, and TIMP-1
MP3 $= 0.5903 \times \log \text{PIIINP (ng/mL)} - 0.1749 \times \log \text{MMP-1 (ng/mL)}$
Enhanced liver fibrosis score (ELF) (iQur Ltd, Southampton, UK) patented formula combining age, hyaluronate, MMP-3, and TIMP-1
Fibrosis probability index (FPI) $= 10.929 + (1.827 \times \text{LnAST}) + (0.081 \times \text{age}) + (0.768 \times \text{past alcohol use}^a) + (0.385 \times \text{HOMA-IR}) - (0.447 \times \text{cholesterol})$
Hepascore (PathWest, University of Western Australia, Perth, Australia) patented formula combining bilirubin, γGT, hyaluronate, α-2-macroglobulin, age, and gender
Fibrometers (BioLiveScale, Angers, France) patented formula combining platelet count, prothrombin index, AST, α-2-macroglobulin, hyaluronate, urea, and age
Lok index $= -5.56 - 0.0089 \times \text{platelet (}10^3/\text{mm}^3) + 1.26 \times \text{AST/ALT ratio} + 5.27 \times \text{INR}$
Goteborg University cirrhosis index (GUCI) $= \text{AST} \times \text{prothrombin-INR} \times 100/\text{platelet}$
Virahep $-$ c model $= 5.17 + 0.20 \times \text{race} + 0.07 \times \text{age (years)} + 1.19 \ln (\text{AST [IU/L]}) - 1.76 \ln (\text{platelet count [}10^3/\text{mL]}) + 1.38 \ln (\text{alkaline phosphatase [IU/L]})$
Fibroindex $= 1.738 - 0.064 \times (\text{platelets [}10^4/\text{mm}^3]) + 0.005 \times (\text{AST [IU/L]}) + 0.463 \times (\gamma - \text{globulin [g/dL]})$
FIB-4 $= \text{age (years)} \times \text{AST [U/L]}/(\text{platelets [}10^9/\text{L]} \times (\text{ALT [U/L]})^{1/2}$
HALT-C model $= -3.66 - 0.00995 \times \text{platelets (}10^3/\text{mL}) + 0.008 \times \text{serum} \times \text{TIMP-1} + 1.42 \times \log (\text{hyaluronate})$
HBV
Hui score $= 3.148 + 0.167 \times \text{BMI} + 0.088 \times \text{bilirubin} - 0.151 \times \text{albumin} - 0.019 \times \text{platelet}$
Zeng score $= 13.995 + 3.220 \log (\alpha\text{-2-macroglobulin}) + 3.096 (\text{age}) + 2.254 \log (\text{GGT}) + 2.437 \log (\text{hyaluronate})$

Measurement of liver stiffness
Transient elastography: FibroScan (Echosens, Paris, France) (results ranging from 2.5 to 75 kPa)
Acoustic radiation force impulse imaging: Acuson 2000 Virtual Touch Tissue Quantification (Siemens Healthcare, Erlangen, Germany) (results ranging from 0.5 to 4.4 meters/sec)
Magnetic resonance elastography (results ranging from 0.5 to 10 kPa)

^{a}Graded as 0–2.

best possible scenario, an AUROC >0.90 cannot be achieved even for a perfect marker of liver disease.[13]

The AUROC can vary based on the prevalence of each stage of fibrosis, described as spectrum bias.[14] Spectrum bias has important implications for the study of noninvasive methods, particularly in comparisons of methods across different study populations. If extreme stages of fibrosis (F0 and F4) are over-represented in a population, the sensitivity and specificity of a diagnostic will be higher than in a population of patients that has middle stages of fibrosis (F1 and F2). Several ways of preventing the "spectrum bias" have been proposed including the adjustment of AUROC using the DANA method (standardization according to the prevalence of fibrosis stages; Difference in Advanced [F2-F3-F4] and Nonadvanced [F0-F1] fibrosis) and nonadvanced (F0-F1) fibrosis)[15,16] or the Obuchowski measure (designed for ordinal gold standards).[17] What really matters in clinical practice is the number of patients correctly classified by noninvasive methods for a defined end point according to the reference standard (ie, true positive and true negative).

Noninvasive Methods

Fibrosis can be measured noninvasively, based on a "biological" approach (quantifying biomarkers in serum samples) or based on a "physical" approach (measuring liver stiffness). Although these approaches are comple-mentary, they are based on a different rationale. Liver stiffness corresponds to a genuine and intrinsic physical property of liver parenchyma, whereas serum biomarkers indicate several, not strictly liver-specific features of blood that have been associated with fibrosis stage, as assessed by liver biopsy.

Markers of Liver Fibrosis in Serum

Many serum biomarkers have been evaluated for their ability to determine stage of liver fibrosis, mainly in patients with chronic hepatitis C (for review, see Pinzani et al,[18] Manning and Afdhal,[19] and Castera[20]). Among the proposed markers, the so–called direct markers reflect the deposition or removal of extracellular matrix in the liver. These include glycoproteins such as serum hyaluronate, laminin, and YKL-40 and collagens such as procollagen III N-peptide and type IV collagen, collagenases, and their inhibitors such as matrix metalloproteases and tissue inhibitory metalloprotease-1. So–called indirect markers include factors that can be measured in routine blood tests, such as the prothrombin index, platelet count, and ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT), which indicate alterations in hepatic function. Results from measurements of direct and indirect markers can be combined and used in diagnosis; the FibroTest (proprietary formula; Biopredictive, Paris, France) was the first algorithm that combined these

Table 2. Respective Advantages and Disadvantages of Currently Available Noninvasive Methods in Patients With Hepatitis B or C

	Serum biomarkers	Measurement of liver stiffness		
		Transient elastography	ARFI	MR elastography
Advantages	• Good reproducibility • High applicability (95%) • Low cost and wide availability (nonpatented) • Well validated	• Liver stiffness is a genuine physical property of liver tissue • Good reproducibility • Well validated • High performance for cirrhosis • User-friendly (rapid, results immediately available; short learning curve) • Can be performed in the outpatient clinic • Prognostic value in cirrhosis	• Liver stiffness is a genuine physical property of liver tissue • Performance likely equivalent to that of TE • Region of interest smaller than TE but chosen by the operator • Can be implemented on a regular ultrasound machine • High applicability: overcomes the limitations of TE (ascites and obesity)	• Liver stiffness is a genuine physical property of liver tissue • Performance may be higher than TE for significant fibrosis • Examination of the whole liver • Can be implemented on a regular MRI machine • High applicability: overcomes the limitations of TE (ascites and obesity)
Disadvantages	• Nonspecific of the liver • Unable to discriminate between intermediate stages of fibrosis • Performance not as good as TE for cirrhosis • Results not immediately available • Cost and limited availability (proprietary) • Limitations (hemolysis, Gilbert syndrome, inflammation. . .) <5%	• Requires a dedicated device • Region of interest cannot be chosen • Unable to discriminate between intermediate stages of fibrosis • Low applicability (80%, obesity, ascites, limited operator experience) • False positive in case of acute hepatitis, extra-hepatic cholestasis, and congestion	• Ongoing validation • Unable to discriminate between intermediate stages of fibrosis • Narrow range of values • Quality criteria not well defined • Prognostic value in cirrhosis?	• Further validation warranted • Not applicable in case of iron overload • Requires an MRI facility • Time-consuming • Costly

data.[21] Several other scores[22–37] have been proposed: 4 are protected by patents and are commercially available (Table 1). Nonproprietary methods use published models, based on routinely available laboratory tests.

The practical advantages of analyzing serum biomarkers to measure fibrosis include their high applicability (>95%) and interlaboratory reproducibility[38,39] and their potential widespread availability (Table 2). However, none are liver specific—their results can be influenced by comorbid conditions, and they require critical interpretation of results. For instance, FibroTest and Hepascore produce false-positive results in patients with Gilbert's syndrome or hemolysis because these patients have hyperbilirubinemia.[40] Similarly, acute hepatitis can produce false-positive results in the aspartate-to-platelet ratio index (APRI), Forns index, FIB-4, or Fibrometer tests, which all measure levels of aminotransferases.

Measuring Liver Stiffness

Transient elastography. Liver fibrosis can be staged using 1-dimensional ultrasound transient elastography (TE),[41] which measures the velocity of a low-frequency (50 Hz) elastic shear wave propagating through the liver. This velocity is directly related to tissue stiffness, called the *elastic modulus* (expressed as $E = 3\rho v^2$, where v is the shear velocity, and ρ is the density of tissue, assumed

to be constant). The stiffer the tissue, the faster the shear wave propagates. TE measures liver stiffness in a volume that approximates a cylinder that is 1-cm wide and 4-cm long, 25–65 mm below skin surface. The results are expressed in kilopascals (kPa) and range from 2.5 to 75 kPa; a normal value is around 5 kPa.[42–44]

Advantages to TE include a short procedure time (<5 minutes), immediate results, and the ability to perform the test at the bedside or in an outpatient clinic: it is not a difficult procedure to learn (Table 2). However, accurate results[45,46] require careful interpretation of data, based on at least 10 validated measurements, a success rate (the ratio of valid measurements to the total number of measurement) above 60%, and an interquartile range (IQR; reflects variations among measurements) of less than 30% of the median value (IQR/M, ≤30%).[47] Although TE analysis has excellent inter- and intraobserver agreement,[48,49] its applicability (80%) is not as good as that of serum biomarkers. Failure to obtain any measurement has been reported in 3% of cases, and unreliable results (not meeting manufacturer's recommendations) have been reported for 16%,[50] mostly because of patient obesity or limited operator experience. A new probe (XL probe; Echosens, Paris, France) has been proposed to overcome these limitations for overweight and obese patients.[51] Apart

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Table 3. Diagnostic Performance of Serum Biomarkers of Fibrosis for Significant Fibrosis (F ≥2) and Cirrhosis (F4) in Patients With Hepatitis B or C

Biomarkers	Etiologies	Year	Patients (n)	F ≥2 (%)	F4 (%)	Cut-offs	AUROC	Se (%)	Sp (%)	CC (%)
FibroTest[21]	HCV	2001	339	80		>0.48	0.87	75	85	46
Forns Index[22]	HCV	2002	476	26		<4.2 >6.9	0.81	30–94	51–95	45
APRI[23]	HCV	2003	270	50		≤0.5 >1.5	0.80	41–91	47–95	44
					17	<1.0 ≥2.0	0.89	57–89	75–93	72
FibroSpectII[24]	HCV	2004	696	52		>0.36	0.83	77	73	75
MP3[25]	HCV	2004	194	45		<0.3 >0.4	0.82	35–65	85–96	NA
ELF[26]	Mixed	2004	1021/496[a]	40		0.102	0.78	87	51	NA
					12	NA	0.89	NA	NA	NA
FPI[27]	HCV	2005	302	48		≤0.2 ≥0.8	0.77	42–85	48–98	20
Hepascore[28]	HCV	2005	211	57		≥0.5	0.82	63	89	92
					16	>0.84	0.89	71	89	NA
Fibrometer[29]	Mixed	2005	598/503[b]	56		NA	0.89	80	84	82
Lok index[30]	HCV	2005	1141		38	<0.2 ≥0.5	0.81	40–98	53–99	52
GUCI[31]	HCV	2005	179		12	>0.1	0.85	80	70	NA
ViraHep-C[34]	HCV	2006	398	37		≤0.22 >0.55	0.83	51–90	54–90	52
Fibroindex[35]	HCV	2007	360	50		≤1.25 ≥ 2.25	0.83	30–40	97–97	35
FIB-4[36]	HCV	2007	847		17[c]	<1.45 >3.25	0.85	38–74	81–98	68
HALT-C model[37]	HCV	2008	512		38	<0.2 ≥0.5	0.81	47–88	45–92	48
Hui Score[32]	HBV	2005	235	25		≤0.15 >0.5	0.79	37–88	50–88	49
Zeng score[33]	HBV	2005	372	58		<3.0 >8.7	0.77	40–98	28–90	35

AUROC, area under ROC curve; CC, correctly classified: true positive and negative; HBV, chronic hepatitis B; HCV, chronic hepatitis C; NA, not available; Se, sensitivity; Sp specificity.
[a]Number of HCV patients.
[b]Number of patients with viral hepatitis.
[c]F3-F4 patients.

from obese patients, TE results can also be difficult to obtain from patients with narrow intercostal space and are impossible to obtain from patients with ascites.[41] The liver is an organ wrapped in a distensible but nonelastic envelope (Glisson's capsule), so additional space-occupying tissue abnormalities, such as edema, inflammation, extrahepatic cholestasis, or congestion, can interfere with measurements of liver stiffness, independently of fibrosis.[52] The influence of steatosis is a matter of debate.[53,54]

Other imaging methods. Several other liver elasticity-based imaging techniques are being developed, including (2-D) acoustic radiation force impulse imaging (ARFI) and 3-D magnetic resonance (MR) elastography. ARFI involves mechanical excitation of tissue using short-duration (~262 μsec) acoustic pulses that propagate shear waves and generate localized, μ-scale displacements in tissue.[55] The shear-wave velocity (expressed in meters/sec) is measured in a smaller region than in TE (10-mm long and 6-mm wide) but can be chosen by the operator. The major advantage of ARFI is that it can be easily implemented on a modified commercial ultrasound machine (Acuson 2000 Virtual Touch Tissue Quantification; Siemens Healthcare, Erlangen, Germany). However, ARFI values, in contrast to TE values, have a narrow range (0.5–4.4 meters/sec). This limits definitions of cut-off values for patient management decisions.

MR elastography uses a modified phase-contrast method to image the propagation characteristics of the shear wave in the liver.[56] Elasticity is quantified by MR elastography (expressed in kilopascals) using a formula that determines the shear modulus, which is equivalent to one-third the Young's modulus used with TE.[57] The theoretical advantages of MR elastography include its ability to analyze almost the entire liver and its applicability to patients with obesity or ascites. However, MR elastography cannot be performed in livers of patients with iron overload because of signal-to-noise limitations and it is too costly and time-consuming to use in routine practice.

Diagnostic Performance

Quantifying Markers of Liver Fibrosis in Serum

The diagnostic performances of serum biomarkers of fibrosis for significant fibrosis and cirrhosis are summarized in Table 3. Overall, biomarkers are less accurate in detecting intermediate stages of fibrosis than cirrhosis. The most widely used and validated are the APRI (a free nonpatented index) and the FibroTest (a patented test that is not widely available). A meta-analysis by the developer[58] that analyzed data from 6378 subjects (individual data from 3282 subjects) who received the FibroTest and biopsies (3501 with hepatitis C virus [HCV] infection and 1457 with hepatitis B virus [HBV]) found that the mean standardized AUROC for diagnosis of significant fibrosis was 0.84, without significant differences between patients with HCV (0.85) and HBV (0.80). Another meta-analysis[59] analyzed results from 6259 HCV patients from 33 studies; the mean AUROC values from the APRI in diagnosis of significant fibrosis and cirrhosis were 0.77 and 0.83, respectively. When compared and validated externally in

Table 4. Diagnostic Performance of Transient Elastography for Significant Fibrosis (F ≥2) and Cirrhosis (F4) in Patients With Hepatitis B or C

Authors	Etiologies	Year	Patient (n)	F ≥2 (%)	F4 (%)	Cut-offs AUROC (kPa)		Se (%)	Sp (%)	CC (%)
Castera et al[66]	HCV	2005	183	74		7.1	0.83	67	89	73
					25	12.5	0.95	87	91	90
Ziol et al[67]	HCV	2005	251	65		8.6	0.79	56	91	68
					19	14.6	0.87	86	96	94
Arena et al[53]	HCV	2008	150	56		7.8	0.91	83	82	83
					19	14.8	0.98	94	92	92
Lupsor et al[68]	HCV	2008	324	65		7.4	0.86	76	84	79
					21	11.9	0.94	87	91	90
Degos et al[64]	HCV	2010	913	62		5.2	0.75	90	32	57
					14	12.9	0.90	72	89	87
Zarski et al[65]	HCV	2012	382	47		5.2	0.82	97	35	64
					14	12.9	0.93	77	90	88
Coco et al[69]	HBV (HCV)	2007	228	62		8.3	0.93	85	91	87
					50[a]	14.0	0.96	78	98	88
Oliveri et al[70]	HBV	2008	188	26		7.5	0.97	94	88	90
					20[a]	11.8	0.97	86	96	94
Marcellin et al[71]	HBV	2009	173	50		7.2	0.81	70	83	76
					8	11.0	0.93	93	87	94
Chan et al[72]	HBV	2009	161		25	12–13.4[b]	0.93	98	75	85
Degos et al[64]	HBV	2010	284	42		5.2	0.78	89	38	59
					10	12.9	0.85	52	93	89

AUROC, area under the receiver operator characteristic curve; CC, correctly classified: true positive and negative; HBV, chronic hepatitis B; HCV, chronic hepatitis C; NA, not available; Se, sensitivity; Sp, specificity.
[a]More than half of patients with clinical cirrhosis.
[b]Adapted to ALT levels.

patients with hepatitis C,[60–65] the FibroTest and biopsy analysis had similar levels of performance in diagnosis of significant fibrosis. The largest study (of 913 HCV and 284 HBV patients) prospectively compared the most popular patented tests (FibroTest, Fibrometre, and Hepacore) with the nonpatented test (APRI); the AUROC values for significant fibrosis ranged from 0.72 to 0.78 with no significant differences among scores.[64] In patients with cirrhosis, the AUROC values were higher, ranging from 0.77 to 0.86, with no significance in differences. Although nonpatented tests such as the Forns index, FIB-4, and APRI could perform less well, they do not incur additional costs, are easy to calculate, and are available almost everywhere.

Measuring Liver Stiffness

Studies have assessed the ability of TE to quantify liver fibrosis in patients with chronic hepatitis C[66,67] and have been largely confirmed[53,64,65,68] and also confirmed in patients with hepatitis B.[64,69–72] TE more accurately detects cirrhosis (AUROC values, 0.87–0.98; correct classification ranging from 85% to 94%) than significant fibrosis (AUROC values, 0.75–0.93; correct classification from 57% to 90%) (Table 4). Interestingly, proposed cut-off values for cirrhosis ranged from 11 kPa in patients with hepatitis B to 14.8 kPa in patients with hepatitis C. Some researchers have proposed that cut-off values be adapted based on causes of liver disease.[73] However, differences among cut-off values could result from differences in prevalence of cirrhosis among study populations (rang-

ing from 8% to 25%). A cut-off value for one population might not be applicable to another, which has a different prevalence of disease. Most studies used single cut-off values for patients with cirrhosis or advanced fibrosis, but more information can be obtained when values are interpreted as a continuum. For example, when liver stiffness values range from 2.5 to 7 kPa, fibrosis is likely mild or absent, whereas when values are above 13 kPa, cirrhosis is likely.[47]

Several meta-analyses[74–77] have confirmed the better diagnostic performance of TE for cirrhosis than for fibrosis, with mean AUROC values of 0.94 and 0.84, respectively.[76] In a meta-analysis of 40 studies (32 papers and 8 abstracts), sensitivity and specificity values were 0.83 and 0.89, respectively, for patients with cirrhosis and 0.79 and 0.78, respectively, for patients with significant fibrosis. However, only 9 studies (comprising 1364 patients) had acceptable standards for liver biopsy and TE, which limit the conclusions. It will therefore be important to perform meta-analyses of data from individual patients.

There are only limited data on the accuracy of ARFI and MR elastography. Preliminary results[78] indicate that the accuracy of ARFI is similar to that of TE. However, most studies are based on small samples of heterogeneous populations and do not always use liver biopsy as reference. A single, pilot study of MR elastography (96 patients) reported that it might be more accurate than TE in diagnosis of significant fibrosis,[79] but validation is required.

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Use in Clinical Practice

Assessing the Stage of Liver Disease

In clinical practice, the determination of fibrosis stage does not need to be as exact as the pathologic scoring system; the absolute stage is less important than determining whether patients have mild or advanced liver disease.

For identifying patients with significant fibrosis, sensitivities and specificities above 85% can be considered sufficient because there are no relevant clinical consequences of false positives or false negatives.[80] Because performances of TE and serum biomarkers have been shown to be equivalent,[64-66] the use of either method could depend on local availability. Strategies that combine 2 serum biomarkers,[81,82] or TE and serum biomarkers,[66,83,84] have been proposed to increase diagnostic accuracy in patients with hepatitis C (Supplementary Figure 1). The advantage of combining 2 unrelated methods, such as TE and biomarkers, over the combination of 2 biomarkers is that TE provides more direct measurement of the liver structure than biomarkers and that there is no relationship between the applicability of TE (success rate and interquartile range) and that of a biomarker.[83,85] Also, the combination of TE and serum biomarkers might be more effective than the combination of 2 biomarkers for detecting significant fibrosis (significantly greater number of saved liver biopsies).[86,87] However, this strategy has only been validated in studies of patients with hepatitis C, is more costly, and could be hampered by the lower applicability of TE, compared with biomarkers.

Identification of patients with cirrhosis requires tests with higher levels of sensitivity because patients might need specific therapies and because patients must be screened for complications. TE appears to be best suited for cirrhosis screening because it has a higher level of performance than biomarker assays[64,84,88]; combining TE with biomarkers does not increase diagnostic accuracy.[65,84,88] However, the applicability of TE is lower (80% vs 95% for biomarker assays), and the performance levels of these diagnostics might not differ for intention-to-diagnose analysis.[65]

In summary, the accuracy and applicability of assays for serum biomarkers and TE differ for patients with hepatitis B or C. For example, strategies to combine noninvasive methods have been shown to increase diagnostic accuracy in patients with HCV but have not yet been validated in patients with HBV.[89-92] Serum levels of aminotransferases should also be taken into account in interpreting results from TE in patients with hepatitis B.[54] To avoid the risk of false-positive results, some authors have proposed to adapt TE cut-offs based on levels of ALT,[72] a strategy that might not apply to patients with fluctuating levels of ALT or hepatitis flares (Table 4). Conversely, in hepatitis e antigen (HBeAg)-negative patients with normal levels of ALT, noninvasive methods, particularly TE, could be used as adjunct tools to measurements of HBV DNA to follow inactive carriers or better identify patients who require liver biopsy (those with ongoing disease activity or significant fibrosis, despite normal levels of ALT).[70,93–95]

Deciding to Provide or Defer Antiviral Therapy

It is important to emphasize that the effects and indications for antiviral treatment differ between patients with hepatitis B and C. For instance, in contrast to hepatitis C, treatment of hepatitis B is not curative and usually prolonged. Apart from fibrosis staging, levels of HBeAg, ALT, and HBV DNA have important roles in treatment decisions for patients with hepatitis B.

In treatment-naïve patients with hepatitis C without comorbidities such as alcoholism or non-alcoholic fatty liver disease, noninvasive methods can be used as first-line assays of fibrosis stage (Figure 1). In that respect, the use of either TE or patented biomarkers (FibroTest, Fibrometer, and Hepascore) was recommended, after an independent systematic review, by the French Health Authorities,[96] and recently endorsed by the European Association for Study of Liver Clinical Practice guidelines.[5] However, the HCV genotype should also be considered, along with local availability of noninvasive methods and clinical relevance.[97] For instance, a liver biopsy might be necessary for patients infected with HCV genotype 1 or 4, if there are discordant results from TE and biomarker assays, before a treatment decision is made. In making the decision to re-treat a patient, a liver biopsy might be required to identify factors that impaired the original response to therapy, such as non-alcoholic steato-hepatitis, if a liver biopsy was not previously performed.

However, with the development of direct-acting agents,[98,99] particularly with next-generation direct-acting agents or interferon-free regimens, which produce higher rates of sustained virologic response,[100,101] discriminating between fibrosis stages F0-F1 and ≥F2 might not be relevant in determining treatment indications.

Noninvasive tests for fibrosis have been less well-incorporated into management of HBV than HCV because there have been fewer studies and because liver inflammation and HBV replication confound interpretation of test results. In treatment-naïve patients, noninvasive tests could be used for patients with levels of ALT <2-fold the upper limit of normal and levels of HBV DNA >20,000 IU/mL (for HBeAg-positive patients) or >2000 IU/mL (for HBeAg-negative patients).[1,2] Results from studies combining TE and biomarker assays remain too preliminary to make recommendations. Some researchers have proposed diagnostic algorithms that use dual TE cut-offs, for positive and negative prediction of significant fibrosis.[102] Obviously, the applicability of this dual cut-off strategy is determined by the setting and the probability that patients have significant fibrosis. For instance, a cut-off value <6.2 kPa could rule out significant fibrosis in virtually all patients (87%) with a low probability for significant fibrosis, such as inactive carriers. Alternatively, a cut-off value of >9.4 kPa accurately predicted fibrosis
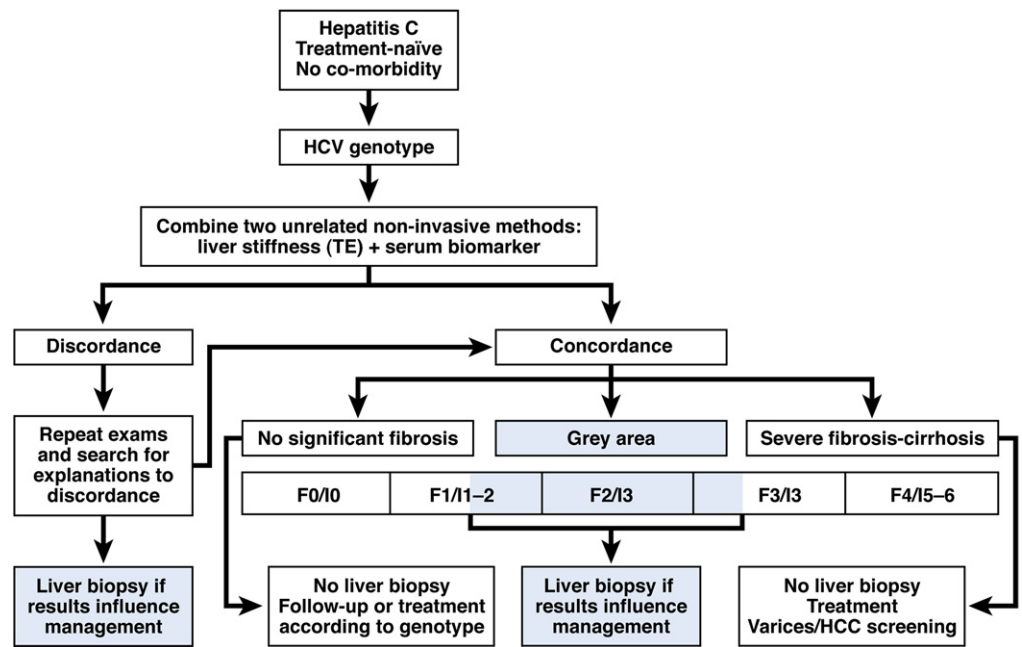
Figure 1. An algorithm that combines 2 unrelated, noninvasive methods to assess liver disease. This algorithm combines data from measurements of liver stiffness (transient elastography) with data from serum biomarker analysis as a first-line assessment of hepatic fibrosis in patients with chronic hepatitis C. The algorithm applies both to significant fibrosis and cirrhosis. F, Metavir fibrosis stage; I, Ishak fibrosis stage.

(92%) in patients with a higher probability of significant fibrosis, such as middle-aged, HBeAg-negative patients with persistently abnormal levels of ALT. The remaining patients should still undergo liver biopsy analysis.[1]

Monitoring Treatment Response

A major advantage of noninvasive methods, compared with liver biopsy, is that the noninvasive assays can be easily repeated over time as patients are followed. For instance, in patients already receiving antiviral therapy, TE and biomarker assays could be used to monitor response to treatment and to evaluate fibrosis regression. Significant histologic improvements have been documented in studies of paired liver biopsies from patients with chronic hepatitis C who achieved sustained viral eradication[103,104] and patients with chronic hepatitis B who received long-term antiviral therapy.[105,106] Several recent studies reported a significant decrease in liver stiffness and biomarkers values, compared with baseline values, in patients with HCV who achieved sustained viral eradication,[107-113] as well as in HBV-infected patients treated with analogues.[114-121]

Despite these encouraging results, following the progress of treated patients with TE or biomarkers can be confounded by changing levels of ALT and inflammation. Some tests for serum biomarkers include parameters that could be affected by the resolution of inflammation (including measurements of ALT and AST). Similarly, a decrease in liver stiffness could result from reductions in inflammatory activity, rather than fibrosis. However, in the only study[113] that assessed liver stiffness kinetics at multiple time points during therapy (weeks 4 and 12) and afterward (week 24), liver stiffness decreased significantly with treatment among patients who did and did not achieve sustain viral eradication; stiffness continued to decrease significantly after the end of treatment only in

patients with sustained viral eradication. Studies with paired liver biopsies are needed to determine whether TE and serum biomarker assays can be used to follow treatment response but are unlikely to be conducted for ethical reasons. Assessments of liver stiffness within 6 months after the end of therapy in patients with HCV infection are probably not clinically meaningful. For patients with HBV infection, serial measurements of liver stiffness should be performed after ALT levels have normalized, over the long-term course of treatment. In patients with cirrhosis, post-treatment assessments of liver stiffness should not substitute for the recommended, periodic surveillance for HCC, using ultrasound examination and measurement of α-fetoprotein levels.[122]

Monitoring Disease Progression

Noninvasive methods can be used to identify patients with cirrhosis who are at risk of disease progression. Compensated cirrhosis is classified as that without varices (stage 1) or with varices (stage 2). Compensated cirrhosis could be further subdivided, as that with no portal hypertension, portal hypertension that is not clinically significant (hepatic venous pressure gradient [HVPG], <10 mm Hg), or clinically significant portal hypertension (HVPG, ≥10 mm Hg).[123]

Measurements of liver stiffness might be used to assess clinical outcomes because they correlate with the severity of liver disease,[124] according to a retrospective study conducted in a single center. This study provided the first "proof of concept" that liver stiffness is a prognostic factor for patients with cirrhosis. Furthermore, liver stiffness correlates with portal pressure (based on the HVPG),[125-128] which accurately predicts clinical events.[129] Interestingly, there was a high degree of correlation between liver stiffness and only HVPG values below 10–12 mm Hg.[126] This indicates that, beyond a certain degree of portal pressure

(above 10–12 mm Hg), development of portal hypertension is at least partially independent from the simple accumulation of fibrillar extracellular matrix, which is responsible for the increase in liver stiffness. Conversely, repeated measurements of liver stiffness, over time, might be made during the first year after liver transplantation to identify patients with early-stage recurrence of severe hepatitis C recurrence and reduce the need for follow-up liver biopsies.[125,130,131]

Liver stiffness values have also been correlated with the presence of esophageal varices. However, the diagnostic accuracy of TE (specificity below 60%) is too low for identification of patients with esophageal varices in clinical practice.[132] When biomarkers were compared, in a large-scale multicenter study of factors to predict which patients would develop high-risk esophageal varices (large esophageal varices, those with red signs, or decompensated cirrhosis), the combination of Lok index and Forns index had the best diagnostic performance, avoiding endoscopy in around one-third of patients.[133] There might be also a role for other noninvasive models combining simple biomarkers such as AST/ALT ratio or platelet count.[134] When compared with serum biomarkers, TE did not perform better for the detection of esophageal varices and large esophageal varices.[88] However, a strategy combining TE with spleen diameter and platelet count (referred as LSPS for LSM-Spleen diameter to platelet ratio score) has been shown to increase diagnostic accuracy for detecting high-risk esophageal varices in patients with HBV-related cirrhosis.[135] Interestingly, Liver Stiffness Measurement-Spleen Diameter and Platelet Count Score (LSPS) appeared as a reliable predictor of esophageal varices bleeding risk in these patients.[136] These findings are consistent with those of a study that reported that liver stiffness values can be as effective as HVPG measurements in predicting which patients will develop clinical decompensation and portal hypertension-related complications.[137] For instance, at a cut-off of 21.1 kPa, TE had a 100% negative predictive value for the occurrence of portal hypertension-related complications; if these results are confirmed, TE could be used as a prognostic tool.[138]

In summary, TE results can identify patients most likely to develop clinically significant portal hypertension but are not sufficient to identify patients with esophageal varices, in clinical practice, or replace endoscopy analysis of cirrhotic patients.[132] Given its likely prognostic value for patients with cirrhosis, TE could be used to rapidly discriminate among patients at different stages of progression of compensated cirrhosis and place them in different risk categories.[139]

Determining Prognosis

Noninvasive methods can also be used in determining prognosis. Large, prospective cohort studies in Asia of patients with hepatitis B or C correlated liver stiffness values with HCC occurrence.[140–142] Among 866 Japanese patients with HCV infection, the cumulative incidence of HCC within 3 years was as high as 38.5%,

among subjects with baseline liver stiffness values >25 kPa, compared with 0.4% among subjects with values ≤10 kPa.[140] Although measurements of liver stiffness could be used to identify patients at risk of developing HCC, more data are needed before they could be integrated into an HCC surveillance program.

Prognosis of patients with chronic liver disease related to viral hepatitis or other causes can be determined using TE[137,143] and assays for serum biomarkers such as FibroTest,[94,144,145] ELF (iQur Ltd, Southsampton, United Kingdom),[146,147] APRI, and FIB-4,[148] as well as for models based on standard laboratory tests.[149,150] A recent French study[143] compared the ability of different noninvasive methods (TE, FibroTest, APRI, and FIB-4) to predict survival and liver-related death of 1457 patients with HCV infection; liver stiffness values and results from the FibroTest had the highest 5-year predictive values, which did not change after adjustment for treatment response, patient age, or estimates of necroinflammatory grade. The potential of noninvasive methods for predicting clinical outcomes seems to be greater than that of liver biopsy; probably the noninvasive tests measure ongoing pathophysiologic processes and functions that a biopsy cannot. Additional advantages of assays for serum biomarkers and TE over histologic scoring systems are that they provide a range of continuous values, instead of a limited number of categories.[151]

Future Directions

Significant progress has been made over the past decade in noninvasive assessment of liver disease in patients with hepatitis B or C, but there is no perfect method. On the one hand, there is increasing awareness that liver biopsy is an imperfect standard. On the other hand, an increasing number of noninvasive methods are available: TE, FibroTest, and APRI are the most widely used and validated worldwide. The introduction of these methods several years ago in France for the management of patients with hepatitis C in routine practice significantly reduced the need for liver biopsy,[152] and this trend has since been observed in most countries where these methods have been implemented. However, noninvasive methods will reduce, but not completely end, the need for liver biopsy.[153] Liver biopsies and noninvasive methods should be used as an integrated system to allow more efficient evaluation of patients with hepatitis B or C.[52]

It is important to investigate the prognostic value of noninvasive methods of fibrosis detection, particularly TE, for patients with cirrhosis; these tests could be used to better classify patients with cirrhosis and assign them to different categories of risk for clinical outcomes. TE has limitations and is challenged by other technologies to measure liver stiffness, such as ARFI and MR elastography, whose place in clinical practice remains to be defined. Other promising techniques, such as supersonic shear imaging[154,155] or measurements of spleen stiffness,[156] could also become available and deserve further evalua-

tion. It has been proposed that noninvasive methods be used to screen the general population for cirrhosis.[157-159] However, this approach is not likely to be cost-effective, given the low prevalence of cirrhosis in the general population.

Supplementary Material

Note: The first 50 references associated with this article are available below in print. The remaining references accompanying this article are avialable online only with the electronic version of the article. To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2012.02.017.

References

1. EASL clinical practice guidelines: management of chronic hepatitis B. J Hepatol 2009;50:227–242.
2. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661–662.
3. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009; 49:1335–1374.
4. Ghany MG, Nelson DR, Strader DB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011;54:1433–1444.
5. EASL clinical practice guidelines: management of hepatitis C virus infection. J Hepatol 2011;55:245–264.
6. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001; 344:495–500.
7. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22:696–699.
8. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR cooperative study group. Hepatology 1996;24:289–293.
9. Maharaj B, Maharaj RJ, Leary WP, et al. Sampling variability and its influence on the diagnostic yield of percutaneous needle biopsy of the liver. Lancet 1986;1:523–525.
10. Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97:2614–2618.
11. Rockey DC, Caldwell SH, Goodman ZD, et al. Liver biopsy. Hepatology 2009;49:1017–1044.
12. Castera L, Pinzani M. Noninvasive assessment of liver fibrosis: are we ready? Lancet 2010;375:1419–1420.
13. Mehta SH, Lau B, Afdhal NH, et al. Exceeding the limits of liver histology markers. J Hepatol 2009;50:36–41.
14. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. N Engl J Med 1978; 299:926–930.
15. Poynard T, Halfon P, Castera L, et al. Standardization of ROC curve areas for diagnostic evaluation of liver fibrosis markers based on prevalences of fibrosis stages. Clin Chem 2007;53:1615–1622.
16. Sebastiani G, Castera L, Halfon P, et al. The impact of liver disease aetiology and the stages of hepatic fibrosis on the performance of non-invasive fibrosis biomarkers: an international study of 2411 cases. Aliment Pharmacol Ther 2011;34:1202–1216.
17. Obuchowski NA. An ROC-type measure of diagnostic accuracy when the gold standard is continuous-scale. Stat Med 2006;25: 481–493.
18. Pinzani M, Vizzutti F, Arena U, et al. Technology insight: noninvasive assessment of liver fibrosis by biochemical scores and elastography. Nat Clin Pract Gastroenterol Hepatol 2008;5:95–106.
19. Manning DS, Afdhal NH. Diagnosis and quantitation of fibrosis. Gastroenterology 2008;134:1670–1681.
20. Castera L. Transient elastography and other noninvasive tests to assess hepatic fibrosis in patients with viral hepatitis. J Viral Hepat 2009;16:300–314.
21. Imbert-Bismut F, Ratziu V, Pieroni L, et al. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet 2001;357:1069–1075.
22. Forns X, Ampurdanes S, Llovet JM, et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. Hepatology 2002;36:986–992.
23. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518–526.
24. Patel K, Gordon SC, Jacobson I, et al. Evaluation of a panel of non-invasive serum markers to differentiate mild from moderate-to-advanced liver fibrosis in chronic hepatitis C patients. J Hepatol 2004;41:935–942.
25. Leroy V, Monier F, Bottari S, et al. Circulating matrix metalloproteinases 1, 2, 9 and their inhibitors TIMP-1 and TIMP-2 as serum markers of liver fibrosis in patients with chronic hepatitis C: comparison with PIIINP and hyaluronic acid. Am J Gastroenterol 2004;99:271–279.
26. Rosenberg WM, Voelker M, Thiel R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. Gastroenterology 2004;127:1704–1713.
27. Sud A, Hui JM, Farrell GC, et al. Improved prediction of fibrosis in chronic hepatitis C using measures of insulin resistance in a probability index. Hepatology 2004;39:1239–1247.
28. Adams LA, Bulsara M, Rossi E, et al. Hepascore: an accurate validated predictor of liver fibrosis in chronic hepatitis C infection. Clin Chem 2005;51:1867–1873.
29. Cales P, Oberti F, Michalak S, et al. A novel panel of blood markers to assess the degree of liver fibrosis. Hepatology 2005; 42:1373–1381.
30. Lok AS, Ghany MG, Goodman ZD, et al. Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: results of the HALT-C cohort. Hepatology 2005;42:282–292.
31. Islam S, Antonsson L, Westin J, et al. Cirrhosis in hepatitis C virus-infected patients can be excluded using an index of standard biochemical serum markers. Scand J Gastroenterol 2005;40: 867–872.
32. Hui AY, Chan HL, Wong VW, et al. Identification of chronic hepatitis B patients without significant liver fibrosis by a simple noninvasive predictive model. Am J Gastroenterol 2005;100:616–623.
33. Zeng MD, Lu LG, Mao YM, et al. Prediction of significant fibrosis in HBeAg-positive patients with chronic hepatitis B by a noninvasive model. Hepatology 2005;42:1437–1445.
34. Fontana RJ, Kleiner DE, Bilonick R, et al. Modeling hepatic fibrosis in African American and Caucasian American patients with chronic hepatitis C virus infection. Hepatology 2006;44:925–935.
35. Koda M, Matunaga Y, Kawakami M, et al. FibroIndex, a practical index for predicting significant fibrosis in patients with chronic hepatitis C. Hepatology 2007;45:297–306.
36. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and Fibrotest. Hepatology 2007;46:32–36.
37. Fontana RJ, Goodman ZD, Dienstag JL, et al. Relationship of serum fibrosis markers with liver fibrosis stage and collagen content in patients with advanced chronic hepatitis C. Hepatology 2008;47:789–798.
38. Cales P, Veillon P, Konate A, et al. Reproducibility of blood tests of liver fibrosis in clinical practice. Clin Biochem 2008;41:10–18.
39. Imbert-Bismut F, Messous D, Thibaut V, et al. Intra-laboratory analytical variability of biochemical markers of fibrosis (Fibrotest) and activity (Actitest) and reference ranges in healthy blood donors. Clin Chem Lab Med 2004;42:323–333.

40. Poynard T, Munteanu M, Imbert-Bismut F, et al. Prospective analysis of discordant results between biochemical markers and biopsy in patients with chronic hepatitis C. Clin Chem 2004;10:10.

41. Sandrin L, Fourquet B, Hasquenoph JM, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003;29:1705–1713.

42. Roulot D, Czernichow S, Le Clesiau H, et al. Liver stiffness values in apparently healthy subjects: influence of gender and metabolic syndrome. J Hepatol 2008;48:606–613.

43. Kim SU, Choi GH, Han WK, et al. What are "true normal" liver stiffness values using FibroScan? A prospective study in healthy living liver and kidney donors in South Korea. Liver Int 2010;30:268–274.

44. Colombo S, Belloli L, Zaccanelli M, et al. Normal liver stiffness and its determinants in healthy blood donors. Dig Liver Dis 2011;43:231–236.

45. Lucidarme D, Foucher J, Le Bail B, et al. Factors of accuracy of transient elastography (Fibroscan) for the diagnosis of liver Fibrosis in chronic hepatitis C. Hepatology 2009:1083–1089.

46. Myers RP, Crotty P, Pomier-Layrargues G, et al. Prevalence, risk factors and causes of discordance in fibrosis staging by transient elastography and liver biopsy. Liver Int 2010;30:1471–1480.

47. Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol 2008;48:835–847.

48. Fraquelli M, Rigamonti C, Casazza G, et al. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. Gut 2007;56:968–973.

49. Boursier J, Konate A, Gorea G, et al. Reproducibility of liver stiffness measurement by ultrasonographic elastometry. Clin Gastroenterol Hepatol 2008;6:1263–1269.

50. Castera L, Foucher J, Bernard PH, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. Hepatology 2010;51:828–835.

Supplementary References (Online-Only)

51. Myers RP, Pomier-Layrargues G, Kirsch R, et al. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. Hepatology 2012;55:199–208.

52. Castera L, Pinzani M. Biopsy and non-invasive methods for the diagnosis of liver fibrosis: does it take two to tango? Gut 2010; 59:861–866.

53. Arena U, Vizzutti F, Abraldes JG, et al. Reliability of transient elastography for the diagnosis of advanced fibrosis in chronic hepatitis C. Gut 2008;57:1288–1293.

54. Fraquelli M, Rigamonti C, Casazza G, et al. Etiology-related determinants of liver stiffness values in chronic viral hepatitis B or C. J Hepatol 2011;54:621–628.

55. Nightingale K, Soo MS, Nightingale R, et al. Acoustic radiation force impulse imaging: in vivo demonstration of clinical feasibility. Ultrasound Med Biol 2002;28:227–235.

56. Muthupillai R, Lomas DJ, Rossman PJ, et al. Magnetic resonance elastography by direct visualization of propagating acoustic strain waves. Science 1995;269:1854–1857.

57. Talwalkar JA, Yin M, Fidler JL, et al. Magnetic resonance imaging of hepatic fibrosis: emerging clinical applications. Hepatology 2008;47:332–342.

58. Poynard T, Morra R, Halfon P, et al. Meta-analyses of Fibrotest diagnostic value in chronic liver disease. BMC Gastroenterol 2007;7:40.

59. Lin ZH, Xin YN, Dong QJ, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology 2011;53:726–736.

60. Parkes J, Guha IN, Roderick P, et al. Performance of serum marker panels for liver fibrosis in chronic hepatitis C. J Hepatol 2006;44:462–474.

61. Halfon P, Bacq Y, De Muret A, et al. Comparison of test performance profile for blood tests of liver fibrosis in chronic hepatitis C. J Hepatol 2007;46:395–402.

62. Leroy V, Hilleret MN, Sturm N, et al. Prospective comparison of six non-invasive scores for the diagnosis of liver fibrosis in chronic hepatitis C. J Hepatol 2007;46:775–782.

63. Cales P, de Ledinghen V, Halfon P, et al. Evaluating the accuracy and increasing the reliable diagnosis rate of blood tests for liver fibrosis in chronic hepatitis C. Liver Int 2008;28:1352–1362.

64. Degos F, Perez P, Roche B, et al. Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: a multicenter prospective study (the FIBROSTIC study). J Hepatol 2010;53:1013–1021.

65. Zarski JP, Sturm N, Guechot J, et al. Comparison of nine blood tests and transient elastography for liver fibrosis in chronic hepatitis C: the ANRS HCEP-23 study. J Hepatol 2012;56:55–62.

66. Castera L, Vergniol J, Foucher J, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343–350.

67. Ziol M, Handra-Luca A, Kettaneh A, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005;41:48–54.

68. Lupsor M, Badea R, Stefanescu H, et al. Analysis of histopathological changes that influence liver stiffness in chronic hepatitis C. Results from a cohort of 324 patients. J Gastrointest Liver Dis 2008;17:155–163.

69. Coco B, Oliveri F, Maina AM, et al. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. J Viral Hepat 2007;14:360–369.

70. Oliveri F, Coco B, Ciccorossi P, et al. Liver stiffness in the hepatitis B virus carrier: a non-invasive marker of liver disease influenced by the pattern of transaminases. World J Gastroenterol 2008;14:6154–6162.

71. Marcellin P, Ziol M, Bedossa P, et al. Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. Liver Int 2009;29:242–247.

72. Chan HL, Wong GL, Choi PC, et al. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. J Viral Hepat 2009;16:36–44.

73. Ganne-Carrie N, Ziol M, de Ledinghen V, et al. Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. Hepatology 2006;44:1511–1517.

74. Shaheen AA, Wan AF, Myers RP. FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy. Am J Gastroenterol 2007;102:2589–2600.

75. Talwalkar JA, Kurtz DM, Schoenleber SJ, et al. Ultrasound-based transient elastography for the detection of hepatic fibrosis: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2007;5:1214–1220.

76. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008;134:960–974.

77. Tsochatzis EA, Gurusamy KS, Ntaoula S, et al. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. J Hepatol 2011;54:650–659.

78. Friedrich-Rust M, Nierhoff J, Lupsor M, et al. Performance of acoustic radiation force impulse imaging for the staging of liver fibrosis: a pooled meta-analysis. J Viral Hepat 2011;19:e212–e219.

79. Huwart L, Sempoux C, Vicaut E, et al. Magnetic resonance elastography for the noninvasive staging of liver fibrosis. Gastroenterology 2008;135:32–40.

80. Martinez SM, Crespo G, Navasa M, et al. Noninvasive assessment of liver fibrosis. Hepatology 2011;53:325–335.

81. Sebastiani G, Vario A, Guido M, et al. Stepwise combination algorithms of non-invasive markers to diagnose significant fibrosis in chronic hepatitis C. J Hepatol 2006;44:686–693.

82. Sebastiani G, Halfon P, Castera L, et al. SAFE biopsy: a validated method for large-scale staging of liver fibrosis in chronic hepatitis C. Hepatology 2009;49:1821–1827.

83. Poynard T, Ingiliz P, Elkrief L, et al. Concordance in a world without a gold standard: a new non-invasive methodology for improving accuracy of fibrosis markers. PLoS ONE 2008;3:e3857.

84. Boursier J, de Ledinghen V, Zarski JP, et al. A new combination of blood test and Fibroscan for accurate non-invasive diagnosis of liver fibrosis stages in chronic hepatitis C. Am J Gastroenterol 2011;106:1255–1263.

85. Poynard T, de Ledinghen V, Zarski JP, et al. Relative performances of FibroTest, Fibroscan, and biopsy for the assessment of the stage of liver fibrosis in patients with chronic hepatitis C: a step toward the truth in the absence of a gold standard. J Hepatol 2012;56:541–548.

86. Castera L, Sebastiani G, Le Bail B, et al. Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C. J Hepatol 2010;52:191–198.

87. Boursier J, de Ledinghen V, Zarski JP, et al. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: new algorithms are more precise and entirely noninvasive. Hepatology 2012;55:58–67.

88. Castera L, Le Bail B, Roudot-Thoraval F, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. J Hepatol 2009;50:59–68.

89. Sebastiani G, Vario A, Guido M, et al. Sequential algorithms combining non-invasive markers and biopsy for the assessment of liver fibrosis in chronic hepatitis B. World J Gastroenterol 2007;13:525–531.

90. Wong GL, Wong VW, Choi PC, et al. Development of a non-invasive algorithm with transient elastography (Fibroscan) and serum test formula for advanced liver fibrosis in chronic hepatitis B. Aliment Pharmacol Ther 2010;31:1095–1103.

91. Kim BK, Han KH, Park JY, et al. A novel liver stiffness measurement-based prediction model for cirrhosis in hepatitis B patients. Liver Int 2010;30:1073–1081.

92. Lee HJ, Seo YS, Kim DJ, et al. Application of the HALF index obviates the need for liver biopsy in half of all patients with chronic hepatitis B. J Gastroenterol Hepatol 2011;26:987–995.

93. Maimone S, Calvaruso V, Pleguezuelo M, et al. An evaluation of transient elastography in the discrimination of HBeAg-negative disease from inactive hepatitis B carriers. J Viral Hepat 2009; 16:769–774.

94. Ngo Y, Benhamou Y, Thibault V, et al. An accurate definition of the status of inactive hepatitis B virus carrier by a combination of biomarkers (FibroTest-ActiTest) and viral load. PLoS One 2008;3:e2573.

95. Castera L, Bernard PH, Le Bail B, et al. Transient elastography and biomarkers for liver fibrosis assessment and follow-up of inactive hepatitis B carriers. Aliment Pharmacol Ther 2011;33: 455–465.

96. Noninvasive methods for the evaluation of hepatic fibrosis/cirrhosis: an update. Available at: http://www.has-sante.fr. Accessed August 2008.

97. Castera L, Bedossa P. How to assess liver fibrosis in chronic hepatitis C: serum markers or transient elastography vs liver biopsy? Liver Int 2011;31(Suppl 1):13–17.

98. Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 2009;360:1839–1850.

99. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet 2010;376:705–716.

100. Gane EJ, Roberts SK, Stedman CA, et al. Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial. Lancet 2010;376:1467–1475.

101. Lok AS, Gardiner DF, Lawitz E, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med 2012; 366:216–224.

102. Vigano M, Paggi S, Lampertico P, et al. Dual cut-off transient elastography to assess liver fibrosis in chronic hepatitis B: a cohort study with internal validation. Aliment Pharmacol Ther 2011;34:353–362.

103. Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002;122:1303–1313.

104. Shiratori Y, Imazeki F, Moriyama M, et al. Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. Ann Intern Med 2000; 132:517–524.

105. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology 2010;52:886–893.

106. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. Gastroenterology 2006;131:1743–1751.

107. Poynard T, Imbert-Bismut F, Ratziu V, et al. Biochemical markers of liver fibrosis in patients infected by hepatitis C virus: longitudinal validation in a randomized trial. J Viral Hepat 2002; 9:128–133.

108. Poynard T, McHutchison J, Manns M, et al. Biochemical surrogate markers of liver fibrosis and activity in a randomized trial of peginterferon alfa-2b and ribavirin. Hepatology 2003;38:481–492.

109. Fontana RJ, Bonkovsky HL, Naishadham D, et al. Serum fibrosis marker levels decrease after successful antiviral treatment in chronic hepatitis C patients with advanced fibrosis. Clin Gastroenterol Hepatol 2009;7:219–226.

110. Ogawa E, Furusyo N, Toyoda K, et al. The longitudinal quantitative assessment by transient elastography of chronic hepatitis C patients treated with pegylated interferon alpha-2b and ribavirin. Antiviral Res 2009;83:127–134.

111. Vergniol J, Foucher J, Castera L, et al. Changes of non-invasive markers and FibroScan values during HCV treatment. J Viral Hepat 2009;16:132–140.

112. Martinez SM, Fernandez-Varo G, Gonzalez P, et al. Assessment of liver fibrosis before and after antiviral therapy by different serum marker panels in patients with chronic hepatitis C. Aliment Pharmacol Ther 2011;33:138–148.

113. Hezode C, Castera L, Roudot-Thoraval F, et al. Liver stiffness diminishes with antiviral response in chronic hepatitis C. Aliment Pharmacol Ther 2011;34:656–663.

114. Poynard T, Zoulim F, Ratziu V, et al. Longitudinal assessment of histology surrogate markers (FibroTest-ActiTest) during lamivudine therapy in patients with chronic hepatitis B infection. Am J Gastroenterol 2005;100:1970–1980.

115. Poynard T, Ngo Y, Marcellin P, et al. Impact of adefovir dipivoxil on liver fibrosis and activity assessed with biochemical markers (FibroTest-ActiTest) in patients infected by hepatitis B virus. J Viral Hepat 2009;16:203–213.

116. Wong GL, Wong VW, Choi PC, et al. On-treatment monitoring of liver fibrosis with transient elastography in chronic hepatitis B patients. Antivir Ther 2011;16:165–172.

117. Fung J, Lai CL, Wong DK, et al. Significant changes in liver stiffness measurements in patients with chronic hepatitis B: 3-year follow-up study. J Viral Hepat 2011;18:e200–205.

118. Ogawa E, Furusyo N, Murata M, et al. Longitudinal assessment of liver stiffness by transient elastography for chronic hepatitis B patients treated with nucleoside analog. Hepatol Res 2011; 41:1178–1188.

119. Enomoto M, Mori M, Ogawa T, et al. Usefulness of transient elastography for assessment of liver fibrosis in chronic hepatitis B: regression of liver stiffness during entecavir therapy. Hepatol Res 2010;40:853–861.

120. Osakabe K, Ichino N, Nishikawa T, et al. Reduction of liver stiffness by antiviral therapy in chronic hepatitis B. J Gastroenterol 2011;46:1324–1334.

121. Lim SG, Cho SW, Lee YC, et al. Changes in liver stiffness measurement during antiviral therapy in patients with chronic hepatitis B. Hepatogastroenterology 2011;58:539–545.

122. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–1236.

123. Garcia-Tsao G, Friedman S, Iredale J, et al. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. Hepatology 2010;51:1445–1449.

124. Foucher J, Chanteloup E, Vergniol J, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006;55:403–408.

125. Carrion JA, Navasa M, Bosch J, et al. Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. Liver Transpl 2006;12:1791–1798.

126. Vizzutti F, Arena U, Romanelli RG, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology 2007;45:1290–1297.

127. Bureau C, Metivier S, Peron JM, et al. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. Aliment Pharmacol Ther 2008;27:1261–1268.

128. Lemoine M, Katsahian S, Ziol M, et al. Liver stiffness measurement as a predictive tool of clinically significant portal hypertension in patients with compensated hepatitis C virus or alcohol-related cirrhosis. Aliment Pharmacol Ther 2008;28:1102–1110.

129. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481–488.

130. Rigamonti C, Donato MF, Fraquelli M, et al. Transient elastography predicts fibrosis progression in patients with recurrent hepatitis C after liver transplantation. Gut 2008;57:821–827.

131. Carrion JA, Torres F, Crespo G, et al. Liver stiffness identifies two different patterns of fibrosis progression in patients with hepatitis C virus recurrence after liver transplantation. Hepatology 2010;51:23–34.

132. Castera L, Pinzani M, Bosch J. Noninvasive evaluation of portal hypertension using transient elastography. J Hepatol 2012;56:696–703.

133. Sebastiani G, Tempesta D, Fattovich G, et al. Prediction of oesophageal varices in hepatic cirrhosis by simple serum non-invasive markers: results of a multicenter, large-scale study. J Hepatol 2010;53:630–638.

134. Fontana RJ, Sanyal AJ, Ghany MG, et al. Factors that determine the development and progression of gastroesophageal varices in patients with chronic hepatitis C. Gastroenterology 2010;138:2321–2331, e1–2.

135. Kim BK, Han KH, Park JY, et al. A liver stiffness measurement-based, noninvasive prediction model for high-risk esophageal varices in B-viral liver cirrhosis. Am J Gastroenterol 2010;105:1382–1390.

136. Kim BK, Kim do Y, Han KH, et al. Risk assessment of esophageal variceal bleeding in B-viral liver cirrhosis by a liver stiffness measurement-based model. Am J Gastroenterol 2011;106:1654–1662, 1730.

137. Robic MA, Procopet B, Metivier S, et al. Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: a prospective study. J Hepatol 2011;55:1017–1024.

138. Bosch J. Soft technique, hard end-points. J Hepatol 2011;55:955–956.

139. Castera L. Liver stiffness and hepatocellular carcinoma: liaisons dangereuses? Hepatology 2009;49:1793–1794.

140. Masuzaki R, Tateishi R, Yoshida H, et al. Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. Hepatology 2009;49:1954–1961.

141. Fung J, Lai CL, Seto WK, et al. Prognostic significance of liver stiffness for hepatocellular carcinoma and mortality in HBeAg-negative chronic hepatitis B. J Viral Hepat 2011;18:738–744.

142. Jung KS, Kim SU, Ahn SH, et al. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). Hepatology 2011;53:885–894.

143. Vergniol J, Foucher J, Terrebonne E, et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. Gastroenterology 2011;140:1970–1979, e1–3.

144. Ngo Y, Munteanu M, Messous D, et al. A prospective analysis of the prognostic value of biomarkers (FibroTest) in patients with chronic hepatitis C. Clin Chem 2006;52:1887–1896.

145. Naveau S, Gaude G, Asnacios A, et al. Diagnostic and prognostic values of noninvasive biomarkers of fibrosis in patients with alcoholic liver disease. Hepatology 2009;49:97–105.

146. Mayo MJ, Parkes J, Adams-Huet B, et al. Prediction of clinical outcomes in primary biliary cirrhosis by serum enhanced liver fibrosis assay. Hepatology 2008;48:1549–1557.

147. Parkes J, Roderick P, Harris S, et al. Enhanced liver fibrosis test can predict clinical outcomes in patients with chronic liver disease. Gut 2010;59:1245–1251.

148. Nunes D, Fleming C, Offner G, et al. Noninvasive markers of liver fibrosis are highly predictive of liver-related death in a cohort of HCV-infected individuals with and without HIV infection. Am J Gastroenterol 2010;105:1346–1353.

149. Ghany MG, Lok AS, Everhart JE, et al. Predicting clinical and histologic outcomes based on standard laboratory tests in advanced chronic hepatitis C. Gastroenterology 2010;138:136–146.

150. Fontana RJ, Dienstag JL, Bonkovsky HL, et al. Serum fibrosis markers are associated with liver disease progression in non-responder patients with chronic hepatitis C. Gut 2010;59:1401–1409.

151. Pinzani M. Noninvasive methods for the assessment of liver fibrosis: a window open on the future? Hepatology 2011;54:1476–1477.

152. Castera L, Denis J, Babany G, et al. Evolving practices of non-invasive markers of liver fibrosis in patients with chronic hepatitis C in France: time for new guidelines? J Hepatol 2007;46:528–529.

153. Sebastiani G, Alberti A. Noninvasive fibrosis biomarkers reduce but not substitute the need for liver biopsy. World J Gastroenterol 2006;12:3682–3694.

154. Muller M, Gennisson JL, Deffieux T, et al. Quantitative viscoelasticity mapping of human liver using supersonic shear imaging: preliminary in vivo feasibility study. Ultrasound Med Biol 2009;35:219–229.

155. Bavu E, Gennisson JL, Couade M, et al. Noninvasive in vivo liver fibrosis evaluation using supersonic shear imaging: a clinical study on 113 hepatitis C virus patients. Ultrasound Med Biol 2011;37:1361–1373.

156. Nedredal GI, Yin M, McKenzie T, et al. Portal hypertension correlates with splenic stiffness as measured with MR elastography. J Magn Reson Imaging 2011;34:79–87.

157. Poynard T, Lebray P, Ingiliz P, et al. Prevalence of liver fibrosis and risk factors in a general population using non-invasive biomarkers (FibroTest). BMC Gastroenterol 2010;10:40.

158. Roulot D, Costes JL, Buyck JF, et al. Transient elastography as a screening tool for liver fibrosis and cirrhosis in a community-based population aged over 45 years. Gut 2011;60:977–984.

159. Castera L. Screening the general population for cirrhosis using transient elastography: finding a needle in a haystack? Gut 2011;60:883–884.
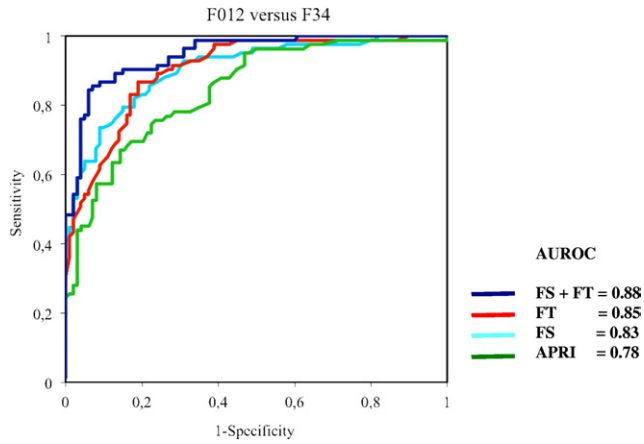
Supplementary Figure 1. ROC curves for FibroScan (FS), FibroTest (FT), and APRI and the combination of FibroScan and FibroTest for significant fibrosis (F0–F2 vs F3-F4). Adapted from Castera et al.[66]