REVIEW ARTICLE

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Use of Liver Imaging and Biopsy in Clinical Practice

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Liver biopsies are traditionally performed to determine the cause and stage of liver disease, as well as to inform treatment decisions and determine prognosis. In 2001, Bravo et al. observed that "liver biopsy is usually the most specific test to assess the nature and severity of liver diseases."[1] During the past 16 years, however, the clinical use of liver biopsies has undergone a profound transformation. Validated alternatives to liver biopsy have proliferated, spurred by concerns about the costs of biopsy and the risk of complications. Furthermore, research has brought a new understanding of the limitations of liver biopsy. In this review, we discuss the role of liver biopsy in the current era, as well as the accuracy of noninvasive evaluations and their use in clinical practice for determining the cause of liver disease and focal liver lesions and for detecting advanced fibrosis and cirrhosis.

Liver Biopsy

Procedure, Indications, and Interpretation

Liver biopsies are usually performed percutaneously but can instead be performed through a laparoscopic, transjugular, or endoscopic route.[2] The specific approach selected depends on chest-wall thickness (since the percutaneous route may be problematic in obese patients) and status with respect to thrombocytopenia or coagulopathy. A typical liver biopsy samples one fifty-thousandth of the liver volume.[1] Histologic assessment requires clinicopathological correlation. Pathologists systematically survey and report on the degree and pattern of inflammation, steatosis, and fibrosis, as well as other notable features such as cellular inclusions, and clinicians provide the clinical context that informs the histologic interpretation.

Most histologic features are not discrete but are part of a continuum. To facilitate comparisons across studies and to evaluate changes during therapeutic trials, pathologists developed categorical scoring systems to grade inflammation, steatosis, and fibrosis.[3] Though staging schema vary slightly according to the underlying disease, the system most often used for fibrosis staging in patients with viral hepatitis ranges from F0 to F4 as follows: no fibrosis (F0), portal fibrosis without septa (F1), portal fibrosis with few septa (F2), bridging septa between central and portal veins (F3), and cirrhosis (F4).[4] Liver biopsies are also used to determine or confirm the cause of the liver disease. The pattern of inflammation can aid in the diagnosis of autoimmune hepatitis (plasma-cell and lymphocytic infiltration in portal tracts and the connective tissue between portal tracts and septa), primary biliary cholangitis (periductular inflammation, or "florid-duct lesions"), and primary sclerosing cholangitis (periductular inflammation and fibrosis, or "onion skin"). Similarly, patterns of cellular proliferation help discern the cause of focal liver lesions.

LIMITATIONS

Much of the interest in noninvasive evaluation of liver disease comes from the risk of complications with liver biopsy and the technical limitations of the procedure. There are several limitations. First, sampling error is common, and many liver diseases do not affect the liver uniformly.[3,5-7] In a study of laparoscopic biopsy samples taken simultaneously from the right and left lobes in 124 patients with hepatitis C virus (HCV), the biopsy findings in 14.5% of the patients were interpreted as cirrhosis in one lobe but as F3 fibrosis in the other lobe.[7] In a sentinel study involving 51 patients with nonalcoholic fatty liver disease in whom two biopsy samples were obtained on the same day, 35% of the patients with F3 fibrosis in one sample had F0 or F1 fibrosis in the other.[6] Complicating matters further, both diagnostic accuracy and disease staging depend on specimen size. Small biopsy samples may be nondiagnostic or may not reveal cirrhosis.[8] Analyzing images of more than 27,000 "virtual" biopsy samples of variable length, Poynard and colleagues found that accuracy was maximized by assessing specimens that were at least 3 cm in length.[9] Such large specimens are rarely obtained in practice. In a clinical trial involving 513 patients, 36% of biopsy samples were less than 1.5 cm in length.[5] Similarly, a single biopsy sample has a negative predictive value no greater than 74% for the presence of steatohepatitis in patients with nonalcoholic fatty liver disease.[6]

Second, biopsy interpretation is subjective. Even among the pathologists involved with the development of staging criteria, the interobserver and intraobserver concordance for fibrosis stage was 78% and 75%, respectively, but concordance for inflammatory activity and fat burden was less than 50%.[3]

Third, biopsies are associated with complications, including pain (in 30 to 50% of patients),[10] serious bleeding (0.6%),[11] injury to other organs (0.08%),[12] and in rare cases, death (up to 0.1%).[2] For these reasons, many patients refuse to undergo liver biopsy.[13]

Fourth, biopsies are costly. Each biopsy involves an expert gastroenterologist or radiologist and a pathologist and must be performed in a facility with adequate periprocedural monitoring by nurses. Consequently, the average direct cost of a percutaneous liver biopsy is $1,558 (in 2016 U.S. dollars),[14,15] which rises substantially for biopsies performed by the transjugular route. There are also unmeasured indirect costs, including lost work productivity for both patients and their caretakers.

NONINVASIVE FIBROSIS ASSESSMENT

The staging of liver disease is essential for risk stratification with respect to complications and death.[16-18] Patients with advanced fibrosis (F3 or F4) have the highest risk of portal hypertensive complications such as variceal hemorrhage, liver failure, and (with specific exceptions) liver cancer.[5,16-19] Unfortunately, the medical history and physical examination do not provide a sufficient basis for detecting advanced fibrosis.[20,21] Classic signs — jaundice, ascites, splenomegaly, and encephalopathy — are absent in early cirrhosis. Similarly, patients with cirrhosis may have normal results of liver chemical profiles.[21]

Several noninvasive methods for the assessment of liver fibrosis have been developed and are widely used. Unlike a biopsy, these methods cannot differentiate the stages of fibrosis but are accurate in discriminating early from advanced fibrosis[22] (Fig. 1 and Table 1).

INDIRECT AND DIRECT SEROLOGIC MARKERS

Indirect serologic markers of fibrosis generally reflect the secondary effects of liver injury. For example, among patients with chronic liver disease due to viral hepatitis or other nonalcoholic causes, aspartate aminotransferase levels exceed alanine aminotransferase levels when cirrhosis develops, probably as a result of decreased clearance of aspartate aminotransferase and decreased production of alanine aminotransferase.[37] Thus, the aspartate aminotransferase level and the ratio of aspartate aminotransferase to alanine aminotransferase are included in many indirect indexes of liver fibrosis[25,28,37,38] (Fig. 1). Thrombocytopenia, however, is the earliest indicator of cirrhosis among routine blood tests, capturing the results of multiple processes associated with advanced liver disease, including, at least, diminished liver function (thrombopoietin underproduction) and portal hypertension (splenic sequestration).[21,39]

Several risk scores use the presence of thrombocytopenia to predict advanced fibrosis or cirrhosis (Fig. 1). Other indexes incorporate proteins that are produced less abundantly by the injured liver (e.g., clotting factors, haptoglobin,

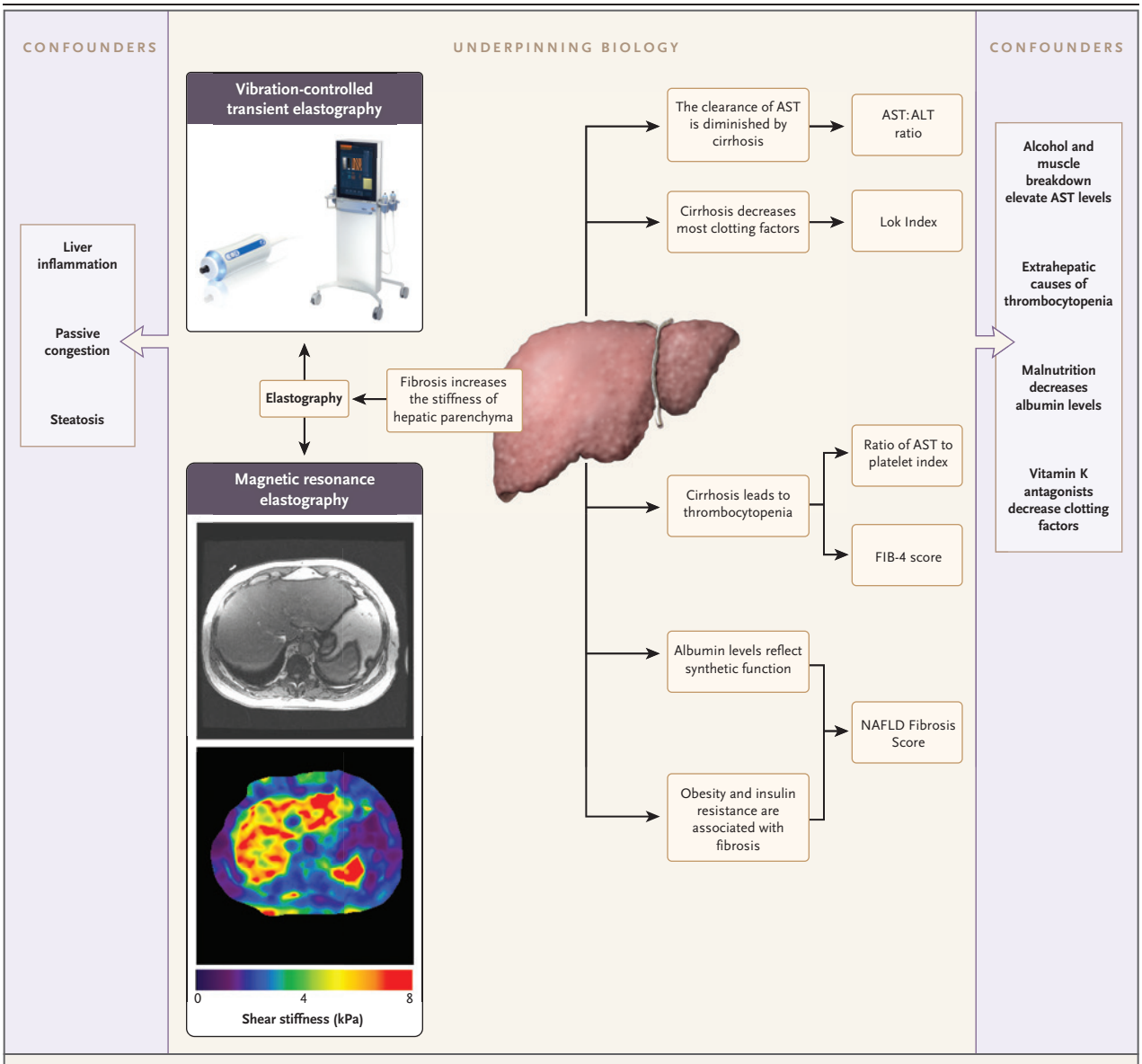


Figure 1. Noninvasive Assessment of Liver Fibrosis.

Imaging techniques and biomarker measurements used to assess the risk of cirrhosis are shown, including the biologic rationale for their use and factors that can confound the results. The ratio of aspartate aminotransferase (AST) to platelet index is calculated as follows: (AST ÷ upper limit of the normal range) ÷ platelet count. The Fibrosis-4 (FIB-4) score is calculated as (age × AST) ÷ (platelet count × √ALT). The Lok Index is calculated as follows: log odds = –5.56 – 0.0089 × platelet + 1.26 × AST:ALT ratio + 5.27 × INR. The NAFLD Fibrosis Score is calculated as follows: –1.675 + 0.037 × age + 0.094 × BMI + 1.13 × IR or diabetes (yes = 1, no = 0) + 0.99 × AST:ALT ratio – 0.013 × platelet count – 0.66 × albumin. ALT denotes alanine aminotransferase, BMI body-mass index (the weight in kilograms divided by the square of the height in meters), INR international normalized ratio, IR insulin resistance, and NAFLD nonalcoholic fatty liver disease.

and apolipoprotein A).[38,40,41] The NAFLD [Nonalcoholic Fatty Liver Disease] Fibrosis Score[31] also includes body-mass index and the status with respect to diabetes or impaired fasting glucose, markers that correlate with advanced fibrosis in nonalcoholic fatty liver disease. Indexes based on routinely available laboratory tests often do not incur added costs and can be used in resource-limited settings.[42] However, there are pitfalls — namely, a false conclusion that thrombocytopenia is due to cirrhosis rather than hematologic causes or that increased aspartate amino-

Table 1. Noninvasive Risk Stratification for Various Liver Diseases.*

Test	Study	Cutoffs for Advanced Fibrosis	Sensitivity	Specificity	Negative Likelihood Ratio	Positive Likelihood Ratio	Probability of Advanced Fibrosis (F3 or F4) after a Negative vs. a Positive Test†
			%				%
Hepatitis C							
AST:platelet ratio index	Lin et al.[25]	>1.0	61	64	0.61	1.7	38 vs. 63
		>1.5	50	87	0.57	3.8	36 vs. 79
FIB-4 score	Vallet-Pichard et al.[26]	<1.45	74	80	0.32	3.7	24 vs. 80
		>3.25	38	82	0.76	2.1	43 vs. 68
VCTE	Castéra et al.[27]	>9.5	73	91	0.30	8.1	23 vs. 89
Hepatitis B							
FIB-4 score	Kim et al.[28]	<1.0	91	73	0.12	3.4	11 vs. 77
		>2.65	39	98	0.63	18.3	39 vs. 95
VCTE	Marcellin et al.[29]	<8.1	86	85	0.16	5.7	14 vs. 85
		>10.5	72	95	0.29	14.4	23 vs. 94
NAFLD							
FIB-4 score	Shah et al.[30]	<1.3	74	71	0.4	2.6	27 vs. 72
		>2.67	33	98	0.7	16.5	41 vs. 94
NAFLD Fibrosis Score	Angulo et al.[31]	<–1.455	77	71	0.3	2.7	24 vs. 73
		>0.676	43	96	0.6	10.8	37 vs. 91
VCTE	Tapper et al.[32]	>9.9	95	77	0.07	4.1	6 vs. 81
MRE	Loomba et al.[33]	>3.64	86	91	0.2	9.6	13 vs. 91
Cholestatic liver diseases							
VCTE for primary biliary cholangitis	Corpechot et al.[34]	>10.7	90	93	0.11	12.9	10 vs. 93
VCTE for primary sclerosing cholangitis	Corpechot et al.[35]	>9.6	93	83	0	5.5	8 vs. 85
All liver diseases							
MRE	Singh et al.[36]	>4.11	85	85	0.2	5.7	15 vs. 85

* The specific calculations of kilopascals differ between elastographic techniques. Thus, the kilopascal calculation determined by means of vibration-controlled transient elastography (VCTE) is not equivalent to the calculation determined by means of magnetic resonance elastography (MRE).[23] Some tests have two cutoffs with indeterminate ranges. Cutoffs and test characteristics for assessment of the risk of cirrhosis (F4) are provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. Cutoffs that indicate a need for antiviral therapy in patients with and those without elevated alanine aminotransferase levels may vary.[24] AST denotes aspartate aminotransferase, FIB-4 Fibrosis-4, and NAFLD nonalcoholic fatty liver disease.

† We applied a Bayesian calculation of post-test probability for each index, assuming a 50% pretest likelihood of advanced fibrosis (F3 or F4) for the purpose of illustration. F3 denotes bridging septa between central and portal veins, and F4 cirrhosis.

transferase levels indicate cirrhosis rather than alcohol abuse or extrahepatic factors (e.g., muscle injury). Finally, some indirect indexes have two cutoffs (to maximize sensitivity or specificity), which create gray zones of indeterminate values (Table 1). A clinical strategy for managing this possibility is discussed below and in Figure 2.

Direct measures of fibrosis assess circulating evidence of fibrogenesis, fibrinolysis, or both. Examples include α_2-macroglobulin, hyaluronic acid, N-terminal propeptide of type III procollagen, and tissue inhibitor of metalloproteinase 1. Proprietary algorithms for these assays are commercially available as FibroTest (BioPredictive) (known as FibroSure [LabCorp] in the United States), FibroMeter (Echosens), HepaScore (Quest

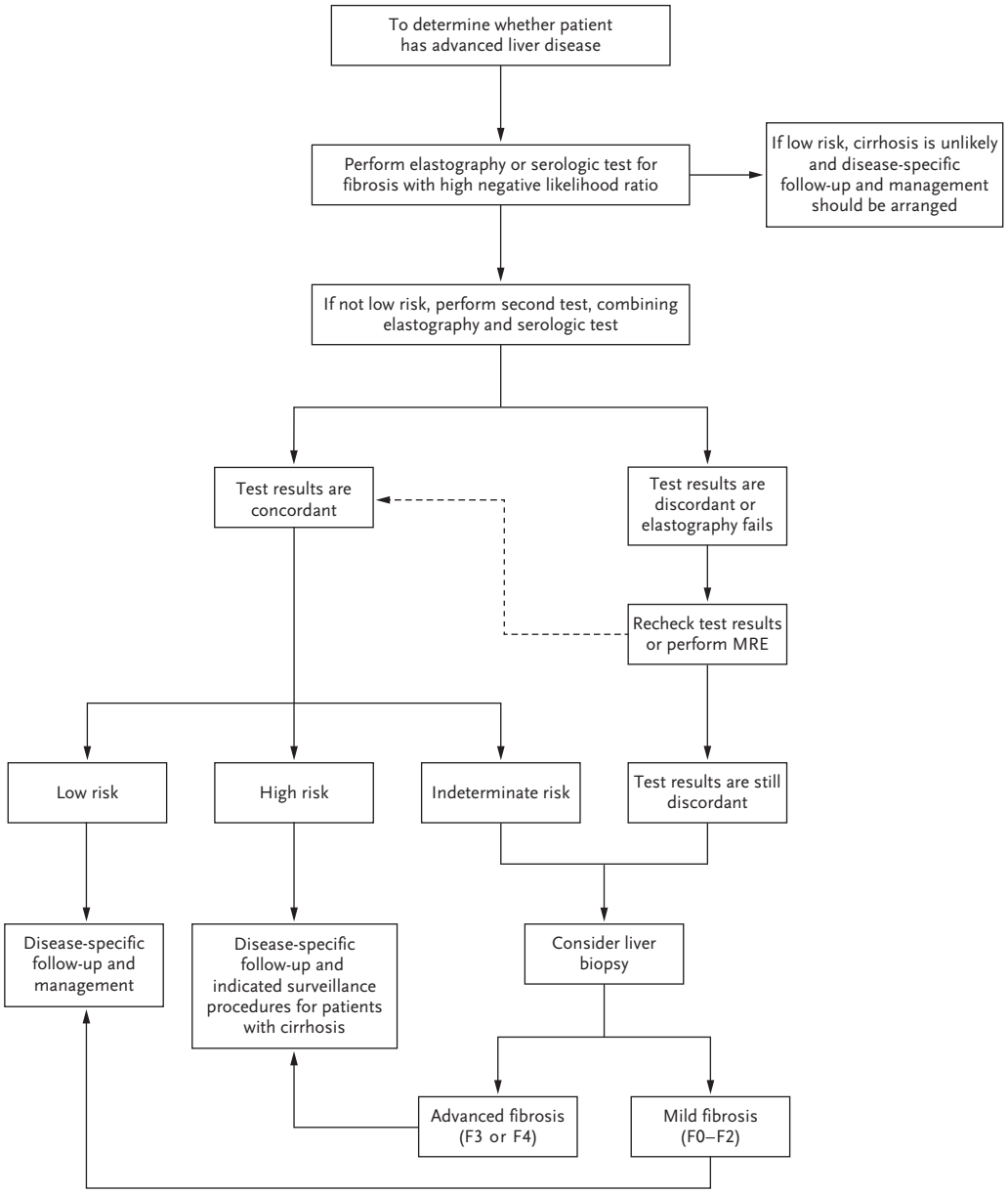


Figure 2. Implementing a Noninvasive Approach to Clinical Staging of Liver Disease.

A strategic approach to noninvasive evaluation of liver fibrosis involves seeking concordance between serologic and elastographic tests. Patients who do not have cirrhosis need only disease-specific treatment (e.g., treatment of hepatitis C). For patients with cirrhosis, surveillance by means of periodic ultrasonography, given the risk of liver cancer, and endoscopy, given the risk of varices, is indicated. This strategy has been evaluated most extensively in patients with hepatitis C and increasingly in patients with nonalcoholic fatty liver disease.[27,32,43,44] MRE denotes magnetic resonance elastography.

Diagnostics), FIBROSpect (Prometheus Laboratories), and the Enhanced Liver Fibrosis Score (Siemens Healthcare Diagnostics). These tests can have false positive results in patients with chronic inflammatory conditions, chronic renal disease, or extrahepatic causes of abnormal fibrogenesis. The assays are also costlier and less widely available than indirect measures.

IMAGING TESTS

Standard imaging tests can suggest the possibility of cirrhosis. Morphologic characteristics that may indicate the presence of cirrhosis include liver nodularity and an enlarged caudate lobe relative to the right lobe. A fibrotic liver may also appear "brighter" on ultrasonography than a nonfibrotic liver. Commonly available imaging techniques are not reliably accurate for diagnosing cirrhosis or ruling it out (e.g., ultrasonographic evaluation of the liver contour has a sensitivity and specificity for cirrhosis of 13 to 88% and 78 to 95%, respectively).[45] The sensitivity of ultrasound-based diagnoses of cirrhosis can be increased by accounting for markers of portal hypertension (e.g., increased spleen size and portal-vein diameter) or the presence of abdominal varices or ascites, but these signs are absent in early cirrhosis. Although the diagnostic test characteristics of conventional computed tomography (CT) or magnetic resonance imaging (MRI) are better (sensitivity, 48.5% to 87.9%; specificity, 55.2% to 100%), the interrater reliability of these measures among radiologists can be inadequate (kappa score, 0.12 to 0.74).[46]

ELASTOGRAPHY

Liver elastography provides more accurate assessments of advanced fibrosis than imaging tests do. There are multiple approaches to the use of this technique: vibration-controlled transient elastography, magnetic resonance elastography, acoustic radiation force–based elastography, and shear wave elastography. Of these approaches, vibration-controlled transient elastography is the most widely used worldwide. In each case, a shear wave is introduced into the liver across the chest wall by means of a probe, and wave propagation is then evaluated by a receiver in the probe, except that with magnetic resonance elastography, the wave is interpreted by the magnetic resonance scanner. The wave's velocity is then converted into a measurement of liver stiffness, expressed in kilopascals, which correlates with the fibrosis burden. Liver stiffness is a continuous measure that does not stage fibrosis. Cutoffs suggestive of advanced fibrosis have been proposed but vary substantially according to the technique used (i.e., kilopascal units for vibration-controlled transient elastography and for magnetic resonance elastography are not interchangeable) and the underlying liver disease; cutoffs also differ among studies of the same disease (Table 1). The use of any cutoff for liver stiffness therefore carries a degree of uncertainty.[26]

In general, elastography offers excellent negative likelihood ratios for advanced fibrosis but much poorer positive likelihood ratios. Other variables such as passive congestion (i.e., heart failure), postprandial hyperemia (with fasting required for 2 to 3 hours before testing), severe inflammation,[47] and steatosis can increase liver stiffness.[43] The technical failure rate of vibration-controlled transient elastography and the accuracy of liver-stiffness measurements are affected by obesity, because obesity increases the distance between the receiver and the liver.[32] This is particularly relevant for patients with nonalcoholic fatty liver disease.[32] Newer probes may have improved the performance of vibration-controlled transient elastography in obese patients[48]; however, patients in whom vibration-controlled transient elastography has failed because of severe obesity may benefit from magnetic resonance elastography. The two techniques are equally able to distinguish between advanced and nonadvanced fibrosis[49]; however, magnetic resonance elastography has a higher success rate among patients with severe obesity.[50]

Confounders of magnetic resonance elastography include inflammation, passive congestion, and a high hepatic iron burden.[51] Though relatively limited availability and cost prohibit widespread use, magnetic resonance elastography complements vibration-controlled transient elastography, playing a critical role in difficult cases. Biopsy is still available when both tests fail.[52]

Vibration-controlled transient elastography and magnetic resonance elastography provide additional information in patients with nonalcoholic fatty liver disease. The same machine can be used to determine whether steatosis is present. Vibration-controlled transient elastography with controlled attenuation parameter[53] and calculation of the proton-density fat fraction or spectros-

copy during MRI[49] are superior to ultrasonography for the detection of hepatosteatosis.

STRATEGIES FOR NONINVASIVE RISK STRATIFICATION

Risk assessment has shifted from fibrosis staging to the dichotomization of fibrosis as advanced or not advanced.[16,17,32] The goal is thus to categorize patients as having a low, an indeterminate, or a high likelihood of advanced fibrosis. Strategies that reserve biopsy for indeterminate results reduce the number of biopsies needed to accurately risk-stratify patients by more than 70%, as compared with biopsy-first approaches.[14,54] To incorporate noninvasive indexes into practice, the simplest strategy is to begin with a test that has a high negative likelihood ratio in order to rule out high-risk cases. Table 1 reviews the test characteristics of common, nonproprietary fibrosis risk scores and elastographic techniques. Serologic tests are readily available, but clinicians need to know that 28% of patients with nonalcoholic fatty liver disease, for example, are classified as having an indeterminate risk on the basis of both the Fibrosis-4 (FIB-4) score[30] and the NAFLD Fibrosis Score.[31] In addition, the positive likelihood ratio of noninvasive tests for fibrosis can be low. A useful strategy is to order two tests and seek concordant results. To this end, clinicians should order both a serologic test and an imaging or elastographic test during a single clinic visit,[15,40,43,54] so that patients can be assigned to one of three risk strata: concordant low risk, concordant high risk, or discordant or indeterminate results.[43,44] Approximately 21% of patients will have discordant or indeterminate results.[27] For these patients, the choice is to repeat the tests or perform a liver biopsy, depending on how the results might change management (Fig. 2). The results of each test can vary slightly on different days, and when tests are repeated at a follow-up visit, concordance is achieved — precluding the need for a biopsy — in as many as 70% of patients with discordant results.[32]

WHEN TO USE NONINVASIVE TESTS

Noninvasive assessments of liver fibrosis can serve many purposes in the management of liver diseases. First, noninvasive assessments can be used to determine whether patients with mild abnormalities in liver chemical values should be referred to liver specialists. This is particularly relevant because of the epidemic of obesity and nonalcoholic fatty liver disease.[31,55] Serologic tests — namely, the NAFLD Fibrosis Score and FIB-4 — provide cost-effective, efficient risk stratification, especially when performed in the primary care clinic to identify patients who have advanced fibrosis or indeterminate scores, warranting referral to a specialist.[14,15]

Second, the likelihood of advanced fibrosis can be used to guide treatment decisions (e.g., in patients with chronic hepatitis B virus [HBV] infection and mildly elevated alanine aminotransferase levels).[24,56] Elevated values for liver stiffness in patients with HBV infection would indicate the need for antiviral therapy, and liver biopsy would not be necessary.[24] Similarly, some insurers require the results of noninvasive tests for prioritizing anti-HCV therapy given the high cost of the direct-acting antiviral drugs.

Third, noninvasive tests can predict which patients are at risk for adverse outcomes, including liver cancer, complications of portal hypertension, and death, with areas under the receiver-operating-characteristic curve of 0.80 or higher.[40,41] The higher the value, the more likely that a patient with any kind of liver disease will be at risk for disease-related complications and death.[34,35,40] For example, though a liver stiffness of 12.5 kPa may be associated with cirrhosis, values exceeding 20 kPa and those exceeding 50 kPa are incrementally more predictive of adverse outcomes.[40,41] Indeed, patients with platelet counts higher than 150,000 per cubic millimeter and liver stiffness below 20 kPa can forgo screening for esophageal varices because of the low risk of associated complications.[57] Although liver stiffness is likely to decrease with disease resolution (e.g., HCV eradication), studies are ongoing to determine whether such changes suggest reduced long-term risks.

NONINVASIVE DIAGNOSIS OF LIVER DISEASES

Roughly 8% of persons in the United States have elevated liver enzyme levels.[58] The medical history in conjunction with a focused serologic and radiologic evaluation is sufficient for diagnosis of liver disease in most instances.[59] The most

Table 2. Undifferentiated Liver Disease.

Disease	Noninvasive Test*	Prevalence†	
		Among Patients with Liver Enzyme Abnormalities (Study)‡	Among Patients Undergoing Biopsy after Negative Preliminary Evaluation
		percent	
NAFLD	Ultrasonography	41	75.7
Alcoholic liver disease	History	13.5	1.9
Hepatitis C	Hepatitis C antibody, confirmed with PCR	7.0	0
Drug-induced liver injury	History — diagnosis by exclusion	4.4 (Van Ness and Diehl[65])	4.7
Hemochromatosis	Transferrin saturation >45%, confirmed with genotyping for hemochromatosis	2.8 (Van Ness and Diehl [65])	0.5
Autoimmune hepatitis	Antinuclear antibody, anti–smooth-muscle antibody, IgG levels	1.8 (Adams et al.[66])	1.8
Hepatitis B	Hepatitis B surface antigen with PCR	0.96	0
Primary biliary cholangitis	Antimitochondrial antibody	0.2	1.2
Primary sclerosing cholangitis	MRCP	0.2	1.1
Wilson's disease	Ceruloplasmin <20 mg/dl, confirmed with urine copper evaluation	0.16 (Tapper et al.[67])	0
Alpha-1 antitrypsin deficiency	Alpha-1 antitrypsin level <80 mg/dl and confirmatory phenotype (e.g., PiZZ)	0.16 (Tapper et al.[68])	0

* MRCP denotes magnetic resonance cholangiopancreatography, PCR polymerase chain reaction, and PiZZ proteinase inhibitor phenotype.
† Data on prevalence are from population studies in the United Kingdom[55] and the United States[58] unless otherwise indicated. The proportion of diseases after biopsy in patients who had undergone serologic and radiologic evaluation was pooled from the three applicable studies.[62-64] The prevalences of other conditions in biopsy studies were 5.6% for normal liver, 1.1% for granulomatous diseases, 0.4% for secondary biliary cirrhosis, and 0.2% each for amyloidosis, glycogen storage disease, and porphyria cutanea tarda.
‡ NAFLD is defined in epidemiologic studies by the presence of steatosis on ultrasonography, which can be insensitive.

common underlying liver diseases are nonalcoholic fatty liver disease,[55,60] alcoholic liver disease,[55,58,60,61] and viral hepatitis.[58] In Table 2, we pooled data on the proportion of specific liver diseases accounting for elevated liver enzyme levels from prospective studies of unselected patients in the third National Health and Nutrition Examination Survey (NHANES III) and a primary care population in the United Kingdom (supplemented with data from other sources for estimates of rare diseases not tested in NHANES).[55,58] The most important determinant of the yield of noninvasive testing is the sensitivity of the medical history for alcoholic liver disease and of imaging for hepatosteatosis, because there are no serologic tests for the diagnosis of these conditions. After excluding patients with these conditions from further evaluation, the pretest probability of testable diseases will rise. When we pooled the three prospective studies that evaluated the usefulness of liver biopsy in patients with unknown diagnoses after preliminary evaluation, the ultimate diagnosis was nonalcoholic fatty liver disease or alcoholic liver disease in 77% of cases (Table 2).[62-64] For patients suspected to have nonalcoholic fatty liver disease because of underlying metabolic syndrome or obesity and nondiagnostic ultrasound results, vibration-controlled transient elastography with controlled attenuation parameter or MRI techniques may confirm the presence of hepatosteatosis.[49,53]

Liver biopsy, however, continues to play a role in the management of nonalcoholic fatty liver disease. Despite poor interobserver concordance,[3] only a biopsy can differentiate simple steatosis from nonalcoholic steatohepatitis. Circulating markers of inflammatory activity such as cytokeratin 18 and plasminogen activator inhibitor 1 appear to be promising,[69,70] but neither is validated for clinical practice. Currently, no drugs have been approved by the Food and Drug Ad-

ministration (FDA) for nonalcoholic fatty liver disease. Given the lack of an established surrogate for clinical outcomes in patients with nonalcoholic fatty liver disease, the FDA requires evidence of histologic improvement and therefore the need for paired biopsies in clinical trials. Drug development for nonalcoholic fatty liver disease is hindered by cost and by the tendency for patients to decline multiple biopsies.[13] Hepatologists have advocated the use of surrogate measures (e.g., vibration-controlled transient elastography or magnetic resonance elastography), but histologic assessment is still required for clinical-trial end points.[71]

Biopsy remains important for the diagnosis of some liver diseases — notably, autoimmune hepatitis, small-duct primary sclerosing cholangitis, and antimitochondrial antibody–negative primary biliary cholangitis — and for treatment decisions in some cases of chronic HBV infection. Finally, in rare cases, biopsy is necessary to diagnose infiltrative diseases such as amyloidosis, lymphoma, and granulomatous hepatitis.

MANAGEMENT OF SOLID LIVER LESIONS

Multiphasic, contrast-enhanced, cross-sectional imaging (CT and MRI) can be used to discern the cause of focal liver lesions on the basis of their vascular and biliary physiological features in relation to the timing of images obtained after the administration of contrast material. Biopsy is now rarely needed to distinguish benign from malignant lesions.

Hepatocellular carcinoma is the most common primary liver cancer.[72] Biopsy of hepatocellular carcinoma is associated with risks, including tumor seeding (in 3% of cases), potentially fatal bleeding (1 to 2%), and, owing to sampling error, a low negative predictive value (14%).[73,74] To avoid these complications, candidacy for transplantation, which is a major method of treatment for hepatocellular carcinoma, is mostly based on a radiologic diagnosis. However, a 2003–2005 study involving 789 patients who underwent liver transplantation for hepatocellular carcinoma showed that 20% of the patients had benign nodules.[75] Diagnostic criteria for hepatocellular carcinoma have since been refined on the basis of the timing of images obtained after intravenous injection of contrast material (Fig. 3). The time required for intravenous contrast material to circulate into the arteries and, ultimately, the portal venous system is well known. Images can thus be obtained during the expected arterial and portal–venous phases of contrast circulation. In contrast to normal liver, which receives most (approximately 80%) of its blood from the portal vein, hepatocellular carcinoma receives blood primarily from the hepatic artery. Accordingly, it receives a contrast load (indicated by hyperintensity) during the arterial phase, with washout, or relative hypointensity, during the portal–venous phase (when the normal liver appears brighter). Use of these findings as diagnostic criteria for hepatocellular carcinoma has a sensitivity of 74 to 80% and a specificity of 89 to 97%.[72] Although imaging is less accurate for the diagnosis of cholangiocarcinoma, biopsy is considered unnecessary for patients with characteristic imaging features (Table 3).[77] If uncertainty remains after imaging, small lesions can be monitored by means of serial imaging in centers where decisions are made at a multidisciplinary tumor conference.[78]

Given the limitations of biopsy, as well as innovations in imaging and systems of care, primary liver cancers are most often diagnosed on the basis of imaging studies alone in clinical practice. Histologic confirmation of the diagnosis is thought to be most useful when imaging is inconclusive. There are two drawbacks of this practice. First, the systematic avoidance of biopsy for the diagnosis of hepatocellular carcinoma may have slowed progress in understanding the biologic features of these tumors and in developing targeted therapies for patients with advanced hepatocellular carcinoma. Second, as noted above, some patients may have benign tumors.[75] Although the use of biopsy has been reduced in the management of liver tumors, future research may point toward a larger role for biopsy.

ROLE OF LIVER BIOPSY IN CURRENT PRACTICE

Multiple forces have radically changed the role of liver biopsy in the management of liver diseases. First, noninvasive alternatives have been shown to be reliable in detecting advanced fibrosis or cirrhosis and in diagnosing many liver dis-

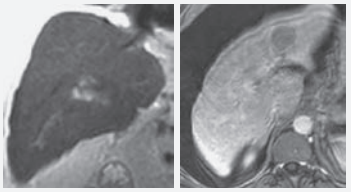
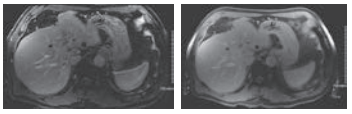
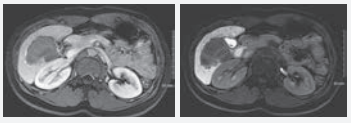
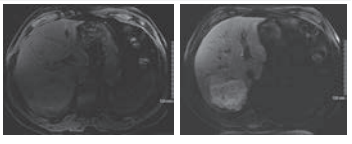
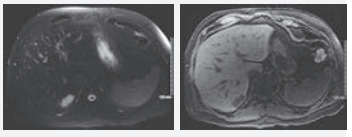
Lesion	Classic Biology	Diagnostic Test	Features	Image
				Panel A / Panel B
Hepatocellular carcinoma	Receives blood supply primarily from the hepatic artery (in contrast to normal liver, which receives most blood from the portal vein)	Multiphasic, contrast-enhanced, cross-sectional imaging (CT or MRI)	Increased contrast enhancement in arterial phase (Panel A), contrast washout during portal venous phase (Panel B), peripheral rim enhancement	
Cholangiocarcinoma	Receives blood from both hepatic artery and portal vein; has an associated extensive desmoplastic reaction	Multiphasic, contrast-enhanced, cross-sectional imaging (CT or MRI)	Progressive contrast enhancement in both arterial and venous phases; early (Panel A) and late (Panel B) venous phases	
Hepatocellular adenoma (HCA)	Receives blood supply primarily from the hepatic artery; lacks bile ducts	Multiphasic MRI with contrast agent that is secreted into bile	Early arterial hyperenhancement, isointense portal venous phase (Panel A), minimal uptake of biliary-specific contrast agents in delayed phases (Panel B)	
Focal nodular hyperplasia (FNH)	Has a central scar (unlike HCA) comprising fat and fibrous tissue	Multiphasic MRI with contrast agent that is readily taken up by hepatocytes; highlights difference between HCA and FNH	Diffuse enhancement in arterial phase, isointense signal in T_1-weighted phase (Panel A), central scar in T_2-weighted phase, with enhancement in late phase (Panel B)	
Hemangioma	Septate clusters of vascular endothelium are lined with hepatic arterial blood supply	Multiphasic MRI; intensity of contrast agent is the same as in the artery	Typically hypointense on T_1-weighted images and hyperintense on T_2-weighted images (Panel A), with peripheral nodular contrast enhancement and centripetal fill-in (Panel B)	

Figure 3. Radiologic Characteristics of Common Liver Lesions.

Grazioli et al.[76] have reported on the differential diagnosis of hepatocellular adenoma and focal nodular hyperplasia.

eases. Long-term clinical outcomes can be predicted by means of noninvasive tests that can accurately differentiate mild from advanced fibrosis.[5,16-18] Furthermore, noninvasive tests are safer and cheaper than biopsy, and they can be repeated over time to monitor disease progression.

Second, many indications for liver biopsy are disappearing. This is most evident in the management of hepatitis C. Until recently, the available therapies were interferon-based, required injections, and had numerous adverse effects and limited efficacy. Biopsy was a means of protecting patients with mild fibrosis from the harms of therapy. Current therapies with direct-acting antiviral drugs are administered orally, have few adverse effects, and can result in a virologic cure in 95% or more of patients, including those with cirrhosis.[79] Consequently, guidelines recommend treatment for all patients with hepatitis C.[80]

CONCLUSIONS

Noninvasive tests have not replaced liver biopsy but have sharply reduced the need for it. This shift has greatly improved our ability to care for patients with liver diseases. However, the limitations of these noninvasive tests must be recognized. Liver biopsy will continue to have a role in diagnosing some liver diseases, resolving indeterminate stages of fibrosis, and addressing specific research questions.

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