Use of FibroScan for Noninvasive Assessments Of Liver Disease

Faculty

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Introduction

The prevalence of chronic liver diseases continues to rise worldwide. The obesity epidemic has led to significant rates of nonalcoholic fatty liver disease (NAFLD), affecting approximately 27% to 34% of individuals in the United States; furthermore, 6 million are expected to have progressed to nonalcoholic steatohepatitis (NASH), and roughly 600,000 have developed NASH-related cirrhosis.[1] Moreover, between 3 and 4 million individuals in the United States have chronic hepatitis C virus (HCV) infections and many of these individuals are unaware of their serostatus.[2] In August 2012, the Centers for Disease Control and Prevention recommended that all baby boomers, a high-risk population of individuals born between 1946 and 1964, undergo HCV testing at least once in their lifetime.[3] In June 2013, the US Preventive Services Task Force made a similar recommendation.[4] As a result, the number of individuals diagnosed with HCV has increased considerably.[3,4]

For patients with chronic liver disease, the early identification of liver fibrosis is critical, particularly for those with cirrhosis who are more likely to develop hepatocellular carcinoma (HCC).[5] Clinical guidelines recommend that cirrhotic patients undergo an ultrasound liver examination every 6 months.[5] Of concern, the annual incidence of HCC between 2001 and 2010 rose from 2.7 to 7.7 cases per 100,000 population, causing 5.5 deaths per 100,000 population.[6] The most common cause of HCC is infection, typically from viral hepatitis, followed by alcoholic liver disease and NAFLD.[7]

Liver biopsy has long been the gold standard to stage liver fibrosis, but it has well-known downsides. It is a costly, invasive procedure that requires patients to miss at least 1 day of work and to avoid strenuous activities for several days thereafter (this has a greater effect on individuals with physically demanding jobs). Biopsies also can be painful and carry a risk for bleeding.[8] Additionally, the accuracy of biopsy results depends on the size of the sample and the pathologist reading it—sampling errors occur in 25% to 30% of liver biopsies.[8]

Due to the increasing rates of liver diseases and the shortcomings of biopsy, alternative diagnostic procedures have been investigated. This article will discuss recent developments in the evaluation of liver fibrosis, including the FibroScan® 502 Touch (Echosens, Sandhill Scientific), which received 510(k) clearance from the FDA in April 2013.

Alternative Diagnostics for Liver Fibrosis

As previously mentioned, several noninvasive tests for staging liver disease have been developed. One such option involves serum biomarker tests that measure variations in biomarkers caused by changes in liver stiffness. In a recent study, researchers compared the diagnostic accuracy of several liver-staging blood tests with that of liver biopsy and concluded that many were "moderately useful" for identifying fibrosis and cirrhosis.[9] The most useful tools were FibroTest™ (LabCorp), FibroIndex (Janssen), simple platelet counts, aspartate aminotransferase/platelet ratio index (APRI), and the Forns Index.[9] Studies have shown that these blood tests work well for staging patients with zero or minimal fibrosis as well as those who have advanced fibrosis or cirrhosis, but they are less helpful for assessing mid-range liver disease or for tracking fibrosis.[8,9]

Another method that clinicians can use to stage liver disease is measuring liver stiffness through transient elastography. This includes ultrasound elasticity imaging and magnetic resonance elasticity imaging. Although these new imaging techniques have a high degree of accuracy for measuring liver stiffness, they are expensive and require sending a patient for scanning at a separate facility, which can delay diagnosis.[9]

FibroScan: A Novel, Noninvasive Technique

FibroScan is a noninvasive test that assesses liver stiffness by employing vibration-controlled transient elastography (VCTE™) to emit a shear wave through the liver and measure its velocity via ultrasound.[8] Although this technology was approved for marketing in the United States in April 2013, it has been available in Europe since 2003, in China since 2008, and in Japan since 2011. It is easy to administer at the point of care, takes only 5 to 7 minutes to conduct, and results are available within 10 minutes. FibroScan is not painful, does not require sedation, and evaluates 100 times more liver volume than biopsy.[8,10]

During the procedure, clinicians induce a 50-Hz shear wave into the liver from a small mechanical actuator on the end of an ultrasound probe during patient expiration. The technology measures the velocity of the shear wave passing through the liver, in meters per second, and then converts the measurement into a liver stiffness value, which is expressed in kilopascals (kPa).[8] Higher kPa values indicate more extensive fibrosis. Results are offered following 10 or more successful measurements and a median interquartile range/median ratio less than 0.30.[8] FibroScan can be used as a standalone tool or as an adjunct to liver biopsy, and it is particularly useful for identifying patients who have very advanced liver disease or cirrhosis.[8] FibroScan is often the first test clinicians order when a patient presents with liver disease.

FibroScan comes with 2 different probes: M and XL. The XL probe, which is indicated for use in obese patients, employs a 2.5-MHz ultrasonic transducer for improved vibration amplitude and measurement depth for accurate measurements in this patient population; the M probe is intended for use in the general population.[11] Clinicians need to be aware of a few subtleties when conducting the test: Patients should be instructed to not consume any food or liquid 2 hours before testing; measurements may be taken anytime during a patient's respiratory cycle; and the physician should be seated on a stool, not standing.

Because FibroScan has not yet received a current procedural terminology (CPT) code, some clinicians are batching the tests, putting their billing in a holding pattern. For patients paying out of pocket, the test costs approximately $131 (North Shore LIJ Health System charges $375), which is much cheaper than biopsies that may cost $1,255 or more once all clinician fees are factored in.[12]

In early 2014, FibroScan was included in joint HCV management guidelines from the Infectious Diseases Society of America and the American Association for the Study of Liver Diseases as a point-of-care option for measuring liver stiffness in order to distinguish the presence of cirrhosis.[13] Doctors are also using it in patients with other types of liver disease, including NAFLD, alcoholic fatty liver disease, hepatitis B virus (HBV) infection, and cholestatic liver disease.[14]

Clinical Data on FibroScan

The most thorough clinical testing of FibroScan has been conducted in patients with chronic HCV. In a prospective multicenter study of 327 patients with chronic HCV, investigators compared results from FibroScan and liver biopsy. FibroScan results were well correlated with fibrosis stage (Kendall correlation coefficient, 0.55; $P<0.0001$).[13] The investigators generated cutoff values with a high degree of accuracy for more

Table 1. Accuracy of FibroScan in Patients With Chronic Hepatitis C

Metavir Score	Cutoff Value, kPa	AUROC
Cirrhosis (F4)	14.6	0.97
Advanced fibrosis (≥F3)	9.6	0.91
Significant fibrosis (≥F2)	8.8	0.79

AUROC, area under the receiver-operator characteristic curve; **kPa,** kilopascal
From reference 15.

Table 2. Recommended Cutoff Values for Different Stages of Fibrosis

	Fibrosis Stage and Cutoff Value			
Disease	F0-F1, kPa	≥F2, kPa	≥F3, kPa	F4, kPa
HBV infection	≤6	7.2	8.1	11
HCV infection	≤7	8.8	9.6	14.6
HIV/HCV coinfection	–	>7	≥11.5	≥14
Cholestatic liver disease	≤7	7.3	9.8	17.3
NAFLD/NASH	≤7	≥7.5	≤10	≥14

HBV, hepatitis B virus; **HCV,** hepatitis C virus; **kPa,** kilopascal; **NAFLD,** nonalcoholic fatty liver disease; **NASH,** nonalcoholic steatohepatitis
Based on references 14, 15, 18, 19, and 21.

serious Metavir fibrosis stages: 8.8 kPa for stage F2 or greater, 9.6 kPa for stage F3 or greater, and 14.6 kPa for stage F4 (Table 1).[15]

Another study involved 109 patients with chronic HCV who underwent a FibroScan test within 6 months of liver biopsy at the National Institutes of Health from 2006 to 2011. With a cutoff value of 13.1 kPa, there was a negative predictive value of 1.0 for the diagnosis of cirrhosis.[16] The specificity of 0.89 resulted in a positive predictive value of 0.58, but 7 of 10 patients with increased liver stiffness consistent with cirrhosis had a noncirrhotic biopsy result.[16] This cohort, however, had other clinical and radiologic features of cirrhosis, which suggests that liver biopsy had understaged the disease.[16] Other researchers have identified the optimal cutoff value for cirrhosis in patients with HCV as 12 kPa.[17]

FibroScan has shown similar utility for patients with HIV/HCV coinfection. One investigation compared the diagnostic accuracy of FibroScan with 4 other noninvasive serum markers for predicting fibrosis among 100 patients with HIV/HCV coinfection: APRI, Forns Index, FIB-4, and HGM2.[18] FibroScan was more accurate for the diagnosis of advanced fibrosis (≥F3) and cirrhosis, resulting in significantly higher area under the receiver-operating characteristic curves compared with FIB-4 (0.92 vs 0.69; *P*=0.06), APRI (0.93 vs 0.77; *P*=0.007), HGM2 (0.92 vs 0.80; *P*=0.03), and the Forns Index (0.92 vs 0.75; *P*=0.002).[18]

Additionally, prospective studies have demonstrated that VCTE is reliable for the evaluation of fibrosis or cirrhosis in patients with HBV, with cutoff values similar to those observed for HCV.[14,19] Research also supports the use of FibroScan for assessing liver fibrosis in patients with cholestatic liver disease and alcoholic liver disease, with precision comparable to that observed in patients with viral hepatitis.[20,21]

At Beth Israel Deaconess Medical Center in Boston, clinicians have been using liver stiffness values between 12 and 15 kPa to indicate a high probability of cirrhosis and a value greater than 15 kPa as a diagnosis of definite cirrhosis.[14] Table 2 provides cutoff values for fibrosis staging across several chronic liver diseases.[14,15,18,19,21] A diagnostic algorithm for the assessment of liver fibrosis is provided in the Figure.

Conclusion

FibroScan has been used extensively as a point-of-contact test in liver clinics throughout Europe. Guidelines from the National Institute for Health and Care Excellence, the European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver recommend using FibroScan technology for the initial evaluation of liver diseases.[8] The procedure has been validated in more than 760 peer-reviewed publications and has been administered to over 100,000 patients. The primary benefit of this procedure is the exclusion or inclusion of advanced fibrosis and cirrhosis, but FibroScan also can be used for serial testing to assess disease progression or treatment response; additionally, it can serve as an adjunct to liver biopsy as well as clinical, radiologic, and serum marker testing.

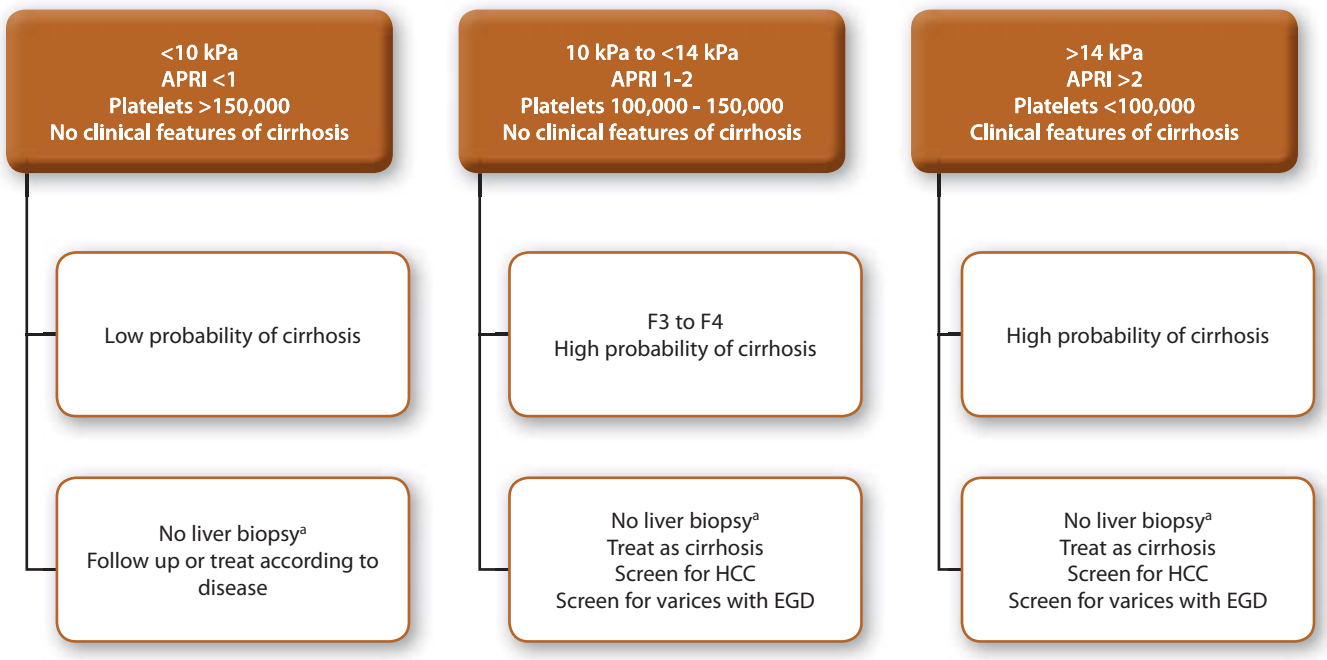

Figure. Procedural workup for assessing fibrosis at North Shore-LIJ Health System.

APRI, aspartate aminotransferase/platelet ratio index; **EGD,** esophagogastroduodenoscopy; **HCC,** hepatocellular carcinoma; **kPa,** kilopascal

[a] Patients receive an annual FibroScan until cirrhosis is detected. The risks of biospy outweigh the benefits gained from annual HCC screening and a single EGD screening for varices.

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