Noninvasive Assessment of Liver Fibrosis

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Case Scenario

A 48-year-old male with a previous longstanding history of intravenous drug abuse is evaluated for a diagnosis of hepatitis C and elevated liver biochemical tests. The aspartate aminotransferase is 59 U/L, and the alanine aminotransferase is 68 U/L. The serum bilirubin is 0.8 mg/dL with an indirect fraction of 0.5 mg/dL, the serum creatinine is 1.1 mg/dL, and the international normalized ratio is 1.0. The serum albumin is 3.9 g/dL. Ultrasound imaging reveals a coarse echotexture without evidence of ascites or intra-abdominal collateral veins. The hepatitis C virus genotype is 1b, and the viral load is 5.6×10^6 IU. You recommend a liver biopsy to determine activity and the stage of fibrosis. The patient asks you whether you can get the same information with blood tests or noninvasive imaging, that is, he wants to know the role of serum markers, ultrasound-based transient elastography (TE), and magnetic resonance elastography (MRE) in such situations.

The Problem

In the United States alone, an estimated 150,000 persons annually are diagnosed with chronic liver disease with nearly 30,000 (20%) individuals having cirrhosis at initial presentation.[1] Disease-related complications of cirrhosis, in turn, are mediated by the development and progression of hepatic fibrosis.

Hepatic fibrogenesis is a maladaptative wound-healing process that occurs in response to chronic, injurious stimuli affecting hepatocytes. This results in a stereotypical inflammatory response leading to hepatic stellate cell activation that produces a nonuniform accumulation of extracellular matrix complexes that constitute hepatic fibrosis. The crosslinking of collagen fibrils within extracellular matrix leads to fibrous scar formation and eventual distortion of the hepatic architecture. Notably, the progression of hepatic fibrosis is not a continuous, linear process but rather a discontinuous, stuttering phenomenon that is greatly influenced by factors such as age, sex, race, alcohol exposure, and obesity.[2]

The gold standard for detecting liver fibrosis remains percutaneous liver biopsy, although this procedure is not without its own inherent limitations. These include (1) a small but significant risk for procedure-related complications such as pain or bleeding, (2) inaccurate staging from sampling error in up to 25% of cases, and (3) inter- and intraobserver variability in biopsy interpretation.[3,4] Because of these reasons and wide availability of serum diagnostic tests, the use of diagnostic liver biopsy in clinical practice is declining.[5]

From a clinical perspective, the greatest limitation with liver biopsy is sampling variability and its effect on fibrosis staging. Several investigations have documented that sampling error is present in a variety of liver diseases.[6,7] Furthermore, the performance of biopsies involving the right and left liver lobes in the same patient does not reduce sampling error, because substantial discordance in fibrosis stage is observed.[7] Although the optimal liver biopsy specimen characteristics ($\geq$20 mm in length with $\geq$11 portal tracts) have been identified to minimize the effects from sampling error,[8] the typical specimen obtained in clinical practice often fails to meet these standards.

Serum Markers and Elastography Imaging

Serum Markers. A variety of serum markers have been developed for identifying patients who are at risk for clinically significant hepatic fibrosis (defined by stages F2-F4). These markers are classified as direct (representing components of extracellular matrix) or indirect (reflecting hepatic inflammation and function). Indirect markers may be used alone or combined with direct markers to form panels. The practical advantages of serum fibrosis markers include their noninvasiveness, potential for widespread availability,

Abbreviations: FDA, U.S. Food and Drug Administration; MRE, magnetic resonance elastography; TE, ultrasound-based transient elastography.

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Table 1. Advantages and Limitations of Biopsy and Noninvasive Tests for Detecting Hepatic Fibrosis

Liver Biopsy	Serum Markers	Transient Elastography	MR Elastography
Advantages			
Direct observation of fibrosis	Noninvasive	Noninvasive	Noninvasive
Staging by accepted classification systems	Reproducible	Reproducible	Reproducible
Evaluation of inflammation and steatosis	Examines indirect or direct markers of fibrosis	Examines 1 cm × 4 cm area over right liver edge	Examines multiple areas within right and left liver
Rule out superimposed diseases	Can be accurate for detecting cirrhosis	Accurate for detecting cirrhosis	Accurate for detecting cirrhosis
Disadvantages			
Invasive with risk of complications	Less accurate for intermediate stages	Less accurate for intermediate stages	More accurate for intermediate stages than TE or serum markers
Contraindicated with coagulopathy	Delays in test result generation with send-out proprietary tests	Failure rate with obesity, narrow rib spaces	Limited by claustrophobia and typical magnetic resonance imaging contraindications
Sampling error and observer variation	False positive values with hemolysis, inflammation, Gilbert's syndrome	False positive values with inflammation, congestion	False positive values with inflammation, congestion
Unsuitable for longitudinal monitoring	Indices may change with disease progression or response to therapy	Liver stiffness does change with disease progression or response to therapy	Liver stiffness does change with disease progression or response to therapy

Adapted from Castera and Pinzani (with permission).[5]

and reproducibility when serial examinations are performed using the same laboratory (Table 1).[9]

Among indirect serum marker panels, the most widely used and validated technique worldwide is called the FibroTest. This proprietary panel contains five variables including total bilirubin, haptoglobin, gamma glutamyl transpeptidase, α2-macroglobulin, and apolipoprotein A. Several independent and combined analyses have demonstrated excellent diagnostic performance for the detection of histological stage F4 fibrosis (i.e., cirrhosis) among patients with chronic hepatitis C. Additional studies in patients with chronic hepatitis B, alcoholic liver disease, nonalcoholic fatty liver disease, as well as studies conducted in the general population, are emerging in support of this method as well. However, serum markers including FibroTest are less accurate in detecting the presence of intermediate stages of fibrosis as compared to the detection of cirrhosis.[9,10]

There are specific limitations associated with the use of FibroTest and serum marker panels in general. False positive results can be attributable to (1) decreases in haptoglobin from hemolysis, (2) increases in total bilirubin from conditions such as Gilbert's syndrome and cholestasis, and (3) increases in α2-macroglobulin and haptoglobin from systemic as well as hepatic inflammation.[9,10] Because of the variability of components in assays and analyzers, FibroTest can only be performed in validated reference laboratories as opposed to local outpatient or hospital-based labs where other testing is typically performed.

Ultrasound-Based TE. This imaging modality uses a transducer probe which emits low-frequency (50 Hz) vibrations into the liver for measuring liver stiffness. The examination is performed over the right lateral intercostal spaces with the patient lying in the dorsal decubitus position and the right arm being in maximal abduction. The propagating shear wave induced by these vibrations is detected by a pulse-echo acquisition, and the velocity of the wave is then calculated. Liver stiffness is proportional to shear wave velocity as expressed by the equation for Young's 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). Liver stiffness is measured in kilopascals. Requirements for accurate TE measurement of mean liver stiffness include (1) an interquartile range for measurements within 30% of the median value and (2) a ratio of successful measurements to the total number of acquisitions $\geq$60%.[11]

In two meta-analyses,[12,13] the pooled estimates for the diagnosis of cirrhosis with TE were excellent, with sensitivity and specificity values approaching 90%. Reported diagnostic threshold (or cutoff) values for cirrhosis have ranged between 11 and 17 kPa in studies of patients with chronic hepatitis C. Results of TE from studies in other etiologies of liver disease such as chronic hepatitis B, alcohol, and nonalcoholic fatty liver disease are emerging. Despite its excellent accuracy for detecting cirrhosis, liver stiffness is an insensitive predictor for esophageal varices and should not dictate which patients should or should not be

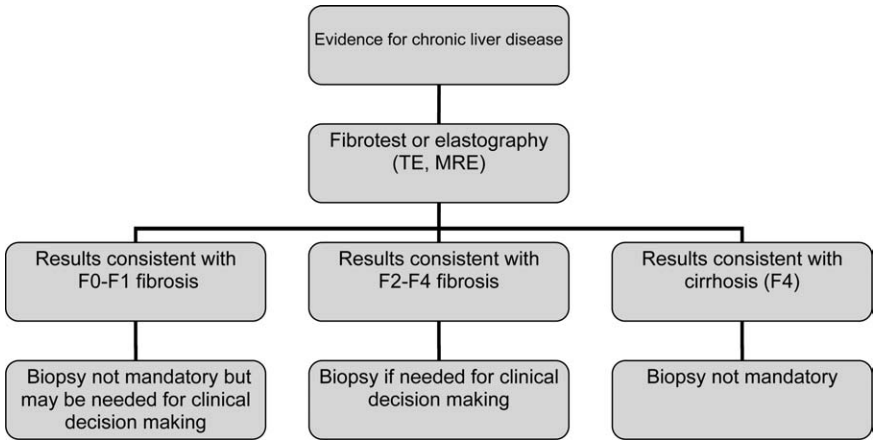

Fig. 1. General algorithm for interpreting results of noninvasive testing for detecting hepatic fibrosis. Biopsy may be required for determining etiology of liver disease or degree of inflammation.

screened for esophageal varices by endoscopy.[14] For the detection of hepatic fibrosis between stages 2-4, however, the pooled estimates of sensitivity and specificity are reduced to between 70% and 80%.[12,13]

Magnetic Resonance Elastography. MRE uses a modified phase-contrast imaging sequence to detect propagating shear waves within the liver. Acoustic shear waves are generated by a pneumatic driver placed directly over the upper abdomen for propagation into liver tissue. Subsequently, liver stiffness values are calculated from wave displacement patterns displayed as color-encoded images (elastograms). Region-of-interest analysis throughout four cross-sectional slices of liver (avoiding vascular structures) is then performed to calculate mean liver stiffness.[15] Elasticity quantification by MRE is based on the formula representing shear modulus, which is equivalent to one-third of the Young's modulus used with TE.

Initial prospective studies have demonstrated the feasibility and diagnostic accuracy in detecting hepatic fibrosis with MRE. As with TE, the detection of cirrhosis by MRE is highly accurate with sensitivity and specificity values exceeding 90%, respectively. In contrast to TE, however, studies of MRE to date identify a higher diagnostic accuracy for detecting intermediate to severe fibrosis (F2-F4) with sensitivity and specificity values each in the 80%-85% range.[16,17]

Although the reproducibility of TE is excellent within experienced centers, its accuracy is diminished when obesity and narrow rib interspaces are encountered.[18] In a recent 5-year prospective study with 13,369 examinations, the probability of technical failure or generation of invalid results was independently associated with a body mass index > 30 kg/m^2.[19] The development of a specialized probe for obese patients may reduce the frequency of technically limited examinations in the future. The reproducibility of MRE is also excellent,[20] yet reliance on individual operators does not exist, because imaging processes are essentially automated. Furthermore, MRE is not significantly affected by obesity or rib interspace width.

For both MRE and TE, it should also be noted that other pathophysiological processes including severe inflammation, cholestasis, and hepatic congestion may independently contribute to liver stiffness.[12,13,18]

Areas of uncertainty

Despite the proliferation of investigations and clinical experiences with noninvasive methods for detecting hepatic fibrosis, there remain a number of critical questions about the clinical effectiveness of these approaches.

For both serum fibrosis markers and elastography imaging techniques, a number of investigators have proposed diagnostic algorithms to assist with defining the stage of fibrosis. For example, it has been suggested that liver biopsy may be deferred in patients with chronic hepatitis C and liver stiffness values from TE ≤ 6 kPa (which suggest nonsignificant fibrosis) or ≥ 12 kPa (which indicate advanced fibrosis). Intermediate values, however, would require liver biopsy for detecting fibrosis stage if relevant for individualized cases. Although these algorithms are intuitively helpful, they have yet to be externally validated among independent populations.

Studies of noninvasive tests to assess disease progression or prognosis with or without liver disease therapy are just beginning to emerge.[21] These results are widely anticipated, because many believe the link between important clinical outcomes and results of noninvasive testing provide the highest level of validation for these methods.

Other potential areas for future research include (1) defining the role of combined versus sequential noninvasive test approaches to improve fibrosis detection, (2) further defining the role of noninvasive testing in special populations (i.e., pediatrics), and (3)

determining the clinical utility of such testing as a screening tool for liver disease in general populations.

Regulatory and Cost Considerations

A major advantage of noninvasive testing is that no serious adverse effects from these techniques is recognized. Economic considerations apply for proprietary serum marker panels as well as TE and MRE. Regarding FibroTest, the U.S. Food and Drug Administration (FDA) has determined that approval is not currently required. FibroTest is currently available in the United States and is marketed as Fibrosure by LabCorp. Recent estimates of cost for this test are approximately US $300 to US $400, which typically includes shipping and processing of the blood sample as well as reporting the test result. At the moment, ultrasound-based TE is not approved for use in the United States by the FDA. In Europe, for example, the price of a TE unit is approximately 80,000 to 100,000 (US $100,000 to US $130,000), and the annual fees for calibrating measurement probes is approximately 3000 to 5000 (US $4000 to US $6500). MRE was first approved by the FDA in 2010, and is becoming available as a commercial upgrade for standard MRI systems. MRE requires less than a minute of acquisition time and can be added as part of a standard MRI examination of the abdomen. The estimated cost of MRE, if performed as a standalone examination, is unknown at this time, but is expected to be similar to that of TE.

Recommendations

There is no evidence for cirrhosis or severe inflammation based on routine clinical studies in the case presented here. The patient's hepatitis C viral genotype is not favorable in terms of probability of treatment response. Thus, obtaining further information about the degree of liver injury from hepatitis C could be an important factor in deciding to pursue or defer antiviral therapy. In this setting, the initial use of a noninvasive test over liver biopsy would be preferred, because it appears the patient may be reluctant to undergo invasive testing (Fig. 1). The use of FibroTest or TE or MRE imaging will be helpful if evidence for cirrhosis or minimal to no fibrosis is predicted by these tests. Should the results of noninvasive testing be indeterminate, then a liver biopsy may need to be performed for stage confirmation. If the patient is discovered to have no or minimal fibrosis and chooses not to pursue antiviral therapy, then longitudinal assessment with elastography imaging to detect fibrosis progression by an increase in liver stiffness is preferred.

References

1. Bell BP, Manos MM, Zaman A, Terrault N, Thomas A, Navarro VJ, et al. The epidemiology of newly diagnosed chronic liver disease in gastroenterology practices in the United States: results from population-based surveillance. Am J Gastroenterol 2008;103:2727-2736.
2. Friedman SL. Mechanisms of hepatic fibrogenesis. Gastroenterology 2008;134:1655-1669.
3. Talwalkar JA, Yin M, Fidler JL, Sanderson SO, Kamath PS, Ehman RL. Magnetic resonance imaging of hepatic fibrosis: emerging clinical applications. HEPATOLOGY 2008;47:332-342.
4. Standish RA, Cholongitas E, Dhillon A, Burroughs AK, Dhillon AP. An appraisal of the histopathological assessment of liver fibrosis. Gut 2006;55:569-578.
5. 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.
6. Garrido MC, Hubscher SG. Accuracy of staging in primary biliary cirrhosis. J Clin Pathol 1996;49:556-559.
7. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97:2614-2618.
8. Bedossa P, Dargère D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. HEPATOLOGY 2003;38:1449-1457.
9. Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. HEPATOLOGY 2006;43:S113-S120.
10. Poynard T, Morra R, Halfon P, Castera L, Ratziu V, Imbert-Bismut F, et al. Meta-analyses of FibroTest diagnostic value in chronic liver disease. BMC Gastroenterol 2007;7:40.
11. Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol 2008;48:835-847.
12. Talwalkar JA, Kurtz DM, Schoenleber SJ, West CP, Montori VM. Ultrasound-based transient elastography for the detection of hepatic fibrosis: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2007;5:1214-1220.
13. Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008;134:960-974.
14. Castéra L, Le Bail B, Roudot-Thoraval F, Bernard PH, Foucher J, Merrouche W, 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.
15. Muthupillai R, Lomas,DJ, Rossman PJ, Greenleaf JF, Manduca A, Ehman RL. Magnetic resonance elastography by direct visualization of propagating acoustic strain waves. Science 1995;269:1854-1857.
16. Yin M, Talwalkar JA, Glaser KJ, Manduca A, Grimm RC, Rossman PJ, et al. Assessment of hepatic fibrosis with magnetic resonance elastography. Clin Gastroenterol Hepatol 2007;5:1207-1213.
17. Huwart L, Sempoux C, Vicaut E, Salameh N, Annet L, Danse E, et al. Magnetic resonance elastography for the noninvasive staging of liver fibrosis. Gastroenterology 2008;135:32-40.
18. Talwalkar JA. Elastography for detecting hepatic fibrosis: options and considerations. Gastroenterology 2008;135:299-302.
19. Castéra L, Foucher J, Bernard PH, Carvalho F, Allaix D, Merrouche W, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. HEPATOLOGY 2010;51:828-835.
20. Hines CD, Bley TA, Lindstrom MJ, Reeder SB. Repeatability of magnetic resonance elastography for quantification of hepatic stiffness. J Magn Reson Imaging 2010;31:725-731.
21. Vergniol J, Foucher J, Castéra L, Bernard PH, Tournan R, Terrebonne E, et al. Changes of non-invasive markers and FibroScan values during HCV treatment. J Viral Hepat 2009;16:132-140.