Evaluation and Staging of Liver Fibrosis

Background

Pathogenesis of Fibrosis with Chronic HCV Infection

Hepatic fibrosis is a dynamic scarring process in which chronic inflammation stimulates production and accumulation of collagen and extracellular matrix proteins.[1, 2] The hepatic stellate cells are the primary cells responsible for producing these extracellular matrix proteins. Over time, with chronic hepatitis C infection, the total extracellular matrix protein content increases and fibrosis can develop, with potential progression to cirrhosis.[3] This dynamic process can also involve remodeling and regression of the fibrous tissue via breakdown of the matrix proteins by the protease enzymes matrix metalloproteinases (MMP).[2, 4] Balance of the remodeling process occurs with inhibition of the remodeling by tissue inhibitors of metalloproteinases (TIMP).[2]

General Approach to Evaluating Liver Fibrosis

Fibrosis is a precursor to cirrhosis and establishing the severity of liver fibrosis helps predict liver-related morbidity and mortality and emergence of complications of portal hypertension. Noninvasive methods to estimate hepatitis fibrosis are commonly used in clinical practice as a more accessible and less costly strategy than liver biopsy for stratifying patients according to risk.[5, 6, 7] These methods include indirect biomarkers, direct biomarkers, and elastography.[7, 8, 9] If a combination of noninvasive methods provides a clear-cut assessment of hepatic fibrosis then further assessment with liver biopsy is generally not needed.[10, 11] Nevertheless, the gold standard evaluation of hepatic fibrosis remains liver biopsy with histologic analysis.[12]
Liver Biopsy and Histologic Assessment of the Liver

Liver Biopsy

Liver biopsy is considered the gold standard for diagnosing and assessing liver fibrosis.[12] The liver biopsy provides information on both the grade (degree of inflammation that reflects ongoing liver disease injury) and the stage (amount of currently established fibrosis). Several factors—alcohol consumption, chronic hepatitis B infection, increased iron stores, and nonalcoholic fatty liver disease—can be associated with accelerated fibrosis progression in those with chronic HCV infection and may elicit concern for advanced fibrosis.[13] Potential liver injury related to any of these factors is best assessed by histology and their presence may contribute to the clinical decision-making process regarding the need for liver biopsy. There are some limitations to the use of liver biopsy: it is invasive and has associated risks, and even in the ideal situation may incorrectly stage fibrosis in 20% of patients due to sampling error and/or interobserver variability.[14,15,16,17,18] Noninvasive methods for assessing fibrosis are therefore increasingly used instead of liver biopsy and may ultimately replace biopsy when the indication is solely to establish fibrosis severity in patients with an established liver disease diagnosis.[19] However, liver biopsy is still currently utilized by clinicians to augment noninvasive fibrosis estimates.

Indications for Liver Biopsy

Prior to the development of widely used noninvasive tests that estimate hepatic fibrosis, such as aspartate aminotransferase-to-platelet ratio index (APRI), FibroSure, FibroTest, and transient elastography (FibroScan), liver biopsy was used to estimate liver fibrosis. Traditionally, the primary reasons for doing a liver biopsy have been to: (1) provide information on fibrosis stage which can help guide therapeutic HCV management decisions, (2) diagnose coexisting liver diseases, and (3) help identify cirrhosis (or advanced fibrosis) that would necessitate routine cancer surveillance. In the current era, liver biopsy is used less frequently, but certain circumstances arise that warrant consideration of liver biopsy and they are:

- When two indirect markers (such as FibroTest and APRI) show discordant results. For example, when an APRI score is in the 0.5 to 1.5 range and the FibroSure/Fibrotest is less than 0.48, then a liver biopsy is warranted to determine the presence or absence of advanced fibrosis/cirrhosis and the need for routine hepatocellular cancer surveillance and follow-up.
- When a second cause of liver disease is suspected. For example, a very high ALT (over 200-300 IU/L) and positive autoimmune markers suggest possible coexisting autoimmune hepatitis.
- When indirect, direct, and transient elastography tests are unavailable.

Approaches to Liver Biopsy

There are three ways to obtain a liver biopsy: (1) percutaneous (the most common method), (2) transjugular or transfemoral, and (3) laparoscopic. Specimens are obtained either with a core aspiration needle (Menghini, Jamshidi, Klatskin style) or sheathed cutting needle (Tru-Cut style) that is at least 16-gauge in caliber. The optimum size of a specimen that offers the least risk of under-staging fibrosis is 3 cm in length after formalin fixation and the sample should include at least 11 portal tracts. The number of portal tracts is relative to biopsy size, and generally samples greater than 2 cm in length are acceptable.[20] In most circumstances, liver biopsy can be done with minimal side effects, but pain and bleeding can occur.[21]

Classification of Liver Histology

Several histologic scoring systems have been developed to grade (inflammation) and stage (fibrosis) hepatic disease caused by hepatitis.[20,22] More complex scoring systems such as Knodell or Ishak are generally limited to use in research including clinical trials.[23,24] For clinical purposes, scoring systems with fewer grade and stage categories are generally utilized; these include Batts and Ludwig, Metavir, and International Association for Study of the Liver (IASL).[15,25] The main determinants of inflammatory activity are
lymphocytic piecemeal necrosis, lobular necroinflammation, and portal inflammation, which are graded 0 to 4 in most classification systems (Figure 1). The main determinants of fibrosis are degree of expansion of fibrotic areas between portal tracts and these changes are staged 0 to 4 in the classification systems commonly used in clinical practice (Figure 2).
Indirect Markers of Fibrosis

In recent years, the use of noninvasive, indirect and direct measures of fibrosis have become commonplace in clinical practice. Initial screening with simple laboratory tests, such as platelet count, prothrombin time, albumin, total bilirubin, and serum aminotransferase levels are commonly performed to estimate fibrosis and identify cirrhosis. Different combinations of these measures have been used to estimate the degree of hepatic fibrosis. Additional serum markers of fibrosis, such as hyaluronic acid (HA), and alpha-2-macroglobulin, have been utilized in tests that include panels of such markers, often combined with standard clinical liver tests.

Aspartate Aminotransferase-to-Platelet Ratio Index (APRI)

The APRI model was developed as a simple, easily calculated method to predict significant, severe fibrosis or cirrhosis and has been tested in patients with HCV monoinfection and those with HCV and HIV coinfection.[26,27] The APRI is calculated using the patient’s aspartate aminotransferase (AST) level, corrected for the upper limit of normal, and platelet count (Figure 3). A meta-analysis of 40 studies found that an APRI cutoff of greater than or equal to 0.7 had an estimated sensitivity of 77% and specificity of 72% for detection of significant hepatic fibrosis (greater than or equal to F2 by Metavir).[28] A cutoff score of at least 1.0 has an estimated sensitivity of 61 to 76% and specificity of 64 to 72% for detection of severe fibrosis/cirrhosis (F3 to F4 by Metavir). For detection of cirrhosis, a cutoff score of at least 2.0 was more specific (91%) but less sensitive (46%). Overall, APRI has good diagnostic utility for predicting severe fibrosis/cirrhosis or low risk of significant fibrosis, but does not accurately differentiate intermediate fibrosis from mild or severe fibrosis. Thus, clinicians should use APRI in combination with other noninvasive markers of fibrosis.

FIB-4

The FIB-4 is an index based on readily available routine laboratory values and has been shown to have good performance characteristics in large observational cohorts.[29,30] Results are generated utilizing age, AST, ALT, and platelet count (Figure 4). A threshold value of less than 1.45 has a sensitivity of 74% and a negative predictive value of 95% for excluding advanced fibrosis (F3-F4).[31] A threshold value of greater than 3.25 has a positive predictive value for advanced fibrosis of 82% with a specificity of 98% in confirming cirrhosis. This model was good at excluding or confirming cirrhosis, but values between 1.45 and 3.25 did not fully discriminate fibrosis and would need an additional method to predict liver fibrosis.

FibroIndex

The FibroIndex is a simple scoring method consisting of three biochemical markers AST, platelet count, and gamma globulin (Figure 5).[32] With a cutoff of less than or equal to 1.25, the sensitivity was 40% and specificity 94% for mild fibrosis (F0 or F1 by Metavir). Using a cutoff of greater than or equal to 2.25, the sensitivity was 36% and specificity 97% for significant fibrosis (F2 or F3 by Metavir). Patients with F4 fibrosis were not included in the study. FibroIndex has good specificity for mild or significant fibrosis, but has low sensitivity. Because of this low sensitivity the FibroIndex is not an adequate tool to be used alone but may serve as an adjunct along with other fibrosis markers.

Forns Index

The Forns Index uses simply obtained parameters—age, gamma-glutamyltransferase (GGT), cholesterol, and platelet count—but it requires a relatively complicated calculation (Figure 6).[33] A cutoff score of less than 4.25 had a negative predictive value of 96% for excluding significant fibrosis (F2, F3, or F4). At a cutoff of greater than 6.9, the positive predictive value was 66% for significant fibrosis (F2, F3, or F4). This tool is useful and has good predictive value in selecting those with low risk of significant fibrosis, but does not reliably predict more advanced fibrosis or cirrhosis. Due to varying cholesterol levels that occur in patients with genotype 3 HCV, this method should not be used in those patients. This method, along with other serum
biomarkers, has also been studied as a predictive tool to evaluate fibrosis regression in response to HCV therapy, and for fibrosis assessment in patients with HIV and HCV coinfection, with comparable predictive value to patients with HCV monoinfection.[34,35]

**HepaScore**

The HepaScore was designed to improve upon nonspecific marker indices in fibrosis models by adding fibrosis specific markers (age, sex, total bilirubin, GGT, alpha-2-macroglobulin, and hyaluronic acid levels).[14] The HepaScore algorithm is more complicated than other indirect markers and the laboratory performing the test utilizes a complex modeling equation model to generate the result (Figure 7). At values less than or equal to 0.2, the negative predictive value to exclude fibrosis is 98%. At values greater than or equal to 0.8 the positive predictive value for predicting cirrhosis is 62%. Given the good negative predictive value with a low HepaScore this method is good at excluding significant fibrosis but not as good at predicting cirrhosis, and it is recommended that for a HepaScore of greater than 0.2 an adjunct marker of fibrosis be used to predict cirrhosis.

**FibroTEST and ActiTest**

The HCV FibroTest and ActiTest are used for the assessment of liver fibrosis and inflammation. The FibroTest uses a proprietary algorithm that includes patient age and gender along with a composite of five biochemical markers associated with hepatic fibrosis: alpha-2-macroglobulin, haptoglobin, GGT, apolipoprotein A1, and total bilirubin. The ActiTest uses a second algorithm that adds a direct marker for inflammatory activity (the ALT value) to the same five parameters in the FibroTest. The FibroTest estimates hepatic fibrosis and the ActiTest estimates hepatic inflammation (necroinflammation activity grade). Commercially, these are typically obtained as a combination test and referred to as the FibroSure Test or the FibroTest-ActiTest. In one meta-analysis of 30 studies with over 2,400 individual patient-level data, the FibroTest was found to be a reasonable alternative to biopsy for estimating hepatic fibrosis with a mean standardized area under the receiver-operator curve of 85% for chronic HCV.[36] Contraindications or caution for use of these methods for fibrosis staging include the presence of any of the following: Gilbert’s disease, acute hemolysis, acute liver inflammation, extrahepatic cholestasis, renal insufficiency, post transplantation, or receipt of medications that may cause unconjugated hyperbilirubinemia. All of these conditions may lead to inaccurate quantitative predictions. The HCV-FibroTest is good at excluding or confirming cirrhosis but, like other biomarkers, this test is indeterminate in discriminating the middle ranges and an adjunct marker of fibrosis would be needed in those situations.
Direct Markers of Fibrosis

Direct markers of fibrosis include procollagen type (I, III, IV), matrix metalloproteinases, cytokines, and chemokines. The direct markers have shown variable effectiveness in predicting liver fibrosis. Among these markers, those currently used involve matrix metalloproteinases. Liver fibrosis/cirrhosis is characterized by enhanced extracellular matrix synthesis by activated stellate cells. Matrix metalloproteinases (MMP’s) are endopeptidases that can degrade collagen and are involved in the tissue remodeling process that takes place with fibrosis.[1] Levels of matrix metalloproteinases are regulated by specific tissue inhibitors of metalloproteinase (TIMPs) and a mismatch between these two is thought to be associated with extracellular matrix deposition and breakdown. Levels of TIMP-1 significantly correlate with fibrosis, with a sensitivity of 100% in diagnosing cirrhosis, but these tests have low specificity. Hyaluronic acid is a glycosaminoglycan secreted by hepatic stellate cells and is one of the chief components of the extracellular matrix. Extensive fibrosis/cirrhosis has been found to be associated with increased serum levels of hyaluronic acid.

FIBROSpect II

The FIBROSpect II is a commercially available test that combines hyaluronic acid, tissue inhibitor of a metalloproteinase-1 (TIMP-1), and alpha-2-macroglobulin in a predictive algorithm for fibrosis stages (F2 to F4). An index score of greater than 0.42 is classified with the presence of stage F2 to F4 fibrosis. Based on data from the test manufacturer involving 696 patients with chronic HCV infection, the overall sensitivity at this cutoff is 80.6% and the specificity 71.4%. [37] Overall, this is a good test for determining presence or absence of significant fibrosis but not useful in differentiating intermediate stages of fibrosis. [38]
Radiologic Modalities to Estimate Fibrosis

Hepatic Ultrasound

Hepatic ultrasound is a noninvasive, lower cost, and reproducible technique for determining focal and parenchymal disease of the liver. Ultrasound can potentially identify various factors that are useful in evaluating chronic liver disease: nodularity of the liver surface (which reflects the presence of regenerative nodules and fibrous septa often seen in cirrhosis), coarseness of the parenchyma, patency and flow of veins and arteries, spleen size (which if enlarged can suggest portal hypertension), hepatocellular carcinoma, and small volume ascites. The use of high-frequency ultrasound transducers is reported to be more reliable than low-frequency ultrasound in diagnosing cirrhosis.\(^\text{39}\) In general, though, a standard ultrasound has been shown to have low sensitivity (in range of 40\%) for the detection of cirrhosis.\(^\text{40}\) In those with HCV, assessment of biochemical markers (prothrombin time, albumin, total bilirubin, and platelet count) is the initial step used by most clinicians in determining the presence or absence of cirrhosis. If biochemical markers are conflicting or suggestive of cirrhosis then abdominal imaging would be used to confirm overt cirrhosis and/or portal hypertension, and screen for hepatocellular carcinoma.

Transient Elastography

Transient elastography (FibroScan) is a noninvasive, easy-to-perform test that takes about 5 to 10 minutes; this test can be done in the clinic setting.\(^\text{41}\) Studies evaluating transient elastography have demonstrated reproducible performance across a variety of patient populations.\(^\text{42, 43, 44}\) Transient elastography examines a larger area of liver tissue (1 cm diameter by 5 cm in length) than liver biopsy and thus may provide a more representative assessment of the entire hepatic parenchyma. The test is performed using an ultrasound transducer probe that is mounted on the axis of a vibrator. Vibration is transmitted through hepatic tissue, mechanically inducing a shear wave, followed by pulse echo that measures the shear wave velocity. The measured velocity correlates directly with liver stiffness. Transient elastography has been validated in multiple studies for detection of advanced fibrosis and cirrhosis. In 2005, Castera and Ziol both published their findings for optimal transient elastography cutoff values that correlate with different Metavir fibrosis scores (Figure 8) and (Figure 9).\(^\text{42, 45, 46, 47}\) Although these studies utilized the same type of transient elastography machine (FibroScan/EchoSens), they derived distinct cut-off values, which may be explained by different study design and patient populations. In both studies, however, the Metavir F3 fibrosis cutoff values were nearly identical (Figure 10). It is important to note that in clinical practice multiple factors, such as hepatic inflammation, obesity, ingestion of a meal within 2 hours of the test, ascites, and elevated central venous pressure can influence the transient elastography result. Transient elastography is contraindicated in those with pacemakers and implantable defibrillators. Thus, most experts utilize transient elastography results in conjunction with other measures of hepatic fibrosis. Despite these limitations, transient elastography is one of the more reliable noninvasive methods for estimating Metavir Fibrosis of F3 or greater.

Shear Wave Elastography

Shear wave elastography (ShearWave Elastography) is a non-invasive sonographic test that can estimate hepatic fibrosis. The test is performed by watching a real-time image with B-mode ultrasound, and then measuring liver stiffness based on anatomical information; the test also can assess liver homogeneity based on the color images it generates that correlates with varying degrees of liver stiffness.\(^\text{48, 49}\) Based on limited data, shear wave elastography performs with similar accuracy as transient elastography in estimating hepatic fibrosis.\(^\text{48, 49}\) In the United States, shear wave elastography is used much less frequently than transient elastography.

Magnetic Resonance Elastography

Magnetic resonance elastography involves applying a probe to the back of a patient, emitting low-frequency vibrations through the liver, which then are measured through magnetic resonance imaging spin echo
sequence. A meta-analysis of five trials comparing magnetic resonance elastography to liver biopsies showed a sensitivity of 94% and specificity of 95% in differentiating F0 to F1 from F2 to F4 as well as a sensitivity of 98% and specificity of 94% in differentiating F0 to F3 from F4.\textsuperscript{[50]} This technique shares the same limitations as transient elastography. The utility of this method in comparison to other modalities is yet to be fully elucidated.\textsuperscript{[51,52]}
Summary Points

- HCV-related hepatic fibrosis is a dynamic scarring process in which chronic inflammation stimulates production and accumulation of collagen and extracellular matrix proteins.
- Simple laboratory tests should continue to be utilized to identify overt cirrhosis, in conjunction with abdominal imaging where appropriate.
- Liver biopsy remains the gold standard for diagnosing other causes of liver disease and for establishing the presence and severity of fibrosis.
- Noninvasive serum markers show clinical utility in predicting presence or absence of significant fibrosis/cirrhosis, but are not as useful in differentiating between intermediate stages of fibrosis.
- In general, the optimal approach to fibrosis assessment is to use noninvasive serum markers/tests in conjunction with transient elastography. If transient elastography is not available then two different noninvasive serum markers/tests should be used.
- Concordance (agreement that advanced fibrosis [F3/F4] is present or absent) between two noninvasive fibrosis methods is usually considered sufficient to avoid liver biopsy. We generally recommend liver biopsy if two noninvasive tests are discordant.
- Relatively little experience exists with the use of direct serum markers and the clinical utility of these markers remains less well defined than for other markers.
- Among the noninvasive tests methods of liver fibrosis estimation, transient elastography is the most accurate for identifying cirrhosis.
Citations


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Figures

Figure 1 Scoring Systems for Histologic Grade (Inflammation)

This table shows three different scoring systems for histologic grade (hepatic inflammation). Abbreviation: International Association for Study of the Liver (IASL)

**Figure 2 Scoring Systems for Histologic Stage (Fibrosis)**

This table shows three different scoring systems for histologic stage (fibrosis). Abbreviation: International Association for Study of the Liver (IASL)

Figure 3 Aspartate Aminotransferase-to-Platelet-Ratio Index (APRI)

The APRI score provides a quick estimate for predicting severe fibrosis or cirrhosis. The AST upper limit of normal should be the upper limit of normal established by the laboratory that performed the test. Most laboratories use an AST upper limit of 40 IU/mL. Abbreviations: AST = aspartate aminotransferase
**Figure 4 Fib4**

The Fib4 represents an easy-to-use test for predicting severe hepatic fibrosis or cirrhosis. Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase

**Figure 5 FibroIndex**

The FibroIndex is a complicated calculation that requires patient platelet count, AST level, and gamma globulin level.

Figure 6 Forns Index

The Forns index incorporates easy-to-obtain parameters but requires a highly complicated calculation.

**Figure 7 HepaScore (FibroScore)**

The HepaScore is a highly complicated calculation and is most useful in excluding advanced fibrosis by using a low cutoff score.

Image 8A: Correlation of Breakpoints and Metavir Fibrosis Scores

Figure 8 (Image Series) - Castera Transient Elastography Cutoffs Correlating with Metavir Fibrosis

Image 8B: Optimal Cutoffs: Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value

Figure 9 (Image Series) - Ziols Transient Elastography Cutoffs Correlating with Metavir Fibrosis

Image 9A: Correlation of Breakpoints and Metavir Fibrosis Scores

Figure 9 (Image Series) - Ziols Transient Elastography Cutoffs Correlating with Metavir Fibrosis

Image 9B: Optimal Cutoffs: Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value

Figure 10 Castera and Ziol Cutoffs for Metavir F3 Fibrosis Score