Evaluation and Staging of Liver Fibrosis

This is a PDF version of the following document:
Module 2: Evaluation, Staging, and Monitoring of Chronic Hepatitis C
Lesson 4: Evaluation and Staging of Liver Fibrosis

You can always find the most up to date version of this document at https://www.hepatitisc.uw.edu/go/evaluation-staging-monitoring/evaluation-staging/core-concept/all.

Background

Pathogenesis of Fibrosis with Chronic Hepatitis C: Hepatic fibrosis is a dynamic scarring process in which chronic inflammation stimulates production and accumulation of collagen and extracellular matrix proteins. The hepatic stellate cells are the primary cells responsible for producing these extracellular matrix proteins. Over time, with chronic hepatitis C infection, the total collagen content increases and fibrosis can develop, with potential progression to cirrhosis. 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). Balance of the remodeling process occurs with inhibition of the remodeling by tissue inhibitors of matrix metalloproteinases (TIMP).

General Approach to Evaluating Liver Fibrosis: Fibrosis is a precursor to cirrhosis and establishing the severity of liver fibrosis may help 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 and these methods include indirect biomarkers, direct biomarkers, and imaging modalities. If noninvasive methods provide a clear-cut assessment of hepatic fibrosis then further assessment with liver biopsy may not be needed. Nevertheless, the most accurate and reliable evaluation of hepatic fibrosis remains liver biopsy with histologic analysis.
Liver Biopsy and Histologic Assessment of the Liver

Liver Biopsy: Liver biopsy is considered the gold standard for diagnosing and assessing liver fibrosis. 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, increased hepatic iron concentration, and steatosis—are associated with accelerated fibrosis progression and may elicit concern for advanced fibrosis. Potential liver injury related to any of these factors is best assessed by histology and the presence of any of these factors 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. In the future, noninvasive methods for assessing fibrosis may completely replace liver biopsy, but currently clinicians often utilize liver biopsy to augment noninvasive estimates of liver fibrosis.

Indications for Liver Biopsy: Prior to the development of widely used non-invasive tests that estimate hepatic fibrosis, such as aspartate aminotransferase-to-platelet ratio index (APRI), FibroSure, and transient elastography (FibroScan), liver biopsy was the best most frequently used test to assess for liver fibrosis. Traditionally, the primary reasons for doing a liver biopsy have been: (1) it can provide information on current status of liver injury and help guide therapeutic hepatitis C management decisions; (2) it can characterize features useful in diagnosing and treating co-existing liver diseases; and (3) it can 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 considering liver biopsy:

- Two indirect markers (such as FibroSure/Fibrotest and APRI) show discordant results. For example, when an APRI is between 0.5 to 1.5 and the FibroSure/Fibrotest is less than 0.48, decision about whether or not to treat may be based on a biopsy.
- When concurrent forms of liver disease in addition to HCV are suspected. For example, if indirect markers or radiologic imaging demonstrate more significant fibrosis than expected, a biopsy can be used to determine whether an additional liver disease is present that is accelerating hepatic fibrosis.
- When indirect, direct, and transient elastography tests are unavailable.
- To determine whether patients require surveillance for hepatocellular cancer.

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 understaging fibrosis is 3 cm in length after formalin fixation and the sample should include at least 11 portal tracts, although the number of portal tracts is relative to biopsy size, and generally samples greater than 2 cm in length are acceptable. In most circumstances, liver biopsy can be done with minimal side effects, but pain and bleeding can occur.

Classification of Liver Histology: Several histologic scoring systems have been developed to grade (inflammation) and stage (fibrosis) hepatic disease caused by hepatitis. Some scoring systems are complex, such as Knodell or Ishak, and because of their complexity are primarily only used in large cohort clinical trials. For general clinical purposes, most use the less complicated scoring systems that have only three to four categories, such as Batts and Ludwig, METAVIR, and International Association for Study of the Liver (IASL). 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 the length in 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 Cirrhosis

Introduction: In recent years, patient and provider concerns regarding liver biopsy have stimulated a growing interest in establishing noninvasive alternatives to liver biopsy for fibrosis staging. Initial screening with simple laboratory tests, such as platelet count, prothrombin time, albumin, total bilirubin, and serum aminotransferase level are commonly performed in clinical practice in an attempt to estimate fibrosis and identify overt cirrhosis. Studies have examined use of different combinations of these measures to evaluate hepatic fibrosis. In addition, some studies have evaluated other serum fibrotic markers, such as hyaluronic acid (HA), and alpha-2-macroglobulin, which is a proteinase inhibitor synthesized by hepatocytes and Ito cells thought to inhibit catabolism of matrix proteins and enhance the fibrotic process in the liver. None of these markers have yet to evolve as standard of practice as the primary means to assess liver fibrosis.

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 both HCV monoinfected and coinfected (HCV and HIV) patients. The APRI is calculated using the patient’s aspartate aminotransferase (AST) level and platelet count, and the upper limit of normal of aspartate aminotransferase (AST) level (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). 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 easy-to-use, quick, and inexpensive test that provides results immediately. 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 specificity of 80% in excluding significant fibrosis. A threshold value of greater than 3.25 has 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: Is a simple scoring method consisting of three biochemical markers AST, platelet count, and gamma globulin (Figure 5). 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). 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 has also been studied as a predictive tool for response (fibrosis regression) to HCV therapy, and histological assessment in patients co-infected with HIV and HCV with similar predictive values.

HepaScore: The HepaScore, also known as a FibroScore, was designed to improve upon nonspecific marker indices fibrosis models by adding fibrosis specific markers (age, sex, total bilirubin, GGT,
alpha-2-macroglobulin, and hyaluronic acid levels). The HepaScore algorithm is more complicated than other indirect markers and the laboratory performing the test utilizes a very complex 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.

**FibroSure, FibroTest-ActiTest:** The HCV-FibroSure and the FibroTest-ActiTest are two identical tests marketed in United States and Europe. FibroSure is the test available in the United States, although not cleared or approved by the Federal Drug Administration (FDA). These tests are used for assessment of liver inflammation and fibrosis. The FibroSure utilizes a proprietary algorithm that includes patient age and gender along with a composite of six biochemical markers associated with hepatic fibrosis: alpha-2-macroglobulin, haptoglobin, GGT, apolipoprotein A1, total bilirubin, and ALT. When compared to liver biopsy histology results in a sample population in which 38% had significant fibrosis (F2, F3, or F4 by METAVIR) the negative predictive value at a cutoff of less than 0.31 for absence of clinical significant fibrosis was 91% and the positive predictive value for presence of significant fibrosis at a cutoff score of greater than 0.48 was 61% and cutoff of 0.72 was 76%. The Acti component of the FibroTest provides estimates of grade (degree of inflammation) and the HCV FibroSure has the measure of inflammation already incorporated into its algorithm and provides estimates of grade and stage in the report. Contraindications for use of the FibroSure method for fibrosis staging include Gilbert’s disease, acute hemolysis, extrahepatic cholestasis, post transplantation, or renal insufficiency, all of which may lead to inaccurate quantitative predictions. This model is good at excluding or confirming cirrhosis but is indeterminate in the middle ranges and an adjunct marker of fibrosis would be needed in those situations.
Direct Markers of Fibrosis

**Introduction:** 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. Levels of MMP’s 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 (HA) 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 chronic HCV-infected patients, the overall sensitivity at this cutoff is 80.6% and the specificity 71.4%. Overall, this is a good test for determining presence or absence of significant fibrosis but not useful in differentiating intermediate stages of fibrosis. It would serve as a good surrogate for determining the presence or absence of cirrhosis in those patients who have a contraindication to liver biopsy, or those who refused it.
Radiologic Imaging to Estimate Fibrosis

**Hepatic Ultrasound**: Hepatic ultrasound is a non-invasive, lower cost, and repeatable 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, size of lymph nodes around the hepatic artery, 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. 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 Ultrasound Elastography (Transient Elastography and Shear Wave Elastography)**: The ultrasound-based transient elastography is a painless, easy-to-perform ultrasound test that takes about 5 minutes to perform. Two transient elastography ultrasound systems are approved for use in the United States: transient elastography (*FibroScan*) and shear wave elastography (*ShearWave Elastography*). Studies using transient elastography have been reproducible and transient elastography examines a large mass of liver tissue (1 cm diameter by 5 cm in length) and thus provides 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 toward hepatic tissue, the vibrations are followed by pulse echo, and their velocities are measured which 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*). Although these two 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, ascites, and elevated central venous pressure and can influence the transient elastography result. Thus, most experts utilize transient elastography results in conjunction with other measures of hepatic fibrosis. Despite these limitations, transient elastography is a potentially very useful non-invasive method in estimating Metavir Fibrosis of F3 or greater.

**Magnetic Resonance Elastography**: This process involves applying a probe to the back of a patient that results in the emission of low frequency vibrations through the liver, which then are measured through MRI spin echo sequence. A meta-analysis of five trials comparing MRE 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. This technique shares the same limitations as ultrasound elastography. The usefulness of this method clinically continues to evolve.
Summary Points

- Hepatitis C-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 in conjunction with abdominal imaging study should continue to be utilized to identify overt cirrhosis.
- Liver biopsy continues to be the gold standard for diagnosing other causes of liver disease and establishing severity of fibrosis.
- Noninvasive serum markers used show clinical utility in predicting presence or absence of significant fibrosis/cirrhosis, but are not useful in differentiating between intermediate stages of fibrosis; these markers may serve as good clinical alternatives in patients who are not candidates for liver biopsy.
- Relatively little experience exists with the use of direct serum markers and the clinical utility of these markers remains relatively poorly defined.
- Radiologic imaging using ultrasound transient elastography shows the most promise of noninvasive techniques for identifying cirrhosis and stratifying stages of liver fibrosis.
References


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)


<table>
<thead>
<tr>
<th>IASL</th>
<th>Batts-Ludwig</th>
<th>Metavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal chronic hepatitis</td>
<td>Grade 1</td>
<td>A1</td>
</tr>
<tr>
<td>Mild chronic hepatitis</td>
<td>Grade 2</td>
<td>A1</td>
</tr>
<tr>
<td>Moderate chronic hepatitis</td>
<td>Grade 3</td>
<td>A2</td>
</tr>
<tr>
<td>Severe chronic hepatitis</td>
<td>Grade 4</td>
<td>A3</td>
</tr>
</tbody>
</table>
**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)


<table>
<thead>
<tr>
<th>Score</th>
<th>IASL</th>
<th>Batts-Ludwig</th>
<th>Metavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Fibrosis</td>
<td>No Fibrosis</td>
<td>No Fibrosis</td>
</tr>
<tr>
<td>1</td>
<td>Mild fibrosis</td>
<td>Fibrous portal expansion</td>
<td>Periportal fibrotic expansion</td>
</tr>
<tr>
<td>2</td>
<td>Moderate fibrosis</td>
<td>Rare bridges or septae</td>
<td>Periportal septae (&gt; 1 septum)</td>
</tr>
<tr>
<td>3</td>
<td>Severe fibrosis</td>
<td>Numerous bridges or septae</td>
<td>Portal-central septae</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis</td>
<td>Cirrhosis</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>
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

\[
\text{APRI} = \frac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}} \times 100
\]

Platelet Count (10^9/L)
The Fib4 represents an easy-to-use test for predicting severe hepatic fibrosis or cirrhosis.
Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase

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

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


**Forns Index**

\[
\text{Forns Index} = 7.811 - 3.131 \times \ln(\text{platelet count} [10^9/L]) + 0.781 \times \ln(\text{GGT [IU/L]}) + 3.467 \times \ln(\text{age}) - 0.014 \times \text{cholesterol [mg/dL]}
\]

\(\ln = \text{natural logarithm}\)

\(\text{GGT} = \text{gamma glutamyl transpeptidase}\)
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.


\[
\text{HepaScore} = \frac{y}{y + 1}
\]

\[
y = \exp[-4.185818 - (0.0249 \times \text{age}) + (0.7464 \times \text{sex})
+ (1.0039 \times \alpha_2\text{-macroglobulin}) + (0.0302 \times \text{hyaluronic acid})
+ 0.0691 \times \text{bilirubin}) - (0.012 \times \text{GGT})]
\]

**Units**
- age = years
- sex (male = 1 and female = 0)
- $\alpha_2$-macroglobulin (g/L)
- hyaluronic acid (µg/L)
- bilirubin (µmol/L)
- GGT = gamma glutamyl transpeptidase (U/L)
Figure 8 (Image Series) - Castera Transient Elastography Cutoffs Correlating with Metavir Fibrosis Scores

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**


<table>
<thead>
<tr>
<th>METAVIR Score</th>
<th>Optimal Cutoff*</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>F ≥ 2 (F0-1 vs. F2-3-4)</td>
<td>7.1 kPa</td>
<td>0.67</td>
<td>0.89</td>
<td>0.95</td>
<td>0.48</td>
</tr>
<tr>
<td>F ≥ 3 (F0-1-2 vs. F3-4)</td>
<td>9.5 kPa</td>
<td>0.73</td>
<td>0.91</td>
<td>0.87</td>
<td>0.81</td>
</tr>
<tr>
<td>F ≥ 4 (F0-1-2-3 vs. F4)</td>
<td>12.5 kPa</td>
<td>0.87</td>
<td>0.91</td>
<td>0.77</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*Optimal Cutoff = value that provided higher total sensitivity and specificity
PPV = Positive Predictive Value
NPV = Negative Predictive Value
Ziol Transient Elastography Breakpoints

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


<table>
<thead>
<tr>
<th>METAVIR Score</th>
<th>Optimal Cutoff*</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>F ≥ 2 (F0-1 vs. F2-3-4)</td>
<td>8.8 kPa</td>
<td>0.56</td>
<td>0.91</td>
<td>0.88</td>
<td>0.56</td>
</tr>
<tr>
<td>F ≥ 3 (F0-1-2 vs. F3-4)</td>
<td>9.6 kPa</td>
<td>0.86</td>
<td>0.85</td>
<td>0.71</td>
<td>0.93</td>
</tr>
<tr>
<td>F ≥ 4 (F0-1-2-3 vs. F4)</td>
<td>14.6 kPa</td>
<td>0.86</td>
<td>0.96</td>
<td>0.78</td>
<td>0.97</td>
</tr>
</tbody>
</table>

*Optimal Cutoff = value that provided higher total sensitivity and specificity
PPV = Positive Predictive Value
NPV = Negative Predictive Value
Figure 10 Castera and Zioli Cutoffs for Metavir F3 Fibrosis Score