Non-Invasive Markers of Liver Fibrosis

Foreword

Non-invasive markers of liver fibrosis include a wide variety of tests and methods for assessing the degree of liver inflammation and scarring. Although these non-invasive markers are not as accurate as the liver biopsy there are many that can provide important information to help monitor the liver health of people with hepatitis C.

The gold standard of care for assessing the health of the liver is the liver biopsy. However since the procedure requires that a needle be inserted through the skin (percutaneous) there is a potential for complications even though the incidence of complications is extremely low. The complications of a liver biopsy can include internal bleeding, and puncturing another organ such as the lungs, stomach, intestines, or any other organs that are close to the liver. In regards to accuracy of the biopsy the sample liver tissue size is important for correctly staging and grading a liver biopsy. Another problem is that the tissue taken from one part of the liver may not be 100% representative of the entire liver. Once the liver tissue sample is collected it is graded and staged by a specialist (usually a pathologist), which could lead to possible human error in interpreting the results. In addition there is no standardized interpretation protocol so it is difficult to compare the results of different biopsies read by different pathologists. Price is also an issue since a typical liver biopsy can cost between $1,500 and $2,000–and up to $2,700 if there are any complications. Given these potential problems it is not surprising that there is a lot of research that is being conducted on the development of non-invasive tests. The tests that have been developed so far have had mixed results in accuracy when compared to the results of a liver biopsy. There have been few prospective clinical trials that have compared the results from various non-invasive markers to the results from a liver biopsy. But recently there have been some advances seen and reported in scientific papers.
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Fibroscan
In 2013 the Food and Drug Administration (FDA) cleared Fibroscan for marketing. Fibroscan is based on ultrasound elastography technology using a machine that sends a vibration wave through the liver. The machine measures how long the wave takes to pass through the liver and estimates the amount of scarring based on the calculation of the Fibroscan. It has been tested extensively in people with hepatitis C. The Fibroscan isn’t 100% accurate, but it is has been shown to have a high degree of accuracy for predicting mild fibrosis, severe fibrosis and cirrhosis. It is less likely to distinguish the difference between no or minimal fibrosis. It is also been shown to be less accurate in people who are obese, and in those who have bile duct damage or ascites (accumulation of fluid in the abdominal cavity). Some medical providers will combine the Fibroscan results with other biochemical tests to provide a better estimation of liver damage.

Non-Invasive Tests
In 2007 the results from a prospective clinical trial that compared six non-invasive tests was published. "Prospective comparison of six non-invasive scores for the diagnosis of liver fibrosis in chronic hepatitis C," by Vincent Leroy and colleagues, was published in the Journal of Hepatology.1 In this study the following serum marker scores were compared to the results obtained from a liver biopsy:

1. MP3: combines PIIIN (a marker of fibrogenesis), and matrix metalloproteinase MMP-1 (involved in fibrolysis).
2. Fibrotest: combines serum concentrations of a2 macroglobulin, haptoglobin, gGT, bilirubin, and apolipoprotein A1.
3. Fibrometer: combines hyaluronate, prothrombin time, platelets, AST, a2 macroglobulin, urea, and age, and the formula is adjusted based on the cause of the liver disease.
4. Hepascore: combines bilirubin, gGT, hyaluronic acid, a2 macroglobulin, age, and gender.
5. Forns’ score: combines age, gGT, cholesterol, and platelet count.
6. APRI: based on AST activity and platelet count.

Liver Biopsy Results
All liver tissue samples were analyzed twice by a single senior pathologist. Liver fibrosis and necroinflammatory activity were evaluated according to the METAVIR scoring system. The METAVIR scoring system was specially designed for patients with hepatitis C. The grade is assigned a number based on the degree of inflammation, which is usually scored from 0-4 with 0 being no activity and 3 or 4 considered severe activity. The METAVIR system also includes scores for necroinflammatory activity ranging from A0 to A3 (A0 = no activity, A1 = minimal activity, A2 = moderate activity, A3 = severe activity.)

The stage score represents the amount of fibrosis:
• Stage F0 = no fibrosis
• Stage F1 = mild fibrosis
• Stage F2 = moderate fibrosis
• Stage F3 = bridging fibrosis
• Stage F4 = cirrhosis

Additionally, sinusoidal fibrosis was staged: 0 = no fibrosis, 2 = moderate to severe fibrosis.
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The overall results found that that 89 (49.4%) patients had no/mild fibrosis (F0/F1), and 51 (28.3%) had extensive fibrosis or cirrhosis (F3/F4). It was also found that the METAVIR fibrosis stage was significantly correlated to sinusoidal fibrosis stage (p<0.001).

Note: The statistical measurement used to establish the overall performance of the serum markers that correlated with the liver biopsies was the AUROC – Area Under the Receiver Operating Characteristic (curve).

The overall diagnostic performance ranged from 0.86 for Fibrometer to 0.78 for Forns’ score (p = ns) for discriminating F0/F1 vs. F2/F3/F4. For discriminating F0/F1/F2 vs. F3/F4, AUROCs ranged from 0.91 for Fibrometer to 0.78 for Forns’ score (p<0.02). Significant or extensive fibrosis was predicted in 10-86% of patients with positive predictive value (PPV) ranging from 55% to 94%. Using a variety of statistical methods the authors stated that, “The best combinations could select one-third of patients for whom either absence of significant fibrosis or presence of extensive fibrosis could be predicted with more that 90% of certainty.”

The study above has confirmed what other smaller studies found: that non-invasive markers are good for detecting either no fibrosis or extensive fibrosis. Unfortunately, the grade and stage in between is more challenging, at least in the setting of non-invasive tests.

The authors also looked at combining various non-invasive tests to increase the accuracy of single marker tests. In this setting the authors found that combining various tests and using cut-off points for determining the likelihood of accurate readings was the best approach. Based on their findings the authors developed an algorithm for detection of fibrosis in hepatitis C patients with elevated transaminases (see diagram on page 2).

In 2010 Carey, DO et al, also reported on non-invasive tests. In their study they compared the tests listed above, and additional tests listed below to the liver biopsy.

- **AST:ALT ratio:** Uses a ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT).
- **PGA index:** A combination of Prothrombin, gamma glutamyl, and apolipoprotein AI levels.
- **FIB-4 index:** A combination of platelet count, AST level, and ALT level.
- **ActiTest:** Combines ALT levels with the Fibrotest.

The authors concluded that the Fibrotest and the ActiTest can be used as reliable alternatives to the liver biopsy.

Carey et al., also studied various imaging technologies, but did not find that magnetic resonance elastography or ultrasound elastography accurately predicted liver damage, but magnetic resonance elastography was very good at predicting liver damage. The authors noted that more studies are needed to confirm their findings before magnetic resonance elastography are routinely used to replace the liver biopsy.

References:
2. Cleveland Clinic Journal of Medicine Volume 77, Number 8, August 2010
HCSP FACT SHEET • HCV DIAGNOSTIC TOOLS
a series of fact sheets written by experts in the field of liver disease

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Related publications:

- An Overview of HCV Diagnostic Tests
- Liver Biopsy
  www.hcvadvocate.org/hepatitis/factsheets_pdf/Biopsy.pdf
- Fibroscan

For more information

- Centers for Disease Control and Prevention
  www.cdc.gov/Hepatitis
- Mayo Clinic:
  www.mayoclinic.com/health/liver-biopsy/MY00949
- MedlinePlus:
- National Digestive Diseases Information Clearinghouse (NDDIC)
  http://digestive.niddk.nih.gov/diseases/pubs/liverbiopsy/

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