

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Serologic Markers of Hepatic Fibrosis

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G&H What are the drawbacks of using liver biopsy or imaging modalities for detecting and staging liver fibrosis?

DR Although liver biopsy is the gold standard for detecting and staging liver fibrosis, it is not ideal. Sampling variability is a significant issue, as only one area of the liver is sampled. This can prove to be quite problematic; the liver in the right lobe, for example, may be less fibrotic than in the left lobe or other portions of the liver, resulting in a wide margin for sampling errors and, potentially, over- or underutilization of therapy. In addition, liver biopsy may be painful, and it is associated with morbidity and even mortality. Finally, analysis of histologic liver fibrosis may be subject to interobserver variability, not to mention that it may be quite expensive.

As for imaging modalities, in particular ultrasound, these techniques are currently not very specific or sensitive for fibrosis.

G&H What fibrotic serologic markers are currently in use?

DR Currently, there are at least a dozen different individual markers or panels of markers available, and there has been much published literature examining many of them. Table 1 lists several of these. In the United States, however, serologic markers are not frequently used to measure fibrosis, in contrast to Europe, where they are more commonly used. Of the markers and panels that are actually used in the United States, the two main ones include HCV FibroSure (LabCorp)—known as

FibroTest (BioPredictive) in Europe—and FibroSpect (Prometheus). HCV FibroSure utilizes 5 different tests as well as age and gender to determine the risk of fibrosis. In contrast, FibroSpect utilizes the 3 markers hyaluronic acid, tissue-inhibited matrix metalloproteinase inhibitor-1, and alpha-2 macroglobulin.

It is also important to note that there is ongoing investigation into the development and improvement of novel markers, both individually and for the various panels, and there will likely be new markers and adjustments to older ones, with time and additional clinical experience.

G&H How do serologic markers represent an improvement over liver biopsy or ultrasound?

DR There are several potential advantages to the use of serologic tests. First, they are not invasive and are associated with essentially no significant risks. Second, at least in theory, by definition they evaluate the entire liver and thus may not be subject to sampling variability.

G&H Could you describe the sensitivity and specificity of serologic markers for detecting fibrosis and differentiating mild fibrosis from moderate-to-severe fibrosis?

DR The sensitivity of serologic markers for detecting advanced fibrosis is generally fairly high, as is the specificity. The main weakness with these tests, however, is that they are not very adept at differentiating mild from moderate fibrosis, as the sensitivity for detecting mild fibrosis is poor. All of the various serologic markers have

Table 1. Combined Panels of Blood Markers for the Detection of Liver Fibrosis

Name	Components
AST/ALT ratio	AST/ALT
*Forns test	platelets, GGT, cholesterol
APRI	AST, platelets
†PGA index	platelets, GGT, apolipoprotein A
FibroTest	GGT, haptoglobin bilirubin, apolipoprotein A, alpha-2-macroglobulin
FibroSpect	HA, TIMP-1, alpha-2-macroglobulin
*FPI	AST, cholesterol, HOMA-IR
ELF	Numerous ECM proteins and proteinases, including collagen IV, collagen VI, PIIINP, MMP-2, MMP-9, TIMP-1, tenascin, laminin, and HA

*Also includes age.

†The index was later modified to the PGAA, which added alpha-2-macroglobulin.

*Also includes age and history of alcohol intake.

ALT=alanine aminotransferase; APRI=AST to platelet ratio index; AST=aspartate aminotransferase; ECM=extracellular matrix; ELF=enhanced liver fibrosis test; FPI=fibrosis probability index; GGT=gamma glutamyl transpeptidase; HA=hyaluronic acid; HOMA-IR=homeostasis model assessment-insulin resistance; MMP-2=matrix metalloproteinase 2; MMP-9=matrix metalloproteinase 9; PGA=prothrombin time, GGT, apolipoprotein A; PIIINP=amino terminal propeptide of type III collagen; TIMP-1=tissue inhibitor of matrix metalloproteinase 1.

Adapted from Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. *Hepatology*. 2006;43(2 suppl 1):S113-S120.

this problem, which is also shared by the gold standard of fibrosis detection, liver biopsy, due to its high sampling variability and errors, as mentioned above. The general lack of sensitivity and specificity in detecting these intermediate grades of fibrosis is the reason that more physicians are not using serologic markers for detecting fibrosis.

It should be noted that the studies evaluating the sensitivity and specificity of serologic markers are limited for the following reasons: studies have not been consistent in terms of measurements; the types of liver disease studied have varied, the numbers of patients studied overall have been limited, though more data are becoming available; the definition of fibrosis has diverged in different studies (and the degree of fibrosis considered to be advanced is variable); and finally, the

use of absolute cutoffs for sensitivity and specificity measurements is arbitrary.

G&H Are serologic markers an option for identifying smaller patient populations that require surveillance screening from at-risk patients with chronic liver disease?

DR The potential use of serologic markers as screening tools is dependent upon their specificity and sensitivity for detecting patients with advanced disease. If a marker is not sensitive, it will not be accurate. Due to their difficulties of differentiating mild from moderate fibrosis, I do not think that using serologic markers as screening tools for the general population would be cost-effective. However, screening with serologic markers or panels may be helpful to identify patients with advanced fibrosis among patients with known liver disease such as hepatitis C, hepatitis B, or autoimmune hepatitis. Serologic markers are quite sensitive and specific in advanced fibrosis, as mentioned above, and would certainly be more effective in populations with advanced fibrosis than with less severe fibrosis.

Another area of related interest is the potential for serologic markers to track the progression of disease. Emerging evidence suggests that this may be a particularly attractive attribute of noninvasive testing.

G&H Has there been any research regarding the cost-effectiveness of using fibrotic serologic markers in general?

DR Although the current cost of many markers and/or panels of markers is less than liver biopsy (including the lower rate of complications), there is currently limited understanding of the cost-effectiveness of serologic markers for fibrosis. Thus, further cost-effectiveness analyses will be useful.

G&H Could you discuss any other noninvasive tools for identifying the presence and severity of liver fibrosis?

DR One promising tool is transient elastography (FibroScan, Echosens), which is a novel noninvasive method that uses pulse-echo ultrasound to measure liver stiffness and predict fibrosis stage. Thus far, transient elastography appears to be a bit more sensitive and specific than serologic markers. In addition, transient elastography is entirely noninvasive (perhaps even less so than serologic markers because there is no need to even draw blood). Transient elastography may have another advantage compared to liver biopsy in

that it is able to evaluate a larger portion of the liver than liver biopsy.

It is noteworthy that there remains the promise that novel imaging techniques will allow noninvasive assessment of liver fibrosis and that investigation in this area is quite active.

Suggested Reading

Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. *Hepatology*. 2006; 43(2 suppl 1):S113-S120.

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