Noninvasive assessment of hepatic fibrosis: Overview of serologic tests and imaging examinations

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INTRODUCTION

Hepatic fibrosis occurs in response to chronic liver injury. Regardless of the cause, the response to liver injury includes collapse of hepatic lobules, formation of fibrous septa, and hepatocyte regeneration with nodule formation. Extracellular matrix components accumulate in the liver as a result of imbalances in their production, deposition, and degradation. This diffuse process may ultimately progress to cirrhosis, with its accompanying consequences of portal hypertension and impaired hepatic function. (See "Pathogenesis of hepatic fibrosis".)

Hepatic fibrosis was originally thought to be irreversible, but it is now recognized as a dynamic process with the potential for significant resolution. Molecular insights into fibrogenesis and fibrosis regression offer potential targets for antifibrotic therapy and increase the need for noninvasive means to measure changes in fibrosis.

Conventional biochemical and serologic tests, when examined alone, are of little value for the assessment of fibrosis. As a result, histopathologic examination of a liver biopsy specimen is the gold standard for staging hepatic fibrosis. However, a liver biopsy has limitations. Because it is invasive, it may be associated with complications. In addition, it can only sample a small portion of the liver and is thereby susceptible to sampling variation and inter- and intraobserver variability. These issues have led to the development of noninvasive means to estimate the amount of hepatic fibrosis present. (See "Approach to liver biopsy".)

This topic will review the serologic tests and imaging examinations used for the noninvasive assessment of hepatic fibrosis. Ultrasound-based elastography is discussed in more detail separately. The histologic assessment of hepatic fibrosis is discussed elsewhere. (See "Noninvasive assessment of hepatic fibrosis: Ultrasound-based elastography" and "Histologic scoring systems for chronic liver disease".)

STAGES OF FIBROSIS

Noninvasive tests of hepatic fibrosis attempt to predict the stage of hepatic fibrosis that would be seen histologically. There are several histologic scoring systems for chronic liver disease. Many use five-point scales such as the METAVIR score (see "Histologic scoring systems for chronic liver disease", section on 'METAVIR score'):

- F0: No fibrosis
- F1: Portal fibrosis without septa
- F2: Few septa
- F3: Numerous septa without cirrhosis
- F4: Cirrhosis

Patients are typically considered to have significant fibrosis if their fibrosis score is ≥F2.

CLINICAL USES

Noninvasive tests of hepatic fibrosis are primarily used for staging of fibrosis in patients with chronic liver disease. We typically consider noninvasive testing for patients with chronic viral hepatitis at the time of initial evaluation to determine the likelihood of advanced liver fibrosis. In patients who are not successfully treated, subsequent testing is useful to determine if there is progression of fibrosis. The tests are also being used in patients with other chronic liver diseases such as nonalcoholic fatty liver disease and primary sclerosing cholangitis. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'Noninvasive assessment of hepatic fibrosis' and "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Transient elastography'.)

The tests are often used to differentiate patients with significant fibrosis (F2 to F4) from those with minimal or no fibrosis (F0 to F1). Many of the tests have been evaluated in specific populations (often patients with chronic hepatitis C virus [HCV]), which should be kept in mind when attempting to generalize the results to other populations.

In patients with chronic HCV, the assessment of fibrosis progression can be valuable for several reasons:

- The presence of advanced fibrosis (bridging fibrosis or cirrhosis) guides certain decisions regarding treatment, including optimal regimen and duration, and is a key factor that determines urgency of treatment. (See 'Stages of fibrosis' above and "Overview of the management of chronic hepatitis C virus infection".)
- The approximate time to the development of cirrhosis can be estimated. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection", section on 'Findings in cirrhosis'.)
- Patients with cirrhosis require screening for complications such as hepatocellular carcinoma and portal hypertension. (See "Surveillance for hepatocellular carcinoma in adults", section on 'Patients with cirrhosis'.)

Noninvasive testing for hepatic fibrosis may also have a role in monitoring patients taking medications associated with chronic liver damage, such as methotrexate [1-5]. In a study of 24 patients who were taking methotrexate and had undergone a liver biopsy, elastography correctly identified 88 percent of patients who did not have significant fibrosis, and FibroTest identified 83 percent of the patients who had significant fibrosis [5]. (See 'Transient elastography' below and 'FibroTest, FibroSure, and ActiTest' below and "Hepatotoxicity associated with chronic low-dose methotrexate for nonmalignant disease".)

CHOICE OF TEST

There are two general categories of noninvasive tests for fibrosis: serologic panels of tests and imaging examinations (table 1). Serologic testing is more widely available. However, while tremendous progress has been made in improving the accuracy of serum markers of hepatic fibrosis, they cannot yet supplant direct histologic analysis. When available, radiologic measurement of elasticity can be used alone or in combination with serologic testing.

We typically use a combination of serologic testing and ultrasound-based transient elastography (TE). The combination of tests results in fewer patients with an indeterminate fibrosis score and an increased specificity. TE is the most commonly used imaging test because it is widely available and has been validated in large populations. Other imaging methods for assessing hepatic fibrosis include magnetic resonance elastography (MRE), acoustic radiation force impulse (ARFI) imaging, and cross-sectional imaging. (See 'Imaging examinations' below.)

The specific serologic test will depend on local availability. We often use the Hepascore panel as we have found it to be widely available and reliable. (See 'Combining tests' below.)

There are four commercial serum marker systems that have been extensively validated: FibroTest/FibroSure (marketed in the United States by LabCorp), Hepascore (Quest Diagnostics), FibroSpect (Prometheus Corp), and the ELF score (European Liver Fibrosis Study Group panel). In addition, the aspartate aminotransferase to platelet ratio (APRI) has also been studied extensively. The APRI has the advantage of being easily calculated using data available from routine laboratory tests. In the case of proprietary panels, the blood samples may need to be sent out for analysis. (See 'Serologic tests' below.)

All the serum tests have limitations:

- They typically reflect the rate of matrix turnover, not deposition, and thus tend to be more elevated when there is high inflammatory activity. By contrast, extensive matrix deposition can go undetected if there is minimal inflammation.
- None of the markers are liver-specific, and concurrent sites of inflammation or fibrosis may contribute to serum levels.
- Serum levels are affected by clearance rates, which may be impaired either due to sinusoidal endothelial cell dysfunction or impaired biliary excretion.
- They are surrogates, not biomarkers.

SEROLOGIC TESTS

A variety of serologic markers have been evaluated to predict the degree of fibrosis in the liver, and panels have been developed that combine assays of multiple markers to improve predictive ability. The most studied panels are the aspartate aminotransferase (AST) to platelet ratio (APRI), FibroTest/FibroSure, Hepascore, and FibroSpect. Overall, studies of the various panels suggest that they have good ability to differentiate patients with significant fibrosis (F2 to F4) from those without significant fibrosis (F0 to F1) [6]. A disadvantage of these panels is that they are not able to reliably differentiate between the different stages of fibrosis, and indeterminate outcomes are common (up to 50 percent with the FibroTest). No panel has yet emerged as the standard of care, and the choice of panel is often dictated by local availability.

Serologic markers of hepatic fibrosis can broadly be categorized as indirect or direct:

- Indirect markers reflect alterations in hepatic function, but do not directly reflect extracellular matrix metabolism. Examples include the platelet count, coagulation studies, and liver aminotransferases. (See 'Panels of indirect markers of fibrosis' below.)

- Direct markers of fibrosis reflect extracellular matrix turnover. Examples include procollagen types I and III, hyaluronic acid, and tissue inhibitor of metalloproteinase (table 2). (See 'Direct markers of fibrosis' below.)

The ability of panels of these markers to detect patients with significant fibrosis was examined in a systematic review of 14 studies of fibrosis panels [7]. The median area under the receiver operating characteristic (ROC) curve was 0.82, suggesting good predictive ability. However, the tests were not able to reliably differentiate between the different stages of fibrosis, and the authors estimated that only 35 percent of patients would be classifiable as either having significant fibrosis or not having significant fibrosis. The remaining patients would have test results that were indeterminate. (See "Evaluating diagnostic tests", section on 'Receiver operating characteristic curves'.)

In addition to detecting significant fibrosis, the panels may also be able to monitor changes in fibrosis over time. This monitoring over time may be more important than assessing the stage of disease at one particular time point since hepatic fibrogenesis is a dynamic process.

Indirect markers of fibrosis — Indirect markers of hepatic fibrosis include serologic biochemical tests that reflect alterations in hepatic function but do not directly reflect extracellular matrix metabolism. The individual markers include serum aminotransferase levels, platelet count, coagulation parameters, gamma-glutamyl transferase (GGT), total bilirubin, alpha-2-macroglobulin, and alpha-2-globulin (haptoglobin). These individual markers have been combined into serologic panels to predict the presence of hepatic fibrosis.

Panels of indirect markers of fibrosis — Interpretation of serum aminotransferase levels, coagulation parameters, and platelet count have been used in clinical practice to predict the presence or absence of cirrhosis. Several studies have also evaluated the accuracy of combinations (or ratios) of these measures [8-12]. The most studied combinations include the APRI, FibroTest/FibroSure, and Hepascore.

AST to platelet ratio index — The APRI is based on the AST level and platelet count and is easy to calculate (calculator 1) [13]. The APRI is calculated using the AST elevation (which is the AST level divided by the upper limit of normal [ULN] for the lab) and the platelet count per mm^3 divided by 1000.

APRI = (AST elevation/platelet count) x 100

As an example, a patient with an AST level of 90 international unit/L in a lab with an ULN = 45 international unit/L and a platelet count of 120,000/mm^3 would have an APRI of:

(2/120) x 100 = 1.67

The APRI has primarily been studied in patients with hepatitis C virus (HCV), human immunodeficiency virus (HIV) and HCV coinfection, or alcoholic liver disease [13-20]. A meta-analysis of 40 studies found that for predicting significant fibrosis (F2 to F4), an APRI cutoff of 0.7 had a sensitivity of 77 percent and a specificity of 72 percent [21]. For predicting cirrhosis (F4), an APRI cutoff of 1.0 had a sensitivity of 76 percent and a specificity of 72 percent. However, accuracy was lower in patients coinfected with HIV and HCV [21]. Thus, the APRI appears most useful for excluding significant fibrosis in patients with chronic HCV.

APRI has also been looked at in patients with nonalcoholic fatty liver disease (NAFLD). The ability of the APRI to predict outcomes in patients with NAFLD was examined in a retrospective series with 320 patients [22]. The area under the ROC curve for predicting adverse liver-related outcomes was 0.80 and for predicting death or liver transplantation was 0.63.

FibroTest, FibroSure, and ActiTest — FibroTest and FibroSure are identical proprietary tests marketed under different names in Europe and America, respectively. ActiTest is a modification of FibroTest. The tests have primarily been studied in patients with hepatitis B and C [23-28].

FibroTest involves assessment of alpha-2-macroglobulin, alpha-2-globulin (haptoglobin), gamma globulin, apolipoprotein A1, GGT, and total bilirubin [29]. It also takes into account the patient's age and sex. Results from the individual assays are combined and are used to classify patients having mild fibrosis (F0 to F1), significant fibrosis (F2 to F4), or an indeterminate stage of fibrosis. The sensitivity for detection of significant fibrosis is approximately 60 to 75 and the specificity is approximately 80 to 90 percent, respectively [23-26,28]. In one study, the severity of disease was correctly identified as being mild or significant in approximately 46 percent of patients [25].

ActiTest is a modification of the FibroTest that incorporates ALT and reflects both liver fibrosis and necroinflammatory activity. ActiTest appears to improve identification of more advanced fibrosis associated with histologic inflammation [30]. Patients with chronic HCV who are treated with pegylated interferon therapy show an improvement in both ActiTest and FibroTest scores compared with an observed untreated control group, supporting a role in monitoring response to treatment [31]. A meta-analysis that included a total of 1570 patients concluded that these tests were reliable alternatives to liver biopsy in patients with chronic HCV [27].

Hepascore — Hepascore involves a combination of bilirubin, GGT, hyaluronic acid, alpha-2-macroglobulin, age, and sex. In one study, Hepascore was no more accurate than the FibroTest in patients with alcoholic liver disease [32]. In other studies, Hepascore was useful for predicting fibrosis in HCV [33,34].

AST/ALT ratio — The AST/ALT ratio is approximately 0.8 in normal subjects. Some studies have suggested that a ratio >1 suggests the presence of cirrhosis [35]. However, study findings have been inconsistent, and the clinical utility of this ratio for diagnosis of cirrhosis remains uncertain [35-38]. The AST/ALT ratio has also been incorporated in predictive models in patients with NAFLD. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults" and "Approach to the patient with abnormal liver biochemical and function tests", section on 'Laboratory tests'.)

Other indirect markers — Tests continue to be developed to detect fibrosis serologically, though they have not been studied as extensively as the APRI or FibroTest/FibroSure. Some of these have been derived for use in specific groups of patients (eg, testing for fibrosis in patients with NAFLD).

- **FIB-4 index** – The FIB-4 index combines biochemical values (platelet count, ALT, and AST) and age. It had good predictive accuracy for advanced fibrosis in at least two studies involving patients with chronic HCV [39,40]. In another report, it performed better than other serologic markers for predicting advanced fibrosis in patients with NAFLD [41]. It also appears to be helpful for predicting outcomes in patients with NAFLD. In a retrospective series with 320 patients with NAFLD, the area under the ROC curve for predicting adverse liver-related outcomes was 0.81 and for predicting death or liver transplantation was 0.67 [22].

  FIB-4 values have also been associated with the risk of developing hepatocellular carcinoma (HCC) among patients who consume alcohol. In a study of 6661 patients who consumed at least 10 g of alcohol per day, those with a FIB-4 index ≥1.75 were more likely than those with an index <1.0 to develop HCC after a median follow-up of 6.2 years (hazard ratio [HR] 5.2; 95% CI 1.1-24) [42]. If the FIB-4 index was ≥2.1, the risk was even higher (HR 13.6; 95% CI 3.8-49). The risk was highest among patients who had a FIB-4 index ≥2.1 and consumed >30 g of alcohol per day (HR 16.6; 95% CI 3.9-71).

- **NAFLD fibrosis score** – The NAFLD fibrosis score is another score used to assess the probability of fibrosis in patients with NAFLD. It takes into account the patient's age, body mass index (BMI), blood glucose levels, aminotransferase levels, platelet count, and albumin. In a validation study, a high NAFLD fibrosis score cutoff (>0.676) was associated

with a positive predictive value for advanced fibrosis (F3 to F4) of 82 percent (sensitivity 43 percent, specificity 96 percent), and a low cutoff value (<-1.455) was associated with a negative predictive value of 88 percent (sensitivity 77 percent, specificity 71 percent) [43]. It has also been used to predict outcomes in patients with NAFLD. In the same retrospective study described above, the area under the ROC curve for predicting adverse liver-related outcomes was 0.86 and for predicting death or liver transplantation was 0.70 [22].

- **PGA index** – The PGA index combines the measurement of the prothrombin index, GGT level, and apolipoprotein A1 level (PGA). It was devised originally as a simple biologic index for detection of alcoholic liver disease [44]. It has been validated in patients with a variety of chronic liver diseases, but particularly alcoholic liver disease. Its accuracy for the detection of cirrhosis has ranged between 66 and 72 percent [44,45].

- **FibroIndex** – The FibroIndex is derived from the platelet count, AST, and gamma globulin measurements [46]. It has been proposed as a marker of significant fibrosis in chronic HCV. Its accuracy is still being determined.

- **Forns index** – The Forns index takes into account age, GGT, cholesterol, and platelet count [47]. It has primarily been studied in patients with HCV. It appears to have performance characteristics similar to those seen with the APRI [48,49].

- **Fibrometer** – The Fibrometer test involves a combination of the platelet count, prothrombin index, AST, alpha-2-macroglobulin, hyaluronic acid, blood urea nitrogen, and age. It performed well in predicting severe fibrosis in patients with chronic viral hepatitis [9,50,51], but was no better than the FibroTest in predicting severe fibrosis in alcoholic liver disease [32].

- **BARD score** – The BARD score was developed to predict fibrosis in patients with NAFLD. The BARD score takes into account BMI, the AST/ALT ratio, and the presence of diabetes mellitus [52]. In a series of 126 patients with NAFLD, the positive and negative predictive values of the BARD score for advanced fibrosis were 69 and 96 percent, respectively, with an area under the ROC curve of 0.87 [53]. In another study, the areas under the ROC curves for the BARD score predicting liver-related adverse outcomes and death or liver transplantation were 0.73 and 0.66, respectively [22].

- **Proteomics and glycomics** – Patterns of proteins or glycoproteins can be assessed by mass spectroscopy of serum samples [54]. These methods represent "surrogate" markers of fibrosis and in fact, the identities of the peaks are generally not known. Nevertheless, impressive correlations have been reported. In a study from Belgium, combining serum

glycomics with FibroTest resulted in a sensitivity for predicting cirrhosis of 100 percent and a specificity of 75 percent [55].

Direct markers of fibrosis — Liver fibrosis results in both qualitative and quantitative changes in extracellular matrix markers. Potential markers of fibrosis include products of collagen synthesis or degradation, enzymes involved in matrix biosynthesis or degradation, extracellular matrix glycoproteins, and proteoglycans/glycosaminoglycans. Direct markers of fibrosis can be divided into (table 2):

- Markers associated with matrix deposition
- Markers associated with matrix degradation
- Cytokines and chemokines associated with fibrogenesis

Panels of direct markers of fibrosis — Direct markers of fibrosis have been combined into panels to predict hepatic fibrosis. The panels may also include indirect markers of fibrosis. These panels include FibroSpect II, Serum Hyaluronic Acid level with serum AST and Albumin level (SHASTA), and the European Liver Fibrosis panel (ELF). As with indirect markers, none have yet evolved as a standard for clinical practice.

FibroSpect II — The FibroSpect II panel uses a combination of serum hyaluronic acid, tissue inhibitor of metalloproteinase-1 (TIMP-1), and alpha-2-macroglobulin. The combination of these assays reliably differentiates patients with chronic HCV with moderate to severe fibrosis from those with no or mild fibrosis [56-58]. In a validation study with 402 patients with chronic HCV, the panel had a sensitivity of 77 percent and a specificity of 73 percent for predicting moderate to severe fibrosis [57].

European Liver Fibrosis panel — ELF is a proprietary algorithm that takes into account hyaluronic acid level, amino-terminal propeptide of type III collagen level, and TIMP-1. In a study that included 1021 patients with chronic liver disease who were undergoing liver biopsy, a threshold score of 0.102 was associated with a sensitivity of 87 to 90 percent and a specificity of 41 to 51 percent for diagnosing moderate or severe fibrosis [59]. If a threshold of 0.457 was used, the specificity increased to 95 percent. While the original calculation included age, it was subsequently removed.

Specific markers — The individual direct markers incorporated into the serologic panels may be associated with matrix deposition or matrix degradation, or they may be cytokines and chemokines associated with fibrogenesis.

Markers associated with matrix deposition — Several markers associated with matrix deposition have been studied (table 2). Most are based upon the detection of various

procollagen peptides, including procollagen type I carboxy-terminal peptide, procollagen type III amino-terminal peptide, type I and type IV collagen, laminin, hyaluronic acid, and YKL-40 (chondrex).

- **Procollagen type I carboxy-terminal peptide (PICP)** – PICP levels are increased in patients with cirrhosis. In patients with alcoholic liver disease, PICP levels are not as accurate as type IV collagen or procollagen type III amino-terminal peptide (PIIINP) levels for detecting the presence of cirrhosis, quantifying disease severity, and indicating the presence of associated alcoholic hepatitis [60].

  PICP levels have also been studied in patients with chronic HCV. In one report, PICP levels were normal in those with mild chronic hepatitis and were elevated in approximately half of the patients with moderate to severe hepatitis or cirrhosis [61]. In contrast to PIIINP, there was no correlation between levels of PICP and a sustained response to interferon-alpha therapy.

- **Procollagen type III amino-terminal peptide (PIIINP)** – PIIINP levels are elevated in acute and chronic liver diseases and correlate with serum aminotransferase levels in patients with active hepatitis and with serum bilirubin levels in those with cirrhosis [62-66]. Serum levels of PIIINP have been shown to correlate with the histologic stage of hepatic inflammation and fibrosis in alcoholic liver disease, viral hepatitis, and primary biliary cirrhosis [62,63,66-74].

  Reduction or normalization of PIIINP levels has been observed in patients who abstain from alcohol [69,70], who successfully respond to immunosuppressive therapy for autoimmune hepatitis [75], or who respond to treatment for HCV [61,76,77]. In patients with primary biliary cirrhosis (PBC), at least one study supported the use of PIIINP as a prognostic marker for survival [67], while other studies demonstrated a correlation with the Mayo risk score [66,78].

- **Type I and type IV collagen** – Levels of type I collagen are increased in all types of liver fibrosis. Messenger RNA (mRNA) levels of type I collagen are increased 60- to 70-fold in activated hepatic stellate cells [79]. In patients with chronic liver disease, serum levels of type I collagen are increased and correlate with fibrosis score but not with the inflammatory activity score [68]. Despite this correlation, there is no association with portal pressure [80].

  Serum type IV collagen levels are increased in patients with chronic liver disease compared with normal controls [81]. Type IV collagen is located in the basement membranes of blood and lymph vessels and bile ducts, around nerve axons, and in perisinusoidal spaces.

One hypothesis suggests that the increased levels may reflect capillarization of the perisinusoidal wall seen in hepatic fibrogenesis [82,83]. Type IV collagen levels have been shown to correlate with fibrotic stage in alcoholic liver disease, hemochromatosis, and HCV [81,84-87]. In one study, type IV collagen was more sensitive than laminin, hyaluronic acid, and PIIINP in diagnosing fibrosis in patients with chronic hepatitis [88].

- **Laminin** – Laminin is noncollagenous glycoprotein synthesized by the hepatic stellate cells and deposited in the basement membrane of the liver. In chronic liver injury, basement membrane components, particularly laminin, are increasingly deposited around the vessels, in the perisinusoidal spaces, and in the portal tracts [82,89]. Laminin appears to be superior to PIIINP, but not as good as collagen type IV, in predicting fibrotic stage in chronic viral hepatitis [90]. Serum levels of laminin and the pepsin-resistant fragment of laminin (laminin P1) are elevated in patients with chronic liver disease associated with alcohol and viral hepatitis, which may reflect an increase in perisinusoidal fibrosis [91]. Serum levels of laminin correlate with the severity of fibrosis and hepatitis, Child-Pugh score, hepatic venous pressure gradient, and complications of liver cirrhosis [14,92-95]. Alcohol abstinence has been associated with a reduction in laminin levels [69,96]. However, a response to treatment for HCV is not always associated with normalization of serum laminin levels [61,76,97].

- **Hyaluronic acid** – Hyaluronic acid, a glycosaminoglycan synthesized by hepatic stellate cells and degraded by the liver sinusoidal cells, is a component of the extracellular matrix [98]. High levels of hyaluronic acid in patients with liver disease (particularly those with cirrhosis) have been related to impaired function of the endothelial sinusoidal cells, and reflect increased fibrogenesis [99]. Elevated hyaluronic acid levels correlate with hepatic inflammation and fibrosis in alcoholic liver disease and with fibrosis in patients with chronic hepatitis B or C virus, NAFLD, and PBC [56,65,74,85,99-108]. A reduction of hyaluronic acid levels was observed in patients with HCV who had a biochemical response to interferon monotherapy [102]. In addition, reduced levels of hyaluronic acid correlated with an improvement in fibrosis, whereas increased levels were associated with worsening of fibrosis. Serum hyaluronic acid levels have the greatest predictive accuracy for advanced fibrosis [56].

- **YKL-40 (chondrex)** – YKL-40 is a 38-kDA glycoprotein. Its function is unknown, but the pattern of its expression in certain tissues such as human liver or cartilage suggests a function in remodeling or degradation of extracellular matrix. Immunohistochemical staining of fibrotic liver tissue has demonstrated YKL-40 in areas of fibrosis and in particular areas with active fibrogenesis [109]. Serum levels of YKL-40 are increased in

patients with alcoholic liver disease, particularly those with alcoholic hepatitis [109,110]. The serum levels are significantly correlated with the degree of liver fibrosis and the plasma level of hyaluronic acid [111]. Elevated serum levels have also been described in patients with posthepatic causes of cirrhosis [109]. Elevation of YKL-40 correlates with the degree of hepatic fibrosis. A study comparing it with the FibroSpect II assay and serum hyaluronic acid levels found that YKL-40 had the highest false-positive rate for predicting fibrosis in patients with chronic hepatitis C [56].

Markers associated with matrix degradation — Matrix degradation occurs predominantly as a consequence of the action of a family of enzymes known as matrix metalloproteinases (MMPs). These enzymes are synthesized intracellularly and are secreted in a proenzyme form, requiring cleavage by cell surface mechanisms for functional activity. They are in turn inhibited by tissue inhibitors of metalloproteinases (TIMPs). (See "Pathogenesis of hepatic fibrosis".)

- **Matrix metalloproteinases** – The observation that MMPs are expressed in liver injury suggests that degradation of normal liver matrix may contribute to the pathogenesis of hepatic fibrosis [97]. The three most important MMPs appear to be: MMP-2 (gelatinase-A), MMP-3 (stromelysin), and MMP-9 (gelatinase-B). However, studies looking to see whether MMP-2, MMP-3, or MMP-9 levels correlate with hepatic fibrosis have reached variable conclusions. Some suggest MMP-2 may predict hepatic fibrosis [85,112], whereas others do not [113]. MMP-3, and MMP-9 levels have not been shown to correlate with fibrosis [114,115].

- **TIMP-1 and -2** – TIMP-1 and -2 inhibit matrix degradation, which may promote the progression of fibrosis. Studies of explanted livers from patients undergoing liver transplantation have demonstrated increased hepatic expression of TIMP-1 and -2 in patients with sclerosing cholangitis, biliary atresia, PBC, and autoimmune hepatitis [116,117]. In patients with chronic HCV, serum TIMP-1 and -2 levels were significantly correlated with the histologic activity index and with fibrosis, respectively [113]. TIMP-1 levels had a sensitivity of 100 percent for diagnosing cirrhosis, but they had a low specificity [118]. In another report, TIMP-1 levels correlated with type IV collagen, PIIINP, and laminin P1 levels [119].

Cytokine and chemokines associated with hepatic fibrosis — A number of cytokines that have a role in hepatic fibrogenesis have been identified, some of which may be useful clinical markers of hepatic fibrogenesis. These include transforming growth factor (TGF)-alpha, TGF-beta, and platelet-derived growth factor (PDGF). (See "Pathogenesis of hepatic fibrosis".)

- **TGF-alpha** – TGF-alpha is a potent stimulator of mitosis of normal and neoplastic hepatocytes. In addition, TGF-alpha also appears to have a pivotal role in hepatocarcinogenesis [120]. TGF-alpha levels are increased in patients with cirrhosis and correlate with bilirubin and Child-Pugh classification, suggesting they are closely correlated with the severity of liver dysfunction [121].

- **TGF-beta** – TGF-beta is the dominant stimulus for the production of extracellular matrix by hepatic stellate cells. Hepatic mRNA levels of TGF-beta are increased in chronic liver disease in association with increases in mRNA levels of type I collagen [122]. Serum levels of total and biologically active TGF-beta are increased in patients with HCV-related chronic liver disease compared with controls, and they correlate with fibrosis score [123]. In patients receiving interferon therapy for HCV, levels of TGF-beta decrease in response to a reduction in necroinflammatory activity, in the absence of changes in fibrosis [124,125]. (See "Pathogenesis of hepatic fibrosis".)

- **PDGF** – PDGF is upregulated following liver injury [126]. At least one study suggested that PDGF levels correlated with the severity of liver disease [127].

IMAGING EXAMINATIONS

Elastography and conventional morphologic cross-sectional examinations (ie, ultrasound, computed tomography [CT], or magnetic resonance imaging [MRI]) are imaging-based procedures to measure liver fibrosis [128].

Elastography — Elastography estimates liver stiffness by applying mechanical waves and measuring their propagation speed through tissue using imaging. Modality options include ultrasound (ie, transient elastography [TE], acoustic radiation force impulse [ARFI] imaging, two-dimensional [2D] shear wave elastography [SWE]), and MRI (ie, magnetic resonance elastography [MRE]). 2D-SWE and MRE can be integrated with conventional morphologic liver imaging in the same sitting.

Strain elastography images tissue motion along the pathway and SWE tangential to the pathway of the applied mechanical force.

Ultrasound-based elastography is discussed in detail elsewhere. (See "Noninvasive assessment of hepatic fibrosis: Ultrasound-based elastography".)

Transient elastography — Vibration-controlled TE uses shear wave imaging to estimate liver stiffness. A mechanical vibrating source is applied to tissue, and shear waves created by the

excitation are measured with an ultrasound detector (image 1). During the imaging examination, the ultrasound operator should acquire at least ten valid measurements. TE does not offer morphologic imaging guidance as the ultrasound detector is one-dimensional (1D).

TE accurately diagnoses cirrhosis (fibrosis stage 4 [F4]) and is useful for distinguishing advanced fibrosis (ie, fibrosis stage 2 [F2] or greater) from minimal or no fibrosis (fibrosis stage 1 [F1] or fibrosis stage 0 [F0]). In a multicenter trial of patients with hepatitis C virus (HCV) or hepatitis B virus (HBV), 1D-TE showed high receiver operating characteristic (ROC) areas under the curve (AUC) in diagnosing fibrosis in the HCV group (fibrosis stage ≥F2: 0.89; fibrosis stage ≥F3: 0.92; fibrosis stage = F4: 0.92) and in the HBV group (fibrosis stage ≥F2: 0.73; fibrosis stage ≥F3: 0.83; fibrosis stage = F4: 0.90) [14,129].

Receiver operating characteristic curves are discussed in more detail, separately. (See "Evaluating diagnostic tests", section on 'Receiver operating characteristic curves'.)

One system for performing TE, FibroScan, has been approved by the US Food and Drug Administration [130].

Acoustic radiation force impulse imaging — ARFI imaging is an ultrasound-based technique that, by evaluating the wave propagation speed, allows assessment of tissue stiffness to estimate liver fibrosis [131]. A short-duration, high-intensity acoustic pulse is applied and tissue displacement in the same direction as the stress is measured. ARFI does not offer morphologic imaging guidance as the ultrasound detector is 1D. (See "Noninvasive assessment of hepatic fibrosis: Ultrasound-based elastography", section on 'Shear wave speed measurements using acoustic radiation force impulse (ARFI)'.)

The diagnostic performance of ARFI and TE may be comparable for detection of early- and late-stage liver fibrosis [132]. In a single-center study of 321 patients with chronic liver disease (eg, viral hepatitis, nonalcoholic steatohepatitis), AUC of the ROC for ARFI versus TE was 0.77 and 0.74 to diagnose fibrosis stage ≥F2, and 0.84 and 0.80 to diagnose fibrosis stage ≥F4. However, ARFI performed slightly better for fibrosis stage ≥F4 diagnosis (AUC of 0.92) in patients without obesity, a difference not noted with TE.

Optimal cutoff values for diagnosis of fibrosis varies among studies and vendor systems [133-145]. In a representative study that included a training set of 88 patients, the sensitivity of ARFI imaging for fibrosis stage ≥F2 was 85 percent using a cutoff of 1.44 m/s, and was 92 percent for fibrosis stage 4 (F4) using a cutoff of 1.9 m/s [144]. The corresponding specificities were 76 and 87 percent, respectively.

Two-dimensional shear wave elastography — Two-dimensional (2D) shear wave elastography (SWE) is another ultrasound-based technique. Because the detector is comprised of a linear array, 2D-SWE offers concurrent real-time grayscale imaging of the target tissue (image 2). As 2D-SWE is integrated into the same scanners that perform a conventional morphologic ultrasound, the two procedures can be performed in the same sitting.

With 2D-SWE, multiple focal zones are interrogated in rapid succession creating a near cylindrical shear wave cone. This enables monitoring of a volume of tissue from which to measure stiffness.

2D-SWE accurately diagnoses early liver fibrosis in patients with chronic liver disease [146-148]. AUC of the ROC for diagnosis of fibrosis stage ≥F2 is typically >0.75. Greater accuracy is observed in diagnosing cirrhosis, with AUC >0.80 for fibrosis stage ≥F4.

In patients with chronic HBV, 2D-SWE is more accurate than serologic tests in diagnosing fibrosis stage ≥F2, primarily because it yields fewer false positives [147]. In a multicenter trial of 402 patients with chronic HBV infection, 2D-SWE, aspartate aminotransferase (AST) to platelet ratio, and FIB-4 index all demonstrated sensitivities of >91 percent; however, specificities were 30 percent (95% CI 20.0-43.0), 11 percent (95% CI 7.0-32.0) and 12 percent (95% CI 5.0-23.0), respectively.

Magnetic resonance elastography — MRE can also be performed to measure liver fibrosis at centers where the necessary technology and expertise are available. Unlike ultrasound-based elastography, MRE interrogates the entire liver and is not limited to a defined target volume for sampling. As MRE is performed on a conventional MRI scanner that has been equipped with added hardware and software, elastography and morphologic imaging can be performed in the same sitting.

With MRE, the mechanical waves are generated by an "active driver," usually located outside the scanner room. Pressure waves are transmitted via tubing to a nonmetallic "passive driver" placed against the patient's right anterior chest wall overlying the liver. A flexible membrane on the surface of the passive driver conducts the vibrations into the body to generate propagating mechanical waves. Imaging with fast pulse sequences measures the speed of the shear waves through the liver and thereby estimates tissue stiffness.

A meta-analysis that included 12 studies of MRE found the following test characteristics [149]:

- Detecting any fibrosis (fibrosis stage ≥F1): Optimal cutoff 3.45 kPa, sensitivity 73 percent, specificity 79 percent

- Detecting significant fibrosis (≥F2): Optimal cutoff 3.66 kPa, sensitivity 79 percent, specificity 81 percent
- Detecting advanced fibrosis (≥F3): Optimal cutoff 4.11 kPa, sensitivity 85 percent, specificity 85 percent
- Detecting cirrhosis (F4): Optimal cutoff 4.71, sensitivity 91 percent, specificity 81 percent

MRE has been compared with ultrasound-based TE. In one report, MRE had similar test characteristics to ultrasound-based TE [150]. Other studies have found that MRE had a higher technical success rate and better diagnostic accuracy [151,152].

Morphologic cross-sectional imaging — CT, MRI, and ultrasound can demonstrate anatomic features of advanced liver disease, such as nodularity and signs of portal hypertension [153]. However, the resolution of hepatic parenchyma with any of the available modalities is insufficient to detect earlier stages of fibrosis. The main roles for imaging are confirming cirrhosis in patients with suspected advanced chronic liver disease and evaluating for complications (eg, hepatocellular carcinoma). (See "Clinical features and diagnosis of hepatocellular carcinoma", section on 'Imaging'.)

In addition, imaging can provide complementary information in patients with indeterminate liver biopsy results or biopsy results that are at variance with the clinical impression.

Morphologic volume measurements of the liver and spleen measured on abdomen CT with contrast can diagnose advanced fibrosis with reasonable accuracy. In one study, for discriminating ≥F3 fibrosis, the liver segmental volume ratio (ratio of the volumes of segments I-III over segments IV-VIII) and the splenic volume demonstrated sensitivities of 72 percent and 81 percent, and specificities of 88 percent and 85 percent, respectively [154]. A model combining the two measurements showed higher accuracy.

Several modifications to standard ultrasonography have been proposed to increase accuracy for the diagnosis of cirrhosis and portal hypertension. Models combining multiple anatomic grayscale and Doppler ultrasound measurements have been reported to detect cirrhosis with accuracies between 82 to 88 percent [155,156]. However, most of these approaches have not been widely validated.

COMBINING TESTS

Using multiple serologic panels or combining serologic panels with imaging may improve the ability to correctly assess the degree of a patient's fibrosis [14,157,158]. In addition, it may be possible to improve the diagnostic performance of these panels if they are used in stepwise

combination [157]. We typically use a combination serologic testing and tissue elastography. The specific tests chosen will depend on local availability. (See 'Choice of test' above.)

For example, the aspartate aminotransferase (AST) to platelet ratio (APRI) has been combined with FibroTest/FibroSure, a strategy referred to as "SAFE" biopsy (sequential algorithm for fibrosis evaluation). In one study, the combination had good overall accuracy for significant fibrosis and reduced the need for liver biopsy in patients with chronic hepatitis C virus (HCV) [158]. (See 'FibroTest, FibroSure, and ActiTest' above.)

FibroTest has also been evaluated in combination with ultrasound-based transient elastography. In a study of 183 patients with chronic HCV, the combination of these tests demonstrated an area under the ROC curve of 0.88 for F ≥2, 0.95 for F ≥3, and 0.95 for F = 4 [14]. When the elastography and FibroTest results agreed, liver biopsy examination confirmed the stage of fibrosis in 84 percent of cases for F ≥2 fibrosis, in 95 percent for F ≥3 fibrosis, and in 94 percent for F = 4 fibrosis. Thus, it is likely that a combination of serum biomarkers and elastography will improve the accuracy of fibrosis detection. (See 'Transient elastography' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hepatitis C virus infection".)

SUMMARY AND RECOMMENDATIONS

- **Clinical uses** – Noninvasive tests of hepatic fibrosis have been used in many clinical scenarios. The majority of studies of serologic markers and imaging tests have looked at the use of these tests for staging of fibrosis in patients with chronic liver disease. We typically consider noninvasive testing for patients presenting for evaluation of chronic viral hepatitis. (See 'Clinical uses' above.)

- **Choice of test** – There are two general categories of noninvasive tests for fibrosis: serologic panels of tests and imaging examinations. When evaluating patients for hepatic fibrosis using noninvasive approaches, we typically use a combination of serologic testing (such as Hepascore) and ultrasound-based transient elastography (TE). The specific tests chosen will depend on local availability. (See 'Choice of test' above.)

- **Serologic tests** – A variety of serologic markers have been evaluated to predict the degree of fibrosis in the liver, and panels have been developed that combine assays of multiple markers to improve predictive ability. The most studied panels are the aspartate aminotransferase (AST) to platelet ratio (APRI) (calculator 1), FibroTest/FibroSure, Hepascore, and FibroSpect. The APRI has the advantage of being easily calculated using data available from routine laboratory tests. Studies suggest they have good ability to differentiate patients with significant fibrosis (F2 to F4) from those without significant fibrosis (F0 to F1). The panels may also be able to monitor changes in fibrosis over time. (See 'Serologic tests' above.)

- **Imaging tests** – Elastography estimates liver stiffness by applying mechanical waves and measuring their propagation speed through tissue using imaging. Modality options include ultrasound (ie, TE, acoustic radiation force impulse [ARFI] imaging, two-dimensional [2D] shear wave elastography [SWE]), and MRI (ie, magnetic resonance elastography [MRE]). 2D-SWE and MRE can be integrated with conventional morphologic liver imaging in the same sitting. (See 'Elastography' above.)

Using multiple serologic panels or combining serologic panels with imaging may improve the ability to correctly assess the degree of a patient's fibrosis. In addition, it may be possible to improve the diagnostic performance of these panels if they are used in stepwise combination. (See 'Combining tests' above.)

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Topic 1239 Version 44.0

GRAPHICS

Advantages and disadvantages of noninvasive methods to evaluate liver fibrosis

Parameters	Transient elastography	pARFI	2D-SWE	MR elastography	Serum biomarke
Advantages	High accuracy, rapid results	High accuracy, rapid results	High accuracy, rapid results	High accuracy	Availability
	Reproducibility	Reproducibility	Reproducibility	Reproducibility	Reproducibilit
	Very easy to learn	Easy to learn	Easy to learn, larger measurement area than other ultrasound techniques	Examination of the whole liver	
		Conventional ultrasound images are also obtained	Conventional ultrasound images are also obtained	Conventional MR images are also obtained	
		Obesity and ascites are not limiting	Ascites is not limiting	Obesity and ascites are not limiting	
Disadvantages	Technical requirements (elastography equipment)	Technical requirements (ultrasound equipment)	Technical requirements (ultrasound equipment)	Technical requirements (MR imaging equipment)	Nonspecific (e hyperbilirubin hemolysis, inflammation)
	Intermediate cost	Intermediate cost	Intermediate cost	High cost, time-consuming	Relatively high cost, limited availability (pa
	Limited recognition of intermediate stages of fibrosis	Limited recognition of intermediate stages of fibrosis	Limited recognition of intermediate stages of fibrosis	Limited recognition of intermediate stages of fibrosis	Limited recogı of intermediat stages of fibrc
	Blind selection of measurement area			Not applicable in case of iron deposition	Results not immediately available

	Restricted value in obese patients and patients with ascites	Narrow range of values, small measurement area			
	False positive values in patients with acute hepatitis, cholestasis, and heart failure	Quality criteria not well-defined	Quality criteria not well-defined		

pARFI: point-shear wave elastography using acoustic radiation force impulse; 2D-SWE: two-dimensional shear wave elastography; MR: magnetic resonance.

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Graphic 97043 Version 1.0

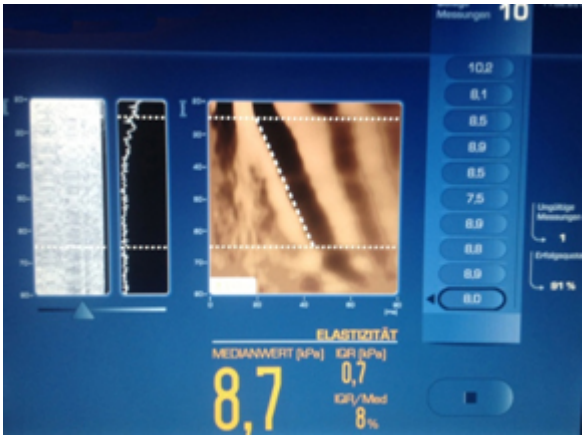
Markers of fibrogenesis and fibrinolysis

Matrix deposition
Procollagen I peptide
Procollagen III peptide
Type I collagen
Type IV collagen
YKL-40 (chondrex)
Laminin
Hyaluronic acid
Matrix degradation
MMP-2
TIMP-1, -2
Cytokines
TGF-beta
TGF-alpha
PDGF

MMP: matrix metalloproteinase; PDGF: platelet derived growth factor; TGF: transforming growth factor; TIMP: tissue inhibitor of metalloproteinase.

Graphic 74005 Version 3.0

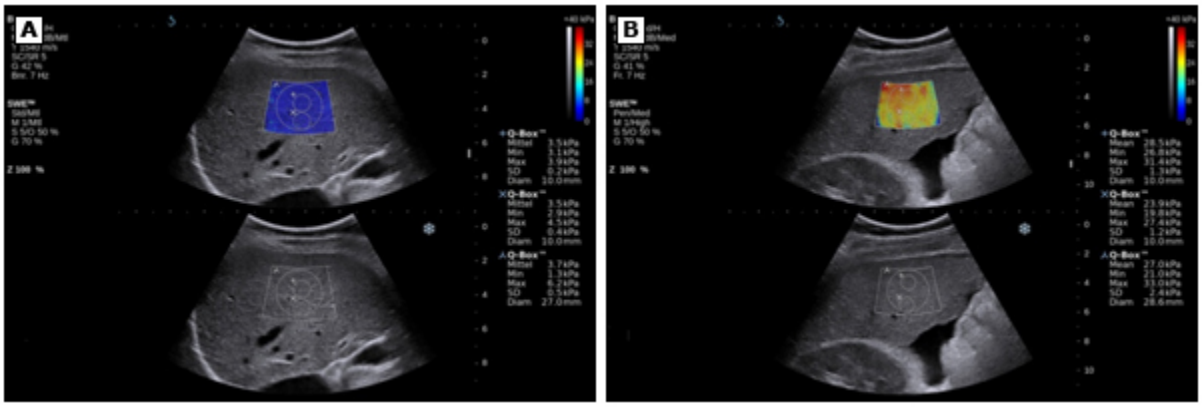
Transient elastography of the liver



Transient elastography showing the measurement of liver stiffness in kilopascals (kPa) along the left side of the screen. An A-mode image is displayed to assist the operator in selecting the measurement zone. On the right side, the values of 10 measurements are shown with the mean value depicted at the bottom of the screen.

Graphic 97037 Version 1.0

Two-dimensional shear wave elastography of the liver



Two-dimensional shear wave elastography in a patient with healthy liver parenchyma (A) and a patient with liver cirrhosis (B). The color indicates the stiffness of the liver: blue means soft, and red means hard. At least one box can be drawn within the area being evaluated; the value of the shear wave speed is shown on the right side of the image either in m/s (top) or in kPa (bottom).

Graphic 97041 Version 1.0

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Conflict of interest policy

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