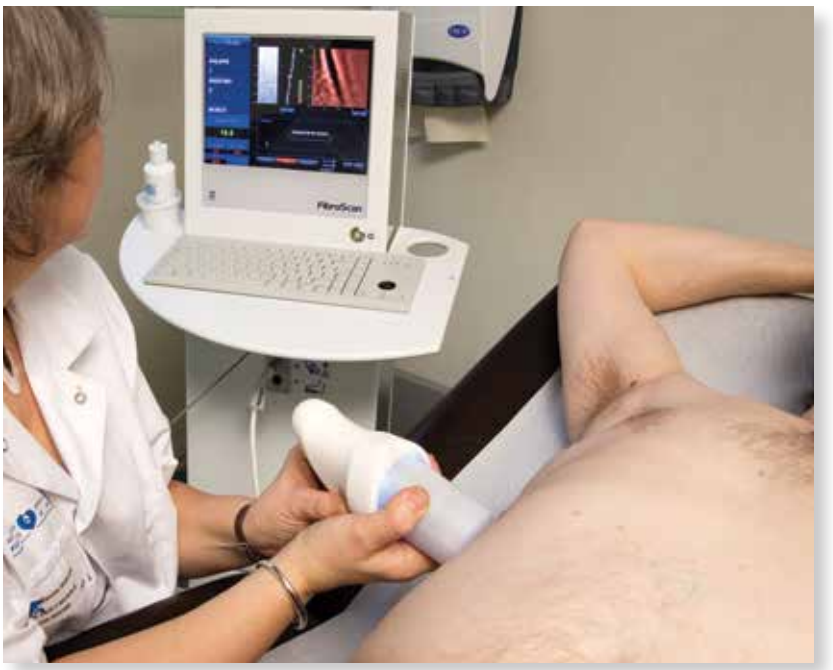
Noninvasive tests for assessing liver fibrosis



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Assessing the degree of liver fibrosis in patients with chronic liver disease assists in management decisions and in determining prognosis. Given that liver biopsy is invasive and carries risks, there is much interest in less invasive technologies to stage liver disease.

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REMEMBER

- Liver fibrosis develops via a common pathway as a result of liver injury and inflammation.[1] In Australia, the most common causes of liver fibrosis are chronic hepatitis B, chronic hepatitis C, alcohol and nonalcoholic fatty liver disease. Interaction between risk factors for liver fibrosis is common, and the final stage of the process is the development of hepatic cirrhosis.
- The identification of patients with hepatic cirrhosis is crucial because all patients with cirrhosis should be checked for oesophageal varices and screened for the development of hepatocellular carcinoma (typically with a liver ultrasound examination every six months).[2,3]
- Histological examination of a liver biopsy specimen remains the reference standard for the assessment of liver fibrosis. However, liver biopsy is invasive, potentially painful and associated with a small but definite mortality rate (0.01%).[4] Also, the small sample obtained by biopsy increases the rate of sampling errors.[5]
- Because of the limitations of liver biopsy, it is reasonable to use noninvasive tests of hepatic fibrosis to assess all patients at risk of chronic liver disease. These will identify most patients with significant hepatic fibrosis or cirrhosis. They will also allow patients to be monitored over time for progression of fibrosis.
- Noninvasive tests to assess liver fibrosis can be broadly divided into two groups: those using serum markers and those using an imaging modality (see the Box).[6]
- Simple indirect noncommercial biochemical markers such as the aspartate aminotransferase to alanine aminotransferase

EXAMPLES OF NONINVASIVE TESTS OF HEPATIC FIBROSIS

Direct serum markers

- Hyaluronic acid
- Collagen IV
- Procollagen type III N-terminal propeptide (PIIINP)
- Tissue inhibitor of metalloproteinase (TIMP)
- Transforming growth factor beta (TGF-β)
- Enhanced liver fibrosis test (based on hyaluronic acid, PIIINP and TIMP1)

Indirect serum markers

- AST to ALT ratio
- AST to platelet ratio index
- FibroTest/Fibrosure (alpha 2-macroglobulin, alpha 2-globulin, γ-globulin, apolipoprotein A1, GGT and total bilirubin)
- Forns index (age, platelet count, cholesterol levels and GGT)
- Hepascore (age, sex, alpha 2-macroglobulin, hyaluronic acid, GGT and bilirubin)
- FibrometerA (age, prothrombin index, alpha 2-macroglobulin and hyaluronic acid)

Imaging techniques

- Transient elastography
- Acoustic radiation force impulse
- Share wave elastography
- Magnetic resonance elastography
- Real time elastography

ABBREVIATIONS: ALT = alanine aminotransferase; AST= aspartate aminotransferase; GGT = gamma glutamyl transferase.

(AST/ALT) ratio and AST to platelet ratio index (APRI) have limited sensitivity.

- Apart from simple indirect serum markers, the most commonly used noninvasive test in Australia is transient elastography (TE) using FibroScan (Figure). TE is now readily accessible through many hospital-based liver clinics, with portable machines servicing rural and remote areas. As TE is quick and noninvasive, it has high patient acceptability. The choice of noninvasive test, however, depends largely on availability, cost and physician preference.
- TE using FibroScan assesses the 'stiffness' of the liver, measured in kPa. This is an indirect measure of hepatic fibrosis. Higher values are associated with higher rates and severity of fibrosis. For example, in patients with hepatitis C, most (80 to 90%) of those with a result of 7.5 kPa or higher have significant hepatic fibrosis. Conversely, a result less than 13.0 kPa excludes cirrhosis. However, the result is also potentially influenced by factors including recent food intake (within the previous two hours), liver inflammation (i.e. high serum ALT levels), liver congestion (in cardiac failure) and cholestasis. These factors can result in falsely elevated readings and hence an overestimation of fibrosis.
- TE measurements are easy to perform, although it may not be possible to obtain a result in patients with obesity. In these patients, an alternative noninvasive test may be necessary and a specialist in liver disease can advise on the most appropriate test.
- Aside from TE, other imaging and proprietary noninvasive tests are not yet widely available in Australia.

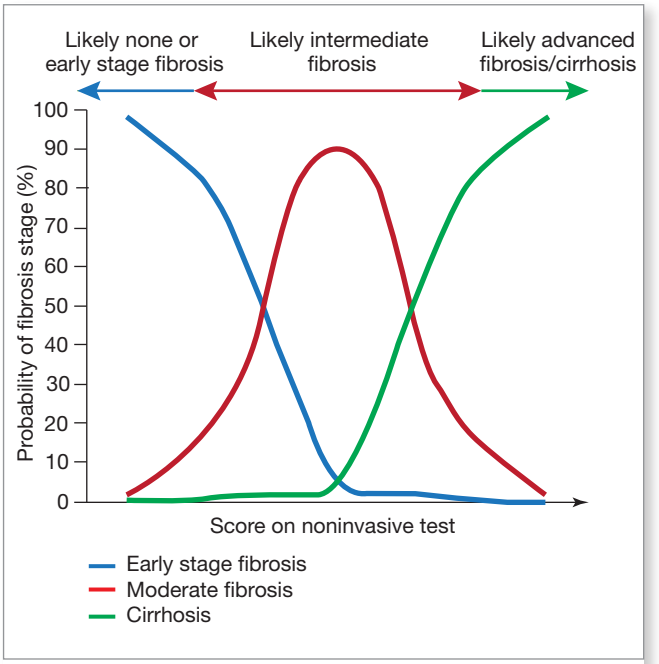

Figure. Probability of fibrosis according to score on the noninvasive liver fibrosis tests.

ASSESSMENT

- The most validated indication for the use of noninvasive tests is in the assessment and monitoring of patients with chronic viral hepatitis B or hepatitis C.[7] In addition, there is emerging literature validating other indications such as nonalcoholic fatty liver disease and alcoholic liver disease.
- International guidelines have integrated the use of noninvasive tests in the assessment of patients with hepatitis C or hepatitis B, particularly those who are not undergoing a liver biopsy.[8,9] The results may help to determine their suitability for antiviral therapy or to establish management priorities.

- Noninvasive tests should be thought of as determining the probability of a particular stage of hepatic fibrosis (Figure). If there is a high pre-test probability of cirrhosis (such as in a patient with a firm liver edge and stigmata of chronic liver disease) then a compatible noninvasive test result can provide a high level of confidence that cirrhosis is present.[10]
- Using a combination of noninvasive tests may increase diagnostic accuracy. A suggested approach is to select tests from different groups, such as a serum test and a physical test.[7]

MANAGEMENT

- Liver biopsy and noninvasive tests such as TE should be used in an integrated way to allow safe, accurate and timely evaluation of all patients with chronic liver disease. There are no guidelines on the use of noninvasive tests specific to an Australian population.
- All patients with chronic hepatitis B or chronic hepatitis C should have an assessment of hepatic fibrosis. In this context, a noninvasive test such as TE is a viable and practical alternative to liver biopsy. A noninvasive test may help to determine:
  - the need for and duration of treatment for chronic hepatitis C
  - the need for antiviral therapy in chronic hepatitis B.
- Interpretation of test results has to be individualised; however, patients with a low reading on TE (less than 7.0 kPa) are very unlikely to have cirrhosis or advanced fibrosis. This may be reassuring for both the patient and clinician. The higher the score, the higher the likelihood of more significant liver disease. In hepatitis C, scores greater than 9.5 kPa are associated with increased mortality. This may influence treatment decisions.
- Results of a noninvasive test need to be interpreted in conjunction with the other available clinical, radiological and biochemical data. Ideally, noninvasive tests are incorporated into patient management as part of specialist care. They should not be used in primary care on their own to determine suitability for treatment or specialist referral.
- The widespread screening of patients at low risk of structural liver disease is unlikely to be cost effective. Therefore, a noninvasive test should be used as a component of the assessment of individuals at increased risk of chronic liver disease (e.g. those with fatty liver).

CONCLUSION

- Noninvasive tests of hepatic fibrosis are safe, rapid and well tolerated and have transformed the way we assess this condition.
- The most frequently used noninvasive test in Australia is transient elastography with FibroScan. This has been validated for the assessment of patients with chronic viral hepatitis and performs well for the detection of a range of degrees of hepatic fibrosis and cirrhosis. MT

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COMPETING INTERESTS: None.

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