Australian Prescriber
VOLUME 44 : NUMBER 6 : DECEMBER 2021

Testing for cirrhosis

SUMMARY

Cirrhosis can be suspected by a thorough clinical assessment, but compensated liver disease is often asymptomatic. Select investigations are therefore critical for identifying patients with advanced liver disease and cirrhosis.

Biomarkers and validated serum tests can evaluate liver damage and synthetic function. The ratio of the concentration of aspartate aminotransferase to the platelet count can predict the presence of cirrhosis.

Non-invasive imaging techniques, from basic ultrasound to elastography, are critical adjuncts to the clinical assessment of cirrhosis. They reduce the need for liver biopsy.

Careful monitoring, prescribing and appropriate specialist referral are key considerations in cirrhosis management. Early diagnosis can help to improve the outcomes for patients.

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Keywords
cirrhosis, liver function, liver biopsy

Aust Prescr 2021;44:197–9
https://doi.org/10.18773/austprescr.2021.053

Introduction

Morbidity and mortality from liver cirrhosis are rising in Australia and worldwide. The diagnosis of cirrhosis is important to guide treatment, determine prognosis, and to monitor for complications in patients with chronic liver disease. The identification of cirrhosis is important for the prescribing of medicines, as its presence will alter the pharmacokinetics of some drugs.

Regardless of the cause of liver disease, cirrhosis results from liver injury that leads to inflammation and fibrogenesis. It causes distortion of hepatic architecture, with micro- and macroscopic nodularity, leading to portal hypertension.[1] Cirrhosis leaves patients vulnerable to life-threatening complications, including variceal bleeding, ascites, infection and hepatocellular carcinoma, and ultimately death.

Clinical features of cirrhosis

Most chronic liver disease is asymptomatic until decompensated cirrhosis develops. The diagnosis of early cirrhosis therefore requires a clinical suspicion of liver disease. Patients in Australia at risk of cirrhosis include those with a history of:

- chronic alcohol misuse
- obesity or other features of metabolic syndrome
- migration from countries with high endemic rates of chronic hepatitis B
- risk factors for chronic hepatitis C, such as a history of intravenous drug use
- haemochromatosis.

Clinical symptoms for those with early or compensated cirrhosis are often non-specific and include anorexia, weight loss and fatigue. Patients with decompensated cirrhosis may present with jaundice, confusion, abdominal distension or easy bruising.

The key findings on physical examination of a patient with chronic liver disease include sarcopenia, spider angiomata, a firm liver edge, splenomegaly, palmar erythema and parotid enlargement. Signs of decompensated cirrhosis are more obvious, such as ascites, jaundice and hepatic flap.

Approach to testing

The gold standard test for diagnosis of cirrhosis has been liver biopsy, however, due to its invasiveness, rare but serious complications and cost, it is now used less frequently. Nowadays, careful clinical assessment, biochemical markers and imaging can provide a reliable evaluation of a patient with cirrhosis.

Biochemical markers

The term 'liver function tests' is commonly used to group the biochemical parameters:

- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- gamma-glutamyl transferase
- alkaline phosphatase.

There can be an excessive focus on these tests when investigating for the presence of liver disease. While alterations in liver function tests can provide clues to the aetiology of chronic liver disease, synthetic function is more specific for detecting the presence and severity of cirrhosis.

Aminotransferases (AST and ALT) can be moderately elevated in chronic liver disease, but are often normal in advanced cirrhosis. Usually, ALT is higher than AST,

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but if alcohol is the main contributor to cirrhosis, this ratio can be reversed with the concentration of AST being over twice that of ALT.

Alkaline phosphatase is often elevated in cirrhosis. Higher concentrations are seen in patients with cirrhosis secondary to cholestatic disease, such as primary sclerosing cholangitis and primary biliary cholangitis.

Gamma-glutamyl transferase is also raised in cholestatic liver disease but is less specific. The most significant confounder is alcoholic liver disease (recent or chronic alcohol ingestion) which can significantly increase the concentration.

Biochemical assessment of synthetic function is a valuable tool in screening a patient for cirrhosis. The markers of hepatic synthetic function include serum albumin and coagulation studies. The albumin concentration falls as cirrhosis progresses. However, it can be reduced in inflammatory states, malnutrition, protein-losing enteropathy or heart failure. The prothrombin time and INR are raised by impaired hepatic synthetic function. This explains the presence of coagulopathy in established liver disease. Although serum bilirubin can be normal in compensated cirrhosis, a rising concentration correlates with disease progression.

Haematological markers

A sensitive marker of cirrhosis is thrombocytopenia. This is secondary to splenic sequestration and congestive splenomegaly resulting from portal hypertension. A platelet count of less than 150 x 10^9/L is often the first marker of cirrhosis, but other cytopenias emerge as the disease progresses.

Tests for fibrosis

There are several tests that combine serum and clinical parameters to predict the presence of cirrhosis. Indirect serum fibrosis tests include the AST:ALT ratio, the AST to platelet ratio index (APRI score) and, in non-alcoholic fatty liver disease (NAFLD), the FIB-4 and NAFLD fibrosis score. The normal AST:ALT ratio is less than 1, so a score greater than 1 is suggestive of advanced fibrosis or cirrhosis.

The APRI score is validated in chronic viral hepatitis. An APRI score greater than 1 has a sensitivity of 76% and specificity of 72% for predicting cirrhosis.[2]

The FIB-4 is a combination of age, AST and platelet count, whereas the NAFLD fibrosis score is a composite of age, body mass index, presence or absence of diabetes, serum aminotransferase concentrations, platelet count and serum albumin. These scores are useful for ruling out the presence of advanced fibrosis with negative predictive values over 90%.[3]

Proprietary tests for fibrosis include the Fibrotest, the Enhanced Liver Fibrosis score (ELF), Fibrospect II and Hepascore, which was developed in Western Australia.[1] These composite scores use a range of clinical parameters and specialised serum markers, some of which are only available in tertiary referral centres.

Ultrasound

Abdominal ultrasound is generally the first imaging modality recommended when liver disease is suspected. It is widely available, low cost and has good sensitivity in excluding biliary obstruction. Features suggestive of cirrhosis on ultrasound include a nodular liver edge, splenomegaly, portal vein dilatation and recanalisation of the umbilical vein. Limitations include overlooking mild hepatic steatosis (<2.5–20%).

Elastography

Elastography is a relatively new, but now widely used imaging modality to non-invasively estimate liver stiffness. Increased liver stiffness correlates with more advanced fibrosis. Elastography does not determine the cause of cirrhosis, but by measuring the propagation speed of mechanical waves through liver parenchyma, it can give a measure of liver stiffness. Elastography is available in conjunction with ultrasound assessment in many radiology practices across Australia, or as FibroScan in most tertiary referral centres.

There are two different kinds of elastography techniques, based on ultrasound or MRI. Ultrasound generates shear waves that travel through the liver tissue at a speed determined by tissue stiffness. The faster the speed, the higher the liver stiffness. In elastography using MRI, mechanical vibration produces waves in the liver that are converted to a tissue stiffness map. This technique is not yet widely available in Australia due to its cost.

Transient elastography, known by its proprietary name FibroScan (Echosens) is the most commonly used form of elastography. It is a one-dimensional form of shear-wave elastography that measures stiffness in kilopascals (kPa). Results range from 2.5–75 kPa, with a normal value of approximately 5 kPa. Cut-offs for the severity of fibrosis (F0–F4) vary depending on the aetiology of liver disease and are best validated in chronic viral hepatitis. In stage 2–3 fibrosis the stiffness is 7–11 kPa and in stage 4 fibrosis (cirrhosis) it is more than 11–14 kPa. Limitations of FibroScan include its low reliability in patients with obesity, ascites and artificially elevated stiffness due to severe liver inflammation or steatosis.[4]

Liver biopsy

Liver biopsy is rarely needed for the diagnosis of cirrhosis, but still has a role in the definitive diagnosis of the underlying cause of liver disease. It is performed percutaneously with ultrasound guidance after confirming that there is no significant coagulopathy.

A trans-jugular liver biopsy, performed in a tertiary referral centre, is safer in patients with an increased risk of bleeding. It also enables measurement of the hepatic vein pressure gradient which is the most accurate measure of portal hypertension, but this is mainly used in research rather than clinical practice.

Monitoring

Once the diagnosis of cirrhosis is made, monitoring for deteriorating liver function or complications is important. This includes referral to a gastroenterologist for consideration of gastroscopy to look for oesophageal varices. These develop as a complication of portal hypertension and are a major cause for mortality in patients with cirrhosis. Pre-emptive treatment of varices with a non-selective beta blocker or band ligation reduces the risk of bleeding and morbidity.

Patients with cirrhosis should have surveillance for hepatocellular carcinoma. Guidelines recommend six-monthly abdominal ultrasound to detect the presence of a new liver lesion and urgent referral to a hepatologist if hepatocellular carcinoma is suspected. Measuring alpha-fetoprotein is no longer recommended as a screening test. Hepatocellular carcinoma is usually asymptomatic until it is very advanced, so surveillance enables earlier diagnosis, better treatment options and improved survival.

Specialist referral

Referral to a hepatologist should be considered for the assessment of all patients with liver cirrhosis, when the diagnosis of chronic liver disease is uncertain and for the management of complications. Patients with early, or well-compensated cirrhosis have a good prognosis, particularly if the underlying liver disease is controlled, by treatment of chronic hepatitis B or C or lifestyle modification, such as alcohol cessation. Early intervention can stabilise disease progression and help to avoid or delay hepatic decompensation.

Conclusion

The prevalence of cirrhosis is increasing. Patients are likely to have a better prognosis if there is an early diagnosis.

Making the diagnosis requires a clinical suspicion of liver disease, particularly in at-risk populations. The initial investigations include biochemical tests and imaging. Serum markers and clinical features can be combined to predict the presence of liver fibrosis. Liver fibrosis can also be assessed by measuring the tissue stiffness with elastography. Biopsy is now rarely used for the diagnosis of cirrhosis. <

Conflicts of interest: none declared

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FURTHER READING

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