GESA
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General Practitioners and Physicians

Understanding Liver Tests

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Key points

- A liver biochemistry panel and coagulation profile, including platelet count, are required to assess the liver when symptoms, signs or risk factors suggest liver injury, or as part of routine health assessments.
- The pattern of abnormalities seen in liver test results can be categorised as hepatocellular, cholestatic or mixed liver dysfunction, with differential diagnoses and investigations tailored to the pattern of dysfunction.
- Patients with liver test results that are persistently abnormal (for more than 3 months) should have an assessment of liver fibrosis using serum-based tests, such as Fibrosis-4 (FIB-4) score or aspartate aminotransferase to platelet ratio index (APRI), or elastography.
- Mild abnormalities in liver test results are often caused by fatty liver associated with metabolic dysfunction (obesity, diabetes, hyperlipidaemia or hypertension) or alcohol consumption, and non-invasive laboratory test-based algorithms (e.g. FIB-4 or APRI) can help to determine the likelihood of advanced fibrosis (portal tract to portal tract bridging, if a liver biopsy is done) or cirrhosis.
- When cirrhosis is suspected based on an elevated non-invasive composite test result, a confirmatory non-invasive test of liver stiffness (FibroScan® or shear wave elastography) is helpful. Liver biopsy is sometimes required.
- In a patient with chronic liver dysfunction or when advanced fibrosis or cirrhosis is suggested, investigations to diagnose and treat the underlying liver disease are required.
- Patients with metabolic-associated fatty liver disease (MAFLD) are at significant risk of cardiovascular morbidity and mortality. Management should include identification and treatment of modifiable risk factors (such as obesity, diabetes and hyperlipidaemia) and cardiovascular complications.

1. Introduction

Testing the health of a patient's liver should be considered when symptoms, signs or risk factors suggest liver injury, or as part of routine health assessments.[1,2]

The set of liver tests within a biochemistry panel includes measurement of albumin, bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) levels (Table 1). Abnormalities in these markers occur in patterns that can suggest hepatocyte injury (AST and ALT) or cholestasis (ALP and GGT). Derangement of international normalised ratio (INR) and/or albumin or bilirubin levels can suggest synthetic dysfunction.

Clinically significant portal hypertension (CSPH), reflecting progression of cirrhosis and risk of decompensation, is suggested by thrombocytopenia. Non-invasive scoring systems, such as the Fibrosis-4 (FIB-4) score, can be used to screen for advanced liver fibrosis and cirrhosis.

Acute liver failure is considered when acute derangement of liver test results is severe and accompanied by hepatic encephalopathy.[1,3,4]

Here, we aim to provide a guide to the indications for liver tests, interpretation of their results and further patient management. The use of non-invasive tests to estimate liver fibrosis and indications for referral to a gastroenterological specialist are also covered.

Table 1: Liver chemistry components

Albumin	Synthesised in liver at 10 g/day with a half-life of 20 days
Bilirubin	By-product of the breakdown of the haem component of haemoglobin, which is conjugated in liver and secreted into bile and gut
ALT	Found in cytoplasm of hepatocytes
AST	Found in cytosolic and mitochondrial compartments in liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes and red cells
ALP	Originates from bile canaliculus of hepatocyte, bone (produced during bone formation) and placenta, with highest concentrations in liver, biliary tract and bone
GGT	Originates from bile canaliculus of hepatocyte, as well as pancreas and biliary tract, with a half-life of 7–10 days, which increases to 28 days in alcohol-associated liver injury

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase.

2. When to test the liver

There are many situations in which liver tests may be indicated. People who might benefit from testing include those who are asymptomatic but known to have risk factors for viral hepatitis (e.g. injecting drug use or born overseas, as most migrants in Australia are from high-prevalence areas) and patients who have metabolic-associated fatty liver disease (MAFLD; obesity, diabetes, hyperlipidaemia or hypertension) or who consume excessive amounts of alcohol or take hepatotoxic medications. Patients with symptoms or signs or with a personal or family history of liver disease should be tested (Table 2).[1,2]

Medications are a common cause of liver dysfunction. To determine if a medication may be hepatotoxic, LiverTox® (https://www.ncbi.nlm.nih.gov/books/NBK547852/) provides referenced, searchable information on patterns, frequency and management of liver injury secondary to prescription or over-the-counter medications.[5]

Liver tests serve as a useful screen for underlying liver disease, but not all patients with abnormal results will have significant liver fibrosis.[2] Although liver test results are often abnormal in the presence of liver disease, standard liver biochemistry does not reflect the degree of underlying liver fibrosis, and results can be mildly deranged or even normal in the presence of cirrhosis.

Table 2: Clinical scenarios in which to consider liver tests

Risk factors	Symptoms	Signs
• Excessive alcohol consumption • Hepatitis B and C risk factors (e.g. illicit drug use, tattoos, overseas-born, received blood transfusion before screening) • Metabolic dysfunction (obesity, diabetes, hyperlipidaemia or hypertension) • Inflammatory bowel disease • Autoimmune conditions and endocrinopathies • Malignancy and oncological therapies • Hepatotoxic medications • Family history of hereditary conditions (e.g. Wilson's disease, haemochromatosis, alpha-1 antitrypsin deficiency, coeliac disease)	• General malaise • Nausea and anorexia • Abdominal pain • Abdominal fullness • Pruritis • Confusion	• Jaundice • Hepatomegaly, tenderness • Splenomegaly • Ascites and peripheral oedema • Hepatic flap (asterixis) or fetor hepaticus • Peripheral stigmata – Palmar erythema – Spider naevi – Gynaecomastia

3. Patterns of liver test abnormality

The pattern of abnormalities seen in liver test results can illuminate both the cause and the next appropriate investigations (Table 3). However, the pattern of dysfunction is often mixed, but a path of investigations will hopefully be suggested by the relative nature of the disturbance.

Hepatocellular injury suggested by elevated AST and ALT levels

A healthy and normal upper limit for ALT level is 19 U/L in women and 30 U/L in men,[6] although these limits are low compared with the reference ranges used by most laboratories. Thresholds for abnormalities also vary between different international expert societies. Reference ranges can be affected by liver conditions with a high prevalence in the general population, such as fatty liver.[7] The Royal College of Pathologists of Australasia classifies the upper limit of normal (ULN) as 35 U/L for ALT and 40 U/L for AST for both men and women.[8,9]

An increase in ALT and AST levels, disproportionate to ALP and GGT levels, is suggestive of hepatocellular injury. The rise in AST and ALT levels can be categorised as mild

Table 3: Characterising abnormal liver test results

	Hepatocellular dysfunction	**Cholestatic dysfunction**
Liver test results	Elevated ALT and AST levels: - Mild (2–5 × ULN) - Moderate (5–15 × ULN) - Severe (>15 × ULN)	Elevated ALP and GGT levels
Most common causes	Fatty liver, viral hepatitis, hepatotoxic medications	Fatty liver, hepatotoxic medications (including illicit, over-the-counter and prescribed drugs)
Initial measures	Mild and moderate: - Reduce or discontinue alcohol consumption	Mild and moderate: - Liver and biliary tract imaging
Laboratory investigations	General: - Albumin, full blood count (especially platelets), prothrombin time/INR, hepatitis A/B/C serology, ANA, coeliac serology, lipids, glucose, HbA1c, iron studies, ceruloplasmin Specific: - Anti-SMA, anti-LKM, ANCA - Severe derangement: paracetamol level, serum and urine drug/toxicology screen	General: - Albumin, full blood count (especially platelets), prothrombin time/INR, hepatitis A/B/C serology, ANA, coeliac serology, lipids, glucose, HbA1c, iron studies, ceruloplasmin Specific: - AMA, ANCA
Imaging	Abdominal ultrasound (CT sometimes required)	Abdominal ultrasound and possibly CT cholangiography or MRCP
Specific measures in patients with severe derangement	If there are signs of acute liver failure (severe dysfunction and encephalopathy): urgent consultation and referral to a tertiary hospital or liver transplant centre If there are no signs of acute liver failure: urgent referral to a hepatologist for further evaluation, which may include a biopsy	In patients with jaundice: emergency review if sepsis is evident If there is persistent elevation without explanation or if above investigations are abnormal: specialist referral recommended

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; ULN = upper limit of normal; INR = international normalised ratio; ANA = anti-nuclear antibodies; SMA = smooth muscle antibodies; LKM = liver–kidney microsome; ANCA = antineutrophil cytoplasmic antibodies; HbA1c = glycated haemoglobin; AMA = anti-mitochondrial antibodies; CT = computed tomography; MRCP = magnetic resonance cholangiopancreatography.

(2–5 × ULN), moderate (5–15 × ULN) or severe (>15 × ULN, and/or ALT >10,000 U/L).[1,3] A mild elevation in transaminase levels is the most common biochemical alteration encountered in everyday clinical practice.[2] The most common causes of mild transaminitis are MAFLD, medications (such as statins) and chronic alcohol consumption.[1,4] Moderate or severe transaminitis can be seen in patients with viral hepatitis (acute or chronic), alcohol-related hepatitis, autoimmune hepatitis, drug-induced liver injury, ischaemic hepatitis and rarer vascular disorders, such as veno-occlusive disease. If accompanied by jaundice, prolonged INR or encephalopathy, liver failure is developing.[3] Non-hepatic causes of elevated levels of these enzymes, such as muscle injury in rhabdomyolysis or myositis, which can result in massive AST elevations, should be considered.[1,10]

If a patient presents with symptoms and signs of acute hepatitis, such as fatigue, fever, anorexia, nausea, vomiting, abdominal pain or jaundice, and/or elevated ALT or AST levels, consider testing for the following, depending on severity and progression: viral infections (e.g. hepatitis A, B, C, D and E; cytomegalovirus; Epstein–Barr virus; and yellow fever), other infections (e.g. leptospirosis and syphilis) and non-infective causes, such as autoimmune hepatitis, drug-induced liver injury and metabolic liver diseases (e.g. Wilson's disease).[11]

Cholestatic injury suggested by elevated ALP and GGT levels

Cholestatic liver injury, reflected by a rise in GGT and ALP levels disproportionate to AST and ALT levels, can be caused by mechanical or functional disruption to bile flow.[12] Mechanical obstruction may be the result of gallstones, a tumour, or bile duct injury within or outside the liver. Functional obstruction can occur at the molecular level of bile transportation, such as from drug-induced, hereditary or other microscopic bile duct injury.

An isolated increase in GGT level can be seen in those with harmful alcohol consumption (although not all patients who drink heavily will have elevated GGT levels) but can also occur in the setting of non-alcohol-related MAFLD or due to induction of bile duct enzymes by certain medications, such as carbamazepine.[2,12] An isolated raised ALP level may also have origins outside the liver, such as from bones during times of rapid growth in children and in people with bone disease (such as metastasis) or even transient hyperphosphataemia. In pregnancy, ALP originates from the placenta. Interestingly, although "cholestasis of pregnancy" is a disorder of biliary excretion, with itch the main clinical manifestation, the liver injury is initially characterised by an elevation in ALT and AST levels.[13]

Imaging with ultrasound, computed tomography (CT)-cholangiography or magnetic resonance cholangiopancreatography (MRCP) is useful to detect mechanical obstruction to bile ducts and intrahepatic space-occupying lesions. In the setting of jaundice, particularly if there are signs of sepsis to suggest cholangitis, urgent biliary assessment and drainage with endoscopic retrograde cholangiopancreatography (ERCP) may be required.[2,14]

Jaundice

Jaundice occurring in combination with abnormalities in synthetic function (INR or albumin level) indicates that liver injury is severe, requiring prompt evaluation of the cause, and consideration of urgent treatment.[10,12] When accompanied by cholestasis, abdominal ultrasound or other imaging (e.g. CT-cholangiography or MRCP) should be performed to identify biliary ductal dilatation and downstream obstruction.[14]

An isolated elevated bilirubin level may not reflect actual liver disease. Determination of the proportions of direct (conjugated) and indirect (unconjugated) hyperbilirubinaemia can identify a defect of bilirubin conjugation enzymes (most often benign Gilbert's syndrome) or overload of the system of conjugation due to red cell haemolysis (in this case, a reduced serum haptoglobin level and elevated reticulocyte count and lactate dehydrogenase level will be evident).[1,2] When less than 20% of bilirubin is conjugated, the jaundice is considered an *unconjugated* hyperbilirubinaemia, whereas if more than 50% of bilirubin is conjugated, it is considered a *conjugated* hyperbilirubinaemia.

4. Advanced fibrosis and cirrhosis

In patients with chronic liver disease, the degree of liver fibrosis determines prognosis and can direct management, such as the need for liver cancer surveillance.[15] Several validated non-invasive screening tools are used to identify patients at high likelihood of significant or advanced fibrosis (portal tract to portal tract bridging, if a liver biopsy is done) or cirrhosis, who may be at risk of complications of liver disease or death.

The validated FIB-4 score has a free online calculator (https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4) using age, AST level and platelet count (Box). Among patients with chronic hepatitis B and C infection, a FIB-4 score <1.45 has 90% negative predictive value (NPV) for advanced fibrosis, whereas a FIB-4 score >3.25 has 97% specificity and 65% positive predictive value (PPV) for advanced fibrosis. In patients with metabolic-dysfunction associated fatty liver disease (MAFLD) or alcohol related liver disease, a FIB-4 score <1.30 is an effective screen to exclude advanced fibrosis.[15,16] Further refinements by international societies (European Association for the Study of the Liver and American Association for the Study of Liver Diseases) suggest that patients with a FIB-4 score >2.7 should be referred for further management, given the higher likelihood of cirrhosis (although not all such patients will turn out to have cirrhosis). Following a FIB-4 screen, those with a score in a "grey zone" (i.e. between 1.3 and 2.7) may benefit from a second non-invasive testing method, such as transient elastography (FibroScan®).[15] For those patients with FIB-4 readings in the grey zone, a liver biopsy may be helpful if management would likely be altered by more accurate fibrosis assessment.

The AST to platelet ratio index (APRI) is an alternative non-invasive tool that is also used to screen for fibrosis (https://www.hepatitisc.uw.edu/page/clinical-calculators/apri) (Box). It is well validated in patients with chronic hepatitis B or C.[17] An APRI threshold of 0.7 has 70% PPV and 79% NPV for significant fibrosis, and a threshold of 1.0 has 76% sensitivity and 72% specificity for predicting cirrhosis.

Although useful at a population level, these non-invasive tests can neither absolutely exclude nor diagnose cirrhosis with great confidence. Further non-invasive assessment and (at times) liver biopsy is recommended when clinical suspicion for significant liver disease is suggested by other modalities of testing or by symptoms.[18,19]

Transient elastography (FibroScan®) and shear wave elastography are also useful as first-line tests to assess fibrosis and can be used to further assess patients with indeterminate FIB-4 scores. They are non-invasive techniques to determine liver stiffness and can be performed at the bedside, with immediate results and good reproducibility.[1,15] FibroScan® is well validated in patients with chronic hepatitis B or C or alcohol-related or metabolic-associated liver disease. Elastography is recommended for patients with indeterminate or high APRI or FIB-4 scores.[20]

Fibrosis-4 (FIB-4) and AST to platelet ratio index (APRI) equations

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST level (U/L)}}{\text{Platelet count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

$$\text{APRI} = \frac{\dfrac{\text{AST level (U/L)}}{\text{AST (upper limit of normal) (U/L)}}}{\text{Platelet count } (10^9/\text{L})} \times 100$$

FIB-4 calculator: https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4
APRI calculator: https://www.hepatitisc.uw.edu/page/clinical-calculators/apri

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

5. Clinically significant portal hypertension

One of the most serious complications of cirrhosis is the development of portal hypertension. Clinically significant portal hypertension (CSPH) identifies those at risk of liver decompensation (ascites, varices or encephalopathy). The presence of CSPH is often suggested by a falling platelet count. Recent guidelines recommend that CSPH can be ruled in with a liver stiffness measurement (LSM) using FibroScan® of ≥25 kPa and ruled out if the LSM is ≤15 kPa and platelet count is ≥150 × 10^9/L.[21]

If CSPH is diagnosed, treatment with beta-blockers can reduce the risk of decompensation events (including variceal bleeding) and avoid the need for regular surveillance endoscopy for varices. Additionally, surveillance endoscopy is not required if patients have an LSM ≤20 kPa and a platelet count ≥150 × 10^9/L, as the probability of their having varices needing treatment is very low.

Surveillance endoscopy should be performed if: (1) the LSM and platelet count cut-offs above are not met; (2) CSPH is present, and beta-blockers are not tolerated or are contraindicated; or (3) there has been previous variceal bleeding.[21]

7. Indications for referral to a hepatologist

The criteria that suggest a significant liver problem are shown in Table 3. Early referral is indicated if abnormal liver test results are accompanied by clinical evidence of decompensated liver disease (Table 2), such as ascites, jaundice or encephalopathy, or when disturbance of test results is severe. Severe derangement is characterised by elevated bilirubin level, prolonged prothrombin time/INR and low albumin level, or low platelet count and splenomegaly, suggesting portal hypertension. Radiological evidence of biliary obstruction, cirrhosis, ascites or space-occupying lesions should also precipitate prompt referral.[2,15]

There is no absolute consensus about when to refer other patients with abnormal liver test results. Investigation and management of any modifiable factors causing liver injury are always a priority. Certainly, referral is recommended if the patient's FIB-4 or APRI score suggests advanced liver fibrosis or cirrhosis. For patients with indeterminate results, especially in those with risk factors or known liver disease (viral hepatitis, metabolic risk factors or hazardous alcohol consumption), a second method to non-invasively clarify the likelihood of advanced liver fibrosis is worthwhile. When abnormalities in liver test results are attributed to MAFLD, and no significant fibrosis is detected by non-invasive serological tests (FIB-4 score <1.3), there is much less need to refer patients to a gastroenterologist. Dealing with modifiable factors, such as optimising weight, controlling diabetes and treating lipid disorders, and risk stratification for associated and more lethal cardiovascular disease are higher priorities in the first instance.[15,22]

Specialist referral may be considered in some cases, such as: patients with genetic haemochromatosis with a ferritin level >1000 microg/L, due to the higher likelihood of advanced fibrosis; patients with hepatitis B with an abnormal ALT level (to assist in decision making about treatment initiation); and patients with hepatitis C with viraemia, although primary care prescribing for HCV cure is encouraged and supported by short training modules. Considering the many possible causes of deranged liver test results during pregnancy, pregnant women with abnormal results may need specialist input, depending on severity (Table 4). Women with intrahepatic cholestasis, or with bile salt levels elevated above 40 IU/mL, may benefit from ursodeoxycholic acid therapy to reduce bile salt burden and the risk of sudden infant death. Urgent delivery of the infant may be needed for women with HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count) or acute fatty liver of pregnancy.[1,4,10]

In the setting of isolated indirect (unconjugated) hyperbilirubinaemia, non-pathological Gilbert's syndrome is the most common explanation and does not require hepatologist review, but a strong clinical suspicion for other causes, including haemolysis, is important. In Gilbert's syndrome, the hyperbilirubinaemia is higher when fasting than non-fasting. Genetic UGT1A1 testing is available through some pathology providers but is usually not necessary.

Table 4: Differential diagnoses of deranged liver chemistries during pregnancy

- Acute viral hepatitis
- Cholelithiasis (gallstones) or choledocholithiasis (bile duct stones)
- Intrahepatic cholestasis of pregnancy (hepatocellular pattern and elevated bile acids)
- Hyperemesis gravidarum, when severe, may be associated with abnormal liver chemistry
- HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count) occurs near term and is usually a feature of pre-eclampsia
- Acute fatty liver of pregnancy occurs late in the last trimester and is a life-threatening liver condition

8. Conclusion

Abnormal liver test results are often encountered in the primary care setting. Investigations should be guided by the specific context to determine characteristics of liver dysfunction, chronicity, severity and aetiology and to guide management. Assessment of liver fibrosis in patients with chronically abnormal liver test results aids decision making regarding the need for specialist referral and consideration of interventions that might prevent life-threatening complications, such as variceal haemorrhage, or the need for liver cancer surveillance. This guide aims to assist a primary care doctor to triage, manage and in some cases refer their patients with abnormal liver test results.

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