Training workshop on screening, diagnosis and treatment of hepatitis B and C
Session 4

Interpretation of liver function tests
Learning objectives

At the end of this session, participants should understand

- Various types of liver function tests
- Clinical application of these tests
- Approach to abnormal liver function test results
- Liver function test abnormalities in patients with
  - Acute hepatitis
    - Uncomplicated
    - Acute liver failure
  - Chronic hepatitis
Liver: Microscopic anatomy

Organized as hepatic lobules

Lobules are penta- to hexagonal structures, with portal tracts at each corner and central vein in the middle

Each liver lobule has the following 3 structures in each corner of its hexagon: bile duct (green), portal vein (blue) and hepatic artery (pink). Usually there is one of each of these but sometimes there may be 2–4 bile ducts and sometimes only 2 structures. In the centre of each lobule there is one central vein (blue), which drains into the hepatic veins.
This is a three-dimensional picture of a hexagonal liver lobule. Each lobule is a three-dimensional structure, which shows the portal tract at each of the corner. Each portal tract has a branch of the portal vein (blue), hepatic artery (red) and bile duct (light green). The entire lobule is packed with hepatocytes organized in the form of plates (brown), which are separated by blood-filled sinusoids (purple).
Portal tract

Direction of flow of blood

Organized as hepatic lobules

Lobules are penta- to hexagonal structures, with portal tracts at each corner and central vein in the middle

In each lobule, blood from the branches of the portal vein and hepatic artery enters from the corner and flows in a centripetal direction to drain into the central vein. This flow of blood is slow and under low pressure, which gives adequate time for exchange between the blood and surrounding hepatocytes.
Liver cells are hexagonal in shape and are arranged in the form of “plates of cells”. The surfaces of these hepatocyte plates are lined with sinusoidal cells and the spaces between the two adjacent hepatocyte plates are called “sinusoids”.

Venous blood, carried into the liver through the portal vein, flows into these sinusoids. Hence, each hepatocyte is bathed in nutrient-rich portal venous blood along its surface.

Inside the hepatocyte plates, the adjoining surfaces of each hepatocyte abut the “bile canaliculi”. These canaliculi collect bile secreted by each hepatocyte and drain into the biliary tree.
Bilirubin metabolism

- Red blood cells
- Liver
- Biliary system

Unconjugated bilirubin

Blood
Bilirubin metabolism

Red blood cells

Liver

Biliary system

Blood

Unconjugated bilirubin → Conjugation → Conjugated bilirubin → Enters bile
Bilirubin metabolism

Red blood cells → Liver → Biliary system

Unconjugated bilirubin → Conjugation → Conjugated bilirubin → Enters bile → Excreted via intestine into faeces
Bilirubin is a substance that is made when your body breaks down old red blood cells. This is a normal process. Bilirubin is also part of the bile that your liver makes to help digest the food you eat. A small amount of bilirubin is normally present in your blood. Healthy adults make 250 to 350 mg of bilirubin each day.

Bilirubin that is bound to a certain protein (albumin) in the blood is called unconjugated, or indirect, bilirubin. Conjugated, or direct, bilirubin travels from the liver into the small intestine. A very small amount passes into your kidneys and is excreted in the urine. This bilirubin also gives urine its distinctive yellow colour.
Jaundice is one of the most common clinical feature in patients with liver disease such as viral hepatitis.

Clinical jaundice represents the elevated serum level of bilirubin. Bilirubin metabolism includes three steps: first, production of unconjugated bilirubin by the destruction of old red blood cells; second, conversion of unconjugated bilirubin into conjugated bilirubin in the liver; and third, excretion of conjugated bilirubin into bile as pile pigment through the biliary tract.

Diseases affecting any of these three steps may lead to jaundice. The pattern of elevation of bilirubin and liver enzymes helps us to differentiate between the causes of jaundice.
Excessive destruction (called haemolysis) of red blood cells, regardless of its cause, will result in haemolytic or unconjugated jaundice. Haemolytic jaundice is commonly seen in patients with haemoglobinopathies such as sickle cell anaemia, thalassaemia, etc. Most of the haemolysis in our body takes place in the spleen and hence majority of the patients with haemolytic jaundice also have splenic enlargement. In most patients, an enlarged spleen is firm and non-tender. In addition, the majority of patients with haemolysis will also have anaemia or low haemoglobin.
The liver is involved in two steps of bilirubin metabolism: conjugation of unconjugated bilirubin and excretion of conjugated bilirubin.

Injuries or diseases affecting the hepatocytes result in a reduction of both of these liver functions but the excretory function is more affected than the conjugatory function. In the presence of liver diseases such as viral hepatitis or liver cirrhosis, conjugated bilirubin is not completely excreted in the bile but is released into the circulation, which results in a mixed pattern of jaundice with a predominance of conjugated bilirubin.
Obstruction of the biliary tree

Several diseases could cause obstruction of the biliary tract. These diseases neither affect the conjugation of bilirubin in the liver nor affect the excretion of conjugated bilirubin from the liver into the bile but they stop the flow of bile into the biliary tree. Because of excessive accumulation, bile is refluxed from the liver into the circulation and results in conjugated hyperbilirubinaemia. The most common causes of biliary tract obstruction are gallstone disease, carcinoma of the gallbladder, cholangiocarcinoma, etc.
Liver function tests include estimation of the serum levels of four important enzymes in the liver. An increase in the serum levels of these enzymes indicates liver injury. Each of these enzymes is located in specific areas within the hepatocytes and cholangiocytes.

Liver injury, induced by various inciting agents such as toxins, pathogens, etc. follows one of the three injury patterns: hepatocellular, cholestatic and mixed patterns. These patterns of liver injuries manifests in form of a particular pattern of elevation of specific liver enzymes.

Hepatitis viruses primarily produce a hepatocellular pattern of liver injury, which is characterized by very high serum levels of the enzymes ALT and AST; serum levels of alkaline phosphatase and gamma glutamyl transpeptidase (GGT) are either normal or mildly elevated.
Infection with the hepatitis viruses results in sudden and massive necrosis of the hepatocytes, which leads to the release of ALT and AST enzymes from the cell cytoplasm into the blood circulation.

Patients with viral hepatitis frequently have jaundice. We must remember that jaundice in a given patient could also be because of biliary obstruction; hence, we need to differentiate between these two different causes of jaundice, whether due to hepatitis viruses or biliary obstruction.

In a jaundiced patient, infection with the hepatitis viruses results in very high serum levels of ALT and AST in contrast to a patient with biliary obstruction, in whom serum levels of alkaline phosphatase and GGT are markedly elevated but ALT/AST are mildly elevated.
Enzymes vary in their subcellular locations

ALT  Alanine aminotransferase (SGPT)
     Cytoplasm
AST  Aspartate aminotransferase (SGOT)
     Cytoplasm, mitochondria
AP   Alkaline phosphatase
     Canaliculi
GGT  Gamma glutamyl transpeptidase
     Canaliculi
LDH  Lactate dehydrogenase
     Mitochondria
<table>
<thead>
<tr>
<th>Condition</th>
<th>Enzyme Activity</th>
</tr>
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<tbody>
<tr>
<td>Injury/death of liver cells</td>
<td>Release of ALT &amp; AST from hepatocyte cytoplasm</td>
</tr>
<tr>
<td>Biliary obstruction</td>
<td>Alkaline phosphatase &amp; GGT from canaliculi</td>
</tr>
<tr>
<td>Long-term injury</td>
<td>AST &gt; ALT</td>
</tr>
<tr>
<td>Alcohol specifically damages mitochondria</td>
<td>(AST &gt; ALT)</td>
</tr>
</tbody>
</table>
Liver functions: Synthesis of proteins

- Liver synthesizes several important body proteins

- These include:
  - Serum albumin (serum albumin level)
  - Clotting factors including prothrombin (prothrombin time)

The liver plays several important roles in our body. The two most important functions of the liver are its synthetic function and excretory function. The synthetic capabilities of the liver are estimated by serum levels of the proteins synthesized and released by the liver. The two most important such proteins are albumin and clotting factors.

In a person with liver disease, if the synthetic function of liver is compromised, it will result in two important problems. First, low serum albumin causes bilateral pitting-type pedal edema, ascites or anasarca. Second, impaired synthesis of clotting factors results in prolongation of the prothrombin time, which may cause spontaneous bleeding such as ecchymosis.

The liver normally excretes bilirubin, which is a waste product of haemoglobin metabolism. Bilirubin is normally excreted in the bile and expelled in the faeces. In the presence of impaired excretory function, bilirubin starts accumulating in the blood and manifests as jaundice or yellow discolouration of the eyes and urine.
# Common tests of liver function

<table>
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<tr>
<th>Test</th>
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<th>Purpose</th>
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<tr>
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<tr>
<td>Conjug. bilirubin</td>
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<td>&lt;15% of total bilirubin</td>
</tr>
<tr>
<td>ALT/SGPT</td>
<td>IU/L</td>
<td>&lt;40</td>
</tr>
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<tr>
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<tr>
<td>GGT</td>
<td>IU/L</td>
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<tr>
<td>Albumin</td>
<td>g/dL</td>
<td>3.5–5.5</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>INR</td>
<td>0.9–1.2</td>
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The reference ranges for these tests may vary slightly between laboratories and populations.

Liver function tests is a name given to a set of biochemical tests. Each of these tests evaluates a specific function of liver cells.

Total bilirubin and conjugated bilirubin tell about the conjugatory and excretory functions of hepatocytes.
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Serum ALT (which was earlier known as SGPT) and serum AST (which was earlier known as SGOT) are released from the hepatocytes into the circulation after hepatocyte injury or death.
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Serum alkaline phosphatase and GGT are located in the cholangiocytes and represent their injury or death. Cholangiocytes are injured in biliary tract diseases such as cholangitis, biliary obstruction, etc.
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<td>&lt;2.0 mg/dL</td>
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<tr>
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<td>3.5–5.5 g/dL</td>
<td>Synthetic function</td>
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Serum albumin and prothrombin time are markers of the synthetic functions of the liver.
Liver function tests has two components: bilirubin and various liver enzymes. For a complete and accurate interpretation of LFT in a person, we need to look at them carefully.

If liver enzymes are predominantly elevated than bilirubin then we need to look which group of enzymes are elevated: those located inside the hepatocytes such as ALT and AST, or those located inside the cholangiocytes such as alkaline phosphatase and GGT.
Liver function tests have two components: bilirubin and various liver enzymes. For complete and accurate interpretation of LFT in a person, we need to look at these carefully.

If liver enzymes are predominantly elevated rather than bilirubin, then we need to look which group of enzymes are elevated: those located within the hepatocytes such as ALT and AST; or those located inside the cholangiocytes such as alkaline phosphatase and GGT.
In a person with jaundice, the first thing we need to see is the proportions of conjugated and unconjugated bilirubin. The presence of less than 20% unconjugated bilirubin fraction indicates an underlying haemolytic disorder. On the other hand, if the fraction of conjugated bilirubin is more than 50%, it is known as conjugated hyperbilirubinaemia and indicates the presence of liver or hepatobiliary disease.

Once conjugated hyperbilirubinaemia has been identified, we need to do an ultrasound abdomen (USG). The radiologist will be informed about what we need to see in the USG. The USG would look for evidence of the following: (i) biliary obstruction such as dilatation of the biliary tract, gallbladder mass or any other mass in the liver; (ii) evidence of chronic liver disease such as liver size, smooth or nodular liver surface, regular or irregular liver margin, portal vein dilatation (normal <12 mm), spleen size, presence of venous collaterals at the splenic hilum and around the portal vein, presence of ascites, etc. A good ultrasound examination can reliably differentiate between liver disease and biliary tract disease as a cause for conjugated hyperbilirubinaemia.

The next step, after the possibility of biliary obstruction has been excluded, is to look into the pattern of liver enzyme elevation, which helps us to identify the possible cause of the liver disease. There are three patterns of liver injury: hepatocellular, cholestatic and mixed patterns. In the hepatocellular pattern of liver injury, there is marked elevation of ALT and AST. In cholestatic liver injury there is marked elevation of alkaline phosphatase and GGT. Patients with a mixed pattern have a variable combination of liver enzyme elevation.
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Approach to a patient with raised bilirubin (jaundice)

1. Elevated serum bilirubin
   - Unconjugated (<20% conjugated)
     - Haemolysis
   - Conjugated (>50% conjugated)
     - Disease of liver or biliary tree
       - Ultrasound
         - No biliary obstruction (hepatic disease)
           - ↑ ALT/AST
             - Hepatitis
           - Mixed
           - ↑ Alk. Phos.
             - Cholestasis
         - Biliary obstruction (biliary disease)
           - Gallstone disease
           - Cancers
Approach to a patient with enzyme elevation

2

Persistent enzyme elevation
Hepatocellular injury may have several causes. The most important causes for marked elevation of ALT/AST are viral hepatitis, alcoholic liver disease, drug-induced liver injury, and autoimmune hepatitis.

Cholestatic liver injury is primarily caused by drugs, liver infiltration due to bacterial (such as tuberculosis) or fungal infections, storage diseases such as amyloidosis, or biliary tract disorders such as primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), etc.
Approach to a patient with enzyme elevation

2 Persistent enzyme elevation

High ALT/AST

Extrinsic causes: often reversible
- Alcohol
- Obesity
- Hepatotoxic drug

High (>2.0 x ULN) alkaline phosphatase

Viral hepatitis
- Hepatitis B virus
- Hepatitis C virus

Intrinsic causes
- Autoimmune, genetic and other diseases

* ULN: Upper limit of normal
Approach to a patient with enzyme elevation

\[
\text{ALT/AP ratio} = \frac{\text{ALT elevation (folds ULN)}}{\text{AP elevation (folds ULN)}}
\]

- If \( \text{ALT/AP ratio} > 5 \), Hepatocellular injury
- If \( \text{ALT/AP ratio} < 2 \), Mixed pattern
- If \( \text{ALT/AP ratio} < 2 \), Cholestatic injury

* Viral hepatitis

* ULN: Upper limit of normal
Approach to a patient with enzyme elevation

1. Persistent enzyme elevation

2. Alk. phosphatase elevation
   (>2.0 x ULN)

* ULN: Upper limit of normal
Approach to a patient with enzyme elevation

Persistent enzyme elevation

ALT/AST elevation (>1.5 x ULN)

Alk. phosphatase elevation (>2.0 x ULN)

GGT

Alcohol Cirrhosis
PBC
PSC
Infiltrative liver disease

GGT elevated
USG abdomen
No biliary obstruction

GGT normal
Non-hepatic causes
Biliary obstruction

ULN: Upper limit of normal
Aminotransferases (ALT/AST)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ALT</th>
<th>AST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ localization</td>
<td>Liver, kidney</td>
<td>Liver, heart, muscle, red blood cells</td>
</tr>
<tr>
<td>Organ specificity</td>
<td>More specific for liver disease</td>
<td>Less specific for liver disease</td>
</tr>
<tr>
<td>Subcellular location</td>
<td>Cytoplasm (easy leakage)</td>
<td>Mitochondria (80%) Cytoplasm (20%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Higher with alcohol</td>
</tr>
<tr>
<td>Half-life</td>
<td>~48 hours (slower drop)</td>
<td>~18 hours (rapid drop)</td>
</tr>
</tbody>
</table>

ALT and AST are two separate enzymes, which are used as markers of liver injury. It is common to see them as synonymous with each other. These two enzymes differ markedly from each other and have their own clinical significance.

ALT is primarily located in the liver and hence it is a more specific enzyme for liver injury than AST, which is more widely distributed in the body. Serum AST levels are frequently elevated in the presence of heart disease such as ischaemic heart disease, haemolysis and muscle injury.

Further, ALT is located in the cytoplasm of the hepatocytes and hence is released by minor injury. This makes ALT a sensitive marker of liver injury.

AST is primarily located inside the mitochondria, and is also found in the cytoplasm of the hepatocyte in a relatively low concentration. AST is released from the hepatocyte after more severe injury, in particular, after injury with an agent that causes injury to the mitochondria such as alcohol.

Hence, AST is a less sensitive and less specific marker of liver injury than ALT. AST is more elevated than ALT in alcohol-induced liver injury.

One important aspect is that ALT has a longer half-life than AST. Hence, the serum ALT level takes a longer time to normalize than the AST after the injury has subsided.

**ALT is indicator of liver injury and AST is indicative of fibrosis. So ALT is used in Hep B management while AST is used in Hep C management.**
In patients with viral hepatitis, in particular, those with hepatitis B infection, serum ALT and AST levels are the cornerstone of diagnosis and management. We need precise estimation of their serum levels. Even a slight change in serum ALT/AST level could change the diagnosis, management and follow-up plan for a given patient.

The serum levels of ALT and AST are sensitive to several common factors such as age, gender, body build (because of liver size, metabolic requirement of the body and muscle mass), fed or fasting state (because liver enzymes are needed for normal metabolism in the liver), exercise (because AST may be released from the muscle after exercise), and delay in sample processing (because AST may be released from the RBCs present in collected blood).

Hence, we must ensure that blood specimens for ALT/AST estimation are collected in the morning after overnight fasting because this will obviate the effect of diet and exercise on serum enzyme levels. Food can increase ALT/AST level by 2–3-fold, so it should be tested while fasting in the morning as morning collection also takes care of a rise due to muscle activity.
Aminotransferases: Important considerations

• Reference range can vary between laboratories and population groups
• Best expressed as multiples of upper limit of normal (ULN)
• Levels do not correlate well with disease severity or outcome
• Repeated measurements have limited role
• No relation with serum bilirubin level

There are a few common myths about serum ALT/AST levels, which must be clarified.

Reports of serum ALT/AST levels are not uniform across the population. Usually, an ALT/AST level up to 40 IU/L is considered normal but the normal limits or reference ranges vary between populations as well as between laboratories. Hence, every value of ALT/AST should be expressed in terms of multiples of the upper limit of normal and the upper limit taken should be that of the laboratory where it is measured.

Serum levels of ALT/AST do not correlate with either liver disease severity or serum bilirubin.
In a normal person as well as most patients with liver disease, ALT is higher than AST. There are two reasons for the higher ALT levels: first, ALT is present in the cytoplasm and is released by minor injuries; second, ALT has a longer half-life than AST and hence remains in the blood for a longer time period.
In some diseases, the AST level tends to be higher than the ALT level:

- Alcoholic liver disease
- Wilson disease
- Liver cirrhosis
- Non-hepatic causes
  - Haemolysis
  - Muscle disease, hectic exercise
  - Heart disease

It is common practice to look at the ALT/AST ratio though it has a limited role in the diagnosis and management of liver diseases. Normal ALT levels are higher than AST levels. In certain conditions, AST could elevated more than ALT like: (i) alcoholic liver disease results in mitochondrial toxicity and pyridoxal phosphate, which is a co-factor for AST; (ii) Wilson disease results in subclinical haemolysis and release of AST; (iii) the presence of liver cirrhosis; once liver cirrhosis is established, AST remains higher than ALT because of destroyed sinusoidal architecture, which results in impaired clearance of AST.

If liver disease is excluded in a patient with a high AST, then extrahepatic sources of AST must be evaluated.
Albumin is the main body protein that maintains the oncotic pressure inside the circulatory system. It is synthesized in the liver and has a half-life of 21 days. This long half-life of albumin helps us use it as a marker to differentiate between and acute and chronic liver injuries. In acute liver injuries such as acute viral hepatitis, serum albumin levels remain normal. In contrast, in the presence of a long-standing chronic injury such as liver cirrhosis, the serum albumin is reduced.

Serum albumin may also be reduced because of excessive loss of albumin such as in patients with renal disease in whom protein is lost in the urine.
Prothrombin time (PT INR)

- A laboratory test that measures some aspects of blood coagulation
- Depends on concentration of clotting factors in the blood
- Prolonged value indicates reduced liver function
- A specific marker of liver failure
- Not a marker of liver injury
- Useful for monitoring degree of liver dysfunction

Prothrombin time, which is commonly known as PT INR, is a composite marker of serum levels of various coagulation factors synthesized in the liver. This reflects the time (in seconds) taken for blood to clot.

In the presence of significant liver disease, the synthetic functions of the liver are compromised and clotting factor levels are reduced in the serum. Reduction in clotting factors leads to prolongation of the PT INR. Mild liver injury does not cause PT prolongation. Only if a severe injury leads to liver failure is the PT prolonged. Hence PT prolongation is a marker of liver failure.
Tests of limited value

- Lactate dehydrogenase
  - Present in many tissues: liver, heart, muscle, kidney, RBCs
  - Not much use since not specific for liver disease

- Serum globulins
  - Level often high in cirrhosis and in autoimmune liver disease
  - But not specific

- Serum total proteins

Several biochemical tests are routinely done as a part of LFT but they have very limited clinical value. These include total serum protein, lactate dehydrogenase, serum globulin, albumin/globulin ratio, etc.

These tests are of little values because they are not specific for liver injury. These enzymes are located in several other organs as well and injury to those organs may cause elevation of these enzymes.
Summary

• Liver function tests are simple tests that help in
  – diagnosing the presence of liver disease
  – differential diagnosis
  – assessing the severity of liver disease
  – monitoring progression of/improvement in liver disease

• Various tests differ in their purpose

• High serum bilirubin indicates impaired excretion, but can occur in other conditions

• ALT or AST levels indicate injury to the liver cells, but do not inform about severity of disease or likely outcome

• Low serum albumin often implies chronic liver disease

• Prothrombin time is a marker of liver failure and helpful in serial monitoring of such patients