The assessment of patients with abnormal liver tests is common in both primary care and gastroenterology clinics. However, among patients with abnormal liver tests, the minority of these will be found to have clinically significant liver disease. Standard laboratory panels include indirect markers of liver disease including hepatic transaminases, alkaline phosphatase, serum bilirubin, serum albumin, and prothrombin time. Additional laboratory tests are available including gamma-glutamyl transpeptidase and 5’-nucleotidase. These blood tests serve as a primary tool by which the clinician can ascertain the presence and severity of liver disease. Through careful assessment of the patient and laboratory data, the nature and severity of liver injury can often be determined.

**Hepatic Transaminases**

The hepatic transaminases are commonly referred to as “liver function tests” though there are no specific liver functions that these tests measure. The hepatic transaminases, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are enzymes that participate in the process of gluconeogenesis and are found in the serum as a product of necrotic or apoptotic hepatocytes. When these are measured in the serum at increased levels, it is inferred that this represents the presence of hepatic inflammation. The AST enzyme is a product of the liver, but lacks specificity in that it is also found in heart, kidney, brain, and striated muscle. The ALT enzyme is more specific to the liver. It is rare that these serological tests are measured individually, and because of the specificity of the ALT, an AST elevation without concurrent ALT increase suggests the presence of cardiac or skeletal muscle injury, such as seen in myocardial infarction or rhabdomyolysis.

The pattern of elevation of hepatic transaminases can provide clues as to the cause of liver injury. AST is located within hepatocytes in both the cytosol as well as mitochondria, whereas ALT is predominantly within the cytosol. Consequently, in conditions such as alcoholic hepatitis where mitochondrial damage is common, the increased measured level of AST is typically higher than the rise seen in measured ALT. Pyridoxine deficiency that is commonly present in patients with chronic alcoholism results in lower concentrations of ALT, for which pyridoxine is a cofactor for synthesis. In presentations of acute biliary obstruction such as choledocholithiasis, the initial laboratory abnormality is an increase in hepatic transaminases because the liver injury that results from acute obstruction of bile flow leads to the release of these already-formed enzymes before other markers of liver injury such as alkaline phosphatase that must be synthesized.

It is rare for any cause of either acute or chronic liver injury to be present without an abnormality of hepatic transaminases. The level to which hepatic transaminases rise can provide clues to the cause of liver injury. Very elevated hepatic transaminases higher than 1000 IU/L are usually seen only in cases of severe medication-induced hepatitis, acute viral hepatitis, or ischemic injury to the liver. In ischemic liver injury due to hypotension, transaminases typically return to normal within just a few days if supportive care is provided and hepatic perfusion is reestablished. Acute viral hepatitis or severe medication-induced hepatitis will result in liver tests that take much longer to normalize as the acute hepatitis resolves. Chronic liver diseases such as non-alcoholic steatohepatitis, chronic viral hepatitis, autoimmune hepatitis, and metabolic diseases of the liver such as Wilson’s disease or hemochromatosis typically present with more modest elevation of hepatic transaminases, although autoimmune hepatitis can present with elevations of AST and ALT to levels near 1000 IU/L and should be kept on the differential diagnosis when severely elevated hepatic transaminases are seen.

Rarely, an isolated AST can exist as a macroenzyme. In this situation, the AST enzyme is complexed with an immunoglobulin and its resultant increase in size results in slow clearance from the blood. This is a benign condition and when suspected, can be confirmed by electrophoresis.
Alkaline Phosphatase

Alkaline phosphatases are a family of enzymes that are present in liver, bone, kidney, intestine, and placenta. The specific physiologic function of alkaline phosphatase is not fully elucidated. Within the liver, alkaline phosphatase is produced by the biliary epithelium. Obstruction or inflammation of the bile ducts at any level of the biliary tree will result in increased synthesis and release into the serum of alkaline phosphatase. If obstruction of even a few bile ducts is present, a measurable increase in alkaline phosphatase can be seen without the development of jaundice. Standard laboratory assays for alkaline phosphatase do not differentiate between the various isoforms of the enzyme. Due to the widespread distribution of alkaline phosphatases, an isolated elevation of measured alkaline phosphatase is nonspecific. Laboratories can typically differentiate the alkaline phosphatase isoenzymes from the liver and bone which permits increased specificity of this test. An elevation of liver alkaline phosphatase significantly out of proportion to the serum bilirubin suggests the presence of an infiltrative liver disease or granulomatous liver diseases that result in obstruction or inflammation of small bile ducts without clinical jaundice developing. Conditions that can produce elevations of alkaline phosphatase of several hundred international units per liter without necessarily an impressive rise in measured serum bilirubin include sarcoidosis, tuberculosis, fungal infections, primary biliary cirrhosis, and lymphoma. Abnormally low levels of alkaline phosphatase can be seen in the setting of acute Wilson’s disease, hypothyroidism, and zinc deficiency.

Bilirubin

There are two types of bilirubin that are routinely measured, conjugated and unconjugated. Unconjugated bilirubin is a product of the degradation of hemoglobin derived from expired red blood cells. Within the liver, bilirubin is glucuronidated to form conjugated bilirubin. Measurement of serum bilirubin is determined by photometric detection of derivatives after bilirubin is subject to the van den Bergh reaction. This reaction allows separation of bilirubin into its conjugated and unconjugated fractions as the conjugated fraction reacts “directly” to produce measured derivatives without the use of a reaction accelerator. The total amount of bilirubin present is measured by the van den Bergh reaction in the presence of a reaction accelerator. The “direct” or conjugated fraction of bilirubin can then be subtracted from the total amount of bilirubin measured to yield the amount of “indirect” or unconjugated bilirubin. Typically, greater than 90% of bilirubin found in the serum is in the unconjugated state.

Unconjugated bilirubin predominates in states that result in high degrees of red cell turnover such as hemolysis. Unconjugated bilirubin is not water soluble and it exists in the serum complexed with albumin. Unconjugated bilirubin complexed to albumin does not get filtered by the kidney and therefore does not result in bilirubinuria. Other states that result in the presence of an elevated level of unconjugated bilirubin are the benign Gilbert’s syndrome, in which an impairment of the promoter for the uridine-diphosphate glucuronosyltransferase (UDPGT) gene results in mildly impaired glucuronidation of bilirubin. Gilbert’s syndrome becomes manifest during periods of stress such as fasting or physical illness when measured levels of unconjugated bilirubin typically rise to levels of no higher than 2-3 mg/dL. The Crigler-Najjar syndrome is a deficiency of the glucuronosyltransferase and presents in two forms. The more severe Type I disease is associated with severe jaundice and encephalopathy with potential for permanent neurological sequelae in infants due to the neurotoxicity of unconjugated bilirubin. Type II disease is associated with less severe elevations in serum concentrations of bilirubin due to the presence of higher amounts (though still markedly reduced from normal) of the UDPGT enzyme.

Conjugated bilirubinemia is found in states where diseases of the hepatobiliary system result in a relative increase in the amount of conjugated bilirubin seen in the serum. Typically, less than 5% of circulating bilirubin is conjugated, but in conditions such as biliary obstruction, obstruction of bile flow causes retention of conjugated bilirubin and its subsequent appearance in the serum as at least 50% of the total amount of bilirubin measured. Extrahepatic obstruction by such causes as choledocholithiasis, common bile duct strictures and pancreatic disease can result in the presence of conjugated bilirubinemia. Similarly, intrahepatic obstruction of bile flow by conditions such as infiltrative diseases of the liver or hepatic tumors can lead to conjugated bilirubinemia.
Inherited conditions such as Rotor syndrome and Dubin-Johnson can result in elevations of conjugated bilirubin in the serum. Rotor syndrome is a benign disorder whereby the hepatic storage of bilirubin is defective, resulting in leakage of conjugated bilirubin into the serum and resultant hyperbilirubinemia. The Dubin-Johnson syndrome is also a benign condition and results from a defect of the biliary excretion of bilirubin and resultant leakage of increased hepatic stores of conjugated bilirubin into the serum. Both of these conditions are rare and their recognition is important primarily in the exclusion of other, more important, liver diseases.

Acute hepatitis and its resultant hepatocellular dysfunction presents with conjugated bilirubinemia that can be indistinguishable from biliary obstruction. Modern imaging techniques such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are often necessary to demonstrate the presence of biliary obstruction. Before these techniques were available, exploratory laparotomy to explore the cause of jaundice in cases of acute hepatitis resulted in high mortality levels.

**Albumin**

Albumin is synthesized exclusively within the liver and has a half-life of 2-3 weeks. In chronic liver disease, the serum albumin can be decreased due to reduced hepatic synthetic function. Measurement of reduced serum albumin levels can be nonspecific as albumin is a negative acute-phase reactant that will exhibit reduced levels during any severe illness. In addition, malnutrition or conditions of protein loss such as the nephrotic syndrome or protein-losing enteropathy can result in low levels of serum albumin. In conditions of chronic liver disease, a low serum albumin has important prognostic implications as a part of the Child-Turcotte-Pugh score.

**Prothrombin Time**

Most of the components of the coagulation pathway are synthesized by the liver, and factors II, VII, IX, and X in particular are dependent upon vitamin K for synthesis. In the non-diseased state, these factors are present in excess. In conditions of chronic liver disease, an impairment in the liver’s ability to synthesize these clotting factors results in prolongation of the measured prothrombin time. Nutritional vitamin K deficiency can be differentiated from hepatic synthetic dysfunction by administering parenteral vitamin K. This should result in correction of the prothrombin time within days if vitamin K deficiency was the only cause of decreased production of clotting factors. An alternative means of differentiating vitamin K deficiency from intrinsic hepatic synthetic dysfunction is to measure factor V levels. This clotting factor is produced by the liver but is not affected by vitamin K. Reduced levels of factor V imply hepatic synthetic dysfunction and not nutritional vitamin K deficiency.

The prothrombin time and calculated international normalized ratio (INR) can be used to quantify hepatic synthetic function but have no role in accurate measurement of clotting ability of the patient with liver disease. Anticoagulant factors such as protein C and protein S are also synthesized by the liver and relevant levels of these important components of the patients clotting ability are not measured by the prothrombin time. A prolongation of the prothrombin time and resultant increase of INR have important prognostic implications in the care of patients with liver disease as an important component of both the Child-Turcotte-Pugh score as well as the Model for Endstage Liver Disease (MELD) score.

**Gamma-glutamyl transpeptidase**

Tissue distribution of γ-glutamyl transpeptidase (GGT) is wide as this enzyme is found in kidney, liver, heart, brain, and pancreas. Within the liver, GGT is found in hepatocytes as well as the entire hepatobiliary tree including the common bile duct. Elevations of GGT are therefore found in multiple medical states including hepatic disease, myocardial infarction, renal failure, and chronic obstructive lung disease. The GGT level is found to often correlate with serum alkaline phosphatase levels and its most common clinical use is for confirmation of the liver origin of alkaline phosphatase, as GGT is not found in bone, as alkaline phosphatase is. An isolated elevation of GGT is not useful clinically due to the widespread distribution of GGT and its subsequent poor specificity. GGT has been used in the past as a surrogate marker of surreptitious alcohol ingestion, taking advantage of its induction by alcohol and its long half-life. The clinical utility of GGT for this purpose is significantly limited due to poor sensitivity and specificity.
With the widespread availability of alkaline phosphatase isoenzymes, the clinical utility of GGT has waned. Laboratory costs of measuring alkaline phosphatase isoenzymes are typically less than for measurement of GGT.

5'- nucleotidase

5'- nucleotidase is present in multiple organ systems such as liver, intestines, brain, pancreas, and vasculature. The specific physiologic function of this enzyme is not clear. Measured serum levels of 5’-nucleotidase typically correlate with measured elevations of alkaline phosphatase and measurement of this enzyme can be used to confirm the liver origin of elevated alkaline phosphatase. Despite the widespread presence of this enzyme, circulating 5’-nucleotidase is felt to be exclusively of liver origin, due to the detergent action of bile salts. 5’-nucleotidase present in other tissues is not felt to be released into the serum in measurable amounts. With the widespread availability of alkaline phosphatase isoenzyme measurements, the measurement of 5’-nucleotidase now has limited clinical utility.

Urinary bilirubin and urobilinogen

Conjugated bilirubin is water soluble and elevated amounts of conjugated bilirubin are filtered by the kidneys such that even modest elevations of serum bilirubin can result in measurable urinary bilirubin. Dark-colored urine as a potential sign of liver disease is commonly recognized by patients and the finding of bilirubinuria can prompt an evaluation for the presence of liver disease. When a patient is unmistakably jaundiced, the finding of bilirubin in the urine is expected and its presence does not provide additional clinical information. In the patient with apparent jaundice in whom bilirubinuria is not seen, one of two states is typically present. In states of elevated unconjugated bilirubin such as hemolysis, unconjugated bilirubin is not water soluble and circulating unconjugated bilirubin must be complexed with albumin which does not get filtered and therefore does not appear in the urine. In states of prolonged jaundice, such as recovery from a bout of acute hepatitis, conjugated bilirubin becomes complexed to albumin, a state referred to as “delta bilirubin.” In this state, the conjugated bilirubin that normally would be filtered by the kidney and therefore appear in the urine can persist for a prolonged duration due to the long half-life of albumin. For this reason, jaundice can persist for a prolonged duration despite intervening recovery of hepatic inflammation.

Normal metabolism of bilirubin involves excretion in the bile after conjugation occurs in the hepatocyte and it is subsequently metabolized by enteric bacteria to form urobilinogen. Urobilinogen is either excreted in the feces or absorbed by the enterohepatic circulation and returned to the liver where it is excreted in bile. A minority of urobilinogen that undergoes enterohepatic circulation enters the systemic circulation and is ultimately excreted in the urine. Urobilinogen is found in the urine commonly during states of bilirubin overproduction. Its absence in the urine in states of jaundice implies that extrahepatic obstruction of bile flow is present resulting in an absence of enteric delivery of bilirubin to the intestines and resulting absence of bacterial metabolism of bilirubin.

Patterns of Liver Test Abnormalities in Specific Disease States

The pattern of liver test abnormalities is an important part of the assessment of patients with chronic liver disease, along with a thorough history and physical examination. Because of the lack of perfect specificity of each individual liver test, it is common for an abnormal laboratory test to be confirmed by another test that measures a similar aspect of liver disease. For example, an AST increase that implies liver injury should be confirmed by evaluation of ALT increase to exclude an alternative source of AST production. Similarly, a reduced serum albumin level should be confirmed by a prolonged prothrombin time, as a condition such as the nephrotic syndrome can result in low measured albumin levels with a normal prothrombin time if liver function is preserved.

Patterns of liver test abnormalities are typically divided into hepatocellular or cholestatic patterns. A predominant rise in hepatic transaminases is seen in common conditions that result in hepatocellular injury such as medication effect, chronic viral hepatitis, alcoholism, or non-alcoholic steatohepatitis (NASH). Metabolic liver diseases such as Wilson’s disease, hemochromatosis, or alpha-1 antitrypsin deficiency also result in a predominant rise of hepatic transaminases, as does autoimmune hepatitis. A careful history, physical examination, and serological evaluation
for these causes of chronic liver disease will often result in a diagnosis without resorting to a liver biopsy. Abdominal imaging with ultrasound, CT, or MRI can demonstrate the presence of hepatic steatosis in suspected NASH.

The cholestatic pattern of liver test elevation is seen when an elevation of alkaline phosphatase and bilirubin are observed predominantly with more modest increases of hepatic transaminases. Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) typically present with a significant elevation of alkaline phosphatase. The presence of an anti-mitochondrial antibody confirms the presence of PBC. Abdominal imaging with ultrasound, CT, or MRI can often demonstrate the presence of either intrahepatic or extrahepatic bile duct obstruction and bile duct imaging by magnetic resonance cholangiography or endoscopic retrograde cholangiography can elucidate bile duct abnormalities such as PSC or obstructing lesion of the biliary tree.

References
Liver function tests can help doctors determine whether a person has liver damage and what might be causing it. Learn about the tests and what the results mean here. Continue reading this article to learn more about liver function tests, including their uses and how to interpret the results.

**What is a liver function test?**

A doctor may order a blood test to measure liver function. Liver function tests, or liver panels, measure the levels of proteins, enzymes, and waste materials (bilirubin) in a person’s blood. Doctors use these tests when they want to evaluate the health of a person’s liver or identify the cause of liver damage. Liver function tests measure the following compounds: Alanine transaminase (ALT) is an enzyme found in liver.

**What does the ‘normal range’ mean in liver function tests?**

The normal range of blood tests is usually dependent on the laboratory that has conducted the tests. The normal range will most often be given along with the result of the test. If it is not given along with the results, it is important to find out about the normal range from the medical specialists as it might have implication in the assessment and management of the liver function test. It is important to highlight here that about 5% of patients with advanced liver disease (cirrhosis) will have normal liver function test.

Therefore, a liver function test will check your liver function and for any signs of inflammation or damage. Since a liver function test measures many different biomarkers, it can help pick up a wide range of issues. High or low levels of certain proteins and enzymes can indicate that there’s a problem with your liver. So if your AST levels are raised, it doesn’t necessarily mean it’s because of a problem with your liver. That’s why it’s important to look at both your AST and ALT levels. High AST levels can be a sign of liver damage.

Liver function tests, also known as liver chemistries, help determine the health of your liver by measuring the levels of proteins, liver enzymes, and bilirubin in your blood. A liver function test is often recommended in the following situations: to check for damage from liver infections, such as hepatitis B. and hepatitis C. Talk to your doctor about the results of your liver function test and what they may mean for you.

What are the most common liver function tests? Liver function tests are used to measure specific enzymes and proteins in your blood. Liver tests can help determine if your liver is working correctly. The liver performs a number of vital bodily functions, such as