Special Considerations in Interpreting Liver Function Tests

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A number of pitfalls can be encountered in the interpretation of common liver function tests. These tests can be normal in patients with chronic hepatitis or cirrhosis, but they are not always normal. Patients with cirrhosis and bleeding esophageal varices can have normal LFTs, only serum albumin, bilirubin and prothrombin time (PT) provide useful information on hepatic function. Indeed, these blood tests may reflect problems arising outside the liver, such as a bilirubin level or bone disease (elevated alkaline phosphatase [AP] level).

Abnormal LFTs often, but not always, indicate that something is wrong with the liver. However, normal LFTs do not always provide clues to the nature of the problem. Indeed, these blood tests may reflect problems arising outside the liver, such as alcoholic hepatitis because aminotransferase levels often rise immediately, but alkylglutamyltransferase levels do not become elevated for several days. As isolated, mild elevation of either the unconjugated bilirubin or the y-glutamyltransferase level usually do not have liver disease and generally do not require extensive hepatic function can be assessed by applying the values for albumin, bilirubin and prothrombin time in the modified Child-Turcotte grading system.

The commonly used liver function tests (LFTs) primarily assess liver injury rather than liver disease. Indeed, these blood tests may reflect problems arising outside the liver, such as bilirubin level or bone disease. The differential diagnosis of abnormal LFTs have been well reviewed. This article discusses some common pitfalls in the interpretation of these tests are presented in Table 1.

TABLE 1
Helpful Hints for Interpreting Liver Function Tests

http://www.aafp.org/afp/1999/0415/p2223.html
<table>
<thead>
<tr>
<th><strong>Situation</strong></th>
<th><strong>Comments</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mildly elevated ALT level (less than 1.5 times normal)</td>
<td>ALT value could be normal for gender, ethn Consider muscle injury or myopathy.</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>Laboratory values can appear cholestatic, and symptoms can mimic cholecystitis.</td>
</tr>
<tr>
<td>AST level greater than 500 U per L</td>
<td>The AST elevation is unlikely to result from alcohol intake alone.</td>
</tr>
<tr>
<td>Common bile duct stone</td>
<td>Condition can simulate acute hepatitis.</td>
</tr>
<tr>
<td>Isolated elevation of GGT level</td>
<td>AST and ALT become elevated immediately, but elevation of AP and GGT is delayed.</td>
</tr>
<tr>
<td>Isolated elevation of AP level</td>
<td>This situation may be induced by alcohol acetaminophen toxicity.</td>
</tr>
<tr>
<td>Isolated elevation of unconjugated bilirubin level</td>
<td>Consider bone growth or injury, or primary biliary cirrhosis.</td>
</tr>
<tr>
<td>Low albumin level</td>
<td>Low albumin is most often caused by acute urinary loss, severe malnutrition or liver disease.</td>
</tr>
<tr>
<td>Blood ammonia level</td>
<td>Blood ammonia values are not necessarily hepatic encephalopathy.</td>
</tr>
</tbody>
</table>

**Markers of Hepatocellular Injury**

The most commonly used markers of hepatocyte injury are aspartate aminotransferase (AST, formerly serum glutamic-pyruvate transaminase [SGPT]) and alanine aminotransferase (ALT, formerly serum glutamic-oxaloacetic transaminase [SGOT]). While ALT is cytosolic, AST has mitochondrial forms.

Hepatocyte necrosis in acute hepatitis, toxic injury or ischemic injury results in the leakage of enzymes into the circulation. However, in chronic liver diseases such as hepatitis C and alcohol liver disease, ALT level correlates only moderately well with liver inflammation. In hepatitis C, apoptosis (programmed cell death) as well as necrosis. Hepatocytes dying from apoptosis synthesize less AST and ALT as they wither away. This probably explains why patients infected with hepatitis C virus have persistently normal serum ALT levels of inflammation on liver biopsy. Patients with cirrhosis often have normal or elevated serum AST and ALT levels. Thus, AST and ALT lack some sensitivity in detecting liver inflammation.

Of course, AST and ALT levels tend to be higher in cirrhotic patients with coexisting chronic liver disease than in those without continuing liver injury.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AP = alkaline phosphatase; GGT = glutamyltransferase.
As markers of hepatocellular injury, AST and ALT also lack some specificity to skeletal muscle. Levels of these aminotransferases can rise to several times normal after severe muscular exertion or other muscle injury, as in polymyositis, or in the presence of hypothyroidism, which can cause mild muscle injury and the release of aminotransferases. In fact, AST and ALT were once used in the diagnosis of myocardial infarction.

Slight AST or ALT elevations (within 1.5 times the upper limits of normal) do not indicate liver disease. Part of this ambiguity has to do with the fact that unlike the values in many other biochemical tests, serum AST and ALT levels do not follow a normal bell-shaped population. Instead, AST and ALT values have a skewed distribution characterized by a long “tail” at higher values (Figure 1). For example, the mean values for ALT are similar from one population to another, but the degree to which the distribution is skewed varies by gender and ethnic group. The ALT distributions in males and nonwhites (i.e., blacks and Hispanics) tend to have a larger tail at the high end, so that more values fall above the upper limits of normal set for the population.

Typical ALT or AST Distribution

![Typical population distribution of serum alanine aminotransferase (ALT) or aspartate transaminase (AST) levels. The population distributions for these aminotransferases do not follow a bell-shaped, normal distribution. Instead, AST and ALT levels have a skewed distribution characterized by a long “tail” at higher values. By convention, values above the 97.5th percentile are considered elevated (shaded area). Although average values for ALT and AST are similar in different populations, the distributions are more skewed in males and in nonwhite ethnic groups (i.e., blacks and Hispanics).](http://www.aafp.org/afp/1999/0415/p2223.html)

AST and ALT values are higher in obese patients, probably because these persons have larger livers. ALT levels have been noted to decline with weight loss. Depending on the view, the upper limits of normal for AST and ALT levels could be set higher.

Rare individuals have chronically elevated AST levels because of a defect in the circulation. For both AST and ALT, the average values and upper limits in patients undergoing renal dialysis are about one half of those found in the general population.

<table>
<thead>
<tr>
<th>A</th>
<th>Autoimmune hepatitis</th>
</tr>
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<tbody>
<tr>
<td>B</td>
<td>Hepatitis B</td>
</tr>
</tbody>
</table>

TABLE 2

Causes of Elevated ALT or AST Values in Asymptomatic Patients

http://www.aafp.org/afp/1999/0415/p2223.html

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Various liver diseases are associated with typical ranges of AST and ALT levels—often rise to several thousand units per liter in patients with acute viral hepatitis levels—often more than 10,000 U per L—are usually found in patients with a subsequent to, for example, acetaminophen overdose or acute ischemic insult levels usually fall rapidly after an acute insult.

Typical AST or ALT Values in Disease

Lactate dehydrogenase (LDH) is less specific than AST and ALT as a marker. However, it is worth noting that LDH is disproportionately elevated after an ischemic liver injury.

It is especially important to remember that in patients with acute alcoholic hepatitis, the serum AST level is almost never greater than 500 U per L and the serum ALT value is almost never greater than 300 U per L. The reasons for these limits on AST and ALT elevations are not well understood. In typical viral or toxic liver injury, the serum ALT level rises more than the AST value, refl
of these enzymes in hepatocytes. However, in alcoholic hepatitis, the ratio of 1 in 90 percent of patients and is usually greater than 2. The higher the AST the likelihood that alcohol is contributing to the abnormal LFTs. In the absence increased AST-to-ALT ratio is often found in patients with cirrhosis.

The elevated AST-to-ALT ratio in alcoholic liver disease results in part from (pyridoxine) in chronic alcoholics. ALT and AST both use pyridoxine as a coenzyme, but the synthesis of ALT is more strongly inhibited by pyridoxine deficiency than is the synthesis of AST. Alcohol also causes mitochondrial injury, which releases the mitochondrial isoenzyme of AST.

Patients with alcoholic hepatitis can present with jaundice, abdominal pain, an elevated AST value, thereby leading to a misdiagnosis of cholecystitis. This is given the high surgical mortality rate in patients with alcoholic hepatitis.

Markers of Cholestasis

Cholestasis (lack of bile flow) results from the blockage of bile ducts or from formation in the liver itself. AP and γ-glutamyltransferase (GGT) levels typic the normal level after several days of bile duct obstruction or intrahepatic cho AP elevations—often greater than 1,000 U per L, or more than six times the r diffuse infiltrative diseases of the liver such as infiltrating tumors and fungal:

Diagnostic confusion can occur when a patient presents within a few hours af obstruction from a gallstone. In this situation, AST and ALT levels often rea the first hours and then decline, whereas AP and GGT levels can take several

Both AP and GGT levels are elevated in about 90 percent of patients with cho GGT alone, with no other LFT abnormalities, often results from enzyme indu aromatic medications in the absence of liver disease. The GGT level is often take three or more alcoholic drinks (45 g of ethanol or more) per day. Thus, immoderate alcohol intake. Phenobarbital, phenytoin (Dilantin) and other ara GGT elevations of about twice normal. A mildly elevated GGT level is a typi taking anticonvulsants and by itself does not necessarily indicate liver disease.

Serum AP originates mostly from liver and bone, which produce slightly diffi The serum AP level rises during the third trimester of pregnancy because of a produced in the placenta. When serum AP originates from bone, clues to bone such as recent fracture, bone pain or Paget's disease of the bone (often found n GGT value, the AP level can become mildly elevated in patients who are tak

If the origin of an elevated serum AP level is in doubt, the isoenzymes of AP electrophoresis. However, this process is expensive and usually unnecessary AP value is usually accompanied by an elevated GGT level, an elevated 5′-n LFT abnormalities.

In one study, isolated AP elevations were evaluated in an unselected group of Affairs hospital. Most mild AP elevations (less than 1.5 times normal) resolved almost all greater elevations had an evident cause that was found on routine c

Persistently elevated liver AP values in asymptomatic patients, especially w primary biliary cirrhosis, which is a chronic inflammatory disorder of the sm antimitochondrial antibody is positive in almost all of these patients.
Indicators of How Well the Liver Functions

BILIRUBIN
Bilirubin results from the enzymatic breakdown of heme. Unconjugated bilirubin is secreted into bile, but most is conjugated with glucuronic acid in hepatocytes to increase its water solubility and is then rapidly transported into bile. The serum conjugated bilirubin level becomes elevated only when the liver has lost at least half of its excretory capacity. Thus, a patient could have obstruction of either the left or right hepatic ducts without a rise in the bilirubin level.

Because the secretion of conjugated bilirubin into bile is very rapid in comparison with other liver functions, healthy persons have almost no detectable conjugated bilirubin in their blood. Healthy persons have almost no detectable conjugated bilirubin in their blood. Liver disease mainly impairs the secretion of conjugated bilirubin into bile. As a result, conjugated bilirubin is rapidly excreted into the urine, where it can be detected by a dipstick test. The finding of bilirubin in urine is a particularly sensitive indicator of the presence of an increased serum conjugated bilirubin level.

In many healthy persons, the serum unconjugated bilirubin is mildly elevated to a mg per dL (34 to 51 μmol per L) or slightly higher, especially after a 24-hour fast. If this is the only LFT abnormality and the conjugated bilirubin level and complete blood count are normal, the diagnosis is usually assumed to be Gilbert syndrome, and no further evaluation is required. Recently, it has been shown to be related to a variety of partial defects in uridine diphosphate glucuronyltransferase, the enzyme that conjugates bilirubin.

Mild hemolysis, such as that caused by hereditary spherocytosis and other disorders, can elevate unconjugated bilirubin values, but hemolysis is not usually present if the hematocrit and blood smear are normal. The presence of hemolysis can be confirmed by testing other markers, such as haptoglobin, or by measuring the reticulocyte count.

Severe defects in bilirubin transport and conjugation can lead to markedly elevated bilirubin levels, which can cause serious neurologic damage (kernicterus) in infants. However, no serious form of liver disease in adults causes elevation of unconjugated bilirubin levels in the blood without also causing elevation of conjugated bilirubin values.

When a patient has prolonged, severe biliary obstruction followed by the restoration of liver function, the serum bilirubin level often declines rapidly for several days and then slowly over a period of weeks. The slow phase of bilirubin clearance results from the presence of a form of bilirubin chemically attached to serum albumin. Because albumin has a plasma half-life of three weeks, delta-bilirubin clears much more slowly than bilirubin-glucuronide. Clinical laboratories can measure delta-bilirubin concentrations, but such measurements are usually unnecessary if the delta-bilirubin phenomenon is understood.

ALBUMIN
Although the serum albumin level can serve as an index of liver synthetic capacity, albumin concentrations are difficult to interpret. The liver can synthesize albumin at a basal rate and thus partially compensate for decreased synthetic capacity or in response to alterations in synthesis. Furthermore, because two thirds of the albumin is located in the extravascular, extracellular space, changes in distribution can alter the serum albumin concentration.

In practice, patients with low serum albumin concentrations and no other LFT abnormalities have a nonhepatic cause for low albumin, such as proteinuria or an acute or chronic inflammatory state.
Albumin synthesis is immediately and severely depressed in inflammatory states such as burns, trauma and sepsis, and it is commonly depressed in patients with active rheumatic disorders or severe malnutrition. In addition, normal albumin values are lower in pregnancy.

**PROTHROMBIN TIME**

The liver synthesizes blood clotting factors II, V, VII, IX and X. The prothrombin time (PT) does not become abnormal until more than 80 percent of liver synthetic capacity is lost; it is relatively insensitive marker of liver dysfunction. However, abnormal PT prolongation may be a sign of serious liver dysfunction. Because factor VII has a short half-life of only about 6 hours, it is sensitive to rapid changes in liver synthetic function. Thus, PT is very useful for follow patients with acute liver failure.

An elevated PT can result from a vitamin K deficiency. This deficiency usually results from chronic cholestasis or fat malabsorption from disease of the pancreas or small K injections (e.g., 5 mg per day administered subcutaneously for three days). To exclude vitamin K deficiency in such patients, the PT should improve within 48 hours of vitamin K injection.

**BLOOD AMMONIA**

Measurement of the blood ammonia concentration is not always useful in patients suspected of hepatic encephalopathy. Ammonia contributes to hepatic encephalopathy, but ammonia concentrations are much higher in the brain than in the blood and therefore do not cross the blood-brain barrier. Furthermore, ammonia is not the only waste product responsible for encephalopathy; other factors, such as ketones and lactate, contribute to encephalopathy. Thus, blood ammonia concentrations show only a mediocre correlation with the level of mental status in patients with liver disease. It is not unusual for the blood ammonia concentration to be normal in a patient who is in a coma from hepatic encephalopathy.

Blood ammonia levels are best measured in arterial blood because venous concentrations can be elevated as a result of muscle metabolism of amino acids. Blood ammonia concentrations are beneficial in evaluating patients with stupor or coma of unknown origin. It is not necessary to evaluate blood ammonia levels routinely in patients with known chronic liver disease who are responding to therapy as expected.

**Grading Liver Function by Child-Turcotte Class**

In communicating among themselves, many physicians use the Child-Turcotte Pugh, often termed the “Child class,” to convey information about overall liver function (Table 3). This grading system can be used to predict overall life expectancy and surgical outcomes for patients with cirrhosis and other liver diseases.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Points</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>More than 3.5 g per dL (35 g per L)</td>
<td>2.8 to 3.5 g per dL (28 to 35 g per L)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Less than 2 mg per dL (34 μmol per L)</td>
<td>2 to 3 mg per dL (34 to 51 μmol per L)</td>
</tr>
<tr>
<td>Prolongation of prothrombin time</td>
<td>Less than 4 seconds</td>
<td>4 to 6 seconds</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Controlled</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Controlled</td>
</tr>
</tbody>
</table>
The Child-Turcotte class, as modified by Pugh, often known simply as the “Child class, adding the points as determined by the patient’s laboratory results: class A = 0 to 1; and higher. The classes indicate severity of liver dysfunction: class A is associated with routine medical therapy” or “refractory to medical therapy.”


For elective general abdominal surgery, perioperative mortality is in the neighborhood of several percent for patients who fall into the Child class A, 10 to 20 percent for those in class percent for those in class C.21 These percentages must be balanced by prognostic considerations when transplantation becomes an option. The presence of cirrhosis by itself is not a contraindication to transplantation, and transplantation is rarely performed in patients who fall in example, the 10-year survival rate is as high as 80 percent in patients with hepatitis C and cirrhosis who have Child class A liver function and no variceal bleeding.22 However, once patients with any type of liver disease fall into the Child-Turcotte class B or class C category, survival following transplantation should be considered.

The Author

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REFERENCES


