

Interpretation of liver chemistry tests

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Liver chemistry tests are frequently used to assess patients with symptomatic and asymptomatic liver diseases. However, these tests are neither sensitive nor specific and should, therefore, be interpreted in conjunction with clinical data and other laboratory investigations as well as imaging studies. Nonetheless, certain patterns in liver tests may be helpful in short listing the differential diagnosis of liver dysfunction. This article discusses the utility and limita-

tions of liver tests in establishing the diagnosis and prognosis in patients with various liver disorders. The paper also addresses non-hepatic causes of abnormal liver chemistry tests.

Key words: Liver tests, aminotransferase, alkaline phosphatase, jaundice.

Bull Kuwait Inst Med Spec 2003;2:27-31

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Introduction

Serum liver chemistry tests are important tools in evaluating patients suspected of having liver disease. Moreover, these tests are frequently obtained on asymptomatic individuals for 'screening' purposes. The approach to biochemical liver tests may be challenging even to the experienced clinician. As with all laboratory tests, interpretation of liver chemistry tests should be done in the context of the patient's demographics, risk factors, symptoms, and findings on physical examination. The magnitude and pattern of abnormal levels may also help interpret these tests.

What are serum chemistry tests?

Liver chemistry tests include several serum chemistries that reflect liver function. How-

ever, not all standard 'liver function tests' truly reflect hepatic function.

The most commonly used serum liver chemistry tests include serum transaminases (alanine aminotransferase ALT, aspartate aminotransferase AST), serum alkaline phosphatase ALP, Gamma-glutamyl transpeptidase (GGT), bilirubin, albumin, and prothrombin time. Serum ALT and AST reflect hepatocellular injury. Serum ALP and GGT reflect impaired bile excretion and bile flow. Only serum albumin and prothrombin time truly represent the synthetic 'function' of the liver.

What is the significance of normal values?

Normal liver chemistry tests are defined as values equal to the mean ± 2 standard deviations obtained in presumably healthy individuals.¹ Thus 2.5% of the healthy population might have elevated serum levels. Moreover, the normal range for children is different from that of adults. It should also be emphasized that normal liver chemistry tests do not rule out liver disease.

What is the role of history taking in interpreting liver tests?

Systemic symptoms of liver disease such as anorexia, nausea, vomiting are non-specific and do not point to specific diagnoses. Moreover, many patients with liver dysfunction may be asymptomatic. However, valuable in-

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formation that helps in the differential diagnosis may be obtained by questions regarding family history, drug history, illicit drug use, alcohol consumption, sexual and menstrual history, travel history, previous surgery and transfusion history (Table 1).²

Table 1. Role of history taking in interpreting liver tests

History	Significance
Age	
Young	Viral hepatitis, Wilson's disease, Gallstones, Autoimmune hepatitis
Middle age	Viral hepatitis, alcoholic liver disease, Hemochromatosis, Gallstones, Primary & secondary liver cancer
Old	PBC, PSC, Malignancy, Stones, Drug induced
Sex	
Females	Autoimmune hepatitis, PBC, Birth control pills, pregnancy-related liver dysfunction, gallstone disease
Nationality	Hepatitis B-endemic areas e.g. South East Asia, Africa, Middle East Hepatitis C – North Africa
Family history	Hepatitis B, Wilson's disease, Hemochromatosis
Alcohol use	Alcoholic fatty liver, hepatitis, cirrhosis
Promiscuity	Hepatitis B, HIV related liver dysfunction
Transfusion	Hepatitis C
Comorbid conditions	DM-steatosis, steatohepatitis, obesity-steatosis and steatohepatitis, Chronic renal failure - Hepatitis B and C, Heart failure – congestive Hepatopathy, Thalassemia – iron overload, hepatitis C, others
General pruritus	Cholestasis due to PBC, PSC, bile duct and ampullary tumors, cholestasis of pregnancy

What physical findings point to liver dysfunction?

Stigmata of chronic liver disease include spider angiomas, palmar erythema, gynecomastia and testicular atrophy. If liver disease had led to portal hypertension, then ascites and splenomegaly may be detected. Leukocytoclastic vasculitic skin lesions may point to HCV-related cryoglobulinemia.

What are the main causes of raised serum AST and ALT?

AST and ALT reflect hepatocellular injury. Common hepatic causes of elevated levels include viral hepatitis, alcohol, drugs, non-alcoholic steatosis and steatohepatitis. Wilson's disease, hemochromatosis, and autoimmune hepatitis are rare causes of raised ALT/AST levels. Both AST and ALT may be elevated in patients with muscle injury due to strenuous exercise, rhabdomyolysis, and myositis (Table 2).³

Table 2. Caveats in the interpretation of elevated AST and ALT

1. ALT may be elevated in myositis, exercise induced muscle injury and myopathy.
2. Markedly raised AST and ALT levels with normal ALP, and total bilirubin should raise the suspicion of non-hepatic origin of serum transaminase elevation.
3. The most common cause of raised serum transaminases in otherwise healthy, low risk individual is fatty liver.

Does the magnitude of AST and ALT elevation help in narrowing down the differential diagnosis of raised liver chemistries?

Mild to moderate elevations in serum ALT and AST levels may be observed in virtually all liver diseases and thus are generally non-specific.⁴ However, ALT and AST levels exceeding 15 times the upper limit of normal are usually found in a limited number of conditions (Table 3).^{5,6}

Table 3. Causes of ALT and AST levels ≥ 1000 iu/L

1. Acute viral hepatitis (A to E, herpes simplex)
2. Drugs (paracetamol, INH, haloalkane anesthetics)
3. Ischemic hepatitis (shock liver)*
4. Autoimmune hepatitis**
5. Common bile duct stones
6. Muscle injury (myositis, rhabdo, exercise)

* Documented Hypotension is not a must to diagnose shock liver in clinical settings associated with visceral hypoperfusion (e.g. heart failure, trauma, burns etc.)

** 40% of patients with autoimmune hepatitis may have a viral hepatitis-like presentation with markedly raised transaminases.

Does the ratio of AST/ALT help in the differential diagnosis?

In most liver diseases AST/ALT ratio is <1. In alcoholic liver disease including alcoholic steatosis, alcoholic hepatitis and cirrhosis AST/ALT is >1, and is usually >2.⁷

In patients with raised serum transaminase levels who are suspected of having viral hepatitis, which viral markers should be performed?

To be cost effective, anti-HAV IgM, HBsAg, and anti-HCV should be obtained first. If the patient is HBsAg positive, the laboratory should test the serum for anti-HBc IgM. If the latter is negative, then the patient is likely to have chronic HBV infection. All

HBsAg positive patients should be tested for anti-Delta.

What are the main causes of raised serum alkaline phosphatase?

Serum alkaline phosphatase activity may originate from liver, bone, intestine and placenta. On rare occasions, patients with a variety of malignant tumors may have elevations in serum ALP that are not caused by metastasis. Table 4 summarizes hepatobiliary and non-hepatic causes of elevated ALP.¹

Table 4. Causes of elevated levels of ALP

Hepatobiliary causes	
	Bile duct obstruction (stone, tumor, benign stricture)
	Drugs
	Primary biliary cirrhosis
	Primary sclerosing cholangitis
	Liver metastasis
	Infiltrative liver disease (granuloma, amyloid)
	Viral hepatitis
	Alcoholic hepatitis
	Cirrhosis
Nonhepatic causes	
	Bone disease
	Pregnancy
	Chronic renal failure
	Congestive heart failure
	Childhood growth
	Malignancy

The most practical and reliable method to determine the origin of ALP is the measurement of GGT which is elevated in patients with hepatobiliary disorders.⁸ ALP isoenzyme determination using urea denaturation or heat inactivation are unreliable. Gel electrophoresis to determine the levels of various ALP isoenzymes is accurate but not available in most clinical laboratories.

What are the causes of low serum ALP levels?

Low serum ALP in patients with biochemical evidence of liver dysfunction may be a clue to Wilson's disease. Also, low ALP may be encountered in hypothyroidism, zinc deficiency, pernicious anemia and congenital hypophosphatemia.

Does the degree of elevation of ALP distinguish intrahepatic cholestasis from extrahepatic biliary obstruction?

No. Typically very high levels (>5 times normal) are not associated with choledocholithiasis.⁹ Very high levels are more typical of PBC, granulomatous liver disease and malignant obstruction of the common bile duct.

How useful is GGT in evaluating patients with liver dysfunction?

GGT is a very sensitive test and is raised in most liver disorders, hence it is not a specific test. The main clinical utility of GGT is to exclude a bone source of ALP elevation.¹⁰

What are the main causes of hyperbilirubinemia?

A useful approach to hyperbilirubinemia is to divide its causes into prehepatic (hemolysis), hepatic, and post-hepatic (biliary obstruction due to stones, tumors or benign strictures) (Table 5).

Table 5. Causes of hyperbilirubinemia

Isolated conjugated hyperbilirubinemia	
	Gilbert's syndrome
	Hemolysis
	Transfusion
	Resorption of hematoma
	Crigler-Najjar Syndrome
	Shunt hyperbilirubinemia (surgical portosystemic shunt)
Conjugated hyperbilirubinemia	
	Bile duct obstruction
	Hepatitis
	Cirrhosis
	PBC (primary biliary cirrhosis)
	PSC (primary sclerosing cholangitis)
	Sepsis
	Total parenteral nutrition
	Cholestasis of pregnancy
	Dubin Johnson syndrome
	Rotor syndrome

How are the various causes of hyperbilirubinemia distinguished?

Prehepatic causes of hyperbilirubinemia can be easily distinguished from hepatic and post-hepatic causes. The former are characterized by bilirubin levels below 120 $\mu\text{mol/L}$

(mainly unconjugated), and by the absence of bilirubin from urine. The distinction between hepatic and post-hepatic causes is more difficult, and a thorough clinical sonographic evaluation is frequently needed. Conjugated hyperbilirubinemia is not synonymous with post-hepatic biliary obstruction (Table 6).

Table 6. Clinical "Pearls" in the interpretation of hyperbilirubinemia

1. If serum bilirubin is ≥ 120 $\mu\text{mol/L}$, fractionation is not useful because the cause is unlikely to be hemolysis.
2. Unconjugated hyperbilirubinemia is usually caused by either Gilbert's syndrome or hemolysis. The latter is associated with increased retics count.
3. Total bilirubin ≥ 120 $\mu\text{mol/L}$ is unlikely to be due to choledocholithiasis unless the latter is complicated by cholangitis.
4. Liver chemical tests, bilirubin level and fractionation (conjugated vs. unconjugated) cannot distinguish between hepatic causes vs. post-hepatic causes of jaundice.
5. Sonography is very important in discriminating hepatic causes (bile ducts not dilated) from post-hepatic causes of jaundice (dilated bile ducts).

What is the significance of hypoalbuminemia?

Albumin is synthesized in the liver and has a half life of 21 days. Hypoalbuminemia may result from decreased synthesis (liver disease) or increased losses by the kidney or the gastrointestinal tract (protein losing enteropathy).

Hypoalbuminemia due to proteinuria can be easily diagnosed by urine analysis. The discrimination between hypoalbuminemia due to liver disease from that secondary to gastrointestinal loss is occasionally difficult. Abnormal serum transaminases, hyperbilirubinemia, and the prolongation of prothrombin time uncorrectable by the administration of vitamin K favor liver disease. Another useful clue is the level of globulins. In most liver diseases complicated by hypoalbuminemia serum globulin levels are either elevated or normal, whereas protein losing enteropathy usually leads to depressed serum globulin levels.

Hypoalbuminemia is an indicator of decompensation in patients with liver disease and is, thus, a poor prognostic sign.

What is the relevance of prolonged prothrombin time in patients with liver disease?

Prolongation of PT can result from vitamin K

deficiency due to malnutrition, malabsorption and cholestatic liver disease. The parenteral administration of vitamin K results in the prompt correction of PT in these settings. However, PT can also be prolonged in severe acute and chronic hepatocellular dysfunction. Vitamin K supplements do not usually correct PT in patients with hepatocellular failure.¹

What are the most useful parameters in determining prognosis of patients with chronic liver disease?

ALT, AST, and ALP are not useful prognostic indicators. However, PT, albumin, and bilirubin, in addition to clinical parameters (encephalopathy and ascites), are currently the most useful tools in predicting prognosis.¹

What is the role of liver biopsy in evaluating patients with abnormal liver chemistry tests?

Liver biopsy is indicated for diagnosis and prognosis. In patients with raised liver tests and unremarkable serologic tests (e.g. viral and autoimmune markers, tests for metabolic liver disease) the most common diagnosis is steatosis or steatohepatitis.¹¹ Even in patients with positive serologic tests prior to liver biopsy, post-biopsy diagnosis was different in 14% of cases.¹² Liver biopsy should be considered in any patient with abnormal liver tests that persist for 6 months or more.

Which has higher diagnostic yield in patients with cholestasis: liver biopsy or endoscopic retrograde cholangiopancreatography (ERCP)?

In general, ERCP should be performed first in patients with evidence of biliary dilatation on ultrasound or CT scan. If bile ducts are not dilated, liver biopsy may be considered first.

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CME Questions

After you have completed reading the above article, take the test given below. Circle T (True) or F (False) in the answer sheet (page 50) to show the correct answer to each question. Questions 11 to 20 are related to the content in this article.

11. ALT greater than 200 iu/L (nml 60) is typical of alcoholic hepatitis.
12. In non-alcoholic steatohepatitis AST to ALT ratio is typically ≥ 1 .
13. ALT may be elevated in muscle disease.
14. Most circulating bilirubin in normal individuals is unconjugated.
15. If all RBC are hemolyzed in a patient with normal liver, total bilirubin will not exceed 120 $\mu\text{mol/L}$.
16. A total bilirubin of 300 $\mu\text{mol/L}$ is typical of common bile duct obstruction by stones.
17. The determination of conjugated versus unconjugated fractions of bilirubin is useful in diagnosing jaundice only if the total bilirubin is less than 120 $\mu\text{mol/L}$.
18. ALT greater than 1000 iu/L may be observed in patients with Paracetamol overdose.
19. The prothrombin time is a useful liver chemistry test for predicting prognosis of chronic liver disease.
20. Serum alkaline phosphatase may be elevated in viral hepatitis.