

Literature Review

How to Interpret Liver Function Test in Daily Practice

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yudith.ermaya@unpad.ac.id**Published:**28th February 2023**DOI:**<https://doi.org/10.58427/apghn.2.1.2023.40-52>**Citation:**Ermaya YS. How to Interpret Liver Function Test in Daily Practice. *Arch Pediatr Gastr Hepatol Nutr.* 2023;2(1):40-52.**Abstract:**

Background: The liver is a multi-function organ that plays a role in producing various important secrete, synthesis and metabolic functions. The term liver function test is also used to refer to the hepatocyte synthesis function, such as serum albumin and prothrombin time. The aim of this literature review is to explain on how to interpret various liver function test results in daily practice as well as approach to abnormal liver function tests.

Discussion: Abnormal result of liver function test is frequently found in asymptomatic healthy patients who are undergoing routine screening. On the contrary, some patients with liver disease may appear with normal liver function test. As such, there are some limitations regarding this particular test. Alanine aminotransferase is the primary marker of hepatocellular injury due to it being more sensitive and specific than aspartate aminotransferase. Conjugated bilirubin level of more than 20% of total bilirubin level is a strong indication of hepato-biliary disease and is always pathogenic. Gamma-glutamyl transferase (GGT) is only increased in cholestatic conditions and not in bone disease. As such, GGT levels can help to distinguish abnormalities in the liver or bones in conditions of increased alkaline phosphatase levels in the blood.

Conclusion: Serum liver biochemistry examination is very useful and effective in assessing liver function. Understanding the proper interpretation of liver enzymes will help clinicians easier to diagnose or predict a disease as well as condition related to the liver in daily practice.

Keywords: interpretation, liver enzyme, liver function test, pediatric

Introduction

The liver is a multi-function organ that plays a role in producing various important secrete, synthesis and metabolic functions. Although in general, the term liver function test is often used, this term actually consists of various types of tests that evaluate not only the liver function but also other essential aspect of the liver, such as transaminase which is an indicator of liver cell destruction.¹ The term liver function test is also used

to refer to the hepatocyte synthesis function, such as serum albumin and prothrombin time. However, in certain circumstances, liver biochemical tests may produce normal values in patients with liver disease such as in compensated cirrhosis as well as abnormal results in healthy children.¹ In this literature review, we will discuss how to interpret various liver function test results in daily practice as well as approach to abnormal liver function tests.

Liver Function Test

Abnormal result of liver function test is frequently found in asymptomatic healthy person who are undergoing routine screening.² On the contrary, some patients with liver disease may appear with normal liver function test. As such, there are some limitations regarding this particular test such as:

1. Normal result of liver function test does not always indicate that the patient does not have liver disease especially in the case of compensated cirrhosis.
2. Some tests do not specifically assess liver function
3. The tests performed do not show a specific etiology but indicate a liver disorder in general, so interpreting any abnormal liver test result must be done case-by-case and may differ for each patient.

There are five categories of liver function tests that evaluate specific aspect of the hepato-biliary system^{3,4}:

1. Liver injury markers which include liver enzymes such as aspartate aminotransferase (AST)/ serum glutamic-oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT)/ serum glutamic-pyruvic transaminase (SGPT).
2. Cholestasis markers such as alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and 5'-nucleotidase.
3. Synthesis function markers such as serum albumin, prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR) and coagulation factor V as well as VII.
4. Excretion function markers which include bilirubin level and bile acid.
5. Liver metabolism function markers which depict the detoxifying role of the liver and the clearance mechanism of endogenous metabolites such as ammonia.

Based on the categories described earlier, liver enzymes such as AST and ALT which are commonly examined in patients with liver disease, actually do not indicate specific liver function disorders but only show the presence of liver damage.^{5,6} As of now, there is no direct relationship between those enzyme levels with the degree or severity of liver damage. Normally, AST and ALT are found in serum at low levels in the healthy population. Evaluation of liver biochemistry test is very useful and provide

the most cost-effective way of assessing liver function. This examination is also routinely performed on asymptomatic people for routine screening, blood banks screening, examinations for insurance purposes, or patients who will perform surgical procedures that are not directly related to liver function.³ The liver function tests that are commonly evaluated are alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (ALP), prothrombin time (PT), serum albumin, gamma-glutamyl transferase (GGT), bile acids, 5'-nucleotidase, and lactate dehydrogenase.¹

Liver Enzyme

Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)

Serum ALT or SGPT is one of the oldest markers used to assess liver disease. This substance is a cytosolic enzyme that is found in high concentrations in the liver and also in the kidneys, heart, muscle, pancreas, spleen, and lung tissue.^{1,3,7} Thereby, increased level of ALT do not always indicate liver disease but may be caused by myocardial infarction, muscular dystrophy, and organ damage.³ This enzyme is a useful serum for measuring liver function because of its high sensitivity and specificity (increase of 2.25 times greater than normal levels predict the presence of liver histological abnormalities). Nevertheless, ALT serum levels are influenced by many other factors, including gender, body mass index, and the use of hepatotoxic drugs.^{8,9} Moreover, a strong relationship was found between ALT and body mass index (BMI). The American Society of Gastroenterology categorizes ALT levels according to the degree of elevation with several differential diagnoses based on the probable cause of liver damage (Table 1).³

Table 1. Degree of Elevation of ALT Level and Possible Etiology.

Mild elevation (<5 times of upper normal limit)	Severe elevation (>15 times of upper normal limit)
Chronic hepatitis B and C	Acute hepatitis (A, B, C, D, E, herpes)
Acute hepatitis (A, B, C, D, E, EBV, CMV)	Drugs or toxins
Steatohepatitis	Ischemia hepatitis
Hemochromatosis	Autoimmune hepatitis
Drugs or toxins	Wilson disease
Autoimmune hepatitis	Acute obstruction of the biliary duct
Alpha-1 antitrypsin deficiency	Budd-Chiari syndrome
Wilson disease	Ligation of the hepatic artery
Celiac disease	
Liver injury due to alcohol	
Cirrhosis	
Non hepatic (hemolytic, myopathy, thyroid disorders)	

In a study conducted at LabCorp America, the normal values of ALT level were categorized based on age and gender (**Table 2**).^{3,10}

Table 2. Normal ALT Value Based on Gender and Age in Pediatric

Gender	Age Interval (years)	ALT/SGPT Level (U/L)
Female	0-11	< 29
	12-17	< 25
	≥ 18	< 33
Male	0-11	< 30
	12-17	< 31
	≥ 18	< 45

The ALT is the primary marker of hepatocellular injury due to it being more sensitive and specific than AST.¹¹ There are several etiologies that may lead to an increase in ALT level such as¹¹:

- a. Highly elevated ALT level (> 15-20 times of upper normal limit)
 - Ischemia (shock, hypotension, congestive heart failure)
 - Viral hepatitis, autoimmune hepatitis
 - Drug toxicity, severe toxic hepatitis
 - Acute Budd-Chiari syndrome
- b. Moderately elevated ALT level (5-15 times of upper normal limit)
 - Liver disease: chronic liver disease (chronic hepatitis, cholestasis with increase in ALP and GGT)
 - Cardiac disease: severe hepatic congestion due to congestive heart failure
 - Other: muscle injury, kidney injury
- c. Mildly elevated ALT level (<5 times of upper normal limit)
 - Liver disease: neonatal hepatitis, hemochromatosis, autoimmune hepatitis, non-alcoholic steatohepatitis (NASH), biliary atresia, alpha-1 antitrypsin deficiency and Wilson disease.
 - Infection: Mononucleosis
 - Drugs: anti-tuberculosis, anti-epileptic, antibiotics and non-steroid anti-inflammatory drugs (NSAID).
- d. False low ALT level such as patient who undergo dialysis or deficiency in pyridoxin.

Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)

Aspartate Aminotransferase is found in both cytosolic and mitochondrial isoenzymes, and is also found in high concentrations in various tissues such as liver, heart muscle,

skeletal muscle, kidney, brain, pancreas, lung, leukocytes and red blood cells.^{10,11} Normally, low concentration of AST is found in the blood, unless there is cellular injury, then large amounts are released into the circulation.¹¹

Aspartate Aminotransferase enzymes can greatly increase in serum during conditions of increased tissue metabolism. If disease or damage occurs to one of these cells, the cell will lyse and consequently AST enzyme will be released into the circulation causing the serum level to increase.^{11,12} The normal value of serum AST is 20-60 U/L in infants, <45 U/L (boys), and <30 U/L (girls) (**Table.3**).¹³ Serum AST will increase 8 hours after damage occurs, with a peak at 24 to 36 hours after damage and returns to normal within 3 to 7 days. If the damage is chronic then the increase will persist. This increase in the AST enzyme indicates liver cell damage, but is less specific for liver disease.¹¹⁻¹³

An increase in AST can be caused by¹¹:

- a. High increase in AST level (>20 times of upper normal limit)
 - Ischemia (Shock, hypotension, Congestive Heart Failure,)
 - Acute viral hepatitis
 - Drug Induced Hepatitis
- b. Moderate increase in AST (15-20 times of upper normal limit)
 - Cardiovascular system: congestive heart failure
 - Infection: infectious mononucleosis
 - Liver: alcoholic cirrhosis
- c. Slight increase in AST (5-10 times of upper normal limit)
 - Liver: chronic hepatitis (alcoholic)
 - Muscle: duchenne muscular dystrophy, dermatomyositis
- d. Very mild increase in AST (< 5 times of upper normal limit)
 - Blood: Hemolytic Anemia, Hemolysis
 - Liver: Fatty liver, liver tumor metastases
 - Others: Acute pancreatitis
 - Drugs: various types of drugs

Table 3. Aspartate Aminotransferase level in infants and children based on age.¹³

Age	AST level, both genders (U/L)	Age	AST Level (U/L)	
			Male	Female
0-5 day	35-140	10-11 yrs	10-60	10-40
6 days–3 yrs	20-60	12-15 yrs	15-40	10-30
4-6 yrs	15-50	16-18 yrs	10-45	5-30
7-9 yrs	15-40	≥ 19 yrs	17-59	14-36

In the following algorithm below from Lab Corp America, a clinical and laboratory assessment can be carried out for very mild increases in ALT and/or AST serum (Figure 1).^{10,14}

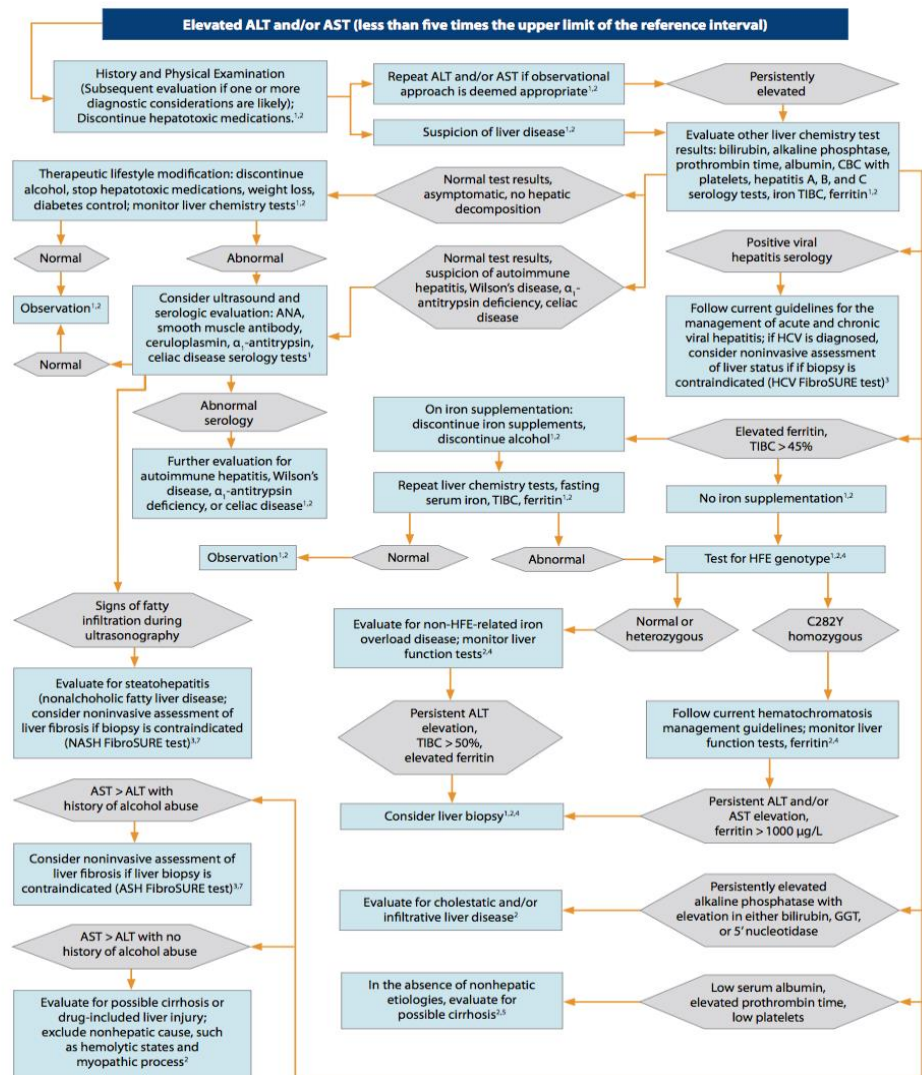


Figure 1. Algorithm for clinical and laboratory evaluation in the case of very mild increase in serum ALT and/or AST.^{10,14}

Bilirubin

Conjugated bilirubin level of more than 20% of total bilirubin level is a strong indication of hepato-biliary disease and is always pathogenic. This is often accompanied by the presence of bilirubin in the urine (causing dark yellow urine) which can also be detected using a dipstick. Bilirubinemia may also be accompanied by clinical jaundice. In cases of acute liver disease that is not accompanied by jaundice (anicteric), it is still possible for the patient to experience fulminant liver failure

accompanied by much later increase in bilirubin levels. As such, serum bilirubin can serve as a prognostic indicator in patients with acute liver diseases.¹

Table 4. Bilirubin level in infants and children based on age.¹³

Age	Bilirubin level (mg/dL)	
	Premature Total	Full Term Total
Up to 23 h	1-8	2-6
24-48 h	6-12	6-10
3-5 days	10-14	4-8
≥1 month		
Conjugated bilirubin		<0.35
Unconjugated bilirubin		<1.0
Total		0.2-1.0

The normal value of conjugated bilirubin for children is 0.0-0.2 mg/dL (**Table.4**).¹³ Cholestasis is a condition of which marked by the failure of the bile to flow into the duodenum in normal amounts. Disturbances of the bile flow can occur anywhere from the basolateral membrane of the hepatocytes to the site of entry of the bile duct into the duodenum.¹⁵ The obstruction of the bile flow causes retention of various substances that should be excreted into the gallbladder with direct bilirubin level 1.0 mg/dL if total bilirubin is under 5 mg/dL or direct bilirubin above 20% of total bilirubin if total bilirubin level is above 5 mg/dL.¹⁶

Based on the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition indicators of cholestasis are¹⁷:

- Direct bilirubin >17µmol/L (1.0 mg/dL)
- Direct bilirubin >20% of total serum bilirubin concentration, if total bilirubin >85µmol/L (5.0 mg/dL)

Currently, the most recent definition of cholestasis is defined when the direct bilirubin level is >1.0 mg/dL.

Gamma-Glutamyl Transferase (GGT)

The enzyme gamma-glutamyl transpeptidase-1 (GGT-1, gamma-GT, gamma-glutamyl transferase) is used as a disease diagnostic marker (**Figure 2**). Gamma-glutamyl transferase (GGT) is a membrane glycoprotein that catalyses the transfer of gamma-glutamyl to other peptides, amino acids or water.

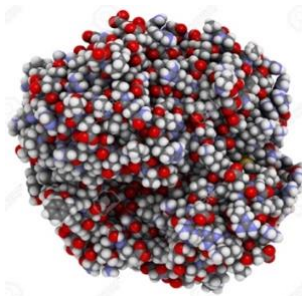


Figure 2. Gamma-glutamyl transpeptidase-1¹⁸

Large amounts of gamma-glutamyl transferase can be found in the kidneys, pancreas, liver, small intestine, and prostate. In the kidney, GGT is abundant on the luminal surface of proximal tubular cells. Meanwhile, in the liver, GGT is abundant in bile epithelial cells and bile canaliculi, GGT is also found in acinar cells of the pancreas, endothelial cells lining the brain, spinal cord, and cells in the male reproductive organs. Gamma-glutamyl transferase which present in astrocyte cells in the blood vessels of the brain has a role in the blood-brain barrier, both in conjugating toxic xenobiotics and metabolizing leukotrienes. GGT can also be found in white blood cells. The function of GGT on white blood cells is still unclear. However, there are two theories which state that GGT protects white blood cells from free radicals, especially during inflammatory processes and helps modify the interaction between receptors and ligands on cell membranes.^{1,19,20}

Gamma-glutamyl transferase is mainly found in organs that have transport function such as the kidney and the biliary system. GGT plays a major role in helping to synthesize glutathione. The specific relationship between GGT and glutathione and the response of GGT to excessive alcohol consumption has led to GGT being used as a marker of excessive alcohol consumption.^{19,20}

Gamma-glutamyl transferase levels are high in neonates, infants up to 1 year of age, and at >60 years of age. Men have higher GGT levels than women. Normal levels of GGT are 0-30 IU/L. (**Table 5**).¹³ During acute viral hepatitis infection, GGT levels will reach their highest levels in the 2nd and 3rd weeks and remain high for 6 weeks. In extrahepatic biliary atresia, GGT levels are also increased. GGT is only increased in cholestatic conditions and not in bone disease. As such, GGT levels can help to distinguish abnormalities in the liver or bones in conditions of increased ALP levels in the blood.^{1,19,20}

Table 5. Gamma-glutamyl transferase level in infants and children based on age.¹³

Age	GGT level, both genders (U/L)	Age	GGT Level (U/L)	
			Male	Female
0-5 day	34-263	10-11 yrs	17-30	17-28
6 days–2 months	10-160	12-13 yrs	17-44	14-25
3-11 month	11-82	14-15 yrs	12-33	14-26
1-3 yrs	10-19	16-18 yrs	11-34	11-28
4-6 yrs	10-22	≥ 19 yrs	10-78	10-78
7-9 yrs	13-25			

Other conditions associated with elevated GGT levels are uncomplicated diabetes mellitus, acute pancreatitis, and myocardial infarction. Drugs such as phenobarbital, phenytoin, paracetamol, tricyclic antidepressants can also increase GGT levels.^{1,19,20} The reference range for normal GGT values is the same for all ages. However, there are significant differences between men and women. Several other factors also affect the normal value of GGT in serum, such as age, sex, pregnancy, childbirth, race, smoking habits, use of oral contraceptives, and exercise.^{1,19,20}

Serum GGT levels are found to be abnormal in liver disease, suggesting that GGT liver function test are sensitive. The highest increase in serum GGT levels was found during conditions of liver inflammation due to excessive alcohol consumption or in conditions of liver inflammation due to drug consumption. However, increased levels of GGT in serum are not specific for liver disease because these increases are also found in conditions of excessive alcohol consumption, pancreatitis and obesity. Serum GGT levels also increase in chronic liver disease associated with hepatitis C infection. Hence, the use of GGT levels in predicting the body's response to interferon administration in individuals with hepatitis C infection have been widely studied. The results showed that GGT levels had a sensitivity of 87% but a specificity of only 27%.^{19,20}

Alkaline Phosphatase (ALP)

Alkaline phosphatase (ALP) is found in a number of tissues including the canalicular membranes of hepatocytes, bone osteoblasts, small intestinal enterocytes, proximal renal tubules, placenta, and white blood cells. ALP is an enzyme synthesized by the cell wall of the bile canaliculi in response to intra- or extrahepatic cholestasis. This enzyme serves as the primary marker of cholestatic disorders before bilirubin level increases. The function of ALP many are unknown, but it plays a role in the transport process. Serum ALP levels often vary with age. Furthermore, ALP is a zinc metalloenzyme group and is present in almost all tissues. In the liver, ALP is present in microvilli along the bile duct canaliculi and on the surface of the hepatocyte sinusoids. The ALP

found in the liver, bone and kidney originate from the same gene, but the ALP found in the small intestine and placenta originate from different genes. ALP can be detected in serum, urine, bile salts, and lymphatic fluids.^{1,11,21}

In healthy person, ALP circulating in the blood originates from the liver or bones. This enzyme levels are relatively higher during childhood and puberty. ALP levels are directly proportional to body weight but inversely proportional to height. The highest ALP levels were found in cholestatic conditions. An increase in ALP occurs due to obstruction to the intrahepatic or extrahepatic flow of bile salts. The mechanism by which ALP is released into the blood is still unknown. There is a theory that damage to the tight junctions in the bile salt canaliculi causes the release of ALP into the hepatocyte sinusoids. Normal ALP level in children is 39-117 U/L (Table 6).¹³ Elevated levels of ALP indicate a biliary obstruction (intrahepatic and extrahepatic), biliary atresia or viral hepatitis.^{1,11}

Table 6. Alkaline phosphatase level in infants and children based on age.¹³

Age	ALP level, both genders (U/L)	Age	ALP Level (U/L)	
			Male	Female
0-5 day	110-300	10-11 yrs	135-530	130-560
6 days–11 months	110-320	12-13 yrs	200-495	105-420
1-3 yrs	145-320	14-15 yrs	130-495	70-230
4-6 yrs	150-380	16-18 yrs	65-260	50-130
7-9 yrs	175-420	≥ 19 yrs	38-126	38-126

In acute viral hepatitis infection, ALP levels may be normal or slightly elevated. During hepatitis A infection, cholestatic conditions can be found which are characterized by itching and increased levels of ALP. On the other hand, tumors can also release ALP into the plasma. Elevated levels of ALP from the small intestine can be found in cirrhotic conditions that are associated specifically with intrahepatic disease. Other conditions that may be associated with elevated ALP levels include bone and liver metastases, infiltrating liver disease, abscesses, granulomatous liver disease, and amyloidosis.^{11,21} Mild elevations in ALP levels can be found in cirrhosis and hepatitis with congestive heart failure. Low ALP levels in the blood can be found in conditions of malnutrition, hypothyroidism, pernicious anemia, zinc deficiency, vitamin C deficiency and congenital hypophosphatemia.^{11,21}

If the serum ALP level increases but is less than 1.5 times of the upper normal limit, then a reexamination must be carried out 3 months later. If the serum ALP level is more than 1.5 times of the upper normal limit and persistently elevated, it is necessary to carry out additional investigations such as ultrasound of the liver to detect

cholestasis or other infiltrating disease. If the examination results are normal and the serum ALP increases to less than 1.5 times of the upper normal limit, then a re-examination should be carried out 6 months later. However, if the serum ALP level increases to more than 1.5 times the upper normal limit and ultrasound as well as serological examinations produce normal results, then the patient should be referred to a hepatologist for a liver biopsy.²¹

If an increase in serum ALP level is found but the GGT level is normal, this indicates that the increased ALP level originates from tissues outside the liver and most likely originates from the bone due to vitamin D deficiency. Therefore, it is necessary to check blood levels of vitamin D. If the vitamin D level is within normal limits and the increase in ALP level is less than 1.5 times of the upper normal limit, then the patient should only be observed.^{21,22}

The following is an algorithm to evaluate the presence of elevated ALP in the blood (Figure 3).²¹

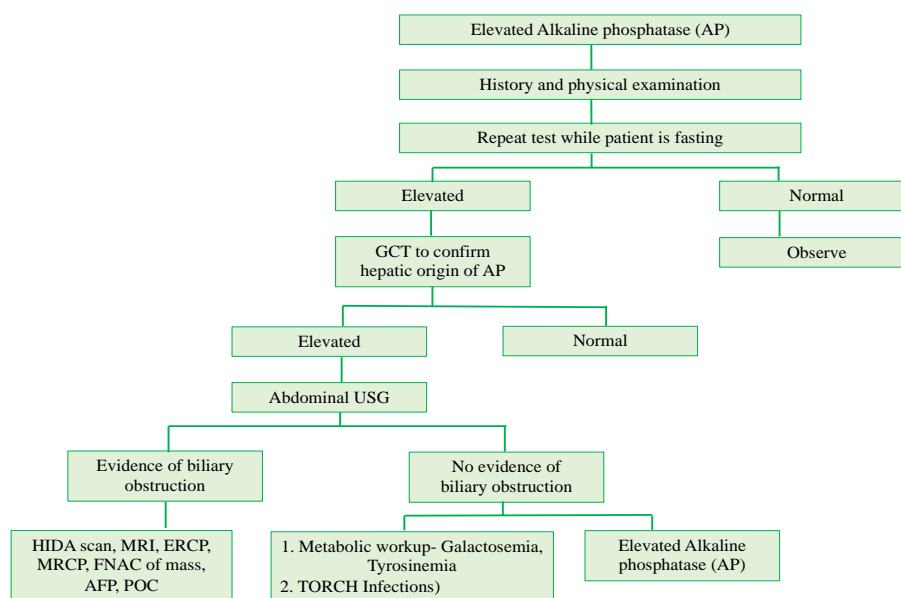


Figure 3. Algorithm for evaluation of increased alkaline phosphatase.²¹

Serum Protein

Albumin

Albumin is a serum protein and is only synthesized in the liver. This protein is synthesized in the endoplasmic reticulum of hepatocytes at a rate of 150 mg/kg/day and has a life span of about 20 days in serum. Taking into account the length of life span, low serum albumin indicates a chronic liver disease.¹ The normal value of albumin in children is 3.5-5.5 g/dL.¹³ In a state of liver disease with an increase in

globulin level but normal albumin level, indicates the presence of infectious process or autoimmune hepatitis. However, in patients with compensated liver disease, serum albumin can be found to have normal values. Hypo-albumin is not specific for liver disease because it can also occur in malnutrition, protein losing enteropathy, chronic infections and nephrotic syndrome.¹

Coagulation Factors

Coagulation disorders are found in patients with liver disease due to disorder of hepatic synthesis of coagulation factors V, VII, IX, X and XI prothrombin, fibrinogen as well as vitamin K deficiency due to inadequate intake or malabsorption and dysfibrinogenemia. Coagulation disorders is often so subtle during mild or moderate liver disease. However, it is often found severe during acute hepatic failure or terminal chronic liver disease.¹

Increase of Liver Enzymes Due to Non-Hepatic Etiology

In certain circumstances, liver enzymes can increase due to abnormalities other than liver disease. If liver disorders have previously been ruled out but liver enzymes are found to be elevated, it is necessary to consider and investigate abnormalities caused by disorders of the muscles, heart, thyroid disease, celiac disease, and, rarely, insufficiency of adrenals. Conditions of increased muscle injury with increased transaminase enzymes may also be accompanied by increased creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). If an elevated ALT and AST condition persist for more than three months, exceeds two times of the normal value and the results of other tests do not produce clear conclusion, then it is necessary to recommend liver function tests.¹

Conclusion

Serum liver biochemistry examination is very useful and effective in assessing liver function. The tests that are commonly evaluated include alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase, prothrombin time, serum albumin, gamma-glutamyl transferase (GGT), bile acids, 5'-nucleotidase, and lactate dehydrogenase. Understanding the proper interpretation of liver enzymes will help clinicians easier to diagnose or predict a disease as well as condition related to the liver in daily practice.

Conflict of Interest

None declared.

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