

## Abnormal liver enzymes: A review for clinicians

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### Abstract

Liver biochemical tests are some of the most commonly ordered routine tests in the inpatient and outpatient setting, especially with the automatization of testing in this technological era. These tests include aminotransferases, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, albumin, prothrombin time and international normalized ratio (INR). Abnormal liver biochemical tests can be categorized based on the pattern and the magnitude of aminotransferases elevation. Generally, abnormalities in aminotransferases can be classified into a hepatocellular pattern or cholestatic pattern and can be further sub-classified based on the magnitude of aminotransferase elevation to mild [ $< 5 \times$  upper limit of normal (ULN)], moderate ( $> 5$ - $< 15 \times$  ULN) and severe ( $> 15 \times$  ULN). Hepatocellular pattern causes include but are not limited to; non-alcoholic fatty liver disease/non-alcoholic steatohepatitis, alcohol use, chronic viral hepatitis, liver cirrhosis (variable), autoimmune hepatitis, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, celiac disease, medication-induced and ischemic hepatitis. Cholestatic pattern causes include but is not limited to; biliary pathology (obstruction, autoimmune), other conditions with hyperbilirubinemia (conjugated and unconjugated). It is crucial to interpret these commonly ordered tests accurately as appropriate further workup, treatment and referral can greatly benefit the patient due to prompt treatment which can improve the natural history of several of the diseases mentioned and possibly reduce the risk of progression to the liver cirrhosis.

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**Core Tip:** Liver function test are one of the most commonly ordered tests. With the automation of test and its inclusion in the complete metabolic profile, the knowledge as it pertains to its interpretation is of paramount importance. It is also important for the clinician to understand the difference between cholestatic and hepatocellular abnormalities. This can be of help for the clinician to formulate appropriate further diagnostic workup and plan the treatment.

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## INTRODUCTION

Liver biochemical tests are some of the most commonly ordered tests in the United States due to the automation of routine laboratory tests. A United States population-based study of 6823 subjects from 1999 to 2002 showed elevated alanine aminotransferase (ALT) in 8.9% of subjects and aspartate aminotransferase (AST) in 4.9% of subjects.

Another population-based study consisting of 15676 subjects was done from 1988 to 1994 which showed elevation in aminotransferases (either ALT or AST) in 7.9%. In that study, 69% of the elevated aminotransferases results were unexplained[1].

Laboratory tests normal ranges are calculated based on the mean value found amongst a group of healthy individuals +/- 2 standard deviations. Hence 5% of healthy individuals' results lie outside the reference range[2].

As a result of the prevalence of liver biochemical tests ordered and abnormal results, we will be writing this review to increase the knowledge about liver tests to clinicians and improve the interpretation of these tests.

Liver function tests (LFTs) are a term commonly used for aminotransferases, alkaline phosphatase (ALP), bilirubin, and albumin which is somewhat of a misnomer as only bilirubin and albumin represent a synthetic function by the liver[3]. Besides, the liver is crucial in clotting factors production and decreased synthetic function of the liver can result in prothrombin time (PT) prolongation and an increase in the international normalized ratio (INR). Consequently, some of the most widely used scores for predicting mortality in cirrhotic patients such as the Child-Pugh score and model for end stage liver disease-Na (MELD-Na) score do not include AST, ALT, or ALP but rather use INR, bilirubin, and albumin in Child-Pugh score and INR and bilirubin in MELD-Na score.

## LIVER BIOCHEMICAL STUDIES

Liver biochemical studies include; ALT, AST, ALP, gamma-glutamyl transferase (GGT), 5' nucleotidase, lactate dehydrogenase (LDH), bilirubin, albumin, PT/INR (Table 1).

### Enzymes

ALT is an enzyme that is found primarily in hepatocytes (lower concentrations in cardiac, renal, and muscle tissue) and thus is specific to the hepatocellular injury. ALT levels often fluctuate throughout the d. ALT facilitates the formation of glutamate and pyruvate in the hepatocyte which is important for energy production[4]. The normal range for ALT in males is between 29-33 IU/L and 19-25 IU/L for females.

**Table 1 Liver biochemical tests and their respective sites and functions**

Interpretation	Test	Site (s)	Function
Hepatocellular integrity	ALT	Hepatocyte (main), cardiac, renal and muscle tissue to smaller extent	Amino acid catabolism. Glutamate and pyruvate production for ATP production
	AST	Hepatocyte, cardiac, muscle and brain tissue	
	LDH	Nonspecific, present widely in the body	Anaerobic glycolysis major enzyme in addition to NADH production. Significant in ischemic hepatitis
Cholestatic pattern	ALP	Hepatobiliary tract, bone, placenta and intestines	Dephosphorylation reactions. Role in bile production
	GGT	Mainly in hepatobiliary tract, present in multiple other organs (nonspecific as an isolate test)	Aids in identification of elevated ALP of biliary origin
	5' nucleotidase	Nonspecific, present widely in the body	Clinical value in hepatobiliary and cholestatic disease specifically when paired with ALP and GGT
	Bilirubin	Serum and liver	End product of heme breakdown. Exists in conjugated and unconjugated form. Elevation in conjugated suggestive of possible cholestasis
Synthetic function	Albumin	Serum	Main protein in the serum, maintains oncotic pressure. Produced by the liver
	PT/INR	Test to measure extrinsic coagulation pathway	Clotting factors primarily produced in the liver. Helpful however does not reflect true coagulation status

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; ATP: Adenosine-triphosphate; PT: Prothrombin time; INR: International normalized ratio.

ALT levels have been a point of debate recently as newer studies are suggesting the need for a lower ALT cutoff to increase the sensitivity of the test. It's believed that the current ALT cutoffs were defined by using patients with possible underlying subclinical liver disease and hence decrease the sensitivity of the test. A retrospective study in 2002 evaluated 6835 patients and hypothesized that undiagnosed hepatitis C and non-alcoholic fatty liver disease (NAFLD) are likely to have skewed the studies previously used to determine normal ALT levels based on the 95<sup>th</sup> or the 97.5<sup>th</sup> percentile.

Suggested new cut-offs from this study are ALT < 30 in men and < 19 in women. It was found that the sensitivity in detecting hepatitis C virus viremia with the lower cut offs was higher than that of the traditional cut-offs. Nonetheless these values should be cautiously interpreted as body mass index, cholesterol levels and age can affect ALT levels[5].

It is important to note that the reference ranges for labs differs across countries and sometimes even between different centers in the same country.

AST is an enzyme which like ALT is also found in the liver however has also other sites where its presence is not as minimal as ALT. These sites are primarily skeletal muscle, cardiac muscle, renal tissue, and brain. It occurs as 2 isoenzymes that are not differentiated on standard testing and hold little clinical value. AST facilitates amino acid metabolism[6]. When it comes to AST, caution must be practiced when evaluating abnormal levels due to its presence in other tissues. The normal range for AST is < 35 IU/L[7].

ALP is an enzyme that is primarily found in the hepatobiliary tract, bone, placenta, and to a smaller extent in intestinal tissue. ALP is involved in multiple dephosphorylating reactions. The normal range for ALP is between 30-120 IU/L. ALP is generally higher in children and adolescents due to the increased osteoblastic activity associated with the bone growth[8].

GGT is an enzyme that is found in multiple organs in the body including the pancreas, seminal vesicles, kidneys, biliary tract, and liver. Its elevation is usually considered significant for a hepatobiliary disease when accompanied by an elevation in other liver biochemical tests. It is generally elevated in biliary disease, cytochrome-inducing medications, and alcohol abuse. GGT is involved in the glutathione metabolism and production in multiple tissues in the body. Normal GGT levels range between 0-30 IU/L. GGT levels are generally 6-8 times higher in infants[9].

5' nucleotidase is an enzyme that is present in many organs however its clinical value holds significance primarily in hepatobiliary or cholestatic disease. It is generally used as a test to help in evaluating whether an isolated elevated ALP is from a hepatobiliary source *vs* an osseous source. Its primary function is in nucleotide hydrolysis reactions. The normal range for 5' nucleotidase 0.3-3.2 Bodansky units (levels need to be corrected with elevated serum ALP)[10].

LDH is an enzyme that is widely present in the body, it has multiple isoenzymes of which one is primarily excreted/taken up by Kupffer cells in the liver[11]. Hence liver disease/injury can result in elevated LDH. This is non-specific and is rarely used as means of evaluating liver disease. Normal LDH ranges between 140-280 U/L (ranges vary slightly between different labs).

### Markers of liver synthetic function

Albumin is one of the major protein constituents in the blood and comprises 50%-60% of total protein in the serum. Albumin synthesis occurs in the liver hence it is considered a marker of the liver's synthetic function. Albumin levels can be influenced by other causes such as systemic inflammation as albumin is a negative inflammatory marker, protein malnutrition, nephrotic syndrome, fluid overload, or protein-losing enteropathy. Albumin has multiple functions such as maintaining serum oncotic pressure and endogenous (*i.e.*, bilirubin) and exogenous (*i.e.*, drugs) substances transport in the blood[12]. Normal albumin levels range between 3.5-5 g/dL.

PT and INR reflect the coagulation cascade and in specific, the extrinsic pathway of the coagulation cascade. The liver is involved in the synthesis of multiple clotting factors including, factors I, II, V, VII, IX, X, XI, and XIII, in addition to protein C, protein S, and anti-thrombin. The reason why PT and INR are primarily elevated rather than activated partial thromboplastin time (aPTT) is due to factor VIII and von Willebrand factor being produced in multiple organs around the body and conceals the aPTT prolongation *in vitro*. Due to deficiency of both pro-coagulant and anticoagulant factors, PT/INR and aPTT are not reliable measures of bleeding risk in cirrhotic patients. Moreover, PT/INR and aPTT are measures of pro-coagulant activity and do not take into consideration defects in anticoagulant pathways. Besides, patients with chronic liver diseases or cirrhosis are likely to have thrombocytopenia due to splenic sequestration and decreased thrombopoietin levels which further increases the risk of bleeding[13].

Bilirubin itself is not a marker of liver synthetic function per se however its excretion and conjugation are closely linked to the liver's conjugating and excreting function. Bilirubin is the end product of heme breakdown and is initially bound to albumin in the serum. In the liver, it is conjugated and excreted in the bile. Elevations in bilirubin levels are further classified as direct hyperbilirubinemia and indirect hyperbilirubinemia. Direct hyperbilirubinemia is generally due to an excretion defect in the liver such as cholestasis or Dubin-Johnson and Rotor syndrome. Indirect hyperbilirubinemia can be due to intrinsic liver injury or hemolysis[14].

## PATTERN RECOGNITION AND INTERPRETATION

Pattern recognition and interpretation are crucial in the evaluation of abnormal liver biochemical tests. Patterns can be primarily divided into hepatocellular and cholestatic. These can be subdivided further into; acute (< 6 wk), subacute (6 wk-6 mo), or chronic (> 6 mo).

In hepatocellular pattern, there is a disproportionate rise in ALT and AST in contrast to ALP and GGT. In hepatocellular injury, there is release of aminotransferases from the hepatocytes resulting in elevated serum levels. *R* value is a proposed score aimed to aid physicians in determining the pattern of liver injury based on the upper limit of normal (ULN) of certain enzymes.  $R \text{ value} = (\text{ALT} \div \text{ULN ALT}) / (\text{ALP} \div \text{ULN ALP})$ . *R* value > 5 is suggestive of hepatocellular pattern, > 2 to < 5 is suggestive of a mixed pattern, and < 2 suggestive of cholestatic pattern (Table 2)[15].

### Hepatocellular pattern

Aminotransferase elevations can be divided into mild, moderate, and severe even though the values for this classification are variable, in this review we will be taking mild as > 2 × - < 5 × ULN lab value, moderate > 5 × - < 15 ×, severe as > 15 × ULN and massive > 10000 IU/L[16]. These values are not accurate measures of the extent of liver injury however can aid in initial workup.

Table 2 R-value calculation and interpretation

R value = (ALT ULN ALT)/(ALP ÷ ULN ALP)	
R value	Interpretation
> 5	Hepatocellular pattern
> 2 but < 5	Mixed pattern
< 2	Cholestatic pattern

ALT: Alanine aminotransferase; ULN: Upper limit of normal; ALP: Alkaline phosphatase.

One of the most commonly known and used ratios is AST:ALT and is generally helpful only for an alcoholic liver disease where AST:ALT > 2. A study done in 1979 among patients with histologic evidence of liver disease demonstrated that 90% of patients with AST:ALT > 2 had alcoholic liver disease and > 96% of patients with AST:ALT > 3 had alcoholic liver disease[17]. This ratio can be explained due to alcohol being a mitochondrial toxin and low pyridoxal phosphate absorption as a result of heavy alcohol use. AST is found in mitochondria and cytoplasm, while ALT is found in cytoplasm but not mitochondria. ALT synthesis is more dependent on pyridoxal phosphate when compared to AST. In alcoholic liver disease, ALT is generally < 300 IU/L and is rarely > 500 IU/L. In situations where ALT > 500 IU/L, even if AST:ALT > 2, other etiologies should be explored. AST:ALT > 1 can be seen in cases of liver cirrhosis. GGT > 2 × the ULN is suggestive of alcohol abuse specifically when paired with AST:ALT > 2, GGT on its own is not a specific indicator of alcohol abuse[1].

Mild elevations in aminotransferases are common to be seen in clinical practice and are generally caused by medications (nontoxic ingestions), alcohol use, and chronic liver diseases such as liver cirrhosis, NAFLD, chronic hepatitis infections (B and C), hemochromatosis, Wilson's disease, autoimmune hepatitis, alpha-1 antitrypsin deficiency (AATD) and celiac disease (CD)[16]. It is advisable in patients with a mild increase in AST and ALT to undergo repeat testing in addition to the investigation of the aforementioned causes.

Moderate and severe elevations of aminotransferases are generally attributed to acute exacerbations of chronic liver diseases (such as exacerbations of hepatitis B virus, Wilson's disease, acute viral hepatitis, autoimmune hepatitis), drug-induced liver injury (DILI), and ischemic liver injury[16]. Also, they can occur in cases of acute biliary obstruction and tend to resolve soon after the obstruction is relieved.

### **Cholestatic pattern**

Elevation of ALP and bilirubin levels often indicate a cholestatic pattern[18]. ALP can be elevated in the presence of liver or bone disease, additionally, it can be elevated due to pregnancy (placenta production). GGT is often used to clarify the origin of ALP elevation. Since ALP is produced in the bile duct epithelia, cholestasis or biliary pathology elevates the enzyme. Both anatomic and autoimmune conditions that affect the biliary system cause a cholestatic pattern. When obstruction of the common bile duct (CBD) is the cause of ALP elevation, the aminotransferases can also be elevated [18].

GGT elevation is also caused by biliary or hepatocyte disease but not bone disease. However, other causes may elevate this enzyme such as drugs (anticonvulsants and oral contraceptives), pulmonary and renal disease. As a marker, it has a high sensitivity for liver disease but low specificity[19,20].

Elevations in bilirubin levels are further classified as direct (conjugated) hyperbilirubinemia and indirect (unconjugated) hyperbilirubinemia. Hemolysis is the most common cause of indirect hyperbilirubinemia followed by Gilbert's syndrome. On the other hand, direct hyperbilirubinemia indicates liver pathology including cholestatic drug reactions, autoimmune cholestatic disease, and biliary obstruction[21].

Further laboratory and imaging studies are essential to work up the causes of a cholestatic pattern[18]. When autoimmune cholestatic liver disease is suspected the presence of anti-neutrophil cytoplasmic antibodies (for primary sclerosing cholangitis) or anti-mitochondrial antibodies (for primary biliary cirrhosis) among other studies help aid in the diagnosis.

## COMMON CONDITIONS ASSOCIATED WITH ABNORMAL LIVER ENZYMES

NAFLD is one of the most common liver diseases, a meta-analysis was done in 2016 demonstrated the global prevalence of NAFLD to be approximately 25.24% [22]. Common condition associated with abnormal liver enzyme is shown in Table 3.

Nonalcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) are diseases in the same spectrum where NAFL can progress to NASH and subsequently liver cirrhosis if no intervention or modification of risk factors was done [23]. These terms are often used interchangeably however it is important to note that the management is different and accurate assessment should be made. The difference between the two is primarily seen on histology as NAFL has only fatty infiltration without inflammation whereas NASH has marked inflammation. AST and ALT levels can be normal in NAFL and are generally mildly elevated in NASH (ALT > AST). NAFL and NASH are diseases of exclusion and general risk factors are metabolic, such as obesity, dyslipidemia, and diabetes mellitus [23]. It is important to note that NAFL is generally reversible with lifestyle modifications in contrast to NASH (Table 4).

Viral hepatitis can result in a mild increase in aminotransferases, specifically chronic viral hepatitis. Hepatitis B and Hepatitis C infections can generally cause chronic infections and also have a risk for developing liver cirrhosis. In a study done in 1988, patients with chronic viral hepatitis without liver cirrhosis had an AST:ALT < 1 (0.59 average), however those with chronic viral hepatitis and liver cirrhosis had an AST:ALT > 1. This was found to be significant and is important to identify in cases of chronic viral hepatitis to aid in recognizing possible concomitant liver cirrhosis [24]. Nonetheless, caution must be practiced when looking at AST:ALT specifically when alcohol use cannot be excluded. Acute viral hepatitis on the other hand can result in moderate to severe elevation in aminotransferases, often with ALT elevations higher than that of AST. Acute hepatitis C virus can result in marked elevations in aminotransferases however generally the elevation is modest compared to hepatitis A and B. Acutely, elevation in aminotransferases levels peak before bilirubin levels, however, begins declining gradually after in contrast to bilirubin [25]. Acute hepatitis A and B in adults are associated with elevations in bilirubin resulting in jaundice (more common with hepatitis A infection) and ALP. The risk of progression to chronic hepatitis is approximately 10% in hepatitis B patients above the age of 6, hepatitis A is not associated with chronic infection [26].

Hereditary hemochromatosis is an autosomal recessive disease caused by over absorption of iron secondary to abnormal iron sensing in the gastrointestinal tract resulting in iron overload [27]. The 2 most common mutations identified are C282Y and H63D on the hemochromatosis (*HFE*) gene. Non-*HFE* hemochromatosis exists, however in this review we will talk only about *HFE* hemochromatosis.

Hemochromatosis causes mild elevations in aminotransferases (ALT > AST), elevations in ALP and bilirubin can also be seen however liver biochemical tests are non-specific in cases of hemochromatosis [27]. Bilirubin elevation is thought to be a protective mechanism to help mitigate oxidative damage caused by excess iron in the liver. Moreover, a study done in 2004 demonstrated that bilirubin level elevation was found to have a positive correlation with serum iron level [28]. In cases of elevated aminotransferases without a clear cause, it would be wise to check iron studies including iron level, ferritin level, total iron-binding capacity, and transferrin saturation. If results suggestive of iron overload, genetic testing and liver biopsy should be considered.

Wilson's disease is an autosomal recessive disease due to mutations in the *ATP7B* gene with a prevalence of approximately 1:30000 worldwide, studies have suggested higher prevalence based on gene mutation frequency. The difference between the 2 reported prevalence could be related to the disease's possible low penetrance [29]. Wilson's disease liver presentation is variable and can be from asymptomatic elevation in aminotransferases to acute liver failure (ALF). Aminotransferase elevation is mild in the majority of cases however can be moderate to severe in patients with Wilson's presenting with ALF. 6%-12% of emergent liver transplant referrals are due to Wilson's disease ALF [30]. Markers that aid in the diagnosis of ALF secondary to Wilson's disease are non-immune hemolytic anemia, acute renal failure, AST:ALT > 2.2, and ALP: Bilirubin < 4. Almost all patients presenting with ALF secondary to Wilson's have underlying liver fibrosis or cirrhosis [31,32].

AATD is an autosomal co-dominant disease with an expected prevalence of 3.4 million globally with combinations for severe AATD [33]. However, this number is thought to be under-representative of the actual prevalence [33]. A study done in 1989

**Table 3 Common condition with abnormal liver biochemical tests**

Condition	AST/ALT	ALP	GGT	Bilirubin	Other
Alcoholic hepatitis	↑↑ AST:ALT > 2	↑	↑	↑	AST/ALT < 500
NAFLD	-/↑ ALT > AST	-/Mild ↑	-/Mild ↑	↑ If progress to cirrhosis	-
Viral hepatitis	↑↑ In acute/↑ in chronic	↑	↑	↑ In chronic	AST:ALT > 1 suggestive of cirrhosis
Hemochromatosis	↑ ALT > AST	↑	↑	↑ Higher levels = higher iron load	↑ Ferritin and transferrin saturation
Wilson's disease	↑/↑↑ AST:ALT > 2.2 in ALF	↑	↑	↑	ALP:Bilirubin < 4
AATD	↑ AST > ALT	-	-	-	-
Celiac disease	↑ ALT > AST	-	-	-	-
Autoimmune hepatitis	↑↑	↑	↑	↑	ALP:AST/ALT < 3
DILI	↑↑/↑↑	↑	↑	↑	↑ PT/INR
Cholestasis	↑	↑↑	↑↑	↑	AST:ALT < 1.5 - Extrahepatic AST:ALT > 1.5 - Intrahepatic

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; NAFLD: Non-alcohol fatty liver disease; AATD: Alpha-1 antitrypsin deficiency; DILI: Drug induced liver injury; PT: Prothrombin time; INR: International normalized ratio.

**Table 4 Non-alcoholic fatty liver disease spectrum**

Non-alcoholic fatty liver disease spectrum		
NAFL	Steatosis changes. No cellular ballooning, hepatocyte inflammation or fibrosis	Prevalence of 25% approximately. Reversible
NASH	Steatosis changes. Cellular ballooning and hepatocyte inflammation. No fibrosis	Prevalence of 1.5%-6.45% approximately. Generally irreversible (has been found to be reversible in some patients)
NASH related liver cirrhosis	Hepatocyte destruction and fibrosis	Prevalence of 1%-2% approximately. Irreversible
Healthy liver ↔ NAFL → NASH → NASH related cirrhosis		

NAFL: Non-alcoholic fatty liver; NASH: Non-alcoholic steatohepatitis.

in St. Louis examined 20000 blood bank samples, 700 blood samples came back positive for homozygous PI\*Z mutation, however, only 28 of those individuals have been diagnosed with AATD[34]. AATD involves multiple alleles however the alleles thought to be contributing to liver disease are M (maltron) and Z allele. In adults with homozygous PI\*Z mutation, 40% were found to have evidence of injury and cirrhosis histologically. Aminotransferases are generally mildly elevated with ALT predominance. Bilirubin levels are elevated in later stages (cirrhosis) along with a decrease in albumin[35].

CD is an autoimmune disease characterized by gluten intolerance which often leads to malabsorption. A study was done where 158 adults recently diagnosed with CD were followed, 42% of patients were found to have mild elevations in aminotransferases. Patients were started on a gluten-free diet and in 95% of cases, the aminotransferases levels normalized at 1 year[36]. Another study was done evaluating patients with chronically elevated aminotransferases, workup on those patients revealed that 9.3% of patients had serological evidence of CD and all but one of the 9.3% had duodenal biopsy findings of CD[37]. Aminotransferases elevation is mild with an AST:ALT < 1, bilirubin levels are generally normal. ALP can be slightly elevated in a subset of patients but is generally normal. Albumin and PT/INR values are not very reliable indicators of hepatic synthetic function in cases of CD as CD is an autoimmune disease, and a state of inflammation could cause a decrease in albumin levels. Moreover, PT/INR values can be elevated due to concomitant vitamin K deficiency secondary to malabsorption[38].

Autoimmune hepatitis is an inflammatory disorder with a female predilection and a prevalence of approximately 1:5000-1:10000 in Europe. At the time of diagnosis, almost 50% of patients have jaundice and approximately 30% have cirrhosis[39,40]. Autoimmune hepatitis affects aminotransferases variably depending on acute *vs* chronic presentations. Acutely, elevations in aminotransferases can be moderate to severe and tend to gradually decline as the disease becomes chronic and/or liver cirrhosis ensues. Bilirubin, ALP, and gamma globulins elevations are also seen in autoimmune hepatitis. ALP:AST or ALT ratio < 3 which is calculated by using the following equation (ALP/ALP ULN)/(AST/AST ULN) (ALT can be used in place of AST for this calculation) and this ratio is thought to be helpful as disproportionate elevation of ALP should prompt exploration of other differentials such as primary biliary cholangitis[41]. Furthermore, it was found that patients with higher elevations in aminotransferases had a better prognosis when compared to those with milder aminotransferase elevations[42].

DILI can cause a multitude of effects on aminotransferases and elevations of aminotransferases can be mild, moderate, or severe. A wide range of medications can cause mild elevations of aminotransferases and those include antibiotics (such as amoxicillin-clavulanic acid, macrolides (cholestatic pattern), ceftriaxone), anticonvulsants (such as Carbamazepine, Phenytoin, Valproic acid, Gabapentin), statins, anti-tuberculosis medications, and herbal supplements. Hence, a thorough history of medication history is crucial in patients with elevated aminotransferases. More commonly, DILI is ALT predominant.

Drugs can also be a cause of moderate to severe aminotransferase elevation with the most commonly implicated drug being acetaminophen. Acetaminophen is advertised as safe with a daily dose < 4000 mg/d[43]. Acetaminophen-induced hepatotoxicity has a prevalence of approximately 30000 cases a year in the United States[44]. Up to 50% of overdoses were found to be unintentional[44]. Studies have been done which showed 6% of acetaminophen prescriptions to be > 4000 mg/d. A study evaluating AST:ALT ratio found that in cases of severe toxicity, an AST:ALT < 0.4 is suggestive of resolving hepatitis and is a positive prognostic marker[45]. Bilirubin, ALP, and PT/INR can all rise in cases of acetaminophen overdose. It is important to note that aminotransferases generally rise 2-3 d after an initial overdose and that an initial normal liver biochemical test does not exclude acetaminophen toxicity[45].

Acute cholecystitis (AC) usually presents as a cholestatic pattern or mixed. The biochemical test abnormalities are associated with obstruction from CBD, reactive hepatitis, fatty liver, direct gallbladder pressure on the biliary tract, or portal tract inflammation[19-21]. Patients with calculous AC may have CBD stones in up to 15% [17]. Gallbladder ultrasound and computed tomography (CT) is not entirely reliable for the diagnosis of CBD stones. Therefore, LFTs may be used for the identification of patients with suspected CBD stones who would benefit from endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) which are more sensitive and specific for this condition[18]. Multiple studies have shown mean values of LFTs higher in patients with AC plus CBD stones[18,22]. Bilirubin, AST, ALP, and GGT are the variables mostly studied to predict CBD stones. Ahn *et al*[18] found GGT to be the most reliable variable for CBD stones prediction with a sensitivity of 80.6% and specificity of 75%. Another study found an elevation in ALP to be the most important predictor for CBD stones[21]. Elevated LFTs in patients with AC without CBD stones are more likely to be transient and resolve within 2-7 d after surgery[18].

Ischemic hepatitis (often also referred to as hypoxic liver injury, shock liver, and hypoxic hepatitis) is a clinical condition characterized by acute liver injury causing severe elevation of aminotransferases secondary to hypoperfusion with a prevalence of approximately 2:1000 admissions and 2.5:100 in intensive care unit admissions. Moreover, it was found that approximately 4 out of 10 admissions with severe elevations in aminotransferases had ischemic hepatitis diagnosis. After further analysis, 78.2% of patients with ischemic hepatitis had a preceding acute cardiac event, 23.4% of patients with ischemic hepatitis had a diagnosis of sepsis and 52.9% of patients had a documented episode of hypotension (unspecified duration)[46].

The aminotransferase elevation is generally severe with level > 75 × ULN being suggestive of ischemic hepatitis, AST:ALT > 1 usually due to the location of AST (zone 3) in the liver and ischemic effect on zone 3. Bilirubin rise is not uncommon yet it can be mild and typically < 3 mg/dL. ALP is usually normal and PT/INR can be mildly elevated[47]. Another ratio that was found to be useful is AST:LDH < 1.5 which helps in differentiating ischemic hepatitis from viral hepatitis[48]. The AST:LDH ratio is thought to be due to the rapid and severe rise of LDH in cases of ischemic hepatitis due to hypoperfusion.



ALF is another potential cause of severe elevation in aminotransferases and cautious identification of this condition is crucial as mortality risk is approximately 40%-80% [49]. ALF is defined as the presence of severe liver injury in addition to clinical and laboratory features of liver failure such as hepatic encephalopathy and elevation in INR specifically in an individual with no prior history of liver cirrhosis or liver disease. Etiologies of ALF include but are not limited to Ischemic hepatitis, Budd Chiari syndrome, Wilson's disease, autoimmune hepatitis, acute viral hepatitis, and drug-induced liver disease. Biochemical test evaluation in ALF can be hepatocellular initially and progress to cholestatic in later stages. Labs are typically significant for severe elevation in aminotransferases, mild to moderate elevation in bilirubin and ALP in addition to INR  $\geq 1.5$ , and in some cases LDH elevation[49]. While declining aminotransferases can be suggestive of recovery, this is not an accurate measure of recovery as it could be indicative of worsening liver failure and severe loss of liver mass. It is more appropriate to follow bilirubin, INR, and clinical features (hepatic encephalopathy) in patients with ALF for possible recovery[49].

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## DIAGNOSTIC TESTS

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The initial evaluation of abnormal biochemical tests will be guided by the pattern (hepatocellular, cholestatic, or mixed). As a first step, the clinician should inquire about the use of medication, herbal therapies, drugs, or alcohol consumption. If a hepatocellular pattern is identified, initial serology should be obtained to rule out infectious and autoimmune etiologies. A right upper quadrant ultrasound (RUQ US) is also justified to evaluate for fatty liver. If the previous workup is unrevealing uncommon causes should be worked up (such as Wilson disease, AATD, *etc.*). If the serologic studies and imaging are unremarkable and ALT/AST is persistently elevated, consider a liver biopsy. When ALP is elevated, GGT and 5' nucleotidase tests are important to identify the source of ALP elevation. If the latter is elevated ALP likely is elevated from hepatobiliary origin. The RUQ US will help to identify ductal dilation or the absence of it. Further workup includes either an MRCP or an ERCP (when ductal dilation is present) or serological studies including AMA if no dilation is identified. Cholestasis can be further divided into intrahepatic or extrahepatic both usually seen with marked elevation of ALP. The workup for extrahepatic cholestasis should aim to rule out choledocholithiasis, malignant obstruction, and biliary strictures. For intrahepatic cholestasis, laboratory works up should aim to rule out primary biliary cholangitis, primary sclerosing cholangitis, sickle cell disease among other causes. In intrahepatic cholestasis imaging or laboratory, workup may not yield a definitive diagnosis and other causes should be considered (*i.e.*, total parenteral nutrition, drugs associated with cholestasis, ischemic, cholestasis of pregnancy, *etc.*)

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## CONCLUSION

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The elevation of liver biochemical studies is a common encounter of all clinicians. The multiple markers used to identify liver injury may be also elevated due to other sources (bone, placenta, kidney, muscle, *etc.*). The biochemical knowledge helps to better understand the behavior of these markers in specific conditions. The proper recognition of hepatocellular or cholestatic pattern prompts further investigations that include imaging and laboratory studies. Other factors highly important to consider when evaluating abnormal liver biochemical patterns are signs and symptoms, medications, degree of liver tests elevation, and other laboratory abnormalities present. Unfortunately, despite the use of additional tests (imaging and laboratory) in some causes the diagnostic is unclear and liver biopsy is recommended.

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