

How to interpret liver function tests

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Careful interpretation of liver function tests within the clinical context can help elucidate the cause and severity of the underlying pathology. Predominantly raised alkaline phosphatase represents the cholestatic pattern of biliary pathology, whilst predominantly raised alanine aminotransferase and aspartate aminotransferase represent the hepatocellular pattern of hepatocellular pathology. The severity of liver dysfunction or biliary obstruction is reflected in the bilirubin level and the degree of liver synthetic function can also be indicated by the albumin level. Beyond the liver function tests, prothrombin time provides another marker of liver synthetic function and a low platelet count suggests portal hypertension.

Key words: Liver function test, cholestatic pattern, hepatocellular pattern, liver synthetic function.

Introduction

Derangement of liver function tests (LFTs) is a common problem that can be difficult to interpret. The clinical context is an important guide, but liver disease can be asymptomatic until the late stages and abnormal blood tests may be the first indication of disease. This review will guide you through the individual LFT's and how to interpret them.

What are the LFTs?

LFTs include liver enzymes, albumin and other proteins, and bilirubin. The liver enzymes are produced by cells within the liver. They include alkaline phosphatase (ALP), γ -glutamyl transpeptidase (GGT), alanine aminotransferase (ALT) and aspartate aminotransferase (AST), but the combination of liver enzyme results you receive depends on your local laboratory. The protein components comprise total protein, albumin and globulin [N.B. Total protein = Albumin + Globulins]. The globulins are a mixture of globular proteins such as immunoglobulins, enzymes, carrier proteins and complement.

The LFT's reflect a limited range of hepatic metabolic processes. Bilirubin is an indication of the detoxification/excretory function and albumin reflects the synthetic function.

Typical normal ranges for LFTs and other blood tests are shown in Table 1, but may vary according to your local laboratory.

Liver enzymes

The liver enzymes are in two main groups – ALP and GGT, produced predominantly by the bile ducts; and ALT and AST, produced predominantly by hepatocytes. Liver enzymes are a poor reflector of liver function, but rather of cholestasis and liver cell integrity, respectively [1].

Liver enzymes have different normal ranges, so assessment of their relative abnormalities by number of

times greater than their upper limit of normal (ULN) can be more informative than the absolute values.

When ALP is raised more times its ULN than either ALT or AST, this suggests a cholestatic pattern indicating biliary pathology. In the acute setting, a cholestatic pattern of LFTs is seen with bile stones, when accompanied by colicky right upper quadrant pain or in cholestatic drug-induced liver injury when there is a history of a new causative medication. A more chronic presentation may be due to pancreatic, liver or bile duct tumours or cholestatic autoimmune liver disease such as primary biliary cholangitis or primary sclerosing cholangitis.

ALP is also produced outside the liver by organs such as bone, placenta, kidneys and gut. Hence ALP may be raised in the presence of normal liver health, most commonly due to bone disease or pregnancy. A raised GGT and/or other abnormalities in the LFTs would indicate a liver source of raised ALP. The ALP isoenzyme can also help differentiate a liver versus bone origin. If all other liver tests are normal, raised calcium or phosphorus levels may also indicate a bone source.

GGT is induced by alcohol and other drugs and so lacks specificity for many liver diseases, except in the context of ALP.

ALT and AST are produced mostly by hepatocytes. However, ALT occurs at low concentrations in skeletal muscle and kidney, and AST is found in kidney, heart, brain, red blood cells and skeletal muscle [1]. Abnormalities in ALT and AST are fairly specific to the liver however.

When ALT or AST are raised more times their ULN than ALP, this is described as a hepatocellular pattern. This state reflects disease processes affecting hepatocytes such as viral hepatitis, metabolic liver diseases, drug or alcohol toxicity and autoimmune hepatitis. Abnormalities in these liver enzymes are generally considered mild if <5 times the ULN, moderate if 5-10 times the ULN or marked if >10 times the ULN.

Table 1. Normal values for blood tests

Component	Abbreviation	Normal range
Bilirubin	Bili	<21 µmol/l
Alkaline phosphatase	ALP	30-130 IU/l
γ-glutamyl transpeptidase	GGT	11-55 IU/l
Alanine aminotransferase	ALT	15-45 IU/l
Aspartate aminotransferase	AST	15-42 IU/l
Albumin	Alb	35-50 g/l
Globulin	Glob	20-40 g/l
Total protein	TP	60-80 g/l
Haemoglobin	Hb	135-185 g/l
Mean cell volume	MCV	78-100 fl
White cell count	WCC	4-11 x10 ⁹ /l
Platelets	Plts	140-400 x10 ⁹ /l
Prothrombin time	PT	9-12 s
International normalized ratio	INR	0.9-1.2
Urea	Urea	2.5-7.8 mg/dl
Creatinine	Creat	60-110 µmol/l
C-reactive protein	CRP	<5 mg/l

In alcoholic hepatitis, an ALT over 300 IU/l is rare, but increased AST/ALT ratio is often observed. In contrast, the AST/ALT ratio is low in non-alcoholic steatohepatitis [2], often accompanied by a modestly elevated GGT. Although there are many differential diagnoses for mild to modest elevations in ALT or AST, marked elevations are usually only caused by acute drug-induced liver injury, viral hepatitis or ischaemic liver injury. Detailed history for drug and toxin exposure, viral hepatitis risk factors and inter-current illness resulting in hypotension should be taken. The patient should also be monitored for fulminant liver failure.

In reality, the pattern of LFTs may not be clear-cut and an apparently hepatocellular pattern can reflect an acute cholestatic cause such as biliary stones. Typically, the raised ALT or AST in this situation resolves quickly once the obstruction is relieved. Clinical context and further assessments are therefore needed to help make the diagnosis.

The timing of liver enzyme abnormalities may differentiate acute from chronic liver disease, but note that in the chronic setting, significant liver damage such as cirrhosis can exist with normal liver enzyme levels. Raised liver enzymes are not a reliable screening test for cirrhosis.

Bilirubin

Bilirubin is the product of haemoglobin breakdown. Lipid-soluble, unconjugated bilirubin is conjugated in the liver, making it water-soluble, and then excreted into bile. When a raised bilirubin or clinical jaundice is found we should consider haemolysis (production of unconjugated bilirubin), liver cell function (conjugation and excretion of bilirubin) and biliary tree function (excretion of bile). A raised bilirubin level is a strong indicator of underlying pathology and should always be investigated with a careful clinical history and appropriate investigations. A liver ultrasound is usually necessary.

In haemolysis, red cell rupture releases free haemoglobin, raising blood levels of unconjugated bilirubin. The diagnosis of haemolysis may be supported by reduced haemoglobin, reduced haptoglobins, increased reticulocyte count and an abnormal blood film, whilst other LFTs and liver ultrasound are normal.

Unconjugated bilirubin is also raised in Gilbert's syndrome, a benign, inherited disease. Patients are well in Gilbert's syndrome, but their bilirubin levels may rise particularly during inter-current illnesses, whilst other liver tests and liver ultrasound remain normal. Gilbert's syndrome can be diagnosed clinically.

In liver cell or biliary pathology with a raised bilirubin, a hepatocellular or cholestatic liver enzyme pattern is often present and possible abnormalities in liver synthetic function. Consideration of these other LFTs, the clinical history and a liver ultrasound to look for biliary obstruction, liver lesions or liver parenchymal change are useful.

Unlike the liver enzymes, the bilirubin can be a useful marker of liver function, as bilirubin rises with increasing severity of liver disease. Bilirubin has been incorporated into a number of composite scores, which assess liver disease severity including the Child Pugh [3] and model for end-stage liver disease (MELD) scores [4].

Albumin

Albumin is a protein synthesized exclusively in the liver. As such it is a marker of liver synthetic function and liver health. The half-life of albumin is 20 days and so a low albumin may be seen in chronic or sub-acute liver disease, but may not be observed in acute liver injury [1]. Albumin levels can be reduced by many kinds of illnesses and so has relatively low specificity as a marker of liver function. None-the-less a low albumin has prognostic significance and forms part of the Child Pugh score.

Other assessments of the liver function

The LFTs are not the only blood tests indicating liver function. In particular the prothrombin time (PT) or international normalised ratio (INR), and platelet count contribute to a more comprehensive assessment.

The PT is governed by the activity of clotting factors,

Table 2. Chronic liver disease screen

Etiology	Investigation
Biliary obstruction, tumours and frank cirrhosis	Abdominal US
Viral hepatitis	Hepatitis B and C serology
Autoimmune hepatitis	Liver autoimmune profile
Haemochromatosis	Ferritin
Hepatocellular carcinoma	α -fetoprotein
Wilson's disease	Caeruloplasmin
α 1- antitrypsin deficiency	α 1 - antitrypsin

which are produced by the liver and have a half-life of about one day [1]. The production of these clotting factors is dependent on adequate vitamin K and so clotting may also be prolonged by vitamin K deficiency. In the absence of vitamin K deficiency or anticoagulants (e.g. warfarin), PT is a good marker of liver function in both acute and chronic settings. The international normalized ratio (INR) also reflects clotting and liver synthetic function in the same way and unlike PT, is standardised across laboratories. Liver function must be quite severely impaired to affect PT or INR and so mild liver disease or a state of compensated cirrhosis will likely have normal values. The PT and INR form part of the Child Pugh and MELD scores, respectively.

Importantly, the liver makes both clotting and fibrinolytic products and so it should not be assumed that a raised PT indicates a hypocoagulable state in the context of liver disease.

Cirrhosis can cause increased pressure in the portal vein that carries blood from the gut and the spleen to the liver. This is called portal hypertension. When this develops, the spleen becomes engorged with blood and consumes platelets. A low platelet count is a marker of portal hypertension [5] and may be the first indicator of chronic liver disease. Portal hypertension causes many of the complications of chronic liver disease such as variceal bleeds, ascites and hepatic encephalopathy and so the finding of a low platelet count in this context is a poor prognostic sign.

The underlying etiology

Despite meticulous interpretation of the LFTs, the underlying cause of liver disease may still not be apparent. When presented with a patient with liver test abnormalities or a clinical suspicion of chronic liver disease, it is often necessary to perform a liver screen. Detailed discussion of the liver screen is beyond the context of this article, but is summarised in Table 2. The liver screen does not contain specific tests for alcohol-related liver disease, non-alcoholic fatty liver disease (NAFLD) or drug-induced liver injury

amongst others, so careful history and assessment of liver disease risk factors are still vital.

In the acute setting, hepatitis A, hepatitis E, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus and stool examination for schistosomiasis ova may also be considered.

Simple non-invasive scores of liver fibrosis

Although the simple presence of raised liver enzyme levels is not a reliable way of diagnosing cirrhosis, liver function blood tests can be used in combination to predict the presence of liver fibrosis. Detailed description and discussion of these scores is beyond the scope of this article, but commonly used scores include the AST/ALT ratio [6], AST to platelet ratio index (APRI) [7], fibrosis 4 (FIB-4) [8] and NAFLD fibrosis risk score [9]. The World Health Organisation recommends the use of APRI or FIB-4 scores for the assessment of chronic hepatitis C related liver fibrosis to aid decision-making on hepatitis C treatment allocation [10].

Summary

Deranged LFTs are a common problem and their interpretation is complicated by the production of liver enzymes from multiple organs and the lack of specificity for markers of liver function. Therefore it is important to interpret liver tests within the clinical context. Raised ALP reflects biliary tree injury and cholestasis, whereas raised AST and ALT levels usually reflect hepatocyte injury. Raised bilirubin and low albumin are the LFT components that can reflect impaired liver function, whilst raised PT or INR also provide a marker of liver synthetic function. A low platelet count may be seen in cirrhosis and signify the onset of portal hypertension.

References

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Quiz on Liver Function Tests (see the article on page 40)

Test your knowledge and find the best matches between the following statements and the blood test results in the table. See page 47 for the answers.

1. A 30-year old female presents to clinic with fevers, vomiting, lethargy and myalgia for 1 week. There is a mild continuous right upper quadrant ache. She takes no medications or alcohol. Two of her family members have also been similarly unwell.
2. A 51-year old male presents with tense abdominal distension. He drinks 80 units of alcohol per week.
3. A 76-year old male with known prostate cancer presents with back pain.
4. A 16-year old male presents with lethargy and breathlessness.
5. A 41-year old female with biopsy-proven HCV cirrhosis who had successful HCV treatment 2 years ago.
6. A 40-year old female presents with 2 days of colicky right upper quadrant pain and nausea.

	A	B	C	D	E	F
Bilirubin (µmol/l)	12	45	63	34	41	15
Alkaline phosphatase (IU/l)	199	338	371	173	49	56
γ-glutamyl transpeptidase (IU/l)	37	182	451	175	31	39
Alanine aminotransferase (IU/l)	18	63	1976	55	16	31
Aspartate aminotransferase (IU/l)	21	63	1883	89	17	34
Albumin (g/l)	35	41	37	22	40	38
Globulin (g/l)	24	20	27	23	29	20
Total protein (g/l)	59	61	64	45	69	58
Haemoglobin (g/l)	136	149	138	115	81	141
Mean cell volume (fl)	98	97	94	108	105	95
White cell count (x10 ⁹ /l)	5.1	8.0	10.0	4.3	5.0	3.9
Platelets (x10 ⁹ /l)	299	307	400	86	249	237
Prothrombin time (s)	11	10	12	15	11	10
International normalized ratio	1.0	1.0	1.1	1.4	1.0	0.9
Urea (mg/dl)	6.5	5.9	6.4	2.0	3.5	3.8
Creatinine (µmol/l)	127	109	97	49	67	57
C-reactive protein (mg/l)	5	9	30	2	3	1