Are **ALT & AST** Elevations Really Liver Function Tests

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Reading time: 6 minutes

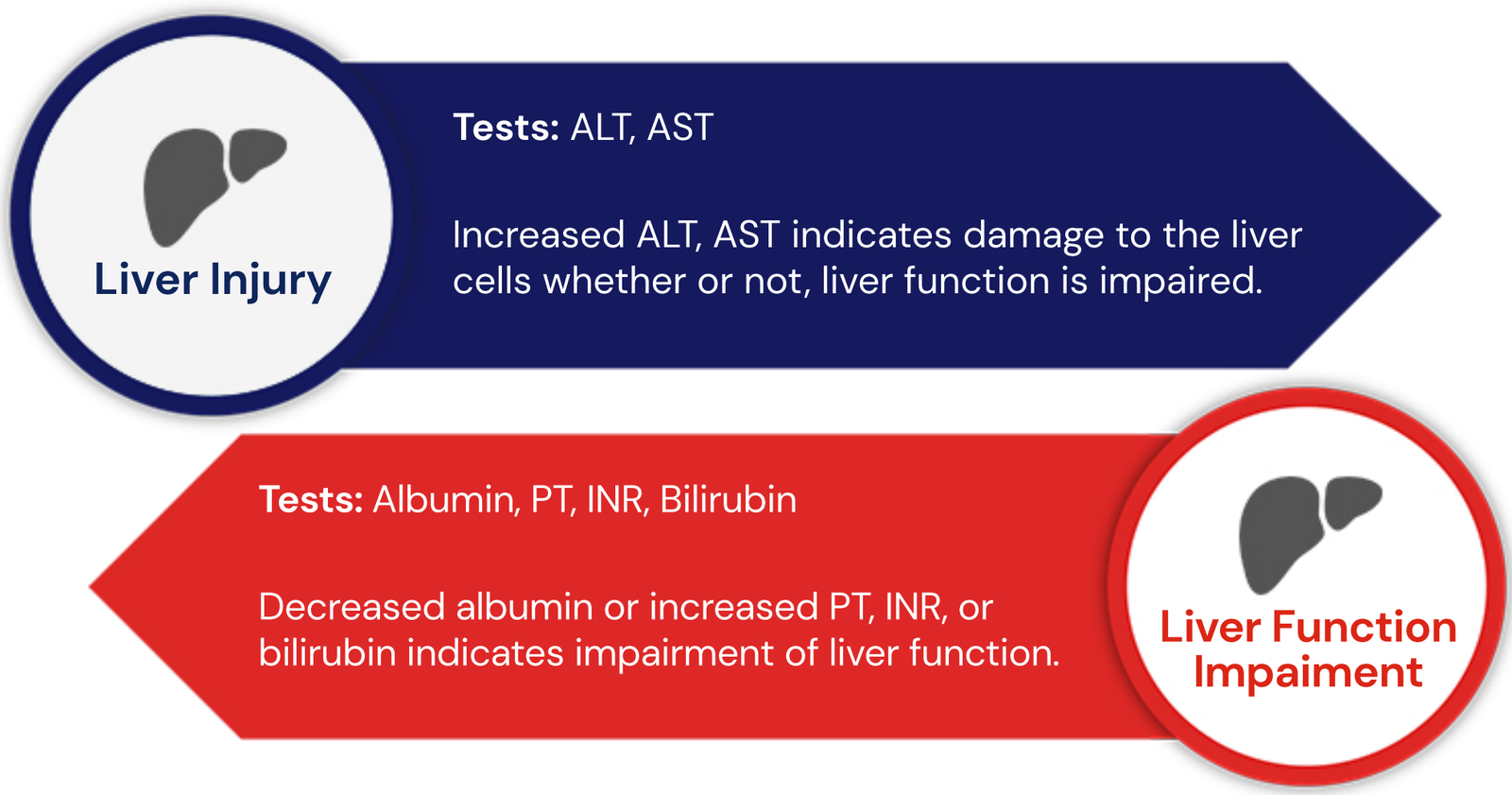
Liver biochemical tests are very commonly performed in clinical studies/clinical practice. These tests include:

- Alanine/aspartate aminotransferases (ALT/AST), Alkaline phosphatase (ALP), Gamma-glutamyl transferase (GGT)
- Bilirubin, Albumin
- Prothrombin time (PT), International normalized ratio (INR)

These tests are commonly used for the diagnosis and evaluation of acute and chronic liver disease, irrespective of the etiology.

Liver Injury Vs. Liver Function

There are two separate concepts for drug-induced liver injury: severity of liver injury and the grade of liver function impairment.



Therefore, the term Liver function tests (LFTs) being used for elevations of ALT and AST is somewhat of a misnomer because these enzymes do not represent liver function, but rather indicate the damage of liver cells. On the other hand, albumin, bilirubin, and vitamin K-dependent clotting factors represent synthetic function of the liver. The decreased synthesis of clotting factors by the liver may lead to prothrombin time (PT) prolongation and an increase in the international normalized ratio (INR).

Some of the commonly used scores to predict mortality in patients with cirrhosis such as the Child-Pugh score and Model for End Stage Liver Disease (MELD) score do not use AST, ALT, or ALP but instead use INR, bilirubin and albumin in Child-Pugh score and INR and bilirubin in MELD score.

The following figure reflects a summary of the commonly used serum liver tests in clinical studies/clinical practice:

Liver Injury Tests

	TEST	SITE OF LOCALISATION	CONDITIONS ASSOCIATED WITH ABNORMAL LIVER INJURY TESTS
Hepatocellular Injury	ALT	Liver, cardiac muscle, skeletal muscle	Hepatocellular injury, muscle injury, rhabdomyolysis
	AST	Liver, cardiac muscle, skeletal muscle, brain, kidney, RBC	Hepatocellular injury, muscle injury, rhabdomyolysis, haemolysis
Cholestasis	ALP	Liver, kidney, bone, intestine, placenta	Cholestasis, biliary injury, bone disorders, late pregnancy
	GGT	Liver, pancreas, kidney, intestine, spleen, prostate	Cholestasis, biliary injury, alcohol intake, obesity, smoking
	Total Bilirubin (Direct + Indirect)	Circulates in blood in unconjugated (indirect) form and undergoes conjugation (direct) in the liver	Direct>Indirect: Hepatocellular injury, cholestasis Indirect>Direct: Haemolysis, Gilbert's syndrome

Liver Function Tests

TEST	SITE & FUNCTION	CONDITIONS ASSOCIATED WITH ABNORMAL LIVER FUNCTION TESTS
Albumin	Main protein that is produced by the liver & circulates in the serum. Maintains serum oncotic pressure.	Acute Liver Disease: Albumin synthesis is usually preserved. Chronic Liver Disease: Low serum albumin indicates cirrhosis.
PT/INR	Indicates function of vitamin K-dependent clotting factors that are mainly synthesized in liver. Test measures extrinsic coagulation pathway.	Aids in the diagnosis of both acute and chronic hepatic disorder.

The below table indicates a pattern of alterations of liver injury tests and liver function tests in hepatocellular injury & cholestasis:

TEST	HEPATOCELLULAR INJURY	CHOLESTASIS
Liver Injury Tests		
ALT/ AST	++/+++	0/+
ALP	0/+	++/+++
Total bilirubin	0/+++	0/+++
Liver Function Tests		
PT/INR	Prolonged	Prolonged
Albumin	-/----	0

Stopping Rules for the Drugs in Premarketing Clinical Studies for Hepatotoxicity

In clinical trials, it is often difficult to determine when the study drug should be stopped. This is because transient increase of ALT or AST are quite common and progression to severe DILI or acute liver failure is usually uncommon, stopping the study drug on an increase in ALT or AST greater than 3xULN may be unnecessary. For most individuals, the liver appears capable of adapting to injury by chemical substances, which may render a person tolerant to the drug despite continued exposure. Stopping a drug at the first indication of mild injury does not allow knowledge if adaptation will occur, as it does for drugs such as tacrine, which cause liver injury but do not cause severe DILI. On the other hand, if there is marked increase in serum aminotransferases or there is evidence of functional liver impairment (as indicated by rising INR or bilirubin) which represent substantial liver injury, continuing with the study drug appears unacceptably dangerous.

Hence, the USFDA guidance[3] mentions that in the premarketing clinical studies, discontinuation of the study drug should be considered if any of the following occurs:

- ALT or AST >8 x Upper Limit of Normal (ULN)
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and (Total bilirubin >2 x ULN or INR >1.5)
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

It is important to note that these stopping rules are guidelines and may further evolve based on advances in medical research and knowledge. The safety of study participants should always be the top priority, and the final decision to stop a study due to hepatotoxicity will be made by the study sponsor in consultation with multiple key stakeholders including regulatory agencies, investigators, and independent safety monitoring committees.

References

1. Drug-induced liver injury (DILI): Current status and future directions for drug development and the post-market setting. A consensus by a CIOMS Working Group. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2020.
2. Ricart A.D. Drug-induced liver injury in Oncology. Annals of Oncology. Volume 28; Issue 8; P2013-2020, August 2017.

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