Interpreting Liver Blood Tests in Primary Care

Medscape UK X Guidelines
Primary Care Hacks

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LBTs have traditionally been referred to as liver function tests (LFTs). However, typical LBTs include measurement of both hepatobiliary enzymes (e.g. ALT and AST) and markers of liver function (e.g. albumin and clotting factors).[1,2] Additionally, many individuals with abnormal LBTs have **normal** liver function.[1,2] Therefore, to avoid confusion and over-investigation, 'LBT' is now the preferred terminology.[1,2]

Key Messages

1. **Standard LBTs usually comprise ALT, AST, ALP, GGT, total bilirubin, and serum albumin**
2. **Abnormal LBTs are very common in primary care!**
3. **LBTs should only be checked when specifically indicated by the clinical situation**
4. **Interpretation of abnormal LBTs should be individualised and in clinical context**
5. **Abnormal LBTs are likely to remain abnormal on repeat testing**
6. **Common patterns of abnormal LBTs are often more helpful than individual markers**
7. **GGT is useful in determining whether raised ALP is of bone or liver origin**
8. **Isolated raised bilirubin is commonly caused by Gilbert's syndrome, but haemolysis should be excluded**
9. **Always consider a possible pharmacological cause for abnormal LBTs**
10. **Liver enzymes are a poor guide to the development of ALD.**

1. Commonly Requested LBTs[1,3–9]

Test	Notes
ALT	• ALT level varies with age, gender, ethnicity, BMI, illness, and exercise • Recent consensus suggests that the current ULN for ALT is too low; updated EASL–EASD–EASO guidance on MASLD[9] suggests that an individual has elevated ALT if >33 U/l in males and >25 U/l in females (usual normal range 10–50 U/l in both men and women).
AST	• Not as liver-specific as ALT; however, in ALD, AST is a more sensitive marker of liver injury than ALT • May be elevated in MI or myositis • The **De Ritis/AST:ALT ratio** may be useful in elevated aminotransferase levels, as most causes of liver injury are associated with a greater increase in ALT than AST. As a general guide: o **AST:ALT <1** (i.e. AST<ALT) is suggestive of MASLD, chronic viral hepatitis B or C, or acute hepatocellular injury o **AST:ALT ≥2** is associated with ALD, cirrhosis (e.g. in MASH), drug-induced liver injury, and primary liver malignancy o **AST:ALT ≥5** warrants suspicion of possible extrahepatic causes (e.g. MI, myositis), particularly if ALT levels are normal.
ALP	• ALP is elevated in **cholestatic liver disease** (e.g. PBC, drug-induced liver injury), **extrahepatic biliary obstruction** (e.g. gallstones, pancreatic cancer), **bone disease** (e.g. bony metastases, vitamin D deficiency, Paget's disease, bone fractures), **renal osteodystrophy**, and **hepatic congestion caused by right-sided HF** • ALP is also higher in pregnancy because of placental production, and in adolescence because of increased bone turnover.
GGT	• **Raised by multiple factors**, particularly excessive alcohol consumption, obesity, and various drugs (e.g. paracetamol. phenytoin, sodium valproate) • Mild elevations are nonspecific, and isolated increases rarely indicate liver disease • Can also be raised in a range of nonhepatic conditions (e.g. COPD or CKD), and for several weeks after acute MI • Despite its low specificity for liver disease, **GGT is one of the best predictors of mortality in those with established liver disease** • **GGT is useful in determining whether raised ALP is of bone or liver origin** (see *7. Interpreting Raised ALP*).
Bilirubin	• Initial testing usually reports **total bilirubin** (including both unconjugated and conjugated fractions) • **Unconjugated hyperbilirubinaemia** is increased primarily in **Gilbert's syndrome and RBC breakdown (i.e. haemolysis)** (see *8. Isolated Raised Bilirubin*) • **Conjugated hyperbilirubinaemia** is usually caused by **impaired liver processing or bile flow**, e.g. from hepatitis, drug-induced cholestasis, or biliary obstruction (e.g. by gallstones or malignancy).
Albumin	• Serum albumin is a **marker of synthetic liver function**; levels are usually reduced in liver failure but may still be normal in severe acute liver damage, as the half-life of albumin in plasma is around 20 days • Levels are also reduced in sepsis, malnutrition, systemic inflammatory disorders, malabsorption, nephrotic syndrome, GI protein loss, acute infection, and HF (all subtypes) • In the absence of other abnormal LBTs, low serum albumin is unlikely to be of liver origin.
PT and INR	• In the presence of significant liver injury (usually >70% loss of synthetic function), production is reduced and PT prolonged/INR raised • Prolonged PT/raised INR can also be caused by warfarin therapy, or by vitamin K deficiency in fat malabsorption or chronic cholestasis • In the presence of otherwise normal LBTs, prolonged PT is unlikely to be of liver origin.

Platelet reduction is also an indicator of advanced liver disease; this is the result of a multifactorial mechanism involving bone marrow suppression, hypersplenism (secondary to portal hypertension), and subsequent splenic sequestration.

Note: the standard set of LBTs differs between areas. The BSG recommends assessing bilirubin, albumin, ALT, ALP, and GGT when first investigating potential liver disease, with an FBC *'if not already performed within the previous 12 months'*.[1]

Abbreviations
AAC=Accelerated Access Collaborative; **AIH**=autoimmune hepatitis; **ALD**=alcohol-related liver disease; **ALP**=alkaline phosphatase; **ALT**=alanine aminotransferase; **AMA**=antimitochondrial antibody; **ANA**=antinuclear antibody; **AST**=aspartate aminotransferase; **AUDIT**=Alcohol Use Disorders Identification Test; **BALLETS**=Birmingham and Lambeth Liver Evaluation Testing Strategies; **BMI**=body mass index; **BSG**=British Society of Gastroenterology; **CKD**=chronic kidney disease; **CMV**=cytomegalovirus; **COPD**=chronic obstructive pulmonary disease; **CVD**=cardiovascular disease; **DMARD**=disease-modifying antirheumatic drug; **EASD**=European Association for the Study of Diabetes; **EASL**=European Association for the Study of the Liver; **EASO**=European Association for the Study of Obesity; **EBV**=Epstein–Barr virus; **FBC**=full blood count; **FIB-4**=Fibrosis-4; **GGT**=gamma-glutamyl transferase; **GI**=gastrointestinal; **HAV**=hepatitis A virus; **HbA_{1c}**=glycated haemoglobin; **HBV**=hepatitis B virus; **HCV**=hepatitis C virus; **HEV**=hepatitis E virus; **HF**=heart failure; **IBD**=inflammatory bowel disease; **INR**=international normalised ratio; **LBT**=liver blood test; **LDH**=lactate dehydrogenase; **LFT**=liver function test; **LKM**=liver kidney microsomal; **MASH**=metabolic dysfunction-associated steatohepatitis; **MASLD**=metabolic dysfunction-associated steatotic liver disease; **MI**=myocardial infarction; **NG**=NICE Guideline; **NSAID**=nonsteroidal anti-inflammatory drug; **OTC**=over-the-counter; **PBC**=primary biliary cholangitis; **PSC**=primary sclerosing cholangitis; **PMH**=past medical history; **PT**=prothrombin time; **PTH**=parathyroid hormone; **RA**=rheumatoid arthritis; **RBC**=red blood cell; **RCGP**=Royal College of General Practitioners; **SMA**=smooth muscle antibody; **T2DM**=type 2 diabetes mellitus; **UGT**=uridine diphosphate glucuronosyltransferase; **ULN**=upper limit of normal; **USS**=ultrasound scan; **U&E**=urea and electrolytes; **WBC**=white blood cell.

2. Contextual Interpretation of Results[1,4,5,10]

- LBTs are regularly checked for unexplained or nonspecific symptoms, almost as a measure of wellbeing
  - in this context, >20% will have abnormal LBTs, and most of these individuals will **not** have significant liver disease[10]
- Moreover, the degree of LBT abnormality does not always correlate with disease severity
  - LBTs may be normal even in advanced liver disease, and are often abnormal in the absence of significant underlying liver disease
- Therefore, interpreting LBTs in isolation is not helpful when diagnosing or ruling out liver disease, and additional history-taking, examination, and/or investigation is usually required (see *4. History, Examination, and Screening* and *5. Further Investigations and Repeat Testing*)
- Review previous LBTs (if available) and assess trends, e.g. mild fluctuation or progressive increase.

4. History, Examination, and Screening[1,3,4,14,18,19]

- Review current clinical status, PMH and comorbidities, family history, travel history, sexual history, occupation, tattoos, prescribed and/or OTC medications, herbal remedies, illicit drug use, and alcohol intake
- Ask about specific signs and symptoms (e.g. jaundice, arthralgia, weight loss, abdominal pain, pruritis, skin hyperpigmentation), as well as tick bites and muscle injury
- Consider assessing BMI and waist-to-height ratio[19], and examining for jaundice, anaemia, ascites, hepatosplenomegaly, and other signs of chronic liver disease (e.g. spider naevi, palmar erythema, gynaecomastia, asterixis)
- Screen for MASLD and features of the metabolic syndrome (see the Primary Care Hack on MASLD/MASH).

3. Indications to Check LBTs[1,4,9,11–17]

- Indiscriminate testing of LBTs in response to nonspecific symptoms that are **not** suggestive of liver disease is likely to lead to unnecessary patient concern, further testing, and investigation
- Opportunistic testing of LBTs is not recommended for asymptomatic people without risk factors for liver disease.

Main Indications for Checking LBTs

- **Nonspecific symptoms suggestive of liver disease**, e.g. fatigue, nausea, or loss of appetite
- **Evidence of chronic liver disease**, e.g. symptoms or signs of portal hypertension, cirrhosis, or liver failure (including ascites, peripheral oedema, hepatosplenomegaly, and spider naevi)
- **Conditions associated with an increased risk of developing liver disease**—including coexisting autoimmune disease, e.g. RA and coeliac disease (increased risk of AIH), and IBD (around 10% risk of comorbid PSC)
- **Monitoring of potentially hepatotoxic drugs** (see *9. Pharmacological Causes*)—various drugs are associated with liver disease and may require LBT monitoring. Notably:
  - **statin monitoring—statins can cause a transient rise in liver aminotransferases but do not cause liver disease;** they are likely to be beneficial in MASLD (note: **CVD is a more common cause of death than liver disease in MASLD**—see the Primary Care Hack on MASLD/MASH) and are associated with reduced primary liver cancer
    - current monitoring of LBTs for statins is unnecessary and costly
    - a single baseline ALT is all that is required—if this is <3x ULN, commence the statin and repeat ALT only if clinically indicated (note: NICE[13] and NHS AAC[16] guidelines do recommend further measurements of ALT/AST as part of early statin monitoring)
  - **DMARD monitoring:**
    - discussion with the specialist team and withholding of therapy may be warranted if ALT and/or AST >100 U/l, or an unexplained reduction in albumin <30 g/l
- **Family history of liver diseases**, e.g. haemochromatosis or Wilson's disease (both autosomal recessive disorders); this may warrant more specific, relevant tests
- **Suspected alcohol misuse and dependence**—to identify physical health complications, e.g. liver inflammation and injury (elevated ALT/AST) and portal hypertension (platelet reduction), and to assess liver synthetic function (PT/INR); see *10. Alcohol-related Liver Disease*
- **Suspected acute or chronic viral hepatitis** (e.g. HBV, HCV, HAV, CMV, EBV)—standard LBTs in addition to hepatitis serology
- **Suspected primary or secondary liver malignancy on examination**, in addition to an urgent, direct-access USS
- As part of **screening for MASLD** in the presence of its cardiometabolic risk factors and/or features of the metabolic syndrome, and/or when hepatic steatosis is found incidentally on USS (see the Primary Care Hack on MASLD/MASH).

5. Further Investigations and Repeat Testing[1,4,9,20,21]

- **Continually repeating LBTs to see whether they normalise is usually an inefficient strategy in primary care**, and is generally only appropriate if transient causes are suspected in the clinical context (e.g. simple viral illness or suspected drug-induced cause)
  - the BALLETS study (2013)[21] found that 84% of abnormal LBTs in primary care remained abnormal on retesting 1 month later, and 75% were still abnormal after 2 years
- Early additional investigation should be considered, informed by LBT results (see Figure 1)
- **Consider an early targeted liver screen, irrespective of level or duration of abnormal LBTs**. Tests to consider are listed to the right.

Tests to consider in a targeted liver screen include:

- HbA_{1c}
- lipid profile
- USS
- coeliac screen
- iron studies
- autoimmune profile (anti-SMA, AMA, anti-LKM antibodies, ANA)
- immunoglobulins
- HBV/HCV serology
- HIV
- TFTs
- alpha-1 antitrypsin
- FIB-4, if MASLD is suspected
- serum or urine copper/caeruloplasmin (if family history of Wilson's disease, and/or aged <45 years)
- if acute hepatitis is suspected, also consider HAV, HEV, CMV, and EBV serology.

6. Common Patterns of Abnormal LBTs[1,3–5,20]

- The pattern of abnormal LBTs is often more informative than individual LBT changes, especially if there is no obvious underlying cause
- The magnitude of LBT abnormality does not necessarily correlate with clinical significance, but as a general guide LBTs <2–3x ULN are considered borderline/mild
- Look for the predominant pattern of enzyme alteration (see table, right).

Pattern	ALT/AST	ALP/GGT	Bilirubin	Notes
Hepatocellular	↑	↔	↑ or ↔	• Causes include MASLD, ALD, viral hepatitis, AIH, and drug-induced liver injury (e.g. paracetamol overdose) • Consider targeted further investigation and USS (see Figure 1).
Cholestatic/ obstructive	↔	↑	↑ or ↔	• Causes include PBC, PSC, biliary obstruction (e.g. from gallstones, strictures, malignancy), drug-induced liver injury, and hepatic congestion (e.g. secondary to HF) • Consider USS and targeted further investigation (see Figure 1).
Mixed hepatocellular/ cholestatic	↑	↑	↑ or ↔	• Often seen in the context of medication use (see *9. Pharmacological Causes*).
Isolated raised bilirubin	↔	↔	↑	• Often suggestive of Gilbert's syndrome, but haemolysis should also be excluded (see *8. Isolated Raised Bilirubin*).
Failure of liver synthetic function	• Jaundice, low albumin, and prolonged PT/INR • See Figure 1.			

↑ = Raised ↔ = Unchanged

7. Interpreting Raised ALP[1,3,4,22]

- **If ALP is raised, check GGT:**
  - if GGT is normal, think 'bone' origin and consider investigations such as calcium, phosphate, magnesium, PTH, U&E, and vitamin D levels (see the Primary Care Hack on abnormal calcium levels)
    - if there is no obvious cause, consider bony metastases
  - if GGT is high, think 'liver' origin and consider a targeted liver screen and USS (see Figure 1)
- **ALP isoenzyme electrophoresis** can also be requested to determine the source of a raised ALP, if unclear
- Consider checking **AMA** and **ANA** if raised ALP of liver origin persists, to exclude PBC
  - PBC is much more common in women and in those aged >50 years, and often presents with intense, widespread itch.

8. Isolated Raised Bilirubin[1,3,4,20,23–25]

- Isolated raised bilirubin is commonly caused by **Gilbert's syndrome**, an inherited condition (**usually autosomal recessive**, but sometimes autosomal dominant) that affects ≥5% of the population and is more commonly identified in males
  - Gilbert's syndrome is a benign congenital defect of the UGT enzyme, which results in a mild, fluctuating **unconjugated hyperbilirubinaemia** with otherwise normal LBTs
  - episodes of jaundice are self-limiting (typically resolving in a few days) and are triggered by physical or psychological stress, e.g. fasting, intercurrent illness, lack of sleep, heavy physical exertion, or surgery
  - bilirubin levels usually do not exceed 80 micromol/l
- Less commonly, **haemolysis** can cause an isolated raised bilirubin; **explore for any signs and symptoms of overt/occult bleeding**, e.g. jaundice, fatigue, haematuria, dyspnoea
  - if suspected (especially if the patient has confirmed anaemia), consider a haemolysis screen—typically, FBC, blood film, reticulocytes, LDH, haptoglobin, and iron studies (see the Primary Care Hack on interpreting iron studies)—and discuss with Haematology
- Consider requesting **conjugated bilirubin** levels to determine whether hyperbilirubinaemia is conjugated or unconjugated.

9. Pharmacological Causes[1,3,4,26]

- Many medications can alter liver enzymes (including prescription and OTC preparations, herbal remedies, dietary supplements, and illicit drugs), but significant drug-induced liver failure is known to be rare
- The pattern of abnormal LBTs associated with medication use **can be hepatocellular, cholestatic, or mixed**, and time to hepatotoxicity usually ranges **from 5 days to 3 months**
- If drug-induced hepatotoxicity is suspected, abnormal LBTs must be interpreted in the context of medication timing and previous LBTs
- Drug-induced liver injury usually resolves within 2–3 months of medication cessation
- LiverTox gives further information about specific drugs with associated hepatotoxicity.

Commonly prescribed drugs in primary care that can cause hepatotoxicity include:

- paracetamol (dose-dependent)
- macrolide antibiotics (dose-independent; e.g. erythromycin)
- nitrofurantoin
- sulfonamides (e.g. co-trimoxazole)
- NSAIDs
- allopurinol
- amiodarone
- anticonvulsants (e.g. carbamazepine, phenytoin, sodium valproate)
- terbinafine
- DMARDS (e.g. methotrexate, azathioprine).

10. Alcohol-related Liver Disease[1,27]

- Liver enzymes offer limited information on the extent of alcohol misuse and development of fibrosis in ALD, but elevated levels may help to facilitate behaviour change in patients
- ALD is not limited to those who are dependent on alcohol, and is affected by other factors; **the risk of liver disease doubles for any given alcohol intake if BMI >35 kg/m²**
- NICE NG50 (updated 2023) recommends screening for cirrhosis using transient elastography in people who have been drinking at harmful levels for several months (>50 units weekly in men and >35 units weekly in women) and in all people diagnosed with ALD
  - note: NG50 reminds us **not** to use routine LBTs to exclude cirrhosis
- The BSG advises considering referral to alcohol services for all adults with ALD with evidence of alcohol dependency, as defined by an AUDIT score >19; referral may also be warranted if AUDIT score is 8–19 and drinking persists, particularly if GGT >100 U/l.

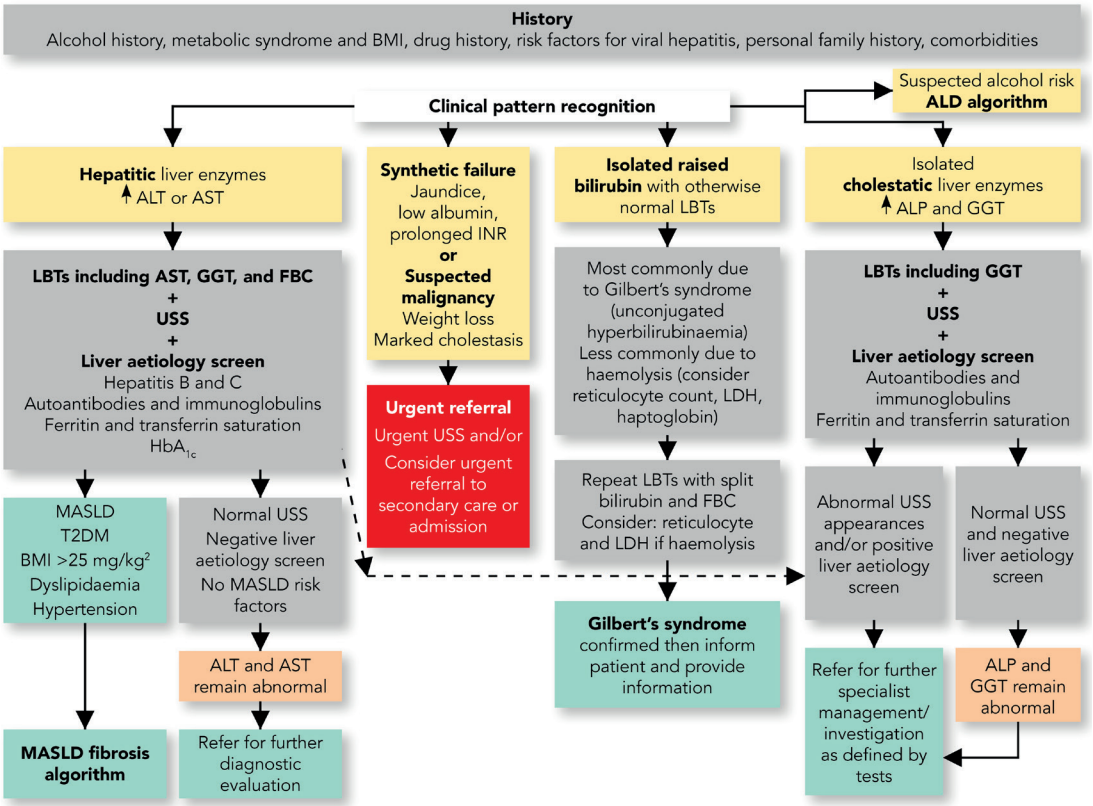

Figure 1: BSG Algorithm—Response to Abnormal Liver Blood Tests[1]

Source: Newsome P, Cramb R, Davison S et al. Guidelines on the management of abnormal liver blood tests. *Gut* 2018; **67** (1): 6–19. Reproduced under the terms of the CC BY 4.0 license.

This figure details the initial response to abnormal LBTs. Boxes in yellow indicate the initial evaluation of the clinical presentation. Patients with marked derangement of LBTs, synthetic failure, and/or suspicious clinical symptoms/signs should be considered for urgent referral to secondary care (red box). For the remainder, a clinical history alongside evaluation of the pattern of LBT derangement will determine choice of pathway and is shown in the grey boxes. A grey box indicates all the tests that should be requested at that stage rather than a hierarchy within it. The presence of metabolic syndrome criteria should be sought to support a diagnosis of MASLD. For children, the [guideline] text should be consulted for modification of recommendation. Areas of diagnostic uncertainty are indicated in orange boxes and the decision for repeat testing or referral to secondary care will be influenced by the magnitude of enzyme elevation and clinical context. Green boxes indicate final/definitive outcomes for users of the pathway.

* Abnormal USS may well include extrahepatic biliary obstruction due to malignancy, which should result in urgent referral.

Useful Resources for Patients, Carers, and Healthcare Professionals

- British Liver Trust—**www.britishlivertrust.org.uk**
- RCGP liver disease toolkit—**bit.ly/4798nAH**
- LiverTox website—**bit.ly/3MpF1UP**
- Alcohol Change UK—**alcoholchange.org.uk**
- AUDIT-C and AUDIT calculators.

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