

Information for Clinicians

Clinical Biochemistry Department

Liver Function Tests in Adults – a guide for GPs

Introduction

Abnormal liver function tests (LFT's) are frequently detected in asymptomatic patients. This may be due to the nature of liver disease often being "silent" and due to the increased frequency of testing now automated assays are readily available. In the ALFIE study 25% of the over 16 year old population had an LFT test over a 10 year period and 1/3 of those were abnormal. Whilst it is often thought that LFTs will return to normal, after 1 month 84% remain elevated and after 2 years 75% (1). Therefore new guidelines suggest clinical evaluation after the initial result (2).

It is important to understand that 2.5% of the normal population will fall outside the upper limit of the reference range as part of the normal statistical distribution of results and test results may fluctuate as a physiological response. However, severe liver disease may be present with little or no liver function abnormality so the level or duration of elevation should not determine the significance but the result should be viewed within the context of trend, past medical and drug history and current symptoms.

Epidemiology

The prevalence of chronic liver disease is increasing in the UK and there is a resultant increase in associated mortality. This is due to an increase in alcohol excess and also the obesity epidemic.

The most common cause of abnormal LFTs in the asymptomatic population is Non Alcoholic Fatty Liver Disease (NAFLD) and this is thought to be present in up to 20% of the UK population. However, in the obese population the incidence can increase to 70%. NAFLD can progress to NASH (Non-alcoholic steatohepatitis) in about 20-30% of cases which can be associated with cirrhosis and hepatocellular carcinoma in approximately 5%. It is a treatable condition like many of the causes of chronic liver disease therefore it is important that LFTs are managed appropriately. Only 5% of those with abnormal liver tests will have a specific condition detected by further investigations but it is important to manage fatty liver proactively in the community.

Other causes of chronic liver disease are hepatitis B/C/D/E, Primary Biliary Cholangitis, Primary Sclerosing Cholangitis, Autoimmune hepatitis, Haemochromatosis, Wilsons disease (usually only presents before the age of 45), and Alpha-1-antitrypsin deficiency.

Management of patients with abnormal liver function tests

Most need further investigations unless there is a high suspicion of a transient process (2). Just repeating the initial liver panel is not recommended, investigating the cause of the liver dysfunction is advised. Three algorithms are included below to support decision making.

Patients need to have a careful evaluation including history, assessment of comorbidities, risk factors and medications.

Those at higher risk of liver disease are:

- Lifestyle (IVDA, Sex workers/promiscuous individuals)
- Prisoners
- Migrants from high prevalence areas of viral hepatitis
- Travel
- Those with other autoimmune conditions
- Those with Inflammatory bowel disease
- Those with a family history of Haemochromatosis, Wilsons or Alpha-1-Antitrypsin disease.
- Those taking hepatotoxic medications (most common cited as carbamazepine, methyl dopa, minocycline, macrolide antibiotics, nitrofurantoin, statins, sulfonamides, terbinafine, chlorpromazine and methotrexate)

Patterns of Liver Function Tests

Predominantly hepatic (ALT and AST most markedly elevated tests)

- An isolated raised ALT is can be transient due to an intercurrent illness such as a viral infection or an intervention (results should normalise after a few weeks if this is the case)
- Other causes of a hepatic picture are viral Hepatitis, NAFLD, Autoimmune hepatitis or Alcohol related liver disease and due to hepatotoxic medications
- AST:ALT ratio >1 can signify a higher risk of fibrosis or cirrhosis
- ALT (and more so AST) can also come from muscle so consider performing a CK if no other cause apparent

Cholestatic (Alkaline phosphatase (ALP) increased significantly more than ALT)

- ALP is an enzyme found in high amounts in the liver and bones; smaller amounts are found in the kidneys, intestine and placenta
- Raised ALP can occur in patients with biliary pathology so if suspicion of malignancy, marked cholestasis or unintentional weight loss refer urgently
- In an asymptomatic individual, it may be necessary to determine the source of raised ALP; repeating LFT's with a gamma glutamyl transferase (GGT) and vitamin D will usually differentiate between liver and bone

- Liver or biliary pathology is supported by a raised GGT. Common biliary causes include biliary obstruction (stones, strictures, neoplasms), Primary Biliary Cholangitis, Primary Sclerosing Cholangitis, hepatic congestion and medications.
- When a bone source is suspected (normal GGT) a vitamin D should be tested as it is the most common cause of non-liver raised ALP; a thorough review of systems should take place and appropriate further investigation of any symptoms. In an asymptomatic individual:
 - ❖ ensure vitamin D replete
 - ❖ ensure results are available for adjusted calcium, thyroid function, renal profile and full blood count
 - ❖ be aware that Paget's disease is increasing in incidence over the age of 55
 - ❖ if ALP<200U/L monitor in 3 months
 - ❖ if ALP >200U/L consider need for further imaging but not always required
 - ❖ telephone the duty biochemist if further advice required 01225 824050
- ALP isoenzymes are reserved for where there is diagnostic uncertainty but are less sensitive at ALP levels below 200U/L

Isolated bilirubin rise

- Most commonly is due to Gilbert's syndrome (5-8% of the population)
- This is a benign condition and does not need referral
- The rise in bilirubin should be unconjugated and direct bilirubin should be less than 30% of the total bilirubin
- Haemolysis and structural liver abnormalities should be ruled out

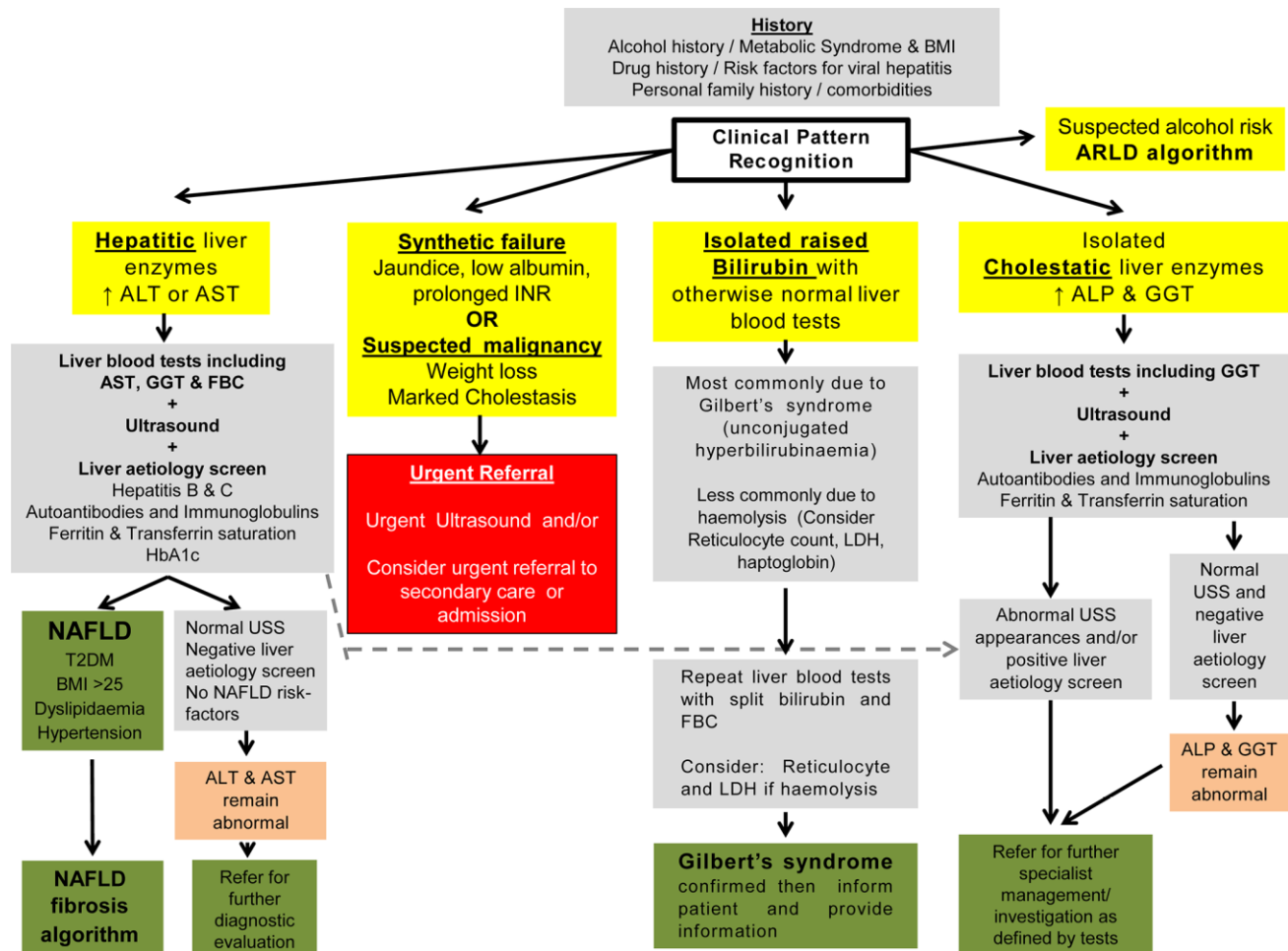


Figure 1 Response to abnormal liver blood tests.

Isolated ALT and Non-invasive liver screen:

There is a chronic liver disease panel available on ICE called a “non-invasive liver screen” that includes LFT and AST, INR, FBC, Ferritin, TTG, Immunoglobulins, Autoimmune profile and cholesterol plus Hepatitis B surface Antigen and anti-Hepatitis B core antibody, Hepatitis C antibodies and Hepatitis A antibodies.

Only those patients with a family history or signs of Wilson’s disease or Alpha-1 antitrypsin deficiency require screening for these.

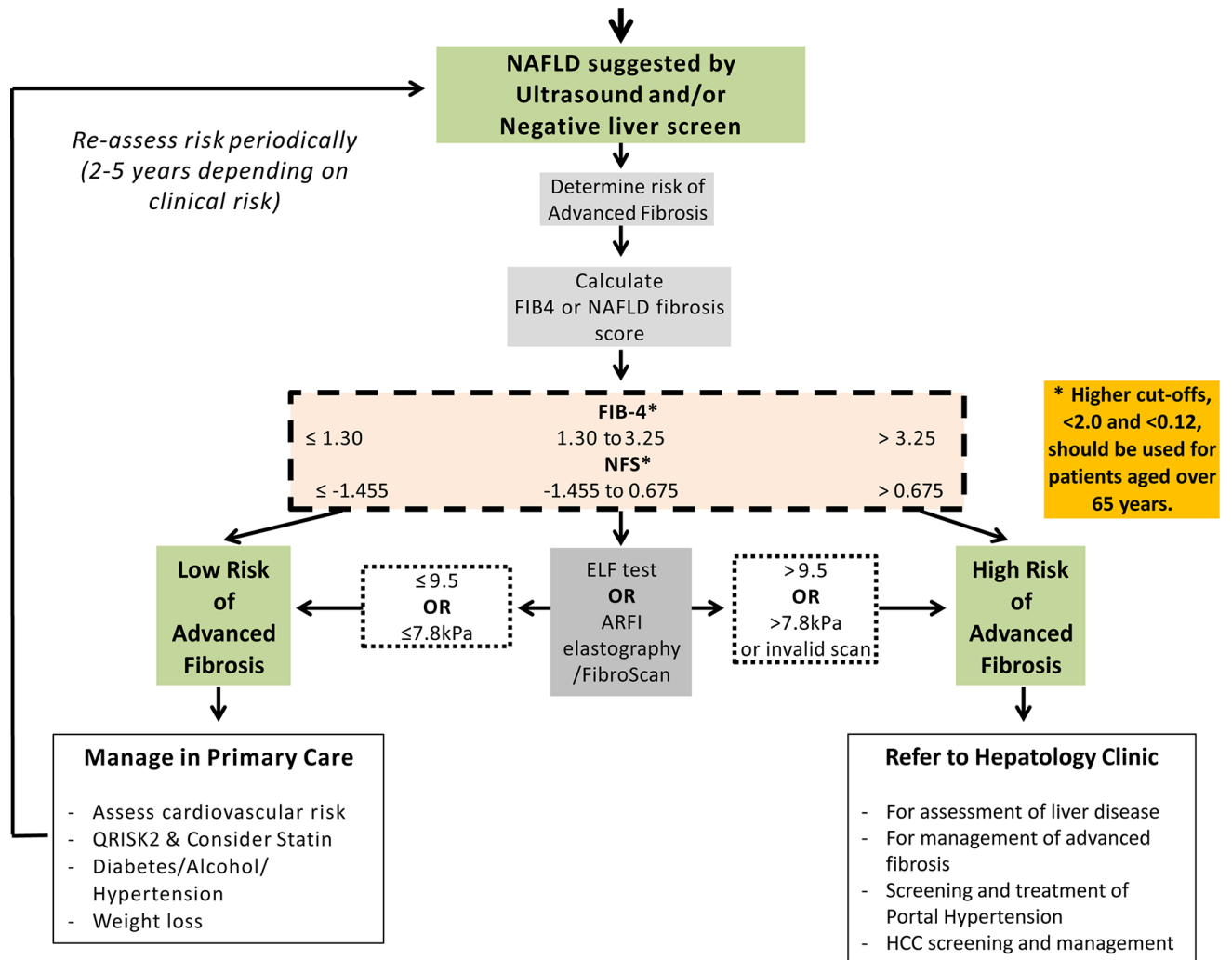


Figure 2 Non-alcoholic fatty liver fibrosis algorithm. For those patients with NAFLD or liver disease of unknown aetiology, the next step is to determine the likelihood of liver fibrosis.

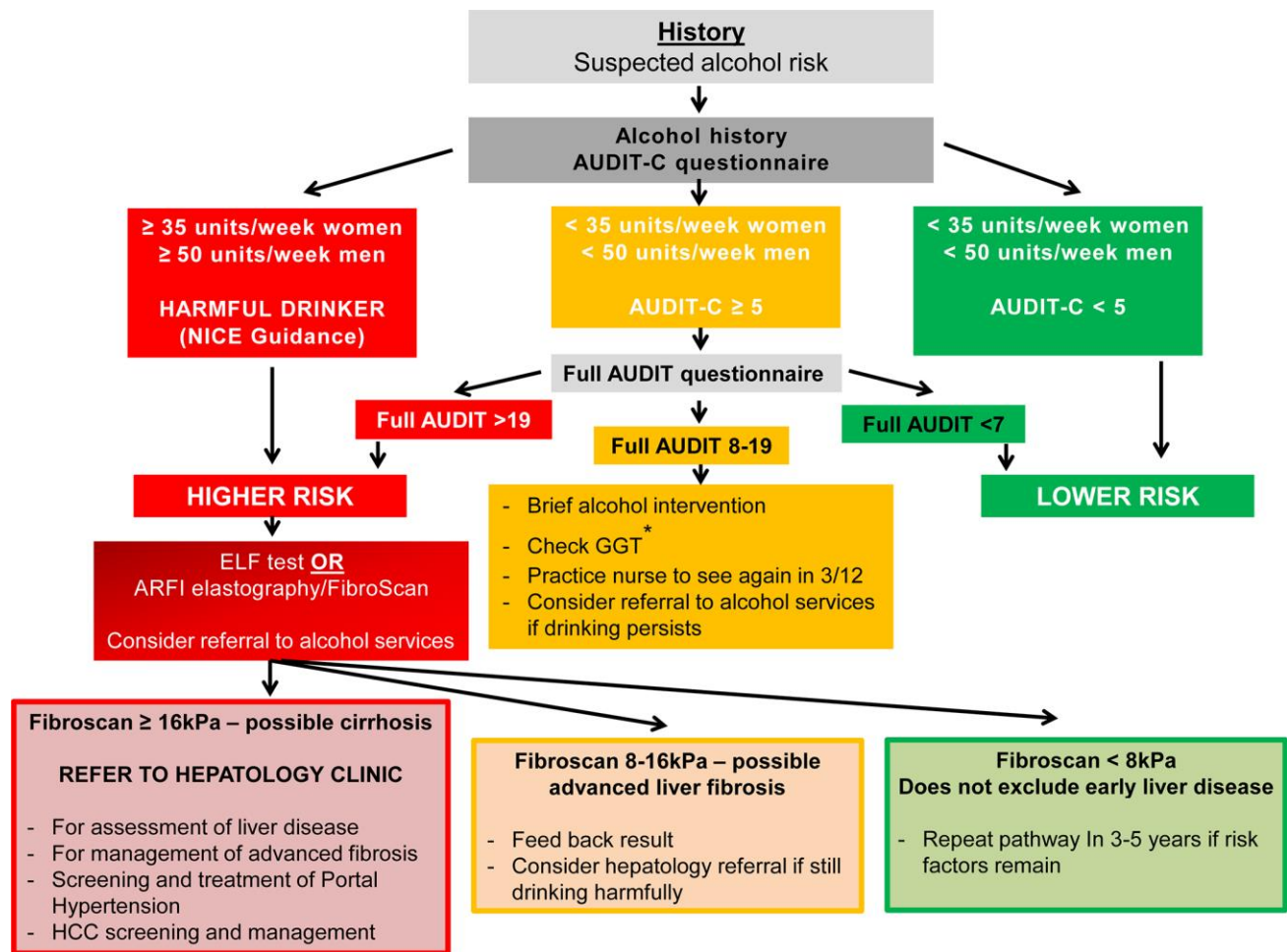


Figure 3 Alcohol-related liver disease algorithm. In patients in whom alcohol is suspected to be the main injurious factor, the extent of consumption influences early decision-making.

References

1. Donnan PT, McLernon D, Dillon JF, et al. Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE). *Health Technol Assess* 2009;13:1–134.
2. Guidelines on the management of abnormal liver tests. Philip N Newsome *Gut* November 9, 2017
3. Interpreting an isolated raised alkaline phosphatase level in an asymptomatic patient. Shipman. *BMJ* 2013;346:f976