

What is the Real Function of the Liver 'Function' Tests?

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ABSTRACT

Liver enzymes are commonly used in the evaluation of patients with a range of diseases. Classically they are used to give information on whether a patient's primary disorder is hepatitic or cholestatic in origin. However, knowledge of enzyme ratios and pattern recognition allow much more information to be derived from these simple tests.

This paper offers an insight to generalists on how to extract greater information from these tests in order to improve the investigation and management of liver disease.

INTRODUCTION

Liver Function Tests (LFTs) are one of the most commonly-requested screening blood tests. Whether for the investigation of suspected liver disease, monitoring of disease activity, or simply as 'routine' blood analysis, these tests can provide a host of information on a range of disease processes. The title 'liver function tests' is, however, somewhat of a misnomer; only the bilirubin and albumin given in this panel offer information regarding the functional capacity of the liver. At a basic level the evaluation of liver enzymes simply gives information as to whether a patient's primary disorder is hepatitic or cholestatic in origin. However, much more may be interpreted from these assays with knowledge of enzyme ratios and pattern recognition. This paper offers an insight to generalists of how to yield greater information from this simple test.

ENZYME PHYSIOLOGY

A basic understanding of each enzyme is fundamental to interpreting the meaning of their titre. The basic pathophysiology of each is delineated in table 1.

PATTERNS AND USE OF HEPATIC ENZYMES IN PRACTICE

The liver enzyme profile should always be assessed in conjunction with a thorough history and clinical examination. Despite these invaluable tools, there are many occasions when doubt persists over an underlying diagnosis. For example, does an overweight diabetic who enjoys a few glasses of wine at the weekend have alcoholic or non-alcoholic fatty liver disease? In such circumstances the absolute liver enzyme levels and ratios may point the clinician in the right direction. Furthermore, the pattern of enzymes will assist, not only with differentiating between cholestasis and hepatitis, but will aid diagnosis when there is a mixed picture.

UNDERSTANDING CHOLESTASIS: MECHANICAL OR MEDICAL?

Mechanical biliary obstruction results in raised levels of ALP,

GGT and often bilirubin. ALP will usually be markedly raised in comparison with ALT. Levels of ALP and GGT elevated in similar proportions signify a hepatobiliary source. Otherwise alternative causes of single enzyme elevation should be considered.

When due to choledocholithiasis, the levels of ALP and GGT tend to fluctuate (in comparison to stricture forming disease) and may be associated with a normal bilirubin.¹ Enzyme titres tend to rise and fall gradually and may be preceded by a peaked rise in liver transaminases which can reach >1000 IU.²

The AST:ALT ratio (De Ritis ratio) may assist in differentiating the site of biliary obstruction. When associated with a cholestatic picture, an AST:ALT ratio of <1.5 suggests an extrahepatic obstruction. In such circumstances the ALT titre is frequently considerably higher than AST. An AST:ALT ratio of >1.5 indicates intrahepatic (mechanical or medical) cholestasis is more likely.³

Drug-induced cholestasis usually presents with a preferential rise in ALP, rather than GGT, or with an ALT:ALP ratio of <2. Causative drugs would include: antibiotics, immunosuppressants, tricyclic antidepressants and angiotensin converting enzyme inhibitors.⁴

In Primary Biliary Cirrhosis, an autoimmune condition of the intrahepatic biliary ducts, the level of ALP is generally greater than that of GGT. In this case, transaminases are invariably normal or only minimally elevated. Both the European Association for Study of the Liver (EASL) and the American Association for Study of Liver Disease (AASLD) recommend that a diagnosis of PBC may be based on cholestatic liver enzyme levels in conjunction with the demonstration of anti-mitochondrial antibodies.^{5,6} If either of these two criteria is absent, imaging and liver biopsy become necessary.

AST and ALP are used within some scoring criteria to monitor the effects of ursodeoxycholic acid in the management of PBC. A recent study has shown that a raised AST:ALT ratio outperforms other non-histological indicators of cirrhosis in PBC, but still only achieves a low sensitivity and a specificity of 65-79%.⁷

As with PBC, liver enzymes play a key role in the diagnosis of Primary Sclerosing Cholangitis (PSC). When other causes of liver disease have been excluded, a raised GGT, and particularly ALP, are diagnostic when associated with

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TABLE 1:

Pathophysiology of liver associated enzymes

<p>Alanine Transaminase (ALT):</p> <ul style="list-style-type: none"> Produced in hepatocytes Very specific marker of hepatocellular injury Relatively low concentrations in other tissues so more specific than AST Levels fluctuate during the day Rise may occur with the use of certain drugs or during periods of strenuous exercise.
<p>Aspartate Transaminase (AST):</p> <ul style="list-style-type: none"> Occurs in two isoenzymes, indistinguishable on standard AST assays. The mitochondrial isoenzyme is produced in hepatocytes and reacts to membrane stresses in a similar way to ALT. The cytosolic isoenzyme is present in skeletal muscle, heart muscle and kidney tissue. Caution must be exercised in its use to evaluate hepatocellular damage. Usually rises in conjunction with ALT to indicate hepatocellular injury: a hepatic picture.
<p>Alkaline Phosphatase (ALP):</p> <ul style="list-style-type: none"> A group of isoenzymes that act to dephosphorylate a variety of molecules throughout the body. Produced in the membranes of cells lining bile ducts and canaliculi. Released in response to the accumulation of bile salts or cholestasis. Non-hepatic production in the kidney, intestine, leukocytes, placenta and bone. Physiological rise in pregnancy or in growing children. Pathological rise in Paget's disease, renal disease and with bone metastases.
<p>Gamma-glutamyl transferase (GGT):</p> <ul style="list-style-type: none"> Present in liver, kidney, pancreas and intestine. It is found in the microsomes of hepatocytes and biliary epithelial cells. Elevation of GGT in association with a rise in ALP is highly suggestive of a biliary tract obstruction and is known as a cholestatic picture. Subject to rise with hepatic enzyme induction due to chronic alcohol use or drugs such as rifampicin and phenytoin.

typical Endoscopic Retrograde Cholangiopancreatography (ERCP) or Magnetic Resonance Cholangiopancreatography (MRCP) findings. This can preclude the need for a liver biopsy.⁵ Transaminase levels may be raised up to 2-3 times normal values in PSC but this is not diagnostic. AST is a component of the Mayo Risk Score, which calculates the risk of disease progression in PSC. A high Mayo Risk Score, and an AST:ALT ratio of >1.12 have been shown to be indicators of risk for the development of oesophageal varices.⁸ In PSC, as with other liver diseases, there are suggestions that an AST:ALT ratio of >1 indicates the development of cirrhosis.⁹

Alcohol induces hepatic enzymes leading to a raised GGT with an ALP which may be normal, or disproportionately lower than the GGT. A GGT:ALP ratio >2.5 in association with jaundice suggests alcohol as a cause of liver disease.^{10,11} The presence of a macrocytosis, due to either an associated dietary deficiency of folate or B12, or due to a direct suppression of bone marrow by alcohol is supportive of the diagnosis of alcoholic liver disease. A raised GGT is not diagnostic of alcohol abuse, with research showing it remains high in former drinkers as well as current drinkers. In men, the highest levels of GGT occur in those who drink daily. In women, binge drinkers and those consuming alcohol without food will have especially high levels. The level of GGT is loosely dose dependant, with those in the top two quartiles of alcohol intake having the highest titres.¹² A diagnostic algorithm for "cholestatic" liver enzymes is shown in figure 1.

THE FATTY LIVER AND THE AST:ALT RATIO

During the last few decades there has been research into using the AST:ALT ratio in the differentiation of alcoholic liver disease (ALD) from other forms of liver disease, particularly the Non-alcoholic Fatty Liver Disease (NAFLD) spectrum. Both AST and ALT enzymes require pyridoxal-5'-phosphate (vitamin B6) to function properly. Its absence in nutritionally-deficient heavy-drinkers has a much larger effect on the production of ALT than that of AST, causing the AST:ALT ratio to rise.^{13,14} A normal AST:ALT ratio should be <1. In patients with alcoholic liver disease, the AST:ALT ratio is >1 in 92% of patients, and >2 in 70%.¹³ AST:ALT scores >2 are, therefore, strongly suggestive of alcoholic liver disease and scores <1 more suggestive of NAFLD/NASH.¹⁵ High ratios reflect the severity of hepatitis or underlying liver disease rather than high alcohol consumption. This means that most heavy-drinkers will not have an AST:ALT ratio >1 as they have not yet developed ALD.^{16,17} No studies have shown that the AST:ALT ratio, either alone or in combination with other factors or models, has the necessary sensitivity or specificity to definitively differentiate between ALD and NAFLD, but it acts as a useful clinical guide when considering the need for liver biopsy. It should also be noted that liver transaminases are known to worsen in response to cessation of alcohol intake (often coinciding with admission to hospital) and that ALT has also been shown to rise simply from admission to hospital, even in patients with no liver disease.^{18,19}

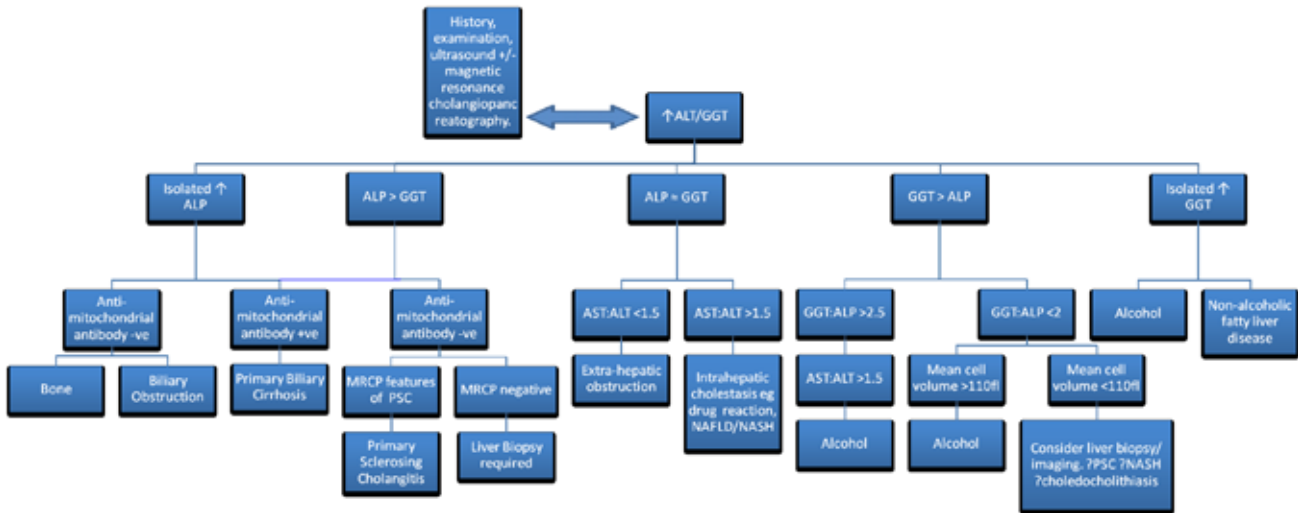


Fig 1. Diagnostic algorithm for cholestatic enzyme pictures

Although models exist which exclude cirrhosis in NAFLD with reasonable accuracy, liver enzyme analysis has so far failed to provide a sensitive and specific enough means to make a diagnosis.²⁰ At present liver biopsy cannot be avoided in cases where confirmation of NASH or cirrhosis is necessary.^{21;22}

The role of liver enzyme analysis in NAFLD lies in both the early identification and modification of associated metabolic risk factors such as hypertension, hyperlipidaemia and glycaemic control and in risk stratification for the future.

A scoring system developed at the Mayo clinic uses age, hyperglycemia, body mass index, platelet count, albumin, and AST:ALT ratio to accurately differentiate patients with advanced fibrosis in NAFLD.²³ The AST:ALT ratio becomes considerably less specific in determining underlying disease with the development of cirrhosis, as the ratio will increase across a broad range of diseases. It is, however, useful in NAFLD patients known not to be abusing alcohol as a score of >1 should lead to the consideration that the patient may have developed cirrhosis.^{24;25}

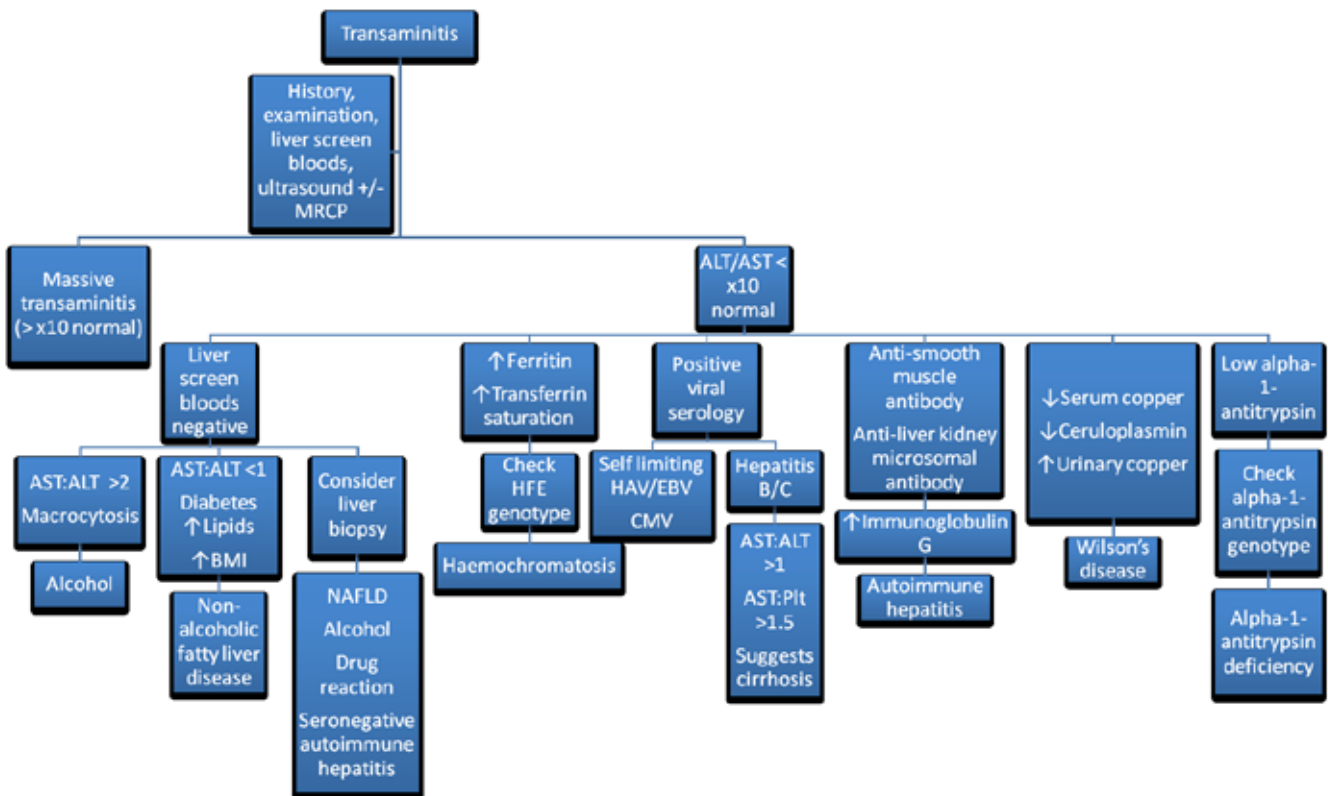


Fig 2: Diagnostic algorithm for transaminitis

TABLE 2:
Summary of enzymes patterns in liver disease

Summary Table

	ALP	AST	ALT	GGT	Other Features
Cholestasis	↑↑	↑	↑	↑↑	AST:ALT <1.5 suggests extrahepatic AST:ALT >1.5 suggests intrahepatic
Primary Biliary Cirrhosis	↑↑↑	↑/N	↑/N	↑↑	Raised AST:ALT may indicate cirrhosis
Primary Sclerosing Cholangitis	↑↑	↑/N	↑/N	↑↑	AST:ALT >1 may indicate cirrhosis AST:ALT >1.12 indicates risk of oesophageal varices
Alcoholic liver disease	↑/N	↑	↑	↑↑	AST:ALT > 2
NAFLD/NASH	↑/N	↑	↑	↑	AST:ALT <1 unless cirrhosis present
Wilson's disease	↑	↑↑	↑↑	↑	ALP:bilirubin < 4 AST:ALT > 2.2
Hepatitis B/C	↑	↑↑/N	↑↑/N	↑	AST:ALT >1 indicates cirrhosis AST:platelet >1.5 indicates at least moderate fibrosis Enzymes may all be normal
Autoimmune hepatitis	↑	↑↑	↑↑	↑	Persistently high transaminases indicate poor prognosis
Ischaemic injury/ shock liver	↑	↑↑↑	↑↑↑	↑	
Toxic injury	↑	↑↑↑	↑↑↑	↑	

USING ENZYME RATIOS TO PREDICT DISEASE SEVERITY, PROGNOSIS AND MANAGE DISEASE

It is possible to predict the severity of some diseases using liver enzyme ratios. The chronic form of the rare genetic disorder Wilson's disease is characterised by a mild liver enzyme alteration, whether its presentation is hepatic or neurological in nature. A compilation of bilirubin, AST level and prothrombin time help to classify patients by disease severity using the Nazer score, which assists clinicians in determining the appropriate management.²⁶ A recent study indicated that in cases of acute liver failure, using the combination of an ALP:bilirubin ratio <4, along with an AST:ALT ratio of >2.2, Wilson's disease can be diagnosed with 100% sensitivity and specificity. Further studies will be required to evaluate whether this is reliable enough to negate the need for other diagnostic tests prior to liver transplantation.²⁷

In patients with chronic viral hepatitis B or C, cirrhosis has been demonstrated in those with a normal ALT, which limits its use as a diagnostic tool.^{28,29} The main use of ALT in viral hepatitis is therefore in the monitoring of anti-viral treatment.³⁰ Again, an AST:ALT ratio >1 suggests cirrhosis. This is a poorly sensitive test, but its specificity for cirrhosis reaches over 99% when used in conjunction with a platelet count of <150,000/mm³ and other variables, such as prothrombin time.³¹ A derivative of this, the AST:platelet ratio index (APRI), is another useful indicator of cirrhosis

in hepatitis patients, but is limited by its poor sensitivity.³² An APRI >1.5 has been used to signify moderate to severe fibrosis. It is hoped that with further analysis of these scores, along with new biomarkers and imaging techniques aimed at detecting liver fibrosis, a significant number of patients may avoid the need for liver biopsy, which at present remains the gold standard for diagnosis and estimating prognosis in liver disease.

The clinical presentation of Autoimmune Hepatitis is widely variable but may include jaundice, pruritis and either gradual or rapid onset of liver failure. The International Autoimmune Hepatitis Group guidelines state that a predominant serum transaminase abnormality, in association with a GGT of >1.5 times normal, is suggestive of AIH when combined with autoantibody and histological data, and when all other causes have been excluded.³³ Liver enzymes are not useful for accurately predicting the presence or absence of cirrhosis.³⁴ However, a sustained rise in transaminases >10 fold, or >5 fold in association with a twofold rise in GGT, is indicative of a higher mortality and the need for aggressive treatment.³⁵ Liver enzymes are used in the initiation of treatment, monitoring of response, remission and relapse, and in aiding decisions to discontinue treatment when enzymes have normalised for a prolonged period. Persistently high transaminases, despite treatment, indicate a high risk of disease progression to cirrhosis and hepatocellular carcinoma, as well as a higher risk of disease recurrence following liver

transplantation.^{36,37} A guide to the diagnostic work-up of a patient with transaminitis is shown in figure 2.

MASSIVE TRANSAMINITIS - WHAT INFORMATION CAN ABSOLUTE ENZYME LEVELS GIVE US?

Liver transaminases are often only mildly increased in ALD, rising to no higher than 6 or 7 times normal in 98% of cases.¹³ Absolute AST and ALT levels of more than 500 are virtually never due to alcohol alone. In the acute setting, the most likely causes for massive transaminitis are paracetamol overdose (the most common cause of acute liver failure in western society), hypoxic liver injury and acute viral hepatitis. This provides diagnostic difficulty where clearly the consequences and treatment of transient infection by a virus, such as Epstein Barr, differs greatly from that of paracetamol overdose and hypoxic injury. In cases of acute liver injury, the measured titre of transaminases offers no prognostic information and is a poor predictor of liver failure in comparison to other indices, such as prothrombin time, renal function and acid base balance. It is important to consider these diagnoses in the broader differential of those patients with a chronic rise in transaminases who present with an acute deterioration.

The majority of patients presenting with extremely high transaminase levels (>75 times normal) have suffered either

ischaemic or toxic injury and a careful history will often elucidate the likely cause. In a typical hepatocyte, zone 3 of the acinus is located centrally, far away from the arterial oxygen supply of the portal triads. It is also the area of the hepatocyte highest in AST concentration. An ischaemic or toxic insult to this zone, which is already starved of oxygen, causes AST levels to peak earlier than ALT, often at extremely high levels. In difficult cases where the enzyme rise is not quite so high, transaminases and bilirubin levels usually normalise quickly in cases of ischaemic and toxic injury, but tend to persist for longer in other causes of acute hepatitis. It is important to note that normalisation of liver enzymes can occur with both the resolution of liver injury as well as with total necrosis. Regular monitoring of the patient's clinical status and markers of hepatic functional capacity are therefore vital. Hypoxic liver injury is often associated with an increased level of LDH, a marker of general ischaemic damage.³⁸

The disease process in adults with hepatitis A is usually self-limiting with ALT levels settling within 4-12 weeks. Serial levels are recommended to ensure resolution. In viral hepatitis, liver transaminase titres range from normal to several thousand (in cases of fulminant hepatitis). They tend to fluctuate over time and occur at lower levels in cases of hepatitis C when compared to A or B.²⁸ The diagnostic considerations for massive transaminitis are shown in figure 3.

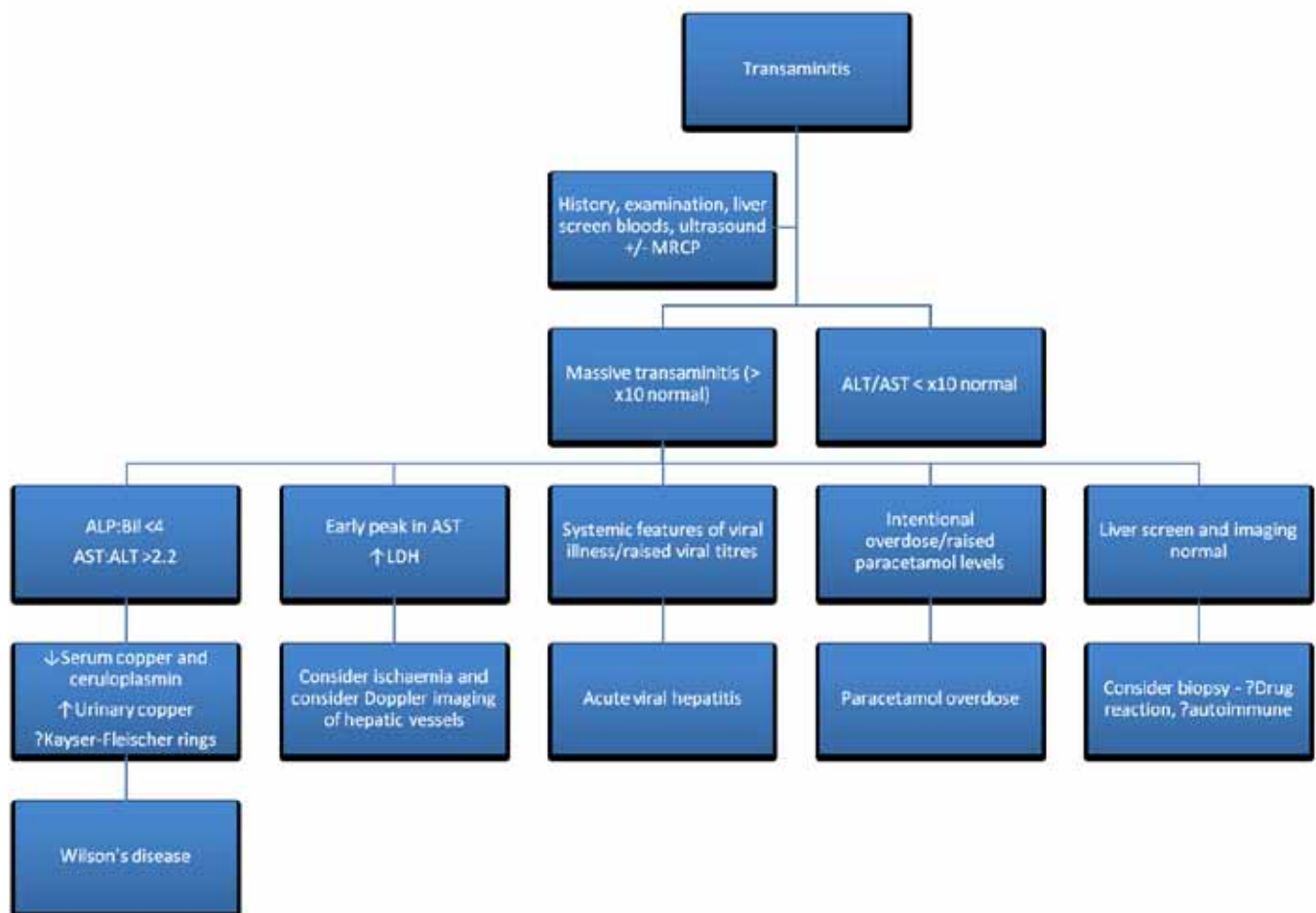


Fig 3. Diagnostic algorithm for massive transaminitis

THE FUTURE OF ENZYME ANALYSIS – OBESITY AND CARDIAC RISK STRATIFICATION

NAFLD accounts for the largest proportion of mild alterations in liver enzymes in western society, with up to 30% of the American population being affected.³⁹ The spectrum encompasses the reasonably benign, simple fatty liver disease (NAFLD), through to Non-alcoholic Steatohepatitis (NASH), which can progress in time to cirrhosis and liver failure. Classical presentation is with a mild elevation in ALT up to 5 times normal, with associated rises in GGT and occasionally ALP. This gives a non-specific picture similar to that of alcoholic liver disease.³⁹ GGT and ALP are of little diagnostic value in NASH; relying on ALT to make a diagnosis is also problematic.⁴⁰ A normal ALT has been demonstrated in patients with disease at all ends of the spectrum, and two thirds of patients with NASH, at any given time, will have a normal ALT.^{21,39} Studies differ in opinion as to whether a high ALT level infers any adverse prognostic value. However, scoring systems such as the Mayo NAFLD/NASH score have shown some correlation.²³

NAFLD falls under the ever-broadening umbrella of conditions associated with the metabolic syndrome. There are many studies linking ALT and GGT levels in particular to the later development of diabetes, hypertension, hyperlipidaemia and coronary atherothrombosis. Indeed, in patients where other causes of liver disease have been excluded, ALT levels are associated with a raised Framingham risk score.⁴¹ Features of the metabolic syndrome may, therefore, point to a diagnosis, but NAFLD also occurs in their absence.³⁸ GGT has been shown to be elevated in only 52% of alcoholic patients in the absence of severe liver disease, but can be raised in up to 50% of patients with NAFLD.^{42,43} This limits its use diagnostically as it is neither sensitive nor specific for alcohol misuse, despite common misconceptions.

CONCLUSION

Knowledge of how to correctly analyse liver enzymes is essential in the diagnosis, monitoring and treatment of liver disease. Although a variety of laboratory and imaging investigations are readily available to aid in this process, an enhanced knowledge of liver enzyme patterns can help prevent unnecessary investigations and expedite interventions, such as liver biopsy, when required. Future research may further define the role of liver enzymes in diagnostic algorithms, or in triggering the need for further investigation of disease by complex biomarkers and new imaging modalities. The relationship of liver enzyme abnormalities in patients with features of the metabolic syndrome is yet to be fully understood, and may provide insight into a condition set to affect many over the coming years.

The authors have no conflict of interest.

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