Review Article

The De Ritis Ratio: The Test of Time

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Abstract
De Ritis described the ratio between the serum levels of aspartate transaminase (AST) and alanine transaminase (ALT) almost 50 years ago. While initially described as a characteristic of acute viral hepatitis where ALT was usually higher than AST, other authors have subsequently found it useful in alcoholic hepatitis, where AST is usually higher than ALT. These interpretations are far too simplistic however as acute viral hepatitis can have AST greater than ALT, and this can be a sign of fulminant disease, while alcoholic hepatitis can have ALT greater than AST when several days have elapsed since alcohol exposure. The ratio therefore represents the time course and aggressiveness of disease that would be predicted from the relatively short half-life of AST (18 h) compared to ALT (36 h). In chronic viral illnesses such as chronic viral hepatitis and chronic alcoholism as well as non-alcoholic fatty liver disease, an elevated AST/ALT ratio is predictive of long terms complications including fibrosis and cirrhosis. There are methodological issues, particularly whether or not pyridoxal phosphate is used in the transaminase assays, and although this can have specific effects when patient samples are deficient in this vitamin, these method differences generally have mild effects on the usefulness of the assays or the ratio. Ideally laboratories should be using pyridoxal phosphate supplemented assays in alcoholic, elderly and cancer patients who may be pyridoxine deplete. Ideally all laboratories reporting abnormal ALT should also report AST and calculate the De Ritis ratio because it provides useful diagnostic and prognostic information.

Introduction

The ratio of the serum activities of AST and ALT was first described by Fernando De Ritis in 1957[1] and has been known ever since as the De Ritis ratio. ALT and AST are commonly requested blood tests for liver disease. They are part of the commonly requested 'Liver Function Test' (LFT) panel, but rather than assessing functions of the liver, the release of ALT and AST from liver cells to the bloodstream represents hepatocellular damage or death. These enzymes are normally released at a constant rate with their usual levels in health representing the equilibrium between the normal turnover of hepatocytes due to programmed cell death (apoptosis) and the clearance of the enzymes from plasma.

ALT is only present in the hepatocyte cytoplasm whereas AST is present in both the hepatocyte cytoplasm and mitochondria. Cytosolic AST (cAST) and mitochondrial AST (mAST) are true isoenzymes and are immunologically distinct. mAST is the more prevalent isoenzyme with approximately 80% of total AST activity in human liver contributed by mAST.[2]

The functions of both these transaminases represent important metabolic links between carbohydrate and protein metabolism. ALT is involved in the 'glucose-alanine cycle' and interchanges alanine and pyruvate and can regenerate glucose consumed by muscle in the same way that lactate dehydrogenase interchanges lactate and pyruvate in the 'Cori cycle' for regeneration of glucose from lactate in anaerobic metabolism (see Figure 1).

AST is even more vital for aerobic glycolysis by allowing the NADH that has been generated in the cytoplasm to be effectively relocated within the mitochondria through the shuffling of malate (as well as α-ketoglutarate, aspartate and glutamate). While these transaminase reactions are particularly important in the liver and muscle, they are important in all cells with a high metabolc activity and Table 1 lists their relative activities.

With the hepatic proportion of AST/ALT of 2.5:1, we might expect that hepatocyte turnover should always result in a much higher amount of AST in serum compared to ALT. However, because AST is removed from serum by the liver sinusoids[4] twice as quickly ($t_{½}$=18 h) compared to ALT

Table 1. Relative activity of transaminases in human tissues.*

	AST Activity	ALT Activity	AST/ALT Ratio	Weight (kg)	AST Total	ALT Total
Liver	7,100	2,850	2.5	1.5	10,650	4,275
Kidney	4,500	1,200	3.8	0.25	1,125	300
Heart	7,800	450	17	0.3	2,340	135
Muscle	5,000	300	17	30	150,000	9,000
Serum	1	1	1.0	3	3	3

*Adapted from King J. Practical Clinical Enzymology, 1965.[3]

($t_{½}$=36 h), the resulting serum levels of AST and ALT are fairly similar in health where the upper reference limits in apparently healthy reference populations are also similar and approximately 30 IU/L to 40 IU/L for both AST and ALT. Furthermore, in health, circulating AST in blood consists mainly of cAST probably due to the process of cytoplasmic leakage believed to be a process of cytoplasmic budding or blebbing. When hepatocellular death is increased beyond the usual 'background' levels, the serum levels of AST compared to ALT will tend to reflect the cellular proportions where AST is over twice as prevalent than ALT.[5]

The Use of Enzyme Ratios

De Ritis described the AST/ALT ratio as being a useful indicator of the aetiology of hepatitis (e.g. acute viral hepatitis)[1] and his work was confirmed and extended by Wroblewski.[6] Over the following decades, subsequent studies using improved transaminase methods continued to confirm the original work.[7-9]

Other enzyme ratios have also been suggested to have similar utility for identification of viral hepatitis such as the ratio of the sum of serum AST+ALT activities divided by the serum

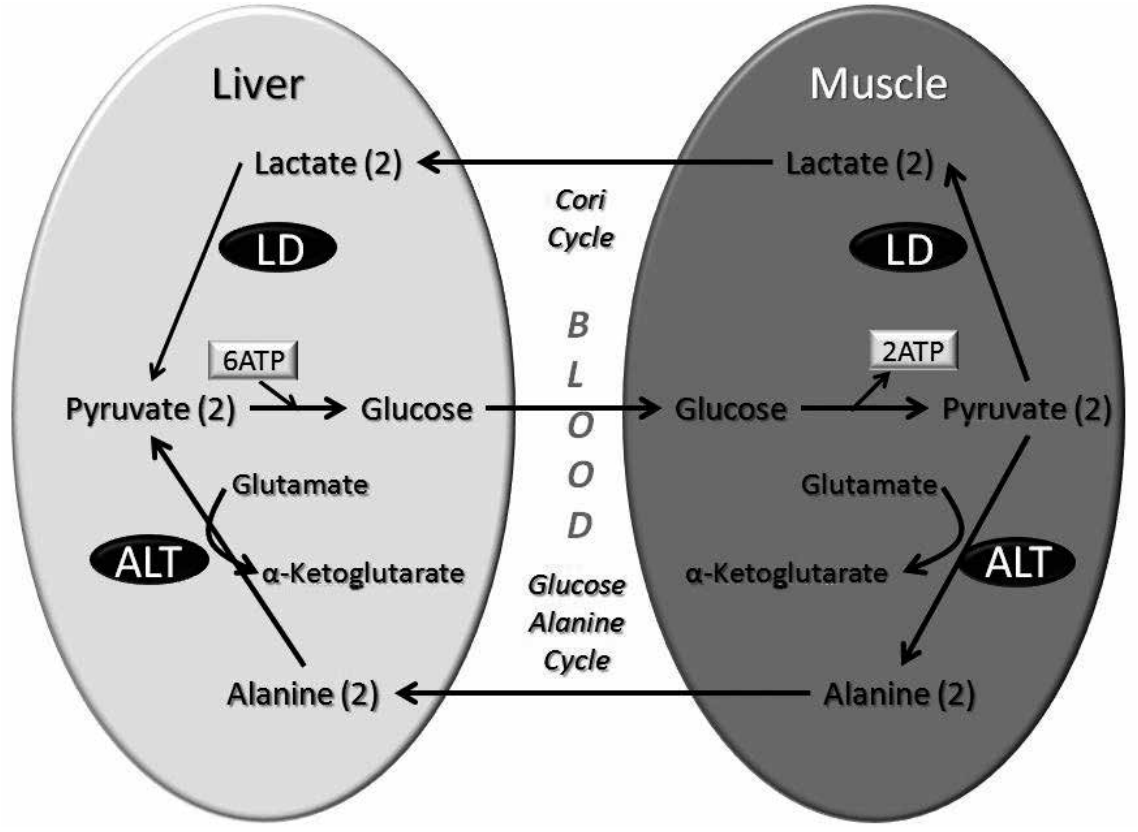

Figure 1. The role of ALT in the glucose-alanine cycle between muscle to liver.

glutamate dehydrogenase activity (GDH) as proposed by Schmidt and Schmidt,[10,11] and the ratio of GDH to ALT as proposed by Forster *et al*,[12] which is considered to be less reliable.[13] Aronsen *et al*. found that the ratio of ALT to alkaline phosphatase (ALP) activity was better than the individual enzymes but not as good as the ALT to gamma glutamyl transpeptidase (GGT) activity in its ability to differentiate between viral hepatitis and obstructive jaundice.[14] The same group also proposed a quotient combining all three enzymes (ALT, GGT and ALP) as a screening test for liver tumours,[15] however it is not ALT but GGT that is required to enable liver enzyme ratios to become selective for cholestatic liver disease whereas ALP may be also increased by bone disease.[16] Despite all these subsequent proposals, the only enzyme ratio that has stood the test of time and is still widely used is the De Ritis ratio.[17]

Measurement of Serum Transaminases

The clinical measurement of serum transaminase activity was first described by Karmen *et al*. in 1954,[18] only three years before De Ritis published on the ratio.[1] The measurement of serum transaminase activity is relatively new compared to other serum enzymes such as ALP (1930)[19] and acid phosphatase (1936).[20]

Serum contains considerably more immunologically active than catalytically active transaminase enzyme[21] and the correlation between the serum concentration of AST protein and AST activity is generally poor.[22] One important reason that transaminases may be present but be enzymatically inactive is that both AST and ALT require the cofactor pyridoxal phosphate, or vitamin B6 (B6). The International Federation of Clinical Chemistry (IFCC) recommends that B6 is added to the reagents for both ALT[23] and AST[24] estimation rather than relying on the concentration of B6 in the patient's serum. This has been debated however with the Japanese Society of Clinical Chemistry (JSCC) recommending that AST and ALT be measured without addition of B6.[25] The omission of B6 from the JSCC method will cause small changes in the AST/ALT ratio.[26] Currently, according to participant information from proficiency testing, most laboratories in Australasia are using the 'modified IFCC method' which has no B6 added. The most likely reason for laboratories selecting non-B6 supplemented transaminase methods is economical rather than technical or clinical.

The addition of B6 into transaminase reagents generally causes a small increase in the serum AST activity, and to a lesser degree ALT, in healthy persons or patients with liver disease.[27] This relative stimulation of AST compared to ALT in chronic liver diseases is typically small resulting in the

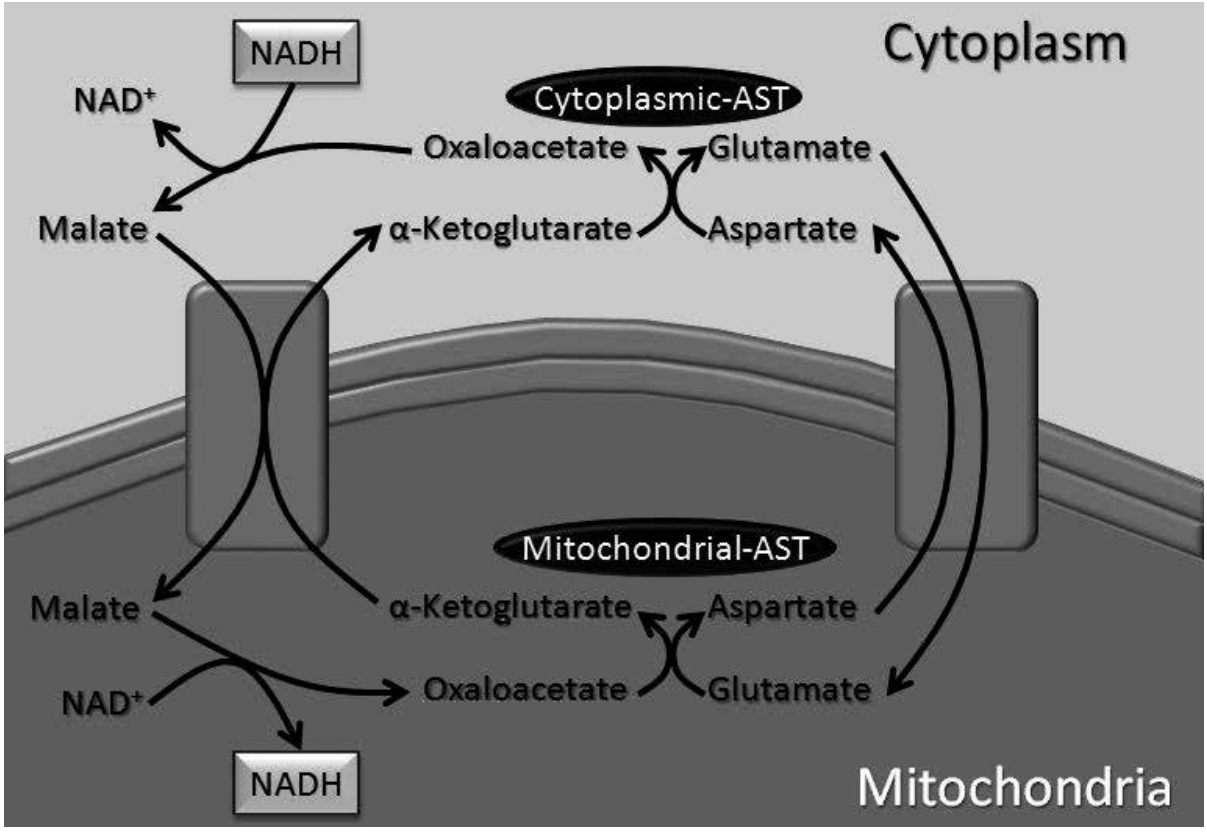

Figure 2. The role of AST in the cytoplasmic-mitochondrial 'malate shuttle'.

diagnostic performance of AST, ALT and their ratio not being significantly improved by the addition of B6.[28-30] Nevertheless, the effect of B6 addition on AST and ALT activities varies markedly from one patient to another[31] and while there may be a small general effect, there may be specific circumstances that argue for the addition of B6.

Alcoholics often have malnutrition, including B6 deficiency, which would translate to decreased transaminase activities.[32] The addition of B6 may therefore be of particular importance for patients with alcoholic hepatitis where low serum B6 levels may give falsely low transaminases levels. A higher AST/ALT ratio has been described in alcoholism (qv) which may be influenced by low B6 levels.[33,34] However others have shown that correction of B6 deficiency does not significantly alter the high AST/ALT ratio often seen in alcoholic hepatitis.[35]

Patients being treated for malignancy may also have low B6 levels and underestimated transaminase levels, so using supplemented assays in these patients has been suggested.[36] Elderly patients may also be at increased risk of nutritional deficiencies and the addition of B6 generally increases AST and ALT levels in the elderly.[37]

Isolated Elevation of AST

In liver disease, where AST is markedly elevated but ALT only mildly elevated, B6 deficiency may be sufficient to normalise the mild elevation of ALT, but not enough to normalise the marked elevation of AST. Otherwise an isolated elevation of AST values suggests a non-hepatic source of AST which often occurs artefactually due to release of AST from blood cells such as occurs in sample haemolysis. While isolated elevation of AST could also theoretically be due to a reduction in AST clearance,[38] in practice an *in vivo* isolated elevation of AST is usually due to injury to non-liver cells, particularly cells that contain mitochondria, and therefore is especially indicative of rhabdomyolysis.

Rhabdomyolysis

Release of muscular AST (and to a much lesser extent muscular ALT) can occur with exercise leading to increased serum transaminases.[39,40] More severe muscle damage or rhabdomyolysis will cause larger elevations of serum AST (and to a lesser extent ALT), however creatine kinase (CK) is the serum enzyme of choice in estimating the degree of rhabdomyolysis, because the levels of CK in muscle are an order of magnitude higher than the transaminases.[41]

Because both CK ($t_{½}$=12 h) and AST ($t_{½}$=18 h) decline rapidly, and ALT ($t_{½}$=36 h) declines relatively slowly,[42] studies have shown that the AST/ALT ratio, which is high in acute skeletal muscle injury, can fall towards 1:1 after a few days due to the faster decline in AST.[43,44] In chronic muscle injury such as polymyositis, the ALT is much the same as the AST[45] and this is consistent with the expected faster clearance of AST compared to ALT.[46]

The persistence of elevated ALT following rhabdomyloysis may also result in the misdiagnosis of hepatitis, such as when hepatitis is attributed to the hepatic effects of anabolic steroids[47] rather than the more obvious association of these substances with skeletal muscle dysfunction. Elevated serum ALT levels in the absence of other evidence of liver disease should lead to consideration of chronic or resolving muscle injury.[48]

Acute Viral Hepatitis

While it is clearly recognised that serum levels of both serum ALT and AST are elevated several fold in 'acute' viral hepatitis (e.g. hepatitis A and E), De Ritis was the first to describe that the ALT is usually higher than the AST with the AST/ALT ratio usually well below 1.0, and typically in the range 0.5 to 0.7.[49-54] It is important to note that the diagnosis of acute viral hepatitis today (when serology and PCR can clearly diagnose a viral cause) is very different to that question 60 years ago. Nevertheless, even today, when transaminases are elevated several fold, a low De Ritis ratio still provides an important clue to aetiology of acute hepatitis.

Investigators have however noted that acute viral hepatitis can occasionally cause a high AST/ALT ratio of up to 2.0, however these are atypical cases representing fulminant hepatitis where there is often a very poor prognosis. This supports the explanation that the reason that AST/ALT ratio in 'acute' viral hepatitis is <1.0 is because the condition is usually resolving when testing occurs. If acute viral hepatitis was not resolving, the AST/ALT ratio will not fall and AST/ALT ratios of 2.0 or greater reflect immediate release of the typical cellular proportions and a potentially fulminant course of acute viral hepatitis. We have recently shown that when ALT is between 200 and 500 U/L and the De Ritis ratio is over 1.5, there is a forty-fold likelihood that the transaminase levels will be over 1000 U/L in a day or two.[55] The 95% confidence limits for the AST/ALT ratio in acute viral hepatitis survivors was 0.3-0.6, while in non survivors the AST/ALT ratio was 1.2-2.3[56]. The De Ritis ratio therefore reflects the time course of acute viral hepatitis and is generally a vital clue to the patient's prognosis.[57]

Chronic Viral Hepatitis

AST/ALT ratios below 1.0 are also typical of chronic viral hepatitis (e.g. hepatitis B and C), however ratios slightly above 1.0 may be found in chronic viral hepatitis but this is particularly when progression to fibrosis and cirrhosis is

present.[58-66] In chronic hepatitis B patients without clinical evidence of cirrhosis, the presence of progressive fibrosis might be predicted using an AST/ALT ratio over 1.0 however the ratio does not go above 2.0 in any patient.[67] In chronic hepatitis C the raised AST/ALT ratio similarly correlates with fibrosis rather than necroinflammatory activity (e.g. Knodel score).[68] The best routine marker of hepatic fibrosis is the De Ritis ratio[69] and although a plethora of better markers have been developed, their use is not routine, other than in specialist settings, and as they are beyond the topic of this review, readers are referred to other recent reviews.[70-73] In patients with hepatitis C, confirmed fibrosis correlates more closely to AST serum activity ($p < 0.002$) than ALT activity ($p < 0.03$)[74] and an increased AST/ALT ratio of over 1.16 is predictive of poor survival as well as correlating with other accepted prognostic scores for liver disease such as the Child-Pugh Test and Model for End Stage Liver Disease (MELD) scores.[75,76] A raised AST/ALT ratio of only slightly above 1 (1.09) is predictive of the progression of chronic viral hepatitis C to cirrhosis.[77]

It is therefore the elevation of AST, rather than ALT, which is predictive of fibrosis and other ratios involving AST, such as the AST to Platelet Ratio Index (APRI)[78] and FIB4 index (which involves the four parameters: AST, ALT, platelets and age) are also more predictive.[79,80] The reason why the AST is more elevated than ALT with progression of fibrosis is uncertain but may be either because of increased production, such as mitochondrial release,[81,82] or a relatively reduced clearance.[83]

Chronic viral hepatitis may also progress to hepatocellular carcinoma, however GGT is the best predictor of this complication, while AST is not predictive in multivariate analysis and ALT is not predictive at all.[84]

Alcoholic Hepatitis

The predominance of AST over ALT in alcohol-related liver disease was first reported by Harinasuta *et al*. in 1967.[85] Many authors have since described AST/ALT ratios greater than 1.5 or greater than 2.0 as being highly suggestive of alcoholic hepatitis.[86-89] Takahashi *et al*. described the ratio in alcoholic liver disease as being as high as 5.090, which is not possible given the cellular proportions of AST and ALT and could be explained by concurrent muscle injury (not unusual in alcoholism) or methodological underestimation of ALT activity.

While many of the studies of the De Ritis ratio in alcoholism are over 25 years old and used outdated formulations of the transaminase assays, more recent papers also quote these ratios of over 1.5 or 2.0 as being strongly suggestive or indicative of alcohol abuse.[91,92] Most patients with alcoholic liver disease will have AST/ALT ratios below 2.0 and many below 1.0, which could conceivably be because some patients could have coexisting alcoholic as well as viral liver disease.[93]

The reasons for a classical 2:1 excess of serum AST activity compared to serum ALT activity in alcoholic hepatitis have been attributed to (i) decreased ALT activity[94] most likely due to B6 depletion in the livers of alcoholics[95] and/or (ii) mitochondrial damage leading to increased release of mAST in serum.[96] This is supported by the finding that normally most of the AST activity in serum is the cytosolic isoenzyme,[97] however in alcoholism mAST is preferentially released.[98] Specificity can be improved using the mAST/AST ratio[99] although sensitivity is decreased.[100,101]

AST/ALT ratios below 1.0 are not uncommon in alcoholic liver disease and in an Australian clinical series of 190 patients with biopsy proven alcoholic cirrhosis one third of patients with cirrhosis exhibited an AST/ALT ratio below 1.0.[102] This may be due to a selection bias in this series which exclude patients with clinical evidence of cirrhosis (e.g. portal hypertension or ascites) but could also be due to the AST/ALT data being recorded in connection with liver biopsies which would generally not be performed during an alcoholic binge and when performed in the following period of days the AST/ALT ratio might have declined because of the relatively shorter half-life of AST (18 h) compared to ALT (36 h). This evidence provides a rationale behind why so many patients who consume high amounts of alcohol display elevated serum aminotransferase levels but do not show a high AST/ALT ratio.[103] One of the main reasons why acute alcoholic hepatitis has a relatively high AST/ALT ratio is because patients are often tested within 24 h of alcohol exposure so the faster clearance of AST ($t_{½}$ =18 h) hasn't had time to take effect. The difference in AST/ALT ratios in viral vs alcoholic liver disease could be partly attributable to disease duration.[104] Therefore a likely explanation of 2:1 AST/ALT ratios in alcoholic hepatitis is the dynamics of serum transaminase release and removal. Many patients with chronic alcohol consumption do not have an AST/ALT ratio above 1 but a high AST/ALT ratio is suggestive of either recent exposure or advanced alcoholic liver disease.[105] The transaminases alone, or in combination, were not helpful in identifying heavy drinking in the NHANES study[106] and others have found that the AST/ALT ratio may fall with increasing consumption.[107]

Another argument that the association of an AST/ALT ratio of over 2.0 with alcoholic cirrhosis is more to do with recent alcohol exposure rather than cirrhosis *per se* is the fact that other causes of liver related death such as primary biliary cirrhosis[108] and primary sclerosing cholangitis[109] are associated with AST/

ALT ratios of above 1.0 but not 2.0. Other non-hepatic alcohol related diseases such as oesophageal cancer also have AST/ALT ratios >2.0 as a risk factor.[110] Furthermore other acute hepatic toxicities, e.g. paracetamol, can have AST/ALT ratios over 2.0.[111] Drug induced hepatitis is typically associated with higher serum AST compared to ALT[112] particularly when the drug is known to damage mitochondria.[113] Some drugs (e.g. cyproterone) have been described as causing a hepatitis with ALT far greater than AST, suggesting that some drugs may effect the release of cytoplasmic enzymes rather than the more prevalent mitochondrial AST enzyme.[114]

Fatty Liver

Almost 10% of Americans in the NHANES survey have elevations of ALT and AST[115] with fatty liver being one of the most common causes.[116,117] Excess alcohol consumption is associated with fatty liver[118,119] with more than three drinks per day causing an elevated ALT and AST in both men and women.[120] Obesity has a greater impact than moderate or heavy alcohol use[121] however when obesity and alcohol are both present they have a multiplicative rather than additive interaction.[122] Paradoxically, obesity is the most likely cause of a raised ALT in men[123] while alcohol was the more likely cause of an elevated ALT in women.

Studies have suggested an integral role of the cytochrome P450 enzyme 'CYP2E1' in the pathogenesis of fatty liver disease due to alcohol and obesity.[124] It is well accepted that both diet-induced obesity and increased alcohol consumption lead to induction of CYP2E1 in the liver, which may explain the synergistic effect of these two factors in causing liver injury or elevated serum ALT and AST.[125]

Non Alcoholic Fatty Liver Diseases (NAFLD)

The prevalence of NAFLD is over 20% in developed countries and nearly 10% in developing nations, making NAFLD the most common liver condition in the world. The pathogenesis of obesity related NAFLD is known to be due to increased *de novo* hepatic lipogenesis, and the hepatic triglyceride production is increasingly thought to be a consequence of increasing sugar intake.[126-131] Dietary 'sugar' is invariably composed of both glucose and fructose regardless of whether the source is cane sugar (sucrose) or high fructose corn syrup (HFCS). Dietary glucose can be stored as muscle and liver glycogen under the control of glucose stimulated insulin secretion. The other 'half' of common sugar (sucrose or HFCS) is fructose which is solely absorbed by the liver. While the liver could convert fructose to glucose, this is not likely to occur when fructose is virtually always ingested with glucose,[132] and obligatory insulin secretion will ensure that hepatic metabolism is directed to convert fructose to triglycerides.[133] There are other causes of NAFLD including viral infection, medications, toxins, surgical procedures, total parenteral nutrition and inborn errors of metabolism.

NAFLD refers to the accumulation of fat in the liver beginning as nonalcoholic fatty liver (NAFL) or simple steatosis, progressing to non-alcoholic steatohepatitis (NASH) and then hepatic fibrosis then cirrhosis.[134] Although the first stage (NAFL) is typically benign, NASH is a potentially serious condition, since as many as 25% of patients with NASH may progress to cirrhosis and experience complications of portal hypertension, liver failure and hepatocellular carcinoma.[135-137]

Fatigue, malaise, and vague right upper quadrant abdominal discomfort can antedate the diagnosis of NASH to medical attention in one third of cases however it is generally asymptomatic and frequently identified incidentally by blood liver function tests or abdominal imaging. Sonographic definitions of NAFLD are required because liver biopsy would rarely be considered. Fatty liver defined by presence of at least two of three findings on abdominal ultrasound including (i) diffusely increased echogenicity (a "bright liver" with greater echogenicity than the kidney), (ii) blurring of hepatic vessels and/or (iii) deep attenuation of ultrasound signal.[138] Clinically evident hepatomegaly occurs in up to 75% of patients with NAFLD and is even greater (85%) when assessed by ultrasound.

Both serum AST and ALT increase with body weight but this is more prominent for ALT rather than AST.[139] Most cases of elevated ALT can be attributed to being overweight (body mass index [BMI] $\geq$ 25 kg/m^2) and obesity (BMI $\geq$ 30 kg/m^2). The five components that compose the metabolic syndrome are central (truncal) obesity, hyperglycaemia, low levels of high-density lipoprotein cholesterol, hypertriglyceridemia, and hypertension. Subjects with specified values for at least three of these components are considered to have metabolic syndrome. All the components of metabolic syndrome are univariate factors associated with elevated ALT. Fasting serum insulin levels and other markers of insulin resistance were associated with elevated ALT independent of BMI and waist circumference. At least 40% of patients with NAFLD fulfil the criteria for metabolic syndrome and subjects with metabolic syndrome are more likely to have elevated ALT.[140,141] Whereas in alcoholic steatohepatitis the De Ritis ratio is always over 1.0,[142] in patients with NASH the AST/ALT ratio is <1 particularly in morbidly obese patients.[143] Not surprisingly, patients with NAFLD have a higher mortality rate than the general population and are at increased risk of developing cardiovascular disease and diabetes in the future.

Increased aminotransferase activities are the most common abnormality reported in patients with NASH, however the

true sensitivity and specificity of liver enzyme elevations for detection of NAFLD is unknown because of the interaction between the relatively small increases in ALT (and AST) but the relatively large differences in laboratory reference limits for these serum enzymes. Reference limits have often been derived using reference populations that include high prevalence of obesity in the mistaken reassurance that excluding alcoholism or known chronic liver disease is a sufficient precaution to ensure the reference population does not have liver dysfunction.

While the elevation in ALT in fatty liver may be assumed to be due to liver damage, evidence of liver damage is not always evident.[144] There is evidence of increased apoptosis, including caspase activation and cytokeratin 18 breakdown. Cytokeratin-18 fragment levels predict NASH and correlate with severity and both AST and ALT correlate with cytokeratin levels with some investigators also suggesting that transaminase transcription may be increased in fatty liver.[145] The AST/ALT ratio however does not correlate with cytokeratin 18.[146]

When ALT is elevated, the AST/ALT ratio has been described as the best routine marker of insulin resistance, in obese and non-obese adults[147] with some authors suggesting that the changes in transaminase levels may precede fatty liver and be caused by increased hepatic transamination of amino acids in the liver especially glutamate.[148] Only ALT levels predict the progression to metabolic syndrome[149,150] while both ALT and AST predict the progression to diabetes.[151]

In NASH, fibrosis may be present with normal transaminase levels[152] particularly if high transaminase reference limits (>>40 IU/L) are used. It is therefore recommended that patients monitored for progressive liver disease should have their AST and ALT compared to appropriate reference limits as well as having the AST/ALT ratio estimated and reported.[153,154] While the AST/ALT ratio is not significantly different across the stages of fibrosis, the ratio may also need to be adjusted for gender.[155] An increased AST to ALT ratio in NASH is associated with the development of cirrhosis.[156,157]

Physiological Determinants of the AST/ALT Ratio

The AST/ALT ratio is typically over 3.0 in a new born infant but should fall by day 5 to below 2.0 and persistent elevation may be due to neonatal asphyxia.[158] The AST/ALT ratio often did not fall below 1.5 in children in the poor-outcome group while it usually decreased below 1.5 in children in the good-outcome group. Calculating the AST/ALT ratio appears to be an easy, early, and reliable prognostic indicator for infants with hepatic disease.[159]

Reference interval studies for AST and ALT have shown that men have higher levels of both of these enzymes. Reference intervals for ALT have been proposed as <30 IU/L for men and <20 IU/L for women.[160] While both AST and ALT are higher in men than women, the AST/ALT ratio is higher in women.[161] In order to accurately use AST/ALT ratios in the assessment of the aetiology or chronicity of liver disease, the patient's gender also should be taken into consideration.[162] The intra-individual variations of both AST (CV_i=13.9%) and ALT (CV_i=20.4%) are relatively large and 30% of patients with a mild increase in transaminase level(s) can be reclassified as 'normal' on repeat testing,[163] however the intraindividual variability of the De Ritis ratio may not necessarily be as large as predicted by the product of the individual variances and further studies are needed in this area.

Table 2. Clinical decision limits that can be applied to the De Ritis ratio. Healthy limits are derived from reference 162.

	De Ritis Ratio Decision Limit			
Condition	**<1.0**	**1.0 to <1.5**	**1.5 to <2.0**	**≥ 2.0**
Healthy	Women (up to 1.7) Men (up to 1.3)		Children	Neonate
Acute Viral Hepatitis	Resolving		Worsening	Fulminant
Alcoholic Hepatitis	Resolving		Alcohol Abuse	Acute Hepatitis
Chronic Liver Disease	Stable	Fibrosis risk		Other Causes
Muscle Disease	Chronic	Resolving		Acute

Conclusion

When medical students are first taught about the clinical value in serum transaminase estimation the name 'De Ritis' is usually mentioned but subsequently enzyme ratios are frequently neglected and possibly despised.[164] Very few laboratory reports include the De Ritis ratio and there are several reasons that could be proposed for its absence. While simple clinical decision limits have been established for the De Ritis ratio (e.g. >2.0 for alcoholic hepatitis or >1.0 for fibrosis/cirrhosis), there aren't any generally accepted reference intervals for the ratio and indeed it is difficult to define 'healthy' limits for the ratio if its main application is when transaminases are abnormal. We have listed the various limits that have been discussed in this review in Table 2.

Many laboratories do not include AST as part of the LFT because it is not a liver specific test. For example, it can also be affected by *in vitro* haemolysis. However in our experience the reason why most laboratories omit AST is economical, which may also be the main reason why laboratories choose non-B6 supplemented transaminase reagents.

We hope that this review provides the evidence that the De Ritis ratio has continued to stand the test of time and remains a useful indicator of liver disease. Its relevance today may be strengthened because of the importance of hepatic diseases such as chronic viral disease and NAFLD. Furthermore serum transaminase estimations are now one of the cheapest laboratory tests available and all laboratory information systems are capable of calculating and comparing simple ratios. Today, patient safety is paramount and practising medicine has also become increasingly litigious, we believe that use of both transaminases and the ratio between them, which has continued to be useful for almost half a century, provides important clinical information which is worth the small additional cost.[165]

Competing Interests: None declared.

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