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Comparative study of transaminase ratio, AST, ALT and GGT in cases of chronic hepatitis

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Abstract
The differential diagnosis between viral hepatitis and other liver diseases (particularly obstructive jaundice) is often difficult on purely clinical grounds. Damage to the liver causes changes in the pattern of the serum enzymes and this has led to the development in recent years of a number of enzyme tests. 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 It is characteristic of viral hepatitis that both levels are greatly increased, but the SGOT/SGPT ratio, normally greater than one, falls considerably below this figure. The AST/ALT ratio is the ratio between the concentrations of the enzymes aspartate transaminase (AST) and alanine transaminase, alanine aminotransferase (ALT) in the blood of a human or animal. It is measured with a blood test and is sometimes useful in medical diagnosis to differentiate between causes of liver damage, or hepatotoxicity. Most causes of liver cell injury are associated with a greater increase in ALT than AST; however, an AST to ALT ratio of 2:1 or greater is suggestive of alcoholic liver disease, particularly in the setting of an elevated gamma-glutamyl transferase. The AST to ALT ratio can also occasionally be elevated in a liver disease pattern in patients with nonalcoholic steatohepatitis, and it is frequently elevated in an alcoholic liver disease pattern in patients with hepatitis C who have developed cirrhosis. In addition, patients with Wilson's disease or cirrhosis due to viral hepatitis may have an AST that is greater than the ALT, though the ratio typically is not greater than two. When the AST is higher than ALT, a muscle source of these enzymes should be considered. For example, muscle inflammation due to dermatomyositis may cause AST>ALT. This is a good reminder that AST and ALT are not good measures of liver function when other sources may increase AST or ALT, because they do not reliably reflect the synthetic ability of the liver, and they may come from tissues other than liver (such as muscle) In a few cases of obstructive jaundice, the serum transaminase picture may initially resemble that in viral hepatitis, but the differential diagnosis can be established by repeating the determinations at intervals. Other enzyme tests, such as determination of alkaline phosphatase and 5'NT, may be used to confirm the biliary obstruction. The present study was undertaken in one hundred patients of hepatitis of sexes ranging 20 to 60 yrs. of age to compare serum levels or alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase & serum bilirubin. Forty of clinically healthy subjects were taken as control group. These were patient's attendants without any evidence of liver disease so as to equilibrate the socioeconomic status and age. The study group patients were either admitted to Rajindra Hospital & GMC, Patiala, or attending the OPD. A detailed clinical examination was carried out in all as per plan mentioned in materials & methods. Diagnosis of these patients was based on clinical findings.

Keywords: hepatitis C virus, disease duration, viral load, inflammation, normal alanine aminotransferase, AST: ALT ratio

1. Introduction
Several markers for high alcohol consumption *per se* have been studied e.g. carbohydrate deficient transferrin (CDT), gamma glutamyl transferase (GGT) and aspartate aminotransferase (AST). Most have fairly low sensitivities and specificities (Conigrave *et al*., 2002) [1]. The use of test combinations significantly improves the information received with single serum enzyme determinations. An elevated serum AST in relation to serum ALT (alanine aminotransferase) has been proposed as an indicator that alcohol has induced organ damage. Thus, when AST/ALT ratio is >1.5, this is considered as highly suggestive that alcohol is the cause of the patient's liver injury (Correia *et al*., 1981; Salaspuro, 1987). However, many patients who doubtless consume high amounts of alcohol and indeed are alcohol-dependent and display elevated serum aminotransferase levels do not show a high AST/ALT ratio. This suggests that additional factors lead to the high AST/ALT ratio seen in some patients. One such factor may be the severity of the liver disease [2]. To test this hypothesis we compared the AST/ALT ratio in three groups of patients with high alcohol consumption: patients hospitalized for treatment of alcohol withdrawal syndromes, patients hospitalized in somatic (medical or surgical) wards for non-liver related causes, (both of which may have contained patients with a mild degree of liver damage) and patients hospitalized with complications from alcoholic liver cirrhosis. The level of ALT also guides the urgency and extent of further investigation. A serum ALT level less than 5 times the upper limit of the normal range should be

rechecked before an extensive work-up is undertaken. If elevated ALT levels are confirmed and if they remain persistently elevated, additional work-up is indicated. ALT levels greater than 5 times the upper limit of the normal range suggest a potentially serious, active liver disease process and work-up should be initiated without waiting to confirm the persistence of abnormal ALT. ALT levels greater than 15 times the normal range indicate severe acute liver cell injury and evaluation should be initiated immediately. The differential diagnosis for patients with severe acute liver injury (ALT levels >15 times the normal range) is relatively limited [3]. Acute viral hepatitis (A-E), ischemic hepatitis or other vascular disorders such as acute venous outflow occlusion (Budd-Chiari), or toxin-mediated hepatitis should be considered. Acute autoimmune hepatitis, hepatic lymphoma or acute biliary occlusion may also present with highly elevated ALT activity [4]. The diagnosis may be made upon historical grounds [ischemic episode, risk factors of acquisition of viral hepatitis, medication or hepatotoxin exposure (*e.g.*, isoniazid) or overdose (*e.g.*, acetaminophen)]. Blood testing (hepatitis and autoimmune serologies) may be helpful where applicable, whereas abdominal imaging may be helpful in other settings (*e.g.*, venous outflow obstruction, biliary obstruction or abnormal lymphadenopathy).

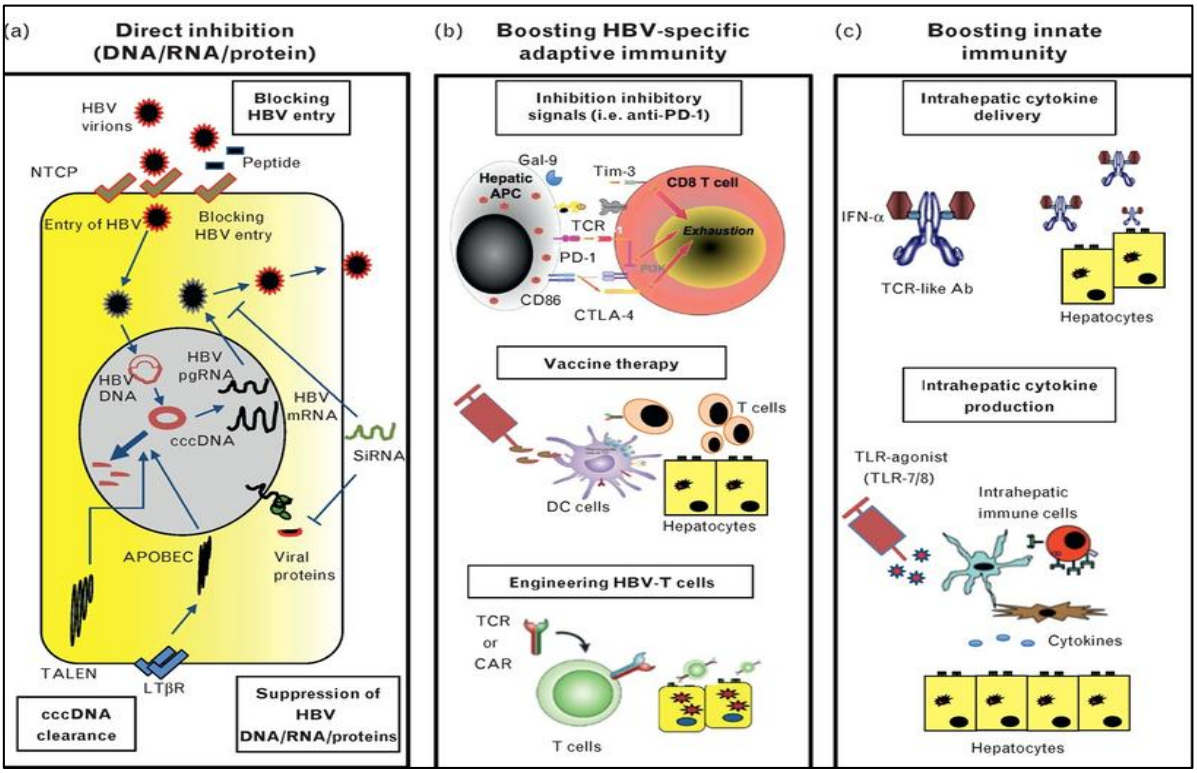

Fig 1: Schematic Representation of New Hepatitis B Virus

2. Materials and Methods

Study sample

A total of 100 patients (50 females, 50 males; mean age: 47.9 ± 13.2 years) with clinically diagnosed hepatitis were studied before the treatment with antiviral drugs. Patients with hemochromatosis, Wilson's disease, autoimmune hepatitis, www.wjgnet.com primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, alpha-1 antitrypsin deficiency, or malignancies were excluded from the present study. None of the subjects was using any medications, including estrogens, amiodarone, steroids, tamoxifen, or herbal supplements. Furthermore we excluded patients with daily alcohol intake exceeding 20 g/d. For control purposes, 100 healthy age- and gender-matched volunteers (56 males, 44 females) were recruited. All controls were judged to be in good health and confirmed as having normal liver by ultrasound. Subjects with a consumption of alcohol > 20 g/d or who were taking any medication were not included in the control group. All subjects underwent physical examination, anthropometric measurements and biochemical screening. A written informed consent was obtained from all participants. Our study was in accordance with the ethical standards for human experimentation and approved by Baba Farid Univ. of Health Sciences, Faridkot.

Laboratory and virology assessment

Blood samples for the evaluation of alanine aminotransferase (ALT), ALT and biochemical parameters were obtained after overnight fasting. Routine biochemical tests were carried out using commercially available kits of Transasia. Ultrasound assessment Liver ultrasound (US) scanning was performed to assess the degree of steatosis. All procedures were performed by the same operator. Liver steatosis was assessed semiquantitatively on a scale of 0 to 3:0, absent; 1, mild; 2, moderate and 3, severe.

Histological analysis

Histological analysis of liver biopsies was performed under conscious sedation using a 16-gauge Klatskin needle in the Pathology section. The hepatitis activity index (HAI), designed by Knodell and Desmet [15, 16], and was used to grade the severity of the necroinflammatory process and fibrosis. Statistical analysis Variables are presented as counts and percentages, mean ± SD. Correlations among the study variables were assessed by means of the Pearson's correlation coefficients.

Table 1: Values of serum aminotransferases and bilirubin in Group W (patients with withdrawal symptoms), Group S (patients with somatic diagnoses in addition to a diagnosis of alcohol abuse or dependence) and Group C (patients with alcoholic cirrhosis)

	W	S	C	Significance of differences
AST (ULN = 0.7 µkat/l)	1.2 ± 1.4*(0.1–12.0)	4.0 ± 13.9*(0.2–120)	3.4 ± 6.0*(0.21–42)	*P < 0.001 for W vs S P = 0.02 for W vs C
ALT (ULN = 0.7 µkat/l)	1.2 ± 1.7 (0.2–20.0)	1.7 ± 2.5 (0.18–18.5)	1.8 ± 2.9 (0.23–15)	NS
AST/ALT	1.0 ± 0.6*(0.3–6.7)	1.7 ± 1.0*(0.4–6.5)	2.6 ± 1.9*(0.03–12.1)	*P < 0.0001 for W vs S, W vs C and S vs C
Bilirubin (ULN = 21 µmol/l)	16.2 ± 11.0*(3–117)	18.1 ± 14.7*(1.8–79)	95.9 ± 133*(2.8–710)	*P < 0.0001 for W vs C and S vs C

3. Results

Steatosis was present in 22 (61%) of the 36 HCV infected patients, of whom 8 (22%) had grade 1, 11 (30%) grade 2, and 3 (9%) grade 3. The histological findings of the study participants are shown in Table 1. In bivariate correlation analyses, ALT levels correlated with duration of HCV infection (r = 0.46, P < 0.01, Figure), HCV-RNA (r = -0.33, P < 0.05, Figure), and the HAI (r = 0.44, P < 0.01, Figure). Among the components of, ALT concentrations were significantly associated with periportal bridging/necrosis (r = 0.50, P < 0.01) and fibrosis (r = 0.37, P < 0.05). Multivariate analysis Multivariate stepwise regression analysis was used to identify independent predictors of ALT levels in our patients with HCV infection. Serum ALT activity was considered as the dependent variable. Alanine aminotransferase levels were significantly raised in viral hepatitis, alcoholic hepatitis and chronic hepatitis patients. The levels were being 737 ±152, 173 ± 89,123±61 respectively as compared to normal control (23.6 ± 15.7). Aspartate aminotransferase levels were significantly raised in viral hepatitis, alcoholic hepatitis and chronic hepatitis patients. The levels being 641 ± 205, 408 ±211, and 183 ± 62.9 respectively as compared to normal control (29.7 ± 21). Alkaline phosphatase levels were significantly raised in viral hepatitis, alcoholic hepatitis and chronic hepatitis patients. The levels being 208±54.4, 180.33±33.29, and 116±11.98 respectively as compared to normal control (74.8 ± 19.6). Gamma glutamyle transpeptidase levels were significantly raised in viral hepatitis, alcoholic hepatitis and chronic hepatitis patients. The levels being 183±47.6, 149 ± 59.6 and 98.7 ± 25.5 respectively as compared to normal control (23.6 ± 11.6). All variables listed in Table 2 were entered into the multivariate model as independent variables.

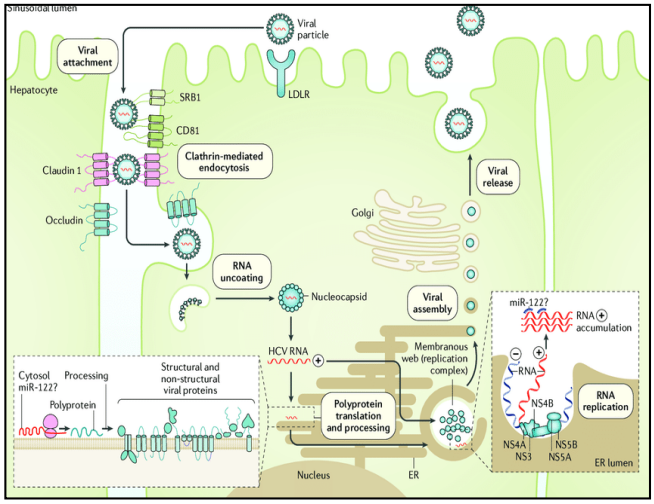

Fig 2: HCV Life Cycle

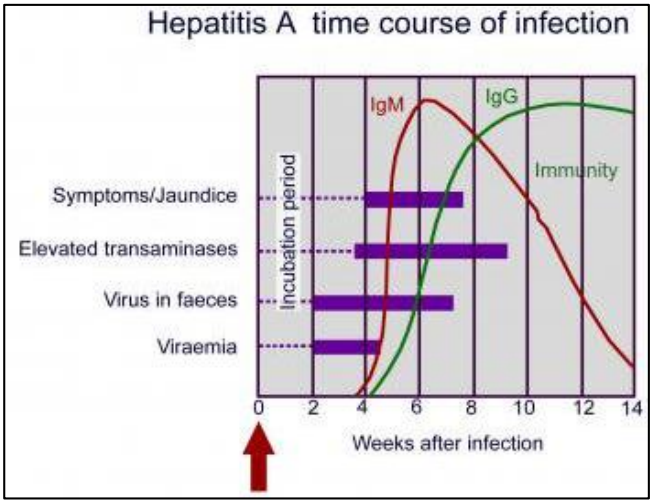

Fig 3: Hepatitis a Type Time Course of Infection

4. Discussion

This study provides insights into the correlates of ALT levels in the setting of patients with HCV infection. We found that, in our sample of patients, serum ALT levels were significantly and independently correlated with periportal bridging/necrosis, viral load and duration of HCV infection [5]. The liver associated enzymes, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) are measures of liver homeostasis [11]. Serum amino transferases such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) indicate the concentration of hepatic intracellular enzymes that have leaked into the circulation. These are the markers for hepatocellular injury [12]. The aminotransferases (transaminases) are sensitive indicators of liver cell injury and are most helpful in recognized acute hepatocellular diseases such as hepatitis. The pattern of the aminotransferase elevation can be helpful diagnostically. In most acute hepatocellular disorders, the ALT is higher than or equal to the AST. An AST: ALT ratio>2:1 is suggestive while a ratio >3:1 is highly suggestive of alcoholic liver disease. The AST in alcoholic liver disease is rarely >300 U/L and the ALT is often normal. A low level of ALT in the serum is due to an alcohol induced deficiency of pyridoxal phosphate [16]. In this study, Table 3 shows the AST: ALT ratios 1 for normal, 0.65(2 for ALD group, which similar to reported by several other studies conducted earlier [18], and 1.24 in cirrhosis, > 1 but < 2 also documented by Nyblom *et al* [19] and others [7]. This helps to differentiate ALD from other liver diseases. In this study AST, ALT ALP, GGT levels were significantly raised in viral hepatitis, alcoholic liver disease and cirrhosis patients as compared to control. In viral hepatitis AST, ALT and ALP Levels were significantly high as compared to alcoholic liver disease and cirrhosis. Moreover alcoholic liver disease patients have more AST, ALT and ALP as compared to cirrhosis. In viral hepatitis ALT is greater than AST. The peak levels of Transminases have been reported to vary from 400- 4000 IU/l or more [20]. In alcoholic liver disease AS

activity has been reported to be greater than ALT and usually does not exceed 300 IU/L. AST/ALT ratio is greater than 2 because of existing mitochondrial damage [20, 21]. This study also confirms that in cirrhosis AST and ALT levels are normal or slightly elevated. If the etiological factors were present or with active alcohol abuse increases AST and ALT levels [2]. The ALP activity has been reported by various workers, minimally increased usually upto 200 -300 U/L in viral hepatitis and in alcoholic liver disease ALP usually up to 300 U/L.In cirrhosis ALP is either normal or slightly elevated [20], increased in serum ALP is associated with liver disease is caused by intra or extra hepatic cholestatis and some destruction of hepatic cell membrane9. Elevation of ALP is observed in patients who have some form of extra hepatic and intra hepatic bile duct obstruction. Any mechanism that impaired excretion of ALP in bile will result in regurgitation of enzyme into circulation via the hepatic sinusoid [8]. The increased ALP present in the patients with disease closely resembles the ALP that can be extracted from liver. The increased cholestatis stimulates the synthesis of ALP by the bile ductules cell providing more ALP which ultimately enters the bloods, the amphillic nature of bile salts facilitates the release of ALP from its membranes bound site and entry into blood [12]. In Viral hepatitis GGT levels were significantly low as compared to cirrhosis and high as compared to alcoholic hepatitis and chronic hepatitis, moreover GGT levels are high in case cirrhosis than alcoholic liver disease. GGT present in the cell membranes of hepatobiliary system, it is an extremely sensitive enzyme to identify cholestatis disease both intra and extra hepatic. In viral hepatitis in the absence of cholestasis, it increases upto 5 times and in the presence of cholestatsis it increases upto 10 times of upper limits [13]. In the alcoholic liver disease it is 8-20 times the upper limits and persistence elevation of GGT may be an indicator if Cirrhosis [4]. In our study we observed the increasing pattern of GGT value in different folds among patients of Viral Hepatitis, Alcoholic hepatitis and chronic hepatitis respectively. Growing evidence has suggested that up to 25% of patients with chronic hepatitis C virus infection have persistently normal aminotransferase levels (10% to 40%, according to different studies) [11, 12, 13]. The normal range for ALT level was set in the 1950 s and has changed little since then. However, several recent studies have questioned whether previously established reference values to define normal ALT range are really accurate. Under these circumstances, it has been repeatedly suggested that the limits of normal ALT activity should be revised [4]. In most countries, the cutoff value for ALT is defined as twice the upper limit of the normal range of healthy individuals [27]. The normal ALT activity for men and women is < 23 IU/L and < 18 IU/L, respectively [7].

Table 2: Showing number of patients with abnormal values of different tests

	Total Bilirubin (>0.8.1mg %)	Total Proteins 6.6-8.7 gm%	Albumi3.5-(5.5gm %)	AST(5-15 IU/l)	ALT(40-60 IU/l)	GGT (30-50 IU/l))
No. of patients normal range	53 (43.9)	35 (32)	30 (18)	36 (34.8)	61 (46.9)	65 (43.8)
No. of patients abnormal range	47 (59.0)	65 (65.8)	70(20)	64(57.9)	39(60.9)	35 (69.9)

Magnitude of AST: ALT Ratio

The magnitude of AST and ALT elevations vary depending on the cause of the hepatocellular injury [16-19]. While values may vary between individuals, the following are typical AST and ALT patterns relating to the "upper limit of normal" (ULN) [5, 6, 7, 8].

- Alcoholic fatty liver disease: AST > 8 times the ULN; ALT > 5 times the ULN
- Nonalcoholic fatty liver disease: AST and ALT > 4 times the ULN
- Acute viral hepatitis or toxin-related hepatitis with jaundice: AST and ALT > 25 times the ULN
- Ischemic hepato Pathy (ischemic hepatitis, shock liver): AST and ALT > 50 times the ULN (in addition the lactate dehydrogenase is often markedly elevated)
- Chronic hepatitis C virus infection: Wide variability, typically normal to less than twice the ULN, rarely more than 10 times the ULN
- Chronic hepatitis B virus infection: Levels fluctuate; the AST and ALT may be normal, though most patients have mild to moderate elevations (approximately twice the ULN); with exacerbations, levels are more than 10 times the ULN

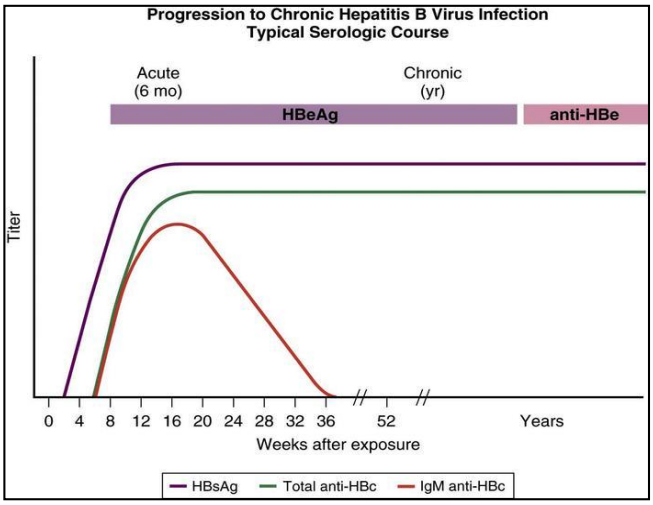

Fig 4: Typical Serological Course in Chronic Hepatitis

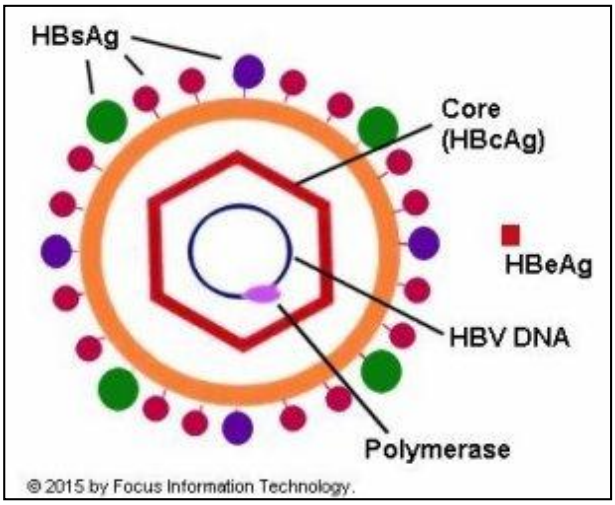

Fig 5: Hepatitis B in Pregnancy

5. Conclusion

ALT is an integral part of the evaluation of patients with liver disease. Its importance as a screening test for liver disease is highlighted by the fact that most patients with common liver diseases such as viral hepatitis B and C and non-alcoholic fatty liver disease have elevated ALT, even though they remain without symptoms to prompt a medical evaluation. Thus, although the interpretation and practical use of ALT analysis may differ across specific liver disease categories, ALT is a sensitive test to detect individuals with liver disease. The importance of ALT activity as an indicator of liver disease has recently been demonstrated in population-based studies which documented a strong association between ALT and subsequent mortality from liver disease. Furthermore, emerging data suggest that ALT has a role as a predictor of mortality independent of liver disease. This association is generally construed to signify NAFLD as a component of the metabolic consequences of insulin resistance, which facilitates the development of atherosclerotic cardiovascular disease. On the other hand the pattern of elevation of aminotransferases, that is, De Ritis ratio is lesser than 1 in viral hepatitis, [2] in ALD. Hence, the level of aminotransferases along with De Ritis ratio can be a useful biochemical test to screen the population of liver disorder, which is noninvasive and cost–effective method in less affluent, undeveloped region where people cannot afford battery of liver function test.

Table 3: Mean Serum levels of AST, ALT, De Ritis ratio in cases & control

Disorder	AST (Mean ± Std.Dev.	ALT	De Ritis ratio
Control	30 ±21.54	30 ±32.0	1 ±.1234.8
ALD	178 ±32.34	80 ±23.98	2 ±.113.6
Viral Hepatitis	78 ±24.23	98 ±34.7	. 9876±.123
NAFLD	121 ±19.42	94 ±23.8	1.2212 ±.1435
Cholestasis	35 ±12.98	24 ±12	1. ±.1896
P Value	0.00	0.011	0.0 ± 0

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