ETIOLOGY OF ELEVATED ALANINE AMINOTRANSFERASE IN A SOUTH INDIAN POPULATION - A COMMUNITY-BASED STUDY

A dissertation submitted in partial fulfillment of the requirements for
DM (Gastroenterology) examination of the
Tamil Nadu Dr. M.G.R. Medical University, Chennai,
to be held in August 2014.

CERTIFICATE

This is to certify that this dissertation entitled **"Etiology of elevated alanine aminotransferase in a south Indian population - a community-based study"** is a bonafide work done by Dr. Ramit Mahajan,Christian Medical College (CMC), Vellore, in partial fulfillment of the rules and regulations for DM Gastroenterology examination of The Tamil Nadu Dr MGR Medical University, to be held in August 2014.

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ETIOLOGY OF ELEVATED ALANINE AMINOTRANSFERASE IN A SOUTH INDIAN POPULATION - A COMMUNITY-BASED STUDY by Ramit Mahajan

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"Appreciation is like looking through a wide –angle lens that lets you see the entire forest, not just the one tree you walked up on."

I bow my head to the almighty God for the strength, endurance and perservance he has granted. I have always felt His presence in the form of my respected teachers while sailing through high and low challenges of my career, thus moving successfully towards my destination and serving the purpose dutifully that I am here for.

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Introduction

INTRODUCTION

Liver diseases are a significant health problem worldwide, leading to considerable morbidity and mortality. Patients with liver diseases require prolonged medical supervision and repeated hospital visits and admissions. The number of deaths due to liver diseases in India reached 208,185 (which accounted for 2.31% of the total deaths) according to the World Health Organisation (WHO) statistics in April 2011(1).

The most common causes of liver disease include alcohol consumption, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, and non alcoholic fatty liver disease (NAFLD). The etiology of liver disease is variable, depending on the geographical areas and populations. Lifestyle changes and epidemics of obesity, diabetes, hypertension, dyslipidemia and ultimately metabolic syndrome have led to an increase in the prevalence of NAFLD in both the developed countries and industrial economies in the Asia Pacific region(2).

The course of liver diseases is long and usually asymptomatic before the development of a late stage disease. During this asymptomatic period, the only markers which may indicate liver damage are liver enzymes, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT). Among the aminotransferases, ALT is a more sensitive indicator of liver cell injury and has been used for almost 60 years for identification of liver diseases(3).

The prevalence and etiology of elevated aminotransferase levels has been studied in blood donors, overweight adolescents and patients with liver disease(4)(5)(6). However such studies are likely to have a selection and referral bias. Population based studies from the US, Italy, Taiwan and China have shown NAFLD to be the commonest cause of elevated ALT and presumed liver injury (7)(8)(9)(10) in these countries. Similar population based studies

are rare in India, but need to be done in different parts of the country in order to assess the potential burden of liver disease in the country.

Review of Literature

REVIEW OF LITERATURE

INTRODUCTION

Liver diseases are among the top ten killer diseases in India. Besides this, liver diseases are associated with lot of morbidity leading to recurrent hospitalizations and prolonged medical attention, leaving the patients physically, mentally, emotionally and financially devastated. The common risk factors for chronic liver disease include non alcoholic fatty liver disease (NAFLD), chronic viral hepatitis and alcohol(8). Other etiologies include autoimmune hepatitis, Wilson's disease, hemochromatosis and vascular diseases of the liver. Knowledge of the cause of liver disease helps predict complications and direct treatment decisions. It also helps to prevent similar diseases in the family by early screening (viral hepatitis B and C) or genetic testing (in Wilson's disease and hemochromatosis).

ALANINE AND ASPARTATE AMINOTRANSFERASES AND LIVER DISEASE IN THE COMMUNITY

Aminotransferases are widely used for screening the presence and assessing the progression of liver diseases. Aspartate aminotransferase (AST) exists in the liver as well as a wide variety of extrahepatic sites (including myocardium, skeletal muscle, kidney, brain, pancreas and blood cells), while alanine aminotransferase (ALT) is localized primarily in the liver, thus, it is more commonly used to detect hepatocyte injury. Both aminotransferases are released into the blood in increasing amounts when the liver cell membrane is damaged. However, there is a poor correlation between the degree of liver-cell damage and the degree of transaminitis.

The normal ranges of ALT and AST were determined as 1–45 U/L and 4–40 U/L respectively in 1950s by Wroblewski *et al* (11). The same has been used in most laboratories

till recently. Several recent studies have highlighted the need to change the upper limit of normal (ULN) as these values were determined in normal healthy medical college students and technicians at that time. They had overlooked the differences between genders and hepatitis C and the metabolic disease such as fatty liver disease were not considered. Many recent studies showed that disease progression was found in chronic hepatitis B and C patients in spite of the normal aminotransferase level (12)(13)(14). Even mild asymptomatic elevations of transaminases can be associated with bridging fibrosis and cirrhosis and should not be ignored(15)(16). High ALT level is associated with higher liver-related mortality and increased overall mortality in both the high risk group and the average risk population(17). Researchers have now proposed that healthy ALT thresholds should be lower than the currently accepted values, and that gender-specific thresholds should be applied. Values of 30 U/L for men and 19 U/L for women have been proposed in Europe by Prati *et al*(18). Ruhl *et al* suggested a new optimal "ULN" of ALT as 29 U/L in men and 22 U/L in women to discriminate persons infected with HCV from those at low risk of liver disease(19). The ULN of ALT among 7403 Asian health check-up participants was studied by Kang *et al* and their value of ULN of ALT was 31 U/L for men, and 23 U/L for women(20).

The normal range of ALT is set at a mean value $\pm$ 2 standard deviation in a group of healthy individuals. Thus mild ALT elevations will be seen in 2.5% of 'normal' individuals. There can also be fluctuation in aminotransferase levels in individual patients. Upon retesting, abnormal ALT levels may turn normal in more than 30 percent of individuals, as was seen in a large, cross-sectional population-based study(21). A normal repeat value may also sometimes reflect a fluctuating biochemical value, as can be seen in diseases such as chronic hepatitis C. Usually, further evaluation is indicated only if the aminotransferases are abnormal on repeated testing. Patients with abnormal liver function tests (LFT) for >6months are considered to have elevated LFT.

The evaluation of etiology of transaminitis starts with a comprehensive history and detailed physical examination. Patients with liver diseases present with nonspecific symptoms (eg, anorexia, weight loss, weakness, fatigue) or signs and symptoms of hepatic decompensation (jaundice, pruritus, signs of upper gastrointestinal bleeding, abdominal distension from ascites, confusion due to hepatic encephalopathy). Physical examination findings may include jaundice, spider angiomata, gynecomastia, ascites, splenomegaly, palmar erythema, digital clubbing, and asterixis. They may also have features related to the underlying cause of cirrhosis such as cryoglobulinemia from hepatitis C, diabetes mellitus and arthropathy in patients with hemochromatosis, or extrahepatic autoimmune diseases (hemolytic anemia or thyroiditis) in patients with autoimmune hepatitis. History should include amount, type and duration of alcohol intake, past history of viral hepatitis or other known liver diseases and history of medication. Previous history of surgeries, blood transfusions, intravenous drug abuse, tattooing, unsafe sexual practices or jaundice in family should be sought.

The etiology of elevated aminotransferases varies, depending upon the population studied. In a study from Texas in a population of 19,877 asymptomatic volunteer blood donors, 0.5 percent had ALT elevation more than 2.25 standard deviation above normal (22). A definite etiology could be found in only 12% of the patients. There were four cases of acute hepatitis B, four with chronic hepatitis C, two with autoimmune liver disease, one with cholelithiasis and another with acute appendicitis. In 87 patients (88%) the elevation in ALT levels was unexplained. In another study, 149 patients with elevated alanine aminotransferase underwent a liver biopsy for evaluation, 56 percent had fatty liver, 20 percent had non-A, non-B hepatitis, 11 percent had changes related to alcohol use, 3 percent had hepatitis B, 8 percent had other causes, and in 2 percent, no cause was identified(23). Daniel et al assessed 1124 consecutive patients with chronic elevations of aminotransferases(6). Eighty-one of

these patients had no definable cause of the elevation and underwent a liver biopsy. Of these 81 patients, 41 had steatosis, 26 had steatohepatitis, 4 had fibrosis, 2 had cirrhosis, and 8 had normal histologic findings. The patients with histologic evidence of fibrosis and cirrhosis also had evidence of fatty metamorphosis.

A leading cause of elevated transaminases is NAFLD, which is associated with metabolic syndrome(24)(25)(26). In industrialized countries, where the prevalence of metabolic disorders is rapidly increasing due to unhealthy eating habits and sedentary lifestyles, NAFLD is becoming the commonest cause of liver disease(27)(28). In a recent study from Jilin, China, abnormal liver functions were noted in 14.77 % of 3791 people screened and metabolic syndrome alone (25%), NAFLD alone(11.61%), and alcohol intake were found to be important etiological factors. Both MS and NAFLD were present in 22.14% individuals(10). In southern Italy, an area where the dietary habits are different from those in industrialized areas, abnormal liver functions have been reported in one eighth of the patients, alcohol was the commonest cause (45.6%) followed by NAFLD (24%), hepatitis C(18.6%) and hepatitis B (8.8%)(8). In a study from All India Institute of Medical Sciences, New Delhi, non-alcoholic steatohepatitis (36%) and chronic viral hepatitis (36%) were the most common causes of elevated ALT in individuals presenting to a tertiary care hospital for check up (29). A diagnosis was reached in 34% of patients with only serological and biochemical investigations, whereas PCR for HBV and HCV could further detect the presence of active HBV or HCV viremia in 21% and a liver biopsy was necessary to establish the diagnosis in 42% patients.

ALCOHOLIC LIVER DISEASE

Alcohol consumption is an important cause of morbidity and mortality worldwide, and most of the burden is from alcohol related hepatotoxicity(30). In addition to the direct hepatotoxicity, alcohol also potentiates the damage caused due to chronic viral hepatitis, non

alcoholic fatty liver disease and drugs(31)(32). This results in earlier development of cirrhosis, higher incidence of hepatocellular carcinoma, and higher mortality. The risk of developing an alcoholic liver disease is dose dependent and is higher in people consuming $\geq$ 30-50 grams of alcohol per day for 5-10 years, but it does not develop in everyone(33). In heavy drinkers (defined as consumption of more than 2 drinks a day), 90-100% develop steatosis, 10-35% have alcoholic hepatitis and 8-20% have cirrhosis(34). The point prevalence of cirrhosis is 1% in persons drinking 30 to 60 g of alcohol daily and up to 5.7% in those consuming 120 g per day(35). Other factors related to environment or the host, like age, gender, obesity, pattern of drinking and amount of alcohol consumed predispose an individual to the development of liver disease. Alcohol consumption is responsible for 3.8% of global mortality and 4.6% of disability-adjusted life-years (DALYs) lost due to premature death (36).The DSM IV criteria for alcohol abuse and dependence were met by 4.65% and 3.81% of the American adults(37). Forty four percent of all deaths due to liver disease were attributed to alcohol in 2003.

There is no single laboratory marker to confirm chronic alcohol consumption. Carbohydrate deficient transferrin (CDT) and gamma glutamyl transferase (GGT) are most commonly used markers for detecting previous alcohol consumption (38). Aminotransferase elevation is also seen. AST can be elevated in alcoholic liver disease with a sensitivity of 50% and a specificity of 80%. AST levels are rarely above 300 IU/ml, while serum ALT levels are lower. This predominance of AST over ALT was first reported in 1967 by Hainasuta *et al*(39). Cohen and Kaplan confirmed that the AST/ALT ratio was elevated in alcoholic hepatitis and cirrhosis(40). The AST/ALT ratio was more than 2 in 70% of patients with alcoholic liver disease as compared to 26% of patients with postnecrotic cirrhosis, 8% with chronic hepatitis, 4% with viral hepatitis and none with obstructive jaundice(40). The percentage increased to more than 96 percent when the ratio was greater than 3:1. Reasons reported behind the high AST/ALT ratio are: (a) decreased hepatic ALT activity (41); (b)

depletion of pyridoxal 5' phosphate in patients with alcoholic liver disease (42) and (c) mitochondrial damage leading to increased levels of mitochondrial aspartate in patients who consume large amounts of alcohol(43). In patients with NAFLD related chronic liver disease and chronic viral hepatitis, the ratio of AST/ALT may be more than one (44)(45)(46)(47). However this has a low predictive value in NAFLD and viral hepatitis(48).

CHRONIC VIRAL HEPATITIS

Chronic viral hepatitis is another cause for asymptomatic transaminitis. Both hepatitis B virus (HBV) and hepatitis C virus (HCV) are important causes of chronic necroinflammatory and neoplastic liver disease worldwide. Approximately one third of the world population has been infected with hepatitis B, with the serological evidence of past or present infection with HBV, as per an estimate by WHO. Of the approximately 2 billion people infected with HBV worldwide, more than 350 million (5-7% of the world's population) suffer from chronic hepatitis B infection(49). Life threatening liver consequences (cirrhosis, liver failure and hepatocellular carcinoma) develop in 15-40% of patients infected with HBV, resulting in 600,000 to 1.2 million deaths a year(50)(51)(52). India has more than 40 million HBV carriers and accounts for 10-15% of the entire pool of HBV carriers of the world, forming the second largest pool of chronic HBV carriers in the world(53). Every year over 100,000 Indians die due to illnesses related to HBV infection.

Hepatitis C is emerging rapidly as an infection which warrants attention(54). Approximately 130-210 million individuals (3% of the world population) are chronically infected with hepatitis C(55). The prevalence ranges from 0.4-3% in Western Europe to 15% in Egypt(56)(57). A community based study from West Bengal, India found a prevalence of 0.9%(58).

Both HBV and HCV are parenterally transmitted and risk factors include blood product transfusions (especially before 1992), unsafe sexual practices, vertical transfusion

during pregnancy, intravenous drug abuse, intranasal cocaine use, hemodialysis, organ transplantation and birth in an endemic region. Most patients with chronic viral hepatitis have no symptoms or only mild symptoms with minimally elevated AST and ALT levels. Hepatitis C can cause transient elevations in liver enzymes (especially ALT) and a repeat testing should be considered even if enzyme testing is normal.

Screening for hepatitis B is done using hepatitis B surface antigen (HBsAg), which is the serological hallmark of HBV infection. HBsAg appears after 1-10 weeks of acute infection and the persistence of HBsAg for more than 6 months implies chronic HBV infection. Chronic HBV infection generally consists of two phases: an early replicative phase with active liver disease, and a low replicative phase with remission of liver disease(59)(60). An immune tolerant phase is also seen in infants with perinatally acquired infection, in which viral replication is not associated with an active liver disease(61). Levels of aminotransferases vary among the various phases depending on the host's immune response. In the immune tolerant phase, the patients are asymptomatic and have normal levels of aminotransferases. The transition from the immune tolerance to the immune clearance phase occurs during the second and third decades, which is characterised by spontaneous HBeAg (hepatitis B e-antigen) clearance. HBeAg seroconversion is frequently accompanied by biochemical exacerbations (elevations of aminotransferases) due to immune mediated lysis of infected hepatocytes(62)(63). Patients in the low or nonreplicating phase/inactive carrier state are HBeAg negative and anti-HBe positive. In some patients, HBV DNA is undetectable in serum and liver disease is in remission as evidenced by normal serum ALT concentrations and the resolution of necroinflammation in liver biopsies. Patients with HBeAg-negative chronic hepatitis are older and have more advanced liver disease with fluctuations in HBV DNA and ALT levels. The frequency of flares was estimated to be 4.3% per year with a cumulative probability of flare of 11% after 5 years and 47% after 10 years in 217

asymptomatic patients with HBeAg negative chronic hepatitis (64). Lok *et al* noted that follow-up every three months captured up to 90 percent of flares(65). Isolated presence of anti-HBc in the absence of HBsAg and anti-HBs has been reported in 0.4 to 1.7 percent of blood donors in low prevalence areas and in 10 to 20 percent of the population in endemic countries(66). The presence of anti-HBc can indicate occult hepatitis B infection which is characterised by clinical and biochemical recovery, serologically undetectable hepatitis B surface antigen (HBsAg-ve), despite the presence of circulating HBV DNA(67). Screening for probable occult HBV infection should be carried out in HCV-infected patients, in patients under immunosuppression, those with unexplained liver diseases and in blood units for immunocompromised recipients(68).

The commonest screening test for hepatitis C infection is anti HCV, which is an enzyme immune assay that detects HCV antibodies. It is easy to use, has low variability, ease of automation and relatively low expense. The sensitivity of the test is 95% and the positive predictive value is 88-95%(69). The positive predictive value is lower (50 to 61 percent) in lower prevalence populations such as blood donors. Overall, enzyme immune assay testing allows detection of anti-HCV in about 95 percent of individuals with HCV as confirmed by highly sensitive molecular tests such as the polymerase chain reaction (PCR) or transcription-mediated amplification (TMA). Gretch *et al* found that the incidence of HCV viremia, determined by the RNA PCR assay, was 73% for confirmed seropositive specimens, 33% for seropositive specimens with indeterminate RIBA results, 12% for seronegative specimens obtained from infected patients, and 2.0% for seronegative specimens obtained from uninfected blood donors. In contrast, serum transaminase testing did not correlate with the RNA PCR assay for HCV. Hence, ALT may not be elevated in chronic hepatitis C, and EIA and immunoblot assay followed by RNA PCR testing should be used to identify most patients who are infected with HCV(70).

Studies from southern India have shown that the community prevalence of HBsAg was 5.7 per cent (CI 4.6- 6.8)(71), while that in antenatal females was1.58%(72) In a meta-analysis of data on 61 populations in 15 Indian states by Batham *et al,* the point prevalence of HBsAg in India has been estimated to be 3.7% (95% CI : 3.17—4.24%), which corresponds to a chronic carrier rate of 2.96%(73). The overall prevalence in Tamil Nadu (four studies) was estimated to be 4.52%. Anti HCV has been found to be positive in 3-13% of the individuals with elevated ALT in various studies from India.

NON ALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease is defined as presence of hepatic steatosis when no other causes for secondary hepatic fat accumulation like heavy alcohol consumption are present. NAFLD can progress to cirrhosis and is probably an important cause of cryptogenic cirrhosis and hepatocellular carcinoma(74)(75). NAFLD is seen worldwide, but the prevalence is greater in developed countries where the major risk factors, obesity, dyslipidemia, diabetes, hypertension are more prevalent (76). The prevalence of NAFLD was noted to have increased from 5.5% between 1988 and 1994 to 9.8% between 1999 and 2004 to 11% between 2005 and 2008 (76). This accounted for 47, 63, 75 percent of chronic liver disease in those time periods respectively. The limitation of the study was that NAFLD was defined as liver disease in patients with unexplained elevated transaminases, hence underestimating the prevalence of NAFLD (which can have normal liver enzymes). Using the ultrasonography data from 12,454 adults who participated in the Third National Health and Nutrition Examination Survey, conducted in the United States from 1988 to 1994, the prevalence of hepatic steatosis and NAFLD was found to be 21.4% and 19.0%, respectively(77). Indian population based studies from Cuttack and Mumbai, found that the prevalence of NAFLD (diagnosed by ultrasonography) was 25% and 16.6%, respectively(78)(79). Insulin resistance and obesity are associated in a proportion of Indian

patients with NAFLD. However, the association with metabolic syndrome in Indian patients is not strong compared to the West. It has been proposed that pathogenetic mechanisms unrelated to MS may contribute to the development of NAFLD in a proportion of Indian patients(80).

Mild to moderate transaminitis is mostly noted in the patients with NAFLD(81). But the pattern of aminotranferase levels bears no correlation with changes in steatosis, inflammation, hepatocyte ballooning, or fibrosis stage as determined by a liver biopsy over time. In a study from the Mayo clinic, it was seen that alanine aminotransferase levels were persistently elevated in 68% of patients, fluctuated between normal and elevated in 22% of patients, and normalized in 10% of patients over a period of 2 years without much change in the weight(82). When the AST and ALT are elevated, the levels are 2 to 5 times the upper limits of normal, with the AST to ALT ratio of less than one (83). The degree of aminotransferase elevation does not predict the degree of hepatic inflammation or fibrosis, and a normal alanine aminotransferase does not exclude a clinically significant histologic injury(84). NAFLD can be diagnosed by imaging features, like increased echogenicity on ultrasound, decreased hepatic attenuation on computed tomography (CT), and an increased fat signal on magnetic resonance imaging (MRI). The gold standard for diagnosis is liver biopsy. Histologic findings in NAFLD include steatosis, inflammation, cell injury, and fibrosis. NAFLD is diagnosed by >5 percent steatotic hepatocytes in a section of liver tissue (85). Steatosis is described as mild if 5 to 33 percent of hepatocytes are steatotic, moderate when 34 to 66 percent of hepatocytes are affected, or severe when >66 percent of hepatocytes show a fatty change(86).

DRUGS

Drugs are an important cause of liver injury. More than 1000 drugs, toxins, and herbs have been reported to cause liver injury(87). Drug-induced liver injury (DILI) is the most

common reason cited for withdrawal of an approved drug. Common hepatotoxic drugs include acetaminophen, NSAIDs, antibiotics (e.g., clavulinic acid-amoxicillin, nitrofurantoin, sulfonamides), HMG-CoA reductase inhibitors (statins), anticonvulsant drugs (e.g., phenytoin, carbamazepine, valproic acid), isotretinoin, immunomodulators (e.g., methotrexate, azathioprine), antituberculous drugs (e.g. isoniazid) and some herbal medications(88). Detailed history-taking and careful reviews of laboratory data are essential for identifying a medication as the cause of elevated aminotransferase levels. Drug induced liver injury should be considered if the increase in the level of liver enzymes was associated with the initiation of the medication.

The incidence of DILI with approved prescription medications is approximately between 1 and 10 per 100,000 persons exposed per year(89)(90)(91)(92)(93). The highest annual incidence rate of DILI (19.1 cases per 100,000 inhabitants) was noted in a population based study from Iceland (90). DILI was caused by a single prescription medication in 75% of cases, dietary supplements in 16% of cases and by multiple agents in 9% of cases. The most commonly implicated drugs were amoxicillin-clavulanate (22%), diclofenac (6%), azathioprine (4%), infliximab (4%), and nitrofurantoin (4%). Thirty percent of patients with acute hepatitis, 10 percent of hepatologist consultations and 1 percent of general medical admissions are due to drug induced liver injury (94)(95)(96).

Clinically, DILI can present like other forms of both acute and chronic liver failure. Acute presentations can range from an asymptomatic elevation of transaminases to fulminant hepatic failure. According to the “Hy’s law”, presence of jaundice (serum bilirubin >2 times the upper limit of normal) in association with an elevation in serum aminotransferases (>3 times the upper limit of normal) is associated with a worse prognosis than that seen in the setting of isolated aminotransferase abnormalities(97). The mortality in this setting is approximately 9 to 12 percent (98). Some drugs are associated with chronic histologic

inflammatory changes and a clinical syndrome resembling autoimmune hepatitis, others cause vascular complications such as sinusoidal obstruction syndrome or Budd-Chiari syndrome by causing endothelial damage or thrombosis. The physician should be alert about the risk of hepatotoxicity because withdrawal of the offending drug usually leads to a reversal of the injury. However, in some types of toxicity can lead to fibrosis or cirrhosis despite discontinuation of the drug.

AUTOIMMUNE LIVER DISEASE

A relatively uncommon but important cause of elevated aminotransferases is autoimmune liver disease. Autoimmune hepatitis (AIH) is characterized by presence of chronic hepatocellular inflammation, serum autoantibodies and hypergammaglobulinemia, with a response to immunosupression in most cases(99). It is a disease of young to middle aged females with a female to male ratio of 4:1(100). The prevalence of AIH in North America and western Europe according to various studies varies from 11-23 %(101)(102). Studies from India have shown a lower prevalence, ranging between 1.5-6.4% of all the liver disease(103)(104)(105). Liver biochemical tests in AIH reveal a "hepatitic" pattern more commonly than "cholestatic" pattern. Levels of transaminases fluctuate, being normal during the quiescent periods and markedly elevated during the disease flare ups. Elevated aminotransferases may be found in asymptomatic patients seeking medical attention for other autoimmune disorders like arthralgias, thyroid or skin diseases(106). Some patients can present as acute liver failure or a recent onset rapidly progressive hepatitic disorder(107)(108). If untreated, AIH has a 5 year mortality of more than 50%. Early diagnosis and immunosuppressive therapy can control the disease activity and result in a normal or near normal life expectancy. The International Autoimmune Hepatitis Group developed a scoring system for diagnosis of AIH in 1993 and subsequently revised it in 1999(109)(110). It has been useful in standardizing the diagnosis for population studies and

clinical trials, but for individual patients the value of the same has been limited. Hence, a simplified criteria for use in individual patients has been proposed, which is based on titres of autoantibodies, IgG levels, liver histology, and the exclusion of viral hepatitis(111). The simplified scoring system has 81 percent sensitivity and 99 percent specificity compared with a clinical and histologic reference standard when using a cutoff of ≥seven. Treatment of AIH needs to be individualized based upon the severity of symptoms, the degree of elevation of serum aminotransferases and gamma globulin levels, histologic findings, and the potential for side effects. According to the AASLD guidelines, treatment with prednisolone and azathioprine should be offered for patients with (a) AST or ALT levels more than 10 times ULN, (b) AST,ALT,gamma globulin levels more than twice the ULN in presence of symptoms, elevated conjugated bilirubin or interface hepatitis on biopsy, (c) histology showing bridging necrosis or multiacinar necrosis, (d) cirrhosis with any degree of inflammation on biopsy, (e) children with AIH(112). Within two weeks of therapy, 90% adults show improvements in serum AST, ALT, bilirubin and gamma globulin levels. Improvement in histology lags behind clinical and laboratory improvement by 3-8 months.

WILSON'S DISEASE

Asymptomatic elevation of transaminases can be seen in Wilson's disease(113). Wilson's disease is an autosomal recessive disease which leads to deposition of copper in the liver, brain and kidneys, due to a defect of copper transport by the hepatic lysosomes(114). Majority of the cases are diagnosed between the ages of 5 and 25 years, but the disease has been diagnosed in younger patients and those upto the age of 70 years. Though there are no population based studies on the prevalence of Wilson's disease in India, hospital based reports have identified this as a leading cause of portal hypertension in children. In a study from Vellore, Wilson's disease was the commonest cause of cirrhosis and portal hypertension (55%) in the paediatric population (115). Another study from Chandigarh revealed that

Wilson's disease was the second most common cause of chronic liver disease (7%) after Indian childhood cirrhosis (17%) (116). The mean age at presentation in 282 southern Indian patients was 16 years, indicating that this disease may also be expected to be found in young adults in this area(117).

Clinical manifestations of Wilson's disease can be predominantly hepatic (18 to 84% patients), neurologic (18 to 73% patients) or psychiatric (10-100% patients), though many patients have a combination of symptoms. Liver disease can range widely and present as asymptomatic transaminitis and steatosis, acute hepatitis and acute liver failure, chronic hepatitis or cirrhosis with or without decompensation. Diagnosing neurologic Wilson disease can be challenging because patients present in a myriad of ways. Dysarthria and/or movement disorders are present in a majority of patients with neurologic Wilson disease. Initial evaluation includes liver biochemical tests, serum ceruloplasmin levels, 24 hours urinary copper and ocular examination. Aminotransferase levels are mostly elevated but do not correlate with the extent of liver damage. The ratio of AST to ALT is often more than 2. Low serum ceruloplasmin (<20 mg/dl) is seen in approximately 85-90% of the patients, and in the presence of Kayser-Fleischer rings this is considered to be diagnostic of Wilson disease(118)(119)(120). Kayser-Fleischer rings are seen in 50 to 60 percent of patients with isolated hepatic Wilson disease and in almost all patients with clinical neurologic involvement (119)(121). The 24-hour urinary copper excretion is Wilson's disease is >100 mcg (>1.6 micromol), but lower values can be seen in about one fourth of asymptomatic patients who have a confirmed disease (122). The gold standard for diagnosis is quantitative hepatic copper determination which is more than 250 mcg (4 micromol) of copper per gram of dry weight(123).

HEMOCHROMATOSIS

Hereditary hemochromatosis is another cause of transaminitis, seen mostly in Caucasian populations in US and Europe(124). It is an autosomal recessive disorder where increased intestinal iron absorption due to mutations in HFE gene result in excessive iron deposition in tissues, especially the liver, heart, pancreas, and pituitary. Patients maybe asymptomatic at the time of presentation, or could present with fatigue, right upper quadrant abdominal pain, arthralgias (typically of the second and third metacarpophalangeal joints), chondrocalcinosis, impotence, decreased libido, and symptoms of heart failure or diabetes. On examination, these patients have an enlarged liver, especially when cirrhosis has developed. They may also have extrahepatic manifestations of chronic liver disease, testicular atrophy, congestive heart failure, skin pigmentation,changes of porphyria cutanea tarda, or arthritis. Progressive deposition of iron in liver can present as asymptomatic transaminitis and eventually progress to fibrosis and cirrhosis.

Abnormal liver enzymes are seen in 75 percent of the patients with hemochromatosis(125). The AASLD guidelines recommend evaluation for hemochromatosis in all patients with liver disease(126). A combination of transferrin saturation and serum ferritin should be used to screen patients who have suggestive symptoms or family history of hemochromatosis. If transferrin saturation is >45% or ferritin is above the upper limit of normal, HFE gene mutation analysis should be performed(126). Therapeutic phlebotomy is the simplest, cheapest, and most effective way to remove accumulated iron in patients with iron overload. The haemoglobin lost with the phlebotomized red cells is compensated by mobilisation of an equal amount of iron from tissue stores, thereby reducing the degree of iron overload.

OTHER RARER CAUSES

A rare cause of aminotransferase elevation is alpha-1 antitrypsin deficiency. It is present in 1 of every 1600 to 1800 live births(127). It is a disease of very young children, but

a small number of these patients can develop an end stage liver disease in the adulthood. The diagnosis should be considered in patients with emphysema or a history of liver failure in a younger sibling. This includes measurement of the alpha-1-antitrypsin level and an assessment for the PiZZ genotype.

Another rare cause of transaminitis mentioned in literature is occult celiac disease. In a series of 140 patients with chronic unexplained transaminitis, 9.3% were positive for antigliadin and anti endomysial antibodies. Duodenal histology was suggestive of celiac disease and AST and ALT levels reduced to normal on a gluten free diet(128). In a recent case report, a patient with cryptogenic hypertransaminasemia, high BMI and grade I fatty liver disease, celiac disease was diagnosed based on serology and presence of subtotal villous atrophy in the duodenal biopsy. Normalization of liver enzymes on a gluten-free diet was noted(129).

Diseases affecting other organs especially striated muscle can also cause elevation of transaminases, though in these cases, aspartate aminotransferase levels are higher. A few examples of such cases included subclinical inborn errors of metabolism or acquired muscle disorders like polymyositis. In a case series of 19 cases of Duchenne's muscular dystrophy, ALT was elevated to nine times the upper limit of normal(130). Aminotransferase elevation can also occur due to strenuous exercise or crush injury. In such cases, the levels of creatine kinase or aldolase are elevated and can help in ruling out a hepatic etiology. Hyperthyroidism has also been shown to increase serum levels of liver enzymes including AST and ALT(131). Genetic factors on the biochemical liver function tests accounts for one-third to two-thirds of the variation among individuals 73-102 years of age(132).

In patients with an undiagnosed chronic transaminitis, a liver biopsy should be considered if the elevation is more than two times the upper limit of normal(113). Das etal assessed the cost utility of liver biopsy in a cohort of patients with chronic (>6 months)

transaminitis and proposed that close clinical follow-up is the most cost-effective strategy for asymptomatic patients with negative tests for viral, metabolic, and autoimmune markers of liver disease(133). This was supported by a study by Sorbi et al who biopsied 36 patients with unexplained elevation of liver enzymes and found that the biopsy led to a change in diagnosis in only five patients and the treatment changed only for two patients(134).

Figure 1 shows the approach to a patient with elevated liver enzymes.

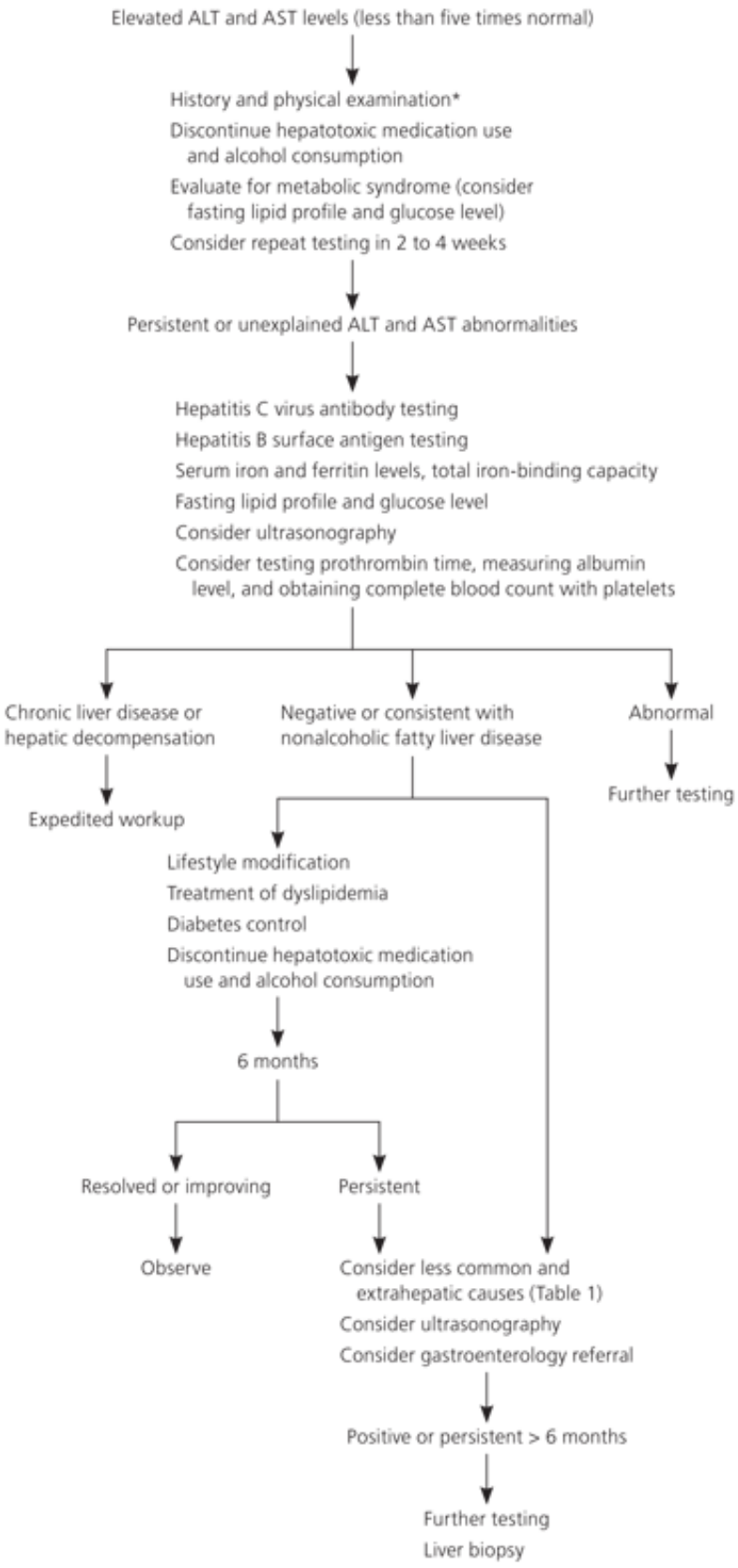


Figure 1 - Management of elevated liver enzymes (from (135))

Aims & Objectives

AIMS AND OBJECTIVES

Our overall aim was to estimate the burden of liver disease in a southern Indian community using elevated alanine aminotransferase as the screening test. The specific objectives were:

1. To determine the prevalence of persistently elevated alanine aminotransferase in a southern Indian population.
2. To determine the etiology of persistent elevation of alanine aminotransferase in this population.

Material & Methods

MATERIAL AND METHODS

STUDY DESIGN:

Population based cross sectional study of adult population in Vellore district in southern India.

SETTING:

A seroprevalence study of celiac disease in southern India was recently conducted by the Christian Medical College, Vellore as part of a three centre study in northern, northeastern and southern India. The study involved a proportional population sampling of the adult population of Vellore city and its neighbouring rural areas. Urban and rural areas covering a total population of approximately 150,000 people (35% urban, 65% rural) were mapped. Eligible households were determined as every third household with a minimum of two adults in the household who were not blood relations. In each selected household, the intent was to obtain a blood sample from one male and one female, not related by blood, for testing for antibody to tissue transglutaminase. After obtaining consent, demographic data of the participants including socioeconomic data, age, sex, height, weight, blood pressure, and waist circumference data were obtained. Blood samples were taken from all consenting participants. Data from 9000 eligible participants (3200 urban, 5800 rural) was analysed. As part of the study, blood samples from these participants were also tested for ALT. The plot of ALT values of all the participants showed a skewed deviation. In consultation with our statistician, it was decided that the upper limit of normal for ALT would be taken as 44 U/l, which represented the mean plus 2 SD of the population sampled. One hundred and ninety nine of 9000 individuals had an ALT>44 U/l on this first testing and they formed the cohort that was investigated in this study.

Of these 199 healthy individuals (145 males) with elevated ALT who were counselled for a repeat ALT testing, 116 individuals (92 males) agreed to participate in further studies to investigate the nature of the elevated ALT. The repeat ALT was normal in 25 of the 116 participants and of the remaining 91 participants (77 males) with a persistently elevated ALT, 35 refused to consent for further evaluation. Hence a total of 56 patients (52 males) underwent further evaluation.

INCLUSION CRITERIA:

1. One hundred and ninety nine apparently healthy individuals aged over 18 years with elevated ALT (>44U/l) identified through a previous survey.

EXCLUSION CRITERIA:

1. Refusal to give consent

DATA COLLECTION:

All one hundred and ninety nine participants with elevated ALT from the celiac screening study were contacted and invited to give a second blood sample to determine whether their ALT remained elevated. Those participants who had persistent elevation of ALT on second testing were called to the hospital for further detailed evaluation as described below. The study protocol was approved by the Institutional Research Board. These individuals provided informed written consent.

INTERVIEW:

An interview using a structured questionnaire (Appendix I) was conducted during the participants' visit to the hospital. The following information was obtained during the interview:

1. Socio-economic and demographic data

2. History of drug intake and alcohol use
3. Previous history of jaundice, surgery, blood transfusion
4. History of intravenous drug abuse, tattooing
5. History of unsafe sexual practices
6. History of jaundice or liver disease in family.

The modified Kuppuswamy score was used to assess the socioeconomic status(136). Alcohol intake was quantified in grams of alcohol consumed per week and an AUDIT questionnaire was administered to screen for risky drinking (score $\geq$ 8)and alcohol dependence(score $\geq$ 20)(137). Excessive alcohol intake was defined as >14 units of alcohol per week (20 grams of alcohol per day) as per the AASLD guidelines(85).

PHYSICAL EXAMINATION:

1. Height was measured without shoes, to the nearest centimetre (cm)
2. Weight was measured while wearing light clothes and without shoes, in kilogram (kg)
3. Waist circumference- Measured at the approximate midpoint between the lower margin of last palpable rib and the top of iliac crest to the nearest centimetre, as per the WHO STEPwise Approach to Surveillance (STEPS) protocol.
4. Hip circumference – Measured around the widest portion of the buttocks to the nearest centimetre(WHO STEPS protocol)
5. Waist Hip Ratio – Waist circumference(cm) / Hip circumference (cm)
6. Body Mass Index – Calculated as Weight (in kg)/ Height (in m^2)

LABORATORY DATA :

Repeat blood samples were obtained from these participants and sent for complete blood counts, liver function tests, and for virology studies as detailed below.

1. Serum biochemistries were performed using a Roche Hitachi P 800 autoanalyser. Both AST and ALT were measured using the α-ketoglutarate reaction.
2. Total cholesterol and triglycerides were measured enzymatically with colour absorbtiometry based on a peroxidise-catalysed reaction.
3. HDL was determined directly by an automated enzymatic colorimetric method using PEG-modified enzymes and dextran sulphate.
4. An automated method using the selective micellary solubilisation of LDL cholesterol by a detergent and interaction of a sugar compound and lipoproteins was used for the direct determination of LDL.
5. Tests for hepatitis B surface antigen were performed using sandwich ELISA (Monolisa HBsAg Ultra , Bio-Rad, Mames La Coquette, France).
6. Specimens were tested for anti- HCV antibody and anti HBc (total core) using the Ortho HCV 3.0 EIA test system enhanced SAVe (Ortho Clinical Diagnostics, Raritan,NJ,USA) and Total anti HBc EIA kit (Diasorin S.p.A. Saluggia, Italy).
7. Ultrasonography of the abdomen was done using the Toshiba Xario SSA 660A machine by a specialist radiologist. The 3-5MHz low frequency curvilinear probe was used to look for evidence of fatty liver, chronic liver disease, portal hypertension and biliary pathology.

DEFINITIONS USED:

1. Obesity : According to the Asian standards, BMI > 23 kg/m^2 was defined as overweight and BMI of >25 kg/m^2 was defined as obese (138).

2. Metabolic Syndrome: Defined as per the modified Adult Treatment Panel III criteria(139). At least 3 of the following 5 components should be present:
    a. Hyperglycemia (fasting Blood sugar >110 mg%)
    b. Central obesity (waist circumference >90 cm for males and >80 cm for females)
    c. Hypertension (BP >130/85 mm of Hg)
    d. Hypertriglyceridemia (serum triglyceride >150 mg %)
    e. Low HDL cholesterol levels (<50mg/dl for women and < 40mg/dl for men)
3. Non Alcoholic Fatty Liver Disease (NAFLD)
    a. Consumption of less than 140 g of alcohol per week (85).
    b. Negative serology for HBsAg or Hepatitis C
    c. Ultrasound imaging suggestive of fatty liver ('bright' liver with stronger echoes in the hepatic parenchyma than in the renal parenchyma, vessel blurring and narrowing of the lumen of the hepatic veins in the absence of findings suggestive of other chronic liver disease)(140)

STATISTICAL ANALYSIS:

This was a cross-sectional descriptive study. Numbers (percentages) are reported. Prevalence rates are reported. Associations of elevated ALT with BMI and other factors were evaluated for significance using Chi square test.

Results

RESULTS

Of the total 9000 people screened, 199 were found to have an elevated ALT and they were all approached for further testing. One hundred and sixteen of these individuals consented to further testing, and 91 of these were found to have a persistently elevated ALT level. At this point, 35 individuals refused to consent for further evaluation. Hence a total of 56 individuals were further evaluated in detail for etiology of the elevated transaminases (Figure 2). During the detailed hospital evaluation, nine individuals had an ALT <44 U/l.

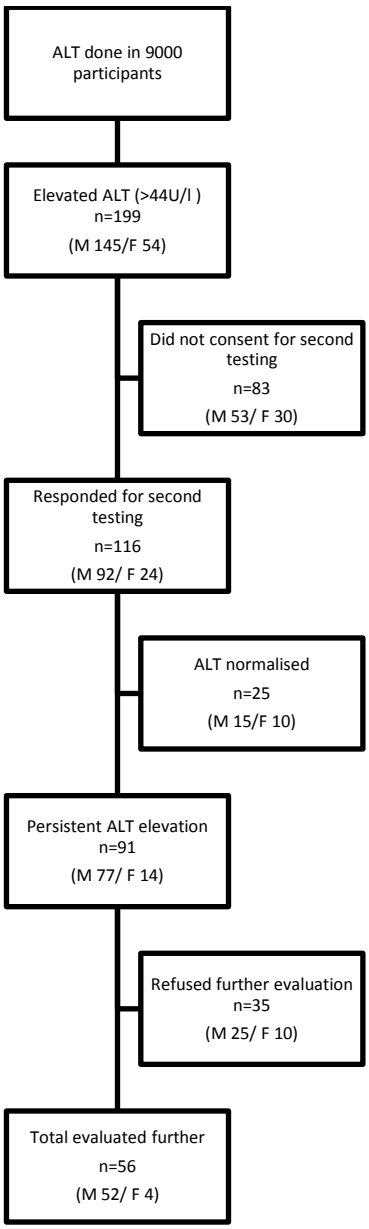


Figure 2. Flowchart of the study cohort *n – number of participants, M- males, F – females.*

ETIOLOGY OF ELEVATED ALT

There were broadly two groups of individuals, the ones with an obvious explanation for ALT elevation like significant alcohol intake (>140g/ week) or positive viral serology and the ones where there was no defined cause. Of the people negative for a history of alcohol or positive viral serology, the majority had a fatty liver on ultrasonography. Liver biopsy and histopathology were not deemed as ethical in these asymptomatic individuals identified on community testing; hence patients with sonological evidence of fatty liver, without history of significant intake of alcohol, and with negative viral markers, were considered to have NAFLD.

As seen in table 1, the most common etiology of elevated ALT was alcohol intake (46.4%) closely followed by NAFLD (42.9%). HBsAg was positive in 6 (10.7%) individuals, of which 3 had a significant alcohol intake. There were no individuals with positive anti HCV. Ceruloplasmin was normal in all participants and transferrin saturation was increased in eight. The etiology of ALT elevation remained unexplained in 3 (5.3%) individuals (Table 2). The ALT levels were persistently high in the above individuals in whom no cause was found for ALT elevation (maximum values being 68, 102 and 190 U/L). These individuals have been counselled to follow up and may require liver biopsy for elucidation of the cause. Among the nine individuals whose ALT normalised on the third testing, eight consumed alcohol (6 had significant alcohol intake) and 3 had NAFLD. Among the six with significant alcohol intake, 3 had fatty liver, two had native drugs and one each had chronic hepatitis B and positive anti tTG in addition.

Table 1 : Etiology of elevated ALT

ETIOLOGY	NUMBER OF INDIVIDUALS
ALCOHOL	23 (41%)
ALCOHOL + HBsAg	3 (5.3%)
NAFLD	24 (42.9%)
HBsAg	3 (5.3%)
UNEXPLAINED	3 (5.3%)

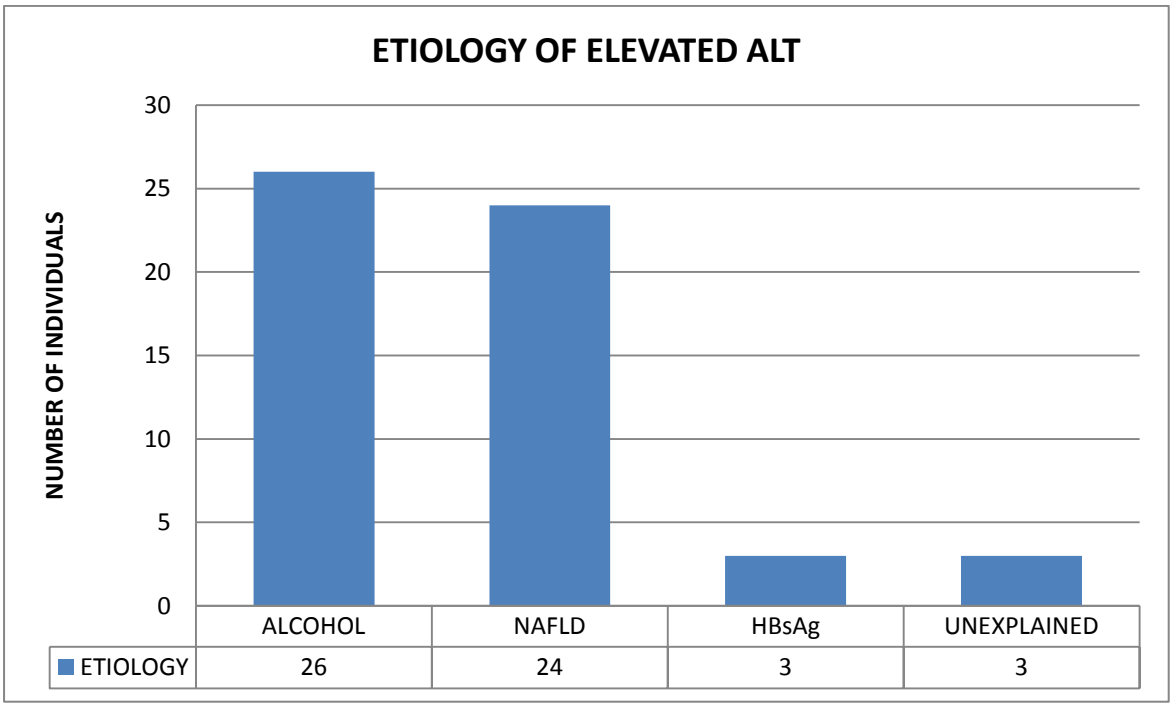


Table 2: Characteristics of 3 participants with unexplained ALT elevation

S.No	**1**	**2**	**3**
ALT1 (U/l)	88	77	51
ALT2 (U/l)	102	190	68
ALT3 (U/l)	90	100	68
Age/Gender	33/F	19/M	32/M
Socioeconomic status	Lower Upper Lower	Upper Middle	Upper
Alcohol (g/week)	0	0	20
Drug history	N	N	N
Past H/O Jaundice	N	N	N
Jaundice in family	N	N	N
Past surgery	N	N	Y
Blood Transfusion	N	N	N
Intravenous drug abuse	N	N	N
Unsafe sexual contact	N	N	N
Tattooing	N	N	N
BMI (kg/m2)	19.5	15.3	27.5
W/H	0.84	0.74	0.9
Fasting blood glucose	94	84	85
Total cholesterol	186	104	183
LDL	128	53	123
HDL	52	41	41
TG	30	54	131
Metabolic Syndrome	N	N	N
AST (U/l)	125	145	48
AST/ALT	1.39	1.45	0.71

ALP (U/l)	66	88	145
HBsAg	Negative	Negative	Negative
anti HBc	Negative	Negative	Negative
anti HCV	Negative	Negative	Negative
Ceruloplasmin (U/l)	685	671	850
Transferrin Saturation	2	24	23.5
Anti TTG	N	N	N
Ultrasonography (Liver and Biliary Tract)	Normal	Normal	Normal

M: male, F : female, N : no, Y : yes, W/H : Waist hip ratio

DEMOGRAPHIC PROFILE

There were 52 males and 4 females in the age group 18-55 years. Median age was 37 years; 19.6% were between 18 and 29 years, 37.5% were between 30 and 39 years and 35.8% were between 40 and 49 years and 7.1% were above 50 years of age.

The most common cause of elevated ALT in younger age group (18 to 39 years, n=32) was non alcoholic fatty liver disease, seen in 16 individuals (50%); of which 15 had metabolic syndrome. The next most common etiology was alcohol (n=11); 9 had fatty liver due to alcohol, 5 had metabolic syndrome in addition. Hepatitis B infection was noted in 3 participants (9%), of which one each had metabolic syndrome and alcohol adding to the morbidity.

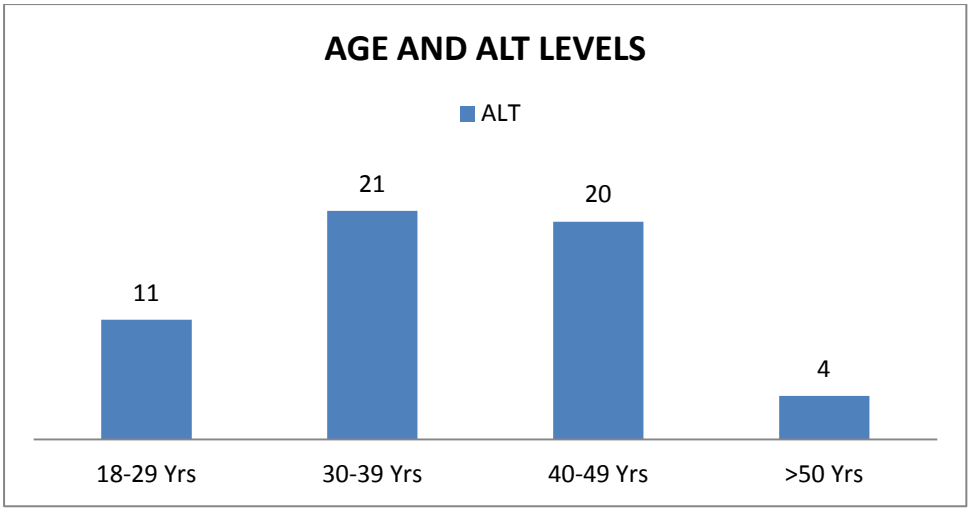
In the middle aged people (40-55 years, n=24), participants with history of significant alcohol (n=15) were almost two times the ones with NAFLD (n=8). Of the 15 individuals with significant alcohol intake, metabolic syndrome was present in 10 and among these 10, seven had fatty liver sonologically and one had features of early chronic liver disease. NAFLD on the other hand was seen in 8 individuals, 7 of whom had metabolic syndrome.

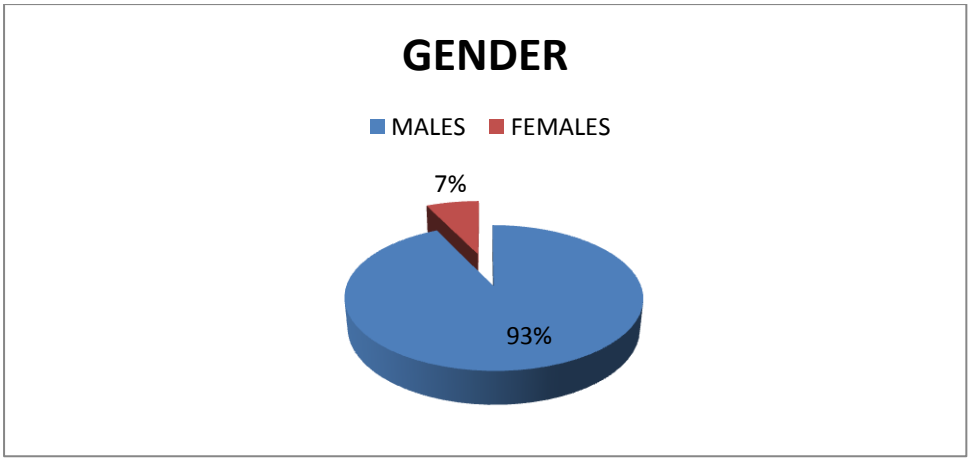
Hence it was noted that ALT levels initially increased and then decreased with increasing age, NAFLD and metabolic syndrome were more common in younger individuals while alcohol related liver disease increased with age. There was no difference in the number of individuals with hepatitis B infection. (Tables 3 and 4).

Majority of the individuals (89.3%) belonged to middle or lower socioeconomic status.

Table 3 : Demographic profile of the individuals with elevated ALT levels

PARAMETERS	NUMBER OF INDIVIDUALS
AGE	
18-29 Yrs	11 (19.6%)
30-39 Yrs	21 (37.5%)
40-49 Yrs	20 (35.8%)
>50 Yrs	4 (7.1%)
GENDER	
Male	52 (92.9%)
Female	04 (7.1%)
SOCIOECONOMIC STATUS	
Upper	01
Upper Middle	05
Middle Lower Middle	21
Lower Upper Lower	28
Lower	01


AGE AND ALT LEVELS
ALT
11
21
20
4
18-29 Yrs
30-39 Yrs
40-49 Yrs
>50 Yrs


GENDER
MALES
FEMALES
7%
93%

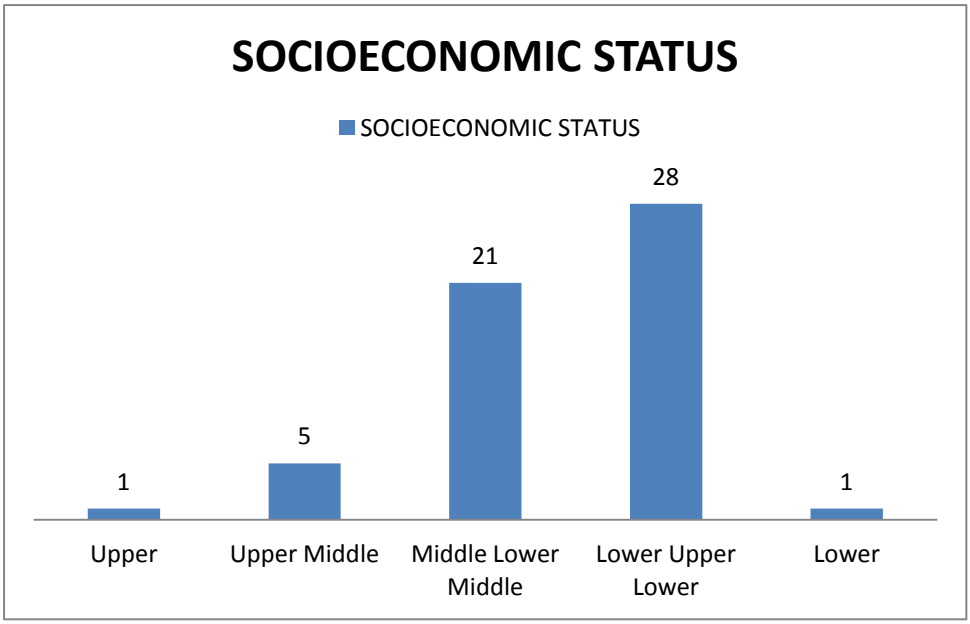

SOCIOECONOMIC STATUS
SOCIOECONOMIC STATUS
1
5
21
28
1
Upper
Upper Middle
Middle Lower Middle
Lower Upper Lower
Lower

Table 4: Etiology of elevated ALT and age distribution

ETIOLOGY	AGE			
	18-29 yrs	30-49	40-49 yrs	>50 yrs
Alcohol	1	0	1	0
Alcohol+MS	1	0	1	1
AFLD	2	1	1	0
AFLD+MS	1	4	7	0
AFLD+HBsAg	1	0	1	0
ACLD+MS	0	0	1	0
ACLD+HBsAg	0	0	1	0
ACLD	0	0	0	1
NAFLD	1	0	1	0
NAFLD+MS	4	11	5	2
HBsAg	0	1	0	0
HBsAg+MS	0	1	1	0
Unexplained	0	3	0	0

AFLD: Alcoholic fatty liver disease, ACLD: Alcohol related early chronic liver disease, NAFLD: Non alcoholic fatty liver disease, MS: Metabolic syndrome, HBsAg: Hepatitis B surface antigen positivity

ANTHROPOMETRY AND PHYSICAL EXAMINATION

Obesity was noted in 80% of the participants (Table 5). As per the Asian standards, 62.5% were obese and 17.9% were overweight. Majority of the individuals had central adiposity. Among the males, 71% had a waist circumference (WC) >90 cm and 88.5% had a waist:hip (W/H) ratio >0.9. A similar trend was seen in females, 75% of them had WC >80 cm and W/H ratio > 0.85.

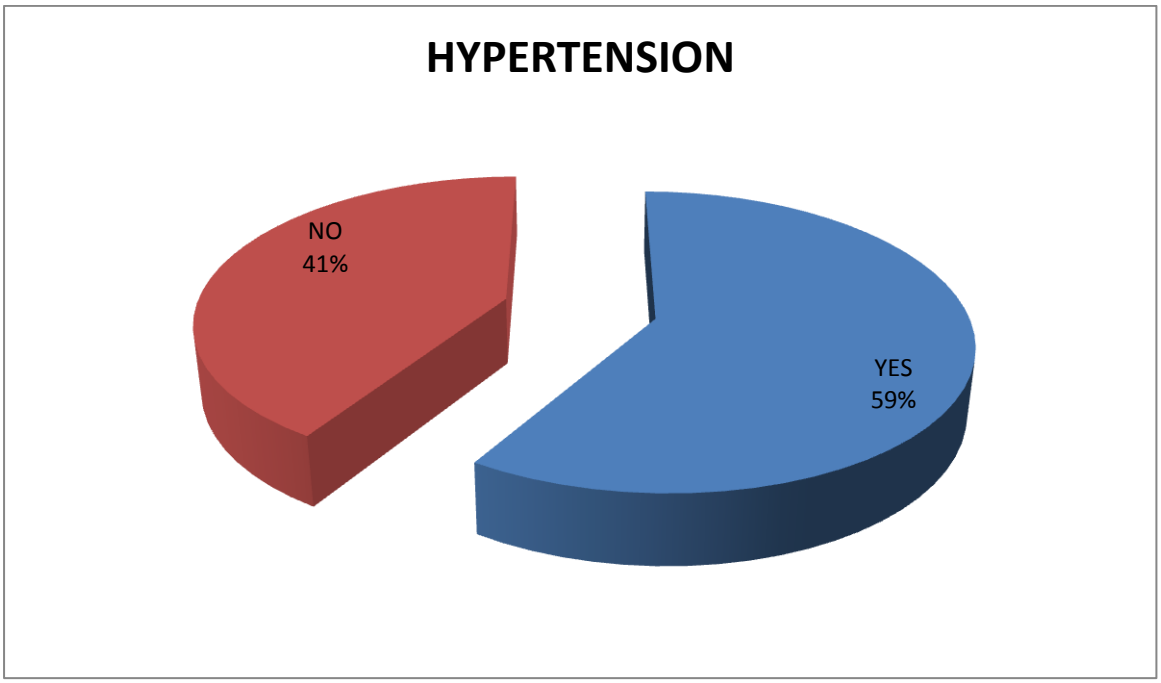
Table 5 : Anthropometric data for individuals with elevated ALT

BMI (Kg/M2)		NUMBER OF INDIVIDUALS	
Underweight (18 kg/ m^2)		1 (1.8%)	
Normal (18-22.9 kg/m^2)		10 (17.9%)	
Overweight (>23 kg/ m^2)		10 (17.9%)	
Obese (>25 kg/ m^2)		35 (62.5%)	
WAIST HIP RATIO			
Gender	Median (Range)	Obesity	Number of individuals
Males (n=52)	0.95 (0.74-1.05)	>0.9	46 (88.5%)
Females (n=4)	0.89 (0.84-1.06)	>0.85	3 (75%)
WAIST CIRCUMFERENCE (CM)			
Gender	Median (Range)	Obesity	Number of individuals
Males (n=52)	93.5 (61-126)	>90 cm	37 (71%)
Females (n=4)	97 (73-106)	>80 cm	3 (75%)

Of the 56 participants with elevated ALT, 33 (58.9%) had hypertension (Systolic Blood Pressure >130 mm Hg and Diastolic Blood Pressure>85 mm Hg). (Table 6)

Table 6 : Blood Pressure(BP) in individuals with elevated ALT (in mm Hg)

	Median (Range)
Systolic BP	130 (92-192)
Diastolic BP	84 (60-100)



ALCOHOL INTAKE

Twenty six (46.4%) of the participants consumed alcohol in significant amounts (>140 grams/ week). Of these participants consuming significant alcohol, 22 (84.6 %) had an AUDIT score of >8, suggestive of risky drinking and six (10.7%) had alcohol dependence (AUDIT score> 20).(Table 7)

None of the females consumed alcohol. Of the males, 8 (15.4%) were teetotallers (Table 8). The number of individuals who had significant amount of alcohol increased with increasing age, 50% of the people with significant alcohol intake were in the age group 40-49 years (Table 9). Most of the individuals had AST elevation upto two times the upper limit of normal, irrespective of the amount of alcohol intake (Table 10). Alcohol intake was more prevalent in the middle and lower socioeconomic groups (Table 11).

Table 7 : Alcohol intake among participants with elevated ALT

	-	AUDIT <8	AUDIT>8
No Alcohol	8	-	-
Alcohol<140g/week	18	16	2
Alcohol>140g/week	26	4	22

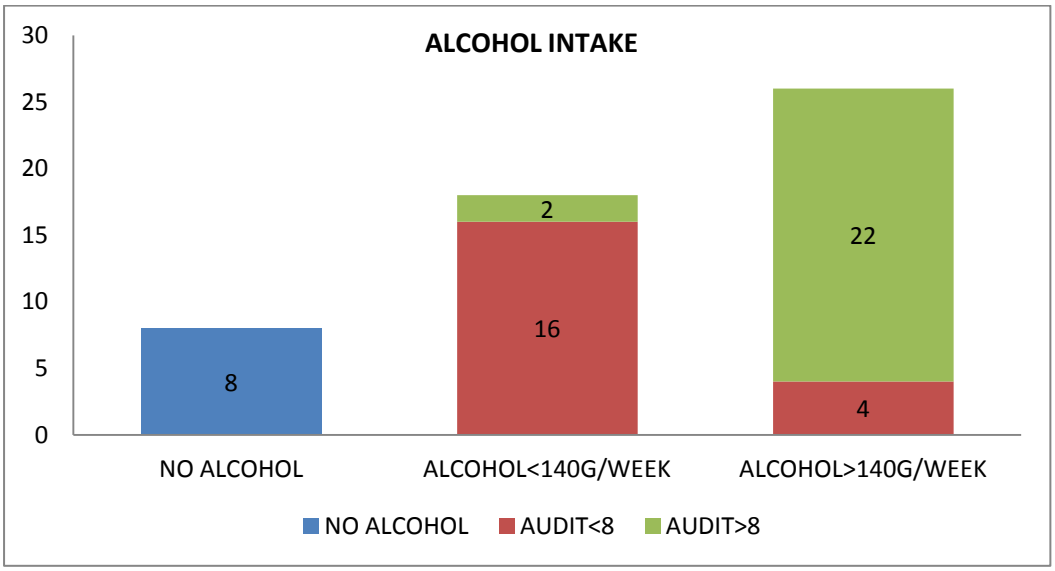


Table 8: Alcohol intake and gender distribution in participants with elevated ALT

	Males	Females
No Alcohol	8	4
Alcohol<140g/week	18	0
Alcohol>140g/week	26	0

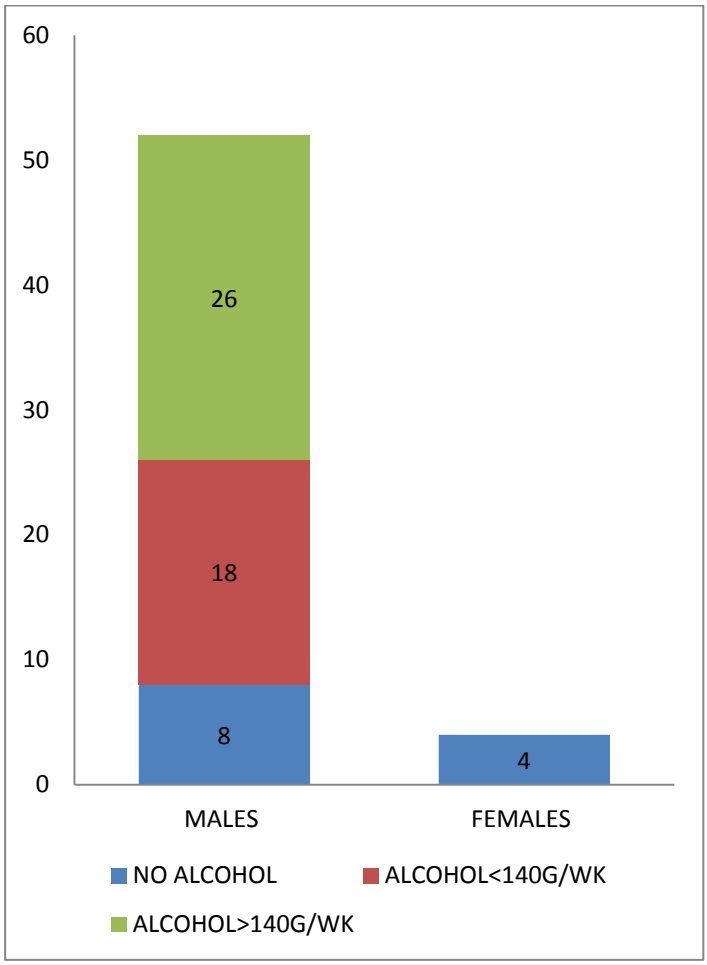


Table 9 : Age and amount of alcohol consumption

Age (Yrs)	NO ALCOHOL	ALCOHOL<140G/WK	ALCOHOL>140G/WK
18-29	4	2	5
30-39	4	11	6
40-49	3	4	13
50-55	1	1	2

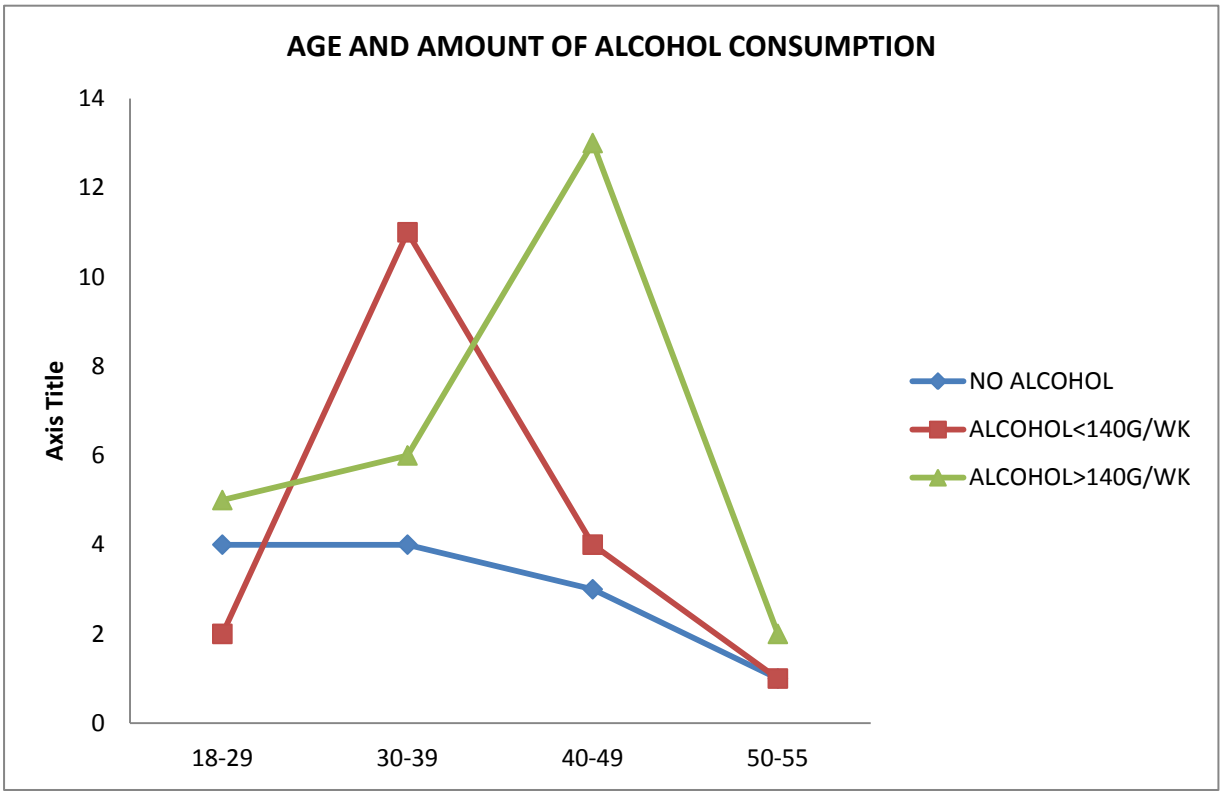


Table 10: Amount of alcohol consumed and pattern of ALT elevation

ALT (U/L)	NO ALCOHOL	ALCOHOL<140G/WK	ALCOHOL>140G/WK
<44[@]	1	2	6
44-88	6	12	14
88-132	4	3	4
132-176	1	1	2

[@]These 9 patients had elevated ALT twice prior to being recruited for detailed hospital evaluation. However, during the detailed hospital evaluation their ALT repeat level was less than 44 U/L.

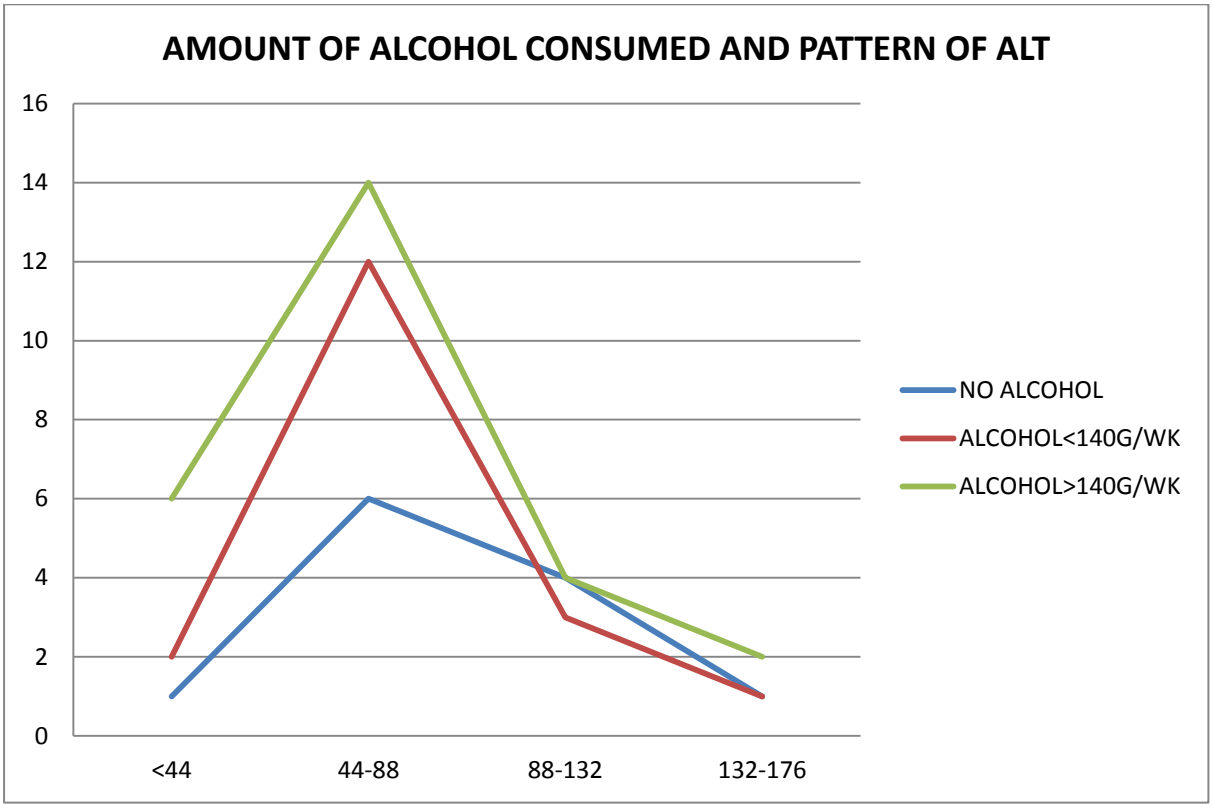
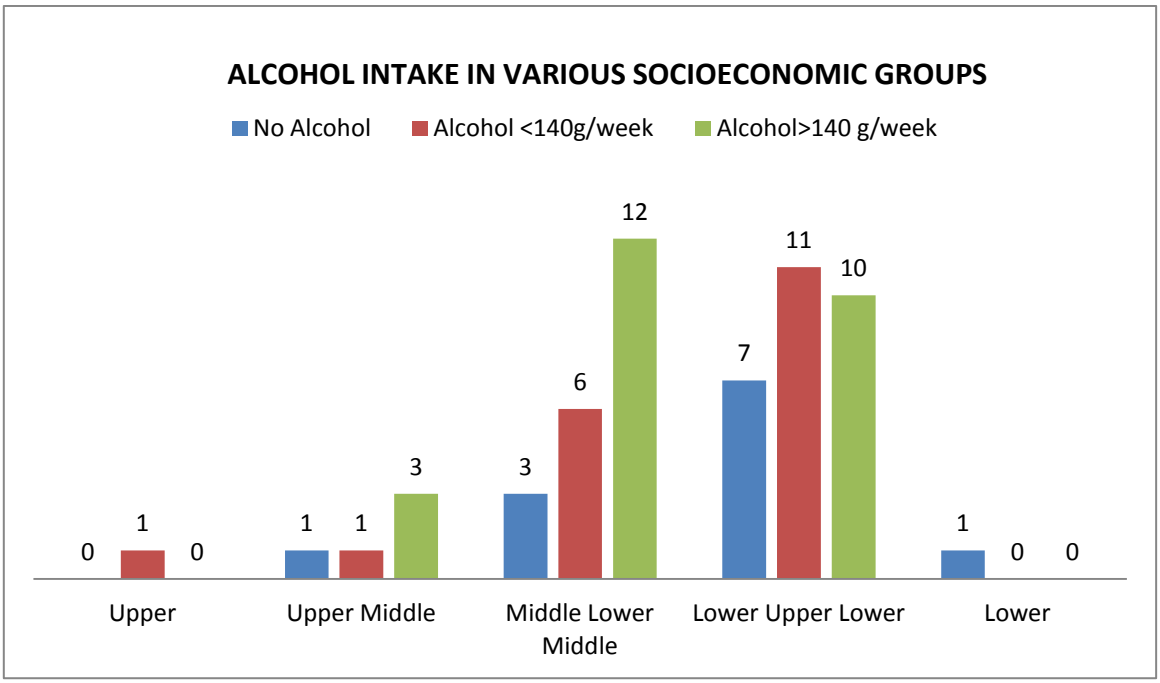


Table 11 : Alcohol intake in various socioeconomic groups

Socioeconomic Status	No Alcohol	Alcohol <140g/week	Alcohol>140 g/week
Upper	0	1	0
Upper Middle	1	1	3
Middle Lower Middle	3	6	12
Lower Upper Lower	7	11	10
Lower	1	0	0



OTHER RISK FACTORS FOR ALT ELEVATION

Fifteen individuals (26.7%) had a history of taking some kind of drug in the last six weeks. The majority had taken the drug over the counter for analgesia, common cough or cold. In most, the nature of the drug was not known. Seven of the patients had taken native medications (once or twice a week for 3-6 weeks) for similar reasons. Three patients were on oral hypoglycaemic agents for diabetes. There was no history of jaundice or hepatic decompensation after starting drugs in any participant.

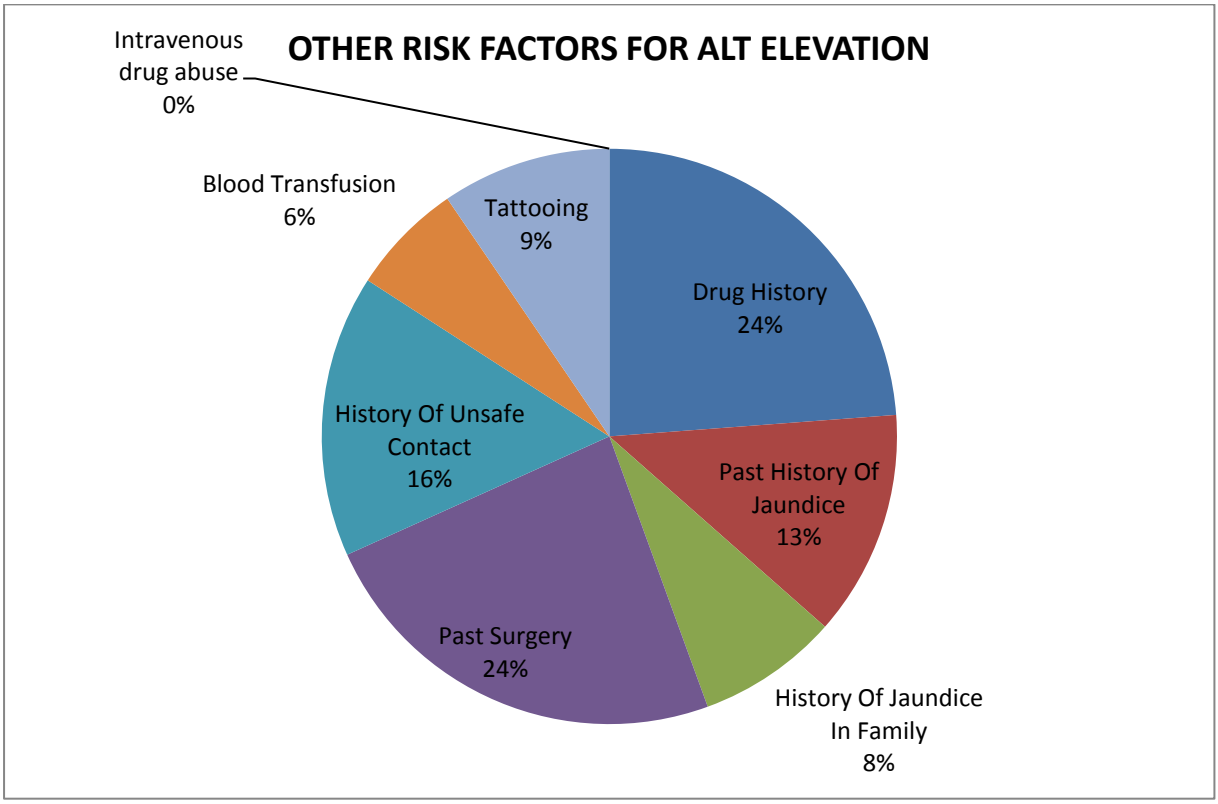
Eight individuals (14.3%) had a past history of uncomplicated and self limiting jaundice. Of these, one was positive for both HBsAg and anti HBc positive and another was HBsAg negative but anti HBc positive. The latter could have probable had a spontaneous HBsAg seroconversion or a HBsAg ‘a’ mutant. Alcohol consumption was significant in 5 of these individuals.

There was a family history of jaundice in 5 participants, none of whom were positive for HBsAg or anti HCV. Ceruloplasmin was normal for all, but one patient had a transferrin saturation of 98% (further evaluation for hemochromatosis was not done).

Other risk factors for parenteral transmission of hepatotropic viruses were assessed. Fifteen individuals had a past history of surgery, 4 of whom had also been transfused blood. There was a history of tattooing in six individuals and 10 had unsafe sexual contact in the past. There were no intravenous drug abusers. One individual who underwent a surgery (no blood transfusion) and three of those who had an unsafe sexual contact were HBsAg positive. No participant with tattoos had any infective etiologies to explain the transaminitis. Anti HCV was negative in all the individuals.

Table 12 : Risk factors for elevated ALT

RISK FACTOR	Number of individuals (%age)
Drug History	15 (26.7%)
Past History Of Jaundice	8 (14.3%)
History Of Jaundice In Family	5 (0.9%)
Past Surgery	15 (26.8%)
History Of Unsafe Contact	10 (17.9%)
Blood Transfusion	4 (0.7%)
Tattooing	6 (10.7%)
Intravenous Drug Abuse	0 (0%)



LABORATORY RESULTS

The mean haemoglobin was 16 g/dl (range 8.4-20.1g/dl). Of the 4 individuals with Hb <12.5 g/dl, three had a very low transferrin saturation (2, 4, and 8% respectively) but none had a positive anti tissue transglutaminase. Platelet count was normal in all participants (Table 13).

None of the participants was clinically icteric, total bilirubin was >1.2 in 5 individuals. Serum protein and albumin were within normal range for all. Aspartate aminotransferase (AST/SGPT) ranged between 18 and 245 U/L, with a median of 46 U/L. ALT ranged between 20 and 167 U/L with a median of 62.5 U/L. The alkaline phosphatase was mildly elevated in 3 patients (maximum of 157 U/L) but none of these had features of biliary obstruction on ultrasonography (Table 13).

ALT levels were seen to fluctuate and normalised in 9 individuals when repeated the third time(Table 14). Among these 9 individuals, there was only one female, who was diabetic, hypertensive and obese. She had a fatty liver on ultrasonography. No other definite etiology of elevated ALT was found. Eight males had fluctuating ALT levels, all of whom consumed alcohol (alcohol intake was significant in six individuals). Two of them had been taking native medications and over the counter drugs and one had a positive HBsAg. Both the individuals with insignificant alcohol intake had NAFLD.

The AST/ALT ratio was >1 in 11/26 (42.3%) of people who consumed alcohol in significant amounts, as compared to 5/30 (16%) in patients who did not (P=0.04) (Table 15). The maximum AST/ALT ratio was 3.8 in a person who consumed 560g of alcohol a day and had features of early chronic liver disease sonologically.

Levels of fasting blood glucose ranged between 72-265 mg/dl. 18.5% individuals had impaired fasting glucose and 24% had diabetes. Median values of triglycerides, HDL, total

cholesterol and LDL were 173, 37,199,131.5 mg/dl; respectively. Metabolic syndrome was seen in 40 (71.4%) of the participants (table 16).

Serum ceruloplasmin was normal in all, while transferrin saturation was more than 45% in 8 participants. Seven of the 8 patients with high transferrin saturation had history of significant alcohol intake and two of them had a transferrin saturation of 98%. ANA was weak positive in 4 (7%), none of whom had hyperglobulinemia. Anti tissue transglutaminase was positive in 5 patients.

Table 13 : Laboratory values

	Mean (Range)
Hemoglobin (g/dl)	16 (8.4-20.1)
Platelet count	251000(109000-415000)
LFTs:	
Bilirubin (mg/dl)	0.7 (0.4-3.3)
Total Protein (g/dl)	7.7 (6.6-8.4)
Albumin (g/dl)	4.6 (3.8-5.2)
AST (U/L)	46 (18-245)
ALT (U/L)[@]	62.5 (20-167)
ALP(U/l)	90 (54-157)
GLUCOSE	
Glucose (Fasting) (mg/dl)	98 (72-265)
LIPID PROFILE	
Triglyceride (mg/dl)	173 (30-767)
HDL (mg/dl)	37 (21-84)
Cholesterol (mg/dl)	199 (104-325)

LDL (mg/dl)	131.5 (53-236)
OTHERS	
Ceruloplasmin (U/l)	638 (415-886)
Transferrin Saturation(%age)	28 (2-98)
ANA	5 (Weak positive)
Anti TTG	5

[@] Nine patients had elevated ALT twice prior to being recruited for hospital evaluation. However, during the detailed hospital evaluation their third ALT level was less than 44 U/L.

Table 14: Fluctuating ALT levels

	Persistent Alt Elevation (47)	Alt Fluctuating(9)
Alcohol (significant)	20 (42.5%)	6 (66.7%)
NAFLD	20 (42.5%)	3 (33%)
HBsAg	3 (6.3%)	-
HBsAg + Alcohol	2 (4.2%)	1 (11%)
Anti Hbc	12 (25.5%)	3 (33%)
Drugs	11 (23.4%)	2 (22%)

Table 15 : AST/ALT ratio and alcohol intake

	Alcohol >100g/week	Alcohol <100 g/week
Total	26	30
Normal	5	7
NAFLD	0	23

Alcoholic Fatty Liver	18	0
Early Chronic Liver Disease	3	0
AST/ALT	0.8 (0.34-3.8)	0.7 (0.44-1.43)
AST/ALT > 1	11 (42.3%)	5 (16%)

METABOLIC SYNDROME

Metabolic syndrome was present in 40 individuals (71.4%). 82.9% of obese and 80% of the overweight individuals had metabolic syndrome as against 27% of those with normal BMI (Table 17). The mean BMI was 26.8±5.1 kg/m2.

A strong association was seen between metabolic syndrome and fatty liver. Of the 40 individuals with metabolic syndrome, 34 (85%) had fatty liver on ultrasound (Table 18). In the participants with fatty liver on ultrasound (n=43), 81.4% had metabolic syndrome. Among these 43 participants, 12 of the 18 individuals (66.7%) who had alcohol related fatty liver also had metabolic syndrome; and 22 of the 24 (91.7%) individuals who had NAFLD had metabolic syndrome. Twenty two of 40 individuals with metabolic syndrome had NAFLD compared to 2 of 16 individuals without metabolic syndrome (P=0.014, chi square test).

Table 16: Metabolic Syndrome

PARAMETER			Number (%age)
Blood Pressure	>130/85		33 (58.9%)
Fasting Plasma Glucose	<100 mg/dl		31/54 (57.4%)
	100-125 mg/dl		10/54 (18.5%)
	>126 mg/dl		13/54 (24%)
Lipid Profile	TG >150 mg/dl		33/55 (60%)
	HDL (mg/dl)	<40 (M)	32/51 (62.7%)
		<50 (F)	3/4 (75%)
	CHOL >200 mg/dl		26/55 (47.3%)
	LDL >100 mg/dl		45/55 (81.8%)

Table 17 : Metabolic Syndrome and Obesity

Metabolic Syndrome	BMI 18.5-22.9kg/m2	BMI 23-24.9 kg/m2	BMI >25 kg/m2
Present	3	8	29
Not Present	8	2	6

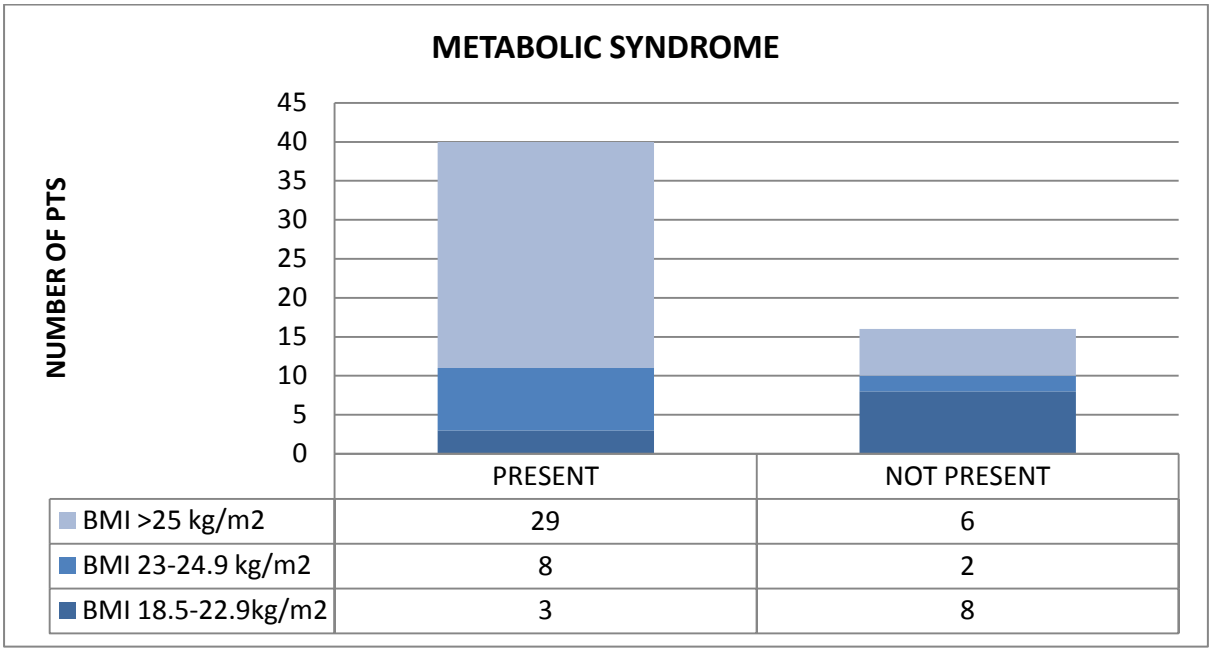
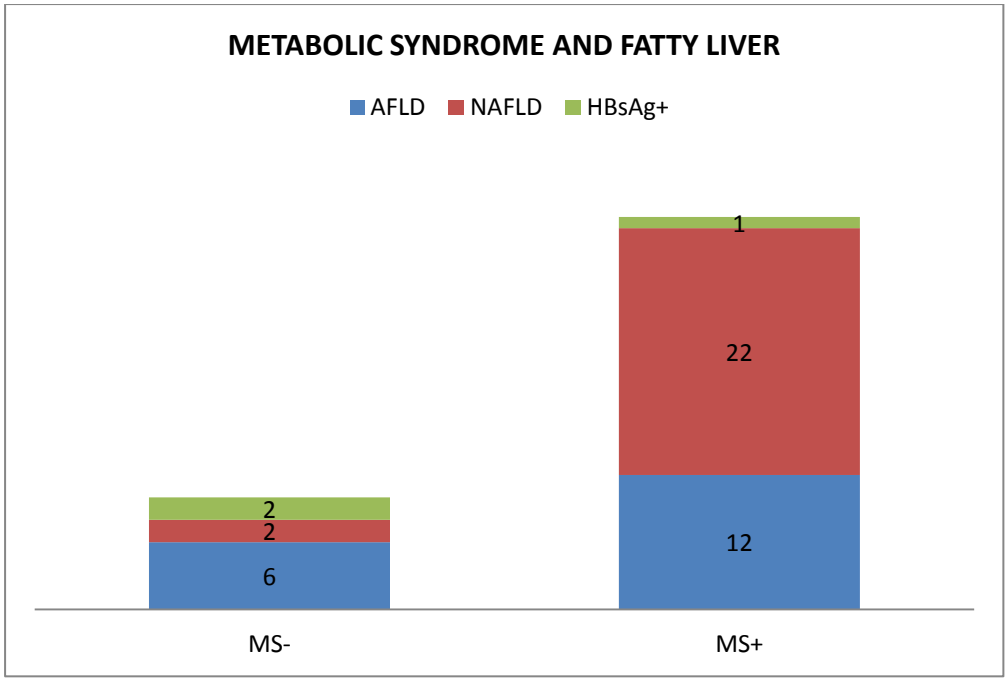


Table 18: Metabolic syndrome and Fatty liver

	AFLD		NAFLD	HBsAg+, Fatty Liver
No MS	HBsAg-	4	2	0
	HBsAg+	2		
MS present	12		22	1


METABOLIC SYNDROME AND FATTY LIVER
AFLD
NAFLD
HBsAg+
2
2
6
1
22
12
MS-
MS+

CHARACTERISTICS OF PATIENTS WITH NAFLD

Twenty four individuals had NAFLD. Majority of the individuals were males (87.5%). Prevalence of NAFLD initially increased and then declined with increasing age, and almost half of the individuals were in their third decade. Median BMI was 27.6 kg/m^2 and BMI decreased with increasing age (Tables 19 and 20). Only one patient had lean NAFLD.

Metabolic syndrome was present in 92% of the patients with NAFLD. Impaired fasting glucose was noted in 8.6% and diabetes mellitus in 39% of the individuals with NAFLD respectively. Ninety two percent of the individuals had at least one component of dyslipidemia (Table 20)

Table 19: Obesity and NAFLD

Age Group	BMI (kg/m2)	Number of individuals
18-29	34.4±6.5	5
30-39	29.57±4	11
40-49	25.73±2.2	6
50-65	24.95±2.5	2

Table 20: Risk factors for patients with NAFLD

Parameters	Range	Median	Mean±SD	Miscellaneous
Age (years)	18-53	37	36.6±9	
Gender	M21/F3			
BMI (kg/m^2)	22.7-43	27.6	28.9±5	>23 (n=23/24)
Waist Circumference(cm)	83-126	98.5	100±9	>90 (n=23/24)
Waist/Hip Ratio	0.87-1.06	0.95	0.96±0.05	>0.9 (n=23/24)
Glucose (mg/dl)	74-262	97	111.4±43	IFG(n=2/23)

				DM(n=9/23)
Cholesterol (mg/dl)	137-325	208	214.4±49.7	>200 (n=14/23)
LDL (mg/dl)	53-191	142	141.6±37.9	>100 (n=18/23)
HDL (mg/dl)	24-56	34	38.6±6	<40 (n=20/23)
TG (mg/dl)	65-529	179	181.8±128	>150 (n=14/23)

VIRAL MARKERS

As described in table 21, six (10.7%) individuals had a positive HBsAg. Fifteen tested positive for anti HBc. Of the six people who were HBsAg positive, 3 also had significant alcohol intake (two of these had fatty liver and one had early CLD) and 2 had features of metabolic syndrome (of whom 1 had fatty liver). Except one individual all others had ALT between 1-2 times the upper limit of normal (Table 22).

The participants were also tested for anti HBc and 15 (26.8%) had a positive result. (Table 23). Of these, 5 individuals were HBsAg positive. Among the 10 individuals with negative HBsAg and anti HBc positivity, ALT varied between 31-102 U/L (median 52 U/L). These patients could theoretically represent a group with occult hepatitis B, seronegative chronic hepatitis b, HBsAg surface antigen mutants or the ones with recovery from a past hepatitis B infection. Further testing like anti HBs and HBV DNA could not be done. All these had other etiologies to explain transaminitis. 50% had significant alcohol intake and another 50% had non alcoholic fatty liver disease. Metabolic syndrome was present in 90%.

Table 21: Viral Markers

VIRAL MARKERS:	**Number of individuals**
HBsAg	6
Anti HBc	15
Anti HCV	0

Table 22: Details of HBsAg positive individuals

Sr No	**ALT**	**ALCOHOL INTAKE (GM/WEEK)**	**METABOLIC SYNDROME**	**ULTRASONOGRAPHY**
1	80	140	N	Fatty Liver

2	35	280	N	Fatty Liver
3	54	140	N	Early CLD
4	47	10	Y	Normal Liver
5	67	40	Y	Fatty Liver
6	53	20	N	Normal Liver

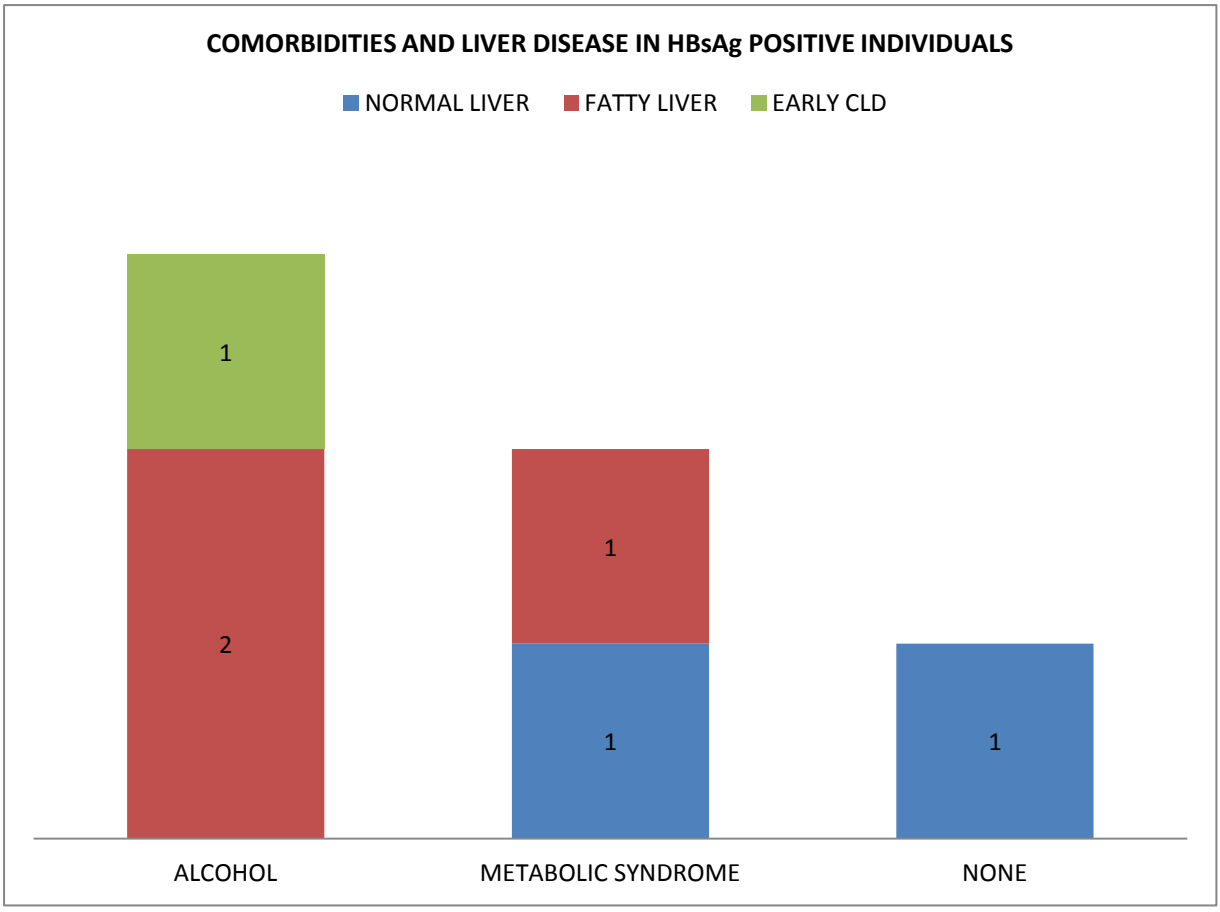
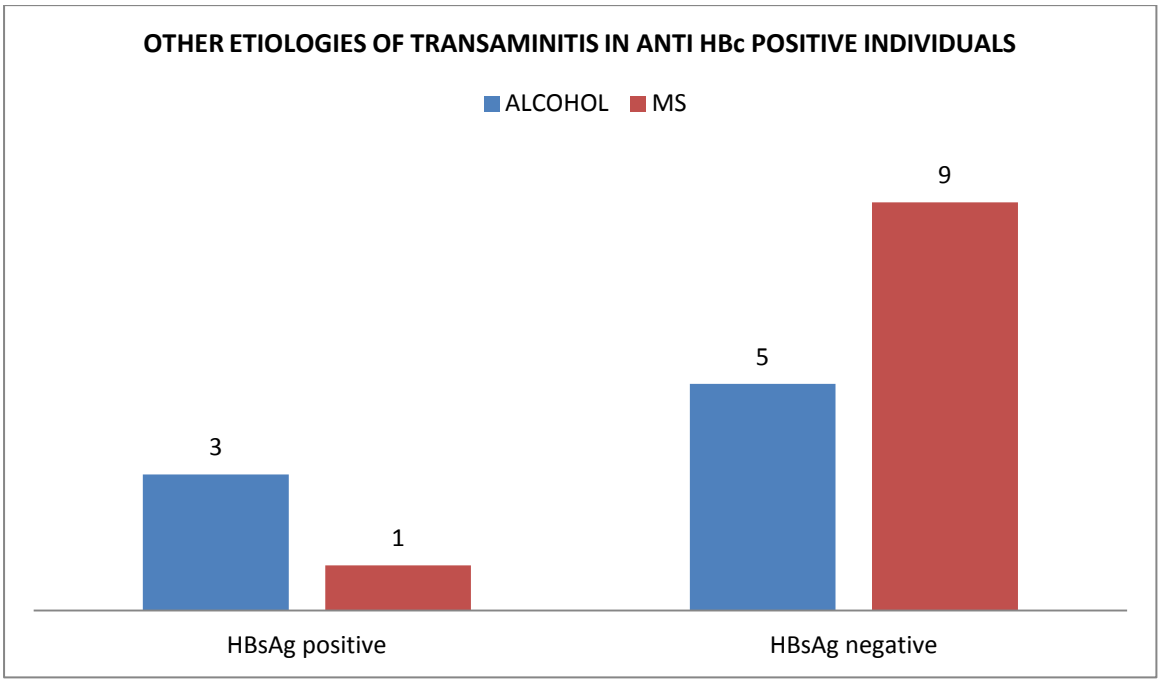


Table 23: Other etiologies of transaminitis in anti HBc positive individuals

anti HBc	**HBsAg**	**ALCOHOL INTAKE**	**METABOLIC SYNDROME**	**ULTRASONOGRAPHY**
Positive	Negative	Significant	P	Fatty Liver
Positive	Negative	Significant	N	Fatty Liver

Positive	Negative	Significant	P	Fatty Liver
Positive	Negative	Insignificant	P	Fatty Liver
Positive	Negative	Insignificant	P	Fatty Liver
Positive	Negative	Significant	P	Normal Liver
Positive	Negative	Insignificant	P	Fatty Liver
Positive	Negative	Significant	P	Normal Liver
Positive	Negative	Insignificant	P	Fatty Liver
Positive	Negative	Insignificant	P	Fatty Liver
Positive	Positive	Significant	N	Fatty Liver
Positive	Positive	Significant	N	Fatty Liver
Positive	Positive	Significant	N	Early CLD
Positive	Positive	Insignificant	P	Normal Liver
Positive	Positive	Insignificant	N	Normal Liver

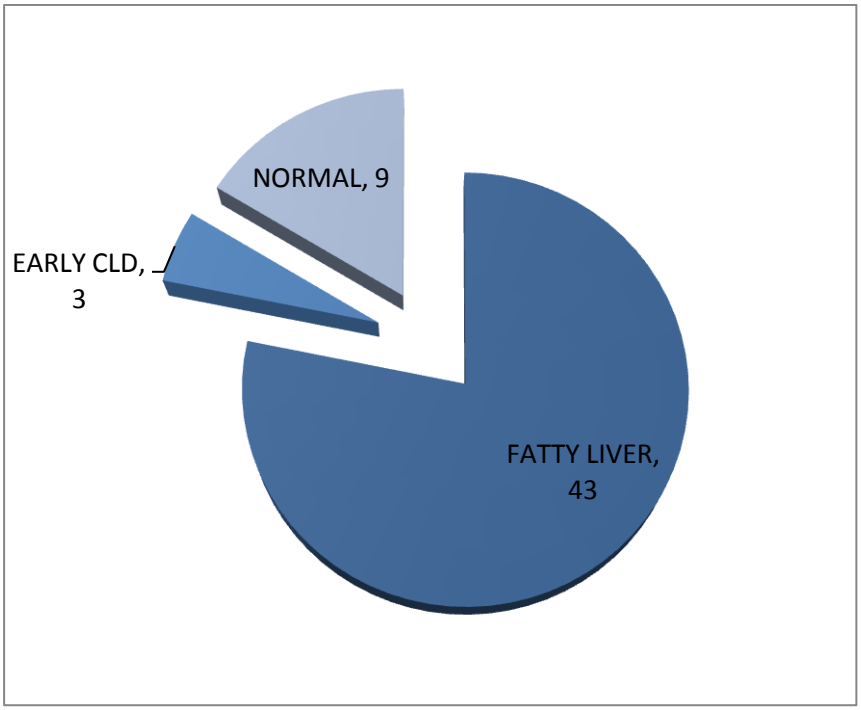
P: Present, N: Not present



ULTRASONOGRAPHY

All participants underwent transabdominal ultrasonography for assessment of the liver and biliary tract. Majority of the individuals (n=43, 76.8%) had a fatty liver. Three had sonological evidence of early chronic liver disease. The remaining 10 had a normal liver on ultrasound.

One person had cholelithiasis and a 13.5 mm calculus in neck of gallbladder. However he was asymptomatic and had normal alkaline phosphatise. Another asymptomatic person had sludge balls in gall bladder. No other biliary tract abnormalities were noted.



Discussion

DISCUSSION

Elevated ALT is a sensitive indicator of hepatocellular damage in acute and chronic hepatitis. Most of the epidemiological data on the prevalence and etiology of transaminitis comes from studies on blood donors or patients seeking medical care which results in a selection and referral bias. We assessed the prevalence and etiology of persistently elevated ALT through a population based cross sectional study to avoid such a bias.

A total of 9000 participants (4439 males, 3200 urban) were included in the study. The surveyed population in Vellore city and surrounding rural areas adequately represents the conditions of villages and towns in southern India, barring a few bigger metropolitan cities like Chennai, Hyderabad and Bangalore.

PREVALENCE OF ELEVATED ALT

The prevalence of elevated ALT at the first measurement was 199/9000 of which only 116 consented for repeat testing, and 91 had persistently elevated ALT. If we assume that only these 91 were "persistent elevated ALT" among the total population of 9000, we arrive at a prevalence rate of elevated ALT of 1% (91/9000) in the adult population. At the other extreme, if we assume that all the 83 participants who refused repeat testing would all have "persistently elevated ALT" then we arrive at a prevalence rate of elevated ALT of 1.93% (174/9000) in the adult population. If we assume that the proportion of "persistent ALT elevation" would have been the same in the 83 participants who refused repeat testing as in the 116 participants who underwent repeat testing that would provide an elevated ALT prevalence rate of 1.73% (153/9000) in the population. We can therefore assume that prevalence of elevated ALT in the adult population surveyed was 1.73% (with a possible range from 1.01% to 1.93%).

Previous community based studies from Europe (Italy) revealed a prevalence of 7.6% in Sicily, 10% in Campania region (single measurement of ALT was done)(141) (142). Both

these towns from southern Italy have a high prevalence of hepatitis C infection and 37-47% of the participants with elevated ALT were HCV RNA positive. The Dionysos Study from northern Italian towns of Campogalliano and Cormons revealed persistently elevated abnormal liver biochemical tests in 17.5% of the individuals studied (143)(144). The Third National Health and Nutrition Examination Survey (NHANES III) conducted in United States between 1988 to 1994 found that prevalence of aminotransferase elevation in adult population was 7.9%(single measurement)(7). Studies from Asia show prevalence of approximately 11% (single measurement) each in Taiwan and China (9)(10), and 7.9%(single measurement); 3.1% (persistent elevation) in Iran(145). There have been no population based studies in India. Elevated ALT levels have been noted in 11.9-16.5% of blood donors (considered to represent normal population) in various studies(146)(147).We have deliberately used a cut-off value for ALT of 44 U/L derived from our measurements in the study population. As the surveyed population was large (9000 individuals) it is likely to be indeed correct. Other studies have used much lower cut-off of ALT level to diagnose liver disease. In our case too, the numbers diagnosed to have liver disease could have increased significantly if we had used a lower cut-off value. However the public health and clinical utility of doing so is a matter of debate (148).

DEMOGRAPHIC PROFILE

Elevated ALT levels were more common in male than in female subjects. The prevalence first increased and then decreased with age, and most of the participants were between 30 and 49 years of age (73%). The commonest etiologies were NAFLD in younger age group (18-39 years) and alcohol consumption in the middle age group(40-55 years) respectively. Population based studies from US, Taiwan and China have shown a similar gender distribution and age distribution(7)(9)(10). However, unlike our study, NAFLD was

more commonly seen in middle aged individuals and HCV infection was noted to increase with increasing age in these studies.

ETIOLOGY OF ELEVATED ALT

Alcohol :

Though India has previously been considered as a traditional 'dry' and abstaining country, there has been an alarming upward trend in the prevalence of alcohol intake recently. There has been an increase in the frequency of alcohol intake, hazardous drinking and chronic use. Age of initiation of alcohol intake has shown a decreasing trend. In the present study, alcohol was the most common etiology of persistently elevated ALT (46.4%). All individuals consuming alcohol were males. Though most of them were in their 3rd and 4th decades, nearly half of the participants below 30 years of age consumed alcohol in significant amounts. Risky drinking was noted in 84.6% of the individuals. Most participants belonged to the middle and lower socioeconomic status. ALT elevation in the majority (59%) was upto 2 times the upper limit of normal. Population based studies assessing alcohol use and its implications on health in southern India have shown a similar age and gender distribution. A recent study from Karnataka showed that 13% of the population consumed alcohol and two thirds of these individuals belonged to the age group 26-45 years(149). Forty percent of the individuals had risky drinking (binge drinking) and 55% drank till intoxication. The proportion of these heavy and long term drinkers was also higher in the rural and slum areas as in our study. The Non-Communicable Disease Risk Factor Survey (2007-08) revealed similar findings in Tamil Nadu.

Alcohol consumption patterns vary considerably among different countries and even among different ethnic groups within one country(150). In southern Italy, excessive alcohol was the most common probable cause of abnormal liver biochemical tests, seen in 45.6 % of the participants(8). Our study had similar results. In other countries with a higher incidence of

NAFLD and viral hepatitis, ALT elevation due to excessive alcohol was seen in lesser number of participants (13.5% and 18.6% in United States(7) and China(10), respectively). A much lower number (0.8%) had alcohol related ALT elevation in Taiwan(9). Studies on etiology of ALT elevation in blood donors have attributed the same to be due to alcohol in 2-14%(151)(152).

NAFLD

With the increasing prevalence of obesity, diabetes and metabolic syndrome, NAFLD is becoming the leading cause of liver disease worldwide. Unlike the prior belief, NAFLD is not a benign disease as it has been shown to progress to advanced fibrosis, liver failure and HCC (153)(154). Large population based surveys in US (NHANES III) and Europe (Dionysus study) have shown that NAFLD is present in at least 20% of the general population in the West (7)(143). NAFLD was considered to be uncommon in the Asia Pacific countries as it is a disease of affluence and these countries have a high burden of viral hepatitis. However, various studies in this region have shown the prevalence of NAFLD ranging between 5-43% (Table 24)

Table 24: Prevalence of NAFLD in SE Asian countries

COUNTRY	PREVALENCE OF NAFLD
Japan	9-43% (155)(156)(157)(158)
China	5-24%(159)(160)(161)
India	5-28%(162)(29)(163)
Korea	18%(164)
Sri Lanka	32%(165)

Indian data on NAFLD has been based on studies on people undergoing master health check ups, ultrasonography for non liver related causes, healthy relatives of the patients and railway employees. These studies have a selection bias, and focus on the economically developed segments of populations. A community based study from a rural population in West Bengal revealed a prevalence of NAFLD, NAFLD with elevated ALT, and cryptogenic cirrhosis of 8.7%, 2.3%, and 0.2%, respectively(166). That study used ultrasound scan and CT scan as the screening modality to identify NAFLD whereas in the present study we focused on ALT elevation and then tried to identify the cause of ALT elevation. It has been seen that Indians have a higher prevalence of diabetes, insulin resistance and fatty liver than the other populations in Asia Pacific.

NAFLD was the second most common etiology of elevated ALT, affecting 43% of the participants in our study. Using a 1% minimal estimate of persistent ALT elevation in our community study, we can then calculate the prevalence of NAFLD in this adult population to be at least 4.3 per thousand individuals, with the mid figure at 7.4 per 1000 and the upper limit of the range of estimated prevalence would be 8.2 per 1000 population.

NAFLD has been considered to be the hepatic component of metabolic syndrome(167). Obesity is a well documented and common risk factor for NAFLD. The prevalence of NAFLD in obese patients undergoing bariatric surgery can exceed 90%(168). High BMI and visceral obesity are known risk factors for NAFLD. Four fifths of the participants in our study were either obese (62.5%) or overweight (18%). Of these, more than half had NAFLD. Mean BMI for these individuals with NAFLD was $28.98\underline{+}5$ kg/m^2. Central adiposity (measured by waist hip ratio) was present in all patients with NAFLD. High prevalence of NAFLD has been noted in diabetic patients(169). In a study done in a diabetic clinic from a tertiary care centre in Mumbai, 127 of 204 diabetic patients had a fatty liver on ultrasonography and 87% patients who underwent a liver biopsy had histologically confirmed

NAFLD(170). In our study, 18.5% of the participants had impaired fasting glucose and 24% were diabetic. Eighty three percent of these patients had a fatty liver, of which 60% were attributed to NAFLD and 34% had an alcohol related fatty liver. High prevalence of NAFLD has been seen in individuals with dyslipidemia (171). High triglyceride levels (>150mg/dl) were seen in 60%, LDL was >100 mg/dl in 82%, high cholesterol levels (>200 mg/dl) was seen in 47% and 63% males and 75% females had low HDL in our study and ninety one percent of participants with NAFLD were dyslipidemic. Age and gender have also been associated with a differential prevalence of NAFLD. In various studies worldwide, NAFLD has been seen to be more common in males and its prevalence increases with an increase in age(79)(169)(172). In our study, 87.5% of the participants with NAFLD were males, but the prevalence of NAFLD was seen to be maximum in the third decade. This was probably because the individuals in this age group had a higher BMI (29.6$\pm$4 kg/m^2) than the older individuals (25.7$\pm$2.2 kg/m^2 and 24.9$\pm$2.5 kg/m^2 in 4th and 5th decades, respectively). This also highlights the increasing trend of obesity related morbidity in the younger age groups in our population. A comparison with the other studies on NAFLD and associated metabolic diseases in India has been tabulated. (Table 25). Like other Indian studies, more males had NAFLD. The mean age was comparable. However, the prevalence of obesity and dyslipidemia in our study was more than other studies.

Table 25 : NAFLD and Metabolic Syndrome in Indian studies

LOCATION	N	M/F	AGE(MEAN)	MEAN BMI(kg/m^2)	CENTRAL OBESITY(%)	OBESITY(%) (BMI>23kg/m2)	DM(%)	↑TG(%)	↑TOTAL CHOL(%)	↓HDL(%)	MS(%)
Vellore (present study)	24	21/3	37	29$\pm$5	100	96	43	65	87	13	92
Lucknow (173)	65	46/19	39	27.4	98	73	8				36

Chandigarh (174)	31	25/6	38	74% had >25	92		10	32		42	
New Delhi(175)	51	46/5	34	26.7		69	10	41		36	21

VIRAL ETIOLOGIES

Chronic viral hepatitis is an important cause of chronic necroinflammatory and neoplastic liver disease worldwide. Chronic hepatitis B and hepatitis C infections affect approximately 5-7% and 3% of the world's population, respectively(49)(55) and can lead to substantial morbidity and mortality from cirrhosis, liver failure and hepatocellular carcinoma. India has more than 40 million HBV carriers, which accounts for the second largest pool of chronic HBV carriers in the world(53). The prevalence of hepatitis C virus infection evaluated by anti HCV antibody positivity is between 1-2% among voluntary blood donors and 0.87% in the community, which is similar to that seen in the developed and industrialized countries like Japan and USA(73)(176).

In our study, HBsAg and anti HBc positivity was noted in 6 (10.7%) and 15 (27%) respectively of the 56 tested participants with elevated ALT. Anti HCV antibody was not detected in any of the participants. If we assume that only these 21 individuals had evidence of current or active HBV infection, the prevalence would be very low (0.23%). In our study, we pre-selected only individuals with elevated ALT for HBsAg and anti-HBc testing, and it is very likely that this will therefore grossly underestimate the prevalence of HBV markers in the community. Many HBV positive individuals in the community may have normal ALT. The primary intent of our study was to evaluate the prevalence of elevated ALT in the community and to ascertain its causes, and our study was neither designed nor powered to assess HBV prevalence in the community.

Anti HBc was positive in 26.8% of the participants (two thirds of these were only anti HBc positive) with persistently elevated ALT in our study. These patients could represent a group with occult hepatitis B, seronegative chronic hepatitis B, HBsAg surface antigen mutants. It could also indicate a phase of late immunity when the original infection has resolved and anti HBs levels fall below detectable limits. The prevalence was similar to a study on blood donors in our centre(16.7%)(177) and in West Bengal (18.3%)(178), but higher than the donors in north India(8.4-10.8%) (179)(180).

Anti HCV has been found to be positive in 3-13% of the individuals with elevated ALT in various studies. However, in our study there were no participants with anti HCV positivity. This may be due to the low prevalence of anti HCV positivity (0.1-0.87%), as noted in other community based studies(181)(58) in India. Another possible reason could be that the cut off for ALT was taken as 44 U/L in our study. Lower values of optimal upper limit of normal (30 U/L for men and 19 U/L for women) have been suggested to discriminate persons infected with HCV from those at lower risks of liver disease(18)(19). Fluctuations in ALT levels in patients with hepatitis C infection and lower incidence of intravenous drug abuse could be the other reasons for the same.

Of the 14% participants with a past history of jaundice in our study, one was HBsAg and anti Hbc positive, and another was only anti HBc positive. The second individual could have had a spontaneous HBsAg seroconversion, or it could have been a HBsAg surface antigen ‘a’ mutant. Among the participants with positive HBsAg and anti HBc, the possible risk factors were unprotected sexual intercourse and past history of surgeries. Only one of these persons had received blood products in the past and had a history of tattooing too.

OTHER ETIOLOGIES:

Drug induced liver injury (DILI) is an important but uncommon cause of elevation of ALT, and it carries a significant morbidity and mortality. The true incidence of the same is unknown as it is vastly unrecognised and under reported. Commonly implicated drugs include paracetamol in the West and antitubercular therapy in India. Except for a study on blood donors with elevated ALT from Morroco(151) which implicated DILI as the commonest etiology of ALT elevation, studies elsewhere have shown a much lesser prevalence. A little more than one fourth of the participants from our study had history of drug intake. Except for native and over the counter drugs, no other common hepatotoxic drugs were identified and all of these individuals either had another etiology (significant alcohol or NAFLD) which explained the ALT elevation.

Wilson's disease is another important, but rarer cause of liver disease. There are no studies on incidence and prevalence of this disease from India. In studies from Europe the prevalence varies between 12 and 29 per 100,000 population(182). Most of the patients are symptomatic at presentation. Our study included asymptomatic individuals with persistent transaminitis and serum ceruloplasmin was normal in all the participants.

In Caucasian populations in US and Europe, hereditary **hemochromatosis** is another cause of transaminitis(124) and abnormal liver enzymes are seen in 75 percent of these patients(125). However, in the most of Asian, Indian subcontinent, African, Australasian, and American Indian populations, frequencies of C282Y mutations are close to zero(183). Fourteen percent of the individuals in our study had a transferrin saturation of >45%, thus warranting a further evaluation for hemochromatosis. Of these individuals, 88% had history of significant alcohol intake.Though the HFE gene mutations were not tested in these individuals, studies have shown that upto 15% of people with significant alcohol intake can have high transferrin saturation, probably due to alcoholic siderosis(184). One third of these

patients had a history of jaundice in family members, further details of which were not available.

Celiac disease is a multisystem disorder which can have a variable clinical expression. Asymptomatic transaminitis may occur in these individuals and can represent parenchymal or vascular liver disease(185)(186). There is a difference in the prevalence of celiac disease in North and South India(187), probably due to differences in staple diets (wheat in north and rice in south India respectively) or differences in genetic makeup. A recent hospital based study from Chennai found a low prevalence of celiac disease in Tamil population(188). In our study, anti tissue transglutaminase was positive in 7% of the patients with persistently elevated ALT. None of these patients had duodenal biopsy to confirm celiac disease.

Autoimmune hepatitis is a rare cause of liver disease in India, with a prevalence of 1.5-6.4% in patients with chronic liver disease(103) (104)(105). In our study, 7% of the individuals had a weakly positive ANA, but there was no hyperglobulinemia. Other etiologies like significant alcohol intake (75%) and NAFLD (25%) were noted among these participants. Further autoimmune workup was not deemed necessary.

Conclusions

CONCLUSIONS

- The estimated prevalence of persistently elevated ALT, suggestive of possible liver damage in this south Indian population is 1.73% (153/9000) in the population.
- The most common etiologies of elevated ALT were alcohol intake (46.4%) and NAFLD (42.9%).
- Among the viral etiologies, HBsAg was positive in 10.7% of the participants and commonly coexisted with history of alcoholism, while no participant had hepatitis C infection.
- A majority (71.4%) of individuals had the 'deadly quartet' of metabolic syndrome. Ninety two percent of these participants had NAFLD.
- From a public health perspective, both early clinical intervention and primary prevention are important and strategies to jointly reduce both alcohol consumption and obesity may lead to reduction in liver disease.

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Appendices

I : Masterchart

No	Age	Gender	Modified Kuppuswamy Scale	Alcohol	Weekly Alcohol	AUDIT	Drugs	Native Med	OTC	Past H/o Jaundice	Jaundice in family	Surgery in past	Blood Transfusion	I/V drug abuse
1	41	F	IV	N	0	0	Y	N	N	N	N	Y	Y	N
2	42	M	IV	N	0	0	N	N	N	N	N	N	N	N
3	48	M	IV	Y	140	10	Y	N	Y	N	N	N	N	N
4	42	M	II	Y	280	16	N	N	N	N	N	Y	N	N
5	31	M	III	Y	280	13	N	Y	Y	N	N	Y	Y	N
6	29	M	III	Y	140	4	N	N	N	N	N	N	N	N
7	28	M	III	Y	140	21	N	N	N	N	N	N	N	N
8	27	F	IV	N	0	0	N	N	N	N	N	N	N	N
9	49	M	III	Y	280	5	N	N	N	Y	N	Y	N	N
10	32	M	III	Y	140	9	N	N	N	Y	N	Y	N	N
11	31	M	IV	Y	180	23	N	N	N	N	N	N	N	N
12	32	M	III	Y	280	19	Y	N	N	N	N	N	N	N
13	39	M	III	Y	10	4	N	N	N	N	N	N	N	N
14	36	M	IV	Y	40	7	N	N	N	N	N	Y	N	N
15	32	M	III	Y	5	3	N	N	N	N	N	N	N	N
16	24	M	III	N	0	0	N	N	N	Y	N	N	N	N
17	44	M	III	Y	280	7	N	N	N	N	N	N	N	N
18	42	M	IV	Y	140	15	N	N	N	N	Y	N	N	N
19	41	M	IV	Y	560	22	N	N	N	N	N	N	N	N
20	34	M	III	N	0	0	N	N	N	N	N	N	N	N
21	47	M	IV	Y	280	8	N	Y	N	Y	Y	N	N	N
22	53	F	V	N	0	0	Y	N	N	N	N	Y	N	N
23	55	M	IV	Y	560	17	Y	N	N	N	Y	N	N	N
24	37	M	IV	N	0	0	Y	N	N	N	N	Y	N	N
25	34	M	III	Y	10	5	N	N	N	N	N	N	N	N
26	40	M	IV	Y	280	20	Y	Y	Y	N	N	N	N	N
27	41	M	IV	Y	140	10	Y	Y	N	N	Y	N	N	N
28	37	M	IV	Y	40	6	N	N	N	N	N	Y	N	N
29	33	F	IV	N	0	0	N	N	N	N	N	N	N	N

30	44	M	III	Y	140	23	N	N	N	N	N	N	N	N
31	19	M	II	N	0	0	N	N	N	N	N	N	N	N
32	26	M	IV	Y	40	5	N	N	N	N	N	N	N	N
33	45	M	III	Y	140	5	N	N	N	N	N	N	N	N
34	40	M	IV	Y	10	1	Y	N	N	N	N	Y	N	N
35	44	M	IV	Y	280	17	N	N	N	N	N	Y	N	N
36	25	M	II	Y	1200	19	N	N	N	Y	N	N	N	N
37	18	M	III	N	0	0	N	N	N	N	N	N	N	N
38	24	M	II	Y	280	14	N	N	N	Y	Y	N	N	N
39	39	M	III	Y	280	11	N	N	N	N	N	N	N	N
40	44	M	IV	Y	20	5	N	N	N	N	N	N	N	N
41	38	M	III	Y	20	2	N	N	N	N	N	N	N	N
42	32	M	II	Y	70	14	N	N	N	N	N	N	N	N
43	49	M	IV	N	0	0	Y	N	N	N	N	N	N	N
44	54	M	IV	Y	560	13	Y	N	Y	N	N	Y	Y	N
45	43	M	IV	Y	5	6	Y	N	N	N	N	N	N	N
46	50	M	III	Y	10	3	N	N	Y	N	N	Y	N	N
47	37	M	IV	N	0	0	Y	Y	N	Y	N	N	N	N
48	28	M	III	Y	140	9	N	N	N	N	N	N	N	N
49	48	M	IV	Y	20	7	Y	Y	N	N	N	N	N	N
50	32	M	I	Y	20	3	N	N	N	N	N	Y	N	N
51	33	M	IV	Y	40	7	N	N	N	N	N	N	N	N
52	20	M	III	Y	10	5	N	Y	Y	N	N	Y	Y	N
53	35	M	IV	Y	140	21	N	N	N	N	N	N	N	N
54	41	M	III	Y	140	18	N	N	N	N	N	N	N	N
55	32	M	IV	Y	20	6	N	N	N	Y	N	N	N	N
56	37	M	IV	Y	20	8	N	N	N	N	N	N	N	N

Sr No	Unsafe sex	Tattooing	Systolic BP	Diastolic BP	Weight (kg)	Height (m)	BMI (kg/m2)	Waist Circumference (cm)	Hip (cm)	W/H	Metabolic Syndrome
1	N	N	106	70	60.7	1.57	24.7	94	102	0.9	y
2	N	N	150	80	77	1.64	28.6	96	104	0.9	y
3	N	N	110	70	56.8	1.6	22.2	82	89	0.9	n
4	N	N	124	80	78	1.69	27.3	96	94	1	y
5	Y	N	112	80	85	1.66	30.8	106	104	1	y
6	N	N	140	90	57.7	1.67	20.7	73	84	0.9	n
7	Y	N	118	70	71.6	1.67	25.7	91	98	0.9	n
8	N	N	130	80	71.8	1.46	33.7	100	115	0.9	y
9	N	N	124	84	82	1.75	26.8	101	100	1	y
10	Y	N	130	88	98	1.6	38.3	114	125	0.9	y
11	N	N	120	66	62	1.75	20.2	82	88	0.9	n
12	N	Y	128	82	55.4	1.62	21.1	71	81	0.8	n
13	N	N	152	90	80	1.65	29.4	95	98	1	y
14	N	N	130	90	91.8	1.75	30	103	109	0.9	y
15	N	N	108	68	70	1.66	25.4	98	99	1	y
16	N	N	130	90	110	1.6	43	126	126	1	y
17	N	N	154	100	75.6	1.67	27	90	96	0.9	y
18	N	N	120	84	58	1.63	21.8	89	84	1.1	n
19	N	N	192	98	73	1.66	26.5	82	90	0.9	y
20	N	N	126	84	68.7	1.71	23.5	100	106	0.9	y
21	Y	N	124	84	87.8	167	31.5	109	112	1	y
22	N	N	134	90	64.5	1.56	26.7	106	100	1.1	y
23	N	Y	150	90	55	1.54	23.2	82	86	1	n
24	N	N	126	86	80.4	1.68	28.5	106	106	1	y
25	N	Y	130	80	84.2	1.64	31.3	99	106	0.9	y
26	N	N	124	80	50.7	1.64	18.7	79	92	0.9	n
27	N	Y	138	90	64	1.67	22.9	92	93	1	y
28	Y	N	160	100	78	1.69	27.3	91	101	0.9	y
29	N	N	160	90	42	1.47	19.4	73	87	0.8	n
30	Y	N	130	80	69.3	1.66	25.1	98	95	1	y
31	N	N	110	70	44.8	1.71	15.3	61	82	0.7	n
32	N	N	130	84	78.5	1.72	26.5	105	112	0.9	y
33	Y	N	112	70	71.5	1.68	25.3	91	100	0.9	n

34	N	N	92	60	75.9	1.65	27.9	98	109	0.9	y
35	N	N	138	90	80.2	1.64	29.8	104	102	1	y
36	N	N	140	90	81.3	1.72	27.5	91	106	0.9	y
37	N	N	130	86	93.8	1.58	37.6	111	115	1	y
38	N	N	122	80	71.2	1.74	23.5	88	93	0.9	n
39	N	N	130	88	75.3	1.6	29.4	96	103	0.9	y
40	N	Y	114	80	66.9	1.61	25.8	93	97	1	n
41	N	N	144	100	88	1.73	29.4	99	106	0.9	y
42	N	N	150	100	93	1.65	34.2	112	108	1	y
43	Y	N	124	80	58	1.6	22.7	83	90	0.9	y
44	Y	Y	140	90	55.4	1.6	21.6	76	84	0.9	y
45	N	N	154	86	63.7	1.61	24.6	94	95	1	y
46	N	N	136	80	67.8	1.71	23.2	90	94	1	y
47	N	N	130	90	72	1.7	24.8	92	93	1	y
48	N	N	140	90	67	1.66	24.3	86	89	1	y
49	N	N	132	90	70	1.58	28	100	98	1	y
50	N	N	128	80	70.5	1.6	27.5	91	101	0.9	n
51	Y	N	120	78	63	1.62	23.9	80	82	1	y
52	N	N	130	86	89	1.74	29.4	94	104	0.9	n
53	N	N	140	100	65	1.68	23	92	93	1	y
54	N	N	154	100	97.5	1.73	32.6	115	109	1.1	y
55	N	N	122	80	64	1.57	26	83	80	1	n
56	N	N	130	88	98.4	1.63	37.3	113	112	1	y

Sr No	**Hemoglobin**	**Platelets**	**ALT (Value 1)**	**ALT (Value 2)**	**Bilirubin (T)**	**Bilirubin (D)**	**Total Protein**	**Albumin**	**AST**	**ALT**	**ALP**	**HBsAg**	**anti HBc**
1	13.7	370000	61	77	0.9	0.2	7.8	4.6	62	86	97	N	N
2	16.4	315000	80	167	1.7	0.5	7.8	4.5	75	150	81	N	N
3	13.7	253000	56	64	1.2	0.6	7.5	3.8	29	20	103	N	N
4	17.6	249000	93	45	0.6	0.2	7.9	4.9	53	42	114	N	P
5	14.5	184000	79	66	0.6	0.2	7.6	4.8	38	54	62	N	N
6	18.1	307000	90	52	0.8	0.2	7.6	4.9	37	45	80	N	N
7	16.7	282000	75	149	1.2	0.3	7.3	4.3	47	80	92	P	P
8	13.9	291000	79	78	0.6	0.1	7.7	4.2	123	97	104	N	N
9	14.5	231000	47	69	0.9	0.3	7.3	4.5	37	48	89	N	N
10	18.8	239000	91	54	1.8	0.6	7.9	4.7	130	93	99	N	N

11	16.7	245000	196	44	0.7	0.3	8	4.7	30	21	73	N	N
12	17.7	233000	56	138	1.1	0.3	7.7	5.2	74	109	82	N	N
13	10.5	158000	48	45	0.7	0.2	7.4	4.4	43	38	76	N	N
14	15.2	261000	129	54	0.4	0.2	7.6	4.6	46	57	54	N	N
15	15	394000	97	61	0.6	0.2	8.2	4.5	49	61	98	ND	ND
16	14.8	350000	54	58	0.6	0.2	7.4	4.4	33	46	111	N	N
17	18.9	206000	87	61	1.8	0.4	7.5	4.4	30	21	106	N	N
18	15.6	342000	72	53	0.6	0.2	8	4.9	40	53	78	N	P
19	16.8	244000	77	190	1.1	0.3	7.6	4.7	89	129	111	N	N
20	15.2	301000	71	59	0.9	0.4	6.8	4.4	45	58	102	N	N
21	16.2	252000	85	49	0.8	0.4	7.7	4.8	63	73	83	N	P
22	15.2	236000	77	53	0.4	0.1	7.1	4.6	32	39	96	N	N
23	13	109000	59	69	3.3	2.5	8.3	3.8	245	64	94	ND	ND
24	16	308000	47	65	0.5	0.2	8.2	4.7	39	63	90	N	P
25	16.2	273000	78	157	0.5	0.2	7.7	4.3	61	113	87	N	N
26	15.2	188000	44	61	0.7	0.3	7.7	4.5	47	35	85	P	P
27	18.3	263000	44	51	1.1	0.4	7.4	4.6	51	52	109	N	N
28	17.6	186000	76	172	0.8	0.2	6.9	4.4	85	99	76	N	P
29	8.4	190000	88	102	0.5	0.1	8.2	5	125	90	66	N	N
30	9.6	278000	54	44	0.4	0.2	7.6	4.2	37	31	85	N	P
31	12.6	322000	77	190	0.4	0.1	8.1	4.5	145	100	88	N	N
32	17.8	195000	46	70	0.6	0.3	7.7	4.6	57	70	111	N	N
33	15.7	220000	55	52	0.8	0.4	7	4.9	35	54	82	P	P
34	14.9	238000	49	101	0.6	0.2	7.7	4.1	29	47	75	P	P
35	15.9	162000	96	143	0.7	0.3	8	4.5	155	144	96	N	N
36	17.1	211000	83	86	0.8	0.2	7.7	4.7	34	65	61	N	N
37	14.1	415000	85	54	0.7	0.2	7.5	4.5	62	68	94	N	N
38	17.2	271000	158	148	0.6	0.2	7.4	4.7	56	167	86	N	N
39	15.9	212000	51	47	0.4	0.2	7.8	4.6	35	47	79	ND	ND
40	17.1	250000	57	60	0.5	0.2	7.7	4.3	18	41	67	N	N
41	14.5	271000	77	77	0.6	0.2	8.1	4.9	64	102	97	N	P
42	15.5	300000	52	60	0.6	0.2	7.9	4.8	32	54	110	N	N
43	15.9	241000	52	65	0.5	0.2	8.4	5.2	39	62	100	N	N
44	14.2	364000	91	114	0.7	0.4	8.1	4.3	77	51	91	N	P
45	15.9	239000	48	73	0.6	0.2	7.7	4.8	34	69	73	N	N
46	16.8	250000	63	85	0.5	0.2	7.1	4.3	46	76	106	N	N
47	16.2	286000	44	72	0.9	0.2	7.2	4.4	71	94	157	N	N

48	20.1	172000	59	69	1.9	0.5	7.8	5	35	58	76	N	N
49	16.8	320000	55	44	1.1	0.3	7.2	4.2	34	45	90	N	P
50	15	333000	51	68	0.8	0.2	8.3	4.8	48	68	145	N	N
51	16.2	192000	45	55	0.4	0.1	7.3	4.6	40	67	61	P	N
52	16.2	254000	71	128	0.8	0.3	7.9	5.1	63	135	74	N	N
53	16.6	256000	134	82	0.9	0.2	8.1	5	60	92	150	N	N
54	17.4	241000	73	69	1.1	0.4	8.3	4.9	117	80	116	N	N
55	17.4	243000	57	86	1.2	0.4	7.5	4.9	31	53	119	P	P
56	16.1	359000	56	52	1.1	0.3	8.1	4.6	35	45	57	N	P

Sr No	anti HCV	Glucose (AC)	Cholesterol	LDL	HDL	TG	Ceruloplasmin	Transferrin Saturation	ANA	ANTI TTG	Ultrasonography	Biliary abnormalities on USG
1	N	151	237	167	33	240	540	29	WP	N	FATTY LIVER	N
2	N	109	169	117	34	66	517	27.5	N	N	FATTY LIVER	N
3	N	80	188	126	45	133	779	24.4	WP	N	NORMAL LIVER	N
4	N	107	295	186	48	420	774	34	N	P	FATTY LIVER	N
5	N	91	255	184	34	280	524	29.4	N	N	FATTY LIVER	N
6	N	99	251	158	44	197	762	19	N	N	FATTY LIVER	N
7	N	90	162	100	45	112	415	65	N	N	FATTY LIVER	N
8	N	153	239	162	34	215	793	30.6	N	N	FATTY LIVER	N
9	N	168	199	143	35	132	733	31.7	N	N	FATTY LIVER	N
10	N	117	220	154	35	160	832	35.9	WP	P	FATTY LIVER	N
11	N	72	214	133	71	57	492	42	N	N	NORMAL LIVER	N
12	N	103	158	87	58	767	592	98	N	N	FATTY LIVER	N
13	N	143	137	53	28	416	497	8	N	N	FATTY LIVER	N
14	N	121	157	94	43	198	812	16	N	N	FATTY LIVER	N
15	ND	93	242	182	34	151	741	28.5	N	N	FATTY LIVER	N
16	N	130	199	135	32	123	592	23	N	N	FATTY LIVER	N
17	N	109	194	131	36	191	734	68	N	N	FATTY LIVER	N
18	N	90	174	105	37	236	565	22.2	N	N	FATTY LIVER	N
19	N	108	196	119	40	289	594	40.9	N	N	FATTY LIVER	N
20	N	88	167	95	33	212	622	26	N	N	FATTY LIVER	N
21	N	104	256	236	48	173	801	25	N	N	FATTY LIVER	N
22	N	130	244	169	35	127	721	24	N	N	FATTY LIVER	N
23	ND	72	240	183	41	165	701	98	N	P	EARLY CLD	N

24	N	89	266	188	35	284	467	33	N	N	FATTY LIVER	N
25	N	262	271	180	24	481	440	39.7	N	N	FATTY LIVER	N
26	N	95	217	109	84	64	623	33.8	N	N	FATTY LIVER	N
27	N	95	205	84	28	646	584	45	N	N	FATTY LIVER	N
28	N	97	325	191	31	529	633	26	N	N	FATTY LIVER	N
29	N	94	186	128	52	30	685	2	N	N	NORMAL LIVER	N
30	N	93	155	107	35	94	635	4	N	N	NORMAL LIVER	N
31	N	84	104	53	41	54	671	24	N	N	NORMAL LIVER	N
32	N	ND	ND	ND	ND	ND	663	25	N	N	FATTY LIVER	N
33	N	99	191	119	50	66	511	41.2	N	N	EARLY CLD	N
34	N	119	197	153	36	63	640	22.4	N	N	NORMAL LIVER	N
35	N	95	154	86	21	243	542	45	N	N	EARLY CLD	N
36	N	ND	158	106	32	112	513	31	N	N	NORMAL LIVER	N
37	N	74	138	83	39	104	708	10.3	N	N	FATTY LIVER	N
38	N	95	126	67	42	98	600	54.8	N	P	FATTY LIVER	N
39	ND	93	180	109	41	185	ND	21	1+	N	FATTY LIVER	N
40	N	89	204	138	42	84	558	33	N	N	FATTY LIVER	SLUDGE BALLS IN GB,
41	N	94	252	174	37	181	649	20.9	N	N	FATTY LIVER	N
42	N	135	266	173	37	350	827	16.7	N	N	FATTY LIVER	N
43	N	162	224	151	36	277	614	21.3	N	N	FATTY LIVER	N
44	N	126	175	124	29	153	622	26.4	N	N	NORMAL LIVER	CHOLELITHIASIS, 13.5 MM CALCULOUS IN NECK OF GB
45	N	179	170	100	56	65	540	28	N	N	FATTY LIVER	N
46	N	98	208	143	37	182	803	36	N	N	FATTY LIVER	N
47	N	92	265	173	38	173	477	27	N	N	FATTY LIVER	N
48	N	76	155	79	35	272	463	30	N	N	FATTY LIVER	N
49	N	85	213	142	34	179	647	46	N	N	FATTY LIVER	N
50	N	85	183	123	41	131	850	23.5	N	N	NORMAL LIVER	N
51	N	101	215	132	37	173	886	34.7	N	N	FATTY LIVER	N
52	N	83	147	112	38	87	684	18.6	N	N	FATTY LIVER	N
53	N	246	264	121	38	741	741	40	N	P	FATTY LIVER	N
54	N	98	237	131	42	447	772	55	N	N	FATTY LIVER	N
55	N	265	198	147	42	106	540	52.4	N	N	NORMAL LIVER	N
56	N	84	194	135	33	125	703	32	N	N	FATTY LIVER	N

II : Proforma

PROFORMA

NAME

HOSPITAL NUMBER

AGE

SEX

ADDRESS

TELEPHONE NUMBER

EDUCATION

OCCUPATION

SOCIOECONOMIC STATUS

MODIFIED KUPPUSWAMY SCALE

(A) Education Score

EDUCATION	SCORE
Profession or Honours	7
Graduate or Post graduate	6
Intermediate or Post High School Diploma	5
High School Certificate	4
Middle School Certificate	3
Primary School Certificate	2
Illiterate	1

(B) OCCUPATION

OCCUPATION	SCORE
Professional	7
Semi Profession	6
Clerical, Shop owner, Farmer	5
Skilled Worker	4
Semi skilled Worker	3
Unskilled Worker	2
Unemployed	1

(C) FAMILY INCOME

FAMILY INCOME PER MONTH IN RS ORIGINAL	SCORE	MODIFIED FOR 1998	MODIFIED FOR 2007
=2000	12	=13500	=19574
1000-1999	10	6750-13459	9788-19574
750-999	6	5050-6749	7323-9787
500-749	4	3375-5049	4894-7322
300-499	3	2025-3374	2936-4893
101-299	2	676-2024	980-2935
=100	1	=675	=979

(D) TOTAL SCORE

26-29 UPPER (I) 16-25 UPPER MIDDLE (II) 11-15 MIDDLE LOWER MIDDLE (III) 5-10 LOWER UPPER LOWER (IV) <5 LOWER (V)

HISTORY

ALCOHOL INTAKE YES/NO

IF YES- AUDIT QUESTIONNAIRE

Table 4. AUDIT Questionnaire[102]

Questions	0	1	2	3	4
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
3. How often doyou have 5 or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
7. how often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year
10. Has a relative, friend, doctor or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year

To score the AUDIT questionnaire, sum the scores for each of the 10 questions. A total ≥ 8 for men up to age 60, or ≥4 for women, adolescents, or men over age 60 is considered a positive screening test.

1. DRUG INTAKE

   Duration of duration intake > 6 weeks

   Yes [ ]

   No [ ]

   1. Native medications
      a. Yes [ ]
      b. No [ ]
   2. Acetaminophen
   3. Anti tubercular drugs
      a. Isoniazid [ ]
      b. Rifampicin [ ]
   4. Nitrofurantoin
   5. Sulfa medications (Trimethoprim / Sulfamethoxone)

6. Amiodarone
7. Alpha methyl dopa
8. Statins
9. Long acting nictonic acid
10. Quinidine
11. Phenytoin
12. Carbamazapine
13. Troglitazone
14. Ibuprofen
15. Diclofenic
16. Chlorzoxazone
17. Azathiprine / 6 MP
18. Methotrexate
19. Fluconazole or Ketoconazole
20. Flutamide
21. Hydralazine
22. Leukotriene synthase inhibitors
    a. Zafirlukast Accolate
    b. Zileuton
23. Perihexiline maleate
24. Phenylbutazone
25. Tacrine
26. Tolcapone
27. Vitamin A (in doses greater than 5000 units/day)
28. Any other over the counter drugs

2. Past history of jaundice
    a. Yes [ ]
    b. No [ ]
3. History of jaundice in family
    a. Yes [ ]
    b. No [ ]
4. History of surgery in past
    a. Yes [ ]
    b. No [ ]
5. History of blood transfusions in past

a. Yes [ ]
b. No [ ]

6. History of intravenous drug abuse
   a. Yes [ ]
   b. No [ ]
7. History of unsafe sexual practices
   a. Yes [ ]
   b. No [ ]
8. History of tattooing
   a. Yes [ ]
   b. No [ ]

PHYSICAL EXAMINATION

Blood Pressure

Height (m)

Weight (kg)

BMI (kg/m2)

Waist circumference (cm)

Hip circumference (cm)

W/H Ratio

LABORATORY INVESTIGATIONS

ALT

DATE	VALUE
1.	
2.	

HEMOGLOBIN

PLATELET COUNT

LFT

BILIRUBIN (T)	
BILIRUBIN (D)	
TOTAL PROTEIN	
ALBUMIN	
AST	
ALT	
ALP	
GGT	

VIRAL MARKERS

HbsAg	
Anti HBc	
Anti HCV	

GLUCOSE (AC)

LIPID PROFILE

TSHCeruloplasminTransferrin SaturationANAAnti TTG	

ULTRASONOGRAPHY

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III : Abbreviations

ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ACLD	Alcohol related early chronic liver disease
AFLD	Alcohol related fatty liver disease
AIH	Autoimmune Hepatitis
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Anti nuclear antibody
anti HBc	Antibody to Hepatitis B core antigen
anti HCV	Antibody to hepatitis C virus
anti TTG	Anti tissue transglutaminase
AST	Aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BMI	Body Mass Index
CDT	Carbohydrate deficient transferrin
CT	Computed Tomography
DILI	Drug Induced Liver Injury
DSM	Diagnostic and Statistical Manual of Mental Disorders
ELISA	Enzyme Linked Immunosorbant Assay
F	Females
GGT	Gamma glutamyl transferase
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High density lipoprotein
kg/m2	Kilogram per square metre
LDL	Low density lipoprotein

LFT	Liver function tests
M	Males
MRI	Magnetic Resonance Imaging
MS	Metabolic syndrome
n	number of participants
N	Negative
NAFLD	Non Alcoholic Fatty Liver Disease
NHANES	National Health and Nutrition Examination Survey
P	Positive
PCR	Polymerase Chain Reaction
RNA	Ribonuclear acid
US	United States of America
USG	Ultrasonography
W/H	Waist Hip Ratio
WC	Waist Circumference
WHO	World Health Organisation