

# Etiological profile of cirrhosis of liver from North-East India with reference to their anti-hepatitis A virus seroprevalence

## Abstract

**Background:** Cirrhosis of liver is common in north-east India. Hepatitis A infection in adults with chronic liver disease can cause acute on chronic liver failure associated with high mortality and morbidity. There have been reports of an epidemiological shift in hepatitis A virus (HAV) seroprevalence from South-East Asia and India. This study evaluated the etiological profile and seroprevalence of anti-HAV IgG in cirrhosis of liver patients. **Patients and Methods:** 160 hospitalized adult cases of decompensated cirrhosis of liver and 200 healthy controls were assessed for etiology and their anti-HAV IgG status by commercially available kits. **Results:** Most common cause of cirrhosis of liver in our region is ethanol related. 95% of cases and 89% of controls were seropositive for anti-HAV IgG ( $P = 0.181$ , insignificant difference). All cases above the age of 40 years were seropositive. Seroprevalence between sexes (M 97% and F 83.3%) was statistically insignificant. Only age showed a high coefficient of correlation ( $r = 0.854$ , statistically significant,  $P < 0.001$ ). **Conclusion:** Alcohol is the most common etiology of cirrhosis of liver in north-east India. Socio-cultural milieu in our part may play a role with alcohol contributing to a major but preventable health burden. Anti-HAV vaccination in our setting is not indicated routinely to cirrhosis of liver patients as it will not be cost-effective. However, young cirrhotics should be screened for anti-HAV antibody and if negative, may be offered vaccination. Screening should target young chronic liver disease patients in view of reports of decreasing seroprevalence across Asia as compared to one or two decades back.

**Key words:** Acute on chronic liver failure, alcoholic liver disease, anti-hepatitis A virus antibody, anti-hepatitis A virus-IgG, cirrhosis of liver, etiology of cirrhosis

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## INTRODUCTION

Common causes of cirrhosis of liver which is a significant health problem worldwide include Hepatitis B, C and alcohol. Literature shows that in India most cases of cirrhosis are due to viral hepatitis B and C. However, of all viral hepatitis globally, hepatitis A virus (HAV) infection is the most common.<sup>[1]</sup> Areas of high endemicity include most of Africa, Asia and Central and South America. Conditions which contribute to the propagation of the virus among young children in these areas include household crowding, poor levels of sanitation and inadequate water supplies.<sup>[2-4]</sup>

Lifelong immunity is conferred by infection or vaccination, so anti-HAV seroprevalence studies can be used to indicate populations which are susceptible to infection. Though HAV infection rarely has sequelae in otherwise healthy subjects, it may have disastrous effects in one with chronic liver disease by causing acute liver failure. Retrospective and prospective studies have demonstrated that the occurrence of acute hepatitis A in patients with chronic liver disease is associated with higher rates of morbidity and mortality compared to previously healthy individuals with acute hepatitis A.<sup>[5]</sup>

Increasing household income, education, water quality and quantity, sanitation, and hygiene leads to decreases in HAV prevalence. Consequently, Japan, Australia, New Zealand, Canada, the United States, and most European nations have low anti-HAV rates. However, anti-HAV rates there remain high in most Latin American, Asian, and Middle Eastern nations, although average seroprevalence rates are declining. Surveys from Africa generally indicate no significant decline in anti-HAV rates. Because the severity

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of illness increases with age, populations with a high proportion of susceptible adults should consider targeted vaccination programmes.<sup>[6]</sup>

Thus, vaccination is advisable in all cases of chronic liver disease to prevent sudden deterioration of liver functioning due to acute hepatitis A infection.<sup>[7]</sup> But to implement hepatitis A vaccination in persons who have already acquired immunity to it, will be a waste of valuable resources in a growing economy like ours.

Though earlier studies had found the incidence of past hepatitis A infection in India up to 100%,<sup>[8]</sup> there has been a decline in the seroprevalence of hepatitis A in South-East Asia as a whole<sup>[9]</sup> including in India. About 15 years ago, the cord blood anti-HAV antibody levels in Indian newborns was nearing 100%, which in turn reflected the maternal antibody prevalence.<sup>[10]</sup> In recent studies however, this level has come down to 50-60%.<sup>[11]</sup>

India seems to be in a transition in respect to seroprevalence of anti-HAV antibody which is showing a decreasing trend similar to European countries as per some recent studies.<sup>[12,13]</sup>

In addition, it has been shown in several studies across the globe that immunity levels in children under 15 years of age have reduced from 18.7% to 5.6% so in the near future all children in the world will progress to non-immune levels of HAV, and therefore public health managers should keep vaccination of children in mind.<sup>[14-16]</sup>

With this background, we attempted to determine the commonest cause and seroprevalence of hepatitis A, and thus the need for HAV vaccination, in cirrhosis of liver patients attending a tertiary care hospital situated in North-East of India. Only hospitalized cases were chosen, as they would be the first candidates if vaccination was proved necessary.

## Objectives

- *Primary aim:* To determine the etiology and seroprevalence of anti-hepatitis A antibody in cirrhotics.
- *Secondary aim:* To investigate the difference of anti-hepatitis A antibody between cirrhotics and a normal control population.

## PATIENTS AND METHODS

This study included all patients, age  $\geq$  18 years with cirrhosis of liver, who attended the Medicine outpatient department or were admitted in the Medicine wards of Assam Medical College and Hospital, Dibrugarh, Assam, (a tertiarycentre situated in Upper Assam area of the North-Eastern India) between 1 September 2009 and 31 August 2013.

Liver biopsy was not done, as clinical, laboratory and imaging are sufficient to establish the diagnosis of cirrhosis<sup>[17-19]</sup> and also because ascites was present in all cases. Our case definition criteria included clinical signs of hepatocellular dysfunction, signs of portal hypertension, and ultra-sonographic findings. Clinical signs were jaundice, encephalopathy, spider angioma, and testicular atrophy. Gastroesophageal varices, splenomegaly, ascites were features

of portal hypertension. Sonographic features were coarsened echotexture, nodular surface, decreased caudate to right lobe ratio, and findings of portal hypertension. Necessary biochemical and serological tests were carried out including liver function tests, renal functions, electrolytes and viral markers.

Since the study was a tertiary hospital-based one, all cases were decompensated having ascites and portal hypertension. Standard care of treatment was followed. No patient had history of previous HAV vaccination. We did not attempt to look into any risk factors for acquiring HAV infection in our cases or controls.

Patients with acute liver failure, malignancy or immunocompromised state, pregnancy or a history of abdominal surgery within last 1 year were excluded. History of alcohol intake with amount and duration was recorded by direct questioning of patients and their relatives.

A total of 200 healthy controls were selected by randomization after excluding significant alcohol intake by direct questioning of self and close relatives.

Informed consent was obtained from both cases and controls. Ethical committee clearance was obtained from the Institutional Ethics Committee.

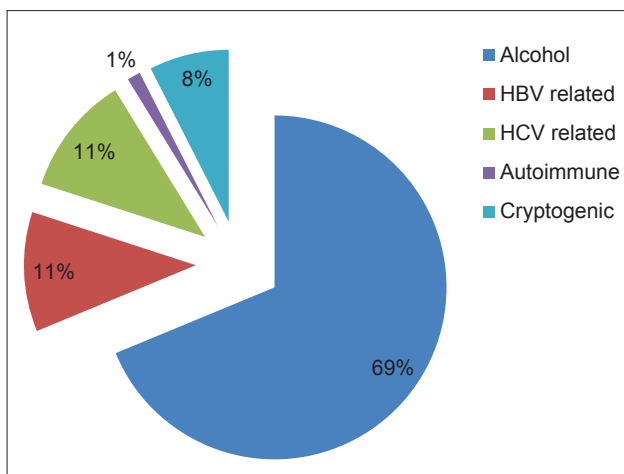
Sera were collected by venipuncture and were tested for IgG anti Hepatitis A antibody with a commercially available ELISA Kit (HEPAVASE, *General Biologicals Corporation, Hsinchu, Taiwan*). All sera were tested in series to detect false negative results. Other investigations included liver function tests, serum creatinine, complete blood count including platelet count, serology for hepatitis B (*Hepacard, Diagnostics Enterprise Parwanoo, Himachal Pradesh*), and C (*Signal Test card, Surat*), by rapid card tests, serum ferritin, serum ceruloplasmin, anti-nuclear antibody, and upper GI endoscopy. Cryptogenic cirrhosis was presumed when history of significant alcohol intake, viral markers and other investigations were negative.

## RESULTS

A total 160 cases of cirrhosis were included. Of them, 110 cases were alcohol related, 18 each were related to hepatitis B and hepatitis C, 2 autoimmune, and 12 cryptogenic [Figure 1]. The youngest cirrhotic was 25 years, the oldest being 72 years, with 61.25% in the age group 40-59 years. Out of all cirrhotics, 24 (15%) were females [Figure 2].

152 (95%) of cirrhosis tested positive for IgG anti-HAV while 178 (89%) out of 200 controls were positive. Table 1 shows a 4 × 4 distribution of this result. Since 1 frequency was less than 5 (i.e. anti-HAV IgG negative cases), we could not apply the  $\chi^2$  test. Fischer's exact *t*-test revealed a *P* = 0.181 showing no statistically significant difference of seroprevalence between case and control.

Of the 136 male cirrhotics, 4 were negative for anti-HAV IgG (3%). Also, 4 out of the 24 female cirrhotics were negative (20%). Fischer's exact test [Table 2] revealed no statistically significant difference in seroprevalence between male and female cirrhotics (*P* = 0.12).



**Figure 1:** Showing etiology of cirrhosis

The distribution of seropositivity across various age groups is shown in Table 3 and Figure 3. To look for correlation between age and seroprevalence, we took the mean age in each group and applied Pearson’s correlation between seroprevalence percentage and the mean age. Pearson’s correlation coefficient of mean age versus seroprevalence (percentage) is 0.854 at  $P < 0.001$ . Thus, the seroprevalence was highly dependent on age of the patient. All cirrhotics >40 years of age were seropositive.

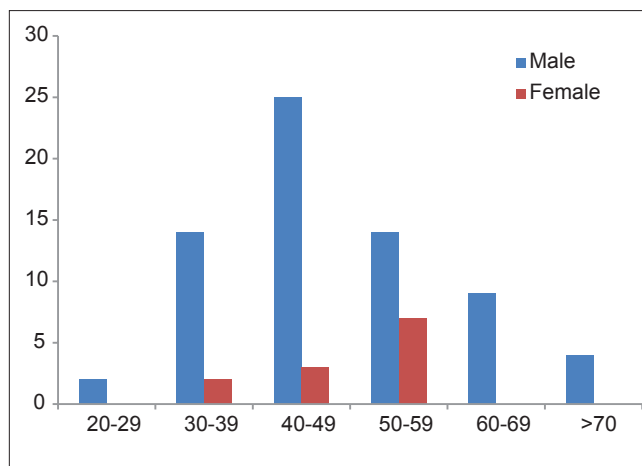
## DISCUSSION

The most common cause of cirrhosis in this study was alcohol related (69%). Chronic hepatitis B and C accounted for 22.5%, while 7.5% were cryptogenic.

More than 60% of cirrhotics were in the age group of 40-59 years. This is in concordance with other Indian studies.<sup>[20,21]</sup> The reported mean age of Indian cirrhotic patients is around 51 years. There was male preponderance with male to female ratio being 5.66:1. This may be explained by the fact that the majority of patients were alcoholic cirrhotics in whom the male to female ratio is around 5:1.<sup>[22]</sup>

95% of cirrhotics and 89% of controls were seropositive with no statistically significant difference between the two groups. Available literature from India show similar rates ranging from 94.6% to 100% [Table 4]<sup>[8,12,13,23-26]</sup> and is similar to our finding.

The deleterious effect of superadded HAV in infection upon chronic liver disease patients are highlighted<sup>[27]</sup> in the 1988 Shanghai acute HAV epidemic ( $n = 310,746$ ) where it was found that the case fatality was 5.6 fold higher in those who had additional chronic HBV infection, compared to those who were HBV negative. This has been confirmed subsequently in other large series reports, including by the CDC, USA, that a) acute HAV superimposed on other chronic liver disease is associated with more severe disease and higher case fatality than due to acute HAV alone,<sup>[28]</sup> b) in USA, such case fatalities are estimated to be 11.7% in HbsAg carriers and 4.6% in other chronic liver disease. Most importantly, these rates were 58- and 23-fold



**Figure 2:** Age distribution of cirrhotics: Males and females shown separately

**Table 1: Seroprevalence of hepatitis A in cirrhotics and healthy controls**

Fischer’s exact test	Anti-HAV IgG positive	Anti-HAV IgG negative	Total
Cirrhotics	152 (95%)	8 (5%)	160
Healthy controls	178 (89%)	22 (11%)	200
Total	330	30	360
Result	Two-tailed $P$ value: 0.1811 (insignificant)		

HAV: Hepatitis A virus, IgG: Immunoglobulin G

**Table 2: Seroprevalence in male and female cirrhotics**

Fischer’s exact test	Anti-HAV IgG positive	Anti-HAV IgG negative	Total
Male	132 (97%)	4 (3%)	136
Female	20 (83%)	4 (17%)	24
Total	152	8	160
Result	Two-tailed $P$ value: 0.105		

HAV: Hepatitis A virus, IgG: Immunoglobulin G

**Table 3: Seroprevalence in different age groups**

Age group (years)	Mean age	No of cases	Positive for IgG Anti-HAV	Percentage
20-29	25.5	4	2	50
30-39	34.5	32	26	81.25
40-49	44.5	56	56	100
50-59	54.5	42	42	100
60-69	64.5	18	18	100
>70	-	8	8	100

HAV: Hepatitis A virus, IgG: Immunoglobulin G

higher respectively, for people without previous chronic liver disease.<sup>[29]</sup> These data show that acute HAV, which has a very low mortality in an otherwise normal individual, can lead to more severe disease (fulminate hepatitis) and sharply increase mortality in people with any type of chronic liver disease, especially in chronic HBV

but also in chronic HCV carriers. Apart from fatalities, higher peak laboratory abnormalities of liver functions occur due to acute HAV superinfection in this susceptible population.

However, the prevalence of hepatitis A is gradually coming down in South-East Asia<sup>[30-33]</sup> [Table 4] as hygienic conditions and general health of the peoples are improving. India will be following this trend because of growing economy, and then the importance of hepatitis A vaccination will increase. There is a significant geographical variation in the seroprevalence across India also, which has been noticeable in the last 10-15 years.

The difference in seroprevalence between males (97%) and females (83.3%) is not statistically significant. Similarly, other Indian studies have found no difference between the sexes.<sup>[25,34]</sup>

Though no other factor was significantly associated with seropositivity, age showed a high coefficient of correlation ( $r=0.854$ ) at statistically significant levels ( $P < 0.001$ ). Seroprevalence of 60-80% by 20 years of age is usual.<sup>[16,34]</sup>

This finding is notable because, the distribution of HAV seroprevalence by age group may reflect current hepatitis A endemicity in countries and regions.<sup>[35]</sup>

In the USA, age-stratified seroprevalence of HAV in patients with CLD of various etiologies is significantly higher than that of the general population, and several independent predictors of prior HAV exposure have been identified.<sup>[36]</sup>

In Iran, the rates of anti-HAV seropositivity across different age groups from three different studies, were reportedly greater than 95% in patients aged >30 years, 71.4% in patients aged 10-20 years and 59.4% in patients aged 10-20 years.<sup>[37-39]</sup> In that country proper vaccination of high-risk groups such as patients with chronic liver disease, especially those younger than 20-30 years old, is suggested.<sup>[16]</sup>

All our cirrhotics were decompensated. Other Indian studies report that decompensated cirrhotics are usually 100% seropositive.<sup>[23]</sup> Seropositivity was 95% in our study, with 100% in those above 40 years. Similar data has been reported by other<sup>[31,35]</sup> implying that

vaccination will not be necessary in relatively older cirrhotics. It is known that the prevalence of anti-HAV is now gradually decreasing in developing countries with age, primarily reflecting declining incidence, changing endemicity and a resultant lower childhood infection rate over time.<sup>[40]</sup> Most cirrhotics in this study were between 40 to 60 year. However, with changing epidemiological patterns, this might change in future. Until then, it might be prudent to advise vaccination for younger cirrhotics. With increasing obesity, especially in urban areas, incidences of Non-Alcoholic Fatty Liver Diseases (NAFLD) associated with metabolic syndrome and Diabetes Mellitus, will increase in India.<sup>[41]</sup> We are likely to encounter more cases of “cryptogenic” cirrhosis due to NAFLD in the near future at a relatively younger age group as a result. This is important to keep in mind, as it has been recently noted that there is now an increasing susceptibility of young and adults to acute HAV infection in Asian countries, with or without chronic liver diseases.<sup>[37]</sup> In future, it will be interesting to concentrate on this group of patients from India in a larger study.

However, at current prices, if the reported or estimated prevalence of HAV antibody in a particular age group and region is >50%, it is worthwhile to screen the individuals before recommending the HAV vaccine. On the other hand, if the probability of an individual having been exposed to HAV is < 50% at a particular age, vaccination can be offered without screening for antibodies.<sup>[42]</sup> As of now, our patients with cirrhosis of liver cannot be advised to go for routine anti-HAV vaccination.

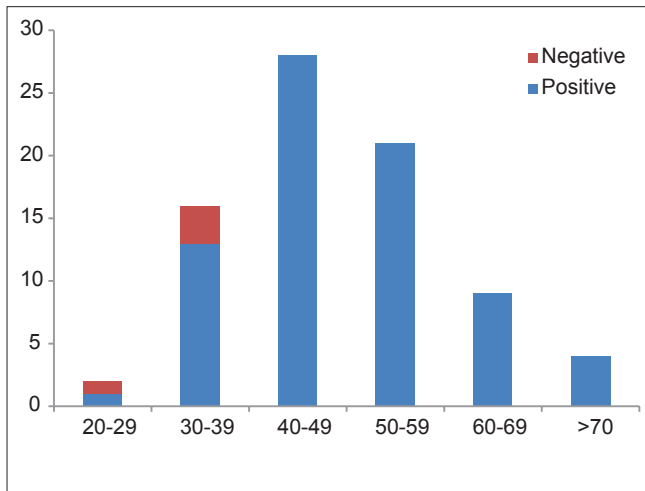
## CONCLUSION

The most common cause of cirrhosis of liver in Upper Assam is alcohol related followed by hepatitis B and C. Anti-HAV seroprevalence in decompensated cirrhosis of liver is nearly 95% and are not at risk of superimposed acute HAV infection. This is not statistically different from that of the general healthy population. Age seems to correlate best with seroprevalence of hepatitis A, as cirrhotics above 40 years almost invariably seroconvert. Thus, in the current scenario, the best recommendation would be to offer only targeted hepatitis A vaccination to younger patients with chronic liver disease to prevent future acute HAV-induced liver failure, and routine vaccination is not indicated in all cirrhotics. But, it is pertinent to screen for antibodies first. It will be informative to study and survey

**Table 4: Seroprevalence of hepatitis A in adult population from some Indian and South-East Asian studies**

Seroprevalence (%)	Author	Country/city	Year of publication	Population
100	Vidya <i>et al.</i> <sup>[8]</sup>	Pune, India	1995	Community based
99	Duseja <i>et al.</i> <sup>[23]</sup>	Chandigarh, India	2004	Hospital based
97.6	Dhotial <i>et al.</i> <sup>[24]</sup>	Delhi, India	2002	Hospital based
94.4	Joshi <i>et al.</i> <sup>[25]</sup>	Hyderabad, India	2000	Community based
93.2	Acharya <i>et al.</i> <sup>[26]</sup>	Delhi, India	2003	Community based
71.2	Das <i>et al.</i> <sup>[12]</sup>	Delhi, India	2000	Community based
65.9 (avg 26.2 to 85.3)	Mall <i>et al.</i> <sup>[13]</sup>	Multicentric (5 Indian cities)	2001	Community based
98.4	Samir <i>et al.</i> <sup>[27]</sup>	Bangladesh	2009	Community based
88.2	Ahmad <i>et al.</i> <sup>[28]</sup>	Malaysia	2011	Hospital based
62.8	Baek <i>et al.</i> <sup>[29]</sup>	Korea	2012	Community based
25.3	Lee <i>et al.</i> <sup>[30]</sup>	Singapore	2011	Community based





**Figure 3:** Age distribution of cirrhotics (seronegative cases shown in red)

different age groups, particularly a large young population with chronic liver disease for anti HAV IgG-M in a well-planned way to generate more data in our country keeping in mind some reports about the epidemiological shift in India. However, in our study we did not include compensated cirrhosis or patients with non-cirrhotic chronic viral diseases which has limited our findings to only a highly specific sub-population of chronic liver disease and is a shortcoming of this study.

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