

Comparing the prevalence of food, water borne, parenterally acquired viral hepatitis in the tribal, non-tribal north east Indian population and its prevalence pre-COVID and during COVID

Abstract

Background: India is rich in tribal population who are concentrated in central India followed by western and north-east Indian locations. Infectious diseases pose a vital threat to the wellbeing of tribals and one such disease is hepatitis. Each tribe has its own unique cultural tradition that could influence hepatitis disease dynamics. This research of ours is based on hepatitis diagnosis and prevalence in the eight north eastern states of India that are in locations bordering other countries like Bangladesh, Bhutan, Nepal. The article intercompares the prevalence pattern in tribal and non-tribals grouped in the north eastern states of India as well as the overall prevalence in COVID-19. COVID-19 had impact on every aspect of health system governance all over the world and did create a major challenge. Viral hepatitis is one major challenge that can be caused by food borne viruses like HAV, HEV or blood borne viruses like HBV, HDV, HCV. **Methodology** This cross-sectional study data on prevalence of viral hepatitis conducted in the 8 north eastern states of India includes inadvertently the data which is two years before the onset of COVID-19 (2018-2019) and 2 years during the COVID (2020-2022). This manuscript presents retrospective observation on viral hepatitis prevalence pre-COVID and during COVID with no planned work done on COVID diagnostics. This work compares viral hepatitis prevalence during these two time periods. **Results:** In this study, young adults of tribal population in northeast India had higher prevalence of viral hepatitis than non-tribal and older adults of non-tribal had higher prevalence of viral hepatitis than tribals. Certain tribes had higher prevalence of particular hepatotropic virus like Lushai tribe for HDV, HCV, HEV. Hepatitis B vaccination was better in non-tribals than tribals in hospitalized patients. Further while comparing the overall prevalence, there was marked difference in pre-COVID and during COVID prevalence of the hepatotropic viruses (HBV, HCV, HAV, HEV) in the 8 north eastern states namely Assam, Arunachal, Nagaland, Sikkim, Tripura, Meghalaya, Manipur, and Mizoram. **Conclusion** Although this observation is retrospective, it could provide insight on the effect of COVID pandemic on hepatitis prevalence in the northeastern states of India. Tribal population included younger adults as major hospitalised patients for hepatitis as compared to older adults in non-tribal patients. Tribal patients indicated very high prevalence of HDV as compared to non-tribal.

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KEY WORDS: COVID19, Hepatitis, HBV, HCV, HAV, HEV, Tribal, Non-tribal, Northeast India

Introduction

The north eastern states of India comprise of Assam (12% of tribal population); Arunachal Pradesh (64% of tribal population); Manipur (35% of tribal population); Meghalaya (86% of tribal population); Mizoram (95% of tribal population); Nagaland (89% of tribal population); Sikkim (23% of tribal population) and Tripura (31% of tribal population) (1). (2). The major tribes of Assam include Boro (or Kachari), Karbi, KochRajbanshi, Mishing, Mishimi and Rabha; Arunachal Pradesh include Galong, Nishi, Wancho and Adi; Manipur include Thadou, Tangkhul, Kabui, Poumai, Kabui, Inpui and Rongmei; Meghalaya include Khasis, Garo and Karbis; Mizoram includes Lusei, Hmar, Paite, Pawi, Mara, Bawm, Tlau, Ralte, Pang, Hualngo and the Bait; Nagaland includes Angami, Ao, Lotha, Sumi, Sangtam, Chang, Khamniungan, Konyak; Sikkim includes Lepchas and Bhutias; Tripura includes Reang, Chakma, Deobarma, Halam and Usai (1),(2).

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Indigenous tribes of India like elsewhere are vulnerable to main-land diseases and hence studying the disease prevalence becomes essential for the wellbeing of the tribal people. Various studies have been conducted in different parts of India focusing on the communicable and non-communicable disease prevalence among the tribal people. India has 28 states and 8 of them falls in the north eastern border adjacent to Bangladesh, Nepal, Bhutan. These 8 north eastern sister states have distinct tribal population and their culture is markedly unique from the mainland. These states include Assam, Sikkim, Nagaland, Tripura, Meghalaya, Arunachal Pradesh, Manipur, Mizoram collectively.

Northeast Indian states have unique cultural and ethnic practices that could have an influence on disease prevalence. In Assamese diet, rice, vegetable and meat based diet fits in. It has been mentioned in literature that during the assamese festival of Rangali Bihu, as far as 108 kind of leafy vegetables are used to prepare dish (3). Unique diets include khar wherein ashes of banana

peel is used for food preparation (3). Probabaly the assamese diet of Tita that includes neem leaf, bitter guard and night gasmine could be beneficial and anti microbial (3). Further assamese cook alongwith rice and vegetables fish, meat of pigeon, duck, chicken, pork, goat etc. This includes by bamboo or leaf cooking, stew or roasting (3).

Basically northeast india has a variety of meat based cuisines and has indigenou delicacies(4). In meghalaya that has 3 major tribes Khasi, Jaintia and Garo, 15 meat based products that are prepared include Dohneiong, Pudoh, Ja snam, Jastem, Dohklong, Dohkpu, Dohsnier, Dohpheret, Dohtyrkhing, Doh jem, Dohsnam, Dohkhlieh, Achardohsniang, Tungrymbai, Jadoh which are pork based dishes (4).

In manipur, the 2 major tribal population include Naga and Kukis and the non tribal population includes Meitei tribe (5).The traditional foods include Hawaichar that is fermented soybean, Hentak from sun dried fish, Ngari from fermented fish, bamboo shoot, rice based food items and alcoholic beverages(5).

Northeastern states of India could have pre disposition towards viral hepatitis (liver inflammation with virus as etiological agent) due to the absence of awareness and presence of risk factors for the blood borne (Hepatitis B and its satellite e virus Hepatitis D, Hepatitis C viruses) and food, water borne (Hepatitis A and Hepatitis E viruses). Studies have been conducted on disease prevalence in other states of India through Indian council of medical research (ICMR) or other research bodies as indicated in literature which includes study on Hepatitis in the primitive tribal population of Odisha (6) study on HCV infection in primitive tribes of eastern India (7), study on hepatitis of trans-Himalayan tribes (8), study on hepatitis of Irula tribes in tamilnadu(9). HCV infections in north eastern Indian population had been detailed by a study that concludes male are prone than female and age group 40-49 are more prone for the infection (10). HCV genotyping in Meghalaya indicates that the genotype found in this area is distinct from mainland (11). Another study on Idu Mishmi tribe of Arunachal Pradesh indicated the presence of HBs antigen (HBs Ag) (12).

Further a study on the prevalence of HDV resulting in severe liver damage in HBV patients in Manipur indicated prevalence of 4.2% which is higher than national average (13). Further, northeastern states share boundaries with other countries and the proven prevalence of Hepatitis in these neighboring countries could possibly influence the prevalence pattern in north eastern states of India bordering these countries. Moreover, seasonal distribution of Hepatitis has been reported in studies conducted in India and neighboring countries. In a meta study done from publications ranging from 1970-2013 spanning 18 countries, indicated summer and spring as possible seasonal peaks for hepatitis (14). In another study conducted at Aligarh in India it has been pointed out that the predominance of Hepatitis was observed in 10 year old children and mostly during the months between June and September (15).

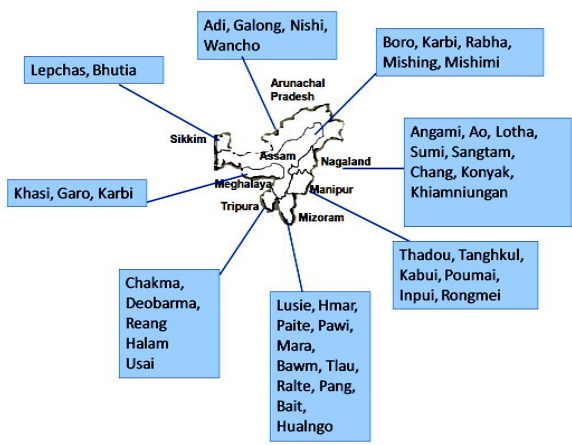


Figure 1 North eastern states with names of few indigenous tribes. The tribes in the 8 different north eastern states (1) are depicted in this figure.

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Scenario during COVID

Different diseases of importance including tuberculosis, hepatitis prevailed globally before the COVID (16) which could have been influenced by the COVID pandemic due to co infection. Viral hepatitis could be caused by blood borne viruses hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV)- which is a satellite virus of HBV and it could also be caused by food or water borne viruses like hepatitis A virus (HAV), hepatitis E virus (HEV). During COVID, co-infection with other diseases

including hepatitis could have occurred and the indirect impact of COVID on health systems also had an impact on treatment of diseases and vaccination for diseases. Studies indicate that HBV co infection with COVID did not lead to severity of COVID (17). In case of patients with HCV infection it did have an accentuated response for SARS COV2 enhancing SARS-COV-2 viral entry (18). In case of HAV, HBV infections, anti HAV, anti HBV antibodies did not influence the outcome Of COVID (19). In a study conducted from 32 European and 12 non-European clinical centers that had data from Jan 2019 to dec 2020, chronic HBV consultations decreased from 32% and 26%; new referrals by 38% and 39%; HBV testing rates by 39% and 21% (for HBs Ag); 30% and 22% (for HBV DNA detection) and new HBV DNA detection; new HBV treatments by 20% and 44% in European and non-European centers respectively. As in case of HCV overall reductions were 39% and 50% for consultation; 49% for new referrals; 11% and 38% for new HCV RNA detection; 51% and 54% for new HCV antiviral treatments for European and non-European centers (20).

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In another study it has been shown that HBV co infection with COVID in pregnant women led to decrease in weight of the infant and also in premature deliveries (21). In a study conducted in HCV infected patients with liver cirrhosis it was observed that COVID was severe (22) but in another study it was shown that SARS COV2 could suppress the HCV replication (8). Globally the COVID had impact on hepatitis B diagnosis, vaccination, treatment (23). It has been reported that hepatitis viral infection can lead to increased chances of mortality in COVID due to impaired immunity (24). Independent of hepatitis, severe form of COVID is known to cause increase in serum bilirubin (25).

The northeastern states of India include Assam, Arunachal Pradesh, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim, Tripura. These states share international boundaries with Bangladesh, Myanmar, Bhutan and China. The first COVID case in north east India was recorded on 24th march 2020 in Manipur followed by Assam on 31 march 2020; Tripura had its confirmed case on April 5 2020; Meghalaya had its first case on 13 April 2020 and a total of 100 cases in all of north east by May 5 2020 (26). India imposed lockdowns in March 2020 that was extended in May 2020. In whole of India, 12.2 crore people lost job and states like Sikkim in north east India dependent on tourism was also affected. Moreover, there was economical loss due to COVID affecting agricultural activities including tea cultivation that north east was dependent on.

This study of ours, primarily was aimed to study prevalence of viral hepatitis with diagnostic markers for the 5 different viruses - HBV (HBsAg, HBeAg, HBcAb IgM/IgG, HBeAb); HCV (Anti HCV); HDV (Anti HDV); HAV (Anti HAV IgM/IgG); HEV (Anti HEV IgM/IgG) in northeast India between 2018 to 2022. But this period overlapped the period of COVID19, that facilitated to compare retrospectively the

prevalence between 2018-2019 vs. 2020-2022. The antigen (Ag) presence could indicate the presence of viral proteins and the antibody (IgG) indicates past infection and (IgM) indicates present infection.

Methodology

Our study was designed to investigate the association of hepatitis viruses in various types of liver diseases in patients attending one teaching hospital in each state or in a selected district hospital, in all the Northeast states of India. Sample Size: 2800 cases from 9 hospitals of the study region over a period from 2018-2022. The hospital study sites included - Assam Medical College Hospital (AMCH), Dibrugarh and Gauhati Medical College Hospital (GMCH), Guwahati Assam; Jawaharlal Nehru Institute of Medical Sciences & Hospital (JNIMS), Imphal, Manipur; North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS), Shillong, Meghalaya; Civil Hospital (CH), Aizawal, District Hospital (DH), Dimapur, Nagaland; Sikkim Manipal Institute of Medical Sciences (SMIMS), Gangtok, Sikkim; Agartala Govt. Medical College (AGMC), Agartala, Tripura; General Hospital (GH), Pasighat, Arunachal Pradesh.

A written informed consent was obtained after careful explanation of the study to each study subjects. After obtaining the informed consent from study subjects / guardians (in case of minor), 5ml of venous blood is collected in K3EDTA tubes & clot activator tubes. Each blood sample collected has a unique sample ID number and the same is matched with the proforma and on the stored sample in the cryovials. The study population included patients with signs and symptoms conferring to the diagnosis of viral hepatitis attending OPD or admitted cases. Each patient was evaluated on the basis of history, physical examination and liver function test profile. All cases of acute viral hepatitis at initial phase were assessed with respect to severity of the diseases. All patients presenting with features of chronic liver disease which confers to the diagnostic criteria of chronic hepatitis, cirrhosis of liver and HCC as per the standard diagnostic criteria of inclusion were admitted into medical wards of the concerned Hospitals. The kits that were used for determination of the serological status of the study participants is listed in the following tables (Table 1, 2).

1.	HAV Ab (competitive), Cat no:AVAB.CE,Company: Diapro, Italy
2.	HAV IgM (capture) Cat no: AVM.CE, Company: Diapro, Italy
3.	HBcAb (screening) Cat no: AVM.CE, Company: Diapro, Italy

4.	HBc IgM (capture quantitative) Cat no: BCM.CE, Company: Diapro, Italy
5.	HDV Ab (total antibody) Cat no: DAB.CE, Company: Diapro, Italy
6.	HDV Ag Cat no: DAG.CE, Company: Diapro, Italy
7.	HDV IgM(capture) Cat no: DIM.CE, Company: Diapro, Italy
8.	HEV Ab (screening) Cat no: EVAB.CE, Company: Diapro, Italy
9.	HEV IgM (sandwich) Cat no: EVM.CE, Company: Diapro, Italy
10.	HEV IgG (qualitative) Cat no: EVG.CE, Company: Diapro, Italy
11.	HBe Ag & Ab Cat no: HBE.CE, Company: Diapro, Italy
12.	HBs Ab (quantitative) Cat no: SAB.CE, Company: Diapro, Italy
13	HBs Ag ULTRA, Cat. No: 72346, USA
14	HCV Ag-Ab, Cat no: 72556,USA

Table 1. ELISA Kits for analysis

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1.	Albumin Cat no. ALB01 Company: DIATEK, INDIA
2.	SGOT Cat no. OT02 Company: DIATEK, INDIA
3.	SGPT Cat no. PT02 Company: DIATEK, INDIA
4.	Alkaline Phosphatase Cat No. ALP02 Company: DIATEK, INDIA
5.	Gamma GT Cat no. GGT01 Company: DIATEK, INDIA
6.	Bilirubin Direct DC Cat no. GBD01 Company: DIATEK, INDIA
7.	Bilirubin Total DC Cat no. GBT01 Company: DIATEK, INDIA
8.	Total Protein Cat no. TP01

Company: DIATEK, INDIA

Table 2 LFT tests used in analysis

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Results and Discussion

North-East India (consists of Meghalaya, Arunachal Pradesh, Manipur, Sikkim, Tripura, Assam, Mizoram, Nagaland) has more than 200 tribes out of the 427 tribal communities present all over India (27) and further has boundaries with Bhutan, Bangladesh, Nepal, Myanmar. The tribes have originated from the ethnic groups of Tibeto-Burmese, Proto Austrioids, Indo-Mongoloids (27).

The diversity and uniqueness of food and culture of northeast India has been described in various studies (28, 29, 30, 31, 32, 33, 34, 35).

The tribal people might have unique culture in terms of their food habits, costume, tattooing, social events that might have act as underlying factor for specific disease prevalence pattern. It has been documented that fermented foods do harbour viruses including that of hepatitis [36] and fermented foods are integral part of the tribal cuisine. Hence such factors can influence disease prevalence. In this study the following factors have been compared between the tribal and nontribal population.

In Assam (site AMCH), 131/300 were tribal patients and 169/300 were nontribal. In Assam (site GMCH), 85/400 were tribal patients and 315/400 were nontribal. In Arunachal, 244/300 was tribal patients and 56/300 were nontribal. In Manipur, 125/400 were tribal patients, 275/400 were nontribal patients. In Meghalaya, 173/240 was tribal patients and 67/240 was non tribal patients. In Mizoram, 294/300 was tribal patients and 6 were nontribal. In Sikkim, 110/300 was tribal patients and 190/300 was nontribal patients. In Nagaland, 132/160 was tribal patients and 28/160 was nontribal. In Tripura, 100/400 patients were tribal and 300/400 were non tribals.

- a. **Socio demographics:** Out of the total 2800 recruited patients of hepatitis in the 8 north-eastern states between 2018-2022, 1394 were tribal, out of which 821 (59%) were from rural background and 573 (41%) from urban background. The remaining 1406 non tribal patients were of 842 from rural background (60%) and 564 from urban background (40%). The tribal patients who were recruited for hepatitis in the study were in the age group of (<18Years: 3%; 18-36Years: 45%; 36-55Years: 37%; >55Years:16%). The nontribal patients who were recruited for hepatitis in the study were in the age group of (<18Years: 2%; 18-36Years: 32%; 36-55Years: 42%; >55Years: 24%). Hence it appears that young adult patients of hepatitis in tribal population were higher (45% of total hospitalized) than nontribal (32% of total hospitalized). Similarly middle-aged and senior citizen hospitalized for hepatitis were higher in nontribal (66%) than in tribals (53%). Male tribal patients were 982/1394 (70%) and female tribal patients were 411/1394 (30%). Male non tribal patients were 1110/1406 (79%) and female non tribal patients (295/1406) (21%).
- b. **Drinking water facility:** Amidst the total hospitalized tribal vs. nontribal patients for hepatitis in the 8 north eastern states at the particular 9 hospital sites as mentioned in methods, 36% vs.26% availed tap water for drinking, 7% vs. 16% availed bore well water, 15% vs. 30% availed hand pump water, 11% vs. 7% availed well water, 5% vs. 13% availed packed drinking water, 29% vs. 21% availed municipal water. Thus tribal population availed more of tap water, well water and municipal water for drinking purpose and non tribal population availed more of bore well, hand pump, packed drinking water.
- c. **Type of hepatitis patients observed:**AVH tribal patients accounted for 441/1394 (32%), ALF tribal patients accounted for 40/1394 (3%), Chronic hepatitis tribal patients accounted for 693/1394 (50%), liver cirrhosis tribal patients accounted for 201/1394 (14%), HCC tribal patients accounted for 19/1394 (1%). AVH nontribal patients accounted for 427/1406 (30%), ALF tribal patients accounted for 28/1394 (2%), Chronic hepatitis tribal patients accounted for 489/1406 (35%), liver cirrhosis tribal patients accounted for 452/1406 (32%), HCC tribal patients accounted for 10/1406 (1%).

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- d. **Hepatotropic viruses prevalence:** HBsAg in nontribal patients accounted for 22% (304/1406), Anti HCV accounted for 20% (278/1405), Anti HDV accounted for 1% (3/260), Anti HEV IgM accounted for 7% (44/627), Anti HAV IgM accounted for 8% (53/649). HAV vaccine was observed in 64/1159 (6%), HBV vaccine in 269/1178 (23%). HBsAg in tribal patients accounted for 33% (458/1394), Anti HCV accounted for 25% (342/1394), Anti HDV accounted for 8% (30/396), Anti HEV IgM accounted for 10% (95/927), Anti HAV IgM accounted for 8% (70/919). HAV vaccine was observed in 31/1184 (3%), HBV vaccine in 166/1168 (14%).
- e. **Literacy status:** Amidst tribal vs. nontribal patients hospitalized for hepatitis, the following was observed as their literacy status. Illiterate were 101/1394 (7%) vs. 72/1406 (5%) in tribal vs. nontribal. Patients with education upto primary school were 364/1394 (26%) vs. 499/1406 (35%). Patients with education upto secondary school were 578/1394 (42%) vs. 598/1406 (43%). Patients with education upto graduation were 330/1394 (24%) in tribal vs. 207/1406 (15%) in nontribal. Patients with education upto post graduation were 17/1394 (1%) in tribals and 25/1406 (2%) in nontribal.
- f. **Risk habits:** Tribal vs. nontribal who had the habit of alcohol consumption included 457/1394 (33%) vs. (543/1406)(39%), smoking (404/1394)(29%) vs. (388/1406)(28%), smokeless tobacco (367/1394) (26%) vs. (299/1404)(21%), marijuana (37/1394) (3%) vs. (73/1406)(5%), hashish (1/1394) vs.(7/1406)(<1%), brown sugar (24/1394) (2%) vs. (41/1406) (3%), opium (3/1394) (<1%) vs. (9/1406)(1%).
- g. **Tribe specific observation:** Different tribes had different trend in the HAV, HBV, HCV, HDV, HEV infection prevalence. Certain tribes like Arunachali had higher level of HBV, HCV; Lushai had higher of HDV, HCV, HEV infection whereas tribes like Rabha, Sherpa, Subha had nil of HCV, HDV, HBs. Certain tribes had higher level of HAV like in Ahom, AO Naga, Bhutia, Boro and some tribes had high of HCV like in Tamang, Nepalese, Lushai.

- h. **Medical treatment opted:** Tribal patients who opted for allopathic included 173/1394 (12%), patients who went for ayurveda included (37/1394) (3%). patients who went for homeopathy included (8/1394) (1%), patients who went for unani (5/1394) (<1%) and patients who went for herbal included 128/1394 (9%). Non tribal patients who opted for allopathic included 289/1406 (21%), patients who opted for ayurveda included (57/1406) (4%), patients who opted for homeopathy included 5/1406 (<1%), patients who opted for unani included (11/1406) (1%), patients who opted for herbal included (202/1406) (14%).
- i. **Cultural practices:** Tribal patients who followed cultural practices of scarification were 0/1394. Those who did body piercing included 375/1394 and those who did tattooing included 249/1394. Non Tribal patients who followed cultural practices of scarification were 1/1406. Those who did body piercing included 490/1406 and those who did tattooing included 199/1406.
- j. **Enrolment of healthy pregnant subjects during this period 2018-2022:**

In tribal antenatal subjects, alcohol consumption was 12/827 (1%) and smokeless tobacco was 221/827 (27%). Tribal pregnant subjects who went for body piercing was 190/827 (23%) and tattooing was 28/827 (3%). In nontribal antenatal subjects, alcohol consumption was 5/3168 (<1%) and smokeless tobacco consumption was 65/3168 (2%). In nontribal antenatal subjects, body piercing was 2906/3168 (92%) and tattooing was 74/3168 (2%).

In Assam, pregnant tribal healthy subject included 67/1000 (7%) as compared to non tribal (933/1000) (93%). In Manipur, pregnant tribal healthy subject included 71/1000 (7%) as compared to non tribal (924/1000) (93%). In Meghalaya, pregnant tribal healthy subject included 634/1000 (63%) as compared to non tribal (366/1000) (37%). In Tripura, pregnant tribal healthy subject included 55/1000 (6%) as compared to non tribal (945/1000)(95%).

In pregnant tribal healthy subjects, 56/827 was vaccinated for HAV and 123/827 were vaccinated for HBV (subjects from 4 states of Assam, Meghalaya, Manipur and Tripura). The number of liver birth in tribal were 437/827, still birth 7/827, dead born

2/827 and abortion was 71/827. The number of tribal who were pregnant <18 years were 18/827 (2%), 755/827 were of age 18-36 years and 54/827 were of age 36-54 years. The number of tribal women who had BMI less than <18 were 70/827 (8%), BMI 18-25 included 563/827 (68%) and BMI>25 included 194/827 (23%).

In pregnant nontribal healthy subjects, 163/3168 was vaccinated for HAV and 293/3168 were vaccinated for HBV (subjects from 4 states of Assam, Meghalaya, Manipur and Tripura). The number of live birth in tribal were 1171/3168, still birth 40/3168, dead born 37/3168 and abortion was 301/3168. The number of nontribal who were pregnant <18 years were 181/3168 (6%), 2892/3168 (91%) were of age 18-36 years and 95/3168 (3%) were of age 36-54 years. The number of tribal women who had BMI less than <18 were 126/3168 (4%), BMI 18-25 included 2400/3168 (76%) and BMI>25 included 622/3168 (20%).

Comparison of Prevalence in northeast viral hepatitis patients between the period 2018-2020 and 2020-2022 (i.e. pre-COVID and during COVID)

During the COVID, many facilities were unavailable and it did affect day to day life of people. COVID did affect the course of normal life and socio-cultural activities. COVID did have impact on dietary practices and negative food habits during lockdown were associated with poor life style, weight gain, mental health issues and limited physical activity (36). Consumption of alcohol, smoking cigarettes, tattooing could have been influenced by COVID lockdown. Alcohol consumption is a known risk factor for HCC (37). COVID19 pandemic had influence on other viral infections as documented in literature either due to the co-infection severity or due to cross reactivity of COVID vaccine or unavailability of healthcare facility during the pandemic. GIS based risk zonation of Indian northeastern states indicated states that are densely populated like Assam, Tripura, Meghalaya, Nagaland had higher COVID-19 risk than the other 4 northeastern states of Arunachal, Manipur, Mizoram, Sikkim (38).

State specific observation:

The prevalence % of hepatotropic viruses in hepatitis patients compared between pre-covid (2018-2019) and (2020-2022) is indicated in Figure 2a-2i. The results have been arranged state wise and in the order of disease markers among the five disease categories.

Assam AMCH	AVH	ALF	CH	LC	HCC
HBsAg	0.72	1	1.1	0.4	0.75
HBcAb IgG	0.5	0.9	1	0.4	0.75
Anti-HBs	0.23	0.7	0.5	0.7	0.75
HBeAb	0.23	0.1	1	0.1	
HBeAg			0.7	0.2	0.75
HBcAb IgM	0.08		0.2	0	
Anti - HCV	0.92		0.8	0.2	
Anti - HDV					
Anti-HEV IgM	0.92				
Anti-HEV IgG	0.92		2.7	3.7	
Anti-HAV IgM	3.69	0.7		0.4	
Anti-HAV IgG	1.6	1.6	1.5	1.4	1.5

Figure 2a Assam AMCH: Positivity ratio (2018-2020 / 2020-2022) of diagnostic markers in the five clinical conditions (AVH, CH, ALF, LC, HCC) of viral hepatitis patients to compare pre-COVID (2018-2020) and during COVID (2020-2022)

Empty values in blue represent positivity only during COVID and empty values in green represent positivity only in pre-COVID. The ratio in blue colored box represents higher positivity during COVID and the ratio in green colored box represents higher positivity during pre-COVID.

Assam GMCH	AVH	ALF	CH	LC	HCC
HBsAg	1.17		0.6		
HBcAb IgG	2.33		0.8	0.5	
Anti-HBs				3.2	
HBeAb	2.84				
HBeAg	2.84				
HBcAb IgM					
Anti - HCV	0.22		1		
Anti - HDV					
Anti-HEV IgM					
Anti-HEV IgG	0.59				
Anti-HAV IgM	0.92				
Anti-HAV IgG	0.94		0.4		

Figure 2b Assam GMCH: Positivity ratio (2018-2020 / 2020-2022) of diagnostic markers in the five clinical conditions (AVH, CH, ALF, LC, HCC) of viral hepatitis patients to compare pre-COVID (2018-2020) and during COVID (2020-2022)

Empty values in blue represent positivity only during COVID and empty values in green represent positivity only in pre-COVID. The ratio in blue colored box represents higher positivity during COVID and the ratio in green colored box represents higher positivity during pre-COVID.

Arunachal Pradesh					
	AVH	ALF	CH	LC	HCC
HBsAg	1.74		1.3		
HBcAb IgG	1.16		1.3		
Anti-HBs	2.12		1.3		
HBeAb			1.1		
HBeAg			1.3		
HBcAb IgM			0.3		
Anti - HCV	1.16		0.2		
Anti - HDV					
Anti-HEV IgM					
Anti-HEV IgG					
Anti-HAV IgM	3.88				
Anti-HAV IgG	1.68				

Figure 2c Arunachal Pradesh: Positivity ratio (2018-2020 / 2020-2022) of diagnostic markers in the five clinical conditions (AVH, CH, ALF, LC, HCC) of viral hepatitis patients to compare pre – COVID (2018-2020) and during COVID (2020-2022)

Empty values in blue represent positivity only during COVID and empty values in green represent positivity only in pre-COVID. The ratio in blue colored box represents higher positivity during COVID and the ratio in green colored box represents higher positivity during pre-COVID.

Manipur					
	AVH	ALF	CH	LC	HCC
HBsAg			0.8	0.3	
HBcAb IgG	0.15		1	0.8	1
Anti-HBs			1.1	1.5	
HBeAb			2.3	3	
HBeAg			0.4		
HBcAb IgM					
Anti - HCV			1.1	1.3	
Anti - HDV					
Anti-HEV IgM					
Anti-HEV IgG			2.3	1.9	
Anti-HAV IgM					
Anti-HAV IgG	0.94		0.9	0.9	

Figure 2d Manipur: Positivity ratio (2018-2020 / 2020-2022) of diagnostic markers in the five clinical conditions (AVH, CH, ALF, LC, HCC) of viral hepatitis patients to compare pre – COVID (2018-2020) and during COVID (2020-2022)

Empty values in blue represent positivity only during COVID and empty values in green represent positivity only in pre-COVID. The ratio in blue colored box represents higher positivity during COVID and the ratio in green colored box represents higher positivity during pre-COVID.

Mizoram	AVH	ALF	CH	LC	HCC
HBsAg	2.15		1.4		
HBcAb IgG	1.01		1.5		
Anti-HBs	0.54		0.6		
HBeAb	1.21		1		
HBeAg	1.25		0.9		
HBcAb IgM	0.98		0.8		
Anti - HCV	0.63		0.8		
Anti - HDV	2.28		3.2		
Anti-HEV IgM	3.54		0.8		
Anti-HEV IgG	3.62		2.1		
Anti-HAV IgM	0.24		0.3		
Anti-HAV IgG	0.82		1.1		

Figure 2e Mizoram: Positivity ratio (2018-2020 / 2020-2022) of diagnostic markers in the five clinical conditions (AVH, CH, ALF, LC, HCC) of viral hepatitis patients to compare pre –COVID (2018-2020) and during COVID (2020-2022)

Empty values in blue represent positivity only during COVID and empty values in green represent positivity only in pre-COVID. The ratio in blue colored box represents higher positivity during COVID and the ratio in green colored box represents higher positivity during pre-COVID.

Meghalaya	AVH	ALF	CH	LC	HCC
HBsAg	0.81		1.3	0.7	0.83
HBcAb IgG	0.74		1.1	1	0.71
Anti-HBs	0.74		0.6	3.6	
HBeAb	1.36		1.5	1.5	0.6
HBeAg	0.61		0.8	1.6	
HBcAb IgM	0.74				
Anti - HCV	0.25		0.8	2.5	1
Anti - HDV			2	1.1	
Anti-HEV IgM					
Anti-HEV IgG	1.47				
Anti-HAV IgM					
Anti-HAV IgG	0.95				

Figure 2f Meghalaya: Positivity ratio (2018-2020 / 2020-2022) of diagnostic markers in the five clinical conditions (AVH, CH, ALF, LC, HCC) of viral hepatitis patients to compare pre –COVID (2018-2020) and during COVID (2020-2022)

Empty values in blue represent positivity only during COVID and empty values in green represent positivity only in pre-COVID. The ratio in blue colored box represents higher positivity during COVID and the ratio in green colored box represents higher positivity during pre-COVID.

Nagaland					
	AVH	ALF	CH	LC	HCC
HBsAg		0	1		
HBcAb IgG		3	0.4	3.5	
Anti-HBs	0.54	0.6	0.3	1.1	
HBeAb	1		1.3	1.6	
HBeAg					
HBcAb IgM			2.3		
Anti - HCV	1.47		0.7	0.4	
Anti - HDV					
Anti-HEV IgM				2.6	
Anti-HEV IgG	3.67			1.6	
Anti-HAV IgM					
Anti-HAV IgG	1.22				1

Figure 2g Nagaland: Positivity ratio (2018-2020 / 2020-2022) of diagnostic markers in the five clinical conditions (AVH, CH, ALF, LC, HCC) of viral hepatitis patients to compare pre-COVID (2018-2020) and during COVID (2020-2022)

Empty values in blue represent positivity only during COVID and empty values in green represent positivity only in pre-COVID. The ratio in blue colored box represents higher positivity during COVID and the ratio in green colored box represents higher positivity during pre-COVID.

Sikkim					
	AVH	ALF	CH	LC	HCC
HBsAg	0.59		8		
HBcAb IgG	1.51	0.8	0.9		
Anti-HBs	1.68	0.2	0.7		
HBeAb					
HBeAg					
HBcAb IgM					
Anti - HCV	1.19				
Anti - HDV					
Anti-HEV IgM	4.21				
Anti-HEV IgG	1				
Anti-HAV IgM					
Anti-HAV IgG	0.95	1.1			

Figure 2h Sikkim: Positivity ratio (2018-2020 / 2020-2022) of diagnostic markers in the five clinical conditions (AVH, CH, ALF, LC, HCC) of viral hepatitis patients to compare pre-COVID (2018-2020) and during COVID (2020-2022)

Empty values in blue represent positivity only during COVID and empty values in green represent positivity only in pre-COVID. The ratio in blue colored box represents higher positivity during COVID and the ratio in green colored box represents higher positivity during pre-COVID.

Tripura	AVH	ALF	CH	LC	HCC
HBsAg	1.33		1.6	0.1	
HBcAb IgG	1.21		0.9	0.3	
Anti-HBs	0.66		1.9		
HBeAb	0.92		1.5	0.8	
HBeAg	0.48		0.5		
HBcAb IgM	0.57		0.5		
Anti - HCV	0.22		0.1		
Anti - HDV					
Anti-HEV IgM	0.6				
Anti-HEV IgG	0.94			0.1	
Anti-HAV IgM	0.6				
Anti-HAV IgG	1.38		1.3	0.7	

Figure 2i Tripura: Positivity ratio (2018-2020 / 2020-2022) of diagnostic markers in the five clinical conditions (AVH, CH, ALF, LC, HCC) of viral hepatitis patients to compare pre –COVID (2018-2020) and during COVID (2020-2022)

Empty values in blue represent positivity only during COVID and empty values in green represent positivity only in pre-COVID. The ratio in blue colored box represents higher positivity during COVID and the ratio in green colored box represents higher positivity during pre-COVID.

In Assam site 1 - AMCH (Figure 2a), HBV, HEV was higher and HCV, HAV were lower in 2020-22 as compared to 2018-2019 in AVH patients. But in case of chronic hepatitis, the trend was opposite. In HCC, the markers were higher in 2018-2019. In liver cirrhosis except HAV IgG, HEV IgG all the markers were higher in 2020-22. HAV IgM was higher in 2020-22 in ALF, chronic hepatitis, liver cirrhosis patients but not in AVH patients.

In Assam site 2- GMCH (Figure 2b), it can be noticed that HBeAb in chronic hepatitis patients was higher in 2018-2019 than in 2020-2022 but HBeAg was higher in 2020-22 than in 2018-19. But in case of AVH patients, both these markers were higher in AVH during 2018-19. Anti HCV was higher in 2020-22.

In Arunachal Pradesh (Figure 2c), it can be noticed that HBeAb in chronic hepatitis patients was higher in 2018-2019 than in 2020-2022 but HBeAg was higher in 2020-22 than in 2018-19. Anti HCV was higher in 2020-22. Anti HEV IgM in AVH patients was higher in 2020-22 but HAV IgM was higher in 2018-19.

In Manipur (Figure 2d), Anti HCV was higher in 2018-19 than in 2020-22 in chronic hepatitis patients, liver cirrhosis patients, ALF patients but in HCC patients it was higher in 2020-22.

In Mizoram (Figure 2e), HBsAg, Anti HDV was higher in 2018-2019 than in 2020-22 in AVH and CH patients. HBeAg, Anti HCV was higher in 2020-22 than in 2018-19 in AVH patients but less in chronic hepatitis patients. HEV and HAV IgM was higher in 2020-22 than in 2018-19. In chronic hepatitis patients, HBeAg was high in 2018-19 than in 2020-22 whereas HBeAb, HBcAbIgM was higher in 2020-22 than in 2018-19 possibly indicating core mutant enrichment. HDV was also higher in 2018-19 than in 2020-22, possibly because of this.

In Meghalaya (Figure 2f), HBsAg was higher in AVH, LC in 2020-22 than in 2018-19 but it was higher in CH in 2018-19. Anti HDV was higher in 2018-19 in chronic hepatitis patients and was higher in 2020-22 in liver cirrhosis, HCC patients. HBeAg was higher in 2020-22 in AVH, CH patients but not in liver cirrhosis patients.

In Nagaland (Figure 2g), HBsAg was high in 2020-22 in ALF patients, chronic hepatitis patients, liver cirrhosis patients and HBeAg was high in chronic hepatitis patients and liver cirrhosis patients. Anti HCV was higher in AVH, ALF, LC but not in CH. HEV IgM was high in AVH, ALF, CH.

In Sikkim (Figure 2h), HBsAg was high in AVH patients in 2020-22 than in 2018-19 and it showed the opposite in chronic hepatitis patients. HEV IgM was high in ALF patients but not in AVH patients during 2020-22. Anti HCV was higher in AVH, CH patients.

In Tripura (Figure 2i), HBsAg was high in AVH, CH, ALF patients pre-COVID but HBeAg was low pre-COVID and high during COVID. Anti HCV was high during COVID in AVH, CH patients.

Overall observation:

HDV cases in males decreased but was increased in female acute liver failure Hepatitis patients during COVID. The influence of COVID infection over a satellite virus infection has not been reported in literature. It was noted that although there was decrease in HBs Ag, there was increase in HDV as measured by anti HDV in female patients during COVID possibly indicating there is possibility of helper independent replication as mentioned in literature (39) and also the possibility of a non HBV virus aiding in HDV replication (40). Further it is also to be noted that HDV replication can be associated with HBV repression (41).

In chronic Hepatitis patients, female patients had an increase in HBV, HCV cases as compared to males post COVID. Possibly this could be influenced by healthcare facilities that were available during the COVID period. Literature suggests that COVID vaccine has no influence on HBV infection (42). But it has been shown that SARS-COV2 infection in inactive HBV carrier state exacerbates the disease (43). The serological parameters of patients with co-infection of SARS-COV2 and HBV have been reported (44).

It has been shown that COVID 19 vaccine had cross reactivity with hepatitis E virus thus confounding its positivity in vaccinated individuals(45). It has also been shown that due to limited medical healthcare facility in COVID, nosocomial infection of HEV occurred(46). Hence during COVID, surge in HEV detection was noticed either due to real infection or probably due to cross-reactivity. In our study, states that indicated increase in HEV during 2020-2022, included Nagaland (acute and chronic viral hepatitis patients), Arunachal Pradesh (acute viral hepatitis patients).

In case of HCV infections, it has been documented that due to use of cortocosteroids in COVID treatment, there was reactivation(47). In our study it was noticed that there was marked increase of HCV in 2020-2022 in the states of Meghalaya, Nagaland in acute viral hepatitis patients and increase of HCV cases in states of Tripura, Arunachal, Assam site 2, Manipur (chronic viral hepatitis patients).

Further, it was noticed that during COVID, HAV IgG positive cases were comparatively less in patients with <1.2 mg/dl bilirubin and hence, there could be a speculation of a scenario like in measles infection that can exhaust antibody repertoire (48). The results also indicate that the patients (Acute viral hepatitis male) with >1.2 mg/dl bilirubin level in post COVID period had more of HBeAb positivity than patients with <1.2 mg/dl bilirubin level. This could possibly indicate an effect of SARS COV2 co-infection in HBV patients or an enrichment of HBecore mutant infection in the post COVID.

Conclusion

The results indicate that COVID did have influence on viral hepatitis infection in northeastern India although the exact mechanism is largely unknown.

Ethical statement:

Samples were collected by informed consent and approval of Institutional ethical committee

Data availability: The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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