ORIGINAL ARTICLE

Comparison of Clinical Features of HBV and HDV Coinfection with HBV Monoinfection: A Study from the Developing World

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Abstract

Hepatitis B infection remains a significant global health concern, with hepatitis D co-infection observed in approximately 5% of the patients. Treatment options for hepatitis D are currently limited, with most therapies awaiting approval by the FDA. However, there is a lack of comprehensive data on the prevalence and clinical presentation of patients with hepatitis B and D coinfection, particularly in Pakistan. In this study, we aimed to compare demographic characteristics, clinical presentations, laboratory, and endoscopic parameters along with the different treatment options between patients with hepatitis B monoinfection and those with hepatitis B and D coinfection.

Keywords: Developing word, Entecavir, Hepatitis B mono-infection, Hepatitis B and D co-infection, Pakistan, Pegylated interferon.

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Introduction

Hepatitis B virus (HBV) remains a significant global public health concern. According to estimates from the World Health Organization (WHO), in 2019, over 296 million people were infected by this virus, with 1.5 million new cases reported annually.[1] Hepatitis D virus (HDV) is found in approximately 5% of individuals with chronic hepatitis B infection.[2] Moreover, the global positivity of anti-HDV is around 12 million.[3]

Hepatitis D, which is a small single-stranded RNA utilizes the hepatitis B surface antigen (HBsAg) for its assembly, transmission between hepatocytes along dissemination amongst the host cells.[4]

According to a WHO approximation, globally around 1 million people die of hepatitis B-related complications.[5] Countries and regions known to have a higher prevalence of hepatitis D include Mongolia, parts of Russia, Romania, Uzbekistan, Pakistan, Vietnam, and the Amazon basin along certain regions of Africa.[6]

Transmission of hepatitis B is generally via the following routes: Perinatal exposure, during sexual intercourse, via the usage of contaminated blood products, and using unsterilized needles.[7] On the other hand, hepatitis D infection is spread from contaminated blood products, in IV drug abusers, men who have sex with men, and through unsafe sexual behaviors. Vertical transmission is rarely noted for hepatitis D.[8,9] A higher number of HDV cases are also observed amongst patients on hemodialysis, those having coinfection with HCV or HIV infection.[10]

While most adults infected with Hepatitis B tend to clear the virus, around 5–10% of the patients tend to develop chronic hepatitis B infection.[11]

In Pakistan, the prevalence of hepatitis B is approximately 2.5%, with a corresponding anti-HDV positivity of 16.6% in those testing positive for HbsAg positive.[12]

There is a paucity of data on the actual prevalence, and clinical presentation of hepatitis D. Our study aims to address this gap by comparing patients having Hepatitis B and D coinfection with hepatitis B moninfection.

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Materials and Methods

All patients initially diagnosed with Hepatitis B or Hepatitis B and D coinfection, attending the Hepatogastroenterology services at our Institute, SIUT, between January 2023 and October 2023 were included in this study (Fig. 1).

Hepatitis B and HDV infections were diagnosed by using commercially available enzyme-linked immunosorbent assays for HBsAg and anti-HDV antibody, while HBV DNA and HDV RNA were detected by using a real-time polymerase chain reaction (PCR).

Those with HbsAg positive for 6 months were labeled as having chronic hepatitis B infection.

After obtaining informed written consent, a questionnaire having the basic demographic data including age, sex, and date of diagnosis of hepatitis B, hepatitis B and D coinfection were noted, and baseline laboratory parameters along with serological work were filled by the principal investigator himself. Following this, quantitative HBV DNA PCR, and quantitative HDV RNA PCR (if required) were requested. Ultrasound abdomen was later on performed to rule out the presence of chronic liver disease (CLD). Those requiring screening EGD as per Baveno VII protocol were advised endoscopy. Endoscopic evaluation of varices was recorded using a video

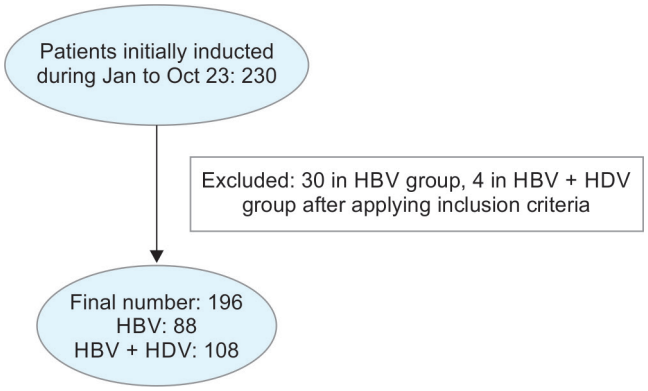

Fig. 1: Flowchart showing the process of induction of patients at our center

endoscope Olympus GIF-H190 (Olympus Medical Systems Corp., Tokyo, Japan) performed by a senior endoscopist (having more than 5 years of experience). The grading system to document the size of varices being followed in our hospital evaluates esophageal varices in the following way: Grade I, varices present, but flatten completely with air insufflations; grade II, non-flattening varices that occupy 10–30% of the esophageal luminal radius; grade III, varices occupy 31–60% of the esophageal luminal radius; and grade IV, varices occupy 61–100% of the esophageal luminal radius.

Abdominal ultrasonography was carried out by an expert sonologist using Toshiba-Aplio 50 (Toshiba Medical Systems Corp., Tochigi, Japan) on the day of presentation. The degree of liver fibrosis was assessed by using the shear wave elastography. All tests were conducted at our hospital and free of cost.

Statistical analysis was carried out using software SPSS version 22 (Statistical Product and Service Solutions; IBM Corporation, Armonk, New York, USA).

Descriptive statistics were computed for all variables. Results were presented as median with SDs for quantitative variables and number (%) for qualitative variables. Pearson χ^2-test was used for qualitative variables. Unpaired *t*-test was applied for normally distributed data while Mann–Whitney *U* test was for data that was not normally distributed. *p*-values of less than 0.05 were taken as statistically significant.

Later on, these patients were advised treatment accordingly, those having hepatitis B and D coinfection and had not decompensated were advised pegylated interferon (PEG-IFN) for a period of 1 year while those who had decompensated were kept on entecavir and advised early induction for liver transplantation. Whereas hepatitis B-infected patients were given tablet entecavir.

Liver-related outcomes were defined as the occurrence of cirrhosis, hepatocellular carcinoma (HCC), undergoing liver transplantation, or death of the patient. These patients were followed up for a period of 6 months and hepatitis B DNA and Hepatitis D RNA were repeated during that time.

Inclusion Criteria

- All patients visiting the gastrointestinal outpatients' department (GI OPD) and recently diagnosed with HBV or HBV and HDV coinfection.
- Age-groups 2–70 years.

Exclusion Criteria

- Those patients who were already on treatment for hepatitis B, or hepatitis B and D.
- Those having HCC.
- Those patients who had concomitant any other liver disease.
- History of use of hepatotoxic agents.
- Those refusing to give consult.

Type of Study

The type of study is a prospective cohort study.

Discussion

Hepatitis B has 10 genotypes from A to J, these vary in their clinic presentations, geographic distribution, clinical course, and genetic expression,[13] While 8 genotypes of Hepatitis D are known to exist.[14]

In Pakistan, the most prevalent genotype of hepatitis B is D,[15] with genotype I being the most common one seen for HDV.[12]

Hepatitis D, being a defective virus, requires the presence of HBsAg for propagation, as a result, Hepatitis D can present with hepatitis B as either a coinfection or a superinfection.[16]

Our study participants had an average age of 35 and were mostly males, a similar finding to what was noted in a Swiss study, which showed an average age of 36 years and with a male predominance.[17]

As shown by many prior studies, diagnosing these infections is challenging, particularly in the developing world and only 10% of chronic hepatitis B patients are aware of their diagnosis.[18]

Coinfection of Hepatitis B with hepatitis D leads to a more severe hepatitis that has two peaks in the ALT/AST levels but with a better chance of clearing the virus. Meanwhile, superinfections lead to severe acute hepatitis leading to chronic hepatitis in 90% of the cases.[19]

Mohsin et al. in their study on the Pakistani population revealed a low viral load of hepatitis B in those having hepatitis B and D coinfection due to the suppression of hepatitis B by the hepatitis D virus,[20] a finding also evident in our study.

Although active HDV infection patients mostly have negative E antigen and negative HBV DNA, this was not the case in our study.[21]

Similar to our findings, another study showed that chronic infection of hepatitis B and D had a higher risk of cirrhosis and HCC compared to hepatitis B alone.[22] While another study pointed out that HDV-infected patients had a lower platelet count and larger size of varices on EGD when compared to those with hepatitis B monoinfection.[23]

According to the AASLD and EASL guidelines, the recommended antiviral therapy for hepatitis B infection is long-term nucleos(t)ide analogues with a high barrier to resistance, these include entecavir, tenofovir alafenamide, tenofovir disoproxil.[24] Our patients mostly received entecavir (60.7%) or TDF (8.7%).

Management for Hepatitis D appears promising but there is currently no FDA-approved oral drug for hepatitis D. The only recommended therapy for hepatitis D remains PEG-IFN alpha.[25] This was used alone in 17.3% of the cases.

A negative HDV RNA after 6 months of therapy with PEG-IFN is said to show a virological response while a treatment duration of 48 weeks is generally recommended.[26]

Newer therapeutic options like bulevirtide, lonafarnib, PEG-IFN lambda, and REP 2139-Ca have emerged, however, none are yet approved by the FDA. Furthermore, their availability in the developing world would face many challenges.[27]

Results

Overall Parameters

Out of 230 patients, 196 patients were included in this study after fulfilling the exclusion criteria (30 patients were excluded in the hepatitis B group while 4 were excluded in the coinfection group).

Hepatitis B and D coinfection was observed in 108 (55.1%) patients, while HBV monoinfection was evident in 88 (44.9 %).

The mean age of all the participants was 35 ± 12.5 years, with most participants following in the 21–49 age bracket, 117 (59.7%) followed by more than 41-year group, 57 (29.1%).

Males predominated, accounting for 150/196 patients (76.5%), while 46 of those included in this study were females (23.5%).

Most of the participants did not have any comorbid condition, 170/196 (86.7%). While in those who did have a comorbid condition 26/196 (13.3%), ESRD was the leading one, seen in 14/196 (7.1%) with chronic kidney disease (CKD) noted in second place, in 3/196 (4.1%).

The majority of our patients were on regular follow-up visits 170/196 (86.7%)

The chief presenting complaint seen was abdominal pain, in 17/196 (8.9%), followed by abdominal distension in 8/196 (4.1%), and decreased urine output and altered level of consciousness in 4/196, (2% each), while melena was evident in 3/196 (1.5%).

When comparing the lab parameters, HbeAg positivity was noted in 40/196 (20.4%), HbeAb positive in 74 (37.8%), and anti-HDV positive in 97 (49.5%).

Initial HBV DNA PCR was detected in 146/196 (74.5%), with a mean value of 3×10^7 (31220546.01) IU/mL.

Meanwhile, the initial HDV RNA PCR was detected in 80/196 (40.8%), having a mean value of 4.8×10^6 (4896002) IU/mL, and was not required in 52/196 (54.2%).

The mean value of the 6th month HBV DNA PCR was 3.1×10^5 (314109) IU/mL and the 6th month HDV RNA PCR was 2×10^6 (2133400) IU/mL.

The mean Child Turcotte Pugh (CTP) score noted in both groups was 7 ± 2.5 and the mean MELD score was 13 ± 7.7; CTP A was noted in 119/196 (60.7%), CTP B in 40/196 (20.4%), and CTP C in 32/196 (16.3%).

Esophageal varices were evident on upper GI endoscopy in 61/196 cases (31.1%), while no evidence of esophageal varices was noted in 18/196 (9.16%) and EGD was not required in 115/196 (58.6%).

Most of our patients had hepatitis encephalopathy grade (G): G1 132/196 (67.3%), G2 34 (17.3%), G3 11 (5.6%), and G4 in 1 (0.5%).

The mean spleen size was 13.2 ± 3.24 cm.

While fibroscan of the liver predominantly showed F1 in 40/196 (20.41%) followed by F2 in 20/196 (10.2%).

In treatment options, out of 196 patients, 119/196 (60.7%) were treated with tablet entecavir while TDF was used in 17/196 (8.7%); PEG-IFN was used in 15/196 (7.65%) and PEG-IFN and Entecavir in 4/196(2%), while 23/196 (11.7%) patients were not given any form of therapy. Pegylated interferon alpha was used in 34 (17.3%) patients, predominantly in those with HBV and HDV coinfection.

Comparison of HBV Monoinfection with HBV + HDV Coinfection

A comparison of hepatitis B ($n = 88$) with hepatitis B and D ($n = 108$) was done on various parameters.

No significant age difference was evident in both groups, with the median age being 33 (IQR 26–41.75) years in HBV-HDV while the median age was 36 (IQR 26-45) in the HBV group, ($p = 0.129$) (Fig. 2).

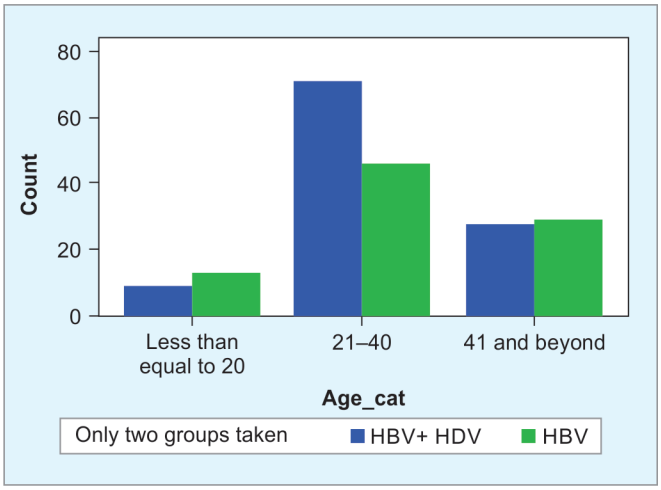

Fig. 2: Division according to the age-groups between HBV monoinfection and HBV+ HDV coinfection

Table 1: Comparison of lab parameters in HBV+ HDV vs HBV monoinfection

	HBV + HDV coinfection	*HBV mono-infection*	
Parameters	*Median (IQR)*	*Median (IQR)*	*p-value*
HB	11.3 (9.3–11.3)	12.5 (11.2–14.1)	0.001
HCT	32.8 (27.6–37.9)	36.2 (31.9–41)	0.022
TLC	5.45 (3.7–7.1)	6.7 (5.5–8.4)	<0.001
Plts	99.5 (65–185)	229.5 (123–288.5)	<0.001
Urea	25 (19–44)	29 (19–37)	0.502
Cr	0.8 (0.6–1.0)	0.865 (0.6–1.2)	0.262
Sodium	137 (134–140)	140 (137–141)	0.006
Potassium	4.2 (3.8–4.5)	4.3 (3.6–4.6)	0.524
Chloride	105 (101.5–108)	103 (101–107)	0.209
Bicarbonate	22 (18–24)	22 (20–25.5)	0.201
INR	1.23 (1–1.45)	1 (0.9–1.2)	<0.001
TBR	1.2 (0.7–2.4)	0.58 (0.39–1.47)	<0.001
ALP	128 (94–195.2)	118 (82–164)	0.097
SGOT	66.5 (41–105)	29 (24–51)	<0.001
SGPT	54 (32–73.5)	29 (23–44)	<0.001
GGT	47 (29–92)	29 (18–49)	<0.001

While male was the predominant gender seen in both the groups, 87 in HBV (80.5%) and HDV while 63 (71.6%) in HBV monoinfection alone with $p = 0.175$.

A significant difference was evident in the presenting complaints in both groups, with the coinfection group presenting more frequently with complaints of abdominal pain, distention, and a decrease in their urine output ($p = 0.013$)

When comparing lab parameters between both the groups, a significant difference was noted (p-value ≤ 0.05) in most apart from urea, creatinine, potassium, chloride, bicarbonate, and alkaline phosphate (Table 1).

Hepatitis B e-Antigen positivity was more noticeable in the HBV and HDV coinfection group, however, the p-value was not significant ($p = 0.062$) (Table 2).

Table 2: Comparison of the overall features between the two groups

Parameters	*HBV-HDV*	*HBV monoinfection*	*p-value*
Number	108	88	–
Gender	Males (80.5%)	Males (63.5%)	0.175
Age (years)	33	36	0.129
Comorbids condition	10.2%	17.0%	0.65
HbeAg positive	21.3%	19.3%	0.062
HbeAb positive	44.3%	32.4%	0.03*
Baseline HBV DNA	1.9 × 107	4.5 × 107	0.26
Baseline HDV RNA	9.0 × 106	–	–
6 months HBV DNA	2.4 × 105	3.9 × 105	0.66
6 months HDV RNA	1.5 × 105	–	0.64
CLD features on US Abdomen	60.2%	22.7%	0.001*
Varices on EGD	48.1%	12.5%	0.001*
Spleen size (cm)	13.6	12	0.000*
HE presence	98%	81.8%	0.001*
CTP B, C	51.9%	18.2%	0.000*
Treatment offered	92%	63%	0.007*
Liver transplanted	7	0	–
Death rates	4	0	–

*$p \leq 0.05$ significant

Hepatitis B, antibody e positivity was more noticeable in the HBV group when compared to the HBV and HDV ($p = 0.03$).

Note that CLD features on ultrasound abdomen were mostly seen in the HBV and HDV coinfection group 65/108 in comparison to 20/88 ($p < 0.001$).

Similarly, the presence of ascites was more evident in the HBV and HDV coinfection group.

66/108 as compared to 22/88 ($p < 0.001$).

Varices on EGD were more evident in the HBV and HDV groups as compared to HBV alone ($p < 0.001$). The majority of those with HBV and HDV coinfection fell in the CTP B and C group ($p < 0.001$). Evidence of HE was more in HBV and HDV groups when compared to groups having HBV alone ($p < 0.001$). The spleen size was 13.6 cm (IQR in the coinfection group vs 12.0 cm (IQR in the monoinfection group ($p = 0.000$).

The majority of the patients in hepatitis B and D coinfection received some form of treatment ($p = 0.007$) when compared to hepatitis B monoinfection alone, with PEG-IFN used in 11 in the coinfection group vs 4 in the monoinfection, entecavir 70 in the coinfection vs 40 in the monoinfection, PEG-IFN and entecavir 4 vs 0.

More patients in Hepatitis B and D coinfection group underwent live-related liver transplant 7 vs 0 in the monoinfection group, while death rates were higher in the coinfection group V vs IV in the monoinfection ($p = 0.052$).

Conclusion

Our study reveals that individuals with HBV+ HDV coinfection were more prone to present with decompensated liver disease, underscoring the tendency for these patients to seek medical attention at later stages and only limited treatment options currently available. Early referral of such cases is crucial to mitigate the risk of further complications. However, the lack of access to novel therapies like bulevirtide in our country further restricts treatment options for these patients.

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