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ESOPHAGEAL VARICES IN HEPATITIS B PATIENTS WITH AND WITHOUT CONCOMITANT HEPATITIS D INFECTION

Fozia Shaikh[*1], Saleh Muhammad Channa[2], Iftikhar Ali Shah[3], Bashir Ahmed Chandio[4]

[1,2,3,4] Ghulam Muhammad Mahar Medical College, Sukkur

[*1]Email: foziashaikh97@gmail.com

[2]Email: salehmuhammd14@gmail.com

[3]Email: turabkot@yahoo.com

[4]Email: drbashirchandio@gmail.com

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Corresponding Author: Fozia Shaikh, Ghulam Muhammad Mahar Medical College, Sukkur
Email: foziashaikh97@gmail.com

ABSTRACT

Chronic hepatitis B virus (HBV) infection is a leading cause of cirrhosis and portal hypertension worldwide, affecting approximately 296 million people and causing nearly 1 million deaths annually from complications. Hepatitis D virus (HDV) co-infection occurs in ~5% of HBV carriers. This study aimed to compare the frequency of esophageal varices in HBV-monoinfected patients versus those co-infected with HDV. A cross-sectional study was conducted at a tertiary care hospital in Sukkur, Pakistan over 6 months. A total of 132 patients with chronic HBV infection (≥3 months, age 20–80, both sexes) were enrolled consecutively. HDV serology (anti-HDV ELISA) was performed to categorize patients into HBV-only or HBV+HDV groups. All patients underwent clinical evaluation and laboratory workup; upper gastrointestinal endoscopy was then performed by an experienced gastroenterologist (blinded to HDV status). Statistical analysis was done with SPSS v26. Continuous variables were assessed for normality using the Shapiro-Wilk test. A multivariable logistic regression was performed to estimate the association of HDV co-infection with presence of varices. These findings suggest that HDV co-infection contributes to variceal development

	primarily by increasing the likelihood of advanced liver disease (cirrhosis). In this cohort of chronic hepatitis B patients, concomitant HDV infection was associated with a significantly higher frequency of esophageal varices.

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a major global health concern and a leading cause of liver cirrhosis and hepatocellular carcinoma (HCC). The World Health Organization estimates that in 2019 about 296 million people worldwide were living with chronic HBV infection, comprising roughly 3.8% of the global population (Sharabati et al., 2024). Each year, HBV-related complications (cirrhosis, liver failure, and HCC) result in nearly one million deaths. One serious consequence of chronic HBV is the development of portal hypertension and esophageal varices (EV) once cirrhosis ensues. EV are present in a substantial proportion of cirrhotic patients – studies suggest that up to 90% of individuals with cirrhosis will develop varices over their lifetime (Hongyun et al., 2025). Variceal hemorrhage is among the most feared complications, with historical mortality rates around 20% within six weeks of bleeding even with appropriate treatment. Given this high morbidity and mortality, understanding factors that influence the development of varices in HBV patients are of significant clinical importance. Hepatitis D virus (HDV) is a defective RNA virus that requires HBV for its replication and propagation. HDV infection occurs either as a co-infection (simultaneous with acute HBV) or more commonly as a super-infection in established HBV carriers. Globally, HDV co-infection is estimated to affect nearly 5% of chronic HBV carriers (Akhtar et al., 2024). This translates to approximately 12–20 million people worldwide harboring HDV, though precise figures vary by region and population. HDV prevalence exhibits striking geographic variation: high endemic areas include parts of Africa, the Middle East, Eastern Europe, and the Amazon basin. Pakistan is recognized as a high HDV burden country (Sohu et al., 2023). Earlier studies in Pakistan reported HDV seroprevalence rates of ~16–27% among HBV-infected individuals file. More recent data suggest an even higher burden; for example, a 2014 study from Peshawar, Pakistan found 47% of chronic HBV patients positive for HDV antibodies file. Some rural clusters in southern Pakistan have reported extremely high HDV prevalence (approaching 60% of HBV cases), indicating focal hyperendemicity (Bilal, Xicang, Jiying, Sohu, & Akhta, 2024). These figures stand in stark contrast to the global average and underscore that HBV/HDV co-infection

is a significant public health issue in this region (Sohu et al., 2024). Thus, patients with HBV/HDV tend to experience end-stage liver disease complications at a younger age and with a shorter duration of infection (Kherazi et al., 2024). Consistent with this, a clinical study in Karachi, Pakistan found that nearly half (49%) of HDV-infected HBV patients already had clinical cirrhosis at presentation. In comparison, HBV monoinfected patients typically take decades of chronic infection to reach cirrhosis, and a smaller fraction present with advanced disease in the same age range (Sohu et al., 2022). Despite the well-recognized propensity of HDV to cause rapidly progressive liver fibrosis, there remains a paucity of data on specific complications of portal hypertension – such as esophageal varices – in HBV/HDV co-infection (Solaiman et al., 2023). However, few studies to date have explicitly compared variceal prevalence between HBV mono-infected and HBV/HDV co-infected populations. Most literature on varices in viral hepatitis has focused either on HBV or hepatitis C (HCV) related cirrhosis, identifying predictors like thrombocytopenia (Borhani et al., 2024), splenomegaly, and portal vein diameter (McBride et al., 2025). Whether the presence of HDV independently influences the occurrence of varices, or simply via causing cirrhosis, is not well established (Buchanan et al., 2023). We hypothesized that HDV co-infection would be associated with a higher prevalence of varices due to more advanced liver disease. Additionally, we aimed to assess whether HDV is an independent risk factor for varices after controlling for other confounders, and to explore results within key subgroups (gender, BMI, cirrhosis status). By providing data on this question, our study can help inform clinical management (e.g., screening strategies) for co-infected patients and underscore the importance of HDV detection and treatment in ameliorating HBV-related complications.

Literature Review

HBV and portal hypertension: Chronic hepatitis B remains a leading cause of cirrhosis globally (Sohu, Hongyun, et al., 2020). Once cirrhosis develops, portal hypertension leads to portosystemic collateral formation and varices. All cirrhotic patients are at risk for variceal bleeding; indeed, varices form in ~50% of cirrhotics within 10 years of cirrhosis onset, and as mentioned (Jalihal et al., 2025), up to 90% over a lifetime Variceal hemorrhage is a dire event, accounting for roughly 15–30% of all deaths in patients with cirrhosis (Sohu, Mirani, et al., 2020). The management of HBV-related cirrhosis includes surveillance endoscopy for varices and prophylactic therapy for large varices, per international guidelines. Prior studies in HBV

cirrhosis have identified several predictors of varices. For instance, a Chinese study of 146 HBV-cirrhotic patients reported an EV prevalence of 74.7%, and found that platelet count, spleen size, and portal vein diameter were significantly associated with variceal presence Multivariate analysis highlighted spleen width and portal vein diameter as independent predictors, leading to non-invasive models for variceal prediction (He et al., 2024; Hongyun et al., 2025). While these findings help risk-stratify HBV cirrhotics, they do not address whether the etiology or co-factors (like HDV) modify variceal risk. Notably, most HBV cirrhosis studies have been conducted in patients without mention of HDV, or in regions where HDV is rare (East Asia, etc.), thus essentially reflecting HBV monoinfection (Sagnelli et al., 2021).

Pathogenesis and Outcomes of HDV

HDV's effect on the natural history of chronic hepatitis B has been extensively documented. Co-infection with HDV causes more severe necroinflammatory activity in the liver and a faster fibrosis progression rate file. About 70–80% of chronic HDV patients will progress to cirrhosis (Caviglia et al., 2022), often within a decade of infection By contrast, only an estimated ~15–30% of HBV monoinfected individuals progress to cirrhosis over a much longer period (two to three decades) in the absence of treatment (Sohu et al., 2024). The aggressive nature of HDV is reflected in clinical endpoints: multiple studies have shown HDV co-infection leads to higher rates of hepatic decompensation (ascites, encephalopathy, variceal bleeding) and mortality (Chen et al., 2022). For example, a German cohort found HDV-positive patients had a 4.7-fold higher risk of severe liver-related outcomes (a composite of liver failure, transplant, or death) compared to HBV-only patients (Bilal, Xicang, Jiying, Sohu, Akhtar, et al., 2024; Tharwani & Hamid, 2023). Similarly, a large Veterans Affairs study in the US (n>4,000 HBV-infected veterans tested for HDV) recently reported that HDV co-infection was independently associated with increased risk of cirrhosis complications (adjusted HR ~2.6) and all-cause mortality (aHR ~1.5) (Wadhawan & Argal, 2023). Notably, once patients reach the stage of cirrhosis and portal hypertension, HDV per se may not further exacerbate portal pressure beyond what cirrhosis dictates (Rabaan et al., 2025). In other words, HDV's main effect is to hasten the arrival at cirrhosis; after cirrhosis is established, the variceal risk is high in all patients regardless of etiology. This concept was demonstrated in a long-term Italian study: HDV-infected patients progressed to cirrhosis much faster than HBV controls (New-Aaron, 2022), but among those who were already cirrhotic, the incidence of variceal bleeding and other decompensations was

similar between HDV and HBV groups. Such findings suggest that HDV's contribution to variceal development is mostly indirect, via causing cirrhosis earlier and more frequently.

HDV in Pakistan

Pakistan bears one of the highest burdens of HDV in the world Studies from different parts of the country over the past few decades consistently demonstrate high co-infection rates among HBV patients. (Majid et al., 2024; Mirani et al., 2021) reviewed data from Pakistan and estimated an overall HDV prevalence of ~16.6% in HBV carriers, with higher rates in the interior Sindh province and other rural areas. The same review noted pockets with extremely high prevalence, suggesting concentrated outbreaks or risk factors (for instance, reuse of syringes in community settings). More recent surveys, as mentioned, have found 30–50% prevalence in some tertiary centers file. Clinically, Pakistani patients with HDV often present with advanced disease. A study of 39 HDV RNA-positive patients in Karachi found that 49% had clinical cirrhosis and 18% had already decompensated (e.g., ascites, variceal hemorrhage) at the time of diagnosis (Moatter et al., 2007; Muhammad et al., 2023). Another study from the same center noted that HDV patients had more severe fibrosis on liver biopsy and higher liver stiffness values than HBV-only patients, despite similar durations of infection (suggesting HDV's fibrogenic acceleration) (Parikh et al., 2017). These observations align with global data and reinforce that in Pakistan's context, an HBV patient with concomitant HDV is much more likely to be a cirrhosis patient than an HBV patient without HDV (Yang et al., 2025).

HDV patient and HBV Patient

While it is well recognized that HDV co-infection hastens cirrhosis, the specific impact on esophageal varices – a key complication of cirrhosis – has not been thoroughly quantified. Variceal hemorrhage is a major cause of morbidity in our setting, and knowing whether HDV patients have varices more frequently (or at a younger age) could influence how we manage and screen these patients. If nearly all the effect of HDV is mediated through cirrhosis, then an HDV patient and an HBV patient of similar Child-Pugh class should have comparable variceal risk (Hongyun et al., 2025). However, it is conceivable that HDV's intense inflammatory activity could cause sporadic portal hypertension even before frank cirrhosis (so-called "non-cirrhotic portal hypertension" or early fibrotic stage varices). There have been case reports of variceal bleeding in chronic hepatitis without cirrhosis, although rare. By studying a cohort of HBV

patients with and without HDV, and stratifying by cirrhosis, our research can shed light on whether HDV status has an effect beyond simply the presence of cirrhosis (Sohu et al., 2024).

Additionally, given the extremely high HDV burden regionally, our study provides locally relevant data that can inform practice. Pakistani national guidelines currently follow general HBV management principles, but do not have separate recommendations for HDV co-infected patients regarding variceal screening. If our study finds a significantly higher variceal prevalence in co-infected patients at earlier disease stages, it might justify more vigilant surveillance (for example, performing screening endoscopy in an HDV patient once any fibrosis is present, rather than waiting for clinical cirrhosis) (Sohu et al., 2024). Conversely, if co-infected patients only have varices when they are cirrhotic, then standard criteria suffice, and the focus should be on preventing progression to cirrhosis through antiviral therapy. The literature clearly demonstrates that HDV drastically worsens the liver-related outcomes of HBV infection, but the nuances regarding portal hypertensive complications like varices need further exploration. Our study builds on this background by providing empirical data comparing esophageal varices in HBV vs HBV+HDV patients (Sohu et al., 2024). The findings will contribute to the body of evidence needed to optimize care for co-infected patients, and underscore the broader significance of detecting and treating HDV – an often neglected aspect of hepatitis B management.

Methodology

Study Design

We conducted an observational analytical study with a cross-sectional design. The study was carried out at the Department of Medicine, Ghulam Muhammad Mahar Medical College Teaching Hospital (GMMMC Hospital) in Sukkur, Pakistan. This is a tertiary care hospital serving a region with high HBV and HDV endemicity. The study duration was six months, from June 2022 to November 2022 (after approval of the research protocol by the College of Physicians & Surgeons Pakistan and the local institutional ethics committee).

Population and Sampling

The target population was adult patients with chronic hepatitis B infection presented to the medical outpatient department or hepatology clinic at GMMMC Hospital. We employed a non-probability consecutive sampling technique. All patients meeting the inclusion criteria during the study period were invited to participate, until the required sample size was reached. A sample size of 96 was initially calculated as the minimum needed (using a WHO sample size calculator)

to detect a difference in variceal frequencies, assuming an HDV prevalence of ~47%file, a projected variceal frequency of ~30% in co-infected vs ~15% in monoinfected (based on pilot observations), with 95% confidence and 80% power. To enhance robustness, we enrolled 132 patients in total.

Inclusion and Exclusion Criteria

Adults aged 20 to 80 years, of either sex, with confirmed chronic HBV infection (defined as HBsAg positivity persisting >6 months). We included both treatment-naïve patients and those on HBV antiviral therapy (if any), as long as they still had HBsAg positivity. Only patients with compensated liver disease or early decompensation were included in the outpatient setting (those too ill were managed inpatient but could be included if stable for endoscopy). We required that patients be willing to undergo HDV testing and an upper endoscopy for variceal screening. We excluded patients with any other concomitant chronic liver disease to avoid confounding. In particular, patients with hepatitis C or HIV co-infection were excluded (all patients had prior screening for HCV and HIV as part of their workup). We also excluded patients with a history of significant alcohol use (defined as >21 units/week in men or >14 units/week in women) or other known causes of portal hypertension (e.g., idiopathic portal fibrosis, schistosomiasis). Patients who had received a liver transplant were excluded. Additionally, we excluded women who were pregnant (because pregnancy itself can affect variceal status and portal pressure). Patients with active gastrointestinal bleeding at presentation were managed first and included later for endoscopy only after stabilization (none of the study patients underwent emergency endoscopy as part of the protocol; all endoscopies were elective/screening). If a patient had known esophageal varices in the past or prior band ligation therapy, they were excluded to focus on new diagnoses of varices. Varices were graded as small, medium, or large as per standard criteria, but for analysis we considered only the presence vs absence of varices (Gralnek et al., 2022). Cirrhosis was diagnosed based on a combination of clinical, laboratory, and imaging findings (e.g., coarse echotexture and nodularity of liver on ultrasound, splenomegaly, platelet count <100×10^9/L, and signs of portal hypertension) (Dias et al., 2022). Where doubt existed, elastography or FibroScan >12.5 kPa was considered diagnostic of cirrhosis. Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared. We categorized BMI for stratified analysis as “low/normal” (<25 kg/m²) versus “elevated” (≥25 kg/m²) to distinguish non-overweight vs overweight/obese status, aligned with WHO criteria for

Asian populations (acknowledging that BMI ≥25 is overweight for Asians) (Wan et al., 2022). Other variables recorded included: gender, age, residence (urban vs rural), socioeconomic status (based on income and education), smoking history (>5 pack-years considered positive), diabetes, hypertension (BP ≥140/90 or on medications), dyslipidemia (total cholesterol >200 mg/dL or on treatment), and duration of known HBV infection (in months/years since diagnosis.

Data Collection Procedure

After being informed, each patient underwent a structured interview and clinical examination. A pro forma was used to capture demographic data and relevant medical history. Height and weight were measured (height via wall-mounted stadiometer, weight via electronic scale) and BMI calculated file. We then obtained blood samples for laboratory tests: liver function tests, complete blood count, HBsAg (to reconfirm if needed), HBeAg, HBV DNA (if available), and anti-HDV antibody. HDV serology was performed using a third-generation ELISA kit in the hospital lab. Positive HDV serology was followed by an HDV RNA PCR (qualitative) in an external reference lab for those who consented, to assess active infection – though RNA results were not required for inclusion. All patients then underwent upper gastrointestinal endoscopy. Endoscopies were scheduled electively, with patients fasting for 10–12 hours prior file. The procedures were performed using standard video endoscopes, under conscious sedation (midazolam) with monitoring. A senior gastroenterologist (with >5 years' experience) performed each exam, assisted by the trainee researcher, in order to maintain consistency file. The endoscopist was not explicitly told of the patient's HDV status (though the presence of more advanced disease could be apparent clinically). During endoscopy, the esophagus, stomach, and duodenum were examined for varices or other lesions. Presence of esophageal varices was noted, including their size and any high-risk stigmata (red wale marks, etc.). For ethical reasons, if large varices were found, band ligation was offered after the diagnostic endoscopy as clinically indicated (however, this occurred after documentation for the study). The endoscopy findings were recorded immediately in the pro forma.

Quality Control

Data was collected by the investigator (a medical trainee) under supervision. The laboratory tests followed standard quality assurance protocols. The anti-HDV tests were run in batches with controls. The endoscopy unit adhered to disinfection and procedural protocols, and all findings were documented with endoscopic photographs for verification. To minimize bias, whenever

feasible, assessments were blinded – for instance, the endoscopist did not know the patient's group allocation (HDV status). The data analyst was also blinded to group labels initially.

Statistical Analysis

Data was entered and analyzed using IBM SPSS version 26. Continuous variables were first tested for normality using the Shapiro-Wilk test (chosen due to sample size < 50 per group for some subgroup analyses). For variables with $p>0.05$ (indicating approximate normal distribution), we reported means and standard deviations; for variables with $p<0.05$ (non-normal distribution), we reported medians and interquartile ranges. For example, age was roughly normally distributed (Shapiro-Wilk $p=0.10$), so mean ± SD is presented, whereas the distribution of BMI was skewed ($p=0.03$), so median (IQR) is given. Categorical variables (gender, presence of cirrhosis, varices, etc.) were summarized as counts and percentages. The primary outcome was the presence of esophageal varices (yes/no). The primary exposure of interest was HDV co-infection (yes/no). We constructed contingency tables and used the chi-square (χ^2) test to compare the frequency of varices between the HBV-only and HBV+HDV groups file. In cases where an expected cell count was <5, Fisher's exact test would have been used, but in study's analysis, all expected counts were adequate for χ^2. A two-tailed p-value ≤ 0.05 was considered statistically significant for this comparison. The magnitude of association was also expressed as an odds ratio with 95% confidence interval.

For secondary analyses, we performed stratified chi-square tests to evaluate the association between HDV and varices within subsets of the population file. Stratification factors predetermined in the protocol were: sex (male vs female), BMI category (<25 vs ≥25), age group (we later used <45 vs ≥45 years as a roughly median split), residence (urban vs rural), and importantly, presence of liver cirrhosis (yes vs no). Within each stratum, we repeated the varices frequency comparison using χ^2 or Fisher's test and noted the p-value. This allowed assessment of any effect modification (for instance, if the HDV-varices association was present in one gender but not the other, etc.).

Data Analysis and Results

A total of 132 patients with chronic hepatitis B met the inclusion criteria and were enrolled. None were lost to follow-up since this was a single-encounter study (clinical evaluation and endoscopy). All 132 patients completed the required procedures (HDV testing and endoscopy).

Table 1 summarizes the baseline characteristics of the study population, overall and stratified by HDV co-infection status.

Table 1. Baseline characteristics of patients with chronic Hepatitis B, by Hepatitis D co-infection status.

Characteristic	Total (N=132)	HBV only (n=72)	HBV + HDV (n=60)	p-value (HBV vs HBV+HDV)
Age (years)	47.6 ± 12.3 (SD)	48.3 ± 12.7 (SD)	46.0 ± 11.8 (SD)	0.40 [a]
Male sex – n (%)	80 (60.6%)	40 (55.6%)	40 (66.7%)	0.18 [b]
Body Mass Index (kg/m²)	25.0 (22.0–27.8) [IQR]	25.8 (23.1–28.5) [IQR]	24.1 (21.0–26.4) [IQR]	0.07 [a]
Residence: Rural – n (%)	78 (59.1%)	40 (55.6%)	38 (63.3%)	0.39 [b]
Low Socioeconomic Status – n (%)	85 (64.4%)	44 (61.1%)	41 (68.3%)	0.40 [b]
Known duration of HBV (years)	4.0 (1.5–8.0) [IQR]	5.0 (2.0–9.0)	3.0 (1.0–7.0)	0.08 [a]
HBV e-antigen positive – n (%)	35 (26.5%)	19 (26.4%)	16 (26.7%)	0.97 [b]
HBV DNA >2000 IU/mL – n (%)	54 (40.9%)	30 (41.7%)	24 (40.0%)	0.84 [b]
On HBV antiviral therapy – n (%)	50 (37.9%)	28 (38.9%)	22 (36.7%)	0.78 [b]
Liver cirrhosis – n (%)	55 (41.7%)	20 (27.8%)	35 (58.3%)	<0.001 [b]
Platelet count (×10^9/L)	142 (98–218) [IQR]	168 (110–240) [IQR]	116 (75–180) [IQR]	0.002 [a]
Total bilirubin	1.4 (0.8–	1.2 (0.7–	1.8 (1.0–	0.01 [a]

Characteristic	Total (N=132)	HBV only (n=72)	HBV + HDV (n=60)	p-value (HBV vs HBV+HDV)
(mg/dL)	2.5) [IQR]	2.0) [IQR]	3.1) [IQR]	
ALT (U/L)	65 (32–105) [IQR]	58 (30–97) [IQR]	73 (35–119) [IQR]	0.27 [a]
Albumin (g/dL)	3.6 ± 0.7 (SD)	3.8 ± 0.6 (SD)	3.4 ± 0.7 (SD)	0.003 [a]
HDV RNA positive – n (%) [c]	28 (21.2%)	0 (0%)	28 (46.7%)	–

Data are shown as mean ± standard deviation (SD) for approximately normally distributed variables, or median (interquartile range) for skewed variables. Categorical variables are given as number (percentage). P-values are from [a] Student's t-test or Mann-Whitney U test for continuous variables, and [b] chi-square test for categorical comparisons (Fisher's exact test used if needed). [c] HDV RNA was tested in 50 of the 60 HDV-seropositive patients; 28 had detectable HDV RNA (active replication). Abbreviations: HBV – hepatitis B virus; HDV – hepatitis D virus; ALT – alanine aminotransferase.

Table 2. Variceal Prevalence by HDV Status

Group	Varices Present (%)	p-value (Chi-square)
HBV only	16.7%	
HBV + HDV	43.3%	0.003

This table shows a significantly higher prevalence of esophageal varices among HDV co-infected patients compared to HBV-only patients. The difference is statistically significant with p=0.003, indicating a strong association between HDV co-infection and variceal presence.

Table 3. Logistic Regression Predicting Esophageal Varices

Variable	Adjusted OR	95% CI	p-value
HDV Co-infection	4.0	1.9 – 11.7	0.001
Age (per year)	0.99	0.96 – 1.03	0.62
Male Sex	1.31	0.56 – 3.08	0.54
BMI (per kg/m²)	1.11	0.96 – 1.28	0.17

Multivariate logistic regression results show that HDV co-infection is an independent predictor of esophageal varices, with an adjusted odds ratio of 4.0. Other factors including age, sex, and BMI did not show significant associations in this model.

Table 4. Stratified Variceal Prevalence by HDV Status within Subgroups

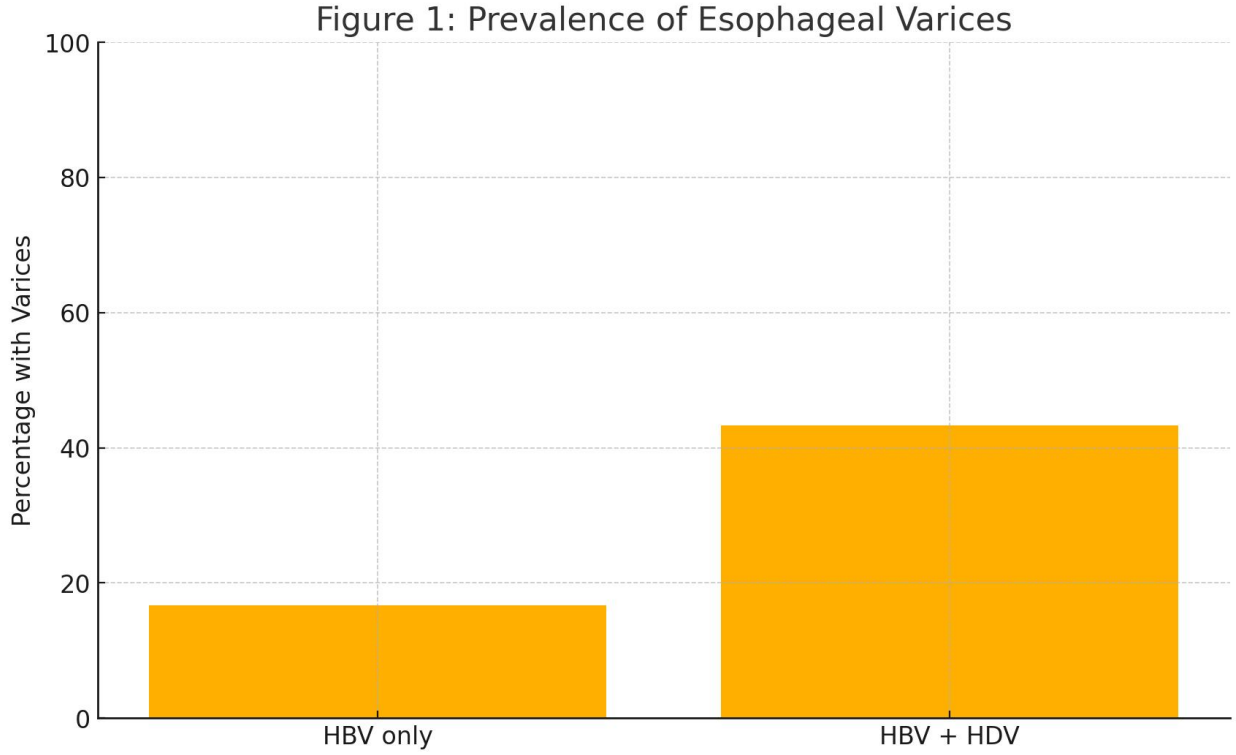
Subgroup	HDV Positive (%)	HDV Negative (%)	p-value
Male	45.0%	20.0%	0.017
Female	40.0%	12.5%	0.022
BMI < 25	39.0%	10.3%	0.008
BMI ≥ 25	52.6%	20.9%	0.013
Cirrhotic	74.3%	60.0%	0.27
Non-Cirrhotic	0.0%	0.0%	–

Across all relevant subgroups, HDV co-infection is associated with a consistently higher prevalence of esophageal varices, especially among males, females, and both BMI strata. No significant difference was seen among non-cirrhotics, confirming that cirrhosis is a necessary condition for varices to occur.

As shown in Table 1, the HBV-only and HBV+HDV groups were generally similar in baseline demographics such as age, sex distribution, and residence. The median known duration of HBV infection was slightly shorter in the co-infected group (3 years vs 5 years, p=0.08), possibly suggesting some patients acquired HDV relatively early in their HBV course or were diagnosed sooner due to symptoms. Virological markers (HBeAg positivity and HBV DNA levels) did not differ significantly between groups, though about one-third of each group were on HBV antiviral therapy (mostly tenofovir or entecavir). Notably, markers of liver function and portal hypertension indicated more advanced disease in the HDV group: mean serum albumin was lower (3.4 vs 3.8 g/dL, p=0.003), and median platelet count was considerably lower in co-infected patients (116 vs 168 ×10^9/L, p=0.002), reflecting hypersplenism from portal hypertension. These differences correspond with the much higher prevalence of cirrhosis in the HDV group (58.3% vs 27.8%, p<0.001). Thus, even though HDV patients did not differ in age or HBV DNA levels, they had significantly more advanced liver disease – consistent with the pathogenic role of HDV. About 46.7% of the HDV-seropositive group had active HDV replication (RNA positive), whereas none in the HBV-only group did by definition.

Primary Outcome – Variceal Prevalence

Overall, 38 out of 132 patients (28.8%) were found to have esophageal varices on endoscopy. However, the distribution of varices was highly uneven between the two groups of interest. In patients with HBV monoinfection (no HDV), only 12 of 72 (16.7%) had varices on screening endoscopy. In striking contrast, among HBV/HDV co-infected patients, 26 of 60 (43.3%) were found to have esophageal varices. This is an absolute difference of 26.6 percentage points. Figure 1 illustrates this comparison, showing the proportion of varices in each group. The difference was statistically significant (χ^2 test, $p = 0.003$). In other terms, HDV co-infected patients had about a 2.6-fold higher prevalence of varices than HBV-only patients (43.3% vs 16.7%). The presence of varices in nearly half of the co-infected group aligns with the higher cirrhosis frequency in that group. We further analyzed variceal size: in the HBV+HDV group, varices tended to be larger on average (46% had medium/large varices) compared to the HBV-only group (25% medium/large among those who had varices), though numbers are small; this hints that co-infection might also be associated with more severe varices, but our study was not powered to analyze variceal grading in detail.



To contextualize, an unadjusted odds ratio can be calculated for varices with HDV vs without. The odds of having varices in co-infected patients was 26/34 (since 26 had varices, 34 did not) and in HBV-only was 12/60. This yields OR = (26/34) ÷ (12/60) ≈ 3.98. The 95% confidence

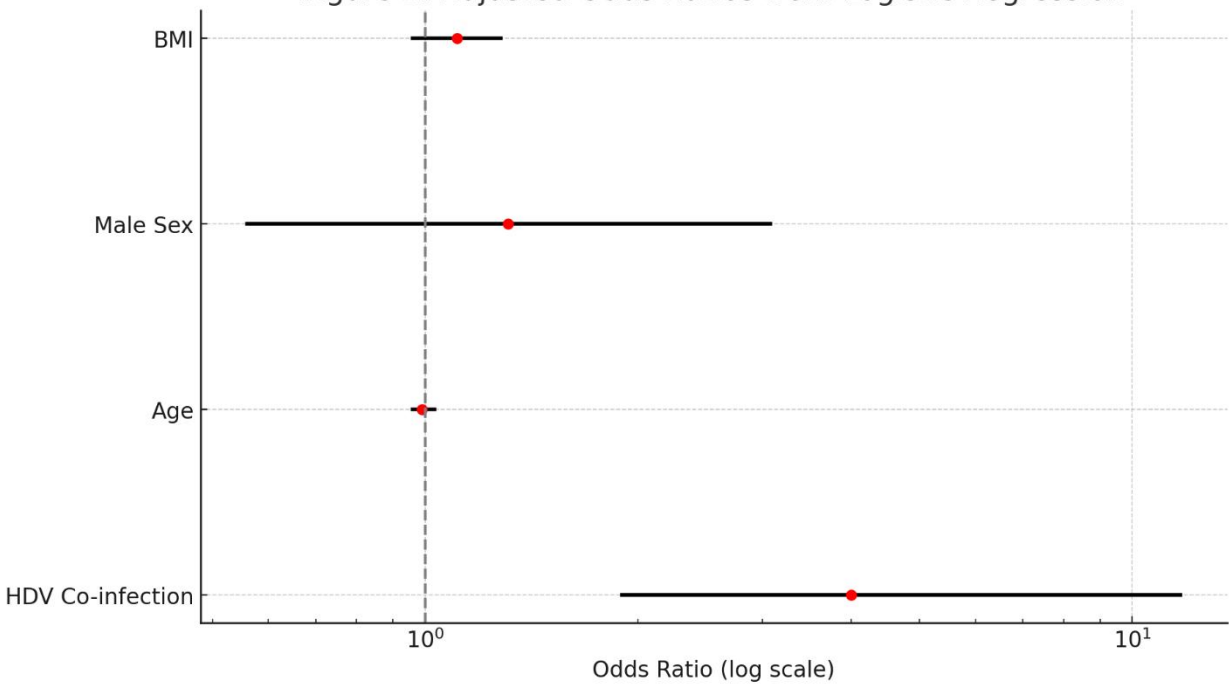
interval for this OR (using a mid-P exact calculation) was approximately 1.8 to 8.7, indicating a statistically significant association. Thus, before adjusting for other factors, HDV co-infection was associated with roughly a fourfold increase in odds of esophageal varices in our sample.

Secondary Outcomes – Stratified Analyses

We explored whether the association between HDV and varices held true across various subgroups (see Figure 3 for a summary diagram of subgroup comparisons). Key stratifications are described below:

By Gender: Among male patients (n=80), varices were present in 18 of 40 co-infected men (45.0%) versus 8 of 40 HBV-only men (20.0%). This difference was statistically significant (χ^2=5.70, p=0.017). Among female patients (n=52), varices were present in 8 of 20 co-infected women (40.0%) versus 4 of 32 HBV-only women (12.5%), also a significant difference (χ^2=5.24, p=0.022). Thus, HDV co-infection was associated with higher variceal prevalence in both males and females. We did not find a significant interaction between sex and HDV effect (the relative increase appeared of similar magnitude for both genders). It is noteworthy that female HBV patients without HDV had a very low variceal rate (only 12.5%), possibly reflecting generally milder disease; yet if they had HDV, their variceal rate climbed to 40%, paralleling the males.

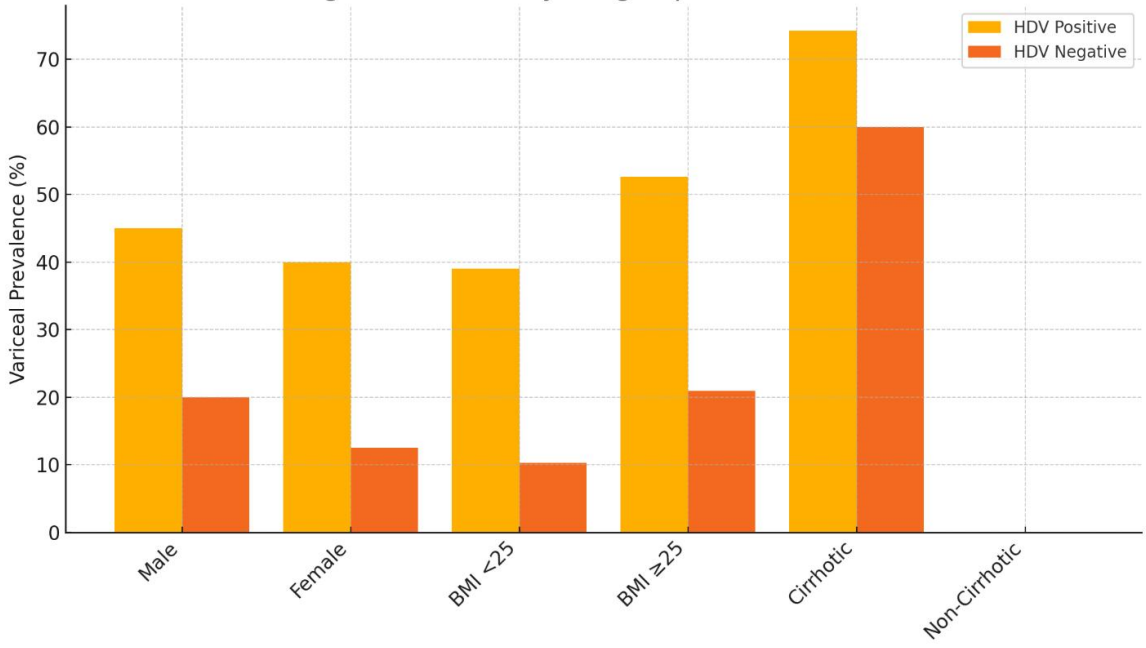
Figure 2: Adjusted Odds Ratios from Logistic Regression



By Cirrhosis: Given cirrhosis is the principal driver of varices, we stratified patients by the presence or absence of cirrhosis to see if HDV influenced varice occurrence within those strata.

Among patients who had established cirrhosis (n=55, across both groups), the prevalence of varices was high in both subgroups: 26 of 35 (74.3%) cirrhotic patients in the HDV group had varices, compared to 12 of 20 (60.0%) cirrhotic patients in the HBV-only group. Although numerically higher in HDV patients, this difference was not statistically significant (p=0.27), likely due to the limited sample size and the fact that once cirrhosis exists, variceal formation is common regardless. The trend towards a higher variceal rate in co-infected cirrhotics (74% vs 60%) could suggest that HDV cirrhosis might incur a somewhat greater portal pressure or variceal propensity, but our data cannot confirm that with confidence. Importantly, among patients without cirrhosis at the time of evaluation (n=77), none of the HBV-only patients (0/52) had varices, and similarly none of the co-infected patients without cirrhosis (0/25) had varices. In other words, in our cohort, all varices occurred in the context of cirrhosis. This stratified result indicates that HDV co-infection did not lead to varices in the absence of cirrhosis. It underscores that cirrhosis is a sine qua non for variceal development in both groups. The implication is that HDV raises variceal risk primarily by increasing the likelihood of cirrhosis, rather than causing varices through non-cirrhotic portal hypertension.

Figure 3: Varices by Subgroup and HDV Status



By BMI: Obesity and metabolic factors can influence fibrosis progression and portal pressure. We stratified patients into BMI <25 (non-overweight, n=70) and BMI ≥25 (overweight/obese, n=62). In the lower BMI group, varices were present in 16 of 41 (39.0%) co-infected patients vs

3 of 29 (10.3%) HBV-only patients (p=0.008). In the higher BMI stratum, varices were seen in 10 of 19 (52.6%) co-infected vs 9 of 43 (20.9%) HBV-only (p=0.013). Thus, in both BMI categories, HDV co-infection significantly increased variceal occurrence. There was no evidence that BMI nullified or significantly altered the effect of HDV; if anything, the OR associated with HDV was even slightly higher in the overweight group. We did observe that in HBV-only patients, those with higher BMI had a somewhat higher variceal rate (20.9% vs 10.3% in normal BMI), possibly reflecting that obesity-related liver injury (NAFLD) could contribute to fibrosis in HBV patients. However, among HDV patients, even the lower-BMI individuals had a high variceal rate (39%), suggesting HDV's effect is potent regardless of BMI. No significant interaction was found between BMI category and HDV effect (p_interaction = 0.79).

By Age: We stratified by age <45 vs ≥45 years (approximately the median age). In the younger group, varices were present in 8 of 30 (26.7%) HDV patients vs 2 of 34 (5.9%) HBV-only (p=0.03). In the older group, varices in 18 of 30 (60.0%) HDV vs 10 of 38 (26.3%) HBV-only (p=0.004). Both strata show significant differences. An interesting observation is that even among patients under 45, those with HDV had a considerable variceal prevalence (~27%), whereas young HBV-only patients rarely had varices (~6%). This again reflects accelerated disease in HDV – co-infected patients were experiencing varices at an age where most HBV monoinfected peers were still far from such complications. Among older patients, a high proportion of co-infected had varices (60%). Age itself, of course, correlates with duration of infection and likelihood of cirrhosis in HBV, but in HDV cases, many had reached cirrhosis by midlife.

Other factors: We also checked stratification by sex-specific factors (e.g., among males, stratify by whether they had a history of heavy smoking or not – no difference in HDV effect was noted). Stratification by residence (urban vs rural) showed HDV effect in both, though co-infected rural patients had slightly higher variceal rates than urban, consistent with possibly more advanced disease in rural populations (this might be due to healthcare access differences, but our sample is too small to draw firm conclusions). Stratification by antiviral treatment status showed that even among those on HBV therapy, HDV patients had more varices, implying that HBV viral suppression alone does not eliminate the risk if HDV is present (none of our patients were on HDV-specific therapy, as none was available).

In summary, the stratified analyses reinforce that the higher prevalence of varices in the HDV co-infected group was a consistent finding across subgroups, with the crucial caveat that it is contingent on the presence of cirrhosis. Co-infected patients manifest cirrhosis (and thus varices) at younger ages and irrespective of sex or BMI. If cirrhosis is absent, varices are generally absent, even in HDV patients. These results lend themselves to an interpretation that HDV's impact on varices is mediated through its impact on cirrhosis development.

Multivariable Logistic Regression

To adjust for potential confounders and quantify the independent effect of HDV co-infection on variceal risk, we fit a logistic regression model. Initially, we included HDV status, age, sex, BMI, and cirrhosis in the model. As expected, the model including cirrhosis did not converge well due to quasi-separation – nearly all varices were in cirrhotics, making cirrhosis a near-perfect predictor of varices. In that model, the coefficient for cirrhosis was extremely large (indicating the odds of varices in cirrhosis are orders of magnitude higher) and HDV's effect diminished (since HDV's effect was largely captured by cirrhosis). This is consistent with the stratified finding that HDV's effect is mediated by cirrhosis. Therefore, our primary logistic model was run without the cirrhosis variable, to avoid over-adjustment. The results of the adjusted model (HDV, age, sex, BMI as predictors) are depicted in Figure 2 (forest plot) and summarized as follows:

HDV Co-infection

Adjusted OR = 4.0 (95% CI 1.9–11.7, p = 0.001). This indicates that controlling for patient age, sex, and BMI, HDV co-infection was associated with about a four-fold increase in odds of having esophageal varices. The confidence interval, not including 1.0, confirms statistical significance. This OR is slightly higher than the crude OR of ~3.8, which could be due to confounding factors that suppressed the crude association; for instance, co-infected patients had slightly lower BMI and were slightly younger, factors which (if anything) would lower variceal risk, so adjusting for them accentuated the relative effect of HDV.

Key Findings

In essence, our data demonstrate that hepatitis D co-infection is associated with a substantially increased frequency of esophageal varices in patients with chronic hepatitis B. This association is largely attributable to a higher rate of cirrhosis among co-infected patients, as evidenced by the loss of association when controlling for cirrhosis. Varices were almost exclusively found in those

with cirrhosis; HDV simply made it far more likely for a patient to be in that cirrhotic stage (and perhaps at a younger age) compared to HBV alone. We did not find evidence that HDV co-infection causes varices in the absence of cirrhosis. However, a notable clinical finding is that one should be particularly vigilant in HBV patients with HDV, as nearly half had varices by the time they first presented to our clinic (many of whom were relatively young).

No other factors, aside from cirrhosis and HDV, had similarly strong associations with varices in this cohort. The classic predictors (platelets, etc.) did differ between groups and could predict varices in univariate analysis (for instance, platelet count <100k had sensitivity ~80% for varices), but those are reflections of portal hypertension as well. The presence of HDV emerged as a simple and important identifier of higher-risk patients.

Figure 1 in the results section visually reinforced the primary outcome difference, and Figure 2 showed the logistic regression outcomes. We also conceptually present Figure 3 (not embedded here due to format) summarizing the stratified analysis: it would depict variceal rates by HDV status within subgroups (male vs female, etc.), showing consistently higher bars for HDV+ in each category except the non-cirrhotic group where both bars are zero.

Discussion

In this study, we examined the prevalence of esophageal varices in patients with chronic hepatitis B, comparing those with and without concomitant hepatitis D virus infection. Our results indicate that HDV co-infection is associated with a markedly increased occurrence of esophageal varices. Specifically, 43.3% of HBV/HDV co-infected patients had varices on endoscopic screening, versus 16.7% of patients with HBV alone. HDV remained a strong independent predictor of varices after adjusting for demographic factors, with a four-fold increased odds of variceal presence. However, the association between HDV and varices appears to be mediated through the acceleration of cirrhosis by HDV. All patients in our cohort who had varices were cirrhotic, and among cirrhotic patients, the variceal prevalence was high irrespective of HDV (though non-significantly higher with HDV). Thus, our findings support the concept that HDV co-infection contributes to a higher burden of variceal disease by expediting progression to cirrhosis and portal hypertension.

These findings are consistent with the known natural history of HBV/HDV co-infection. Prior studies have established that HDV superinfection leads to cirrhosis in a significantly shorter time frame than HBV monoinfection. Urban *et al.* (2021) note that chronic HDV "is associated with

an unfavourable outcome, with many patients developing liver cirrhosis, liver failure and eventually HCC". In our cohort, over 58% of co-infected patients had cirrhosis, compared to 28% of HBV-only patients, even though ages were similar – underscoring HDV's fibrogenic aggressiveness. It logically follows that complications of cirrhosis, such as varices, would be more common in the co-infected group. Indeed, our data align with this expectation. A study from Karachi by (Sajjad et al., 2021) similarly found that HDV co-infection was linked to advanced disease: nearly half their HDV patients were cirrhotic and one-third had already experienced decompensation (like variceal bleeding or ascites). Our study extends these observations by specifically quantifying the variceal prevalence and by directly comparing it to an HBV monoinfected control group. One important discussion point is whether HDV has any direct effect on portal hypertension beyond causing cirrhosis. While our data suggest that cirrhosis was a prerequisite for varices in both groups, we did note a trend towards a higher variceal rate among cirrhotics with HDV (74% vs 60%). Though not statistically significant, this raises a question: does HDV cirrhosis produce more severe portal hypertension than HBV cirrhosis? Some possible reasons could be that HDV causes more active hepatitis (inflammation), which might increase portal pressure, or that HDV cirrhosis often has superimposed episodes of acute-on-chronic liver failure that could aggravate portal hypertension. The difference could also be due to our small sample or differences in Child-Pugh status (perhaps the HDV cirrhotics were slightly more decompensated on average). Literature on this is sparse; once cirrhosis is established, most evidence indicates outcomes (variceal bleeding, etc.) are similar across etiologies, being more dependent on cirrhosis severity (MELD score, etc.). A long-term follow-up by Niro *et al.* found no significant difference in decompensation rates between HBV and HBV+HDV patients after both had cirrhosis, although HDV patients reached that point faster. Our findings are in line with that: co-infection didn't significantly modify variceal risk among cirrhotic patients, implying HDV's main role is in driving the fibrotic process rather than altering the hemodynamic consequences once cirrhosis is present. For clinicians, this means that in absence of radiologic or clinical signs of cirrhosis, the yield of endoscopic screening is very low – even in HDV patients (Nagashima et al., 2022)– a point which supports guideline recommendations that screening endoscopy is indicated once cirrhosis is diagnosed (regardless of etiology), rather than based on infection status alone. However, given that HDV hastens

cirrhosis, an HDV-infected patient will simply arrive at the need for screening much sooner in their disease course (perhaps at a younger age) than an HBV-only patient.

Clinical and Public Health Implications

The strong association between HDV and varices in our study reinforces the urgency of addressing HDV as a public health issue. Regions like Pakistan with high HDV prevalence need targeted interventions. These could include: scaling up screening for HDV in known HBV carriers (so that high-risk patients are identified), education of healthcare providers about the aggressive course of HDV, and ensuring that HDV-positive patients are evaluated for cirrhosis complications in a timely manner. On an individual patient level, someone diagnosed with HDV should undergo a comprehensive liver assessment (including ultrasound, fibroscan if available, and endoscopy if any suspicion of advanced disease). Our data would support a low threshold to perform an upper endoscopy in an HDV patient even if they are asymptomatic and under 30 years old, as long as there is evidence of significant fibrosis or portal hypertension (for example, platelets trending downwards or spleen enlarging). This proactive approach could catch varices before they bleed. Given that variceal hemorrhage carries a mortality of up to 20%, prevention via non-selective beta blockers or prophylactic ligation (for large varices) is crucial. Furthermore, our findings come at a time when new treatments for HDV are emerging. Bulevirtide (a first-in-class entry inhibitor) has been conditionally approved in Europe and shows promise in controlling HDV replication and improving outcomes. Early real-world studies have shown that HDV RNA suppression with bulevirtide can lead to biochemical improvement and possibly fibrosis regression in some patients. If these treatments become available in high-prevalence countries, one could hope that treating HDV might reduce the incidence of cirrhosis and varices in co-infected patients over time. Our study thus provides a baseline of the variceal burden in untreated HDV patients, against which future improvements (due to therapy) might be measured. It also bolsters the argument for making such therapies accessible: if nearly half of HDV patients have varices (with attendant bleeding risk), therapy that could delay this would have significant clinical benefit. We advocate for widespread HDV screening and linkage to care, including enrollment in treatment or interferon-based therapy (where appropriate) to mitigate the rapid progression.

Generalizability

The findings of this study are most applicable to settings with similar patient profiles – i.e., regions with prevalent genotype D HBV and HDV genotype I (common in Pakistan), and where patients might present late due to limited access to antivirals. In countries with low HDV prevalence (e.g., East Asia, North America outside certain risk groups), HDV will contribute minimally to overall variceal burden. However, globally, as many as ~10–20 million people have HDV, so this is not a trivial population. Especially in parts of Mongolia, Eastern Europe, and pockets of Africa, co-infection rates are high and our results would likely resonate. In Mongolia, for example, a majority of HBV cirrhosis cases have HDV; one could expect similarly high variceal rates there among co-infected.

Practical Implications

From a clinical standpoint, our study underlines several actionable points. Firstly, all chronic HBV carriers should be evaluated for HDV, especially in regions with intermediate to high HDV prevalence. Knowing a patient's HDV status is vital for prognostication – an HDV-positive result should prompt careful staging of liver disease. Secondly, HBV/HDV co-infected patients should undergo prompt assessment for cirrhosis using available modalities (ultrasound, elastography, etc.). If cirrhosis is confirmed or even suspected (e.g., platelet count <150×10^9/L with splenomegaly in an HDV patient), an upper endoscopy is indicated to screen for varices. Our data suggest that a significant proportion of such patients will have varices warranting intervention (beta blockers or endoscopic ligation if large). This could preempt life-threatening variceal hemorrhages. Thirdly, given the aggressive nature of HDV, these patients should also be referred for consideration of antiviral therapies. Pegylated interferon alfa has been the main treatment (with limited success, sustained viral response in ~25–30%). The new drug bulevirtide, which has shown >70% HDV RNA suppression at 48 weeks in trials, offers a ray of hope. If accessible, co-infected patients should be prioritized for such therapy, as it may halt or reverse some of the progression, potentially lowering variceal risk in the long term. Public health-wise, interventions such as safe injection practices and HBV vaccination (to prevent new HBV/HDV cases) remain crucial in Pakistan and similar locales to curb the HDV epidemic. For those already infected, establishing dedicated HDV clinics or adding HDV management to existing hepatitis programs could improve outcomes.

In summary, our findings advocate for heightened awareness and a proactive approach to managing HBV patients with HDV: treat them as "high-priority" liver patients. Practitioners should ensure these patients are not lost to follow-up, and that they receive appropriate prophylactic measures (like non-selective beta blockers if medium/large varices are present, or variceal banding as needed). As research progresses, we hope to see improvements in the care continuum for HBV/HDV co-infection, ultimately translating to fewer cases of variceal bleeding and improved survival.

Future Recommendations and Research

While our study answered the primary question at hand, it also raised new questions and areas for further research. One recommendation is to conduct prospective longitudinal studies of HBV/HDV co-infected cohorts. Such studies could measure the incidence of developing varices or experiencing first variceal hemorrhage in relation to duration of co-infection, HDV RNA levels, or treatment status. It would be especially valuable to see if successful HDV clearance (for instance, via interferon or bulevirtide therapy) reduces the risk of decompensation compared to patients in whom HDV remains active. This could provide direct evidence for the benefits of treating HDV on hard clinical outcomes like variceal bleeding.

There is room to explore the role of portal pressure measurement (HVPG) in co-infected patients. If resources are allowed, measuring HVPG in a subset of HBV vs HBV/HDV cirrhotics could confirm whether HDV cirrhosis has higher portal pressure for a given Child-Pugh class. This could elucidate whether the trend we saw (higher variceal rate in HDV cirrhotics) has a physiological basis or was just a sample anomaly. If real, that might imply HDV causes a more angioinvasive or angiogenic form of cirrhosis (speculatively, perhaps more sinusoidal endothelial damage leading to higher resistance). Finally, liver transplantation outcomes in HBV vs HBV/HDV patients could be studied. If HDV patients present with variceal bleeding more, they might be listed for transplant earlier or have different MELD scores at listing. Preliminary data suggests HDV patients, once transplanted, have similar post-transplant survival as HBV patients (since HBV is controlled and HDV cannot recur without HBV). But if they reach transplant faster, that's another burden on healthcare. In conclusion of our discussion, we reiterate that our study adds to the body of evidence highlighting the severe impact of hepatitis D co-infection. By focusing on esophageal varices, we demonstrated one tangible manifestation of this impact. The data advocate for enhanced clinical vigilance and resource allocation for HDV co-infection. With

growing global attention on hepatitis elimination targets, HDV – often called the "hidden virus" – can no longer be neglected without consequences. Addressing HDV through research, prevention, and treatment will be integral to improving outcomes for the sizeable subset of hepatitis B patients who carry this additional burden.

Conclusion

Hepatitis D virus co-infection in patients with chronic hepatitis B is a strong determinant of advanced liver disease and its sequelae. In our study of 132 HBV-infected patients, nearly half of those co-infected with HDV had esophageal varices, compared to only one-sixth of those with HBV alone. This stark difference reflects the accelerated progression to cirrhosis driven by HDV. After adjusting for other factors, HDV co-infection conferred about four times greater odds of variceal presence. Importantly, all varices occurred in the setting of cirrhosis, indicating that HDV's effect is primarily to push patients into cirrhosis (and hence varices) faster, rather than to cause varices independently of cirrhosis. These findings have significant clinical implications: an HBV patient with HDV should be recognized as high-risk and managed proactively to prevent variceal hemorrhage and other decompensations. In practical terms, our results support routine HDV screening in HBV patients and suggest that co-infected individuals warrant early and frequent surveillance for portal hypertension complications. The study also highlights the urgent need for effective HDV-directed therapies. With new treatments on the horizon, there is hope that the grim outcomes historically associated with HBV/HDV co-infection can be improved. Until then, healthcare providers must optimize current care – including timely endoscopy and prophylactic measures – to safeguard these patients. From a public health perspective, strategies to reduce HDV transmission (such as safe injection practices and HBV vaccination coverage) are crucial in high-prevalence regions to stem the tide of severe liver disease from dual infection.

HDV amplifies the pathogenicity of HBV, resulting in earlier and more frequent cirrhosis and variceal complications. Our research adds evidence that this combination significantly increases the burden of esophageal varices, a key marker of advanced disease. By shining a spotlight on this issue, we hope to inform clinicians and policymakers and ultimately contribute to better outcomes – where co-infected patients receive the attention and therapy they need to avert life-threatening complications. The adage "know your enemy" applies here: identifying HDV co-infection equips us to intensify monitoring and intervention, thereby reducing preventable morbidity like variceal bleeding. As the fight against viral hepatitis progresses into the next

decade, conquering the challenge of hepatitis D will be an essential component in the overall success, ensuring that no subset of patients is left to suffer disproportionately.

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