Journal of Clinical and Translational Hepatology **2025** vol. 13(4) | 278–283
DOI: 10.14218/JCTH.2024.00313

Original Article

Prevalence of Hepatitis D Virus Antibody Positivity in Chinese Patients with Chronic Hepatitis B Virus Infection

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Received: August 29, 2024 | **Revised:** December 10, 2024 | **Accepted:** January 20, 2025 | **Published online:** February 24, 2025

Abstract

Background and Aims: Large-scale data on the hepatitis D virus (HDV)/hepatitis B virus (HBV) co-infection rate is needed to estimate the current epidemiology of HDV in China. This study aimed to estimate the current epidemiology of HDV. ***Methods:*** Patients with chronic HBV infection, with documented serum hepatitis B surface antigen (HBsAg) positivity for more than six months, were enrolled across China. Blood samples were collected at baseline for central evaluations of HDV antibody and HBsAg quantification. Assessments for antibodies of hepatitis A virus, hepatitis C virus, hepatitis E virus, and human immunodeficiency virus, as well as HDV RNA quantification, were performed in patients who tested positive for HDV antibodies. ***Results:*** Of the 5,044 enrolled patients between September 24, 2021, and December 28, 2022, 4,936 patients were included in the analysis. The mean age (±standard deviation) was 42.9 ± 9.9 years, and 69.8% of patients were male. The mean alanine aminotransferase level was 34 ± 58 U/L, and 1,509 (30.6%) patients were hepatitis B e antigen-positive. The mean (standard deviation) HBsAg level at baseline was 3,535 ± 11,292 IU/mL among 4,842 patients who were HBsAg positive. The rate of HBV infection and HDV antibody positivity was 0.24% (95% confidence interval: 0.1–0.4%), and only one patient was HDV RNA positive. ***Conclusions:*** The prevalence of HDV antibody positivity was 0.24% in Chinese patients with chronic HBV infection, and only one patient with both anti-HDV antibody and HDV RNA positivity was observed in this study.

Citation of this article: Liang X, Chen Q, Tang H, Guan Y, Liang M, Hu P, *et al*. Prevalence of Hepatitis D Virus Antibody Positivity in Chinese Patients with Chronic Hepatitis B Virus Infection. J Clin Transl Hepatol 2025;13(4):278–283. doi: 10.14218/JCTH.2024.00313.

Introduction

Hepatitis D virus (HDV)/hepatitis B virus (HBV) co-infection is considered the most severe form of chronic viral hepatitis due to its unfavorable clinical outcomes.[1] HDV does not form its own viral envelope and relies on the surface glycoproteins of HBV to replicate.[2,3] The global prevalence of HDV infection is estimated to be 0.98%, while the prevalence of HDV among hepatitis B surface antigen (HBsAg)-positive patients is reported to be around 4.5–14.6%.[4,5]

HDV infection can occur as a simultaneous infection of HBV and HDV (acute hepatitis) or in patients with chronic HBV (superinfection).[6] Acute hepatitis due to simultaneous HBV and HDV infections rarely leads to chronic hepatitis D (<10%),[7] but the chronicity rate in HDV superinfection is high. Chronic HBV/HDV co-infection accelerates the progression of hepatitis to a more severe stage compared to HBV mono-infection.[6,8] The relative risk of developing cirrhosis doubles in patients with HDV/HBV co-infection compared with those with HBV alone. Approximately 15% of patients with HDV/HBV co-infection develop cirrhosis within one to two years, and 70–80% within five to ten years.[6] Furthermore, persistent HDV infection is associated with the development of hepatocellular carcinoma and deaths related to liver disease.

Keywords: Hepatitis D virus; Hepatitis B virus; Antibody; Prevalence; Co-infection; Virus RNA; Chinese.
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China has the world's largest burden of HBV infection.[9] A study that extracted data from the Global Burden of Disease 2019 database suggested that 23,355,000 patients are infected with HBV in China, accounting for 29% of global HBV infections.[10] However, despite the higher prevalence of HDV infection in patients with HBV compared to the general population, HDV infection testing is not routinely performed for chronic HBV patients in clinical practice in China. A study retrospectively analyzing 3,065 HBsAg-positive patients in China showed that HDV was unevenly distributed among HBsAg carriers.[11] The study revealed that the geographic hotspots for HDV in China were concentrated around Inner Mongolia and Xinjiang, with co-infection rates of 13.9% (35/251) and 3.9% (7/180), respectively. No HDV infection was observed in 2,634 samples from other provinces or cities. These studies indicate that the prevalence of HDV varies widely across different regions in China. However, the current evidence may be limited by study design, selection biases, and differing diagnostic methods, which could explain the discrepancies in prevalence rates between studies. Therefore, more studies are needed to better understand the epidemiological distribution of HDV among patients with HBV or severe liver disease.

Currently, no drug is approved for the treatment of chronic HDV infection in China. Pegylated interferon-α has been commonly used to treat HDV for the past 30 years.[12] Suppression of HDV replication with pegylated interferon-α could only be observed in 20–30% of patients, with frequent off-treatment virological relapse and significant side effects during treatment.[12] More recently, bulevirtide was granted conditional approval by the European Medicines Agency for the treatment of chronic HDV infection in adult patients with compensated liver disease.[13,14] Other modes of action that interfere with steps of the HDV replication cycle are currently in clinical evaluation.[15,16]

With the current study, we provide further insights into the prevalence and distribution of HBV/HDV co-infection across China, with the goal of identifying the target patient population for developing HDV treatments.

Methods

Study design and patients

This prospective exploratory study was conducted to enroll up to 5,500 patients with chronic HBV infection at nine hospitals across China. Study sites were selected based on feasibility and to cover geographic locations across North, South, West, and East China. These tertiary hospitals were higher-tier institutions, serving a larger population in the region. The study was divided into part 1 (first 5,000 patients) and part 2 (additional up to 500 patients enrolled under protocol amendment 2). An additional inclusion criterion was added for part 2 to increase the chances of identifying patients with active HDV/HBV co-infection. Eligible patients for both parts were aged 18–65 years; had chronic HBV infection with documented serum HBsAg positivity for more than six months before screening, or alternative markers (hepatitis B e antigen [HBeAg] positivity or HBV DNA positivity at least six months prior to screening); and had HBV DNA, alanine aminotransferase (ALT), and HBeAg test results within six months before screening. For part 2, patients additionally had to have high ALT (>40 U/L) and low HBV DNA ($<10^4$ IU/mL) test results within six months before screening. There were no further exclusion criteria in this study.

Serum samples were collected within 14 days after screening. Detection of antibodies against HDV, hepatitis A virus (HAV), hepatitis C virus (HCV), hepatitis E virus (HEV), and human immunodeficiency virus (HIV), and quantification of HBsAg and HDV RNA, were performed at central laboratories (HDV antibodies and HBsAg tests: Guangzhou Huayin Medical Research Institute Co. Ltd, Guangzhou, China; HDV RNA tests: Fenglin Clinical Laboratory, Shanghai, China; HAV, HCV, HEV, and HIV tests: Guangzhou Huayin Medical Laboratory Center Co. Ltd, Guangzhou, China). Clinical information, such as age, sex, serum levels of HBV DNA and ALT, HBeAg status, prior interferon treatment, liver disease status (decompensated or not), and liver stiffness (measured by FibroScan®) or biopsy (if available), was collected from patients' medical history recorded at local sites within six months before screening. The study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. The protocol and all amendments were approved by the Institutional Review Board before implementation. All patients provided informed consent prior to enrollment. This study was reported following the STROBE checklist for cohort studies (https://www.strobe-statement.org/checklists/).

Assessments and study endpoints

All patients were screened for anti-HDV antibodies (HDV Ab ELISA kit, Dia.Pro Diagnostic Bioprobes Srl, Milan, Italy) and evaluated for HBsAg quantification (Elecsys HBsAg II Kit, Roche Diagnostics, Rotkreuz, Switzerland). HDV status was determined by the signal-to-cutoff (Co/S) value of the antigen, where specimens with a result of Co/S values > 1.1, 0.9 ≤ Co/S values ≤ 1.1, and Co/S values < 0.9 were considered HDV antibody positive, gray-zone, and HDV antibody negative, respectively. Quantification of HDV RNA (RoboGene HDV RNA Quantification Kit 2.0, Roboscreen Diagnostics, Leipzig, Germany) and detection of HAV IgM (Detection Kit for IgM Antibody to Hepatitis A Virus [ELISA], Beijing Wantai BioPharm-Engineering Co. Ltd, Beijing, China), HCV IgG (Diagnostic Kit for Antibody to Hepatitis C Virus [ELISA], Shanghai Kehua Bio-Engineering Co. Ltd, Shanghai, China), HEV IgM (Detection Kit for IgM antibody to Hepatitis E Virus [ELISA], Beijing Wantai BioPharm-Engineering Co. Ltd, Beijing, China), and HIV antibodies (Diagnostic Kit for Antibody to Human Immunodeficiency Virus [ELISA], Shanghai Kehua Bio-Engineering Co. Ltd, Shanghai, China) were performed in patients with HDV antibodies. All assays (including HDV antibody and HDV RNA assays) conducted by the central laboratory were validated. The lower limit of quantification for the HDV RNA test was 57.50 IU/mL. No study treatment was administered to the enrolled patients; only serious adverse events related to the study procedure (blood sample collection) were recorded.

The primary endpoints were the proportion of HDV infection (HDV antibody positivity) in Chinese patients with chronic HBV infection (part 1) and active HDV infection (positivity of both HDV antibody and HDV RNA) in Chinese patients with chronic HBV infection whose ALT was >40 U/L and HBV DNA was $<10^4$ IU/mL (part 2). Secondary endpoints were the proportion of patients positive for HDV RNA among those with HDV antibodies and their HDV RNA levels. Co-infection rates of HAV/HCV/HEV/HIV in patients with HDV antibodies, the correlation between HBsAg and HDV RNA levels, and the risk factors for HDV infection were predefined exploratory endpoints.

Statistical analysis

No formal sample size estimation was performed for this exploratory study. An estimated 5,000 patients were needed for part 1 (assuming a 1% HBV and HDV co-infection rate

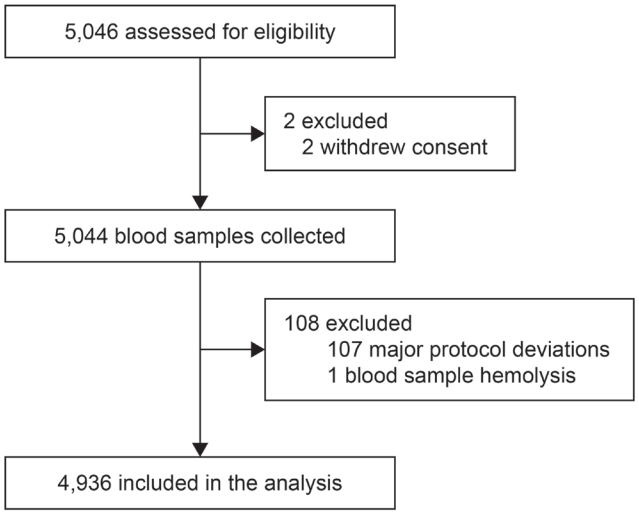

Fig. 1. Trial profile.

and 10% of those having ALT > 40 U/L and HBV DNA < 10^4 IU/mL) and 500 for part 2 (assuming a 10% HBV and HDV co-infection rate with the additional inclusion criteria) so that approximately 10 potential patients with HBV and HDV co-infection, with ALT > 40 U/L and HBV DNA < 10^4 IU/mL, could be identified for a phase II study. Results were summarized using descriptive statistics, and 95% confidence intervals (CIs) were calculated with the Clopper–Pearson method. Missing values were not imputed. All statistical analyses were performed using R software (version 4.1.2, Vienna, Austria).

Results

Between September 24, 2021, and December 28, 2022, 5,046 patients were screened, and blood samples were collected from 5,044 patients (Fig. 1). In total, 108 patients were excluded from the analysis due to major protocol deviations (n = 107) and blood sample hemolysis (n = 1). The most common major protocol deviation was failure to provide HBV DNA, ALT, or HBeAg results assessed within six months prior to screening.

A total of 4,936 patients were included in the analysis—4,891 patients from part 1 and 45 patients from part 2. The mean age was 42.9 ± 9.9 years, and 3,443 (69.8%) patients were male (Table 1). Based on the medical history within six months before screening, the mean ± SD ALT was 33.9 ± 57.3 U/L, and 1,509 (30.6%) patients were HBeAg positive. The mean baseline HBsAg level was 3,534.7 ± 11,291.9 IU/mL among 4,842 patients who had qualitative results. Most patients (n = 4,363 [88.4%]) were on nucleos(t)ide analog treatment, and 4,231 (85.7%) patients had low HBV DNA (<100 IU/mL). Based on medical history, 105 (2.1%) patients had signs of liver decompensation. The mean liver stiffness (measured by FibroScan®) was 7.6 ± 5.7 kPa among 3,323 patients with available data.

All 12 patients who tested positive for HDV antibodies were enrolled in part 1. The co-infection rate based on HDV antibody positivity was 0.25% (12/4,891; 95% CI: 0.1–0.4%) in patients with chronic HBV infection (part 1) and none (0/45) in patients with chronic HBV infection and ALT > 40 U/L and HBV DNA < 10^4 IU/mL (part 2). Among the 4,936 patients (parts 1 and 2) included in the analysis, the overall co-infection rate of HBV and HDV was 0.24% (95% CI: 0.1–0.4%); the HDV antibody status was positive in 12 patients, gray-zone in 35 patients, and negative in 4,889 patients. The geographic location and HDV antibody positivity of each study site are shown in Table 2 and Figure 2. None of the 107 patients who were excluded from the analysis due to major protocol deviations tested positive for HDV antibodies.

Among the 12 patients who tested positive for HDV antibodies, the mean age was 45.3 ± 9.4 years, and 10 (83.3%) patients were male (Table 1). Based on the medical history within six months before screening, the mean ± SD ALT was 110.7 ± 311.6 U/L, and four (33.3%) patients were HBeAg positive. The mean baseline HBsAg level was 1,032.6 ± 1,280.5 IU/mL. Ten (83.3%) patients had low HBV DNA (<100 IU/mL). No patients had signs of liver decompensa-

Table 1. Demographic and baseline characteristics

	Total (n = 4,936)	**HDV Ab+ (n = 12)**
Age, mean (SD), years	42.9 (9.9)	45.3 (9.4)
Sex, *n* (%)		
Male	3,443 (69.8)	10 (83.3)
Female	1,493 (30.2)	2 (16.7)
ALT, mean (SD), U/L	33.9 (57.3)	110.7 (311.6)
HBeAg status, *n* (%)		
Positive	1,509 (30.6)	4 (33.3)
Negative	3,427 (69.4)	8 (66.7)
HBsAg quantity, mean (SD), IU/mL	3,534.7 (11,291.9)[a]	1,032.6 (1,280.5)
HBV DNA, *n* (%)		
Low (<100 IU/mL)	4,231 (85.7)	10 (83.3)
Medium to high (≥100 IU/mL)	705 (14.3)	2 (16.7)
Decompensated liver, *n* (%)	105 (2.1)	0 (0)
Liver stiffness[b], mean (SD), kPa	7.6 (5.7)[c]	7.0 (3.5)[d]

[a]n = 4,842; [b]measured by FibroScan®; [c]n = 3,323; [d]n = 6. Ab, antibody; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis D virus; SD, standard deviation.

Table 2. Geographic location and HDV antibody positivity of each study site

Study site	Geographic location in China	Number of enrolled patients	Number of patients with HDV Ab+	Incidence of HDV Ab+ (%)
West China Hospital, Sichuan University	Southwestern	1,117	2	0.18
The Second Affiliated Hospital of Chongqing Medical University	Southwestern	564	1	0.18
Nanfang Hospital of Southern Medical University	Southern	1,052	2	0.19
Guangzhou Eighth People's Hospital	Southern	1,001	4	0.4
The First People's Hospital of Foshan	Southern	945	1	0.11
Beijing Ditan Hospital, Capital Medical University	Northern	174	0	0
Peking University People's Hospital	Northern	50	2	4
The First Hospital of Jilin University	Northeastern	24	0	0
Shanghai Public Health Clinical Center	Eastern	9	0	0

Ab, antibody; HDV, hepatitis D virus.

tion. The mean liver stiffness (measured by FibroScan®) was 7.0 ± 3.5 kPa among six patients with available data.

Statistical estimation of HDV RNA levels in patients with HDV antibodies was not feasible, as HDV RNA (302 IU/mL) was only measurable in one patient who tested positive for HDV among those with HDV antibody positivity and gray-zone results. Among HDV antibody-positive patients, the rate of HCV antibody positivity was 25% (95% CI: 5.5–57.2%, n = 3), and no patients tested positive for HAV, HEV, or HIV antibodies.

Patients with HDV antibodies had statistically significantly lower levels of HBsAg than patients who were negative for

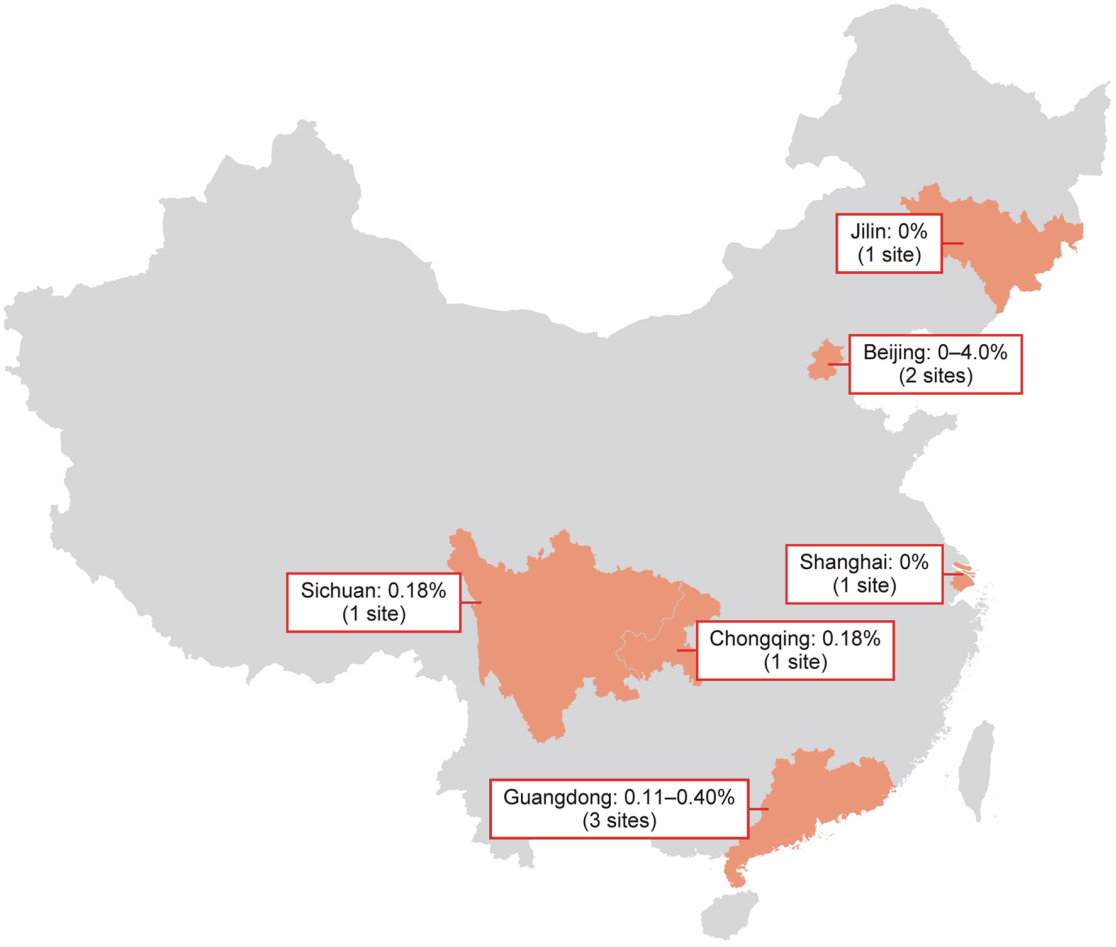

Fig. 2. Incidence of HDV antibody based on geographic locations in China. HDV, hepatitis D virus.

HDV antibodies at baseline (mean ± SD: 1,032.6 ± 1,280.5 IU/mL [n = 12] vs. 3,540.9 ± 11,305.0 IU/mL [n = 4,830], p-value of Welch 2-sample t-test = 1.37×10^{-5}).

No adverse events were reported in the study.

Discussion

In this study, we screened 5,046 patients with chronic HBV infection at nine hospitals across China, of which the prevalence of HDV antibody positivity was 0.24%. The evaluation of the HBV and HDV co-infection rates across China is crucial due to the lack of robust epidemiological data for HDV. This seroprevalence study provides insights into the prevalence of HDV, which could be useful for patient recruitment in future clinical studies.

Available epidemiological data for HDV in China have either been outdated,[17] limited to local populations,[18] or based on extrapolation.[4,5] A previous epidemiological survey conducted more than two decades ago showed that the prevalence of HDV in the general population from disease surveillance points in Fujian was low (2.10%).[17] More recent studies on HDV prevalence in China have included a limited number of patients from local populations[18] or analyzed blood samples retrospectively.[11] The current study suggests that the prevalence of HDV in China is much lower than the 5.57% reported in a recent meta-analysis that included 17,163 patients with HBsAg positivity from 20 studies.[4] The discrepancy in HDV prevalence between our study and the literature could be attributed to improvements in the specificity of detection methods for HDV antigen and antibody compared to those used decades ago. Decreasing HBV infection rates in China[19] may also have contributed to a lower HDV co-infection rate. Furthermore, patient populations differed across studies. Most patients enrolled in the current study were from outpatient settings and did not have liver cirrhosis or decompensation; thus, the co-infection rate is expected to be higher in patients with late-stage liver disease. Additionally, we did not recruit patients from Inner Mongolia and Xinjiang, where geographic hotspots of HDV in China have been reported.[11]

HDV is usually dominant over HBV in patients with co-infection,[20] leading to suppressed HBV DNA and detectable HDV RNA in most cases. Clinical symptoms of HBsAg positivity, combined with low or suppressed HBV DNA and increased inflammatory activity (*e.g.,* fluctuating ALT levels), are suggestive of HBV/HDV co-infection.[6,8] Our study showed that chronic HBV-infected patients with HDV antibodies had higher ALT levels and statistically significantly lower HBsAg levels than those without HDV co-infection. However, the difference in HBsAg (1,000 IU/mL vs. 3,500 IU/mL) has limited clinical implications, as the degree of difference could not be used to identify patients with HDV. Furthermore, the current study suggests that the combination of suppressed HBV DNA ($<10^4$ IU/mL) and increased inflammation (ALT > 40 U/L) is rare in Chinese patients with chronic HBV infection, as evidenced by the low enrollment rate after the implementation of additional inclusion criteria.

It was noted that three of the twelve (25%) patients with chronic HBV and HDV antibodies tested positive for HCV antibodies, and none of the 12 patients tested positive for HAV, HEV, or HIV antibodies. A previous report showed that a delay in the identification of HDV infection can be a diagnostic problem and therapeutic challenge in patients with HBV and HCV co-infection.[7] Furthermore, patients with triple infection of HBV, HCV, and HDV have an increased risk for progression to hepatocellular carcinoma.[21] Therefore, HDV screening should be considered in patients with HBV/HCV co-infection, especially in those who continue to have elevated ALT levels despite nucleos(t)ide analog treatment for HBV.

The study had several strengths. To our knowledge, this was the largest study in China to prospectively assess HDV antibodies, HDV RNA, and HAV/HCV/HEV/HIV antibodies robustly in a central laboratory using high-quality test kits among the HBV-infected population. Furthermore, the current study enrolled patients across various regions in China to avoid extrapolating the prevalence of HBV and HDV co-infection from a single site or area and did not recruit patients from geographic hotspots of HDV in China. The study also had some limitations. First, there might be potential sampling bias since patients were enrolled from nine hospitals. Additionally, results of HBV DNA and ALT were collected from patients' medical history within six months before screening, and the status of patients may have changed by the time of screening. Furthermore, different local hospitals used different detection methods and cutoffs for clinical laboratory assessments (*e.g.,* normal range of ALT). Another limitation was that many other planned analyses could not be performed due to the low rates of HDV antibodies and HDV RNA, which restricted the study's capacity to estimate co-infection rates of HAV/HCV/HEV/HIV in patients with HDV antibodies, explore the correlation between HBsAg and HDV RNA levels, and identify risk factors associated with HDV infection. Nonetheless, our study provides an accurate assessment of HDV prevalence based on a larger patient population and broader geographical coverage. Future studies could include other regions in China, such as Inner Mongolia and Xinjiang, to provide a more comprehensive assessment of the incidence and prevalence of HDV in China. Furthermore, in-depth analyses of viral load, genotype, and clinical characteristics in patients with HDV RNA positivity, as well as analyses of the dynamics of HDV infection, could assist in developing effective treatment strategies and formulating public health policies.

Conclusions

This large-scale exploratory study demonstrated that the prevalence of HDV antibody positivity was very low (0.24%) in Chinese patients with chronic HBV infection, with only one of the 4,936 patients enrolled in the study testing positive for HDV RNA.

Acknowledgments

The authors would like to thank the patients, investigators, and site staff for their participation in the study. We also thank Deng Jun from Janssen Research & Development for supporting the execution of the study. Medical writing assistance was provided by Shao-Hua Chin and Lawrence Law from Parexel (funded by Janssen).

Funding

This study was supported by Janssen Research & Development.

Conflict of interest

XC, XLi, YZ, OL, MB, and QC are employees of Janssen Pharmaceuticals and stockholders in Johnson & Johnson. JH has been an Executive Associate Editor of *Journal of Clinical and Translational Hepatology* since 2013, PH has been an Associate Editor of *Journal of Clinical and Translational Hepatology* since 2013, and HR has been an Editorial Board Members of

Journal of Clinical and Translational Hepatology since 2023. The other authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (XLiang, JH, QC, XC, MB, OL), acquisition of data (JH, XLiang, HT, YG, ML, PH, WX, HR, JN, LC, LY, YZ, XLi, XC), analysis of data (XC), drafting of the manuscript (QC, XC, MB, OL, XLiang, JH), administrative support (YZ, XLi), and study supervision (XLi). All authors had the opportunity to review and comment on the manuscript before publication and shared the final responsibility for the decision to submit it for publication.

Ethical statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1975 Helsinki Declaration, as revised in 2008. The study protocol was approved by the institutional review board or independent ethics committees at all participating sites (NFEC-2020-215). The study was not registered in any clinical trial registry. Informed consent was obtained from all patients for inclusion in the study.

Data sharing statement

Although these data are not currently publicly available for sharing, requests for data sharing can be sent to the corresponding author and will be evaluated on an individual basis.

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