



# Anti-HDV Seroprevalence Among Patients with Chronic Hepatitis B Infection in Diyarbakır

Diyarbakır'da Kronik Hepatit B Enfeksiyonu Olan Hastalarda Anti-HDV Seroprevalansı

● Muhammed Bekçibaşı<sup>1</sup>, ● Eyüp Arslan<sup>2</sup>

<sup>1</sup>University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Diyarbakır, Turkey  
<sup>2</sup>Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey

## ABSTRACT

**Objectives:** This study identifies the hepatitis delta virus (HDV) antibodies (anti-HDV) seroprevalence in patients with chronic hepatitis B (CHB) infection in a region highly endemic for HDV.

**Materials and Methods:** A total of 306 patients with CHB infection, who were followed up regularly between January 2016 and December 2019, were retrospectively analyzed. Demographic characteristics, hematological parameters, liver function tests, abdominal ultrasonography, hepatitis serologies, and liver biopsy results of the patients were analyzed through patient follow-up forms.

**Results:** Anti-HDV was positive in 43 (14.1%) of 306 patients, 129 (42.1%) of whom were female and had a mean age of 41.5±13.4 years. Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase levels of delta hepatitis (DH) patients were significantly higher than those of CHB patients (p=0.019, p<0.001; p=0.027; p=0.001, respectively), whereas albumin, white blood cell, and platelet levels were significantly lower (p<0.001; p=0.001; p<0.001, respectively). 55.8% of patients with DH were with the diagnosed with cirrhosis.

**Conclusion:** Anti-HDV was positive in 14.1% of patients diagnosed with CHB in the Diyarbakır region. The progression to liver cirrhosis and hepatocellular carcinoma is faster in DH; therefore, more efforts should be made to identify and treat this patient group.

**Keywords:** Anti-HDV, hepatitis B virus, hepatitis delta virus, seroprevalence

## ÖZ

**Amaç:** Bu çalışmanın amacı hepatit delta virüsü (HDV) için yüksek oranda endemik olan bir bölgede kronik hepatit B (KHB) enfeksiyonu hastalarında HDV antikorları (anti-HDV) seroprevalansını belirlemektir.

**Gereç ve Yöntemler:** Ocak 2016-Aralık 2019 tarihleri arasında düzenli takipleri yapılan 306 KHB enfeksiyonu tanılı hasta retrospektif olarak analiz edildi. Hastaların demografik özellikleri, hematolojik parametreleri, karaciğer fonksiyon testleri, abdominal ultrasonografi raporları, hepatit serolojileri ve karaciğer biyopsi sonuçları hasta takip formları aracılığıyla incelendi.

**Bulgular:** Yüz yirmi dokuzu (%42,1) kadın ve yaş ortalaması 41,5±13,4 olan 306 hastanın 43'ünde (%14,1) anti-HDV pozitifliği. Delta hepatiti (DH) hastalarının alanin aminotransferaz, aspartat aminotransferaz, alkalen fosfataz ve gama-glutamil transferaz seviyeleri KHB hastalarına göre anlamlı derecede yüksek (sırasıyla; p=0,019; p<0,001; p=0,027; p=0,001), albümin, beyaz kan hücresi ve trombosit değerleri ise anlamlı derecede düşük izlendi (sırasıyla; p<0,001; p=0,001; p<0,001). DH hastalarının %55,8'inde siroz tanısı mevcut idi.

**Sonuç:** Diyarbakır bölgesinde KHB tanılı hastaların %14,1'inde anti-HDV pozitif bulunmuştur. DH'de karaciğer sirozu ve hepatosellüler karsinomaya gidiş daha hızlı olduğundan, bu hasta grubunun tespiti ve tedavisi için daha fazla çaba sarf edilmelidir.

**Anahtar Kelimeler:** Anti-HDV, hepatit B virüsü, hepatit delta virüsü, seroprevalans

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**Address for Correspondence:** Muhammed Bekçibaşı MD, University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Diyarbakır, Turkey

**Phone:** +90 537 027 12 32 **E-mail:** m\_bekcibas@hotmail.com **ORCID ID:** orcid.org/0000-0003-0230-9127 **Received:** 06.08.2021 **Accepted:** 13.09.2022

## Introduction

Hepatitis delta virus (HDV) is a small, defective RNA virus with a viroid structure. HDV can only spread to an individual with hepatitis B virus (HBV) by simultaneous transmission of two viruses (coinfection) or by the infection of an HBV carrier with HDV (superinfection) (1). Spontaneous recovery occurs in 95% of the patients with HBV/HDV coinfection. However, it may cause extensive hepatic necrosis in the remaining patients and lead to a presentation of fulminant hepatitis with high mortality rates (2). Superinfection of people with chronic hepatitis B (CHB) infection with HDV results in turning into chronic at a rate of 80%, which leads to accelerated progression to cirrhosis and an increased risk of hepatocellular carcinoma (HCC) compared to CHB infection alone (3). It is estimated that 0.16% of the general population, which approximately equals 12 million people, are anti-HDV positive worldwide. The prevalence of anti-HDV was reported to be 4.5% among all HBsAg-positive individuals and 16.4% among those presenting to hepatology clinics (4). In Turkey, the lowest prevalence of delta hepatitis (DH) in CHB patients is observed in the West with 4.8%, while the highest prevalence is observed in the Southeast with a rate of 27.1%. In recent years, there has been a decrease in DH in Turkey after the national HBV vaccination program; however, the prevalence is still high in the Southeastern and Eastern Anatolia Regions and continues to be an important health problem (5). The study aims to identify the anti-HDV seroprevalence in CHB patients in a region highly endemic for HDV.

## Materials and Methods

### Study Design

This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital (approval number: 725, date: 26.03.2021).

This study is a retrospective analysis of medical data obtained from the Infectious Diseases Outpatient Clinic of Diyarbakır Bismil State Hospital. A total of 306 patients diagnosed with CHB infection, who were followed up regularly between January 2016 and December 2019, were included in the study. Demographic characteristics, hematological parameters, liver function tests, abdominal ultrasonography, hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), anti-HBe, anti-HDV immunoglobulin G, HBV-DNA, HDV-RNA, and liver biopsy results of the patients were analyzed through patient follow-up forms. Serological tests were performed using the macro-ELISA method (Architect i2000SR, Abbott Diagnostics, Chicago, IL, USA). Anti-HDV presence was analyzed using the Triturus (Triturus, Grifols, Spain) and the micro-ELISA (HDV Ab, Enzyme Immunoassay Test Kit, Delta Biologicals, Italy) systems according to the manufacturer's instructions. The presence of HBV-DNA and HDV-RNA was evaluated by real-time polymerase chain reaction (PCR) using the Rotor-Gene Q (Qiagen, Germany) system and the HBV QS-RG PCR kit (Qiagen, Hilden, Germany) with a linear range of detection of  $25.6\text{-}4.21 \times 10^8$  IU/mL.

## Definitions

CHB infection was defined as the patient group known to be HBsAg positive for more than six months with serological and molecular test confirmation.

The diagnosis of liver cirrhosis was defined in patients who met at least one of the following items:

1. Hepatic surface irregularity, caudate lobe hypertrophy, splenomegaly, or hepatic parenchymal damage on ultrasonography,
2. Laboratory and histological analysis results,
3. Esophageal varices confirmed by endoscopy.

Patients with co-infection with hepatitis C virus and human immunodeficiency virus, or chronic liver diseases such as primary biliary cirrhosis, autoimmune hepatitis, and alcoholic hepatitis, and patients under the age of 16 were excluded from the study. Patients with acute hepatitis B, defined by the presence of HBsAg for less than six months and a clinical presentation compatible with recent HBV infection, were excluded from the study.

## Statistical Analysis

Continuous variables were compared using the Independent samples t-test. Categorical variables were compared using the Pearson chi-square or the Fisher's exact test. All tests were performed using the SPSS for Windows version 18.0 software (SPSS Inc. Chicago, IL, USA). A p-value of  $<0.05$  was considered statistically significant.

## Results

A total of 129 (42.1%) of the 306 patients included in the study were female and the mean age was  $41.5 \pm 13.4$  years. HBeAg was positive in 9.1% of the patients. 28.4% of the patients had undetectable HBV-DNA and 20.9% of HBsAg (+) patients were receiving oral antiviral therapy for HBV. HDV antibodies (anti-HDV+) were positive in 43 (14.1%) of the patients. HDV-RNA was above the detectable level in 17 (39.5%) of the anti-HDV (+) patients. Pegile interferon alfa 2 treatment was given to 19 (44.1%) of the anti-HDV positive patients for 48 months, and 4 (9.3%) for a total of 96 months. Liver transplantation was performed in 2 (4.6%) anti-HDV positive patients. The mean age of the anti-HDV (+) patients was significantly higher than that of the anti-HDV (-) patients ( $p < 0.001$ ). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) levels in anti-HDV (+) patients were significantly higher than those of anti-HDV (-) patients based on the analysis of the biochemical data ( $p = 0.019$ ;  $p < 0.001$ ;  $p = 0.027$ ;  $p = 0.001$ , respectively). The anti-HDV (+) patients had significantly lower albumin, white blood cell count (WBC), and platelet levels compared to the anti-HDV (-) patients ( $p < 0.001$ ;  $p = 0.001$ ;  $p < 0.001$ , respectively). While more than half of the anti-HDV (+) patients were diagnosed with liver cirrhosis, this rate was very low in the anti-HDV (-) patient group (55.8% vs 1.9%,  $p < 0.001$ ). The distribution of demographic, biochemical, and hematological characteristics of the study participants according to the groups is shown in Table 1.

## Discussion

It is estimated that more than 15 million of the 350 million CHB carriers worldwide are exposed to HDV (6). Similar to HBV, HDV is transmitted parenterally through exposure to infected blood or body fluids. Therefore, transmission rates are high in intravenous drug users (7). There is evidence of sexual transmission, and people with high-risk sexual activity are at greater risk for infection (8). Intrafamilial transmission, known as non-specific parenteral transmission, is common in areas with high HDV prevalence. On the other hand, perinatal transmission of HDV is rare. Despite the antiviral therapies used in HDV treatment, these patients are subject to increased liver decompensation, which leads to faster progression to cirrhosis and death, compared to those with HBV infection alone (9). In a viral hepatitis prevalence study in which a large population was screened in Turkey, a middle-endemic country for HBV, anti-HDV positivity was found in 2.8% of the patients with HBsAg positivity (10). The eastern and southeastern parts of Turkey are especially the regions with the highest prevalence of DH. The prevalence of DH in the east and southeast of the country has been associated with the low socioeconomic status of these regions which represent the poorest regions of Turkey (5).

In the present study, anti-HDV positivity was identified in 14.1% of HBsAg (+) patients. More than half of the DH patients (55.8%) were diagnosed with cirrhosis. In a meta-analysis study in which studies conducted in Turkey between 1995 and 2004 were evaluated, anti-HDV seropositivity in patients diagnosed with CHB was reported to be the lowest in the western region with a rate of 5% and the highest in the southeast region with a rate of 27%. In the same study, anti-HDV seropositivities in patients with cirrhosis caused by hepatitis B were at a rate of 20% in the western region and 46% in the southeast region (5). In studies conducted after

2010, anti-HDV positivity in HBsAg (+) patients has been reported to be the lowest in the Western regions, within a range of 1.4-4.1% (11,12,13,14). The rate was within the range of 0.9-4.2% in studies conducted in the middle Anatolia regions (15,16,17). As in previous years, the highest rates have been observed in the East (8.8-15.2%) and Southeast (3.2-27.8%) regions in studies conducted after 2010 (18,19,20,21,22,23,24). Recent studies in Turkey are summarized in Table 2.

In the present study, ALT, AST, ALP, and GGT levels of the DH patients were significantly higher than those of the CHB patients ( $p=0.019$ ;  $p<0.001$ ;  $p=0.027$ ;  $p=0.001$ , respectively), while albumin, WBC, and platelet levels were significantly lower ( $p<0.001$ ;  $p=0.001$ ;  $p<0.001$ , respectively). The presence of cirrhosis in 55.8% of the DH patients suggests the laboratory changes that occurred. Studies have shown that DH patients have significantly higher ALT levels and histological activity compared to CHB patients who are not infected with HDV (25). In a recent meta-analysis, it was shown that DH progresses to cirrhosis within a mean of five years and HCC within a mean of 10 years (26).

## Study Limitations

There are some limitations to the present study. It was single-centered, retrospective, and had a relatively small sample size. Moreover, sequential HDV-RNA monitoring could not be performed in some of the patients.

## Conclusion

In the present study, the anti-HDV seroprevalence of the patients with CHB infection was identified above the Turkey average and close to the average of the data reported from the Eastern and Southeastern regions with a rate of 14.1%. Agents

**Table 1.** Clinical, demographic features, and laboratory data of the participants

	Anti-HDV positive	Anti-HDV negative	p-value
Patient count, n (%)	43 (14.1)	263 (85.9)	
Age, years, mean $\pm$ SD	51.7 $\pm$ 11.3	39.9 $\pm$ 12.9	<0.001
Sex, female n (%)	17 (39.5)	112 (42.6)	0.834
ALT (U/L)	50.7 $\pm$ 32.2	37.0 $\pm$ 35.9	0.019
AST (U/L)	50.2 $\pm$ 28.4	29.0 $\pm$ 16.1	<0.001
ALP (U/L)	105.8 $\pm$ 47.8	87.2 $\pm$ 45.4	0.027
GGT (U/L)	68.4 $\pm$ 69.2	24.2 $\pm$ 18.9	0.001
Albumin (g/dL)	3.86 $\pm$ 0.59	4.39 $\pm$ 0.40	<0.001
Total bilirubin (mg/dL)	0.80 $\pm$ 0.57	0.67 $\pm$ 0.47	0.091
Creatinine (mg/dL)	0.82 $\pm$ 0.14	0.86 $\pm$ 0.16	0.154
White blood count (mm <sup>3</sup> )	6375 $\pm$ 1841	7450 $\pm$ 2019	0.001
Hemoglobin (g/dL)	14.6 $\pm$ 1.8	14.8 $\pm$ 1.8	0.620
Platelet (mm <sup>3</sup> )	150198 $\pm$ 56492	211630 $\pm$ 59039	<0.001
INR	1.14 $\pm$ 0.13	1.08 $\pm$ 0.69	0.609
AFP	8.21 $\pm$ 21.15	7.18 $\pm$ 20.13	0.778
Liver cirrhosis n (%)	24 (55.8)	5 (1.9)	<0.001
CTP score	5.3 $\pm$ 0.9	5.1 $\pm$ 0.3	0.054

HDV: Hepatitis delta virus, SD: Standard deviation, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, INR: International normalized ratio, AFP: Alpha-fetoprotein, CTP: Child-Turcotte-Pugh

Table 2. Anti-HDV positivity in patients with chronic hepatitis B in Turkey			
Region	Study period	Researcher	Anti-HDV (+)
<b>West Turkey</b>			
İstanbul	2015-2017	Yolcu et al. (14)	4.1%
İstanbul	2015-2019	Ergen et al. (11)	2.9%
İzmir	2016-2018	Kaya et al. (13)	2.8%
Sakarya	2015-2018	Aydemir et al. (12)	1.4%
<b>Central Turkey</b>			
Ankara	2010-2013	Gürkan et al. (15)	4.2%
Ankara	2012-2014	Yozgat et al. (17)	3.0%
Eskişehir	2012-2013	Korkmaz et al. (16)	0.9%
<b>East Turkey</b>			
Elazığ	2017-2019	Eser-Karlıdağ (20)	8.8%
Malatya	2012	Duman et al. (19)	15%
Van	2012-2014	Dulger et al. (18)	15.2%
<b>Southeast Turkey</b>			
Adıyaman	2010-2012	Kölgelir et al. (23)	3.2%
Diyarbakır	2012-2017	Ayaz and Sarı (21)	4.4%
Siirt	2017-2018	Bal (22)	27.8%
Şanlıurfa	2011-2012	Uyanıkoğlu et al. (24)	5.0%

HDV: Hepatitis delta virus

that can be used in the treatment of DH are limited, and response rates are very low; therefore, more efforts should be made to minimize the proportion of undiagnosed or not regularly followed-up CHB patients. In addition, HBV vaccination should be applied effectively not only in childhood but also in all risk groups in endemic regions.

### Ethics

**Ethics Committee Approval:** This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital (approval number: 725, date: 26.03.2021).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.B., E.A., Concept: M.B., E.A., Design: M.B., Data Collection or Processing: M.B., E.A., Analysis or Interpretation: M.B., Literature Search: M.B., Writing: M.B.

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