Research Article

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Find HDV and Determine Its Status in Türkiye "SITU(HD) VATION TÜRKİYE"

Türkiye'de HDV'yi Bulmak ve Durumunu Belirlemek: SITU(HD)VATION TÜRKİYE

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ABSTRACT

Objectives: Hepatitis delta virus (HDV) infection is detectable in hepatitis B surface antigen (HBsAg) positive patients and is more significant than other viral hepatitis in terms of the risk of liver cirrhosis/liver cancer. This study aimed to determine the prevalence of HDV and the clinical and histological status of patients with HDV in the southeastern region of Türkiye.

Materials and Methods: A total of 250 family physicians in the provinces of Diyarbakır, Şanlıurfa, Batman, and Mardin were trained on the importance of HDV infection and the follow-up of patients with HBsAg positivity. The importance of HDV was emphasised. For this purpose, the importance of prospectively screening 20,000 HBsAg-positive patients under the care of family physicians for HDV was highlighted. Human immunodeficiency virus (HIV) testing was also conducted in patients who tested positive for anti-delta. Patients who tested positive for HDV were referred to gastroenterology/infectious diseases specialists. Liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) values were measured using Fibroscan® in patients who tested positive for HDV.

Results: A total of 20,000 HBsAg-positive patients were included in the study. The mean age of the patients was 38.2 years; 64.3% of the patients were male. Anti-delta seropositivity was detected in 1,019 (5.1%) of HBsAg-positive patients. Patients with anti-

ÖZ

Amaç: Hepatit delta virüsü (HDV) enfeksiyonu, hepatit B yüzey antijeni (HBsAg) pozitif bireylerde saptanabilmekte olup, siroz ve hepatoselüler karsinom gelişimi açısından diğer viral hepatitlere kıyasla daha yüksek riskle ilişkilidir. Bu çalışmanın amacı, Türkiye'nin Güneydoğu bölgesinde HDV prevalansını ve HDV ile enfekte hastaların klinik/histolojik durumlarını ortaya koymaktır.

Gereç ve Yöntemler: Diyarbakır, Şanlıurfa, Batman ve Mardin illerinde görev yapan toplam 250 aile hekimine, HBsAg pozitif hastalarda HDV enfeksiyonunun önemi ve izlemi konusunda eğitim verilmiştir. Bu kapsamda, aile hekimliği izleminde bulunan 20.000 HBsAg pozitif hastanın prospektif olarak HDV açısından taranmasının gerekliliği vurgulanmıştır. Anti-delta pozitif saptanan hastalara ayrıca insan immün yetmezlik virüsü (HIV) testi uygulanmıştır. HDV pozitif olgular gastroenteroloji/enfeksiyon hastalıkları uzmanlarına yönlendirilmiştir. HDV pozitif hastalarda karaciğer sertlik ölçümü (LSM) ve kontrollü atenüasyon parametresi (KAP) değerleri Fibroscan® ile değerlendirilmiştir.

Bulgular: Çalışmaya toplam 20.000 HBsAg pozitif hasta dahil edilmiştir. Hastaların yaş ortalaması 38,2 olup olguların %64,3'ü erkektir. HBsAg pozitif hastaların 1.019'unda (%5,1) anti-delta pozitifliği saptanmıştır. Anti-delta pozitif hastalar tanı ve izlem amacıyla uzman hekimlere yönlendirilmiştir. HDV-ribonükleik asit (RNA) >500 kopya/mL olan hasta sayısı 367 (%36) olarak

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delta positivity were referred to a specialist physician for diagnosis and follow-up. HDV-ribonucleic acid (RNA) >500 copies/mL was detected in 367 patients (36%). Vibration-controlled transient elastography was performed with the M530 Fibroscan® device in 992 HDV-positive patients to assess LSM and CAP. Liver cirrhosis was detected in 5.5% of patients. Among patients with liver cirrhosis, HDV-RNA was positive in 92.8% and alanine aminotransferase levels above the upper limit of normal were detected in 71.4%. The mean LSM in delta patients was 8.7 kPa, compared with 17.2 kPa in cirrhotic HDV-infected patients (p<0.05). HIV testing was performed on 1,019 HDV-positive patients, and HIV was detected in 18 patients (1.8%). Of these patients, 38.8% reported a history of intravenous drug use. CAP values were significantly higher in patients with hepatitis B virus+HDV+HIV coinfection. The metabolic dysfunction-associated steatotic liver disease rate was 72.2% in these patients.

Conclusion: Anti-delta positivity was detected in 5.1% of HBsAg-positive patients in the southeastern region of our country. Liver cirrhosis was observed in 5.5% of these patients. HIV positivity was also observed in 1.8% of HDV-positive patients. HDV is a significant problem in our country; therefore, HBsAg-positive patients should be evaluated for HDV. Additionally, HDV/HIV co-infection is a significant issue, particularly among intravenous drug users.

Keywords: Chronic hepatitis D, hepatocellular carcinoma, liver cirrhosis, hepatitis B virus (HBV), hepatitis D virus (HDV)

belirlenmiştir. HDV pozitif 992 hastada M530 Fibroscan® cihazı ile titreşim kontrollü geçici elastografi uygulanarak LSM ve KAP düzeyleri değerlendirilmiştir. Karaciğer sirozu hastaların %5,5'inde saptanmıştır. Sirozu olan hastaların %92,8'inde HDV-RNA pozitifliği mevcutken, %71,4'ünde alanin aminotransferaz düzeyi üst normal sınırın üzerinde bulunmuştur. Delta hepatitli hastalarda ortalama LSM değeri 8,7 kPa iken, sirotik HDV enfeksiyonlu hastalarda ortalama LSM değeri anlamlı derecede daha yüksek saptanmıştır (17,2 kPa; p<0,05). Anti-delta pozitif 1.019 hastaya uygulanan HIV testinde 18 hastada (%1,8) HIV pozitifliği tespit edilmiştir. HIV pozitif hastaların %38,8'i intravenöz madde kullanımı öyküsü bildirmiştir. Hepatit B virüs+HDV+HIV koenfeksiyonu olan hastalarda KAP değerleri anlamlı derecede daha yüksek bulunmuş ve bu grupta metabolik disfonksiyonla ilişkili steatotik karaciğer hastalığı sıklığı %72,2 olarak saptanmıştır.

Sonuç: Ülkemizin Güneydoğu bölgesinde HBsAg pozitif bireylerde anti-delta pozitifliği %5,1 olarak saptanmış, bu hastaların %5,5'inde siroz varlığı belirlenmiştir. HDV pozitif hastalarda HIV pozitifliği oranı %1,8 olup, özellikle intravenöz madde kullanan bireylerde HDV/HIV koenfeksiyonunun önemli bir sorun olduğu görülmüştür. HDV, ülkemizde klinik açıdan ciddi sonuçlara yol açabilen önemli bir halk sağlığı problemidir; bu nedenle HBsAg pozitif hastaların HDV açısından da sistematik biçimde değerlendirilmesi gereklidir.

Anahtar Kelimeler: Kronik hepatit D, hepatoselüler karsinom, karaciğer sirozu, hepatit B virüsü (HBV), hepatit delta virüsü (HDV)

Introduction

Liver cirrhosis and hepatocellular carcinoma (HCC) constitute a significant global public health problem, particularly due to their interrelated pathophysiological mechanisms and the increasing burden of hepatitis infections (1,2). Liver cirrhosis is a common terminal outcome of chronic liver disease, which can arise from various etiologies, including viral infections such as hepatitis B virus (HBV) and hepatitis C virus (HCV), alcohol use, and metabolic dysfunction-associated steatotic liver disease (MASLD). In the latest European endocrinology guidelines, the term non-alcoholic fatty liver disease has been abandoned due to its inadequate definition and exclusionary approach; instead, the term MASLD has been proposed. This new definition provides a more inclusive, pathophysiology-based disease classification defined by positive criteria related to metabolic risk factors (2,3,4). MASLD is diagnosed in individuals with clinical or imaging [ultrasonography, Fibroscan® controlled attenuation parameter (CAP) measurement] evidence of hepatic steatosis, absence of alcohol consumption, and at least two criteria of metabolic dysfunction. According to the 2023 guidelines, criteria for metabolic dysfunction include type 2 diabetes, obesity (body mass index ≥30 kg/m^2), dyslipidaemia, hypertension, insulin resistance, hypertriglyceridaemia, low high-density lipoprotein cholesterol, and elevated C-reactive protein levels. Metabolic dysfunction-associated steatohepatitis (MASH) is an inflammatory form within the MASLD spectrum, characterised histologically by liver steatosis, hepatocyte damage, and lobular inflammation. In a patient with MASLD, if alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels are above normal and liver stiffness measurement (LSM) at >5.5 kPa, the patient is diagnosed with MASH. If ALT/AST are within normal limits, both the MASLD criteria and the LSM >7.0 kPa criterion must be met (5). The pathogenesis of liver cirrhosis involves progressive fibrosis, which causes structural and functional impairment of the liver and ultimately results in advanced stages, in which the risk of liver cancer significantly increases (6).

Epidemiological and experimental studies strongly support the link between liver cirrhosis and liver cancer. Cirrhosis is not only a predisposing factor for the development of HCC but also complicates the treatment and prognosis of individuals diagnosed with liver cancer. Inflammation, oxidative stress, and cellular apoptosis play important roles in the transition from cirrhosis to HCC, and specific cellular responses, such as the activation of hepatic stellate cells, contribute to the fibrotic environment that promotes tumour formation (1,7). Evidence indicates that impaired liver function in cirrhotic patients significantly increases the risk of HCC development, highlighting the critical role of preserving liver function in reducing cancer risk (1,6). The relationship between cirrhosis and liver cancer, particularly in the context of co-infection with HBV, hepatitis delta virus (HDV), and human immunodeficiency virus (HIV) is a significant concern in hepatology. Co-infections can exacerbate liver disease through various mechanisms that affect viral replication, hepatic inflammation, and fibrosis progression, thereby increasing the risk of developing severe conditions such as cirrhosis and HCC (8,9,10,11).

Chronic HBV involves persistent hepatocyte inflammation that can lead to fibrosis and ultimately cirrhosis and HCC (2,8). In particular, patients co-infected with HDV and HBV have worse outcomes than those with HBV infection alone. Approximately 5% of chronic HBV carriers are infected with HDV. HDV co-infection, which accompanies HBV infection, exacerbates the clinical picture and significantly worsens disease course (12). Studies have shown that individuals co-infected with HBV and HDV may have a threefold higher risk of developing HCC compared to those with

HBV infection alone. Therefore, screening for HDV is recommended for all detectable in hepatitis B surface antigen (HBsAg)-positive patients. If HDV serology is positive, screening for HDV replication should be performed (9).

The HDV is a defective ribonucleic acid (RNA) virus that can replicate in the presence of HBV, and its contribution to hepatic damage is mediated not only by viral replication but also by cytopathic effects and by exacerbation of the immune response (13). Cirrhosis develops both more frequently and at an earlier stage in individuals coinfected with HDV. Indeed, HDV infection accelerates progression to cirrhosis and results in earlier and more frequent liver-related clinical endpoints (12,13,14). High HDV viremia are directly associated with progressive liver disease, including cirrhosis and HCC (10).

In the context of HIV co-infections, this interaction becomes even more complex. HIV not only increases the severity of HBV-related liver disease but also promotes HBV replication, leading to elevated HBV-DNA levels in co-infected individuals (15). The immunodeficiency observed in HIV-positive populations often leads to reduced clearance of HBV and increased risk of liver-related mortality. This situation is further exacerbated by the effects of antiretroviral therapy (ART), which, despite effectively controlling HIV, fails to adequately treat the underlying liver complications arising from co-infection (16). In developed countries, intravenous drug use (IVDU), previously the primary route of HDV transmission among HIV-infected individuals, has been supplanted by sexual transmission. In individuals co-infected with HIV, HBV, and HDV, liver disease progresses more aggressively and is associated with a significantly increased risk of cirrhosis and liver-related mortality. The presence of HDV accelerates the progression of liver fibrosis and increases the risk of decompensation and death in HIV-positive individuals. Therefore, screening for HBV and HDV is recommended for HBsAg-positive and HIV-infected individuals, and antiviral treatment should be planned for patients with viremia (17). A study conducted in India investigated the prevalence and clinical effects of HIV and HDV co-infections and triple infections (HIV/HBV/HDV) in individuals with chronic HBV infection. Triple infection was particularly prevalent in the 21-40 year age group and was associated with chronic hepatitis and cirrhosis. The prevalence of HDV infection was lower in HIV-negative individuals, whereas it was higher in HBV/HIV-coinfected individuals. These findings suggest that the presence of HIV may increase the risk of HDV infection and that this patient group should be closely monitored (18).

This study aims to determine the seroprevalence of HDV among HBsAg-positive individuals receiving follow-up in primary care and to assess the epidemiological burden of HDV in our region. Within this scope, 250 family physicians from four provinces were trained on HBV/HDV, and anti-HDV (anti-delta) positivity was assessed among approximately 20.000 HBsAg-positive individuals. Additionally, HIV seroprevalence was assessed in a subgroup of HDV-positive individuals, and HDV-RNA levels were used to determine the presence of active HDV infection. The presence of cirrhosis was assessed by measuring LSM (kPa) and liver steatosis (dB/m) using vibration-controlled elastography (VCTE/FibroScan®). This study aims to determine the prevalence of HDV infection among HBsAg-positive individuals, assess the clinical and histological stages of the disease, and elucidate the HDV status in our region.

Materials and Methods

Study Design

This prospective, multicentre, observational study was designed to investigate the prevalence, virological profile, and liver fibrosis status of HDV infection in the southeastern region of Türkiye. Our study was previously presented as a poster at the 2025 Congress of the Asian Pacific Association for the Study of the Liver. The study was conducted in four provinces in our region (Diyarbakır, Mardin, Batman, and Şanlıurfa), which are among the largest provinces in Türkiye. These provinces have among the highest incidence rates of HDV-related cirrhosis and HCC in Türkiye, and the lack of regional seroprevalence data underscores the need for this study. The study population comprised HBsAg-positive adult patients who were followed by family physicians in these regions.

Participants and Inclusion Criteria

A total of 20.000 Turkish citizens aged ≥18 years with HBsAg positivity confirmed for at least six months were included. There were no exclusion criteria. All participants provided written informed consent prior to enrolment.

Data Collection and Work Procedures

The study was carried out in several stages:

1. Training Phase: Between April and July 2024, 250 family doctors were trained by infectious disease or gastroenterology specialists in the natural course and complications of HBV and HDV infections. The training aimed to improve primary care physicians' HDV screening practices and to highlight the importance of anti-HDV testing, particularly in HBsAg-positive individuals.

2. Screening and Assessment: All HBsAg-positive patients under the care of participating family physicians were screened for anti-delta antibodies. Anti-delta-positive individuals were subsequently tested for HIV and HCV to assess co-infection rates. Given that current literature suggests that HIV seroprevalence may be higher in individuals with HDV infection and that IVDU may be a route of transmission, HIV testing was performed in approximately 1.000 HDV-positive individuals.

3. Liver Fibrosis Assessment: Liver fibrosis in HDV-positive patients was assessed using non-invasive methods such as FibroScan®, fibrosis-4 index, and Child-Pugh scoring. Liver stiffness measured by FibroScan® in 992 patients was compared with established cirrhosis threshold values to calculate the prevalence of cirrhosis. MASLD-compatible steatosis findings were also evaluated. Additionally, HDV-RNA testing was performed to determine viraemia status and to identify the rate of active infection. Correlation analyses were conducted between liver enzyme levels and HDV-RNA positivity among HDV-positive individuals.

4. Physician Knowledge Survey: A structured five-question survey was administered to family physicians before and after educational sessions to assess knowledge development. Data were collected via Slido®.

5. Timeline:

- Planning and preparation: 01.02.2024-31.03.2024
- Data collection and training: 01.04.2024-30.09.2024
- Data analysis and writing: 01.10.2024-31.12.2024
- Final reporting and presentation: by 31.01.2025.

Endpoints

The primary endpoint is the incidence of HDV infection among HBsAg-positive individuals. Secondary endpoints include:

- Virological and fibrosis profile of HDV-infected patients
- HIV co-infection rates
- Demographic characteristics of HDV-infected cases
- Vertical transmission rates and treatment needs
- Liver enzyme levels and clinical correlations in HDV-RNA positive patients
- Incidence of cirrhosis and HCC
- Prevalence of cirrhosis-equivalent stiffness and MASLD/MASH compatible findings in patients evaluated with FibroScan®
- Referral of HIV-positive patients to specialised outpatient clinics and initiation of treatment.

Ethical Approval

The study protocol was approved by the Dicle University Medical Faculty Ethics Committee for Non-Interventional Studies (approval no: 12, date: 20.12.2023), and the study was conducted in accordance with ethical principles and the Helsinki Declaration.

Statistical Analysis

All statistical analyses were performed using IBM SPSS v25.0. Continuous variables were presented as mean ± standard deviation. Categorical data were presented as frequencies and percentages. The normality of the data distribution was assessed using the Kolmogorov-Smirnov or Shapiro-Wilk tests. Chi-square (χ^2) tests were used for categorical variables. For comparisons of numerical data between independent groups, the Student's t-test was used, and single and multiple regression analyses were applied to evaluate the relationship between these data and cirrhosis. Correlations between continuous variables were analysed using Pearson or Spearman's correlation coefficients. Odds ratios were used to assess risk and diagnostic value. All test results with $p<0.05$ were considered statistically significant.

Results

A total of 20.000 HBsAg-positive individuals were included in the study. The ages of the participants ranged from 19 to 61 years, with an average age of 38.20±11.06 years. The average duration of HBsAg positivity was 4.99±2.38 years. The study group comprised 7.147 (35.7%) females and 12.853 (64.3%) males. Of the individuals, 51.7% were from Diyarbakır (n=10.333), 23.6% were from Batman (n=4.718), 16.4% were from Mardin (n=3.286), and 8.3% were from Siirt (n=1.663). Anti-HDV testing revealed a positivity rate of 5.1% (n=1.019) among the individuals tested (Table 1).

HDV-RNA positivity (>500 copies/mL) was detected in 36.0% (n=367) of the 1,019 HDV-positive patients. Anti-HIV tests were positive in 1.8% (n=18) of 1,000 patients with HDV infection. IVDU was identified in 7 (38.8%) of 18 HIV-positive patients. Additionally, MASLD was detected in 13 (72.2%) of the 18 patients. A specialist physician treated all HIV-positive patients. ALT levels were above the normal limits in 25.7% (n=262) of patients. Cirrhosis was detected in 5.5% (n=56) of patients. HCC was not detected in any of these patients. Among 992 HDV-positive patients, LSM and CAP values were assessed using VCTE with FibroScan® M530. The mean LSM in these patients was 8.7±2.7 kPa, whereas this value was significantly higher in cirrhotic HDV-infected patients (17.2 kPa; p=0.019). The mean CAP value measured in the same group was 231.7±41.6. In patients with HBV+HDV+HIV co-infection, the CAP value was significantly higher (260.6±41.7; p=0.012) (Table 2).

Discussion

Infection with HBV can become chronic. It affects hundreds of millions of people worldwide and has serious public health consequences. Current data indicate that approximately 5-10% of HBV carriers are coinfected with HDV. HDV is a structurally incomplete RNA virus that requires the HBsAg for replication; therefore, it can only cause infection in individuals with HBV infection. HDV infection causes more severe liver damage than HBV infection. In this co-infection, serious complications such as cirrhosis and HCC may develop earlier. HDV can be transmitted simultaneously with HBV (co-infection) or acquired later (superinfection). In particular, cirrhosis develops within 5-10 years in cases of superinfection, and this risk is much higher than that observed with HBV infection alone. Therefore, the presence of HDV is considered a factor that significantly worsens the course of the disease (13,18,19,20).

In the study by Ton et al. (21), 324 HBV patients were evaluated, and HDV co-infection was detected in 22 (6.7%) of them. In another study, Gish et al. (22) evaluated 1,191 patients with chronic HBV infection, and HDV co-infection was detected in 8% of them. In a study by Da et al. (23), 652 HBV patients were examined; HDV co-infection was detected in 91 (14%) of them. In a study by Ho et al. (24), HDV co-infection was detected in 5.5% (n=44) of the 800 HBV patients screened. In the study by Genné and Rossi (25), HDV positivity was detected in 5.9% of 1,699 HBV patients. In the study by Heidrich et al. (26), this rate was reported as 11% (258/2.363). In a 2020 review, Vlachogiannakos and Papatheodoridis (27). examined regional HDV co-infection rates. In European countries, the rates ranged from 2% to 23.1%, while in the Americas, they ranged from 0.9% to 32.8%. In Asian and Middle Eastern countries, rates ranged from 0.9% to 28.8%, while in African countries, they ranged from 1.3% to 43%. Among the studies reviewed, the largest number of patients was reported in China (n=17.163), was 5.6% (27). In our study, the HDV co-infection rate was 5.1%; the number of patients evaluated (20.000) was significantly higher than reported in similar studies.

Co-infection with HBV and HIV, and HBV/HDV/HIV triple infections, are also of clinical importance because they significantly alter the clinical course of these patients. HBV and HIV co-infections continue to pose a serious risk of liver-related complications and

Table 1. Demographic characteristics of patients and HDV positivity

	n	Minimum	Maximum	Mean	Std. deviation
Patient age (year)	20000	19.00	61.00	38.20	11.06
HBsAg positivity duration (year)	20000	1.00	23.00	4.99	2.38
		n		%	
Gender	Female	7147		35.7	
	Male	12853		64.3	
City	Diyarbakır	10333		51.7	
	Batman	4718		23.6	
	Siirt	1663		8.3	
	Mardin	3286		16.4	
Anti-delta	Negative	18981		94.9	
	Positive	1019		5.1	

HBsAg: Hepatitis B surface antigen, Anti-delta: Antibody against hepatitis D virus, Std.: Standard, HDV: Hepatitis delta virus

Table 2. Clinical characteristics of HDV-positive patients

Patients with positive HDV (n=1019)		n	%
HDV-RNA	Negative	652	64.0
	Positive	367	36.0
Anti-HIV	Negative	1001	98.2
	Positive	18	1.8
ALT	Within normal limits	757	74.3
	Above normal limits	262	25.7
Cirrhosis	Negative	963	94.5
	Positive	56	5.5
	n	Mean	Std. deviation
LSM (kPa)	992	8.7	2.7
CAP	992	231.7	41.6

Std.: Standard, HDV: Hepatitis delta virus, RNA: Ribonucleic acid, Anti-HIV: Antibody against human immunodeficiency virus, ALT: Alanine aminotransferase, LSM: Liver stiffness measurement, CAP: Controlled attenuation parameter, kPa: Kilopascal

non-acquired immune deficiency syndrome (AIDS)-related mortality. This co-infection accelerates the progression of HIV infection to AIDS in HBV carriers. Additionally, in individuals co-infected with HBV and HIV, there is a decrease in the cluster of differentiation 4+T-lymphocyte immune response and an impairment of specific immune mechanisms directed against HBV. Furthermore, the likelihood of HBV reactivation or reverse seroconversion increases in HIV-positive individuals with suppressed immune systems. HBV/HIV co-infection rates range from 6-14% in Europe, while in Asian and African countries, this rate can reach up to 20% (28,29,30,31,32). The risk of HBV infection among HIV-infected patients is 40% higher than among HIV-negative patients, and HBV co-infection is a leading cause of increased morbidity and mortality among individuals living with HIV (33,34). The course of liver disease in individuals co-infected with HBV/HDV/HIV is more rapid than in HIV-negative individuals (35,36). The literature shows regional differences in the prevalence of this triple infection, ranging from 1.2% to 22.2% (35,36,37,38,39,40,41,42). In our study, among 20.000 HBV-infected patients, 1.019 patients co-infected with HDV were screened for HIV. HIV co-infection was detected in 1.8% of these HDV-positive patients.

The co-existence of viral infections significantly affects the course of the disease in patients. In Ton et al.'s (21) study, the rate of liver fibrosis was reported as 40% in HDV co-infected patients, which was higher than the rate in HBV mono-infected individuals (10%). In the same study, levels of ALT, AST, bilirubin, and albumin were also higher in HDV-infected individuals. These findings have been supported by other studies (43,44,45). In a study by Da et al. (23), independent risk factors for HDV included IVDU, HBV-DNA <2.000 IU/mL, ALT >40 U/L, and residence in a country where HDV is endemic. Among patients with HDV, blood transfusion (4.5%), male-to-male sexual intercourse (9.1%), and IVDU (4.5%) were reported; these rates were not significantly different from those in the HBV mono-infected group (21). According to the literature, in HDV infections, cirrhosis develops within 5 years, and HCC develops on average within 10 years. HDV infection has a clinically more aggressive course than HBV and is associated with a threefold higher risk of developing cirrhosis (10,46,47). In a study using Fibroscan®, 33.3% of HDV-positive patients had elevated ALT levels, 63.6% had liver fibrosis, and 45.5% had cirrhosis; these figures were reported to be significantly higher than those in patients with HBV infection without HDV (48). In our study, when HDV-infected patients were evaluated using Fibroscan®, elevated ALT levels and cirrhosis were detected in 25.7% and 5.5% of patients, respectively. No HCC was detected in any patient. The mean LSM was 8.7 kPa and significantly higher among cirrhotic patients. The low rate of cirrhosis observed in our study, compared with the high rates reported in the literature, is related to the characteristics of the patient population. Our study included individuals screened at primary care centres who were representative of the general population. The HDV-RNA positivity rate was also relatively low in this group. However, patients followed up in gastroenterology clinics are generally drawn from those with advanced-stage disease, resulting in higher cirrhosis rates reported in these centres. In our study, active delta infection was not considered in HDV-RNA-negative patients, and the risk of liver disease

progression in this group was considered limited. On the other hand, the presence of cirrhosis in HDV-RNA-positive patients further underscores the role of HDV infection in the development and progression of liver fibrosis to cirrhosis. This finding demonstrates how differences between the screening population and the patient profile observed in advanced centres affect the results.

Studies conducted in Europe have found that the rate of anti-HDV positivity is higher among HIV/HBV co-infected patients who inject drugs intravenously (49). However, Motamedifar et al. (35) reported that this is not a significant risk factor. Although MASLD prevalence in people living with HIV varies across cohorts, the available evidence suggests a substantial overall burden and a predominant association with metabolic risk factors (e.g., adiposity, dyslipidaemia, and insulin resistance). The study by Kalopitas et al. (50) also supports these findings, indicating that, in addition to classic metabolic risk factors, HIV-specific mechanisms contribute to MASLD development, including ART-associated mitochondrial toxicity, lipodystrophy, insulin resistance, gut microbiota dysbiosis, and direct hepatic effects of HIV. Collectively, these data underscore the importance of early diagnosis and metabolic risk-focused screening strategies in HIV-positive individuals. In our study, 1.8% (n=18) of HDV-positive patients were anti-HIV positive. IVDU was identified in 38.8% of the 18 HIV-positive patients. Additionally, MASLD was detected in 72.2% (n=13) of these 18 patients. CAP values were also significantly elevated in individuals co-infected with HBV, HDV, and HIV.

Study Limitations

This study has several limitations. Limiting the study population to HBsAg-positive individuals followed in primary care settings in four provinces in southeastern Türkiye may restrict the generalisability of the findings to other regions and to patient groups managed in tertiary care centres. Moreover, because data on behavioural risk factors, such as intravenous drug use, were based on physician records and reports, under-reporting is possible. These issues should be taken into account when interpreting the study results.

Conclusion

In this large-scale study, we evaluated the prevalence of HDV and HIV co-infections in individuals with HBV infection and their impact on liver disease. The data indicate that liver damage is more severe and the risk of cirrhosis is increased when HBV infection is accompanied by HDV co-infection. However, the rate of cirrhosis among delta patients receiving primary care was found to be lower than that observed in specialist clinics. Significantly elevated CAP values in patients with HIV co-infection also indicate an increased metabolic burden. Although HDV infection was infrequently detected, screening for HDV is important in all HBsAg-positive individuals because of its clinical consequences. Similarly, routine evaluation of HBV and HDV infections is recommended in HIV-positive patients. HDV screening in HBsAg-positive individuals revealed an HDV prevalence of 5.1% in our region. Evaluation of HDV patients using VCTE has shown that it is essential for detecting liver cirrhosis (5.5%). This study has demonstrated the importance of screening all HBsAg-positive patients for HDV and of screening HDV-positive patients for HIV.

Ethics

Ethics Committee Approval: The study protocol was approved by the Dicle University Medical Faculty Ethics Committee for Non-Interventional Studies (approval no: 12, date: 20.12.2023), and the study was conducted in accordance with ethical principles and the Helsinki Declaration.

Informed Consent: All participants provided written informed consent prior to enrolment.

Footnotes

Authorship Contributions

Concept: M.K.Ç., Ç.M., Y.T., Y.B., Design: M.K.Ç., Ç.M., Y.T., Y.B., Data Collection or Processing: M.K.Ç., Ç.M., Y.T., İ.Y., Y.D., P.Ç., T.D.Ç., Ü.Y., Y.B., Analysis or Interpretation: M.K.Ç., İ.Y., Y.B., Literature Search: M.K.Ç., Ç.M., Y.T., Y.B., Writing: M.K.Ç., Ç.M., Y.T., Y.B.

Conflict of Interest: One of the authors of this article (Mustafa Kemal Çelen) is a member of the Editorial Board of this journal. He/she was completely blinded to the peer review process of the article.

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