VIRAL HEPATITIS SOCIETY

E-ISSN: 2147-2939

Viral Hepatitis Journal

VİRAL HEPATİT DERGİSİ

RESEARCH ARTICLES

www.viralhepatitisjournal.org

December 2025
3
Volume 31

galenos

VIRAL HEPATITIS SOCIETY

Viral Hepatitis Journal

VİRAL HEPATİT DERGİSİ

Address for Correspondence:
Viral Hepatitis Prevention Society
Sağlık Mahallesi, Süleyman Sırrı Caddesi No: 2/15
Sıhhıye, Ankara, Türkiye
Phone: +90 312 433 74 26
Fax: +90 312 433 06 54
E-mail: info@viralhepatitisjournal.org

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Türkiye
Phone: +90 (539) 307 32 03
E-mail: info@galenos.com.tr
yayin@galenos.com.tr
Web: www.galenos.com.tr

Yayıncı Sertifika No: 14521
Online Publication Date: January 2026
E-ISSN: 2147-2939
International scientific journal published quarterly.

VIRAL HEPATITIS SOCIETY

Viral Hepatitis Journal

VİRAL HEPATİT DERGİSİ

Please refer to the journal's webpage **(https://viralhepatitisjournal.org/)** for **"About Us"**, **"Instructions to Authors"** and **"Peer Review & Ethics"**.
The journal's editorial policies are based on "ICMJE Recommendations" rules.
Viral Hepatitis Journal is indexed in **Emerging Sources Citation Index (ESCI), EBSCO, Gale, ProQuest, Embase, CABI, CINAHL Database, Tübitak/Ulakbim Turkish Medical Database, British Library, J-Gate, IdealOnline, Türk Medline Index** and **Turkiye Citation Index databases**.
The journal is published online.
Owner: Viral Hepatitis Society
Responsible Manager: Fehmi TABAK

VIRAL HEPATITIS SOCIETY

Viral Hepatitis Journal

VİRAL HEPATİT DERGİSİ

CONTENTS

Research Article

DOI: 10.4274/vhd.galenos.2025.2025-8-1
Viral Hepat J 2025;31(3):72-77

Evaluation of Health-related Quality of Life among Patients with Chronic Viral Hepatitis and Non-alcoholic Fatty Liver Disease

Kronik Viral Hepatit ve Alkolsüz Yağlı Karaciğer Hastalığı Olan Hastalarda Sağlıkla İlişkili Yaşam Kalitesinin Değerlendirilmesi

Ayşe Merve Ok Kurt[1], Emine Satır[2], Tuğçe Eşkazan[3], Deniz Eyice Karabacak[4], Enes Ali Kurt[5], Abdullah Sonsuz[3], Billur Canbakan[3], Sebati Özdemir[3], Murat Tuncer[3], İbrahim Hatemi[3]

[1]*University of Health Sciences Türkiye, Kocaeli City Hospital, Clinic of Endocrinology and Metabolism, Kocaeli, Türkiye*
[2]*Acıbadem International Hospital, Clinic of Gastroenterology, İstanbul, Türkiye*
[3]*İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Internal Medicine, Division of Gastroenterology, İstanbul, Türkiye*
[4]*University of Health Sciences Türkiye, Kocaeli City Hospital, Clinic of Immunology and Allergy, Kocaeli, Türkiye*
[5]*University of Health Sciences Türkiye, Kocaeli City Hospital, Clinic of Gastroenterology, Kocaeli, Türkiye*

ABSTRACT

Objectives: Chronic viral hepatitis may reduce quality of life (QoL). In this study, our aim was to assess the QoL of patients with chronic hepatitis B virus (HBV) infection and to compare these results with those of patients with non-alcoholic fatty liver disease (NAFLD) and chronic hepatitis C virus (HCV).

Materials and Methods: A total of 299 consecutive patients with chronic HBV, 92 patients with chronic HCV, and 64 patients with NAFLD were included. Short form-36 (SF-36), the liver disease symptom index 2.0 (LDSI 2.0), and the sociodemographic data form were completed. Child-Pugh and the model for end-stage liver disease scores were also calculated.

Results: Patients with chronic HCV had the worst scores on the SF-36 and the LDSI 2.0, followed by patients with HBV and NAFLD. Factors associated with QoL were, among patients with HCV, employment status, medical treatment, income level, presence of cirrhosis, and number of comorbid conditions; among patients with HBV, gender and presence of cirrhosis; and among patients with NAFLD, number of children, duration of disease, number of comorbid conditions, and body mass index.

Conclusion: Chronic viral hepatitis had a negative impact on QoL. Patients with chronic HCV had the lowest QoL, followed by patients with chronic HBV and NAFLD.

Keywords: Chronic HCV infection, chronic hepatitis B infection, NAFLD, quality of life

ÖZ

Amaç: Kronik viral hepatit, yaşam kalitesini (YK) olumsuz etkileyebilir. Bu çalışma, kronik hepatit B virüs (HBV) hastalarında YK'yi değerlendirmek ve sonuçlarını alkole bağlı olmayan yağlı karaciğer hastalığı (NAFLD) ve kronik hepatit C virüs (HCV) hastalarıyla karşılaştırmak amacıyla yapılmıştır.

Gereç ve Yöntemler: Çalışmaya 299 HBV, 92 HCV ve 64 NAFLD hastası dahil edildi. Kısa form-36 (KF-36), karaciğer hastalığı semptom indeksi 2.0 (LDSI 2.0) ve sosyodemografik form kullanıldı. Sirozu olan hastalarda Child-Pugh ve model for end-stage liver disease skorları hesaplandı.

Bulgular: Kronik HCV'li hastalar KF-36 ve LDSI 2.0'da en kötü puanları alırken, bunu HBV ve NAFLD'li hastalar izledi. Yaşam kalitesiyle ilişkili faktörler, HCV'de çalışma durumu, tıbbi tedavi, gelir düzeyi, siroz ve ek hastalık sayısı; HBV'de cinsiyet ve siroz; NAFLD'de çocuk sayısı, hastalık süresi, ek hastalık sayısı ve vücut kitle indeksi YK ile ilişkili bulundu.

Sonuç: Kronik viral hepatitler YK'yi olumsuz etkilemektedir. HCV hastalarında YK en düşük, HBV'de orta, NAFLD'de ise en yüksek düzeydedir.

Anahtar Kelimeler: Kronik HCV enfeksiyonu, kronik hepatit B enfeksiyonu, NAFLD, yaşam kalitesi

Address for Correspondence: Ayşe Merve Ok Kurt, MD, University of Health Sciences Türkiye, Kocaeli City Hospital, Clinic of Endocrinology and Metabolism, Kocaeli, Türkiye
E-mail: a.merve52@gmail.com **ORCID ID:** orcid.org/0000-0002-1074-1801

Received: 10.08.2025 **Accepted:** 24.11.2025 **Epub:** 05.01.2026 **Publication Date:** 26.01.2026

Cite this article as: Ok Kurt AM, Satır E, Eşkazan T, Eyice Karabacak D, Kurt EA, Sonsuz A, Canbakan B, Özdemir S, Tuncer M, Hatemi İ. Evaluation of health-related quality of life among patients with chronic viral hepatitis and non-alcoholic fatty liver disease. Viral Hepat J. 2025;31(3):72-77

Introduction

Chronic viral hepatitis is a major cause of chronic liver disease worldwide, posing a substantial healthcare burden (1). Beyond managing the illness itself, patients face socioeconomic and psychological challenges.

Health-related quality of life (HRQoL) refers to the perceived physical, mental, emotional, and social well-being of patients, based on the World Health Organization's holistic perspective introduced in the late 20th century. This concept has gained importance due to increased life expectancy resulting from improved treatments, which, in turn, leads to a higher prevalence of chronic diseases. Today, therapeutic success is measured not only by clinical outcomes but also by its effects on QoL, making HRQoL assessments an essential part of medical research (2,3).

HRQoL tools are generally either generic or disease-specific. Generic tools assess QoL regardless of diagnosis, are applicable to the general population, and allow comparisons between different chronic diseases (4,5). However, they may lack sensitivity to detect subtle, clinically relevant changes linked to treatment or disease progression. Disease-specific tools, in contrast, are often more sensitive to such changes, which may be important for patients and physicians. When used together, these tools provide complementary perspectives on the impact of chronic diseases (6).

Poor QoL may contribute to or result from issues such as poor treatment adherence, missed follow-ups, social withdrawal, and family conflicts. In chronic hepatitis B virus (HBV), treatment often requires prolonged, sometimes lifelong, medication. Uncontrolled treatment discontinuation can have severe consequences. Thus, evaluating HRQoL is crucial for optimal management and follow-up.

This study aimed to assess the QoL in patients with chronic HBV, considering sociodemographic factors and disease subgroups.

Materials and Methods

Consecutive patients aged ≥18 years who were treated at our outpatient clinic between March and June 2016 and who provided informed consent were enrolled. Exclusion criteria included: significant hepatic encephalopathy; Child-Pugh score >10; recent (<1 month) gastrointestinal bleeding or spontaneous bacterial peritonitis; use of lactulose or psychoactive drugs; neurological, psychiatric, or dementing disorders; non-hepatic metabolic encephalopathy; stage 3-4 cardiac failure; stage 4-5 chronic renal failure; severe chronic pulmonary disease; uncontrolled diabetes or hypertension; active malignancy; alcohol intake >50 g/day within the past 3 months; prior portal hypertension shunt or transjugular intrahepatic portosystemic shunt; solid organ or bone marrow transplantation; immunosuppression; other chronic liver diseases; or hospitalization for unrelated conditions within the past month.

This cross-sectional study involved completion of the short form-36 (SF-36), the liver disease symptom index 2.0 (LDSI 2.0), and a 16-item sociodemographic form following brief oral instructions. Questionnaires were completed under physician supervision without interference; additional clinical data (medications, comorbidities) were extracted from records. Child-Pugh and model for end-stage liver disease (MELD) scores for patients with cirrhosis were calculated using same-day laboratory results. Physical component scores (PCS) and mental component scores (MCS) from SF-36 were computed using dedicated software. The study received ethical approval from the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (approval no: A-34, date: 03.05.2016).

Short Form-36

Developed by Ware and Sherbourne (7) and adapted for clinical use by the RAND Corporation, the SF-36 was validated in Turkish by Kocyigit et al. (8). This generic, self-administered tool assesses eight domains over the preceding 4 weeks and summarizes them into PCS and MCS scores (range: 0-100; higher scores indicate better QoL).

Liver Disease Symptom Index 2.0

Developed by van der Plas et al. (9) and validated in Turkish by Eraydın et al. (10), LDSI 2.0 is a disease-specific instrument with 24 items in two sections: Appendix I comprises 18 questions covering the past week (9 main and 9 supplementary), and Appendix II comprises 6 questions on disease impact since diagnosis. Scores range from 1-5, with higher scores indicating poorer QoL.

The LDSI 2.0 is a disease-specific QoL scale developed for patients with chronic liver disease. The SF-36 is a general QoL scale that is independent of disease. We used both measures to assess disease-specific and overall impairments in QoL. This approach ensures the validity of findings for both specific patient subgroups and the general population and captures subtle and broad changes through the psychometric complementarity among these instruments.

Sociodemographic Data Form

A 16-item form, designed by the research team, was used to collect demographic and socioeconomic data, including marital status, education, occupation, and income level.

Statistical Analysis

Data were analyzed with SPSS 21.0. Descriptive statistics included frequencies, percentages, means, and standard deviations. Normality was assessed using the Kolmogorov-Smirnov test. Pearson's chi-square test was used to compare qualitative data. Non-normally distributed quantitative variables were compared using the Kruskal-Wallis test with post-hoc analysis. Linear regression was used to assess the associations between the independent and the dependent variables. Statistical significance was set at $p<0.05$; 95% confidence interval were reported.

Results

A total of 455 patients were included: 299 with chronic HBV, 92 with chronic hepatitis C virus (HCV), and 64 with non-alcoholic fatty liver disease (NAFLD). Table 1 summarizes the characteristics. The gender distribution differed significantly, with more females in the NAFLD group and fewer females in the HBV group ($p<0.001$). HCV patients were significantly older than both HBV and NAFLD patients ($p<0.001$). NAFLD patients had a higher body mass index

(BMI) than the other groups (p<0.001). Marital status differed: there were fewer married and more widowed individuals in the HCV group (p=0.003). NAFLD patients had fewer children than HCV patients (p=0.048). HCV patients had lower education levels (p=0.023), lower employment rates (p=0.043), and lower income levels (p=0.023). Disease duration was longer in patients with HBV and HCV than in patients with NAFLD (p<0.001). HBV patients had fewer comorbidities (p<0.001) but had higher rates of smoking and drug use (p<0.001).

Table 2 shows the results of QoL assessments. PCS were higher in HBV (47.72±9.08) and in NAFLD (50.91±5.91) than in HCV (43.81±9.67). MCS were highest in NAFLD (49.91±6.84), followed by HBV (46.28±9.00) and HCV (42.56±9.66). Appendix I scores were higher in HBV (27.98±8.81) and HCV (30.90±11.37) than in NAFLD (24.41±6.81). Appendix II scores were highest in HCV (12.32±5.04), followed by HBV (10.55±4.54), and lowest in NAFLD (8.33±3.53). Total Appendix scores were highest in the HCV group (43.22±15.30), followed by the HBV group (38.56±12.02) and the NAFLD group (32.73±8.90).

Table 3 presents the assessment tool scores. Subgroup analyses revealed that PCS was lower in cirrhotic HBV and HCV patients than in non-cirrhotic patients. Cirrhotic HBV patients, HCV patients, and treated HCV patients had lower PCS than NAFLD patients. MCS was lower in cirrhotic HCV patients than in HCV patients with virological response; no differences were observed among HBV subgroups. Appendix I scores were higher in cirrhotic HCV patients than in untreated patients or those with a virological response; cirrhotic HBV and HCV patients had lower Appendix I scores than patients with NAFLD. Appendix II scores were higher in cirrhotic than in non-cirrhotic HBV patients; no significant differences were observed among HCV subgroups. Appendix total scores were higher in cirrhotic HBV and HCV patients than in non-cirrhotic counterparts, but lower than in NAFLD patients.

Discussion

QoL includes physical, mental, and social well-being. In modern medicine, which primarily focuses on symptom management, QoL assessments enable patients to communicate their experiences and help healthcare providers understand their needs more effectively. This multidimensional approach is particularly important in the management of chronic diseases, where personalised strategies can improve patient outcomes.

Several studies have compared QoL among patients with chronic HBV, HCV, and NAFLD. Younossi (6) evaluated 160 patients with NAFLD, 56 with HBV, and 65 with HCV using both generic

Table 1. Demographic characteristics of study groups

		HBV (n=299)	HCV (n=92)	NAFLD (n=64)
Gender	Male	171 (57.2%)	41 (44.6%)	24 (37.5%)
	Female	128 (42.8%)	51 (55.4%)	40 (62.5%)
Age, mean ± SD		49.5±12.6	60±11.9	51.8±12.4
BMI		27.3±4.4	27.6±4.6	29.741±4.3
Marital status	Married	249 (83.3%)	63 (68.5%)	53 (82.8%)
	Single	27 (9.0%)	9 (9.8%)	6 (9.4%)
	Widow/divorced	23 (7.7%)	20 (21.7%)	5 (7.8%)
Children	No	42 (14.0%)	13 (14.1%)	10 (15.6%)
	Yes	257 (86.0%)	79 (85.9%)	54 (84.4%)
Number of children		2.2±1.7	2.4±1.7	1.9±1.3
Level of education	None	15 (5.0%)	15 (16.3%)	3 (4.7%)
	Elementary	157 (52.5%)	42 (45.7%)	31 (48.4%)
	High school	68 (22.7%)	19 (20.7%)	15 (23.4%)
	University	59 (19.7%)	16 (17.4%)	15 (23.4%)
Duration of education		8.540±4.449	7.480±4.846	8.770±4.468
Employment status	Unemployed	101 (33.8%)	40 (43.5%)	26 (40.6%)
	Employed	131 (43.8%)	24 (26.1%)	24 (37.5%)
	Retired	67 (22.4%)	28 (30.4%)	14 (21.9%)
Financial difficulties	No	176 (58.9%)	52 (56.5%)	40 (62.5%)
	Yes	123 (41.1%)	40 (43.5%)	24 (37.5%)
Monthly income	<300 euro	68 (22.7%)	34 (37.0%)	17 (26.6%)
	300-800 euro	164 (54.8%)	49 (53.3%)	31 (48.4%)
	800-1600 euro	53 (17.7%)	7 (7.6%)	10 (15.6%)
	>1600 euro	14 (4.7%)	2 (2.2%)	6 (9.4%)

BMI: Body mass index, HBV: Hepatitis B virus, HCV: Hepatitis C virus, NAFLD: Non-alcoholic fatty liver disease, SD: Standard deviation

Table 2. The results of the assessment tools according to disease groups

Test name Mean ± SD		HBV (n=299)				HCV (n=92)				NAFLD (n=64)		
		Median	IQR		Mean ± SD	Median	IQR		Mean ± SD	Median	IQR	
SF-36	Physical component score	47.718±9.083	49.5	42.4	54.8	43.809±9.669	44.45	35.75	51.8	50.906±5.906	51.6	47.7
	Mental component score	46.277±9.002	47	39.7	53.5	42.560±9.662	44.35	34.6	49.75	49.905±6.835	52.05	44.4
LDSI 2.0	Appendix I	27.977±8.808	26	22	32	30.902±11.369	29	23	34	24.406±6.807	22	20
	Appendix II	10.552±4.540	9	6	14	12.315±5.038	11	8	16	8.328±3.528	6	6
	Appendix total	38.562±12.019	35	29	45	43.217±15.301	41	31.25	52	32.734±8.897	30	26

SD: Standard deviation, IQR: Interquartile range, SF-36: Short form-36, LDSI 2.0: Liver disease symptom index 2.0, HBV: Hepatitis B virus, HCV: Hepatitis C virus, NAFLD: Non-alcoholic fatty liver disease

Table 3. Assessment tool scores in study groups

SF-36 PCS*	NAFLD>HBV>HCV
SF-36 MCS*	NAFLD>HBV>HCV
LDSI 2.0 Appendix 1**	NAFLD<HBV<HCV
LDSI 2.0 Appendix 2**	NAFLD<HBV<HCV
LDSI 2.0 Appendix total**	NAFLD<HBV<HCV

*: Higher scores indicate better quality of life, **: Higher scores indicate worse quality of life, SF-36: Short form-36, LDSI 2.0: Liver disease symptom index 2.0, HBV: Hepatitis B virus, HCV: Hepatitis C virus, NAFLD: Non-alcoholic fatty liver disease, PCS: Physical component scores, MCS: Mental component scores

and disease-specific tools, reporting that QoL was worst in patients with NAFLD, followed by those with HCV and HBV. That study included cirrhotic NAFLD patients but excluded HCV patients on interferon (IFN) therapy. In a later study of 3,333 patients with NAFLD, 346 with HCV, and 5,982 healthy controls, the worst scores were observed in the HCV group, followed by the NAFLD group and healthy controls (11). Our findings align more closely with the latter, with HCV patients being most affected, followed by HBV and NAFLD patients.

Recent studies published after 2020 have continued to confirm these trends. In a meta-analysis including over 10,000 HBV patients, Fu et al. (12) reported significantly impaired HRQoL, particularly in the physical component domains, compared with healthy controls. Similarly, Zhang et al. (13) demonstrated that fatigue, sleep disturbance, and social isolation are strong mediators of poor QoL in HBV-related cirrhosis, independent of MELD or alanine aminotransferase levels.

In NAFLD, Golubeva et al. (14) and Hwang and Han (15) found that higher BMI, metabolic comorbidities, and advanced fibrosis were associated with lower SF-36 physical functioning and vitality scores. Importantly, weight reductions exceeding 5% resulted in significant improvements in the physical and mental health subdomains, underscoring the dynamic and reversible nature of QoL impairment in metabolic liver disease (13).

In our study, no significant differences were observed between patients with cirrhosis due to HCV and those with cirrhosis due to HBV, suggesting that cirrhosis has a similar impact on QoL regardless of etiology. PCS values in cirrhotic HCV patients were lower than in most other subgroups, including NAFLD. Treated HCV patients also showed poorer PCS, likely reflecting IFN-related adverse effects during the study period. In regression analyses, drug use and cirrhosis were associated with lower PCS and MCS in HCV, while employment was associated with improved PCS and higher income with improved MCS.

Cirrhotic HBV patients also had lower PCS scores than other HBV subgroups and NAFLD patients. A Canadian study of 433 HBV patients found QoL impairment primarily in those with decompensated cirrhosis or HCV coinfection, with no significant differences between compensated patients and those on antiviral therapy (16). In our study, only cirrhotic HBV patients had worse scores. Treated HBV patients had similar QoL to cirrhotic patients, possibly because daily antiviral use serves as a constant reminder of illness. A Korean study of 7,098 HBV patients and 35,090 controls found that higher socioeconomic status and higher education levels were associated with greater QoL impairment among people with HBV (17).

Consistent with these earlier findings, Ibrahim et al. (18) found that even clinically stable HBV carriers report poorer HRQoL and higher fatigue scores than uninfected individuals, despite having normal liver enzymes and no fibrosis. These data collectively emphasize that the burden of chronic hepatitis extends beyond biochemical or histological markers and significantly impacts psychosocial well-being.

Multivariate analysis in our study showed that female gender negatively affected all QoL domains, while cirrhosis affected all domains except MCS. Education and income were not significant predictors, possibly because only a small proportion (4.7%) of HBV patients had higher monthly incomes (>1,600 EUR), which limited statistical power.

NAFLD patients had the highest QoL scores. A greater number of children were associated with lower PCS and Appendix I scores, whereas longer disease duration was linked to improvements in the LDSI total score. This may reflect both reduced anxiety over time, as disease stability is observed during follow-up visits and a generally low public awareness of NAFLD consequences in Türkiye. Consistent with prior research, higher BMI was associated with worse LDSI total scores.

Study Limitations

This study has certain limitations. First, its cross-sectional design prevents assessment of causality or temporal changes in QoL. Second, the study was conducted at a single tertiary center, which may limit generalizability to broader populations with different socioeconomic or healthcare backgrounds. Additionally, the use of self-reported questionnaires such as SF-36 and LDSI 2.0 introduces potential recall and reporting biases despite physician supervision.

The disease groups also exhibited clinical heterogeneity, including differences in cirrhosis status, treatment exposure, comorbidities, and demographic characteristics, which may have influenced HRQoL outcomes.

Finally, the study did not include a healthy control group, limiting the interpretation of absolute impairment levels compared with the general population.

Conclusion

Overall, both our data and recent literature confirm that chronic HCV has the greatest negative impact on QoL, followed by HBV, while NAFLD patients—particularly those without advanced fibrosis—are relatively less affected. The strong influence of cirrhosis across etiologies emphasizes the need for early diagnosis, effective antiviral or metabolic therapy, and multidimensional care strategies that incorporate patient-reported outcomes to preserve long-term well-being.

Ethics

Ethics Committee Approval: The study received ethical approval from the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (approval no: A-34, date: 03.05.2016).

Informed Consent: Who provided informed consent were enrolled.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.M.O.K., D.E.K., Concept: A.M.O.K., A.S., M.T., İ.H., Design: A.M.O.K., A.S., İ.H., Data Collection or Processing: A.M.O.K., E.S., D.E.K., Analysis or Interpretation: T.E., B.C., S.Ö., Literature Search: A.M.O.K., Writing: A.M.O.K., E.A.K., İ.H.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare no financial support.

References

1. Seto WK, Lo YR, Pawlotsky JM, Yuen MF. Chronic hepatitis B virus infection. Lancet. 2018;392:2313-2324.
2. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA. 1995;273:59-65.
3. Edisan Z, Kadıoğlu FG. Health related quality of life questionnaires: an assessment from ethical point of view. Turkiye Klinikleri J Med. 2011;19:8-15.
4. de Bruin AF, de Witte LP, Stevens F, Diederiks JP. Sickness impact profile: the state of the art of a generic functional status measure. Soc Sci Med. 1992;35:1003-1014.
5. Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. Med Care. 1996;34:702-722.
6. Younossi ZM. Chronic liver disease and health-related quality of life. Gastroenterology. 2001;120:305-307.
7. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-483.
8. Kocyigit H. Kısa form-36 (KF-36)'nın Türkçe versiyonunun güvenilirliği ve geçerliliği. İlaç ve Tedavi Dergisi. 1999;12:102-106.
9. van der Plas SM, Hansen BE, de Boer JB, Stijnen T, Passchier J, de Man RA, Schalm SW. The liver disease symptom index 2.0; validation of a disease-specific questionnaire. Qual Life Res. 2004;13:1469-1481.
10. Eraydın A, Akarsu M, Derviş Hakim G, Keskinoğlu P, Ellidokuz H. The validity and reliability of "the liver disease symptom index 2.0" for Turkish society. Turk J Gastroenterol. 2014;25:531-538.
11. Golabi P, Otgonsuren M, Cable R, Felix S, Koenig A, Sayiner M, Younossi ZM. Non-alcoholic fatty liver disease (NAFLD) is associated with impairment of health related quality of life (HRQOL). Health Qual Life Outcomes. 2016;14:18.
12. Fu MX, Lambert G, Cook A, Ndow G, Haddadin Y, Shimakawa Y, Hallett TB, Harvala H, Sicuri E, Lemoine M, Nayagam S. Quality of life in patients with HBV infection: a systematic review and meta-analysis. JHEP Rep. 2025;7:101312.
13. Zhang Q, Zhong C, Cai S, Yu T, Xu X, Yin J. Risk factors associated with quality of life in patients with hepatitis B virus related cirrhosis. Front Psychol. 2022;12:770415.
14. Golubeva JA, Sheptulina AF, Yafarova AA, Mamutova EM, Kiselev AR, Drapkina OM. Reduced quality of life in patients with non-alcoholic fatty liver disease may be associated with depression and fatigue. Healthcare (Basel). 2022;10:1699.
15. Hwang TI, Han AL. Quality of life in adults with metabolic dysfunction-associated fatty liver disease. Int J Environ Res Public Health. 2021;18:13145.
16. Woo G, Tomlinson G, Yim C, Lilly L, Therapondos G, Wong DK, Ungar WJ, Einarson TR, Sherman M, Heathcote JE, Krahn M. Health state utilities and quality of life in patients with hepatitis B. Can J Gastroenterol. 2012;26:445-451.
17. Kim SJ, Han KT, Lee SY, Park EC. Quality of life correlation with socioeconomic status in Korean hepatitis-B patients: a cross sectional study. Health Qual Life Outcomes. 2015;13:55.
18. Ibrahim Y, Umstead M, Wang S, Cohen C. The impact of living with chronic hepatitis B on quality of life: implications for clinical management. J Patient Exp. 2023;10:23743735231211069.

Liver Disease Symptom Index 2.0 (LDSI-2.0)

Original Questionnaire Format (0-4 Likert Scale)

Scoring scale for all items:

0=Not at all

1=A little

2=Moderate

3=Quite a bit

4=Very much

Instruction

During the past 7 days, how much have you been bothered by the following symptoms? Please circle one number (0-4) for each item.

Appendix 1 - Core Symptoms (18 Items)

Itching (pruritus) [0] [1] [2] [3] [4]

Joint pain [0] [1] [2] [3] [4]

Pain or discomfort in the right upper abdomen [0] [1] [2] [3] [4]

Abdominal swelling [0] [1] [2] [3] [4]

Shortness of breath [0] [1] [2] [3] [4]

Muscle cramps [0] [1] [2] [3] [4]

Difficulty concentrating [0] [1] [2] [3] [4]

Memory problems [0] [1] [2] [3] [4]

Fatigue [0] [1] [2] [3] [4]

Sleepiness during the day [0] [1] [2] [3] [4]

Difficulty sleeping at night [0] [1] [2] [3] [4]

Decreased appetite [0] [1] [2] [3] [4]

Nausea [0] [1] [2] [3] [4]

Feeling depressed [0] [1] [2] [3] [4]

Worry related to liver disease [0] [1] [2] [3] [4]

Fear of complications [0] [1] [2] [3] [4]

Yellowing of the skin or eyes (jaundice) [0] [1] [2] [3] [4]

Decreased sexual interest [0] [1] [2] [3] [4]

Appendix 2 - Additional NLV Items (7 Items)

Fluid retention in the legs [0] [1] [2] [3] [4]

Tendency to bruise easily [0] [1] [2] [3] [4]

Muscle weakness [0] [1] [2] [3] [4]

Difficulty performing daily activities [0] [1] [2] [3] [4]

Emotional instability [0] [1] [2] [3] [4]

Social withdrawal [0] [1] [2] [3] [4]

Reduced tolerance for physical activity [0] [1] [2] [3] [4]

Research Article

DOI: 10.4274/vhd.galenos.2025.2025-9-1
Viral Hepat J 2025;31(3):78-85

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

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

Mustafa Kemal Çelen[1], Çiğdem Mermutluoğlu[1], Yeşim Taşova[2], İsmail Yıldız[3], Yakup Demir[4], Pınar Çakmak[5], Tuba Damar Çakırca[6], Ülkiye Yetim[7], Yaşar Bayındır[8]

[1]*Dicle University Faculty of Medicine, Department of Clinical Microbiology and Infectious Disease, Diyarbakır, Türkiye*
[2]*Çukurova University Faculty of Medicine, Department of Clinical Microbiology and Infectious Disease, Adana, Türkiye*
[3]*Dicle University Faculty of Medicine, Department of Biostatistics, Diyarbakır, Türkiye*
[4]*Memorial Dicle Hospital, Clinic of Clinical Microbiology and Infectious Disease, Diyarbakır, Türkiye*
[5]*Mardin Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Mardin, Türkiye*
[6]*Şanlıurfa Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Şanlıurfa, Türkiye*
[7]*Batman Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Batman, Türkiye*
[8]*Ankara Güven Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Ankara, Türkiye*

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

Address for Correspondence: Çiğdem Mermutluoğlu, Asst. Prof., Dicle University Faculty of Medicine, Department of Clinical Microbiology and Infectious Disease, Diyarbakır, Türkiye
E-mail: cigdemmermut@gmail.com **ORCID ID:** orcid.org/0000-0003-1836-6281

Received: 02.09.2025 **Accepted:** 24.11.2025 **Epub:** 23.12.2025 **Publication Date:** 26.01.2026

Cite this article as: Çelen MK, Mermutluoğlu Ç, Taşova Y, Yıldız İ, Demir Y, Çakmak P, Damar Çakırca T, Yetim Ü, Bayındır Y. Find HDV and determine its status in Türkiye "SITU(HD)VATION TÜRKİYE". Viral Hepat J. 2025;31(3):78-85

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.

Financial Disclosure: This work was supported by Gilead Sciences (grant number: IN-TR-980-7061).

References

1. Pinter M, Trauner M, Peck-Radosavljevic M, Sieghart W. Cancer and liver cirrhosis: implications on prognosis and management. ESMO Open. 2016;1:e000042.
2. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol. 2006;45:529-538.
3. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, Zelber-Sagi S, Wai-Sun Wong V, Dufour JF, Schattenberg JM, Kawaguchi T, Arrese M, Valenti L, Shiha G, Tiribelli C, Yki-Järvinen H, Fan JG, Grønbæk H, Yilmaz Y, Cortez-Pinto H, Oliveira CP, Bedossa P, Adams LA, Zheng MH, Fouad Y, Chan WK, Mendez-Sanchez N, Ahn SH, Castera L, Bugianesi E, Ratziu V, George J. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol. 2020;73:202-209.
4. Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology. 2020;158:1999-2014.e1.
5. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024;81:492-542.
6. Dhar D, Baglieri J, Kisseleva T, Brenner DA. Mechanisms of liver fibrosis and its role in liver cancer. Exp Biol Med (Maywood). 2020;245:96-108.
7. Xiang Z, Li Y, Zhu C, Hong T, He X, Zhu H, Jiang D. Gastrointestinal cancers and liver cirrhosis: implications on treatments and prognosis. Front Oncol. 2021;11:766069.
8. Cheng Z, Lin P, Cheng N. HBV/HIV coinfection: impact on the development and clinical treatment of liver diseases. Front Med (Lausanne). 2021;8:713981.

9. Hajiabdolbaghi M, Abdiliae Z, Bayani J, Qaempanah M, Ghiasvand F. Characteristics of hepatitis B and D co-infection: a descriptive study. Hepatitis Monthly. 2021;21.
10. Romeo R, Foglieni B, Casazza G, Spreafico M, Colombo M, Prati D. High serum levels of HDV RNA are predictors of cirrhosis and liver cancer in patients with chronic hepatitis delta. PLoS One. 2014;9:e92062.
11. Vali B, Yue FY, Jones RB, Sheth PM, Kaul R, Betts MR, Wong D, Kovacs C, Loutfy M, Common A, Halpenny R, Ostrowski MA. HIV-specific T-cells accumulate in the liver in HCV/HIV co-infection. PLoS One. 2008;3:e3454.
12. Bockmann JH, Grube M, Hamed V, von Felden J, Landahl J, Wehmeyer M, Giersch K, Hall MT, Murray JM, Dandri M, Lüth S, Lohse AW, Lütgehetmann M, Schulze Zur Wiesch J. High rates of cirrhosis and severe clinical events in patients with HBV/HDV co-infection: longitudinal analysis of a German cohort. BMC Gastroenterol. 2020;20:24.
13. Sagnelli C, Sagnelli E, Russo A, Pisaturo M, Occhiello L, Coppola N. HBV/HDV co-infection: epidemiological and clinical changes, recent knowledge and future challenges. Life (Basel). 2021;11:169.
14. Wranke A, Heidrich B, Deterding K, Hupa-Breier KL, Kirschner J, Bremer B, Cornberg M, Wedemeyer H. Clinical long-term outcome of hepatitis D compared to hepatitis B monoinfection. Hepatol Int. 2023;17:1359-1367.
15. Thio CL. Hepatitis B and human immunodeficiency virus coinfection. Hepatology. 2009;49(5 Suppl):S138-S145.
16. Rivera MM, Soza A, Jazwinski A, Mi L, Kleiner DE, Zhao X, Zuber C, Brust D, Hsu E, Simpson J, Hoofnagle JH, Heller T. HIV through the looking glass: insights derived from hepatitis B. J Acquir Immune Defic Syndr. 2015;68:123-127.
17. Calle Serrano B, Manns MP, Wedemeyer H. Hepatitis delta and HIV infection. Semin Liver Dis. 2012;32:120-129.
18. Saravanan S, Madhavan V, Velu V, Murugavel KG, Waldrop G, Solomon SS, Balakrishnan P, Kumarasamy N, Smith DM, Mayer KH, Solomon S, Thyagarajan SP. High prevalence of hepatitis delta virus among patients with chronic hepatitis B virus infection and HIV-1 in an intermediate hepatitis B virus endemic region. J Int Assoc Provid AIDS Care. 2014;13:85-90.
19. World Health Organization. Hepatitis B. Geneva: World Health Organization; 2025. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
20. Demirel A, Uraz S, Deniz Z, Daglilar E, Basar O, Tahan V, Ozaras R. Epidemiology of hepatitis D virus infection in Europe: is it vanishing? J Viral Hepat. 2024;31:120-128.
21. Ton JT, Passos-Silva AM, Ton ET, de Castro Silva E, Santos AO, Araújo A, Vieira D, Salcedo JMV, Vasconcelos MPA. Clinical evaluation of the progression of liver disease in patients coinfected with HBV and HDV in the western Amazon region of Brazil. Int J Hepatol. 2025;2025:2054487.
22. Gish RG, Yi DH, Kane S, Clark M, Mangahas M, Baqai S, Winters MA, Proudfoot J, Glenn JS. Coinfection with hepatitis B and D: epidemiology, prevalence and disease in patients in Northern California. J Gastroenterol Hepatol. 2013;28:1521-1525.
23. Da BL, Rahman F, Lai WC, Kleiner DE, Heller T, Koh C. Risk factors for delta hepatitis in a north American cohort: who should be screened? Am J Gastroenterol. 2021;116:206-209.
24. Ho E, Deltenre P, Nkuize M, Delwaide J, Colle I, Michielsen P; Belgian Association for the Study of the Liver. Coinfection of hepatitis B and hepatitis delta virus in Belgium: a multicenter BASL study. Prospective epidemiology and comparison with HBV mono-infection. J Med Virol. 2013;85:1513-1517.
25. Genné D, Rossi I. Hepatitis delta in Switzerland: a silent epidemic. Swiss Med Wkly. 2011;141:w13176.
26. Heidrich B, Deterding K, Tillmann HL, Raupach R, Manns MP, Wedemeyer H. Virological and clinical characteristics of delta hepatitis in central Europe. J Viral Hepat. 2009;16:883-894.
27. Vlachogiannakos J, Papatheodoridis GV. New epidemiology of hepatitis delta. Liver Int. 2020;40(Suppl 1):48-53.
28. Kellerman SE, Hanson DL, McNaghten AD, Fleming PL. Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus-infected subjects. J Infect Dis. 2003;188:571-577.
29. Konopnicki D, Mocroft A, de Wit S, Antunes F, Ledergerber B, Katlama C, Zilmer K, Vella S, Kirk O, Lundgren JD; EuroSIDA Group. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. AIDS. 2005;19:593-601.
30. Lee HC, Ko NY, Lee NY, Chang CM, Ko WC. Seroprevalence of viral hepatitis and sexually transmitted disease among adults with recently diagnosed HIV infection in Southern Taiwan, 2000-2005: upsurge in hepatitis C virus infections among injection drug users. J Formos Med Assoc. 2008;107:404-411.
31. Diop-Ndiaye H, Touré-Kane C, Etard JF, Lô G, Diaw P, Ngom-Gueye NF, Gueye PM, Ba-Fall K, Ndiaye I, Sow PS, Delaporte E, Mboup S. Hepatitis B, C seroprevalence and delta viruses in HIV-1 Senegalese patients at HAART initiation (retrospective study). J Med Virol. 2008;80:1332-1336.
32. Nyirenda M, Beadsworth MB, Stephany P, Hart CA, Hart IJ, Munthali C, Beeching NJ, Zijlstra EE. Prevalence of infection with hepatitis B and C virus and coinfection with HIV in medical inpatients in Malawi. J Infect. 2008;57:72-77.
33. World Health Organization. Management of hepatitis B and HIV coinfection: clinical protocol for the WHO European Region [Internet]. Copenhagen: WHO Regional Office for Europe; 2011 [cited 2025 Aug 1]. Available from: http://www.euro.who.int/__data/assets/pdf_file/0011/152012/e95792.pdf
34. Alberti A, Clumeck N, Collins S, Gerlich W, Lundgren J, Palù G, Reiss P, Thiebaut R, Weiland O, Yazdanpanah Y, Zeuzem S; ECC Jury. Short statement of the first European consensus conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. J Hepatol. 2005;42:615-624. Erratum in: J Hepatol. 2005;43:1098.
35. Motamedifar M PhD, Taheri M MSc, Lankarani KB Md, Gholami M Bc, Lari MA Md, Faramarzi H Md, Sarvari J PhD. The prevalence and risk factors of hepatitis delta virus in HIV/HBV co-infected patients in Shiraz, Iran, 2012. Iran J Med Sci. 2015;40:448-453.
36. Coffie PA, Tchounga BK, Bado G, Kabran M, Minta DK, Wandeler G, Gottlieb GS, Dabis F, Eholie SP, Ekouevi DK. Prevalence of hepatitis B and delta according to HIV-type: a multi-country cross-sectional survey in West Africa. BMC Infect Dis. 2017;17:466.
37. Salpini R, Fokam J, Ceccarelli L, Santoro MM, Nanfack A, Sosso SM, Kowo M, Cento V, Torimiro J, Sarmati L, Andreoni M, Colizzi V, Perno CF, Njoya O. High burden of HBV-infection and atypical HBV strains among HIV-infected Cameroonians. Curr HIV Res. 2016;14:165-171.
38. Chambal LM, Gudo ES, Carimo A, Corte Real R, Mabunda N, Maueia C, Vubil A, Zicai AF, Bhatt N, Antunes F. HBV infection in untreated HIV-infected adults in Maputo, Mozambique. PLoS One. 2017;12:e0181836. Erratum in: PLoS One. 2017;12:e0190460.
39. Sheng WH, Hung CC, Kao JH, Chang SY, Chen MY, Hsieh SM, Chen PJ, Chang SC. Impact of hepatitis D virus infection on the long-term outcomes of patients with hepatitis B virus and HIV coinfection in the era of highly active antiretroviral therapy: a matched cohort study. Clin Infect Dis. 2007;44:988-995.
40. Braga WS, da Costa Castilho M, dos Santos IC, Moura MA, Segurado AC. Low prevalence of hepatitis B virus, hepatitis D virus and hepatitis C virus among patients with human immunodeficiency virus or acquired immunodeficiency syndrome in the Brazilian Amazon basin. Rev Soc Bras Med Trop. 2006;39:519-522.
41. Soriano V, Vispo E, Labarga P, Medrano J, Barreiro P. Viral hepatitis and HIV co-infection. Antiviral Res. 2010;85:303-315.
42. Mendes-Correa MC, Gomes-Gouvêa MS, Alvarado-Mora MV, Da Silva MH, Lázari C, Cavalcanti NC, Alonso FK, Carpinelli CC, Uip DE, Pinho JR. Hepatitis delta in HIV/HBV co-infected patients in Brazil: is it important? Int J Infect Dis. 2011;15:e828-e832.

43. Glynn M, Cohen C, Gish RG, Andrews R, Trang A, Zovich B, Hall W, Clary R, Balestreri J, Scott L, Scott R, Jackson T, Ntiri-Reid B, Southworth A, Dieterich D, Sepe T. Advancing research, awareness, screening, and linkage to care to eliminate HDV in the U.S. Hepatol Commun. 2023;7:e00168.
44. Lucifora J, Alfaiate D, Pons C, Michelet M, Ramirez R, Fusil F, Amirache F, Rossi A, Legrand AF, Charles E, Vegna S, Farhat R, Rivoire M, Passot G, Gadot N, Testoni B, Bach C, Baumert TF, Hyrina A, Beran RK, Zoulim F, Boonstra A, Büning H, Verrier ER, Cosset FL, Fletcher SP, Salvetti A, Durantel D. Hepatitis D virus interferes with hepatitis B virus RNA production via interferon-dependent and -independent mechanisms. J Hepatol. 2023;78:958-970.
45. Bach C, Lucifora J, Delphin M, Heydmann L, Heuschkel MJ, Pons C, Goto K, Scheers E, Schuster C, Durantel D, Pauwels F, Baumert TF, Verrier ER. A stable hepatitis D virus-producing cell line for host target and drug discovery. Antiviral Res. 2023;209:105477.
46. Alfaiate D, Dény P, Durantel D. Hepatitis delta virus: from biological and medical aspects to current and investigational therapeutic options. Antiviral Res. 2015;122:112-129.
47. Lago BV, Mello FCA, Barros TM, Mello VM, Villar LM, Lewis-Ximenez LL, Pardini MIMC, Lampe E; Brazilian Hepatitis B Research Group. Hepatitis D infection in Brazil: prevalence and geographical distribution of anti-delta antibody. J Med Virol. 2018;90:1358-1363.
48. Aberra H, Gordien E, Desalegn H, Berhe N, Medhin G, Mekasha B, Gundersen SG, Gerber A, Stene-Johansen K, Øverbø J, Johannessen A. Hepatitis delta virus infection in a large cohort of chronic hepatitis B patients in Ethiopia. Liver Int. 2018;38:1000-1009.
49. Soriano V, Grint D, d'Arminio Monforte A, Horban A, Leen C, Poveda E, Antunes F, de Wit S, Lundgren J, Rockstroh J, Peters L. Hepatitis delta in HIV-infected individuals in Europe. AIDS. 2011;25:1987-1992.
50. Kalopitas G, Arvanitakis K, Tsachouridou O, Malandris K, Koufakis T, Metallidis S, Germanidis G. Metabolic dysfunction-associated steatotic liver disease in people living with HIV-limitations on antiretroviral therapy selection. Life (Basel). 2024;14:742.

Research Article

DOI: 10.4274/vhd.galenos.2025.2025-7-1
Viral Hepat J 2025;31(3):86-90

Evaluation of Hepatitis A Seroprevalence in Patients Admitted to a University Hospital

Bir Üniversite Hastanesine Başvuran Hastalarda Hepatit A Seroprevalansının Değerlendirilmesi

Yunus Emre İbik, Hacer Özlem Kalaycı, Mustafa Kerem Çalgın

Ordu University Faculty of Medicine, Department of Medical Microbiology, Ordu, Türkiye

ABSTRACT

Objectives: Hepatitis A virus (HAV) is a ribonucleic acid virus that usually causes acute self-limiting liver disease and is transmitted via the fecal-oral route. The prevalence of HAV is an indicator of socioeconomic level and closely related to geographical differences and hygiene.

Materials and Methods: This study aimed to investigate the seropositivity of anti-HAV immunoglobulin G (IgG) and anti-HAV IgM in patients of different age groups admitted to our hospital. A total of 3,110 cases were analyzed using the electrochemiluminescence immunoassay method and patients were divided into four age groups: 0-12 years, 13-17 years, 18-35 years, and over 35 years old. The chi-square test was used to evaluate the anti-HAV IgG serological variable about the independent variables such as age and gender.

Results: There was no significant difference between genders. However, a statistically significant difference was observed between the 0-12 and 13-17 age groups, as well as between the 18-35 and >35 age groups. Anti-HAV IgM reactivity was detected only in a 43-year-old female. HAV seropositivity between 13 and 35 years of age is significantly lower, suggesting that the vaccine should also be administered to young adults.

Conclusion: Seroprevalence data is crucial for outbreak prevention, guiding public health measures such as sanitation and hygiene, and particularly for planning vaccination programs.

Keywords: Hepatitis A, seroprevalence, anti-HAV IgM, anti-HAV IgG, vaccination

ÖZ

Amaç: Hepatit A virüsü (HAV), genellikle kendi kendini sınırlayan akut karaciğer hastalığına neden olan ve fekal-oral yolla bulaşan bir ribonükleik asit virüsüdür. HAV prevalansı sosyoekonomik düzeyin bir göstergesidir ve coğrafi farklılıklar ve hijyen ile yakından ilişkilidir.

Gereç ve Yöntemler: Bu çalışmada hastanemize başvuran farklı yaş gruplarındaki hastalarda anti-HAV immünoglobulin G (IgG) ve anti-HAV IgM seropozitifliğinin araştırılması amaçlanmıştır. Toplam 3.110 olgu elektrokemolüminesans immünoassay yöntemi kullanılarak analiz edilmiş ve hastalar dört yaş grubuna ayrılmıştır: 0-12 yaş, 13-17 yaş, 18-35 yaş ve 35 yaş üstü. Anti-HAV IgG serolojik değişkenini yaş ve cinsiyet gibi bağımsız değişkenler açısından değerlendirmek için ki-kare testi kullanılmıştır.

Bulgular: Cinsiyetler arasında anlamlı bir fark bulunmamıştır. Ancak, 0-12 ve 13-17 yaş grupları ile 18-35 ve >35 yaş grupları arasında istatistiksel olarak anlamlı bir fark gözlenmiştir. Anti-HAV IgM reaktivitesi sadece 43 yaşında bir kadında tespit edilmiştir. HAV seropozitifliğinin 13 ve 35 yaş arasında önemli ölçüde düşük olması, aşının genç yetişkinlere de uygulanması gerektiğini düşündürmektedir.

Sonuç: Seroprevalansın değerlendirilmesi, salgınların önlenmesi, sanitasyon ve hijyen önlemleri gibi koruyucu politikaların oluşturulması ve özellikle etkili aşılama programlarının oluşturulması için gereklidir.

Anahtar Kelimeler: Hepatit A, seroprevalans, anti-HAV IgM, anti-HAV IgG, aşı

Address for Correspondence: Yunus Emre İbik, Asst. Prof., Ordu University Faculty of Medicine, Department of Medical Microbiology, Ordu, Türkiye
E-mail: yeibik28@gmail.com **ORCID ID:** orcid.org/0000-0002-6298-6181

Received: 18.07.2025 **Accepted:** 17.12.2025 **Epub:** 06.01.2026 **Publication Date:** 26.01.2026

Cite this article as: İbik YE, Kalaycı HÖ, Çalgın MK. Evaluation of hepatitis A seroprevalence in patients admitted to a university hospital. Viral Hepat J. 2025;31(3):86-90

Introduction

Hepatitis A virus (HAV) is a 27-32 nanometer diameter non-enveloped ribonucleic acid virus and a member of the genus *Hepatovirus* of the *Picornaviridae* family (1). It is considered highly contagious due to its resistance to disinfectants and heat (2). HAV infection is an acute, self-limiting liver disease that has been known for centuries, causing jaundice epidemics and is usually transmitted by oral ingestion of contaminated water and food. The clinical picture shows a wide spectrum ranging from asymptomatic infection to fulminant hepatitis with high mortality (3). The incubation period of the disease is 15-50 days with an average of 30 days. The severity of the disease is age-related, jaundice is usually not seen in children and most infections are mild or asymptomatic. In adulthood, the disease can lead to severe clinical pictures. Since there is only one serotype of HAV, the infection leads to lifelong immunity and the immunoglobulin G (IgG) antibodies formed remain for a lifetime. Detection of anti-HAV IgG is the standard method for seroprevalence studies (4,5,6). Although the incidence of HAV infection varies based on socio-economic status and regions, it is common all over the world. It has been reported that anti-HAV IgG seropositivity is decreasing significantly and the cases are shifting towards older ages as socio-economic conditions improve (7).

In a meta-analysis conducted in our country, data from 63 studies were evaluated, it was shown that the average seroprevalence was 53% and the importance of age-specific prevalence studies was emphasized (8). The study aimed to investigate the seropositivity of anti-HAV IgG and anti-HAV IgM in patients of different age groups admitted to our hospital.

Materials and Methods

Between May 2021 and May 2024, patients who were admitted to Ordu University Training and Research Hospital were retrospectively included in this study. The anti-HAV IgM and IgG parameters of the 3,110 cases were analyzed using the electrochemiluminescence immunoassay method on the Cobas e601 (Roche, Germany) device. Patients were divided into four age groups: 0-12 years, 13-17 years, 18-35 years, and over 35 years old. The seropositivity of HAV in each group was determined.

Statistical Analysis

Statistical evaluation was performed with SPSS 22.0. The chi-square test was used to evaluate anti-HAV IgG serological variables according to independent variables such as age and gender and p-value <0.05 was considered significant. This study was carried out in compliance with the Declaration of Helsinki with the approval of Ordu University Non-Interventional Scientific Research Ethics Committee dated October 11, 2024 and numbered 2024/142.

Results

Among the 3,110 cases included in the study, 1,848 (59.4%) were female and 1,262 (40.6%) were male. Anti-HAV IgG reactivity was detected in 60.9% of the female and 60.2% of the male cases, with no statistically significant difference between genders (p=0.691). The anti-HAV IgG reactivity results by age distribution are shown in Table 1.

When examining the age distribution of the cases, anti-HAV IgG seropositivity was significantly higher in the 0–12 age group (72.4%) compared to the 13-17 age group (10.8%) (p<0.001). Similarly, seropositivity significantly increased to 88.6% in the >35 age group compared to 46.7% in the 18-35 age group (p<0.001).

Anti-HAV IgM reactivity was detected in only one case, a 43-year-old female patient admitted to the physical therapy and rehabilitation outpatient clinic.

Discussion

HAV is the leading cause of viral hepatitis in children. It has shifted to affecting older age group as a result of improved hygiene and sanitation conditions (9,10). The infection is usually self-limiting, asymptomatic, non-chronic and rarely fulminant when acquired at an early age. The prevalence of HAV infection depends on many factors such as age, socioeconomic level, hygiene and sanitation conditions. It varies between countries and even among regions within the same country. To take preventive measures against the infection and determine vaccination policies, it is important to assess the prevalence of HAV infection in the community (11). This study was conducted to determine HAV seroprevalence rates in our region and to emphasize the need for preventive measures.

HAV has a low mortality rate but it is recognised as a public health problem that needs to be addressed as it causes outbreaks leading to workforce loss (12). The prevalence of HAV infection shows three endemicity patterns: high, intermediate and low (13). While certain developed countries exhibit low levels of endemicity, regions including the Middle East and Southern Europe are classified as areas of intermediate endemicity (14). Türkiye is categorised as

Table 1: Anti-HAV IgG reactivity by age groups

	Anti-HAV IgG		Total	p-value
Age groups	Reactive (%)	Non-reactive (%)		
0-12	42 (72.4%)	16 (27.6%)	58	p<0.001
13-17	14 (10.8%)	116 (89.2%)	130	
18-35	848 (46.7%)	966 (53.3%)	1,814	p<0.001
>35	982 (88.6%)	126 (11.4%)	1,108	
Total	1,886 (60.6%)	1,224 (39.4%)	3,110	

P-values indicate the difference between 0-12 and 13-17 years; 18-35 and >35 years age groups
HAV: Hepatitis A virus, IgG: Immunoglobulin G

intermediately endemic in terms of HAV seroprevalence (15). The prevalence of HAV infection is decreasing in developing countries of the world. The general serological prevalence of HAV was determined as 38.3% in a study conducted in Jordan in 2021 and 25.1% in a study conducted in Kuwait in 2023 (16,17).

Different HAV seroprevalence rates have been reported in various studies conducted in Türkiye: 67.2% in İstanbul in 2024, 88.25% in Gaziantep in 2024, 73.89% in Uşak in 2021, 48.6% in Van in 2021, 87.3% in Erzurum in 2020, 57% in Karabük in 2020, 79.1% in Yozgat in 2019, 74% in İzmir in 2019, 58.9% in Samsun in 2019, 97.4% in Bingöl in 2018 (15,18,19,20,21,22,23,24,25,26,27). Different socio-economic conditions are thought to be the primary determinant for the regional differences in HAV seroprevalence in Türkiye. In our study, the anti-HAV seroprevalence was found to be 60.6%, which is below the average HAV seroprevalence in our country, but similar to that of Samsun and Karabük cities in our region (21,23).

While the impact of gender on HAV seroprevalence has been widely studied, our findings indicate no significant difference between genders in HAV seroprevalence. In studies conducted by Vilibic-Cavlek et al. (28) in Croatia, and Ayouni et al. (29) in Tunisia, no significant difference in HAV seropositivity was reported in terms of gender. In a study conducted in Lisbon, Cortes-Martins et al. (30) reported that HAV IgG seroprevalence rates of 44.4% among women and 53.6% among men with no statistically significant difference detected. In a study conducted in İstanbul, HAV seroprevalence was significantly higher in men with 70.69% (15). A study by Alkan Ceviker et al. (21) showed HAV seropositivity was found to be 75.3% in women and 33.1% in men. In Yilmaz's (26) study, it was noted that a significantly higher HAV IgG seropositivity in men. Kalaycı and Çalgın (27) determined anti-HAV IgG positivity as 54.7% in women and 56.6% in men in their study with healthcare workers and found no statistically significant difference. In the study by Tuna et al. (25), in patients applying to primary health care institutions, no significant relationship was found between anti-HAV IgG seropositivity and gender.

In alignment with World Health Organization recommendations, the HAV vaccine was included in Türkiye's national childhood vaccination schedule in 2012, with a two-dose regimen at 18 and 24 months of age. Our study compared anti-HAV IgG seropositivity rates across age groups. The prevalence of anti-HAV IgG was 72.4% in the 0-12 age group, 10.8% in the 13-17 age group and 46.7% in the 18-35 age group. The vaccination program appears to be a major factor in these results. Similar results showing the effect of the vaccination programme were found in other studies conducted in our country (15,19,22). We think that the low immunity in adolescents and young adults is a result of these age groups not yet being routinely vaccinated against HAV in our country. In our study, seroprevalence was 88.6% after 35 years of age. A 2022 study in Somalia showed the lowest seroprevalence (29.4%) in the 1-2 age group, with the highest (88.9%) observed in individuals over 41 years old (31). Similarly, Ciftci et al. (32) observed an increase in HAV IgG seropositivity in the 0-5 age group between 2015 and 2023.

According to a study conducted in 2023, anti-HAV IgG positivity was found to be 16.8% in children aged 13-17 years (33). In the study conducted by Yiş and Değirmenci (34) in unvaccinated children, seropositivity rates were found to be 19.25% in the 0-6 age group and 41.52% in the 7-15 age group. In 2019, in a study conducted by Alkan Ceviker et al. (21) in Samsun, it was reported that the seroprevalence of anti-HAV IgG was 40.9% and 34.4% under the age of 18 and under the age of 30, respectively. In another study conducted in 2014 evaluating HAV seroprevalence, the anti-HAV IgG positivity rate was reported as 66.4% in the 13-18 age group (35). In our study, the reason for the low anti-HAV IgG seropositivity in the 13-18 age group may be that the incidence of infection has decreased in recent years due to increased public awareness about viral hepatitis, better knowledge of the transmission routes of the disease and breaking the chain of infection. The ongoing childhood HAV vaccination program since 2012 has been quite effective in breaking the chain of infection in society. However, the high proportion of children in the 13-17 age group who have not been exposed to HAV highlights the need for vaccination in this age group as well.

Evidence from various studies indicates a shift of HAV infection affecting older age groups, which is associated with more severe clinical manifestations and increased mortality (14,36). Acikgoz et al. (37) showed that anti-HAV IgG seropositivity was 34.9% in first-year health students in their study and recommended vaccination for acute HAV infection in the patient group between the ages of 18-37. Similar to our study, Düzenli et al. (38) also found high vaccine-associated anti-HAV IgG positivity in children under ten and high HAV susceptibility in adults over thirty. In parallel, Akman et al. (39) reported that vaccine-associated anti-HAV IgG seronegativity shifted to adolescents. Kalaycı and Çalgın (27) found the anti-HAV IgG positivity rate to be 35.8% in the 16-25 age group among healthcare workers. The data of our study are consistent with the literature and show that the age of exposure to the virus has shifted towards young adulthood.

Although HAV seroprevalence in Türkiye is decreasing, it remains a significant public health issue. The anti-HAV IgM rate in our study was 0.03%, much lower than the national prevalence, reported between 0.18% and 1.2% in recent studies (18,38,40). Due to the higher incidence of complications due to acute HAV in older age groups, it has become necessary to vaccinate especially seronegative adults (21). Our findings also suggest that seronegative adults should be included in vaccination programs. In a study conducted in Beijing, it was highlighted that adults would be susceptible to HAV due to attenuation of antibodies resulting from vaccination, which would lead to a possible HAV epidemic. Future studies are essential to establish the need for booster immunization (41).

Study Limitations

This study is subject to several limitations. The study did not achieve a sufficient sample size and data were obtained from a single-center. To contribute to the epidemiological data of our country, the study should be supported by a multicenter study.

Conclusion

The results of this study can serve as a guide for HAV seroprevalence in the Central Black Sea region. Routine HAV

vaccination programs implemented since 2012 have significantly increased seropositivity among children aged 0-12. In addition, HAV seropositivity between 13 and 35 years of age is significantly lower, indicating that HAV vaccine should also be considered for young adults. Seroprevalence data is crucial for outbreak prevention, guiding public health measures such as sanitation and hygiene, and particularly for planning vaccination programs.

Ethics

Ethics Committee Approval: This study was carried out in compliance with the Declaration of Helsinki with the approval of Ordu University Non-Interventional Scientific Research Ethics Committee dated October 11, 2024. and numbered 2024/142.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.İ., H.Ö.K., Concept: Y.İ., M.K.Ç., Design: Y.İ., H.Ö.K., Data Collection or Processing: Y.İ., H.Ö.K., Analysis or Interpretation: Y.İ., H.Ö.K., M.K.Ç., Literature Search: Y.İ., H.Ö.K., Writing: Y.İ., H.Ö.K., M.K.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare no financial support.

References

1. Hokinson D, Sanjaya A, Jo J. Severe acute hepatitis of unknown etiology in Indonesia: what has been learned? Explor Res Hypothesis Med. 2023;8:257-268.
2. Di Cola G, Fantilli AC, Pisano MB, Ré VE. Foodborne transmission of hepatitis A and hepatitis E viruses: a literature review. Int J Food Microbiol. 2021;338:108986.
3. Webb GW, Kelly S, Dalton HR. Hepatitis A and hepatitis E: clinical and epidemiological features, diagnosis, treatment, and prevention. Clin Microbiol Newsl. 2020;42:171-179.
4. Agrawal A, Singh S, Kolhapure S, Hoet B, Arankalle V, Mitra M. Increasing burden of hepatitis A in adolescents and adults and the need for long-term protection: a review from the Indian subcontinent. Infect Dis Ther. 2019;8:483-497.
5. Gholizadeh O, Akbarzadeh S, Ghazanfari Hashemi M, Gholami M, Amini P, Yekanipour Z, Tabatabaie R, Yasamineh S, Hosseini P, Poortahmasebi V. Hepatitis A: viral structure, classification, life cycle, clinical symptoms, diagnosis error, and vaccination. Can J Infect Dis Med Microbiol. 2023;2023:4263309.
6. Herzog C, Van Herck K, Van Damme P. Hepatitis A vaccination and its immunological and epidemiological long-term effects: a review of the evidence. Hum Vaccin Immunother. 2021;17:1496-1519.
7. Sa-nguanmoo P, Posuwan N, Vichaiwattana P, Vuthitanachot V, Saelao S, Foonoi M, Fakthongyoo A, Makaroon J, Srisingh K, Asawarachun D, Owatanapanich S, Wutthiratkowit N, Tohtubtiang K, Vongpunsawad S, Yoocharoen P, Poovorawan Y. Declining trend of hepatitis A seroepidemiology in association with improved public health and economic status of Thailand. PLoS One. 2016;11:e0151304.
8. Karakaya Suzan Ö, Bektaş M, Altındiş M, Kaya Ö, Eroğlu A, Çetinkaya Özdemir S, Tecik S, Emecen AN, Çınar N. Examining the changes in the prevalence of hepatitis A in Türkiye: systematic review and metaanalysis. BMC Public Health. 2024;24:3280.
9. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine. 2010;28:6653-6657.
10. Melhem NM, Jaffa M, Zaatari M, Awada H, Salibi NE, Ramia S. The changing pattern of hepatitis A in Lebanese adults. Int J Infect Dis. 2015;30:87-90.
11. Kurkela S, Pebody R, Kafatos G, Andrews N, Barbara C, Bruzzone B, Butur D, Caplinskas S, Davidkin I, Hatzakis A, Hellenbrand W, Hesketh LM, Nardone A, Nemecek V, Pistol A, Sobotová Z, Vranckx R, Anastassopoulou CG. Comparative hepatitis A seroepidemiology in 10 European countries. Epidemiol Infect. 2012;140:2172-2181.
12. Snyder MR, McGinty MD, Shearer MP, Meyer D, Hurtado C, Nuzzo JB. Outbreaks of hepatitis A in US Communities, 2017-2018: firsthand experiences and operational lessons from public health responses. Am J Public Health. 2019;109:S297-S302.
13. Aggarwal R, Goel A. Hepatitis A: epidemiology in resource-poor countries. Curr Opin Infect Dis. 2015;28:488-496.
14. Ariyarathna N, Abeysena C. Sero-prevalence of viral hepatitis A in a district of Sri Lanka: a community based cross-sectional study. BMC Infect Dis. 2019;19:443.
15. Karabey M, Alacam S, Karabulut N, Uysal H, Gunduz A, Aydina OA. Hepatitis A virus infection and seroprevalence, Istanbul, Turkey, 2020-2023. Ann Saudi Med. 2024;44:386-393.
16. Ismail M, Naseem M, Khan B, Baloch MC. Study on the prevalence, risk factors and clinical aspects of hepatitis A and B in different ethnic groups of Quetta district. Pak-Euro Journal of Medical and Life Sciences. 2023;6:31-38.
17. Kareem N, Al-Salahat K, Bakri FG, Rayyan Y, Mahafzah A, Sallam M. Tracking the epidemiologic shifts in hepatitis A sero-prevalence using age stratification: a cross-sectional study at Jordan University Hospital. Pathogens. 2021;10:1081.
18. Aslan S, Şahin A, Doğantekin E, Doğantekin A, Gürbüz H. Hepatitis A seroprevalence and endemic change in Gaziantep province. J Harran Univ Med Fac. 2024;21:113-117.
19. Calik S, Tosun S, Ari A, Coskuner SA, Bayik H, Aygun O, Demir S, Hassoy H. Hepatitis A seroprevalence in different age groups in a region with low and moderate socioeconomic level in Izmir province: results of a fieldwork. KLIMIK J. 2019;32:310-315.
20. Bilger Çavuş, M, Alagöz M, Gürkan Y. Evaluation of hepatitis A and isolated anti-HBc IgG prevalences in a city of Eastern Anatolia. Arch Clin Biomed Res. 2018;2:85-92.
21. Alkan Ceviker S, Gunal O, Kilic SS, Koksal E, Tahmaz A. Seroprevalence of hepatitis A virus among different age groups in the province of Samsun. BAUN Health Sci J. 2019;8:81-86.
22. Güngör SE. Status of viral hepatitis in Uşak province, Turkey: a 9-year retrospective analysis. Acta Med Mediterranea. 2021;37:2089-2095.
23. İnci H, Aşgın N, İnci F, Adahan D. Viral hepatitis seroprevalence by age groups among individuals admitted to a university hospital family medicine outpatient clinic. Konuralp Med J. 2020;12:34-38.
24. Kader Ç, Göçmen AY, Demir MI, Çolak NY, Gök SE, Arkan FI, Sara MY, Erbay A. Hepatitis A immunity in Yozgat, Turkey. Ann Saudi Med. 2019;39:37-41.
25. Tuna DK, Dicle Y, Aydın E. Two-year hepatitis and HIV seroprevalence in samples of patients admitted to primary health care centers. Van Med J. 2021;28:404-411.
26. Yilmaz A. Hepatitis A seroprevalence in Erzurum, Turkey. Ann Agric Environ Med. 2020;27:481-484.
27. Kalaycı HÖ, Çalgın MK. Investigation of hepatitis A, hepatitis B, hepatitis C and human immunodeficiency virus seroprevalence in healthcare workers in a training and research hospital. Sağlık Bil Değer. 2025;15:15-19.
28. Vilibic-Cavlek T, Kucinar J, Ljubin-Sternak S, Kolaric B. Seroepidemiology of hepatitis A in the croatian population. Hepat Mon. 2011;11:997-999.
29. Ayouni K, Kharroubi G, Mallekh R, Hammami W, Marouani R, Mhamdi M, Ben Salah A, Triki H, Bettaieb J. Seroprevalence of hepatitis A virus infection in Central-West of Tunisia. J Med Virol. 2021;93:3666-3671.

30. Cortes-Martins H, Matos R, Moura S, Almeida L, Ferreira S, Manita C, Santos J, Pinto S, Nunes B, Roquette R, Cardoso C. Anti-HAV IgG seroprevalence in Lisbon region residents: preliminary results from the National Serological Survey 2015-2016. J Clin Virol. 2016:S79-S80.
31. Akbulut UE, Arslan E. Hepatitis A seroprevalence in Mogadishu, Somalia. J Trop Pediatr. 2022;68:fmac009.
32. Ciftci IH, Koroglu M, Demiray T, Terzi HA, Kahraman Kilbas EP. Age-specific seroprevalence of hepatitis A virus in Turkey between 2000 and 2023: systematic review and meta-analysis. Diagnostics (Basel). 2024;14:2464.
33. Mıngır S, Şensoy N, Demirtürk N. Evaluation of hepatitis A and hepatitis C serology and responses to hepatitis B vaccination in adolescent children. Turk J Fam Med Prim Care. 2023;17:126-131.
34. Yiş R, Değirmenci S. Evaluation of hepatitis A seroprevalence in a children's hospital located in Southeastern Anatolia. Bozok Med J. 2020;10:30-35.
35. Aşcı Z, Akgün S, Keşli R, Demirtürk N. Seroprevalence rates of hepatitis A virus in different age groups in the province of Afyonkarahisar. Goztepe Med J. 2014;29:94-98.
36. Mantovani SA, Delfino BM, Martins AC, Oliart-Guzmán H, Pereira TM, Branco FL, Braña AM, Filgueira-Júnior JA, Santos AP, Arruda RA, Guimarães AS, Ramalho AA, Oliveira CS, Araújo TS, Arróspide N, Estrada CH, Codeço CT, da Silva-Nunes M. Socioeconomic inequities and hepatitis A virus infection in Western Brazilian Amazonian children: spatial distribution and associated factors. BMC Infect Dis. 2015;15:428.
37. Acikgoz A, Cimrin D, Kizildag S, Esen N, Balci P, Sayiner AA. Hepatitis A, B and C seropositivity among first-year healthcare students in western Turkey: a seroprevalence study. BMC Infect Dis. 2020;20:529.
38. Düzenli T, Köseoğlu H, Üçer Ş, Comba A, Sezikli M. Seroprevalence of hepatitis A virus according to age groups in Northern Anatolia of Turkey. The Turkish Journal of Academic Gastroenterology. 2021;20:136-142.
39. Akman AÖ, Burhan BY, Uzun AK, Taş D. Hepatitis A virus age-specific seroprevalence after the implementation of a Toddlers' vaccination in Turkey: shifting susceptibility to adolescents. Turk Pediatri Ars. 2020;55:370-375.
40. Ertürk A, Çiçek AÇ, Akdoğan RA, Öztürk Ç. Seroprevalence of hepatitis A in Rize province and different adult age groups. Viral Hepatit J. 2013;19:85-88.
41. Wang H, Gao P, Chen W, Bai S, Lv M, Ji W, Pang X, Wu J. Changing epidemiological characteristics of hepatitis A and warning of anti-HAV immunity in Beijing, China: a comparison of prevalence from 1990 to 2017. Hum Vaccin Immunother. 2019;15:420-425.

Research Article

91

DOI: 10.4274/vhd.galenos.2026.2025-10-1
Viral Hepat J 2025;31(3):91-96

Hepatitis B Reactivation and Antiviral Prophylaxis in Patients on Immunosuppressive Therapy

İmmünosüpresif Tedavi Alan Hastalarda Hepatit B Reaktivasyonu ve Antiviral Profilaksi

Yakup Gezer, Arzu Tarakçı

University of Health Sciences Türkiye, Konya City Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Konya, Türkiye

ABSTRACT

Objectives: Hepatitis B virus reactivation (HBVr) may occur in patients receiving immunosuppressive therapy. The risk of HBVr varies depending on the immunosuppressive agent used and hepatitis serology. This study aimed to evaluate HBVr among immunosuppressed patients with and without antiviral prophylaxis.

Materials and Methods: HB surface antigen (HBsAg)-positive and/or HB core antibody-positive patients receiving immunosuppressive therapy were retrospectively evaluated at a single-center, tertiary-care hospital.

Results: A total of 224 patients were initially screened, and 153 were included in the study. The median age was 62 years (range, 52.5-72), and 50.3% were female. The rate of HBsAg positivity was 21.6%, while HB surface antibody positivity was detected in 52.3% of patients. Antiviral prophylaxis was administered to 81.7% of patients: entecavir (75.2%), tenofovir disoproxil fumarate (TDF) (19.2%), and tenofovir alafenamide (TAF) (5.6%). HBVr was not observed in patients receiving antiviral prophylaxis, whereas two cases occurred in patients not receiving prophylaxis (p=0.033). One of these patients was receiving rituximab-based therapy, and the other was on corticosteroid treatment. When patients were stratified by risk group, rates of HBVr among patients who did not receive prophylaxis were 50% in the high-risk group, 25% in the moderate-risk group, and 0% in the low-risk group.

Conclusion: HBVr may occur in immunosuppressed patients. In these patient groups, hepatitis serologic testing should be performed, and antiviral prophylaxis should be administered according to the immunosuppressive regimen. Entecavir, TDF, and TAF appear to be both effective and safe. Patients without antiviral prophylaxis should be closely monitored.

Keywords: Anti-HBc-positive, antiviral prophylaxis, corticosteroids, HBsAg positive, immunosuppressive therapy, rituximab

ÖZ

Amaç: Hepatit B virüs reaktivasyonu (HBVr), immünosüpresif tedavi gören hastalarda ortaya çıkabilir. HBVr riski, kullanılan immünosüpresif ajana ve hepatit serolojisine bağlı olarak değişir. Bu çalışmanın amacı, antiviral profilaksi alan ve almayan immünosüprese hastalarda HBVr'yi değerlendirmektir.

Gereç ve Yöntemler: HB virüsünün yüzey antijeni (HBsAg) pozitif ve/veya HB çekirdek antikoru pozitif hastalar, retrospektif olarak tek merkezli, üçüncü basamak bir hastanede incelendi.

Bulgular: Başlangıçta 224 hasta tarandı ve 153 hasta çalışmaya dahil edildi. Hastaların medyan yaşı 62 (52,5-72) yıl ve %50,3'ü kadındı. HBsAg pozitifliği %21,6 ve HB yüzey antikoru pozitifliği %52,3 idi. Antiviral profilaksi hastaların %81,7'sine başlandı; kullanılan ilaçlar entekavir (%75,2), tenofovir disoproksil fumarat (TDF) (%19,2) ve tenofovir alafenamid (TAF) (%5,6) idi. Profilaksi alan grupta HBVr gözlenmezken, profilaksi almayan iki hastada HBVr saptandı (p=0,033). Bu hastalardan biri rituksimab bazlı tedavi, diğeri ise kortikosteroid alıyordu. Risk gruplarına göre sınıflandırıldığında, profilaksi almayan hastalarda HBVr oranı yüksek risk grubunda %50, orta risk grubunda %25 iken, düşük risk grubunda gözlemlenmedi.

Sonuç: HBVr immünosüprese hastalarda görülebilmektedir. Bu hasta gruplarında hepatit serolojisi taranmalı ve immünosüpresif rejime göre uygun antiviral profilaksi uygulanmalıdır. Entekavir, TDF ve TAF etkili ve güvenli seçenekler olarak görünmektedir. Antiviral profilaksi almayan hastalar takip sırasında yakından izlenmelidir.

Anahtar Kelimeler: Anti-HBc pozitif, antiviral profilaksi, kortikosteroidler, HBsAg pozitif, immünosüpresif tedavi, rituksimab

Address for Correspondence: Yakup Gezer, MD, University of Health Sciences Türkiye, Konya City Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Konya, Türkiye
E-mail: dryakupgezer@gmail.com **ORCID ID:** orcid.org/0000-0002-1582-7313
Received: 08.10.2025 **Accepted:** 12.01.2026 **Publication Date:** 26.01.2026

Cite this article as: Gezer Y, Tarakçı A. Hepatitis B reactivation and antiviral prophylaxis in patients on immunosuppressive therapy. Viral Hepat J. 2025;31(3):91-96

Introduction

Hepatitis B virus reactivation (HBVr) is a complication that can develop in patients receiving immunosuppressive therapy for autoimmune or rheumatologic diseases, or chemotherapy for cancer. People who have been previously exposed to HBV are at risk of developing this complication. Although it depends on the immunosuppressive agent used, this risk is higher in people with HB surface antigen (HBsAg)-positive/HB core antibody (anti-HBc)-positive serology than in those with HBsAg-negative/anti-HBc-positive serology. The clinical presentation of HBVr can range from asymptomatic infection to liver failure (1,2). In people with prior HBV infection, the cccDNA of HBV remains latent in hepatocytes, and when immunity is reduced by various immunosuppressive drugs, reactivation of HBV can occur (3,4). There is still no standardized approach for the prevention of HBVr. For this reason, different groupings have been made to determine the risk of HBVr, and it has been suggested that the decision regarding antiviral prophylaxis should be made according to these groupings. The risk of HBVr is classified as high if it is greater than 10%, moderate if it is between 1% and 10%, and low if it is less than 1%. Antiviral prophylaxis is recommended to be initiated two weeks before the start of immunosuppressive therapy and discontinued 6 to 12 months after the end of immunosuppressive therapy. The immunosuppressive agents responsible for HBVr are mainly cytotoxic chemotherapeutics, B-cell suppressors, anti-tumor necrosis factor (TNF) agents, immune checkpoint inhibitors, tyrosine kinase inhibitors, and corticosteroids. New targeted biologic agents are introduced daily, and the effects of many of these agents on HBVr are not fully understood (5,6,7,8). The aim of this study was to evaluate the presence of HBVr in patients receiving immunosuppressive therapy.

Materials and Methods

We retrospectively collected and analyzed the medical records of patients for whom the infectious diseases department was consulted for evaluation of HBV prophylaxis at a tertiary care hospital between January 2021 and March 2024. Patients from different departments with hepatitis serology who were scheduled for immunosuppressive treatment for primary diseases were evaluated.

In our institution, the departments of hematology, oncology, rheumatology, gastroenterology, and neurology routinely request HBV screening prior to initiating immunosuppressive therapy. At baseline, HBV serology [HBsAg, HB surface antibody (anti-HBs), and anti-HBc] is assessed in all patients. Patients with HBsAg positivity or isolated anti-HBc positivity are referred for an infectious diseases consultation to guide antiviral prophylaxis and follow-up care planning. According to the available medical records, patients underwent liver function testing, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), approximately every three months to monitor for signs of active hepatitis. In cases of elevated liver enzyme levels, HBsAg and HBV-DNA levels were subsequently evaluated.

Patients aged 18 years and older were included in the study. Patients on antiviral therapy for chronic HBV and those with insufficient documentation were excluded. Age, sex, primary disease, immunosuppressive therapy, HBV serology, AST, ALT, HBV-DNA, and antiviral agents initiated for prophylaxis were recorded. Patients were categorized as being at high, moderate, or low-risk of HBVr according to guideline recommendations (9). HBVr was defined as either the de novo detectability of HBV-DNA in patients with previously undetectable levels or a ≥10-fold increase in HBV-DNA from baseline values (9).

Statistical Analysis

Statistical analyses were performed with SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to assess the distribution of continuous variables. The median and interquartile range (IQR) (IQR: 25^{th}-75^{th} percentile) are reported for continuous variables that are not normally distributed, and categorical variables are presented as frequencies and percentages. Categorical variables were compared using the chi-square test. Fisher's exact test was employed when the expected cell counts were fewer than five. A p-value of <0.05 was considered statistically significant.

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from KTO-Karatay University Non-Drug and Non-Medical Device Research Ethics Committee (approval no: 2024/013, date: 07.06.2024).

Results

Hepatitis serology was analyzed in 224 patients who were referred from different departments of the hospital to the infectious diseases department for HBV prophylaxis. When the retrospective records were analyzed, 22 patients with missing data on immunosuppressive treatment were excluded. The 49 anti-HBc-negative patients were excluded from the study because they were not at risk of HBVr. One hundred and fifty three patients with HBsAg(+/-) and anti-HBc(+) status were included (Figure 1). Of the 153 patients, 33 (21.6%) were HBsAg-positive and 80 (52.3%) were anti-HBs-positive. The median (IQR) age of the patients was 62 (52.5-72) years, and 77 (50.3%) were female (Table 1). Among patients with detectable baseline HBV-DNA levels, the median (IQR) was 230 IU/mL (90-3009).

Patients were grouped according to the immunosuppressive treatments they received with regard to HBvr. Of the study population, 53 patients (34.6%) were classified as high-risk, 37 (24.2%) as moderate-risk, and 63 (41.2%) as low-risk.

HBV antiviral prophylaxis was initiated in 125 (81.7%) patients (Table 2). The antivirals used were entecavir (n=94, 75.2%), tenofovir disoproxil fumarate (TDF) (n=24, 19.2%), and tenofovir alafenamide (TAF) (n=7, 5.6%). One patient receiving entecavir was switched to TDF due to an allergic reaction. The median follow-up duration (IQR) was 10 (6-18) months.

Among the 28 patients (18.3%) who did not receive antiviral prophylaxis, two were classified as high-risk and were receiving rituximab-based regimens and anthracycline-group immunosuppressive agents. HBVr occurred in one patient

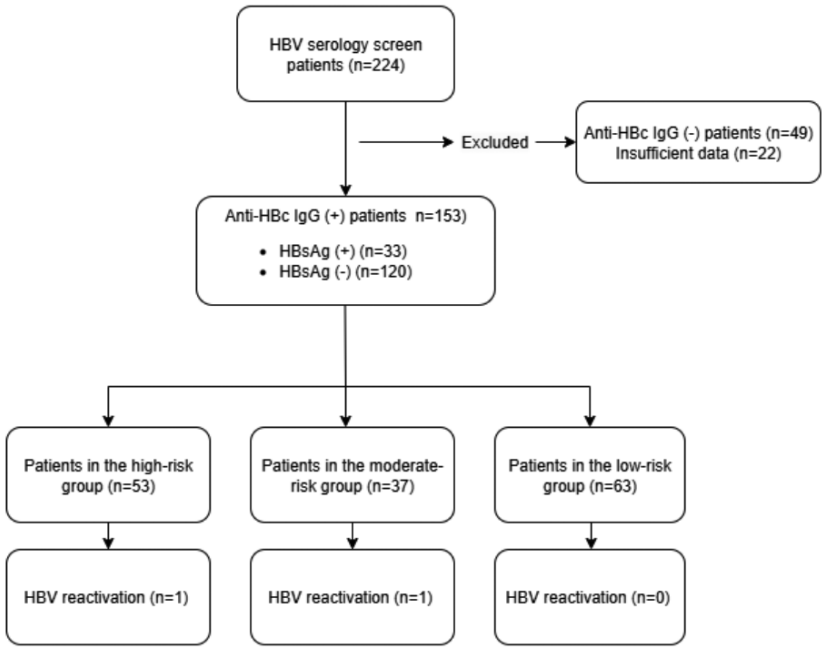

Figure 1. HBV reactivation associated with serologic profiles and antiviral prophylaxis
HBV: Hepatitis B virus, HBsAg: Hepatitis B surface antigen, Anti-HBc: Hepatitis B core antibody, IgG: Immunoglobulin G

treated with a rituximab-based regimen. Four patients in the moderate-risk group did not receive prophylaxis. These patients were receiving corticosteroid therapy, and one had HBVr. Twenty-two patients were identified as low-risk, including seven on corticosteroids, six on conventional synthetic disease-modifying antirheumatic drugs (DMARDs), and nine on anti-TNF agents. All nine patients receiving anti-TNF therapy (including four receiving etanercept, three receiving golimumab, and two receiving adalimumab) were HBsAg-negative. No HBVr was observed in this low-risk group.

HBVr was not observed in HBsAg-positive or anti-HBs-positive patients; two cases occurred in HBsAg-negative patients (0/33 vs. 2/120; p=1.000) and in anti-HBs-negative patients (0/80 vs. 2/73; p=0.226). In contrast, HBVr occurred only in patients who did not receive antiviral prophylaxis (0/125 vs. 2/28; p=0.033). Table 3 summarizes the characteristics of patients who developed HBVr.

Discussion

In this study, antiviral prophylaxis was administered to 96.2% of high-risk, 89.2% of moderate-risk, and 65.1% of low-risk patients. Entecavir was the predominant antiviral agent (75.2%). No cases of HBVr occurred among patients receiving prophylaxis, whereas HBVr was observed in two of 28 patients (7.1%) without prophylaxis. When stratified by risk, the HBVr rate in patients without prophylaxis was 50% (1/2) in the high-risk group, 25% (1/4) in the moderate-risk group, and not observed in the low-risk group.

In countries with HBsAg prevalence above 2%, hepatitis serology screening is recommended before initiating immunosuppressive therapy (5). In Türkiye, a seroprevalence study reported HBsAg and anti-HBc positivity rates of 4% and 30.6%, respectively (10). Because Türkiye is a country of moderate endemicity for HBV, HBV serology screening is required prior to immunosuppressive treatment.

In a multicenter study of patients with hematologic malignancies receiving rituximab-based chemotherapy, HBVr was more common in those without antiviral prophylaxis (11). In our study, among 34 patients receiving rituximab-based therapy, only one patient—who did not receive prophylaxis—developed HBVr. No cases occurred among patients receiving prophylaxis. Current guidelines classify rituximab-containing regimens as high-risk and recommend antiviral prophylaxis (5,9). Although the number of cases in our study was small, our findings support these recommendations and highlight the importance of guideline implementation.

HBVr has been frequently reported in patients receiving anti-CD20 or anti-TNF therapy, though data on newer monoclonal antibodies remain limited (12). Recent evidence suggests that treatment with biologic or targeted synthetic DMARDs in patients with rheumatoid arthritis who are HBsAg-negative/anti-HBc-positive may increase the risk of HBVr (13). While some studies report minimal risk in anti-TNF-treated HBsAg-negative/anti-HBc-positive patients, others indicate a risk ranging from 0.4% to 6% (14,15,16,17). In our cohort, none of the nine low-risk, isolated anti-HBc-positive patients who received anti-TNF therapy without prophylaxis developed HBVr. These findings suggest that HBsAg-negative/anti-HBc-positive patients, unlike patients with HBsAg-positive serology, have a lower risk of HBVr with anti-TNF therapy. Accordingly, close clinical and laboratory monitoring with a preemptive strategy appears preferable to routine prophylaxis, minimizing unnecessary antiviral exposure.

In patients with multiple sclerosis (MS) receiving ocrelizumab, HBVr occurred in 28.6% of patients not receiving antiviral prophylaxis, while no cases were observed in those receiving prophylaxis (18). However, a multicentre study reported no cases

Table 1. Demographic and clinical characteristics of the patients	
Variables	**n=153**
Age, years, median (IQR)	62 (52.5-72)
Gender, n (%)	
Male	76 (49.7)
Female	77 (50.3)
Follow-up duration, months, median (IQR)	10 (6-18)
Diseases, n (%)	
Rheumatoid arthritis	33 (21.6)
Lymphoma	29 (18.9)
Multiple myeloma	22 (14.4)
Ankylosing spondylitis	17 (11.1)
Leukemia	15 (9.8)
Immune thrombocytopenic purpura	11 (7.2)
Multiple sclerosis	6 (3.9)
Autoimmune hemolytic anemia	6 (3.9)
Psoriatic arthritis	3 (2)
Others	11 (7.2)
Baseline hepatitis serology, n (%)	
HBsAg (+)	33 (21.6)
HBsAg (-)	120 (78.4)
Anti-HBs (+)	80 (52.3)
Anti-HBs (-)	73 (47.7)
Anti-HBc (+)	153 (100)
Anti-HBs titer** (IU/L), median (IQR)	160 (60-1000)
Baseline AST level (U/L), median (IQR)	24 (19-29)
Baseline ALT level (U/L), median (IQR)	25 (20-30)
Baseline HBV-DNA status	
Detectable	19 (45.2)
Undetectable	23 (54.8)
Immunosuppressive agents used, n (%)	
Hematological diseases	
Rituximab-based regimens	34 (22.2)
Corticosteroids	20 (13.1)
Bortezomib-based regimen	15 (9.8)
Anthracyclines	6 (3.9)
Antimetabolites	4 (2.6)
Tyrosine kinase inhibitor	3 (2)
B-cell lymphoma 2 inhibitors	2 (1.3)
Others	7 (4.6)
Rheumatological diseases	
Anti-TNF	30 (19.6)
csDMARDs	9 (5.9)
csDMARS+corticosteroids	9 (5.9)
Anti-TNF+csDMARDs	8 (5.2)
Neurological diseases	
Ocrelizumab	6 (3.9)

Table 1. Continued	
Variables	**n=153**
Antiviral prophylaxis agent, n (%)	
Entecavir	94 (75.2)
Tenofovir disoproxil fumarate	24 (19.2)
Tenofovir alafenamide	7 (5.6)

Numerical variables were shown as median (IQR 25-75%). **: Median anti-HBs titer was calculated among patients with anti-HBs positive patients (≥10 IU/L); categorical variables were expressed as number (%). Anti-TNF: Anti-tumor necrosis factor, csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HBV: Hepatitis B virus, IQR: Interquartile range, HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, Anti-HBc: Hepatitis B core antibody

of HBVr among anti-HBc-positive patients with MS who received rituximab or ocrelizumab, irrespective of antiviral prophylaxis (19). Although data in the literature differ regarding the risk of HBVr, the recently published American Gastroenterological Association guideline places ocrelizumab in the same high-risk category as rituximab (9). In our study, all patients treated with ocrelizumab received antiviral prophylaxis, and no cases of HBVr were observed.

The degree of immunosuppression induced by corticosteroids depends on dose and duration. In patients receiving moderate- to high-dose corticosteroids for more than four weeks, HBsAg-positive individuals are classified as high-risk, while HBsAg-negative/anti-HBc-positive individuals are considered moderate-risk. When treated with low-dose corticosteroids for four weeks, HBsAg-positive and HBsAg-negative/anti-HBc-positive patients are classified as moderate- and low-risk, respectively (9). In our study, nine HBsAg-negative/anti-HBc-positive patients received corticosteroids without antiviral prophylaxis (two moderate-risk and seven low-risk). HBVr occurred in one of the two moderate-risk patients (50%, 1/2). Risk stratification for HBVr should consider corticosteroid dose and duration; and clinicians should remain vigilant even for moderate-risk patients.

Previous studies have suggested that anti-HBs positivity, particularly an anti-HBs titer above 100 IU/L, may have a protective effect against HBVr (13,20). The findings of our study are consistent with this observation. Among the 14 patients who were anti-HBs positive and did not receive antiviral prophylaxis (11 of whom had anti-HBs titers >100 IU/L), none experienced HBVr. These patients were classified as belonging to the low-risk group. Although a generalization cannot be made because of the small sample size and inclusion of only low-risk patients, anti-HBs positivity may contribute to the prevention of HBVr; this finding should be investigated further in larger patient populations.

Increasing awareness of HBVr has led to more frequent hepatitis serological screening and identification of patients who are HBsAg(-)/anti-HBc(+). However, this has also resulted in unnecessary antiviral prophylaxis among low-risk individuals (21). Consistent with this observation, 65.1% of our low-risk group received prophylaxis. In accordance with current guidelines, close clinical and laboratory monitoring may be preferred for these patients.

Table 2. Use of HBV antiviral prophylaxis according to immunosuppression risk stratification

	High (n=53)	Moderate (n=37)	Low (n=63)	Total (n=153)
Use of antiviral prophylaxis (yes)	51 (96.2%)	33 (89.2%)	41 (65.1%)	125 (81.7%)
Use of antiviral prophylaxis (no)	2 (3.8%)	4 (10.8%)	22 (34.9%)	28 (18.3%)

HBV: Hepatitis B virus

Table 3. Clinical and demographic characteristics of patients with HBV reactivation

Patient characteristics	Patient 1	Patient 2
Age	49	78
Gender	Male	Female
Disease	Non-Hodgin's lymphoma	Autoimmune hemolytic anemia
Treatment for the primary disease	Rituximab-based chemotherapy (cyclophosphamide, adriamycin, vincristine, methylprednisolone)	Dexamethasone+mycophenolate mofetil
Antiviral prophylaxis	No	No
HbsAg	Negative	Negative
Anti-HBc	Positive	Positive
Anti-HBs (IU/L)	Negative	Negative
HBV-DNA (IU/mL)	-	967
HBVr risk status	High	Moderate
After reactivation		
HBV-DNA (IU/mL)	20000000	8560518
ALT (U/L)	45	223
Initiated antiviral therapy	Entecavir	Tenofovir disoproxil fumarate
6th month follow-up		
HBV-DNA (IU/mL)	18193	2670
ALT (U/L)	42	53
12th month follow-up		
HBV-DNA (IU/mL)	0	0
ALT (U/L)	31	34

HBVr: Hepatitis B virus reactivation, ALT: Alanine aminotransferase, HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, Anti-HBc: Hepatitis B core antibody

Study Limitations

This study has some limitations because it was a single-center, retrospective study. Because the number of patients who did not receive antiviral prophylaxis was small, the results cannot be generalized. We believe that this study contributes to the literature by reporting outcomes for patients who did or did not receive antiviral prophylaxis with respect to HBVr.

Conclusion

The incidence of HBVr may vary depending on the patient's immunosuppressive status. Therefore, these patients should undergo hepatitis serology screening. The decision to administer antiviral prophylaxis should be based on the patient's level of risk. In this study, no cases of HBVr were observed among patients who received prophylaxis. Entecavir, TDF, and TAF represent effective and safe options for HBVr prevention. Patients not receiving antiviral prophylaxis should be closely monitored for HBVr.

Ethics

Ethics Committee Approval: Ethical approval was obtained from KTO-Karatay University Non-Drug and Non-Medical Device Research Ethics Committee (approval no: 2024/013, date: 07.06.2024).

Informed Consent: It was waived due to the retrospective nature of the study.

Footnotes

Authorship Contributions

Concept: Y.G., A.T., Design: Y.G., A.T., Data Collection or Processing: Y.G., A.T., Analysis or Interpretation: Y.G., A.T., Literature Search: Y.G., A.T. Writing: Y.G., A.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare no financial support.

References

1. Visram A, Feld JJ. Defining and grading HBV reactivation. Clin Liver Dis. 2015;5:35-38.
2. Hoofnagle JH. Reactivation of hepatitis B. Hepatology. 2009;49(5 Suppl):S156-S165.
3. Lok ASF, Liang RHS, Chiu EKW, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy: report of a prospective study. Gastroenterology. 1991;100:182-188.
4. Mason AL, Xu L, Guo L, Kuhns M, Perrillo RP. Molecular basis for persistent hepatitis B virus infection in the liver after clearance of serum hepatitis B surface antigen. Hepatology. 1998;27:1736-1742.
5. Lau G, Yu ML, Wong G, Thompson A, Ghazinian H, Hou JL, Piratvisuth T, Jia JD, Mizokami M, Cheng G, Chen GF, Liu ZW, Baatarkhuu O, Cheng AL, Ng WL, Lau P, Mok T, Chang JM, Hamid S, Dokmeci AK, Gani RA, Payawal DA, Chow P, Park JW, Strasser SI, Mohamed R, Win KM, Tawesak T, Sarin SK, Omata M. APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy. Hepatol Int. 2021;15:1031-1048.
6. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370-398.
7. Papatheodoridis GV, Lekakis V, Voulgaris T, Lampertico P, Berg T, Chan HLY, Kao JH, Terrault N, Lok AS, Reddy KR. Hepatitis B virus reactivation associated with new classes of immunosuppressants and immunomodulators: a systematic review, meta-analysis, and expert opinion. J Hepatol. 2022;77:1670-1689.
8. Cohen EB, Regev A, Garg A, Di Bisceglie AM, Lewis JH, Vierling JM, Hey-Hadavi J, Steplewski K, Fettiplace A, Chen CL, Pehlivanov N, Kendrick S, I Avigan M. Consensus guidelines: best practices for the prevention, detection and management of hepatitis B virus reactivation in clinical trials with immunosuppressive/immunomodulatory therapy. Drug Saf. 2024;47:321-332.
9. Ali FS, Nguyen MH, Hernaez R, Huang DQ, Wilder J, Piscoya A, Simon TG, Falck-Ytter Y. AGA clinical practice guideline on the prevention and treatment of hepatitis B virus reactivation in at-risk individuals. Gastroenterology. 2025;168:267-284.
10. Tozun N, Ozdogan O, Cakaloglu Y, Idilman R, Karasu Z, Akarca U, Kaymakoglu S, Ergonul O. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect. 2015;21:1020-1026.
11. Clerico M, Dogliotti I, Ghione P, Zilioli VR, Merli F, Botto B, Al Essa W, Battaglini M, Grimaldi D, Cervi L, Ragaini S, Ferrero S, Peri V, De Luca G, Marzano A, Cavallo F. HBV reactivation in patients with past infection affected by non-Hodgkin lymphoma and treated with anti-CD20 antibody based immuno-chemotherapy: a multicenter experience. J Pers Med. 2022;12:285.
12. De Pauli S, Grando M, Miotti G, Zeppieri M. Hepatitis B virus reactivation in patients treated with monoclonal antibodies. World J Virol. 2024;13:1-6.
13. Tien YC, Yen HH, Li CF, Liu MP, Hsue YT, Hung MH, Chiu YM. Changes in hepatitis B virus surface antibody titer and risk of hepatitis B reactivation in HBsAg-negative/HBcAb-positive patients undergoing biologic therapy for rheumatic diseases: a prospective cohort study. Arthritis Res Ther. 2018;20:1-8.
14. Sayar S, Kürbüz K, Kahraman R, Öztürk O, Çalışkan Z, Doğanay HL, Özdil K. Risk of hepatitis B reactivation during anti-TNF therapy; evaluation of patients with past hepatitis B infection. Turkish J Gastroenterol. 2020;31:522-528.
15. Taş Aygar G, Haykır Solar A, Yılmaz OK, Karataş H, Çevirgen Cemil B, Kartal SP. Risk of HBV reactivation during immunosuppressive therapy in psoriasis: a retrospective analysis.Viral Hepat J. 2025;31:59-65.
16. Fidan S, Capkın E, Arıca DA, Durak S, Okatan IE. Risk of hepatitis B reactivation in patients receiving anti-tumor necrosis factor-αtherapy. Int J Rheum Dis. 2021;24:254-259.
17. Pappa M, Koutsogianni A, Karamanakos A, Kyriazi N, Cheila M, Moschou D, Mole E, Gazi S, Papadimitriou E, Atzeni F, Sebastiani M, Argyropoulou OD, Vasilakis KD, Papagoras C, Fragoulis GE, Androutsakos T. Similar hepatitis B virus reactivation risk for patients with inflammatory arthritis or connective tissue diseases: a multicenter retrospective study. Rheumatol Int. 2025;45:15.
18. Çelik M, Baba C, Irmak Ç, Özakbaş S, Avkan-Oğuz V. Risk of hepatitis B virus reactivation in people with multiple sclerosis treated with ocrelizumab: an observational study from Turkey. J Neurol. 2024;271:4131-4137.
19. Buonomo AR, Viceconte G, Calabrese M, De Luca G, Tomassini V, Cavalla P, Maniscalco GT, Ferraro D, Nociti V, Radaelli M, Buscarinu MC, Paolicelli D, Gajofatto A, Annovazzi P, Pinardi F, Di Filippo M, Cordioli C, Zappulo E, Scotto R, Gentile I, Spiezia AL, Petruzzo M, De Angelis M, Brescia Morra V, Solaro C, Gasperini C, Cocco E, Moccia M, Lanzillo R; Raising Italian Researchers in Multiple Sclerosis (RIREMS) study group. Management of hepatitis B virus prophylaxis in patients treated with disease-modifying therapies for multiple sclerosis: a multicentric Italian retrospective study. J Neurol. 2022;269:3301-3307.
20. Poola S, Kratzer M, Sewell K, Tillmann HL. Size matters! Anti-HBs titer and HBV reactivation during anti-TNF therapy. Dig Dis Sci. 2023;68:4511-4520.
21. Yenilmez E, Cetinkaya RA. Overuse of prophylaxis in HBSaG and/or anti-HBC positive patients after increasing awareness to prevent reactivation in patients receiving immunosuppressive therapies: how rational are our prophylaxis decisions according to the literature? Infez Med. 2019;27:299-307.

2025 Referee Index