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A Decade of HBV-DNA Testing: Trends in Positivity and Viral Load in a Tertiary Referral Laboratory in Türkiye

Türkiye'de Bir Üçüncü Basamak Referans Laboratuvarında On Yıllık HBV-DNA Testi: Pozitiflik ve Viral Yük Eğilimleri

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ABSTRACT

Objectives: Hepatitis B virus (HBV) infection is a leading cause of liver-related morbidity and mortality worldwide. HBV-DNA tests, used to detect viremic patients and monitor viral load, may also provide insights into transmissibility and public health implications. This study aimed to analyze HBV-DNA tests performed in our hospital over a period of 10.5 years.

Materials and Methods: Results of 45,624 HBV-DNA tests performed in the molecular microbiology laboratory between January 1, 2015, and July 31, 2025 were collected from the electronic records. The HBV-DNA test was performed using real-time polymerase chain reaction. Annual test numbers, positivity rates, and viral load changes were analyzed using linear regression.

Results: On average, 4,310 tests were performed annually, of which 27.4% were positive. Throughout the study period, the median age of the tested patient population increased significantly by 7-8 years; the positivity rate of the tests declined from 37% to 25.6%; and the median viral load of patients testing positive and the quartile extremes decreased significantly by 1-log. The number of tests conducted and the positivity rate decreased significantly during the coronavirus disease 2019 (COVID-19) pandemic compared to previous years, by 35.4% and 37.6%, respectively. Although the COVID-19 pandemic and regional earthquakes temporarily reduced access to testing, these short-term disruptions did not alter the overall downward trends.

Conclusion: The decline in positivity and the increase in patient age suggest that vaccination reduced infections in younger populations, thereby leading to an aging HBV-positive cohort. The reduction in viral load reflects effective treatment and monitoring; however, follow-up may have been disrupted by the pandemic. Strengthening access to antiviral therapy among individuals with undiagnosed chronic HBV could accelerate reduction in HBV prevalence.

Keywords: HBV, HBV-DNA, PCR, viral load, trend analysis

ÖZ

Amaç: Hepatit B virüsü (HBV) enfeksiyonu, dünya genelinde karaciğerle ilişkili morbidite ve mortalitenin önde gelen nedenlerinden biridir. Viremik hastaların tespitinde ve viral yük takibinde kullanılan HBV-DNA testleri, aynı zamanda bulaştırıcılık ve halk sağlığı açısından da önemli bilgiler sağlayabilir. Bu çalışmada hastanemizde 10,5 yıllık bir dönemde yapılan HBV-DNA testlerinin analiz edilmesi amaçlanmıştır.

Gereç ve Yöntemler: 1 Ocak 2015-31 Temmuz 2025 tarihleri arasında moleküler mikrobiyoloji laboratuvarında gerçekleştirilen toplam 45.624 HBV-DNA testinin sonuçları elektronik kayıt sisteminden alınmıştır. HBV-DNA testi gerçek zamanlı polimeraz zincir reaksiyonu yöntemiyle yapılmıştır. Yıllık test sayıları, pozitiflik oranları ve viral yük değişimleri doğrusal regresyon analizi ile değerlendirilmiştir.

Bulgular: Yıllık ortalama 4.310 test yapılmış olup, bunların %27,4'ü pozitif bulunmuştur. Çalışma dönemi boyunca, test edilen hasta popülasyonunun ortalama yaşı 7-8 yıl artmış, testlerin pozitiflik oranı %37'den %25,6'ya düşmüş, pozitif hastaların medyan viral yükü ve çeyrek değer aralıkları ise 1-log azalmıştır. 2019 koronavirüs hastalığı (COVID-19) pandemisi döneminde yapılan test sayısı ve pozitiflik oranı, önceki yıllara göre sırasıyla %35,4 ve %37,6 oranında azalmıştır. COVID-19 pandemisi ve bölgesel depremler testlere erişimi geçici olarak azaltmış olsa da, bu kısa süreli aksamalar genel düşüş eğilimini değiştirmemiştir.

Sonuç: Pozitiflik oranındaki düşüş ve hasta yaşındaki artış, aşılama programlarının genç popülasyondaki enfeksiyonları azalttığını ve HBV pozitif hasta grubunun yaşlandığını göstermektedir. Viral yükteki azalma etkin tedavi ve izlem uygulamalarını göstermektedir; ancak pandemi sürecinde hasta takibinde aksamalar yaşanmış olabilir. Tanı almamış kronik HBV hastalarında antiviral tedaviye erişimin kolaylaşması, ülkemizde HBV prevalansını hızla azaltabilir.

Anahtar Kelimeler: HBV, HBV-DNA, PCR, viral yük, trend analizi

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Introduction

Human hepatitis B virus (HBV) is a hepatotropic virus belonging to the family *Hepadnaviridae*, with an icosahedral symmetry, an enveloped capsid structure, and a circular, partially double-stranded DNA genome (1). The relatively small genome (3.2 kb) transforms into the covalently closed circular DNA form in the nucleus of the infected cell and encodes the viral polymerase, core, envelope, surface, and X antigens (2). Similar to retroviruses, HBV replicates via an RNA intermediate and causes persistent infection by integrating into the host cell genome. To date, at least 10 genotypes (A-J) of HBV have been identified, each with distinct geographical distribution patterns and varying clinical severity (3).

The HBV forms a stable virion that can remain infectious for months under appropriate conditions outside the human body. It spreads through various transmission routes, primarily parenteral, sexual, and vertical (4). Following infection of a susceptible host, HBV leads to two main outcomes: acute infection or chronic infection. The risk of chronic infection is particularly high when infection occurs in early childhood, whereas infections in young adults are cleared without progressing to chronicity in about 90% of cases (5).

Chronic HBV infection is the most important clinical condition in which the pathogen threatens human health, and is one of the leading causes of chronic liver failure and hepatocellular carcinoma (HCC). A modeling study based on data from 170 countries reported that nearly 270 million people worldwide were living with chronic HBV infection by 2022 (6). The World Health Organization (WHO) announced that 1.2 million people are infected with HBV each year and that 1.1 million deaths occur annually due to chronic HBV-related complications, particularly cirrhosis and HCC (7). Due to this major global health burden, WHO has classified HBV as a major public health threat and set a target of reducing new cases by 90% by 2030 (8).

Türkiye is among the countries with a low-to-moderate prevalence of HBV. According to the 2017 report by the Ministry of Health, there were approximately 3 million chronic HBV patients in the country, and the incidence of the disease significantly decreased following the implementation of vaccination programs (9). Shortly after the licensing of antiviral drugs that inhibit viral replication, they were reimbursed under the national health insurance scheme and administered to patients with chronic HBV who had indications for treatment. In addition, numerous awareness programs have been carried out in the country to increase public knowledge about HBV. Despite all these efforts, there is insufficient scientific data on changes in the prevalence of HBV-DNA-positive patients in our community and on their viral loads.

Monitoring HBV-DNA is critical for establishing treatment indications for an individual patient, as well as for tracking viral concentrations, liver inflammation, and disease progression. Furthermore, analyzing cumulative HBV-DNA test results collected from a population over an extended period can provide valuable information about the effectiveness of preventive measures implemented to date and allow us to predict disease progression within the community prospectively. In this study, we aimed to investigate positivity rates and changes in patients' viral load over the past decade by examining HBV-DNA tests performed in our hospital, which is a tertiary regional referral center for molecular diagnosis.

Materials and Methods

Study Design and Scope

This study was conducted in the molecular microbiology laboratory of a tertiary university hospital with 1,500 beds. HBV-DNA real-time polymerase chain reaction (PCR) test results generated in the laboratory between January 1, 2015, and July 31, 2025, were retrospectively retrieved from the hospital's electronic database. Patient demographic data (age and sex), HBV-DNA results (positive or negative) obtained by PCR, and viral load levels detected in the serum samples of positive patients were evaluated in this study. Regardless of the test request date, HBV-DNA test results completed within the study period were included in the analysis. For repeated tests in the same patient within six months, if positive, the result with the highest viral load was included; if negative, the result of a single test was considered.

HBV-DNA Analysis

Blood samples collected from patients were centrifuged at 3,000 rpm to separate the serum. Viral DNA in serum samples was extracted using the EZ1 Virus Mini Kit (Qiagen, Germany) on the QIAsymphony SP instrument (Qiagen, Germany), according to the manufacturer's instructions. Detection of viral DNA was performed by real-time PCR using artus HBV QS-RGQ kits and the Rotor-Gene Q system (Qiagen, Germany).

Statistical Analysis

Patients' demographic data and their HBV-DNA-positive or -negative status were expressed as numbers (n) and percentages (%). Viral loads detected in positive patients were expressed in copy/mL, and annual median viral load values were calculated. For each year, viral loads of positive patients were ranked from highest to lowest, and median viral load values for the quartiles (the upper 25%, upper-middle 25%, lower-middle 25%, and the lowest 25%) were calculated. Over the study period, which exceeded 10 years, annual changes in patients' median age, positivity rates, median viral load among positive patients, and median viral load across quartiles were evaluated using linear regression analysis. Categorical variables were compared using Pearson's chi-square test. A p-value <0.05 was considered statistically significant.

Ethical Approval

This study was approved by the İnönü University Health Sciences Scientific Research Ethics Committee (approval no: 2025/8344, date: 16.09.2025). Consent was not obtained because the study was retrospective.

Results

A total of 45,624 test results were included in the study. The average numbers of tests per month and per year during the study period were 359 and 4,310, respectively. Among the patients, 37.5% were female and 62.5% were male. During the study, 12,520 (27.44%) samples were HBV-DNA positive, with a female-to-male distribution of 39.7% and 60.3%, respectively. Notably, the number of tests conducted in 2020 decreased significantly by 35.4% compared with the average of the previous five years (3058 vs. 4731, p=0.008), and the positivity rate in 2021 was significantly lower than that of the previous six years (19.1% vs. 30.6%, p=0.033). The gender characteristics, number of tests performed, and results by year are shown in Table 1.

The median age of patients who underwent HBV-DNA testing increased from 46 years in 2015 to 54 years in 2025. The median age of positive patients rose from 42 years in 2015 to 49 years by the end of the study, while that of negative patients increased from 49 to 56 years over the same period. Linear regression analysis confirmed a significant annual increase in median age [estimate=0.836, standard error (SE)=0.045, p<0.001, 95% confidence interval (CI): 0.736-0.937]. Changes in patients' ages across the study years are shown in Figure 1.

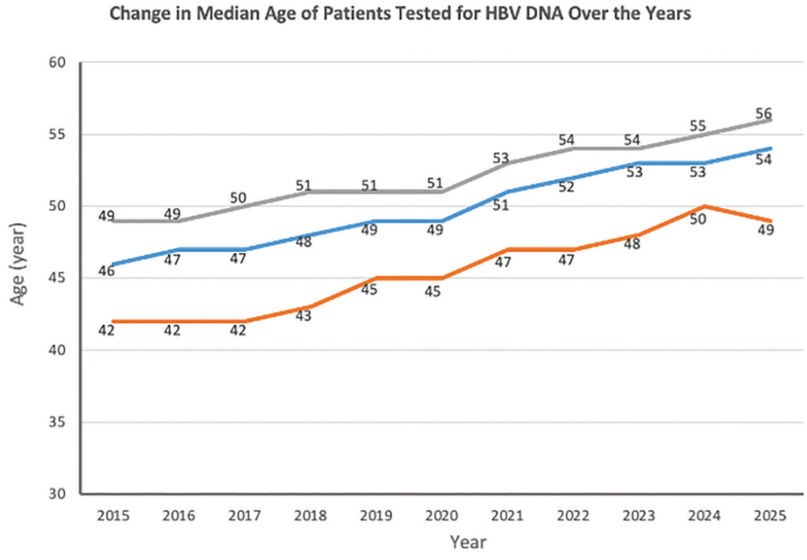

Figure 1. Median age of patients tested for HBV-DNA by year (2015-2025). The blue line represents all patients, the orange line indicates HBV-DNA positive patients, and the grey line indicates HBV-DNA negative patients

HBV: Hepatitis B virus

Table 1. HBV-DNA test data by year and demographic characteristics of tested patients

Years	HBV-DNA				Sex (n)		Age (median; year)
	No of tests	Positive (n, %)		Negative (n)	Female	Male	
2015	4526	1705	37.7	2821	1673	2853	46
2016	4739	1424	30.04	3315	1724	3015	47
2017	5029	1578	31.4	3451	1899	3130	47
2018	4593	1405	30.6	3188	1773	2820	48
2019	4771	1320	27.7	3451	1796	2975	49
2020	**3058***	743	24.3	2315	1122	1936	49
2021	3904	746	**19.1****	3158	1453	2451	51
2022	4791	1099	22.9	3692	1818	2973	52
2023	3378	728	21.6	2650	1262	2116	53
2024	4171	1091	26.2	3080	1612	2559	53
2025	2664	681	25.6	1983	956	1708	54

*: The annual number of HBV-DNA test was significantly lower than the annual average of the test numbers conducted in the previous five years (3058 vs. 4731, p=0.008).
**: The positivity rate detected in 2021 was found to be significantly lower than the annual average of previous six years positivity rate (19.1% vs. 30.6%, p=0.033). Pearson chi-square test
HBV: Hepatitis B virus

The positivity rate of HBV-DNA tests decreased from 37.7% in 2015 to 25.6% in 2025. Linear regression analysis confirmed a significant decreasing trend in HBV-DNA positivity (estimate=-1.175, SE=0.352, p=0.009, 95% CI: -1.972 to -0.378).

The median viral load of positive patients decreased from 16,625 copies/mL in 2015 to 6,730 copies/mL in 2025. Trend analysis revealed a statistically significant 1-log reduction in the median viral load over the study period (β=1070.8, SE=187.4, p<0.001, R^2=0.784).

The change in the median viral load of positive patients is shown in Figure 2. Considering the quartiles based on viral load values, patients in the highest (p=0.016, R^2=0.491) and lowest quartiles (p<0.001, R^2=0.491) demonstrated a significant 1-log reduction in median viral load over the years. However, the decreases observed in the upper-middle and lower-middle quartiles were not statistically significant. The changes in median viral load levels across quartiles over the study period are presented in Figure 3.

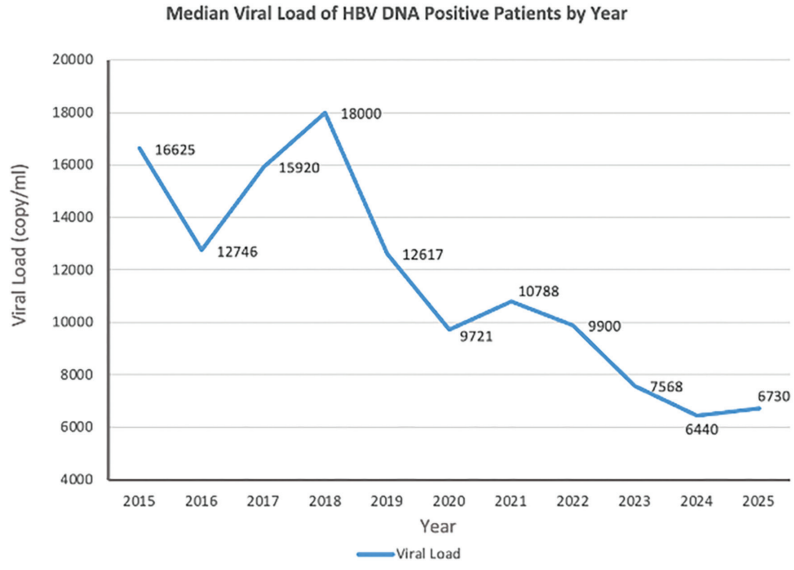

Figure 2. Median viral load of HBV-DNA positive patients by year (2015-2025)
HBV: Hepatitis B virus

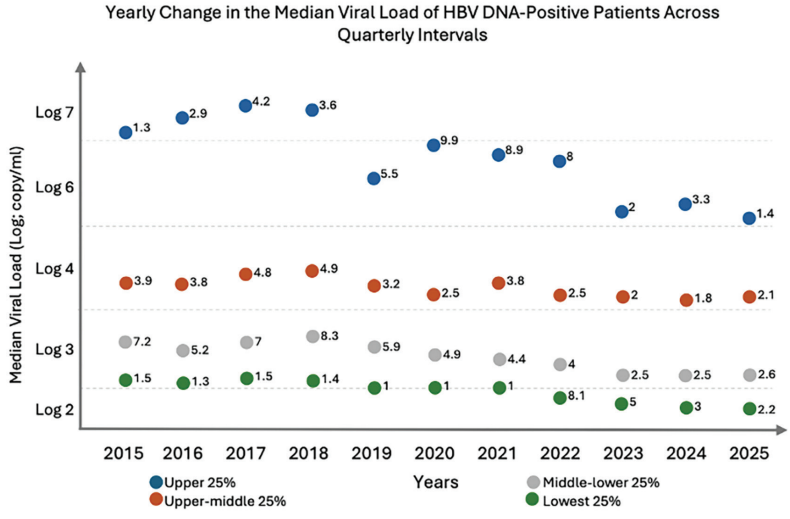

Figure 3. Changes over the years in the median viral load measured in quartile groups formed by ranking viremic patients from highest to lowest viral load. A significant 1-log reduction was observed in patients in the upper and the lowest quartiles during the study period; however, although a decrease in median viral load was also noted in the two middle quartiles, these were not statistically significant
HBV: Hepatitis B virus

Discussion

Liver diseases caused by HBV are an important public health problem both in our country and worldwide. Published data have reported that one in three individuals in Türkiye has been exposed to HBV, and that 40-50% of liver transplantations are HBV-related (9). In a study included 334 liver transplant patients in Türkiye, liver failure due to HBV was found in 115 patients (34.4%) (10). Therefore, important strategies have been adopted in Türkiye to combat HBV, and the country has begun aligning with the WHO's 2030 HBV elimination targets.

Nationwide vaccination campaigns play a major role in prevention strategies. First introduced into the immunization schedule in 1998 under the hepatitis B control program, the HBV vaccine has already been administered to every child within the expanded vaccination program from birth as part of the routine schedule (11). According to Ministry of Health data, supplementary vaccination campaigns for primary and secondary school students, especially between 2005-2009, played a major role in reducing the incidence of acute HBV from 12.0 per 100,000 in 2005 to 1.9 in 2017 (9). Another strategy implemented to curb transmission has been the strict legal regulation and control of other high-risk routes of HBV spread, such as blood transfusion, dental procedures, cosmetic practices, and sex work. In addition, since spousal transmission has been identified as an important route in Türkiye, (4,12) individuals applying for marriage have been included in HBV screening, and when one partner is found positive, awareness programs are conducted to prevent viral transmission among them. Another preventive measure has included community awareness activities, such as public information campaigns on World Hepatitis Day (July 28).

In Türkiye, treatment services have also been implemented to reduce HBV-related health problems. For this purpose, antivirals and immunomodulatory drugs, once licensed for clinical use, began to be reimbursed by the national health insurance scheme for eligible patients. According to the joint guidelines prepared by the Turkish Association for the Study of the Liver and the Viral Hepatitis Society, all first-degree relatives and sexual partners of HBV-positive individuals are recommended to undergo testing for HBV serological markers. If negative, vaccination is advised, and patients with chronic HBV infection should be closely monitored both for antiviral treatment indications and potential complications (13).

The initial diagnosis of HBV patients is most often made serologically by detecting viral antigens and antibodies. In particular, HBV-DNA tests are used in chronic infections both for monitoring viral load and for evaluating treatment response. In this study, HBV-DNA test results from a regional molecular microbiology laboratory, spanning more than 10 years, were analyzed to assess the possible impact of HBV control efforts in Türkiye over the past 20 years on patients and test outcomes. Patient age was analyzed according to three parameters: the ages of all patients tested, positive patients, and negative patients. Over the 10.5-year study period, all three parameters showed a significant and progressive increase of 7-8 years (Figure 1). This finding is one of the most important results of our study, indicating that the HBV-tested population in our region is aging steadily, without a substantial influx of younger patients. If this trend continues, chronic HBV infection will become a disease that characteristically affects the geriatric population, while the HBV-positive burden will significantly decrease over the coming decades. In its 2017 report, the Ministry of Health noted an increase in the ages of chronic HBV patients (9). However, detailed information on the extent and trend of this increase is lacking, and developments after 2017 have not been investigated. A multicenter community survey published in 2015 found that the median age of hepatitis B surface antigen (HBsAg)-positive individuals in Türkiye was between 40-49 years, (12) coherent with the median age of 46 years for our HBV-positive patients in that year. Importantly, our study shows that HBV-positive individuals have continued to age steadily since 2015. This change is likely driven by the widespread vaccination campaigns implemented over the last 30 years, which have rendered children and young people immune to HBV and protected them against infection.

Another key finding of our study was a downward trend in both the number and proportion of HBV-DNA-positive patients. The average positivity rate was above 32% during the first four years (2015-2018) and dropped to around 23% during 2022-2025. Additionally, the median viral concentration in positive patients has shown a significant decrease of 1-log. When viral loads among viremic patients were analyzed by quartile, the median viral load in both the highest and lowest quartiles declined significantly over time. The concurrent decrease in both the proportion of viremic patients and the viral loads of these patients suggests that antiviral treatment has been effective in Türkiye. Antiviral agents suppress viral replication, markedly reducing the viral load, even below the limit of detection. A meta-analysis of 328 published studies found that antiviral treatment, without causing major adverse effects, was an independent factor associated with HBsAg loss, HBV-DNA clearance, and reduced cirrhosis and HCC in chronic HBV patients (14). In a Turkish study involved 17 pregnant women with chronic HBV infection and high viral loads, antiviral therapy reduced viral load to below 10,000 IU/mL without significant adverse effects in mothers or fetuses, achieved an average 2-log reduction in two-thirds of patients, and reduced liver enzyme levels in about 90% of patients (15). These results highlight the potential of antiviral therapy to significantly reduce vertical transmission, a critical route of HBV spread in the community.

By suppressing HBV replication to such an extent, antiviral therapy reduces hepatic inflammation and hepatocyte damage, halts progression to cirrhosis and HCC, and lowers the likelihood of transmission to others. Nevertheless, a multicentre Turkish study in 2015 involving approximately 5,500 participants found that only a small proportion of HBsAg-positive individuals were aware of their condition (12). Moreover, given that treatment non-adherence in Türkiye ranges from 18-30%, with even higher rates in some particular groups (16,17), ensuring that as many HBV patients as possible receive therapy, and improving adherence and continuity among those under treatment, appears as major goals of the HBV control program today.

In our study, the number of tests was significantly lower in 2020, and the positivity rate was lowest in 2021, coinciding with the coronavirus disease 2019 pandemic. This may have been due to hospitals being overwhelmed with pandemic cases, curfews, and public announcements advising older adults to stay at home. Similarly, another decline was observed in 2023 after the major earthquakes in our region on February 6, although it was not significant. Following this disaster, many people experienced housing problems; about one-quarter of the city's population migrated to other regions. Indeed, notable declines have been reported in the detection of many infectious diseases after both the pandemic and the earthquakes (18-20), and our study confirmed that HBV diagnosis and follow-up processes were significantly affected by these unexpected events. Taking appropriate precautions and ensuring preparedness can help minimize the impact of such disasters on HBV control programs.

On the other hand, in light of our results and the available literature, we believe that the emergence of antiviral resistance or the spread of non-vaccine HBV serotypes could threaten the success of control programs. To sustain the decreasing trend in HBV infection in the community, it is essential not only to provide broader vaccine coverage but also to monitor rare vaccine-breakthrough cases and treatment-resistant strains.

Study Limitations

This study has some limitations. First, it is a retrospective study conducted at a single-center and based on laboratory records. Second, detailed clinical information such as patients' treatment status, disease stage, and vaccination history was not available in the laboratory database.

Conclusion

In this study, more than ten years of data from a laboratory serving as the sole molecular microbiology facility for a population representing approximately 1% of Türkiye were analyzed. The findings indicate that the HBV-infected population has been gradually ageing as a result of vaccination and other preventive measures. Transmission among the young population has effectively decreased, and both the proportion of viremic patients and their viral loads have fallen, indicating reduced transmissibility. Although unforeseen events such as the pandemic and earthquakes have disrupted diagnostic and follow-up processes, they have not yet had a significant negative impact in the short term. For Türkiye to achieve full success in HBV control, identifying and enrolling undiagnosed and untreated HBV patients in care and treatment programs will be crucial

Ethics

Ethics Committee Approval: This study was approved by the İnönü University Health Sciences Scientific Research Ethics Committee (approval no: 2025/8344, date: 16.09.2025).

Informed Consent: Consent was not obtained because the study was retrospective.

Footnotes

Authorship Contributions

Concept: E.S.T, Y.Y., B.O., Design: E.S.T, Y.Y., B.O., Data Collection or Processing: E.S.T., M.G., Analysis or Interpretation: Y.Y., M.G., Literature Search: E.S.T., M.G., B.O., Writing: E.S.T., Y.Y., B.O.

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

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Research Article

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Tenofovir Disoproxil Fumarate and Entecavir in Patients with Chronic Hepatitis B: Efficacy and Safety Comparison

Kronik Hepatit B Hastalarında Tenofovir Disoproksil Fumarat ve Entecavir: Etkinlik ve Güvenlik Karşılaştırması

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ABSTRACT

Objectives: Two potent nucleoside analogues frequently used to treat chronic hepatitis B (CHB) are entecavir (ETV) and tenofovir disoproxil fumarate (TDF). The purpose of this study was to examine the virological and biochemical therapeutic responses to TDF and ETV in CHB patients and to assess their effects on renal function.

Materials and Methods: This was a single-center retrospective study. The study comprised patients diagnosed with CHB who had been treated with TDF or ETV for at least a year.

Results: A total of treatment-naive 269 patients were analyzed, of whom 29% were hepatitis B e antigen positive. Among the patients, 26% (n=70/269) received ETV, whereas 74% (n=199/269) received TDF treatment. Patients receiving TDF were younger than those treated with ETV. The TDF group had significantly higher baseline hepatitis B virus DNA levels (log_{10} IU/mL) than the ETV group. Complete virological response was achieved in 232 (86.2%) of patients. Antiviral efficacy was comparable between treatments; however, a greater decline in estimated glomerular filtration rate was observed among patients receiving TDF.

Conclusion: This study showed that TDF and ETV had comparable antiviral effectiveness. These findings provide updated real-world evidence supporting individualized selection of first-line antiviral therapy based on patients' renal profiles.

Keywords: Chronic hepatitis B, nucleos(t)ide analogues, entecavir, tenofovir disoproxil fumarate, virological response

ÖZ

Amaç: Kronik hepatit B (KHB) tedavisinde sıklıkla kullanılan iki güçlü nükleozit analoğu entecavir (ETV) ve tenofovir disoproksil fumarattır (TDF). Bu çalışmanın amacı, KHB hastalarında TDF ve ETV'ye karşı virolojik ve biyokimyasal tedavi yanıtlarını incelemek ve böbrek fonksiyonları üzerindeki etkilerini değerlendirmektir.

Gereç ve Yöntemler: Bu çalışma tek merkezli, retrospektif bir araştırma olarak tasarlanmıştır. Çalışmaya, en az bir yıl süreyle TDF veya ETV tedavisi alan KHB tanılı hastalar dahil edilmiştir.

Bulgular: Toplamda tedavi görmemiş 269 hasta analiz edildi; bunların %29'u hepatit B e antijeni pozitifti. Hastaların %26'sı (n=70/269) ETV alırken, %74'ü (n=199/269) TDF tedavisi aldı. TDF alan hastalar, ETV ile tedavi edilenlerden daha gençti. TDF grubunun, ETV grubuna göre anlamlı derecede daha yüksek başlangıç hepatit B virüsü DNA seviyelerine (log_{10} IU/mL) sahip olduğu görüldü. Hastaların 232'sinde (%86,2) tam virolojik yanıt elde edildi. Antiviral etkinlik her iki tedavi grubu arasında benzer bulunmakla birlikte, tahmini glomerüler filtrasyon hızındaki düşüş TDF kullanan hastalarda daha belirgin olarak saptandı.

Sonuç: Bu çalışmanın sonuçları, TDF ve ETV'nin antiviral etkinliklerinin benzer olduğunu göstermektedir. Bulgularımız, ilk basamak antiviral tedavinin hastaların renal profilleri dikkate alınarak bireyselleştirilmesi gerektiğini destekleyen güncel gerçek yaşam verileri sunmaktadır.

Anahtar Kelimeler: Kronik hepatit B, nükleoz(t)id analogları, entekavir, tenofovir disoproksil fumarat, virolojik yanıt

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Introduction

Chronic hepatitis B (CHB) continues to represent a major global health burden, affecting 254 million individuals worldwide, with 1.2 million new cases reported each year (1). In about 5% of adults and more than 90% of newborns infected with hepatitis B virus (HBV), the infection results in chronicity (2,3). Patients with CHB remain at lifelong risk for complications such as cirrhosis and hepatocellular carcinoma (HCC) (4).

The key objective of treatment is to achieve a functional cure, which is defined as the complete elimination of hepatitis B surface antigen, with or without seroconversion, as current antiviral drugs cannot completely eliminate HBV due to the persistence of covalently closed circular DNA in hepatocytes (5,6). Additional treatment goals, as outlined in international guidelines, include long-term virological suppression, normalization of serum aminotransferase levels, and achievement of serological endpoints (7,8).

Effective suppression of serum HBV-DNA has been as been related to a reduced risk of HCC and progressive liver disease (9,10). Nevertheless, a functional cure may still be achieved during long-term therapy. This usually follows a period of treatment during which HBV-DNA and hepatitis B e antigen (HBeAg) remain continuously undetectable (11,12). The purpose of this study was to assess and compare the therapeutic efficacy of tenofovir disoproxil fumarate (TDF) and entecavir (ETV) in patients with CHB, with a focus on suppression of HBV-DNA levels and normalization of alanine aminotransferase (ALT). Additionally, the impact of both drugs on renal function was examined by assessing changes in estimated glomerular filtration rate (eGFR). The study investigated evolving patterns in the choice of oral antiviral drugs for the management of CHB.

Materials and Methods

Between January 2015 and January 2022, a retrospective study was performed at a 507-bed tertiary hospital in İstanbul, Türkiye. Patients' demographic characteristics, biochemical and hematological laboratory parameters, and radiological imaging findings were obtained from the hospital's institutional clinical database. Treatment-naive patients with CHB who were started on TDF (300 mg once daily) or ETV (0.5 mg once daily) as initial treatment were included in the study. Patients who had co-infections with hepatitis C, hepatitis D, and human immunodeficiency viruses were excluded. Additional exclusion criteria included the presence of chronic liver diseases other than CHB and prior or ongoing immunosuppressive therapy during the study period. Real-time polymerase chain reaction assays were used to quantify serum HBV-DNA levels. The Artus HBV QS-RGQ Kit (Qiagen GmbH, Germany; lower limit of detection: 10.2 IU/mL) and COBAS AmpliPrep/COBAS TaqMan HBV assay version 2.0 (Roche Molecular Diagnostics, Pleasanton, CA, USA; lower limit of detection: 20 IU/mL) were used to measure viral load. The nucleic acid extraction and amplification procedures followed the manufacturer's standard protocols.

A complete virological response (CVR) was defined as undetectable serum HBV-DNA levels after 12 months of therapy. A partial virological response was defined as a decrease in HBV-DNA levels of more than 1 $\log_{10}$ IU/mL. Classification of HBeAg-negative and HBeAg-positive CHB was defined according to the 2025 European Association for the Study of the Liver guidelines, and HBV-DNA values >5 $\log_{10}$ IU/mL were considered as high viral load (13).

The Ishak-modified histological activity index was used to assess necroinflammatory and fibrotic activity in liver biopsy specimens (14). The biochemical response was determined by ALT normalization. Biochemical and virological responses were evaluated and compared between treatment groups at weeks 24 and 48. Achievement of a complete virological and biochemical response at one year was defined as the primary endpoint, while secondary endpoints included partial virological response and changes in renal function.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range), as appropriate, while categorical variables were presented as frequencies and percentages. Data distribution was assessed using the Kolmogorov-Smirnov test. Group comparisons were conducted using the Student's t-test or Mann-Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. A two-sided p-value <0.05 was considered statistically significant.

Ethics Statement

The study received ethical approval from the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no: 2023-02-19, date: 23.01.2023).

Results

The study comprised 269 patients, 60.2% of whom were male, with a mean age of 44.1±13.4 years. HBeAg positivity was present in 29% of patients; 74% were treated with TDF and 26% with ETV. The median ALT level was 44 IU/L, whereas the median serum HBV-DNA level was 6.16 $\log_{10}$ IU/mL. Patients treated with TDF were younger than those receiving ETV (41.9±12.9 vs. 50.4±12.8 years; p=0.001). Table 1 summarizes the demographic, biochemical, viral, and histopathological features of the patients.

The TDF group had higher initial HBV-DNA levels than the ETV group (6.43 vs. 5.78 $\log_{10}$ IU/mL; p=0.016). A CVR was observed in 86.2% of patients and was comparable between the TDF and ETV groups (p=0.339). There was no significant difference between treatment groups (p=0.905), and most patients (68.5%) who achieved CVR had high baseline HBV-DNA levels. At 12 months, the median HBV-DNA level in patients without CVR was 1,490 IU/mL (minimum:

Table 1. Demographic characteristics, biochemical and virological responses of patients with chronic hepatitis B

	Total	ETV	TDF	p
Number of patients (%)	269 (100)	70 (26)	199 (74)	
Age (mean ± SD)	44.1±13.4	50.4±12.8	41.9±12.9	0.001
Gender, n (%) Male Female	 162 (60.2) 107 (39.8)	 38 (54.3) 32 (45.7)	 124 (62.3) 75 (37.7)	0.238
HBeAg-positive (%)	78 (29)	19 (27.9)	59 (30.3)	0.719
Anti HBe-positive (%)	186 (69.1)	49 (72.1)	137 (70.3)	0.779
ALT (IU/L) (median)	44	42	44	0.960
AST (IU/L) (median)	34	39	34	0.385
Creatinin (mg/dL) (median)	0.7	0.7	0.7	0.310
AFP (IU/mL) (median)	3.1	3.1	3.1	0.761
Albumin (g/dL) (median)	43	42	44	0.076
PLT (103/µL) (median)	218	226	215	0.692
HAI (median)	6	6	6	0.575
Fibrosis (median)	2	2	2	0.233
HBV-DNA PCR (log_{10} IU/mL) (median)	6.16	5.78	6.43	0.016
HBV-DNA PCR-negative at 24 weeks (%)	168 (71.8)	47 (77)	121 (69.9)	0.289
CVR (%)	232 (86.2)	58 (82.9)	174 (87.4)	0.339
ALT normalization at 48 weeks (%)	88 (86.3)	20 (83.3)	68 (87.2)	0.632

ETV: Entecavir, TDF: Tenofovir disoproxil fumarate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, AFP: Alfa feto protein, PLT: Platelet count, HAI: Histology activity index, CVR: Complete virological response, HBV: Hepatitis B virus, HBeAg: Hepatitis B e antigen, Anti HBe: Antibodies against hepatitis B e antigen, SD: Standard deviation, PCR: Polymerase chain reaction

51, maximum: 10348) for patients without a CVR. Initially, 43.9% of patients had elevated ALT levels. ALT normalization occurred in 21.2% of these patients at month 6 and increased to 74.6% by the end of the first year (p=0.632). However, when comparing the groups with respect to ALT normalization, no statistically significant differences were observed at either the six-month [p=0.394, odds ratio (OR): 0.65, 95% confidence interval (CI): 0.24-1.73] or the one-year (p=0.735, OR: 1.36, 95% CI: 0.38-4.80) follow-ups.

Clinical and virological characteristics were compared between patients achieving partial and CVRs. Patients older than 40 years and those with elevated baseline HBV-DNA levels showed higher CVR rates; however, these differences were not statistically significant (p=0.16 and p=0.14).

Histological activity index scores (p=0.98) and fibrosis stages (p=0.34) were similar between patients with partial and CVRs (Table 2).

At 12 months, renal function data were available for 242 patients (180 in the TDF group and 62 in the ETV group). The mean eGFR in the TDF group decreased considerably from 115.2±14.9 mL/min/1.73 m^2 at baseline to 109.1±8.7 mL/min/1.73 m^2 after one year (p<0.001) (Figure 1a). Patients receiving ETV did not have a significant change in renal function, with mean eGFR values of 107.0±16.1 mL/min/1.73 m^2 at treatment initiation and 109.8±9.3 mL/min/1.73 m^2 at one-year follow-up (p=0.586). (Figure 1b). Changes in eGFR differed significantly between the treatment groups (p<0.001) (Figure 1c).

Discussion

Due to their potent antiviral activity and high genetic barriers to resistance, ETV and TDF are frequently used as first-line treatments (15,16). Although both agents are well established, treatment selection should balance antiviral efficacy with long-term safety considerations. In the current study, we evaluated the efficacy and clinical outcomes of TDF or ETV in treatment-naive patients, offering valuable insights that could shape treatment decisions and improve patient care.

In treatment-naive patients with CHB, TDF and ETV have shown similar and high rates of CVR (17,18,19). CVR rates at week 48 were reported to be 92.5% in the TDF group and 83.3% in the ETV group in a large cohort study by Riveiro-Barciela et al. (20) involving 611 treatment-naive patients. Park et al. (21) found CVR rates of 81% in patients receiving TDF and 72% in those receiving ETV, whereas Batirel et al. (22) reported lower rates of 74.7% and 58.4%, respectively. Variations among studies may result from differences in HBV-DNA level thresholds, treatment adherence, or patient characteristics.

Ha et al. (23) reported that patients treated with TDF were younger than those treated with ETV, while Alkan et al. (24) found no significant age difference. The younger age of patients receiving TDF may reflect a clinical preference to avoid potential renal and bone toxicity in older individuals. Despite higher baseline HBV-DNA levels in the TDF group, pretreatment viral load did not

Table 2. Evaluation of the parameters affecting CVR

	PVR	CVR	p
Number of patients, n (%)	37 (13.8)	232 (86.2)	
Gender, n (%) Male Female	 19 (51.4) 18 (48.6)	 143 (61.6) 89 (38.4)	0.23
Age (mean ± SD)	46.35±13.87	43.81±13.33	0.28
Age ≥40 years, n (%)	26 (70.3)	135 (58.2)	0.16
HBV-DNA>100000 IU/mL, n (%)	21 (56.8)	160 (69)	0.14
Higher baseline ALT level, n (%)	13 (44.8)	105 (54.1)	0.35
HAI, n (%)			0.98
<6	11 (31.4)	65 (29.8)	
6-8	18 (51.4)	115 (52.8)	
≥9	6 (17.1)	38 (17.4)	
Fibrozis, n (%)			0.34
0-2	31 (86.1)	173 (79.7)	
3-4	3 (8.3)	37 (17.1)	
≥5	2 (5.6)	7 (3.2)	
ALT, median (IQR)	39 (22.5-74)	44 (26.75-90)	0.43
HAI, median (IQR)	6 (5-7)	6 (5-7)	0.71
Fibrozis, median (IQR)	2 (2-2)	2 (2-2)	0.15
PLT, median (IQR)	225.5 (176.5-283.75)	216.5 (182-248)	0.32

IQR: Interquartile range, ALT: Alanine aminotransferase, HAI: Histology activity index, SD: Standard deviation, CVR: Complete virological response, PVR: Partial virological response, PLT: Platelet count, HBV: Hepatitis B virus

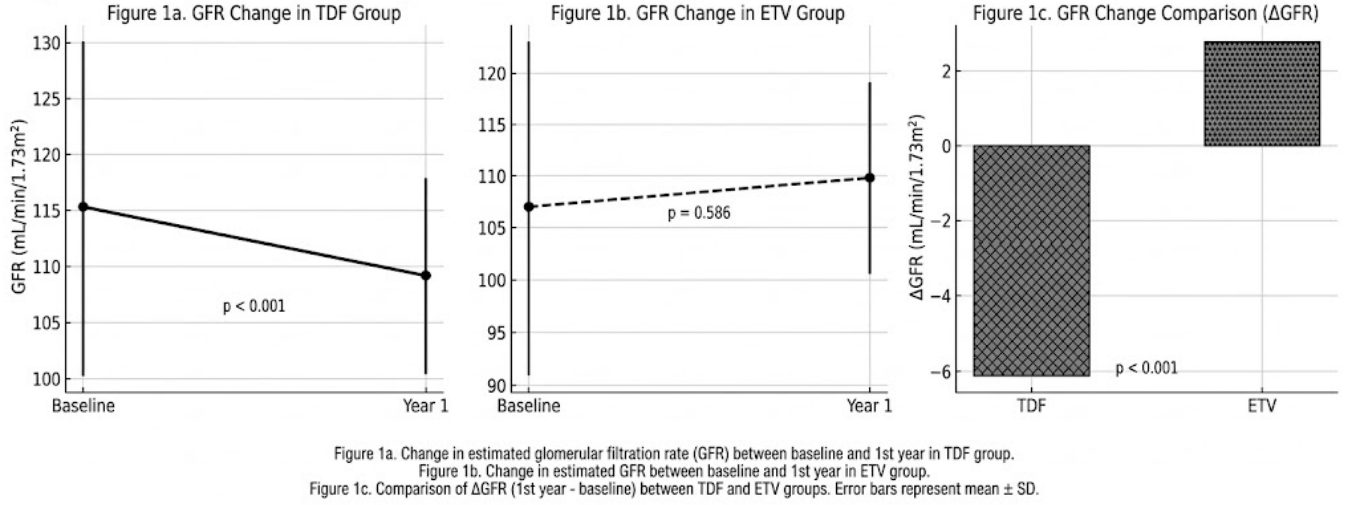

Figure 1. a. Changes in estimated glomerular filtration rate (GFR) between baseline and the first year in the TDF group. b. Changes in estimated GFR between baseline and the first year in the ETV group. c. Comparison of GFR change (ΔGFR) between the TDF and ETV groups

TDF: Tenofovir disoproxil fumarate, ETV: Entecavir

independently affect virological response, indicating that ETV and TDF are comparably effective across different viral load levels. In accordance with our findings, Yang et al. (25) reported higher baseline HBV-DNA levels in patients treated with TDF than in those receiving ETV, while similar trends were observed by Li et al. (26). These data highlight differences in baseline viral load distribution between treatment groups and underscore the clinical importance of HBV-DNA monitoring in therapeutic decision-making.

Biochemical response, as reflected by normalization of serum ALT levels, is among the earliest treatment outcomes observed in clinical practice. ALT levels are often used as an indirect marker of hepatic activity, and their normalization after antiviral therapy

suggests improvement in liver inflammation. Ha et al. (23) evaluated 557 treatment-naive patients and reported ALT normalization rates of 80.1% and 85.6% with TDF and ETV, respectively, at week 48. According to Güzelbulut et al. (18), there was not a significant difference in ALT normalization rates between TDF and ETV (79.2% vs. 85%). ALT normalization rates were similar between TDF and ETV in our study (87.2% vs. 83.3%, p=0.632), consistent with previous studies (17,27,28).

TDF treatment was associated with higher serum creatinine levels and a more marked decline in eGFR at one year compared with ETV. Long-term exposure to TDF is associated with a higher decline in renal function than ETV in patients with CHB, according to prior studies by Jung et al. (29) and Lee et al. (30). Therefore, for patients with baseline renal impairment or those at risk for nephrotoxicity, ETV should be considered a safer therapeutic option. Overall, these results support current evidence and emphasize that careful, sustained monitoring of renal function is essential when TDF is used for long-term antiviral therapy.

Study Limitations

Our study had some limitations. Initially, it was designed as a retrospective study, was carried out at a single-center, and included patients followed in an infectious diseases outpatient clinic. Second, the follow-up period was limited to 48 months, which prevented the assessment of long-term outcomes such as liver decompensation, HCC, or overall survival. Moreover, the lack of detailed data regarding concomitant medications with potential renal effects may have influenced renal outcome assessments. Therefore, studies with longer follow-up and larger patient populations are required. This study is strengthened by its large sample size and the high proportion of patients who underwent liver biopsy.

Conclusion

The research presented here reveals our preference for ETV and TDF as well as a comprehensive review of their therapeutic efficacy, highlighting the advantages of each in therapy. High and comparable rates of virological and biochemical responses were observed with TDF and ETV. However, TDF was associated with a significantly greater decline in eGFR compared with ETV, indicating a greater adverse effect on renal function. These findings are consistent with previous studies but provide updated evidence from a contemporary real-world cohort, reflecting current treatment practices. By simultaneously evaluating antiviral efficacy and renal safety, this study contributes to a more balanced understanding of the risk–benefit profile. ETV may be preferred in patients with pre-existing renal impairment, while TDF remains an effective option for patients with preserved renal function requiring potent viral suppression. This study, therefore, contributes timely clinical data to the ongoing discussion on optimizing the management of CHB in the era of lifelong antiviral therapy.

Ethics

Ethics Committee Approval: The study received ethical approval from the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no: 2023-02-19, date: 23.01.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.B., A.İ.S., F.B.E., E.C.Ü., Concept: D.B., Y.E.Ö., S.Ş., Z.Ç., H.K.K., K.K.Y., Design: D.B., Y.E.Ö., Z.Y., Data Collection or Processing: D.B., E.S.D., A.S.D., Analysis or Interpretation: D.B., Y.E.Ö., Z.Y., S.Ş., Z.Ç., H.K.K., K.K.Y., Literature Search: D.B., Writing: D.B.

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

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Research Article

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Real-World Evaluation of APRI and FIB-4 Scores in Patients with Chronic Hepatitis C Treated with Direct-Acting Antivirals

Kronik Hepatit C Hastalarında Doğrudan Etkili Antiviral Tedavi Sonrası APRI ve FIB-4 Skorlarının Gerçek Yaşam Verileriyle Değerlendirilmesi

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ABSTRACT

Objectives: This study aimed to evaluate biochemical response, sustained virological response (SVR) rates, and changes in non-invasive fibrosis markers [aspartate aminotransferase (AST) to platelet ratio index (APRI) and fibrosis-4 index (FIB-4)] using real-world data in patients with chronic hepatitis C virus (HCV) treated with direct-acting antivirals (DAAs).

Materials and Methods: Patients aged ≥18 years with chronic HCV who were followed between January 2018 and December 2024 and treated with glecaprevir/pibrentasvir, sofosbuvir/velpatasvir/voxilaprevir, or ledipasvir/sofosbuvir were retrospectively analyzed. Alanine aminotransferase (ALT), AST, platelet count, and HCV-RNA levels were recorded at baseline, at treatment week 4, at end of treatment, and at 12 and 24 weeks after treatment completion. APRI and FIB-4 scores were calculated at each time point.

Results: A total of 43 patients were included; the median age was 57 years (interquartile range: 43-65), and 58% were male. ALT and AST levels decreased significantly from treatment week 4 onward ($p<0.001$). APRI scores showed a significant early decline that persisted throughout the follow-up period ($p<0.001$). FIB-4 scores decreased significantly at week 4; however, this reduction was not sustained during follow-up. A strong correlation was observed between changes in APRI and ALT, whereas the association between FIB-4 and ALT was weak and limited. SVR12 and SVR24 rates were 100% among patients with available HCV-RNA data.

Conclusion: In real-world settings, DAA therapy achieves high SVR rates and rapid biochemical improvement. The early and persistent decline in APRI reflects regression of inflammatory activity, while the limited change in FIB-4 suggests that longer follow-up may be required to adequately assess fibrosis regression.

Keywords: Chronic hepatitis C, direct-acting antivirals, APRI, FIB-4, real-world data

ÖZ

Amaç: Bu çalışmada, doğrudan etkili antiviral (DAA) tedavi alan kronik hepatit C virüs (HCV) hastalarında gerçek yaşam verileri kullanılarak biyokimyasal yanıt, kalıcı virolojik yanıt (SVR) oranları ve invaziv olmayan fibrozis belirteçleri olan aspartat aminotransferaz (AST) trombosit oranı indeksi (APRI) ve fibrozis-4 indeksi (FIB-4) skorlarındaki değişimlerin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Ocak 2018-Aralık 2024 tarihleri arasında kronik HCV tanısıyla izlenen ve glekaprevir/pibrentasvir, sofosbuvir/velpatasvir/voxilaprevir veya ledipasvir/sofosbuvir ile tedavi edilen ≥18 yaş hastalar retrospektif olarak analiz edildi. Alanin aminotransferaz (ALT), AST, trombosit sayısı ve HCV-RNA düzeyleri; başlangıçta, tedavinin 4. haftasında, tedavi sonunda ve tedavi bitiminden 12 ve 24 hafta sonra kaydedildi. APRI ve FIB-4 skorları her zaman noktasında hesaplandı.

Bulgular: Çalışmaya toplam 43 hasta dahil edildi; medyan yaş 57 (çeyrekler arası aralık: 43-65) yıl olup hastaların %58'i erkekti. ALT ve AST düzeyleri tedavinin 4. haftasından itibaren anlamlı olarak azaldı ($p<0,001$). APRI skorlarında erken dönemde anlamlı bir düşüş saptandı ve bu düşüş izlem boyunca sürdü ($p<0,001$). FIB-4 skorları 4. haftada anlamlı olarak azalsa da, izlem süresince bu düşüş korunmadı. APRI değişimi ile ALT değişimi arasında güçlü bir ilişki saptanırken, FIB-4 değişimi ile ALT değişimi arasında zayıf ve sınırlı bir ilişki izlendi. HCV-RNA verisi bulunan hastalarda SVR12 ve SVR24 oranları %100 idi.

Sonuç: Gerçek yaşam koşullarında DAA tedavisi yüksek SVR oranları ve hızlı biyokimyasal düzelme sağlamaktadır. APRI skorlarındaki erken ve kalıcı düşüş enflamatuvar aktivitenin gerilemesini yansıtırken, FIB-4 skorlarındaki sınırlı değişim fibrozis regresyonunun yeterli şekilde değerlendirilebilmesi için daha uzun izlem sürelerine ihtiyaç olabileceğini düşündürmektedir.

Anahtar Kelimeler: Kronik hepatit C, doğrudan etkili antiviraller, APRI, FIB-4, gerçek yaşam verisi

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Introduction

Hepatitis C virus (HCV) infection remains a major global public health problem (1). According to World Health Organization data, approximately 50 million people worldwide are living with chronic HCV infection, and nearly 1 million new cases are reported annually (2). HCV is one of the leading causes of chronic hepatitis, cirrhosis, and hepatocellular carcinoma, and it is a major cause of mortality from chronic viral hepatitis.

In Türkiye, the prevalence of HCV infection in the general population has been reported to range between 0.3% and 1%; however, this rate is significantly higher among risk groups such as intravenous drug users and patients undergoing hemodialysis (3,4). Genotype 1b is the most frequently observed HCV genotype in Türkiye and plays a determinant role in both the natural course of the disease and treatment response (5).

In recent years, the introduction of direct-acting antiviral (DAA) agents into clinical practice has represented a revolutionary milestone in the treatment of HCV infection. These agents provide high rates of virological response with interferon-free regimens of short duration and offer substantial advantages in terms of both efficacy and safety (6). Although the effectiveness of DAA therapies is well established, real-world data regarding the short- and mid-term behavior of non-invasive fibrosis scores following treatment remain limited and heterogeneous.

The present study aimed to evaluate real-world data from patients with chronic HCV infection receiving DAA therapy and to assess post-treatment biochemical responses and changes in non-invasive fibrosis scoring systems.

Materials and Methods

This single-center observational study was designed as a retrospective analysis of patients diagnosed with chronic HCV who were followed between 01 January 2018 and 31 December 2024 and who received new-generation DAA therapy. Patients aged ≥18 years with a diagnosis of chronic HCV infection who were followed in our outpatient clinic and treated with glecaprevir/pibrentasvir (G/P), sofosbuvir (SOF)/velpatasvir (VEL)/voxilaprevir (VOX), or ledipasvir (LDV)/SOF were included. Patients with a history of liver transplantation, those with poor treatment adherence, or those who did not complete treatment were excluded. Treatment duration was determined in accordance with national and international guidelines.

Patient age, treatment history, year of diagnosis, interval between diagnosis and initiation of DAA therapy, genotype, and the presence of cirrhosis, hepatocellular carcinoma, and coinfections were recorded. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count, and HCV-RNA levels were recorded at baseline, at week 4 of treatment, at the end of treatment (EOT), and at weeks 12 sustained virological response (SVR12) and 24 (SVR24) after treatment completion. AST to platelet ratio index (APRI) and fibrosis-4 index (FIB-4) scores were calculated at each time point.

Biochemical response was defined as a serum ALT level below 40 IU/L. Virological response was defined as undetectable HCV-RNA levels measured by polymerase chain reaction. SVR was defined as continued HCV-RNA negativity for at least 12 weeks after completion of treatment.

Statistical Analysis

Statistical analyses were performed using Jamovi software (version 2.7.13). Continuous variables were presented as median [interquartile range (IQR)] or mean ± standard deviation, depending on distribution. Paired continuous variables measured before and after treatment were compared using the Wilcoxon signed-rank test. Comparisons between APRI ≥1.5 and <1.5 subgroups were performed using the Mann-Whitney U test. Associations between variables were assessed using Spearman's correlation coefficient based on distributional assumptions. A p-value <0.05 was considered statistically significant.

Ethical approval for the study was obtained on 17 December 2024 from the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (approval number: 4669). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was waived due to the retrospective design of the study.

Results

During the study period, 62 patients were evaluated; however, DAA therapy could not be initiated in 19 patients due to administrative and reimbursement-related constraints. A total of 43 patients were ultimately included in the analysis. Baseline demographic and clinical characteristics are summarized in Table 1. The median age was 57 years (IQR: 43-65), and 58.1% of patients were male. Most patients were treatment-naïve (90.7%), and cirrhosis and hepatocellular carcinoma were present in one patient each (2.3%).

Among the 34 patients with available genotype data, genotype 1b was predominant (n=21, 61.8%), followed by genotype 1a (n=7, 20.6%), genotype 3 (n=4, 11.8%), and genotype 4 (n=1, 2.9%); one patient had a mixed genotype 3 and 4 infection. Treatment regimens

Table 1. Baseline characteristics

Variable	Value
Age, median (IQR), years	57 (43-65)
Male sex, n (%)	25 (58.1)
Treatment-naïve, n (%)	39 (90.7)
Cirrhosis, n (%)	1 (2.3)
Hepatocellular carcinoma, n (%)	1 (2.3)
HBV coinfection, n (%)	3 (7.0)
HIV coinfection, n (%)	2 (4.7)
Genotype 1b, n/N (%)	21/34 (61.8)
Time from diagnosis to treatment, months, median (IQR)	5 (2-36)

IQR: Interquartile range, HBV: Hepatitis B virus, HIV: Human immunodeficiency virus

included G/P for 8 weeks in 38 patients; SOF/VEL/VOX for 8 weeks in 3 patients; LDV/SOF for 24 weeks in 1 patient; and LDV/SOF plus ribavirin for 4 weeks in 1 patient.

At baseline, ALT elevation (>40 U/L) was present in 58.1% of patients, and AST elevation was observed in 37.2% of patients. Median ALT was 45 U/L (IQR: 27.5-65.5), median AST was 37 U/L (IQR: 27-48), and median platelet count was 240×10^9/L (IQR: 206.5-274). The median HCV-RNA level was 6.03×10^5 IU/mL (IQR: 1.48×10^5-1.59×10^6).

Baseline medians for APRI and FIB-4 scores were 0.369 (IQR: 0.272-0.552) and 1.272 (IQR: 0.849-1.659), respectively. According to APRI categories, 65.1% of patients had APRI <0.5, 27.9% had APRI between 0.5 and 1.5, and 7.0% had APRI ≥1.5. According to FIB-4 categories, 60.5% had FIB-4 <1.45, 34.9% had FIB-4 between 1.45 and 3.25, and 4.7% had FIB-4 ≥3.25.

At week 4 of treatment, ALT and AST levels decreased significantly compared with baseline ($p<0.001$), with normalization observed in all patients; this biochemical response was maintained at EOT and during post-treatment follow-up at weeks 12 and 24 (Table 2).

Both APRI and FIB-4 scores showed a decreasing trend during treatment. Reductions in APRI and FIB-4 at week 4 were statistically significant compared with baseline (both $p<0.01$). APRI demonstrated an early and sustained decline throughout follow-up ($p<0.001$), whereas FIB-4 showed a significant reduction only at week 4, with no statistically significant changes at EOT or SVR24. At EOT, no patients had APRI ≥1.5, whereas two patients had FIB-4 >3.25. A borderline decrease in FIB-4, observed at SVR12, should be interpreted cautiously due to the limited sample size and missing data (Table 2).

A strong positive correlation between the reduction in APRI scores (ΔAPRI) and the decrease in ALT levels (ΔALT) was observed at week 4 (Spearman's $\rho=0.822$, $p<0.001$; n=38) and persisted at EOT ($\rho=0.894$, $p<0.001$; n=33). Although correlation coefficients declined during follow-up, the associations remained statistically significant (SVR12: $\rho=0.693$, $p<0.001$; n=21; SVR24: $\rho=0.715$, $p<0.001$; n=20).

In contrast, no significant correlation was found between changes in FIB-4 scores (ΔFIB-4) and ALT reduction at week 4 (Spearman's $\rho=0.227$, $p=0.159$). A weak-to-moderate association was observed at EOT ($\rho=0.423$, $p=0.011$), but this relationship was not sustained during follow-up.

At week 4 of treatment, HCV-RNA was undetectable in all but three patients, whose HCV-RNA levels were 70, 80, and 135 IU/mL, respectively. At EOT and week 12, all 23 patients with available data were HCV-RNA negative. Similarly, all 19 patients with available data at week 24 remained HCV-RNA negative. Both SVR12 and SVR24 rates were 100%.

In subgroup analyses based on fibrosis level, patients with baseline APRI ≥1.5 showed more pronounced reductions in ALT and AST levels compared with those with APRI <1.5 (Mann-Whitney U test, $p<0.05$).

Comparisons between treatment regimens could not be performed due to a disproportionate distribution. All treatment regimens were well tolerated, with no treatment discontinuations or serious adverse events reported.

Discussion

In this study, biochemical and virological responses, as well as changes in non-invasive fibrosis markers, were evaluated using real-world data from patients with chronic HCV infection treated with DAAs. Our findings demonstrate marked biochemical improvement during the early treatment period, high rates of SVR, and distinct temporal dynamics of non-invasive fibrosis indices.

Randomized controlled trials have reported SVR rates of 95-99% with DAA therapies across different genotypes (7,8,9,10,11,12,13). In our study, the observation of 100% SVR12 and SVR24 rates among patients with available data further supports the high efficacy and reliability of current DAA regimens in real-world clinical practice.

Regarding the biochemical response, ALT and AST levels normalized rapidly and markedly, particularly during the early treatment period. Early normalization of transaminases following DAA therapy reflects the prompt resolution of biochemical inflammation. Previous studies have reported ALT normalization rates of approximately 85% as early as two weeks after treatment initiation, increasing to over 90% at SVR12. An early biochemical response not only reflects virological suppression but also serves as an important indicator of treatment response in clinical practice. Long-term follow-up studies have shown that biochemical improvement is largely sustained, although a small proportion of patients may exhibit persistent or recurrent ALT elevation despite achieving SVR, often due to non-HCV-related factors such as

Table 2. Biochemical and fibrosis markers over time

Parameter	Baseline	Week 4	EOT	SVR12	SVR24	p-value*
ALT (U/L), median (IQR)	45 (27.5-65.5)	15 (12.75-20.25)	15 (13-18)	12 (10.5-16)	15 (14-17)	<0.001
AST (U/L), median (IQR)	37 (27-48)	19.5 (18-24.25)	21 (17-24.5)	19 (17-22.5)	21 (16.25-21)	<0.001
APRI, median (IQR)	0.369 (0.272-0.552)	0.21 (0.17-0.30)	0.232 (0.178-0.284)	0.240 (0.18-0.29)	0.199 (0.176-0.258)	<0.001
FIB-4, median (IQR)	1.272 (0.849-1.659)	1.10 (0.86-1.58)	1.151 (0.978-1.542)	1.40 (0.91-1.74)	1.174 (0.696-1.740)	0.08
APRI ≥1.5, n (%)	3 (7.0)	0	0	0	0	—
FIB-4 >3.25, n (%)	2 (4.7)	2	2	0	0	—

*p-values represent comparisons between baseline and the last available follow-up using the Wilcoxon signed-rank test. SVR: Sustained virological response, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, IQR: Interquartile range, FIB-4: Fibrosis-4 index, APRI: AST to platelet ratio index, EOT: End of treatment

metabolic syndrome, non-alcoholic fatty liver disease, or alcohol use (14,15).

When evaluated together, APRI and FIB-4 demonstrated different response patterns to antiviral therapy. The early and marked decline in APRI scores suggests that individuals with higher inflammatory activity may exhibit a more pronounced biochemical response to antiviral treatment. The greater reduction in ALT levels among patients with baseline APRI ≥1.5 further supports this observation.

Although a statistically significant reduction in FIB-4 scores was observed at week 4, the lack of sustained significance during follow-up suggests that this index may be less influenced by short-term biochemical changes and, therefore, represent a more stable marker of fibrosis burden. The weak and inconsistent association between changes in FIB-4 scores and reductions in ALT further supports this interpretation. Previous studies have similarly reported significant and sustained decreases in APRI scores after DAA therapy, whereas changes in FIB-4 scores were more limited and occurred later in the follow-up period (16). These findings indicate that APRI and FIB-4 should not be considered interchangeable markers reflecting the same biological process, but rather complementary parameters representing different pathophysiological components that evolve on different time scales following DAA therapy.

All treatment regimens were well tolerated, with no serious adverse events or treatment discontinuations, consistent with existing real-world safety data on DAA therapies (17).

Study Limitations

This study has several limitations. Its retrospective and single-center design, relatively small sample size, and limited follow-up duration limit assessment of long-term fibrosis regression. The retrospective design and limited sample size reduced statistical power in some subgroup analyses, and comparisons between treatment regimens could not be performed because of unequal distribution across regimens. The absence of histological confirmation or elastography data limited the assessment of fibrosis to serological scores. Nevertheless, the presentation of real-world data, demonstration of virological success at all follow-up points, and detailed evaluation of the temporal behavior of APRI and FIB-4 scores represent notable strengths of this study.

No external financial support was received for this study. The authors declare no conflicts of interest.

Conclusion

G/P and other DAA regimens provide high SVR rates and rapid biochemical improvement under real-world conditions. The marked reduction in APRI scores suggests regression of inflammatory activity, whereas the limited change in FIB-4 scores indicates that longer follow-up periods may be required to assess fibrosis regression. These findings provide real-world evidence from Türkiye, supporting the effectiveness and safety of DAA therapies in clinical settings aligned with global HCV elimination goals.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained on 17 December 2024 from the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (approval number: 4669).

Informed Consent: Written informed consent was waived due to the retrospective design of the study.

Footnotes

Authorship Contributions

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

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Molecular Evaluation of Concomitant HBsAg, and Anti-HBs Positivity in Chronic Hepatitis B Patients

Kronik Hepatit B Hastalarında Eş Zamanlı HBsAg ve Anti-HBs Pozitifliğinin Moleküler Değerlendirmesi

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ABSTRACT

Objectives: The hepatitis B virus (HBV) has a high mutation rate during replication, leading to the production of different variants. However, such atypical profiles could also be due to variant strains resulting from mutations. This study aimed to determine the mutations responsible for this profile and the presence of mutant strains by performing sequence analysis of the HBV pol/S gene regions in patients with chronic HB infection who were found to have coexisting HB surface antigen (HBsAg) and anti-HBs positivity during their follow-up.

Materials and Methods: The study group consisted of patients who were found to be simultaneously positive for HBsAg and anti-HBs during routine follow-up for chronic HBV infection between 2021 and 2022. Mutations in the pol/S gene regions of HBV-DNA- positive patients were investigated using HBV-DNA sequencing technology.

Results: The coexistence of HBsAg and anti-HBs was observed in 33 patients (3.8%). Anti-HBe was positive in all cases. Thirteen (39.4%) patients were HBV-DNA positive (minimum 6.9+E1 IU, maximum 3.7+E6 IU). All patients had HBV genotype D, and the D1/D2 ratio was 45.5%/54.6%. Among HBV-DNA-positive patients, 11 (84.6%) had pol/S gene mutations. Sixty-eight HBsAg mutations (42.8%) and 91 reverse transcriptase (RT) mutations (57%) were detected in these cases, representing a total of 159 mutations. In total, three patients (27.2%) had clinically significant HBsAg mutations, and four (36.3%) had RT mutations. Drug resistance was detected in 18.2% of cases. A vaccine-escape HBsAg mutation was detected in two cases (18.1%).

ÖZ

Amaç: Hepatit B virüsü (HBV), replikasyon sırasında yüksek bir mutasyon oranına sahiptir ve bu durum çeşitli varyantların oluşmasına yol açmaktadır. Ancak, bu atipik profiller, mutasyonlardan kaynaklanan varyant suşlardan da kaynaklanabilir. Bu çalışma, kronik HB enfeksiyonu olan ve takipleri sırasında eş zamanlı HB yüzey antijeni (HBsAg) ve anti-HBs pozitifliği saptanan hastalarda HBV pol/S gen bölgelerinin sekans analizi yapılarak, bu profili oluşturan mutasyonları ve mutant suşların varlığını belirlemeyi amaçlamıştır.

Gereç ve Yöntemler: Çalışma grubu, 2021 ve 2022 yılları arasında kronik HBV enfeksiyonu için rutin takip sırasında eş zamanlı olarak HBsAg ve anti-HBs pozitifliği saptanan hastalardan oluşmuştur. HBV-DNA pozitif hastaların pol/S gen bölgelerindeki mutasyonlar, HBV-DNA sekanslama teknolojisi kullanılarak araştırılmıştır.

Bulgular: HBsAg ve anti-HBs'nin birlikte bulunması 33 (%3,8) hastada saptanmıştır. Tüm olgularda anti-HBe pozitifti. On üç (%39,4) hastada HBV-DNA pozitifliği saptandı (minimum 6,9+E1 IU, maksimum 3,7+E6 IU). Tüm hastalarda HBV genotipi D idi ve D1/D2 oranı %45,5/%54,6 idi. HBV-DNA pozitif hastaların 11'inde (%84,6) pol/S gen mutasyonu bulundu. Bu olgularda 68 (%42,8) HBsAg mutasyonu ve 91 (%57) ters transkriptaz (RT) mutasyonu saptandı ve toplamda 159 mutasyon tespit edildi. Toplamda üç hastada (%27,2) klinik olarak anlamlı HBsAg mutasyonu, dört hastada (%36,3) RT mutasyonu saptandı. Olguların %18,2'sinde ilaç direnci saptandı. İki olguda (%18,1) aşıdan kaçış HBsAg mutasyonu saptandı.

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Conclusion: The mutations detected in the pol/S gene sequence analyses of patients with HBsAg and anti-HBs coexistence seen in the course of chronic HB infection are naturally occurring, and the coexistence of HBsAg and anti-HBs could not be explained by these mutations.
Keywords: HBsAg, anti-HBs, chronic hepatitis B, coexistence, mutation

Sonuç: Kronik HB enfeksiyonu sürecinde HBsAg ve anti-HBs birlikteliği görülen hastalarda pol/S gen sekans analizlerinde saptanan mutasyonlar genellikle doğal olarak oluşan mutasyonlardır ve HBsAg ile anti-HBs birlikteliği bu mutasyonlarla açıklanamayacağı düşünüldü.
Anahtar Kelimeler: HBsAg, anti-HBs, kronik hepatit B, birliktelik, mutasyon

Introduction

Hepatitis B virus (HBV) is a double-stranded DNA virus belonging to the family *Hepadnaviridae* and is part of the *Orthohepadnavirus* group. It has 10 different genotypes (A-J) and several subgenotype (1,2). Among the polymorphism patterns of genotype D, the model types D1, D2, and D6 were commonly observed. Genotypes influence the natural history and clinical outcomes of HBV and response to treatment in chronic patients (3,4,5). Chronic HB (CHB), characterized by HB surface antigen (HBsAg) positivity for more than six months, has emerged as a major public health problem worldwide (1). The most common genotype in Türkiye is genotype D (3,6,7,8).

The S region of HBV-DNA comprises the S gene and pre-S gene regions. This gene region encodes three envelope proteins of the HBsAg: small (S protein), medium (M protein), and large (L protein). Differences in these proteins are caused by synthesis starting from different codons within on the same gene (9). Serological and molecular tests, including HBsAg and anti-HBs antibodies, are used for the diagnosis and follow-up of HB infection. Although HBsAg is a marker of HBV infection, anti-HBs is a marker of immunity to HBV infection. Anti-HBs generally appear after the loss of HBsAg. Simultaneous HBsAg and anti-HBs positivity is not an expected condition (10). The mechanisms leading to simultaneous HBsAg and anti-HBs antibody positivity remain controversial. This atypical serological profile may result from laboratory error or be caused by viral and host-related factors (11).

Although the HBV is a DNA virus, it has a high replication capacity ($>10^{12}$ virion/day). Because the viral polymerase enzyme lacks proofreading activity during the reverse transcription process, it is susceptible to mutation during replication and has a high mutation frequency (10^{5} substitutions/base/cycle) (6). These mutations result in a large number of variants. Although most mutations are single nucleotide substitutions, they can sometimes occur as deletions or insertions. The coexistence of HBsAg and anti-HBs can be caused by mutant HBV strains escaping the immune system, point mutations occurring in the S gene, and rarely, pre-S and S gene deletion mutations, particularly mutations in the determinant "a" or polymerase region (12,13,14,15,16).

The aim of this study was to determine the presence of mutant strains by sequencing HBV gene regions and performing pol/S gene mutation analysis in patients with concurrent HBsAg and anti-HBs positivity who were followed up for CHB infection.

Materials and Methods

Between 2021 and 2022, patients aged >18 years who were diagnosed with CHB and followed up in the department of infectious diseases and clinical microbiology, and who simultaneously tested positive for both HBsAg and anti-HBs by ELISA (ARCHITECT HBsAg Qualitative II Reagent Kit, ARCHITECT Anti-HBs Qualitative II Reagent Kit, and ARCHITECT i2000SR Immunoassay Analyzer) were included in the study. Patients who did not simultaneously test positive for both HBsAg and anti-HBs or who had decompensated cirrhosis, delta virus, hepatitis C, or human immunodeficiency virus infection were excluded from the study. Mutation analysis was performed on serum samples from HBV-DNA positive patients, and the pol gene was amplified and sequenced. This is shown in the flowchart (Figure 1).

Written informed consent was obtained from all patients who agreed to participate in this study. Age, gender, HBsAg, anti-HBs, HBeAg, anti-HBe levels, HBV-DNA load, and current treatments were recorded. A 10-mL whole-blood sample was obtained from each patient. The separated sera were stored at -20 °C until the time of the study.

HBV-DNA Quantitation

A QIAsymphony SP magnetic particle isolation platform (QIAGEN GmbH, Hilden, Germany) was used to isolate HBV-DNA. HBV-DNA was quantified by real-time polymerase chain reaction using an artus HBV-DNA RGQ kit on the RotorGene platform (QIAGEN GmbH, Hilden, Germany).

HBV Genotyping and Resistance Analysis

HBV genotyping was performed by sequencing all known primary/compensatory nucleos(t)ide analogs, resistance mutations, and mutations of the S gene (HBsAg protein; amino acids 111-227) that overlap with the reverse transcriptase (RT) domain (RT region, amino acids 80-250) (17). Forward (F: 5'-TCGTGGTGGACTTCTCTCAATT-3') and reverse (R: 5'-CGTTGACAGACTTTCCAATCAAT-3') primers were used to amplify the HBV pol gene (742 bp). Phire Hot Start DNA polymerase (Finnzymes Oy, Finland) was used in the sequencing protocol. Sequencing was performed using the BigDye Terminator v3.1 Cycle Sequencing Kit (Amersham Pharmacia Biotech Inc., USA) according to the manufacturer's recommendations. Sequencing was performed using the ABI PRISM 3130 platform (Applied Biosystems Inc., USA). Vector NTI v5.1 software (InforMax, Invitrogen, Life Science Software, USA) was used to generate electropherograms. Sequences were analyzed using the Geno2pheno Drug Resistance software (Center of Advanced European Studies and Research, Germany).

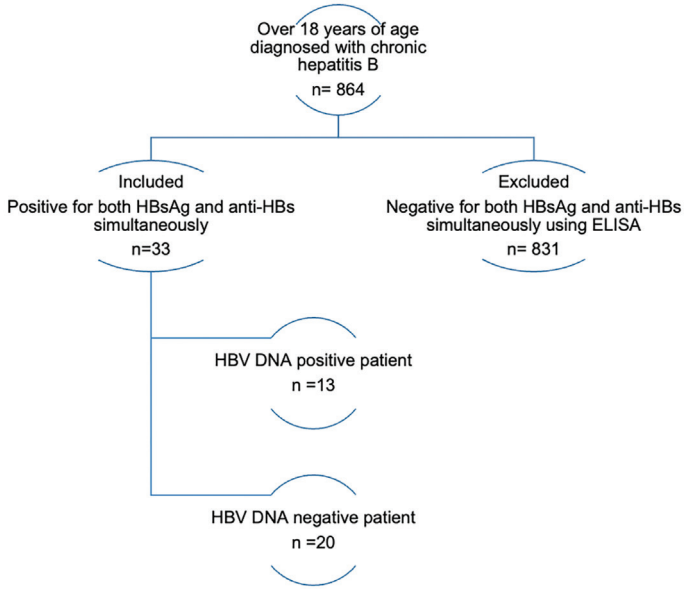

Figure 1. Patient selection flowchart
HBV: Hepatitis B virus, HBsAg: HB surface antigen, ELISA: Enzyme-linked immunosorbent assay

Statistical Analysis

Statistical analyses were performed using the SPSS (version 26.0) software package. Descriptive statistics were presented as mean ± standard deviation for normally distributed continuous data, median (minimum-maximum) for continuous variables with non-normal distribution, and numbers (n) and percentage (%) for categorical data.

Ethics Committee Approval

This study was approved by the Ethics Committee of the Faculty of Medicine, Hitit University (date: 28.04.2021, approval no: 457). This study was supported by the Scientific Research Project Unit of Hitit University (project number: TIP19001.21.004).

Results

A total of 864 patients diagnosed with CHB were followed up at the department of infectious diseases and clinical microbiology between 2021 and 2022. Of these, 33 patients (3.8%) with concurrent HBsAg and anti-HBs positivity were included in the study. Anti-HBe positivity was found in all cases (100%). HBV-DNA positivity was detected in 13 patients (39.4%). Among HBV-DNA-positive patients, 76.9% were male, and the mean age was 54.9 years. HBV-DNA results were negative in 20 of 33 (60.6%) patients with concurrent HBsAg and anti-HBs positivity (non-replicative) (Table 1).

The median anti-HBs titers were 51.4 mIU/mL in HBV-DNA-negative cases, 17.6 mIU/mL in HBV-DNA-positive cases, and 38.7 mIU/mL overall. Anti-HBs antibodies in HBV-DNA positive patients ranged from 11.1 to 25.9 mIU/mL (Table 1).

All HBV-DNA-positive had HBV genotype D (100%). An analysis of their sub-genotype showed that the D/D1 and D/D2 ratios were 45.5% and 54.6, respectively. Mutational analysis was performed on serum samples from 13 HBV-DNA-positive patients (3.8%) and the pol gene was amplified and sequenced. Codon analyses of the RT domain (polymerase/pol mutation) and of the HBsAg protein (S gene) were performed in all patients. In two of the 13 (15.4%) HBV-DNA-positive patients (P3, P7), sequence-based mutation analysis of the pol/S gene was not performed. Pol/S gene mutations were detected in 11 (84.6%) of the 13 patients. In these patients, 68 HBsAg mutations (42.8%) and 91 RT mutations (57.2%) were identified, resulting in a total of 159 mutations. While three patients (27.2%) were found to have a clinically significant HBsAg mutation, four patients (36.3%) were found to have an RT mutation. Three patients were found to have anti-HBs levels above 20 mIU/mL, and no pol/S gene mutation was detected in two of them. The mean HBV-DNA level was 2.8+E5 IU/mL (range, 6.2+E1-3.7+E6) (Table 1). Only one patient was found to have clinically significant concurrent HBsAg and RT mutations, and this patient had the highest viral replication (HBV-DNA: 3.7+E6) (Table 2).

Two patients (15.4%) received antiviral therapy, whereas 11 patients (84.6%) did not receive treatment. While one HBV-DNA-positive patient received entecavir, another received tenofovir disoproxil fumarate (Table 1). Drug resistance to nucleoside/nucleotide analogs was observed in 18.2% (n=2) of patients. While one patient (P1) had primary resistance to entecavir, telbivudine, and lamivudine, another patient (P4) had primary resistance to telbivudine and lamivudine. The same patient was moderately susceptible to entecavir. None of the patients with resistance mutations received antiviral therapy. Two cases (18.18%) were found to have the HBsAg vaccine escape mutation (Table 2).

Table 1. Demographic and laboratory characteristics of HBsAg, anti-HBs positive patients

Group	Age	Gender	Anti-HBs unit, mIU/mL	HBV-DNA load, IU/mL	Anti-HBe status	Treatment history
HBV-DNA positive patient						
P1	58	Female	12.4	6.9+E1	Positive	None
P2	51	Male	11.1	1.1+E3	Positive	None
P3	37	Female	34.2	4.3+E2	Positive	None
P4	68	Male	13.7	6.0+E2	Positive	None
P5	54	Male	14.8	1.6+E3	Positive	None
P6	51	Female	17.7	6.2+E3	Positive	TDF*
P7	50	Male	21.9	1.2+E3	Positive	None
P8	45	Male	17.2	4.0+E3	Positive	None
P9	76	Male	18.8	9.9+E2	Positive	None
P10	64	Male	11.8	1.4+E2	Positive	None
P11	38	Male	17.4	3.7+E6	Positive	None
P12	63	Male	25.9	3.4+E2	Positive	None
P13	58	Male	12.2	9.2+E2	Positive	ETV
			Median: 17.6	Median: 2.8+E5		
HBV-DNA negative patient						
P14	76	Male	46.4	Negative	Positive	None
P15	33	Female	276	Negative	Positive	None
P16	65	Female	17.9	Negative	Positive	None
P17	45	Male	10.9	Negative	Positive	None
P18	70	Male	12.9	Negative	Positive	None
P19	80	Male	22.5	Negative	Positive	TDF
P20	48	Female	16.7	Negative	Positive	None
P21	57	Female	18.4	Negative	Positive	None
P22	61	Female	42.1	Negative	Positive	None
P23	30	Female	20	Negative	Positive	None
P24	42	Female	12	Negative	Positive	None
P25	49	Female	11.5	Negative	Positive	None
P26	55	Male	11.9	Negative	Positive	None
P27	42	Male	14.6	Negative	Positive	None
P28	50	Female	16.5	Negative	Positive	None
P29	62	Female	11.4	Negative	Positive	None
P30	62	Male	25.4	Negative	Positive	None
P31	67	Female	19.9	Negative	Positive	None
P32	64	Male	19.3	Negative	Positive	None
P33	62	Female	401.5	Negative	Positive	TDF
			Median: 51.4			

HBV: Hepatitis B virus, HBsAg: HB surface antigen, anti-HBe: HB e-antibody, TDF: Tenofovir disoproxil fumarate, ETV: Entecavir, P: Patient

Table 2. Mutations in the pol/S gene in HBsAg/anti-HBs antibody-positive patients

Case	The HBV genotype	HBV sub-genotype	Clinically significant RT mutation	Clinically significant HBsAg mutation	Antiviral resistance	Clinical significance
P1	D	D1	ND	ND	Lamivudin, entecavir and telbivudin resistant	
P2	D	D2	ND	ND	ND	
P4	D	D1	ND	ND	Lamivudin and telbivudin resistance, entecavir is moderately susceptible	
P5	D	D1	ND	**W172L**	ND	W172L; mutations in the HBsAg caused by acyclic phosphonate. Naturally occurred
P6	D	D2	**Q215H**	ND	ND	Q215H; accessory mutation. Repair of HBV replication/ viral fitness
P8	D	D1	ND	ND	ND	
P9	D	D2	ND	**S193L**	ND	S193L; HBsAg vaccine escape mutation. Naturally occurred
P10	D	D2	**Q149K**	ND	ND	Q149K; accessory mutation. Repair of HBV replication/ viral fitness
P11	D	D2	**Q149K, A194T**	**S193L**	ND	S193L; HBsAg vaccine escape mutation. Naturally occurred
P12	D	D2	**A194T**	ND	ND	A194T; mutation occurring in TDV treatment; repairs HBV replication/viral fitness
P13	D	D1	ND	ND	ND	

P3 and P7 were not sequenced. HBV: Hepatitis B virus, HBsAg: HB surface antigen, ND: Not detected, P: Patient, TDV: Tenofovir disoproxil, RT: Reverse transcriptase

Discussion

In patients with CHB, the coexistence of HBsAg and anti-HBs may be detected during follow-up. Studies conducted in Turkey and other parts of the world have reported that the prevalence of serological profiles with simultaneous HBsAg and anti-HBs positivity ranges from 2.8% to 9% (10,18,19,20). In our study, the coexistence of HBsAg and anti-HBs was observed in 3.8% of patients with CHB infection, which is consistent with the literature.

Although the underlying molecular mechanisms for the coexistence of HBsAg and anti-HBs in patients with CHB infection are not clear, it may be due to the selection of immune escape mutants of HBV during chronic process, and pre-S and S gene deletion mutations have been identified in such cases (9,21,22). Some studies have shown that this is usually caused by S gene point mutations, but it is rarely associated with pre-S and S gene mutations (18,23). In our patients with HBsAg and anti-HBs positivity who were followed up with CHB, mutation analysis of pol/S genes by sequence analysis of HBV gene regions showed that a total of 159 mutations were observed, including sixty-eight HBsAg mutations (42.8%) and 91 RT mutations (57.2%); of these, a clinically significant HBsAg mutation was detected in three cases (27.27%) and an RT mutation in four cases (36.36%). The presence of these mutations is important in the context of treatment and immunosuppression.

When the relationship between the observed mutations and the HBV-DNA result was evaluated, a patient with a combination of clinically significant mutations in HBsAg and RT had the highest rate of viral replication (HBV-DNA: 3.7+E6). It has been reported that the pre-S/S and polymerase genes sometimes overlap during replication, and some codons may overlap. Increased HBV replication leading to a severe clinical course has been observed in HBV variants with combinations of HBsAg and RT mutation (18). This case was closely monitored clinically. Mutations were not analyzed in 60.6% of patients with negative HBV-DNA and in two patients with positive HBV-DNA (P3 and P7) because sequencing could not be performed. The presence of these mutations in individuals testing negative for HBV-DNA suggests they may originate from remnants of a previously formed viral variant or a low-level persistent mutant virus.

Analysis of the relationship between these mutations and genotype shows that pre-S/S mutations (HBsAg mutation) are more common in genotype D infection, which is associated with fulminant

hepatitis (18). Despite this study, other studies have reported that genotype C has more mutations (16,24). In our study, genotype D was found in all included patients, and no mixed isolates were observed. In patients with genotype D, fewer clinically significant HBsAg mutations (27.2%) were detected than RT mutations (36.3%). D2 was the dominant sub genotype in our cohort (54.6%). In Türkiye, genotype D is dominant, as in Southern Europe, the Middle East, and India. The sub-genotypes observed in Türkiye range from D1 to D4. D1 is the most common sub-genotype. Although HBeAg seroconversion is observed at lower rates in patients infected with genotype D (7,25), all of our patients had HBeAg seroconversion. We must always consider the presence of these mutations when monitoring our patients.

Mutant HBV variants can also infect vaccinated individuals and are not neutralized by vaccine-derived anti-HB antibodies; these are known as vaccine escape mutations. The emergence and predominance of vaccine escape mutants may pose a serious threat to the control of HBV infection. Some common immune escape mutants are G145R, D144A, P142S, Q129H, I/T/126N/A and M133L (18,24). A study in which genotypes D (81.3%) and E (17.3%) were dominant reported that vaccine escape mutations (P120T, D144E/A and G145R) were detected in genotype D isolates (19). All patients in our study were genotype D, and 18.2% had the S193L HBsAg mutation, a vaccine escape mutation. This mutation can occur with entecavir use (24), but it was not associated with drug use in our study because the patients were not receiving antiviral drugs. This mutation developed naturally. This suggests that HB infection can develop despite the presence of immunoglobulin.

Nucleoside analogs can induce point mutations in the pol gene. The formation of point mutations can lead to drug resistance (17). These mutations can be divided into two main groups: primary drug resistance mutations, which result in non-response to treatment, and compensatory mutations, which affect viral fitness (increased viral load and restored replication capacity). The W172L mutation in HBsAg caused by acyclic phosphonate has been frequently observed in patients receiving lamivudine (17,26). In our study, two patients who developed drug resistance had no prior exposure to antiviral therapy. This situation suggests to us that it may be an infection caused by a resistant strain or it may have developed spontaneously through mutation. Close monitoring of these patients is important.

When the relationship between the observed mutations and the anti-HBs titers was evaluated, the anti-HBs levels of our patients ranged from 11.1 to 25.9 mIU/mL. The median anti-HBs titer was 51.4 in the HBV-DNA-negative group and 17.6 in the HBV-DNA-positive group. Anti-HBs titers were lower in the HBV-DNA- positive group. This interpretation may be supported by the increase in anti-HBs levels, which suggests a weak immune response. No mutation was detected in two of the three cases (P3, P7, P12) with anti-HBs levels above 20 mIU/mL (P3 and P7). Thus, in proportion to the anti-HB titer, more amino acid mutations are observed in HBsAg and anti-HBs positive patients (27).

In our study no correlation was found between the number of mutations observed and the anti-HB titer. Given the small number of cases, this approach should be supported by studies with larger sample sizes.

Study Limitations

1. No patients under the age of 18.
2. The number of cases is small.

Conclusion

During the follow-up of patients with CHB, HBsAg and anti-HBs may be observed together. The mutations detected in the pol/S gene analyses of the HBV genomes of these patients are not clinically significant; these mutations are naturally occurring, and the association of HBsAg and anti-HBs could not be explained by these mutations.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Faculty of Medicine, Hitit University (date: 28.04.2021, approval no: 457).

Informed Consent: Written informed consent was obtained from all patients who agreed to participate in this study.

Footnotes

Authorship Contributions

Concept: Ö.A., N.B., A.K.Ç., Design: Ö.A., M.S., N.B., A.K.Ç., Data Collection or Processing: Ö.A., D.Y., Ü.S., G.K., Analysis or Interpretation: Ö.A., M.S., Ü.S., N.B., A.K.Ç., Literature Search: Ö.A., D.Y., M.S., N.B., A.K.Ç., Writing: Ö.A., D.Y., M.S., N.B., A.K.Ç.

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

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Case Report

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Transient HBsAg Positivity Following Hepatitis B Vaccination in a Patient Undergoing Hemodialysis: Case Report

Hemodiyaliz Tedavisi Uygulanan Bir Hastada Hepatit B Aşısı Sonrası Geçici HBsAg Pozitifliği: Olgu Sunumu

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ABSTRACT

Transient hepatitis B surface antigen (HBsAg) positivity following hepatitis B (HB) vaccination is a rare occurrence and, particularly in hemodialysis patients, may lead to unnecessary clinical interventions if misinterpreted. A 42-year-old male with a history of myasthenia gravis, nephrotic syndrome, and thymic carcinoma was admitted to the clinic to initiate chronic hemodialysis for steroid-resistant focal segmental glomerulosclerosis. Since baseline serology was negative for HBsAg and anti-HBs, the patient was administered a double dose of recombinant HB vaccine. One day after vaccination, HBsAg positivity was detected, and the patient was dialyzed using an isolated dialysis machine. The positivity persisted on the second day but completely resolved by day 12. The final test was negative for HBsAg, with an anti-HBs titer of 10.85 IU/L. Additional vaccine doses were administered, and HBsAg remained negative on follow-up evaluations. To prevent misdiagnosis and unnecessary isolation or interventions, accurate interpretation of serological findings and effective interdisciplinary communication in dialysis centers are critically important.

Keywords: Hepatitis B surface antigen, hepatitis B vaccine, hemodialysis, glomerulosclerosis, focal segmental, chronic kidney disease

ÖZ

Hepatit B (HB) aşısı sonrasında geçici HB yüzey antijeni (HBsAg) pozitifliği nadir görülen bir durumdur ve özellikle hemodiyaliz hastalarında yanlış yorumlandığında gereksiz klinik müdahalelere yol açabilir. Miyastenia gravis, nefrotik sendrom ve timik karsinom öyküsü bulunan 42 yaşında erkek hasta, steroid-dirençli fokal segmental glomerüloskleroz tanısı ile kronik hemodiyaliz başlatılmak üzere kliniğe yatırıldı. Başlangıç serolojisinde HBsAg ve anti-HBs negatif saptandığı için hastaya rekombinant HB aşısı çift doz uygulandı. Aşılamadan bir gün sonra HBsAg pozitifliği görüldü ve hasta izole makinede diyalize alındı. İkinci günde devam eden pozitiflik, 12. gün itibarıyla tamamen düzeldi. Son testte HBsAg negatif, anti-HBs titresi ise 10,85 IU/L olarak ölçüldü. Takip eden aşı dozları uygulandı ve HBsAg negatif kaldı. Yanlış tanı ve gereksiz izolasyon/müdahalelerin önüne geçebilmek için serolojik bulguların doğru yorumlanması ve hemodiyaliz merkezlerinde disiplinler arası iletişimin sağlanması kritik öneme sahiptir.

Anahtar Kelimeler: Hepatit B yüzey antijeni, hepatit B aşısı, hemodiyaliz, glomerüloskleroz, fokal segmental, kronik böbrek hastalığı

Introduction

Patients with chronic kidney disease (CKD) on hemodialysis are at an increased risk for hepatitis B virus (HBV) infection due to frequent vascular accesses and exposure to blood and its products (1). The repeated invasive procedures required for their care further heighten their susceptibility to infections, including HBV, which can progress to severe liver disease if left unaddressed. Routine HB vaccination is, therefore, a critical preventive measure recommended by healthcare guidelines to protect this vulnerable population from HBV infection (1). Despite the high efficacy of recombinant HB vaccines, rare events such as transient HB surface antigen (HBsAg) positivity following vaccination have been documented. Such occurrences can pose diagnostic challenges, leading to unnecessary isolation or treatment modifications, particularly in the hemodialysis setting (2,3).

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Transient HBsAg positivity may reflect the detection of HBsAg in the absence of an active infection. This generally occurs because the highly sensitive assays detect circulating non-infectious viral particles from the vaccine itself (4,5). Although infrequent, identification of this transient response is important to avoid unnecessary clinical interventions. Moreover, the transient nature of such a serological finding underlines the importance of proper follow-up testing to confirm true infection status (2,3,6). This case report describes a patient with a complex medical history, including myasthenia gravis, nephrotic syndrome, and prior thymic carcinoma, who developed transient HBsAg positivity following a double-dose recombinant HB vaccination at the initiation of chronic dialysis. The findings provide insight into the interpretation of serological results in CKD patients undergoing HB vaccination and highlight the need to distinguish antigenemia due to vaccination from active HBV infection through appropriate clinical evaluation and follow-up.

Case Report

A 42-year-old male patient, with a medical history of myasthenia gravis, nephrotic syndrome, and previously treated thymic carcinoma, was admitted to the nephrology department on September 5, 2024, for the management of focal segmental glomerulosclerosis refractory to both steroid and immunosuppressive therapies. Due to progressive renal insufficiency and persistent refractory proteinuria, medical nephrectomy was performed, followed by initiation of hemodialysis three times per week.

On October 15, 2024, the patient commenced hemodialysis at the unit. Initial serological screening revealed negative HBsAg and anti-HBs. Consequently, a double-dose recombinant HB vaccine (Elovac-B) was administered to enhance the immunogenic response, in accordance with standard recommendations for hemodialysis patients. The vaccination schedule was meticulously planned to optimize the patient's immunological response, with doses administered as follows: the first dose on October 16, 2024; the second dose on November 16, 2024; the third dose on December 16, 2024; and the fourth dose on January 16, 2025. The fifth dose is yet to be administered.

During routine pre-dialysis screening at another dialysis center on October 18, 2024, the patient tested positive for HBsAg. As a precautionary measure, he was placed on an isolated dialysis machine designated for HBsAg-positive cases. Concerned about this unexpected result, the patient informed his primary nephrology team. Repeat serological testing performed at the same dialysis center on October 26, 2024, revealed that the patient had become negative for HBsAg. Additionally, anti-HBs was detected at a low titer of 10.85 IU/L. Molecular testing for HBV-DNA and HBV-RNA yielded negative results, further supporting the absence of active infection. The serological timeline is detailed in Table 1.

The patient continued on hemodialysis without recurrence of HBsAg positivity. The planned vaccination schedule was adhered to without interruption, and no adverse events were observed following the administration of subsequent vaccine doses. Anti-HBs titers demonstrated a progressive increase over time, confirming the development of a successful immunological response to the vaccination.

Discussion

Transient HBsAg positivity following HB vaccination has been rarely reported, primarily in immunocompromised individuals or patients undergoing chronic dialysis. The recombinant HB vaccine contains non-infectious HBsAg particles that can circulate transiently and may be detected by sensitive assays, leading to false-positive results. This may result in unnecessary patient isolation, modifications to dialysis arrangements, and undue concern among healthcare workers, particularly when vaccination schedules overlap with routine serological testing. Early recognition of this transient response is crucial to minimize unwarranted anxiety and prevent unnecessary clinical interventions (2,3,4,5,6,7,8).

The duration of HB surface antigenemia after vaccination is brief, usually 1-7 days, however, this may be prolonged up to 4 weeks in patients on hemodialysis (8). Janzen et al. (4) was the first one to report positive HBsAg among hemodialysis patients, where they turned negative within 20 days of vaccination. Shortly after that, Brodersen et al. (5) also reported a case of transient antigenemia in hemodialysis patient subsequent to third dose of HB vaccine, which cleared one week after vaccination. In early 2000s, Ly et al. (9) found nine hemodialysis patients to be HBsAg positive attributed to vaccine that was also transient. Olde and Garcia (10) has reported HBsAg positive results as 50% among hemodialysis patients and concluded that it lasted no more than two weeks. In the present

Table 1. Test results

Date	HBsAg	Anti-HBs	HBV-DNA	HBV-RNA
Before vaccination	Negative	NA	NA	NA
2 days post-vaccination	+	NA	NA	NA
6 days post-vaccination	Borderline	10.85 IU/L	Negative	Negative
12 days post-vaccination	Negative	5.58 IU/L	NA	NA
19 days post-vaccination	NA	5.58 IU/L	NA	NA
Post 3rd dose vaccination	Negative	2.0 IU/L	NA	NA

HBsAg: Hepatitis B surface antigen, HBV: Hepatitits B virus, DNA: Deoxyribonucleic acid, RNA: Ribonucleic acid, NA: Non-applicable

case, transient HBsAg positivity was noted two days following vaccination and resolved by day 12. The absence of detectable HBV-DNA or HBV-RNA supported vaccine-induced antigenemia rather than active infection (2,5,6). Thus, low post-vaccination anti-HBs titers reflect impaired active immunization in patients with CKD and prior immunosuppressive therapies. The transient response noted in this complex patient, with numerous comorbid conditions and therapy for immunosuppression, draws into light certain unique challenges with which patients suffering from CKD may have to bear in an immunization schedule (2,3,4). Moreover, distinguishing between transient antigenemia and active HBV infection is critical to avoid inappropriate clinical decisions, such as unnecessary antiviral treatment or prolonged patient isolation. This case has provided valuable information on the uncommon but clinically significant transient HBsAg positivity and its implications for patient care and institutional policies. This case highlights the importance of cautious interpretation of serological results obtained after HB vaccination in patients with CKD. Transient HBsAg positivity needs to be recognized to avoid inappropriate interventions, which include isolation and modification of dialysis practice. Liaison between dialysis units and the renal team ensures good patient care and prevents inappropriate isolation of the patient (2,6,7,8). All healthcare professionals should be aware of such possibilities when planning routine serological testing shortly after vaccination, to avoid confusion and simplify patient management.

Study Limitations

This case report has some limitations that should be acknowledged. First, the findings are based on a single patient and therefore cannot be generalized to all patients undergoing hemodialysis or HB vaccination. Second, the patient had multiple comorbidities and a history of immunosuppressive treatment, which may have influenced the immune response to vaccination and limited the interpretation of the findings in otherwise healthy dialysis populations. Despite these limitations, the report provides clinically important insights into a rare but potentially misleading phenomenon in dialysis practice.

Conclusion

This report describes a rare yet clinically significant case of transient HBsAg positivity following HB vaccination in a patient undergoing chronic dialysis. Accurate recognition and appropriate management of this phenomenon rely on heightened awareness among healthcare providers and robust interdisciplinary coordination. By recognizing and addressing this rare occurrence, clinicians can improve patient care and optimize institutional protocols.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.Y., S.Ö., Concept: M.Y., N.Ö., C.P.D., S.Ö., Design: M.Y., N.Ö., S.Ö., Data Collection or Processing: M.Y., N.Ö., C.P.D., S.Ö., Analysis or Interpretation: M.Y., N.Ö., S.Ö., Literature Search: M.Y., N.Ö., S.Ö., Writing: M.Y., N.Ö., C.P.D., S.Ö.

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World Hepatitis Day-July 28; "Hepatitis A and E Getting Serious, C is in Decline, but B and D Remain Concerns"

Dünya Hepatit Günü-28 Temmuz; "Hepatit A ve E Ciddileşiyor, C Düşüşte, Ancak B ve D Endişe Kaynağı Olmaya Devam Ediyor"

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Dear Editor,

Viral hepatitis remains a critical yet unevenly addressed component of the global public health agenda. Although the World Health Organization has set ambitious targets for the elimination of viral hepatitis as a public health threat by 2030, progress across different hepatitis viruses has been inconsistent. The marked decline in hepatitis C virus (HCV) prevalence driven by the scale-up of direct-acting antivirals stands in contrast to the growing concern surrounding hepatitis A virus (HAV) and hepatitis E virus (HEV), as well as the persistent threat of hepatitis B virus (HBV) and hepatitis D virus (HDV) (1,2).

HAV and HEV, historically regarded as self-limiting and endemic infections, have demonstrated a concerning epidemiological shift. In recent years, sporadic outbreaks have increasingly been reported in urban and high-income settings, refugee camps, and among immunocompromised populations, including solid-organ transplant recipients and pregnant women (3,4). The zoonotic and waterborne nature of HEV, together with environmental instability and inadequate sanitation, has resulted in large-scale outbreaks with disproportionately high case-fatality rates among pregnant women (5). These trends emphasize the need to reframe HAV and HEV as significant clinical and public health threats rather than transient or low-priority infections.

In parallel, HBV and its satellite virus HDV continue to exert a disproportionate burden of chronic liver disease, hepatocellular carcinoma, and liver-related mortality. Despite universal HBV vaccination programs and antiviral therapies, global HBV diagnosis and treatment rates remain below 10%, with millions unaware of their chronic infection (1). The situation for HDV is even more concerning, owing to limited access to diagnostics, lack of routine screening, and the absence of standardized management strategies. Despite the significant therapeutic progress represented by new drugs like bulevirtide, access remains severely limited in many regions where it is endemic (6).

On World Hepatitis Day (July 28), themed "We're not waiting," it is essential to expand our collective attention beyond HCV to acknowledge the increasing importance of HAV and HEV, as well as the persistent public health failures to control HBV and HDV. These infections necessitate heightened urgency, particularly in nations with transitional economies, vulnerable health systems, and substantial migration pressures.

Overall, these epidemiological and clinical issues emphasise that elimination goals cannot be accomplished solely through antiviral therapies; rather, they necessitate collaborative efforts across clinical practice, laboratory evaluations, public health policy, and medical education. Clinical microbiology and virology laboratories should integrate routine HAV, HEV, HBV genotyping, and HDV testing into diagnostic algorithms, particularly for high-risk populations and outbreak settings. Healthcare professionals must remain vigilant for atypical manifestations of HAV and HEV in immunocompromised individuals, while public health authorities ought to prioritise surveillance, vaccination strategies, and educational programs.

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Medical education and research initiatives must confront the ongoing oversight of non-HCV hepatitis viruses to prevent isolated eliminatin measures.

In this context, scaling up universal childhood HAV vaccination in regions affected by climate-driven outbreaks and shifting age-related immunity patterns is essential (7). Similarly, sustainable global access to HEV vaccines should be prioritised, especially for pregnant women and immunocompromised individuals. The reinforcement of birth-dose HBV vaccination, maternal screening, extended HCV testing approaches, and routine HDV screening within HBV care pathways are essential measures for comprehensive hepatitis control.

In summary, the future of viral hepatitis elimination depends on our ability to respond to evolving epidemiological patterns, diagnostic gaps, and therapeutic inequities across all hepatitis viruses. Elimination is not merely an ambition—it is a global obligation.

Footnotes

Authorship Contributions

Concept: M.A., Design: M.A., A.R.U., Data Collection or Processing: M.A., A.R.U., Analysis or Interpretation: M.A., A.R.U., Literature Search: M.A., A.R.U., Writing: M.A., A.R.U.

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