ORIGINAL ARTICLE

DOI: 10.4274/hamidiyemedj.galenos.2026.76598

Hamidiye Med J

Evaluation of Clinical and Laboratory Findings in HBsAg Positive Patients: A Comprehensive Retrospective Study

HBsAg Pozitif Hastalarda Klinik ve Laboratuvar Bulgularının Değerlendirilmesi: Kapsamlı Retrospektif Bir Çalışma

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ABSTRACT

Background: Hepatitis B virus (HBV) infection remains a major global health concern. This study aimed to evaluate the clinical and laboratory characteristics of patients with positive hepatitis B surface antigen (HBsAg) results and to provide real-world insights into HBV detection, serological profiles, and clinical management.

Materials and Methods: This retrospective study included patients with positive HBsAg results between August 2023 and May 2025. Data on indications for testing, requesting departments, accompanying serological markers, current antiviral regimens, and previous treatment modifications were obtained from hospital records. HBsAg-positive patients were compared according to anti-HBs status. Patients receiving antiviral therapy were also evaluated with respect to their history of modifications to previously used nucleos(t)ide analogues.

Results: A total of 295 patients were included. The most common reason for HBsAg testing was routine chronic hepatitis B follow-up (52.2%), followed by preoperative or screening evaluations (32.2%). Concurrent HBsAg and anti-HBs positivity was detected in 5.9% of tested patients and was associated with significantly lower HBsAg cut-off index values ($p < 0.001$). Among the 64 patients receiving antiviral therapy on the index date, 19 (29.7%) had a history of modification to a previously used antiviral agent. Tenofovir disoproxil fumarate was the most frequently modified of the previously used agents, and the documented reasons for these modifications were predominantly renal- and bone-related conditions. No modification involving the discontinuation of previously used tenofovir alafenamide fumarate was documented. A history of treatment modification was associated with a longer total duration of antiviral treatment ($p = 0.004$).

Conclusion: The findings provide an integrated perspective on the circumstances of HBsAg detection, atypical serological profiles, and antiviral treatment histories. They support appropriate evaluation following HBsAg detection, the individualized selection of antivirals, and careful long-term monitoring.

Keywords: Hepatitis B, HBsAg, anti-HBs, chronic hepatitis B, tenofovir, serological markers

ÖZ

Amaç: Hepatit B virüsü (HBV) enfeksiyonu küresel ölçekte önemli bir halk sağlığı sorunu olmaya devam etmektedir. Bu çalışmada HBsAg pozitifliği saptanan hastaların klinik ve laboratuvar özelliklerinin değerlendirilmesi ve HBV'nin saptanma koşulları, serolojik profiller ve tedavi yönetimine ilişkin gerçek yaşam verilerinin sunulması amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya Ağustos 2023 ile Mayıs 2025 tarihleri arasında HBsAg pozitifliği saptanan hastalar dahil edildi. Test istem endikasyonları, istem yapan klinikler, eşlik eden serolojik belirteçler, mevcut antiviral tedaviler ve geçmiş tedavi değişikliklerine ilişkin veriler hastane kayıtlarından elde edildi. HBsAg pozitif hastalar anti-HBs durumuna göre karşılaştırıldı. Antiviral tedavi alan hastalar ayrıca daha önce kullanılan nükleoz(t)id analoglarında değişiklik yapılma öyküsüne göre değerlendirildi.

Bulgular: Toplam 295 hasta çalışmaya dahil edildi. HBsAg testinin en sık istem nedeni kronik hepatit B'nin rutin takibi (%52,2) olup bunu preoperatif değerlendirme veya tarama amaçlı istemler (%32,2) izledi. Test edilen hastaların %5,9'unda eş zamanlı HBsAg ve

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Received: 18.04.2026 **Accepted:** 02.10.2026 **Epub:** 30.10.2026

Cite this article as: Öksüz C, Öz M, Çubuk F. Evaluation of clinical and laboratory findings in HBsAg positive patients: A comprehensive retrospective study. Hamidiye Med J. [Epub Ahead of Print]

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ÖZ

anti-HBs pozitifliği saptandı ve bu durum anlamlı derecede daha düşük HBsAg cut-off indeks değerleriyle ilişkiliydi (p < 0,001). İndeks tarihinde antiviral tedavi alan 64 hastanın 19'unda (%29,7), daha önce kullanılan bir antiviral ajanda değişiklik yapılma öyküsü vardı. Tenofovir disoproksil fumarat, daha önce kullanılan ve en sık değişiklik yapılan ajan olup belgelenen değişiklik nedenleri ağırlıklı olarak renal ve kemikle ilişkili durumlardı. Daha önce kullanılan tenofovir alafenamid fumaratın kesilmesini içeren herhangi bir tedavi değişikliği belgelenmedi. Tedavi değişikliği öyküsü, daha uzun toplam antiviral tedavi süresiyle ilişkiliydi (p = 0,004).

Sonuç: Bulgular, HBsAg'nin saptanma koşulları, atipik serolojik profiller ve antiviral tedavi öyküleri hakkında bütüncül bir bakış açısı sunmaktadır. Sonuçlarımız HBsAg pozitifliği saptandıktan sonra uygun klinik değerlendirme yapılmasını, antiviral tedavinin bireyselleştirilmesini ve uzun dönem dikkatli izlem uygulanmasını desteklemektedir.

Anahtar Kelimeler: Hepatit B, HBsAg, anti-HBs, kronik hepatit B, tenofovir, serolojik belirteçler

Introduction

Hepatitis B virus (HBV) remains a primary cause of viral hepatitis, which frequently progresses to liver cirrhosis, hepatocellular carcinoma (HCC), and hepatic failure. It is estimated that HBV-related malignancies and cirrhosis account for nearly 600,000 deaths annually (1). As of 2022, the global burden of chronic hepatitis B (CHB) infection was estimated at approximately 254 million individuals (2).

HBV is a hepatotropic DNA virus belonging to the *Hepadnaviridae* family (3). The virus can induce both acute and chronic clinical manifestations. During acute infection, approximately 70% of cases are asymptomatic or anicteric, while the remaining 30% present with classical icteric hepatitis (4). Although CHB is typically clinically silent, patients may occasionally report non-specific symptoms such as fatigue. In many instances, the diagnosis is incidental, occurring during routine screenings or laboratory evaluations of high-risk groups. Chronic infection is formally defined as the persistence of HBsAg in serum for more than six months. A definitive assessment of HBV-related liver disease necessitates an integrated approach involving clinical, serological, biochemical, and histopathological parameters (2).

The management of acute HBV is primarily supportive. However, antiviral intervention may be warranted in cases of prolonged coagulopathy (exceeding four weeks), persistent severe symptoms, or profound jaundice (4). Current therapeutic options for CHB management include pegylated interferon and oral nucleos(t)ide analogues (NAs), the latter being the most widely used worldwide. Nevertheless, these treatments face challenges regarding long-term tolerability and various adverse effect profiles (5).

Previous studies have characterized atypical HBV serological profiles, particularly concurrent HBsAg and anti-HBs positivity, or have evaluated antiviral effectiveness and treatment-related adverse events among established CHB cohorts (6-11). However, these components of HBV care have generally been investigated separately. Evidence integrating the clinical context in which HBsAg positivity is encountered with subsequent serological characterization and antiviral treatment modification remains limited. Therefore, the present study aimed to provide an integrated real-world assessment of HBsAg-positive patients by examining (i) the indications for HBsAg testing and the requesting departments, (ii) the frequency and clinical correlates of concurrent HBsAg/Anti-HBs positivity, and (iii) current NAs use and the patterns and reasons for treatment modification. By including both patients under routine CHB follow-up and those identified during preoperative or screening evaluations, this study sought to provide a broader understanding of HBV detection, serological assessment, and treatment management in routine secondary-care practice.

Materials and Methods

Ethical approval was obtained from the Sivas Cumhuriyet University Ethics Committee (approval number: 2025-06/03; date: 12 June 2025).The study adhered to the Declaration of Helsinki. Given the retrospective nature of the study and the use of anonymized clinical data, informed consent from patients was not required in accordance with the institutional ethics committee's decision. This single-center retrospective study was conducted at a secondary-care hospital located in the city center, and providing inpatient and outpatient services to the local population. Because the hospital lacks a gastroenterology department, HBV-related evaluation and follow-up are primarily undertaken by the department of infectious diseases and clinical microbiology. The study population comprised patients aged ⩾18 years who had at least one positive HBsAg result at the Medical Microbiology Laboratory between August 2023 and May 2025. Data regarding the requesting departments, indications for HBsAg testing, concurrent hepatitis markers, and antiviral treatments were retrospectively extracted from the institutional database.

Laboratory records were matched at the patient level using unique patient identifiers. For patients with more than

one positive HBsAg measurement during the study period, the first positive result was defined as the index result. All subsequent HBsAg measurements were removed as duplicate records, ensuring that each patient was included only once.

Patients with previously established CHB and those in whom HBsAg positivity was identified during preoperative, pre-hospitalization, screening, or administrative evaluations were eligible for inclusion. A single positive HBsAg result was not considered sufficient to classify a newly identified patient as having CHB unless chronicity had previously been documented in the medical records. For anti- hepatitis B surface (HBs), hepatitis B e antigen (HBeAg), anti hepatitis B e antibody (HBe), anti hepatitis B core antibody (HBc), and HBV DNA, the result obtained on the index date was used; if none was available on that date, the closest measurement within the study period was recorded. Missing ancillary serological or molecular test results were not considered patient-level exclusion criteria, and the corresponding analyses were performed using the available data.

Acute HBV infection was not a prespecified exclusion criterion. However, medical records were reviewed for a documented diagnosis of acute hepatitis B, and available anti-HBc immunoglobulin (Ig) M results were evaluated.

The antiviral agent used on the index date was recorded as the current treatment, while modifications to previously used antiviral agents were evaluated separately from patients' treatment histories. Treatment modification was defined as the discontinuation or replacement of a previously used NA for a documented clinical reason.

Reasons for previous NA treatment modifications were retrospectively identified in the patients' medical records. Renal- and bone-related treatment modifications were classified according to the criteria specified in the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines, which were applicable during the study period (12). A modification was categorized as renal-related when at least one of the following was documented on or nearest to the date of treatment modification: an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, albuminuria >30 mg/24 h, moderate proteinuria on dipstick testing, a serum phosphate level <2.5 mg/dL, or the requirement for hemodialysis. A modification was categorized as bone-related when osteoporosis, a history of fragility fracture, or the use of medications associated with reduced bone mineral density was documented. These findings were accepted as reasons for treatment modification only when the treating physician had explicitly associated the renal or bone condition with the decision to change therapy. These criteria were used to classify documented treatment modifications retrospectively and did not constitute a prospectively applied treatment-switching protocol.

For serological evaluation, 3–5 mL of venous blood was collected, and serum was isolated via centrifugation for analysis within two hours. Antigens (HBsAg and HBeAg) and antibodies (anti-HBs, anti-HBe, anti-HBc IgM, and Anti-HBc IgG) were detected using the electrochemiluminescence method on a Roche cobas e411 analyzer (Roche Diagnostics, Germany) using Elecsys kits. Hemolyzed or lipemic samples from the same patient were excluded. HBsAg results were reported as cut-off index values (COI; sample signal/cut-off) generated by the qualitative Elecsys HBsAg II assay. Therefore, the numerical values represent assay signal values and not standardized quantitative HBsAg concentrations expressed in IU/mL.

Nucleic acid extraction was performed using the Magnesia 16 automated system and Magnesia Viral DNA/RNA Extraction Kits (Anatolia GeneWorks, Türkiye). Quantitative HBV DNA levels were determined using the Montania 4896 real-time polymerase chain reaction (PCR) system with Bosphore HBV Quantification Kits (Anatolia GeneWorks, Türkiye). The analytical lower limit of detection was 10 IU/mL. On-treatment virological suppression at the index date was defined as undetectable HBV DNA by real-time PCR (<10 IU/mL). For the retrospective classification of treatment-modification reasons, absence of virological response included primary non-response, defined as a decline of <1 $\log_{10}$ IU/mL in HBV DNA after three months of therapy, and partial virological response, defined as a decline of >1 $\log_{10}$ IU/mL from baseline with persistently detectable HBV DNA after at least 12 months of adherent NA therapy (12). A virological reason was accepted only when it had been explicitly documented by the treating physician as the reason for treatment modification and was not retrospectively inferred from incomplete serial HBV DNA measurements.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). The distributions of continuous variables were assessed using the Shapiro–Wilk test. Because the normality assumption was not satisfied in at least one of the relevant comparison groups, continuous variables were presented as median and interquartile range (IQR). Comparisons between two independent groups were performed using the Mann–Whitney U test, while comparisons among three independent groups were performed using the Kruskal–Wallis test. When the Kruskal–Wallis test indicated a statistically significant difference, post-hoc pairwise comparisons were conducted using the Mann–Whitney U test with Bonferroni correction.

Categorical variables were presented as n (%). For

variables with missing observations, results were presented as n/N (%), where N represents the number of patients with available data. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. The Fisher–Freeman–Halton exact test was used for contingency tables larger than 2 × 2 when expected cell counts were insufficient for the chi-square test. Missing measurements were not considered exclusion criteria; analyses were performed using the available data for each variable, and no imputation was undertaken. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

Results

A total of 295 patients were included in the study. The age range was 21 to 87 years, with a median age of 55 years (IQR: 42–63). Of the patients, 142 (48%) were female. The reasons for presentation among HBsAg-positive patients were evaluated; 154 (52.2%) were CHB patients presenting for routine follow-up. These were followed by: preoperative or pre-hospitalization assessments and health board applications (n = 95, 32.2%); prescriptions for continuation of CHB treatment (n = 26, 8.8%); and reports for continuation of CHB treatment (n = 20, 6.8%).

Of the clinical departments requesting HBsAg tests, 55.6% were from the department of infectious diseases and clinical microbiology. This was followed by internal medicine (24%), general surgery (5.4%), occupational health (4.1%), orthopedics (3.4%), urology (2.4%), emergency medicine (1.4%), ophthalmology (1.4%), psychiatry (1%), palliative care (0.7%), otorhinolaryngology (0.3%), and home healthcare services (0.3%). Notably, there is no gastroenterology department in our hospital.

Among the HBsAg-positive patients, one tested positive for anti-HIV and another tested positive for anti-HCV. Anti-HBs was tested in 270 patients; sixteen had positive anti-HBs results. No patient had a documented clinical diagnosis of acute hepatitis B. Anti-HBc IgM results were available for 180 patients and were negative in all of them. Anti-HBc IgG was tested in 186 patients; only 4 (2.1%) had negative results. Their HBsAg values ranged from 1.02 to 3.56. All four were tested for HBV DNA, and all tests were negative. HBeAg and Anti-HBe results were available for 184 patients; HBeAg positivity was detected in 5/184 (2.7%), and Anti-HBe positivity was detected in 167/184 (90.8%). HBV DNA results were available for 202 of 295 patients (68.5%), and detectable HBV DNA was identified in 134 of these 202 patients (66.3%).

Patients were divided into two groups based on Anti-HBs positivity and were compared on several parameters. A statistically significant difference was observed only for HBsAg COI values, which were lower in the Anti-HBs-positive group (p < 0.001). These findings are presented in Table 1.

On the index date, 64 patients were receiving antiviral treatment for CHB. Among them, 24 were receiving tenofovir disoproxil fumarate (TDF), 26 were receiving entecavir (ETV), 12 were receiving tenofovir alafenamide fumarate (TAF), and two were receiving lamivudine (LAM). Virological suppression, defined as HBV DNA <10 IU/mL, was observed in 56 of the 64 treated patients (87.5%). By antiviral agent, suppression was achieved in 22/24 (91.7%) patients receiving TDF; 20/26 (76.9%) receiving ETV; 12/12 (100%) receiving TAF; and 2/2 (100%) receiving LAM. The differences among the TDF, ETV, and TAF groups were not statistically significant (p = 0.129).

A review of previous treatment histories showed that 19 patients (29.7%) had undergone at least one modification of a previously used antiviral agent. Because some patients had undergone more than one treatment modification and more than one reason could be documented for an individual modification, a total of 26 reasons were recorded. Of these, 19 were related to renal- or bone-related conditions, while 7 were attributed to an inadequate virological response. TDF was the most frequently modified agent among those previously used. The previously used agents and the documented reasons for their modification are presented in Table 2.

Patients with a history of modification of a previously used antiviral agent and those without such a history were compared in Table 3. No statistically significant differences in age, sex, HBsAg COI values, or HBeAg positivity were observed between the groups (all p > 0.05). However, total antiviral treatment duration was significantly longer among patients with a history of treatment modification than among those without modification (median, 11.0 [IQR, 9.0–15.0] vs. 8.0 [IQR, 3.0–10.0] years; p = 0.004). At the index date, virological suppression was observed in 18/19 patients (94.7%) with a history of treatment modification and in 38/45 patients (84.4%) without such a history; the difference between groups was not statistically significant (p = 0.418).

Comparisons by the current antiviral agent are presented in Table 4. Age differed significantly among the TDF, ETV, and TAF groups (p = 0.001). Patients receiving TDF were younger than those receiving ETV (median, 50.5 [IQR, 35.8–59.0] vs. 61.0 [IQR, 56.0–68.0] years; adjusted p=0.005) or those receiving TAF (median, 63.5 [IQR, 56.3–68.0] years; adjusted p = 0.009), whereas age did not differ between the ETV and TAF groups. The proportion of male patients differed among the groups and was highest in the TDF group (79.2%, 46.2%, and 50.0%, respectively; p = 0.044). No statistically significant differences were identified among the TDF, ETV, and TAF groups with respect to HBsAg COI

Table 1. Comparison of anti-HBs positive and negative patients in the HBsAg positive patient group.

Variables	Anti-HBs positive (n = 16)	Anti-HBs negative (n = 254)	p
Age, median (IQR), (years)	56 (46-62)	54 (41-63)	0.707
Male sex, n (%)	5 (31%)	129 (50%)	0.130
HBsAg COI value, median (IQR)	72 (2-875)	4166 (1308-5930)	**<0.001**
Anti-HBe positivity, n/N (%)	10/12 (83%)	157/172 (91%)	0.306

Data are presented as median (interquartile range [IQR]) or n (%), as appropriate. For variables with missing observations, categorical data are presented as n/N (%), where N represents the number of patients with an available result. HBsAg values represent assay-derived cut-off index (COI) values and not quantitative HBsAg concentrations. HBsAg, hepatitis B surface antigen.

Table 2. Reasons for modification of previously used antiviral agents.

Previously used agent	Renal-related reason, n (%)	Bone-related reason, n (%)	Absence of virological response, n (%)
TDF (19 modification events)	9 (47.4%)	10 (52.6%)	0 (0.0%)
ETV (3 modification events)	0 (0.0%)	0 (0.0%)	3 (100%)
LAM (4 modification events)	0 (0.0%)	0 (0.0%)	4 (100%)

Categorical variables are presented as n (%). Data are descriptive and represent the documented reasons for modification of previously used nucleos(t)ide analogues. More than one reason may have been recorded for an individual patient. Because the total number of patients previously exposed to each agent and the corresponding exposure durations were not evaluated, these findings should not be interpreted as agent-specific treatment-modification or adverse-event rates. No treatment modification involving the discontinuation of TAF was documented. TDF, tenofovir disoproxil fumarate; ETV, entecavir; LAM, lamivudine.

Table 3. Comparison of patients with and without treatment modification in chronic hepatitis b therapy.

Variables	Patients with treatment modification (n = 19)	Patients without treatment modification (n = 45)	p
Age, median (IQR), years	62 (57-68)	57 (49-64)	0.063
Male sex, n (%)	9 (47.4%)	29 (64.4%)	0.204
HBsAg COI value, median (IQR)	5576 (3778-6301)	4652 (2509-6759)	0.959
HBeAg positivity, n/N (%)	1/19 (5.3%)	3/43 (7.0%)	1.000
Total treatment duration, median (IQR), years	11.0 (9.0–15.0)	8.0 (3.0–10.0)	**0.004**
Virological Suppression, n/N (%)	18/19 (94.7%)	38/45 (84.4%)	0.418

Data are presented as median (interquartile range [IQR]) or n (%), as appropriate. For variables with missing observations, categorical data are presented as n/N (%). Virological suppression was operationally defined as an HBV DNA level <10 IU/mL at the index date. HBsAg values represent assay-derived cut-off index (COI) values.

Table 4. Unadjusted descriptive comparison of patient characteristics according to current nucleos(t)ide analogue regimen.

Variables	TDF (n = 24)	ETV (n = 26)	TAF (n = 12)	p
Age, median (IQR), years	50.5 (35.8–59.0)	61.0 (56.0–68.0)	63.5 (56.3–68.0)	**0.001**
Male sex, n (%)	19 (79%)	12 (46%)	6 (50%)	**0.044**
HBsAg COI value, median (IQR)	5371.5 (4012.8–6743.8)	4843.5 (2291.3–6078.0)	5570.0 (2134.8–6732.8)	0.329
Anti-HBe Positivity, n/N (%)	17/24 (70%)	20/24 (83%)	11/12 (91%)	0.348
Total treatment duration, median (IQR), years	10.0 (4.3–10.0)	6.5 (2.0–12.0)	11.0 (6.3–14.5)	0.092
Virological Suppression, n/N (%)	22/24 (91.7%)	20/26 (76.9%)	12/12 (100%)	0.129

Data are presented as median (interquartile range [IQR]) or n (%), as appropriate. For variables with missing observations, categorical data are presented as n/N (%). Virological suppression was operationally defined as an HBV DNA level <10 IU/mL at the index date. The two patients receiving LAM were not included in between-group comparisons. TDF, tenofovir disoproxil fumarate; ETV, entecavir; TAF, tenofovir alafenamide fumarate; LAM, lamivudine; COI, cut-off index.

values, anti-HBe positivity, virological suppression, or total antiviral treatment duration (p = 0.329, p = 0.348, p = 0.129, and p = 0.092, respectively).

Discussion

The main contribution of this study is not a new prevalence estimate in isolation, but rather the integrated evaluation of three interconnected aspects of HBV care within the same HBsAg-positive population: the clinical context in which HBsAg positivity was encountered, the presence of atypical serological profiles, and the patterns of antiviral treatment modification. Previous studies have generally examined these domains separately. For example, Ayaz et al. (13) selected and characterized 145 patients with atypical serological profiles from a larger cohort of patients followed for HBV infection, whereas Bulut et al. (11) evaluated antiviral effectiveness and treatment-related adverse events among 572 patients receiving treatment for CHB. In contrast, our cohort included both patients attending routine CHB follow-up and individuals identified during preoperative, prehospitalization, screening, or administrative evaluations. The present findings, therefore, provide a pragmatic cross-sectional view of HBsAg-positive patients managed at a secondary-care hospital without a gastroenterology department. This perspective complements earlier descriptive cohorts by evaluating the setting of HBsAg detection, laboratory phenotype, and observed treatment patterns within the same real-world population.

In our study, using real-world data, we evaluated patients with HBsAg positivity at a secondary-level public hospital . We found that 55.6% of HBsAg requests were made by the Department of infectious diseases and clinical microbiology. In the absence of a gastroenterology department at our hospital, the remaining requests were primarily submitted by the Department of Internal Medicine and other hospital units. This finding highlights the need for appropriate referrals from other departments to ensure proper follow-up and treatment of patients with hepatitis B.

When evaluating the reasons for HBsAg testing, screening prior to hospital admission, surgery, or medical board applications was the second most common (n = 95, 32.2%). These screenings should be seen as an opportunity, and patients identified through such evaluations should be referred to Infectious Diseases or Gastroenterology Departments. Raising awareness in this regard is essential.

Serological tests are widely used to diagnose HBV infection and detect viral markers. However, atypical serological profiles are sometimes encountered. In our study, 5.9% (16/270) of patients were positive for both HBsAg and Anti-HBs. Among these, 43.7% (7/16) were also HBV DNA positive. Viral mutations, host-related factors, and methodological influences can all lead to the coexistence of HBsAg and anti-HBs (6). Reported prevalence rates for this serological profile range between 2.8% and 3.6% across different cohorts (7), and a study from Türkiye found this rate to be 3.6% (8). Our study found a higher frequency than previously reported. The clinical significance and long-term outcomes of concurrent HBsAg and Anti-HBs positivity are not well understood. However, a study investigating long-term outcomes reported higher HCC incidence and greater HBsAg seroclearance in patients with concurrent HBsAg and Anti-HBs positivity compared to those with HBsAg alone (7). This indicates that such patients require closer follow-up.

When we compared anti-HBs-positive (n = 16) and anti-HBs-negative (n = 254) groups within our HBsAg-positive cohort, no differences were observed in age, sex, or Anti-HBe positivity. However, HBsAg COI values were significantly lower in the Anti-HBs positive group (p < 0.001). Similarly, Thi Cam Huong et al. (9) found no differences in age, sex, or Anti-HBe positivity between groups with concurrent HBsAg and Anti-HBs positivity and those with HBsAg alone. Although they reported lower median HBsAg levels in the co-positive group, the difference was not statistically significant (p = 0.052). Additionally, infections with genotype C and HCC were more common in the co-positive group (9). G enotype analysis was not performed in our study, and no HCC cases were identified in our cohort. Liu et al. (10), who studied the clinical and virological features of patients with concurrent HBsAg and anti-HBs positivity, also found significantly lower HBsAg levels in this group compared with those who were anti-HBs-negative. Moreover, they observed more amino acid substitutions in the “a determinant” of the S gene among patients with genotype C and concurrent positivity (10). Our study does not include data on mutation analysis.

The clinical interpretation of the lower HBsAg COI values observed in patients with concurrent positivity for HBsAg and anti-HBs requires caution. In the present study, HBsAg was assessed using an immunoassay and expressed as a cut-off index rather than as a quantitative HBsAg concentration in IU/mL. Therefore, a lower COI value indicates lower assay reactivity relative to the cut-off but cannot be directly interpreted as indicating a lower circulating HBsAg concentration or used alone to infer inactive infection, imminent HBsAg seroclearance, or a favorable prognosis. Although concurrent positivity may occur during an immune-mediated decline in HBsAg preceding seroclearance, it may also result from immune-escape mutations in the S gene, heterologous subtype-specific anti-HBs, circulating antigen–antibody complexes, or assay-related factors (6,7,9,10). Notably, HBV DNA remained detectable in 7 of the 16 patients (43.7%) who had concurrent positivity,

indicating that the presence of anti-HBs did not necessarily indicate viral clearance. Accordingly, this atypical profile should be interpreted together with HBV DNA, alanine aminotransferase, HBeAg status, liver disease stage, and longitudinal serological findings. Because quantitative HBsAg, genotype, mutation, and longitudinal outcome data were unavailable, the prognostic significance of the lower COI values could not be determined in the present study.

Among patients receiving treatment for CHB, 19 (29.7%) underwent changes in their therapy. The most frequent change observed in those receiving TDF was statistically significant ($p < 0.001$). In a retrospective study conducted between January 2005 and November 2017 evaluating treatments in CHB patients, 23.8% (136 patients) underwent treatment changes, with the highest rate in LAM users (52%) (11). The discrepancy with our findings may be due to the earlier period during which that study was conducted.

In our study population, treatment changes in TDF users were attributed to renal (n = 9) and bone (n = 10) disorders. TDF is a prodrug of tenofovir, a nucleotide reverse transcriptase inhibitor with a high resistance barrier, and is considered a first-line agent in international liver disease guidelines for the treatment of CHB (14). No treatment changes were due to lack of efficacy. Bone disorders were the most common reason for switching from TDF. TDF use has been associated with reductions in bone mineral density. A study conducted in Hong Kong with 41,531 CHB patients found that those treated with TDF had a higher risk of fractures than those on ETV after two years of treatment (15). This underscores the importance of monitoring bone health in TDF-treated patients and modifying treatment when necessary. Another significant reason for TDF discontinuation was the development of renal disease. Evidence of renal tubular dysfunction in TDF users primarily comes from HIV-related studies (16). Today, TDF-related renal dysfunction is generally considered mild and tolerable, with severe forms such as Fanconi syndrome or acute tubular necrosis being rare. The estimated GFR decline associated with TDF is usually mild and is thought to result from mitochondrial toxicity in renal tubular cells due inhibition of mitochondrial DNA polymerase-γ. Regular monitoring of renal function with serum creatinine, phosphate levels, and urine dipstick tests is recommended during TDF treatment (17).

In selected patient populations, particularly those with renal impairment, osteoporosis, or relevant risk factors, TAF may offer a more favorable renal and bone safety profile than TDF (18-20). No modification involving TAF, the previously used antiviral agent, was documented. The duration of exposure to TAF was unavailable; therefore, this finding may reflect shorter agent-specific exposure and treatment-selection practices. Nonetheless, this observation should not be interpreted as evidence that TAF was safer than TDF or ETV. Antiviral treatment was not randomly assigned, and the choice of agent was likely influenced by age, treatment history, renal function, bone health, comorbidities, and clinician preference. Indeed, patients receiving TDF were significantly younger than those receiving ETV or TAF, indicating that the treatment groups differed in clinically relevant baseline characteristics. In addition, patients with renal or bone-related risk factors may have been preferentially started on or switched to TAF or ETV, resulting in confounding by indication. Therefore, the observed treatment patterns represent unadjusted real-world clinical practice and do not permit causal or comparative safety conclusions regarding individual NAs.

These considerations are consistent with current international guidelines, which emphasize individualized NA selection rather than a universal preference for a single agent. The 2025 EASL guidelines recommend TAF over TDF in patients with hypophosphatemia, osteoporosis, renal insufficiency, or risk factors for TDF-related nephrotoxicity. The 2024 World Health Organization guidelines identify TDF and ETV as preferred treatment options and indicate that TAF may be considered for patients with impaired renal function and/or osteoporosis. For long-term safety, regular monitoring of serum creatinine and eGFR is recommended during NA therapy, with additional assessment of phosphate and urinary protein in patients receiving TDF. Lipid and metabolic considerations should also be taken into account during TAF therapy. These recommendations support individualized treatment selection and modification based on renal, bone, metabolic, and previous treatment-related factors, together with continued long-term monitoring (19,20).

The side effects of TDF mentioned above and the resulting treatment changes have also affected our cohort of CHB patients. When patient groups receiving TDF, ETV, and TAF were compared, patients treated with TDF were younger ($p = 0.001$). This suggests that antiviral therapy should be selected based on the patient's age and comorbidities.

Additionally, when comparing patients with and without treatment changes, the only significant difference was the total duration of therapy, which was longer in those who experienced treatment changes ($p = 0.004$). This finding highlights the need for close monitoring of patients receiving long-term treatment for potential side effects.

Study Limitations

This study has several limitations inherent to its retrospective and single-center design. Because inclusion

was based on HBsAg positivity identified by routine clinical testing at a secondary-care hospital, selection and referral biases cannot be excluded. Patients already undergoing CHB follow-up or being evaluated by the Department of Infectious Diseases and Clinical Microbiology may be overrepresented; therefore, the findings may not fully reflect undiagnosed individuals in the community or patients managed in tertiary-care settings. In addition, clinical and laboratory assessments were performed according to clinical indications rather than a standardized study protocol, resulting in incomplete data for some variables. Consequently, formal HBV phase and cirrhosis status could not be reliably assigned across the entire cohort, and screening before immunosuppressive therapy was not recorded as a separate testing category. The findings should therefore be interpreted as representing a heterogeneous hospital-based HBsAg-positive population rather than a cohort stratified according to specific HBV disease stages. The same data limitations precluded detailed clinical, virological, and longitudinal characterization of patients with concurrent HBsAg and Anti-HBs positivity; analyses of genotype, mutation, and antiviral resistance were unavailable. Comparisons among the current TDF, ETV, and TAF treatment groups were unadjusted and may have been affected by confounding by indication and treatment-selection bias. Although age and treatment duration were available, pretreatment renal function, bone health, comorbidities, liver disease stage, and other factors that could influence antiviral selection were not consistently recorded. These limitations, together with the small number of treated patients, particularly those receiving TAF, precluded a reliable adjusted comparative analysis. Therefore, the antiviral treatment findings should be considered descriptive and should not be interpreted as evidence of comparative safety or effectiveness. Finally, the relatively small overall sample size and the absence of long-term clinical outcome data limit the precision and broader interpretation of the findings.

Conclusion

This study provides an integrated real-world perspective on the clinical contexts in which HBsAg positivity is encountered, the accompanying serological profiles, and the antiviral treatment patterns observed in a secondary-care setting. Although routine CHB follow-up was the most common context, 32.2% of HBsAg-positive encounters occurred during preoperative, pre-hospitalization, or health board evaluations, highlighting the importance of appropriate clinical assessment and follow-up when HBsAg positivity is identified outside routine CHB care. Concurrent HBsAg/Anti-HBs positivity was detected in 5.9% of tested patients and was associated with significantly lower HBsAg COI values, emphasizing the need for careful interpretation of atypical HBV serological profiles. Among patients receiving antiviral therapy, 29.7% had a history of treatment modification, and longer treatment duration was associated with such modification; renal and bone-related concerns were among the documented reasons for these changes. However, comparisons among the current NA treatment groups were unadjusted, and pretreatment renal function and bone health data were unavailable; therefore, the findings do not support conclusions regarding the comparative safety of TDF and TAF. Overall, these results support appropriate evaluation following HBsAg detection, individualized antiviral selection, and careful long-term monitoring; however, larger prospective multicenter studies are needed to confirm these findings.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Sivas Cumhuriyet University Ethics Committee (approval number: 2025-06/03; date: 12 June 2025).

Informed Consent: Given the retrospective nature of the study and the use of anonymized clinical data, informed consent from patients was not required in accordance with the institutional ethics committee's decision.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.Ö., Concept: C.Ö., M.Ö., F.Ç., Design: C.Ö., M.Ö., F.Ç., Data Collection or Processing: C.Ö., F.Ç., Analysis or Interpretation: C.Ö., M.Ö., Literature Search: C.Ö., Writing: C.Ö.

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

Financial Disclosure: The authors declared that this study received no financial support.

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