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Research Article

Relationship of HBV-DNA levels with biochemical and microbiological markers in chronic hepatitis B patients

Kronik hepatit B hastalarında HBV-DNA düzeylerinin biyokimyasal ve mikrobiyolojik belirteçlerle ilişkisi

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Abstract

Aim: HBV-DNA levels are used to diagnose Chronic Hepatitis B (CHB), determine the stage of infection, decide on treatment and determine the course of the disease. HBeAg is a marker of active viral replication and transcription, Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) are markers of liver inflammation. This study aims to investigate the relationship between HBV-DNA levels and age, biochemical and microbiological parameters in patients followed up with a preliminary diagnosis of CHB in our hospital.

Material and Methods: HBV-DNA, microbiological and biochemical parameters test results from blood samples of 264 patients followed up in our hospital with a preliminary diagnosis of CHB between May 2021 and May 2024 were retrospectively analyzed. HBV-DNA levels were divided into three groups as HBV-DNA Negative (Group 1), HBV-DNA 10-2000 IU/mL (Group 2) and HBV-DNA >2000 IU/mL (Group 3). Statistical analyses were performed with the MedCalc (version 20.009; Ostend, Belgium) statistical package program.

Results: HBeAg positivity was significantly lower in HBV-DNA negative patients compared to patients with HBV-DNA 10-2000 IU/mL and HBV-DNA >2000 IU/mL and in patients with HBV-DNA 10-2000 IU/mL compared to patients with HBV-DNA >2000 IU/mL ($p < 0.05$). ALT and AST values were significantly higher in patients with HBV-DNA >2000 IU/mL compared to patients with HBV-DNA negative and HBV-DNA 10-2000 IU/mL. No statistically significant correlation was found between HBV-DNA levels and WBC, HGB, MCV, RDW, GGT, ALP, Total protein, albumin, PT, aPTT, INR values.

Conclusion: A significant relationship was found between HBeAg and ALT, AST values and HBV-DNA levels in CHB patients. These parameters can be used together to diagnose CHB disease, establish the stage of infection, decide on treatment and determine the course of the disease.

Keywords: HBV-DNA, HBeAg, ALT, chronic hepatitis B

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Öz

Amaç: HBV-DNA seviyeleri, Kronik hepatit B (KHB) hastalığını teşhis etmek, enfeksiyon evresini belirlemek, tedaviye karar vermek ve hastalığın seyrini belirlemek için kullanılır. HBeAg aktif viral replikasyonun ve transkripsiyonun, Alanin aminotransferaz (ALT) ve Aspartat aminotransferaz (AST) karaciğer inflamasyonunun bir belirtecidir. Bu çalışma ile hastanemizde KHB ön tanısıyla takip edilen hastaların HBV-DNA düzeylerinin yaş, biyokimyasal ve mikrobiyolojik parametreler arasındaki ilişkinin araştırılması amaçlanmaktadır.

Gereç ve Yöntemler: Mayıs 2021- Mayıs 2024 tarihleri arasında hastanemizde KHB ön tanısı ile takip edilen 264 hastanın kan örneklerinden HBV-DNA, mikrobiyolojik ve biyokimyasal parametrelere ait test sonuçları retrospektif olarak incelenmiştir. HBV-DNA düzeyleri HBV-DNA Negatif (Grup 1), HBV-DNA 10-2000 IU/mL (Grup 2) ve HBV-DNA>2000 IU/mL (Grup 3) olmak üzere üç gruba ayrılmıştır. İstatistiksel analizler MedCalc (version 20.009; Ostend, Belgium) istatistik paket programı ile yapılmıştır.

Bulgular: HBV-DNA negatif hastalarda HBV-DNA 10-2000 IU/mL ve HBV-DNA >2000 IU/mL olan hastalara göre, HBV-DNA 10-2000 IU/mL olan hastalarda da HBV-DNA >2000 IU/mL olan hastalara göre HBeAg pozitifliği anlamlı derecede düşük tespit edilmiştir ($p < 0,05$). ALT ve AST değerleri ise HBV-DNA >2000 IU/mL olan hastalarda HBV-DNA negatif ve HBV-DNA 10-2000 IU/mL olan hastalara göre anlamlı derecede yüksek saptanmıştır. HBV-DNA düzeyleri ile WBC, HGB, MCV, RDW, GGT, ALP, Total protein, albümin, PT, aPTT, INR değerleri arasında istatistiksel olarak anlamlı bir ilişki bulunmamıştır.

Sonuç: KHB hastalarında HBeAg ve ALT, AST değerleri ile HBV-DNA düzeyleri arasında anlamlı bir ilişki saptanmıştır. Bu parametreler birlikte KHB hastalığını teşhis edip enfeksiyon evresini oluşturmak, tedaviye karar vermek ve hastalığın seyrini belirlemek için kullanılabilir.

Anahtar Kelimeler: HBV-DNA, HBeAg, ALT, kronik hepatit B

Introduction

Approximately 400 million people worldwide are infected with hepatitis B virus (HBV), which can cause outcomes ranging from asymptomatic carriage to hepatocellular carcinoma (HCC) [1]. Various biomarkers associated with liver diseases are used in the clinic to monitor and predict disease progression. HBV-DNA is a quantitative virological marker of the level of HBV replication. HBV-DNA levels are used to diagnose chronic hepatitis B (CHB), determine the stage of infection, decide on treatment, and determine the course of the disease [2]. Previous studies have shown that high serum HBV-DNA levels are a risk factor for advanced liver diseases such as liver damage and cirrhosis. Hepatitis B surface antigen (HBsAg) is the primary marker of HBV infection, and HBsAg clearance indicates viral clearance. Hepatitis B e antigen (HBeAg) indicates active viral replication and transcription and is a marker of infectivity. Alanine aminotransferase (ALT) is a marker of liver inflammation; levels at the upper limit of normal are indicative of damage to hepatocytes.

CHB infection is classified according to serum HBV-DNA level, ALT level and HBeAg status; the infection process is assessed by serial HBV-DNA and ALT measurements [3]. HBsAg, HBeAg and HBV-DNA reach high levels in the early stages of CHB infection [4]. High serum HBV-DNA and normal ALT levels are striking in HBeAg-positive patients in the immune tolerance (IT) stage. High HBV-DNA and high ALT levels are reached in most patients later in the IT stage, during the immune clearance (IC) stage [5]. HBeAg negativity and anti-HBe positivity, normal serum ALT concentration, low or undetectable HBV-DNA (<2000 IU/mL) are seen in inactive CHB (carrier) patients with absent or low replicative phase [1,2].

ALT >2-fold and HBV-DNA>20000 IU/mL are criteria for treating all HBeAg-positive or HBeAg-negative chronic HBV patients with immunoreactive phases. In HBeAg-negative CHB patients with normal ALT and HBV-DNA levels between 2000 and 20000 IU/mL, urgent liver biopsy or treatment is not required unless there is evidence of liver disease. However, careful follow-up with serial ALT and HBV-DNA measurements is recommended. Biopsy and treatment are not necessary in inactive CHB, but lifelong follow-up with ALT and HBV-DNA determinations is required [6].

Biochemical [Aspartate aminotransferase (AST) and ALT, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), serum albumin, complete blood count and prothrombin time (PT)] and microbiological (HBsAg, HBeAg, Anti-HBe) parameters are used for the detection of liver disease, treatment

decision and HCC surveillance. This study aims to investigate the relationship between HBV-DNA levels and age, biochemical and microbiological parameters in patients followed up with a preliminary diagnosis of chronic hepatitis B in our hospital.

Material and Methods

The test results of HBV-DNA, microbiological and biochemical parameters from blood samples of 264 patients followed up in our hospital with a preliminary diagnosis of CHB between May 2021 and May 2024 were retrospectively examined. Patients diagnosed with acute viral hepatitis were excluded from the study. The relationship between HBV-DNA levels and biochemical parameters such as complete blood count parameters, AST, ALT, ALP, GGT, albumin, total protein, prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR) and microbiological parameters such as HBsAg, HBeAg and anti-HBe was analyzed.

For viral load determination, HBV-DNA levels were measured using Real-Time PCR (Cobas TaqMan HBV, Roche Diagnostics, USA) according to the manufacturer's instructions. Biochemical and microbiological parameters were studied on an automatic immunoassay analyzer (cobas 6000 c 501, cobas 6000 e 601, Roche Diagnostics, Mannheim, Germany) and complete blood count parameters were studied on a Sysmex XN 1000 hematology analyzer. HBV-DNA levels were divided into three groups as HBV-DNA Negative (Group 1), HBV-DNA 10-2000 IU/mL (Group 2) and HBV-DNA>2000 IU/mL (Group 3). The lower detection limit of HBV-DNA was 10 IU/mL and the upper detection limit was 170,000,000 IU/mL.

After the approval of the study protocol of the Non-Interventional Scientific Research Ethics Committee No. 93 dated 12.07.2024 by our Institution's Ethics Committee, the patients' data were retrospectively examined in accordance with the Declaration of Helsinki Principles.

Statistical Analysis

Statistical analyses were performed using the MedCalc (version 20.009; Ostend, Belgium) statistical package program. In the statistical description of the data, numbers and percentages were used for categorical variables. In the statistical description of the data, numbers and percentages were used for categorical variables. For numerical variables, numbers, arithmetic mean, standard deviation (SD), median, 25th and 75th percentile values were used. Kolmogorov-Smirnov normality test was used to assess the normality of the groups. Chi-square test was used to compare groups of categorical data. In the comparative analysis of more than two groups for numerical data, if the groups were normally distributed, one-way analysis of variance was used, and if the groups were not normally distributed, Kruskal-Wallis test was used. Pairwise comparisons were made by assuming Bonferroni correction for post-hoc analysis. In the tables, data that were normally distributed were expressed as mean and standard deviation (SD), and data that were not normally distributed were expressed as median and (25.p – 75.p). Categorical data are expressed as numbers and percentages (%). Visually, groups that conform to normal distribution are shown as mean±2SD, and groups that do not conform to normal distribution are shown as box-whisker graphs. Categorical data are shown as stacked percentage column graphs. In the interpretation of the results, the significance level was taken as $p < 0.05$.

Results

109 (41.3%) of the patients were female, and 155 (58.7%) were male. No statistically significant relationship was found between HBV-DNA levels and gender. The age range of HBV-DNA negative patients was 52.7 ± 12.1, the age range of patients with HBV-DNA 10-2000 IU/mL was 47.8 ± 13.3, and the age range of patients with HBV-DNA>2000 IU/mL was 40.5 ± 14.2. A statistically significant relationship was found between HBV-DNA levels and the age of the patients ($p < 0.001$) (Figure 1).

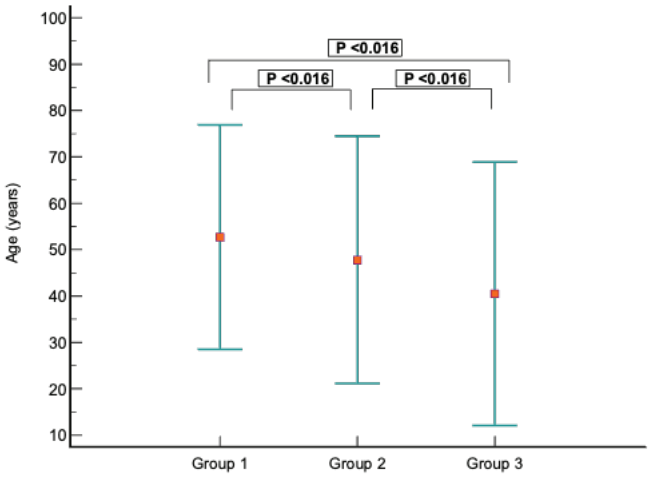

Figure 1. Distribution of HBV-DNA levels by age.

Serum HBV DNA levels were found to be <10 IU/mL in 114 patients (43.2%), between 10-2000 IU/mL in 124 patients (47%), and >2000 IU/mL in 26 patients (9.8%). All patients in this study were HBsAg positive. However, 57 patients (85.1%) were HBeAg negative, and 10 patients (14.9%) were HBeAg positive. In our study, 14 (21.5%) patients were anti-HBe negative, and 51 (78.5%) patients were anti-HBe positive.

The comparison of microbiological and biochemical parameters according to HBV-DNA levels is shown in Table 1. In HBV-DNA negative patients, HBeAg positivity was found to be significantly lower than in patients with HBV-DNA 10-2000 IU/mL and HBV-DNA >2000 IU/mL ($p < 0.05$). HBeAg positivity was found to be significantly lower in patients with HBV-DNA 10-2000 IU/mL than in patients with HBV-DNA >2000 IU/mL ($p < 0.05$). According to HBV-DNA levels, ALT and AST values were found to be significantly higher in patients with HBV-DNA >2000 IU/mL than in patients with HBV-DNA negative and HBV-DNA 10-2000 IU/mL (Figures 2,3). No statistically significant relationship was found between HBV-DNA levels and WBC, HGB, MCV, RDW, GGT, ALP, Total protein, albumin, PT, aPTT, INR values.

Table 1. Comparison of age. gender and laboratory findings by groups.

		Groups									
		Group 1 (G1)		Group 2 (G2)		Group 3 (G3)		P-Value	Post-hoc Analysis		
		HBV-DNA <10 IU/mL		HBV-DNA 10-2000 IU/mL		HBV-DNA >2000 IU/mL		P-Value			
		N=114		N=124		N=26			G1-G2	G1-G3	G2-G3
Age (years)		52.7	12.1	47.8	13.3	40.5	14.2	<0.001*	0.003	<0.0001	0.013
Gender	Female	46	40.4%	52	41.9%	11	42.3%	0.964			
	Male	68	59.6%	72	58.1%	15	57.7%				
HBe Ag	Negative	18	94.7%	27	90.0%	12	66.7%	0.034***			
	Positive	1	5.3%	3	10.0%	6	33.3%				
Anti Hbe	Negative	3	15.8%	5	17.9%	6	33.3%	0.354			
	Positive	16	84.2%	23	82.1%	12	66.7%				
HBs Ag (IU/mL)		5596	(2877-6826)	4221	(2098-6369)	4905	(2603-6920)	0.096			
ALT (IU/L)		17	(13-22)	20.5	(15-26.9)	25	(18.5-61.3)	<0.0001**	0.002	0.000	0.009
AST (IU/L)		19	(16-22)	20	(17-24)	23	(20-41.3)	<0.001**	0.0433	0.0005	0.008
GGT (IU/L)		17	(13.3-24)	16	(13.5-23.5)	17	(11.75-36.5)	0.965			
ALP (IU/L)		84	(74.5-102)	82	(70-93)	81	(70.5-103)	0.556			
Total protein (g/L)		74	(70.9-76.7)	71.8	(69.4-74)	76.8	(71-78.6)	0.384			
Albumin (g/L)		45	(43.2-47.3)	45	(43.3-47)	46.2	(44-47)	0.852			
APTT (second)		27	(26-28.2)	27.5	(25.6-29)	27.6	(26-29.3)	0.754			
PT (second)		9.2	(8.7-10.3)	8.7	(8.4-9)	9.2	(9-9.6)	0.091			
INR		1.02	(0.97-1.13)	0.97	(0.94-1.02)	1.02	(0.98-1.03)	0.082			
WBC (10^3/L)		6.7	(5.1-8.4)	6.5	(5.5-8)	6.6	(6-7.7)	0.972			
NEU (%)		58.8	(50.8-64)	56.8	(51.3-61.4)	59.7	(52-64.2)	0.209			
LYMPH (%)		30.1	(25.4-36.4)	32.6	(27-38)	29.3	(24-32)	0.214			
MONO (%)		7.5	(6.3-8.7)	7.8	(6.7-9)	7.8	(6-9.6)	0.656			
EOS (%)		2.2	(1.5-3.2)	2.4	(1.5-4)	2.4	(1.7-3.7)	0.453			
BASO (%)		0.6	(0.4-0.8)	0.5	(0.4-0.8)	0.6	(0.4-0.8)	0.973			
IG (%)		0.3	(0.2-0.4)	0.3	(0.2-0.4)	0.3	(0.2-0.3)	0.429			
RBC (10^6/L)		4.9	(4.6-5.3)	5.0	(4.6-5.3)	5.1	(4.7-5.2)	0.940			
Hb (g/dL)		14.5	(13.6-15.4)	15	(13.6-15.7)	14.2	(13.3-15.4)	0.550			
Hct (%)		43.5	(40.5-45.6)	43.7	(40.3-46.7)	43	(39.9-44.7)	0.410			
MCV (fl/L)		87.7	(84.5-89.8)	87.5	(85.1-90.4)	86.4	(84.6-88)	0.151			
MCH (pg/L)		29.6	(28.5-30.6)	29.6	(28.6-30.6)	29.1	(28-30.1)	0.423			
MCHC (g/dL)		33.8	(33-34.4)	33.65	(32.8-34.4)	33.65	(32.4-34.6)	0.982			
RDW-CV (%)		13.2	(12.8-13.6)	12.8	(12.3-13.3)	13.25	(12.7-14.2)	0.058			
PLT (10^3/L)		222.0	(179.4-272)	227.5	(190.5-257)	210	(180-266)	0.846			
PCT (%)		0.20	(0.18-0.27)	0.23	(0.19-0.25)	0.22	(0.18-0.27)	0.622			
MPV (fl/L)		10.2	(9.4-10.9)	10.2	(9.9-10.8)	10.3	(9.7-10.6)	0.646			

* Significant difference at <0.05 level according independent t-test. Means and Standart deviations (SD) are presented ** Significant difference at <0.05 level according to Mann-Whitney U test. Medians are presented and 25p-75p are shown in parentheses

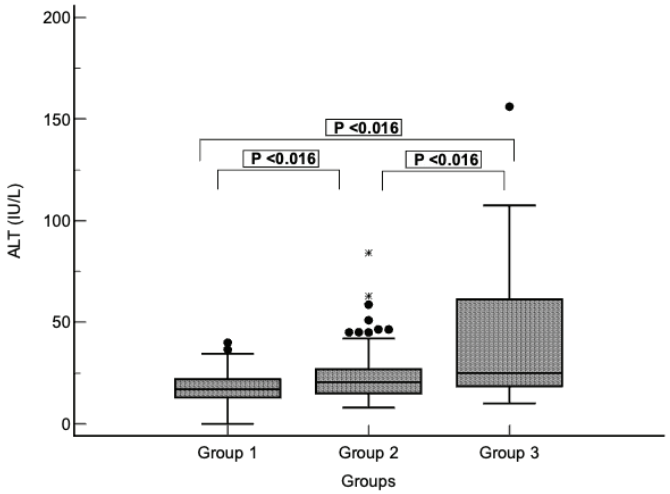

Figure 2. ALT values according to HBV-DNA levels.

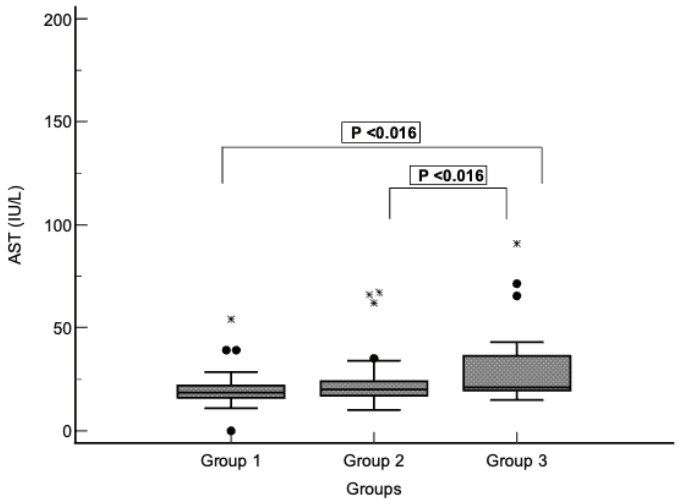

Figure 3. AST values according to HBV-DNA levels.

Discussion

Hepatitis B infection is a major public health problem affecting approximately 400 million people worldwide [7]. HBV causes hepatocellular injuries mediated by the host immune response to inflammatory damage in hepatocytes. Chronic hepatic inflammation also promotes the development of liver fibrosis, cirrhosis, and even HCC [8]. Therefore, the diagnosis of severe liver inflammation is important for physicians to evaluate the prognosis of patients with CHB infection and to decide on initiating treatment [2,9,10].

Liver biopsy is the gold standard for the diagnosis of hepatitis. However, liver biopsy is an invasive procedure and carries the risk of rare but potentially life-threatening complications [11]. In addition, the cost of a liver biopsy is high, which limits its use for mass screening purposes. These limitations of liver biopsy have led to the development of noninvasive markers of hepatitis. Biochemical tests are generally used to diagnose hepatitis due to their advantages of being cheap and noninvasive. In our study, we investigated the relationship between biochemical and microbiological parameters according to HBV-DNA levels.

Molecular detection of HBV-DNA is now widely used to detect viral replication. Patients should be evaluated for HBV-DNA levels, HBeAg status, and if possible, liver biopsy and HBV genotype. Guidelines recommend antiviral therapy for patients with HBV-DNA levels >2000 Iu/mL, ALT levels greater than twice the upper limit of normal, and significant liver fibrosis. HBV-DNA testing should be repeated at 3-6 month intervals, and increases in ALT and AST levels should be detected [5,11,12]. Further studies should be conducted to examine non-invasive parameters to reduce invasive methods in the evaluation of CHB.

The most commonly used biochemical tests reflecting liver inflammation are ALT and AST [13]. However, the degree of liver inflammatory activity does not always correlate well with ALT and AST [14,15]. Previous studies have shown that significant liver inflammation can be found in 20–34% of CHB patients with detectable HBV DNA and normal ALT levels [16,17]. Another study found that 5.7% of CHB patients with undetectable HBV DNA and normal ALT levels had severe liver inflammation [18]. In the study by Günal et al., a significant relationship was found between ALT levels and HBV-DNA levels [19]. In another study conducted in Türkiye, high viral load (HBV-DNA) and ALT levels were noted in the HBeAg positive patient group [20]. Yuan et al. found a weak correlation between HBV-DNA load and ALT ($p < 0.05$) [21]. In this study, we found a statistically significant correlation between HBV-DNA load and ALT and AST, which are markers of liver damage. According to our study, ALT and AST values were found to be higher in CHB patients with HBV-DNA >2000 IU/mL ($p < 0.001$, $p < 0.001$). Therefore, antiviral treatment is needed more in CHB patients with HBV-DNA >2000 IU/mL.

In order to precisely determine the stage of chronic hepatitis in patients, HBeAg values should also be evaluated. HBeAg is usually detected during active viral replication in patients with positive serum HBV DNA. In the study by Zhao et al., when HBeAg positive and HBeAg negative CHB patients were compared, HBV-DNA levels were found to be significantly higher in HBeAg positive patients [15]. Various studies

conducted in Türkiye have also shown that ALT and HBV-DNA levels are higher in HBeAg positive patients [22,23]. Ergunay et al. detected significantly higher HBV-DNA levels in HBeAg positive patients [24]. In our study, we also found a statistically significant relationship between HBV-DNA levels and HBeAg positivity and ALT levels. In our study, statistically significant higher HBeAg positivity ($p < 0.05$) was found in patients with HBV-DNA >2000 IU/mL compared to patients with HBV-DNA <2000 IU/mL. This indicates that CHB patients with HBV-DNA>2000 IU/mL require treatment.

Serum GGT level is an indicator of hepatobiliary diseases and alcohol consumption. Serum GGT has been accepted as a potential biomarker in the diagnosis and treatment of HBV infection. Huang et al. found a significant positive correlation between serum GGT levels and serum ALT levels in a cohort of 215 patients with CHB, but no significant correlation was observed between serum GGT levels and HBV DNA levels [25]. Previous studies have shown that serum GGT levels are independently associated with severe liver inflammation in CHB patients [11,26,27]. In one study, significant decreases in GGT, ALT and AST values were also found in patients with CHB, in addition to decreased HBV-DNA values [28]. In the Gecgel study, no correlation was found between GGT values and HBV-DNA values [29]. In our study, no relationship was found between HBV-DNA levels and GGT values.

Albumin is an acute phase protein synthesized by the liver. Albumin synthesis and functions are reduced in patients with liver failure. A study has shown that a lower albumin level or a higher AST or ALT level is associated with higher hepatitis B viral load in liver diseases [30]. Nakamuta et al. showed that albumin levels are associated with HBV-DNA levels but not with ALT levels [31]. Gecgel reported that albumin is the biomarker that most affects HBV-DNA after ALT [29]. In our study, no significant relationship was found between albumin and HBV-DNA levels.

As previously reported, age is significantly associated with liver inflammation activity in CHB patients [26]. However, other recent studies have not found a significant association between age and liver inflammation activity in CHB patients [32,33]. In our study, a significant association was found between age and HBV-DNA levels ($p < 0.05$).

The levels of hematological biomarkers also define the severity of liver disease [34]. Various hematological markers, especially RDW, are the main indicators of adverse outcomes in HBV-related liver diseases [35,36]. In the study of Yang et al., it was reported that MCV is associated with the severity of liver failure and may be a predictor of mortality in patients with HBV-related decompensated cirrhosis [37]. In the Gecgel study, it was found that the hematological markers WBC, HGB and RDW did not change according to HBV-DNA values, and MCV values were higher in patients with HBV-DNA >20000 IU/mL [29]. In our study, no significant relationship was found between HBV-DNA levels and hematological markers.

Limitations of the study

The limitation of our study is that it is retrospective and does not compare with biopsy results of chronic hepatitis B patients.

In conclusion, as a result, a significant relationship was found between HBeAg and ALT, AST values and HBV-DNA levels in CHB patients. These parameters can be used together to diagnose CHB disease, establish the stage of infection, decide on treatment and determine the course of the disease. However, a low HBV-DNA load does not indicate better liver function. In order to reduce invasive methods in the evaluation of CHB patients, further studies are needed to examine noninvasive parameters.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Ethics approval

This study was approved by the Non-Interventional Scientific Research Ethics Committee of Ordu University Ethics Committee with protocol number 93 and date 12.07.2024.

Author Contributions

Concept: HÖK, ABG, Design: HÖK, ABG, Data Collection and Processing: HÖK, ABG, Analysis and Interpretation: HÖK, ABG, Writing: HÖK, ABG

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