Research Article

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Relationships Between Liver Histopathology with Biochemical Parameters, and Hepatitis B Virus-DNA in Chronic Hepatitis B Infection

Kronik Hepatit B Enfeksiyonunda Karaciğer Histopatolojisi ile Biyokimyasal Parametreler ve Hepatit B Virüs DNA Arasındaki İlişkinin Araştırılması

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ABSTRACT

Objectives: We investigated the relationship between serum hepatitis B virus (HBV)-DNA levels and biochemical parameters and liver histopathology in patients with chronic hepatitis B (CHB).

Materials and Methods: In this single-center retrospective study, treatment-naive hepatitis B e antigen (HBeAg) negative CHB patients between 2015 and 2022 years were included.

Results: A total of 316 patients were included. There were significant correlations between the histological activity index (HAI) score and HBV-DNA (r=0.522, p<0.001), alanine aminotransferase (ALT) (r=0.349, p<0.001), aspartate aminotransferase (r=0.414, p<0.001), and fibrosis score (r=0.111, p=0.049). The fibrosis score did not have a significant correlation other than the HAI. Patients with normal ALT levels had higher minimal inflammation (19.6% vs. 4.7%, p<0.001) and mild fibrosis (88.7% vs. 80.4%, p=0.042) than patients with elevated ALT levels. High HBV-DNA (>2,000,000 IU/mL) (60.8% vs. 36.7%, p=0.003) and moderate inflammation (27.6% vs. 13.9%, p=0.042) were higher in patients with ALT >2x upper limit of normal (ULN) than in patients with ALT 1-2xULN. For predicting HAI ≥6, the area under the receiver operating characteristics (AUROC) values of HBV-DNA (cut-off: 33,427) and ALT (cut-off: 40.5) were 0.726 and 0.664, respectively. For predicting ≥F2 the AUROC values of HBV-DNA (cut-off: 721,062) and ALT (cut-off: 44.5) were 0.624 and 0.597, respectively.

Conclusion: This study revealed positive correlations between laboratory parameters and HAI score, but not with fibrosis score. In

ÖZ

Amaç: Çalışmamızda, kronik hepatit B (KHB) hastalarında serum hepatit B virüs (HBV)-DNA düzeyleri ve biyokimyasal parametreler ile karaciğer histopatolojisi arasındaki ilişkinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Tek merkezli, retrospektif olarak yürütülen çalışmamıza, 2015-2022 yılları arasında tedavi naif hepatit B e antijeni (HBeAg) negatif KHB hastaları dahil edildi.

Bulgular: Toplam 316 hasta çalışmaya alındı. Histolojik aktivite indeksi (HAİ) skoru ile HBV-DNA (r=0,522, p<0,001), alanin aminotransferaz (ALT) (r=0,349, p<0,001), aspartat aminotransferaz (r=0,414, p<0,001) ve fibroz skoru (r=0,111, p=0,049) arasında anlamlı korelasyon mevcuttu. Fibroz skorunun ise HAİ dışında korelasyon gösterdiği bir parametre yoktu. ALT seviyeleri normal aralıkta olan hastalarda minimal enflamasyon (%19,6'ya karşı %4,7, p<0,001) ve hafif fibroz (%88,7'ye karşı %80,4, p=0,042), ALT seviyeleri yüksek olan hastalara göre daha fazla saptandı. ALT seviyeleri >2x normal üst sınır (NÜS) olan hastalarda ise yüksek viral yük (>2,000,000 IU/mL) (%60,8'e karşı %36,7, p=0,003) ve orta derecede enflamasyon (%27,6'ya karşı %13,9, p=0,042), ALT değeri 1-2xNÜS aralığında olan hastalara göre daha fazla saptandı. HAİ ≥6'yı öngörmede HBV-DNA (sınır değer: 33,427) ve ALT (cut-off: 40,5) için alıcı çalışma özelliklerinin altındaki alan (AUROC) analiz değerleri sırasıyla 0,726 ve 0,664 idi. ≥F2'yi öngörmek için HBV-DNA (sınır değer: 721,062) ve ALT'nin (sınır değer: 44,5) AUROC değerleri ise sırasıyla 0,624 ve 0,597 idi.

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addition, HBV-DNA and ALT showed poor diagnostic performance in predicting ≥F2. Therefore, while viral load and ALT are useful predictors of hepatic inflammation, the role of these markers in predicting fibrosis remains unclear.
Keywords: ALT, chronic hepatitis B, fibrosis score, HAI score, HBV-DNA

Sonuç: Çalışmamız, laboratuvar parametreleri ile HAİ skoru arasında pozitif korelasyon olduğunu, ancak fibrozis skoru ile olmadığını ortaya koymaktadır. Ek olarak, HBV-DNA ve ALT, ≥F2'yi öngörmede zayıf tanısal performans göstermiştir. Sonuç olarak; viral yük ve ALT, hepatik enflamasyonun belirteçleri olarak yararlı olabilir, fakat bu belirteçlerin fibrozu öngörmedeki rolü belirsizdir.
Anahtar Kelimeler: ALT, fibroz skoru, HAİ skoru, HBV-DNA, KHB

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Introduction

Hepatitis B virus (HBV) infection remains a serious public health problem as an important cause of cirrhosis and hepatocellular cancer, despite reduction in treatment management and vaccination policies (1). Worldwide, approximately 300 million people live with chronic HBV infection, and approximately one million deaths occur annually due to complications of this disease (2). Countries are divided into 3 classes according to the prevalence of hepatitis B surface antigen (HBsAg) as low (<2%), intermediate (2-7%), and high endemic (≥8%) (3). Turkey is in the intermediate endemic group with an HBsAg prevalence of 4.57%, comprising approximately 3.3 million people living with HBV (4).

Chronic HBV infection can be classified into five different clinical forms by evaluating serological markers, liver function tests, HBV-DNA levels, and liver biopsy results. The need for antiviral treatment in these patients was determined on the basis of alanine aminotransferase (ALT) and serum HBV-DNA levels. In patients whose treatment criteria are not fully met, it is recommended to evaluate inflammation and fibrosis scores by performing liver biopsy (5,6,7). In Turkey, health insurance covers antiviral treatment for patients with cirrhosis findings or any contraindications for liver biopsy, such as coagulopathy. Otherwise, to access HBV treatment covered by health insurance, histopathological examination with liver biopsy is mandatory for all patients who need to be treated with antivirals. Therefore, centers that follow patients living with HBV in Turkey have many liver histopathology results in chronic hepatitis B (CHB).

As the viral load increases, deterioration in hepatic histology is usually expected. However, there is no threshold for HBV-DNA levels to determine histological deterioration (8). In studies focused on this subject, heterogeneous populations (HBeAg positive and negative) were generally included. (8,9). In this study, we aimed to investigate the relationship between serum HBV-DNA levels and biochemical parameters and liver histopathology in treatment-naive hepatitis B e antigen (HBeAg) negative CHB patients.

Materials and Methods

In this retrospective study, patients aged 18 years who underwent liver biopsy with treatment-naive HBeAg-negative chronic HBV infection between 2015 and 2022 years were included. Patients co-infected with hepatitis C, delta virus, or human immunodeficiency virus and those non-compliant with treatment were excluded from the study. Demographic characteristics (age, gender), serological (HBsAg, HBeAg), and biochemical parameters including HBV-DNA, ALT, aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase, creatinine, albumin, platelet count, and liver biopsy results were retrospectively retrieved from patients' medical charts and electronic medical records.

The definition of "HBeAg-negative CHB" was provided by the European Association for the Study of the Liver (EASL) 2017 (5). Histopathological evaluation of liver biopsies was performed according to Ishak's scoring system for fibrosis and Knodell's histological activity index (HAI) for necroinflammation (10). The HAI score was classified as minimal inflammation (HAI: 1-3), mild inflammation (HAI: 4-8), moderate inflammation (HAI: 9-12), and severe inflammation (HAI: 13-18). The fibrosis score was classified as mild fibrosis (F0-F2) and moderate/severe fibrosis (F3-F6).

Patients were divided into three groups according to ALT levels [<upper limit of normal (ULN), 1-2xULN, >2xULN] and six groups according to HBV-DNA levels (IU/mL) (<$2x10^4$, $2x10^4$-$2x10^5$, $2x10^5$-$2x10^6$, $2x10^6$-$2x10^7$, $2x10^7$-$2x10^8$, >$2x10^8$). The primary outcome was detecting the correlations between the HAI score, fibrosis score, HBV-DNA, and ALT levels. Secondary outcomes were HAI ≥6 and fibrosis ≥2 in determining the diagnostic performance of ALT and HBV-DNA.

Statistical Analysis

Categorical variables are expressed as numbers and percentages. Continous variables are expressed as median (minimum-maximum) and mean ± standard deviation. To compare categorical variables, the chi-square test was performed. While the Student's t-test was used to compare normally distributed continuous variables, the Mann-Whitney U test was used to compare non-normally distributed continuous variables. Spearman correlation analysis was performed to explore possible relationships between HBV-DNA, ALT, and AST levels and HAI and fibrosis. Reciever operating characteristic (ROC) curve analyzes were performed for predicting HAI ≥6 and fibrosis ≥2. Results with a p-value <0.05 were accepted as statistically significant. Statistical analyzes were performed using the IBM SPSS-21 package program.

Ethical Approval

This study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital

Clinical Research Ethics Committee (approval number: 2023-03-03, date: 06.02.2023). Written informed consent was waived because this study was conducted retrospectively.

Results

A total of 316 patients were included. Of these patients, 61% (n=193) were male, and the mean age was 47.3±11.3 years. In the liver biopsies of the patients, 12.7% (n=40) had minimal inflammation, 72.5% (n=229) had mild inflammation, 13.9% (n=44) had moderate inflammation, and 0.9% (n=3) had severe inflammation. In addition, 84.8% (n=268) had mild fibrosis and 15.2% (n=48) had moderate/severe fibrosis. The demographic characteristics, laboratory parameters, and liver biopsy results of the patients are presented in Table 1, 2.

Spearman's correlation analysis revealed significant correlations between HBV-DNA levels with ALT (r=0.449, p<0.001), AST (r=0.560, p<0.001) and HAI score (r=0.522, p<0.001), but not with fibrosis score (r=-0.011, p=0.849). There were significant correlations between HAI score with ALT (r=0.349, p<0.001), AST

Table 1. Demographic characteristics and laboratory parameters of patients with chronic hepatitis B

	Mean ± SD/n (%)	**Median (min.-max.)**
Age	47.3±11.3	47 (23-80)
Gender		
Male	193 (61.1)	
Female	123 (38.9)	
ALT (IU/L)	**77.4±161.3**	
<41 (ULN)	168 (53.2)	**38.5 (7-1,870)**
41-80 (1-2xULN)	79 (25.0)	
>80 (>2xULN)	69 (21.8)	
AST (IU/L)	50.6±93.3	29 (10-1190)
Albumin (g/dL)	4.35±0.59	4.40 (2.60-5.60)
ALP (U/L)	79.3±41.5	74 (7-449)
GGT (U/L)	34.0±38.3	23 (6-343)
Creatinine (mg/dL)	0.73±0.19	0.70 (0.30-2.70)
PLT (10^3/µL)	226±60	219.5 (71-455)
HBV-DNA (IU/mL)	**148,148,732±1,917,824,655**	**240,701 (2,045-33,915,235,786)**
2,000-20,000	80 (25.3)	
20,000-200,000	73 (23.1)	
200.000-2,000,000	72 (22.8)	
2,000,000-20,000,000	52 (16.5)	
20,000,000-200,000,000	28 (8.9)	
>200,000,000	11 (3.5)	
HAI score	6.2±2.1	6 (2-14)
Fibrosis score	2.0±0.8	2 (0-6)

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, HAI: Histologic activity index, PLT: Platelet count, SD: Standard deviation, ULN: Upper limit of normal, min.: Minimum, max.: Maximum

Table 2. Histopathological findings of patients with chronic hepatitis B

Fibrosis score	**Minimal inflammation (HAI 1-3) (n=40)**		**Mild inflammation (HAI 4-8) (n=229)**		**Moderate inflammation (HAI 9-12) (n=44)**		**Severe inflammation (HAI 13-18) (n=3)**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
F0 (n=10)	0	0.0	9	3.9	1	2.3	0	0.0
F1 (n=43)	0	0.0	41	17.9	2	4.5	0	0.0
F2 (n=215)	38	95.0	154	67.2	22	50.0	1	33.3
F3 (n=40)	1	2.5	21	9.2	17	38.7	1	33.3
F4 (n=6)	1	2.5	2	0.9	2	4.5	1	33.3
F5 (n=0)	0	0.0	0	0	0	0.0	0	0.0
F6 (n=2)	0	0.0	2	0.9	0	0.0	0	0.0

HAI: Histological activity index, F: Fibrosis

(r=0.414, p<0.001) and fibrosis score (r=0.111, p=0.049). On the other hand, the fibrosis score did not have a significant correlation other than the HAI score (Figure 1).

Regarding viral load, 70.9% of patients with normal ALT levels and 22.9% of patients with elevated ALT levels had HBV-DNA <200,000 IU/mL (p<0.001). Patients with normal ALT levels had higher minimal inflammation (19.6% vs. 4.7%, p<0.001) and mild fibrosis (88.7% vs 80.4%, p=0.042) than patients with elevated ALT levels. Patients with elevated ALT levels were divided into two groups (1-2xULN vs. >2xULN). High HBV-DNA (>2,000,000 IU/mL) (60.8% vs. 36.7%, p=0.003) and moderate inflammation (27.6% vs. 13.9%, p=0.042) were higher in patients with ALT >2 ULN than in patients with ALT 1-2 ULN (Table 3). The distributions of HBV-DNA and ALT according to HAI grade and fibrosis stage are shown in Figure 2, 3.

According to the ROC curve, for predicting HAI≥ 6, the area under the ROC (AUROC) values of HBV-DNA (cut-off: 33,427 IU/mL) and ALT (cut-off: 40.5 IU/L) were 0.726 (sensitivity: 78.4%, specificity: 61.8%, p<0.001) and 0.664 (sensitivity: 53.7%, specificity: 70.8%, p<0.001), respectively (Figure 4A). For predicting ≥F2 the AUROC values of HBV-DNA (cut-off: 721,062 IU/mL) and ALT (cut-off: 44.5 IU/L) were 0.624 (sensitivity: 56.7%, specificity: 65.0%, p=0.004) and 0.597 (sensitivity: 56.6%, specificity: 61.2%, p=0.026), respectively (Figure 4B).

Discussion

In this study, we presented a detailed analysis of the liver biopsy results, biochemical features, and virological parameters of 316 patients with treatment-naïve HBeAg negative CHB. We demonstrated positive correlations between HBV-DNA, ALT,

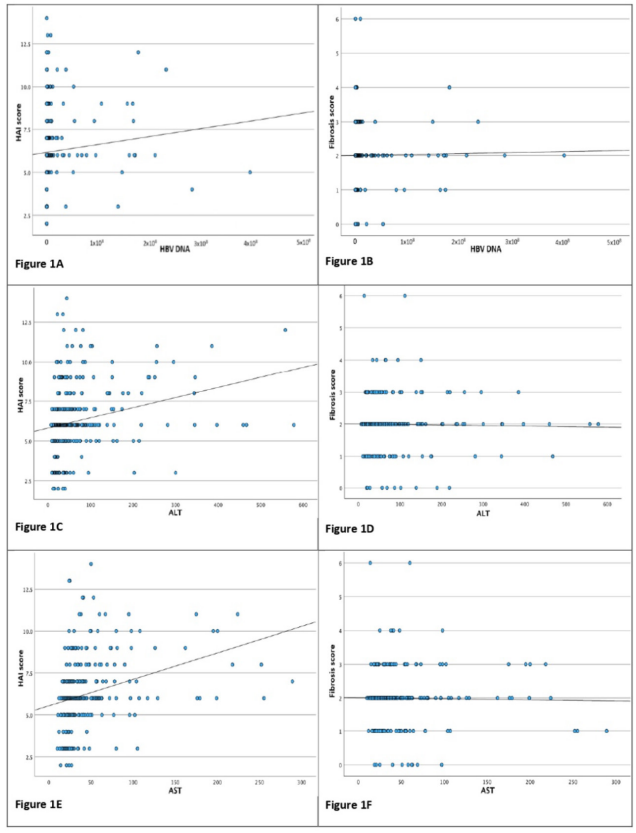

Figure 1. Correlations between HBV-DNA, ALT, and AST with HAI and fibrosis scores

HBV: Hepatitis B virus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HAI: Histologic activity index,

Table 3. Comparison of virological and histopathological findings of patients according to ALT levels

	Normal ALT (n=168)		Elevated ALT (n=148)					
			1x2 ULN (n=79)		>2xULN (n=69)		p[1]	p[2]
	n	%	n	%	n	%		
HBV-DNA (IU/mL)								
2000-20,000	67	39.9	8	10.1	5	7.2	0.538	**<0.001**
20,000-200,000	52	31.0	10	12.7	11	15.9	0.568	**<0.001**
200,000-2,000,000	29	17.3	32	40.5	11	15.9	**0.001**	**0.013**
2,000,000-20,000,000	12	7.1	17	21.5	23	33.3	0.108	**<0.001**
20,000,000-200,000,000	6	3.6	8	10.1	14	20.3	0.082	**0.001**
>200,000,000	2	1.2	4	5.1	5	7.2	0.581	**0.033**
HAI score								
1-3	33	19.6	4	5.1	3	4.3	0.884	**<0.001**
4-8	119	70.9	63	79.7	47	68.1	0.108	0.484
9-12	14	8.3	11	13.9	19	27.6	**0.043**	**0.003**
13-18	2	1.2	1	1.3	0	0.0	0.551	0.642
≥6**	105	62.5	63	79.7	59	85.5	0.360	**<0.001**
Fibrosis score								
F0-2	149	88.7	65	82.3	54	78.3	0.539	**0.042**
F3-6	19	11.3	14	17.7	15	21.7		

ALT: Alanine aminotransferase, ULN: Upper limit of normal, HAI: Histological activity index. p[1]: Comparison of 1x2 ULN with >2 x ULN, p[2]: Comparison of normal ALT with elevated ALT

and AST with HAI score, but not with fibrosis score. However, patients with normal ALT levels had a lower fibrosis score (F0-2). In addition, HBV-DNA and ALT showed poor diagnostic performance in predicting ≥F2, while HBV-DNA had moderate diagnostic performance in predicting HAI ≥6.

International guidelines, including EASL, the Asian Pacific Association for the Study of the Liver (APASL), and the American Association for the Study of Liver Diseases (AASLD), have recommended that the decision to initiate antiviral treatment should be planned according to HBV-DNA and ALT levels (5,6,7). In all three guidelines, elevation of ALT levels more than 2 times the ULN are indicated as the initiation criterion for treatment. However, although 40 IU/L is accepted as the upper limit of ALT in the EASL and APASL guidelines (5,6), the limit value is 35 IU/L for men and 25 IU/L for women in the AASLD guidelines (7). In

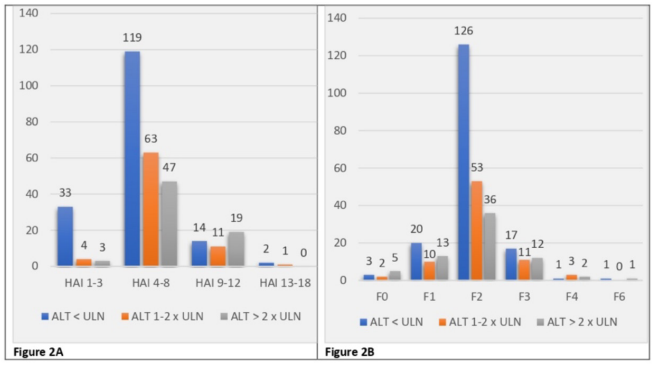

Figure 2. Comparison of ALT levels according to HAI grade and fibrosis stage

ALT: Alanine aminotransferase, HAI: Histologic activity index, ULN: Upper limit of normal

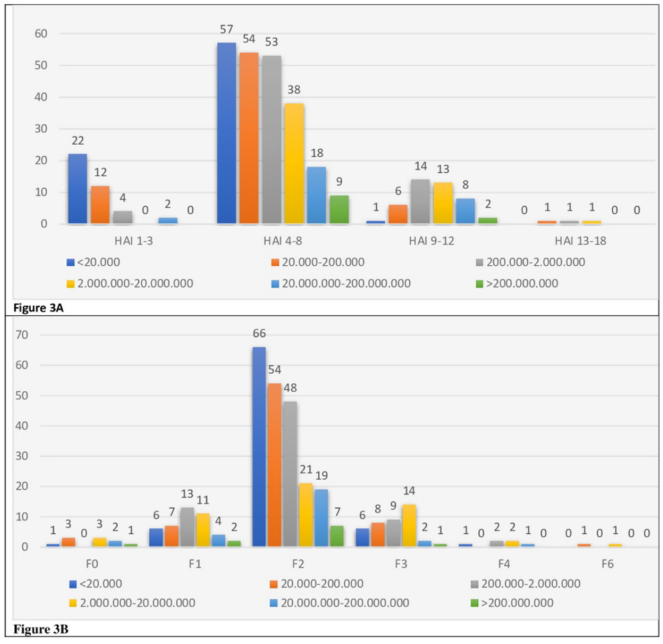

Figure 3. Comparison of HBV-DNA levels according to HAI grade and fibrosis stage

HBV: Hepatitis B virus, HAI: Histologic activity index

our study, approximately half of the patients receiving antiviral therapy had ALT levels in the normal range. In addition, moderate inflammation, which is accepted as the criterion for initiating antiviral treatment in international guidelines (5,6,7), was more common in patients with ALT >2xULN than in patients with ALT 1-2xULN. However, we found the ALT cut-off values to be 40.5 IU/L and 44.5 IU/L, respectively, in predicting HAI ≥6 and F ≥2, which are the indications for initiating antiviral treatment in our country. In the study by Alam et al. (11), 286 HBeAg-negative CHB patients were evaluated. Moderate to advanced inflammation (HAI ≥9) was 30.6% in the group with ALT 1-2xULN, whereas it was 51.0% in the group with ALT >2xULN (p=0.001). In the prediction of moderate inflammation, the sensitivity of ALT (cut-off 58.5 IU/L) value was 63% and the specificity was 65% (11). In the study by Seto et al. (12), ALT and fibrosis levels were compared. They reported that there was no significant difference between the group with ALT 1-2xULN and the group with ALT >2xULN in terms of significant fibrosis (≥F3) development. Similarly, in our study, there was no difference between the two groups (ALT 1-2xULN vs. ALT >2xULN) was detected in terms of significant fibrosis (≥F3) development.

In HBeAg-negative CHB patients, the HBV-DNA cut-off value, which is the treatment initiation criterion, is 20,000 IU/mL in the EASL guidelines (5), whereas it is 2,000 IU/mL in the APASL and AASLD guidelines (6,7). In our study, the HBV-DNA value of approximately a quarter of the patients who met the criteria (HAI ≥6 or ≥F2) for starting antiviral treatment with biopsy was between 2,000 IU/mL and 20,000 IU/mL. In addition, we found that the HBV-DNA cut-off values for predicting HAI ≥6 or ≥F2 were 33,427 IU/mL and 721,662 IU/mL, respectively. However, almost all patients (98.7%) with HBV-DNA between 2,000 and 20,000 IU/mL had minimal to mild inflammation (HAI ≤8). In the study of Yıldız Kaya et al. (13), although quantitative HBsAg levels were high (>1000 IU/mL) in patients with HBV-DNA values of 2,000-20,000 IU/mL, 78.9% of these patients had no fibrosis (<F2) and 57.9% had minimal inflammation (HAI <4). In another study, patients were divided into 2 groups according to their HBV-DNA values (<100,000 IU/mL vs. ≥100,000 IU/mL). Mild inflammation (81% vs. 19%, p<0.001) and mild fibrosis (81% vs. 21%, p<0.001) were found to be significantly lower in the group with HBV-DNA <100,000 IU/mL than in the group with HBV-DNA ≥100,000 IU/mL (14).

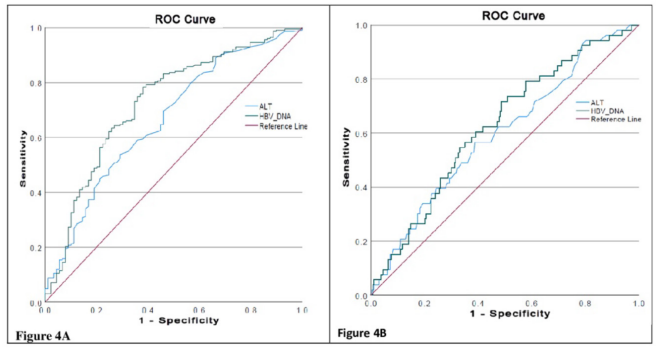

Figure 4. Receiver operating characteristic curves of the HBV-DNA and ALT in predicting ≥F2 and HAI ≥6

HBV: Hepatitis B virus, ALT: Alanine aminotransferase, HAI: Histologic activity index, ROC: Receiver operating characteristics

In our study, we showed that ALT, AST, HBV-DNA, and HAI scores were positively correlated with each other. No biochemical or virological parameters correlated with the fibrosis score. Shao et al. (9) reported that HBV-DNA levels were positively correlated with ALT (r=0.351, p=0.042), but not with AST, HAI score, and fibrosis score. In addition, no correlation was reported between ALT, AST with HAI and fibrosis scores (9). In the study of Diktas et al. (15), a positive correlation was found between HAI score and HBV-DNA (r=0.45, p<0.001), ALT (r=0.28, p=0.003) and AST (r=0.28, p=0.003), while only HBV-DNA was correlated with fibrosis score (r=0.21, p=0.024). In another study, a significant correlation was reported between AST, ALT, HBV-DNA, and HAI scores, similar to our study. However, the only parameter that correlated with the fibrosis score was AST levels (16).

Study Limitations

This study had several limitations. First, this was a single-center study enrolling patients admitted to an infectious diseases outpatient clinic and receiving antiviral therapy. Therefore, there may have been bias in the selection of inclusion. Second, the sampling error of liver biopsy, which is the gold standard reference method, was ignored. Third, instant virological and biochemical parameters were included. Therefore, ALT and HBV-DNA fluctuations in the natural history of HBeAg-negative CHB disease could not be detected and evaluated. However, our study had some strengths. First, we included only HBeAg -negative patients, and the number of patients was relatively high. Second, the diagnostic performance of virological and biochemical parameters was determined in the definition of histopathological findings, which is the indication for initiating antiviral treatment in our country.

Conclusion

In conclusion, although HBV-DNA and ALT are useful predictors of hepatic inflammation, the role of these markers in predicting fibrosis remains unclear. However, although the optimal ALT and HBV-DNA levels that predict hepatic damage remain uncertain, we emphasize that patients with both ALT levels in the normal range and HBV-DNA values <20,000 should be closely followed up for the need for antiviral treatment, considering our results.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval number: 2023-03-03, date: 06.02.2023).

Informed Consent: Written informed consent was waived because this study was conducted retrospectively.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.C.Ü., A.İ.S., Design: K.K.Y., Data Collection and Processing: E.S.D., A.S.D., Analysis or Interpretation: Y.E.Ö., O.F.B., Literature Search: D.B., Writing: Y.E.Ö., D.B.

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

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