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Evaluation of the Relationship of HBsAg Serum Plasma Values with HBV DNA and Other Serologic Markers in the Diagnosis of Hepatitis B

Hamdi Karahan[1,a], Cem Çelik[1,b*]

[1]*Department of Medical Microbiology, Faculty of Medicine, Sivas Cumhuriyet University, Sivas, Turkiye*
**Corresponding author*

Research Article

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ABSTRACT

Objective: Hepatitis B virus (HBV) infections cause a major public health problem worldwide diagnosis and treatment of HBV infection is an important issue. Detection of HBV DNA by polymerase chain reaction (PCR) and demonstration of viral replication together with serologic and biochemical indicators are very useful in diagnosis and treatment. In this study, we aimed to evaluate the relationship between HBsAg serum concentration values and other serologic parameters related to HBV in the diagnosis of hepatitis B.

Methods: HBsAg, HBV DNA, Anti HBc IgG, Anti HBc IgM, HBeAg, and Anti HBe values obtained from blood sera taken from patients in Sivas Cumhuriyet University Application and Research Hospital Microbiology Laboratory between 2012-2020 were retrospectively analyzed from laboratory records.

Results: A positive correlation was found between HBsAg serum titers and HBV DNA and between HBeAg and HBV DNA. It was found that HBV DNA positivity rates increased as HBsAg titers increased. Similarly, it was found that HBc IgG positivity increased as HBsAg titers increased. HBeAg positivity increased with increasing HBsAg titers up to a certain point, while HBeAg positivity decreased after a certain titer. When HBV DNA results were compared with HBeAg results, the relationship between the two values was found to be significant.

Conclusion: We think that it is useful to investigate the relationship between serum concentrations of HBsAg and HBV DNA and other serologic parameters in the accurate identification of HBV infection and monitoring of treatment.

Keywords: HBsAg, HBV DNA, Anti HBc IgG, Anti HBc IgM, HBeAg, Anti HBe

Hepatit B Tanısında HBsAg Serum Plazma Değerlerinin HBV DNA ve Diğer Serolojik Belirteçlerle İlişkisinin Değerlendirilmesi

Araştırma Makalesi

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ÖZET

Amaç: Hepatit B virüsü (HBV) enfeksiyonları tüm dünyada çok önemli bir toplum sağlığı problemi oluşturmaktadır. HBV enfeksiyonunun tanı ve tedavisi önemli bir konudur. HBV DNA'nın polimeraz zincir reaksiyonu (PCR) yöntemi ile saptanarak viral replikasyonun gösterilmesi, serolojik ve biyokimyasal göstergelerle birlikte tanı ve tedavinin takibinde oldukça yararlıdır. Bu çalışmada, Hepatit B tanısında HBsAg serum konsantrasyon değerlerinin, HBV ile ilgili diğer serolojik parametreler ile karşılaştırılarak aralarındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Yöntem: Sivas Cumhuriyet Üniversitesi Uygulama ve Araştırma Hastanesi Mikrobiyoloji Laboratuvarına 2012–2020 yıllarında hastalardan alınan kan serumlarından elde edilen HBsAg, HBV DNA, Anti HBc IgG, Anti HBc IgM, HBeAg ve Anti HBe değerleri laboratuvar kayıtlarından geriye dönük olarak incelenmiştir.

Bulgular: HBsAg serum titreleri ile HBV DNA arasında ve HBeAg ile HBV DNA arasında pozitif bir ilişki bulunmuştur. HBsAg titreleri arttıkça HBV DNA pozitiflik oranlarının arttığı görülmüştür. Aynı şekilde HBsAg titreleri arttıkça HBc IgG pozitifliklerinin arttığı tespit edilmiştir. Belirli bir noktaya kadar artan HBsAg titreleri ile HBeAg pozitifliği artarken, belirli bir titreden sonra HBeAg pozitifliği düşmüştür. HBV DNA sonuçları ile HBeAg sonuçları karşılaştırıldığında iki değer arasındaki ilişki önemli bulunmuştur.

Sonuç: HBV enfeksiyonun doğru bir şekilde tanımlanmasında ve tedavinin izlenmesinde HBsAg'nin serum konsantrasyonlarının, HBV DNA ve diğer serolojik parametreler ile ilişkilerinin araştırılmasının yararlı olduğunu düşünmekteyiz.

Anahtar Kelimeler: HBsAg, HBV DNA, Anti HBc IgG, Anti HBc IgM, HBeAg, Anti HBe

[a] *hmdkrhn@gmail.com* *0000-0002-4801-2217* [b] *cemcelik58@gmail.com* *0000-0002-7141-5874*

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Introduction

Hepatitis B virus (HBV) infections are a very important public health problem all over the world. Many people around the world are infected with HBV and 300 million people are chronically infected. Approximately one million people die each year due to HBV infection and HBV-related complications[1].

Liver diseases caused by HBV are one of the important health problems all over the world[2]. HBV infection can lead to a wide range of liver diseases, from HBV carriage to liver cirrhosis and hepatocellular carcinoma[3].

Differences in the virus or patients cause different clinical manifestations of HBV infection. The clinical presentation of HBV infection depends on the age of infection, the genetic structure of the virus, the presence of other viral hepatitis viruses, and the immune status of the host. While 90% of infections acquired in the neonatal period become chronic, the rate of chronicity is 25-30% until the age of 5 and less than 5% in adulthood[4].

Diagnosis and treatment of HBV infection is an important issue. Detection of viral replication by polymerase chain reaction (PCR) of Hepatitis B virus deoxyribonucleic acid (HBV DNA), together with other serologic indicators, is very useful in diagnosis and monitoring of treatment[5]. In recent years, it has become important to investigate the relationship between serum concentrations of Hepatitis B surface antigen (HBsAg) and HBV DNA and other serologic parameters[6]. Molecular, serological, and biochemical tests are used together in the diagnosis, clinical, and treatment management of HBV infection[7]. This study aimed to evaluate the relationship between HBsAg serum concentration values and HBV DNA, Anti HBc IgG (Hepatitis B virus core G antibody), Anti HBc IgM (Hepatitis B virus core M antibody), HBeAg (Hepatitis B virus e antigen) and Anti HBe (Hepatitis B virus e antibody) in the diagnosis of Hepatitis B.

Materials and Methods

In this study, HBsAg, HBV DNA, anti-HBc IgG, anti-HBc IgM, HBeAg, and anti-HBe levels obtained from blood sera of patients of different age and gender groups in Sivas Cumhuriyet University Application and Research Hospital Microbiology Laboratory between 2012 and 2020 were retrospectively analyzed from laboratory records.

In the study, the blood samples analyzed were evaluated once a year for each patient; repeated patient results within the same year were not evaluated. In addition to HBsAg positivity, patients with one or more positive anti HCV, anti HDV and anti HIV tests were excluded from the study to avoid confusion in the evaluation of other study parameters.

In this study, the presence of antigen/antibody used in HBV diagnosis in serology tests was analyzed. Blood samples taken from the patients in EDTA tubes were separated by centrifugation without waiting. HBsAg, Anti HBc, Anti HBc IgM, HBe Ag, Anti HBe, HBe IgM, HBe Ag, Anti HBe, tests of serum samples from 2012-2019 were analyzed using the Chemiluminescent Microparticle Enzyme Immunoassay (CMIA) method by the procedure recommended by the manufacturer (Architect System, Abbott, Germany). HBsAg, Anti HBc, Anti HBc, Anti HBc IgM, HBeAg, Anti HBe, tests from serum samples in the 2019-2020 years were analyzed using the electrochemilluminescence Immunoassay (ECLIA) method by the procedure recommended by the manufacturer (Roche Diagnostics, Germany).

Each stage of the study was conducted with ethical principles. Before the application, the necessary permissions were obtained from the Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (dated 25.05.2022, numbered 11/41).

Statistical Analysis

The data obtained from this study were uploaded to the SPSS program (ver:22.0). In the evaluation of the data, when the parametric test assumptions were fulfilled (Kolmogorov-Smirnov), the significance test of the difference between two means was used when comparing the measurements obtained from two independent groups, Man Whitney U test was used when the parametric test assumptions were not fulfilled, Correlation analysis was used to determine the relationships between variables, Khi-Square test was used in 2x2 and multi compartment arrangements in the evaluation of data obtained by counting, and the error level was taken as 0.05.

Results

In this study, a total of 3788 patients were tested for HBsAg and HBV DNA. Of these patients, 1536 were female (40.6%) and 2252 were male (59.4%). In the 3788 patients in the study, the youngest age was 0 and the oldest age was 94, with a mean age of 49.43 years. The mean age was 49.65 years for females and 49.30 years for males. HBV DNA, Anti HBc IgG, Anti HBc IgM, HBeAg, and Anti HBe tests were performed in the patient group included in the study and their relationships with HBs Ag titers were compared (Table 1-6).

HBV DNA positivity rate of individuals with HBsAg titer <1 IU/ml was 1.3% and the negativity rate was 98.7%, while HBV DNA positivity rates increased as HBsAg titers increased. When the HBsAg titers and HBV DNA cross table were examined in detail, the relationship between HBV DNA positivity according to titers was found to be significant (X^2=1913.70) (p=0.001) (Table 1).

Table 1. HBsAg Titer and HBV DNA Cross Table

HBsAg Titer (IU/ml)		HBV DNA			
		Negative	Positive	Pos./Neg.	Total
<1 IU/ml	Number of patients	1299	17	0	1316
	%	98.7	1.3	0	100.0
1-10 IU/ml	Number of patients	102	11	0	113
	%	90.3	9.7	0	100,0
11-100 IU/ml	Number of patients	153	185	1	339
	%	45.1	54.6	0.3	100.0
101-1000 IU/ml	Number of patients	0	4	0	4
	%	0	100.0	0	100.0
1001-2000 IU/ml	Number of patients	32	162	0	194
	%	16.5	83.5	0	100.0
2001-4000 IU/ml	Number of patients	199	628	4	831
	%	23.9	75.6	0.5	100.0
4001-5000 IU/ml	Number of patients	133	493	0	626
	%	21.2	78.8	0	100.0
>5001 IU/ml	Number of patients	106	259	0	365
	%	29.0	71.0	0	100
Total	Number of patients	2024	1759	5	3788
	%	53.4	46.4	0.2	100.0

When the cross tabulation of HBsAg titers and Anti HBc IgG is analyzed, it is seen that HBc IgG positivity increases as HBsAg titers increase. While HBc IgG positivity was 68.6% at HBsAg titer <1 IU/ml, this rate reached up to 100% as the titers increased. Accordingly, the relationship between HBsAg titers and anti HBc IgG was found to be significant (X^2=489.20) (p=0.001) (Table 2).

Table 2. HBsAg Titer and HBc IgG Cross Table

HBsAg Titer (IU/ml)		HBc IgG		
		Negative	Positive	Total
<1 IU/ml	Number of patients	160	350	510
	%	31.4	68.6	100.0
1-10 IU/ml	Number of patients	14	29	43
	%	32.6	67.4	100.0
11-100 IU/ml	Number of patients	9	165	174
	%	5.2	93.8	100.0
101-1000 IU/ml	Number of patients	0	2	2
	%	0	100.0	100.0
1001-2000 IU/ml	Number of patients	0	127	127
	%	0	99.2	100.0
2001-4000 IU/ml	Number of patients	2	550	552
	%	0.4	99.6	100.0
4001-5000 IU/ml	Number of patients	2	417	419
	%	0.5	99.5	100.0
>5001 IU/ml	Number of patients	0	247	247
	%	0	100.0	100.0
Total	Number of patients	187	1887	2074
	%	9.2	90.8	100.0

The first antibody that develops against hepatitis B Cor antigen is Anti HBcIgM. This antibody disappears after a while and is replaced by HBcIgG. When HBsAg titers and Anti HBcIgM values were analyzed in our study, Anti HBcIgM positivity was found between 0% and 7% in HBsAg titers. (X^2=71.14)(p=0.021) (Table 3).

Table 3. HBsAg Titer and HBcIgM Cross Table

HBsAg Titer (IU/ml)		HBcIgM			
		Negative	Positive	Pos./Neg.	Total
<1 IU/ml	Number of patients	501	10	1	512
	%	97.8	1.9	0.3	100.0
1-10 IU/ml	Number of patients	42	1	0	43
	%	97.7	2.3	0	100.0
11-100 IU/ml	Number of patients	164	11	0	175
	%	93.7	6.3	0	100.0
101-1000 IU/ml	Number of patients	2	0	0	2
	%	100.0	0	0	100.0
1001-2000 IU/ml	Number of patients	119	9	0	128
	%	93.0	7.0	0	100.0
2001-4000 IU/ml	Number of patients	542	11	0	553
	%	98.8	2.0	0	100.0
4001-5000 IU/ml	Number of patients	415	5	0	420
	%	98.8	1.2	0	100.0
>5001 IU/ml	Number of patients	247	0	0	247
	%	100.0	0	0	100.0
Total	Number of patients	2032	47	1	2080
	%	97.3	2.3	0.04	100.0

HBeAg is formed during similar periods as HBsAg. HBeAg disappears and Anti HBe is formed in certain groups during the progression of the disease. When the HBsAg titers and HBeAg cross-tabulation were examined, HBeAg positivity ranging from 0.5% to 32.7% was observed at different HBsAg titers. While HBeAg positivity increased with increasing HBsAg titers up to a certain point, HBeAg positivity decreased after a certain titer (X^2=297.81)(p=0.001) (Table 4).

Table 4. HBsAg Titer and HBeAg Cross Table

HBsAg Titer (IU/ml)		HBeAg		
		Negative	Positive	Total
<1 IU/ml	Number of patients	590	3	593
	%	99.5	0.5	100.0
1-10 IU/ml	Number of patients	51	1	52
	%	98.1	1.9	100.0
11-100 IU/ml	Number of patients	167	56	223
	%	74.9	25.1	100.0
101-1000 IU/ml	Number of patients	2	0	2
	%	100.0	0	100.0
1001-2000 IU/ml	Number of patients	105	51	156
	%	67.3	32.7	100.0
2001-4000 IU/ml	Number of patients	582	85	667
	%	87.3	12.7	100.0
4001-5000 IU/ml	Number of patients	508	14	522
	%	97.3	2.7	100.0
>5001 IU/ml	Number of patients	297	7	304
	%	97.7	2.3	100.0
Total	Number of patients	2302	217	2519
	%	91.4	8.6	100.0

When the HBsAg titers and Anti HBe cross table are analyzed, it is seen that Anti HBe positivity increases as HBsAg titers increase. Anti HBe positivity, which was 21.4% at HBsAg <1 IU/ml, increased to 74.3% as the titers increased. The relationship between HBsAg titers and Anti HBe was found to be significant (X^2=374.06) (p=0.001) (Table 5).

Table 5. HBsAg Titer and Anti-HBe Cross Table

HBsAg Titer (IU/ml)		Anti-HBe Negative	Anti-HBe Positive	Total
<1 IU/ml	Number of patients	447	122	569
	%	78.6	21.4	100.0
1-10 IU/ml	Number of patients	28	22	50
	%	56.0	44.0	100.0
11-100 IU/ml	Number of patients	120	99	219
	%	54.8	45.2	100.0
101-1000 IU/ml	Number of patients	1	1	2
	%	50.0	50.0	100.0
1001-2000 IU/ml	Number of patients	69	86	155
	%	44.5	55.5	100.0
2001-4000 IU/ml	Number of patients	238	419	657
	%	36.2	63.8	100.0
4001-5000 IU/ml	Number of patients	133	384	517
	%	25.7	74.3	100.0
>5001 IU/ml	Number of patients	109	193	302
	%	36.1	63.9	100.0
Total	Number of patients	1145	1326	2471
	%	46.3	53.7	100.0

When HBV DNA results were compared with HBeAg results, HBeAg positivity was found to be 2.5% in HBV DNA negative patients, while this rate was 13.5% in HBV DNA positive patients. When HBV DNA results were compared with HBeAg results, the relationship between the two values was found to be significant (X^2=95.43) (p=0.001) (Table 6).

Table 6. HBV DNA and HBeAg Cross Table

HBVDNA		HBeAg Negative	HBeAg Positive	Total
Negative	Number of patients	1073	27	1100
	%	97.5	2.5	100.0
Positive	Number of patients	1221	190	1411
	%	86.5	13.5	100.0
Pos.Neg.	Number of patients	4	0	4
	%	100.0	0	100.0
Total	Number of patients	2298	217	2515
	%	91.4	8.6	100.0

Discussion

The issue of which serologic and virologic tests to use in the diagnosis of HBV-related diseases is important. The diagnosis of HBV is based on clinical, biochemical, histological and serological findings[8].

HBsAg is the first antigen of the virus detected in the diagnosis of acute hepatitis B. Primary HBV infection can

be serologically determined by the appearance of HBsAg and HBeAg. Clinical symptoms appear around 10 weeks after infection and during this period elevated liver enzymes and anti-HBc IgM antibodies are detected. Shortly after the appearance of HBsAg, HBeAg also appears. The presence of HBeAg is associated with transmissibility and active viral infection. When HBeAg disappears, Anti-HBe appears and remains positive for years. In acute hepatitis B, there may be a window period when both HBeAg and Anti HBe are negative. Anti-HBc IgM is positive during the window period and is therefore important. Anti-HBc IgM level decreases within 12-48 weeks, while Anti-HBc IgG level increases and can be positive in serum for life. Detection of Anti-HBc IgG and Anti-HBs IgG antibodies together is an indication that the disease has been transmitted and immunity is formed. Anti HBcTotal and anti HBs tests are not useful in diagnosis. Because they are indicators of previous infection. Persistent HBsAg positivity for at least 6 months suggests the presence of chronic hepatitis B[9].

The treatment of chronic HBV infections is difficult and complex. Due to the persistence of HBV covalently closed circular DNA (cccDNA), most patients require indefinite treatment. A durable treatment response often fails to develop. Therefore, efforts to prevent the disease and to screen risk groups are of vital importance[10]. Measurement of HBV DNA load and serum HBsAg is important in accurately defining HBV infection, monitoring treatment, and determining prognosis. Sağlık et al.[11] reported a positive correlation between HBsAg measurement values and HBV DNA levels in chronic hepatitis B patients. Zhu et al.[12] reported a positive correlation between increasing HBV load and serum HBsAg levels in patients divided into 3 groups according to HBV DNA load. Demirelli et al.[13] investigated the relationship between serum HBsAg and HBV DNA in 71 patients treated for chronic hepatitis B infection. Researchers have found a positive correlation between serum HBsAg levels and HBV DNA in patients. In our study, similar results were obtained between HBsAg serum titer and HBV DNA. As HBsAg titer increased, the HBV DNA positivity rate increased.

Karra et al.[14] categorized HBV infection into 4 phases: immune tolerance phase, immune clearance phase, low replicative phase, and HBeAg negative hepatitis. In a total of 976 HBV-associated patients, the investigators reported that HBsAg titers were different in each phase of HBV infection, and HBsAg and HBV DNA levels were significantly correlated in all groups. Özaras et al.[15] performed HBsAg quantitation and HBV DNA measurements at certain weeks in 18 patients with chronic hepatitis B receiving pegylated interferon ± lamivudine and reported a significant correlation between these results. Researchers have reported that the HBsAg test is associated with HBV DNA and may be a valuable marker during the monitoring of the effectiveness of HBV treatment. Similarly, in our study, the HBV DNA positivity rate increased as the HBsAg titer increased. The relationship between HBsAg titers and HBV DNA positivity was found to be significant ($p<0.05$).

The presence of HBe Ag antigen is associated with increased infectivity and an increased risk of chronic hepatitis b carriers progressing to cirrhosis. The HBe Ag antigen can be used to help monitor the evolution of chronic HBV[8]. Shao et al.[16] evaluated HBV DNA levels in HBeAg positive and negative patients in their study. The researchers found HBeAg test positive in 178 and negative in 35 of 213 patients with HBV DNA levels above 10^5 copies/mL. In our study, similar results were obtained between HBV DNA and HBeAg status similar to Shao et al. HBV DNA was found positive in 190 of 217 HBeAg positive patients. Wang et al.[17] grouped 1020 patients into HbeAg positive and HbeAg negative groups and high and low HBV DNA levels. The researchers reported that when the HBeAg level was higher than 16.15 S/CO, they were four times more likely to have high HBV DNA levels. Bizim çalışmamızda HBeAg pozitif olan hastaların büyük çoğunluğunda HBV DNA pozitif bulunması yönünden Wang ve arkadaşlarının çalışmasının sonuçları ile benzer görünmektedir. Çeviker et al.[18] formed two groups according to HBeAg positive and negative status among 231 patients diagnosed with chronic hepatitis B. Among these patients, 198 were anti HBe positive and 33 were HBeAg positive. HBV DNA levels were found to be significantly higher in HBeAg positive patients. The results of our study seem to be similar to the results of this study.

HBV inactive carriers are difficult to differentiate from HBeAg negative patients. Martinot-Peignoux et al.[19] classified 129 HBeAg-negative CHB patients as inactive carriers, active carriers and reactivation patients. The researchers reported that combined HBsAg and HBV DNA cut-off values should be applied to baseline measurements and HBsAg should be included in the monitoring of asymptomatic HBeAg-negative CHB patients. Akın et al.[20] reported HBeAg negative anti HBe positive results in 94% of 233 patients and HBV DNA positive results in 13 patients. In our study, 90.7% of HBeAg negative patients were also found to be anti HBe positive. The results of the study by Akın et al. and the anti HBe positivity in our study seem to be similar. Tezcan Ülger et al.[21] compared HBV DNA results with HBeAg results in 91 patients with chronic hepatitis B and reported that the relationship between HBsAg measurement values and HBV DNA levels was statistically significant. The researchers found that HBsAg levels in HBeAg positive patients were significantly higher than HBeAg negative patients.

In cases where HBsAg is negative, the presence of HBV DNA at low titer is known as latent HBV. Even if the HBsAg test is negative, HBV may be present in the body in some patients. These patients may continue to be infectious. Savcı et al.[22] reported that they found isolated HBV DNA positivity (occult hepatitis B infection) in 18 of 160 HBsAg negative patients on hemodialysis. Latent HBV infection is a significant threat to the safety of the blood supply. Svicher et al.[23] investigated occult HBV infection in their study. HBsAg and nucleic acid tests were performed on a total of 422278 blood donors. The researchers reported that they identified occult HBV in 26 of them. In our study,

of the 1316 patients with HBsAg titer <1 IU/ml, 1299 were HBV DNA negative and 17 were HBV DNA positive. Our study results are similar to the results of the above studies in this respect.

Isolated anti HBc positivity may be indicative of different conditions ranging from false reactivity to chronic HBV infection. Further investigation and monitoring are important in these patients. Bozdemir et al.[24] retrospectively analyzed the serologic parameters of 22333 patients whose HBsAg, anti HBc, and anti HBs tests were performed on the same date. It was reported that isolated anti-HBc positivity was detected in 837 (3.74%) of these patients. Of 180 patients who were tested for HBV DNA, 16 (8.8%) were found to be positive. In our study, anti HBcIgM test was performed in 2090 of 3788 patients. Anti HBcIgM test was found to be negative in 2032 patients, positive in 47 patients, and pos. neg in 1 patient. HBV DNA positivity was found to be higher in our study compared to this study.

HBsAg as an indicator of HBV infection is being evaluated. The clinical use of plasma concentrations of serum HBsAg is becoming increasingly important. HBsAg and other serologic parameters alone are insufficient in the evaluation of the course of HBV infection, response to antiviral treatment, and prognosis. Detection of HBV DNA is recognized as the most sensitive method in treatment and follow-up. A positive correlation has been found between HBsAg serum titers and HBV DNA and between HBeAg and HBV DNA. We think that HBV DNA levels are very important in the accurate identification of HBV infection and monitoring of treatment.

Conflicts of interest

There are no conflicts of interest in this work.

Authors' contributions

HK: Analyses, design, supervision, resources, materials, data collection, literature review, reporting. CÇ: Project administration, concept, Writing – review and editing, Research, Methodology, Verification.

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