İstanbul Med J 2024; 25(3): 229-35
DOI: 10.4274/imj.galenos.2024.55491

The Role of Quantitative HBsAg Levels in Chronic Hepatitis B Infection

Merve Kılıç Tekin[1], Serkan Sürme[1,2], Mustafa Yıldırım[3]

[1]University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey
[2]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Medical Microbiology, Institute of Graduate Studies, İstanbul, Turkey
[3]İstanbul Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey

ABSTRACT

Introduction: Chronic hepatitis B (CHB) infection is essential for patient management, including treatment and follow-up. Therefore, quantitative hepatitis B surface antigen (qHBsAg) may help physicians identify the stages of hepatitis B virus (HBV) infection. This study aimed to examine the variance in qHBsAg levels across various stages of viral infection.

Methods: This cross-sectional study, 183 patients who attended the Infectious Diseases outpatient clinic at Haseki Training and Research Hospital between July and December 2020, tested positive for HBsAg, and did not undergo prior treatment.

Results: Among the 183 patients, 54.1% were male. The mean qHBsAg level was 2,155 IU/mL (interquartile range: 625-12,759). Correlation analysis revealed that qHBsAg was significantly associated with age, laboratory results, and HBV-DNA. In the receiver operating characteristic analysis, which evaluates the predictive power of qHBsAg for chronic hepatitis, the area under the curve was 0.749, and the optimal cut-off value for qHBsAg was 3,081 IU/mL. The cutoff value for the 95% specificity of qHBsAg in predicting chronic hepatitis was 38,641 IU/mL.

Conclusion: Quantitative HBsAg is an easily applicable and relatively inexpensive test for distinguishing different stages of chronic hepatitis. Therefore, qHBsAg can help clinicians assess liver injury and plan treatment at the most appropriate time for patients with CHB infection. In patients with HBV-DNA levels exceeding 2,000 IU/mL, commencement of treatment without the necessity of liver biopsy may be considered when the qHBsAg exceeds 38,000 IU/mL.

Keywords: HBeAg, HBV DNA, chronic hepatitis B, qHBsAg, liver biopsy

Introduction

Hepatitis B virus (HBV) is a member of the Hepadnaviridae family that is characterized by its double-stranded DNA structure (1). Hepatitis B surface antigen (HBsAg) is secreted into the circulation in tubular or spherical forms by hepatocytes infected with the (HBV). Quantitative hepatitis B surface antigen (qHBsAg) levels reflect transcriptional activity originating from closed circular DNA (cccDNA) and integrated DNA within hepatocytes. Therefore, qHBsAg levels can be used as an auxiliary indicator during the course of chronic hepatitis B (CHB) (2).

The standardization of HBsAg quantification has been achieved, leading to an increased utilization of this method in current practice. HBsAg quantification is a valuable parameter that can guide the staging and follow-up of CHB infection and can be used to predict complications of CHB infection and to determine treatment initiation and cessation (3,4).

This finding does not necessarily indicate that patients with infection have CHB. Hence, the identification of individuals with chronic HBV infection and persistent HBV infection holds significant importance in patient management, including treatment decisions and follow-up protocols. In this regard, qHBsAg can help physicians identify the stages of HBV infection (3). The primary objective of this study was to examine variations in qHBsAg levels among distinct infection stages. Additionally, the relationship between qHBsAg and the tested parameters was investigated.

Methods

Patients

In this single-center, cross-sectional study, a total of 183 patients with hepatitis B who applied to the Department of Infectious Diseases and Clinical Microbiology, Haseki Training and Research Hospital between July and December 2020 were included.

The inclusion criteria were age 18 years, confirmed HBsAg positivity for a minimum duration of 1 year, and no history of prior HBV treatment.

Address for Correspondence: Merve Kılıç Tekin MD, University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey
Phone: +90 534 790 70 96 **E-mail:** drmervetekin@gmail.com **ORCID ID:** orcid.org/0000-0003-3208-6331

Cite this article as: Kılıç Tekin M, Sürme S, Yıldırım M. The Role of Quantitative HBsAg Levels in Chronic Hepatitis B Infection. İstanbul Med J. 2024; 25(3): 229-35

Received: 27.03.2024
Accepted: 10.06.2024

The exclusion criteria were coinfection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatocellular carcinoma (HCC), pregnancy, and findings indicative of alcoholic hepatitis.

We recorded the following data for each patient: age, gender, HBsAg, hepatitis B envelop antigen (HBeAg), anti-HBe, HBV-DNA levels, anti-HDV, anti-HCV, anti-HIV, biochemical values such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) total bilirubin, alkaline phosphatase, gamma-glutamyl transferase, albumin, globulin, alpha-feto protein, hemogram, prothrombin time, international normalized ratio values, and abdominal ultrasonography findings. The biopsy findings [fibrosis and histological activity index (HAI)] of patients who underwent liver biopsy within the last 1 year were also recorded.

qHBsAg levels were correlated with biochemical results and HBV-DNA levels obtained concurrently, whereas liver biopsies were performed within 1 year of blood sample collection.

According to the 2017 Classification by the European Association for the Study of the Liver (EASL), patients were categorized into four groups: HBeAg-positive chronic infection (HBV-DNA >10^7 IU/mL, normal ALT); HBeAg-positive chronic hepatitis (HBV-DNA 10^4-10^7 IU/mL, elevated ALT); HBeAg-negative chronic infection (HBV-DNA <2000 IU/mL, normal ALT); and HBeAg-negative chronic hepatitis (HBV-DNA >2000 IU/mL, elevated ALT) (3).

The study was approved by the University of Health Sciences Turkey, Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 2020 -111, date: 08.07.2020).

Informed consent was obtained from the patients prior to their participation in the study.

Definitions and Reference Ranges

In the present study, biochemical analyses, including serum urea, serum creatinine, AST, and alanine transaminase levels, were performed using kits applied to the Beckman AU2700 auto analyzer devices of the Biochemistry Laboratory of Haseki Training and Research Hospital.

Serological and virological tests were performed using the Abbott Architect I-2000 Device and the Architect Alinity Kit in the microbiology laboratory of Haseki Training and Research Hospital.

For HBsAg quantification, serum samples obtained from patients were stored at 40 °C, and qHBsAg levels were measured using the chemiluminescent microparticle immunoassay technique with the Elecsys HBsAg II (Roche Diagnostics, Indianapolis, USA) kit.

Statistical Analysis

For statistical analyses, SPSS 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used. The chi-square test was used for categorical variables. Mann-Whitney U test was used for subgroup analyses, and results were interpreted with Bonferroni correction. The Kruskal-Wallis test was used to compare continuous variables between the four groups. The relationships between numerical variables were analyzed using Pearson's correlation analysis when the parametric test conditions were met and Spearman's correlation analysis (Spearman's RHO test) when the parametric test conditions could not be met. Statistical significance was given as $p<0.05$.

Receiver operating characteristic (ROC) analysis was performed with reference to the HAI, fibrosis, and chronic hepatitis classifications, and ROC graphs were used to determine the diagnostic performance of the qHBsAg variable, which is clinically predicted to be effective in determining the risk group. Variables with an area under the curve (AUC) of >0.500 that had a certain sensitivity and specificity for determining chronic hepatitis, HBV-DNA levels, liver fibrosis, and HAI were also calculated.

Results

A total of 183 patients were included in this study, and 84 (45.9%) were women. The median age of the patients was 40 years (range: 30-48).

Liver needle biopsy was performed in 77 patients within the last 1 year. There were 64 (83.1%) patients with fibrosis between 0 and 2 and 13 (16.9%) with fibrosis 3-4 among patients who underwent biopsy. Fibrosis 5 or 6 was not detected in any patient. A total of 58 (75.3%) patients had HAI between 0-6, and 19 (24.7%) had HAI >6.

According to the hepatitis classification, 13 (7.1%) patients had HBeAg (+) chronic infection, 40 (21.9%) HBeAg (+) chronic hepatitis, 96 (52.5%) HBeAg (-) chronic hepatitis, and 34 (18.6%) were in the HBeAg (-) chronic hepatitis group.

The demographic characteristics and fundamental test outcomes are presented in Table 1.

The comparison of the patient groups in terms of clinical and demographic characteristics, such as sex, age, laboratory results, HBV-DNA, qHBsAg, fibrosis, HAI scores, and hepatosteatosis, are presented in Table 2. Subgroup analyses performed according to Bonferroni correction for these features are presented in Table 3.

In the correlation analysis, qHBsAg was significantly associated with age, ALT, AST, albumin, PTZ, AFP, and HBV-DNA in the general study group. Furthermore, notable correlations were observed between qHBsAg levels and factors such as age, total protein, albumin, and HBV-DNA in HBeAg-positive patients. Similarly, significant associations were identified between qHBsAg and the fallowing variables; age, ALT, and HBV-DNA in HBeAg-negative patients (Table 4).

A moderate positive correlation was detected between qHBsAg and HBV-DNA in the cohort ($r=0.626$, $p<0.001$) and HBeAg (+) group ($r=0.602$, $p<0.001$). A weak positive correlation was detected between qHBsAg and HBV-DNA in HBeAg (-) group ($r=0.375$, $p<0.001$). In HBeAg (+) and HBeAg (-) patient groups, as the HBV-DNA value increased, the qHBsAg value also increased in Table 4.

The ability of qHBsAg to predict fibrosis and HAI in patients with biopsy results was calculated using an ROC curve. In the ROC analysis, in which the predictive power for fibrosis ≥2 was evaluated, qHBsAg was insufficient to evaluate fibrosis ($p>0.086$) (Figure 1).

In the ROC analysis, the AUC for HAI ≥6 was not statistically significant (AUC=0.611, $p=0.15$). The AUC for HAI ≥9 was statistically significant (AUC=0.742, $p=0.008$).

In the ROC analysis performed to predict chronic hepatitis, the AUC for qHBsAg was statistically significant (AUC=0.749, p<0.001). The cut-off point of qHBsAg for determining chronic hepatitis was 3,081 IU/mL. The sensitivity and specificity were 70.3% and specificity 70.6% for qHBsAg ≤3,081 IU/mL. In recognizing chronic hepatitis, the limit value was 38,641 IU/mL with 95% specificity, and the sensitivity was 18% for this value in Figure 2.

In the ROC analysis to evaluate the power of qHBsAg for HBV DNA >2,000 IU/mL in patients, the AUC for HBV-DNA >2,000 IU/mL was statistically significant (AUC=0.790, p<0.001) in Figure 3. For HBV-DNA >2,000 IU/mL, the cutoff value of qHBsAg was 1.924.5 IU/mL. The sensitivity and specificity of qHBsAg 1.924.5 were 72.3% and specificity was 70.4% for qHBsAg ≥1.924.5.

In the ROC analysis performed to evaluate the predictive power of qHBsAg for HBV-DNA >20.000 IU/mL in patients, the AUC was found to be statistically significant (AUC=0.814, p<0.001) in Figure 4. For HBV-DNA >20,000 IU/mL as the reference, the cut-off value for qHBsAg was determined to be 3.081 IU/mL. The sensitivity was 75% and specificity was 71.3% for qHBsAg ≥3,081.

No significant cutoff values were detected for qHBsAg to predict HBV-DNA between 2,000-20,000 IU/mL (AUC=0.475, p=0.615).

Table 1. Demographic characteristics, laboratory parameters, and liver biopsy findings

Characteristics	Median (IQR)
Age (years)	40 (30-48)
Gender	
Female (n, %)	84 (45.9)
Male (n, %)	99 (54.1)
ALT (IU/L)	28 (19-49)
AST (IU/L)	26 (20-38)
Total bilirubin level (mg/dL)	0.50 (0.40-0.70)
Direct bilirubin administration (mg/dL)	0.10 (0.10-0.14)
Total protein (g/dL)	72.2 (70-75.8)
Albumin (g/dL)	42 (40-45)
INR	1 (0.90-1)
Prothrombin time (sec)	11.2 (11-12)
AFP (IU/mL)	2.83 (1.9-4)
HBeAg	
Positive	53 (29.0)
Negative	130 (71.0)
HBV-DNA (IU/mL)	5.271 (623-444.240)
qHBsAg (IU/mL)	2.155 (625.1-12.759)
Fibrosis in biopsy specimens	
0-2	57 (74.0)
≥2	20 (26.0)
HAI in biopsy specimens	
0-6	48 (62.3)
≥6	29 (37.7)
Hepatosteatosis	
Grade-1	38 (67.9)
Grade-2	18 (32.1)
HBeAg + Chr. infection	13 (7.1)
HBeAg + Chr. hepatitis	40 (21.9)
HBeAg - Chr. infection	96 (52.5)
HBeAg - Chr. hepatitis	34 (18.6)

IQR: Interquartile range, n: number of data, ALT: Alanine aminotransferase, IU/L: International unit/liter, AST: Aspartate aminotransferase, INR: International normalized ratio (international standardized ratio), sec: second, AFP: Alpha fetoprotein, HBeAg: Hepatitis B envelop antigen, HBV-DNA: Hepatitis B virus deoxyribonucleic acid, qHBsAg: Quantitative Hepatitis B surface antigen, HAI: Histologic activity index, Chr. hepatitis: Chronic hepatitis, Chr. infection: Chronic infection

Discussion

In total, 183 nave patients diagnosed with CHB were evaluated in this study. Upon evaluation of the correlation analyses, a positive association was identified between qHBsAg levels and ALT, HBV-DNA, and HAI. Consequently, we deduced that employing qHBsAg could be efficacious in determining the necessity for treatment initiation and monitoring patient follow-up.

Quantitative HBsAg is a factor affecting the prognosis of the disease, such as HBeAg positivity, HBV-DNA elevation, and genotype. Previous studies have shown that qHBsAg level >1000 IU/mL in HBeAg-negative CHB patients were associated with disease progression and HCC development (5,6). Additionally, the EASL and American Association for the Study of Liver Diseases guidelines stated that the most important determinant of the decision to treatment cessation is HBsAg loss. There is an annual average loss of HBsAg of 0.4-2.3% depending on the stage of liver disease and patient age. Given that most strategies for the functional cure of HBV infection involve combination therapy with nucleos(t)ide analogs, monitoring HBsAg is crucial for assessing response to novel therapeutic approaches. In addition to HBsAg loss, the degree of HBsAg

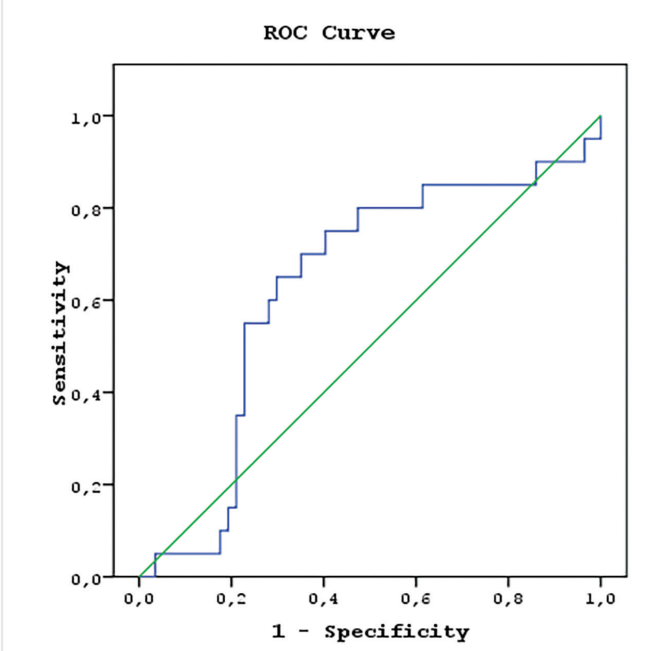

Figure 1. Examining the predictor power of qHBsAg Fibrosis 2 and over with the receiver operating characteristic curve

decline or specific cutoff values can serve as secondary endpoints in early clinical trials. However, the precise magnitude of HBsAg reduction or the threshold for treatment success remains uncertain (3,7). This condition is often difficult to achieve and requires long-term treatment. Some studies have examined whether monitoring the qHBsAg level is a predictive value of HBsAg loss during the natural course of the disease. It was concluded that low qHBsAg levels before treatment (<1,000 IU/mL) and a decrease in the early stages of the treatment (e.g. 1-2 log IU/mL) were indicative of the development of HBsAg loss, but the limit value was not determined clearly (5,6).

Many studies on HBsAg quantification have emphasized that qHBsAg measurement is a dynamic parameter that may differ according to the natural course of the disease (8,9). However, it was also shown that qHBsAg can be used as a reference to determine disease severity, evaluate compliance with treatment, and decide whether to terminate

Table 2. Comparison of clinical and demographic characteristics according to EASL classification

Characteristics	HBeAg (+) Chr. infection, (n=13)	HBeAg (+) Chr. hepatitis, (n=40)	HBeAg (–) Chr. infection, (n=96)	HBeAg (–) Chr. hepatitis, (n=34)	p-value
Gender					
Female n (%)	10 (76.9%)	15 (37.5%)	51 (53.1%)	8 (23.5%)	0.002
Male n (%)	3 (23.1%)	25 (62.5%)	45 (46.9%)	26 (76.5%)	
Age (years)					
Median	26	31	42	40	<0.001
IQR	20-31	27-47	37.25-50.75	32-47.25	
ALT (IU/L)					
Median	23	62.5	20	43.5	<0.001
IQR	17-29.5	43.5-93.5	16.25-26	33.75-85.75	
AST (IU/L)					
Median	24	43.5	20	36.5	<0.001
IQR	19-27.5	30.25-62	18-25.75	27-56	
Total bilirubin (mg/dL)					
Median	0.45	0.535	0.5	0.625	0.002
IQR	0.325-0.525	0.4925-0.7875	0.4-0.7	0.5-0.9	
Total protein (g/dL)					
Median	74.7	72	72.25	72.95	0.205
IQR	68.7-75.9	67.9-75	69.525-75.175	71-77.05	
Albumin (g/dL)					
Median	41	40.5	43	44	<0.001
IQR	40-43.5	37-43	41-45	42-46.25	
INR					
Median	0.9	0.995	0.9	1	0.048
IQR	0.9-1	0.9-1.1	0.9-1	0.975-1	
Prothrombin time (sec)					
Median	11.2	11.15	11.2	11.3	0.197
IQR	11.15-12.55	11-12.175	10.9-11.875	11-12.025	
AFP (IU/mL)					
Median	3.41	3.275	2.525	2.575	0.092
IQR	1.33-3.815	2.555-4.5375	1.9-3.645	1.875-4.17	
HBV-DNA (IU/mL)					
Median	146.861	20,000,000	739.5	36.557	<0.001
IQR	3.464-92.645.057	182.179.8-486.041	107-2.921	11.893.25-758.476.5	
qHBsAg (IU/mL)					
Median	37.510	20.717	874.1	2.506.5	<0.001
IQR	24.742.5-170.410	11.789.5-143.825	275.325-2.172.25	1082.75-6.708.75	

EASL: European Association for the Study of the Liver, HBeAg: Hepatitis B envelop antigen, Chr. infection: Chronic infection, Chr. hepatitis: Chronic hepatitis, n: Number of data, IQR: Interquartile range, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, IU/L: International unit/liter, qHBsAg: Quantitative hepatitis B surface antigen, INR: International normalized ratio (international standardized ratio), sec: Second, AFP: Alpha fetoprotein, HBV-DNA: Hepatitis B virus deoxyribonucleic acid, qHBsAg: Quantitative hepatitis B surface antigen

treatment (10,11). In this regard, qHBsAg is considered a reliable marker that can be used for patient follow-up.

HBsAg seroclearance and anti-HBs formation are the ultimate targets to be called functional cures and to discontinue treatment in patients who receive such treatments. For this reason, the quantitative measurement of HBsAg level plays an important role in patient follow-up (12). HBsAg seroclearance is an important parameter for predicting decreased HBsAg titers (especially HBsAg <10 IU/mL) and spontaneous HBsAg loss, which is used in treatment follow-up. Other markers reported to be advanced age, low ALT, high platelet, and leukocyte counts (13).

Many studies have reported that quantitative HBsAg can be used to differentiate between chronic infection and hepatitis (8,9). In a study by Brunetto et al. (14), it was reported that a qHBsAg level of 1000 IU/mL is an appropriate limit for differentiating between active and inactive hepatitis B in genotype D patients. In contrast, in our study, the sensitivity was calculated to be 86.5% and specificity 45.9% for qHBsAg 1000 IU/mL in predicting chronic hepatitis. In the present study, the AUC was statistically significant as a result of the qHBsAg level with reference to chronic hepatitis (AUC=0.749) (p<0.001). The cut-off value of qHBsAg for determining chronic hepatitis was 3,081 IU/mL. The sensitivity was calculated as 70.3%, and specificity was 70.6% at this cut-off point. The 95% specificity limit of qHBsAg for recognizing chronic hepatitis was determined to be 38.641 IU/mL. The initiation of antiviral treatment without liver biopsy may be considered because of the high specificity values at this and above the qHBsAg levels.

Different qHBsAg results were found at different disease stages because of the qHBsAg dynamism. In a study conducted in China, in which

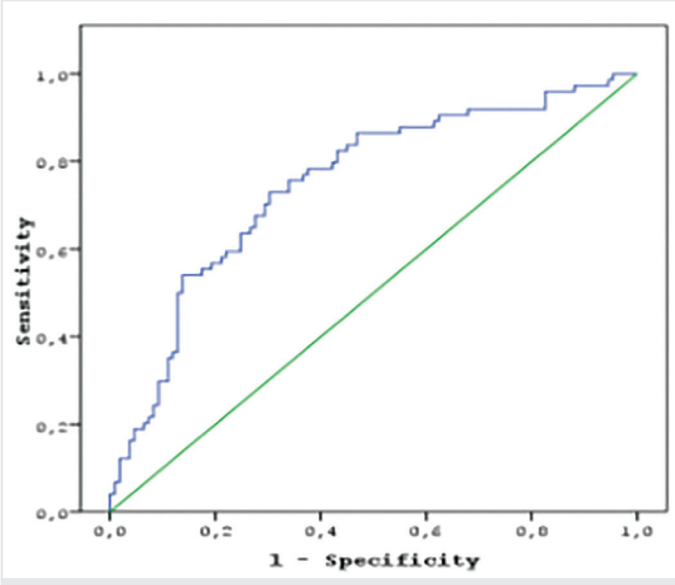

Figure 2. Examining the predictor power of qHBsAg for chronic hepatitis with ROC curve

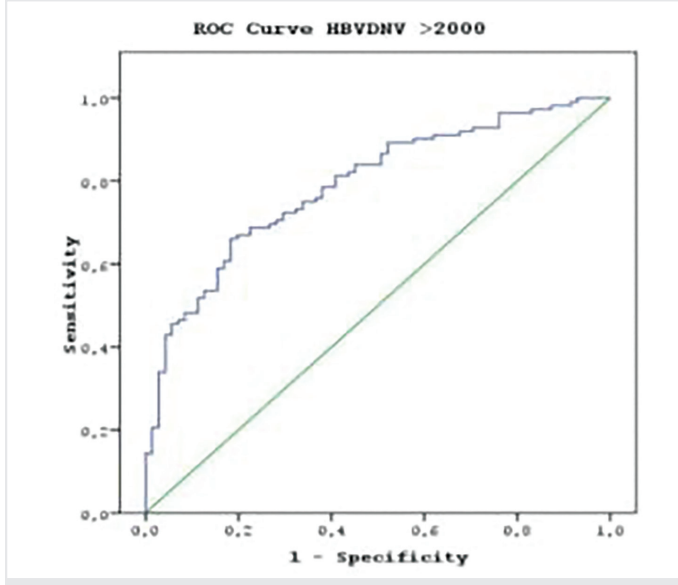

Figure 3. Examining the predictor power of qHBsAg for HBV DNA >2.000 IU/Ml using the receiver operating characteristic curve

Table 3. Subgroup analyses of the clinical and demographic characteristics of the patient groups

Characteristics	HBeAg (+) Chr vs. Infection		HBeAg(+) vs. Chr. Hepatitis		HBeAg (-) vs. Chr. infection	
	HBeAg (+) Chr. hepatitis	HBeAg (-) Chr. infection	HBeAg (-) Chr. hepatitis	HBeAg (-) Chr. infection	HBeAg (-) Chr. hepatitis	HBeAg (-) Chr. hepatitis
	p	p	p	p	p	p
Gender	0.031	0.185	0.002	0.097	0.196	0.002
Age (years)	0.006	<0.001	0.001	0.001	0.252	0.084
ALT (IU/L)	<0.001	0.381	<0.001	<0.001	0.045	<0.001
AST (IU/L)	<0.001	0.209	<0.001	<0.001	0.237	<0.001
Total bilirubin (mg/dL)	0.014	0.225	0.006	0.056	0.198	0.003
Direct bilirubin (mg/dL)	0.061	0.268	0.026	0.057	0.153	0.001
Albumin (g/dL)	0.355	0.187	0.019	0.001	<0.001	0.047
INR	0.338	0.728	0.200	0.053	0.649	0.013
HBV-DNA (IU/mL)	0.077	<0.001	0.739	<0.001	<0.001	<0.001
qHBsAg (IU/mL)	0.148	<0.001	<0.001	<0.001	<0.001	0.001

HBeAg: Hepatitis B envelope antigen, Chr. hepatitis: Chronic hepatitis, Chr. infection: Chronic infection, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, IU/L: İnternational unit /liter, INR: International normalized ratio (international standardized ratio), HBV-DNA: Hepatitis B virus deoxyribonucleic acid, qHBsAg: Quantitative hepatitis B surface antigen, Bonferroni correction p<0.0083 (the significance value of p-value was evaluated according to Bonferroni correction)

623 people with different stages of hepatitis B were examined, the patients were evaluated in 5 stages, and the disparities in qHBsAg levels throughout the natural course of the disease were examined. In this study, it was found that median qHBsAg levels differed in each stage of CHB, and statistically significant differences were observed between them (p<0.001). Additionally, HBsAg titers were found to be at the highest level in immune-tolerant patients and lowest in inactive carriers. In addition, serum HBsAg levels were positively and strongly correlated with HBV-DNA in the immune clearance stage (r=0.683, p<0.001) (15). Similarly, in the present study, the qHBsAg median values were found to be different in all four groups, and there was a statistically significant difference between them (p<0.001). Also, similarly, the median value was found to be at the highest level in the HBeAg (+) chronic infection group and the lowest in the HBeAg (-) chronic infection group. In the present study, similarly, the total patient group (r=0.626, p<0.001), HBeAg (+) patient group (r=0.602, p<0.001), and HBeAg (-) patient group (r=0.375, p<0.001) had varying degrees of positive correlations between qHBsAg and HBV DNA. In this regard, qHBsAg can provide us with an idea regarding the natural course of the disease.

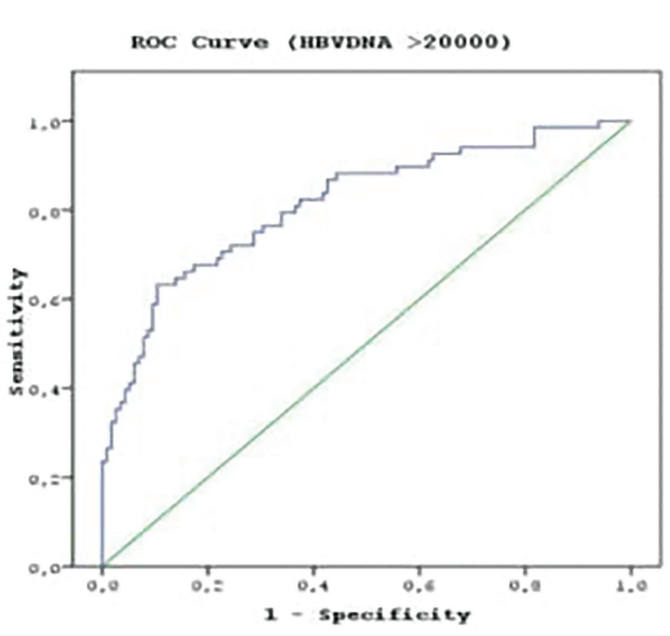

Figure 4. Examining the predictor power of qHBsAg for HBV DNA>20.000 IU/Ml using the receiver operating characteristic curve

qHBsAg levels can provide information about disease activation in patients who did not or could not undergo a biopsy. However, the current literature showed that qHBsAg was insufficient for evaluating significant fibrosis. For this reason, non-invasive fibrosis tests (elastography, etc.) can be considered as an alternative to liver biopsy for identifying significant fibrosis.

In several studies conducted in recent years, qHBsAg was shown to be useful in predicting the stage of liver damage (7,16). In a previous investigation, a robust and positive correlation was identified between ALT, HBV-DNA, HAI score, and qHBsAg levels (8). In the present study, as in this study, it was shown that there was a positive correlation between the quantitation of HBsAg in the entire patient group and ALT (p<0.001) and HBV-DNA (p<0.001). These findings may enable the assessment of whether qHBsAg indicates a low or high risk of progressive liver damage, akin to ALT and HBV-DNA levels. In addition, they may offer guidance for physicians in the timing of treatment planning for patients.

The study has some strengths. First, we evaluated a homogenous group of treatment-naive patients. Second, we performed various analysis methods, including correlation and receiver operating characteristic (ROC) curve analysis. Third, we performed HBeAg subgroup analysis.

Study Limitations

There were several limitations in this study. First, it was conducted at a single center, potentially limiting the generalizability of the findings. Second, the sample size was relatively modest, which may have affected the statistical power and reliability of the findings. Third, liver biopsy

Table 4. Correlations of quantitative HBsAg levels with other parameters

Characteristics	Total		HBeAg (+)		HBeAg (-)	
	qHBsAg		qHBsAg		qHBsAg	
	r	p	r	p	r	p
Age	-0.397	<0.001	-0.342	0.012	-0.259	0.003
ALT (IU/L)	0.386	<0.001	-0.213	0.125	0.236	0.007
AST (IU/L)	0.354	<0.001	-0.208	0.135	0.151	0.086
Total bilirubin (mg/dL)	0.050	0.503	-0.216	0.120	0.120	0.172
Direct bilirubin (mg/dL)	-0.001	0.988	-0.221	0.112	0.038	0.670
Total protein (g/dL)	0.021	0.780	0.300	0.029	0.060	0.498
Albumin (g/dL)	-0.158	0.032	0.315	0.022	-0.011	0.905
INR	0.106	0.153	-0.133	0.341	0.119	0.177
PT	0.152	0.040	-0.115	0.411	0.120	0.172
AFP (IU/mL)	0.155	0.036	0.058	0.681	0.110	0.212
HBV-DNA (IU/mL)	0.626	<0.001	0.602	<0.001	0.375	<0.001

HBsAg: Hepatitis B surface antigen, HBeAg: Hepatitis B envelop antigen, qHBsAg: Quantitative hepatitis B surface antigen, r: Correlation coefficient, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, IU/L: International unit/liter, INR: International normalized ratio (international standardized ratio), PT: Prothrombin time, AFP: Alpha fetoprotein, HBV-DNA: Hepatitis B virus deoxyribonucleic acid

outcomes were assessed retrospectively over a 1-year period and were not conducted concurrently with other assessments. Additionally, budget constraints prevented genotype determination was not feasible for patients. Finally, the qHBsAg measurements were based on a single assessment, precluding a longitudinal analysis.

Conclusion

The quantitative HBsAg is an easily applicable and relatively inexpensive test that can be used to differentiate between different stages of CHB. In this respect, qHBsAg may help stratify patients with CHB into chronic infection and hepatitis and manage treatment decision. If the qHBsAg level is >38,000 IU/mL in patients with CHB, treatment initiation may be considered without liver biopsy.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 2020 -111, date: 08.07.2020).

Informed Consent: Informed consent was obtained from the patients prior to their participation in the study.

Authorship Contributions: Surgical and Medical Practices - M.K.T., M.Y.; Concept - M.K.T., S.S.; Design - M.K.T.; Data Collection or Processing - M.K.T.; Analysis or Interpretation - M.K.T., S.S., M.Y.; Literature Search - M.K.T., S.S., M.Y.; Writing - M.K.T.

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

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

References

1. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th Edition 145, 1940-1963.e7
2. Chan HL, Wong VW, Tse AM, Tse CH, Chim AM, Chan HY, et al. Serum hepatitis B surface antigen quantitation can reflect hepatitis B virus in the liver and predict treatment response. Clin Gastroenterol Hepatol. 2007; 5: 1462-8.
3. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017; 67: 370-98.
4. Seto W, Wong DK, Fung J, Huang F, Liu KS, Lai C, et al. Linearized hepatitis B surface antigen and hepatitis B core-related antigen in the natural history of chronic hepatitis B. Clin Microbiol Infect. 2014; 20: 1173-80.
5. Liu J, Yang HI, Lee MH, Lu SN, Jen CL, Wang LY, et al. Incidence and determinants of spontaneous hepatitis B surface antigen seroclearance: a community-based follow-up study. Gastroenterology. 2010; 139: 474-82.
6. Yıldız Kaya S, Mete B, Kaya A, Balkan II, Saltoglu N, Tabak ÖF. The role of quantitative HBsAg in patients with HBV DNA between 2000-20,000 IU/ml. Wien Klin Wochenschr. 2021; 133: 647-53.
7. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018; 67: 1560-99.
8. Chu CM, Liaw YF. HBsAg seroclearance in asymptomatic carriers of high endemic areas: appreciably high rates during a long-term follow-up. Hepatology. 2007; 45: 1187-92.
9. Buti M, Riveiro-Barciela M, Rodríguez-Frías F, Tabernero D, Esteban R. Role of Biomarkers in Guiding Cure of Viral Hepatitis B. Semin Liver Dis. 2020; 40: 49-60.
10. Tseng TC, Liu CJ, Yang HC, Su TH, Wang CC, Chen CL, et al. Determinants of spontaneous surface antigen loss in hepatitis B e antigen-negative patients with a low viral load. Hepatology. 2012; 55: 68-76.
11. Li M, Zhang L, Lu Y, Chen Q, Lu H, Sun F, et al. Early Serum HBsAg Kinetics as Predictor of HBsAg Loss in Patients with HBeAg-Negative Chronic Hepatitis B after Treatment with Pegylated Interferonα-2a. Virol Sin. 2021; 36: 311-20.
12. Cornberg M, Wong VW, Locarnini S, Brunetto M, Janssen HLA, Chan HL. The role of quantitative hepatitis B surface antigen revisited. J Hepatol. 2017; 66: 398-411.
13. Han ZG, Qie ZH, Qiao WZ. HBsAg spontaneous seroclearance in a cohort of HBeAg-seronegative patients with chronic hepatitis B virus infection. J Med Virol. 2016; 88: 79-85.
14. Brunetto MR, Oliveri F, Colombatto P, Moriconi F, Ciccorossi P, Coco B, et al. Hepatitis B surface antigen serum levels help to distinguish active from inactive hepatitis B virus genotype D carriers. Gastroenterology. 2010; 139: 483-90.
15. Zeng LY, Lian JS, Chen JY, Jia HY, Zhang YM, Xiang DR, et al. Hepatitis B surface antigen levels during natural history of chronic hepatitis B: a Chinese perspective study. World J Gastroenterol. 2014; 20: 9178-84.
16. Tseng TC, Kao JH. Clinical utility of quantitative HBsAg in natural history and nucleos(t)ide analogue treatment of chronic hepatitis B: new trick of old dog. J Gastroenterol. 2013; 48: 13-21.