Original Article

Are Serum Quantitative Hepatitis B Surface Antigen Levels, Liver Histopathology and Viral Loads Related in Chronic Hepatitis B-infected Patients?

Ayhan Balkan, Mustafa Namıduru[1], Yasemin Balkan[2], Ayşe Özlem Mete[2], İlkay Karaoğlan[1], Vuslat Keçik Boşnak[1]

Departments of Gastroenterology and [1]Infectious Diseases and Clinical Microbiology, Gaziantep University, [2]Department of Infectious Diseases and Clinical Microbiology, 25 Aralık State Hospital, Gaziantep, Turkey

Address for correspondence:
Dr. Ayhan Balkan, Department of Gastroenterology, Gaziantep University, Faculty of Medicine, Üniversite Bulvarı Şehitkamil, Gaziantep - 27310, Turkey.
E-mail: drayhanbalkan27@gmail.com

ABSTRACT

Background/Aims: Fluctuations in hepatitis B virus (HBV) DNA and alanine transaminase (ALT) levels complicate assessment of the phases of chronic hepatitis B (CHB) infection and correct identification of the inactive HBV carrier state. In this study, we aimed to examine the role of HBsAg quantification (qHBsAg) in the identification of the phases of HBV and to evaluate its association with liver histopathology. **Patients and Methods:** Inactive HBV carriers (IC) (n = 104) and CHB patients (n = 100) were enrolled in the study. Demographic characteristics of patients were evaluated; biochemical parameters and serum qHBsAg levels were studied, and liver biopsy and histopathology were assessed. **Results:** Serum qHBsAg levels were found to be significantly low in IC (5150.78 ± 8473.16 IU/mL) compared with the HBeAg-negative CHB (7503.21 ± 8101.41 IU/mL) (P = 0.001) patients. The diagnostic accuracy of qHBsAg to differentiate HBeAg-negative CHB from IC was found to be moderate (c-statistic: 0.695) and the cutoff level for qHBsAg in diagnosis was found as 1625 IU/mL (specificity: 80%; sensitivity: 49%). No correlation was noted between serum qHBsAg level and ALT, histologic activity index (HAI), and fibrosis in IC and CHB. A moderate and positive correlation was observed between the serum qHBsAg level and HBV-DNA in HBeAg-positive CHB patients. **Conclusions:** Serum qHBsAg levels may prove to be useful in the differentiation between IC and HBeAg-negative CHB when used in conjunction with HBV DNA. Furthermore, patients diagnosed solely on the basis of HBV DNA and ALT may present with higher grade and stage of liver histopathology than expected.

Key Words: Adult, biopsy, carrier state, hepatitis B e antigens, hepatitis B virus

Received: 20.08.2015, Accepted: 09.12.2015

How to cite this article: Balkan A, Namiduru M, Balkan Y, Mete AO, Karaoglan I, Bosnak VK. Are serum quantitative hepatitis b surface antigen levels, liver histopathology and viral loads related in chronic hepatitis b-infected patients?. Saudi J Gastroenterol 2016;22:208-14.

Hepatitis B virus (HBV) infection is a major health concern worldwide. Globally, approximately two billion individuals have been exposed to HBV, with nearly 240 million estimated cases of chronic hepatitis B infection. HBV and related conditions are also thought to be responsible for 500,000 to 700,000 deaths annually.[1] Turkey is an endemic region with regard to hepatitis B infection; its seroprevalence of HBsAg positivity is 2%–7% and the prevalence of HBV exposure is 20%–60%.[2] For this reason, treatment and follow-up of chronic HBV infection is crucial.

The course of chronic hepatitis B (CHB) infection may vary in a broad clinical spectrum from an inactive carrier state to cirrhosis or even to hepatocellular carcinoma.[3,4]

The natural history of the disease was divided into five different phases in the European Association for the Study of Liver (EASL) Clinical Practice Guidelines for CHB. These are as follows: "Immune tolerant phase, immune reactive

Access this article online

Quick Response Code:

Website: www.saudijgastro.com

DOI: 10.4103/1319-3767.182454

HBeAg-positive phase, inactive HBV carriers (IC) state, HBeAg-negative CHB, and HBsAg-negative phase."[5] These phases are very important in terms of clinical approach, the necessity of biopsy and the treatment decision, although it is difficult to differentiate these clinical phases. The differentiation between HBeAg-negative CHB patients and IC specially, can be sometimes difficult.Recent studies are focused on a noninvasive procedure that can serve this purpose and reflect liver histopathology. In these studies, the latest biomarker investigated was the "serum qHBsAg level."[6,7] These studies have shown that HBsAg quantification may help in evaluating the phases of HBV infection. In the present study, we examined the association between qHBsAg levels and HBV DNA, alanine transaminase (ALT), and liver histopathology in IC and CHB patients, and sought to determine the diagnostic value of qHBsAg in HBeAg-negative CHB patients.

PATIENTS AND METHODS

Patients

The study was carried out at the Gaziantep University Medical Faculty Hospital between December 2009 and June 2010. Patients were selected from treatment-naive patients who applied to the Infectious Diseases and Clinical Microbiology and Gastroenterology Outpatient Departments. Patients who had received an antiviral treatment in the past, patients with decompensated hepatic cirrhosis, cancer patients, and patients with insufficient biopsy were not enrolled. Moreover, patients with positive anti-HDV, anti-HCV, anti-HIV, antinuclear antibodies (ANA), antismooth muscle antibodies (ASMA), and antimitochondrial antibodies (AMA) were excluded from the study.

Methods

IC (n = 104) and active CHB patients (n = 100) were enrolled in the study. IC state was defined as HBsAg in serum >6 months, HBeAg negative and anti-HBe positive, HBV DNA level <2000 IU/mL, persistently normal ALT/aspartate transaminase (AST) levels (<40 U/L). IC patients were followed-up for at least one year by analyzing the HBV-DNA and ALT levels every 3 months. Documented evidence of HBsAg positive for more than 6 months, HBeAg (−) or (+) patients with ALT levels above the upper limit of normal or normal (>40 U/L) and HBV-DNA level >2000 IU/mL were considered to have CHB infection.

Laboratory testing

Body mass indexes (BMIs) of the patients were calculated. Complete blood cell count, hepatic function tests [ALT, AST, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin, direct bilirubin, albumin, international normalized ratio (INR)], fasting blood glucose (FBG), total cholesterol, triglyceride, urea, creatinine, HBsAg, Anti-HBs, HBeAg, Anti-HBe, Anti-HBc IgM, Anti-HBc IgG, Anti-Delta, HBV-DNA (Amplicor HBV Monitor™ test, Roche Diagnostic Systems, Inc., Branchburg, NJ), Anti-HCV, Anti-HIV, and alpha fetoprotein (AFP) were studied. IC, HBeAg-negative and HBeAg-positive CHB patients were differentiated on the basis of HBsAg, HBeAg, Anti-HBe, HBV-DNA, and ALT results. The ELISA method was used in the assessment of HBsAg, HBeAg, Anti-HBe, Anti-HDV, Anti-HCV, and Anti-HIV tests in all patients, whereas HBV-DNA was assayed using quantitative polymerase chain reaction (PCR). All patients underwent an abdominal ultrasonography and a liver biopsy and the liver histopathology of patients was examined. Blood samples were obtained concurrently on the day of the liver biopsy. The blood samples were kept at room temperature for 30–60 min, and then were centrifuged at 3000–5000 rpm for 10–15 min. The serum samples obtained were then kept at −80°C until the time of qHBsAg quantification, which was approximately 6 months later after initial sampling. Serum qHBsAg quantification was performed using an Elecsys HBsAg II (Roche Diagnostics, Indianapolis, USA) device and its kits. This device utilizes an electro-chemiluminescence immunoassay technique.

- Incubation: Two samples of 50 μL, two biotins with monoclonal Anti-HBs antibodies, and a mixture of ruthenium complex-labeled polyclonal Anti-HBs antibody and monoclonal Anti-HBs antibody comprised the sandwich complex
- Incubation: Addition of streptavidin-coated microparticles is followed by the solid complex phase, which is the result of the interaction between biotin and streptavidin. The reaction mixture is transferred into the measurement chamber, where microparticles are trapped on the surface of the electrode with a magnetic effect. The dissolving substances are removed by Procell. Application of voltage on the electrode initiates chemiluminescent emission, which is measured by the photomultiplier. The results are measured using a calibration curve.[8]

Liver biopsy

All patients received ultrasonography-guided percutaneous biopsy of the right lobe of the liver. A quick-cut and 16-gauge cutting needle (Disposable Automatic Biopsy Gun with variable throw, Gallini Medical Devices, Mantova, ITALY) was used for this procedure. The biopsy dimensions were 1.5-2.0 cm with seven or more available portal areas. The biopsy specimens were fixed with 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin for morphologic evaluation and Masson's trichrome stain for the assessment of fibrosis. A single pathologist examined the liver specimens in the pathology laboratory. Histopathologic examinations were carried out according to the Modified Ishak scoring system.[9] HAI < 4/18, HAI = 4/18–8/18,

and HAI > 8/18 were referred as mild, moderate, and severe inflammation, respectively. Nevertheless, during the histopathologic examination, if the stage of fibrosis was <2/6 this was considered as mild fibrosis, a fibrosis of between 2/6 and 3/6 was considered as moderate fibrosis, whereas a fibrosis >3/6 was considered as severe fibrosis. HAI ≥ 6/18 or fibrosis ≥2/6 was considered starting points for treatment.

Ethics statement

The study was carried out in accordance with principles of the Helsinki Declaration of 1975 as revised in 2008, and with the approval number 05.05.2011/32 of the University of Gaziantep Faculty of Medicine Clinical Research Ethics Committee. All patients provided written consent prior to the liver biopsy and study entry with all clinical investigations conducted according to the principles expressed in the Declaration of Helsinki.

Statistical analyses

Statistical analyses were performed using the SPSS version 15.0 (SPSS, Inc., Chicago, IL, USA) software package. In the comparison of independent groups, the *t*-test was used for the comparison of numeric variables when the normal distribution condition was met; when the normal distribution condition was not met, the Mann–Whitney *U* test was used. The Spearman's rho analysis is used to determine the relationship between quantitative HBsAg levels and the other parameters. Spearman correlation method (nonparametric method for correlation) was used to find correlation coefficient because of skewed-distributed values. Analysis of the curve of receiver operating characteristics (ROC) and the cutoff value were determined to make a correct diagnosis of HBeAg-negative and CHB patients, by making use of the quantitative levels of HBsAg. The level of statistical significance was considered as a state where the *P* value was less than 0.05.

RESULTS

Patient characteristics

Demographic data of the 204 cases enrolled were evaluated. Patients were divided into two groups: IC (n = 104) and CHB patients (n = 100). Of the cases with CHB infection, 62 (62.0%) were HBeAg-negative CHB, whereas 38 (38.0%) of the cases were HBeAg-positive CHB patients. There was no significant difference in terms of age, gender, white blood cell count, levels of hemoglobin, hematocrit, ALP, GGT, total bilirubin, direct bilirubin, FBG, total cholesterol, triglyceride, urea, creatinine, AFP, hepatosteatosis in ultrasonography, cirrhosis in biopsy, steatosis, ground glass and hydropic degeneration, in both groups. Body mass index ($P < 0.05$), platelet count ($P = 0.001$), and albumin level ($P = 0.001$) were significantly higher in inactive carriers compared with CHB patients. Serum qHBsAg levels ($P = 0.001$), INR ($P = 0.001$), ALT ($P = 0.001$), AST ($P = 0.001$), and HBV-DNA ($P = 0.001$) were significantly lower in inactive carriers compared with CHB patients [Table 1]. In the histopathologic examination for both groups, there was no significant difference in terms of cirrhosis, level of steatosis, ground glass, and hydropic degeneration. However, HAI severity and fibrosis stage were significantly lower in IC than in CHB patients ($P = 0.001$). In the IC group, the number of cases with moderate-to-severe levels of inflammation (HAI ≥ 4/18) was 25 (24%) and the number of cases with severe fibrosis (fibrosis ≥2/6) was found to be 34 (33%). In the CHB group, the number of cases with

Table 1: Comparison of inactive HBV carriers and CHB cases in terms of demographic, histopathologic, and laboratory characteristics

Patient characteristics	Inactive HBV carriers (n=104)	Chronic hepatitis B patients (n=100)	*P* value*
Age	38.26±11.70	33.54±11.74	0.395
Gender, female (%)	41 (39)	37 (37)	0.280
BMI, (kg/m²)	26.86±5.00	25.31±4.95	<0.05*
Hemoglobin, g/dl	14.75±1.80	15.06±1.58	0.637
Thrombocyte, ×10³/μL	241.30±56.40	222.30±54.06	0.001*
ALT, U/L	31.82±21.78	83.51±73.84	0.001*
AST, U/L	26.15±10.35	50.05±37.02	0.001*
ALP, U/L	193.45±58.04	191.98±76.56	0.129
GGT, U/L	23.02±23.14	25.93±17.26	0.237
Total bilirubin, mg/dL	0.54±0.26	0.61±0.38	0.326
Direct bilirubin, mg/dL	0.13±0.09	0.15±0.12	0.644
Albumin, g/dL	4.40±0.32	4.35±0.34	0.001*
INR	1.00±0.11	1.08±0.09	0.001*
AFP, IU/mL	2.60±2.06	3.15±4.11	0.168
HBV DNA, ×10³ IU/mL	0.640±0.584	59900.47±140555.35	0.001*
qHBsAg, IU/mL	5150,78±8473,16	31959,96±62370,80	0.001*
HAI			
Mild	79	28	0.001*
Moderate	25	65	
Severe	0	7	
Fibrosis			
Mild	70	35	0.001*
Moderate	28	56	
Severe	6	9	
Cirrhosis, *n* (%)	0 (0)	1 (1)	0.248
Steatosis,			
Nonexistent	84	86	0.504
Mild	12	9	
Moderate	7	3	
Severe	1	2	
Ground glass, *n* (%)	22 (21)	25 (25)	0.264
Hydropic degeneration, *n* (%)	6 (6)	2 (2)	0.309

AFP: Alpha fetoprotein, FBG: Fasting blood glucose, ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate transaminase, GGT: Gamma glutamyl transferase, HAI: Histologic activity index, HBV: Hepatitis B virus, INR: international normalized ratio, N: Normal, qHBsAg: HBsAg quantitation, BMI: Body mass index. *Statistically significant

moderate-to-severe inflammation (HAI ≥ 4/18) was 72 (72%) and cases with moderate-to-severe fibrosis (fibrosis ≥2/6) were found to be 65 (65%) [Table 1].

Comparison of inactive HBV carriers with HBeAg-negative CHB patients

The comparison of patients with CHB infection was made by dividing them into two groups, as HBeAg positive and HBeAg negative. Serum qHBsAg levels were found to be significantly high in HBeAg-negative CHB patients compared with the IC ($P = 0.001$), while in HBeAg-positive CHB patients they were significantly higher ($P = 0.001$) than HBeAg-negative CHB patients [Figure 1]. In this study, the diagnostic efficacy of serum levels of qHBsAg for IC individuals and HBeAg-negative CHB patients was examined. The demographic characteristics, laboratory and histopathologic results of both groups were compared [Table 2].

Diagnostic value of qHBsAg

The diagnostic efficacy of the serum level of qHBsAg for IC individuals and HBeAg-negative CHB patients was examined. For this, ROC analysis was performed. As a result, the diagnostic efficacy of qHBsAg levels was found to be low to moderate [c-statistics: 0.695, 95% CI (0.619–0.764)] [Figure 2].

The cutoff value of qHBsAg was determined as 1625 IU/mL by this analysis. Patients under 1625 IU/mL fell largely into the group of inactive carriers (specificity was 80%; negative likelihood ratio was 0.38). Patients above 1625 IU/mL were HBeAg-negative CHB patients (sensitivity was 49%; positive likelihood ratio was 1.65). Three different values were used in the diagnosis of HBeAg-negative CHB patients. When the qHBsAg value was 1589 IU/mL, sensitivity and specificity were 51% and 80%, respectively. For a qHBsAg value of 1625 IU/mL, sensitivity, specificity, positive likelihood ratio, and negative likelihood ratios were 49%, 80%, 1.65, and 0.38, respectively; whereas for a qHBsAg value of 1800 IU/mL, sensitivity and specificity were 49% and 77%, respectively [Table 3].

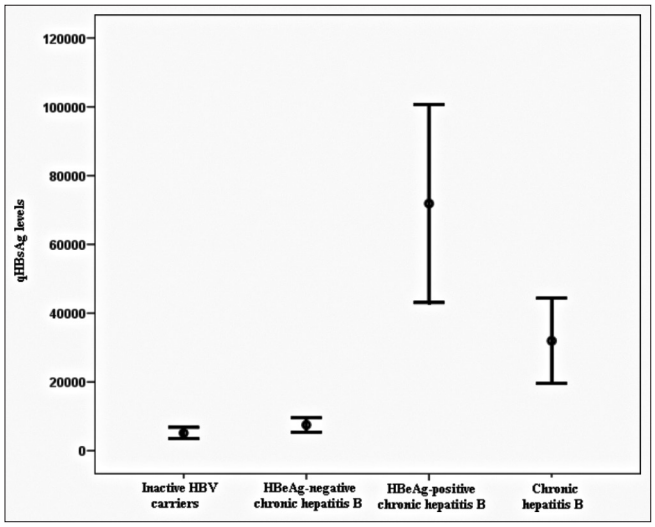

Figure 1: Inactive HBV carriers, HBeAg-negative CHB patients, HBeAg-positive CHB patients, and qHBsAg levels of CHB patients

Correlation between qHBsAg and HBV DNA levels

Finally, in this study the correlation analysis between the serum qHBsAg level and ALT, HBV-DNA, HAI severity, and the fibrosis stage was performed in IC and CHB patients. No correlation was found between the serum qHBsAg level and ALT, HBV-DNA, HAI severity, and the fibrosis stage in IC. No correlation was found between the serum qHBsAg

Table 2: Clinical and laboratory characteristics of inactive HBV carriers and HBeAg-negative CHB patients

Patient characteristics	Inactive HBV carriers (*n*=104)	HBeAg-negative CHB patients (*n*=62)	*P* value*
Age	38.26±11.70	36.56±11.44	0.408
Gender, female (%)	41 (39)	18 (29)	0.305
BMI, (kg/m²)	26.86±5.00	26.08±4.79	0.237
Hemoglobin, g/dL	14.75±1.80	15.25±1.40	0.327
Thrombocyte, ×10³/μL	241.30±56.40	217.82±58.90	0.009*
ALT, U/L	31.82±21.78	83.71±84.64	0.001*
AST, U/L	26.15±10.35	48.98±41.47	0.001*
ALP, U/L	193.45±58.04	188.77±69.01	0.509
GGT, U/L	23.02±23.14	27.06±15.78	0.642
Total bilirubin, mg/dL	0.54±0.26	0.62±0.43	0.235
Direct bilirubin, mg/dL	0.13±0.09	0.17±0.14	0.508
Albumin, g/dL	4.40±0.32	4.37±0.30	0.129
INR	1.00±0.11	1.08±0.09	0.001*
AFP, IU/mL	2.60±2.06	3.65±4.74	0.137
HBV DNA, ×10³ IU/mL	0.640±0.584	8286.70±26069.77	0.015*
qHBsAg	5150.78±8473.16	7503.21±8101.41	0.001*
HAI severity			
Mild	79	18	0.001*
Moderate	25	38	
Severe	0	6	
Fibrosis stage			
Mild	70	21	0.001*
Moderate	28	37	
Severe	6	4	
Cirrhosis, *n* (%)	0 (0)	1 (1.6)	0.329
Steatosis; nonexistent	84	51	0.066
Mild	12	6	
Moderate	7	3	
Severe	1	2	
Ground glass, *n* (%)	22 (21)	19 (30)	0.437
Hydropic degeneration, *n* (%)	6 (6)	2 (3)	0.638

AFP: Alpha fetoprotein, FBG: Fasting blood glucose, ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate transaminase, G: Grade, GGT: Gamma glutamyl transferase, HAI: Histologic activity index, HBV: Hepatitis B virus, INR: International normalized ratio, N: Normal, qHBsAg: HBsAg quantitation, BMI: Body mass index. *Statistically significant

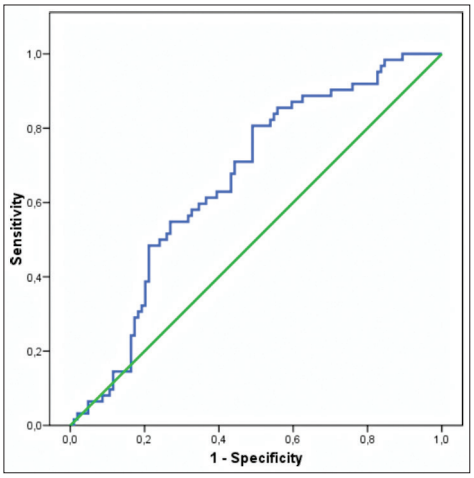

Figure 2: The diagnostic efficiency of qHBsAg value among inactive HBV carriers and HBeAg-negative chronic hepatitis B patients group. The area under the curve when tested with receiver operating characteristic analysis = 0.660; 95% CI (0.577–0.743)

Table 3: The diagnostic value of the serum qHBsAg levels in the diagnosis of HBeAg-negative CHB patients

	Cut off value of qHBsAg levels (IU/mL) (%)		
Accuracy measurement	1589.0	1625.0	1800.0
HBeAg-negative CHB (*n*=62)			
Sensitivity	51	49	49
Specificity	80	80	77
Positive likelihood ratio		1.65	
Negative likelihood ratio		0.38	

HBV: Hepatitis B virus, CHB: Chronic hepatitis B, qHBsAg: HBsAg quantitation

level and ALT, HAI severity, and the fibrosis stage in CHB patients. In CHB patients, a moderate positive correlation between the serum qHBsAg level and HBV-DNA was detected (rho = 0.533, $P < 0.001$). A moderate positive correlation was detected between the serum qHBsAg level and HBV-DNA in HBeAg-positive CHB patients (rho = 0.513, $P = 0.001$), whereas no correlation was detected between the serum qHBsAg level and HBV-DNA in HBeAg-negative CHB patients (rho = 0.087, $P = 0.500$). Moreover, no correlation was detected between the serum qHBsAg level and HBV-DNA in IC (rho = −0.046, $P = 0.643$) [Figure 3].

DISCUSSION

The natural history of the disease was divided into five different phases in the EASL Clinical Practice Guidelines for CHB. It is not always easy to make an accurate distinction between these phases. It is especially quite difficult to make a definite distinction between IC and HBeAg-negative CHB patients. Today, non-invasive tests (ALT and HBV-DNA level) and liver histopathology are used for this distinction.[10] However, ALT and serum HBV-DNA levels are insufficient for identifying each phase, whereas liver biopsy is an impractical invasive procedure. In this regard, we need tests and/or tests with high sensitivity and specificity, which can reflect liver histopathology, be used in disease follow-up and enable us to better evaluate the phases of chronic hepatitis.

In this study, serum qHBsAg levels in IC and CHB patients, and the correlation between ALT, HBV-DNA, HAI severity, and the stage of fibrosis were examined. No correlation was noted between serum qHBsAg levels and ALT, HBV-DNA, HAI severity, and the stage of fibrosis in IC. A moderate and positive correlation was observed between serum qHBsAg level and HBV-DNA in HBeAg-positive hepatitis B patients. However, no correlation was found between serum qHBsAg levels and ALT, severity of HAI, and fibrosis in CHB patients. In the study of Chan *et al.*,[6] where the relationship between HBV-DNA and qHBsAg was investigated, and samples were taken from 49 HBeAg-positive and 68 HBeAg-negative patients at different times, a moderate relationship between qHBsAg levels and HBV-DNA was determined (r = 0.61, $P < 0.001$). In this study, a moderate positive correlation was determined between serum qHBsAg levels and HBV-DNA in the HBeAg-positive CHB patients (rho = 0.435, $P = 0.009$); however, no correlation was noted between the serum qHBsAg levels and HBV-DNA in HBeAg-negative CHB patients (rho = 0.087, $P = 0.500$). Thompson *et al.*[11] found that quantitative HBeAg and qHBsAg levels may be used as markers in deciding about the initiation of the treatment as well as in the follow-up of treatment. In this study, it is suggested that the relationship between quantitative serum HBsAg and HBeAg titers and serum HBV-DNA is complex and probably reflects an interaction between virologic and host immunologic factors. This explanation also defines results of the correlation analysis of this study.

In a recent study on this subject, the relation between the qHBsAg level and clinical and viral dynamics in patients with CHB infection was investigated. The qHBsAg levels were found to be significantly different among groups consisting of a total of 434 CHB patients including 62 immunotolerant patients, 103 HBeAg-positive CHB patients, 151 HBeAg-negative CHB patients and 218 IC. Following evaluation of the qHBsAg level together with HBV-DNA level, it suggested that they could be used as markers for distinguishing HBeAg-negative CHB and IC groups.[7]

In this study, the qHBsAg level of 204 patients with CHB infection was investigated in addition to the routine laboratory examination and liver histopathology. Apart from diagnosis, the efficiency of qHBsAg in distinguishing HBeAg-negative CHB patients from IC was examined. Accordingly, the diagnostic efficacy of qHBsAg levels was found to be at moderate level

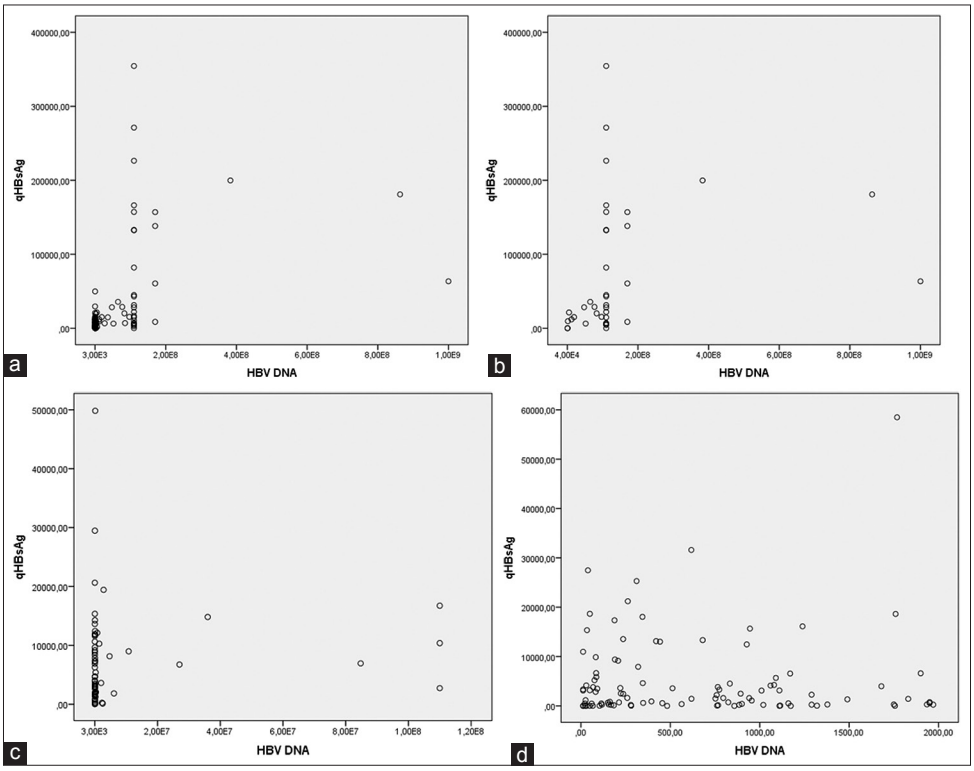

Figure 3: Correlation between qHBsAg and HBV-DNA in (a) chronic hepatitis B patients (rho = 0.533, $P < 0.001$); (b) HBeAg-positive chronic hepatitis B patients (rho = 0.513, $P = 0.001$); (c) HBeAg-negative chronic hepatitis B patients (rho = 0.087, $P = 0.500$); and (d) inactive HBV carriers (rho = –0.046, $P = 0.643$). Spearman correlation method (nonparametric method for correlation) was used to find correlation coefficient because of skewed-distributed values

and the cutoff value of qHBsAg in diagnosis was determined as 1625 IU/mL (specificity: 80%, sensitivity: 49%, positive likelihood rate: 1.65, negative likelihood rate: 0.38).

Wustorn *et al*.[12] and Chan *et al*.[6] demonstrated that cccDNA is strongly related to qHBsAg and they suggested that serial monitoring of qHBsAg during antiviral treatment can be an additional marker for evaluating treatment response. In these studies, qHBsAg values were determined to be less than 10,000 IU/mL in patients after PEG-IFN-LAM treatment. Sensitivity, specificity, positive predictive value, and negative predictive value for the qHBsAg value obtained with regard to virologic response were 86%, 56%, 43%, and 93%, respectively. It was suggested that when evaluating qHBsAg response to treatment, a 0.5 log or 1.0 log decrease in weeks 12 and weeks 24 had a high predictive value for sustained viral response (SVR). Based on previous experiences and long-term follow-up data, it was observed that most patients with SVR obtained in the first year tended to stay in remission.

In another recent study, 102 HBeAg-negative patients treated with PEG-IFN were examined, and an end point was demonstrated where HBV-DNA and qHBsAg levels concurrently declined from baseline by weeks 12 of treatment. The decline at week 24 was the best predictor of SVR. Serum qHBsAg levels did not decrease and serum HBV-DNA levels decreased for less than 2 logs. SVR was not observed in any of the 20 patients (20% of the study group).[13]

In a study where patients with different phases of the CHB infection were followed for eight years, the natural course of serum qHBsAg changes during different phases of the CHB infection was demonstrated. The qHBsAg levels were reported to be stable at a positive phase, whereas HBeAg tended to decrease in a negative phase, when the disease was not treated. Although a decrease of more than 1 log in qHBsAg seemed to indicate an immune control, further studies examining the use of decreased qHBsAg as a predictor of treatment response should be conducted.[12] The studies that contain particularly post-treatment qHBsAg results may help us to understand the value and the dynamics of this new parameter. Our study is not a prospective study and does not involve the long-term follow-up results of the patients. This is the major limitation of our study. In a Taiwanese study involving genotype B and C patients with chronic hepatitis B infection, it was found that low HBsAg

levels alone or in conjunction with low HBV-DNA levels were able to predict HBsAg loss when used one year after HBeAg seroconversion.[14] In another study from the same country, combining low HBsAg (<1000 IU/mL) with low ALT and HBV-DNA levels were again found to be beneficial in defining "minimal risk" levels in inactive HBV carriers.[15]

All these studies indicate that investigating qHBsAg levels can be an important test in identifying different phases and in evaluating the treatment response in CHB patients.

In this study, the diagnostic efficacy of qHBsAg was found to be at a moderate level with regard to distinguishing HBeAg-negative CHB patients from HBsAg carriers. As the qHBsAg cutoff value is 1625 IU/mL, its sensitivity was found to be at a moderate level although the specificity was high. These results show that qHBsAg is quite useful as a test when used together with ALT and HBV-DNA levels in distinguishing IC from HBeAg-negative CHB patients.

CONCLUSION

These studies questioned the use of serum qHBsAg levels as a screening biomarker (screening test for identifying phases of the disease) and as a follow-up marker for the evaluation of response to treatment (especially for the determination of sustained viral response). However, further prospective studies with a larger population requiring a long-term follow-up are needed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. World Health Organization 2012. Prevention and Control of Viral Hepatitis Infection: Framework for Global Action. WHO/HSE/PED/HIP/GHP 2012.1. Available from: http://www.who.int/csr/disease/hepatitis/GHP_framework.pdf. [Last accessed on 13 July 2015].
2. Özdemir D, Kurt H. HBV'larının epidemiyolojisi. In: Tabak F, Balık İ, Tekeli E, editors. Viral Hepatit. İstanbul: Viral Hepatit Savaşım Derneği Inc; 2007. p. 108-17.
3. Bergsland EK, Venook AP. Hepatocellular carcinoma. Curr Opin Oncol 2000;12:357-61.
4. Ganem D, Prince AM. Hepatitis B virus infection-natural history and clinical consequences. N Engl J Med 2004;350:1118-29.
5. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57:167-85.
6. 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.
7. 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.
8. Martinot-Peignoux M, Moucari R, Leclere L, Carvalho R, Cardoso AC, Boyer N, *et al*. Quantitative HBsAg: A new specific marker for the diagnosis of HBsAg inactive carriage. J Hepatol 2010;52(Suppl 1):S282.
9. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, *et al*. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22:696-99.
10. Koziel MJ, Thio CL. Hepatitis B virus and Hepatitis D virus. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and Practice of Infectious Diseases. 7th ed. New York: Churchill Livingstone; 2010. p. 2059-86.
11. Thompson AJ, Nguyen T, Iser D, Ayres A, Jackson K, Littlejohn M, *et al*. Serum hepatitis B surface antigen and hepatitis B e antigen titers: Disease phase influences correlation with viral load and intrahepatic hepatitis B virus markers. Hepatology 2010;51:1933-44.
12. Wursthorn K, Lutgehetmann M, Dandri M, Volz T, Buggisch P, Zollner B, *et al*. Peginterferon alpha-2b plus adefovir induce strong cccDNA decline and HBsAg reduction in patients with chronic hepatitis B. Hepatology 2006;44:675-84.
13. Rijckborst V, Hansen BE, Cakaloglu Y, Ferenci P, Tabak F, Akdogan M, *et al*. Early on-treatment prediction of response to peginterferon alfa-2a for HBeAg-negative chronic hepatitis B using HBsAg and HBV DNA levels. Hepatology 2010;52:454-61.
14. Tseng TC, Liu CJ, Su TH, Wang CC, Chen CL, Chen PJ, *et al*. Serum hepatitis B surface antigen levels predict surface antigen loss in hepatitis B e antigen seroconverters. Gastroenterology 2011;141:517-25, 525.e1-2.
15. Tseng TC, Liu CJ, Yang HC, Su TH, Wang CC, Chen CL, *et al*. Serum hepatitis B surface antigen levels help predict disease progression in patients with low hepatitis B virus loads. Hepatology 2013;57:441-50.