Original Article

Quantitative HBsAg levels do not identify hepatic fibrosis in HBeAg-negative chronic hepatitis B patients

Fatima A. Ahmed, Maryam S. Bajaifar[1], Mohammed A. Ahmed, Abduljaleel Alalwan[2,3], Faraaz A. Sanai[4], Khalid Albeladi[5], Abdulrahman A. Aljumah[2,3], Faisal M. Sanai[5,6]

College of Medicine, Ibn Sina National College for Medical Studies, [1]College of Medicine, King Abdulaziz University, [4]Emergency Department, King Fahd Hospital, [5]Gastroenterology Unit, Department of Medicine, King Abdulaziz Medical City, Jeddah, [2]Hepatology Division, Department of Hepatobiliary Sciences and Organ Transplant Center, King Abdulaziz Medical City, [3]King Saud bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center, Ministry of National Guard Health Affairs, [6]Liver Disease Research Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Abstract

Background/Aims: Quantitative serum hepatitis B surface antigen (qHBsAg) has been evaluated in limited patient groups as a marker of histological fibrosis. The accurate identification of inactive chronic hepatitis B virus (HBV) carriers from those with active carriers is difficult because of wide and frequent HBV DNA fluctuations. We aimed to assess the utility of qHBsAg in distinguishing histologically significant fibrosis in untreated HBeAg-negative chronic HBV patients.

Patients and Methods: qHBsAg levels were measured at baseline as single-point quantification and correlated with virologic and biochemical profiles of consecutive carriers (median, 29; range, 12-110 months). HBeAg-negative patients ($n = 75$) with HBV DNA <2000 ($n = 5$), 2000-20,000 ($n = 16$) and >20,000 IU/mL ($n = 54$) were included and all had liver biopsy. A qHBsAg cutoff point of 1000 IU/mL was assessed to demonstrate whether it better delineated patients with non-significant histology (F0-1, inflammatory grade A0-1).

Results: Mean age of the patients was 39.4 ± 11.4 years and 58 (77.3%) were male. Patients with qHBsAg levels >1000 IU/mL were more likely to be males (84.5%, $P = 0.006$) or with elevated AST (68.4%, $P = 0.0002$) and ALT levels (72.4%, $P < 0.0001$), higher HBV DNA ($\log_{10}$ 6.4 ± 1.4, $P < 0.0001$) and those with F2-4 fibrosis (48.3%, $P = 0.028$). Serum $\log_{10}$ qHBsAg were significantly lower in patients with HBV DNA <2000 (2.80 ± 1.47) and HBV DNA 2000-20,000 (2.71 ± 0.83) vs. >20,000 IU/mL (3.89 ± 0.61, $P < 0.0001$). Overall, qHBsAg were not different in patients with F0-1 (3.44 ± 0.91) and F2-4 fibrosis (3.74 ± 0.85, $P = 0.161$). Serum qHBsAg were higher in patients with significant (A2-3) inflammation (3.85 ± 0.72) compared to A0-1 (3.38 ± 0.95; $P = 0.018$). Serum qHBsAg demonstrated poor accuracy (AUROC, 0.61, $P = 0.111$) in identification of F2-4 fibrosis.

Conclusion: Serum qHBsAg levels do not help differentiate between those with HBV DNA <2000 or 2000 – 20,000 IU/mL or distinguish patients with significant fibrosis. Moreover, more than half of the patients with non-significant fibrosis have a qHBsAg level greater than 1000 IU/mL.

Keywords: Fibrosis, hepatitis B surface antigen, hepatitis B virus, levels, quantitative

Address for correspondence: Dr. Faisal M. Sanai, Gastroenterology Unit, Dept. of Medicine, King Abdulaziz Medical City, PO Box: 9515, Jeddah 21423, Saudi Arabia.
E-mail: sanaifa@ngha.med.sa

Access this article online	
Quick Response Code:	Website: www.saudijgastro.com
	DOI: 10.4103/sjg.SJG_80_19

How to cite this article: Ahmed FA, Bajaifar MS, Ahmed MA, Alalwan A, Sanai FA, Albeladi K, *et al*. Quantitative HBsAg levels do not identify hepatic fibrosis in HBeAg-negative chronic hepatitis B patients. Saudi J Gastroenterol 2019;25:286-92.

INTRODUCTION

Chronic hepatitis B (CHB) is an immune-based disease in which the host immunological response greatly affects the extent of disease in addition to the frequency and quality of virologic response.[1] CHB represents a crucial health concern worldwide, with most recent studies reporting global prevalence estimates of over 290 million individuals with hepatitis B virus (HBV) infection.[2] HBV constitutes a crucial healthcare burden in Saudi Arabia and significant challenges remain in the management of CHB.[3,4]

Chronic hepatitis B is a dynamic disease, with patients passing through different stages back and forth, and also from one status to another.[5] There is variability in conditions associated with chronic hepatitis B e antigen (HBeAg) negative HBV infection, varying from inactive carrier (IC) status to active CHB status. Assessment of disease activity and progression is of immense importance in the management of such patients and is based on surrogate markers such as the alanine aminotransferase (ALT) and HBV DNA levels.[6,7] However, patients with normal ALT levels and low viremia may harbor significant fibrosis.[8,9] The most reliable parameter to determine proper treatment alternatives is assessing liver fibrosis by biopsy. However, due to the invasiveness of the liver biopsy procedure, the need for developing innovative non-invasive approaches to diagnose fibrosis is crucial.

The presence of hepatitis B surface antigen (HBsAg), which is secreted by infected hepatocytes, characterizes overt HBV infection.[5,10] An essential diagnostic marker of HBV infection is detecting HBsAg in serum. Obtaining quantitative HBsAg (qHBsAg) levels may reveal the existence of covalently closed circular DNA and predict favorable response to antiviral therapy and HBsAg sero-clearance.[11,12] A qHBsAg of 1000 IU/mL has been suggested as an appropriate cutoff to distinguish active from inactive HBV.[13] In combination with HBV DNA, qHBsAg has been proposed as a new diagnostic tool for the characterization of HBV disease state due to the presence of significant variations of total serum qHBsAg in the variable phases of HBV infection.[12]

Previous studies have shown that median qHBsAg levels vary throughout the different phases of HBV infection,[11-16] and serum levels correlate, albeit poorly, with HBV DNA levels.[11,15,16] While these correlations between HBV DNA and qHBsAg are well described, there is scant information describing the association between qHBsAg and liver pathology in patients with CHB infection in the IC phase.[17] Therefore, additional studies are needed to fully understand the key tenets of qHBsAg levels and its association with liver pathology.

In this study, we aimed to evaluate the relationship of qHBsAg with serum HBV DNA levels in Saudi patients with HBeAg-negative chronic HBV and to evaluate qHBsAg as a non-invasive biomarker of liver inflammation and fibrosis in CHB patients.

PATIENTS AND METHODS

Study patients

Untreated chronic adult HBV (HBsAg detection >6 months) HBeAg-negative patients (n = 75) with mean HBV DNA <2000, 2,000 – 20,000 and >20,000 IU/mL were included from the hepatology clinics of King Abdulaziz Medical City in Riyadh, Saudi Arabia, and all had a liver biopsy. The Institutional Review Board approved the study. Clinical records and hospital databases were searched for consecutive HBeAg-negative patients between 16 and 80 years of age for the period between January 2006 and January 2012. Virologic and biochemical profiles of the consecutively followed-up carriers (median, 8; range, 4–17 months) were assessed in relation to liver histology. These patients were part of a cohort of 366 HBeAg-negative carriers previously reported by us in relation to liver histological fibrosis.[18]

Study design

A minimum of three ALT recordings for patients with normal levels and two recordings for those with elevated levels were required. The last three levels prior to the intervention were recorded. The reference ULN for ALT assays (as provided by the manufacturer) varied considerably at different time points (≤55, ≤65 or ≤40 U/L with values not being gender-specific). Since the ULN for ALT levels are assay-determined and not equivalent in absolute values across different assays, we corrected for the differing ULN in various assays used and expressed ALT levels as a ratio in relation to the ULN.[18] Commercially available autoanalyzers and enzyme-linked immunoassays were utilized for liver biochemical tests and hepatitis serological markers.

The qHBsAg levels (Abbott ARCHITECT® Assay, Architect i2000SR, Abbott Diagnostics; Abbott Laboratories, Chicago, IL, USA) were measured at baseline as single-point quantification and correlated with virologic and biochemical profiles of consecutive carriers. The detection value of quantitative HBsAg ranged from 0.05 to 250 IU/mL and samples with HBsAg titers >250 IU/mL required a 1:500 dilution. A qHBsAg cutoff point of

1000 IU/mL was assessed to demonstrate whether it better delineated patients with non-significant histology (F0-1, inflammatory grade A0-1). Minimum of three HBV DNA recordings (Abbott Real*Time* assay, Abbott Molecular, Inc., Des Plaines, IL, USA; lower detection limit of 10 IU/mL) were required. Reference value utilized for analysis was based on the pre-biopsy level.

Patients with co-infection with hepatitis C, delta virus, or HIV were excluded. Chronic HBV patients with superimposed other liver diseases or alcohol consumption >20 g/d were also excluded, including those with previous immunosuppressive or antiviral therapy or prior organ transplantation. Also, decompensated cirrhosis with a Child-Pugh score >6, or evidence of portal hypertension, variceal bleeding laboratory findings of a platelet count <100 (10^9/L) an international normalized ratio ≥1.3 were part of the exclusion criteria. We also excluded patients with hepato-biliary malignancy or renal impairment with a creatinine >135 μmol/L.

Liver histology

All biopsies were stained with hematoxylin and eosin for morphological evaluation and with reticulin for the assessment of fibrosis. The number of portal tracts considered sufficient on which to report a biopsy was ≥10. All specimens were centrally assessed and scored according to the METAVIR system by a hepatopathologist who was blinded to all clinical information. An inflammatory score of ≥A2 and fibrosis score of ≥F2 were defined as significant.

Statistical analyses

Quantitative variables were expressed as mean ± standard deviation or the median with IQR (25^{th} – 75^{th} percentile), and categorical variables as frequencies and proportions. Comparisons between groups were performed using the Mann-Whitney test, Chi-square test, and Fisher's exact test as appropriate. Means of quantitative variables were compared using one-way analysis of variance (ANOVA) with Post-hoc test (Turkey's) as needed. All analyses related to HBV DNA and qHBsAg were conducted after logarithmically transforming the values (Ln) to account for the skewed distribution. The area under receiver operating characteristics (AUROC) was calculated to obtain the optimal cut-off point to discriminate F2-4 (METAVIR) with qHBsAg. A *P* value of <0.05 was considered statistically significant. Statistical Package for Social Sciences (*SPSS, version* 17.0; Chicago, IL, USA) and MedCalc (MedCalc Software, Inc, Mariakerke, Belgium) were used for data analysis.

RESULTS

Baseline characteristics of patients

A total of 75 patients with mean HBV DNA <2000 ($n = 5$), 2,000–20,000 ($n = 16$) and >20,000 IU/mL ($n = 54$) were included in this analysis. The mean age of the patients was 39.4 ± 11.4 years and 58 were male (77.3%). Baseline characteristics of all patients are shown in Table 1. ALT levels were normal in 30 (40%) with the median ALT of the overall cohort being 1.2 ULN (IQR 0.6 – 1.6). The $\log_{10}$ qHBsAg level of the overall cohort was 3.4 ± 0.9 IU/mL.

Prevalence of significant fibrosis

Baseline parameters of patients with significant fibrosis (F2-4) and those without significant fibrosis (F0-1) are shown in Table 2. Significant fibrosis (F2-4) was seen in 31 (41.3%) and these patients were more likely to have

Table 1: Characterization of patients based on qHBsAg levels

Parameters	Overall (*n*=75)	HBsAg <1000 IU/mL (*n*=17)	HBsAg >1000 IU/mL (*n*=58)	*P*
Age (yrs)	39.4±11.4	42.6±11.2	38.5±11.4	0.197
Male gender (%)	58 (77.3)	9 (52.9)	49 (84.5)	0.006
Body mass index (Kg/m^2)	27.4±5.0	29.0±5.6	26.9±4.8	0.186
Diabetes mellitus (%)	4 (5.3)	2 (11.8)	2 (3.4)	0.219
Hyperlipidemia (%)	16 (21.3)	5 (29.4)	11 (19.0)	0.501
HBV DNA $\log_{10}$ (IU/mL)	5.8±1.7	4.0±1.2	6.4±1.4	<0.0001
HBV DNA >2000 IU/mL	70 (93.3)	14 (82.4)	56 (96.6)	0.073
HBV DNA <2000 IU/mL	5 (6.7)	3 (17.6)	2 (3.4)	
Platelet (10^9/L)	249.3±79.2	280.4±101.3	239.5±69.2	0.136
AST (x ULN)*	1.2 (0.7-1.8)	0.6 (0.5-1.0)	1.3 (0.9-1.9)	<0.0001
Normal AST (%)	31 (41.9)	13 (76.5)	18 (31.6)	0.0002
Elevated AST (%)	43 (58.1)	4 (23.5)	39 (68.4)	
ALT (x ULN)*	1.2 (0.6-1.6)	0.4 (0.2-0.7)	1.4 (1.0-2.0)	<0.0001
Normal ALT (%)	30 (40.0)	14 (82.4)	16 (27.6)	<0.0001
Elevated ALT (%)	45 (60.0)	3 (17.6)	42 (72.4)	
Fibrosis stage				
F0-1	44 (58.7)	14 (82.4)	30 (51.7)	0.028
F2-4	31 (41.3)	3 (17.6)	28 (48.3)	

Data represented as *n* (%) and mean±standard deviation, or *median (25^{th} - 75^{th} interquartile range). HBV: Hepatitis B virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase

Table 2: Baseline parameters of patients with significant fibrosis (F2-4) and those without (F0-1)

Parameters	Fibrosis F0-1 (*n*=44)	Fibrosis F2-4 (*n*=31)	*P*
Age (yrs)	38.2±9.7	41.2±13.4	0.257
Male gender (%)	32 (72.7)	26 (83.9)	0.401
BMI (Kg/m^2)	27.4±4.6	27.4±5.6	0.955
Diabetes mellitus (%)	1 (2.3)	3 (9.7)	0.300
Hyperlipidemia (%)	12 (27.3)	4 (12.9)	0.162
HBV DNA log$_{10}$ (IU/mL)	5.5±1.6	6.4±1.7	0.020
Platelet (10^9/L)	282.4±79.0	201.3±50.3	<0.0001
AST (x ULN)*	0.9 (0.6-1.5)	1.4 (1.0-2.0)	0.008
Normal AST (%)	24 (54.5)	7 (23.3)	
Elevated AST (%)	20 (45.5)	23 (76.7)	0.008
ALT (x ULN)*	1.0 (0.5-1.6)	1.4 (1.0-2.3)	0.039
Normal ALT (%)	22 (50.0)	8 (25.8)	
Elevated ALT (%)	22 (50.0)	23 (74.2)	0.035
qHBsAg log 10 (IU/mL)	3.4±0.9	3.7±0.9	0.166

Data represented as *n* (%) and mean±standard deviation, or *median (25th - 75th interquartile range). HBV: Hepatitis B virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase

higher Log$_{10}$ HBV DNA (6.4 ± 1.7 vs. 5.5 ± 1.6 IU/mL), elevated ALT (74.2 vs. 50.0%) and AST (76.7 vs. 45.5%), and lower platelets (201.3 ± 50.3 vs. 282.4 ± 79.0 10^9/L). In patients with HBV DNA >2000 IU/mL, when qHBsAg levels were >1000 IU/mL (*n* = 56, 74.7%) F2-4 fibrosis was more frequently seen (50.0%) as opposed to those with qHBsAg <1000 IU/mL (7.1%, *P* = 0.005). However, in one-half of the patients who fulfilled these criteria of HBV DNA >2000 IU/mL and qHBsAg >1000 IU/mL nonsignificant (F0-1) fibrosis was found [Table 3].

Predictors of high quantitative HBsAg levels

Characteristics of patients with high qHBsAg (>1000 IU/mL) are shown in Table 1. Most patients (77.3%) had qHBsAg levels >1000 IU/mL and these were more likely to be males (84.5%, *P* = 0.006) or with elevated AST (68.4%, *P* = 0.0002), ALT levels (72.4%, *P* < 0.0001), higher HBV DNA (log$_{10}$ 6.4 ± 1.4, *P* < 0.0001) and those with F2-4 fibrosis (48.3%, *P* = 0.028). Serum log$_{10}$ qHBsAg were significantly lower (*P* < 0.0001) in patients with HBV DNA <2000 (2.80 ± 1.47) and 2000-20,000 (2.71 ± 0.83) compared to >20,000 IU/mL (3.89 ± 0.61, Figure 1). Few patients with HBV DNA <2000 IU/mL had qHBsAg >1000 (*n* = 2) or <1000 IU/mL (*n* = 3). Multivariate analysis showed that only high HBV DNA levels was independently associated with higher qHBsAg levels (OR 3.4, 95% CI 1.7 – 6.7; *P* < 0.0001; Table 4).

Table 3: Combination of fixed HBV DNA and qHBsAg cutoffs in identifying significant fibrosis

Fibrosis stage	Overall (*n*=70)	HBV DNA >2000 & qHBsAg <1000 IU/mL (*n*=14)	HBV DNA >2000 & qHBsAg >1000 IU/mL (*n*=56)	*P*
F0-1	41 (58.6)	13 (92.9)	28 (50.0)	0.005
F2-4	29 (41.2)	1 (7.1)	28 (50.0)	

Data expressed as *n* (%)

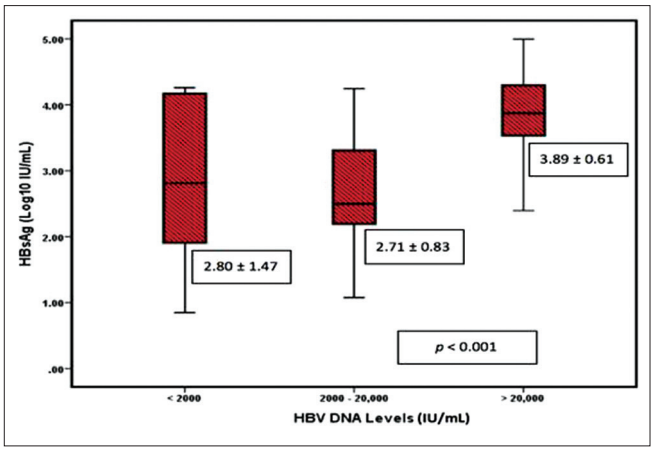

Figure 1: Relationship of serum qHBsAg with different threshold levels of HBV DNA

Quantitative HBsAg in relation to histology

The relationship between log$_{10}$ qHBsAg levels and liver histology is demonstrated in Figure 2. Overall, levels were not different in patients with F0-1 (3.44 ± 0.91) and F2-4 (3.74 ± 0.85, *P* = 0.161). Levels were higher in patients with significant inflammation, A2-3, (3.85 ± 0.72) compared to A0-1 (3.38 ± 0.95; *P* = 0.018). Patients with qHBsAg levels >1000 IU/mL were more likely to have F2-4 fibrosis (48.3%) compared to those with <1000 IU/mL (17.6%, *P* = 0.028). Serum qHBsAg demonstrated poor accuracy (AUROC, 0.61, *P* = 0.111) in identification of F2-4. Based on the ROC curve of qHBsAg levels, we determined threshold values with the best compromise between sensitivity and specificity for the detection of F2-4 fibrosis. The optimum qHBsAg threshold was 5185 IU/mL for distinguishing F2-4, with a sensitivity of 67.7% and a specificity of 59.1% [Figure 3].

DISCUSSION

In this study, we evaluated whether qHBsAg levels may contribute to the identification of significant fibrosis (F2-4) in untreated HBeAg negative carriers. Our results show that qHBsAg do not distinguish patients with F2-4 fibrosis. Mean levels were similar in patients with significant and non-significant fibrosis, and in those with levels >1000 IU/mL less than half had significant fibrosis. More than half the patients with nonsignificant fibrosis were also found to have a qHBsAg level >1000 IU/mL. More importantly, patients with qHBsAg <1000 IU/mL had a presence of significant fibrosis similar to those with levels >1,000 IU/mL. Brunetto *et al*. previously proposed a qHBsAg level of >1000 IU/mL to be an accurate cut-off to differentiate active from inactive HBV in Italian patients,[13] although liver histological assessment and profiling was not included, and disease characterization

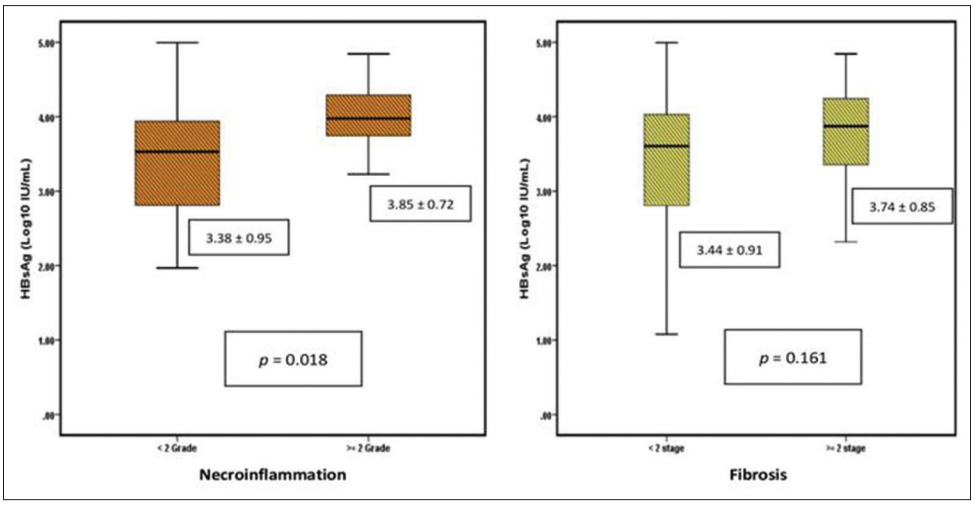

Figure 2: Relationship of serum qHBsAg with liver fibrosis and necroinflammation

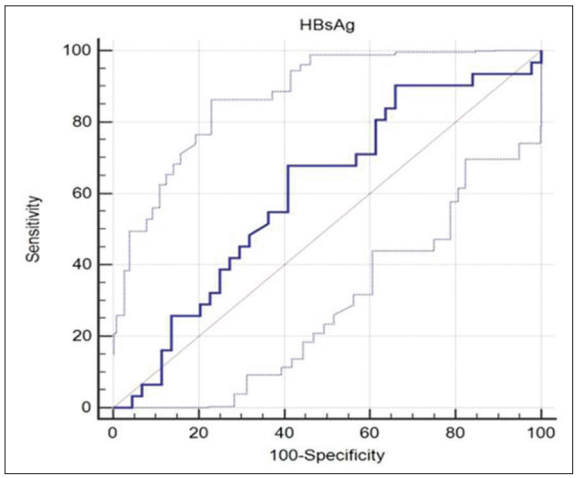

Figure 3: Receiver operating characteristic curve of qHBsAg in identifying significant fibrosis F2-4. In patients meeting the threshold qHBsAg (5185 IU/mL), the sensitivity is 67.7% and specificity 59.1% (AUROC, 0.61; 95% CI: 0.49–0.72)

was carried out principally on the basis of serial HBV DNA and ALT levels. This clearly does not address the issue that significant fibrosis in patients with low viremia (the so-called "inactive carriers") does occur[8,9] and that liver biopsy remains the preferred means for its assessment. It was thus hoped that the level of qHBsAg could fill this gap by serving as a proxy biomarker of fibrosis, where a better stratification of HBV disease could be made. However, our results show that this disease stratification is not feasible with qHBsAg levels, with results being in conformity with other studies in HBeAg-negative patients where higher qHBsAg levels did not identify significant fibrosis.[19-21]

The relationship between qHBsAg and hepatic necroinflammation has rarely been described. Chakrabarty *et al*. showed an inverse relationship with lower qHBsAg levels in HBeAg-negative genotype E patients with higher necroinflammatory scores. Along the same lines, lower qHBsAg were also found more frequently in those with advanced fibrosis.[9] Nonetheless, the natural history of chronic HBV infection might be another reason for the lack of relationship between qHBsAg with histological disease evolution in HBeAg-negative patients. Chronic HBV infection is a dynamic process reflecting the relationship between viral replication and the host immune response. There is an increased likelihood of significant inflammation while transitioning from immune-tolerant to the immune-active phase where HBV virus is no doubt being cleared. This may explain the higher necroinflammatory scores in patients with higher qHBsAg levels in our study.

In clinical practice HBV DNA levels of 2000 – 20,000 IU/mL pose a particular difficulty where different guidelines offer conflicting guidance on management.[6,7] We have previously reported that histological fibrosis in both these groups occurs at a similar rate.[9] In this study, we found that serum qHBsAg levels do not differentiate between patients with HBV DNA <2000 and 2000 – 20,000 IU/mL. While a weak correlation existed between HBV DNA and qHBsAg levels, mean qHBsAg levels were similar between those with HBV DNA <2000 and 2000 – 20,000 IU/mL. On the other hand, natural history studies have clearly shown that the viremia level of 2000 – 20,000 IU/mL is distinguished by a higher likelihood of developing cirrhosis and HCC as compared to <2000 IU/mL.[22] Hence, it appears that the clinical utility of qHBsAg levels is further hindered by this limitation.

Previous studies have studied whether qHBsAg serum levels may contribute to the diagnosis of different HBV

Table 4: Univariate and multivariate analysis of predictors of quantitative HBsAg >1000 IU/mL

Variables	Univariate	Multivariate	*P*
	Odds Ratio (95% CI)	Odds Ratio (95% CI)	
Gender	0.21 (0.06-0.68)	0.2 (0.0-1.2)	0.085
HBV DNA $\log_{10}$ (IU/mL)	3.09 (1.74-5.47)	3.4 (1.7-6.7)	<0.0001
AST (x ULN)	1.40 (0.74-2.64)	0.8 (0.4-1.5)	0.532
ALT (x ULN)	1.38 (0.88-2.17)	0.8 (0.5-1.4)	0.515
Fibrosis stage	4.35 (1.13-16.78)	3.8 (0.6-25.2)	0.171

HBV: Hepatitis B virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase

phases in untreated HBeAg-negative asymptomatic carriers. Brunetto *et al*. identified a threshold qHBsAg level of 1000 IU/mL as a means of distinguishing patients with "inactive carrier" state, where a single point combined quantification of HBsAg (1000 IU/mL) and HBV DNA (2000 IU/mL) permits the identification of inactive carriers with a diagnostic accuracy of 94.3%. In our study 82% of the patients with qHBsAg levels <1000 IU/mL had nonsignificant (F0-1) fibrosis. However, the relevance of this finding is dampened by the analysis that over half of the patients with qHBsAg >1000 IU/mL exhibited nonsignificant fibrosis. Serum qHBsAg demonstrated poor accuracy (AUROC, 0.61) in the identification of fibrosis, with poor overall sensitivity and specificity. While our ROC analysis identified a qHBsAg level of 5185 IU/mL as an optimum threshold for significant fibrosis, the modest corresponding sensitivity (67.7%) and specificity (59.1%) would make such a distinction clinically irrelevant.

Perhaps the utility of qHBsAg levels lies in distinguishing nonsignificant fibrosis in the minority group of high viremia patients but with qHBsAg <1000 IU/mL (18.7% of our cohort). In this cohort, an overwhelming 93% had non-significant fibrosis. However, the number of patients with combined HBV DNA <2000 and qHBsAg <1000 IU/mL were low in our study (n = 3) making a realistic identification of a true "inactive carrier state" as demonstrated by Brunetto *et al*. impractical.[13] As such, the true value of utilizing lower qHBsAg levels to exclude significant fibrosis must be studied in larger cohorts of HBeAg-negative patients.

Admittedly, an obvious bias existed in performing liver biopsy in favor of those with higher HBV DNA levels. Our population of HBV patients does not essentially represent an unselected cohort, given the impracticality of performing a liver biopsy in all HBeAg-negative patients. It is feasible that a proportion of these patients may have been biopsied as a consequence of subtle hints for the presence of fibrosis, and others excluded where the justification or rationale for performing a biopsy did not exist. Since practice guidelines currently do not recommend liver biopsy in patients with low levels of viremia, an alternative approach would be to use non-invasive tests and imaging techniques in such patients and reserve biopsy for those who show possible advanced fibrosis based on such tests. Moreover, chronic HBV is a dynamic process evolving over many years, with liver biopsy merely offering a snapshot image of underlying histology at a given time-point. Hence, histological disease estimation at any time-point is prone to under- or over-estimation of fibrosis. This aspect could only be convincingly addressed by performing serial non-invasive assessments in untreated patients over an extended period of time to control for subsequent disease evolution.

CONCLUSION

In conclusion, our study shows that serum qHBsAg levels in Saudi HBeAg-negative chronic hepatitis B patients do not help differentiate between those with HBV DNA <2000 or 2000 – 20,000 IU/mL or distinguish patients with significant fibrosis. Although patients with qHBsAg >1000 were more likely to harbor significant fibrosis, as opposed to those with levels <1000 IU/mL, the value of this observation was diminished by the finding that more than half the patients with nonsignificant fibrosis also have a qHBsAg level >1000 IU/mL. The value of supplementing these non-invasive markers of histological disease with other tests such as transient elastography should be assessed prospectively, with a larger number of patients particularly with low viremia, so that a better stratification of disease phase can be achieved.

Financial support and sponsorship

This Work was funded by the National Plan for Science, Technology and Innovation (MAARIFAH), King Abdulaziz City for Science and Technology, Kingdom of Saudi Arabia, grant number 08-MED512-02.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Perrillo R. Therapy of hepatitis B — Viral suppression or eradication? Hepatology 2006;43:S182-93.
2. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: A modelling study. Lancet Gastroenterol Hepatol 2018;3:383-403.
3. Sanai FM, Alghamdi H, Alswat KA, Babatin MA, Ismail MH, Alhamoudi WK, *et al*. Greater prevalence of comorbidities with increasing age: Cross-sectional analysis of chronic hepatitis B patients in Saudi Arabia. Saudi J Gastroenterol 2019;25:194-200.
4. Aljumah AA, Babatin M, Hashim A, Abaalkhail F, Bassil N, Safwat M, *et al*. Hepatitis B care pathway in Saudi Arabia: Current situation, gaps

and actions. Saudi J Gastroenterol 2019;25:73-80.
5. Rotman Y, Brown T, Hoofnagle J. Evaluation of the patient with hepatitis B. Hepatology 2009;49:S22-7.
6. 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.
7. Abaalkhail F, Elsiesy H, AlOmair A, Alghamdi MY, Alalwan A, AlMasri N, *et al*. SASLT practice guidelines for the management of hepatitis B virus. Saudi J Gastroenterol 2014;20:5-25.
8. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ; Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-In HBV (the REVEAL-HBV) Study Group. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006;130:678-86.
9. Abdo AA, Bzeizi KI, Babatin MA, AlSohaibani F, AlMana H, Alsaad KO, *et al*. Predictors of significant fibrosis in chronic hepatitis B patients with low viremia. J Clin Gastroenterol 2014;48:e50-6.
10. Blumberg BS, Alter HJ, Visnich S. A "New" antigen in leukemia sera. JAMA 1965;191:541-6.
11. Jaroszewicz J, Serrano B, Wursthorn K, Deterding K, Schlue J, Raupach R, *et al*. Hepatitis B surface antigen (HBsAg) levels in the natural history of hepatitis B virus (HBV)-infection: A European perspective. J Hepatol 2010;52:514-22.
12. Chan H, Thompson A, Martinot-Peignoux M, Piratvisuth T, Cornberg M, Brunetto M, *et al*. Hepatitis B surface antigen quantification: Why and how to use it in 2011 – A core group report. J Hepatol 2011;55:1121-31.
13. Brunetto M, 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.
14. Chan H, Wong V, Wong G, Tse C, Chan H, Sung J. A longitudinal study on the natural history of serum hepatitis B surface antigen changes in chronic hepatitis B. Hepatology 2010;52:1232-41.
15. 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.
16. Alghamdi A, Aref N, El-Hazmi M, Al-Hamoudi W, Alswat K, Helmy A, *et al*. Correlation between hepatitis B surface antigen titers and HBV DNA levels. Saudi J Gastroenterol 2013;19:252-7.
17. Seto W, Wong D, Fung J, Ip P, Yuen J, Hung I, *et al*. High hepatitis B surface antigen levels predict insignificant fibrosis in hepatitis B e antigen positive chronic hepatitis B. PLoS One 2012;7:e43087.
18. Sanai FM, Babatin MA, Bzeizi KI, Alsohaibani F, Al-Hamoudi W, Alsaad KO, *et al*. Accuracy of international guidelines for identifying significant fibrosis in hepatitis B e antigen--negative patients with chronic hepatitis. Clin Gastroenterol Hepatol 2013;11:1493-9.e2.
19. Chakrabarty G, Bruce M, Horner M, Wang B, Agarwal K, Carey I. Can quantitative hepatitis B surface antigen levels predict the severity of liver disease in genotype E Patients? J Viral Hepat 2018;25:80-7.
20. Li Q, Li W, Lu C, Huang Y, Chen L. Serum hepatitis B surface antigen levels predict insignificant fibrosis and non-cirrhosis in hepatitis B e antigen positive patients with normal or mildly elevated alanine transaminase levels. Oncotarget 2017;8:86463-70.
21. 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.
22. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, *et al*. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65-73.