HBsAg Serum Level And Viral Load In Egyptian HBV-Infected Patients: Is There A Correlation?

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Abstract: Background and aim: HBsAg is the hallmark of overt HBV infection, and detection of HBsAg in serum is the fundamental diagnostic marker of HBV infection. Given that viral load assays are more expensive than quantitative HBsAg, a critical question is whether HBsAg can be used instead of, or must be used in conjunction with, HBV-DNA levels. The aim was to study the relationship between HBsAg serum level and HBV-DNA in chronic Hepatitis B infected patients. **Patients and methods**: HBsAg quantification, using the Abbott ARCHITECT assay, was done in 2oo treatment naïve patients having chronic HBV infection. Serum HBV-DNA was measured by use of COBAS AmpliPrep/ COBAS TaqMan with detection limit of 12 IU / ml. **Results**: Divided into two groups; group I included patients with HBV-DNA <2000 IU/ml, while group II included patients with HBV-DNA ≥2000 IU/ml. Group (I) included 83 males and 17 females with their mean age (33.21±9.37 years), while group (II) included 84 males and 16 females with their mean age (31.27 ± 6.51 years). All patients in group (I) were HBeAg negative, while in group (II) two patients (2%) were HBeAg positive. Each studied group was further divided into two subgroups according to serum ALT level; elevated versus normal. HBV DNA in group (C) and (D) were significantly higher than group (A) and (B) ($1.5x10^7$±46204315.2 and 661348±4063280 versus 415.6±195.27 and 724.52±531.99 IU/ml) ($p< 0.001$). Significant positive correlation was found between HBsAg titer and HBV- DNA level among all studied patients ($p < 0.001$). However, when the correlation was studied in different groups there was a significant positive correlation in group (C) ($p < 0.001$) and group (D) ($p < 0.001$), but it didn't reach significant level in group (A) ($p > 0.05$) and group (B) ($p > 0.05$). A cut-off HBsAg titer of 425 IU/ml could predict serum HBV DNA levels ≥ 2000 IU/ml with 85% sensitivity, 97% specificity and 91% Accuracy. **Conclusions**: HBsAg titer is significantly correlated to HBV-DNA level. Baseline HBsAg quantification may help to refine future treatment algorithms for both immune-modulator therapy and oral nucleos(t)ide analogue therapy.

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Key words: HBsAg Quantification, HBV-DNA, Diagnostic Marker, Abbott ARCHITECT Assay, Ampliprep/ COBAS Taqman.

1. Introduction

The spectrum of chronic HBV infection and disease is diverse and variable, ranging from a low viremic in-active carrier state to progressive chronic hepatitis, which may evolve to cirrhosis and hepatocellular carcinoma (HCC). HBV-related end stage liver disease or HCC are responsible for over 1 million deaths per year and currently represent 5−10% of cases of liver transplantation **(Lok and McMahon, 2007).**

The natural history of chronic hepatitis B (CHB) is typically regarded as consisting of five phases; immune-tolerant (IT), immune-clearance (IC), non/low-replicative (LR), hepatitis B e antigen negative hepatitis (ENH), and HBsAg-negative phase. These phases have been classified by specific biochemical, serological and virological characteristics, including serum ALT levels, hepatitis B e antigen (HBeAg) serostatus, and hepatitis B virus DNA (HBV DNA) titre. It is important to note that these phases do not occur in all individuals, and do not always necessarily occur sequentially **(Nguyen *et al.*, 2010).**

In the era of molecular diagnostics, significant progress has been made in the understanding of the lifecycle, clinical course, and pathogenesis of the hepatitis B virus (HBV). Quantitative serologic assessment of virologic factors plays a pivotal role in the diagnosis and effective management of chronic hepatitis B **(Chen *et al.*, 2006).** Highly sensitive assays for the quantification of HBV DNA have become a primary tool in selecting patients who are candidates for therapy, monitoring response to therapy, and detecting the emergence of drug resistance **(Lok and McMahon, 2007).**

In addition to HBV DNA levels, several clinical investigations have provided evidence that relationships exist between other viral antigens, such as hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg), and the natural course of disease as well as patients' response to antiviral therapy **(Wursthorn *et al.*, 2006).**

Given that viral load assays are more expensive than quantitative HBsAg, a critical question is whether HBsAg can be used instead of, or must be used in conjunction with, HBV DNA levels **(Su *et al.*, 2008).**

2. Patients & Methods

This study was conducted in outpatient clinics, Hepatology department, National Liver Institute, Menoufiya University, Egypt. It included 200 treatment naive patients diagnosed as having chronic HBV infection based on positivity for HBsAg and HBV DNA PCR, and divided into two groups; group I included patients with HBV DNA <2000 IU/ml. While group II included patients with HBV DNA ≥2000 IU/ml. Group (I) included 83 males and 17 females with their mean age (33.21±9.37 years), while group (II) included 84 males and 16 females with their mean age (31.27 ± 6.51 years). All patients in group (I) were HBeAg negative, while in group (II) 98% were HBeAg negative and the remaining two patients (2%) were HBeAg positive. None of the individuals included had hepatitis delta virus (HDV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV) co-infection. Further exclusion criteria were Patients with liver cirrhosis and/ or hepatocellular carcinoma, concurrent chronic disease as DM, chronic kidney disease, heart failure as well as autoimmune disease.

Serum HbsAg quantification by chemiluminescent microparticle assay:

Serum HBsAg levels were quantified using the Abbott ARCHITECT assay. The ARCHITECT quantitative HBsAg assay is a chemiluminescent microparticle assay internally calibrated using the World Health Organization (WHO) standard for HBsAg. Quantitative HBsAg levels were reported in IU/ml, with a dynamic range of 0.05–250 IU/ml. Given that most serum HBsAg titres were above this range, samples were initially tested at dilutions of 1 in 100 or 1 in 1000. ARCHITECT HBsAg Manual Diluent (Abbott Diagnostics) was used to dilute patient sera.

HBV DNA measurement by real time PCR (Roche):

Serum HBV-DNA was measured by use of COBAS AmpliPrep/COBAS TaqMan with detection limit of 12 IU/ml. HBV-DNA levels were expressed in IU/ml.

Statistical analysis:

The data collected were tabulated & analyzed by SPSS (statistical package for the social science software) statistical package version 11 on IBM compatible computer.

Quantitative data were expressed as mean & standard deviation (X+SD) and analyzed by applying student **t**-test for comparison of two groups of normally distributed variables and Mann whiteny test for none normally distributed ones. ANOVA test for analysis of variance (**f**-test) was used for comparison of more than two groups of normally distributed variables and Kruskal Wallis test was used for comparison of more than two groups of none normally distributed variables. Qualitative data were expressed as number and percentage (No & %) and analyzed by applying chi-square test. Pearson correlation (**r**) was used to detect association between quantitative variables. The ROC (receiver operating characteristic) curve was used to detect the cutoff value with highest sensitivity and specificity. All these tests were used as tests of significance at $P<0.05$.

3. Results

Two hundred treatment naive patients with chronic hepatitis B (CHB) recruited into the current study and divided into two groups; group I included patients with HBV DNA <2000 IU/ml, While group II included patients with HBV DNA ≥2000 IU/ml. Each one of the studied groups was further divided into two subgroups according to serum ALT level; Group (A) included 5 patients with HBV DNA <2000 IU/ml and elevated serum ALT. Group (B) included 95 patients with HBV DNA <2000 IU/ml and serum ALT not exceeding the upper limit of normal (35 IU/ml). Group (C) included 39 patients with HBV DNA ≥2000 IU/ml and elevated serum ALT. Group (D) included 61 patients with HBV DNA ≥2000 IU/ml and serum ALT not exceeding the upper limit of normal (35 IU/ml) table (1).

Table (1) Comparison between patients with HBV DNA level below 2000 IU/ml & ≥2000 IU/ml regarding percentage of patients with elevated versus normal Liver enzyme (ALT).

Parameter	**Group I HBV DNA<2000 IU/ml (n = 100)**		**Group II HBV DNA≥2000 IU/ml (n = 100)**		**X^2**	***P*. value**
ALT (N: up to 35 IU/ml)	A (elevated)	B (Normal)	C (elevated)	D (Normal)	33.68	**<0.001**
No	5	95	39	61		
%	5%	95%	39%	61%		

As shown in table (2) HBV DNA in group (C) and (D) were significantly higher than group (A) and (B) ($1.5x10^7$±46204315.2 and 661348±4063280 versus 415.6±195.27 and 724.52±531.99 IU/ml) ($p< 0.001$), also HBV DNA in group (C) was significantly higher than group (D) ($1.5x10^7$±46204315.2 versus 661348±4063280 IU/ml) ($p< 0.001$).

Table (2) Comparison between the four studied groups regarding HBsAg titre & HBV DNA level.

Parameter	Group A (n=5) mean± SD	Group B (n=95) mean± SD	Group C (n=39) mean± SD	Group D (n=61) mean ± SD	*P*. value
HBsAg Titre(IU/ml)	260 ±151.66	104.4±98.20	7052.04±6128.8	3804.56±4823.8	*<0.05
HBV DNA level(IU/ml)	415.6±195.27	724.52±531.99	$1.5x10^7$±46204315.2	661348±4063280	*<0.001

The mean value of HBsAg titre in group (C) and (D) were significantly higher than group (A) and (B) (7052.04±6128.8 and 3804.56±4823.8 versus 260 ±151.66 and 104.4±98.20 IU/ml) ($p < 0.05$), in addition to that the mean value of HBsAg titre in group (C) was significantly higher than group (D) (7052.04±6128.8 versus 3804.56±4823.8 IU/ml) ($p < 0.05$) , the mean value of HBsAg titre in group (A) was significantly higher than group (B) (260 ±151.66 versus 104.4±98.20 IU/ml) ($p < 0.05$).

As shown in tables (3 & 4) and figures (1-5) significant positive correlation was found between HBsAg titre and HBV DNA level among all studied groups (R = 0.48, $p< 0.001$). However, when the correlation was studied in different groups there was a significant positive correlation in group (C) (R = 0.58, $p< 0.001$) and group (D) (R = 0.39, $p < 0.001$), but it didn't reach significant level in group (A) (R = 0.31, $p > 0.05$) and group (B) (R = 0.09, $p > 0.05$).

Table (3) Pearson correlation between HBV DNA level & HBsAg titre in all studied patients.

Parameter	HBV DNA level (IU/ml)	
	R	*p*. value
HBsAg titre (IU/ml)	0.48	< 0.001

Table (4) Pearson correlation between HBV DNA level & HBsAg titre in each group.

Parameter	Group A HBV DNA level (IU/ml)		Group B HBV DNA level (IU/ml)		Group C HBV DNA level (IU/ml)		Group D HBV DNA level (IU/ml)	
	R	*p*. value	R	*p*. value	R	*p*. value	R	*p*. value
HBsAg Titre (IU/ml)	0.31	>0.05	0.09	>0.05	0.58	<0.001	0.39	<0.001

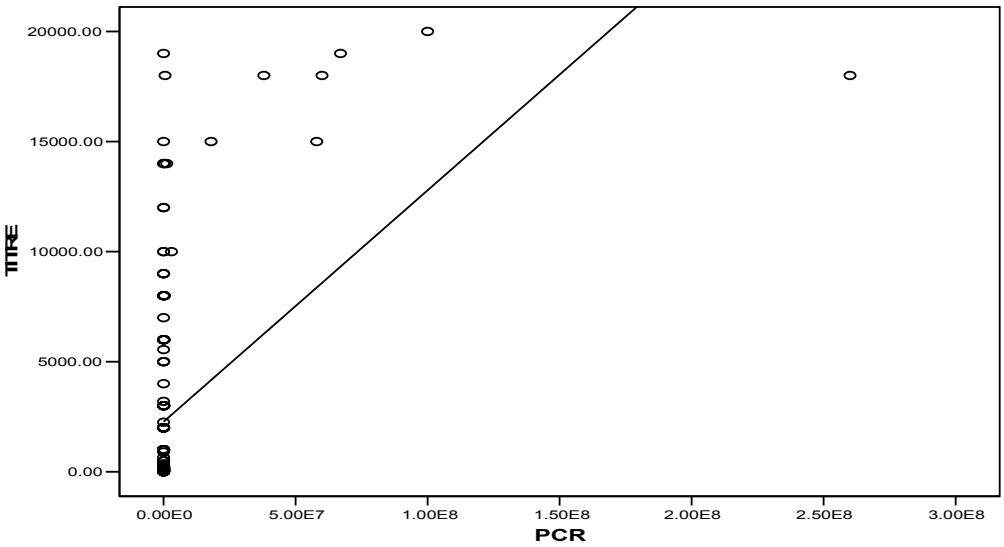

Fig. (1) Pearson correlation between HBV DNA level & HBsAg titre in all studied patients.

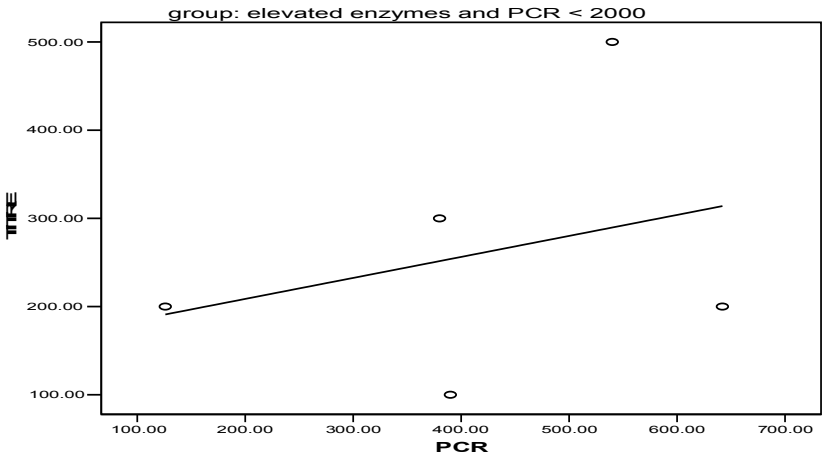

Fig. (2) group A: included 5 patients with elevated serum ALT and HBV DNA <2000 IU/ml

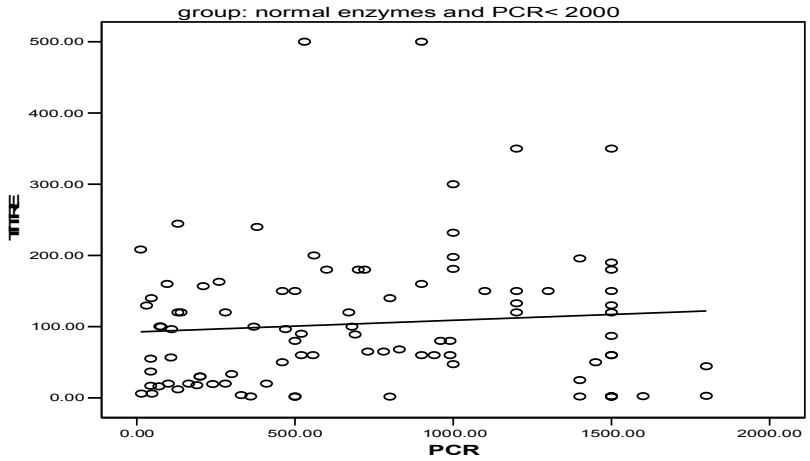

Fig. (3) group B: included 95 patients with serum ALT not exceeding the upper limit of normal (35 IU/ml) and HBV DNA <2000 IU/ml.

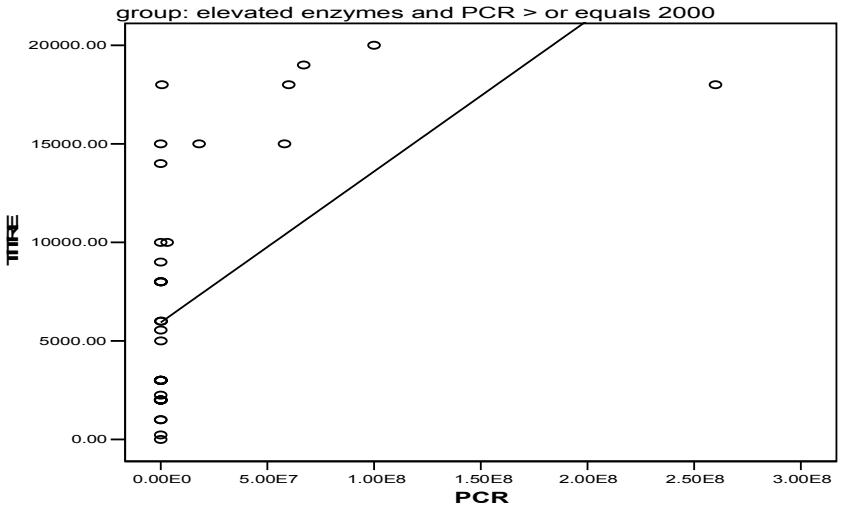

Fig. (4) group (C): included 39 patients with elevated serum ALT and HBV DNA ≥2000 IU/ml

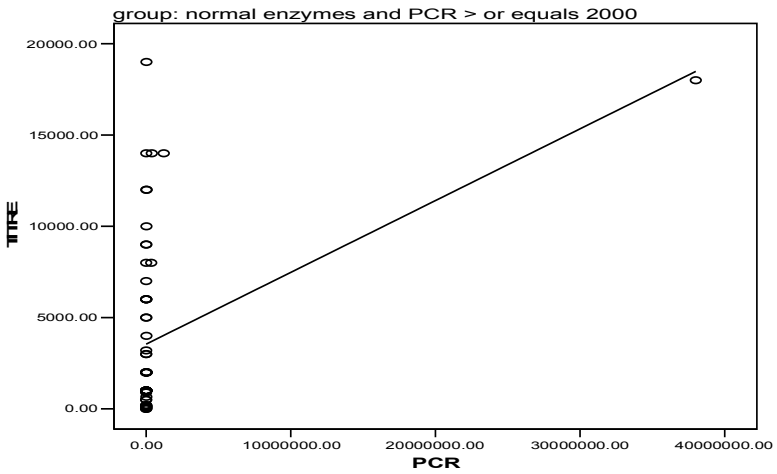

Fig. (5) group (D): included 61 patients with serum ALT not exceeding the upper limit of normal (35 IU/ml) and HBV DNA ≥2000 IU/ml.

As shown in tables (5 & 6) and (fig. 6) a cut-off HBsAg titer of **425 IU/ml** could predict serum HBV DNA levels ≥ 2000 IU/ml with 85% sensitivity, 97% specificity, 91%Accuracy, 97% PPV and 87% NPV.

Table (5) Validity of HBsAg titre in detecting cases with elevated HBV DNA level (≥ 2000 IU/ml).

Parameter	%
Cut off	425
Sensitivity	85
Specificity	97
Accuracy	91
PPV	97
NPV	87

Table (6) Relation between HBV DNA level & HBsAg titre at a cut 0ff point = 425 (IU/ml).

HBsAg Titre (IU/ml)	HBV DNA level (IU/ml)				Total
	≥ 2000		< 2000		
	No	%	No	%	
≥ 425	85	85	3	3	88
< 425	15	15	97	97	112
Total	100	100	100	100	200

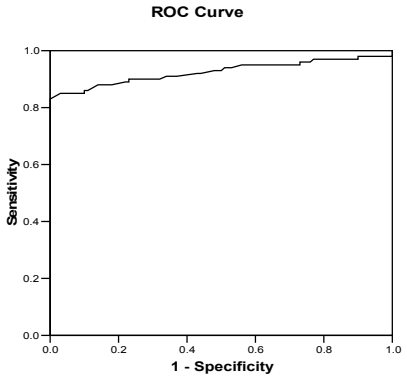

Fig. (6) The ROC (receiver operating characteristic) curve was used to detect the cutoff value with highest sensitivity and specificity.

4. Discussion

HBsAg was the first hepatitis B virus (HBV) protein to be discovered. It was discovered about 40 years ago and called the 'Australia antigen'. HBsAg is the hallmark of overt HBV infection, and the detection of HBsAg in serum is the fundamental diagnostic marker of HBV infection **(Rotman *et al.*, 2009).**

In chronic hepatitis B, HBsAg seroconversion is considered the preferred end point because it is believed to represent successful immunologic control of HBV. Multiple studies have demonstrated that HBsAg seroconversion is associated with a favorable prognosis. Spontaneous HBsAg loss is rare, however, with a 1–2% annual rate. Although HBsAg seroconversion is the closest end point to a ''clinical cure,'' it is important to note that intrahepatic cccDNA

can still be detected at low levels and, as such, represents a reservoir for potential disease reactivation **(Chen *et al.*, 2004).**

HBV DNA quantification is currently the standard in selecting patients who are candidates for therapy, monitoring response to therapy, and detecting the emergence of drug resistance. Currently, real-time PCR using the TaqMan probe is the most sensitive quantitative HBV DNA assay and is able to detect as few as 10 copies/mL **(Manesis *et al.*, 2008).**

Quantification of HBsAg was introduced more than 20 years ago, but recently new quantitative HBsAg assays have been developed that fulfill the prerequisites of a biomarker: reproducibility, automated quantification with high-throughput platforms, relatively low cost (<10% of the cost of a serum HBV DNA assay) and standardization (IU/ml) **(Nguyen *et al.*, 2009).** Interest in quantitative HBsAg serology as a clinical biomarker has been based upon studies which showed a positive association with intrahepatic cccDNA levels **(Rodella *et al.*, 2006)** and HBV DNA **(Chen *et al.*, 2004).** However, the utility of HBsAg titres as a reliable surrogate for both cccDNA and HBV DNA remains unclear **(Manesis *et al.*, 2008).**

This study aimed to evaluate the correlation between serum levels of HBsAg and HBV DNA in chronic Hepatitis B infected patients. This study involved 200 patients with chronic hepatitis B. Most of them were found to be HBeAg negative 99%, and only 1% was HBeAg positive. This finding goes in line with **(El-Zayadi *et al.*, 2009)** who reported that HBeAg-negative variant accounts for more than 80 % of CHB in Egypt. This is due to replication of naturally occurring HBV variants with nucleotide substitutions in the pre core and/or basic core promoter regions of the genome and represents a later phase of chronic HBV infection **(Rizzetto and Ciancio, 2008).**

In this study serum HBsAg levels varied significantly between patients in the different groups. The lowest levels of HBsAg were evident in group (B) which included patients with serum ALT levels not exceeding the upper limit of normal and HBV DNA <2000 IU/ml {low-replicative phase (LR)}, the mean value of serum HBsAg titer in this group was found to be (104.4±98.20 IU/ml). Among other patients, the particularly high levels of HBsAg were observed in group (C) which included patients with elevated serum ALT and HBV DNA ≥2000 IU/ml, the mean value of serum HBsAg titer in this group was found to be (7052.04±6128.8 IU/ml).This is in agreement with Nguyen and his colleagues who found that the median HBsAg titres were (2.86 $\log_{10}$ IU/ml) in patients described as being in low replicative phase, and (3.35 $\log_{10}$ IU/ml) in patients with elevated serum ALT and HBV DNA ≥2000 IU/ml (HBeAg negative hepatitis phase, ENH) **(Nguyen *et al.*, 2010).** Also Jaroszewicz and his co-workers concluded that among patient with HBeAg negative, HBsAg titre was lower in LR phase the mean value was (1230 IU/ml), and higher in ENH phase the mean value was (7545 IU/ml) **(Jaroszewicz *et al.*, 2010).**

The current study observed significant positive correlation between HBsAg titre and HBV DNA among all studied patients (R = 0.48, p< 0.001). However, when the correlation studied in different groups there was significant positive correlation among patients with viral load (≥ 2000 IU/ml with or without elevated liver enzyme) group (C) and (D) (R = 0.58, p< 0.001) (R = 0.39, p< 0.001). While in patients with viral load (< 2000 IU/ml with or without elevated liver enzyme) group (A) and (B) there was no significant correlation (R = 0.31, p> 0.05) (R = 0.09, p> 0.05).On the same page, Thompson and colleagues concluded that the HBsAg-titer and viral load were correlated in the overall HBeAg-negative cohort (R = 0.28, P = 0.012). Among HBeAg-negative patients in the inactive phase (<2,000 IU/mL), HBsAg titer did not correlate with HBV DNA (R = 0.15, P = 0.53) **(Thompson *et al.*, 2010).** In similar vein Jaroszewicz and colleagues, reported that in all studied patients with chronic HBV-infection, serum HBsAg was correlated with HBV-DNA levels (R = 0.75, p < 0.001); however this strong association was no longer observed in consecutive phases of HBV-infection, in Low-replicative phase (HBeAg negative, HBV DNA <2000 IU/ml, normal serum ALT) (R = 0.22, p =0.07), HBeAg negative hepatitis (HBeAg negative, HBV DNA >2000 IU/ml, serum ALT >2xULN) (R = 0.26, p =0.05), Immune tolerance phase (HBeAg positive, high viral load, serum ALT <2xULN) (R = 0.34, p =0.07), and finally in Immune clearance phase (HBeAg positive, elevated viral load, serum ALT >2xULN) (R = 0.11, p =0.48) **(Jaroszewicz *et al.*, 2010).**

Furthermore Nguyen and colleagues reported that there was a modest correlation observed in the Immune clearance phase (R = 0.77, p = 0.0001), but poor correlation between serum HBsAg and HBV DNA in either the Immune tolerance phase (R = 0.30, p = 0.09), the Low-replicative phase (R = 0.22, p = 0.11) or HBeAg negative hepatitis (R = 0.29, p = 0.008) **(Nguyen *et al.*, 2010).** In addition Brunetto and associates in their study on HBsAg as a guide to sustained response to peginterferon alfa-2a in HBeAg-negative chronic hepatitis B found that pretreatment HBsAg showed a positive correlation with baseline HBV DNA level (R = 0.38), also they found that significant on-treatment decline in HBsAg was observed during treatment with peginterferon alfa-2a alone or combined with lamivudine but not during treatment with lamivudine alone **(Brunetto *et al.*,** The findings of the this study are contrary to the results of Ozdil and colleagues who reported a significant

negative correlation between viral load and HBsAg levels in the non-cirrhotic chronically HBV-infected patients ($p<0.01$) **(Ozdil *et al.*, 2009).**

The current study has demonstrated that cut-off HBsAg titers of 425 IU/ml could predict serum HBV DNA levels ≥ 2000 IU/ml with 85% sensitivity and 97% specificity. On the same page a recent study in Taiwan suggested that cut-off HBsAg titers of 314 and 768 IU/ml could predict serum HBV DNA levels of 2000 and 20,000 IU/ml, respectively (~80% sensitivity and 50–60% specificity) **(Su *et al.*, 2008).**

Since HBV-infection is a highly dynamic disease, an appropriate follow-up is of highest importance especially in low replicative HBeAg negative patients because of the possible fluctuating profile. A limitation of this study is being across-sectional design; it would have been useful to follow patients longitudinally through different phases of infection. However, such longitudinal follow- up is difficult given that patients can remain in either the immune tolerant or non/low-replicative phases for years. Also patients in the immune-clearance and HBeAg negative hepatitis phases are potential treatment candidates.

In conclusion

This study revealed a significant positive correlation between serum HBsAg titre and HBV DNA in all studied patients ($R = 0.48$, $p< 0.001$). Moreover, the correlation remains positive in patients with viral load ≥ 2000 IU/ml ($p< 0.001$) and became non-significant in those having viremia <2000 IU/ml ($p> 0.05$). More importantly cut-off level for serum HBsAg titers of 425 IU/ml could predict serum HBV DNA levels ≥ 2000 IU/ml with 85% sensitivity, 97% specificity, 91% Accuracy, 97% PPV and 87% NPV.

In the future, baseline HBsAg quantification may help refine future treatment algorithms for both immune-modulator therapy and oral nucleos(t)ide analogue therapy. Larger prospective studies are now required to evaluate longitudinal changes in serum HBsAg, and evaluating their significance in predicting the ultimate goal of antiviral therapy. Future studies may also evaluate whether the achievement of serum HBsAg levels similar to those typically seen in the low replicative phase could be a therapeutic end point on the way to potential HBsAg seroclearance.

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