

THE CLINICAL SIGNIFICANCE OF QUANTITATIVE HBSAG IN PATIENTS WITH HBEAG NEGATIVE CHRONIC HEPATITIS B

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ISSN 0350-364X

DOI: 10.5457/517

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ABSTRACT

Background: The quantification of HBsAg provides different and complementary information that helps in determination of the different phases of chronic hepatitis B viral infection, evaluation and follow-up of liver disease progression as well as in treatment individualization.

Aim: To evaluate the clinical significance of quantitative HBsAg (qHBsAg) in patients with HBeAg negative chronic hepatitis (CHB) and its correlation with the serum levels of alanine aminotransferase (ALT), quantitative HBV DNA and liver fibrosis.

Subjects and Methods: The study included 53 treatment naïve patients with HBeAg negative chronic hepatitis B. All patients underwent complete laboratory and serology testing, quantification of HBV DNA and HBs antigen. The liver stiffness was measured with elastography. Patients' demographic characteristics, viral and biochemical markers were recorded at one point of time.

Results: Correlation analysis between the qHBsAg and ALT showed a significant, positive correlation between the parameters for $R=0.42$ and $p<0.05$; there was statistically non-significant positive correlation for $R=0.25$ and $p>0.05$ between qHBsAg and HBV DNA. There was a positive correlation between qHBsAg and liver fibrosis for $R=0.08$ and $p>0.05$. The serum levels of HBsAg had greater impact on the serum levels of ALT compared to that of HBV DNA for $R=0.15$ and $p>0.05$.

Conclusion: Patients with higher ALT values and higher liver fibrosis score have higher qHBsAg; qHBsAg can reflect the serum HBV DNA levels.

Key words: hepatitis B virus, HBsAg, HBeAg, quantitative HBsAg, quantitative HBV DNA

INTRODUCTION

Chronic hepatitis B virus (CHB) infection affects 248 to 257 million people worldwide and is associated with 1 million mortalities every year [1]. While the persistence of HBsAg for more than 6 months defines chronic HBV state, its clearance from serum is considered the nearest-to-cure outcome of HBV infection. The process of seroconversion from HBeAg to anti-HBe is usually associated with remission of liver disease, but certain proportion of HBe negative, anti-HBe-positive patients with precore/core promoter mutations continue to have viral replication with ongoing progression of the diseases [2]. This HBeAg-negative phase of HBV infection is heterogeneous, and encompasses a wide spectrum ranging from non-progressive inactive infection to active chronic hepatitis B infection, with high risk of liver cirrhosis

and hepatocellular carcinoma (HCC)[2-4]. The HBeAg-negative chronic hepatitis B is characterized by fluctuating levels of hepatitis B virus deoxyribonucleic acid (HBV DNA) and aminotransferases, with temporary remissions [2-5]. Usually, quantification of HBV DNA is widely used as an indicator of viral replication and a mandatory virology marker for a timely and appropriate initiation of antiviral therapy as well as for monitoring the antiviral response, but it is an expensive test and not always readily available [5-7]. As it is widely known, serum hepatitis B surface antigen (HBsAg) is a reliable biomarker of apparent hepatitis B virus infection. It is secreted as a subviral particles by infected cells in a larger extent than the infectious virions [2,8-10]. It has been proposed that the serum concentration of HBV surface antigen (HBsAg) reflects the amount of covalently closed circular DNA (cccDNA) in the liver, where it acts as template for

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the transcription of viral genes [9-11]. Namely, HBsAg is derived for HBV DNA and it is integrated in the host cell genome, either by the host cells' enzymes or by the process of translation via transcriptionally active cccDNA. It has been an established fact that cccDNA represent a minichromosome (endosome) and acts as a viral matrix which serves for continuing renewal of the amount of HBsAg. This process represents a quintessential factor for sustainable chronic hepatitis B viral infection. It is necessary to potentiate that cccDNA continuously synthesizes HBsAg regardless of the fact whether there is an active replication of the hepatitis B virus. Thus, many studies suggest that qHBsAg represent more reliable marker for chronic HBV infection than HBV DNA itself [12-13].

Quantitative HBsAg is a surrogate marker which reflects the quantity of the transcriptional activity of cccDNA in hepatocytes. The quantification of HBsAg provides different, but complementary information that can help clinicians in determination of the different phases of chronic hepatitis B viral infection, follow-up and evaluation of liver disease progression as well as in treatment individualization [10,13-15]. Lately, quantification of the serum levels of HBsAg has been standardized which allows for easier and more routine administration of this test in every day practice [16].

The aim of this study was to evaluate the clinical significance of quantitative HBsAg and its correlation with the serum levels of alanine aminotransferase (ALT), quantitative HBV DNA and liver fibrosis in our cohort of patients with HBeAg negative chronic hepatitis B.

SUBJECTS AND METHODS

The study included 53 treatment naïve patients with serologically confirmed HBeAg negative anti-HBe-positive chronic hepatitis B, followed-up at the Clinic for infectious diseases and febrile conditions in Skopje, Republic of North Macedonia. A prospective non-randomized study was conducted on patients who were HBsAg-positive for at least six months, HBeAg-negative, anti-HBe-positive and had HBV DNA levels above 2000 IU/ml. Patients under the age of 18 years, all patients who tested positive for hepatitis A, hepatitis C and HIV were not included in the study. Patients with previous or current exposure to antiviral hepatitis B treatment, alcoholic and autoimmune liver diseases, incomplete serum profile and a follow-up period of less than six months, patients with hepatocellular carcinoma (HCC), decompensated liver disease and pregnant patients were not included in the study. All patients underwent evaluation of liver fibrosis with Fibroscan®. Patients' demographic characteristics, viral and biochemical markers were recorded at one point of time. Complete serology profile (HBsAg, anti-HBsAg, antibody (anti-HBs), hepatitis B e antigen (HBeAg) and antibodies (anti-HBe)) was performed with ELISA (enzyme linked immune assay) tests.

The upper normal limit of serum transaminase both for alanine aminotransferase (ALT) and aspartate aminotransferase (ALT) was 40 U/L, according to the traditional cut-off values. Quantification of the serum level of HBV DNA was performed in-house, by real time polymerase chain reaction (RT-PCR) on COBAS AmpliPrep COBAS TaqMan HBV test and Abbott m 2000 sp / m 2000 rt with a lower detection limit of 10 IU/mL. The serum level of HBsAg (qHBsAg) was quantified with Architect HBsAg assay (Abbott Laboratories) in-house, according to the manufacturers' protocol. The detection level of HBsAg varies from 0.05 to 250 IU/ml. HBsAg levels above 250 IU/ml were further diluted in a ratio of 1:500. Transient elastography (TE) was performed in order to measure the speed of the shear wave which is directly associated with the liver stiffness. TE measures the liver stiffness (LS) which by itself is associated with the degree of fibrosis¹⁷.

The value of ALT and AST were expressed in units international per litre (UI/L) and those of qHBsAg and HBV DNA in international units per millilitre (IU/ml). The study was approved by the Ethics Committee of the Medical Faculty in Skopje.

STATISTICAL ANALYSIS

All data were processed using a statistical computer program Statistica 7.1 for Windows and SPSS Statistics 17.0. Series with attributive variables were analysed with percentages of structure. For numerical variables descriptive statistics ((Mean; Std.Deviation; ± 95 , 00%CI; Minimum; Maximum) was used, where frequencies and percentages were used for description of the categorical variables. Distribution of the data was tested with Kolmogorov-Smirnov tests; Lilliefors test; Shapiro-Wilks test (p). Spearman Rank Order (R/p); was used to test the relationship between qHBsAg and HBV DNA, qHBsAg and ALT, qHBsAg and liver fibrosis. Multiple Regression (R/p) was used to determine the correlation between ALT, qHBsAg and HBV DNA. For all analyses P values of <0.05 were considered significant.

RESULTS

From 53 patients 39 (73.58%) were male and 14 (26.42%) were female. The median age of the patients varied in the interval od 43.91 \pm 11.72 years; ± 95.00 CI, the minimal age was 22 years and the maximum age of the patients was 74 years. The median value of alanine aminotransferase was 50.45 \pm 38.53 UI/L and of aspartate aminotransferase was 34.74 \pm 19.46 UI/L. The serum value of qHBsAg varied in the interval of 12556, 06 \pm 27188.85 IU/ml and of HBV DNA in the interval od 7237363.98 \pm 46513427.91 IU/ml (Table 1). Only six patients (11.32%) had qHBsAg <1000 IU/ml, and 47 (88.68%) had qHBsAg >1000 IU/ml (Figure 1).

Table 1. The demographic, biochemical and virological parameters of the cohort

Parameter	N	Average	Confidence -95.00%	Confidence +95.00%	Minimum	Maximum	Std.dev.
Age	53	43.91	40.67	47.14	22	74	11.72
ALT U/L	53	50.45	39.83	61.07	10	173	38.53
AST U/L	53	34.74	29.37	40.10	12	101	19.46
qHBsAg IU/ml	53	12556.06	5062	20050	12.95	155311.00	27188.85
HBV DNA IU/ml	53	7237363.98	-5583325	20058053	2061	338999252	46513427.91

Abbreviations: ALT- alanine aminotransferase; AST-aspartate aminotransferase, qHBsAg- quantitative HBsAg; HBV DNA- hepatitis B virus deoxyribonucleic acid

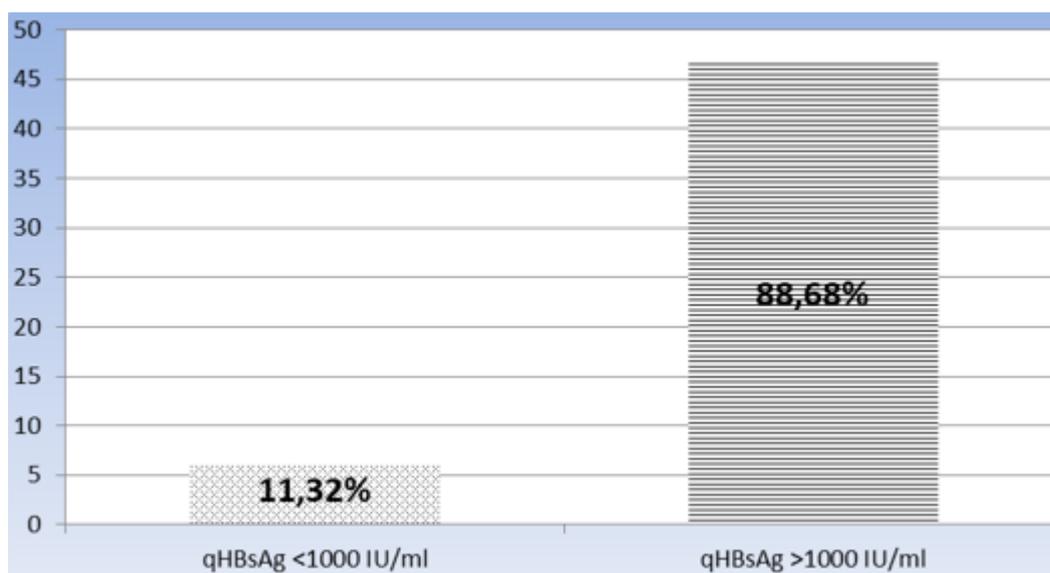


Figure 1. Distribution of quantitative HBsAg (qHBsAg) in the cohort

The results of Fibroscan® showed that 30 patients (56.60%) had fibrosis Fo/F1, 6 (11.32) had fibrosis F2, 6 (11.32%) had fibrosis F2/F3, 6 (11.32%) had fibrosis F3/F4, 3 (5.66%) had fibrosis F4 and 2 patients (3.77%) had fibrosis F3 (Table 2).

Table 2. Liver fibrosis measured by transient elastography

Fibroscan®	Number	Cumulative No.	%	Cumulative %
f0/f1	30	30	56,60	56,60
f2/f3	6	36	11,32	67,92
f4	3	39	5,66	73,58
f2	6	45	11,32	84,91
f3/f4	6	51	11,32	96,23
f3	2	53	3,77	100,00
Missing	0	53	0,00	100,00

Correlation analysis between the serum levels of HBsAg and alanine aminotransferase indicated that there was statistically significant positive correlation between the parameters for $R=0.42$ and $p<0.05$. Namely, each single increase of the value of quantitative HBsAg was followed with a significant increase of the serum value of alanine aminotransferase (Figure 2).

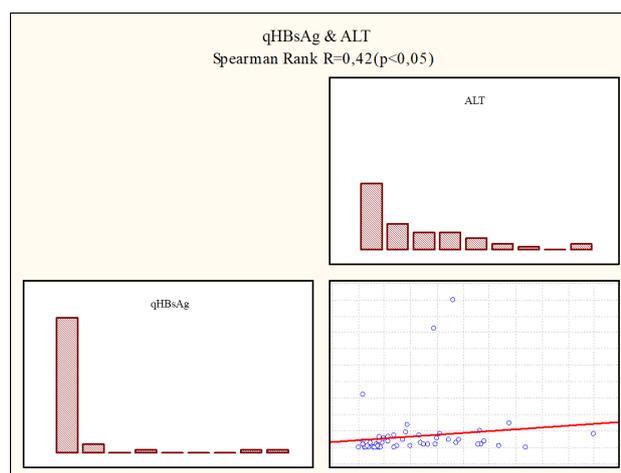


Figure 2. Correlation between qHBsAg (quantitative HBsAg) and ALT (alanine aminotransferase)

A correlation analysis between qHBsAg and HBV DNA showed that there was statistically non-significant positive correlation for $R=0.25$ and $p>0.05$. Namely, each single increase of qHBsAg was followed with non-significant increase of the serum value of HBV DNA (Figure 3.)

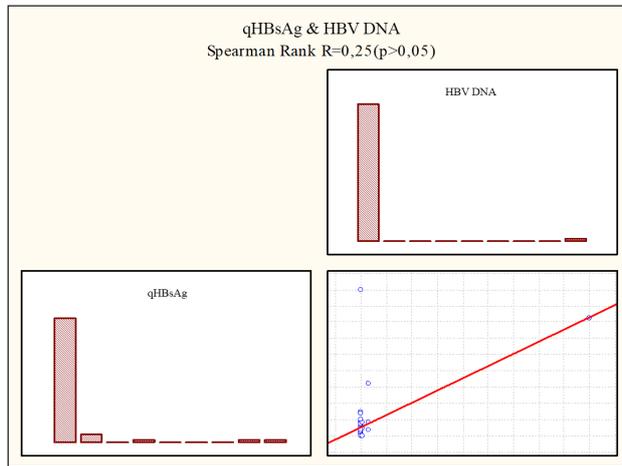


Figure 3. Correlation between the serum levels of quantitative HBsAg and HBV DNA (hepatitis B virus deoxyribonucleic acid)

The serum level of HBsAg is in positive correlation with the degree of liver fibrosis, measured with transient elastography, but statistically non-significant. Each increase of the qHBsAg is followed with the increase in the FibroScan score, for $R=0.08$ and $p>0.05$ as shown on Figure 4.

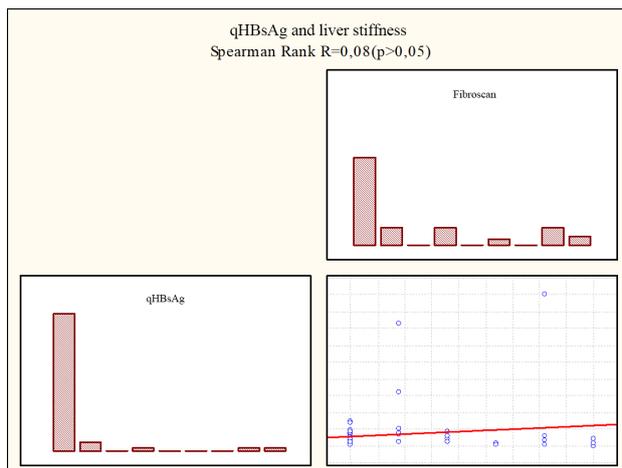


Figure 4. Correlation between the serum level of HBsAg and liver fibrosis.

In order to determine the interactions between the qHBsAg and HBV DNA on the serum levels of alanine aminotransferase, a multiple regression analysis for performed. The multiple regression analysis showed that the serum levels of HBsAg had greater impact on the serum levels of ALT compared to that of HBV DNA, and this influence was positive, although non-significant for $R=0.15$ and $p>0.05$. Namely, each increase of qHBsAg was followed with an increase of the serum level of ALT (Table 3).

Table 3. Multiple regression analysis between ALT and qHBsAg and HBV DNA

Dependent Variable: ALT; $R= 0,15$; $F(2,50)=0,59$ and $p<0,66$

	Beta	Std.Err. of Beta	B	Std.Err. of B	t(53)
Intercept			47.64	5.93	8.03
qHBsAg	0.17	0.17	0.0002	0.000	0.99
HBV DNA	-0.04	0,17	-0.000	0.000	-0.22

Abbreviations:

ALT- alanine aminotransferase;

qHBsAg- quantitative HBsAg;

HBV DNA –hepatitis B virus deoxyribonucleic acid.

DISCUSSION

It has been proposed that the quantitative HBsAg can be used to monitor the activity of HBV infection. It is observed that the reduction of serum HBsAg concentration is associated with the reduction of cccDNA in the liver [11], which might represent improved immune control over viral replication [18]. It can be stated that the level of HBsAg is higher proportionally to the higher levels of cccDNA in CHB patients and that a 2 logio drop of qHBsAg to below 100 IU/ml is associated with a high likelihood of HBsAg clearance. Moreover combined quantification of HBsAg (<1000 IU/ml) and HBV DNA (≤ 2000 IU/ml) at one point of time can determine the phases of chronic HBV infection with a 94.3% diagnostic accuracy, and 87,9 % PPV in the identification of inactive carrier versus HBeAg negative CHB [10,19]. By using the same thresholds in HBeAg-negative, the diagnostic accuracy and the PPV for genotype B and C infected carriers was 78% and 83% respectively [20]. Ramachandran et al. [21], divided 131 non-treated hepatitis B patients into two groups as HBeAg positive and negative, and divided the “e” positive patients as immune tolerance and immuno-clearance as well as categorized the “e” negative patients as low replication phase and “e” negative CHB. HBV DNA and qHBsAg levels were found to be higher in HBeAg positive patients and a statistically significant correlation was found between these two parameters. In our cohort patients the mean value of qHBsAg was 12556.06 IU/ml, and only in 6 patients the serum values of qHBsAg was less than 1000 IU/L whereas in all patients HBV DNA was ≥ 20000 IU/ml, showing that in these patients there was an active hepatitis.

When we evaluated the correlation between the serum levels of HBsAg and alanine aminotransferase it was shown that there was a statistically significant positive correlation between them and that each single increase of the value of quantitative HBsAg was followed with a significant increase of the serum value of alanine aminotransferase, meaning that patients with higher ALT values had higher qHBsAg. Papatheodoridis et al. [22], indicated in their study that ALT-AST activity and serum HBV DNA levels were very significant in

diagnosis and treatment of HBeAg-negative chronic HBV infection. When patients were divided into three groups (Group 1: 0-1999, Group 2: 2000-19999, Group 3: ≥ 20000), and they were compared for ALT and HBsAg levels, there were significant differences in ALT levels between Groups 1 and 3 ($p=0.002$), and Groups 2 and 3 ($p=0.025$). For HBsAg levels, there were again significant differences between Groups 1 and 3 ($p=0.001$), and Groups 2 and 3 ($p=0.005$). Gunal et al.[23] revealed a significant correlation between the serum levels of ALT and qHBsAg levels.

When the correlation between the serum levels of HBsAg and HBV DNA was investigated in our cohort of HBeAg negative chronic hepatitis B patients, it showed that there is a positive correlation between the investigated parameters. Namely, with each single increase of the serum level of HBsAg there was an increase of the serum value of HBV DNA, but non-significant. Similar to results found in our study, Zhu et al.[24], investigated 124 patients with chronic hepatitis B and found a positive correlation between serum HBsAg and HBV DNA levels, and the serum value of HBsAg was significantly higher in patients with serum levels of HBV DNA $>1 \times 10^3$ cp/ml compared to patients with serum levels of HBV DNA $< 1 \times 10^3$ cp/ml ($t=5.983$, $p=0.000 < 0.05$). The study of Ganji et al.[25] which also investigated the correlation between HBsAg quantitative assay results and HBV DNA levels in chronic HBV patients, found a significant relationship in HBeAg positive patients, but no meaningful relationship was found in "e" negative patients. Yet, in another study, Alghamdi et al.[26] demonstrated a significant relationship between these markers in HBeAg negative patients and stated that they could be considered as predictor of diseases outcome if they are used together.

Most of the studies found in the medical literature considering the correlation between qHBsAg levels and liver histopathology, have shown that lower HBsAg level was found to reflect the status of advanced liver fibrosis, especially in HBeAg positive chronic hepatitis B subjects [27-29]. A significant correlation between serum HBsAg and fibrosis was not reported in HBeAg-negative patients [27], however several studies showed a trend for lower HBsAg levels in cirrhotics which was explained with the possibility of existing viral quasispecies with prevalent preS/S variants (selected during the long lasting immuno-elimination phase. Larsson et al.[30] showed that in patients with HBeAg negative hepatitis the serum level of HBsAg $< 3 \log_{10}$ IU/ml favors minimal liver injury, with a predictive value of 92 %, and when combined with serum HBV DNA levels $< 4.0 \log_{10}$ cp/ml the predictive value was 96%. Serum level of HBsAg above $3.5 \log_{10}$ IU/ml, identifies patients with more extensive liver injury with a predictive value of 16% and in combination with HBV DNA $> 5.0 \log_{10}$ cp/ml the positive predictive value was 33%. The authors conclude that the serum levels of HBsAg reflect the clinical stadium as well as the degree of liver injury. Our study also showed that

there is a positive correlation between the qHBsAg and liver fibrosis, indicating that in patients with higher serum HBsAg levels more advanced liver disease is to be expected.

The multiple regression analysis between ALT, HBsAg and HBV DNA levels in our patients showed that the increase of qHBsAg was followed with an increase of the serum level of ALT, while the increase of the level of HBV DNA was followed with a non-significant decrease of ALT level. In this multiple regression analysis the impact of quantitative HBsAg on the level of ALT is more profound than of HBV DNA. From this analysis is to be expected that the increase of qHBsAg will be associated with a rise of serum levels of ALT, i.e. hepatic inflammation, while the increase of HBV DNA (viral replication) will be associated with a decrease in the serum ALT values. The latter might be explained that in cirrhotic patients with an advanced liver diseases, due to the decrease of hepatic mass there might be lower serum values of ALT, or an increase of AST values. The study of Günal et al.[23] showed a positive but statistically weak correlation between serum levels of HBsAg, ALT and HBV DNA. The findings in our study is discordant to the findings of Mahdavi et al.[31], where there was no significant correlation between quantitative HBsAg and HBV DNA serum levels and HBsAg and ALT levels.

CONCLUSION

In conclusion, quantification of HBsAg serum levels represents a useful tool which can help in the management of patients with chronic hepatitis B. Serum levels of HBsAg are higher in patients with higher ALT values and liver fibrosis, and HBsAg can reflect the serum HBV DNA levels. It is necessary, at the same time to monitor biochemical and virology factors, as well as the clinical presentation of the patient. The combined use of these factors can help and guide the clinician in timely and proper selection of patients in need for prompt antiviral therapy. The drawback of our study was that the sample size was maybe too small and the lack of tests to perform control qHBsAg in the follow up of patients. Further studies involving more patients and regular monitoring of these parameters will improve the evaluation of the patients with HBeAg negative CHB as well as determine the applicability of these tests.

SAŽETAK

Uvod: Kvantifikacija HBs antigena omogućava različitu, ali komplimentarnu informaciju koja služi u procesu određivanja različitih faza kod pacijenata sa hroničnim hepatitisom B, evaluaciju i praćenje progresije hepatalne bolesti, kako i individualizaciju antivirusnog tretmana.

Cilj: Evaluacija kliničkog značaja kvantitativnog HBsAg (qHBsAg) kod pacijenata sa HBeAg-negativnim hroničnim hepatitisom B (CHB) i njegova korelacija sa serumskim nivoima alanin aminotransferaze (ALT), kvantitativne HBV DNA i hepatalne fibroze.

Ispitanici i metode: Studija je obuhvatila 53 tretmana naivnih pacijenata sa HBeAg-negativnim hroničnim hepatitisom B. Kod svih pacijenata je bila urađena kompletna laboratorija, serologija, kvantifikacija HBV DNA i HBs antigena. Hepatalna krutost je bila određena preko elastografije. Demografske, virusološke i biohemiske karakteristike svih pacijenata su bili određeni u jednoj vremenskoj tački.

Rezultati: Korelacijska analiza između qHBsAg i ALT ukazala je da postoji statistički signifikantna pozitivna korelacija između parametara za $R=0.42$ i $p<0.05$; postoji statistički nesignifikantna korelacija za $R=0.25$ i $p>0.05$ između qHBsAg i HBV DNA. Postoji pozitivna korelacija za qHBsAg i hepatalne fibroze za $R=0.08$ i $p>0.05$. Serumski nivo HBsAg ima veći uticaj od serumskog nivoa ALT u usporedbi sa HBV DNA za $R=0.15$ i $p>0.05$.

Zaključak: Veći qHBsAg je za očekivati kod pacijenata sa višim vrednostima ALT i naprednom fibrozom; qHBsAg može reflektirati serumске nivoe HBV DNA.

Ključne reči: hepatitis B virus, HBsAg, HBeAg, kvantitativan HBsAg, kvantitativna HBV DNA

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