Association of liver fibrosis based on transient elastography and quantitative HBsAg levels in HBeAg-positive chronic hepatitis B patients

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Research Article

Association of Liver Fibrosis based on Transient Elastography and Quantitative HBsAg Levels in HBeAg-Positive Chronic Hepatitis B Patients

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ABSTRACT

Background: The data of lower quantitative hepatitis B surface antigen (HBsAg) level were associated with more severe liver fibrosis in HBeAg-positive chronic hepatitis B. This study aimed to analyze correlation between liver fibrosis based on transient elastography and quantitative HBsAg levels in HBeAg-positive chronic hepatitis B patients.

Methods: We conducted a cross-sectional study of 32 treatment-naive HBeAg-positive chronic hepatitis B patients. Liver fibrosis was measured using transient elastography, and quantitative HBsAg level was measured using automated Chemiluminescence Enzyme Immunoassay.

Results: Quantitative HBsAg levels were highest in the F1 group, followed by F2, F3 and lowest in the F4 group. A strong negative correlation between transient elastography and quantitative HBsAg level was revealed in HBeAg-positive chronic hepatitis B patients (r=-0.706, p=0.000). Quantitative HBsAg levels were found to be higher in the immune-tolerant phase which liver fibrosis was minimal compared to the immune clearance phase which liver fibrosis was more severe. Patients with more severe liver fibrosis showed lower quantitative HBsAg levels.

Conclusion: We found a negative correlation between liver fibrosis based on transient elastography and quantitative HBsAg levels in HBeAg-positive chronic hepatitis B.

Keywords: Liver fibrosis, transient elastography, quantitative HBsAg, chronic hepatitis B

INTRODUCTION

The high incidence, natural history and chronicity of infections with the symptoms of chronic hepatitis B (CHB) tend to be severely affected as a result of not optimal treatment. Indonesia has a moderate to high hepatitis B endemicity. CHB is determined by seropositivity of hepatitis B surface antigen (HBsAg) of more than 6 months [1]. Among 2-6% of adults, 30%-60% of young children and 90% of infants (< 1 year of age) are diagnosed with CHB infections [2]. In Indonesia, the number of people with hepatitis B infection are estimated 4.0-20.3%, which prevalence of HBsAg positive in islands outside of Java is significantly higher than in Java [3, 4].

The natural history of chronic hepatitis B infection is a dynamic process which can progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma. HBeAg-positive CHB infection characterized by varying levels of ALT, HBV DNA, qHBsAg, and liver fibrosis. HBeAg-positive CHB infection is early phase and associated with more active liver inflammation and high risk for being hepatocellular carcinoma. Early detection of significant liver disease can improve patient outcomes [5, 6]. Hepatitis B is a viral infection that has the potency to become a chronic infection and causes serious complications such as liver cirrhosis and hepatocellular carcinoma [7]. Hepatitis B virus (HBV) infection persist within nuclei of infected hepatocytes as covalently closed circular DNA (cccDNA) minichromosomes which acts as a template for the transcription of viral genes. Data presented imply that a depletion of cccDNA by cell death may be clarified [8]. HBV spreads through blood, sperm fluid, or other body fluids from patients infected with HBV [9]. HBV is percutaneously spread by contact from

patients with Hepatitis B to contaminate blood or other body fluids [10].

Liver fibrosis is a condition that liver cell damage is replace with connective tissue, so it is suggested that in liver fibrosis the number of healthy liver cells decrease, nuclei of infected hepatocytes reduce, consequently cccDNA will also reduce. HBsAg is generally called a diagnosis of HBV infection, containing the virus' protein envelope. Quantitative HBsAg (qHBsAg) can reflect the concentration and transcription activity of cccDNA. Quantitative HBsAg examination was also reported to correlate with HBV DNA and cccDNA [11, 12]. Quantification HBsAg has been recognized as valuable for monitoring the natural history of chronic hepatitis and predicting treatment outcome [13].

The main pathogens that contribute to cirrhosis are liver fibrosis. Fibrosis in the early stages is also necessary to identify. Liver biopsy is a gold standard to diagnose the degree of liver fibrosis [14]. The invasive procedure and the possibility of severe complications are however limited. A variety of non-invasive methods for predicting liver fibrosis have therefore been developed. Several studies have suggested that transient elastography can be used to assess liver fibrosis, including to assess liver fibrosis in CHB infection [15]. Quantitative HBsAg level is reported to correlate with liver fibrosis and may represent liver damage [16]. Several studies have shown a negative correlation between liver fibrosis with quantitative HBsAg levels in the HBeAg-positive CHB [17–19]. Whereas another research showed high quantitative HBsAg levels indicating more severe fibrosis [20].

There were limited studies about correlation of liver fibrosis with quantitative HBsAg levels in Indonesia, so we conducted this study. In this study, it is expected that quantitative HBsAg examination can be used as a consideration for examining liver fibrosis, especially by using transient elastography, that might be useful for determining treatment strategies.

MATERIALS AND METHODS

This cross-sectional study included eligible consecutive patients with HBsAg positive for at least 6 months conducted in tertiary hospital of Dr. Soetomo General Hospital, Surabaya, Indonesia from August 2019 to November 2019. The inclusion criteria were: (i) age 19-59 years; (ii) HBeAg-positive. The exclusion criteria were: (i) treatment with antiviral therapy, (ii) infection with hepatitis C, HIV (iii) Non Alcoholic Fatty Liver Disease/NAFLD, (iv) alcoholic, (v) autoimmune hepatititis, (vi) hepatocellular carcinoma, (vii) decompensated liver cirrhosis, (viii) diabetes mellitus, (ix) corticosteroid/immunosupresant agent. The study was approved by the local ethics committees in Dr. Soetomo General Hospital, Surabaya. All patients provided written concent to this study.

Liver fibrosis measurements were using transient elastography by fibroscan (Echosens, Paris, France), the results in kilopascal (kPa). Classification of fibrosis was based on: F1 (5-8.0 kPa); F2 (8.1-10.9 kPa); F3 (11-18.1 kPa) and F4 (≥18.2 kPa). Quantitative HBsAg levels were measured using automated Chemiluminescence Enzyme Immunoassay (Sysmex, Japan) with a diagnostic range of 0.03 – 2500 IU/mL.

All data were analyzed using Statistical Package for the Social Sciences version 23 (SPSS version 23). Patients characteristics are presented as mean with standard deviation or median with minimum and maximum range for continuous variables. The number of subjects for categorical data are presented as percentage. Spearman's correlations were used to evaluate the correlation between liver fibrosis and qHBsAg levels. The p-values were two-tailed, and $p<0.05$ was considered statistically significant.

RESULTS

Patients' Characteristics

The baseline characteristics are summarized in Table 1. The mean age of 32 patients (18 males, 14 females) was 32±10.812 years. Median ALT was 50.5 IU/L (range 20-210 IU/L).

Table 1: Patients' characteristics

Characteristics	Subjects (n=32)			
	n (%)	Mean±SD	Median	min-max
Age (years)		32±10.812	28.5	19-59
Sex				
Male	18 (56.3)			
Female	14 (43.8)			
AST (IU/L)		40.31±26.079	33	14-143
ALT (IU/L)		67.63±46.514	50.5	20-210
Hb (g/dL)		14.431±1.801	14.4	9.1-17.1

WBC (/uL)		7162.19±1132.8	6945	4650-10100
PLT (10^3/uL)		307.46±79.471	255.5	142-421
Albumin (g/dL)		4.384±0.335	4.2	3.6-5
BUN (mg/dL)		10.72±4.567	10	6-26
SK (mg/dL)		0.836±0.132	0.8	0.6-1.2

Table 2 shows that the median fibrosis value using transient elastography is 7.05 kPa (range 5.1-33.4 kPa). Twenty one patients (65.6%) were classified as F1, five patients (15.6%) as F2, two patients (6.3%) as F3, and four patients (12.5%) as F4.

Table 2: Liver fibrosis based on transient elastography

Variables	Subjects (n=32)				
	n (%)	Mean±SD	Median	min-max	P value
Transient elastography (kPa)		9.328±6.319	7.05	5.1-33.4	0.000
Liver fibrosis					
F1	21 (65.6)	6.114±1.086	5.9	5.1-7.9	
F2	5 (15.6)	9.7±0.418	9.8	9-10.1	
F3	2 (6.3)	13.25±2.05	13.25	11.8-14.7	
F4	4 (12.5)	23.775±6.491	21.15	19.4-33.4	

In this study, if qHBsAg level was >3.4 log10 IU/mL, we analyzed as 3.4 log10 IU/mL. The median qHBsAg level was 3.397 log10 IU/mL (range 2.32 log10 IU/mL – >3.4 log10 IU/mL). Quantitative HBsAg level was highest in F1 with median value of qHBsAg level 3.397 log10 IU/mL (range 3.397 log10 IU/mL – >3.4 log10 IU/mL).

Table 3: Quantitative HBsAg level in fibrosis liver

	Transient elastography		
	r	P value	
Quantitative HBsAg	-0.706	0.000	Significant

Quantitative HBsAg level was lowest in F4 with median value qHBsAg level 2.725 log10 IU/mL (range 2.32 log10 IU/mL – 2.95 log10 IU/mL), as seen in Table 3.

Correlation between liver fibrosis using transient elastography and qHBsAg level

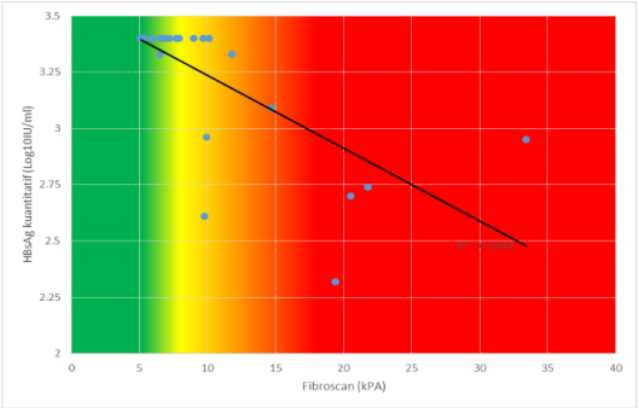

Fig.1:Scatter plot of transient elastography value and qHBsAg level

There was strong negative correlation between liver fibrosis using transient elastography and quantitative HBsAg levels (r = -0.706, p <0.000; Table 4). The results showed the more severe the fibrosis, the lower the qHBsAg level (Figure 1).

DISCUSSION

In HBeAg-positive CHB patients (r = -0,706 and p = 0,000), this analysis showed a strong, negative association between liver fibrosis dependent on transient elastography with quantitative HBsAg. The previous study reported a negative correlation between transient elastography with quantitative HBsAg levels (r = -0.576 and p <0.001) [19]. Quantitative HBsAg level describes the amount and transcription activity of cccDNA in hepatocytes. Thus, quantitative HBsAg can provide information about disease activity above an estimated viral replication [21]. Elimination of cccDNA is affected by the cell death of infected hepatocytes [8]. The more severe the fibrosis, the number of hepatocytes decreases, cccDNA decreases so that the level of quantitative HBsAg is low. The previous research presents a cross-sectional study of 103 patients showing different results, high quantitative HBsAg levels indicating more severe fibrosis [20]. This is likely because the analysis did not distinguish between HBeAg-positive and HBeAg-negative groups.

The number of male subjects in this study were larger than female (56.3% vs 43.8%) that were consistent with other previous study [18, 19, 22]. The demographics in Southeast Asia showed a higher HBsAg positive prevalence rate for men than for women (10% vs 6%) [23]. The mechanism underlying sex differences related to hepatitis B virus infection remains unclear. It is suspected that mechanism of sex differences is related to the presence of sexual hormone factors, gender behavior, and environmental factors [24]. This study showed that the average age of the subjects were young which also consistent with the previous reports. In accordance with the natural course of hepatitis B infection, young age is more often found in the HBeAg-positive CHB. In this study, the average ALT was 67.63±46.514 IU/L. In a previous study the average ALT was 32.3±17.7 IU/L [19]. The previous research also found an ALT of 168.3±220 IU/L [22]. This variation in ALT values is influenced by differences in inclusion criteria, exclusion criteria, and phase of chronic hepatitis B infection in the study subjects. ALT levels varied in the HBeAg-positive group. In the immune tolerant phase the ALT levels are normal, whereas in the immune reactive phase ALT levels increase [6].

In this study, quantitative HBsAg levels were highest in the F1 group, followed by F2, F3 and lowest in the F4 group. This is consistent with the previous study, patients with fibrosis <F2 had higher levels of quantitative HBsAg than ≥F2 (4.4±0.8 log10 IU/mL vs 3.5±1.2 log10 IU/mL, p <0.001) [19]. Another research also mentions that fibrosis ≤F1 has higher levels of quantitative HBsAg than fibrosis >F1 [25]. Although the exact mechanism of the inverse association between the qHBsAg level and staging of liver fibrosis is not fully understood, previous researchers speculate that decreasing HBsAg levels with increasing fibrosis severity might be caused by greater HBsAg retention in cells than HBsAg secretion into the circulation, or reduced host ability to support viral replication with increased severity of liver fibrosis [17]. In addition, the natural course of chronic HBV infection is another reason for lower HBsAg levels along with the development of liver fibrosis in HBeAg-positive patients. Quantitative HBsAg levels were found to be higher in the immune-tolerant phase which liver fibrosis was minimal compared to the immune clearance phase which liver fibrosis was more severe [26, 27].

Our study had several limitations. First, it was a cross sectional study in which qHBsAg levels and transient elastography were only done once, so it could not be able to evaluate the changes that might change over time. Therefore, longitudinal studies are needed to further explore and exact correlation between liver fibrosis and qHBsAg level. Further researches are required regarding quantitative HBsAg levels as a marker of fibrosis with gold standard liver biopsy in chronic hepatitis B patients. Second, we did not do complete examination such as HBV DNA, liver biopsy, and HBV genotypes. The quantitative HBsAg levels were not diluted if the levels > 2500 IU/mL (3.4 log10 IU/mL).

CONCLUSION

We found a negative correlation between liver fibrosis based on transient elastography and quantitative HBsAg levels in HBeAg-positive CHB. Low level of qHBsAg can be considered to get starting liver fibrosis test, especially by using transient elastography, which might be useful for determining treatment strategy.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflicts of interest in this study.

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