Treatment Response Monitoring of Chronic Hepatitis B Patients using Transient Elastography and Aspartate Aminotransferase-to-Platelet Ratio Index (APRI)

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ABSTRAK

Latar belakang: *prevalensi Hepatitis B di Indonesia masih tinggi dan pengobatan dengan obat antivirus memerlukan pamantauan untuk menilai respons terapi. Salah satu metode pemantauan respons terapi yang non-infasif dan mudah dilakukan di Indonesia adalah dengan pengukuran derajat kekerasan hati atau transient elatography (TE)dan alanine aminotransferase-to-platelet ratio index (APRI) yang merupakan metode alternatif untuk mendeteksi fibrosis hati. Meskipun demikian, akurasinya dalam mengevaluasi respon terapi pada pasien hepatitis B kronik di Indonesia masih belum diketahui. Penelitian ini bertujuan untuk mengetahui perubahan derajat kekerasan hati dengan menggunakan transient elastography (TE) dan APRI sebelum dan setelah terapi antiviral per oral selama satu tahun pada pasien hepatitis B kronik dan korelasi antara TE dan APRI.* ***Metode:*** *desain penelitian yang digunakan adalah studi kohort retrospektif pada pasien hepatitis B kronik di Rumah Sakit Cipto Mangunkusumo Jakarta yang diberikan terapi selama bulan Januari 2012 hingga Desember 2014. Pasien diberikan antiviral dengan analog nukleosida terbaru (entecavir atau telbivudine) selama minimal satu tahun. TE dan APRI diperiksakan sebelum dan setelah terapi. Reduksi TE dan APRI diuji secara statistik menggunakan korelasi Spearman.* ***Hasil:*** *penelitian ini mengikutsertakan 41 pasien dan mendapatkan nilai median kekerasan hati berkurang secara signifikan dari 10,8 menjadi 5,9 kPa setelah terapi antiviral per oral ($p<0,001$, Uji Wilcoxon). Nilai median APRI juga berkurang secara signifikan dari 1,13 menjadi 0,43 setelah terapi ($p<0,001$, Uji Wilcoxon). Sebelum terapi dimulai nilai korelasi antara derajat kekerasan hati dan APRI menunjukkan hasil 0.40 dan nilai korelasi setelah terapi antiviral menjadi 0,73.* ***Kesimpulan:*** *derajat kekerasan hati yang diukur menggunakan TE dan APRI berkurang secara signifikan setelah terapi antiviral selama satu tahun pada pasien hepatitis B kronik. Terdapat korelasi yang signifikan antara TE dan APRI.*

Kata kunci: *terapi antiviral, indeks aspartate aminotransferase-to-platelet ratio(APRI), hepatitis B kronik, derajat kekerasan hati, transient elastography.*

ABSTRACT

Background: *Hepatitis B is endemic in Indonesia and treatment response need to be monitored during and after antiviral therapy. Liver stiffness measurement and alanine aminotransferase-to-platelet ratio index (APRI) are noninvasive method to detect liver fibrosis available in Indonesia. However, little is known about their ability to evaluate treatment response in chronic hepatitis B (CHB) patients in Indonesia. This study aimed to investigate liver stiffness changes by transient elastography (TE) and APRI before and after one-*

year oral antiviral treatment in CHB patients and the correlation between TE and APRI. ***Methods:*** *this study was retrospective cohort on CHB patients in CiptoMangunkusumo Hospital, Jakarta who uderwent treatment between January 2012 and December 2014. Patients received oral antiviral treatment with newer nucleoside analogues (entecavir or telbivudine) for at least one year. TE and APRI were obtained before and after treatment. TE and APRI reductions were analyzed statistically with Spearman's test.* ***Results:*** *a total of 41 patients were enrolled in this study. Median liver stiffness value was significantly reduced from 10.8 to 5.9 kPa after oral antiviral treatment (p<0.001, Wilcoxon's test). Median APRI was also significantly reduced from 1.13 to 0.43 after treatment (p<0.001, Wilcoxon's test). The correlation between liver stiffness and APRI before treatment was weak (r=0.40), but it was strong after treatment (r=0.73).* ***Conclusion:*** *the liver stiffness measured with transient elastography and APRI significantly decreased after one year of antiviral treatment in chronic HBV patients. There was a significant correlation between TE and APRI after one year of treatment.*

Keywords: *antiviral therapy, aspartate aminotransferase-to-platelet ratio index (APRI), chronic hepatitis B, liver stiffness measurement, transient elastography.*

INTRODUCTION

Hepatitis B infection is a public health problem in Indonesia. Based on the National Basic Health Research 2007, the prevalence of HBsAg-positive case was 9.7% in men and 9.3% in women. The highest prevalence was found among 45-49 years age group (11.9%).[1] Hepatitis B virus (HBV) is responsible for various medical conditions from asymptomatic carriers to cirrhosis and hepatocellular carcinoma. It is the cause of 500.000 to 1.2 million deaths annually, which is related to cirrhosis and hepatocellular carcinoma.[2] Obviously, antiviral treatment and prevention of disease progression is the main goal of chronic hepatitis B (CHB) management.

Patients treated with oral antiviral therapy should be regularly monitored. The current practice of treatment monitoring is done by measuring serum liver enzymes, HBV-DNA and serological markers such as hepatitis B e antigen (HBeAg), hepatitis b surface antigen (HBsAg), and anti-HBs.[3] The Asian-Pacific Association for the Study of the Liver (APASL) 2012 guidelines recommended to start evaluation using viral seromarkers at 3 months after treatment and should be repeated every 3 months during treatment.[4] The guidelines also recommended assessing fibrosis stage before treatment either invasively with liver biopsy or non-invasively.[5]

Transient elastography (TE) is one of the most widely used non-invasive methods to assess liver fibrosis.[6] Initial TE studies were done on Caucasian chronic hepatitis C patients.[7,8] Other studies on TE have also been done in alcoholic fatty liver disease,[9] primary biliary cirrhosis[10] and hepatitis B.[11,12]

Combination of biochemical markers is another alternative to assess liver fibrosis in CHB patients.[13] One of the most economical methods is by calculating the aspartate aminotransferase (AST)-to-platelet-ratio index (APRI).[14] Liver fibrosis stage and APRI is significantly correlated in CHB patients.[15] Theoretically, platelet count is reduced when fibrosis stage increases. This is caused by increased portal hypertension in advanced fibrosis thereby increasing platelet sequestration and its destruction in the enlarged spleen.[16]

A cross-sectional study in Jakarta has shown that liver stiffness tend to increase parallel to fibrosis stage. The median of liver stiffness in F0-F1, F2, F3, and F4 were 5.45, 5.8, 7.8, and 29.3 kPa, respectively. The APRI also tends to increase when the fibrosis stage increases.[17] Both TE and APRI has good diagnostic accuracy to detect significant liver fibrosis (>F2) in CHB patients.[17]

Study on CHB patients has shown that long-term antiviral treatment might improve liver histology and produce liver fibrosis regression.[18-20] Treatment response monitoring with TE showed that entecavir treatment for at least 12 months may reduce liver stiffness from 11.2 kPa to 7.8 kPa.[21] Non-invasive methods like TE and APRI has not been well studied in Indonesia to monitor treatment response of CHB patients. Therefore, this study was aimed to know

the alterations of liver stiffness using TE and APRI after oral antiviral treatment for at least one year in CHB patients.

METHODS

This was a cohort retrospective study conducted at Cipto Mangunkusumo Hospital (CMH), Jakarta between January and June 2013. The study was cohort retrospective using data of CHB patients who had been diagnosed and treated in CMH before 2013 and were followed-up during the study period. Patients were included when they had a record of liver stiffness measurement with TE, had complete initial laboratory data (blood chemistry and liver function test) and had been treated with oral antiviral for at least one year. The minimum number of subjects was calculated using the analytical numeric formula for paired subjects with 5% type I error and 80% research power. The standard deviation of liver stiffness difference between before and after treatment was estimated at twice of the minimum mean difference (2 kPa) or equal to 4 kPa. Therefore, the minimum sample size needed was 31 patients. Patients were excluded when there was a co-infection with hepatitis C virus (HCV) or human immunodeficiency virus (HIV), failure of TE readings, and hepatocellular carcinoma.

Liver Stiffness Measurement

Liver stiffness was measured by using transient elastography (TE) machine (FibroScan®, Echosens, Paris, France) according to the instructions provided by the manufacturer.[22] It is equipped with a probe that includes a ultrasound (US) transducer mounted on a vibrator.

The measurement depth was between 25 and 65 mm. Measurement was considered valid if 10 successful acquisitions were obtained with success rate (SR) of at least 60% and the ratio of interquartile range over median (IQR/M) was 30% less.[23] Results were expressed in kilopascals (kPa).TE was considered normal if liver stiffness was 5.0 kPa or lower. In patients with normal ALT levels, fibrosis stage measured by TE was categorized as: F1 (>5-6 kPa), F2 (>6-9 kPa), F3 (>9-12 kPa), F4 (>12 kPa). In patients with elevated ALT levels, fibrosis was staged as follows: F1 (>5-7.5 kPa0), F2 (>7.5-12 kPa), F3 (>12-13.4 kPa), and F4 (>13.4 kPa).[12]

Calculation of APRI

APRI was calculated twice, before and after oral antiviral therapy. APRI was calculated as [(AST/ ASTULN) x100] / platelet count (109/ L). ASTULN is the upper limit of the normal AST value, which were 35 IU/mL in women and 50 IU/mL in men. The cut-off value of APRI to detect significant liver fibrosis was set to 0.5.[24]

Liver Biopsy

Liver biopsy was done percutaneously under local anesthesia. A specimen was adequate when it at least contained six portal tracts and measured 1.5 cm in length. Specimens were fixed in 4% buffered formalin and embedded in paraffin. Specimens were cut in 4-μm thickness and were stained with haematoxyllin eosin and Masson's trichrome staining.

Fibrosis stage was evaluated using METAVIR scoring system as follows: F0 indicated no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with a few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis.[25] Significant fibrosis was defined as F2 or more.

Data Management and Statistic Analysis

Characteristics of the study subjects were presented descriptively. The difference of liver stiffness and APRI before and after treatment was assessed using the Wilcoxon test (for skewed data). A p value of less than 0.05 was considered significant. Correlation between TE and APRI was expressed as Spearman's coefficient of correlation (r). A correlation was considered weak if $r < 0.5$, moderate if $r = 0.5$-0.7 and strong if $r > 0.7$ Analysis was done with the SPSS version 17 (SPSS Inc., Chicago, Illinois, USA).

Patients signed a written informed consent before involvement in the study. Ethical approval was obtained from the Ethical Committee for Medical Research, Faculty of Medicine, University of Indonesia. No 05/H2.F1/ETIK/ 2013 dated January 7th, 2013.

RESULTS

A total of 41 CHB patients were enrolled. More than two-thirds of them were men. The median age was 50 years old. Twenty-three patients were HBeAg-positive and had high serum HBV-DNA levels (**Table 1**). The mean

period of antiviral treatment was 18.1 (4.1) months.

Table 1. Characteristics of the study subjects (n=41)

Variables	Value
Male gender, n (%)	29 (70.7)
Age (years), median (range)	50 (22-67)
Platelet count (x109/μL), mean (SD)	194.4 (71.3)
AST (U/L), median (range)	52 (18–530)
ALT (U/L), median (range)	49 (16-850)
- Normal ALT, n (%)	10 (24.4)
- ALT 1-2xULN, n (%)	12 (29.3)
- ALT >2xULN, n (%)	19 (46.3)
HBeAg-positive, n (%)	23 (56.1)
HBV-DNA (log copies/mL), mean (SD)	5.5 (2.1)

Initial Liver Fibrosis Evaluation

Based on liver stiffness measurement algorithm, significant liver fibrosis was correctly detected in 26 (78.8%) patients. Using a cut-off value of 0.5 for significant fibrosis, APRI could correctly identifymost patients with F2-F4 (**Table 2**).When analyzed further, fibrosis stage assessment by TE can correctly classified F0-F1 patients and F3-F4 patients, but not the F2 category (**Table 3**).

Evaluation of Treatment Response

The median of initial liver stiffness was 10.8, ranging from 4.1 to 61.5 kPa. It was significantly reduced after treatment (p<0.001). Median APRI was reduced from 1.13 (range, 0.20 – 21.13) at baseline to 0.43 (range, 0.12-2.00) after treatment (p<0.001). Reduction of TE and APRI was similar between HBeAg-positive and HBeAg-negative patients (**Figure 1A** and **1B**). There was a moderate correlation between initial TE and APRI (r=0.40, Spearman's correlation test). After oral antiviral treatment, there was a strong correlation between TE and APRI (r=0.73; Spearman's correlation test).

Evaluation of liver fibrosis stage using TE showed that liver stiffness reduction could be reasonably translated into fibrosis stage. None of patients with initial liver histopathology showing F2 and F3 fibrosis underwent disease progression. On the contrary, improvement occurred in 7/8 (87.5%) of F2 patients, 7/8 (87.5%) of F3 patients, and 13/17 (76.5%) of F4 patients (**Table 4**).

DISCUSSION

Treatment monitoring with TE or APRI has not been routinely done in Indonesia. However, guidelines on CHB management have included

Table 2. The association between liver fibrosis proven by biopsy and non-invasive measures of fibrosis stage

Fibrosis stage by	Fibrosis stage based on histopathology		p value*
	F0-F1 - n (%)	F2-F4 - n (%)	
TE			
F0-F1	5 (62.5)	7 (21.2)	0.034
F2-F4	3 (37.5)	26 (28.8)	
APRI			
F0-F1 (<0.5)	6 (75.0)	7 (21.2)	0.007
F2-F4 (>0.5)	2 (26.0)	26 (78.8)	

* Fisher exact test; p value <0.05 was considered statistically significant

Table 3. Concordance of fibrosis stage by histopathology assessment and transient elastography (n=41)

Fibrosis stage by TE*	Fibrosis stage by histopathology (n, %)				
	F0	F1	F2	F3	F4
F0 (≤ 5 kPa)	0	1 (12.5)	2 (25.0)	0	0
F1 (>5-6 or >5-7.5 kPa)	0	4 (50.0)	5 (62.5)	0	0
F2 (>6-9 or >7.5-12 kPa)	0	3 (37.5)	1 (12.5)	4 (50.0)	1 (5.9)
F3 (>9-12 or >12-13.4 kPa)	0	0	0	3 (37.5)	2 (11.8)
F4 (>12 or >13.4 kPa)	0	0	0	1 (12.5)	14 (82.4)

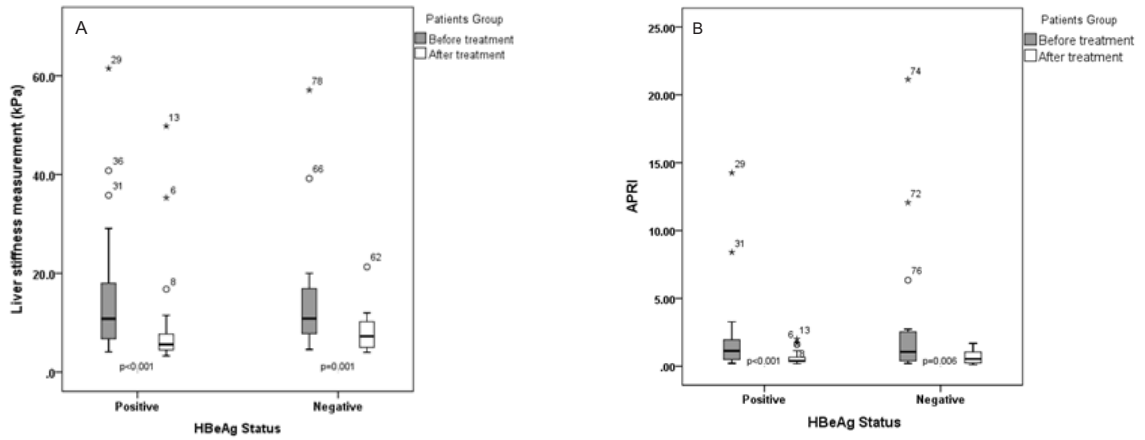

Figure 1. (A) Reduced liver stiffness after oral antiviral therapy in chronic hepatitis B patients. (B) Reduced APRI after oral antiviral therapy in chronic hepatitis B patients (n=41)

Table 4. Liver fibrosis improvement by transient elastography assessment after oral antiviral therapy in chronic hepatitis B patients (n=41)

Fibrosis stage after treatment by TE*	Initial fibrosis stage by histopathology, n (%)			
	F1	F2	F3	F4
F0 (≤5 kPa)	5 (62.5)	3 (37.5)	2 (25.0)	3 (17.63)
F1 (>5-6 or >5-7.5 kPa)	2 (25.0)	4 (50.0)	1 (12.5)	1 (5.9)
F2 (>6-9 or >7.5-12 kPa)	1 (12.5)	1 (12.5)	4 (50.0)	3 (17.6)
F3 (>9-12 or >12-13.4 kPa)	0	0	1 (12.5)	6 (35.4)
F4 (>12 or >13.4 kPa)	0	0	0	4 (23.5)

*liver stiffness measurement was categorized based on ALT normal vs. 1-5x ULN[12]

Table 5. Liver fibrosis improvement after oral antiviral therapy in chronic hepatitis B patients (n=41)

Fibrosis stage	Fibrosis stage based on histopathology	
	F0-F1, n (%)	F2-F4, n (%)
TE		
F0-F1	7 (87.5)	29 (87.9)
F2-F4	1 (12.5)	4 (12.1)
APRI		
F0-F1 (≤0.5)	6 (75.0)	18 (54.5)
F2-F4 (>0.5)	2 (26.0)	15 (45.5)

histological response in addition to virological and biochemical responses. Evaluation of liver fibrosis may be done invasively by biopsy or non-invasively.[26]

Our study showed that liver stiffness was reduced after treatment which may indicate histological improvement. Assessment of liver fibrosis in CHB patients should be based on ALT levels. Using the ALT-based algorithm, TE could detect advanced fibrosis more accurately than fibrosis stage F2. This category has been regarded as gray zone with TE values between 6 and 9 kPa (or 7.5 to 9 kPA in elevated ALT) which need liver biopsy for confirmation.[13] Research on TE to show fibrosis regression had been shown in other studies.[21,27] TE could also be used to evaluate disease progression. A study reported that untreated patients had increased liver stiffness from 6.1 to 6.3 kPa with mean observation period of 422 (358-709) days.[28]

Liver stiffness has been known to increase when there was active inflammation such as acute flare with ALT elevation. In this case, liver stiffness may be 1.5 times higher than its value when the ALT levels return to normal.[29] Nevertheless, TE has a good reproducibility to be used in daily practice. The inter- and intra-examiner variation ranges from 3.2 to 3.3%. Other study found high correlation between to examiners (r=0.98).[30] However, reliability decrease in lower

fibrosis stage (F0-F1) compared to higher fibrosis stage (>F2). Measurement reliability is also reduced when hepatic steatosis is present in more than 25% of liver tissue and if body mass index is 25 kg/m^2 or more.[29]

In this study, median APRI was reduced significantly after antiviral treatment. APRI was initially used in chronic hepatitis C patients to predict significant fibrosis and cirrhosis.[31] Other study involving both chronic hepatitis C and B with negative HBeAg showed that APRI was significantly associated with fibrosis stage.[32]

The reported APRI cut-off level for significant fibrosis is 0.76 (95%CI 0.74-0.79) in CHC patients.[33] In CHB patients, two studies reported that APRI's AUC for significant fibrosis were 0.63 and 0.72.[20,34] Previous study in Jakarta found a much lower cut-off (0.22) for significant liver fibrosis; however, that study only includes 4 patients with cirrhosis that may have skewed the distribution of APRI values.[21] A recent study suggested an APRI value of 0.5 in detecting significant fibrosis in CHB patients which had 87.7% sensitivity and 90.8% specificity.[35]

TE and APRI have a similar accuracy in detecting liver fibrosis in CHB patients. However, the cost of performing TE is much higher than APRI. Therefore, APRI should be used in primary care when TE facility is not available.[21]

This study has several limitations. Firstly, the study subjects were not pre-selected based on their ALT levels. Some patients had ALT levels more than 5 times the ULN when TE was performed thereby it might cause higher liver stiffness measurement. Secondly, liver fibrosis stage after treatment was not confirmed by histopathological assessment.

CONCLUSION

This study showed that liver stiffness measured by transient elastography (TE) and aspartate-to-platelet ratio index (APRI) significantly reduce after 12-month oral antiviral treatment in chronic hepatitis B patients. Liver stiffness was strongly correlated with APRI in these patients. Both TE and APRI are potentially used for treatment monitoring in CHB patients receiving oral antiviral therapy.

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