Original Article

Transient Elastography for the Assessment of Liver Fibrosis in Chronic Hepatitis B in Patients with End-Stage Renal Disease *versus* Those with Normal Renal Function

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ABSTRACT

Background: Liver stiffness as measured by transient elastography (Fibroscan®) is correlated with the degree of liver fibrosis in HBV-infected patients with normal renal function. The usefulness of Fibroscan® in assessing liver fibrosis in HBV-infected patients with end-stage renal disease (ERSD) is unknown. The study were aimed to compare the performance of Fibroscan® for the assessment of significant liver fibrosis in HBV-infected patients with ESRD to those having normal renal function and to investigate the effect of serum alanine aminotransferase (ALT) levels on liver stiffness measurement.

Methods: We prospectively enrolled renal transplant candidates with chronic HBV infection who underwent liver biopsy and liver stiffness measurement to evaluate the severity of liver disease. The cohort was compared to patients with chronic hepatitis B who underwent liver biopsy prior to antiviral treatment in the same calendar year. Liver histology was evaluated and graded by METAVIR scoring system and liver stiffness was expressed as kPa.

Results: Patients with ESRD had a mean (SEM) age of 40.5 ± 3.1 years and 83% were male. Eleven patients were on hemodialysis and 4 were received oral antiviral agents with a median duration of 22 months (ranged from 17 to 31 months) prior to histologic evaluation. The HBeAg was negative in 10 (83%) patients, and two were HBeAg-positive. Alanine aminotransferase activities ranged from 9 to 77 U/L (median level of 22 U/L). None of the patients had criteria for liver cirrhosis and ascites in the ultrasound examination. According to the METAVIR classification, 7 patients had stage 0-I, 4 had stage II, and 1 had stage III disease. Compared to patients with normal renal function, ESRD group had significantly lower body mass index (21.4 ± 0.7 vs. 23.9 ± 0.3 kg/m^2, p = 0.01), HBV DNA (× 10^6 IU/ml) 5.1 ± 3.6 vs. 13.8 ± 2.3, p = 0.0007, AST (22 ± 3.5 vs. 44 ± 3.8 units/L, p = 0.0002), ALT (25 ± 5.3 vs. 62 ± 6.8 units/L, p = 0.0009) and hemoglobin level (11.4 ± 0.7 vs. 14 ± 0.1 g/dL, p = 0.0004). Liver stiffness values were similar between both groups. To predict significant fibrosis (grade II), optimal cutoff value of Fibroscan® at 5.9 kPa with the area under the curve (AUC) of 0.86 in ESRD patients yielded a sensitivity of 100%, specificity of 71%, positive predictive value (PPV) of 71%, and negative predictive value (NPV) of 100%. Whereas in patients with normal renal function, optimal liver stiffness value of 6.8 kPa with the AUC of 0.76 provided a sensitivity of 74%, specificity of 75%, PPV of 75%, and NPV of 74%.

Conclusions: Fibroscan® is a reliable mean for evaluating the severity of liver disease in HBV-infected patients with ERSD, with higher performance compared to patients with normal renal function at the same stage of liver fibrosis. As elevated serum ALT levels have the influence on the diagnostic performance of liver stiffness measurement, a lower liver stiffness measurement may be needed to diagnose different degrees of liver fibrosis in HBV-infected patients with ESRD.

Key words : transient elastography, liver stiffness, chronic hepatitis B, end-stage renal disease

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INTRODUCTION

Since its discovery in 1965 known as "Australian antigen", hepatitis B virus (HBV) infection has been a worldwide health problem. Viral hepatitis has been recognized as a major complication of renal replacement therapy. Patients undergoing maintenance dialysis have potentially increased risk of exposure to viral hepatitis. These infections are of clinical importance as they become chronic and progress to chronic liver diseases including chronic hepatitis, cirrhosis or hepatocellular carcinoma. The relative risk of death was increased in dialysis patients with viral hepatitis infections[1].

Since the 1977 release of guidelines from the Centers for Disease Control and Prevention (CDC) to prevent transmission of HBV infection in dialysis units, the incidence of chronic hepatitis B in patients with end-stage renal disease (ESRD) has significantly declined[2]. However, the management of HBV infection in patients with kidney failure remains an important clinical issue, since the presence of chronic hepatitis B is associated with decreased patient survival after kidney transplantation[3]. Although chronic hepatitis B is not a contraindication for kidney transplantation, all potential kidney transplant recipients with HBV infection should undergo complete evaluation, which may include liver biopsy to assess the severity of liver disease[4]. Patients with underlying cirrhosis should be considered for combined liver-kidney transplantation, if liver failure and criteria for liver transplantation are present, as isolated kidney transplantation may be associated with hepatic decompensation or complications of portal hypertension[3]. Currently, percutaneous liver biopsy remains the gold standard for grading necroin-flammation and staging fibrosis in patients with liver diseases. In addition, liver histology can help clinicians determine the eligibility of renal transplantation, prognosis, and necessity of antiviral therapy in dialysis patients with chronic viral hepatitis. However, liver biopsy is an invasive procedure with several limitations including, sampling error, variability in histopathologic interpretation and patient acceptability.

From these limitations, many non-invasive methods have been developed including many biochemical tests and transient elastography (Fibroscan®, Echosens, Paris, France). Fibroscan® is a novel, rapid, and noninvasive technique to measure liver stiffness[5]. In HBV-infected patients, liver stiffness as measured by Fibroscan® is strongly associated with the degree of liver fibrosis[6]. Despite these promising results, several studies showed that elevated aminotransferase levels in these patients could interfere with fibrosis assessment by Fibroscan®. Moreover, all published data of Fibroscan® are derived from patients with normal renal function. The usefulness of Fibroscan® in assessing liver fibrosis in HBV-infected patients with ESRD remains unknown.

Thus, the aims of the present study were (1) to compare the performance of Fibroscan® for the assessment of significant liver fibrosis in HBV-infected patients with ESRD to those having normal renal function and (2) to investigate the effect of serum alanine aminotransferase (ALT) levels on liver stiffness measurement.

MATERIALS AND METHODS

Study design:

Cross-sectional study

Patients:

We prospectively enrolled renal transplant candidates with chronic HBV infection who underwent liver biopsy examination and liver stiffness measurement to evaluate the severity of liver disease at Siriraj Hospital from May 2007 to September 2008. The exclusion criteria were patients who have contraindication for liver biopsy, massive ascites, decompensated liver cirrhosis, morbid obesity (BMI >40 kg/m^2), hepatitis B and C co-infection, and co-infection with HIV

The cohort was compared to patients with chronic hepatitis B who underwent liver biopsy prior to antiviral treatment in the same calendar year. Normal renal function determines as estimated creatinine clearance rate was more than 60 ml/min using Cockcroft-Gault formula. ALT was divided in 3 categories: normal (<40 U/L), >1 to 2 times ULN, and >2 times ULN.

The following parameters were collected; age, sex, BMI, dialysis treatment and duration, serological testing for HBsAg, HBeAg, HBV DNA viral load, aspartate aminotransferase (AST), alanine aminotransferase (ALT), CBC with platelet count, coagulogram, BUN, and Cr.

Liver stiffness measurement:

Liver stiffness was measured with Fibroscan® by a single experienced operator who was unaware of the clinical, biochemical and radiological data.

Liver stiffness measurements were performed on the right lobe of the liver through intercostal spaces on

patients lying in the dorsal decubitus position with the right arm in maximal abduction.

The tip of the probe transducer was covered with coupling gel and placed on the skin, between the rib bones at the level of the right lobe of the liver. The operator, assisted by an ultrasonic image, located a liver portion of at least 6 cm thick free of large vascular structure. Once the measurement area had been located, the operator pressed the probe button to start an acquisition. Measurement depth was between 25 mm and 65 mm below the skin surface. Ten successful measurements were performed on each patient. Success rate was calculated as the ratio of the number of successful measurement over the total number of acquisition. The results were expressed in kilopascal (kPa). Median value of the successful measurements was kept as representative of liver stiffness. The whole examination duration was less than five minutes. Only liver stiffness measurements obtained with at least 10 successful measurements and a successful rate of at least 80% were considered reliable.

Liver histology and assessment of liver fibrosis:

Liver biopsy was fixed in formalin and paraffin-embedded. All biopsy specimens were analyzed by an experienced pathologist who was blinded to the clinical data and the results of Fibroscan®. Fibrosis and necro-inflammatory activity were staged according to METAVIR scoring system. Fibrosis was staged on a 0-4 scale: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. Activity was graded as: A0, none; A1, mild; A2, moderate; and A3, severe.

Statistical analysis

Patient characteristics were analyzed by descriptive statistics and reported as mean ± SEM and number with percentage. Linear regression analysis was used to identify factors associated with higher liver stiffness measurement. The receiver operative characteristic curve (ROC) was constructed for detection of the optimal cut-off value of liver stiffness measurement which chosen to maximize the sum of sensitivity and specificity. All statistical testing was done at the conventional 2-tailed α level of 0.05.

RESULTS

There were a total of 12 HBV-infected patients with ESRD enrolled in the study. Eleven of 12 HBV-infected patients with ESRD were on hemodialysis. The HBeAg was negative in 10 (83%) patients, and two were HBeAg-positive. Four patients received oral antiviral agents with a median duration of 22 months (ranged from 17 to 31 months) prior to histologic evaluation. All patients except one had serum ALT less than 40 U/L with a median level of 22 U/L (ranged from 9 to 77 U/L). None of the patients had criteria for liver cirrhosis and ascites on the ultrasound examination. The clinical and demographic data of the patients as indicated in Table 1.

Liver histology was staged according to the

Table 1. Characteristics of patients with ESRD and patients with normal renal function.

	ESRD (n = 12)	Normal Renal Function (n = 152)	*p* value
Age (yr)	40.5 ± 3.1	46.2 ± 0.8	0.04
Sex (F/M)	2/10	61/91	0.1
BMI (kg/m^2)	21.4 ± 0.7	23.9 ± 0.3	0.01
HBeAg-positive, n (%)	2 (17%)	32 (21%)	1.0
HBV DNA ($\times 10^6$ IU/ml)	5.1 ± 3.6	13.8 ± 2.3	0.0007
AST (U/L)	22 ± 3.5	44 ± 3.8	0.0002
ALt (U/L)	25 ± 5.3	62 ± 6.8	0.0009
Alkaline phosphatase (U/L)	69 ± 5.9	69 ± 1.8	0.9
Prothrombin time (sec.)	12.1 ± 0.2	11.8 ± 0.1	0.1
Hemoglobin (g/dL)	11.4 ± 0.7	14.0 ± 0.1	0.0004
Platelet ($\times 10^3$/ml)	120 ± 19	228 ± 4	0.08
Calculated GFR (ml/min)	8.1 ± 0.6	94 ± 1.8	<0.0001
Liver stiffness	8.6 ± 1.5	8.1 ± 0.4	0.9

METAVIR scoring system. In HBV-infected patients with ESRD, 92% had fibrosis score F0 - F2 and 8% had F3 fibrosis. None of the patients had F4 fibrosis in this group. Liver histology was showed in Table 2.

The performance of Fibroscan® in patients with ESRD and those with normal renal function

To predict significant fibrosis (grade II), the optimal cut-off value of Fibroscan® at 5.9 kPa with the area under the curve (AUC) of 0.86 in ESRD patients yielded a sensitivity of 100%, specificity of 71%, positive predictive value (PPV) of 71%, and negative predictive value (NPV) of 100%. Whereas in patients with normal renal function, optimal liver stiffness value of 6.8 kPa with the AUC of 0.76 provided a sensitivity of 74%, specificity of 75%, PPV of 75%, and NPV of 74% as shown in Table 3.

Factors associated with higher liver stiffness measurement

Univariate analysis:

BMI and serum ALT level were significantly associated with higher liver stiffness measurement (p <0.0001). Liver histology according to METAVIR scoring system, both histologic activity and fibrosis score were also significantly associated with higher liver stiffness measurement (p <0.0001). (Table 4).

Multivariate analysis:

Among overall HBV-infected patients with ESRD, two variables were independently associated with higher liver stiffness measurement: serum ALT level (p <0.0001) and fibrosis score (p <0.0001). (Table 4.)

The performance of Fibroscan® for assessing significant fibrosis in different ALT categories

In HBV-infected patients with normal serum ALT level, the optimal cut-off value of Fibroscan® at 6.8 kPa with the AUC of 0.77 yielded a sensitivity of 68%, specificity of 83%, PPV of 65%, and NPV of 84%. Whereas in patients with elevated serum ALT level 2-5 times of upper normal limit, optimal liver stiffness value of 8.0 kPa with the AUC of 0.68 provided a sensitivity of 71%, specificity of 75%, PPV of 94%, and NPV of 33% as shown in Table 5.

Table 2. Liver histology of patients with ESRD and patients with normal renal function.

	ESRD (n = 12)	Normal Renal Function (n = 152)	*p* value
Histologic activity (METAVIR)			0.5
A0-1	1 (83%)	94 (61%)	
A2	2 (17%)	51 (34%)	
A3	0	7 (5%)	
Fibrosis score (METAVIR)			0.3
F0-1	7 (58%)	77 (51%)	
F2	4 (34%)	47 (31%)	
F3	1 (8%)	26 (17%)	
F4	0	2 (1%)	

Table 3. The performance of Fibroscan® in patients with ESRD and those with normal renal function.

Group	Kilopascal	AUROC	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
ESRD						
Stage 2	5.9	0.86	100 (57-100)	71 (36-92)	71 (36-92)	100 (57-100)
Stage 3	8.8	0.73	100 (21-100)	73 (45-90)	25 (5-70)	100 (68-100)
Normal renal function						
Stage 2	6.8	0.76	74 (63-82)	75 (64-83)	75 (64-83)	74 (63-87)
Stage 3-4	7.6	0.79	86 (69-95)	68 (60-76)	39 (28-51)	95 (89-98)

Table 4. Factors associated with higher liver stiffness measurement.

variable	Unadjusted (Univariate)		Adjusted (Multivariate)	
	Regression coefficient	*p* value	Regression coefficient	*p* Value
Age (year)	0.055	0.2		
Female	-0.692	0.1		
BMI	0.428	<.001		
HBeAg-positive	0.5444	0.3		
ALT (U/L)	0.038	<.0001	0.032	<.0001
Hemoglobin (g/dL)	-0.250	0.3		
End-stage renal disease	0.015	0.2		
Calculated GFR (ml/min)	0.015	0.8		
Histologic activity (METAVIR)	3.086	<.0001		
Fibrosis score (METAVIR)	2.459	<.0001	1.767	<.0001

Table 5. The performance of Fibroscan® for assessing significant fibrosis in different ALT categories.

Group	Kilopascal	AUROC	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
ESRD						
Overall	5.9	0.86	100 (57-100)	71 (38-92)	71 (36-92)	100 (57-100)
Normal renal function						
Overall	6.8	0.76	73 (63-82)	75 (64-83)	75 (64-83)	74 (63-84)
Normal ALT	6.8	0.77	68 (48-83)	83 (70-91)	65 (46-810	84 (72-92)
ALT 1-2 × UNL	6.6	0.66	76 (58-88)	62 (41-79)	73 (56-86)	65 (43-82)
ALT 2-5 × UNL	8.0	0.68	71 (50-86)	75 (30-95)	94 (72-99)	33 (12-65)

DISCUSSION

This cross-sectional study is the first study evaluating the performance of transient elastography (Fibroscan®) for the assessment of significant liver fibrosis in HBV-infected patients with ESRD. We compared liver stiffness measurements with fibrosis stages assessed on liver biopsy in a population of patients with chronic hepatitis B and normal renal function. Our study showed that Fibroscan® was easy to perform, and was strongly associated with the degree of liver fibrosis (sensitivity 100%, specificity 71% in stage 2 fibrosis), with higher performance compared to patients with normal renal function at the same stage of liver fibrosis.

While liver biopsy remains the gold standard in establishing the diagnosis and the assessment of hepatic damage in patients suffering liver disease, it is an invasive procedure carrying significant risk of mortality and morbidity especially for patients with bleeding tendency such as dialysis patients who are known to have uremic state related platelet dysfunction. Reproducibility of liver biopsy is also poor, owing to heterogeneity in liver fibrosis and sample size, and also to variability within and between pathologists[7]. Even when an experienced physician performs liver biopsy and an expert pathologist interprets the results, liver biopsy has up to a 20% error rate in disease staging. In a recent study, Bedossa *et al*[8]. showed that, using the METAVIR scoring system, only 65% of 15-mm biopsies (the currently recommended length) were correctly classified in terms of fibrosis stage. This increased to 75% for 25-mm specimens. Regev *et al*[9]. reported a difference of at least one fibrosis stage between the right and left lobes in 33% of 124 patients, while Siddique *et al*[10]. showed a difference, in 45% of patients, of at least one fibrosis stage between two specimens (at least 15 mm long) obtained at the same puncture site.

Based on previous studies which demonstrated a

significant association between serum hepatic transaminase levels and hepatic inflammation shown in histology, biochemical parameters including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have long been playing a major role serving as non-invasive surrogate parameters to reflect the activity and severity of liver disease in patients with HBV infection. In the present study, as elevated serum ALT levels have the influence on the diagnostic performance of liver stiffness measurement, a lower liver stiffness measurement may be needed to diagnose different degrees of liver fibrosis in HBV-infected patients with ESRD.

Fibroscan® may also be a valuable tool to quantify the severity of liver disease among HBV-infected patients with ESRD. Therefore, and since Fibroscan® is very convenient, the usefulness of Fibroscan® for the follow-up of chronic hepatitis B patients with ESRD, especially for significant liver fibrosis, should be of great interest and needs further evaluation.

The limits of the present study are (1) the small number of HBV-infected patients with ESRD, (2) patients were not equally distributed over stages F1-F4, none of the patients had F4 fibrosis in ESRD group.

CONCLUSION

Transient elastography (Fibroscan®) is a reliable mean for evaluating the severity of liver disease in HBV-infected patients with ESRD, with higher performance compared to patients with normal renal function at the same stage of liver fibrosis.

Future studies are required to compare the use of Fibroscan® versus other serum markers for the diagnosis of liver fibrosis in HBV-infected patients with ESRD.

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