The Diagnostic Value of FibroScan in Assessing Significant Liver Fibrosis in Patients with Chronic Hepatitis B

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ABSTRACT

Objective: *Significant liver fibrosis is recognized as the key link of therapy and prognosis in patients with chronic hepatitis B infection (CHB). The present study is designed to estimate the benefits of FibroScan (FS) in diagnosing significant fibrosis in patients with CHB.*

Methods: *Two hundred and eight consecutive CHB patients, who underwent liver biopsy, FS and laboratory tests, were recruited. The receiver operating characteristic (ROC) curves were generated to assess the performance of non-invasive models.*

Results: *Liver stiffness measurement (LSM) and aspartate transaminase (AST) to platelet (PLT) ratio index (APRI), but not age-platelet index (API) or AST to alanine aminotransferase (ALT) ratio (AAR), were closely correlated with significant fibrosis; areas under ROC curves (AUROC) were 0.817 (*$p < 0.001$*), 0.705 (*$p = 0.003$*), 0.626 (*$p = 0.065$*) and 0.631 (*$p = 0.055$*), respectively. When combining LSM with APRI, the AUROC was 0.813,* $p < 0.001$.

Conclusion: *FibroScan can predict the presence of significant liver fibrosis, so as to avoid liver biopsy. It seems that the combination of FS and APRI does not significantly improve the ability to predict significant fibrosis.*

Keywords: Chronic hepatitis B, FibroScan, liver stiffness measurement, liver biopsy, non-invasive, significant liver fibrosis

El Valor Diagnóstico del FibroScan a la Hora de Evaluar la Fibrosis Hepática Significativa en Pacientes con Hepatitis B Crónica

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RESUMEN

Objetivo: *La fibrosis hepática significativa es reconocida como el vínculo clave de la terapia y el pronóstico en pacientes con infección por hepatitis B crónica (HBC). El presente estudio se diseñó con el fin de evaluar los beneficios del FibroScan (FS) en el diagnóstico de la fibrosis significativa en pacientes con HBC.*

Métodos: *Se alistaron doscientos ocho pacientes consecutivos de HBC, a los que se les había practicado biopsia del hígado, FS y pruebas de laboratorio. Las curvas de la característica operativa del receptor (ROC) fueron generadas para evaluar el funcionamiento de los modelos no invasivos.*

Resultados: *La medición de la rigidez hepática (MRH) y el índice APRI resultante de la relación aspartato-aminotransferasa (AST)/plaquetas (PLT), guardaron una estrecha correlación con la fibrosis significativa, lo cual no fue el caso con el índice de edad-plaqueta (IEP) ó el índice (AAR) resultante de la relación aspartato-aminotransferasa (AST)/alanina transaminasa (ALT). Las áreas bajo las curvas ROC (AUROC) fueron 0.817 (*$p < 0{,}001$*), 0.705 (*$p = 0.003$*), 0.626 (*$p = 0.065$*) y 0.631 (*$p = 0.055$*), respectivamente. Al combinarse la MRH con el índice APRI, el AUROC era 0.813,* $p < 0.001$.

Conclusión: *El FibroScan puede predecir la presencia de fibrosis hepática significativa, de manera que puede evitarse la biopsia del hígado. Según parece, la combinación de FS y APRI no mejora significativamente la capacidad para predecir la fibrosis significativa.*

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Palabras claves: Hepatitis B crónica, FibroScan, medición de la rigidez hepática, biopsia del hígado, no invasivo, fibrosis hepática significativa

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INTRODUCTION

Hepatitis B virus (HBV) infection remains a huge public burden and the major cause of chronic liver diseases, with an estimated 350 million or more affected individuals worldwide (1). Liver fibrosis, in patients with chronic hepatitis B (CHB), is easy to develop into cirrhosis or hepatocellular carcinoma. Therefore, detection of liver fibrosis is proven to be very important in the management of patients with CHB. In particular, according to the guidelines of American Association for the Study of Liver Diseases (AASLD), the presence of significant liver fibrosis is a strong signal to initiate antiviral therapy (2).

Liver biopsy and transient elastography (TE) are the main methods for diagnosing and staging liver fibrosis in clinical practice. Although the gold standard, liver biopsy is invasive and has sampling errors and complications *etc*. Transient elastography is a new, non-invasive and reproducible apparatus for estimating the progression of liver diseases, which is based on the measurement of liver stiffness. This study was to investigate the accuracy of TE, namely FibroScan (FS), combined with other tests, particularly aspartate aminotransferase-to-platelet ratio index (APRI), in assessing significant liver fibrosis in CHB patients.

SUBJECTS AND METHODS

A total of 208 consecutive patients with CHB who underwent TE and liver biopsy at the Department of Infectious Diseases, Southwest Hospital, from October 2012 to April 2014, were included in this study. Chronic hepatitis B was diagnosed on the condition that serum hepatitis B surface antigen (HBsAg) was positive for more than six months (3). Patients with elevated alanine aminotransferase (ALT; normal value $\leq$ 40 IU/L) more than five times the upper limit of normal (ULN) were excluded, because inflammation might influence the results of FS (4, 5). None of the patients had concurrent other viruses or suffered from decompensated cirrhosis, hepatocellular carcinoma, hepatic failure and other diseases.

Laboratory tests, FS and liver biopsy were all carried out on the same day. This research was in accordance with the ethical guidelines of the Declaration of Helsinki, 2008. All people enrolled gave approval to be in the study and signed an informed consent as well.

Laboratory procedure

Serologies for HBsAg were tested in all patients with an automated blood analyser (Advia-Bayer, Leverkusen, Germany). Serum HBV DNA levels were measured using a fluorescent probe-based detection kit (PCR-Fluorescence Probing, Shanghai, China) on real-time polymerase chain reaction system (Roche LightCycler®480II, Basel, Switzerland) with a range of detection from 500 to 10^7 IU/mL. The parameters of routine blood (measured by XT-2000i, SYSMEX, Kobe, Japan) and biochemical tests (measured by 7600 Series, HITACHI, Tokyo, Japan), including platelet (PLT), ALT, aspartate transaminase (AST), gamma-glutamyl trans-peptidase (GGT), total bilirubin (TBIL), serum albumin (ALB), alkaline phosphatase (ALP), globulin and international normalized ratio (INR), were performed before breakfast. In addition, the age-platelet index (API), AST to ALT ratio (AAR) and AST to PLT ratio index (APRI), which were considered to be non-invasive models to evaluate liver fibrosis in patients with CHB (6), were determined.

FibroScan

After having breakfast and prior to liver biopsy, liver stiffness was measured independently by an experienced physician (more than 1000 TE measurements) using FibroScan® (Echosens, Paris, France). The examination procedure was done following the steps described previously (7). The median value of ten successful measurements was the reliable result, provided that interquartile range (IQR) was under 30% of the median value and the success rate, which was calculated as the number of validated measurements divided by the total number, exceeded 60%.

Liver biopsy

Ultrasonography-guided percutaneous biopsy using 16 G disposable needles (Hepafix, B. Braun, Melsungen, Germany) was done on all patients under local anaesthesia. They all had their INR and blood pressure checked before and after biopsy for the sake of security. The specimens with a minimum length of 10 mm and six portal triads were fixed in 10% formalin immediately (8, 9) and they were subsequently sent to the Department of Pathology in our hospital for further analysis. All biopsy samples were reviewed independently by two histopathologists without knowledge of the clinical data.

Liver fibrosis was divided into five stages according to the METAVIR scoring system as follows (10): F0, no fibrosis; F1, mild fibrosis without fibrous septum; F2, fibrosis with few fibrous septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. F2 or more levels ($F \geq 2$) was defined as significant liver fibrosis.

Statistical analysis

Baseline characteristics of patients were represented as mean ± standard deviation (SD) or median and range as appropriate; categorical variables were expressed as number (percentage). All statistical analyses were carried out by the SPSS statistical

software (version 18.0) and Stata statistical package (release 11, 1, 2010, Stata Corporation). For each statistical test, it was statistically significant if *p*-value was less than 0.05. We also obtained 95% confidence intervals (95% CI).

To extend the validation of FS for estimating the progression of CHB, the receiver operating characteristic (ROC) curves and area under ROC (AUROC) curve were adopted here; values closer to 1.0 indicated higher diagnostic accuracy.

RESULTS

Of 46 patients who were excluded from the study, the liver stiffness measurement (LSM) values of 16 patients obtained by FS were invalid due to low success rates or high IQR; 10 had daily alcohol intake of > 40 g/day for at least 10 years; five patients had hepatitis C virus (HCV) or hepatitis E virus (HEV) co-infection. Three patients with hepatocellular carcinoma and 12 patients with hepatitis exacerbations were also ruled out. Thus, the final analysis comprised 162 patients whose baseline characteristics are summarized in Table 1.

Comparisons of baseline characteristics categorized by presence or absence of significant liver fibrosis, based on the METAVIR scoring system, are also listed in Table 1. The majority of CHB patients were male (67.9%) and middle-aged (37.0 ± 11.5 years). Between the two groups, levels of AST, TBIL, ALB and GGT were statistically significantly different ($p < 0.05$), while levels of age, body mass index (BMI), globulin, PLT, ALT, ALP and HBV DNA were not ($p > 0.05$).

The diagnostic performance and corresponding ROC curves of LSM and other non-invasive models for predicting significant fibrosis is shown in the Figure.

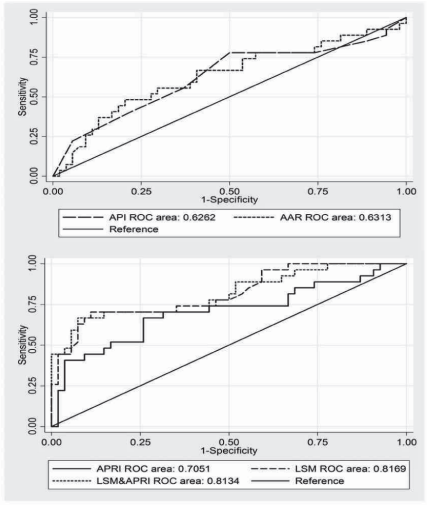

Figure: The receiver operating characteristic (ROC) curves of non-invasive models of liver fibrosis. According to the area under ROC curves, liver stiffness measurement (LSM) and aspartate aminotransferase-to-platelet ratio index (APRI) showed a good value in predicting significant liver fibrosis. However, the diagnostic value of combination of LSM and APRI has not increased significantly. In addition, there were no diagnostic value of age-platelet index (API) and aspartate aminotransferase-to-alanine aminotransferase ratio index (AAR).

Table 1: Baseline characteristics of chronic hepatitis B infection patients with different fibrosis stages

Characteristics	All patients	Group F0–F1	Group F2–F4	*p*-value
Males (n, %)	110/162 (67.9%)	60/108 (55.6%)	50/54 (92.6%)	0.071
Age (years)	37.0 ± 11.5	35.6 ± 10.2	39.8 ± 13.4	0.157
BMI (kg/m^2)	23.2 ± 3.1	23.4 ± 3.1	22.8 ± 3.3	0.662
PLT (10^9/L)	137 (32–304)	141 (52–304)	128 (32–260)	0.194
AST (IU/L)	51 (19–322)	44 (19–322)	64 (20–160)	0.002
ALT (IU/L)	59 (12–199)	54 (12–170)	70 (13–199)	0.091
GGT (IU/L)	53.2 (9.0–330)	39 (9–330)	82 (16–304)	< 0.001
ALP (IU/L)	97.7 (28–398)	87 (28–301)	119 (51–398)	0.056
Globulin (g/L)	30.2 ± 4.3	29.7 ± 4.0	31.3 ± 4.8	0.080
ALB (g/L)	43.6 ± 7.4	44.9 ± 4.6	41.2 ± 10.7	0.032
TBIL (μmol/L)	27.7 (6.1–249.5)	22.2 (6.7–198.3)	38.7 (6.1–249.5)	0.035
HBV DNA (log10 of copies/mL)	5.8 ± 1.9	6.1 ± 1.9	5.2 ± 1.7	0.071
LSM (kPa)	12.8 (3.5–75.0)	8.2 (3.5–31.6)	22.0 (6.3–75.0)	< 0.001

BMI: body mass index; PLT: platelet count; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transpeptidase; ALP: alkaline phosphatase; ALB: albumin; TBIL: total bilirubin; HBV: hepatitis B virus; LSM: liver stiffness measurement

There were 54 (33.3%), 54 (33.3%), 18 (11.1%), 16 (9.9%) and 20 (12.4%) patients with F0, F1, F2, F3 and F4 fibrosis stage, respectively. Consequently, according to the pathological observation, 54 patients had significant fibrosis (Group F2–F4) and 108 patients did not (Group F0–F). As expected, median LSM value was higher in patients with significant fibrosis (22.0 kPa *vs* 8.2 kPa, $p < 0.001$).

The AUROC of API, AAR, APRI and LSM for significant fibrosis (F0–1 *vs* F2–4) was 0.626 (95%CI: 0.489, 0.764, $p = 0.065$), 0.631 (95%CI: 0.496, 0.767, $p = 0.055$), 0.705 (95%CI: 0.575, 0.836, $p = 0.003$) and 0.817 (95%CI: 0.715, 0.919, $p < 0.001$), respectively (11). When combining LSM and APRI, the AUROC was 0.813 (95%CI: 0.707, 0.920, $p < 0.001$). As shown in Table 2, LSM cut-off value of 6.7 kPa had 96.30% sensitivity and 95.65% negative predictive value to

exclude significant fibrosis. Similarly, the APRI value of 0.6583 could detect significant fibrosis with 74.07% sensitivity and 45.45% positive predictive value.

Table 2: Optimal cut-offs for the diagnosis of significant fibrosis

	LSM	APRI	LSM and APRI
Optimal cut-off (#)	6.7	0.6583	0.4357
Sensitivity (%)	96.30	74.07	66.67
Specificity (%)	40.74	55.56	90.74
Positive predictive value (%)	44.83	45.45	78.26
Negative predictive value (%)	95.65	81.08	84.84

LSM: liver stiffness measurement; APRI: aspartate aminotransferase-to-platelet ratio index
#The optimal cut-off value was determined by the maximum value of sensitivity plus specificity

DISCUSSION

Chronic hepatitis B patients with significant fibrosis are considered candidates for antiviral treatment (2). In view of the limitations of biopsy, FS is gradually being recommended as an alternative to the assessment of significant fibrosis by measuring liver stiffness. Therefore, the study was designed to evaluate diagnostic performance of FS in detecting significant fibrosis of CHB patients.

In agreement with other results, middle-aged men were high risk for infection with HBV (12). Serum HBV DNA levels were previously found to correlate with the development of liver fibrosis independent of other parameters (13). In this study, HBV DNA almost remained at the lowest level in F4 stage. However, there was no significant difference in HBV DNA levels between Group F0–F1 and Group F2–F4 due to the small volume of F4 subjects (14); $p = 0.071$.

Some experts argued that AST, GGT, TBIL, ALB and PLT were the most powerful predictors of fibrosis and were further used to create several non-invasive models to evaluate fibrosis (15–21). Here, levels of AST, TBIL, ALB and GGT exhibited the diagnostic performance of significant fibrosis for their statistical differences between the two groups. Platelet count in subjects with significant fibrosis decreased to some extent, though no significant difference existed. This study managed to validate that the serum-marker models of liver fibrosis, including AAR and API, had little predictive value for significant fibrosis, which was not coincident with that reported previously (6). Others supported our findings that neither AAR nor API was deemed diagnostically adequate (22, 23).

In addition, it was observed that LSM and APRI were promising tools for detecting significant fibrosis. Receiver operating characteristic curves showed that the accuracy of LSM in confirming significant fibrosis tended to be superior to APRI, yet combination of them did not significantly improve the performance to a higher level and was not recommended, just as Lesmana *et al* did (24). Aspartate transaminase and PLT are the conventional clinical test items; APRI was a good and feasible screening tool to detect significant liver fibrosis, especially in primary care and obese patients.

The first and foremost problem of our study was the limited number of patients recruited. Moreover, the small proportion of significant fibrosis patients (only one-third) might cause a selection bias and probably lead to the low cut-off points of FS.

In conclusion, FS showed a great diagnostic accuracy in detecting significant fibrosis in patients with CHB and could be applied in clinical practice. Combination of LSM and APRI did not add much benefit in detecting significant liver fibrosis.

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