Research Article

Xian-Zhi Han#, Shu-Feng Zhang*,†, Jia-Yin Yi, Bin Wang, Hui-Qing Sun

Effect of FibroScan test in antiviral therapy for HBV-infected patients with ALT <2 upper limit of normal

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Abstract

Objective – The objective of this study is to detect the liver stiffness of hepatitis B virus (HBV)-infected patients with an alanine aminotransferase (ALT) level of <2 upper limit of normal (2ULN) by FibroScan and compare histological changes to assess the progression of liver lesions and its test results.

Methods – There were 36 patients who had a liver FibroScan degree of >7.3 KD (F1), and a liver biopsy was conducted. Along with serology of liver fibrosis, indexes and hierarchical processing were used for evaluation. The correlation between these factors was analyzed.

Results – The histopathological results of the liver were closely correlated with liver hardness. In the pathological diagnosis of chronic hepatitis, G represents the grade of inflammation and S represents the stage of hepatic fibrosis. Pathological examination results of H&E staining of liver tissue sections revealed that the area under the work characteristic curve of the subjects in G2S1, G2S2, G3S2, and G3S3 stages was 0.923, 0.916, 0.955, and 0.971, respectively, with diagnostic cut-off values of 9.03, 9.85, 15.14, and 30.67, respectively. Furthermore, hydroxyapatite, type III procollagen, laminin, and type IV collagen of serum fibrosis indexes are associated with liver stiffness values (P < 0.05).

Conclusion – FibroScan can be used as an alternative to liver biopsy. It is meaningful in determining whether HBV infected patients with an ALT level of <2 ULN should receive antiviral therapy.

Keywords: FibroScan, HBV infection, ALT <2 ULN, antiviral therapy opportunity

1 Introduction

The incidence of hepatitis B virus (HBV) in the young- and middle-aged population remains relatively high in China and is also the main cause of cirrhosis in China. Determining the correct timing for the administration of antiviral therapy for HBV infection plays an important role in its treatment and prognosis [1]. According to the Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2015 Edition), the time of antiviral treatment for chronic HBV infection is when alanine aminotransferase (ALT) levels are >2 upper limit of normal (ULN). When the ALT level is <2 ULN, only patients with histopathological changes need to receive the antiviral treatment [2]. Liver biopsy is the gold standard for histopathological results. However, it is an invasive procedure, and as such, patient acceptance is low. Due to this, liver biopsies are unable to be routinely conducted. Furthermore, the uneven distribution of hepatic fibrosis and differences in subjective observations can often lead to misdiagnosis. An alternative to this is FibroScan, which is a non-invasive device that can be repeatedly carried out [3,4]. In patients with normal liver function, some may have occult hepatitis, hepatic fibrosis, and F2 or above and require a selective liver biopsy to determine whether antiviral therapy is necessary. Hence, FibroScan is a great alternative to these patients.

2 Data and methods

2.1 Clinical data

From July 1, 2015, to June 30, 2017, 36 patients with HBV infection who were diagnosed with hepatic
fibrosis with a degree of >7.3 KD (F1 or above) underwent liver biopsy. There were 28 males and 8 females. The average age of these patients was 50.2 ± 11.3 years, with a mean body mass index of 22.53 ± 2.67. The diagnosis conformed to the diagnostic criteria within the Guidelines for the Prevention and Control of Chronic Hepatitis B (2010 Edition), which was jointly established by the Chinese Medical Association Liver Disease Branch and the Association of Infectious Diseases of the Chinese Medical Association [5]. The patients were divided into three groups, according to their liver hardness values: F1–F2 (7.3–9.7), F2–F3 (9.7–12.4), and F3 (12.4 or above).

Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

2.2 Methods

Enzyme-linked immunosorbent assay was used to measure hepatitis B. The HBV DNA was detected by polymerase chain reaction, and patients with high values subsequently underwent a high-sensitivity test. Liver fibrosis was detected by the FibroScan502 system (France). Color Doppler ultrasound, α-fetoprotein detection, and routine biochemical tests (ALT, aspartate transaminase, total bilirubin, hydroxyapatite [HA], laminin [LN], etc.) were also conducted. Liver hardness was measured using the FibroScan system. For each patient, two measurements were taken on the same day by the same technician, once in the morning and once in the evening 2 h after dinner. The final result was the mean value of these two tests. Patients with a FibroScan result of >7.3 KD (F1) and abnormal hepatic fibrosis indexes were stratified. Patients in each group underwent a liver biopsy within 1 week.

2.3 Statistical analysis

The experimental data were subjected to statistical and correlation analyses using the SPSS 25.0 software. Measurement data were expressed as mean ± standard deviation (x ± SD) and compared among groups using univariate analysis of variance (ANOVA). Data were compared between two groups using independent sample t-test. The diagnostic accuracy of FibroScan results was evaluated through the receiver operating characteristic (ROC) curve. The sensitivity and specificity of the FibroScan diagnostic technique were calculated with a P < 0.05 that was considered to be statistically significant.

3 Results

3.1 General data of the included patients

A total of 623 chronic HBV-infected patients had an ALT level of <2 ULN. Furthermore, 66 patients had abnormal FibroScan and serological results (10.59%), and 36 patients met the inclusion criteria and underwent a liver biopsy. Among these 36 patients, 15 patients were at F1–F2 stage, 17 patients were at F2–F3 stage, and 4 patients were at F3 or above stage (Table 1). A comparison of histology sections of these three different pathological stages is presented in detail in Figure 1.

3.2 Evaluation results of FibroScan diagnostic test

With the results of the 36 patients serving as the standard, the diagnostic value of FibroScan was evaluated using the diagnostic ROC curve, and the cut-off value was obtained through the Jordan index. These results suggest that the area under the curve (AUC) was >0.9 at all stages, and both the sensitivity and specificity were high. This shows that the diagnostic value of FibroScan is high (Table 2).

| Groups/pathology | N   | G1S0 | G2S1 | G2S2 | G3S2 | >G3S3 |
|------------------|-----|------|------|------|------|-------|
| F1–F2            | 15  | 11   | 2    | 2    | 0    | 0     |
| F2–F3            | 17  | 2    | 10   | 4    | 1    | 0     |
| >F3              | 4   | 0    | 2    | 1    | 1    |       |
### 3.3 Correlations between FibroScan and serological indicators

The one-way ANOVA of the correlations between serological indexes and liver hardness in the 36 patients showed statistically significant ($P < 0.05$) differences in HA, type III procollagen (PCIII), LN, and type IV collagen (CIV) levels among patients with different liver hardness (Table 3).

### 3.4 Correlation between the FibroScan result and HBV DNA load

The high-sensitivity test revealed low virus replication in all the 36 patients. Furthermore, there was no significant correlation between liver fibrosis and virus DNA levels (Table 4).

### 4 Discussion

Due to hepatitis B immunization, the growth rate of HBV infection in China has decreased to a certain extent. However, the total number of infected patients remains large [6]. The early screening of hepatitis B and timely administration of antiviral therapy are important measures to reduce the risk of liver failure and death [7]. This is particularly important in patients with chronic HBV infection. According to the Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2015 Edition), for patients with HBV infection, when the ALT level is $<2$ ULN, only those with pathological changes are required to undergo antiviral treatment [2]. Recently updated guidelines by the American Association for the Study of Liver Diseases (AASLD) recommend that patients with HBV infection and cirrhosis undergo antiviral therapy. In addition, patients with HBV DNA levels of $>2,000$ IU/mL regardless of ALT level should receive antiviral therapy. When the ALT level is $<2$ ULN, the pathological changes of the liver are taken into account to determine whether antiviral treatment is required [8,9].

Hepatic fibrosis refers to the condition when excessive extracellular matrix (ECM) deposition occurs in the liver, and the abnormal hyperplasia of a large number of fibrous tissues occurs in the portal area. This is a reversible pathological condition during the process where various chronic liver diseases develop to cirrhosis [10–12]. The ECM production is the core link of hepatic fibrosis. This occurs by the synthesis and decomposition of collagens in the liver, including HA, CIV, PC III, and LN, and lose dynamic balance, which causes oxidative

#### Table 2: Diagnostic indexes of FibroScan

| Stages | AUC   | 95% confidence interval | Critical value | Sensitivity (%) | Specificity (%) |
|--------|-------|-------------------------|----------------|----------------|-----------------|
| ≥G2S1  | 0.923 | 0.832–1.000             | 9.03           | 91.3           | 84.6            |
| ≥G2S2  | 0.916 | 0.821–1.000             | 9.85           | 90.9           | 84.0            |
| ≥G3S2  | 0.955 | 0.866–1.000             | 15.14          | 80.0           | 99.8            |
| ≥G3S3  | 0.971 | 0.916–1.000             | 30.67          | 99.9           | 78.6            |
Table 3: Correlation between FibroScan and serum fibrosis for 36 HBV-infected patients with ALT <2 ULN

| Groups | N   | HA (µg/L)      | PCIII (µg/L) | LN (ng/mL)   | CIV (ng/mL)   |
|--------|-----|----------------|--------------|--------------|---------------|
| F1–F2  | 15  | 241.80 ± 131.70| 209.36 ± 46.25| 185.17 ± 18.69| 210.27 ± 141.97* |
| F2–F3  | 17  | 402.36 ± 134.82*| 225.64 ± 58.75*| 209.48 ± 55.35*| 260.20 ± 97.80* |
| >F3    | 4   | 483.55 ± 142.24*| 267.61 ± 48.40*| 251.90 ± 35.90*| 288.74 ± 87.86* |
| F      |     | 9.428          | 7.241        | 5.806        | 7.106         |
| P      |     | 0.001          | 0.019        | 0.034        | 0.022         |

Note: Compared with F1–F2, *P < 0.05; compared with F2–F3, ▲P < 0.05.

Table 4: Correlation between FibroScan and HBVDNA for 36 HBV-infected patients with ALT <2 ULN

| Groups | N/HBV DNA (IU/mL) | <5 × 10⁵ | 5 × 10⁵–10⁶ | 10⁶–10⁷ | >2 × 10⁷ |
|--------|-------------------|----------|------------|---------|---------|
| F1–F2  | 15 (367)          | 5        | 5          | 4       |         |
| F2–F3  | 17 (450)          | 5        | 3          |         |         |
| >F3    | 4 (201)           | 5        | 1          | 0       |         |

Antiviral treatment in patients with HBV infection has been shown to reduce the viral load [1,23], and monitoring is needed during the process of antiviral treatment [24]. A study reported that hepatic stiffness was measured to monitor the outcomes of hepatic fibrosis in antiviral therapy, and the result confirmed that long-term viral inhibition was correlated with the outcomes of hepatic fibrosis [25]. Therefore, monitoring the degree of hepatic fibrosis is useful during antiviral treatment. In China, the Guidelines for the Prevention, Management, and Treatment of Chronic HBV Infection (2015 Edition) also emphasize that FibroScan can be used to monitor hepatic hardness in chronic HBV infection, to improve the success rate and speed of detection [2]. Thus, identifying the degree of hepatic fibrosis is not only the key to knowing when to start antiviral treatment but also of importance for the evaluation during antiviral therapy and post-treatment. In our study, the accuracy of FibroScan to assess hepatic hardness in hepatic fibrosis was evaluated.

The levels of HA, LN, and serum albumin, hepatic hardness, and biopsy results were compared among all selected patients. The results revealed that relevant serum biochemical parameters and hepatic hardness were correlated with the stage and grade of hepatic biopsy (P < 0.005). This demonstrates the detection accuracy of FibroScan and reveals that hepatic stiffness is significantly correlated with hepatic fibrosis. However, there are limitations to the current study. This includes that all the selected patients were patients with viral hepatitis. We did not investigate whether there was a difference in hepatic hardness in patients with different types of chronic liver diseases, and further investigations are required to elucidate this.

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Conflict of interest: The authors state no conflict of interest.

Data availability statement: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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