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Case Report

# The Diagnostic value of FibroScan for the degree of liver fibrosis in patients with ALT<2×ULN chronic hepatitis B

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## Abstract

**Objective:** This paper studied the diagnostic value of FibroScan (FS) for the degree of liver fibrosis in patients with ALT<2×ULN chronic hepatitis B(CHB).

**Methods:** 100 ALT<2×ULN CHB patients, who also with liver biopsy in our hospital from January 2017 to May 2019 were enrolled. According to the results of liver biopsy, patients that below G2 were classified as mild inflammation group. patients that above G2 were classified as moderate inflammation group; patients that below S2 were designated as non-significant fibrosis group, patients that above S2 and equal to S2 were designated as significant fibrosis group, then compared it with the results of Liver Stiffness Measurement (LSM) which measured by FS respectively.

**Results:** 91 out of 100 patients had complete data, there were 60 patients in mild liver inflammation group, 31 in the moderate inflammation group, 53 patients belong to no significant fibrosis group and 17 patients belong to significant fibrosis group, comparison, there were statistically significant between the two groups of LSM ($Z= 3.303$, $P = 0.001$; $Z= 4.944$, $P < 0.001$); FS diagnosis of significant liver fibrosis area under the curve (ACU) were 0.851, 95% CI (0.765-0.937), when the Yoden index is 0.59, the LSM optimal cut-off value is 5.35, and the corresponding sensitivity value is 86.4%, the specificity value is 72.5%.

**Conclusion:** For patients with ALT<2×ULN CHB, the liver stiffness measurement (LSM) measured by FS is related to the degree of fibrosis in the liver tissue. When the optimal cut-off value of LSM is 5.35, its diagnosis is most effective in significant liver fibrosis.

## Backbround

Liver fibrosis is a pathological process in the development of chronic hepatitis B to cirrhosis, accurate evaluation of the degree of liver fibrosis is helpful to guide clinical diagnosis and treatment. At present, the gold standard for liver fibrosis evaluating is liver pathological examination of liver biopsy, however, due to invasiveness, sampling error, observer error and inability to observe dynamically, it is difficult to conduct as a general survey or routine examination, and also limits the application in clinic. FibroScan (FS) is a non-invasive ultrasound technique for survey the liver stiffness rapidly, it reflect liver fibrosis by measuring Liver Stiffness Measurement (LSM), because of its non-invasive, simple, rapid, easy to operate,



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reproducible, safe and well tolerated characteristics, it has been recommended as an important means of clinical evaluation for hepatitis B and C virus-related liver fiber by AASLD, EASL and China Guidelines for the prevention and treatment of CHB [1-3]. In addition, China guidelines for the prevention and treatment of CHB (2015 update) indicated that: people who in ALT <2×ULN and with normal bilirubin level and never received antiviral therapy, when LSM was greater than or equal to 10.6 kPa can be diagnosed as cirrhosis; LSM≥9.4 kPa can be diagnosed as significant liver fibrosis; and LSM<7.4 kPa can be excluded progressive liver fibrosis; people with LSM between 7.4-9.4 kPa, if it is difficult to make a correct clinical decision, liver biopsy can be considered [4]. In this study, FS and liver biopsy were performed on 100 CHB patients with normal bilirubin levels and ALT<2×ULN to observe the diagnostic value of LSM to liver stiffness.

## Subjects and methods

### Subjects

A total of 100 patients with CHB who are in the Second People's Hospital of Lanzhou, Gansu province, P. R. China from January 2017 to May 2019 were invited in this study as below inclusion criteria: the diagnostic criteria were based on the guidelines for the prevention and treatment of CHB formulated by the Chinese Medical Association in 2015 [2], and excluded from clear interference factors, at the same time conform to the following conditions: patients with the ALT normal or increased twice as much as normal, total bilirubin was normal and HBV-DNA positive, body mass index <28kg / $m^2$, has not received antiviral and anti-enzyme drugs, and exclude alcoholic liver disease, drug-induced hepatitis, non-alcoholic fatty liver, overlap with other hepadnavirus infections, no autoimmune liver disease and congenital genetic diseases. All patients underwent blood cell analysis, and biochemistry, coagulation, HBV-M, HBV-DNA, liver biopsy examination.

### Laboratory test

Blood cell analysis, biochemistry and HBV-M, HBV-DNA detection were tested in all patients with blood cell analyzer (BC-3000, Shenzhen Maiduan Company), Beckman biochemical analyzer (AU680, American Beckman Olympus Company), Abbott automatic chemiluminescence analyzer(American), Step one plus PCR fluorescence analyzer (American) respectively, and relevant test results were collected.

### Liver biopsy and pathological diagnosis

The liver tissue was located and obtained by ultrasound-guided puncture. Observed under light microscope after fixation, embedding, sectioning, HE staining and modified Goniri reticular fiber staining. The staging (S) criteria of liver fibrosis was in accordance with the "Hepatic Fibrosis Diagnosis and Efficacy Assessment Consensus" developed by the Liver Fiber Chemistry Group of the Chinese Liver Disease Society in 2002.

### Fibroscan

The FS (purchased from Echosens, France, probe M) was used to measure the patient's LSM within one week before liver biopsy, refer to the FS user manual for specific methods.

### Definition

Significant fibrosis: fibrosis stage 2 or above (≥S2); moderate inflammatory necrosis: inflammation grade 2 or higher(≥G2); upper limit of ALT normal value (upper limit of Normal, ULN) is 40 U/L [5,6].

### Statistical methods

All statistical analyses were carried out by the SPSS 19.0 and MedCalc 9.3 statistical software, the measurement data conforming to the normal distribution was represented by ($\overline{x} \pm s$), we used t-test of two independent samples for comparison between groups; the data of non-normal distribution was indicated by M (P25, P75), and adopted Wilcoxon W test; the count data is analyzed by chi-square test. Taking liver histopathological changes as the gold standard, using the receiver operating characteristic curve (ROC), calculating the area under the curve (AUC), calculating the Youden's index, then get the optimal cut-offs and its sensitivity and specificity were calculated to evaluate the diagnostic value of FS, the difference was statistically significant at P<0.05.

## Results

### General information

91 patients with complete data who were enrolled in 100 patients, including 58 males and 33 females, aged (17-63) years old, were recruited, their blood cells, liver function, INR, HBV-M, HBV-DNA and other indicators.

### Pathological results according to the patient's liver biopsy

The inflammatory activity was divided into mild inflammation group (<G2) and moderate. Inflammation group (≥G2), the former had a total of 61 patients, including 42 males and 19 females, with an average age of (34.4±10.1) years old, and the latter a total of 30 patients, 16 males and 14 females, mean age (38.5±12.6) years old, there was no statistical significance in gender composition and age difference between the two groups ($\chi^2$= 2.095, P= 0.148; t= 1.987, P= 0.050); Similarly, the degree of fibrosis was divided into no significant fibrosis group (<S2) and significant fibrosis group (≥S2), 22 patients had significant fibrosis and 69 patients did not, the significant fibrosis group including 13 males and 9 females and middle-aged(37.7±12.9), another group had 45 males and 24 females, and also middle-aged(35.4±10.1), there was no statistical significance in gender composition and age difference between the two groups ($\chi^2$= 0.271, P= 0.603; t= 0.871, P= 0.386); Compared the LSM levels of patients in different liver biopsy group, there were statistically significant in difference between the two groups.

### The diagnosis value of FS for significant liver fibrosis

Liver biopsy was used as the gold standard, and the degree of fibrosis ≥S2 was determined to be significant fibrosis. The area under the curve (ACU) for FS diagnosis of liver fibrosis was



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0.851, 95% CI (0.765-0.937), as shown in Figure 1, When the Yoden index is 0.59, LSM cut-off value of 5.35 kPa had 86.4% sensitivity and 72.5% specificity.

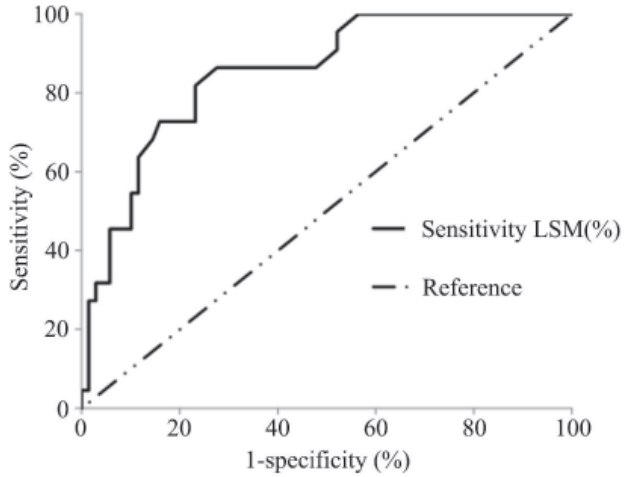


**Figure 1:** LSM diagnosis of CHB fibrosis ROC curve.

## Discussion

The liver is a silent organ, most chronic hepatitis and even early cirrhosis without specific symptoms, signs and biochemical indicators, however, once patients have been found some obvious symptoms and signs, most of them have cirrhosis and even liver failure [7-9]. In consequence, the diagnosis of liver fibrosis is of great value in the prognosis evaluation and treatment decision of chronic liver disease, it is a key step in the management of chronic liver disease to timely evaluate and find advance liver fibrosis and early diagnosis of liver cirrhosis. As a relatively mature non-invasive inspection, TE has the advantages of simple operation, good reproducibility, and accurate identification of mild liver fibrosis and progressive liver fibrosis or early cirrhosis [2,10]. After a decade of development, it has been verified that FS can be used to assess the degree of liver fibrosis in different liver diseases, but its clinical diagnostic threshold still lacks a large number of liver biopsy to be clear [10,11]. Yuan lichao et al. performed liver biopsy and pathological staging on 45 patients with CHB, and diagnosed of liver fibrosis with FS, then the analysis of the receiver operating characteristic curve found that the degree of liver fibrosis ≥Sl, ≥S2, ≥ S3 and ≥S4, the area under the receiver operating characteristic curve were 0.889, 0.941, 0.908 and 0.911, respectively, it indicates that FS is effectly in staging diagnosis of liver fibrosis. A meta-analysis of a total of 2772 patients with CHB , included 18 studies showed that when the liver fibrosis stage≥S2, S3-S4, S4 ,and thresholds were 7.9 kPa, 8.8 kPa, 11.7 kPa, respectively, and LSM values of 11.7 kPa as diagnose cirrhosis, the critical value has a sensitivity of 84.6% and a specificity of 81.5% [12]. The FS principle uses liver stiffness to reflect the degree of liver fibrosis, but the measured value does not depend entirely on the degree of liver fibrosis. Some experts argued that FS measurements have many influencing factors, such as body weight, gender, diabetes, ALT and liver steatosis, jaundice, inflammation, diet, etc [13-16].

In this study, patients with the ALT standard, or increased but less two times higher than the standard value total bilirubin normal, HBV-DNA positive, body mass index <28kg / m$^2$, has not received antiviral and anti-enzyme drugs, and exclude alcoholic liver disease, drug-induced hepatitis, non-alcoholic fatty liver, overlap with other hepadnavirus infections, no autoimmune liver disease and congenital genetic diseases were be choosen as the research object, exclude the impact of the above factors on FS measurements, the results showed that there were differences between LSM, hepatic inflammatory activity and the degree of fibrosis in 91 patients with CHB, here, we found when the LSM optimal cut-off value of patients with significant fibrosis in liver biopsy was 5.35, the sensitivity was 0.824 and the specificity was 0.736, therefore, for patients with CHB and HBV-DNA positive, if the transaminase is normal or slightly elevated, and the liver hardness value reaches 5.35, the liver tissue may be fibrotic, in addition, it is different from the previous study that LSM less than 7.4KPa can rule out progressive liver fibrosis, the intensive research is needed by further expand the number of cases.

### Compliance with ethical standards

Ethical approval This present study was approved by the Ethics Committee of Lanzhou Second People's Hospital.

Informed consent Informed consent was obtained from each participant before enrolling in this study.

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