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Original Article

Diagnostic value of transient elastography combined with noninvasive scores for the detection of advanced liver fibrosis in chronic hepatitis B patients

Xueju Zhang[1], Yu Zhang[2], Qianyi Qiu[1], Chunmei Zhang[1], Changjun Wu[1]

[1]Department of Ultrasound, No. 1 Hospital of Harbin Medical University, Harbin 150001, China; [2]Department of Radiology, Aerospace 731 Hospital, Beijing 100074, China

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Abstracts: Introduction: To explore whether a noninvasive scores could improve the diagnosis value of liver stiffness measurement (LSM) with transient elastography (TE) for detecting advanced liver fibrosis in patients with chronic hepatitis B. Methods: LSM by TE, APRI, FIB-4 and BARD scores were conducted in 93 chronic hepatitis B patients. And liver biopsy was recognized as gold standard to identify the histopathological type of tissue samples. The area under the receiver operating curve (AUROC) was used to assess the diagnostic value. Results: No or insignificant fibrosis (fibrosis stage ≤ 2) was found in seventy patients (75.27%); advanced fibrosis (stage > 2) was found in 23 patients (24.73%). The sensitivity of LSM by TE, APRI, BARD and FIB-4 scores for advanced fibrosis was 78.3, 73.9, 78.3, and 69.9%, respectively, and the specificity was 91.4, 75.7, 72.9, and 81.4%, respectively. Even though the AUROC of LSM combined with noninvasive scores was larger than LSM alone, there have no significant statistical difference between LSM alone and LSM combined with noninvasive scores. Conclusion: In the present study, both LSM by TE and noninvasive indices/scores (APRI, BARD and FIB-4 scores) were discovered to be similarly reliability for noninvasive diagnosis of advanced hepatic fibrosis of chronic hepatitis B. However, their combination cannot significantly improve the diagnostic accuracy of LSM by TE.

Keywords: Transient elastography, biopsy, fibrosis, hepatitis B, noninvasive evaluations, diagnosis

Introduction

As we known that, hepatitis B virus (HBV) still remains a public health problem (especially in East Asia), affecting more than 350 million people worldwide [1]. Various etiologies including HBV infection can trigger chronic hepatic injury of patients, and results in persistent hepatic inflammation and progressive fibrosis [2]. Different with acute injury, chronic hepatic injury promote the progression and resolution of fibrosis through induces repetitive tissue damage and wound healing process [3]. And the severity of liver fibrosis predicts the speed of disease progression (cirrhosis, portal hypertension and hepatocellular carcinoma (HCC)). Therefore, the accurate diagnosis of liver fibrosis is critical for the management of Chronic HBV infection (CHB).

Liver biopsy is a recognized "gold standard" for diagnosing and staging liver fibrosis [4]. However, there have several shortcomings limit its reduplicative application in clinical work. Firstly, liver biopsy is invasive and have a certain chance to cause complications even death [5]. In addition, the diagnostic accuracy of liver biopsy is mainly depends on the biopsy specimens and the experience of observer. Sampling errors (such as small and fragmented) can result in mistaken estimation of the degree of liver fibrosis. Intraobserver and interobserver variability also can significantly impact the interpretation of liver fibrosis.

On the other hand, there have two kinds of noninvasive assessment of liver fibrosis including noninvasive combined indices/scores and liver stiffness measurement (LSM) with transient elastography (TE). TE (FibroScan®, EchoSens, Paris, France) is a rapid, objective, promising and reproducible technique for estimating liver fibrosis [6]. Even though TE has been well vali-

Table 1. Baseline characteristics of the 93 included chronic hepatitis B patients

General characteristics	Mean ± SD
Age (years)	45.92 ± 6.00
BMI (kg/m^2)	29.05 ± 5.24
Waist circumference (cm)	102.59 ± 11.12
Hip circumference (cm)	109.78 ± 9.56
Systolic BP (mmHg)	127.98 ± 23.30
Diastolic BP (mmHg)	85.32 ± 15.83
Diabetes mellitus (yes/no)	21/73
AST (U/L)	54.39 ± 34.56
ALT (U/L)	81.76 ± 60.01
Triglycerides (mg/dL)	180.85 ± 86.47
Total cholesterol (mg/dL)	199.07 ± 110.30
HDL (mg/dL)	42.96 ± 18.69
LDL (mg/dL)	119.57 ± 50.37
Ferritin (ng/mL)	157.48 ± 49.32
Glucose (mg/dL)	120.54 ± 61.56
Hb (g/dL)	15.43 ± 3.29
CRP (mg/dL)	6.02 ± 12.37
Platelet count (10^9/L)	243.98 ± 89.33

dated in chronic hepatitis C patients, however, limited data are available in patients with other liver diseases, including chronic hepatitis B [7]. Besides LSM by TE, numerous noninvasive combined indices/scores have been formulated to estimate the degree of liver fibrosis, such as aspartate aminotransferase/platelet ratio (APRI) [8], FIB-4 score [9], and BARD score [10].

In the present study, we hypothesized that the combinational use of TE and noninvasive combined indices/scores could improve the noninvasive detection and characterization of liver fibrosis in patients with chronic hepatitis B. We therefore tested whether adding noninvasive combined indices/scores of APRI, FIB-4 score and BARD score to TE could elevate its diagnostic value for the detection of advanced fibrosis in patients with chronic hepatitis B.

Methods

Patients

The current study was designed as a retrospective study. Between March 2013 and April 2015, a total of 93 CHB patients who were consecutively included at No. 1 Hospital of Harbin Medical University, China. We defined that the presence of serum hepatitis B surface antigen (HBsAg) should persist for at least 6 months and HBV DNA positivity on a polymerase chain reaction (PCR) assay. The study protocol was prepared in accordance with the ethical guidelines of the 1995 Declaration of Helsinki and was approved by the independent ethics committees of No. 1 Hospital of Harbin Medical University. All included patients provided written consent prior to liver biopsy.

All included patients were filtrated by clinicians according to the following inclusion and exclusion criteria. Inclusion criteria: (1) 18 to 64 years old; (2) HBsAg presence time ≥ 6 months; and (3) availability of records of patients' demographics, liver biochemistries, HBV DNA levels, and HBV genotypes. Exclusion criteria: (1) liver cirrhosis or HCC; (2) infection with hepatitis A, hepatitis C, hepatitis D, hepatitis E, or human immunodeficiency virus; (3) drug hepatitis, Wilson disease, alcohol-related liver disease (> 30 g/day for > 5 years), and autoimmune hepatitis drug hepatitis; (4) hemolytic diseases or jaundice caused by obstructive; (5) prolonged prothrombin time induced by blood system diseases; (6) LSM failure, invalid LSM (defined as an interquartile range (IQR) to median value ratio (IQR/M) > 0.3, success rate < 60%, or < 10 valid measurements); (7) co-morbid condition, uncontrolled metabolic condition or psychiatric condition; and (8) antiviral treatment within the previous 6 months.

LSM by TE

LSM was determined using Fibroscan® (Echosens, Paris, France) as described by Sandrin [6]. The TE operator was a physician who had previously performed LS by Fibroscan® on at least 100 patients (D. C.). Patients with LSM failures or unreliable examinations were excluded (n=2). LSM failure was defined as zero valid shots and unreliable examinations were defined as fewer than 10 valid shots, an interquartile range/LSM more than 30%, or a success rate less than 60%. A reliable LSM result was defined as at least 10 valid shots, a success rate of at least 60%, and interquartile range less than 30% of the median LSM value.

Liver biopsy

Liver biopsy was conducted by using a 16-gauge needle (Bard, Germany, 1620) according to the standard Menghini technique. Two experienced

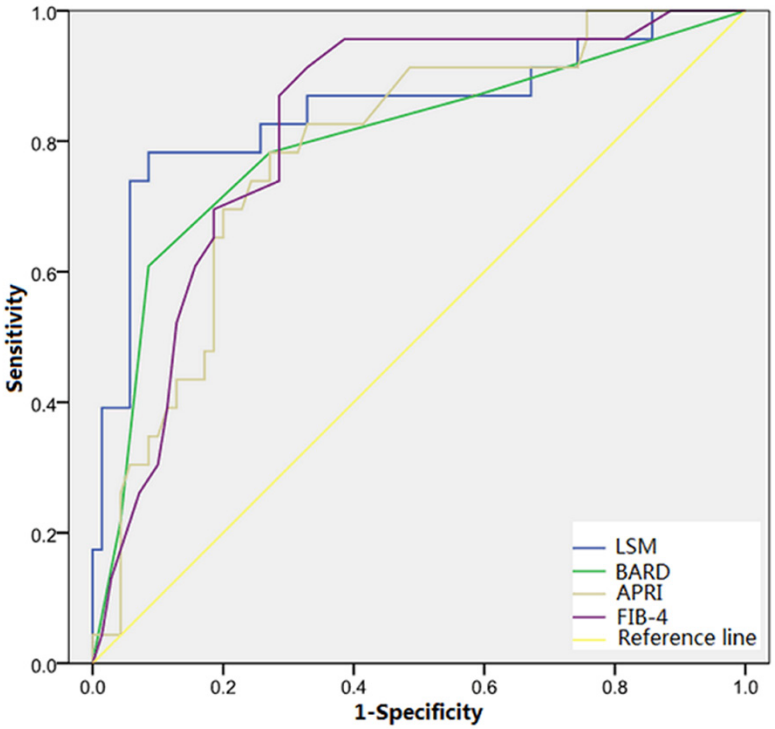

Figure 1. ROC curves of the LSM by TE, APRI, BARD, and FIB-4 scores for detecting advanced liver fibrosis (F ≥ 3) in patients with chronic hepatitis B.

pathologists were assigned to assess the liver specimens, independently. Any disagreement was settled by consensus. Only specimens of more than 20 mm and with ≥ six completely portal tracts were accepted for histological analysis. Specimens were staged for fibrosis according to the METAVIR classification: no fibrosis (F0); portal fibrosis with-out septa (F1); portal fibrosis with few septa (F2); numerous septa without cirrhosis (F3); and cirrhosis (F4). A cut-off value of F ≥ 3 was considered to indicate advanced fibrosis [11].

Noninvasive indices/scores

According to Wai's formula [8], the APRI score was calculated as follows: (AST/upper limit of normal considered as 40 IU/l)/platelet count (expressed as platelets × 10^9/l) × 100. The BARD score is composed of three variables and the possible score ranges from 0 to 4 points, that is AST/ALT ratio at least 0.8 (2 points); a BMI at least 28 kg/m^2 (1 point); and presence of diabetes (1 point) [10]. According to Harrison et al. [10], BARD scores equaling 0 or 1 have a high (96%) negative predictive value for the presence of advanced fibrosis. The FIB-4 score was formulated using Sterling's formula [9] as follows: age (years) × AST (IU/l)/platelet count [(expressed as platelets × 10^9/l) × ALT$^{1/2}$ (IU/l)].

Statistical analysis

The statistical computations were conducted using the Statistical Package for the Social Sciences (SPSS), version 19.0 (IBM Corporation, Somers, New York, USA). Quantitative variables are reported as means ± SDs, and categorical variables are reported using absolute frequencies. The sensitivities and specificities were calculated for each diagnostic modality using receiver operator characteristic (ROC) curves. The AUROCs for different noninvasive tests were compared using paired significance tests by MedCalc, version 15.6 (MedCalc Software, Belgium). If $P < 0.05$ was considered statistically significant (two-tailed).

Results

Patient characteristics

The general characteristics of included patients are summarized in **Table 1**. The mean age of the 93 patients (47 males, 46 females) was 45.92 ± 6.00 years (range, 25-67 years). There were 61 patients infected with genotype B HBV and 32 patients infected with genotype C HBV. Twenty patients (21.51%) were classified as F0, thirty-three patients (35.48%) were classified as F1, seventeen (18.28%) patients were classified as F2, fifteen (16.13%) patients were classified as F3, and eight (8.60%) patients were classified as F4. No or insignificant fibrosis (fibrosis stage ≤ 2) was found in seventy patients (75.27%); advanced fibrosis (stage > 2) was found in 23 patients (24.73%).

Diagnostic value of noninvasive indices/scores

According to the formulas of APRI score, BARD score and FIB-4 score, we calculated their ROC curves for detecting advanced fibrosis of CHB

Table 2. AUROCs and sensitivities/specificities of the LSM by TE, APRI, BARD, and FIB-4 scores for detecting advanced liver fibrosis (F > 2) in patients with chronic hepatitis B

Covariate	AUC	Optimal cutoff	Standard error	Gradual Sig. b	LL of 95% CI	UL of 95% CI	Sensitivity (%)	Specificity (%)
LSM	0.849	10.5	0.055	0.000	0.741	0.957	78.3	91.4
BARD	0.798	2.0	0.059	0.000	0.682	0.915	78.3	72.9
APRI	0.785	0.72	0.053	0.000	0.682	0.889	73.9	75.7
FIB-4	0.821	0.85	0.048	0.000	0.727	0.915	69.6	81.4

Table 3. Transient elastography parameters of the 93 included chronic hepatitis B patients

TE parameters	Mean ± SD
LSM (kPa)	5.18 ± 4.79
Valid shot (n)	12.3 ± 2.4
Success rate (%)	87.5 ± 7.6
Interquartile range LSM	2.0 ± 1.5
Interquartile range LSM/median	14.8 ± 5.8

patients and used the results of FB as gold standard (**Figure 1**). The sensitivity of APRI, BARD and FIB-4 scores for advanced fibrosis was 73.9, 78.3, and 69.9%, respectively, and the specificity was 75.7, 72.9, and 81.4%, respectively. For each noninvasive indices/scores, the optimal cutoff, AUROCs (95% confidence interval (CI)) and sensitivities/specificities are summarized in **Table 2**.

Diagnostic value of LSM by TE (alone or combined with noninvasive scores)

The mean LSM value of all 93 patients was 5.18 ± 4.79 kPa (range from 3.92 to 19.73 kPa). And the results of LSM assessment are shown in **Table 3**. At an optimal cutoff value of 10.5 kPa, LSM had an AUROC of 0.849 [95% CI=0.751-0.957] for the prediction of significant fibrosis (P=0.000) (**Figure 1**).

After combined with noninvasive scores, the ROC curves for the detection of advanced fibrosis were then generated using the results of FB as gold standard (**Figure 2**). The sensitivity of LSM combined with APRI, BARD and FIB-4 scores for advanced fibrosis was 87.0, 82.6 and 91.3%, respectively, and the specificity was 90.0, 91.4 and 92.9%, respectively. Even though the AUROC of LSM combined with noninvasive scores larger than LSM alone, there have no significant statistical difference between LSM alone and LSM combined with noninvasive scores (**Table 4**).

Discussion

Various types of chronic hepatic diseases, including CHB, will develop to a certain stage of liver fibrosis. As we known that advanced liver fibrotic change of patient is strongly predict a highly risk of mortality. Liver biopsy (LB) is a traditional method to discover hepatic fibrosis, and it is also the gold standard for detecting hepatic fibrosis. However, LB have several short-comes which limited its duplicative use to detect liver fibrosis for one patient. Latterly, numerous noninvasive methods were implemented, including noninvasive indices/scores (APRI, Fibrometer, FibroIndex, BARD and FIB-4 et al.), LSM by TE, serum biomarkers (glycoproteins, collagenases and collagenase inhibitors), real-time tissue elastography, magnetic resonance (MR) elastography, combinations of serum markers and imaging, and acoustic radiation force impulse methods [2].

Although most of the noninvasive indices/scores were initially implemented based on the data of patient with chronic hepatic C, researchers [12-14] found that they also have significant diagnostic value for detecting advanced fibrotic change in patient with chronic hepatitis B. Sebastiani G et al. [15] found that stepwise combination algorithms of APRI, Fibrotest and biopsy showed excellent performance (0.96 AUC, 100% NPV) for significant fibrosis and 0.95 AUC, 98% NPV for cirrhosis, with 50%-80% reduced need for liver biopsy. Our results confirmed that APRI, BARD and FIB-4 scores can reliably detect advanced hepatic fibrosis of patient with chronic hepatitis B. The AUROC of APRI, BARD and FIB-4 scores was 0.798, 0.785 and 0.821, respectively.

Because the LSM by TE have been found significantly correlate with the proportion of the liver affected by fibrosis, TE is becoming popular equipment for staging hepatic fibrosis. More and more associated data were reported for its

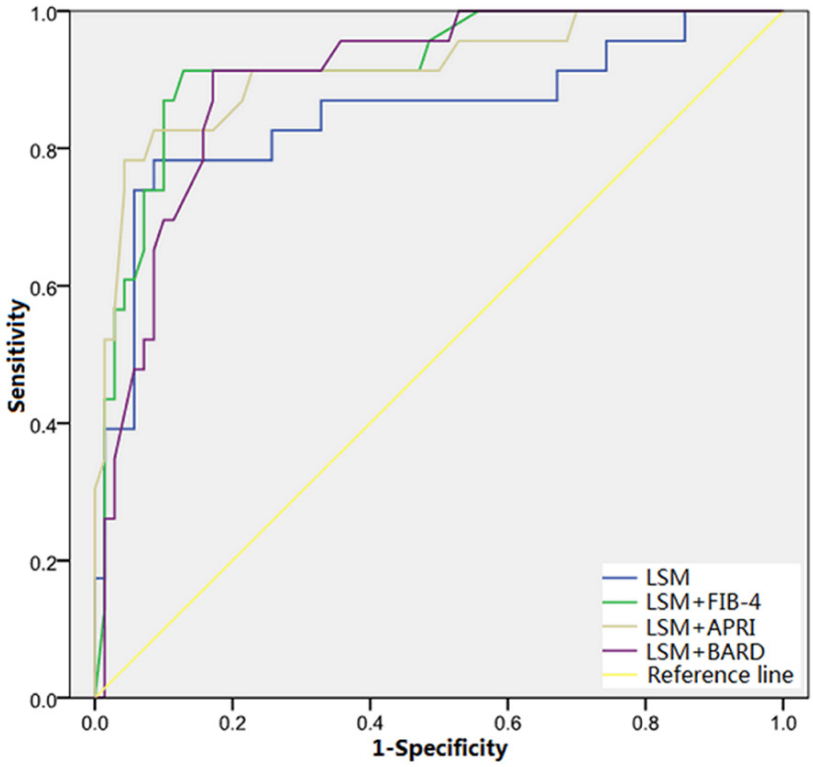

Figure 2. ROC curves of LSM by TE alone and combined with noninvasive indices/scores (APRI, BARD, and FIB-4 scores) for predicting advanced liver fibrosis (F > 2) in patients with chronic hepatitis B.

use in patients with chronic hepatic diseases (especially in chronic hepatitis C), however, there have no enough available data for chronic hepatitis B. According to the present researches, LSM by TE is less accurate in patients with chronic hepatitis B than in those with chronic hepatitis C. Therefore, we have not only assess the diagnostic value of LSM by TE alone, but also assess the diagnostic value of LSM by TE combined with noninvasive indices/scores. In the present study, ROC curves analysis showed that LSM by TE also can reliably exclude advanced liver fibrosis of patients with chronic hepatitis B. After combined with noninvasive indices/scores, LSM by TE showed a higher AUROC. However, the difference of AUROC between LSM by TE alone and combined with noninvasive indices/scores have no statistical significance.

Several limitations of the present study also should be put forward: firstly, our research is a retrospective study. As we know that the results of a prospective research are more reliable than results of retrospective study. Secondly, the small sample size of our study may impact the reliability of our results, and larger sample sizes is needed to verify our data. Thirdly, more noninvasive indices/scores should be included to test which formula can improve the diagnostic value of LSM by TE. Fourthly, the race of our included patients is Han nationality and our data may not reflect the truly situation of other populations.

Conclusion

In the present study, both LSM by TE and noninvasive indices/scores (APRI, BARD and FIB-4 scores) were discovered to be similarly reliability for noninvasive diagnosis of advanced hepatic fibrosis of chronic hepatitis B. However, their combination cannot significantly improve the diagnostic accuracy of LSM by TE. A broader range of indices/scores should be identified whether a formula could improve the diagnostic accuracy of LSM by TE.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Changjun Wu, Department of Ultrasound, No. 1 Hospital of Harbin Medical University, No. 23 Youzheng Street, Nangang District, Harbin 150001, China. Tel: 86-0451-

Table 4. AUROCs and sensitivities/specificities results for LSM by TE alone and combined with noninvasive indices/scores (APRI, BARD, and FIB-4 scores) for predicting advanced liver fibrosis (F > 2) in patients with chronic hepatitis B

Covariate	AUC	Standard error	Gradual Sig. b	LL of 95% CI	UL of 95% CI	Sensitivity (%)	Specificity (%)	comparison of ROC curves (*P*)
LSM	0.849	0.055	0.000	0.741	0.957	78.3	91.4	--
LSM+FIB-4	0.918	0.033	0.000	0.853	0.984	87.0	90.0	0.3048
LSM+APRI	0.914	0.038	0.000	0.839	0.989	82.6	91.4	0.3698
LSM+BARD	0.899	0.034	0.000	0.833	0.966	91.3	92.9	0.4050

85556000; Fax: 86-0451-53670428; E-mail: wcj_hmu@sina.cn

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