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TOPIC HIGHLIGHT

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Noninvasive assessment of liver fibrosis in patients with chronic hepatitis B

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Abstract

Infection with hepatitis B virus is an important health problem worldwide: it affects more than 350 million people and is a leading cause of liver-related morbidity, accounting for 1 million deaths annually. Hepatic fibrosis is a consequence of the accumulation of extracellular matrix components in the liver. An accurate diagnosis of liver fibrosis is essential for the management of chronic liver disease. Liver biopsy has been considered the gold standard for diagnosing disease, grading necroinflammatory activity, and staging fibrosis. However, liver biopsy is unsuitable for repeated evaluations because it is invasive and can cause major complications, including death. Several noninvasive evaluations have been introduced for the assessment of liver fibrosis: serum biomarkers, combined indices or scores, and imaging techniques including transient elastography, acoustic radiation force impulse, real-time tissue elastography, and magnetic resonance elastography. Here, we review the recent progress of noninvasive assessment of liver fibrosis in patients with chronic hepatitis B. Most noninvasive evaluations for liver fibrosis have been validated first in patients with chronic hepatitis C, and later in those with chronic hepatitis B. The establishment of a noninvasive assessment of liver fibrosis is urgently needed to aid in the management of this leading cause of chronic liver disease.

Key words: Acoustic radiation force impulse; Biomarkers; Biopsy; Elastography; Fibrosis; Hepatitis B; Noninvasive evaluations

Core tip: The usefulness of noninvasive evaluations for predicting liver fibrosis remains to be fully evaluated in chronic hepatitis B. Few indices/scores based on combinations of serum biomarkers were originally proposed for use in patients with chronic hepatitis B. Transient elastography is less accurate for chronic hepatitis B than for chronic hepatitis C. Limited data are available regarding the usefulness of acoustic radiation force impulse, real-time tissue elastography, and magnetic resonance elastography in chronic hepatitis B. However, these methods are suitable for repeated evaluations and can be useful for assessing the clinical stage of disease, predicting complications of cirrhosis, and monitoring the response to treatment.

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INTRODUCTION

Hepatic fibrosis, regardless of the underlying etiology, is a consequence of the accumulation of extracellular matrix components in the liver. This process is caused by persistent liver damage and consequent wound healing re-

action and can progress to cirrhosis, portal hypertension, and hepatocellular carcinoma (HCC), leading to increased morbidity and mortality[1,2]. An accurate diagnosis of liver fibrosis is thus essential for the management of chronic liver diseases.

Liver biopsy has been considered the "gold standard" for diagnosing chronic liver disease, grading necroinflammatory activity, and staging liver fibrosis[3,4]. However, sampling error can lead to underestimation of the degree of liver fibrosis, especially when the biopsy specimens are small or fragmented. In addition, interpretation of the results is subject to significant intraobserver and interobserver variability. Moreover, liver biopsy is unsuitable for repeated evaluations because it is invasive and can cause major complications, including death[5,6]. Therefore, several serum biomarkers, combined indices/scores, and imaging techniques for the noninvasive assessment of liver fibrosis have been introduced.

Infection with hepatitis B virus (HBV) is an important health problem worldwide: it affects more than 350 million people and is a leading cause of liver-related morbidity, accounting for 1 million deaths annually[7-9]. However, most noninvasive evaluations of liver fibrosis have been validated first in patients with chronic hepatitis C and only then in patients with chronic hepatitis B. Herein, we review the recent progress in the noninvasive assessment of liver fibrosis in patients with chronic hepatitis B.

SERUM MARKERS

Several surrogate serum markers have been proposed as alternatives for the noninvasive assessment of liver fibrosis[10-12]. In general, markers of fibrosis can be divided into two groups: direct and indirect. Serum direct markers reflect extracellular matrix turnover. They include glycoproteins such as serum hyaluronate, laminin, and YKL-40; collagens such as procollagen Ⅲ N-terminal propeptide and type Ⅳ collagen 7S; collagenases and collagenase inhibitors such as matrix metalloproteases and tissue inhibitory metalloprotease-1. Indirect markers reflect alterations in hepatic function rather than metabolism of the hepatic extracellular matrix. They include the platelet count, coagulation studies, and the levels of aspartate and alanine aminotransferases (AST and ALT). The advantages of biomarkers as measures of fibrosis include their high applicability and interlaboratory reproducibility and their wide availability for repeated assays. However, none is liver-specific: the results of all such tests can be influenced by comorbid conditions.

Several algorithms, indices, or scores derived from combinations of serum biomarkers have been proposed, namely, the Fibrotest[13], Forns index[14], AST-to-platelet ratio index (APRI)[15], FIB-4[16], Fibrometer[17], FibroIndex[18], and ELF[19]. Table 1 shows the diagnostic performance of several combined indices/scores in patients with chronic hepatitis B. Although most indices/scores were originally established using data from patients with chronic hepatitis C, their diagnostic accuracies have been validated in patients with chronic hepatitis B[20-23]. Sebastiani *et al*[20] reported that the area under the receiver operating characteristic (AUROC) curve values for identification of both significant fibrosis (≥ F2) and cirrhosis (F4) in patients with chronic hepatitis B were better for the Fibrotest than for the APRI and Forns index. Combined indices/scores including hepatic aminotransferase levels are unsuitable for monitoring liver fibrosis during treatment, as the serum levels of aminotransferases decrease rapidly after initiation of therapy. As the Fibrotest includes the serum haptoglobin, bilirubin, and γ-glutamyltranspeptidase levels, false-positive results may occur in patients with hemolysis or cholestasis and in those who have recently consumed alcohol[24]. Hui *et al*[25] and Zeng *et al*[26] have developed liver fibrosis scores specifically for patients with chronic hepatitis B, although their usefulness remains to be validated by other groups.

TRANSIENT ELASTOGRAPHY

Transient elastography (FibroScan®, EchoSens, Paris, France), which has become a popular tool, is a rapid, objective, and promising technique for staging liver fibrosis by measuring the stiffness of the liver, expressed in units of kilopascals (kPa)[27,28]. This system is equipped with a probe including an ultrasonic transducer mounted on the axis of a vibrator. The vibration transmitted from the vibrator toward the tissue induces an elastic shear wave that propagates through the liver. These propagations are followed by pulse-echo ultrasound acquisition, and their velocity, which is directly related to tissue stiffness, is measured. In a morphometric analysis, Wong *et al*[29] found that the liver stiffness as assessed by transient elastography correlates significantly with the proportion of the liver affected by fibrosis, particularly pericellular fibrosis rather than periportal or perivenular fibrosis.

Liver stiffness measurement has generally been considered reliable when it fulfills all of the following criteria: ≥ 10 valid measurements, a success rate of ≥ 60%, and an interquartile range/median ratio (IQR/M) of ≤ 0.30. However, in multivariate analyses of 1165 patients with various chronic liver diseases, Boursier *et al*[30] recently reported that the reliability of measurement of liver stiffness depends on the IQR/M according to the median level of liver stiffness, thus defining three categories of reliability: "very reliable" (IQR/M ≤ 0.10), "reliable" (0.10 < IQR/M ≤ 0.30, or IQR/M > 0.30 with a median value of < 7.1 kPa), and "poorly reliable" (IQR/M > 0.30 with a median value of ≥ 7.1 kPa).

In a meta-analysis of 50 elastography studies performed mainly in patients with chronic hepatitis C, the mean AUROC curves for the diagnosis of significant fibrosis (≥ F2), severe fibrosis (F3/F4), and cirrhosis (F4) were 0.84, 0.89, and 0.94, respectively[31]. The diagnostic accuracy of transient elastography was generally high for cirrhosis but poorer for significant fibrosis[32]. The results of liver stiffness measurement can be affected by factors other than fibrosis, including necroinflammatory activ-

Table 1 Performance of serum fibrosis markers for identification of significant fibrosis (≥ F2) and cirrhosis (F4) in patients with hepatitis B

Ref.	Year	Patients (*n*)	Diagnosis for ≥ F2				Diagnosis for F4			
			Patients (%)	AUROC	Cutoff (kPa)	Se/Sp (%)	Patients (%)	AUROC	Cutoff (kPa)	Se/Sp (%)
Originally for patients with HCV										
Fibrotest (includes α2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, and GGT)										
Sebastiani *et al*[20]	2007	110	68	0.85	F2	81/90	20	0.76	F4	56/96
[1]Bottero *et al*[21]	2009	108	56	0.77	0.48	70/72	15	0.87	0.73	75/85
Forns index (includes age, platelet count, cholesterol, and GGT)										
Sebastiani *et al*[20]	2007	110	68	0.63	4.20	58/78	20	-	-	-
Wong *et al*[22]	2010	156 +	75	0.70	5.20	28/91	26	-	-	-
		82	59	0.72	8.40	43/93	20			
[1]Bottero *et al*[21]	2009	108	56	0.72	-	-	15	0.81	-	-
APRI (includes AST and platelet count)										
Sebastiani *et al*[20]	2007	110	68	0.72	0.50	71/87	20	0.64	2.00	43/85
Kim *et al*[23]	2010	668	79	0.70	-	-	34	0.73	-	-
[1]Bottero *et al*[21]	2009	108	56	0.73	-	-	15	0.76	-	-
FIB-4 (includes age, AST, ALT, and platelet count)										
Kim *et al*[23]	2010	668	79	0.86	1.00	91/73	34	0.93	1.60	88/84
[1]Bottero *et al*[21]	2009	108	56	0.74	-	-	15	0.80	-	-
Fibrometer (includes age, platelet count, PT index, AST, α2-macroglobulin, hyaluronate, and urea)										
[1]Bottero *et al*[21]	2009	108	56	0.74	0.46	73/68	15	0.89	0.83	81/85
Originally for patients with HBV										
Hui score (includes body mass index, bilirubin, albumin, and platelet count)										
Hui *et al*[25]	2005	235	25	0.79	0.15	88/50	-	-	-	-
Zeng score (includes age, α2-macroglobulin, hyaluronate, and GGT)										
Zeng *et al*[26]	2005	372	58	0.77	3.00	98/28	-	-	-	-

[1]Study subjects were coinfected with human immunodeficiency virus. APRI: AST to platelet ratio index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; AUROC: Area under the receiver operating characteristic curve; GGT: γ-Glutamyltranspeptidase; HBV: Hepatitis B virus; HCV: Hepatitis C virus; PT: Prothrombin.

ity[33-35], obesity[36], and extrahepatic cholestasis[37].

The usefulness of transient elastography has been well validated in patients with chronic hepatitis C; however, limited data are available for its use in patients with other liver diseases[38], including chronic hepatitis B. Table 2 shows the diagnostic performance of elastography for significant fibrosis (≥ F2) and cirrhosis (F4) in patients with chronic HBV infection[22,32,39-42]. In some studies[43,44], measurement of liver stiffness has been less accurate in patients with chronic hepatitis B than in those with chronic hepatitis C. One possible explanation for the difference in diagnostic accuracy is that chronic hepatitis B is associated with acute exacerbations, in which severe/moderate necroinflammation can lead to overestimation of fibrosis, more frequently than is chronic hepatitis C[45]. On the other hand, liver stiffness measurement exhibits good diagnostic accuracy with a high negative predictive value[46].

In previous studies that addressed both chronic hepatitis B and chronic hepatitis C[47,48], the median liver stiffness at each stage of fibrosis was lower in patients with chronic hepatitis B than in those with chronic hepatitis C. The reported cutoff values for predicting cirrhosis in patients with chronic hepatitis B ranged from 9.4 to 12.9 kPa[32,39-42]; all of these values are lower than the optimal cutoff value of 13.0 kPa derived from a meta-analysis of 17 studies (mostly concerning chronic hepatitis C)[51]. The amount of fibrosis in the cirrhotic liver is generally lower for chronic hepatitis B than for chronic hepatitis C because macronodular cirrhosis, characterized by large nodules delimited by thin septa, is more common in patients chronically infected with HBV.

Some studies have proposed the adoption of different cut-off values for each cause of liver disease[43]. To avoid overestimation of fibrosis, other studies have proposed basing the cut-off value on the ALT level[41]. Diagnostic algorithms using dual cut-offs, for positive and negative prediction of liver fibrosis, have also been proposed[49].

ACOUSTIC RADIATION FORCE IMPULSE

Acoustic radiation force impulse (ARFI; Siemens AG, Erlangen, Germany) imaging involves mechanical excitation of tissue using short-duration acoustic pulses to generate localized tissue displacement[50-52]. The harder the tissue, the faster the shear wave spreads. The displacement results in shear-wave propagation, which is tracked using correlation-based ultrasonic methods and recorded in m/s. This examination is performed during B-mode ultrasonography.

Sporea *et al*[53] showed that the mean liver stiffness values obtained by ARFI were similar between patients with chronic hepatitis B and those with chronic hepatitis C at the same stage of fibrosis. Friedrich-Rust *et al*[54] reported that the diagnostic accuracy of ARFI for the histological staging of liver fibrosis in patients with chronic hepatitis

Table 2 Performance of transient elastography for identification of significant fibrosis (≥ F2) and cirrhosis (F4) in patients with hepatitis B

Ref.	Year	Patients (*n*)	Diagnosis for ≥ F2				Diagnosis for F4			
			Patients (%)	AUROC	Cutoff (kPa)	Se/Sp (%)	Patients (%)	AUROC	Cutoff (kPa)	Se/Sp (%)
Oliveri *et al*[39]	2008	188	26	0.97	7.5	94/88	20	0.97	11.8	86/96
Marcellin *et al*[40]	2009	173	50	0.81	7.2	70/83	8	0.93	11.0	93/87
Chan *et al*[41]	2009	161	-	-	-	-	25	0.93	12.0-13.4[2]	98/75
Degos *et al*[32]	2010	284	42	0.78	5.2	89/38	10	0.85	12.9	52/93
Wong *et al*[22]	2010	156 + 82	68	0.80	9.0-12.0[2]	54/99	23	-	-	-
[1]Miailhe *et al*[42]	2011	57	61	0.85	5.9	81/87	20	0.96	9.4	92/94

[1]Study subjects were coinfected with human immunodeficiency virus; [2]Adapted to ALT values. AUROC: Area under the receiver operating characteristic curve; Se: Sensitivity; Sp: Specificity.

B was comparable to that of transient elastography.

REAL-TIME TISSUE ELASTOGRAPHY

Real-time tissue elastography (Hitachi Medical Systems, Tokyo, Japan) is a new ultrasound-based diagnostic method for the evaluation of tissue elasticity and can be performed during routine B-mode screening of the liver[55-57]. This technology has already been proven diagnostically valuable for the detection of mass lesions in the breast, prostate, and pancreas. A computer-assisted apparatus is used to calculate the relative hardness of the tissue from the degree of tissue distortion and displays this information as a color image. Ultrasound elastography does not demonstrate physical elasticity directly but rather shows the relative degree of tissue strain under subtle compression.

A Chinese study of real-time tissue elastography in 71 patients with chronic hepatitis B found a strong negative correlation between the elastic strain ratio and the histological stage of fibrosis[58]. The AUROC curve for detection of significant fibrosis (≥ F2) was higher for real-time elastography than for blood parameters, such as the APRI and Forns index. Similar results were also reported in another Chinese study[59].

MAGNETIC RESONANCE ELASTOGRAPHY

Magnetic resonance (MR) elastography is a promising imaging technique that noninvasively measures the stiffness of the liver as well as that of other organs by analyzing the propagation of mechanical waves through tissue[60-62]. Its clear advantages include the potential to assess the entire liver parenchyma, the dispensability of an acoustical window, and operator independence. In addition, this method may be useful for quantifying hepatic fat content.

Venkatesh *et al*[63] examined 63 patients with chronic hepatitis B and reported that MR elastography was significantly more accurate for the detection of biopsy-confirmed significant fibrosis and cirrhosis than were serum fibrosis markers such as APRI. As there are only limited data on the accuracy of MR elastography in patients with chronic hepatitis B, further studies are required for validation.

COMBINATIONS OF BIOMARKERS AND IMAGING METHODS

Combinations of serum markers and imaging studies can detect advanced fibrosis in patients with chronic hepatitis B with a high degree of accuracy. A Korean study developed a liver stiffness measurement-spleen diameter to platelet ratio index (LSPI) for the assessment of liver fibrosis: (liver stiffness measurement × spleen diameter/platelet count) × 100[64]. Another Korean study established a model for predicting significant fibrosis, called the HALF index, consisting of liver stiffness values and the serum haptoglobin, apolipoprotein A1, and α2-macroglobulin levels[65].

CLINICAL APPLICATIONS

Assessing the clinical stage of disease

The natural course of chronic HBV infection acquired perinatally or during infancy consists of four distinct phases: "immune tolerance," "immune reactivity," "inactive carrier state," and "reactivation"[7-9]. Assessment of the clinical stage of disease is usually based on the ALT activity, HBV DNA level, and titers of hepatitis e antigen (HBeAg) and anti-HBe antibodies; however, noninvasive evaluations could also be helpful to discriminate HBeAg-negative patients who have significant fibrosis despite normal ALT activity from inactive carriers of HBV[66-68]. Some patients may then require further assessment by liver biopsy for proper evaluation of indication of antiviral therapy.

Predicting complications of cirrhosis

Noninvasive methods can be used to predict complications of cirrhosis. In a Korean prospective study of 1130 patients with chronic hepatitis B[69], 57 patients developed HCC during the 24-51-mo follow-up period. Multivariate analysis showed that patients with higher liver stiffness measurements by transient elastography were at significantly greater risk of developing HCC, with the following hazard ratios: 3.07 for 8.1-13 kPa; 4.68 for 13.1-18 kPa; 5.55 for 18.1-23 kPa; and 6.60 for > 23 kPa. Wong *et al*[70] proposed the LSM-HCC score, a liver stiffness-based HCC risk score based on transient elastography data

from 1555 consecutive patients with chronic HBV infection. This score was constructed from the liver stiffness measurement, age, serum albumin level, and HBV DNA level and ranges from 0 to 30. When a cutoff value of 11 was used, the score excluded future HCC with a high negative predictive value (99.4%-100%) after 5 years.

Liver stiffness values have also been shown to correlate with the presence and severity of esophageal varices. Using transient elastography data from 577 consecutive patients with B-viral cirrhosis, a Korean group developed a liver stiffness measurement-based model, the liver stiffness measurement-spleen diameter to platelet ratio score liver stiffness measurement (LSPS × spleen diameter/platelet count), for assessment of the cumulative risk of future esophageal variceal bleeding[71]. Multivariate analysis found an LSPS of ⩾ 6.5 ($P = 0.003$), along with large variceal size and Child-Pugh classification B/C, to be a significant predictor of a first occurrence of esophageal variceal bleeding. A Chinese study found significant linear correlations between liver and spleen stiffness as measured by ARFI and the stage of fibrosis in 138 patients with hepatitis B-related cirrhosis[72]. As there was also a significant linear correlation between spleen stiffness and the varix grade, ARFI can be used as a noninvasive method for assessing the presence and severity of esophageal varices.

Monitoring response to treatment

Several studies have reported significant decreases in liver stiffness and biomarker levels in patients with chronic hepatitis B who were treated with interferon-α or nucleos(t)ide analogues[73-81] as well as in patients with chronic hepatitis C who achieved sustained virologic response to interferon[82]. We studied the liver stiffness measurement by transient elastography in 20 patients with chronic hepatitis B[80]. The liver stiffness values in patients treated with entecavir decreased significantly from 11.2 kPa (range: 7.0-15.2 kPa) to 7.8 kPa (range: 5.1-11.9 kPa; $P = 0.0090$) during 12 mo of treatment. Fung *et al*[81] also repeated liver stiffness measurement during antiviral therapy in 58 chronic HBV infected patients with baseline ALT levels from × 1 to × 10, the upper limit of the normal. The ALT level became normal after a median of 3 mo of antiviral therapy. The AUROC curve for diagnosis of significant fibrosis by liver stiffness was 0.68 in patients with an elevated ALT level at baseline versus 0.73 after ALT level normalization, suggesting that even mild-to-moderate elevation in the ALT level may increase liver stiffness. The decrease in liver stiffness during the first few months of nucleos(t)ide analogue treatment may be attributable to improvement in necroinflammation rather than regression of liver stiffness.

CONCLUSION

The usefulness of noninvasive evaluations for predicting liver fibrosis has been less extensively studied and validated for chronic hepatitis B than for chronic hepatitis C. Few algorithms or indices/scores based on combinations of serum biomarkers were originally proposed for use in patients with chronic hepatitis B. Transient elastography is less accurate in patients with chronic hepatitis B than in those with chronic hepatitis C. Limited data are available on the usefulness of ARFI, real-time tissue elastography, and magnetic resonance elastography in patients with chronic hepatitis B. In addition, these methods do not provide information on necroinflammatory activity, steatosis, iron deposition, or other findings that can be obtained by liver biopsy. However, they are suitable for repeated evaluations and can be useful for assessing the clinical stage of disease, predicting complications of cirrhosis, and monitoring the response to treatment.

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