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REVIEW

Noninvasive models for assessment of liver fibrosis in patients with chronic hepatitis B virus infection

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Abstract

There are approximately 240 million patients with chronic hepatitis B virus (HBV) infection worldwide. Up to 40% of HBV-infected patients can progress to liver cirrhosis, hepatocellular carcinoma or chronic end-stage liver disease during their lifetime. This, in turn, is responsible for around 650000 deaths annually worldwide. Repeated hepatitis flares may increase the progression of liver fibrosis, making the accurate diagnosis of the stage of liver fibrosis critical in order to make antiviral therapeutic decisions for HBV-infected patients. Liver biopsy remains the "gold standard" for diagnosing liver fibrosis. However, this technique has recently been challenged by the development of several novel noninvasive tests to evaluate liver fibrosis, including serum markers, combined models and imaging techniques. In addition, the cost and accessibility of imaging techniques have been suggested as additional limitations for invasive assessment of liver fibrosis in developing countries. Therefore, a noninvasive assessment model has been suggested to evaluate liver fibrosis, specifically in HBV-infected patients, owing to its high applicability, inter-laboratory reproducibility, wide availability for repeated assays and reasonable cost. The current review aims to present the status of knowledge in this new and exciting field, and to highlight the key points in HBV-infected patients for clinicians.

Key words: Liver biopsy; Hepatitis B; Noninvasive; Serum biomarkers; Fibrosis

Core tip: An accurate diagnosis of liver fibrosis is essential to make therapeutic decisions in patients with chronic hepatitis B (CHB). However, liver biopsy, the "gold standard" for assessing the degree of liver fibrosis, has been limited by its complications. Although noninvasive models composed with serum biomarkers were applied to assess fibrosis in patients with CHB, they have been suggested owing to their high applicability, inter-laboratory reproducibility, wide availability for repeated assays and cost. Previous data

presented on the noninvasive models for assessing liver fibrosis from different levels of alanine aminotransferase have been limited.

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INTRODUCTION

Past or current hepatitis B virus (HBV) infection has been confirmed in an estimated 2 billion people worldwide, and approximately 240 million patients are chronically infected[1]. In China, the prevalence of hepatitis B surface antigen (HBsAg) for people aged 1-4 years, 5-14 years and 15-29 years has been shown to be 0.32%, 0.94% and 4.38%, respectively[2]. The major complications of chronic hepatitis B (CHB) are liver cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC), which account for approximately 650000 deaths annually worldwide[3]. Chronic hepatitis has been shown to lead to liver fibrosis, the final pathway from chronic parenchymal injury to development of cirrhosis. Different stages of liver fibrosis can influence the clinical strategies. Therefore, assessing the stage of liver fibrosis is critical for the decision of antiviral strategies, which can potentially prevent the progression of HBV-related diseases.

Current guidelines for HBV management (APASL, EASL and AASLD)[4-6] recommend consideration of serum alanine transaminase (ALT), HBV DNA, hepatitis B e antigen (HBeAg) status and/or hepatic necroinflammation/fibrosis stage for deciding antiviral therapy. Liver biopsy remains the "gold standard" of assessing hepatic fibrosis. However, it has limitations, such as high cost, invasiveness, associated risk for complications and sampling variability. Liver biopsy has recently been challenged by the development of novel noninvasive methodologies, including serum direct and/or indirect markers of hepatic fibrosis, noninvasive models of predicting fibrosis and imaging techniques, including transient elastography (TE), ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). TE is a relatively new technique for assessment of hepatic fibrosis[4,7,8]. However, the cost of the equipment may limit the use of TE in some institutions with limited resources. The present study reviews the noninvasive models for liver fibrosis in HBV-infected patients.

NONINVASIVE MODELS FOR ASSESSING HEPATIC FIBROSIS: ARE THEY NECESSARY?

Liver biopsy is still the standard method to diagnose liver fibrosis. However, it has limitations of sampling error and inter-/intra-observer variability. In addition, the APASL clinical practice guidelines recommended that core lengths of the biopsy specimens obtained by at least a 16G biopsy needle should be at least 15 mm in length and/or should have more than 10 portal tracts[9]. The AASLD guidelines recommended that the biopsy specimens should be more than 3 cm in length, with at least 11 portal tracts[10]. These liver biopsy specimen characteristics have been identified to minimize the risk of sampling error. However, few percutaneous needle biopsies in clinical practice meet these criteria[10]. Moreover, up to 2% of patients have been reported to develop potential complications from this procedure, with 0.57% of the patients having experienced severe complications; in general, repeat liver biopsy is poorly tolerated by patients[10,11].

Although traditional imaging techniques, including US, CT or MRI, have been applied to assess liver cirrhosis and signs of portal hypertension, they cannot be used to identify minimal fibrosis[12-15]. Recently, new technologies have been used to assess liver fibrosis. Magnetic resonance elastography or acoustic radiation force impulse (ARFI) has been applied to assess liver fibrosis and may provide an accurate diagnosis of advanced liver fibrosis and liver cirrhosis[16,17]. Both represent a potential method for assessing liver fibrosis[18] but require further validation. TE (FibroScan) was first applied to assess liver stiffness in 2003, and it is probably a reliable method to diagnose fibrosis in patients with chronic hepatitis C (CHC). Although TE has shown good performance in assessing HBV-related significant fibrosis (F2 stage) and cirrhosis (F4 stage), with areas under receiver operating curves (AUCs) of 0.65-0.97 and 0.8-0.97, respectively[8], it has some limitations. For example, it is less accurate in predicting the existence of significant fibrosis, and it has been unsuccessful in individuals with high levels of ALT/bilirubin, obesity and/or ascites. An optimal diagnostic cutoff for the stage of liver fibrosis in HBV has not been determined[8]. In addition, TE is more expensive than the noninvasive models.

Serum markers are another attractive alternative for assessing liver fibrosis. In general, these serum markers are classified into direct and indirect types. Direct markers represent the pathophysiology of liver fibrogenesis and include glycoproteins, collagens, collagenases and collagenase inhibitors. Indirect markers reflect the consequences of liver damage

Table 1 Advantages and disadvantages of liver biopsy and noninvasive models for detecting liver fibrosis

	Liver biopsy	Noninvasive models
Advantages	Gold standard to assess fibrosis	Non-invasive
	Direct observation and quantitative assessment of fibrosis, inflammation and steatosis	Inter-laboratory reproducibility
	Different stage by different scoring systems	High applicability and wide availability for repeated assays
	Diagnosing different forms of liver disease	Reasonable cost
	Accurately assessing progression of liver disease or the effect of therapy	Accurate assessment of cirrhosis and minimal/no fibrosis
Disadvantages	Invasive	Less accurate for intermediate fibrosis stages
	Sampling error and inter-observer differences	False positive values
	Unsuitable for repeated assays	Scores may change in different disease stages
	Risk of complications, rare major complications, morbidity and mortality	Unsuitable for diagnosing liver disease
	Expensive	Not quantitative

and their correlation with the evolution of liver fibrosis and include the platelet (PLT) count, aspartate transaminase (AST) and ALT, globin, serum HBsAg, ceruloplasmin, red blood cell distribution width, IL-2R, TGF-α and serum Golgi protein 73 (GP73)[19-23]. Direct or indirect markers could be individually used to assess liver fibrosis. However, currently, no single marker is sufficiently liver-specific to accurately reflect fibrosis. Therefore, serum markers are commonly combined to achieve good diagnostic sensitivity and specificity.

Determining the stage of hepatic fibrosis in HBV-infected patients is very important for deciding antiviral therapy and for monitoring the responses to antiviral treatment, especially in patients who do not accord with the recommendations of clinical practice guidelines[2,4,6]. Although liver biopsy still plays an important role in diagnosing the extent of fibrosis, it is essential to build noninvasive, accurate and reproducible methods for this purpose. The advantages and disadvantages of liver biopsy and noninvasive models for assessing liver fibrosis are summarized in Table 1.

NONINVASIVE MODELS FOR GENERAL ASSESSMENT OF HEPATIC FIBROSIS

The majority of noninvasive tests for assessing hepatic fibrosis were first established to evaluate hepatitis C virus (HCV)-infected patients. These tests include FIB-4, FibroTest, APRI, European Liver Fibrosis score and Hepascore[24-28], and have been validated. However, they might not be suitable for patients with CHB, because HBV and HCV infections may have different effects on the measurements of fibrosis. A comprehensive review[29] showed that the accuracy and applicability of noninvasive methods varied between patients with HBV and HCV, and some methods were shown to be invalid in patients with HBV. Therefore, recent studies have focused on developing several new noninvasive models for assessing liver fibrosis, specifically in HBV-infected patients[19,30-32].

Recent guidelines[4-6] recommend treatment of CHB based on ALT levels, HBV DNA, HBeAg status and/or liver histology. These guidelines recommend treating patients with ALT $\geqslant$ 2 the upper limit of normal (ULN) and HBV DNA > 20000 IU/mL and > 2000 IU/mL for HBeAg-positive and -negative patients, respectively. Patients with high HBV DNA levels but ALT < 2 ULN should undergo noninvasive assessment of inflammation and fibrosis. Patients with compensated cirrhosis and detectable HBV DNA should be advised antiviral therapy, regardless of the ALT level. Therefore, in some conditions, antiviral therapy is based on ALT levels or the extent of liver fibrosis. The assessment of liver fibrosis is more essential to make antiviral therapy decisions in patients with ALT < 2 ULN than in patients with ALT $\geqslant$ 2 ULN. Noninvasive models for estimating liver fibrosis are recommended to select patients for liver biopsy[2,4].

NONINVASIVE MODELS FOR ASSESSING HEPATIC FIBROSIS IN HBV INFECTIONS

The diagnostic parameters for significant fibrosis and cirrhosis by various noninvasive tests are summarized in Table 2. To date, FIB-4 and APRI have been the most extensively studied, and they were first applied to assess liver fibrosis in patients with CHC. They have also been validated in HBV-infected patients, and have been recommended to assess liver fibrosis for making decisions with regard to antiviral treatment and to monitor disease progression[2,4,7]. The diagnostic values of FIB-4 and APRI are attractive and reliable because they are simple tests that are readily available, and are inexpensive in the clinical laboratory or in an outpatient setting. They are easy to calculate, and both of the tests use two cutoff points for distinguishing different liver fibrosis stages. A high cutoff is used for diagnosing patients with significant, advanced fibrosis or cirrhosis, and a low cutoff is used for excluding the presence of a minimal fibrosis.

The FIB-4 index has been assessed to evaluate significant fibrosis and liver cirrhosis in HBV-infected patients in numerous studies[19,21,30,32-37]. Although several studies showed that the diagnostic value of FIB-4 was better than other non-invasive indices[33,34], the diagnostic values of FIB-4 remain controversial. A meta-analysis[38] including 1908 subjects from

Table 2 Performance of noninvasive tests for diagnosis of significant fibrosis (≥ F2) and cirrhosis (F4) in hepatitis B virus-infected patients

Ref.	Year	*n*	Diagnosis of significant fibrosis				Diagnosis of cirrhosis			
			AUC	Cutoff	Se/Sp (%)	PPV/NPV (%)	AUC	Cutoff	Se/Sp (%)	PPV/NPV (%)
Myers *et al*[68]	2003	209	0.78	< 0.2	89/52	43/92	NA			
				> 0.8	18/99	92/75	NA			
Zeng *et al*[52]	2005	373	0.84	< 3.0	94.8/44.1	70.1/86.1	0.84	> 8.7	35.3/95.2	91.1/51.6
Hui *et al*[51]	2005	235	0.79	≤ 0.15	51.5/84.6	74.5/66.7	NA			
				> 0.5	16.2/97.4	84.6/57.1	NA			
Zeng *et al*[19]	2013	198	NA				0.89	-1.03	88.0/88.1	68.7/96.1
Zeng *et al*[21]	2015	237	NA				0.87	-1.89	88.6/78.2	48.2/96.8
Seto *et al*[59]	2011	237	0.776	< 1.662	73.3/78.2	56.4/88.4	NA			
Zhang *et al*[31]	2008	137	NA	NA	45.3/98.9	93.7/91.3	NA			
Kim *et al*[55]	2007	346	NA				0.89	> 12	35.6/99.6	96.3/82.8
			NA					< 5	100/32	32/100
Chen *et al*[56]	2008	653	NA				0.907	0.1	92.8/74.1	52/97.1
Zhou *et al*[57]	2010	386	0.81	< 0.1	90.41/23.95	60.92/65.57	0.89	≥ 1.5	27.27/97.73	52.94/93.50
Taefi *et al*[62]	2015	152	NA				0.77	0.0880	82.7/61.0	52.4/87.1
Gümüşay *et al*[48]	2013	58	NA	NA	90/100	100/96.4	NA			
Wang *et al*[42]	2013	349	0.856	0.75	56.5/94.1	92.9/61.5	0.956	0.9800	64.3/94.6	47.4/97.2
Lee *et al*[63]	2015	482	0.747	0.0625	72.3/67.7	93.4/58.0	0.811	0.0685	88.6/66.0	67.6/87.9
Liu *et al*[32]	2012	114	0.762	< 1.68	72.4/69.6	71.2/70.8	0.781	< 2.53	72.7/84.5	33.4/96.7
Mohamadnejad *et al*[66]	2006	276	0.91	4.72	97/52	26/99	NA			
Fung *et al*[67]	2008	1268	0.85	6.87	82.1/73.5	67.6/85.9	0.89	8.93	78.0/85.7	69.6/90.3

AUC: Area under receiver operating curve; NA: Not available; NPV: Negative predictive value; PPV: Positive predictive value.

12 studies and 2105 subjects from 10 studies for evaluating significant fibrosis and cirrhosis, respectively, used the low and high cutoffs for FIB-4 of 1.45 and 1.62, respectively, for assessment of significant fibrosis (METAVIR ≥ F2). The mean standardized AUC, specificity and sensitivity were 0.78 (95%CI: 0.74-0.81), 77.0% (95%CI: 70.0%-83.0%) and 65.0% (95%CI: 56.0%-73.0%), respectively. For cirrhosis, the low and high cutoffs for FIB-4 were 2.9 and 3.6. The mean standardized AUC, specificity and sensitivity were 0.96 (95%CI: 0.92-1.00), 96.0% (95%CI: 95.0%-97.0%) and 42.0% (95%CI: 36.0%-48.0%), respectively. Recently, another meta-analysis[39] analyzed results from 6455 patients to assess significant fibrosis and from 6068 patients to evaluate cirrhosis. The summary AUC values for significant fibrosis and cirrhosis were 0.7844 (95%CI: 0.7450-0.8238) and 0.8448 (95%CI: 0.7742-0.9154), respectively. Several studies, including two meta-analyses[33,34,38-43], have been conducted to evaluate the potential diagnostic values of significant fibrosis and cirrhosis. These studies showed that FIB-4 has optimal accuracy in identifying cirrhosis and suboptimal accuracy in excluding significant fibrosis.

A recent meta-analysis of 8855 patients for detecting significant fibrosis and 8777 patients to evaluate cirrhosis used low and high cutoffs for APRI such as 0.5 and 1.5, respectively, for significant fibrosis (METAVIR ≥ F2). The mean standardized AUC, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 0.7407 (95%CI: 0.7033-0.7781), 70.0% (95%CI: 35.0%-97.0%) and 60.0% (95%CI: 34.0%-86.7%), 34.1% (95%CI: 14.0%-75.0%) and 89.5% (95%CI: 81.6%-100.0%), 61.7% and 52.9%, and 83.2% and 52.0%, respectively. For cirrhosis, the low and high cutoffs for APRI were 0.5 and 1.5. The mean standardized AUC, sensitivity, specificity, PPV and NPV were 0.7268 (95%CI: 0.6578-0.7958), 82.4% and 36.9% (95%CI:25.2%-48.5%), 38.5% and 92.5% (95%CI:85.9%-99.1%), 23.2% and 52.6%, 90.7% and 86.7%, respectively. Ray Kim *et al*[44] showed that the AUC for APRI was 0.65 and 0.69 for diagnosing cirrhosis and advanced fibrosis, respectively. Hence, the assessment of liver fibrosis according to Ishak's stage in patients with CHB seemed unsuitable in clinical practice. Although APRI has been recommended as the "perfect non-invasive model" to evaluate liver fibrosis by APASL HBV and the World Health Organization HBV guidelines[4,7], most studies[31,40,41,43-50] concluded that APRI has only a moderate sensitivity and accuracy for assessing HBV-related fibrosis. Therefore, APRI was not an ideal substitute for liver biopsy.

In recent years, studies on noninvasive models for assessing fibrosis in patients with CHB have been published[19-21,30,31,51-67]. Myers *et al*[68] reported a study on FibroTest including α2-macroglobulin, apolipoprotein A1 and haptoglobin to evaluate liver fibrosis in 209 treatment-naive patients with CHB. The test could accurately predict F2-F4 fibrosis with an AUC of 0.78, and NPV and PPV of 92%. Zeng *et al*[52] constructed a noninvasive test consisting of a combination of four variables, namely α2-macroglobulin, gamma glutamyl transpeptidase, age and hyaluronic acid, in 372 HBeAg-positive patients with CHB. To exclude the presence of significant fibrosis, the test had a high accuracy (sensitivity of 94.8%, NPV of 86.1% and

Table 3 Performance of noninvasive tests for identification of fibrosis in hepatitis B virus-infected patients with normal or minimally elevated serum alanine transaminase

Ref.	Year	*n*	Fibrosis	Cutoff	AUC	Se/Sp, %	PPV/NPV, %
Zeng *et al*[30]	2014	278	F4	0.62	0.830	86.7/75.0	49.6/95.2
FIB-4							
Seto *et al*[59]	2011	237	F2		0.726	NA	NA
Wang *et al*[35]	2013	239	F2		0.770	54/85	86/78
			F3		0.810	67/80	37/97
APRI							
Seto *et al*[59]	2011	237	F2		0.727	NA	NA
Wang *et al*[35]	2013	239	F2		0.770	59/79	59/70
			F3		0.770	63/72	28/94
Park *et al*[69]	2011	124	F3	16.5	0.800	90.6/50.0	NA
				18.5	0.800	31.3/89.5	NA
Seto *et al*[59]	2011	237	F2		0.797	NA	NA
Wang *et al*[70]	2015	283	F2		0.820	NA	NA

AUC: Area under receiver operating curve; NA: Not available; NPV: Negative predictive value; PPV: Positive predictive value.

PPV of 70.1%). Similarly, to identify the presence of significant fibrosis, the test had a high PPV of 91.1%, NPV of 51.6% and specificity of 95.2%. However, the predictive markers of α2-macroglobulin, haptoglobin and apolipoprotein A1 are not commonly applied as routine laboratory parameters in most hospitals. Hui *et al*[51] developed a test comprising serum albumin, body mass index, total bilirubin and PLT count to exclude the presence of significant fibrosis in 235 treatment-naive patients with CHB, using the optimal cutoff value of 0.15 and NPV of 92%. Recently, several serum markers have been used to increase the diagnostic values of liver fibrosis. Zeng *et al*[19] developed a noninvasive test consisting of alpha-fetoprotein, PLT, prothrombin time (PT) and ceruloplasmin, which had a high AUC of 0.893, sensitivity, specificity, PPV and NPV of 88%, 88.1%, 68.7% and 96.1% for detecting cirrhosis, respectively. An IC-model[21] including HBsAg, HBeAg, age and international normalized ratio had an AUC of 0.87, a specificity and sensitivity of 88.64 and 78.24%, respectively, and a PPV and NPV of 48.15% and 96.79%, respectively, to detect cirrhosis in patients with CHB in the immune clearance phase.

Although the AUCs of most noninvasive models were mostly greater than 0.85, some serum tests are not commonly used in most centers. Moreover, no independent study has confirmed their validity yet. More studies are essential to validate these results.

NONINVASIVE MODELS IN PATIENTS WITH NORMAL OR MINIMALLY ELEVATED SERUM ALANINE TRANSAMINASE LEVELS

The diagnostic performances for significant fibrosis, advanced fibrosis and cirrhosis using various tests in patients with normal minimally elevated ALT are summarized in Table 3. International guidelines (APASL, EASL and AASLD) state that antiviral treatment should be initiated in patients with CHB with ALT ⩾ 2 ULN, and liver biopsy should be performed to guide treatment decisions in patients with an ALT level < 2 ULN, particularly in those aged above 40 years. Most of the noninvasive models have included patients with HBV infection. A few noninvasive tests have been developed to evaluate liver fibrosis in HBV-infected patients with normal and minimally raised ALT.

Park *et al*[69] developed a noninvasive test by combining the age-AST to predict significant fibrosis and cirrhosis in 124 patients. This simple age-AST model was applied to assess advanced fibrosis (F3) with an AUC of 0.82 and to make decisions on liver biopsy. Liver biopsy was found to be unnecessary in 37% of the patients. Wang *et al*[35] validated the performance of APRI and FIB-4 in 239 HBV-infected patients with low serum ALT activity. To assess significant fibrosis (⩾ S2), the AUC was 0.77 for both FIB-4 and APRI in the whole cohort. The PPV was 59% for both. To assess advanced fibrosis (⩾ S3), the AUC was 0.81 for FIB-4 in the whole cohort, which was superior to that for APRI 0.77, but the PPVs were 37% and 28%, respectively. In patients with minimally raised ALT, the AUC was decreased to 0.71 and 0.73 for FIB-4 and 0.72 and 0.76 for APRI, and the PPV was 59% for both for FIB-4 and 56% for both for APRI to assess significant fibrosis and advanced fibrosis. However, the prediction of significant fibrosis by FIB-4 and APRI was poor because of the poor PPV. Zeng *et al*[30] analyzed several routine laboratory parameters in a cohort of 278 patients with CHB who had undergone liver biopsy. They showed that the PPT (PLT, PT and total bile acid) test was very useful for cirrhosis with an AUC of 0.83. Using this test, 86.7% of patients with cirrhosis and 95.2% of patients without cirrhosis could be accurately identified. At the same time, the PPT test had a higher likelihood than APRI, FIB-4, APGA and the AP index (*i.e.,* greater AUC; $P < 0.05$) of predicting cirrhosis. Deng *et al*[22] investigated the utility of IL-2R

and TGF-α in diagnosing liver fibrosis in patients with CHB with ALT < 2 ULN. The noninvasive model of fib-index was superior to FIB-4 and APRI in diagnosing significant fibrosis with AUCs of 0.82, 0.67 and 0.74, respectively. However, the main limitation was that the circulating cytokines of IL-2R and TGF-α are not routinely available tests. Wang *et al*[70] established the Fibro-score test with an AUC of 0.82, which is higher than the APRI (0.78). The test was convenient to use to identify patients with significant fibrosis.

Several studies have suggested that 28%-37% of patients with CHB with persistently normal ALT may have significant histological liver injury[71,72]. Especially in patients in the immune tolerance (IT) phase, liver biopsy revealed liver injury and histological characteristics[73,74]. Antiviral therapy is currently not recommended for patients in the IT phase, which is marked by high serum HBV DNA, positive results for HBeAg but normal ALT level. However, clinical evidence has shown that a proportion of patients at this phase may experience active liver injury, necessitating antiviral therapy. Given that a normal ALT level does not exclude the absence of significant liver injury, it is necessary to predict liver fibrosis in order to decide the antiviral therapy. A recent meta-analysis including 830 patients with CHB with ALT ⩽ 40 IU/L concluded that approximately 20.7% of patients had significant fibrosis (stage ⩾ 2) regardless of HBV DNA levels, HBeAg status, age or ethnicity. Significant fibrosis still existed in more than 20% of patients with CHB with ALT ⩽ 30 IU/L (males) and 19 IU/L (females)[75], even in patients with undetectable HBV DNA and normal serum ALT. Alam *et al*[76] showed that about 17% patients with CHB had severe liver fibrosis. It is essential to provide clear management guidelines for patients with CHB with normal ALT. Several studies have shown that there is a clear association between normal ALT and liver inflammation and liver fibrosis[71,72,75-83].

Tan *et al*[83] used age to evaluate significant fibrosis in HBeAg-positive and -negative patients with normal ALT levels. To evaluate significant fibrosis, the AUC, sensitivity and specificity of age in HBeAg-positive and -negative patients was 0.612 and 0.672, 54.5% and 66.7%, and 64.6% and 75.4%, respectively. Wang *et al*[35] validated the performance of APRI and FIB-4 in 140 HBV-infected patients with normal ALT. To evaluate significant fibrosis, the AUC was 0.81 for FIB-4 and 0.80 for APRI, the PPV and NPV was 61% and 59%, and 93% and 70%, respectively. To evaluate advanced fibrosis, the AUC was increased to 0.83 for FIB-4 and 0.81 for APRI, the NPV was 96% and 94%, but the PPV was 38% and 28%, respectively. Although neither test had a high PPV, using FIB-4 to exclude the presence of significant fibrosis showed a slightly high NPV in patients with normal ALT levels. In fact, the AUC, specificity and sensitivity were greater for patients with normal ALT levels than for patients with elevated ALT levels.

Although APRI and FIB-4 are the most widely used and validated tests, and the APASL HBV guidelines[4] recommend biopsy if APRI suggests evidence of significant fibrosis, these tests are less validated in patients with CHB than in patients with CHC. Therefore, better predicting noninvasive models for patients with CHB with normal or minimally elevated serum ALT levels are warranted.

METHODS TO INCREASE DIAGNOSTIC ACCURACY

Recently, some studies have shown the combination of serum tests or TE and serum biomarkers in order to increase diagnostic accuracy[84-88]. These strategies have mostly been validated in studies on patients with CHC. However, there are fewer studies in patients with CHB infection. Liu *et al*[89] evaluated the combination of two imaging techniques (ARFI and TE) and one noninvasive model (APRI) for the assessment of liver fibrosis in 108 patients with CHB. The AUC and accuracy of the combination were 0.92 and 83.86%, and 0.98 and 91.88% for significant fibrosis and cirrhosis, respectively. The combination also improved the diagnostic values of sensitivity (90.25% and 93.88%) and NPVs (93.30% and 87.96%) for significant fibrosis and liver cirrhosis, respectively. Sebastiani *et al*[90] reported that combination of FibroTest and APRI could achieve an AUC of 0.96, NPV of 100% and accuracy of 97.2% for significant fibrosis and an AUC of 0.95, NPV of 98% and accuracy of 95.8% for cirrhosis. In another study[60], the combination of TE and Forns score also increased the diagnostic accuracy of significant fibrosis and cirrhosis.

However, combinations of serum markers and TE are more expensive than non-combination tests, and may not be widely available. There is a potential influence of ALT, AST and total bilirubin when interpreting the results of TE[91], and TE is not widely available. Combination algorithms for noninvasive assessment of CHB-related fibrosis and cirrhosis are available in resource-limited settings of developing countries. Salkic *et al*[92] assessed the diagnostic accuracy of six free noninvasive tests in a cohort of 211 patients with CHB who had undergone liver biopsy. A combination of FIB-4 and APRI had a high diagnostic accuracy of 93.5% in excluding patients without significant fibrosis. The combination of GUCI and Lok score had an accuracy of 97.8% in excluding patients without cirrhosis.

LIMITATIONS

There are some limitations of noninvasive tests. Their main disadvantage is the low diagnostic accuracy to identify intermediate stages rather than advanced stages of fibrosis. For evaluation of diagnostic effectiveness, AUC is the standard parameter. However,

the AUC for fibrosis evaluation never reaches the maximum theoretical value (1.0). Noninvasive models used to identify significant fibrosis and cirrhosis in order to decide the antivirus treatment require very high sensitivity. On the contrary, tests used to exclude significant fibrosis in order to relieve the economic burden of antivirus therapy require very high specificity. In fact, none of the models can achieve both perfect sensitivity and specificity. "Spectrum bias" of over-representation of extreme stages of fibrosis (F0 and F4) is difficult to avoid. A study population with an excess of patients with severe fibrosis will automatically generate higher sensitivity and specificity values compared to populations of patients with lower stages of fibrosis (F1 and F2). There may be delays in procuring the results of tests that need to be sent out of the laboratory. Moreover, the indices may change with disease progression or response to therapy.

CONCLUSION

Continued research in this area will provide opportunities to offer more precise and noninvasive diagnostic models to patients. This will eventually result in the incorporation of noninvasive models into clinical guidelines, leading to their wider use in clinical practice. In particular, in resource-limited settings, precise noninvasive diagnostic models will be popular for simple serum markers because they are inexpensive, easy to calculate, and widely available. Although liver biopsy will still be a part of clinical practice in the coming years, noninvasive methods will be increasingly applied.

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