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Review

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Personalized management of cirrhosis by non-invasive tests of liver fibrosis

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Owing to the high prevalence of various chronic liver diseases, cirrhosis is one of the leading causes of morbidity and mortality worldwide. In recent years, the development of non-invasive tests of fibrosis allows accurate diagnosis of cirrhosis and reduces the need for liver biopsy. In this review, we discuss the application of these non-invasive tests beyond the diagnosis of cirrhosis. In particular, their role in the selection of patients for hepatocellular carcinoma surveillance and varices screening is highlighted. **(Clin Mol Hepatol 2015;21:200-211)**

Keywords: Transient elastography; FibroScan; FibroTest; Hepatocellular carcinoma; Varices

INTRODUCTION

Despite geographical differences, chronic liver diseases are highly prevalent worldwide. It is estimated that at least 350 million and 120 million people globally are chronically infected with hepatitis B virus (HBV) and hepatitis C virus, respectively.[1,2] Non-alcoholic fatty liver disease (NAFLD) affects 15-40% of the general population and is particularly prevalent in patients with diabetes and obesity.[3-5] Alcoholic liver disease affects both developed and developing countries and may account for up to 9.2% of all disability-adjusted life years in some regions.[6] Although the etiologies are different, chronic liver disease leads to liver injury, progressive liver fibrosis, and finally to the stage of cirrhosis and liver decompensation. As a result, cirrhosis remains the twelfth global leading cause of death in 2010.[7]

The diagnosis of cirrhosis is not as simple as it seems. Evidently, the diagnosis is straightforward when a patient has already developed clinical manifestations of portal hypertension such as ascites, varices and hypersplenism. Nonetheless, these signs are absent in patients with early cirrhosis, and the radiological features of early cirrhosis are subtle and unreliable.[8] Liver biopsy is traditionally the gold standard for the diagnosis of cirrhosis. However, it is an invasive procedure with a small risk of bleeding. The poor patient acceptance and the risk of sampling error (understaging due to inadequate sample) further limit the widespread application of liver biopsy.

In recent years, the development and application of non-invasive tests of liver fibrosis have revolutionized hepatology practice. Numerous studies have confirmed the accuracy of these tests in fibrosis staging and the diagnosis of cirrhosis. In general, the tests have high negative predictive value in excluding advanced fibrosis and cirrhosis and have been recommended by the European Association for the Study of the Liver as initial assessment in patients with various liver diseases.[9]

Abbreviations:

ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; CHB, chronic hepatitis B; CHC, chronic hepatitis C; EGD,esophagogastroduodenoscopy; ELF, enhanced liver fibrosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; HVPG, hepatic vein pressure gradient; LSM, liver stiffness measurement; NAFLD, non-alcoholic fatty liver disease

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In addition, cirrhosis is not one single disease but encompasses a broad spectrum of clinical condition ranging from compensated disease to decompensated disease. As the disease progresses, various complications of portal hypertension may develop. The development of hepatocellular carcinoma (HCC) further drifts the clinical course and leads to major morbidity and mortality. Therefore, one important part of the management of cirrhosis is to identify and treat major complications early. In this review, we first provide an overview on non-invasive tests of liver fibrosis. Since the diagnosis of cirrhosis is only the first step in the management of cirrhosis, we further discuss the potential application of these tests in the risk stratification of cirrhosis and prediction of cirrhotic complications.

NON-INVASIVE TESTS OF LIVER FIBROSIS

Non-invasive tests of liver fibrosis have been a hot research area in the past decade. At the beginning, the main focus was to reduce the burden of liver biopsy by confidently identifying patients who are very unlikely to have significant fibrosis on one hand and those who are very likely to have advanced fibrosis or cirrhosis on the other. Treatment decisions can then be made accordingly, and patients in the middle (gray zone cases) may undergo liver biopsy or be observed over time. In general, non-invasive tests of liver fibrosis can be divided into serum tests and physical measurements.

Serum tests

The advantages of serum tests include high applicability (successful measurements can be made in most cases) and relatively simple logistics. Doctors may obtain blood samples at their clinics and send them to designated laboratories even for more specific biomarkers. Serum tests can be divided into class I biomarkers and class II biomarkers. Class I biomarkers specifically measure the activity of fibrogenesis or fibrinolysis. In contrast, class II biomarkers do not measure fibrosis directly but represent parameters that correlate with fibrosis. For example, aspartate aminotransferase (AST) is a marker of hepatic necroinflammation and not fibrosis. However, patients with fibrosis and cirrhosis often have increased AST levels. Although class I biomarkers are expected to directly reflect fibrosis and be more accurate than class II biomarkers, this has not been consistently demonstrated in prospective studies.

In any case, at present there is no single marker that can adequately reflect fibrosis. Therefore, in most situations several biomarkers or a combination of biomarkers and other clinical features are used. Some of the combined panels such as FibroTest, FibroMeter and enhanced liver fibrosis (ELF) score have been commercialized. It should be noted that such combined tests are modeled against liver histology, which is an imperfect reference standard. In other words, even if the models can 100% faithfully reflect liver histology, the accuracy of liver histology to diagnose fibrosis and cirrhosis will be the ceiling of accuracy of the new models.[10]

Some of the class II biomarkers are more generic. Examples include the AST-to-alanine aminotransferase (ALT) ratio and the AST-to-platelet ratio index (APRI). In other cases, owing to the pathophysiology of different liver diseases, the class II biomarkers are more disease-specific. For instance, metabolic factors are overrepresented in the NAFLD fibrosis score, which should only be applied in patients with NAFLD.[11,12]

Physical measurements

The other main class of non-invasive tests of liver fibrosis relies on physical measurement of liver stiffness and elasticity. Although the cutoffs of the measurements are determined with reference to histology, these tests are not modeled against histology and theoretically may achieve better prediction than histology. In fact, studies in patients with chronic viral hepatitis suggest that transient elastography may be better than histology in predicting overall mortality.[13,14]

Transient elastography by FibroScan (Echosens, Paris, France) is currently the most commonly used method to measure liver stiffness.[15] It estimates liver fibrosis by measuring the velocity of a shear wave in the liver parenchyma. This is based on the physical principle that waves travel faster in a stiffer medium. The main advantage of transient elastography is the ease of use and high reproducibility.[16] Compared with serum tests, transient elastography is less applicable in obese patients, although the new XL probe partially compensates for that.[17] Liver stiffness is also affected by high ALT level, hepatic congestion, food intake and amyloidosis. Because the correlation between liver stiffness and fibrosis is a generic phenomenon, the technique can be applied to patients with different liver diseases, though the appropriate cutoffs are higher in patients with alcoholic liver disease.[18]

Newer techniques such as acoustic radiation force impulse and shear-wave elastography allow simultaneous visualization of the liver parenchyma and measurement of liver elasticity.[19,20] This can thus combine HCC surveillance and liver fibrosis assessment in a single examination. Magnetic resonance elastography appears to

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be highly accurate and is not affected by obesity, but machine availability and the costs of examination can be prohibitive.[21] These new techniques also have not been as extensively validated as transient elastography.

For simplicity, doctors usually adopt one or more recommended cutoff values in the interpretation of any of the non-invasive tests above. In reality, however, the more extreme the values of the non-invasive tests are, the more we are confident in whether a patient has fibrosis/cirrhosis or not. For example, a probability-based interpretation of liver stiffness measurements (LSM) has been proposed.[22] Based on the exact LSM, the probability of a patient having different fibrosis stages can be determined. The complexity of this approach limits its use in real life practice. Nonetheless, as a patient is more likely to have cirrhosis and advanced cirrhosis when he has more extreme non-invasive tests results, this forms the basis of extending the tests to stratify the risk and predict complications in cirrhotic patients.

HEPATOCELLULAR CARCINOMA

Current recommendations and unmet need

HCC is one of the most important complications in patients with chronic liver diseases.[23] HCC surveillance is an indispensable part of the management of liver patients. The current Asian Pacific guidelines recommend 6-monthly trans-abdominal ultrasonography and serum alpha-fetoprotein (AFP) testing for HCC surveillance.[24] Despite the fact that AFP has been widely adopted for decades, it has been criticized as neither sensitive nor specific.[25] Hence the latest American guidelines stopped recommending the use of AFP in the surveillance program.[26] Nonetheless, a recent study demonstrated a satisfactory sensitivity and specificity of AFP for HCC in CHB patients received antiviral therapy.[27] Therefore some experts believed that the calls for abandoning the monitoring of AFP levels might be premature, especially given the already low HCC surveillance rate in developing countries and at primary care settings.[28]

HCC surveillance improves the prognosis of patients by identifying tumors of smaller sizes, fewer numbers of tumors, and longer overall survival.[29] Unfortunately, the 5-year mortality rate was still close to 40% despite the regular HCC surveillance. This observation points towards the fact that the current HCC surveillance recommendation is still far from satisfactory.

The key components of an optimal surveillance program include accurate risk stratification and reliable surveillance tools. Hence there is a need for accurate HCC risk prediction to assist prognostication as well as decision on the need for HCC surveillance.

Non-invasive tests and HCC risk

Liver stiffness measurements

Various non-invasive tests of liver fibrosis have been tested to predict the risk of HCC. Among them LSM with transient elastography is the most widely-studied. A dose–response relationship between LSM and HCC risk was demonstrated in patients with either chronic hepatitis B (CHB) or chronic hepatitis C (CHC).[30,31] In a prospective cohort of study of 1,130 Korean CHB patients, the hazard ratios (HRs) of developing HCC were 3.1, 4.7, 5.6, and 6.6 in patients with LSM at 8.1–13.0 kPa, 13.1–18.0 kPa, 18.1–23.0 kPa, and >23.0 kPa, respectively, when compared to those with LSM LSM ≤ 8.0 kPa.[30] A similar relationship was demonstrated in

Table 1. CU-HCC score vs. LSM-HCC score [Modified from reference Wong VW et al. JCO 2010 & Wong GL et al. J Hep 2014]

Factors	CU-HCC score*	LSM-HCC score†
Age		
> 50 years	+3	+10
≤ 50 years	0	0
Albumin		
≤ 35g/L	+20	+1
> 35g/L	0	0
Total bilirubin (μmol/L)		
> 18	+1.5	
≤ 18	0	
HBV DNA		
> 200,000 IU/mL	+4	+5
2,000–200,000 IU/mL	+1	0
≤ 2,000 IU/mL	0	0
Cirrhosis		
Yes	+15	
No	0	
Liver stiffness measurement		
≤ 8.0 kPa		0
8.1-12.0 kPa		+8
> 12.0 kPa		+14

HBV, hepatitis B virus; LSM, liver stiffness measurement.
*Total CU-HCC score ranges from 0 to 44.5. Scores of 0 to 4, 5 to 19 and 20 to 44.5 indicate low, intermediate and high risk respectively.
†Total LSM-HCC score ranges from 0 to 30. Scores of 0 to 10, 11 to 20 and 21 to 30 indicate low, intermediate and high risk respectively.

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Table 2. The application of non-invasive tests of fibrosis in the prediction of portal hypertension

Author	N	Non-invasive tests	Cutoff	Endpoint	AUROC	Sensitivity	Specificity
Ultrasound techniques							
Tasu 2002[53]	50	Hepatic arterial acceleration index by duplex ultrasound	1 ms-2	HVPG 12 mmHg	0.83	65%	95%
		Portal vein velocity	17cm/s	HVPG 12 mmHg	-	69%	67%
Bolognesi 2001[73]	40	Estimated portal pressure by echo-color Doppler		HVPG 16 mmHg	-	82%	70%
Berzigotti 2006[56]	31	Renovascular impedance	0.7	HVPG 16 mmHg	-	52%	100%
Kim 2007[59]	76	Damping index by Doppler hepatic vein waveform	0.6	HVPG 12 mmHg	0.86	76%	82%
Choi 2003[54]	138	Portal vein velocity & flow		HVPG		No correlation	No correlation
		Splenic vein velocity & flow		HVPG		No correlation	No correlation
		Pulsatility index		HVPG		No correlation	No correlation
		Resistive index		HVPG		No correlation	No correlation
		Portal vein velocity		Change in HVPG with terlipressin		No correlation	No correlation
Taurel 1998[55]	40	Portal vein time-average mean blood velocity	-	HVPG 12 mmHg	-	-	-
		Portal vein flow	-	HVPG 12 mmHg	-	-	-
		Hepatic artery resistance index	-	HVPG 12 mmHg	-	No correlation	No correlation
		Superior mesenteric artery resistance index	-	HVPG 12 mmHg	-	No correlation	No correlation
Baik 2006[60]	78	Hepatic waveforms by Doppler ultrasound	Mono-phasic waveform	HVPG 15 mmHg	-	74%	95%
Physical measurements							
Robic 2011[48]	65	LSM	21.1 kPa	Portal hypertension-related complications	0.734	100%	41%
Lemoine 2008[47]	92	LSM	20.5kPa	HVPG 10 mmHg	0.76	63%	70%
		LSM	34.9kPa	HVPG 10 mmHg	0.94	90%	88%
Procopet 2015[49]	202	LSM	13.6kPa	HVPG 10 mmHg	Training cohort- 0.94 Validation cohort- not reported	Training cohort- 95.6% Validation cohort- 86.7%	Training cohort- 75.3% Validation cohort- 69.3%
		LSM	21.1kPa	HVPG 10 mmHg	Training cohort- 0.94 Validation cohort- not reported	Training cohort- 88.9% Validation cohort- 80%	Training cohort- 87.6% Validation cohort- 96.6%
		Lok score	0.73	HVPG 10 mmHg	Training cohort- 0.84 Validation cohort- not reported	Training cohort- 87% Validation cohort- 66.7%	Training cohort- 80.6% Validation cohort- 88.5%