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EDITORIAL

Evolving strategies for liver fibrosis staging: Non-invasive assessment

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Abstract

Transient elastography and the acoustic radiation force impulse techniques may play a pivotal role in the study of liver fibrosis. Some studies have shown that elastography can detect both the progression and regression of fibrosis. Similarly, research results have been analysed and direct and indirect serum markers of hepatic fibrosis have shown high diagnostic accuracy for advanced fibrosis/cirrhosis. The prognosis of different stages of cirrhosis is well established and various staging systems have been proposed, largely based on clinical data. However, it is still unknown if either non-invasive markers of liver fibrosis or elastography may contribute to a more accurate staging of liver cirrhosis, in terms of prognosis and fibrosis regression after effective therapy. In fact, not enough studies have shown both the fibrosis regression in different cirrhosis stages and the point beyond which the prognosis does not change - even in the event of fibrosis regression. Therefore, future studies are needed to validate non-invasive methods in predicting the different phases of liver cirrhosis.

Key words: Elastography; Non-invasive methods; Chronic liver diseases; Stiffness; Non-invasive serum markers

Core tip: Several studies have demonstrated the accuracy of non-invasive methods to predict significant/advanced fibrosis and cirrhosis and to identify the presence/absence of fibrosis. However, it is still unknown if either non-invasive markers of liver fibrosis or elastography may contribute to a more accurate staging of liver cirrhosis, in terms of prognosis and fibrosis regression after effective therapy. Therefore, future studies are needed to validate non-invasive methods in predicting the different phases of liver cirrhosis.

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INTRODUCTION

Transient elastography and acoustic radiation force impulse (ARFI) method can play a key role in the assessment of hepatic fibrosis[1-4]. Liver stiffness is particularly convenient either in confirming significant fibrosis and cirrhosis, or in confirming the absence of fibrosis. In some cases, liver biopsy is needed because the histological analysis contributes to establishing the aetiology of the disease. In this case, a non-invasive test should not substitute a hepatic biopsy but can be used to monitor patients previously biopsied.

Recently, longitudinal studies[5-7] have shown that transient elastography can detect changes in hepatic stiffness in hepatitis C virus (HCV) patients during antiviral treatment. In these patients, non-invasive serum markers, both indirect and direct, have been proposed as alternative tests to a liver biopsy. All non-invasive serum markers showed a satisfactory accuracy for the diagnosis of significant and/or advanced fibrosis and cirrhosis.

As regarding hepatitis B virus (HBV) infection, in particular, some studies suggest that the complete long-term suppression of HBV replication by nucleosides/nucleotides results in a long-term improved outcome that significantly reduces the risk of developing liver cirrhosis, hepatocellular insufficiency, and hepatocellular carcinoma (HCC)[8]. Moreover, longitudinal histopathological evaluation has demonstrated a regression of liver tissue fibrosis during nucleos(t)ide analogue therapy[9]. Liver biopsy still is the gold standard, and in some cases it is still required for a proper staging in HBV patients. The research results seem to indicate that non-invasive methods may also be useful in these patients, but further study is needed before any firm conclusion can be drawn.

In patients with primary biliary cholangitis (PBC), several staging systems[10-13] have been suggested to describe the evolution from the characteristic early lesions of chronic non-suppurative destructive cholangitis to cirrhosis. Although each staging system has been shown to have a predictive value for outcomes PBC-related and patient survival[14], the quest for a better staging system is still active. However, one should keep in mind that any staging systems considering the role of fibrosis in prognosis should take into account that cirrhotic patients with different aetiology may develop complications in a wide range of fibrotic tissue. In fact, Hall *et al*[15], in a study of liver explants collected at the time of orthotopic liver transplantation, showed that hepatic fibrosis was more present in alcoholic liver disease (30%), PBC (23.5%) and primary sclerosing cholangitis (22.5%), than autoimmune hepatitis (18.5%), HCV (17%) and HBV (16.5%).

On the other hand, in PBC patients, complications may also develop before cirrhosis[16], thus prompting research to identify additional parameters that may better predict clinically significant events.

Floreani *et al*[17] demonstrated that transient elastography accurately assesses liver fibrosis in PBC, whereas non-invasive surrogate markers proved unsatisfactory in predicting significant fibrosis.

Some studies[17,18] demonstrated that generally the non-invasive markers' values were not significantly different between the different stages of PBC.

Stasi *et al*[18] showed a significant correlation between histomorphometric values of hepatic fibrosis and all non-invasive markers, even though indirect serum markers did not show significant differences between Ludwig's stages, suggesting that non-invasive methods could be better descriptors of fibrosis in PBC in comparison with traditional semi-quantitative staging methods.

Recently, Sheptulina *et al*[19] evaluated the capacity of non-invasive markers [fibrosis-4 (FIB-4), aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AAR), AST to platelet count ratio (APRI), and platelet count to spleen diameter (PC/SD) ratio] compared to percutaneous liver biopsy to classify significant fibrosis, advanced fibrosis and cirrhosis in patients with autoimmune hepatitis. The authors showed that the PC/SD ratio correctly identifies autoimmune hepatitis patients with advanced fibrosis and cirrhosis, thereby decreasing the execution of liver biopsy in these patients.

However, despite a number of non-invasive markers having been validated to differentiate chronic liver disease from cirrhosis, they are still scarcely used in the clinical setting.

EMERGING NON-INVASIVE ASSESSMENT OF EXTENSIVE FIBROSIS OR CIRRHOSIS

D'Amico *et al*[20] showed that the different phases of end-stage liver disease consist of different mortality rate/year, ranging from 1% in cirrhosis without varices to 57% in complicated cirrhosis. The various cirrhosis phases may have distinct responses to therapy, meaning that a better staging of cirrhosis phases may have prognostic significance. The identification of the different phases of liver cirrhosis, each characterized by its own cumulative risk of non-response to treatment in terms of clinical response rather than as virus eradication, could contribute to the management of these patients. Different staging systems for cirrhosis have been proposed, some of which have a defined prognostic value relative to survival. For some of these (Child and MELD) the prognostic value for the direct-acting antiviral agents (DAAs) therapy was calculated, although it is unclear whether those patients who

responded to therapy had different survival rates. It remains to be seen whether any of the alternative fibrosis staging systems, such as the evaluation of stiffness, which is known to have a wide range of values in cirrhotic patients, or non-invasive fibrosis markers can offer different prognostic implications for patients undergoing antiviral treatment.

Currently, liver biopsy is the most reliable method for evaluating the severity of hepatic fibrosis, in particular the use of collagen proportionate area (CPA) determinations. Therefore, the staging of liver fibrosis during cirrhosis may have a high clinical/prognostic value. Probably, there is a "point of no return" at which the regression of fibrosis in patients with cirrhosis after antiviral treatment with DAAs does not change the prognosis, probably because the neoangiogenesis and liver regeneration continue to support the evolution to HCC. Moreover, portal hypertension established at this point does not regress. The biopsy provides helpful information and offers valid help in disease prognosis. However, it is also an invasive procedure in decompensated cirrhosis patients for the presence of complications such as ascites, prolonged clotting time and infections[21].

Xie *et al*[22] analysed the CPA of 53 resected liver tissue samples from HBV-related decompensated cirrhotic patients, and examined the association between the CPA and liver functional reserve. Lower CPA values were found in patients who had largely macronodular cirrhosis. In these patients, liver transplants were executed, especially for severe portal hypertension (gastrointestinal bleeding) although their liver functional reserve was still at the compensated stage. This study demonstrated that the number of hepatocytes diminishes with an increasing fibrosis and CPA value, and it showed a robust correlation between MELD score, serum total bilirubin level, international normalized ratio (INR) and CPA, and showed significant differences among three CPA groups (< 0.22, 0.22-0.48 and > 0.48).

Liang *et al*[23] retrospectively evaluated patients with HBV and they demonstrated that combining routine markers ameliorates the accuracy of transient elastography for cirrhosis diagnosis in these patients.

Leroy *et al*[24] compared the overall diagnostic performances of serum markers of liver fibrosis (FibroTest®, FibroMeter®, and HepaScore®) in 510 HBV or HCV monoinfected patients and found that these were similar between HBV and HCV, with the area under the receiver operating characteristic (AUROC) curve ranging from 0.82 to 0.85 for advanced fibrosis and 0.84 to 0.87 for cirrhosis, respectively[24].

A recent meta-analysis demonstrated a good correlation between transient elastography and hepatic venous pressure gradient (HVPG) for the prediction of clinically significant portal hypertension, such as HVPG $\geqslant$ 10 mmHg. This cut-off level indicates the absence/presence of clinically significant portal hypertension in compensated cirrhosis[25].

Several studies have been carried out using transient elastography to assess its accuracy in describing the occurrence of portal hypertension and oesophageal varices. An extensive range of cut-off levels have been described so far, and transient elastography cannot consequently be considered reliable in describing portal hypertension[26]. Deng *et al*[27] investigated the role of APRI, AAR, FIB-4, fibrosis index (FI), and King scores and they confirmed that diagnostic accuracy of oesophageal varices was modest in liver cirrhosis. Therefore, they might not be able to predict oesophageal varices in liver cirrhosis.

Diagnostic imaging techniques to estimate liver cirrhosis phases include abdominal ultrasound (US), used for diagnosis and monitoring of chronic liver disease patients, the contrast-enhanced ultrasonography, used especially to study liver tumours, and the Doppler US signs for studying portal hypertension. Using US, liver cirrhosis is characterized by atrophy of the right lobe associated with hypertrophy of the left lobe, whereas complete liver atrophy indicates the advanced phase. The echo-pattern of cirrhosis has been described as a *coarse* pattern, without posterior beam attenuation; however, the coarse pattern increases hepatic echogenicity, causing some difficulty in differentiating between cirrhosis and steatosis. Liver surface irregularities such as micro- or macro-nodularity in liver cirrhosis are considered among the most sensitive and more reproducible US signs[28]. The US is able to identify the third phase of liver cirrhosis (presence of ascites), but it is inaccurate for the identification of the second phase (early detection of varices). Although, spleen bipolar diameter of > 12 cm or largest splenic cross-sectional area passing through the hilum of > 45 cm^2 and reduced portal vein blood flow velocity (time-averaged mean velocity of < 14-16 cm/s^2) may indicate portal hypertension[29,30].

It has been suggested that a combination of imaging data and blood parameters may provide a better staging of liver fibrosis.

Berzigotti *et al*[31] proposed an association of hepatic stiffness and spleen diameter and platelet count estimation to detect patients with portal hypertension.

Recently, serum markers have been proposed as possible tools for non-invasive staging of cirrhosis. Moreover, some studies have shown that spleen stiffness value acquired using ARFI may predict the presence of oesophageal varices in cirrhotic patients. In particular, Park *et al*[32] demonstrated that the AST to ALT ratio score, APRI score, PLT, PLT/spleen diameter ratio and spleen elastography variables were all independently associated with oesophageal varices. However, the multivariate analysis revealed that only spleen elastography was associated with oesophageal varices. However, in cases of alcohol-induced liver cirrhosis, spleen stiffness was not reliable for the prediction of oesophageal varices.

Cassinotto *et al*[33] showed that liver and spleen stiffness were correlated with cirrhosis severity, with

Table 1 Prediction of any grade of oesophageal varices by some non-invasive methods

Method	Aetiology	Cut-off value	PPV	NPV
Liver stiffness (kPa) Castéra *et al*[40], 2009	HCV	⩾ 21.5	68	84
Liver stiffness (kPa) Hassan *et al*[41], 2014	HCV	> 18.2	89	49
FIB-4 Hassan *et al*[41], 2014	HCV	> 2.8	92.7	50
Forns index Hassan *et al*[41], 2014	HCV	> 6.61	88.4	45.5
Lok score Hassan *et al*[41], 2014	HCV	> 0.63	78	42.9
Lok index Sebastiani *et al*[42], 2010	CLD	0.9	80	64
Forns index Sebastiani *et al*[42], 2010	CLD	8.5	81	57
Minimum slice thickness by CT (mm) Karatzas *et al*[39], 2016	CLD	0.625-1.2	77.5	70.6
Platelet count/spleen diameter ratio Giannini *et al*[43], 2010	CLD	909	76.6	87

FIB-4: Fibrosis-4; CT: Computer tomography; HCV: Hepatitis C virus; CLD: Chronic liver diseases independent of aetiology; PPV: Positive predictive value; NPV: Negative predictive value.

values increasing according to Child-Pugh subclasses and the presence of complications. With a negative predictive value of > 90%, liver stiffness cut-offs for high-risk oesophageal varices, history of ascites, Child-Pugh B/C, variceal bleeding and clinical decompensation were 12.8, 19, 21.4, 30.5 and 39.4 kPa, respectively. Cho *et al*[34] analysed the diagnostic and prognostic values of non-invasive fibrosis markers in comparison with HVPG in patients with alcoholic cirrhosis. For the diagnosis of clinically significant portal hypertension in compensated patients, liver stiffness and the liver stiffness-spleen diameter to platelet ratio score showed significantly higher accuracy with area under the curves (AUCs) of 0.85 and 0.82, respectively, than APRI, FIB-4, Forns index, Lok index, (platelet count)2/[monocyte fraction (%) × segmented neutrophil fraction (%)], and PC/SD ratio. Nevertheless, none of these methods showed accurate diagnosis for the diagnosis of high-risk varices.

On the contrary, Stefanescu *et al*[35] proposed an algorithm combining hepatic stiffness, spleen stiffness and serum markers to predict patients with low-risk varices and who may benefit from more distanced endoscopic evaluation.

Cho *et al*[34], in the course of a median follow-up of 42.6 mo, showed that only Lok index and FIB-4 were independently associated with cause of death in decompensated patients and only the Lok index significantly ameliorated the discrimination function of MELD score in prognostication of overall survival.

Recently, the indocyanine green retention test at 15 min (ICG-r15; routinely used for evaluating hepatic function in patients undergoing hepatic surgery for liver tumour) has been investigated and has been proposed and clinically evaluated as a prognostic marker in patients with advanced cirrhosis[36]. In patients with compensated cirrhosis, this test correlated to the degree of portal hypertension and oesophageal varices. ICG-r15 appears to be accurately related to liver decompensation, confirming the preliminary findings of its association with portal hypertension in compensated patients, and can be used for patient prognostication[36]. Li *et al*[37] assessed the hepatic functional reserve in patients with HCC through the use of magnetic resonance elastography (MRE). Regions of interest were identified in different slices of the liver parenchyma free of tumour to measure average stiffness. In addition, the ICG test was performed within 1 wk before or after magnetic resonance examination and the ICG-r15 and the ICG plasma clearance rate (ICG-K) were evaluated. The authors found that the liver stiffness value of the tumour-free parenchyma was positively related to the ICG-r15 and negatively related to the ICG-K. Therefore, it could be used to evaluate the liver functional reserve of HCC patients.

Antil *et al*[38] evaluated the performance of hepatic venous waveform, damping index (DI; the ratio between the minimum velocity and maximum velocity of the hepatic venous flow, with DI of > 0.6 suggestive of portal hypertension and higher DI values tending to give flat hepatic venous waveforms) and splenoportal index (SPI; denoting the splenic index, which is a product of maximum transverse and vertical diameter of the spleen in centimetres) in patients with cirrhosis on colour Doppler US in predicting the severity of portal hypertension and presence of oesophageal varices. They concluded that a change in triphasic to monophasic waveform and DI of > 0.6 indicate severe liver dysfunction and severe portal hypertension. Hepatic venous waveform pressure changes, DI and SPI have no value in predicting oesophageal varices.

Karatzas *et al*[39] compared multidetector computed tomography and the PC/SD ratio for the diagnosis of gastroesophageal varices. Multidetector computed tomography was accurate for this diagnosis, especially for that of gastroesophageal varices with clinically significant size (> 5 mm), and superior to the PC/SD ratio. The authors suggested that multidetector computed tomography could replace, in selected patients, upper gastrointestinal (GI) endoscopy as a method for diagnosing gastroesophageal varices in cirrhotic patients.

In Table 1[39-43] we have summarized the cut-off values of some non-invasive methods for the diagnosis of oesophageal varices.

CONCLUSION

Although increasing evidence has been reported for the prognostic value of non-invasive evaluation of liver fibrosis, the staging of hepatic fibrosis during the different phases of liver cirrhosis has little evidence,

and future studies are needed to validate non-invasive methods in predicting the different phases of liver cirrhosis.

In fact, several non-invasive methods have been suggested for the diagnosis of oesophageal varices, including serum markers, liver stiffness measurements and US parameters. These methods are useful to detect patients in whom the gastroesophageal evaluation is indicated with a certain level of urgency, but cannot replace the GI endoscopy.

There is a continuous lead-up to fibrosis staging, including the validation of different methods. However, it is not the proper tools that we lack, rather the answers to some basic questions. Not enough studies have shown both the fibrosis regression in different cirrhosis stages and the point beyond which the prognosis does not change - even in the event of fibrosis regression. Such information could enhance our understanding of when eradicating therapies against HCV are most likely to radically change the patients' prognoses, and when such changes would be rather unlikely.

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