1 Noninvasive markers of fibrosis: how reliable are they?

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LEARNING POINTS

- Noninvasive tests must always be interpreted critically, according to the context of use and setting (primary healthcare or tertiary referral center and clinical context), taking into account the recommended quality criteria for each test and its possible pitfalls.
- Limitations include cost and availability for patented serum markers, and operator experience and obesity for transient elastography.
- The most validated serum markers are APRI and FIB-4 (nonpatented) and FibroTest® (patented).
- Transient elastography is a point-of-care technique and the most validated and accurate for diagnosing cirrhosis (better at ruling out than ruling in), outperforming serum markers.
- Noninvasive tests (transient elastography >> serum markers) are recommended as first line for detection of cirrhosis before antiviral treatment in patients with viral hepatitis.
- In patients with cirrhosis, posttreatment decrease in liver stiffness should not substitute for the recommended, periodic surveillance for hepatocellular carcinoma.

Introduction

Staging of liver fibrosis and early detection of compensated cirrhosis are critical in the management and surveillance of patients with chronic viral liver disease. For many years, liver biopsy has been considered the "gold standard" for evaluation of hepatic fibrosis. However, liver biopsy is an invasive procedure with rare but potentially life-threatening complications and prone to sampling errors. These limitations, as well as the availability of powerful virologic tools and antiviral agents, have rapidly decreased the use of liver biopsy in patients with chronic viral hepatitis and led to the development of noninvasive methods. These methods are now widely used in clinical practice and recommended by international and European Association for the Study of the Liver (EASL) guidelines [1–5].

Currently available noninvasive methods

Among the currently available noninvasive methods, there are two distinct approaches: (i) a "biological" approach based on the dosage of serum markers of fibrosis; (ii) a "physical" approach based on the measurement of liver stiffness, using either ultrasound (US) or magnetic resonance (MR)-based elastography techniques. Although complementary, these two approaches are based on different rationales and conceptions: liver stiffness is related to elasticity, which corresponds to a genuine and intrinsic physical property of liver parenchyma, whereas serum biomarkers are combinations of several, not strictly liver-specific, blood parameters optimized to mimic fibrosis stages as assessed by liver biopsy. The critical endpoint in clinical practice is the detection of cirrhosis as the choice of direct-acting antiviral agents in hepatitis C virus (HCV) patients and the posttreatment prognosis depend on the stage of fibrosis. Finally, treatment with nucleoside analogs should not be stopped in hepatitis B virus (HBV) patients with cirrhosis.

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Serum markers of liver fibrosis

Many serum markers have been evaluated for their ability to detect cirrhosis in patients with chronic viral liver disease. Details can be found elsewhere [1]. Their respective advantages and limitations are summarized in Table 1.1. Nonpatented tests are cost-free, easy to calculate, and almost universally available, whereas patented tests are commercially available proprietary formulae.

Liver stiffness measurement

Transient elastography (TE) was the first commercially available ultrasound-based elastography method developed for the measurement of liver stiffness, using a dedicated device (FibroScan®, Echosens, Paris, France). Several other liver elasticity-based imaging techniques challenging TE have been developed, including point shear wave elastography (pSWE), also known as acoustic radiation force impulse imaging (ARFI), (2-D) shear-wave elastography (2D-SWE), and magnetic resonance elastography (MRE) [6]. Their respective advantages and limitations are summarized in Table 1.1. The units and scales are different between the different techniques. The main limitation of TE in clinical practice is its limited applicability in cases of obesity, which is solved with the use of an XL probe. Confounding factors for liver stiffness, whatever the technique, include inflammation (transaminases >5 × upper limit of normal [ULN]), liver congestion, food intake, and extrahepatic cholestasis. Procedures should be performed using a standardized protocol in fasting patients (for at least two hours).

Diagnostic performance of noninvasive methods for diagnosing cirrhosis

Serum biomarkers of fibrosis

Among nonpatented tests, the AST to Platelet Ratio Index (APRI) and the Fibrosis-4 (FIB-4) are the most extensively studied and validated with evidence based on large meta-analyses [7,8], including several thousands of patients reporting area under the receiver operating characteristic curve (AUROC) for diagnosing cirrhosis ranging from 0.73 to 0.84 (Table 1.2). They all perform better at ruling out than ruling in cirrhosis with high negative predictive value (>90%).

As for patented tests, the FibroTest® is the most extensively studied, mainly in patients with viral hepatitis. However, all patented tests lack external validation, and metaanalyses independent from the developers are very few [9]. When compared with nonpatented tests, patented tests offer slight improvement in accuracy but their widespread application is limited by cost and availability.

Liver stiffness measurement

The diagnostic accuracy of TE for cirrhosis is based on large metaanalyses including several thousands of patients with viral hepatitis [10,11] and considered excellent with AUROCs of 0.93–0.94, and sensitivities and specificities of 86–87% and 89–91%, respectively (Table 1.2). However, a metaanalysis based on individual data is still awaited. Actually, TE is better at ruling out than ruling in liver cirrhosis (with negative predictive value higher than 90%).

Different cut-offs have been proposed for HBV and HCV but no consensus has been reached. As shown in Table 1.2, cut-offs for cirrhosis ranged from 9.0 to 16.9 kPa in HBV. This may be related to the so-called spectrum bias, depending on the uneven distribution of different fibrosis stages in different cohorts. In that respect, the 2015 Baveno VI consensus workshop recommended a diagnosis of compensated liver cirrhosis in asymptomatic patients using TE, if liver stiffness values are repeatedly (two different days, fasting) >15 kPa [12]. When compared head to head with serum markers, TE outperforms all of them. ARFI performance for diagnosing cirrhosis has been evaluated mainly in viral hepatitis with high accuracy (AUROC 0.91) and cut-off of 2.42 m/sec [13]. When compared with TE, ARFI has equivalent results. 2D-SWE has been evaluated in a single metaanalysis [14], based on individual data in 1340 patients with chronic liver disease, reporting high accuracies (AUROCs 0.93–0.95) for cirrhosis with an optimal cut-off of 13.5 kPa. When compared to TE in this metaanalysis, no significant difference was found, if the quality criteria of TE were respected. As for MRE, evidence is based on a few hundred patients, but with excellent accuracy (97%) for diagnosing cirrhosis [15]. However, widespread use of this method will depend on cost and availability.

Finally, it should be kept in mind that cut-offs for cirrhosis are system specific.

Use in clinical practice

Before starting antiviral treatment

The EASL clinical practice guidelines recommend that all patients with chronic hepatitis B or C should be assessed for liver disease severity before antiviral therapy using noninvasive tests as first line [2,3]. Serum levels of

Table 1.1 Respective advantages and limitations of currently available non-invasive methods in patients with chronic liver disease

Serum markers	Measurement of liver stiffness			
	Transient elastography (TE)	**ARFI (pSWE)**	**2D-SWE**	**MR elastography**
Advantages				
• Good reproducibility • High applicability (95%) • No cost and wide availability (nonpatented) • Well validated • Can be performed in primary healthcare setting	• Most widely used and validated technique: standard to be beaten • Point-of care technique • Can be performed by nurses • High range of values (2-75 kPa) • Quality criteria well defined (IQR/M <30%) • Good reproducibility • High performance for cirrhosis • Quantification of steatosis (CAP) • Low failure rate in obese patients when using XL probe (3%)	• Can be implemented on a regular US machine • ROI smaller than TE but location chosen by the operator • Higher applicability than TE (ascites and obesity) • Performance equivalent to TE for cirrhosis	• Can be implemented on a • regular US machine • ROI can be adjusted in size and location and chosen by the operator • High range of values • (2-150 kPa) • Good applicability • Performance equivalentto TE for cirrhosis	• Can be implemented on a regular MRI machine • Examination of the whole liver • Higher applicability than TE (ascites and obesity) • High performance for cirrhosis
Limitations				
• Nonspecific for the liver • Unable to discriminate between intermediate stages of fibrosis • Performance not as good as TE for cirrhosis • Cost and limited availability (patented) • Limitations (hemolysis, Gilbert syndrome, inflammation…)	• Requires a dedicated device • ROI cannot be chosen • Unable to discriminate between intermediate stages of fibrosis • Applicability (80%) lower than serum markers (obesity, ascites, operator experience) • False positive in cases of acute hepatitis, cholestasis, liver congestion, food intake, and excessive alcohol intake	• Unable to discriminate between intermediate stages of fibrosis • Units (m/sec) different from that of TE (kPa) • Narrow range of values (0.5-4.4 m/sec) • Quality criteria not well defined • Cannot be perfomed by nurses	• Further validation warranted • Unable to discriminate between intermediate stages of fibrosis • Quality criteria not well defined • Cannot be perfomed by nurses	• Further validation warranted, especially in comparison with TE • Small range of values (2-11 kPa) • Not applicable in case of iron overload • Time-consuming • Limited availability • Costly

Source: Adapted from reference [1].
ROI, region of interest.

Table 1.2 Diagnostic performances (metaanalyses) of serum markers and elastography techniques for cirrhosis taking liver biopsy as reference

	Etiology	Patients (n)	Cut-offs	Area under receiver operating characteristic	Sensitivity (%)	Specificity (%)e
Serum markers						
Nonpatented						
APRI [8]	HBV	8773	1.0–2.0	0.73	66–31	74–89
[7]	HCV	4548	1.0–2.0	0.83	76–46	72–91
FIB-4 [8]	HBV	6068	1.05–2.65	0.84	87–64	65–86
Patented						
FibroTest [9]	HBV	1754	0.74	0.87	62	91
Liver stiffness						
Ultrasound-based elastography						
Transient elastography [11]	HBV	4386	9.0–16.9 kPa	0.93	86	87
[10]	CLD (HCV)	8206	13.0 kPa	0.94	91	89
ARFI [13]	HBV/HCV	2691	2.42 m/sec	0.91	86	84
2D-SWE [14]	HBV	400	11.5 kPa	0.95	80	93
	HCV	379	13.0 kPa	0.93	86	88
Magnetic resonance-based elastography						
[15]	HBV	1470	4.6 kPa	0.97	89	92

CLD, chronic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus.

aminotransferases should be taken into account in interpreting TE results in patients with hepatitis B. To avoid the risk of false-positive results, some authors have proposed adopting TE cut-offs based on levels of alanine aminotransferase (ALT). In cases of unexplained discordance or suspected additional etiologies of liver disease, a liver biopsy is still recommended [2,3].

Monitoring of fibrosis regression in treated patients

Several studies have reported a significant decrease in liver stiffness and biomarker values, compared with baseline values, in HBV patients treated with analogs and in HCV patients who achieved sustained virologica response (SVR), consistent with significant histologic improvement documented in studies of paired liver biopsies in these patients. It should be stressed, however, that these studies suffer from several methodologic shortcomings: most are retrospective, with small sample size and short follow-up and, most importantly, no paired liver biopsies.

Nevertheless, in a recent metaanalysis based on 24 studies (10 with DAA), including a total of 2934 HCV patients, SVR was associated with a significant decrease in liver stiffness, particularly in patients with high baseline level of inflammation or patients who received direct-acting agents [16]. Almost half the patients considered to have advanced fibrosis, based on TE, before therapy achieved posttreatment liver stiffness levels <9.5 kPa. Similarly, in a recent study in 164 HBV Chinese patients treated with telbivudine and paired with liver biopsies (baseline and week 104), a two-phase decline in liver stiffness was observed: rapid within the first 24 weeks (−2.2 kPa/24 weeks) in parallel with ALT levels, then slower (−0.3 kPa/24 weeks) but continous from week 24 to week 104 while ALT levels remained within the normal range [17]. This pattern suggests that the first phase decline was mostly related to inflammation whereas the second phase could be related to fibrosis improvement. Although this study is the only one to date with paired liver biopsies, only 10 patients had baseline cirrhosis and no information was available regarding the regression of cirrhosis. Finally, in a large cohort of HBV patients (n = 575) treated with tenofovir and baseline liver biopsy, APRI or FIB-4 reduction did not correlate with fibrosis regression after 240 weeks of antiviral therapy [18].

Thus, although it is tempting to use noninvasive tests to assess fibrosis regression in treated patients with chronic

hepatitis B or C, no recommendation can be made, given the influence of inflammation on serum biomarkers and liver stiffness. In patients with cirrhosis, posttreatment decrease in liver stiffness should not replace the recommended periodic surveillance for hepatocellular carcinoma, using ultrasound examination and measurement of alpha-fetoprotein levels.

Monitoring of disease progression

In patients with liver stiffness values in the range of liver cirrhosis, screening for portal hypertension and hepatocellular carcinoma (HCC) is also recommended without prior liver biopsy. A metaanalysis based on 17 studies in 7058 patients with chronic liver diseases (mainly related to viral hepatitis) has shown that baseline liver stiffness, measured using TE, was significantly associated with risk of hepatic decompensation (six studies; relative risk [RR] 1.07; 95% confidence interval [CI] 1.03–1.11), hepatocellular carcinoma (nine studies; RR 1.11; 95% CI 1.05–1.18), death (five studies; RR 1.22; 95% CI 1.05–1.43), or a composite of these outcomes (seven studies; RR 1.32; 95% CI 1.16–1.51) [19]. Thus, the potential of liver stiffness values for predicting clinical outcomes seems to be greater than that of liver biopsy, probably because liver stiffness measures chart ongoing pathophysiologic processes and functions that a biopsy cannot. As for other elastography techniques, data are currently lacking in viral hepatitis B or C.

The 2015 Baveno VI consensus recommendations stated that: (i) in patients with viral-related compensated advanced chronic liver disease (cACLD), TE (≥20–25 kPa) alone or combined with platelets and spleen size is sufficient to rule in clinically significant portal hypertension, defining the group of patients at risk of having endoscopic signs of portal hypertension; (ii) in patients with a liver stiffness <20 kPa and a platelet count >150 000, the risk of having varices requiring treatment is very low and screening endoscopy can be avoided [12]. Interestingly, the performance of these criteria has been confirmed independently in various populations and all studies confirmed that about 20% of upper gastrointestinal (GI) endoscopies could be safely avoided, missing less than 4% of patients with varices needing treatment [20]. These recommendations represent a significant advance in the management of patients with viral hepatitis and early cirrhosis and can be confidently applied in everyday practice. Recently, expanded Baveno VI criteria (liver stiffness <25 kPa and platelet count >110 000) have been proposed [21], allowing avoidance of around 40% of endoscopies and missing less than 5% of patients with varices needing treatment. As for ARFI and 2D-SWE, given the very limited number of studies reporting on their performance for detection of esophageal varices, no recommendation can be made [20].

Conclusions and perspectives

Considerable progress has been made over the past decade in noninvasive assessment of liver disease in patients with hepatitis B and C. Noninvasive tests are now widely used in clinical practice and recommended by national and international guidelines as first-line tools for the management of these patients together with transaminases and serologic and virologic markers. The choice of test may depend on accuracy, reliability and local availability, as well as cost. Importantly, clinicians need to keep in mind the importance of interpreting critically the results of the different noninvasive tests with the risk of false-positive results, given the frequence of flare of necroinflammation in patients with chronic hepatitis B. In doubtful cases or in those with comorbidities, a liver biopsy should still be performed, especially before starting antiviral treatment. TE as a point-of-care technique remains the most widely used and validated method. There is also growing evidence for the prognostic value of liver stiffness in the context of cirrhosis, which can be used to stratify patients at risk of developing complications. There are, however, promising challengers for the measurement of liver stiffness, such as ARFI and 2D-SWE, whose place in practice remains to be better defined. Finally, noninvasive tests may also be used for screening liver fibrosis in populations at risk for hepatitis B and C or in the general population [22]. This is now becoming an area of active research.

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