

# Non-invasive diagnostic and prognostic evaluation of liver cirrhosis and portal hypertension

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**Abstract.** Cirrhosis is the final stage of most of chronic liver diseases, and is almost invariably complicated by portal hypertension, which is the most important cause of morbidity and mortality in these patients. This review will focus on the non-invasive methods currently used in clinical practice for diagnosing liver cirrhosis and portal hypertension. The first-line techniques include physical examination, laboratory parameters, transient elastography and Doppler-US. More sophisticated imaging methods which are less commonly employed are CT scan and MRI, and new technologies which are currently under evaluation are MR elastography and acoustic radiation force imaging (ARFI). Even if none of them can replace the invasive measurement of hepatic venous pressure gradient and the endoscopic screening of gastroesophageal varices, they notably facilitate the clinical management of patients with cirrhosis and portal hypertension, and provide valuable prognostic information.

Keywords: Ultrasound, transient elastography, serum markers, cirrhosis, varices

## 1. Introduction

Portal hypertension is a key event in the evolution of chronic liver disorders when severe fibrosis or cirrhosis develops. Once portal pressure exceeds 10 mmHg (clinical significant portal hypertension – CSPH), patients are at risk of experiencing severe complications such as variceal bleeding or ascites. In patients with chronic liver disease, histopathological examination of biopsy samples has traditionally been considered the gold standard for staging the severity of fibrosis and for diagnosing progression to cirrhosis. However, liver biopsy has important limitations (it is invasive and sampling error is very frequent), and in the last decade many studies have been devoted to the search of non-invasive

methods to diagnose fibrosis and cirrhosis. The ideal test for fibrosis and cirrhosis diagnosis should be safe, easy to perform, inexpensive, reproducible (within patients and between and within laboratories) and should provide an accurate assessment of the degree of liver fibrosis from pre-cirrhotic scarring, through very early and early compensated cirrhosis. The test should be predictive of long term outcomes such as portal hypertension, decompensation, need for transplantation, and death.

On the other hand, HVP measurement is the gold standard technique to evaluate the presence and severity of portal hypertension. Also in this case some limitations exist, since HVP measurements are not available in all centers, the technique is invasive and some patients are unwilling to be submitted to it. This is even more relevant when the repetition of the procedure is needed to monitor treatment response. These issues have raised interest to non-invasively determine when CSPH is present, so allowing defining a patient at risk of developing portal hypertension-related complications.

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The aim of this review is to depict the non-invasive tools used to diagnose and monitor treatment of cirrhosis and portal hypertension (Table 1).

## 2. Physical examination

The cheapest and readily available information to detect cirrhosis and/or of portal hypertension is that obtained by physical examination (Fig. 1). Physical stigmata of liver cirrhosis are: a firm left hepatic lobe [1], gynaecomastia, testicular atrophy, parotidomegaly, features of hepato-cellular failure such as jaundice, vascular spiders, leuconychia, palmar erythema or of hepatic encephalopathy, presence of abdominal wall collateral circulation, ascites, leg oedema and splenomegaly (which can be considered the single most important clinical diagnostic sign of portal hypertension). In addition, hypotension and tachycardia may be found reflecting the frequent hyperdynamic circulation found in patients with cirrhosis.

All these findings can be found in decompensated disease with features of portal hypertension, and are obviously highly specific of the syndrome [2]. However, decompensated cirrhosis does not represent the population where non-invasive diagnosis is more needed, and unfortunately, the sensitivity of physical signs in patients with compensated cirrhosis is low.

As for CSPH detection, in a recent study by our group performed in a homogeneous population of patients with well compensated cirrhosis in which HVPG was measured, none of the physical signs was useful to identify patients with HVPG over 10 mmHg. On the other hand spider naevi were independently predictive of esophageal varices [3].

## 3. Laboratory tests

Serum markers of fibrosis have the advantage over liver biopsy of offering a sampling of the all liver, allowing frequent repetition, being far less invasive and having less dependence on professional expertise. Moreover, as we will discuss below, they may reflect the severity of liver fibrosis and predict clinically relevant outcomes. In the following we will focus on the ability of these tests to detect cirrhosis appearance. It is out the scope of the review to analyze in depth the utility of these tests in grading fibrosis.

### 3.1. Indirect markers of fibrosis (Class II, simple laboratory tests)

The diagnostic performance of single or combined hematological and biochemical parameters routinely available, which may “indirectly” reflect (*surrogate markers*) the effect of fibrosis on the liver has been extensively studied. These include indicators of cytolysis (AST, ALT), cholestasis ( $\gamma$ GT, bilirubin), hepatocytes synthetic function (i.e. INR, cholesterol, ApoA1, haptoglobin, N-glycans), and hypersplenisms due to portal hypertension (i.e. platelet count). These parameters may also be surrogates of inflammation and steatosis, which have a significant predictive value for the progression of fibrosis [4,5].

About 20 numerical scores or indices are reported for parameters which are mostly routine laboratory tests and frequently multiparametric. Among them, Fibrotest and AST to Platelet ratio index (APRI) have been proposed for clinical application [6,7]. The FibroTest, which is a combination of  $\alpha$ 2-macroglobulin ( $\alpha$ 2M), ApoA1, Bilirubin,  $\gamma$ GT, Haptoglobin measurements, is the most validated indirect test for liver fibrosis [8–10]. It has been shown to accurately predict the presence of severe fibrosis/cirrhosis with an AUC of 0.92. APRI has also been found to be a reliable predictor of severe fibrosis/cirrhosis in patients with chronic hepatitis C (AUC: 0.80) [11].

However, a recent meta-analysis of 14 studies examining 10 panels of indirect blood markers in chronic hepatitis C [12], including Fibrotest and APRI, demonstrated that in individual patients they cannot reliably differentiate stages of fibrosis. This makes non-invasive markers of fibrosis still insufficient to “monitor” the evolution of chronic liver diseases. In addition, accuracy of serum markers may be reduced by multiple factors, such as co-morbidity of the patients (connective tissue disease among others) and ongoing drug therapies.

As for portal hypertension, Child-Pugh score and its objective component (albumin, bilirubin, INR) correlate with HVPG [13–15] and with the prevalence and grade of esophageal varices in cirrhotic patients. Interestingly this correlation is observed also in patients with compensated cirrhosis [3], suggesting that a close relationship exists between the structural changes which give onset to portal hypertension and hepatocellular dysfunction. In our study, a model obtained by the combination of biochemical parameters, namely albumin, ALT, and INR, had an area under the curve (AUROC) of 0.952 in the prediction of CSPH [3].

Table 1

Non-invasive methods currently available to diagnose cirrhosis and portal hypertension. As shown, none of them holds all the characteristics of an ideal method; however, their combination might help overcome the limitation of the individual tests. Nonetheless a “portal sphygmomanometer” is not yet available

		Characteristics needed for an ideal non-invasive method						
		Safe	Quantitative	Accurate	Objective	Reproducible	Cheap	Validated
Non-invasive methods available for diagnostic/prognostic purposes in patients with portal hypertension	Physical examination	+++	-	-	++	++	+++	++
	Standard Laboratory Tests	+++	+++	+	+++	+++	++	+++
	Direct serum markers of fibrosis	+++	+++	++	+++	+++	-	++
	Transient elastography	+++	+++	++	+++	++	++	++
	Ultrasound and Doppler-Ultrasound	+++	+	+	+	+	+++	+++
	Abdominal CT-scan	+(*)	+	++	++	+++	+	++
	Abdominal MRI	++	+	++	++	+++	+	++

\*Cumulative radiation exposure and subsequent risk should be carefully evaluated [78].

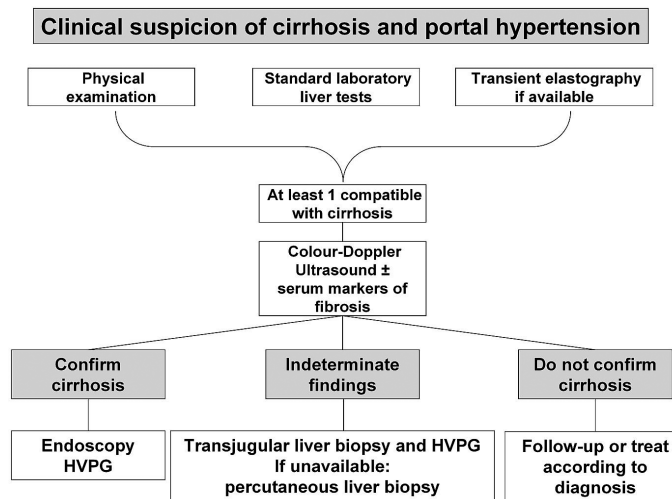


Fig. 1. Proposed algorithm for the non-invasive diagnosis of cirrhosis and portal hypertension. As shown, in indeterminate cases requiring liver biopsy the transjugular modality has to be preferred since this allows the simultaneous measurement of the HVPG. If hepatic vein catheterization is not available a percutaneous liver biopsy should be obtained.

Platelet count is independently correlated with the prevalence and grade of esophageal varices in several studies [16,17], and platelet count to spleen diameter ratio > 909 had a 100% negative predictive value for the presence of esophageal varices in one study [18] suggesting that it could be of help in avoiding unnecessary endoscopies; however in subsequent series its predictive value was lower, and should be further investigated before being accepted in clinical practice.

### 3.2. Direct markers of fibrosis (Class I)

Class I markers, also called *direct* or *true markers*, are biochemical parameters measurable in the periph-

eral blood that express liver matrix constituents or enzymes involved in their regulation, which allow a quantitative assessment of the total amount of hepatic extracellular matrix, and its deposition or removal [19]. Their determination is expensive, and the ability of single markers in the assessment of the severity and progression of liver fibrosis is poor. A systematic review of serum markers of liver fibrosis concluded that panels of markers evaluated in combination are more accurate than single tests [20].

The European Liver Fibrosis (ELF) study evaluated the relationship between different algorithms incorporating serum levels of a panel of direct markers and in-

dividual histology scores in 1000 patients with a wide range of chronic liver disease [21]. Overall, the algorithm discriminant score allowed a good differentiation between patients with and without cirrhosis at biopsy and might be a promising approach in the future.

### 3.3. Panels combining direct and indirect markers

Some scores combine direct and indirect non-invasive markers to diagnose significant fibrosis or cirrhosis. For example, Fibrometer [22] includes platelets, prothrombin time, AST,  $\alpha$ 2M, age, urea and hyaluronan (HA), and Hepascore [23] includes bilirubin,  $\gamma$ GT, TIMP-1,  $\alpha$ 2M, age, and sex. Prospective evaluation [24] has shown improved accuracy of Fibrometer compared to Fibrotest, in particular in diagnosing severe fibrosis and cirrhosis, but further external validation is needed.

### 3.4. Prognostic value of serum markers

Serum markers showed predictive value for liver-related morbidity and mortality.

The results from ELF study in a subgroup of 120 patients followed-up for 5–8 years suggest that serum markers of fibrosis are as good as liver histology in the prediction of liver related death. In this study, the sensitivity of F3-F4 fibrosis at enrolment in the prediction of liver-related mortality at 8 years was 80.7%, while that of serum markers was 84.0%. In a study in patients with alcoholic liver disease [25], Nojgaard reported that YKL-40 and collagen propeptide PIIINP were predictive of short survival and increased relative risk of death. In a cohort of patients with primary biliary cirrhosis treated with UDCA [26], HA was the only independent predictor of poor outcome.

Some studies evaluated the prognostic value of serum markers of fibrosis in patients with cirrhosis. Guechot and colleagues looked at the predictive value of Hyaluronic acid (HA) in a series of patients with HCV-cirrhosis, followed-up for a median of 38 months [27]. In this study, HA had a predictive value equivalent to Child-Pugh score for the prediction of severe complications of cirrhosis or death.

## 4. Transient Elastography (TE)

Transient elastography (measured by *Fibroscan*<sup>®</sup>, Echosens, Paris, France) has been recently developed for the non-invasive assessment of liver stiffness. Mea-

surements are performed with an ultrasound transducer probe built on the axis of a vibrator; a vibration of mild amplitude and low frequency is transmitted, inducing a wave that propagates through the liver tissue, and pulse-echo acquisitions are performed to measure the velocity of propagation of the wave, which is directly related to the tissue stiffness. The volume of liver parenchyma which can be studied by Fibroscan is about 100 times greater than that obtained by biopsy, and has therefore a potentially lower sampling error.

Since fibrosis within the liver increases the organ's stiffness, TE has been used to assess the presence of fibrosis and cirrhosis, and has proved an excellent tool in this setting [28]. Liver stiffness has been shown to correlate with fibrosis severity in HCV [29], and in other chronic liver disease [30]. The best cut-off to detect cirrhosis is not exactly defined since it appears to vary according to the etiology of liver disease; however, in a recent prospective study performed in patients with liver disease values over 12.5 kPa strongly suggested cirrhosis [31].

The value of TE in the non-invasive prediction of portal hypertension has also been evaluated. In a study performed in patients with hepatitis C recurrence after liver transplantation, liver stiffness showed an excellent correlation with fibrosis and with HVPG [32]. In this study, a liver stiffness value  $\geq 8.74$  kPa had a sensitivity and specificity of 90% and 81% for the diagnosis of any grade of portal hypertension (HVPG  $\geq 6$  mm Hg).

In addition, in the setting of cirrhosis, liver stiffness has been shown to correlate with the presence of large esophageal varices; specifically, in the study by Kazemi and colleagues, a liver stiffness value above 19 kPa predicted the presence of large esophageal varices [33]. In another study published as an abstract [34] the authors found a good direct correlation between HVPG and liver stiffness in a population of uncomplicated alcoholic and HCV-related cirrhotic patients; a cut-off value of 17 kPa had a sensitivity of 90% for the diagnosis of HVPG over 12 mmHg. In two additional studies the cut-off values of respectively 23 and 13.6 kPa had a good capacity to predict the presence of CSPH in patients with chronic liver disease [35,36]. It should be underlined that in the study by Vizzutti et al. [35], it was shown that above the threshold value of 13.6 kPa there was not a good correlation between liver stiffness and HVPG, probably since once portal hypertension increases above a the threshold HVPG value of 10–12 mmHg porto-systemic collaterals develop and fibrosis is no longer the only mechanisms inducing portal hypertension, since increase of porto-collateral blood flow importantly contributes [35].

Table 2  
Main ultrasonographic signs of cirrhosis and portal hypertension

		Refs	Sensitivity	Specificity
<b>US signs of cirrhosis</b>				
<b>Liver</b>	Nodular liver surface	(42;45;79;80)	55–91%	82–95%
	Coarse echopattern	(81;82)	20% overall 51% HBV-HDV	90%
	Left lobe/ right lobe ratio > 1.30	(83)	74%	100%
	Caudate lobe/ right lobe ratio $\geq$ 0.65 (hypertrophy of caudate lobe)	(84)	43–84%	100%
	Reduction of the medial segment of left hepatic lobe	(85)	74%	100%
<b>Hepatic veins</b>	Narrowing and loss of normal phasicity of flow by Doppler	(86)	Not reported	Not reported
	Altered straightness	(87)	97%	91% 86%
	Nonuniformity of hepatic vein wall echogenicity		88%	
<b>Hepatic artery</b>	Increased diameter	(88)	Not reported	Not reported
<b>US signs of portal hypertension</b>				
<b>Portal venous system</b>	Dilatation of portal vein ( $\geq$ 13 mm)	(16;47)	< 50%	90–100%
	Reduction of portal vein blood flow velocity (Max vel < 16 cm/s; mean vel < 13 cm/s)	(89;90)	80–88%	80–96%
	Inversion of portal vein blood flow	(91)d}2}	Not reported; sign prevalence: 8.3% of unselected pts	100%
	Increased portal vein congestion index ( $\geq$ 0.08)	(49;90)	67–95%	100%
	Dilatation of splenic vein (SV) and superior mesenteric vein (SMV) ( $\geq$ 11 mm)	(92;93)	72%	100%
	Reduction of respiratory variation of diameter in SV or SMV (< 40%)	(47)	79.7%	100%
<b>Spleen</b>	Splenomegaly (diameter > 12 cm and/or area $\geq$ 45 cm <sup>2</sup> )	(3)	93%	36%
<b>Splenic artery</b>	Increased resistive index of the intraparenchymal branches ( $\geq$ 0.60)	(94)	84.6%	70.4%
<b>Hepatic artery</b>	Increased resistive index of artery at the porta hepatis (> 0.78)	(95)	50%	100%
	Increased resistive index of the intrahepatic branches			
<b>Renal artery</b>	Increased resistive index of the right interlobar renal artery ( $\geq$ 0.65)	(94)	79.5%	59.3%
<b>SMA</b>	Decreased pulsatility index ( $\leq$ 2.70)	(94)	85.7%	65.2%
<b>Presence of porto-systemic collateral circulation</b>		(58)	83%	100%

In a study recently performed in our unit, TE was tested for the diagnosis of CSPH in the setting of patients with potentially resectable hepatocellular carcinoma. The results suggested that TE is not an ideal method to rule-out or confirm CSPH in this population, and should not be used as a non-invasive surrogate for indicating or contraindicating surgery [37].

Given these observations, it can be suggested that even if high values of liver stiffness at TE are strongly predictive of cirrhosis and of the presence of CSPH, the technique is not accurate enough to assess the severity of portal hypertension.

## 5. Ultrasound and colour-Doppler-ultrasound

Ultrasonography (US) is a non-invasive and inexpensive technique frequently used as first line examina-

tion in the diagnosis and follow-up of hepatic diseases (Fig. 1).

Doppler-US is very accurate in diagnosing thrombosis in large vessels. Therefore, it is extremely useful to identify causes of portal hypertension different than cirrhosis, such as portal vein and hepatic veins thrombosis, and should be performed routinely for this purpose at the beginning of the diagnostic work-up of cirrhosis and portal hypertension [38–40].

Findings of cirrhosis on conventional US include changes in liver morphology and signs of portal hypertension (Table 2). US findings are usually highly specific, and can be considered sufficient to confirm the diagnosis [41], so a positive result “rules-in” cirrhosis. On the other hand, the sensitivity of individual US findings is low, indicating that a negative result cannot fully rule-out cirrhosis.

The most accurate single sign for the diagnosis of cirrhosis, which can be found even in early phases, is nodularity of liver surface [42]; this should be specifically investigated. The use of high frequency transducers increases the diagnostic performance of conventional abdominal US probes, and should be preferred. Few false positive have been described [43].

The combination of nodular liver surface and portal vein mean velocity below 12 cm/s holds 80% accuracy for discriminating between patients with chronic hepatitis with severe fibrosis and those with cirrhosis [44].

In patients with *clinical suspicion of cirrhosis and confounding conditions* the detection of nodular liver surface is an excellent non-invasive method to rule-in cirrhosis, while the combination of US and transient elastography allows the best diagnostic performance [45].

As for the assessment of portal hypertension in cirrhosis, all US signs of portal hypertension are very specific, while their sensitivity is low, especially in compensated cirrhosis; therefore, while the presence of a sign or a combination of signs definitely rules-in portal hypertension, its absence cannot exclude the diagnosis.

Spleen dimension is the US sign most commonly associated to the presence of portal hypertension; contrarily to other signs its sensitivity is high, while its specificity ranges 50–80% according to different series. It is an independent predictor of esophageal varices, and is associated to CSPH in compensated cirrhotic patients [3].

The presence of porto-collateral circulation such as paraumbilical vein, spontaneous spleno-renal circulation, dilated left and short gastric veins, and the inversion of flow within the portal system are 100% specific US signs of CSPH.

Other US signs of CSPH include dilatation of portal vein (diameter > 13 mm) [46]; lack or reduced respiratory variations of splenic and superior mesenteric vein diameter [47]; reduced portal vein velocity (maximal and mean velocimetry of portal vein flow, respectively < 16 cm/s and < 10–12 cm/s) [48]; increased congestion index of portal vein [49]; altered hepatic venous Doppler pattern [50]; increased intraparenchymal hepatic and splenic artery impedance [51–53]; increased intraparenchymal renal artery impedance [54] and reduced mesenteric artery impedance [55].

HVPG significantly correlates with some US parameters such as portal vein velocity and volume of blood flow [55], hepatic artery resistance index, splenic and renal artery resistance and pulsatility index. However the degree of correlation is only slight to moderate and

these parameters can not be used as reliable surrogates of HVPG.

Some US-Doppler parameters hold prognostic value in cirrhosis.

As for the presence of *varices and variceal formation, growth and bleeding*, models for the prediction of varices of any size or of large varices include portal vein diameter or spleen size in combination with blood tests (platelet count and prothrombin time). Prospective studies in compensated cirrhosis [56,57] initially suggested a good discriminating ability. Nonetheless, validation studies in subsequent series failed to confirm an adequate accuracy for varices prediction. Porto-systemic collaterals such as left gastric vein > 3 mm and short gastric veins (collaterals at upper spleen half) strongly suggest the presence of esophageal varices [58], and their development/increase in number have been associated with a greater proportion of variceal formation and growth [59]. Similarly, progressive spleen enlargement may predict variceal formation and growth [60].

Congestion index of the portal vein (ratio between the cross-sectional area and blood flow velocity) independently predicted first variceal bleeding in a prospective study in patients with varices [61].

As for the prediction of *first clinical decompensation of any kind*, spleen enlargement (> 1 cm) on follow-up might be associated with a higher probability of developing the first clinical decompensation of cirrhosis [60].

A portal vein averaged maximum velocity <15 cm/s was the only variable independently associated with a high risk of non-malignant *portal vein thrombosis* in a recent prospective study [62].

The presence of porto-systemic collateral circulation predicted *hepatocellular carcinoma* appearance in a recent study performed in 129 unselected cirrhotic patients [63], probably since porto-systemic collaterals are signs of clinically significant portal hypertension, which is independently related with HCC occurrence [64].

US is highly sensitive in diagnosing *ascites*, which is the most common clinical decompensation of cirrhosis and holds a severe prognostic significance.

The increase of intrarenal arteriolar RI in patients with cirrhosis is related to arterial vasoconstriction; it is observed in about 40% of patients with ascites, is accurate for detecting *hepato-renal syndrome* [65].

A small liver size, spleen size over 14.5 cm, mean portal vein velocity below 10 cm/s and loss of pulsatility of hepatic veins have been associated to higher

mortality on follow-up in patients with compensated cirrhosis [66].

**Monitoring of treatment of portal hypertension.** There is currently no room for performing US-Doppler monitoring of HVPG response to medical therapy of portal hypertension, since changes of Doppler parameters do not accurately reflect changes in HVPG [66]. However, in a recent study, CDUS pattern at baseline was shown to be different, showing a greater baseline splanchnic vasodilatation (as indicated by a low pulsatility and resistance index in splenic, mesenteric and hepatic artery) in HVPG non-responders than in responders after chronic nadolol treatment [67], and overall the high negative predictive value of Doppler parameters may help to detect non-responders.

On the other hand, US-Doppler is useful in the non-invasive follow-up of transjugular intrahepatic portosystemic shunt (TIPS), and allows saving unnecessary invasive hemodynamics procedures [68].

## 6. Second line imaging techniques and new methods needing validation

**Computed tomographic scan (CT) and magnetic resonance (MRI)** allow an accurate visualization of the liver parenchyma and the portal venous system.

Three studies demonstrated that single detector or multidetector CT scanning are reliable in detecting large esophageal varices (specificity 90–100% and sensitivity 84–100%), with moderate inter-observer variability; however the sensitivity for small varices detection is lower. A cost-effectiveness analysis showed that straight CT screening of varices was more cost-effective than endoscopy screening and than CT followed by endoscopy for patients with small varices on CT [69].

Dynamic contrast-enhanced single-section CT scans and MRI (compartmental analysis of intensity versus time curves for magnetic resonance images of the liver after injection of a gadolinium chelate), and phase contrast MR angiography allow a quantitative measurement of portal [70] and azygos [71] blood flow. Azygos blood flow, as measured by MRI, correlates with the presence of esophageal varices at endoscopy, and with the risk of bleeding from varices. Portal fraction of liver perfusion and mean transit time at MRI have been recently showed to have a good correlation with HVPG [72]. Whether any of these sophisticated and expensive techniques add to clinical, biochemical, US

or transient elastography parameters should be evaluated in future studies.

**MR elastography (MRE)** is a novel method proposed to evaluate liver stiffness. The measurement is obtained by synchronizing motion-sensitive imaging sequences with the application of acoustic waves in tissue media [73]. It has been tested in human subjects, and the preliminary results support its practicability in predicting the stage of fibrosis in patients with chronic liver disease [74]. MRE is repeatable and changes correlate well with changes in tissue fibrosis [75]. MRE has been successfully applied to measure spleen stiffness, which was highly correlated with hepatic stiffness and might have a closer correlation with portal pressure [76].

Although MR elastography has some technical advantage over Fibroscan (no need an acoustical window, a freely-oriented field of view, lack of sensitivity to body habitus) it is more expensive and time consuming and it will only be used as an additional tool in patients that already need to be submitted to MRI for other reasons.

**Acoustic radiation force impulse imaging (ARFI)** is a novel technology that provides information about the local elasticity of tissues in real-time. Short-duration ( $\sim 262 \mu\text{s}$ ) acoustic pulses are produced and induce the propagation of shear waves which generate minimum displacements within the target tissue. The shear wave velocity (metres per second) is measured in a small portion of the parenchyma (10 mm long  $\times$  6 mm wide). It has the advantage of being integrated in a conventional ultrasound system, so allowing controlling the sampling position within the liver. Recent data suggest that ARFI is as accurate as transient elastography by Fibroscan for fibrosis and cirrhosis detection in patients with chronic liver diseases [77].

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