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**Non-invasive diagnosis of liver fibrosis in chronic hepatitis C**

Schiavon LL *et al*. Non-invasive diagnosis of liver fibrosis

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**Abstract**

Assessment of liver fibrosis in chronic hepatitis C virus (HCV) infection is considered a relevant part of patient care and key for decision making. Although liver biopsy has been considered the gold standard for staging liver fibrosis, it is an invasive technique and subjected to sampling errors and significant intra- and inter-observer variability. Over the last decade, several noninvasive markers were proposed for liver fibrosis diagnosis in chronic HCV infection, with variable performance. Besides the clear advantage of being noninvasive, the more objective interpretation of tests results may overcome the mentioned intra- and inter-observer variability of liver biopsy. In addition, these tests can theoretically offer a more accurate view of fibrogenic events occurring in the entire liver with the advantage of providing frequent fibrosis evaluation without additional risk. However, in general, these tests show low accuracy to discriminate between intermediate stages of fibrosis and may be influenced by several hepatic and extra-hepatic conditions. These methods are either serum markers (usually combined in a mathematical model) or imaging modalities that can be used separately or combined in algorithms to improve the accuracy. In this review we will discuss the different noninvasive methods that are currently available for the evaluation of liver fibrosis in chronic hepatitis C, its advantages, limitations and application in clinical practice.

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**Key words:** Liver fibrosis; Liver cirrhosis; Hepatitis C; Diagnosis; Elasticity Imaging Techniques

**Core tip:** There is an increase interest in non-invasive markers of fibrosis, especially in chronic hepatitis C virus infection. Although several methodologies have been proposed over the last few years, the limited availability and concerns about the true accuracy of these techniques has restricted its clinical application. In this review we will discuss the different noninvasive methods that are currently available for the evaluation of liver fibrosis in chronic hepatitis C, its advantages, limitations and application in clinical practice.

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**INTRODUCTION**

Assessment of liver fibrosis in chronic hepatitis C virus (HCV) infection is considered a relevant part of patient care and key for decision making. Liver fibrosis stage is probably the most robust prognostic factor in several liver diseases; including hepatitis C. Higher stages of fibrosis have shown to be associated with progression to decompensated cirrhosis, need for liver transplantation and liver-related death in HCV infection[[1](#_ENREF_1),[2](#_ENREF_2)]. In addition, the severity of fibrosis may be used as selection criteria for antiviral therapy and also can indicate the need for further evaluations, such as surveillance for hepatocellular carcinoma (HCC) and esophageal varices screening[[3](#_ENREF_3),[4](#_ENREF_4)]. For many years, liver biopsy has been considered the gold standard for staging liver fibrosis. Histological evaluation also provides information on necroinflammatory activity and other features such as steatosis and iron overload. Several scoring systems have been developed, the most common being the METAVIR, the Scheuer's, the Batts-Ludwig, the International Association for the Study of the Liver (IASL) and the Ishak Scoring systems[[5-9](#_ENREF_5)]. However, besides its advantages, liver biopsy is an invasive technique with associated morbidity. Minor complications are relatively common and about one fourth of the patients have pain in the right upper quadrant or right shoulder after liver biopsy[[10](#_ENREF_10)]. Severe complications are infrequent, with significant bleeding rates varying from 0.05% to 5.3% and mortality of less than 0.15% in the largest series[[10](#_ENREF_10)]. The performance of liver biopsy for fibrosis staging has also been questioned and concerns about the possibility of sampling errors and significant intra- and inter-observer variability were raised over the last years. Since biopsy represents 1/50000 of the liver, the heterogeneity of liver fibrosis in HCV infection and the inadequacy of sample size can cause considerable bias in the assessment of hepatic histology[[11-13](#_ENREF_11)]. A study that included 124 patients with chronic HCV infection who underwent simultaneous laparoscopy-guided biopsies of the right and left hepatic lobes showed that 33.1% of the subjects had a difference of at least one stage between the two lobes[[11](#_ENREF_11)]. Likewise, a study on virtual liver biopsy has indicated that a non-fragmented specimen of at least 25 mm in length would be necessary to correctly evaluate fibrosis with a semiquantitative score, a goal not always achievable in daily practice[[14](#_ENREF_14)].

Over the last few years, several noninvasive markers were proposed for liver fibrosis diagnosis in chronic HCV infection. Table 1 summarizes the major advantages and limitations of those methods in relation to liver biopsy. Besides the clear advantage of being noninvasive, the more objective interpretation of tests results may overcome the mentioned intra- and inter-observer variability of liver biopsy. In addition, these tests can theoretically offer a more accurate view of fibrogenic events occurring in the entire liver with the advantage of providing frequent fibrosis evaluation without additional risk. However, in general, these tests show low accuracy to discriminate between intermediate stages of fibrosis and may be influenced by several hepatic and extra-hepatic conditions. In this review we will discuss the different noninvasive methods that are currently available for the evaluation of liver fibrosis in chronic hepatitis C, its advantages, limitations and application in clinical practice.

**NONINVASIVE MARKERS OF LIVER FIBROSIS**

***General considerations of noninvasive fibrosis markers***

Because fibrosis denotes morphological changes, liver biopsy became the natural gold standard for staging the disease. However, the mentioned limitations of biopsy make it very difficult to interpret the “real” performance of surrogate markers of fibrosis in the studies. In the vast majority of studies, the diagnostic performance of noninvasive markers of liver fibrosis was evaluated by calculating the area under the receiver operating characteristic (ROC) curve. The ROC curve is the plot that depicts the trade-off between the sensitivity and 1-specificity across a series of cut-off points when the diagnostic test is continuous variable[[15](#_ENREF_15)]. Mehta *et al*[[16](#_ENREF_16)] demonstrated that, when a range of accuracies of biopsy and a range of prevalence of fibrosis are taken into account, even in the ‘best’ scenario an AUROC > 0.90 cannot be achieved even for a perfect marker. The perceived limitation in diagnostic accuracy of noninvasive markers of liver fibrosis is probably the major reason that explains why these tests have not been widely adopted in clinical practice.

Noninvasive markers of liver fibrosis can be divided into two groups: serum biomarkers and imaging techniques. These methodologies will be presented separately and a combined approach will also be discussed in this review.

***Serum biomarkers***

**Indirect (or class II) markers of liver fibrosis:** This group comprises, in general, routine tests usually combined with other laboratory or clinical parameters in a specific model. The most common studied indirect markers in HCV infection include aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, gamma-glutamyltransferase (GGT), bilirubin, haptoglobin, apolipoprotein A1, alpha-2-macroglobulin. Models that combined indirect markers are usually devised from retrospective studies and, as a rule for noninvasive fibrosis markers, are limited in discriminating between intermediate stages of fibrosis. Table 2 depicts the most common models including indirect markers proposed for fibrosis estimation in hepatitis C.

The AST/ALT ratio has been used for several years as a noninvasive method for assessing the severity of chronic liver diseases, including chronic HCV infection[[17-20](#_ENREF_17)]. Although some studies have found promising results, its performance as a noninvasive marker of fibrosis is generally low, especially in the diagnosis of less advanced stages of fibrosis[[21](#_ENREF_21),[22](#_ENREF_22)]. In a recent study, we have shown a low diagnostic accuracy of AST/ALT ratio in detecting significant fibrosis (AUROC of 0.661) as compared to other simple models, such as APRI (AUROC 0.793) and FIB-4 (AUROC 0.811)[[23](#_ENREF_23)].

The AST-to-Platelet Ratio Index (APRI) is calculated as (AST/upper limit of normal range)/platelet count (109/L) × 100. This index was originally proposed by Wai *et al*[[24](#_ENREF_24)] in 2003and became one of the most studied noninvasive fibrosis markers in chronic HCV infection. The APRI is based on the rationale that worsening of fibrosis and increasing of portal pressure is associated with reduced production of thrombopoietin by the hepatocytes, increased platelet sequestration within the spleen and reduced clearance of AST[[25-27](#_ENREF_25)]. A meta-analysis exploring the performance of this model in HCV infection was published in 2011 and included 40 studies and a total of 8,739 subjects[[28](#_ENREF_28)]. This study showed only a moderate degree of accuracy for APRI in the detection of HCV-related fibrosis. The summary AUROC of the APRI for the diagnosis of significant fibrosis (≥ F2 according to METAVIR), severe fibrosis (≥ F3), and cirrhosis was 0.77, 0.80, and 0.83, respectively[[28](#_ENREF_28)]. In this meta-analysis, the best cutoff for diagnosing significant fibrosis was 0.7, with summary sensitivities and specificities of 77% and 72%, respectively. For the detection of cirrhosis, the optimal cutoff was 1.0, with summary sensitivities and specificities of 76% and 72%, respectively. A threshold of 2.0 exhibited 91% specificity for diagnosing cirrhosis, however with low sensitivity (46%)[[28](#_ENREF_28)]. A major advantage of APRI is that it was validated in special populations, such as HIV/HCV co-infection[[28-37](#_ENREF_28)], in whom the overall performance seems to be lower than in HCV mono-infected individuals [[28](#_ENREF_28)] and adjusted cutoffs may increase sensitivity and specificity, as we previously demonstrated[[30](#_ENREF_30)]. APRI also proved to be a valuable tool in hemodialysis patients with chronic HCV infection. In a study that included 203 subjects, we demonstrated a good performance of this model, especially in excluding significant fibrosis, with a negative predictive value (NPV) of 93% for a prevalence of significant fibrosis of 24%[[38](#_ENREF_38)]. These results were further validated in a cohort of 279 hemodialysis patients[[39](#_ENREF_39)] and Canbakan *et al*[[40](#_ENREF_40)] showed that APRI was superior to FibroTest® in this population.

The *FIB-4* is also a noninvasive method for the evaluation of liver fibrosis, based on simple variables such as age, AST, ALT and platelet count. It was initially proposed by researchers of the APRICOT study (AIDS Pegasys Ribavirin International Coinfection Trial) to evaluate the presence of liver fibrosis in HIV/HCV coinfected patients[[41](#_ENREF_41)]. It was subsequently validated in a large cohort of HCV mono-infected patients in whom values < 1.45 had a NPV of 94.7% to exclude severe fibrosis (F3-F4) with a sensitivity of 74.3%[[42](#_ENREF_42)]. A FIB-4 value higher than 3.25 had a positive predictive value (PPV) of 82.1% with a specificity of 98.2%[[42](#_ENREF_42)]. The authors also showed a similar performance between FIB-4 and FibroTest®[[42](#_ENREF_42)]. Several other studies reported variable degree of accuracy of FIB-4 index in HCV-infected subjects[[43-47](#_ENREF_43)]. We have performed a comparison between FIB-4 and APRI and have found similar AUROCs for both models (0.811 *vs* 0.793)[[23](#_ENREF_23)]. However, the proportion of biopsies that could have been correctly avoided was substantially higher with FIB-4 than with APRI (63% *vs* 47%) suggesting that FIB-4 is probably a more useful tool for incorporation into daily practice[[23](#_ENREF_23)].

The Forns index is based on age and three additional simple tests: platelet count, cholesterol levels, and GGT[[48](#_ENREF_48)]. In the original study, the AUROC was 0.86 for the estimation group and 0.81 for the validation group in diagnosing significant fibrosis [[48](#_ENREF_48)]. However, in a recent systematic review, the median AUROC from 22 studies was 0.76 for significant fibrosis and 0.87 for cirrhosis[[49](#_ENREF_49)]. When evaluating those studies that performed direct comparisons, Forns index and APRI showed a very similar performance for both significant fibrosis and cirrhosis[[49](#_ENREF_49)].

The Fibroindex was originally proposed for diagnosis of HCV-related fibrosis and includes the following variables: platelet count, AST, and gamma globulin[[50](#_ENREF_50)]. In the original study, this model exhibited a higher AUROC (0.83) for diagnosing significant fibrosis as compared to APRI and to Forns index[[50](#_ENREF_50)]. Fibroindex was also correlated significantly with variation in fibrosis stage when a subset of 30 patients who had undergone a liver biopsy twice was evaluated[[50](#_ENREF_50)]. Nevertheless, in the mentioned systematic review, the median AUROC for significant fibrosis detection was 0.76 and for cirrhosis was 0.86[[49](#_ENREF_49)]. Direct comparisons showed no superiority of Fibroindex over APRI for both significant fibrosis and cirrhosis detection[[49](#_ENREF_49)].

**Direct (or class I) markers of liver fibrosis:** Multiple etiologies of liver disease, including chronic HCV infection, can lead to liver fibrosis through integrated signaling networks that regulate the deposition of extracellular matrix[[51](#_ENREF_51)]. This sequence of events drives the activation of hepatic stellate cells into a myofibroblast-like phenotype that is contractile, proliferative and fibrogenic[[51](#_ENREF_51)]. Collagen and other extracellular matrix (ECM) components are deposited as the liver generates a wound-healing response to encapsulate injury[[51](#_ENREF_51)]. The direct (or class I) markers of liver fibrosis are usually fragments of the liver matrix components produced by hepatic stellate cells during the process of ECM remodeling, usually reflecting the deposition or removal of ECM[[52](#_ENREF_52)]. The most studied direct markers are the hyaluronic acid (HA), YKL-40, laminin, fibronectin, alpha-2-macroglobulin, procollagen type I carboxy terminal peptide (PICP), procollagen type III amino-terminal peptide (PIIINP), N-terminal propeptide of type II collagen, Metalloproteinases (MMPs), tissue inhibitors of matrix metalloproteinases (TIMPs) and transforming growth factor-b1 (TGF-b1).

As stated for indirect tests, direct biomarkers are usually combined in composite scores to increase the diagnostic performance (Table 3). It is important to point that these models are not liver-specific and also present limitations, such as the low accuracy for intermediate stages of fibrosis and limited availability (patented formulas or tests not routinely performed). Below, we discuss the most studied models combining direct and indirect biomarkers for the diagnosis of liver fibrosis in chronic hepatitis C.

The FibroTest*®* score was originally proposed in 2001 and is one of the most validated models for predicting liver fibrosis in HCV-infected patients[[53](#_ENREF_53)]. It is computed by accessing a proprietary website and entering the patient’s age, sex, and serum haptoglobin, α2-macroglobulin, apolipoprotein A1, GGT, and total bilirubin. A meta-analysis published in 2007 showed a pooled adjusted AUROC of 0.83 for FibroTest® in HCV patients[[54](#_ENREF_54)]. However, the systematic review published by Chou and Wasson revealed that, when considered only studies that performed direct comparisons, the APRI was associated with only a slightly lower AUROC than FibroTest® for significant fibrosis (median difference between AUROCs, - 0.03; range, - 0.10-0.07), but there was no difference for cirrhosis (median difference between AUROCs, 0.0; range, - 0.04-0.06)[[49](#_ENREF_49)]. The FibroTest® was also not superior to FIB-4 and other models such as Fibrometer® and Hepascore® for the diagnosis HCV-related fibrosis, as shown in the same review[[49](#_ENREF_49)]. Beyond the absence of a clear superiority of FibroTest® over other free and readily available models, given the variability of component of assays and analyzers, FibroTest® assays can only be performed in validated laboratories. In addition, the existence of hemolysis or Gilbert syndrome can lead to false-positive results and must be taken into account[[55](#_ENREF_55)].

The Enhanced liver fibrosis (ELF) score provides a single value by an algorithm combining age as well as quantitative serum measurements of TIMP-1, PIIINP and HA[[56](#_ENREF_56)]. Age was removed from the simplified ELF score[[56](#_ENREF_56)]. It was originally proposed in a cohort study including 1,021 subjects with various chronic liver diseases (496 with chronic hepatitis C). In contrast to the good performance observed for alcoholic liver disease (AUROC 0.944) and non-alcoholic fatty liver disease (AUROC 0.870), a relatively low accuracy was observed in chronic HCV infection (AUROC 0.773)[[56](#_ENREF_56)]. ELF was further validated in HCV patients[[57-59](#_ENREF_57)] but it was not superior to APRI for the detection of both significant fibrosis and cirrhosis in studies that performed direct comparison between the two models[[49](#_ENREF_49),[58](#_ENREF_58)]. A recent study has shown that ELF score is significantly influenced by gender (higher values in men) and age (higher scores in older persons), and this fact should be taken into account when interpreting its results[[60](#_ENREF_60)].

The Fibrometer® is a patented and commercially available proprietary panel of tests that combines platelet count, prothrombin index, AST, 2-macroglobulin, HA, blood urea nitrogen and age[[61](#_ENREF_61)]. In addition to the typical results of fibrosis stage corresponding to the METAVIR system, Fibrometer® may also indicate the amount of liver fibrosis as a percentage of fibrous tissue within the liver (area of fibrosis)[[62](#_ENREF_62)]. In the systematic review published by Chou and Wasson, Fibrometer® exhibited a pooled AUROC of 0.82 for significant fibrosis and 0.91 for cirrhosis[[49](#_ENREF_49)]. Direct comparisons showed better performance for Fibrometer® over APRI and FibroTest® in detecting both significant fibrosis and cirrhosis[[43](#_ENREF_43),[49](#_ENREF_49)].

FIBROspect II® is also a commercially available panel that includes TIMP-1, 2-macroglobulin and HA levels[[63](#_ENREF_63)]. It was generated from a cohort of 696 HCV-infected patients and exhibited an AUROC of 0.831 for diagnosing significant fibrosis in the original study[[63](#_ENREF_63)]. The FIBROspect II® was subsequently validated[[64](#_ENREF_64),[65](#_ENREF_65)] and the pooled AUROC in the mentioned systematic review was 0.86 for significant fibrosis[[49](#_ENREF_49)].

The Hepascore*®* is a patented model that combines age, sex and four biomarkers (2-macroglobulin, HA, GGT and total bilirubin)[[66](#_ENREF_66)]. It was devised in a cohort of chronic HCV patients [[66](#_ENREF_66)] and further validated in several studies[[67-72](#_ENREF_67)]. An interesting advantage of Hepascore® is that it can be totally automated using a single analyzer and only one serum sample[[69](#_ENREF_69)]. However, data from comparative studies showed that this test was not superior to APRI and FibroTest® in diagnosing significant fibrosis and only slightly better for the detection of cirrhosis[[49](#_ENREF_49)].

***Imaging techniques***

Transient hepatic elastography (TE) by FibroScan®: TE, as assessed by FibroScan® (Echosens, Paris, France), is a simple non-invasive method to measure liver stiffness, based on the unidimensional transient elastography, a technique that uses elastic waves and low frequency ultrasounds (50 Hz). The equipment is composed of a probe, an in-built ultrasound system and an electronic unit for data processing. Through a transductor, low amplitude vibrations produced by the probe are transmitted to liver tissue. Simultaneously, the ultrasound system generates pulses that track and determine the rapidity of propagation of elastic waves within the parenchyma. The velocity of propagation is directly related to elasticity: the harder the tissue, the faster the propagation of elastic waves. Hence, tests with high results generally indicate the presence of significant fibrosis in liver parenchyma. The final result is the median of all valid acquisitions, which is considered to be representative of the hepatic elasticity, expressed in kilopascals (kPa), within a range of 2.5-75.0 kPa. The test is simple, fast (usually performed in less than 5 min), and can be easily carried out in both inpatient and outpatient settings. Neither special preparation nor lab tests are necessary.

TE has been evaluated in several non-viral chronic liver diseases[[73-75](#_ENREF_73)] in both adults and children[[76](#_ENREF_76)], it was, initially projected and then validated in patients with chronic hepatitis C[[77-81](#_ENREF_77)].

Several studies have shown significant correlation between TE and fibrosis stage, as assessed by the METAVIR score system[[78-80](#_ENREF_78)], as well as by computer-assisted morphometric image analysis[[81](#_ENREF_81)]. TE by FibroScan® shows a similar performance for predicting significant fibrosis and higher accuracy to identify liver cirrhosis, as compared to other noninvasive tests. This has been shown by Castera *et al*[[78](#_ENREF_78)] who evaluated and compared the performance of FibroScan®, FibroTest® (FT, Biopredictive, Paris, France) and the AST-to-platelet ratio index (APRI) in 183 HCV patients. The areas under the curve (AUROCs) of FibroScan®, FibroTest® and APRI for the diagnosis of significant fibrosis (F ≥ 2) were 0.83, 0.85 and 0.78, respectively. To predict the presence of cirrhosis (F4), the AUROCs for each method were 0.95, 0.87 and 0.83, respectively. The diagnostic superiority of TE was further confirmed by a study with 298 HCV patients comparing the performance of FibroScan®, FT, APRI, Lok index, platelet count (PC), prothrombin index (PI) and AST/ALT ratio (AAR) for the early detection of cirrhosis. In this study, TE was the most accurate method for predicting cirrhosis (AUROCs: TE 0.96 vs. FT 0.82, Lok and APRI 0.80, PC 0.79, PI 0.73, AAR 0.61; *P* < 0.0001)[[82](#_ENREF_82)].

The most validated TE cutoff points are 7.1 kPa to identify patients with significant fibrosis and 12.5 kPa to recognize those with cirrhosis[[78](#_ENREF_78),[82](#_ENREF_82),[83](#_ENREF_83)]. TE values ≥ 14.6 kPa exhibit a positive predictive value of 90% to predict liver cirrhosis, with a positive likelihood ratio of 35.5[[82](#_ENREF_82)].

TE was also evaluated in special populations of HCV patients, such as HCV-HIV co-infection[[84](#_ENREF_84),[85](#_ENREF_85)] and post-transplant hepatitis C[[86-88](#_ENREF_86)], with similar accuracy to that observed in the general population of HCV patients.

Besides estimating fibrosis stage, TE has been used to identify cirrhotic patients under risk of development of portal hypertension and liver-related complications[[82](#_ENREF_82),[85](#_ENREF_85),[89](#_ENREF_89),[90](#_ENREF_90)]. However, several cutoff values have been used and many of these studies have found weak correlation coefficients, particularly among patients with high HVPG (> 10 mmHg). Altogether, these data indicate that the relationship between TE and HVPG is insufficiently linear to be clinically useful.

In contrast to HCV, few studies with appropriate methodology evaluated the accuracy of TE in patients with chronic hepatitis B virus (HBV) infection[[83](#_ENREF_83),[91-94](#_ENREF_91)]. An algorithm has been proposed to adjust the interpretation of TE values according to ALT levels. Values < 6.0 kPa and < 7.5 kPa accurately predict the absence of advanced fibrosis or cirrhosis in patients with serum ALT levels inferior to the upper limit of normality (ULN) and in subjects with ALT activity between 1 and 5 times the ULN, respectively[[93](#_ENREF_93)]. Likewise, TE values > 9.0 kPa and > 12.0 kPa predict advanced fibrosis or cirrhosis in subjects with normal ALT and in those with ALT 1-5 times the ULN. A recent study suggested that TE exhibits similar diagnostic performances in HBV infection as compared to HCV patients[[83](#_ENREF_83)].

**Acoustic radiation force impulse imaging (ARFI):** Although the ARFI technique has been developed by two companies, Siemens and Philips, most clinical studies with the method have used a Siemens S2000 conventional ultrasound equipment that uses short-duration acoustic pulses (push-pulses) emitted with a frequency around 2.6 MHz. The compression induced by the pulse in the evaluated tissue generates shear waves which propagate perpendicularly into the tissue. These shear waves are tracked by the pulse-echo ultrasound acquisitions and their velocity of propagation is measured inside a small region-of-interest (ROI) of 5 mm × 10 mm located up to 8 cm of depth. The stiffer the tissue, the faster the shear wave velocity, which means that the speed of the shear wave increases with the severity of the liver fibrosis[[95-97](#_ENREF_95)]. The results are expressed in meters per second (m/s), ranging from 0.5 to 4.4 m/s (± 20% accuracy over the range). Higher values are generally found in the left hepatic lobe, but higher accuracy is obtained with ARFI measurements in the right hepatic lobe [[98-100](#_ENREF_98)]. Even though not formally recommended by the manufacturer, good quality technical parameters (especially an interquartile ratio < 30%) yielded better correlations between elastometry measurements and liver fibrosis, as well as higher accuracies for predicting fibrosis stages than those with inadequate parameters[[101](#_ENREF_101),[102](#_ENREF_102)]. Evaluating 106 subjects with HCV infection, Bota *et al*[[101](#_ENREF_101)] observed discordance of at least two stages of fibrosis between ARFI results and histological assessment in 31.7% of the patients; in multivariate analysis, female gender and IQR ≥ 30% were associated with discordances. Finally, as observed with TE, high aminotransferases levels (> 5 times the upper limit of normal) are associated with higher liver stiffness as assessed by ARFI, which should be taken into account in order to interpret results adequately[[103](#_ENREF_103)]. It is intuitive to consider that the impact of higher aminotransferase levels reflects the influence of higher levels of necroinflammatory activity, which has indeed been demonstrated by Chen *et al*[[104](#_ENREF_104)].

ARFI elastography is an easy, fast (usually performed within five minutes), and reproducible noninvasive method for liver fibrosis assessment, especially in cirrhotic patients. However, ARFI reproducibility was lower in women, in patients with high BMI (≥ 25 kg/m2), in the presence of ascites and in the absence of liver cirrhosis[[105](#_ENREF_105)]. Being included into a conventional ultrasound machine and the possibility of being performed in patients with ascites are relevant advantages of ARFI elastography over TE by FibroScan®. A standard procedure should include measuring in a supine position with the convex transducer (4C1) without specific breathing maneuvers (the patient is simply asked to stop breathing for a moment). Elastometry values increase after food intake, and measurements should be performed in the fasting state (or at least 3 hours after the last meal)[[106](#_ENREF_106),[107](#_ENREF_107)].

Although in a limited number of studies, the method has been evaluated in a variety of liver conditions, such as metabolic liver diseases[[108-112](#_ENREF_108)], autoimmune liver diseases[[113](#_ENREF_113)], hepatic tumors[[114](#_ENREF_114),[115](#_ENREF_115)], and chronic hepatitis B[[116](#_ENREF_116),[117](#_ENREF_117)]. However, like TE, ARFI has been most studied in patients with chronic hepatitis C virus (HCV) infection[[118-128](#_ENREF_118)]. In a pooled meta-analysis, Friedrich-Rust et al. evaluated original data of 518 patients from eight studies (73% with HCV)[[129](#_ENREF_129)]. The optimal cut-offs for diagnosing significant fibrosis (F ≥ 2), advanced fibrosis (F ≥ 3) and cirrhosis were 1.34, 1.55, and 1.80 m/s, respectively, with diagnostic accuracies (represented by AUROCs) of 0.87, 0.91, and 0.93, respectively. In a large, international multicenter study, Sporea et al. evaluated retrospectively 914 HCV subjects[[119](#_ENREF_119)]. They observed a significant positive correlation between liver stiffness by ARFI and fibrosis stage (Spearman *r* = 0.654; *P* < 0.0001), and a good diagnostic performance for predicting fibrosis stage according to the METAVIR score. Although with significant overlapping of ARFI measurements for fibrosis F0–F2, advanced fibrosis (F ≥ 3) and cirrhosis could be accurately excluded. Generally, correlation with histological fibrosis was similar between TE and ARFI elastography. Nevertheless, TE was better than ARFI for predicting the presence of liver cirrhosis and fibrosis (F ≥ 1)[[119](#_ENREF_119)]. A recent meta-analysis including 13 studies and 1,163 patients with different hepatopathies demonstrated that for the detection of both significant fibrosis (F ≥ 2) and cirrhosis, the diagnostic performance of ARFI and TE were comparable, but with ARFI showing higher rate of reliable measurements as compared to TE[[130](#_ENREF_130)].

**Combined approach (algorithms):** Algorithms combining different fibrosis tests have been proposed to improve the accuracy of noninvasive methods for the correct diagnosis of liver fibrosis in HCV infection. They use two serum-based models either simultaneously or in a sequential procedure[[72](#_ENREF_72),[131](#_ENREF_131),[132](#_ENREF_132)]. They may also be based on agreement between a blood test and an imaging technique[[133](#_ENREF_133),[134](#_ENREF_134)]. Leroy algorithm has been proposed in a study that evaluated six non-invasive scores in 180 HCV patients[[72](#_ENREF_72)]. In this approach, the APRI and FibroTest® were calculated simultaneously and concordant results bellow the lower cutoffs (FibroTest® < 0.22 and APRI < 0.5) could rule out significant fibrosis with NPV of 94.1%. Results above the upper cutoffs (FibroTest® > 0.59 and APRI > 2) exhibited PPV for significant fibrosis of 96.7% and for extensive fibrosis (F3-F4) of 92.2%[[72](#_ENREF_72)]. However, only 32% of the patients presented concordant results. Therefore, a significant proportion of subjects are expected to require a liver biopsy when using this system[[72](#_ENREF_72)]. The SAFE (sequential algorithm for fibrosis evaluation) biopsy algorithm has been proposed in study that included 2035 HCV patients[[131](#_ENREF_131)]. The SAFE biopsy for simultaneous detection of significant fibrosis and cirrhosis produced only 52 (2.6%) misclassified cases, with an overall accuracy of 97.4%. However, as stated for the Leroy algorithm, liver biopsy would be required in the majority of the cases (64%)[[131](#_ENREF_131)].

A different approach was proposed by Castera *et al*[[133](#_ENREF_133)] in an algorithm combining FibroTest® and TE simultaneously. In this method (called Castera algorithm or Bordeaux algorithm), the diagnosis of significant fibrosis is based in the finding of concordant results for both methods, and liver biopsy is recommended in discordant results or for those individuals in whom liver stiffness measurement was not possible[[133](#_ENREF_133)]. For the diagnosis of significant fibrosis, the number of saved liver biopsies was significantly higher using Castera than SAFE biopsy algorithm (71.9% *vs* 48.3%, respectively). However, accuracy of SAFE biopsy algorithm was significantly higher than Castera algorithm (97.0% *vs* 87.7%, respectively).

More recently, a combination of Fibrometer® and FibroScan® was proposed in a study including 1785 patients with chronic hepatitis C[[134](#_ENREF_134)]. The so-called FM+FS classification includes 6 fibrosis classes (F0/1; F1/2; F2±1; F2/3; F3±1 and F4) and requires no liver biopsy[[134](#_ENREF_134)]. By using this approach, the proportion of discordant results has decreased as compared to SAFE biopsy and Castera algorithm. Even though this new classification of liver fibrosis appears to be more a formalization of uncertainty, it may also be an astute tactic for practical application of noninvasive fibrosis markers, allowing a more precise interpretation of its results. However, the employment of two relatively expensive methods will increase costs and may limit the application of FM+FS classification.

Although algorithms including every previously studied noninvasive marker are obviously not available, based on the above data, a simple and plausible approach would be to simultaneously perform two tests (serum and imaging technique), reserving liver biopsy for discordant results (Figure 1). We suggest using models based in simple blood tests, such as APRI or FIB-4, as there are no clear evidence for the use of more complex and expensive tests in this setting. Similar methodology was proposed in other review articles[[135](#_ENREF_135),[136](#_ENREF_136)]. By using this system, it is probable that liver biopsy will still be necessary in a significant proportion of patients. However, the number of misclassification is likely to be low.

**COST-EFFECTIVENESS OF NONINVASIVE MARKERS OF FIBROSIS**

The total cost of each strategy for diagnosing liver fibrosis depends on several factors such as the need for hospitalization or sedation in the case of liver biopsy, potential risks, the modality of noninvasive test and finally, the diagnostic accuracy. Although the procedure protocol varies greatly, liver biopsy usually requires a short-term hospitalization, the administration of sedatives and specialized nursing staff for post-biopsy care. In addition, ultrasonography is often used to mark or guide the biopsy. These particularities and the need for interpretation are responsible for the relatively high cost of liver biopsy, ranging from $ 1200 in the United Kingdom[[137](#_ENREF_137)] to $ 2200 in the United States[[138](#_ENREF_138)]. There are limited data regarding the cost-effectiveness of noninvasive strategy for liver fibrosis assessment, especially for the indirect markers. However, recent studies evaluating the FibroScan® and FibroTest® showed favorable cost-effectiveness profile for both noninvasive tests as compared to the traditional approach based on liver biopsy[[139-142](#_ENREF_139)]. There is a need for studies evaluating the cost-effectiveness of different strategies of noninvasive liver fibrosis assessment, such as the combined approach and the use of indirect markers. This information would be of special interest in low-income countries where the costs of liver biopsy are expected to be lower, but also with a limited availability.

**CONCLUSION**

The accurate diagnosis of liver fibrosis is essential for decision-making in chronic hepatitis C. Even though, over the last decade, remarkable achievements were made in noninvasive diagnosis of fibrosis, this is an evolving field and there is still room for improvement. It is possible that, in the near future, the incorporation of other methodologies such as genetic, proteomic, and metabolomics profiles allows the diagnosis of fibrosis in earlier stages, even permitting the identification of stellate cell activation in pre-fibrotic stages. In addition, extensive validation of currently available tools, including the investigation of their prognostic value may extend the applicability of noninvasive fibrosis markers in clinical practice.

Although noninvasive tests are now routinely used in several countries, they are still very limited in differentiating between early stages of fibrosis, and this fact, at least in part, may be related to liver biopsy limitations. Along with the improvement of the current noninvasive markers, there is also a need for changes in our way to look at fibrosis in the near future.

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**Figure 1 Suggested algorithm for diagnosing liver fibrosis in chronic hepatitis C.** Patients with concordant results in two techniques (serum and imaging) may be followed without liver biopsy and histological analysis can be reserved for those with discordant results. HCV: Hepatitis C Virus.

**Table 1 Major advantages and limitations of liver biopsy and noninvasive fibrosis markers**

|  |  |  |
| --- | --- | --- |
|  | **Liver Biopsy** | **Noninvasive markers** |
| Advantages |  |  |
|  | Validated scoring systems | Absence of significant discomfort and risks |
|  | Differential diagnosis and associated conditions | Allows frequent revaluation |
|  | Simultaneous evaluation of necro-inflammation | Objective interpretation |
|  |  | Patient acceptance |
| Limitations |  |  |
|  | Invasive | Low accuracy to discriminate between intermediate stages of fibrosis |
|  | High cost | Nonspecific for the liver (biomarkers) |
|  | Sampling errors and intra- and inter-observer variability | Influence of several extra-hepatic factors |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 2 Selected models including indirect markers of liver fibrosis** | | | | | | | |
| **Score (original reference)** | **Variables** | **Performance in HCV patients1** | | | | | |
| **Significant fibrosis (≥ F2)** | | | **Cirrhosis (≥ F4)** | | |
| **Median AUROC** | **Median Sensitivity2**  **(%)** | **Median Specificity2**  **(%)** | **Median AUROC** | **Median Sensitivity2**  **(%)** | **Median Specificity2**  **(%)** |
| APRI[24] | AST and platelet count | 0.77 | 81 | 95 | 0.84 | 77 | 94 |
| 3FIB-4[41] | Age, AST, ALT and platelet count | 0.74 | 64 | 79 | 0.87 | 90 | 92 |
| Forns index[48] | Age, platelet count, cholesterol levels, and GGT | 0.76 | 88 | 94 | 0.87 | 98 | 91 |
| Fibroindex[50] | Platelet count, AST, and gamma globulin | 0.76 | 94 | 97 | 0.86 | 70 | 91 |
| 1Based on reference number 49; 2Sensitivity values are present for the lower cutoff and specificity for the upper cutoff (when multiple cutoffs are presented); 3Model originally proposed for HIV/HCV co-infected patients. HCV: Hepatitis C virus; AUROC: Area under the receiver operating characteristic curve; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyltransferase. | | | | | | | |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 3** **Most studied models combining direct and indirect biomarkers for the diagnosis of liver fibrosis in chronic hepatitis C** | | | | | | | |
| **Score (original reference)** | **Variables** | **Performance in HCV patients1** | | | | | |
| **Significant fibrosis (≥ F2)** | | | **Cirrhosis (≥ F4)** | | |
| **Median AUROC** | **Median Sensitivity2**  **(%)** | **Median Specificity2**  **(%)** | **Median AUROC** | **Median Sensitivity2**  **(%)** | **Median Specificity2**  **(%)** |
| FibroTest[53] | Age, sex, serum haptoglobin, 2-macroglobulin, apolipoprotein A1, GGT, and total bilirubin | 0.79 | 92 | 96 | 0.86 | 85 | 81 |
| ELF[56] | Age, TIMP-1, PIIINP and hyaluronic acid | 0.81 | 85 | 70 | 0.88 | - | - |
| Fibrometer[61] | platelet count, prothrombin index, AST, 2-macroglobulin, hyaluronic acid, blood urea nitrogen and age | 0.82 | 69 | 81 | 0.91 | - | - |
| FIBROspect II[63] | TIMP-1, 2-macroglobulin and hyaluronic acid | 0.86 | 80 | 70 | - | - | - |
| Hepascore[66] | Age, sex, 2-macroglobulin, hyaluronic acid, GGT and total bilirubin | 0.79 | 66 | 79 | 0.89 | 72 | 86 |
| 1Based on reference number 49; 2Sensitivity values are present for the lower cutoff and specificity for the upper cutoff (when multiple cutoffs are presented). ELF: Enhanced liver fibrosis;HCV: Hepatitis C virus; AUROC: Area under the receiver operating characteristic curve; GGT: Gamma-glutamyltransferase; TIMP: Tissue inhibitor of matrix metalloproteinases; PIIINP: Procollagen type III amino-terminal peptide; AST: Aspartate aminotransferase. | | | | | | | |