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REVIEW ARTICLE

Non-invasive assessment of liver fibrosis in chronic hepatitis C

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Abstract Quantification of hepatic fibrosis is of critical importance in chronic hepatitis C not only for prognosis, but also for antiviral treatment indication. Two end points are clinically relevant: detection of significant fibrosis (indication for antiviral treatment) and detection of cirrhosis (screening for eosphageal varices and hepatocellular carcinoma). Until recently, liver biopsy was considered the reference method for the evaluation of liver fibrosis. Limitations of liver biopsy (invasiveness, sampling error, and inter-observer variability) have led to the development of non-invasive methods. Currently available methods rely on two different approaches: a "biological" approach based on the dosage of serum fibrosis biomarkers; and a "physical" approach based on the measurement of liver stiffness, using transient elastography (TE). This review is aimed at discussing the advantages and limits of non-invasive methods and liver biopsy and the perspectives for their rational use in clinical practice in the management of patients with chronic hepatitis C.

Keywords Chronic hepatitis C · Liver fibrosis · Non-invasive · Transient elastography · FibroScan · Serum biomarkers · Liver biopsy

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Introduction

In patients with chronic hepatitis C, precise staging of liver fibrosis is important not only for estimation of prognosis, but also for indication of antiviral therapy. Two end points are clinically relevant: detection of significant fibrosis, which is an indication for antiviral treatment, and detection of cirrhosis, which is an indication for specific monitoring of complications related to portal hypertension and to the increased risk of developing hepatocellular carcinoma [1].

Liver biopsy has traditionally been considered the reference method for the evaluation of liver fibrosis in chronic hepatitis C [2]. However, liver biopsy is an invasive procedure, associated with pain in around 30% of cases [3–5], and potentially life-threatening complications (hemorrhage in 0.3% of cases and mortality in 0.01%) [6]. The accuracy of liver biopsy to assess fibrosis has also been questioned in relation to sampling errors and intra- and inter-observer variability that may lead to over- or under-staging [7–10]. Finally, liver biopsy does not allow dynamic evaluation of liver fibrosis over time.

These limitations have led to the development of non-invasive methods [11]. Currently available methods rely on two different, but complementary, approaches: [1] a "biological" approach based on the dosage of serum biomarkers of fibrosis; and [2] a "physical" approach based on the measurement of liver stiffness, using transient elastography (TE) [12]. Although the large number of publications over the past decade confirms the growing interest regarding these new non-invasive methods, there is a need for clarification and guidance on their use and interpretation. This review is aimed at discussing the advantages and limits of these methods, and the perspectives for their rational use in clinical practice in the management of patients with chronic hepatitis C.

Biological approach: serum fibrosis biomarkers

Individual surrogate serum markers of liver fibrosis

A variety of "direct" serum markers of fibrosis, reflecting either the deposition or the removal of extracellular matrix in the liver have been evaluated for their ability to assess liver fibrosis. These include: glycoproteins, such as serum hyaluronate [13–17], laminin [18, 19], and YKL-40 [20]; the collagens family, such as procollagen III N-peptide (PIIINP) [13] and type IV collagen [21]; collagenases and their inhibitors, such as matrix metalloproteases (MMP) [22] and tissue inhibitory metalloprotease-1 (TIMP-1) [23].

"Indirect" serum markers including simple routine blood tests, such as prothrombin index [19], platelet count [24], and AST/ALT ratio [25–27] have also been proposed.

The performances of "direct" and "indirect" serum markers have been evaluated in chronic hepatitis C (reviewed in [12, 28–30]), with hyaluronate being the most extensively studied. Apart from hyaluronate [14, 15, 31], "direct" and "indirect" markers, when used individually, are useful for the diagnosis or the exclusion of cirrhosis, but have limited accuracy for the diagnosis of significant fibrosis [32].

Scores combining indirect and direct markers of liver fibrosis

The limitations of individual markers to assess liver fibrosis have led to the development of more sophisticated scores combining the results of panels of markers that substantially improved diagnostic accuracy for which the FibroTest has been the pioneer [33]. Several other scores have been developed since then [34–48] (Table 1). The diagnostic performances for significant fibrosis and cirrhosis of proposed scores are summarized in Tables 2 and 3, respectively.

Five scores are protected by patents and are currently commercially available: the FibroTest® in Europe (Biopredictive, Paris, France) licensed under the name of Fibrosure® in the USA (LabCorp, Burlington, NC, USA), the Fibrometers® (BioLiveScale, Angers, France), the FibroSpectII® (Promotheus Laboratory Inc. San Diego, Ca, USA), the ELF® (Enhanced Liver Fibrosis Test, iQur Ltd, Southampton, UK), and the Hepascore® (PathWest, University of Western Australia, Australia).

To date, FibroTest® and aspartate to platelet ratio index (APRI) have been the most extensively studied. In a meta-analysis [49], which pooled 6,378 subjects (with analysis of individual data in 3,282) with both FibroTest and biopsy (3,501 HCV), the mean standardized area under the ROC curve (AUROC) for diagnosing significant fibrosis was 0.84 (95% CI, 0.83–0.86). In another meta-analysis [50], which pooled 4,266 HCV patients from 22 studies, the mean AUROCs of APRI for diagnosing significant fibrosis and cirrhosis were 0.76 (0.74–0.79) and 0.82 (0.79–0.86), respectively.

When compared and validated externally in patients with hepatitis C [51–56], the different patented scores have similar performances for the diagnosis of significant fibrosis. In the largest study to date ($n = 1{,}307$) [56], comparing prospectively several patented and non-patented scores (FibroTest®, Fibrometre®, Hepacore® and APRI), the AUROCs ranged from 0.72 to 0.78 for significant fibrosis and from 0.77 to 0.86 for cirrhosis. Although non-patented scores, such as the Forns index, FIB-4, and APRI may have slightly lower performance, they are cost-free, easy to calculate, and available almost everywhere.

Limitations

One of the main limitations to the clinical use of "direct" markers of liver fibrosis is that they are not routinely available in most hospital settings. Another limitation of these markers is that none is liver-specific and they may be influenced by changes in their clearance and excretion. For instance, increased levels of hyaluronate occur in the postprandial state [57] or in aged patients with chronic inflammatory processes such as rheumatoid arthritis. Also, the reproducibility of measurement of some parameters included in "indirect" serum markers, such as AST levels or platelet count, is questionable [58]. Conversely, the inter-laboratory reproducibility of scores, such as FibroTest® and Fibrometers® has been shown to be satisfactory for use in clinical practice [59–61]. However, when using FibroTest®, the interpretation should be done critically, taking into account each of the five components individually to avoid false-positive results related to hemolysis (decrease in haptoglobin) and Gilbert syndrome (increase in bilirubin), or false-negative results related to inflammation [62].

Physical approach: transient elastography

Principle

TE (FibroScan®, Echosens, Paris, France) has been proposed for the measure of liver stiffness [63]. Briefly, an ultrasound transducer probe is mounted on the axis of a vibrator. Vibrations of mild amplitude and low frequency are transmitted by the transducer, inducing an elastic shear wave that propagates through the underlying tissues. Pulse-echo ultrasound acquisitions are used to follow the propagation of the shear wave and to measure

Table 1 Proposed serum scores for non-invasive evaluation of liver fibrosis in chronic hepatitis C

– Fibrotest® (α-2-macroglobulin, γGT, apolipoprotein A1, haptoglobin, total bilirubin, age, and gender)
– Forns Index (age, platelet count, cholesterol, and γGT)
– AST to platelet ratio (APRI) (AST and platelet count)
– FibroSpect® (α-2-macroglobulin, hyaluronate, and TIMP-1)
– MP3 (MMP-3 and TIMP-1)
– Enhanced Liver Fibrosis score® (ELF) (age, hyaluronate, MMP-3, and TIMP-1)
– Fibrosis Probability Index (FPI) (age, past alcohol intake, AST, cholesterol, and HOMA-IR)
– Lok Index (platelet count, AST/ALT ratio, and INR)
– Gotebörg University Cirrhosis Index (GUCI) (AST, INR, and platelet count)
– Hepascore® (bilirubin, γGT, hyaluronate, α-2-macroglobulin, age, and gender)
– Fibrometers® (platelet count, prothrombin index, AST, α-2-macroglobulin, hyaluronate, urea, and age)
– Virahep-C model (AST, platelet count, alkaline phosphatase, and age)
– Fibroindex (platelet count, AST, and γ-globulin)
– FIB-4 (Platelet count, ALT, and AST)
– HALT-C model (hyaluronic acid, TIMP-1, and platelet count)

Table 2 Diagnostic performance of non-invasive serum scores of liver fibrosis for significant fibrosis in chronic hepatitis C

Scores	Year	Patients (*n*)	Significant fibrosis (%)	Cutoffs	AUROC	Se	Sp	+LR	−LR
FibroTest® [33]	2001	339	80	>0.48	0.87	75	85	5	0.3
Forns Index [34]	2002	476	26	<4.2 >6.9	0.76–0.86	30–94	51–95	1.9–6.0	0.1–0.7
APRI [35]	2003	270	50	≤0.5 >1.5	0.69–0.88	41–91	47–95	1.7–8.2	0.2–0.6
FibroSpect® [36]	2004	696	52	>0.36	0.83	77	73	2.9	0.3
MP3 [37]	2004	194	45	<0.3 >0.4	0.82	35–65	85–96	4.3–8.8	0.4–0.7
ELF® [38]	2004	1,021[a]	40	NA	0.78	90	30	1.3	0.3
FPI [39]	2005	302	48	<0.2 ≥0.8	0.77	42–85	48–98	1.6–21.0	0.3–0.6
Hepascore® [40]	2005	211	57	≥0.5	0.82	63	89	5.7	0.4
Fibrometer® [41]	2005	598[b]	56	NA	0.89	80	84	5	0.2
ViraHep-C [42]	2006	859	37	≤0.22 >0.55	0.83	51–90	54–90	2.0–5.1	0.2–0.5
Fibroindex [43]	2007	360	50	≤1.25 ≥2.25	0.83	30–40	97–97	10.0–13.3	0.6–0.7

AUROC Area under ROC curve, *Se* sensitivity, *Sp* specificity, *+LR* positive likelihood ratio, *−LR* negative likelihood ratio, *NA* not available
[a] 496 HCV patients; [b] 383 with viral hepatitis in the exploratory population and 120 HCV in the validation population

Table 3 Diagnostic performance of serum non-invasive scores of liver fibrosis for cirrhosis in chronic hepatitis C

Scores	Year	Patients (*n*)	Cirrhosis (%)	Cut-offs	AUROC	Se (%)	Sp (%)	+LR	−LR
FibroTest® [56]	2001	1,197	14	>0.74	0.82	63	84	4	0.4
APRI [35]	2003	476	17	<1.0 ≥2.0	0.94	57–89	75–93	3.6–8.1	0.1–0.5
Glycocirrhotest [44]	2004	106[a]	45[b]	NA	0.87	79	86	5.6	0.2
ELF® [38]	2004	1,021[c]	NA	NA	0.89	91	69	2.9	0.4
Lok Index [45]	2005	1,141	38	<0.2 ≥0.5	0.81	40–98	53–99	2.1–40.0	0.04–0.6
Hepascore® [40]	2005	211	16	>0.84	0.89	71	89	6.5	0.3
GUCI [46]	2005	179	12	>1.0	0.85	80	78	3.6	0.3
FIB-4 [47][d]	2007	847	17$	<1.45 >3.25	0.85	38–74	81–98	3.9–19.0	0.3–0.6
HALT-C model [48]	2008	512	38	<0.2 >0.5	0.81	47–88	45–92	1.6–5.9	0.3–0.6

AUROC Area under ROC curve, *Se* sensitivity, *Sp* specificity, +LR positive likelihood ratio, −LR negative likelihood ratio, *NA* not available
[a] 71 HCV patients; [b] 24% with decompensated cirrhosis; [c] 496 HCV patients; [d] F3F4 patients

its velocity, which is directly related to tissue stiffness of the elastic modulus: the stiffer the tissue, the faster the shear wave propagates. TE measures liver stiffness in a volume that approximates a cylinder of 1-cm wide and 4-cm long, between 25 and 65 mm below the skin surface. This volume is at least 100 times bigger than a biopsy sample and is therefore far more representative of the hepatic parenchyma. TE is painless, rapid (less than 5 min), and easy to perform at the bedside or in the outpatient clinic. The results are immediately available and expressed in kilopascals (kPa), corresponding to the median value of ten validated measurements and range from 2.5 to 75 kPa [64], with normal values around 5.5 kPa [65].

Reproducibility

Reproducibility is an important prerequisite for a widespread application of TE in clinical practice. TE reproducibility has been shown to be excellent for both inter-observer and intra-observer agreement, with intra-class correlation coefficients (ICC) of 0.98 [66, 67]. However, inter-observer agreement was significantly reduced in patients with lower degrees of hepatic fibrosis, with hepatic steatosis, and with increased body mass index [66], as well as for liver stiffness values <9 kPa [67].

Diagnostic performance

The two index studies suggesting the interest of TE in the assessment of liver fibrosis were conducted in patients with chronic hepatitis C [68, 69]. Many other groups have confirmed these results [56, 70–72] with a strong correlation of liver stiffness values with Metavir fibrosis stages and AUROCs ranging from 0.75 to 0.91 for the diagnosis of significant fibrosis and from 0.90 to 0.98 for cirrhosis. Cutoff values with optimal diagnostic accuracy were defined for each stage of fibrosis (Tables 4, 5). It should be stressed, however, that despite high AUROC values, a substantial overlap of liver stiffness values was observed between adjacent stages of hepatic fibrosis, particularly for lower fibrosis stages.

Three meta-analyses recently addressed the issue of diagnostic performance of TE [73–75]. In the most comprehensive meta-analysis, based on 50 studies (15 full papers and 35 abstracts) [75], the mean AUROC was 0.84 (95% confidence interval (CI), 0.82–0.86) for the diagnosis of significant fibrosis with a suggested optimal cutoff of 7.6 kPa, and 0.94 (95% CI, 0.93–0.95) for the diagnosis of cirrhosis with a suggested optimal cutoff of 13.0 kPa. Meta-analyses with individual data are awaited.

TE appears to be a reliable method for the diagnosis of cirrhosis, better at excluding than at predicting cirrhosis. For instance, in a population of 1,007 patients with different chronic liver diseases, a cutoff value of 14.6 kPa yielded positive and negative predictive values of 74 and 96%, respectively [76].

Monitoring of disease progression

Another promising application of TE is for monitoring the progression of liver fibrosis. The clinical significance of the wide range of liver stiffness values observed in patients with cirrhosis (13–75 kPa) remains uncertain. Preliminary results suggested that liver stiffness values in cirrhotic patients increased as the liver disease progressed [77]. For instance, cutoff values of 27.5, 37.5, 49.1, 53.7, and 62.7 kPa, respectively, had >90% negative predictive value for the presence of stage 2/3 esophageal varices, Child–Pugh score B or C, and a past history of ascites, HCC, and esophageal bleeding. Although retrospective and conducted in a single centre, this study provided the first "proof of concept" that liver stiffness values may have prognostic value in a context of cirrhosis. In addition, several studies [78, 79] have shown a correlation between liver stiffness values and portal hypertension diagnosed by means of hepatic venous pressure gradient (HVPG) measurement, the gold standard for the diagnosis and staging of portal hypertension and a reliable predictor of clinical decompensation [80]. A correlation between liver stiffness

Table 4 Diagnostic performance of transient elastography for significant fibrosis in chronic hepatitis C

Authors	Patients (*n*)	Significant fibrosis (%)	Cutoffs (kPa)	AUROC	Se (%)	Sp (%)	+LR	−LR
Degos et al. [56]	913	62	5.2	0.75	90	32	1.3	0.3
Sporea et al. [72]	191	84	6.8	0.77	60	93	8.6	0.4
Castera et al. [69]	183	74	7.1	0.83	67	89	6.1	0.4
Lupsor et al. [71]	324	65	7.4	0.86	76	84	4.8	0.3
Arena et al. [70]	150	56	7.8	0.91	83	82	4.6	0.2
Ziol et al. [68]	251	65	8.6	0.79	56	91	6.6	0.5

AUROC Area under ROC curve, *Se* sensitivity, *Sp* specificity, *+LR* positive likelihood ratio, *−LR* negative likelihood ratio

Table 5 Diagnostic performance of transient elastography for cirrhosis in chronic hepatitis C

Authors	Patients (*n*)	Cirrhosis (%)	Cutoffs (kPa)	AUROC	Se (%)	Sp (%)	+LR	−LR
Lupsor et al. [71]	324	21	11.9	0.94	87	91	9.7	0.1
Castera et al. [69]	183	25	12.5	0.95	87	91	9.7	0.1
Castera et al. [83]	298	23	12.5	0.96	83	95	16.6	0.2
Degos et al. [56]	913	14	12.9	0.9	72	89	6.8	0.3
Ziol et al. [78]	251	19	14.6	0.97	86	96	23.1	0.1
Arena et al. [70]	150	19	14.8	0.98	94	92	11.3	0.1

AUROC Area under ROC curve, *Se* sensitivity, *Sp* specificity, *+LR* positive likelihood ratio, *−LR* negative likelihood ratio

values and the presence of esophageal varices has also been reported [79, 81–84]. However, liver stiffness measurement (LSM) cannot yet confidently predict the presence of esophageal varices in clinical practice and thus avoid the need for upper GI endoscopic screening of cirrhotic patients [85].

TE could be also valuable for assessing the severity of recurrent hepatitis C after liver transplantation, reducing the need for follow-up liver biopsies [78, 86–90]. It has been recently suggested that TE may perform better for significant fibrosis than serum (direct and indirect) biomarkers [91].

Finally, TE could be useful for evaluating fibrosis regression in patients with chronic hepatitis C achieving sustained viral eradication [92–94] or for monitoring fibrosis progression in untreated patients.

Long-term prospective follow-up studies are now awaited to see whether liver stiffness values can predict the occurrence of clinical events in patients with compensated cirrhosis. Interestingly, a recent Japanese prospective study has shown in a large cohort of patients with chronic hepatitis C a correlation between liver stiffness values and the risk of hepatocellular carcinoma [95]. Although these findings need to be confirmed in other settings (Caucasian patients or HBV-infected patients) and with longer follow-up, they suggest that TE could be used as a rapid screening tool to allocate cirrhotic patients to specific risk categories [96].

Limitations

The interpretation of TE results should be always in the hands of an expert clinician and should be made having at disposition information regarding patient demographics, disease etiology, and essential laboratory parameters, as well as carefully following the manufacturer's recommendations (number of valid shots $\geq$ 10; success rate (the ratio of valid shots to the total number of shots) $\geq$60%; and interquartile range (IQR, reflecting the variability of measurements) less than 30% of the median LSM value (IQR/LSM $\leq$ 30%) [64]). Indeed, in a recent prospective 5-year study based on more than 13,000 examinations, LSM failure (no value after ten measurements or more) has been shown to occur in 3.1% of cases and LSM results to be uninterpretable (not meeting manufacturer's recommendations) in an additional 15.8% [97]. Limited operator experience, obesity, and more generally features of the metabolic syndrome were the main determinants of LSM failure or unreliable results. This challenges previous claims [67, 98] that LSM requires no learning curve and that a novice can consistently obtain reliable results after a short training period. Operator experience influenced not only the success rate, as previously reported [67, 98], but also the IQR/LSM ratio, which was recently shown to be critical for LSM accuracy [99]. These findings emphasize the need for rigorous scientific evaluation of all novel procedures, such as TE before their widespread uptake. Further technological refinements are required for specific populations, such as those with the metabolic syndrome.

Finally, as the liver is an organ wrapped in a distensible but non-elastic envelope (Glisson's capsula), additional space-occupying tissue abnormalities, such as edema and inflammation, cholestasis and congestion may interfere with LSM, independently of fibrosis. Indeed, as previously mentioned, the extent of necro-inflammatory activity has been shown to influence TE measurements in patients with viral hepatitis with a steady increase of liver stiffness values in parallel with the degree of histological activity [66, 70, 100]. Consistent with these results, the risk of overestimating liver stiffness values has been reported in case of ALT flares in patients with acute viral hepatitis or chronic hepatitis B [101–103], as well as in cases of extrahepatic cholestasis [104] or congestive heart failure [105].

Comparison and combination of approaches

For the diagnosis of significant fibrosis, performances of TE and serum biomarkers have been shown to be equivalent in patients with chronic hepatitis C [56, 69]. For the diagnosis of cirrhosis, the situation is different as TE

appears to be the most accurate non invasive method in HCV patients when compared with currently available biomarkers and routine blood tests [56, 69], allowing the avoidance of liver biopsy in around 90% of cases. TE is thus "the test to be beaten" for those developing alternative methods [106].

In order to increase diagnostic accuracy, new approaches using a combination of TE and serum markers [69, 107, 108] have been proposed. For instance, using an algorithm to evaluate the agreement between TE and FibroTest®, liver biopsy can be avoided for the diagnosis of significant fibrosis in around 75% of patients with chronic hepatitis C [69].

Also, a sequential algorithm (SAFE Biopsy), using APRI as screening test, followed by Fibrotest® in APRI non-classified cases and restricting liver biopsy to patients classified as F0–F1 by non-invasive tests, has been proposed, allowing avoidance of liver biopsy for the diagnosis of significant fibrosis in around 50% of cases [109]. These results have been confirmed in a large-scale, multicenter international validation study of more than 2,000 patients with chronic hepatitis C [110]. Other groups have proposed alternative algorithms combining FibroTest® and APRI [53] either with Forns index (Fibropaca) [111] or Hepascore [112].

In a recent study where these two approaches were compared in the same population of patients with chronic hepatitis C, the number of saved liver biopsies was significantly higher using the combination of TE and Fibrotest® than SAFE Biopsy algorithm for detecting significant fibrosis (72 vs. 48%, respectively; $P < 0.0001$) [113].

A combination of two unrelated methods, such as TE and Fibrotest®, may have certain advantages over the combination of two biomarkers, in that TE provides more direct measurement of the liver structure than serum markers and that there is no relationship between the applicability of TE (success rate and interquartile range) and Fibrotest® (Gilbert's syndrome, hemolysis, and sepsis) [107].

Novel imaging techniques

New alternative imaging techniques may also become available: magnetic resonance (MR) elastography, which can be implemented readily on standard MR imaging systems with additional hardware; diffusion weighted MR imaging, which measures the apparent diffusion coefficient of water, a parameter that is dependent on the tissue structure; optical digital analysis of computed tomography images of the liver and sonography-based real-time elastography, which can be performed with conventional ultrasound probes during a routine sonography examination [114]. The theoretical advantages of these methods include the ability to analyze almost the entire liver and the applicability to patients with obesity or ascites. Preliminary studies in human subjects have confirmed the feasibility of these techniques for quantitative assessment of hepatic fibrosis [115–119]. In addition, a recent prospective comparative study in 96 patients with chronic liver disease [120] has suggested that MR elastography had a better diagnostic accuracy than TE for the diagnosis of significant fibrosis (AUROC: 0.99 vs. 0.84, respectively $P < 0.05$). Although such results are encouraging, these techniques remain so far too expensive and time-consuming for implementation in clinical practice for screening hepatic fibrosis.

Very recently, a novel imaging technology (ARFI acoustic radiation force impulse imaging), involving the mechanical excitation of tissue using short-duration ($\sim$262 μs) acoustic pulses producing shear waves propagation generating localized micron-scale displacements in the tissue, has been proposed [121]. The shear wave velocity (expressed in meters per second) is measured in a region of interest smaller than that of TE (10-mm long and 6-mm wide), but that can be chosen by the examiner. Preliminary results suggest that at least in patients with chronic hepatitis C, its performance is very similar to that of TE, although further validation is warranted [122–126]. The major advantage of this novel technology is that it can be easily implemented on a modified commercial ultrasound machine. However, as compared with LSM values (2.5–75 kPa), ARFI values are in a very narrow range (0.5–4.4 m/s), which could represent a limitation to its use for making decision in clinical practice. More data are also awaited regarding the intra- and inter-observer reproducibility of ARFI.

Conclusion

Significant progress has been made in the non-invasive diagnosis of hepatic fibrosis in patients with chronic hepatitis C. An increasing number of reliable tests are now available: TE, Fibrotest® and APRI have been the most extensively studied and validated. These tests are already widely used in routine clinical practice in France resulting in a significant decrease in the need for liver biopsy [127]. However, it is likely that non-invasive methods will reduce but not completely abolish the need for liver biopsy [28]. The most rational way of using these tools is to make a compromise: use non-invasive methods to classify those patients in whom they perform with high accuracy, limiting liver biopsy to the subset of patients in whom precise non-invasive staging is not possible. In that respect, the use of TE and several patented scores (FibroTest®, Fibrometer®,

and Hepascore®) has been recently approved, after an independent systematic review by the French Health Authorities, for the first-line assessment of fibrosis in naïve patients with chronic hepatitis C without co-morbidities [128]. Interpretation of the results of non-invasive methods should always be done critically by an expert clinician according to clinical context and taking into account patient demographics, essential laboratory parameters, and manufacturer's recommendations. Apart from cases where cirrhosis is clinically obvious, a combination of two unrelated methods should be used rather than a single method. A liver biopsy should be performed in case of discordance between results of non-invasive tests, when non-invasive methods are not applicable, or if co-morbidities such as alcoholism or metabolic syndrome are present. In any case, a large specimen (ideally 20–25 mm) should be obtained and reading should be done by an experienced liver pathologist.

In conclusion, we believe that liver biopsy and non-invasive methods, particularly TE, should be employed as an integrated system to allow a more efficient and convenient management of patients with chronic hepatitis C [129].

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