World Journal of Gastroenterology

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DOI: 10.3748/wjg.v22.i4.1711

World J Gastroenterol 2016 January 28; 22(4): 1711-1720
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Non-invasive assessment of liver fibrosis: Between prediction/prevention of outcomes and cost-effectiveness

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Author contributions: Stasi C designed the review, wrote and revised the manuscript; Milani S critically revised the manuscript for important intellectual content and has given final approval of the version to be published.

Conflict-of-interest statement: The authors have no conflicts of interest to disclose.

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Received: July 27, 2015
Peer-review started: July 30, 2015
First decision: September 9, 2015
Revised: September 26, 2015
Accepted: December 12, 2015
Article in press: December 14, 2015
Published online: January 28, 2016

Abstract

The assessment of the fibrotic evolution of chronic hepatitis has always been a challenge for the clinical hepatologist. Over the past decade, various non-invasive methods have been proposed to detect the presence of fibrosis, including the elastometric measure of stiffness, panels of clinical and biochemical parameters, and combinations of both methods. The aim of this review is to analyse the most recent data on non-invasive techniques for the evaluation of hepatic fibrosis with particular attention to cost-effectiveness. We searched for relevant studies published in English using the PubMed database from 2009 to the present. A large number of studies have suggested that elastography and serum markers are useful techniques for diagnosing severe fibrosis and cirrhosis and for excluding significant fibrosis in hepatitis C virus patients. In addition, hepatic stiffness may also help to prognosticate treatment response to antiviral therapy. It has also been shown that magnetic resonance elastography has a high accuracy for staging and differentiating liver fibrosis. Finally, studies have shown that non-invasive methods are becoming increasingly precise in either positively identifying or excluding liver fibrosis, thus reducing the need for liver biopsy. However, both serum markers and transient elastography still have "grey area" values of lower accuracy. In this case, liver biopsy is still required to properly assess liver fibrosis. Recently, the guidelines produced by the World Health Organization have suggested that the AST-to-platelet ratio index or FIB-4 test could be utilised for the evaluation of liver fibrosis rather than other, more expensive non-invasive tests, such as elastography or FibroTest.

Key words: Stiffness; Serum markers; Liver fibrosis; Hepatitis C virus; Public health

Core tip: The results of several studies have shown that non-invasive methods are becoming increasingly precise in predicting non-significant and advanced liver fibrosis, thus reducing the need for liver biopsy in a relevant

number of patients. However, when both serum markers and transient elastography values fall, liver biopsy may be still needed. Recently, the guidelines for the screening, care, and treatment of hepatitis C virus infected patients produced by the World Health Organization suggested that the AST-to-platelet ratio index or FIB-4 test could be used for the evaluation of liver fibrosis rather than other, more expensive non-invasive tests in a resource-limited setting.

Stasi C, Milani S. Non-invasive assessment of liver fibrosis: Between prediction/prevention of outcomes and cost-effectiveness. *World J Gastroenterol* 2016; 22(4): 1711-1720 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i4/1711.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i4.1711

INTRODUCTION

The evolution of chronic hepatitis C (CHC) into liver cirrhosis is correlated with an extensive accumulation of extracellular matrix, leading to the formation of large amounts of fibrotic tissue that is initially concentrated in periportal areas and in later stages completely surrounds the nodules of regenerating hepatocytes[1].

The progressive increase of the fibrotic matrix, in addition to its deleterious effects on hepatocyte function and solute exchange between hepatocytes and portal blood, contributes both to the vascular disturbances that favour the development of irreversible portal hypertension and to the microenvironmental changes that facilitate the occurrence of hepatocellular carcinoma.

In addition to its prognostic value in the evaluation of liver disease progression and decompensation, liver fibrosis is also a well-recognised negative prognostic factor of the viral response to interferon-based therapies[2].

Many studies have shown that treatment with both double therapy [pegylated interferon (PEG-IFN) and ribavirin] and triple therapies (PEG-IFN, ribavirin, and either telaprevir or boceprevir) are indeed significantly less effective in patients with severe fibrosis or cirrhosis[2-5].

For these reasons, clinical practice guidelines for the therapy of CHC recommend evaluating liver fibrosis to help in treatment decision making and the proper choice of treatment timing[6].

The demonstration that a sustained viral response is associated with fibrosis regression even in patients with severe fibrosis and cirrhosis[7,8] suggests that the evaluation of fibrosis after antiviral therapy could be of clinical interest for the management of these patients.

Liver biopsy has long been considered the "gold standard" for the evaluation of hepatic fibrosis.

The attempt to stage the fibrosis by liver biopsy has led to the proposal of different types of scoring systems[9-11]. The first of these was proposed by Knodell in 1981[9], which described 4 classes from 0 to 4. Each of the proposed scores[9-11] considered some aspects that could describe the fibrotic evolution, though not giving a quantitative assessment. Therefore, the attempt of researchers has been to obtain a better quantization. All proposed scores are burdened by possible sampling error, observer-dependent diagnostic variability and lack of standardization of staining utilized to highlight the fibrous connective tissue. For example the trichrome stain is performed to assess the extent of liver fibrosis; the Sirius red and aniline blue stains are used for selective staining of collagen when quantitative evaluation of fibrosis by morphometry is required, thus contributing to the variability of the diagnosis[12].

The ability to use immunohistochemical components to highlight specific components of fibrotic tissue, such as α-smooth muscle actin[13], may introduce additional variability. The proposal to get a better staging by a quantitative analysis of the surface occupied by collagen, probably will not overcome the issues relating to sampling, since liver biopsy involves only a very small part of the hepatic parenchyma (approximately 1/50000). However, in addition to its diagnostic variability[14], concerns have been raised regarding its invasiveness and potential for adverse events[15,16], stimulating research for alternative, non-invasive diagnostic tools for the measurement of liver fibrotic tissue. In the last 40 years, since the pioneer study of Rohde *et al*[17], who established the first radioimmunoassay for the determination of the fragments of procollagen type Ⅲ in the body fluids of acute and chronic hepatitis patients, several studies have been published analysing various non-invasive techniques for the evaluation of hepatic fibrosis. In the last decade, transient elastography (TE) and magnetic resonance (MR) elastography have also been suggested as non-invasive techniques for the detection of liver fibrosis[18,19], raising wide interest because of their potential as a substitute for liver biopsy.

The aim of this review is to analyse the most recent data on non-invasive techniques for the evaluation of hepatic fibrosis before, during, and after antiviral therapy in hepatitis C virus (HCV) infected patients, with particular attention to cost-effectiveness.

INDIRECT MARKERS OF LIVER FIBROSIS

"Indirect markers" are panels of clinical and biochemical parameters not directly related to extracellular matrix metabolism that have been tested for their ability to predict and differentiate various stages of liver fibrosis.

Among them, the AST-to-platelet ratio index (APRI) test, Forns test, and FibroTest (FT) have demonstrated a satisfactory diagnostic accuracy for the detection of significant and/or advanced fibrosis and cirrhosis (Table 1)[20-25].

Castera *et al*[26] compared the diagnostic effectiveness to discriminate between significant fibrosis and

Table 1 Cut-off values of the first indirect markers of fibrosis in the diagnosis of significant fibrosis and cirrhosis[1]

Markers	Algorithm	Aetiology	Cut-off values of some indirect markers	
			⩾ Significant fibrosis	Extensive fibrosis or cirrhosis
APRI		HCV	> 1.5	⩾ 2
Wai *et al*[20], 2003	AST (UI/L)/platelet count (10^9/L) × 100			
FORNS INDEX		HCV	> 6.9	
Forns *et al*[21], 2002	7.811-3.131 × ln (platelet count) + 0.781 × ln (GGT) + 3.467 × ln (age [years]) - 0.014 × ln (cholesterol)			
FIBROTEST®	Formula combining α-2-macroglobulin, γGT, apolipoprotein	HCV	⩾ 0.6	
Imbert-Bismut *et al*[22], 2001	A1, haptoglobin, total bilirubin, age and gender			
LOK	Log odds = -5.56-0.0089 × platelet count (× 10^3/mm^3) + 1.26	HCV		⩾ 0.5
Lok *et al*[23], 2005	× AST/ALT ratio + 5.27 × INR			
FIBROINDEX		CLD	⩾ 2.25	
Koda *et al*[24], 2007	1.738–0.064 [platelet counts (10^4/mm^3)] + 0.005 × AST (UI/L) + 0.463 [gamma-globulin (g/dL)]			
FIB-4		CLD		> 3.25
Vallet-Pichard *et al*[25], 2007	Age (yr) × AST (UI/L)/[platelet count (10^9/L)] × [ALT (UI/L)]$^{1/2}$			

[1]According to either METAVIR or Ishak scoring system. CLD: Chronic liver disease; AST: Aspartate aminotransferase; GGT: Gamma glutamiltranspepsidasi; ALT: Alanine aminotransferase; INR: International normalized ratio.

cirrhosis of two algorithms including either TE and FT (Castera) or APRI and FT (SAFE biopsy). The former algorithm used the combination of TE and FT (named the Castera algorithm) as the first-line evaluation of fibrosis. Using this algorithm, they used liver biopsy when the two methods were in disagreement in the diagnosis of fibrosis stage (when liver stiffness was ⩾ 7.1 but FT was ⩽ 0.48 and when liver stiffness was ⩽ 7.1 but FT was ⩾ 0.48). The second algorithm consisted of the sequential use of APRI, FT, and liver biopsy for the diagnosis of significant fibrosis (> F2 by Metavir) when the cut-off value for FT is ⩽ 0.48 and in the diagnosis of the need for cirrhosis liver biopsy when the FT score ranged from 0.49 to 0.74. The study demonstrated that, for the detection of significant fibrosis, the number of saved biopsies was significantly higher using the Castera algorithm rather than the SAFE biopsy algorithm. In contrast, the accuracy of the SAFE biopsy algorithm was significantly higher than that of the Castera algorithm. The authors suggested, however, that the Castera algorithm may be less cost-effective because it required both TE and FT in all cases, whereas the SAFE biopsy, using APRI in all cases and FT in half of the patients, was much less expensive. For the diagnosis of cirrhosis, the number of saved liver biopsies did not differ between the Castera and SAFE biopsy algorithms, but the accuracy of Castera was significantly higher than that of the SAFE biopsy.

Bota *et al*[27] evaluated the performance of several non-invasive techniques for estimating hepatic fibrosis, including TE, APRI score, Lok score, Forns score, FIB-4 score, fibrosis index, King score, and Bonacini score in comparison with the effectiveness of liver biopsy. On the basis of the results, a new algorithm was validated for fibrosis prediction (named the predicted liver fibrosis score) derived from TE and multiple serological tests. The predicted liver fibrosis score was more strongly correlated with fibrosis stage in predicting significant and severe fibrosis than individual tests when used alone, while their predictive values for cirrhosis were similar. Sirli *et al*[28] compared various non-invasive methods (platelet count, APRI score, Forns score, Lok score, FIB-4, TE) for the evaluation of hepatic fibrosis with biopsy taken as a reference method. In this study, the APRI score and Forns scores correctly identified most of the patients having or lacking significant fibrosis. TE was the best method for estimating cirrhosis, but all the evaluated tests had excellent predictive value.

Liu *et al*[29] assessed the cost-effectiveness of FT and liver biopsy used either alone or sequentially in six different strategies: FT only; FT with liver biopsy for ambiguous results; FT followed by biopsy to exclude or confirm significant fibrosis; biopsy only; and treatment without screening. The results of this study suggested that the early treatment of CHC was the best cost-effective strategy and that it was superior to the other fibrosis screening strategies. However, when using the new triple therapy and when testing was required, FT only was cost-effective. Bousier *et al*[30] showed that the accuracy of the third-generation Fibrometer (the first-generation Fibrometer bringing together platelets, prothrombin index, aspartate aminotransferase, α2-macroglobulin, hyaluronate, urea, and age[31], the second generation added sex, as gender interferes with fibrogenesis in CHC, and the third generation was obtained by replacing the hyaluronic acid with gamma-

glutamyl transferase, GGT[32]) was significantly higher than that of other non-invasive tests (Fibrometer second generation, FibroScan, and FT). A new fibrosis index (the fibro-stiffness index), consisting of liver stiffness measurement, platelet count, and prothrombin time, was validated in HCV patients who underwent liver biopsy. Its accuracy was compared with that of APRI, the Forns index, and FibroIndex, and with hepatic stiffness measured by FibroScan, and it was found superior to liver stiffness alone, APRI, the Forns index, and FibroIndex for $F \geqslant 2$, $F \geqslant 3$, and $F = 4$[33].

It is important to underline that almost all studies conducted so far have used biopsy as the gold standard for non-invasive methods. Most recently, Poynard *et al*[34] assessed the accuracy of FT, liver stiffness, and biopsy using methods without the reference method in 1289 HCV patients and 604 healthy volunteers. In this study, four different tests (FT, liver stiffness measurement, ALT, and biopsy) were applied in all patients, and each test produced a dichotomous test result (*e.g.*, the test was either positive or negative). None of these tests was error-free. Moreover, the inclusion of a control group without any risk factor for chronic liver disease, consequently having a very low risk of advanced fibrosis, permitted assessment of the effectiveness of the fibrosis tests in screening programs. Statistical analysis was performed using the latent class model with random effects. This method permits testing of the accuracy of diagnostic tests when the results of a reference method are missing or not error-free (*e.g.*, liver biopsy). This statistical model without a reference standard validated the accuracy of FT and FibroScan in the detection of severe fibrosis and cirrhosis in HCV patients. Crisan *et al*[35] determined the accuracy of TE and non-invasive biological tests such as APRI, HAPRI (an algorithm that combines hyaluronic acid and the prothrombin index), Forns, Lok, and Bonacini scores to prospectively evaluate the stage of hepatic fibrosis in chronic HCV treated *vs* non-treated patients. They found a significant decrease in liver stiffness in sustained virological responders (SVR) and in non-responders (NR) that gained biological response (patients who had normal ALT levels 24 wk after the end of antiviral therapy).

In a recent prospective study, Poynard *et al*[36] estimated the impact of sustained virological response on the dynamics of fibrosis. In the study, in which 933 patients with both repeated FT and TE were prospectively evaluated, the authors showed that SVR had significantly higher fibrosis regression rates compared with non-treated patients. However, 10 years after virological cure, only 49% of SVR with severe fibrosis at baseline had a significant improvement, and the net reduction of cirrhosis prevalence was only 5%. Liver cancer occurred in 4.6% of SVR and in 5.6% of NR.

In summary, these studies demonstrated that a combination of non-invasive tests may improve accuracy, particularly when they include TE and FT.

Direct markers of liver fibrosis

Several researches have analysed the diagnostic values of direct markers of hepatic fibrosis, *i.e.*, the serum levels of molecules diffused into the systemic circulation, that are related to the metabolism of the extracellular matrix. Some of these molecules reflect matrix accumulation (fibrogenesis), whereas others are more related to its degradation (fibrolysis). Serum levels of different fibrotic markers have been studied: type Ⅳ collagen, hyaluronic acid, laminin, collagen VI, transforming growth factor beta 1 (TGF β1) and metalloproteinases or tissue inhibitors of metalloproteinases (TIMPs), YKL-40. Many signalling pathways are involved in myofibroblast activation, such as TGF β1. One activated, TGF β1 signals induce collagen production[37]. Quiescent hepatic stellate cells are induced by TGF β1 to transdifferentiate into myofibroblasts that secrete extracellular matrix. The major limitation of direct serum markers is that extracellular matrix serum levels are influenced not only by fibrogenesis but also by the production in other organs and by liver inflammation[38].

It has been suggested that an association of different serum markers may enhance sensitivity and specificity for the diagnosis of hepatic fibrosis stage. Among others, YKL-40 has been proposed as a non-invasive serum marker of liver fibrosis. Serum levels of YKL-40, a growth factor for fibroblasts and endothelial cells[39], have been evaluated in CHC[38]. Saitou *et al*[40] determined the concentrations of type Ⅳ collagen, procollagen Ⅲ propeptide, hyaluronic acid, and YKL-40 before and after interferon treatment. They found that YKL-40 was most useful for monitoring liver fibrosis and for discriminating advanced from mild hepatic fibrosis. It predicted severe fibrosis with an 80% positive predictive value[40]. Berres *et al*[41] analysed promoter polymorphisms of the *CHI3L1* gene, encoding for the YKL-40 protein. In this study, CHC patients underwent percutaneous liver biopsy prior to antiviral therapy. They showed that a homozygous minor allele (classified as GG polymorphism) is protected from severe fibrosis and influences the serum levels of YKL-40. In a subsequent study, Fontana *et al*[42] determined YKL-40 polymorphisms in patients enrolled in the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial. The minor allele (classified as T polymorphism) in these HALT-C Trial patients was similar to that found in other patient populations by Berres *et al*[41], but, contrary to the data of Berres *et al*[41], Fontana *et al*[42] showed that YKL-40 promoter polymorphisms were not associated with disease progression and the evolvement of advanced liver fibrosis.

The enhanced liver fibrosis (ELF) score test, derived from an algorithm combining three fibrosis

markers (hyaluronic acid, amino-terminal propeptide of type Ⅲ collagen, and tissue inhibitor of matrix-metaloproteinase-1) and age, was analysed retrospectively in patients with chronic liver disease such as HCV, hepatitis B virus infection, and primary biliary cirrhosis who underwent liver biopsy, TE, and FT using histology as the reference method[43]. The results of this study showed that the three non-invasive methods were comparable in diagnostic accuracy for the detection of significant fibrosis and cirrhosis. Lichtinghagen *et al*[44] measured ELF scores in 400 healthy controls and 79 CHC patients. Analysis of ELF scores in healthy subjects revealed that afternoon values were slightly higher than morning values, possibly as a result of food intake. All of the aforementioned serum markers were capable to distinguish between the absence of fibrosis and severe fibrosis/cirrhosis, but a so-called "grey area" still existed in which liver biopsy was needed for correct staging. For this reason, Gangadharan *et al*[45] investigated additional candidate serum fibrosis markers and identified 20 molecules of potential interest. Plasma from healthy controls and patients with cirrhosis was compared by proteomics using two-dimensional gel electrophoresis. These molecules were characterised as fibrosis markers by Western blotting using plasma from patients across all Ishak fibrosis scores. The same plasma samples were blotted for the protein markers present in the FT, ELF, Hepascore, and Fibrospect, and they were compared to new fibrosis markers. This technique identified proteins whose levels were increased or decreased in hepatic cirrhosis. The serum levels of five of these molecules (lipid transfer inhibitor protein, complement C3d, corticosteroid-binding globulin, apolipoprotein J, and apolipoprotein L1) changed with the Ishak fibrosis stage more consistently compared to the other markers used, such as FT, ELF, Hepascore, and FibroSpect.

Zarski *et al*[46] sought to establish the best algorithms in terms of accuracy for the diagnosis of significant fibrosis in HCV patients using Fibrometer, FT, Hepascore, APRI, ELFG, MP3, Forns, hyaluronic acid, collagen Ⅳ, and, when possible, FibroScan. In this study, the best screening strategies for the diagnosis of significant fibrosis were Fibrometer, FT, or Hepascore in combination with the ELFG score. The performance of the combination of FibroScan and ELFG was similar to those combining two blood tests. The number of avoided liver biopsies ranged from 50% to 55%. In terms of cost-benefit analysis, they found that the lowest cost strategies included ELFG. FibroScan results were also cost-effective, but only when the use of FibroScan was intensive, enough to accommodate for its price of acquisition.

Martinez *et al*[47] validated ELF, FIB-4 index, APRI, and Forns scores in 340 patients who underwent the antiviral therapy with weekly PEG-IFN plus ribavirin for 24 or 48 wk, according to the HCV genotype. A significant decrease in all the components of the ELF score was observed in SVR, whereas HA and PⅢNP remained unchanged and the TIMP-1 increased in non-sustained responders. ELF scores persisted unchanged or increased in non-SVR. The Forns score, APRI, and FIB-4 index decreased significantly in SVR. This normalisation was mainly due to their respective components (particularly AST and ALT).

Fontana *et al*[48] examining 462 prior NR to PEG-IFN and ribavirin enrolled in the randomised phase of the HALT-C trial, studied the association between a panel of serum markers such us hyaluronic acid, N-terminal peptide of procollagen type 3, TIMP-1, YKL-40, and histological stage of liver disease after two and four years of treatment. Values derived from an algorithm containing baseline total bilirubin, albumin, INR, and YKL-40 levels were strongly associated with the likelihood of clinical disease progression. All of these markers significantly decreased at week 72 compared with pre-treatment baseline levels in SVR patients following 48 wk of full-dose PEG-IFN and ribavirin treatment[49]. Taken together, these studies suggest that direct markers of liver fibrosis are useful in predicting fibrogenesis.

ULTRASOUND-BASED TRANSIENT ELASTOGRAPHY

In the last decade, elastographic techniques have emerged as an important field of research complementary to ultrasound. Elastography refers to a variety of techniques that are capable of characterising the response and mechanical properties of tissues using non-invasive methods. In previous studies (summarized in Ref.[13]), hepatic elastography has proven to be a valid method on one side for detecting severe fibrosis or cirrhosis and for excluding significant fibrosis. It has been suggested that it may be used to decide clinical priorities and reduce the number of liver biopsies (Table 2)[50-56].

Ferraioli *et al*[57] compared the results of liver stiffness obtained in 246 patients (79.3% HCV) with the results considered in a recent meta-analysis by Tsochatzis *et al*[58]. The cut-off of the single-centre study by Ferraioli *et al*[57] was comparable to that obtained in the meta-analysis that included 40 studies. In this meta-analysis, the cut-off values were 7.6 (range 5.1-10.1), 10.9 (8.0-15.4), and 15.3 (11.9-26.5) kPa for F = 2, 3 and 4, respectively, in chronic HCV. It is important to define these because the cut-off values are often used improperly by matching a lower cut-off to severe fibrosis and thus justifying the use of triple therapy that would otherwise be inappropriate and without any advantage according to the cost/benefit ratio. Crisan *et al*[35] prospectively assessed treated *vs* untreated liver fibrosis for 24 wk after treatment in 224 HCV patients using biological scores (APRI, HAPRI, Forns, Bonacini, and Lok) and TE. Fibrosis decreased significantly in

Table 2 Cut-off values of stiffness in relation to METAVIR score based on the prevalence of disease in studies conducted before 2009

Authors	Aetiology	Cut off values of stiffness			PPV/NPV (%)
		⩾ F2	⩾ F3	⩾ F4	
Castera *et al*[50]	HCV	7.1			95/48
			9.5		87/81
				12.5	77/95
Ziol *et al*[51]					
	HCV	8.8			88/56
			9.6		71/93
				14.6	78/97
Carrion *et al*[52]					
	HCV post-LT	8.5			79/92
				12.5	50/100
Foucher *et al*[53]					
	CLD	7.2			90/52
			12.5		90/80
				17.6	91/92
Gomez-Dominguez *et al*[54]					
	CLD	4.0			88/50
			11.0		78/76
				16.0	80/98
Kim *et al*[55]					
	CLD	7.3			96/50
			8.8		78/95
				15.0	33/97
Arena *et al*[56]					
	HCV	7.8			83/79
			10.8		89/95
				14.8	73/98

CLD: Chronic liver disease; post-LT: After liver transplantation; HCV: Hepatitis C virus; PPV: Positive predictive value; NPV: Negative predictive value.

sustained virological response patients. Isgro *et al*[59] showed that the histological measurement of collagene proportionate area by quantitative image analysis was better related to liver stiffness than the Ishak stage. A previous study[60] determined the relationship between computer-assisted digital image analysis, hepatic venous pressure gradient, and Ishak score. The quantity of collagen in the liver was expressed as the percentage area stained with specific collagen staining in histological liver sections. Previous studies (listed in Table 1) have suggested that stiffness values can be influenced by the degree of necroinflammation, particularly in the absence of severe fibrosis. In contrast, the presence of mild steatosis does not seem to affect stiffness values. Moreover, TE is characterised by high intra- and inter-observer repeatability. However, meals can affect the reliability of stiffness measurement and, subsequently, in the diagnosis of fibrosis stage in HCV infected patients[61,62]. Arena *et al*[62] suggested that a fasting period of 120 min is warranted before liver stiffness measurements. In this study, hepatic stiffness was measured in 125 consecutive HCV infected patients in different stages of fibrotic evolution. Stiffness was measured at different time points after a standardised liquid meal. A peak in the increase of stiffness values was observed between 15-45 min after the start of the meal, with a return to pre-meal baseline values within 120 min in all patients. The delta peak post-meal of stiffness progressively increased for increasing stages of fibrosis, and it was greatest in cirrhotic patients. However, the probability of identifying the METAVIR stage of fibrosis, the Child-Pugh class, or the presence/absence of oesophageal varices with the increase in delta post-meal stiffness values was lower than that obtained with the basal values. Recently, some studies[63-68] have estimated the usefulness of TE for the evaluation of longitudinal changes in hepatic fibrosis in HCV infected patients undergoing antiviral treatment. The results of these researches showed that this method can also detect longitudinal variation in liver fibrosis. Moreover, Stasi *et al*[5] showed that hepatic stiffness, although not representative of hepatic fibrosis, may also have a negative predictive value. In this study[5], patients with stiffness values greater than 12 kPa had a significantly lower response to antiviral therapy, suggesting that the hepatic stiffness values could be considered together with other predictors of response when considering antiviral therapy[5,68,69], in whom antiviral therapy was contraindicated or not tolerated. Stasi *et al*[70] showed that, in patients with HCV-related mixed cryoglobulinemia syndrome undergoing rituximab therapy, a reduction in hepatic stiffness was associated with B-cell depletion, thus reinforcing the concept that stiffness values may be influenced by liver infiltrates and liver necro-inflammation.

Recently, other liver elasticity-based imaging methods have been introduced in clinical practice:

acoustic radiation force impulse imaging (ARFI) and 2D-shear wave elastography (2D-SWE). pSWE/ARFI implies the mechanical excitation of tissue using short-duration acoustic pulses that propagate shear waves and produce localised, μ-scale displacements in tissue[71]. 2D-SWE is based on the association of a radiation force determined in tissues by focused ultrasonic beams and a sequence of ultrasound imaging able to capture in real time the transient propagation of resulting shear waves[72].

An international multicentre study[73] compared the reliability of ARFI elastography to liver biopsy and TE. The results of this study showed that TE performed better in predicting all stages of fibrosis ($F \geqslant 1$) and cirrhosis, while the performance of ARFI and TE is similar for the detection of significant ($F \geqslant 2$) and severe fibrosis ($F \geqslant 3$).

The recent Clinical Practice Guidelines (CPGs)[74] developed by a panel of experts chosen by the European Association for the Study of the Liver and the Asociacion Latinoamericana para el Estudio del Higado Governing Boards, considered the pSWE/ARFI or 2D-SWE alternative techniques, for the staging of fibrosis. Ferraioli *et al*[75] outlined that these techniques can be utilised to evaluate the severity of hepatic fibrosis in patients with chronic viral hepatitis, particularly with HCV. Nonetheless, the evidence that is available is still limited, and quality criteria for correct interpretation are not yet well defined.

Poynard *et al*[34] assessed the performance of a new test, the Elasto-FT® (EFT), that combines FT® and liver stiffness measurement because they are the most well-validated methods for the non-invasive evaluation of fibrosis in HCV patients. The performance of EFT for the detection of cirrhosis is higher than that of FT or FibroScan® alone, but no improvement in performance was observed for the diagnosis of advanced fibrosis.

MAGNETIC RESONANCE ELASTOGRAPHY

It is well established that "conventional" MR imaging is not accurate in the diagnosis of the pre-cirrhotic stages of liver fibrosis and early cirrhosis. In MR images, hepatic parenchyma appears to be normal. However, the use of contrast agents may improve the detection of fibrosis[76]. In particular, double contrast-enhanced MR imaging generates high image contrast between the low-signal-intensity fibrotic reticulations. The main disadvantage of this method is the high cost and the need to use two contrasts[76].

MR elastography is a new method that quantifies the liver stiffness with a sufficient reproducibility and high diagnostic accuracy for staging liver fibrosis[77,78]. Ichikawa *et al*[79] compared the ability of MR elastography and serum fibrosis markers to discriminate each stage of fibrosis. They found that the mean liver stiffness value increased as the liver fibrosis stage progressed. In comparison with TE, the advantage of MR elastography is that this technique visualises the whole liver and does not require a precise acoustic window. Its main limitations are high costs and the interference of potential confounding factors such us hepatic inflammation[80], hepatic vascular congestion, cholestasis, and portal hypertension[76]. Although steatosis itself might not affect stiffness measurements, fat deposition can cause inflammation, with a consequent increase in hepatic stiffness[80].

In addition, as it is for transhepatic elastometry, a meal can affect the accuracy of stiffness measurements.

WHERE WE ARE

The results of several studies show that non-invasive methods are becoming increasingly precise in predicting non-significant and advanced liver fibrosis, reducing the need for liver biopsy in a relevant number of patients. However, when both serum markers and TE values fall, liver biopsy may be still needed. Recently, the guidelines on the management of HCV infected patients produced by the World Health Organization and addressed to healthcare providers in resource-limited settings (in low- and middle-income countries)[81] suggested that the APRI or FIB-4 tests could be utilised for the evaluation of liver fibrosis rather than other, more expensive non-invasive tests, such as elastography or FT. The FIB-4 index permitted the correct detection of severe fibrosis (METAVIR F3-F4), in particular an FIB-4 index higher than 3.25 is able to confirm the presence of fibrosis, with a positive predictive value of 82.1%, and an FIB-4 index lower than 1.45 had a negative predictive value of 94.7% to exclude severe fibrosis (F3-F4)[25]. The staging of fibrosis is very important in resource-limited settings. In this case, it may be utilised to prioritise antiviral therapy for patients with more advanced disease. In many high-income countries, all HCV infected patients, who do not have a contraindication for treatment, are considered eligible for therapy. Among the techniques developed to assess liver fibrosis stage, TE has been the most widely evaluated. The main limits for its use include the high cost of the equipment and the need for regular recalibration and trained operators.

A public healthcare-based approach to ameliorate access to health care for HCV patients could result in improved medical care in many resource-limited settings.

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P- Reviewer: Gassler N, Lakatos PL **S- Editor**: Gong ZM
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ISSN 1007-9327
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