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TOPIC HIGHLIGHT

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Noninvasive diagnosis of cirrhosis: A review of different imaging modalities

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Abstract

Progressive hepatic fibrosis can lead to cirrhosis, so its early detection is fundamental. Staging fibrosis is also critical for prognosis and management. The gold standard for these aims is liver biopsy, but it has several drawbacks, as it is invasive, expensive, has poor acceptance, is prone to inter observer variability and sampling errors, has poor repeatability, and has a risk of complications and mortality. Therefore, non-invasive imaging tests have been developed. This review mainly focuses on the role of transient elastography, acoustic radiation force impulse imaging, and magnetic resonance-based methods for the noninvasive diagnosis of cirrhosis.

Key words: Liver; Cirrhosis; Elastography; Acoustic radiation force impulse imaging; Magnetic resonance elastography

Core tip: In order to overcome the well-known drawbacks of liver biopsy, different non-invasive imaging tests have been developed for diagnosing and staging liver fibrosis. At present, transient elastography and acoustic radiation force impulse imaging are the most widely used. Reviewing literature, it seems that acoustic radiation force impulse imaging, having the advantage of being included in ultrasound equipments, could provide higher reproducibility and successful measurements rate, with a more precise examination than transient elastography. Magnetic resonance-based methods, especially hepatospecific contrast medium uptake/excretion measurements and elastography, are promising but still not universally available tools.

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INTRODUCTION

Fibrosis is the common result of several chronic hepatic diseases that, if progressive, can lead to cirrhosis, which is developed by 20%-30% of patients. Since fibrosis can be reversible, its early detection is fundamental[1,2]. Staging is also needed, because it is critical for prognosis and management, especially for chronic viral hepatitis: antiviral therapy is recommended in chronic hepatitis B (CHB) with cirrhosis, while in chronic hepatitis C (CHC) the treatment may not be indicated with minimal or absent fibrosis[3,4]. Furthermore, the assessment of residual

fibrosis in CHC patients who achieved a sustained virological response to interferon is of strategic importance, for prognostication and to define a cost-effective surveillance, especially for patients with eradicated infection but ongoing complications[5]. Moreover, staging is needed for the treatment of CHC with protease inhibitors, which are effective but expensive[6]. Finally, staging is important in human immunodeficiency virus/hepatitis C virus co-infection, because of the more rapid progression and to the diminished response to therapy[7]. The gold standard for diagnosing and staging fibrosis is liver biopsy (LB), which gives information on presence and extent of fibrosis but also on other concomitant processes. Fibrosis is mainly staged with the METAVIR system, which comprises five stages: F0 (no fibrosis), F1 (portal fibrosis without septa: minimal fibrosis), F2 (portal fibrosis with few septa: moderate fibrosis or clinically significant fibrosis), F3 (septal fibrosis with many septa but no cirrhosis: severe fibrosis) and F4 (cirrhosis). LB has several drawbacks, as it is invasive, expensive, has poor acceptance, is prone to interobserver variability and sampling errors, has poor repeatability, and has a risk of severe complications of 0.57%, and a mortality rate of 0.009%-0.12%[8-10]. Therefore, non-invasive imaging tests for evaluation of liver fibrosis have been developed. This review focuses on the most widely used imaging methods and on possible future developments for the non-invasive diagnosis of cirrhosis, with particular emphasis on transient elastography, acoustic radiation force impulse imaging, and magnetic resonance (MR) elastography.

ELASTOGRAPHIC TECHNIQUES

This group comprises imaging techniques that observe tissue deformation after applying a force, that can be so slow that is considered "quasi-static" [strain elastography (SE) and strain-rate imaging (SRI)] or dynamic [acoustic radiation force impulse (ARFI), transient elastography (TE), point shear-wave elastography (pSWE), shear wave elastography (SWE)].

TE

Technical aspects

TE is a dynamic quantitative technique, which uses acoustic waves ("thumps"-50 Hz), generated by an external driver. Liver stiffness (LS) measurement is performed in the right lobe, with patient in dorsal decubitus, with the right arm above the head. A portion of parenchyma free of large vessels, > 6 cm thick, must be chosen; LS is measured at depth of 25-65 mm, in a 1 cm × 4 cm area. At least 10 valid measurements must be obtained, with a success rate, defined as the number of valid acquisitions divided by the attempts, > 60%, and a ratio of the interquartile range to the median of 10 measurements ⩽ 0.3. Liver elasticity is expressed in kilopascals (kPa).

Clinical applications, normal and pathological values

LS ranges from 2.5 kPa to 75 kPa; mean LS in normal adults is 5.81 ± 1.54 and 5.23 ± 1.59 kPa, respectively for men and women[11]. The main published meta-analyses have proved the reliability of TE and its usefulness (Table 1). Different cut-off values for different etiologies have been proposed for the diagnosis of cirrhosis: 12.5 kPa in CHC, 13.4 kPa in CHB, 10.3 kPa in non-alcoholic fatty liver disease (NAFLD), 22.4 kPa in alcoholic steatohepatitis (ASH), 17.3 kPa in primary biliary cirrhosis and primary sclerosant cirrhosis[12-16]. Liver biopsy is often not recommended in the NAFLD patients, because of its cost, the potential risk of complications and the absence of consensus regarding the histopathological criteria that firmly differentiate between the NAFLD entities; because of the remarkable increase in the prevalence of NAFLD, which represents the most common chronic liver disease in the general population and is expected to increase in future as a result of an ageing population, and the concomitant efforts in developing novel therapies, a non-invasive, simple and reproducible technique as TE is needed in the clinical practice[17]. TE does not always provide a perfectly corresponding estimation of fibrosis stage; one of the known reasons for this is that LS is affected by other histological findings, as edema, steatosis, inflammation or necrosis. Acute or chronic inflammation, in fact, can produce higher LS, indicating the presence of falsely higher fibrosis stages[18]. Several studies have reported the usefulness of TE for longitudinal monitoring of antiviral treatment, mainly reporting a decrease in LS, which could indicate a regression of fibrosis. Particularly, Martinez *et al*[19] performed TE at baseline and at weeks 24, 48, and 72 in patients with CHC: LS significantly decreased in treated patients and remained stable in untreated patients. These results are not universally accepted; it must be kept in mind that both reduction in fibrosis and necroinflammation might contribute to the decrease of LS. For example, Wong *et al*[20] reported that the absolute change in LS poorly correlated with the modifications of fibrosis stage, and resolution of advanced fibrosis could only be assumed with significantly decreased liver stiffness to 5.0 kPa or less after treatment.

Pros and cons

TE is rapid and easy to perform and can be repeated over time. TE can assess a sample area about 100 times bigger than a biopsy sample; therefore it should be more representative. Despite this, with TE is impossible to be sure that the chosen area is free of parenchymal inhomogeneities, which could affect the measurement. The success rate of TE is dependent on operator expertise, as well as on other factors (age, width of the intercostal space, ascites, BMI, visceral fat). Sporea *et al*[21] reported a rate of reliable measurements of 81.6%, which is in line with Castera *et al*[22]. The obesity problem has been partially solved by the development of XL probe, increasing the success rate in obese patients from 45%-50% to about 75%[23,24]. As above mentioned, necroinflammation influences LS. D'Ambrosio *et al*[25] reported that 30% of patients with persistent F4 had LS values suggestive of a less severe disease, and this was explained by the

Table 1 Diagnostic performance of transient elastography for the diagnosis of cirrhosis in different chronic liver disease from different etiology, data from meta-analysis

Meta-analysis	No. of studies	Etiology	Cut-off (kPa)	Sensitivity	Specificity	AUROC
Bota *et al*[53]	13	Various	-	89%	87%	-
Shaheen *et al*[107]	4	HCV	12.5	86%	93%	0.95
Talwalkar *et al*[108]	9	Various	-	87%	91%	-
Friedrich-Rust *et al*[109]	50	Various	-	-	-	0.94
Tsochatzis *et al*[110]	40	HCV	15 ± 4.1	83%	89%	-
Adebajo *et al*[111]	5	HCV	-	98%	84%	-
Stebbing *et al*[112]	22	Various	15.08	84.45%	94.69%	-
Abd El Rihim *et al*[113]	23	Various	-	83.40%	92.40%	-
Chon *et al*[114]	18	HBV	11.7	84.60%	81.50%	0.929

AUROC: Area under receiver operating characteristic; HCV: Hepatitis C virus; HBV: Hepatitis B virus.

onset of liver remodelling and necroinflammation. Park *et al*[26] reported that 3 mo after acute exacerbation ALT levels decreased and stabilised, while LS required 3 more months for stabilisation: LS should be postponed for > 3 mo after stabilisation of ALT levels to restore the reliability. As patients with higher ALT levels tend to have higher LS, several authors suggested to use different cut-offs to adjust the inflammation-induced overestimation. In particular, Chan *et al*[27] proposed that for patients with normal ALT, a LS value > 12 kPa would indicate F4, while for patients with ALT 1-5-times > ULN, this value should be > 13.4 kPa. Kim *et al*[28] reported that the cut-off value for F4 was 10.1 kPa in patients with normal ALT, whereas it was 15.5 kPa in those with elevated ALT.

ARFI

Technical aspects

ARFI is a dynamic technique that uses ultrasound-induced radiation force impulses to obtain both qualitative measure of displacement, both quantitative measure of shear waves speed (ARFI quantification). It involves targeting a region of interest (ROI) of 5 mm × 10 mm, at maximum depth of 8 cm, chosen while performing B-mode imaging. The ultrasound probe produces short-duration acoustic "push" pulses (262 ms), with a transmission frequency of 2.67 MHz, which generate shear waves, propagating perpendicularly, tracked using ultrasound, thus obtaining the shear wave speed quantification in m/s. Patients should be supine, with the right arm in maximum abduction. Probe is placed parallel to the intercostal space. 5-10 measurements are performed in the right lobe, with the patient holding breath gently. Several technical aspects must be taken into account. The influence of deep inspiration on measurement is still debated, as Karlas *et al*[29] reported that it could increases values by an average of 13%, while Horster *et al*[30] and Goertz *et al*[31] did not report differences. Eiler *et al*[32] evaluated 132 healthy children, reporting a shear waves speed (SWS) of 1.16 ± 0.14 m/s, stating that neither age or depth had influence on results. This is in contrast with the study by Lee *et al*[33], who evaluated the age-related modifications in 202 healthy children, founding a mean SWS of 1.14 ± 0.020 < 5 years and of 1.08 ± 0.023 > 10 years. Eiler's *et al*[32] study is in contrast also with other two studies: Sporea *et al*[34], which found a poor correlation between subcapsularly-measured values and fibrosis; and Chang *et al*[35], which found that the measurement depth with lower variability was 4 cm. Moreover, also D'Onofrio *et al*[36] reported that higher values could be obtained in the superficial right lobe: the absence of this aspect in children is probably due to a lower age-related fibrosis in the superficial parenchyma. In the study of Eilers *et al*[32], an interlobar difference was found, with lower values in the right lobe. This difference has been reported also by other authors, reporting both higher both lower values in the left lobe[33-39]. Rifai *et al*[40], instead, reported that ARFI values of both lobes were comparable; in addiction, Goertz *et al*[41] reported a lower number of faulty measurements in right posterior segments. There is no definite explanation for this: probably the presence of heart-beating artifacts in the left lobe and the direct compression with the probe during the examination can be issues; these aspects, however, should not to be considered as a limitation of ARFI, since they can also reflect real interlobar differences and heterogeneity in disease progression. Regarding this, it was demonstrated that biopsies taken in both lobes during laparoscopy presented differences in fibrosis stage in up to 33% of cases[42]. However, since the reference standard for the assessment of fibrosis is LB of the right lobe, it is recommend to measure LS in this lobe[43]; an approach with bilateral multiple measurements is worthy of further investigation, as it may lead to interesting diagnostic results. ARFI must be performed in fasting conditions: Popescu *et al*[44] reported that mean LS increased significantly 1 h after food intake, but 3 h after the meal the difference was no longer significant.

Clinical applications, normal and pathological values

It is still difficult to definitely determine the real value of ARFI for the early diagnosis of fibrosis; it is also difficult to compare the large amount of published papers on this issue. It must be noted that the newest release of the Siemens ARFI system is based on two acoustic pulses, and the maximum depth nowadays achievable is 8 cm, so the more recent published data should be more indicative of what can be obtainable. Moreover, high variability in normal values has been reported; for example, in both

Table 2 Diagnostic performance of acoustic radiation force impulse for the diagnosis of cirrhosis in different chronic liver disease from different etiology, data from main published meta-analysis

Meta-analysis	No. of studies	Etiology	Cut-off (m/s)	Sensitivity	Specificity	AUROC
Bota *et al*[53]	13	Various	-	87%	87%	-
Friedrich-Rust *et al*[57]	9	Various	1.80	-	-	0.93
Nierhoff *et al*[115]	36	Various	1.87	-	-	0.91

AUROC: Area under receiver operating characteristic.

the preliminary studies from the Verona group, D'Onofrio *et al*[36] and Gallotti *et al*[45] reported a mean value of about 1.5 m/s: these results should be considered a outliers, if compared to other studies, but however possible, as it has been also reported by other authors[46]. The main published meta-analyses suggest that ARFI is a reliable method for the diagnosis of cirrhosis (Table 2). Almost all published studies report an increase in SWS with the increase of fibrosis, despite there is a wide overlap between consecutive stages; moreover, mean values indicating cirrhosis have a wide range, while cut-offs have a narrower range. For these reasons, what it seems most important, more than the accurate staging, is to give the correct task to this new technique, as previously stated by D'Onofrio *et al*[47]: the correct use of ARFI must be based on the possibility of this technique to detect significant modifications of LS, related to the development of a significant amount of fibrosis. In fact, as for TE, it seems unreal that this technique could identify very small and localized amount of fibrosis, as it happens in F1, or to differentiate between early stages; it seems to be more "real", technically feasible and clinically useful the differentiation between the two extremes of the grading scale, i.e. the distinction between non-cirrhotics and cirrhotics. For example, in the study by Fierbinteanu-Braticevici *et al*[48] there is a wide overlap between F0-F1 and F2 stages, and the increase in SWS is more significant between F2 and F3 than between F1 and F2, and this is consistent with the more important increase in fibrosis deposit between stages F2 and F3 than between F1 and F2. In the international multicentric study by Sporea *et al*[49], the chosen cut-offs were really strict: F = 1 > 1.19 m/s; F = 2 > 1.33 m/s; F = 3 > 1.43 m/s; F = 4 > 1.55 m/s. The difference between non-cirrhotics and cirrhotics was just 0.12 m/s. In order to make ARFI a useful tool, the chosen cut-off values must not be too strict, but they should be adapted in relation to clinical aspects, imaging findings and technical settings, in order to avoid an overestimation of pathology and to identify inconsistent diseases. This is a further evidence of the necessity of placing ARFI in the right setting, in a protocol that includes an ultrasound (US) evaluation of the liver and a clinical evaluation of the patient, rather than use its results alone.

As above mentioned, liver biopsy is often not recommended in patients with non-alcoholic fatty liver disease (NAFLD), because of its cost, the potential risk of complications and the absence of consensus regarding the histopathological criteria that firmly differentiate between the NAFLD entities. ARFI can represent a useful tool in diagnosing the onset of fibrosis in NAFLD and non-alcoholic steatohepatitis (NASH), in which B-mode evaluation can be inaccurate; Fierbinteanu-Braticevici *et al*[50] reported a high diagnostic performance in predicting cirrhosis in these patients (AUROC = 0.984). Most studies report at least equivalence between TE and ARFI: Friedrich-Rust *et al*[51] (AUROCs of 0.91 and 0.91 for cirrhosis), Piscaglia *et al*[37] (high correlation, $r = 0.891$), Vermehren *et al*[52] ($r = 0.75$, $P < 0.001$), Bota *et al*[53] (mean difference in rDOR = 0.12), Cassinotto *et al*[54] (no significant difference). Some other studies reported a superiority of ARFI: in the 2013 multicentric study by Friedrich-Rust *et al*[55], the diagnostic accuracy for cirrhosis of ARFI and TE was 0.97 and 0.93; similarly, Rizzo has shown a superiority of ARFI *vs* TE regardless of fibrosis stage[56]. Other studies reported a slightly lower diagnostic accuracy of ARFI: the Friedrich-Rust *et al*[57] pooled meta-analysis reported a comparable accuracy of ARFI and TE for the diagnosis of significant and severe fibrosis in 2012, with a trend to be inferior for the diagnosis of cirrhosis; also in the 2012 international multicentric study by Sporea *et al*[49] TE was better than ARFI for predicting cirrhosis.

Pros and cons

A first advantage of ARFI is its integration into conventional US equipment, as opposed to TE: this enables the preliminary evaluation of the whole liver, seeking for signs of cirrhosis and for focal lesions. Then, ARFI is US-guided, so it should be more reliable than TE, for the possibility to position the ROI in an area free of vessels, lesions, biliary ducts or other inhomogeneities. Moreover, ARFI is easy, rapid, and painless; results are immediately available; intra-operator and inter-operator correlation is good[58]. Several studies reported higher rates of valid measurements in comparison to TE: Crespo *et al*[59] reported that ARFI was successfully performed in its whole cohort, while TE failed in 11% of patients; Rifai *et al*[40] reported that ARFI was feasible in all patients, while TE gave invalid results in 34% of patients. Then, ARFI can be performed in patients with ascites or in obese patients. Some limits of ARFI are that the elasticity measurement cannot be performed a posteriori; the ROI has a predetermined and not-changeable size. The influence of necroinflammation on measurements is a debated issue, as it initially appeared poorly relevant. However, a multicentric study[60] showed that, for the same fibrosis degree, the threshold was slightly lower for patients with normal ALT and higher for those with altered ALT; this

study concluded that necroinflammation partially affects ARFI, but with lower extent than TE. The influence of steatosis is another debated issue: Guzman-Aroca *et al*[61] reported that ARFI was not influenced by the severity of steatosis; Marginean *et al*[39] found that SWS in patients with steatosis was statistically higher compared to healthy controls. Righi *et al*[62] reported the influence of chronic autoimmune diseases (primary biliary cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis, overlap syndromes) on ARFI: SWS was significantly higher.

SWE

SWE is a dynamic technique, which does not require manual compression, similar to ARFI; it provides a quantitative measure of SWS using ultrasound-induced radiation forces to create a Mach cone. SWS is calculated as a colorimetric elastographic map, showing quantitative tissue stiffness, expressed as kilopascal. Few and controversial papers focus on the application of SWE in chronic liver diseases. In particular, Leung *et al*[63] reported that the AUROC of SWE and TE was respectively 0.98 and 0.92 for F4; SWE had significantly higher accuracy than TE in all stages and a higher successful rate. Poynard *et al*[64] reported that the performance of SWE for staging was lower than those of TE. Ferraioli *et al*[65] reported an AUROC of 0.98 for SWE and 0.96 for TE when comparing F0-F3 *vs* F4.

REAL-TIME STRAIN ELASTOGRAPHY

It is based both on strains and on shear waves; the stress is manually induced or by internal body movements. Qualitative maps of the strain are produced, in which colors range from red for soft components to blue for hard components. LS evaluation can be either qualitative or semi-quantitative, by analyzing strain histograms and distribution pattern of the pixels in the ROIs[66]. Different quantitative assessment methods as elastic ratio or liver fibrosis index were proposed by Koizumi *et al*[67] and Tomeno *et al*[68]. Real-time strain elastography (RTE) has several advantages over TE, as it allows the evaluation of LS while performing the US exam. RTE does not seem to suffer from breathing artifacts, nor from ascites, steatosis, BMI, or skin thickness[69]. Some studies reported the utility of RTE to evaluate liver stiffness, but with controversial results[67-72].

CONTRAST-ENHANCED ULTRASOUND

Very few studies have tested contrast-enhanced ultrasound (CEUS) for fibrosis assessment. Orlacchio *et al*[73] used time intensity curve analysis and found an AUROC of 0.88 for the distinction between F0-2 *vs* F3-4. Sugimoto *et al*[74] proposed a subjective assessment of CEUS images to identify morphologic changes of portal vein branches, reporting AUROCs of 0.96 for F1 *vs* F2-4 distinction, 0.97 for F1-2 *vs* F3-4, and 0.91 for F1-3 *vs* F4.

PERFUSION COMPUTED TOMOGRAPHY

Few studies have been performed on perfusion computed tomography applied to fibrosis evaluation; Ronot *et al*[75] found that mean transit time could differentiate F1 from F2-3 with a sensitivity of 0.71 and a specificity of 0.65. Motosugi *et al*[76] reported that portal venous perfusion in cirrhotics was significantly lower than in patients without cirrhosis. Kanda *et al*[77] reported that mean hepatic arterial perfusion and arterial perfusion fraction were significantly higher in cirrhotics than in healthy controls.

MR

Several MR-based techniques can be used to evaluate cirrhosis. Regarding unenhanced MR, Banerjee *et al*[78] reported that T1 mapping strongly correlated with fibrosis degree, with AUROC of 0.94; Hshiao *et al*[79] reported that standard deviation, mean, and entropy of pixel intensity in selected ROIs of dynamically grey-level scaled T2-weighted images were significantly smaller in patients with cirrhosis. Balassy *et al*[80] studied the modifications induced by fibrosis in susceptibility-weighted images and found that liver-to-muscle signal intensity (SI) ratio decreased in parallel with the increase of fibrosis and performed well in grading fibrosis (AUROC = 0.93 for F4). Regarding contrast-enhanced MR, especially with gadolinium-EOB-DTPA, a reduced SI in patients with cirrhosis is mostly reported. Particularly, Feier *et al*[81] found that relative enhancement values correlated strongly with fibrosis stage, with an AUC of 0.83 for > F4; Norén *et al*[82] found that liver-to-spleen contrast ratios at 10 and at 20 min and contrast uptake rate had AUROCs values of respectively 0.80, 0.78, and 0.71 with regard to severe *vs* mild fibrosis; Verloh *et al*[83] found that the mean relative enhancement in patients with Child-Pugh Score A cirrhosis had significant increase between arterial, late arterial, portal and hepato-biliary phases, while for Child-Pugh B+C cirrhosis, relative enhancement increased until portal phase and was significantly reduced in C cirrhosis during hepatobiliary phase; Nojiri *et al*[84] found that SI at 25 min could discriminate F = 0-3 *vs* F = 4, with AUROC of 0.87; Goshima *et al*[85] reported that sensitivity, specificity, and AUROC demonstrated by linear regression formula generated by volumetric ratio and contrast enhancement index in predicting fibrous scores were 91%, 100% and 97% for F4. Kim *et al*[86] reported that the relative enhancement [(hepatocyte phase SI - precontrast SI)/pre-contrast SI] of patients with Child-Pugh cirrhosis was significantly higher than that of patients with Child-Pugh B or C cirrhosis. Few studies have been performed on perfusion MRI. Nilsson *et al*[87] quantitatively assessed hepatic uptake of gadolinium in the whole liver as well as on a segmental level, finding a larger parenchymal liver volume, lower hepatocyte function and more inhomogeneous distribution of function in cirrhotics. Hagiwara *et al*[88] reported that the most discriminating perfusion parameter to differentiate F0-2 *vs* F 3-4 was

distribution volume (AUROC = 0.82, sensitivity = 0.77, specificity = 0.79). Diffusion-weighted imaging (DWI) uses the diffusion properties of water molecules in biological tissues; the microscopic movement of water molecules in biological tissues can be measured by apparent diffusion coefficient (ADC) values derived from DWI. Fibrosis should modify this movement, and this has been proved by several studies: Cece *et al*[89] found a significant difference between patients and controls and between different METAVIR stages in respect of liver mean ADC values. DWI images analysis could be also performed directly evaluating the SI of DWI images: Tosun *et al*[90] reported that the SI of cirrhotic liver in b = 1000 images was significantly higher than those of the normal volunteers. Despite these encouraging results, the correlation between ADC values of different diffusion b values and the influence of necroinflammation have not been definitely determined; for example, Onur *et al*[91] found that mean ADC values of CHC patients were significantly lower than mean ADC values of the control group at b = 100 and b = 600 gradients, while no significant difference was found at b = 1000 gradient; moreover, no significant correlation was found between ADC values and histopathologic scores of CHC; Bulow *et al*[92] stated that ADC values can be confounded by fat and iron. Finally, the Wang *et al*[93] reported that MRE outperformed DWI: the AUROC for DWI was 0.86 for F0 *vs* F1-4, 0.83 for F0-1 *vs* F2-4, and 0.86 for F0-2 *vs* F3-4, all significantly lower than the equivalent AUROCs for MRE. Diffusion tensor imaging (DTI) is an evolution of DWI, which uses additional gradients to detect the degree of diffusion in multiple dimensions. Tosun *et al*[90] reported that ADCs reconstructed from conventional DWI and DTI of the patients were significantly lower than those of the normal volunteers; despite this, DWI performed better than DTI for the diagnosis of fibrosis and inflammation. MR spectroscopy has been poorly used in the assessment of fibrosis. Some authors found that 31P-MR spectroscopy measurements correlate with the fibrosis stage whereas others found no correlation[94-99].

MR ELASTOGRAPHY

Technical aspects

MR elastography (MRE) provides a qualitative and quantitative imaging of LS by measuring acoustic shear waves progression. It uses vibrations produced by an external driver; the shear modulus of tissues can be then assessed using a specific MRI sequence. The resulting data are processed to generate quantitative maps (elastograms), displaying LS. The external device is triggered and synchronized with the MR pulse sequence. Different driving mechanisms have been developed, as electromechanical drivers, piezoelectric stack drivers, focused-ultrasound-based radiation force systems. Different pulse sequences can be used.

Clinical applications, normal and pathologic values

Although not as widely available as TE or ARFI, many studies confirm the usefulness of MRE in fibrosis detection. Yin *et al*[100] reported that a cut-off of 2.93 kPa is optimal for distinguishing healthy livers from fibrotic ones (sensitivity = 98%, specificity = 99%); Kim *et al*[101] reported that the best cut-off for advanced fibrosis was 4.15 kPa (AUROC = 0.954, sensitivity = 0.85, specificity = 0.929). Ichikawa *et al*[102] found that mean stiffness value increased with increasing stages of fibrosis: F0 = 2.10 ± 0.10 kPa; F1 = 2.42 ± 0.29 kPa; F2 = 3.16 ± 0.32 kPa; F3 = 4.21 ± 0.78 kPa; and F4 = 6.20 ± 1.08 kPa; the mean AUROC values for discriminating fibrosis stages were F1 = 0.984; F2 = 0.986; F3 = 0.973; and F4 = 0.976. Wang *et al*[93] reported an overall sensitivity, specificity, and AUROC of 0.83, 0.99, and 0.95 for the distinction between F0 and F1-4. Venkatesh *et al*[103] found that MRE was significantly more accurate than serum fibrosis markers for the detection of significant fibrosis (AUROC 0.99 *vs* 0.55-0.73) and cirrhosis (AUROC 0.98 *vs* 0.53-0.77); sensitivity, specificity, positive predictive and negative predictive values for MRE for significant fibrosis and cirrhosis were 97.4%, 100%, 100% and 96%, and 100%, 95.2%, 91.3% and 100%, respectively. Choi *et al*[104] found that LS values measured on MRE were more strongly correlated with fibrosis stage than with the contrast enhancement index (SIpost/SIpre, where SIpost and SIpre are, respectively, the liver-to-muscle signal intensity ratio on hepatobiliary phase images and on unenhanced images): MRE showed higher sensitivity and specificity for predicting F1 (91% and 87%), F2 (87% and 91%), F3 (80% and 89%), and F4 (81% and 85%) compared with contrast enhancement index.

Regarding NAFLD, Kim *et al*[101] reported that the best cutoff for advanced fibrosis was 4.15 kPa (AUROC = 0.954, sensitivity = 0.85, specificity = 0.929), concluding that MR elastography can be a useful diagnostic tool for detecting advanced fibrosis in NAFLD. Chen *et al*[105] reported that the mean hepatic stiffness for patients with simple steatosis (2.51 kPa) was lower than that for patients with inflammation but no fibrosis (3.24 kPa). The mean hepatic stiffness for patients with inflammation but no fibrosis was lower than that for patients with hepatic fibrosis (4.16 kPa). Liver stiffness had high accuracy (AUROC = 0.93) for discriminating patients with NASH from those with simple steatosis, with a sensitivity of 94% and a specificity 73% by using a threshold of 2.74 kPa; the author concluded that in patients with NAFLD, hepatic stiffness measurements with MR elastography can help identify individuals with steatohepatitis, even before the onset of fibrosis; NAFLD patients with inflammation but no fibrosis have greater liver stiffness than those with simple steatosis and lower mean stiffness than those with fibrosis.

Pros and cons

The main advantage of MRE is that the acquisition time is relatively short, so it could be included in standard protocols, providing a comprehensive evaluation of the liver. Second, it provides quantitative maps of tissue stiffness over large regions, so it is much less operator dependent

than ultrasound-based techniques, and can accurately reflect the distribution of fibrosis in the whole liver. Finally, MRE has been reported to be more accurate than any non-invasive alternative, with a success rate higher than TE; moreover, it can be suitable for patients with obesity or ascites[106]. Despite these pros, MRE remains poorly available, more expensive and not suitable for patients with contraindications to MR.

CONCLUSION

At present, TE and ARFI are the most widely used non-invasive methods for the diagnosis of cirrhosis. ARFI has the great advantage of being included in standard US equipment, so it can be used as a complement to the conventional B-mode whole-liver evaluation, with higher reproducibility and success rate, providing also a more precise examination than TE. MR-based methods, especially hepatospecific contrast medium uptake/excretion measurement and MRE, are promising tools; in the future, a wider availability of these techniques should be expected, in order to add these measurements to standard MRI protocols, to obtain a better comprehensive liver assessment.

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