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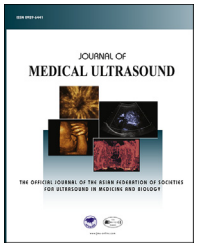

EDUCATIONAL FORUM

Ultrasound Evaluation of Liver Fibrosis

CME Credits

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Abstract Early diagnosis of liver fibrosis is an important factor affecting the efficacy of chronic hepatitis treatment. In the past, the diagnosis of liver fibrosis was dependent on a liver biopsy which has several shortcomings as sampling error, intra- or inter-observation variations and possible procedure-related complications. Ultrasound-based elastography, tissue elastography (TE) and acoustic radiation force impulse (ARFI) have been developed to assess liver fibrosis. Current clinical evidence indicates that TE and ARFI had high sensitivities and specificities to diagnosis from significant fibrosis to liver cirrhosis. TE and ARFI can not only assess liver fibrosis but can also be used to predict prognosis.In practical, ARFI can also be used on a regular basis to evaluate the degree of liver fibrosis for chronic hepatitis B and C, nonalcoholic fatty liver disease, and alcoholic liver disease.
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Introduction

Recent progress in the treatment of chronic hepatitis has provided a better understanding of the damage caused to the liver by long-term chronic hepatitis. In particular, liver fibrosis is considered to be an important factor affecting the efficacy of chronic hepatitis treatment. While it was previously thought that liver fibrosis was irreversible, recent evidence suggests that liver fibrosis is reversible if additional inflammation of the liver can be prevented.

In the past, the diagnosis of liver fibrosis was dependent on liver biopsy. The patient's resistance to liver biopsies has driven the ongoing development of various noninvasive methods of detecting liver fibrosis, such as through the use of ultrasound. In general, ultrasound examinations of the liver use B-mode real-time ultrasound (commonly known as "black-and-white ultrasound"), and this type of examination can aid in the understanding of morphological changes affecting the liver as a whole. In addition, ultrasound

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evaluation of the liver can detect liver calculus, liver cirrhosis, hepatic cysts, liver abscess, and liver nodules or tumors. However, assessment of the degree of liver fibrosis has gradually become the purview of the gastroenterologist. The METAVIR system, which is currently in widespread use, can assess the degree of liver fibrosis by assigning a grade. A grade of F2 or above indicates significant fibrosis, which implies that a patient's fibrosis has progressed and clinical treatment is urgent. A grade of F4 indicates advanced fibrosis or precirrhosis.

Liver stiffness depends on numerous factors, and fibrosis is an important factor influencing liver stiffness. However, additional factors that may affect liver stiffness include (1) acute or chronic hepatitis (inflammation), (2) blood volume, (3) liver perfusion, (4) fatty infiltration, (5) cholestasis, (6) heart failure/central venous pressure, and (7) whether the patient is fasting [1,2]. As a consequence, when performing an examination, it is important to exclude patients with cardiopulmonary diseases. At the same time, patients must fast before the examinations. At present, the consensus in Taiwan is that patients must fast for at least 4 hours prior to examination.

In the past, the assessment of liver fibrosis was dependent on a liver biopsy, which has the following shortcomings: (1) it is an invasive procedure, (2) rare but severe complications may occur (0.5%), and (3) there is sampling error and variation between the interpretations of different pathologists (intraobserver and interobserver variations). To overcome these problems, serology and imaging tools have been developed to assess liver fibrosis. In particular, ultrasound-based elastography can be used as an assessment tool, and tissue elastography (TE) and acoustic radiation force impulse (ARFI) are the ultrasonic methods most commonly used for this purpose.

Tissue elastography

TE involves the use of low-frequency (50 Hz), low-amplitude sound waves emitted by a probe to detect the transmission velocity at a depth of 2.5 cm to 6.5 cm beneath the skin. This information is used to determine the tissue elasticity at that depth. The results are expressed in kilopascal, and have a typical range from 2.5 kPa to 75 kPa. When this method is used to diagnose significant fibrosis (METAVIR system: F $\geq$ 2) or liver cirrhosis (F4), the cutoff values are >7 kPa in the case of significant fibrosis (F2 to F4) and >11 kPa to 14 kPa in the case of liver cirrhosis [3] (Figure 1). The optimal cutoff value used in the diagnosis of liver cirrhosis is apparently lower for chronic hepatitis B than chronic hepatitis C. According to the results of research involving Asian patients, suitable cutoff values for liver cirrhosis (in the diagnosis of chronic hepatitis B) are in the range from 9.0 kPa to 10 kPa [4].

TE is chiefly used in the assessment of patients with chronic hepatitis C and a small number of Asian patients with chronic hepatitis B. TE is generally used to diagnose significant fibrosis, and has a 70% sensitivity and 84% specificity for this purpose [5]. When used to diagnose liver cirrhosis, the sensitivity and specificity of TE are estimated at 87% and 91%, respectively, and TE also has excellent intraobserver and interobserver variations [6].

Liver stiffness can be used to evaluate chronic hepatitis prognosis. According to a meta-analysis of 17 studies involving chronic hepatitis patients, initial liver stiffness correlated with risk of liver function decompensation [relative risk (RR), 1.07; 95% confidence interval (CI), 1.03–1.11], incidence of liver cancer (RR, 1.11; 95% CI, 1.05–1.18), and death (RR, 1.22; 95% CI, 1.05–1.43) [7].

Apart from being noninvasive and compared with conventional liver biopsies, TE has the capability of evaluating more than 100 times the volume of tissue. In addition, studies are easily repeated and TE also has a high diagnostic reliability in cases of significant fibrosis. However, TE cannot make effective measurements in patients with excessive obesity, ascites, liver tumors, or excessively small intercostal spaces. In addition, the accuracy of TE in cases of no fibrosis (F0) and mild fibrosis (F1) awaits further improvement. Finally, in cases of abnormal liver function, TE may overestimate the degree of liver fibrosis [8]. The XL probe, which is currently available, may improve accuracy in the case of very obese patients.

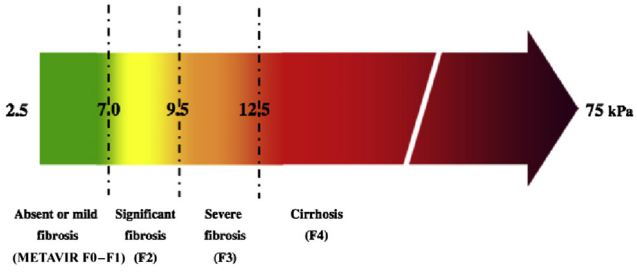

Figure 1 F4 cutoff values are >7 kPa in the case of significant fibrosis (F2 to F4) and >11 kPa to 14 kPa in the case of liver cirrhosis [3].

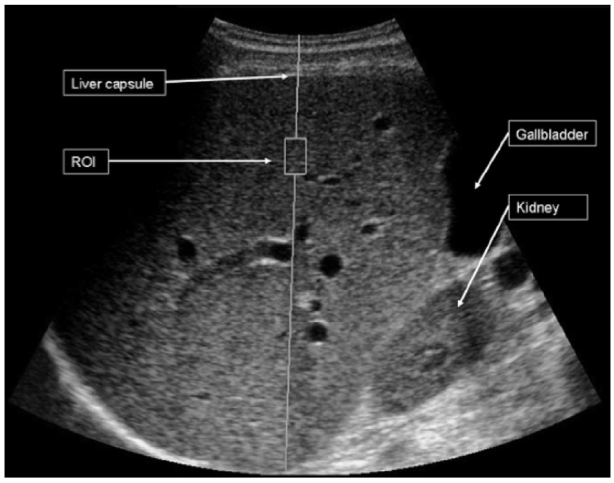

Figure 2 Acoustic radiation force impulse is used to measure shear waves; its major advantage over tissue elastography is that it can be used in conjunction with conventional ultrasound and shear wave velocity to gauge liver stiffness [9]. ROI = region of interest.

Acoustic radiation force impulse

ARFI is used to measure shear waves and its major advantage over TE is that it can be used in conjunction with conventional ultrasound and shear wave velocity to gauge liver stiffness (Figure 2) [9]. Besides, ARFI can make more efficient measures than TE in patients with ascites [10] and obesity [11]. ARFI measurements are guided using conventional gray-scale ultrasound; the same transducer is also used to generate shear waves, and the resulting information is transmitted in graphic form. ARFI has a sensitivity of approximately 75% when used to diagnose significant fibrosis, and a sensitivity of approximately 90% when used to diagnose liver cirrhosis, with a specificity of approximately 85% and 87%, respectively, for those two applications [10,12].

ARFI is performed in much the same manner as TE. Measurements are performed within the right intercostal space, and it is recommended that minimal pressure should be applied to the transducer during scanning. In the middle of the normal breathing cycle (when the patient avoids deep breaths followed by breath holds), the patient temporarily holds his or her breath, which enhances the repeatability of measurements. Liver stiffness measurements are recorded as the mean value within a region of interest, and the results are expressed as meter/second or converted to kilopascal (as the velocity of shear waves is directly proportional to the square root of tissue elasticity). ARFI has been applied to the diagnosis of chronic hepatitis B and C [13], nonalcoholic fatty liver disease [14], and alcoholic fibrosis [15]. A meta-analysis of 518 cases of chronic liver disease found that the optimal cutoff values for the diagnosis of liver fibrosis were (1) F $\geq$ 2: 1.34 m/s, sensitivity 79%, specificity 85%; (2) F $\geq$ 3: 1.55 m/s, sensitivity 86%, specificity 86%; and (3) F4: 1.80 m/s, sensitivity 92%, specificity 86% [10].

A meta-analysis of 1163 cases of chronic liver disease compared the accuracies of ARFI and TE. ARFI had a relatively low measurement failure rate compared with TE (2.1% vs. 6.6%) [12]. ARFI and TE had similar sensitivities of 74% and 78%, respectively, when used to diagnose significant fibrosis, and 87% and 89%, respectively, when used to diagnose liver cirrhosis. Specificity was also similar, at 83% and 84%, respectively, in the case of significant fibrosis, and 87% and 87%, respectively, in the case of liver cirrhosis [12].

The limitations of ARFI are similar to those of conventional ultrasound and include high operator dependence. In addition, ARFI has a narrow range of values (0.5—4.4 m/s), which may restrict optimal cutoff values. A further restriction involves the amount of necroinflammatory activity [16], which may lead to the overestimation of liver fibrosis.

Conclusion

Liver biopsy is an invasive procedure and has rare but severe complications. Because liver biopsies only sample a small portion of the liver parenchyma (1/50,000th), there is a relatively high risk of sampling error. To overcome these problems, alternative methods of assessing liver fibrosis, such as those based on ultrasound, have been developed in recent years. Current clinical evidence indicates that TE and ARFI are able to not only assess liver fibrosis, but can also be used to predict prognosis.

In practical, ARFI can also be used on a regular basis to evaluate the degree of liver fibrosis for chronic hepatitis B and C, nonalcoholic fatty liver disease, and alcoholic liver disease.

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