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## Endoscopic Ultrasound Real-Time Elastography in Liver Disease

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See “A Prospective Blinded Study of Endoscopic Ultrasound Elastography in Liver Disease: Towards a Virtual Biopsy” by Allison R. Schulman, Ming V. Lin, Anna Rutherford, et al., on page 181-185.

In patients with chronic liver disease (CLD), persistent inflammation and tissue injury lead to liver fibrosis. The degree of hepatic fibrosis should be evaluated accurately for therapeutic decision-making and estimation of prognosis.<sup>1</sup> Liver biopsy is still recommended as the gold standard for assessment of the degree of hepatic fibrosis<sup>2</sup> but it is not suitable for serial monitoring of the dynamic changes in fibrosis because of its invasiveness.<sup>3</sup>

Recently, non-invasive methods to assess the extent of hepatic fibrosis have emerged as substitutes for liver biopsy. Among these, ultrasound elastography techniques to assess liver stiffness related to hepatic fibrosis have been introduced, including transient elastography (TE), real-time elastography (RTE), acoustic radiation force impulse imaging (ARFI), and shear wave elastography (SWE).<sup>4</sup> Although TE, ARFI, and SWE provide quantitative values of liver stiffness by measuring the speed of shear waves, the computation processes and results are different among these modalities. A shear wave is produced by an acoustic pulse or a vibration, and spreads through the tissue examined. Strain elastography is an operator-dependent procedure and can be influenced by surrounding tissues or ascites. Different from other ultrasound elastography techniques,

RTE can measure heartbeat-induced strain and thus provide relatively objective qualitative (color-coded strain map) and semiquantitative results (scores such as liver fibrosis index [LFI], elasticity index, and elastic ratio).<sup>5</sup>

Among the above-mentioned ultrasound-based techniques, TE (FibroScan<sup>TM</sup>) was introduced first and is now used globally in clinical settings. Its usefulness was reported in many previous studies that demonstrated reliable diagnostic accuracy for the evaluation of fibrosis in CLDs with various etiologies.<sup>6,7</sup> The limitation of TE is the difficulty of measuring liver stiffness in patients with high body mass index (BMI), narrow intercostal spaces, severe hepatic atrophy, and ascites.<sup>8</sup> In a prior study, BMI >28 kg/m<sup>2</sup> was significantly associated with failure of liver stiffness measurement using TE.<sup>9</sup> Transabdominal RTE is a more sensitive method of hepatic fibrosis measurement than TE. Compared to TE, RTE sometimes has shown slight inferior diagnostic accuracy but is known to have few or no limitations. Among many previous studies, Koizumi et al.<sup>3</sup> reported that skinfold thickness and BMI did not significantly affect the elastic ratio determined when examiners measured liver stiffness at four sites through intercostal body surface using RTE. Another more recent study by Marques et al.,<sup>10</sup> however, showed that abdominal wall thickness of ≥23 mm was significantly associated with unsuccessful measurement of LFI using RTE.

While many studies to date have paid attention to transabdominal RTE, the article in this issue of *Clinical Endoscopy* by Schulman et al.<sup>11</sup> introduced a pilot study of endoscopic ultrasound (EUS) RTE for distinguishing normal liver, fatty liver, and cirrhosis in patients with CLD. It is a reasonable idea that EUS RTE may be more sensitive than transabdominal RTE in assessing the stage of liver fibrosis because of the shorter

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penetration depth in the EUS approach than in the transabdominal approach (thin gastric wall vs. thick abdominal wall). The study evaluated 50 prospectively enrolled patients who underwent EUS RTE and abdominal imaging prior to EUS. The patients were divided into normal liver ( $n=26$ ), fatty liver ( $n=16$ ), and cirrhosis groups ( $n=8$ ). LFI computed from the EUS RTE was statistically different among the normal liver, fatty liver, and cirrhosis groups. The cirrhotic group had a significantly higher mean LFI than the fatty liver (3.2 vs. 1.7,  $p<0.001$ ) and normal groups (3.2 vs. 0.8,  $p<0.001$ ). When applying a previously reported LFI cut-off value,<sup>12</sup> the area under the receiver-operating characteristic curve for LFI in predicting cirrhosis on imaging was 0.865.

When evaluating the results of this study, some limitations should be considered. First, it is not clear what kind of abdominal imaging was used to distinguish normal liver, fatty liver, and cirrhosis. Furthermore, the definitions of normal liver, fatty liver, and cirrhosis were not described in detail. Abdominal ultrasonography is the most common first-line imaging study for patients with CLD. However, ultrasonography does not perform well in obese patients<sup>13</sup> and may miss the diagnosis of fatty liver if steatosis is  $\leq 30\%$ .<sup>14</sup> In this study, the mean BMIs of the patients were relatively high at 29.6 kg/m<sup>2</sup>, 30.8 kg/m<sup>2</sup> and 28.3 kg/m<sup>2</sup> in the normal, fatty liver, and liver cirrhosis groups, respectively. If abdominal ultrasonography is used for imaging, mild fatty liver may be misdiagnosed as normal liver. Second, liver biopsy was performed not in all patients; thus, no data were available for fibrosis stage in this study. Although liver biopsy has several limitations, it is still considered as the gold standard assessment for liver fibrosis stage. Many previous studies that used noninvasive methods validated their ability to identify significant fibrosis and cirrhosis in comparison with liver biopsy.<sup>3,6,10,12</sup> Those studies suggested a cutoff value for each fibrosis stage on the basis of liver biopsy results. Fatty liver is comprised of a broad spectrum of characteristics, including isolated steatosis, steatohepatitis, advanced fibrosis, and cirrhosis. The role of liver biopsy is to establish a diagnosis, assess fibrosis stage, and correlate histological lesions with potential clinical outcomes.<sup>15</sup> Without performing liver biopsy, broad-spectrum characteristics could not be interrogated properly and taken into account. Thus, the LFI of the fatty liver group could not be generalized to every patient with fatty liver. Another significant limitation of this study was its small sample size ( $n=50$ ), especially in the cirrhosis group ( $n=8$ ), which comprised 16% of all recruited patients. This limits the strength to differentiate the three groups and predict cirrhosis on imaging using the LFI.

Although this study has some limitations, it demonstrates that EUS RTE might be a potentially effective method for non-invasive assessment of liver fibrosis, especially in obese pa-

tients. However, invasiveness of EUS RTE compared to transabdominal RTE and sedation needed for EUS are drawbacks and obstacles for implementation of EUS RTE. Increased sedation requirement in patients with obesity may raise the risk of adverse events such as obstructive sleep apnea.<sup>16</sup> Further studies are required to compare the efficacy of EUS RTE with that of transabdominal RTE and liver biopsy to determine the cut-off value for EUS RTE according to fibrosis stage and to determine the safety of EUS RTE.

### Conflicts of Interest

The authors have no financial conflicts of interest.

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