Digestive Diseases and Sciences (2020) 65:928–930
https://doi.org/10.1007/s10620-019-05923-w

EDITORIAL

MRE and ELF in Liver Fibrosis Assessment: Are Two Better Than One?

Phyllis C. Tien[1,2] · Maria Duarte[1] · Annelys Roque[1] · Jennifer Price[1]

Published online: 11 December 2019

Assessment of liver fibrosis severity is clinically important in persons at risk for liver disease and also in research studies aimed at better understanding the factors associated with liver fibrosis progression. Liver biopsy has long been considered the clinical "gold standard" for staging liver fibrosis. Yet, its use in monitoring liver fibrosis progression has been limited since it is invasive, the samples of liver tissue are obtained randomly, and the method may not be acceptable to patients in whom progression is monitored. Although the need for an invasive liver biopsy to stage liver fibrosis prior to HCV treatment initiation has become less urgent with the advent of direct-acting antiviral agents, the emergence of nonalcoholic fatty liver disease (NAFLD) as a leading cause of cirrhosis and liver transplantation has expanded the need for fibrosis staging and longitudinal monitoring. This, combined with the lack of effective treatments for NAFLD, has led to a growing need to identify noninvasive markers that are accurate and reproducible for monitoring disease progression and in therapeutic clinical trials, disease regression.

Current noninvasive methodologies used to assess the severity of liver fibrosis include imaging and serum biomarkers of liver fibrosis. Serum biomarkers offer the advantages of being minimally invasive and safe. Both indirect and direct serum biomarkers of liver fibrosis have been studied relative to histologic assessment of liver fibrosis and validated in large cohorts. Among indirect serum biomarkers, AST to Platelet Ratio Index (APRI) and fibrosis (FIB)-4 are widely used, since they can be readily calculated using standard clinical laboratory values including platelet count, AST, and ALT. Indirect serum markers have been validated in diverse populations, but are less accurate than imaging modalities.

Direct serum biomarkers of liver fibrosis generally include proteins that are components of extracellular matrix metabolism. The Enhanced Liver Fibrosis (ELF) score, for example, is calculated using an equation that incorporates serum levels of three proteins: hyaluronic acid (HA), procollagen III amino acid terminal peptide (PIIINP), and tissue inhibitor of metalloproteinase I (TIMP-1). The ELF score, one of the most well-studied direct serum biomarkers of liver fibrosis, was derived and validated in a cohort of 921 patients with a spectrum of liver diseases including NAFLD, alcoholic liver disease, viral hepatitis infection, and autoimmune liver disease. The ELF score distinguished histologic ≥ F3 fibrosis with an area under the receiver operating characteristics curve (AUROC) of 0.804 [1]. The ELF score is also an accurate prognostic marker for all-cause mortality and complications of cirrhosis, further confirming its clinical utility [2]. In a study of HIV/HCV-coinfected women, ELF was superior to APRI and FIB-4 in predicting mortality [3]. Recently, a panel of experts employed the Delphi method (using a sensitivity of 85% for the detection of fibrosis and > 95% specificity for cirrhosis) to identify ELF thresholds correlating with histologic fibrosis stage [4]. An ELF cutoff of ≥ 9.8 demonstrated a sensitivity of 76% for cirrhosis, whereas a cutoff of ≥ 11.3 was 97% specific for cirrhosis. Based on these findings, the group selected ELF thresholds of ≥ 7.7, ≥ 9.8, and ≥ 11.3 to correspond to mild-moderate fibrosis, advanced fibrosis, and cirrhosis, respectively. These thresholds predicted adverse liver-related events within the cohort in which they were derived and should prove useful in both interpreting and explaining test results in the clinical setting. The ELF score is approved for commercial use in Europe, but not in the USA, where it is available via a commercial laboratory only for research purposes at this time.

Among the imaging-based fibrosis assessment methods, vibration-controlled transient elastography (VCTE), which assesses liver stiffness by measuring the speed of acoustic shear waves passing through the liver, is the most commonly used method in the USA. It can be performed at the bedside in an ambulatory setting in a short amount of time. It has been validated in large cohorts worldwide and in a spectrum

✉ Phyllis C. Tien
Phyllis.Tien@ucsf.edu

[1] Department of Medicine, University of California, San Francisco, San Francisco, CA, USA

[2] Department of Veterans Affairs Medical Center, San Francisco, CA, USA

of liver diseases including viral hepatitis, fatty liver disease, and autoimmune liver disorders. VCTE has several limitations, however, including anatomical limitations due to large body habitus, narrow inter-rib space, the presence of ascites, and is also confounded by liver inflammation, hepatic congestion, cholestasis, and food intake within 2–3 h of VCTE.

Magnetic resonance elastography (MRE) images the propagation of acoustic shear waves in a larger volume of the liver and applies a mathematical algorithm to compute cross-sectional images displaying the magnitude of the complex shear modulus of liver tissue. Unlike VCTE, obesity and the degree of necro-inflammatory activity on liver biopsy does not seem to influence the diagnostic accuracy of MRE for the detection of significant or advanced liver fibrosis. Nevertheless, MRE is expensive, requires more time (including scheduling and transportation to a radiology suite) than either VCTE or phlebotomy and may not be acceptable to patients with claustrophobia. In a study that assessed the pooled effect estimates of test characteristics in 13 studies evaluating MRE and 36 studies evaluating VCTE in adults with chronic HCV infection [5], MRE showed little or no difference in accuracy over VCTE in identifying patients with cirrhosis; rates of misclassifying patients with cirrhosis versus no cirrhosis were comparable. By contrast, in a pooled analysis of 230 adults with biopsy-proven NAFLD from three studies [6], MRE had statistically significant higher diagnostic accuracy than VCTE in detection of each stage of histologic fibrosis. Cluster-adjusted AUROC of MRE versus VCTE for detection of fibrosis stages ≥ 1 was 0.87 (95% CI 0.82–0.91) versus 0.82 (95% CI 0.76–0.88) ($p = .04$); for stage ≥ 2 was 0.92 (95% CI 0.88–0.96) ($p = .03$) versus 0.87 (95% CI 0.82–0.91); for stage ≥ 3 was 0.93 (95% CI 0.89–0.96) versus 0.84 (95% CI 0.78–0.90) ($p = .001$); for stage ≥ 4 was 0.94 (95% CI 0.89–0.99) versus 0.84 (95% CI 0.73–0.94) ($p = .005$). Using a fixed sensitivity or specificity of 90%, that study [6] established optimal thresholds of MRE (2.61, 2.97, 3.62, and 4.69 kPa, respectively) and VCTE (6.2, 7.6, 8.8, and 11.8 kPa, respectively) for the detection of any fibrosis (stage ≥ 1), significant fibrosis (stage ≥ 2), advanced fibrosis (stage ≥ 3), and cirrhosis (stage ≥ 4) in patients with NAFLD. One limitation of both MRE and VCTE is that optimal cutoff points vary by study, which typically focus on patients with a specific liver disease. The ELF thresholds by contrast were developed from a large cohort of adults with chronic liver disease regardless of type.

In this issue of *Digestive Diseases and Sciences*, Sherman et al. [7] compare MRE and the ELF score in 283 participants of whom 56% had HIV monoinfection, 17% had HIV/HCV coinfection, 2% had HCV monoinfection, and 25% had neither infection. The ELF score had a high specificity for advanced liver fibrosis and cirrhosis, which were defined using MRE cutoffs previously determined from studies comparing MRE-measured fibrosis to liver biopsy [8]. They concluded that ELF could be a viable alternative to MRE for the diagnosis of advanced liver fibrosis and cirrhosis in persons with HIV and/or HCV infection.

Sherman et al. showed that high ELF scores were strongly associated with advanced fibrosis or cirrhosis as detected by MRE [7]. A previous study similarly found that ELF scores correlated with VCTE-measured liver stiffness [9]. While identifying optimal cutoff points for noninvasive modalities, including ELF, VCTE, and MRE, is valuable when interpreting and explaining results to patients, a strength of noninvasive markers is the ability to continuously monitor changes in liver fibrosis. It may be cost-effective to use multiple noninvasive modalities to risk-stratify patients and monitor change in liver fibrosis over time. The study findings by Sherman et al. [7] suggest that in patients with HIV and/or HCV infection who meet criteria for MRE-defined advanced fibrosis and cirrhosis, the ELF score could be used to assess the rate of progression and inform the timing of follow-up MRE, possibly simultaneously with MRI screening for hepatocellular carcinoma if indicated.

The current study adds to the growing literature addressing noninvasive methodologies used to stage liver fibrosis and provides new information regarding the use of both MRE and ELF in the setting of HIV infection. Noninvasive methods to accurately stage liver disease are greatly needed in people living with HIV, since HCV coinfection is highly prevalent and NAFLD is now on the rise. Nevertheless, an unanswered question remains whether a combination of both modalities might be superior to using one or the other to assess progression of liver fibrosis and predict liver-related morbidity and mortality. Additional longitudinal studies are needed to determine the optimal use of noninvasive imaging and serum biomarkers such as MRE and ELF to best predict progression to liver-related morbidity and mortality.

References

1. Rosenberg WM, Voelker M, Thiel R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. *Gastroenterology*. 2004;127(6):1704–1713.
2. Parkes J, Roderick P, Harris S, et al. Enhanced liver fibrosis test can predict clinical outcomes in patients with chronic liver disease. *Gut*. 2010;59(9):1245–1251.
3. Peters MG, Bacchetti P, Boylan R, et al. Enhanced liver fibrosis marker as a noninvasive predictor of mortality in HIV/hepatitis C virus-coinfected women from a multicenter study of women with or at risk for HIV. *AIDS*. 2016;30(5):723–729.
4. Day J, Patel P, Parkes J, Rosenberg W. Derivation and performance of standardized enhanced liver fibrosis (ELF) test thresholds for the detection and prognosis of liver fibrosis. *J Appl Lab Med*. 2019;3(5):815–826.
5. Lim JK, Flamm SL, Singh S, Falck-Ytter YT, Clinical Guidelines Committee of the American Gastroenterological A. American

Gastroenterological Association Institute guideline on the role of elastography in the evaluation of liver fibrosis. *Gastroenterology*. 2017;152(6):1536–1543.
6. Hsu C, Caussy C, Imajo K, et al. Magnetic resonance versus transient elastography analysis of patients with nonalcoholic fatty liver disease: a systematic review and pooled analysis of individual participants. *Clin Gastroenterol Hepatol*. 2019;17(4):630–637.
7. Sherman KE, Abdel-Hameed EA, Ehman RL, et al. Validation and refinement of noninvasive methods to assess hepatic fibrosis: magnetic resonance elastography versus enhanced liver fibrosis index. *Dig Dis Sci.* (Epub ahead of print). https://doi.org/10.1007/s10620-019-05815-z.
8. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver versus nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol*. 2015;13(4):643–654.
9. Swanson S, Ma Y, Scherzer R, et al. Association of HIV, Hepatitis C virus, and liver fibrosis severity with the enhanced liver fibrosis score. *J Infect Dis*. 2016;213(7):1079–1086.