# Serum biomarkers for the evaluation of liver fibrosis: The need for better tests

Müjdat Zeybel[1] (iD), Ramazan İdilman[2] (iD)

[1]Department of Gastroenterology and Hepatology, Koç University School of Medicine, İstanbul, Turkey
[2]Department of Gastroenterology Ankara University School of Medicine, Ankara, Turkey

See "Köksal İ, Yılmaz G, Parlak M, et al. Diagnostic value of combined serum biomarkers for the evaluation of liver fibrosis in chronic hepatitis C infection: A multicenter, noninterventional, observational study" on page 464-72.

Liver fibrosis is a major predictor of disease progression and liver-related mortality, irrespective of the etiology. Hepatic fibrosis has traditionally been diagnosed and staged by liver biopsy (1). Several limitations of the routine use of liver biopsies have been identified, including sampling error, inter- and intra-observer variability, and complications leading to morbidity, along with low tolerability. Consequently, liver biopsy has been accepted as an "imperfect gold standard" by many experts (2,3). The implementation of non-invasive approaches, including biomarkers, scoring systems, and imaging techniques, for the assessment of liver fibrosis evolved rapidly to yield several scoring systems (e.g., AAR, BARD, APRI, FIB-4, and NAFLD fibrosis score) and commercial non-invasive tests (e.g., the Enhanced Liver Fibrosis score and Fibrotest®) (4). Reportedly, many of these tests result in high specificity and negative predictive values and have frequently been used to rule out significant fibrosis and cirrhosis prior to liver biopsies. Original and validation studies have observed diagnostic accuracy in the determination of significant fibrosis with area under the receiver operating characteristic curve levels of 74%–88% (5). However, most tests have much more limited precision in the detection of intermediate levels of fibrosis (6). Further research in the field has explored novel fibrosis biomarkers, such as miRNA's and circulating cell free DNAs (7,8). Liver stiffness measurement by transient elastography, acoustic radiation force impulse imaging, shear wave elastography, and magnetic resonance (MR) elastography have been a major step forward in the assessment of hepatic fibrosis (2). However, these techniques are expensive and not widely available, particularly in developing countries. Current evidence noticeably indicates that liver fibrosis is a rather dynamic process ranging from stable, progressive, and regressive states (9). Currently, the causative agents of hepatic damage can be prevented by antivirals and further treatment for non-alcoholic steatohepatitiz (NASH) and other liver diseases at the development stage. It is now not uncommon to observe regression of established cirrhosis. Thus, to predict and monitor clinically significant liver fibrosis with a reliable, reproducible, and non-invasive method is still an unmet clinical challenge, and new methods are awaited.

Taking into account the requirement of multicenter studies to test biomarkers' performance, a study by Köksal and colleagues highlighted the diagnostic value of combined serum biomarkers for the assessment of hepatic fibrosis in this issue of the Turkish Journal of Gastroenterology. This study included 182 patients with chronic hepatitis C infection from several Turkish centers. Patients were categorized into two groups: mild fibrosis (Metavir, F0–F1) or advanced fibrosis (Metavir, F2–F4). Among the studied tests, APRI, FIB-4, and Fibrotest showed sensitivities of 69%, 69%, and 75%, respectively, and specificities of 77%, 60%, and 71%, respectively, for the detection of severe fibrosis. Another interesting point of the study is that to better discriminate mild vs significant hepatic fibrosis, the combined factors of Fibrotest, FIB-4, APRI, and AAR were examined in the hepatitis C cohort. Combinations of the tests did not improve negative predictive values significantly, and Fibrotest alone performed better with a negative predictive value of 85.5%. However, the combination of APRI and AAR improved the positive predictive value. Although this study noted evidence of

*Corresponding Author:* **Müjdat Zeybel; mzeybel@ku.edu.tr**

Zeybel and İdilman. Serum biomarkers for the evaluation of liver fibrosis

Turk J Gastroenterol 2018; 29: 377-8

slightly better results with the combination of the tests, area under the ROC curve of the tests remained lower than those reported in previous studies; it is unclear if this could avoid the need for liver biopsy. It is also important to note that a relatively small group of F2–F4 patients enrolled in this study precludes the effective assessment of the current tests.

Liver fibrosis will continue to pose important diagnostic and therapeutic challenges to hepatologists. The robust and accurate detection of fibrosis severity is important for various clinical decisions, including monitoring, prognosis, and treatment. Several points need to be addressed in future studies. Current biomarkers have possibly reached their limits for the stratification of patients according to fibrosis stages. Upcoming studies using novel biomarkers for both fibrosis assessment and prognostic prediction are required. Understanding the pathophysiology of hepatic fibrosis better with regard to the generation and degradation of extracellular matrix components could lead to the discovery of advanced methods. This approach may also help in determining the speed of fibrosis progression and regression. Direct-acting antivirals have been introduced for hepatitis C and novel therapeutic options under clinical evaluation as fibrosis modifiers for non-alcoholic fatty liver disease. Future studies should aim to not only include treatment-naïve patients but also focus on patients with sequential biopsies from clinical trials. This method could be more helpful for establishing the fibrosis stage and for predicting disease outcomes. It is also noteworthy that some of the suggested tests perform less accurately in elderly patients,

particularly in those with NASH (10). Research including elderly patients will also demonstrate the value of current and future tests. To avoid invasive liver biopsy and to stratify patients according to disease stages, further studies combining scoring systems and novel biomarkers are required for viral hepatitis, NASH, and other hepatic disorders.

### REFERENCES

1. Friedman SL, Liver fibrosis - from bench to bedside. J Hepatol 2003; 38 (Suppl 1): S38-53.
2. Castera L, Pinzani M, Biopsy and non-invasive methods for the diagnosis of liver fibrosis: does it take two to tango? Gut 2010; 59: 861-6.
3. Martinez SM, Crespo G, Navasa M, Forns X. Noninvasive assessment of liver fibrosis. Hepatology 2011; 53: 325-35.
4. Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology 2012; 142: 1293-302.
5. Adams LA. Biomarkers of liver fibrosis. J Gastroenterol Hepatol 2011; 26: 802-9.
6. Parkes J, et al., Performance of serum marker panels for liver fibrosis in chronic hepatitis C. J Hepatol 2006; 44: 462-74.
7. Pirola CJ, Fernández Gianotti T, Castaño GO, et al. Circulating microRNA signature in non-alcoholic fatty liver disease: from serum non-coding RNAs to liver histology and disease pathogenesis. Gut 2015; 64: 800-12.
8. Yiğit B, Boyle M, ÖZler O, et al. Plasma cell-free DNA methylation: a liquid biomarker of hepatic fibrosis. Gut 2018; pii: gut-jnl-2017-315668. doi: 10.1136/gutjnl-2017-315668. [Epub ahead of print]
9. McPherson, S., et al., Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol 2015; 62: 1148-55.
10. McPherson S, Hardy T, Dufour JF, et al. Age as a Confounding Factor for the Accurate Non-Invasive Diagnosis of Advanced NAFLD Fibrosis. Am J Gastroenterol 2017; 112: 740-51.