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**Editorial**

# Non-invasive biomarkers of liver fibrosis in non-alcoholic fatty liver disease

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The search for reliable and non-invasive biomarkers of liver fibrosis has been a focus of intense medical research, with the aim of improving patient outcomes through early diagnosis and effective treatment. The purpose of this editorial is to raise awareness about the importance of non-invasive biomarkers for liver fibrosis and the impact of fibrosis on overall well-being.

Various predictive tests have been developed as non-invasive tests alternative to either imaging or liver biopsy.[1-3] The Fibrosis Risk Stratification includes three levels: Low risk if (fibrosis-4 [FIB-4]: <1.30, liver stiffness measurement [LSM] <8 kPa, enhanced liver fibrosis [ELF] <7.7); Indeterminate risk if (FIB-4: 1.30–2.67, LSM 8–12 kPa, ELF 7.7–9.8) and high risk if (FIB-4: >2.67, LSM >12 kPa, ELF >9.8). However, these tests have often not met quality metrics for diagnostic tests, leaving the clinician with a fair degree of uncertainty.[4-8] In this issue of the *Clinical and Molecular Hepatology*, Reinson et al.[9] clearly showed that there are several biomarkers that have been studied for their ability to identify individuals with F2-F3 degree of fibrosis in the liver. These markers includes FibroTest, NAFLD fibrosis score, Fibro Scan, acoustic radiation force impulse, Aspartate aminotransferase-to-Platelet Ratio Index (APRI), magnetic resonance elastography (MRE), FibroScan-AST (FAST) score and ELF tests.[9] It is important to note that these biomarkers are not perfect and their performance may vary depending on age, body mass index and the underlying cause of fibrosis. Therefore, it is important to use them in combination with other diagnostic tools, such as clinical examination and imaging exams, to make a definitive decision.

Machine learning algorithms have been studied as a future potential alternative for identifying individuals with F2-F3 fibrosis or higher; But their performance ability needs to be confirmed.[10,11]

Noninvasive serum biomarkers have been studied for their utility in predicting liver-related outcomes.[11] Serial measurement of specific biomarkers could be used in order to monitor liver disease progression and response to treatment.[11] Some examples include tracking fibrosis by using FibroTest and APRI, monitoring cirrhosis by prothrombin time, and monitoring liver cancer by α-fetoprotein. Increase of 20% in

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vibration controlled transient elastography (≥16.6 kPa) predicts progression to cirrhosis and ≥30.7 kPa predicts decompensation. Increase of 15% in MRE is associated with fibrosis progression and increase of 19% in MRE associated with poor outcomes.[12-14] In viral hepatitis, measuring viral load, liver enzymes and FibroTest or FIB-4 at different intervals can help to assess the effectiveness of antiviral therapy. It is also important to consider that some biomarkers may not significantly change even with an effective treatment, or may take longer time to show improvement.[12-14]

Non-invasive biomarkers can be also useful tools in drug trials for non-alcoholic steatohepatitis (NASH). These tools could help in monitoring progression and regression of liver fibrosis. However, it is important to use them in conjunction with other diagnostic tools and to have a clear understanding of their limitations and potential biases. Higher baseline, greater change in ELF (>9.76) is associated with an increased risk of progression to cirrhosis. ELF greater than 11.3 predicts liver-related clinical events.[15]

Liver stiffness measurement by transient elastography, platelet counts and spleen stiffness could be also used for assessment of the degree of portal hypertension and the extent of liver fibrosis.[16] A level of transient elastography above 15 kPa and platelet counts below 150K indicate significant portal hypertension.[16]

How best can I Identify who needs to be treated without a liver biopsy?

There are three scores to answer that:

1. The FAST score (Fibroscan AST) provides an efficient way to non-invasively identify patients at risk of progressive NASH for clinical trials or treatments, and thereby reduce unnecessary liver biopsy in patients unlikely to have significant disease. Performance of FAST score is good with AUC 0.71, positive predictive value (PPV) 33-85% and negative predictive value (NPV) 73-100%.[17]

2. The MAST score (MRI-PDFF-AST) outperforms previous scores with AUC 0.93; In the validation cohorts, the 90% specificity cut-off of 0.242 corresponded to a sensitivity of 75%, PPV of 50% and NPV of 97%, whereas the 90% sensitivity cut-off of 0.165 corresponded to a specificity of 72%, PPV of 29%, and NPV of 98%.[18]

3. Finally the MRE combined with FIB-4: (FIB-4 [if ≥1.6]+MRE ≥3.3 kPa) score is superior to FAST in detecting patients "at risk" for NASH among patients with biopsy-proven NAFLD with AUC 0.88.[19]

Future Perspective: metabolomics, lipid omics, and multiomics (gut microbiome) studies could help the clinicians in identify biomarkers associated with the pathophysiology of NAFLD and NASH. Integration of artificial intelligence and machine learning techniques to improve diagnostic accuracy and to develop personalized treatment plans for patients.

These biomarkers offer a more reliable, non-invasive, and cost-effective alternative to liver biopsy for diagnosing liver fibrosis. Combining several tests and scores, and creating charts for risk stratification and management, help the primary physician manage such patients and refer them to specialized centers.

## Authors' contribution

NIMER Assy wrote the manuscript. Maamon Basheer and Mohamed Naffah revised it.

## Conflicts of Interest

The authors have no conflicts to disclose.

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**Abbreviations:**

FIB-4, fibrosis-4; LSM, liver stiffness measurement; ELF, enhanced liver fibrosis; ARFI, acoustic radiation force impulse; NFS, NAFLD fibrosis score; APRI, aspartate aminotransferase-to-platelet ratio index; MRE, magnetic resonance elastography of liver; FAST score, FibroScan-AST score; VCTE, vibration controlled transient elastography; NASH, non-alcoholic steatohepatitis; PPV&NPV, positive and negative predictive values; NAFLD, non-alcoholic fatty liver disease; MAST score, The MRI-aspartate aminotransferase score; MEFIB, MRE combined with FIB-4

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