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Exploring non-invasive diagnostics for metabolic dysfunction-associated fatty liver disease

Non-invasive diagnostics for MAFLD

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Abstract

The population of metabolic dysfunction-associated fatty liver disease (MAFLD) is increasingly common worldwide. Identification of people at risk of progression to advanced stages is necessary to timely offer interventions and appropriate care. Liver biopsy is currently considered the gold standard for the diagnosis and staging of MAFLD, but it has associated risks and limitations. This has spurred the exploring non-invasive diagnostics for MAFLD, especially for steatohepatitis and fibrosis. These non-invasive approaches mostly include biomarkers and algorithms derived from anthropometric measurements, serum tests, imaging or stool metagenome profiling. However, they still need rigorous and widespread clinical validation for the diagnostic performance.

Key Words: Metabolic dysfunction-associated fatty liver disease; Non-invasive diagnostics; Circulating biomarkers; Imaging biomarkers; Stool microbial biomarkers

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Core Tip: Metabolic dysfunction-associated fatty liver disease (MAFLD) is a burdensome public health problem. The diagnostic assessment of MAFLD is an important step for timely management. Extensive effort and encouraging progress have been made to establish non-invasive tests to diagnose steatohepatitis and fibrosis.

TO THE EDITOR

We read with great interest the article by Trinks *et al*^[1] on the omics-based biomarkers as diagnostic tools for metabolic dysfunction-associated fatty liver disease (MAFLD). Since its global epidemic, MAFLD becomes a burdensome public health problem^[2]. The development of steatohepatitis, especially liver fibrosis, is most strongly associated with poorer long-term outcomes and increased incidence of liver-related mortality^[3-5]. It is in

this context that identification of people at risk of progression to advanced stages is necessary to timely offer interventions and appropriate care. Currently, liver biopsy is still the reference standard for diagnosis and staging of MAFLD. However, it is an invasive approach with poor compliance and a small but appreciable risk of complications^[6]. Besides, it is also expensive, prone to sampling bias, and has high intra- and interobserver variability^[6-8]. These inherent limitations have driven the need for non-invasive approaches to replace liver biopsy in severity assessment and risk stratification of patients with MASLD. In this regard, extensive effort and encouraging progress have been made in this field. There is now increased availability of non-invasive tests, and some become increasingly incorporated into routine clinical practice^[9-12]. These non-invasive approaches mostly include biomarkers and algorithms derived from anthropometric measurements^[9], serum tests^[10], imaging^[11] or stool metagenome profiling^[12].

Anthropometric measurements: Anthropometric indicators have been used for prediction of MASLD, such as body mass index, abdomen, waist and chest circumferences, and trunk fat. These indicators are easy to be determined by simple and affordable equipment, thus making them ideal for use in remote areas or in primary clinical practice^[9]. Recently, artificial intelligence (AI), such as machine learning and deep learning, has been applied to assist anthropometric diagnostics of MAFLD^[13]. However, these indicators still limited by suboptimal accuracy, especially in detecting fibrosis^[13].

Serum biomarkers and related panels: Increased serum triglycerides, alanine amino-transferase (ALT), aspartate amino-transferase (AST) or ALT/AST are not accurately predictive of MAFLD severity^[14, 15]. Related panels derived from these biochemical indicators are also subject to low accuracy and specificity, such as FLI (fatty liver index) for hepatic steatosis, and BARD score (BMI, AST: ALT ratio, presence of diabetes) for hepatic fibrosis^[16, 17]. Despite these limitations, they are still commonly used for screening owing to general applicability. Recently, some novel serum biomarkers have been proposed as promising alternatives for diagnosis of NASH and fibrosis.

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Circulating concentrations of cytokeratin-18 (CK-18) fragments were proposed to be the most reliable predictors of steatohepatitis^[18], and its combination with other indicators in a biomarker panel could further increase the diagnostic performance^[19]. However, it has relatively low power to determine the severity of NASH fibrosis^[20]. Serum Pro-C3 and metalloprotease-1 inhibitor (TIMP1), are emerging biomarkers for fibrosis with excellent diagnostic performance^[21, 22]. Subsequently, several biomarker panels are proposed, such as MACK-3 (HOMA-IR, AST, and CK-18 M30)^[23] and ADAPT (age, platelet count, diabetes, and PRO-C3)^[24], and their diagnostic performance is evaluated in comparative diagnostic accuracy studies^[10, 25]. In addition, the application of innovative omics technologies have screened out some novel serum biomarkers^[26, 27], but their accuracy, reproducibility or reliability are not yet gone through analytical/biological and clinical cohort validation.

Imaging biomarkers: Conventional ultrasonography is the first-line imaging test for detecting hepatic steatosis^[28], and newer quantitative ultrasound-based techniques demonstrate superior performance^[29]. As a contrast, magnetic resonance imaging proton density fat fraction (MRI-PDFF) is considered more accurate at quantifying liver fat than ultrasonography^[30], and even liver biopsy^[31]. Current imaging-based biomarkers have poor diagnostic performance for steatohepatitis, especially distinguishing steatohepatitis from fibrosis^[32]. Ultrasound-based measurements of liver stiffness by vibration-controlled transient elastography (VCTE), commercially marketed as FibroScan have demonstrated very good diagnostic accuracy for advanced fibrosis^[33]. Likewise, magnetic resonance elastography (MRE) shows low failure rate in diagnosis of advanced fibrosis^[34]. More importantly, MRE outperforms VCTE in diagnostic accuracy for earlier stages of fibrosis^[30].

Gut-microbiome-derived biomarkers: Dysregulation of the gut microbiome is implicated in the progression of MAFLD as evidenced by several studies^[35, 36]. This association could be translated into diagnostic capacity for MAFLD. A latest study characterized the gut microbiome compositions using metagenomic sequencing of stool samples from patients with biopsy-proven MAFLD, and establish gut microbiome-

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based metagenomic signature to differentiate between mild or moderate and advanced fibrosis^[12]. These microbial biomarkers achieved robust diagnostic accuracy in small samples, and further studies are needed to validate the clinical utility.

In summary, progress has been made in the identification of novel non-invasive diagnostics for MAFLD, including biomarkers and algorithms integrating biomarkers. Although none of biomarkers achieved the sufficient performance to replace liver biopsy in diagnosis of steatohepatitis and fibrosis, some diagnostics are promising tools for identifying advanced fibrosis.

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PRIMARY SOURCES

- 1** [Julieta Trinks, María F Mascardi, Adrián Gadano, Sebastián Marciano. "Omics-based biomarkers as useful tools in metabolic dysfunction-associated steatotic liver disease clinical practice: How far are we?", World Journal of Gastroenterology, 2024](#) 25 words — 2%
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