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Editorial

Non-invasive imaging biomarkers for liver steatosis in non-alcoholic fatty liver disease: present and future

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in the United States.[1] It is not only associated with cirrhosis but is also considered a significant risk factor for cardiovascular disease and other complications related to the metabolic syndrome.[2] NAFLD is considered an umbrella term for a group of diseases; the spectrum starts with nonalcoholic fatty liver (NAFL), which is defined as liver fat content of more than 5% of the hepatocyte and is characterized histologically by macrovesicular hepatic steatosis. NAFL can progress into non-alcoholic steatohepatitis (NASH) which is characterized by the presence of inflammation and cellular injury, specifically ballooning, with or without fibrosis. However, both NAFL and NASH are associated with an increased risk of fibrosis and identifying it at an early stage is key. NAFL progresses to NASH in up to 30% of cases, leading to significant liver fibrosis with detrimental consequences.[2] Although liver biopsy remains the gold standard to diagnose NASH and liver steatosis, it is associated with risks and challenges. In addition, the rise of noninvasive testing (NITs) is found to be easier to perform, cost-effective, and less invasive.[2]

Given the prevalence of NAFLD worldwide, it is not feasible to perform liver biopsies on all patients with the suspected disease. There are several limitations of liver biopsy including sampling error, inter- and intra-observer variability, risks, and complications. Since only around 1/50,000 of the whole liver tissue is sampled during one biopsy, this by itself raises the concern of sampling error.[3] Hepatocyte ballooning is a histological key feature differentiating steatosis (NAFL) from NASH yet expert liver pathologists disagree in many instances on the presence or absence of ballooning.[4] Moreover, every procedure is associated with risks, and the incidence of serious complications and mortality has been reported to be 0.3–0.57% and 0.01% respectively.[5] As mentioned by Nogami et al.[6], the importance of assessing the degree of fibrosis rather

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than diagnosing NAFL or NASH or evaluating liver steatosis is key. Nogami et al.[6] also mentioned the importance of appropriately evaluating liver steatosis as studies have shown higher risk of mortality from extrahepatic cancer, cardiovascular disease, cirrhosis and hepatocellular carcinoma with different liver steatosis levels. Nevertheless, NITs play a significant role nowadays in diagnosing and managing multiple aspects of NAFLD including identifying disease severity, monitoring response to therapy, and predicting outcomes.

FIRST GENERATION TESTS

There are different serum biomarkers and composite scores used to evaluate hepatic fibrosis such as the Enhanced Liver Fibrosis (ELF) test and Fibrosis-4 (FIB-4), but the scope of this editorial revolves around the role of imaging in liver steatosis. As mentioned in the recently published review article by Nogami et al.[6], multiple tests exist to identify steatosis including abdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI). US is a simple and popular type of imaging to diagnose fatty liver. B mode findings such as bright liver, vascular blurring attenuation, and hepatorenal echo contrast indicate fatty liver however the sensitivity and specificity decrease when intra-hepatic steatosis is less than 30%.[6] CT scans can identify fatty liver, yet they are costly, time-consuming, a relatively poor indicator to quantify steatosis, and are associated with inevitable radiation exposure.[6] On CTs, fatty liver is usually diagnosed by comparing the liver fat content relative to that of the spleen. MRI is an excellent method to quantify fat content in the liver as the signals are obtained from protons belonging to water and fat molecules, and there is no risk of exposure compared to CT. However, it has not been used in general practice due to high costs.

Vibration-Controlled Transient Elastography (VCTE) (e.g., FibroScan®) was discovered in 2003 and is used to obtain a liver stiffness measurement (LSM) that correlates with fibrosis.[2] It is widely available and can be used as a point-of-care test. In 2010, the controlled attenuation parameter (CAP) was introduced to measure the degree of fat attenuation, allowing it to quantify liver steatosis.[6] Initially, obesity was considered a limitation until the XL probe was introduced, which allows for deeper penetration to generate signals in patients with a higher body mass index (BMI). As mentioned by Nogami et al.[6], CAP is essential in evaluating S ≥1, 2, and 3 however it has not been reported whether the measurement of liver steatosis is useful for long term follow up. On the other hand, changes in liver stiffness can be used to identify disease progression.[6]

Newer MR-based modalities are used to quantify hepatic fat. MRI proton density fat fraction (MRI-PDFF) is a MR technique that accurately quantifies hepatic fat by decomposing the signals obtained from the liver into its fat and water components.[7] It minimizes most confounding factors, including patient factors such as body mass index (BMI), sex, age, or etiology of liver disease, or other liver abnormalities such as iron overload.[7] Although MR approaches are considered the gold standard NIT to detect steatosis, they are not used as frequently due to limited availability and high cost.[7] Importantly, MRI-PDFF can be coupled with magnetic resonance elastography (MRE) which is more sensitive than VCTE in the detection of fibrosis stage ≥2 and is considered the most accurate noninvasive imaging-based test in fibrosis assessment in NAFLD.[7]

SECOND GENERATION TESTS

Steatohepatitis remains the driver of the disease, and thus regulators have considered NASH patients with the histological NASH activity score of 4 and higher and fibrosis stage 2 and higher (also known as at-risk NASH) as the targeted group for pharmacological therapy, especially in NASH phase 3 registry studies. Combining serologic markers with imaging is an improved way to assess at-risk NASH patients and has been studied recently. A newer predictive score combines LSM, CAP, and aspartate aminotransferase (AST) to-

Abbreviations:

NAFLD, nonalcoholic fatty liver disease; NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NITs, Noninvasive testing; ELF test, Enhanced Liver Fibrosis (ELF) test; FIB-4, Fibrosis-4; US, abdominal ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; VCTE, Vibration-Controlled Transient Elastography; LSM, liver stiffness measurement; CAP, controlled attenuation parameter; BMI, body mass index

gether, known as FAST (FibroScan-AST), which is an efficient way to identify these individuals and minimize unnecessary liver biopsies. In a prospective multicenter study of 350 patients, the FAST score was internally and externally validated with a cutoff of 0.35 and 0.67 for ≥0.90 sensitivity and specificity, respectively, in the derivation cohort.[8] Moreover, Agile 3+ and 4 are other non-invasive scores based on VCTE that accurately identify fibrosis (≥F3) and F4 (cirrhosis), respectively, but also predict adverse outcomes such as major adverse liver outcomes (MALO), hepatocellular carcinoma (HCC), the requirement for liver transplant (LT), and death.[9] Last but not least, the MAST score (MRI-AST) is an MRI serum-based score that, by far, outperforms previous scores (FAST and FIB-4) in identifying at-risk NASH patients.[10] The MEFIB score has also shown an ability to predict at-risk NASH patients and MALO.[11] Nevertheless, the dichotomous nature of the test gives less flexibility to its use in comparison to MAST and FAST.

In terms of correlation between NITs and MALO, a study by Younossi et al.[12] has shown that baseline FIB-4, NFS, ELF, and VCTE correlated with clinical liver outcomes. Boursier et al.[13] have shown significant increases in patients' risk for MALO with "FIB4 ≥1.30 then VCTE 8.0-12.0 kPa" (aHR 3.8; 95% CI 1.3–10.9) and even more for those with "FIB4 ≥1.30 then VCTE >12.0 kPa" (aHR 12.4; 95% CI 5.1–30.2). Two studies have shown that increases in MRE stiffness correlate with MALO and that a cutoff of 6.48 is a threshold of decompensation.[14,15] In another study with six international cohorts, MRE was shown to be associated with liver outcomes; the MEFIB (a combination of MRE and FIB-4) had an excellent negative predictive value for hepatic decompensation. MAST has also shown a correlation with clinical liver events with c-Statistic of >0.92.[10]

CONCLUSION

NAFLD is a progressive liver disease that can lead to cirrhosis. Its worldwide prevalence is high and continues to rise. In clinical practice, NITs are being used more frequently to identify steatosis, fibrosis, and high-risk NASH instead of liver biopsy, which is invasive, expensive, and associated with risks. Quantifying liver fat content is important however identifying "at risk NASH" is more essential. The future of NASH diagnosis and management is heading towards non-invasive methods, as there is robust evidence that NITs can assess disease severity and predict liver-related events. Ongoing studies are being conducted to support the use of NITs in monitoring responses to available treatments.

Authors' contribution

Lynna Alnimer drafted the manuscript. Mazen Noureddin revised and finalized the manuscript.

Conflicts of Interest

The authors have no conflicts to disclose.

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