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Editorial

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

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We read with great interest the review article by Yip and colleagues.[1] We could not agree more that the histological diagnosis of nonalcoholic steatohepatitis (NASH) can be substantially limited by sampling variability and observer variability. In one of the cited studies,[2] there was only fair to moderate agreement between pathologists for the grading of lobular inflammation and hepatocyte ballooning and for the diagnosis of NASH. Importantly, there was an alarming disagreement rate between pathologists (i.e., in up to 23% of cases) for the diagnosis of NASH resolution without worsening of fibrosis (which is one of the key endpoints for NASH clinical trials). Furthermore, the semi-quantitative nature of grading and staging of the histological components may obscure changes following an intervention. We also agree with the authors that the liver biopsy procedure is invasive (with a small risk of serious complications, including mortality), and we have no reservation in stating that a liver biopsy is not feasible for routine clinical use for initiation of treatment and for monitoring of response in patients with nonalcoholic fatty liver disease (NAFLD), now or in the future.

While liver biopsy is a requirement for NASH clinical trials, it is also a major deterrent for patients to participate due to the fear of procedural risk. Furthermore, histology is a major cause of screen failures in clinical trials, which is partly attributable to its inherent limitations, as aforementioned. A prescreening strategy using one or more non-invasive tests is often employed to reduce screen failure rates. However, as non-invasive tests were developed using histology as a reference standard, we are using tests that were constructed based on a problematic test to then select patients to be subjected to the problematic test for screening and enrolment into clinical trials. As much as the emphasis that has been placed on histological endpoints, they are but surrogate to clinical endpoints such as decompensation and liver-related mortality. There is an urgent need to demonstrate that non-invasive tests could act as a surrogate for these clinical endpoints and to determine the corresponding level and

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the desired change for initiation of treatment and for monitoring of response, respectively.

In their review, Yip and colleagues pointed out that serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) may be normal in patients with NASH and may even paradoxically decrease in patients with progressive fibrosis. We similarly observed that serum AST level has very poor negative predictive value for NASH. However, elevated serum AST level, especially when more than twice the upper limit of normal, has excellent positive predictive value for NASH.[3] Moreover, a decrease in serum ALT level of 17 U/L or more has been found to be significantly associated with histological response.[4] Importantly, these biomarkers are cheap and readily available. Although cytokeratin-18 (CK-18), an apoptotic marker, has limited role when used as a single test,[5,6] combination of the test with other biomarkers have been found to correlate better with liver inflammation than routine tests. For example, we found that MACK-3 (combination of homeostatic model assessment [HOMA], AST and CK-18) has high diagnostic value for fibrotic NASH with an area under the receiver operating characteristic curve (AUROC) of 0.80. We also found that the diagnostic accuracy of MACK-3 for active NASH was the highest among the evaluated tests with AUROC, sensitivity and specificity of 0.81, 84.2% and 81.4%, respectively.[7] Although HOMA, a marker of insulin resistance, is not routinely performed, its additional use in a fibrosis score with potentially improved performance may increase its role in the evaluation of patients with NAFLD.[8]

Imaging studies, including ultrasound, vibration-controlled transient elastography (VCTE), computed tomography and magnetic resonance imaging (MRI) are useful as diagnostic modalities for NAFLD. However, only FibroScan-AST score, which utilizes VCTE and AST, and several MRI-based tests has been found to be promising in the measurement of liver inflammation.[9,10] VCTE has the advantage of being non-invasive, reliable, easily performed and relatively affordable. In contrast, although the combinations of AST or fibrosis-4 index with MRI-proton density fat fraction, magnetic resonance (MR) elastography and/or iron-corrected mapping in MRI have high accuracy, the high cost and lack of availability may limit their use to only selected settings. Interestingly, Yip and colleagues[1] also described the role of artificial intelligence in evaluating NASH. Supervised or unsupervised machine learning and deep learning models were able to improve the diagnostic accuracy of fibrotic NASH.[11] For example, Fialoke et al.[12] developed a machine learning model using large electronic health records from the United States and accurately predicted NASH based on longitudinal data of ALT, AST, platelet count, basic demographic information and diabetes status with AUROC of 0.83 to 0.88. Although machine learning models appear promising, more validation studies are needed before they can be applied to routine clinical use.

Due to the high prevalence of NAFLD but only a small yet significant proportion of patients have more severe liver disease, a simple assessment and referral pathway is necessary to ensure that patients with more severe liver disease are referred to specialist for further management. On the other hand, patients who are unlikely to have severe liver disease should remain in primary care, where they are best managed.[13] An example of such assessment is the use of serum ALT and/or AST level among patients with type 2 diabetes mellitus, who are at higher risk of more severe liver disease, to identify patients who may have NASH.[13,14] As serum ALT and AST level may be normal in patients with NASH, simultaneous assessment of liver fibrosis (e.g., with fibrosis-4 index, followed by liver stiffness measurement for patients with elevated fibrosis-4 index)[15,16] will complement the evaluation and can serve as a safety net to identify patients with more severe liver disease but normal serum ALT and/or AST level. Another example is the use of a scoring system based on readily available parameters, for example, the Asia Pacific NASH Risk Score, which uses body mass index, diabetes mellitus, dyslipidemia, ALT and AST level. A score of 4 to 6 is considered as high-risk for NASH with NASH seen in 80% to 82.7% of patients.[17] Until a more reliable and cost-effective screening or diagnostic test for liver inflammation becomes available, these simple and readily available tests may serve as part of the strategy to manage patients with NAFLD.

Abbreviations:

NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-18, cytokeratin-18; HOMA, homeostatic model assessment; AUROC, area under the receiver operating characteristic curve; VCTE, vibration-controlled transient elastography; MRI, magnetic resonance imaging

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Authors' contribution

KHC and WKC drafted the manuscript and edited it for important intellectual content. Both authors reviewed and agreed with the content of the final manuscript.

Conflicts of Interest

The authors have no conflicts to disclose.

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