Editorial

Hepatic inflammation: an important target for biomarker development in nonalcoholic fatty liver disease

Hiba Khan[1], Mohammad Shadab Siddiqui[2]

[1]Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA, USA; [2]Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, Richmond, VA, USA

Correspondence to: Mohammad Shadab Siddiqui, MD. Division of Gastroenterology, Virginia Commonwealth University, 1200 East Broad Street, P.O. Box 980204, Richmond, VA 23298, USA. Email: mohammad.siddiqui@vcuhealth.org.

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Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease globally and liver biopsy remains central to diagnosis and risk stratification (1,2). There is currently an immense unmet need to develop non-invasive biomarkers to help establish the diagnosis, disease activity, and disease severity in NAFLD in clinical practice to reduce the need for liver biopsies (3). Unable to identify patients with nonalcoholic steatohepatitis (NASH), the clinically aggressive variant of NAFLD, or significant fibrosis readily in clinical practice presents challenges in management of patients with NAFLD and is one of the reasons why incidence of NASH related cirrhosis is rapidly increasing. Furthermore, as there is currently no approved therapy for treatment of NASH, there are several novel therapeutics in clinical trials for treatment of NASH. However, enrollment in these clinical trials has been challenging due to high screen failure rates with the most common reason being disqualifying liver biopsy. Better non-invasive risk stratification to identify patients with suspect NASH undergoing liver biopsy for clinical trial consideration to reduce the screen failure rates will not only facilitate development of therapeutics but also diagnostics. Thus, non-invasive and cheap biomarkers that can be readily deployed in wide clinical settings are urgently needed in clinical and research setting to mitigate the projected increase in NASH related cirrhosis.

The biomarker development in NAFLD can be largely divided into two eras, with the first era focusing on risk stratification via fibrosis quantification and the second (i.e., current) era that aims to develop diagnostics for identification of 'at risk' NASH, defined as NASH with NAFLD activity score (NAS) of 4 or higher and at least stage 2 fibrosis. Fibrosis utilized serum based biomarkers of fibrosis such enhanced liver fibrosis (ELF) panel, elastography based modalities [i.e., vibration controlled transient elastography (VCTE), magnetic resonance elastography (MRE)] and clinical prediction rules [i.e., Fibrosis-4 (FIB-4)] (4,5). Innovation in technology and statistical science have allowed for expansion into detection of NASH. Historically, the fibrosis-based biomarkers had excellent 'rule-out' ability [i.e., high negative predictive value (NPV)] but had suboptimal 'rule-in' or positive predictive value (PPV). While initial studies reported diagnostic performance of study Implementation of two-cutoff values, one as a rule-out value and the other as the rule-value, the recent elastography based measurements that include Fibroscan aspartate aminotransferase (AST) (FAST) and magnetic resonance imaging (MRI)-AST (MAST) scores have demonstrated significantly higher PPV at identifying at-risk NASH (6). Technologically, magnetic resonance imaging (MRI)-based parameters such as corrected T1 (cT1) have also enhanced the ability to identify patients with NASH non-invasive with improved accuracy (7).

In this issue of *HepatoBilliary Surgery and Nutrition*, Dr. Chen and colleagues present novel data using radiomics to identify hepatic inflammation in patients with histologically established NAFLD (8). Hepatic inflammatory activity score (IAS) was used to quantify inflammation and was the unweighted sum of lobular inflammation and cytological ballooning as assessed on liver histology. Subsequently, a radiomics signature based on T2-weighted imaging (T2WI) was developed for each subject based on weighted select radiomics features. The study utilized patients from two validation cohorts (Wenzhou Medical University and Guangdong Province Traditional Chinese Medical Hospital). A total of 18 radiomics features were identified as significant and incorporated into the final model for identification of hepatic inflammation. The diagnostic area under the receive operative curve (AUROC) [95% confidence interval (CI)] was 0.80 (0.71–0.89) for the training set, 0.77 (0.61–0.93) for validation in the Wenzhou cohort, and 0.75 (0.63–0.84) in the Guangdong cohort. The PPV for the T2WI radiomics signature (T2-RS) was relatively high for significant hepatic inflammation, however, the NPV was low in the Guangdong cohort (45%). The study offered an external and internal validation group, thereby, providing further validity to the study results. Incorporating MRI parameters that can be readily obtained conventional standard of care MRI has the potential to implement T2-RS more widely in clinical setting, without the potential of added cost that can accompany proprietary MRI-based biomarkers.

The study adds to the rapidly evolving MRI-based technology to provide better risk stratification for patients with NAFLD. Prior studies, have attempted to utilize hepatic inflammation whether it was done based solely on MRI-based parameters such as that multiparametric MRI protocol or combing MRI proton density fat fraction (PDFF), MRE with serum AST levels as done with MAST score (7,9). The T2-RS was developed in a relatively small cohort of patients (both internal and external validation) its performance needs to be further validated and confirmed in larger and ethnically diverse patient population. As MRI-based risk stratification is not part of routine clinical practice due to cost consideration, a potential role for MRI-based risk stratification technologies is identification of 'at-risk' NASH patients for enrollment into clinical trials (9). In the present study, NASH was defined as NAS ≥5, however, higher NAS scores are not synonymous with diagnosis of definitive NASH. Thus, the performance of T2-RS for identification of NASH and 'at-risk' NASH needs to be better defined. While the study evaluated the effect of hepatic fibrosis on T2-RS, the number of patients with advanced hepatic fibrosis was low ranging from 0 to 9.9%, thus, it is not entirely clear from the present study how presence of advanced fibrosis might affect the diagnostic performance of T2-RS. In a more specialized setting or clinical trial setting, where the prevalence of at-risk NASH and advanced fibrosis might be significantly higher, the diagnostic performance of T2-RS needs to be delineated better. Finally, the diagnostic performance of T2-RS could have been reported to allow for better incorporation into clinical or research setting by optimizing sensitivity ('rule-out') or specificity ('rule-in). Moreover, recent studies aimed at evaluating biomarkers in NAFLD utilizing dual cutoff values aimed at ruling out patients at lower risk for disease (i.e., high NPV) or ruling disease in by opting for higher PPV. Such an approach reduces the number of patients in the indeterminate or grey zone, thereby, minimizing the need for a liver biopsy while simultaneously increasing the yield of a liver biopsy to detect advanced hepatic fibrosis or at-risk NASH. As the current study provides the foundational data for T2-RS for discrimination of patients with low versus high hepatic inflammation, future investigations are needed to determine if two cutoff values might allow for better differentiation of patients with low versus high hepatic inflammation compared to a single cutoff value (8).

In summary, the current study by Dr. Chen uses MRI-based parameters to quantitate hepatic inflammation non-invasively with promising results. The proposed methodology requires further validation in larger and more diverse cohorts to better define how T2-RS can be used for risk stratifying patients with NAFLD.

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Safety Monitoring Board of Sagimet and is a member of AMRA's Advisory board. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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