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LETTERS TO THE EDITOR

Biomarkers for noninvasive biochemical diagnosis of nonalcoholic steatohepatitis: Tools or decorations?

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Abstract

In light of the growing epidemics of nonalcoholic fatty liver disease (NAFLD), identification and validation of the novel biochemical surrogate markers for nonalcoholic steatohepatitis (NASH) are paramount to reduce the necessity for liver biopsy. The availability of such markers has tremendous potential to radically alter the management strategies of NAFLD patients and to monitor the disease activity. Although current biomarkers do not entirely fulfill the many requirements for the identification of patients with NASH, they should not discourage our quest, but remind us that we need to cognize the challenges ahead.

Key words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Biomarkers; Liver biopsy

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TO THE EDITOR

In light of the dramatic increase in the prevalence of nonalcoholic fatty liver disease (NAFLD), noninvasive, simple, reproducible, and reliable biomarkers that can allow identifying patients with nonalcoholic steatohepatitis (NASH) among NAFLD patients are greatly needed[1]. The availability of such biomarkers has tremendous potential to radically alter the diagnostic and monitoring strategies through the reduction in the need for liver biopsy[2].

To be introduced in the clinical practice, the ideal biomarker for NASH must fulfill many requirements, such as ease of interpretation by clinicians, accurateness, reproducibility obtained in a standardized fashion, as well as high sensitivity and specificity. This latter point is both important and dependent on the design of study.

The recent report by Uslusoy *et al*[3] published in the *World Journal of Gastroenterology* has provided evidence that certain noninvasive markers for liver injury, including aminotransferase levels and AST/ALT ratio, do not entirely reflect the histological aspects of liver biopsy in patients with NASH. Based on their results, the authors concluded that aminotransferase levels and AST/ALT ratio do not seem to be reliable predictors for NASH. Although numerous non-invasive biomarkers are available, all patients with fatty liver should undergo liver biopsy[3]. It is feasible, however, that this radical conclusion may be too far to reach given the important caveats of this study. Firstly, the authors limited their analysis to aminotransferase levels. It has been previously shown, in this regard, that serum levels of caspase-cleaved cytokeratin 18 may be a potential biochemical marker for NASH in NAFLD patients with normal aminotransferase levels[4]. Secondly, the statistical analysis of data, demonstrating the lack of an association of aminotransferase levels and AST/ALT ratio with NASH, is likely to be underpowered as the study enrolled too few participants to identify such differences. Underpowered studies are overly prone to making false-negative conclusions, or committing what epidemiologists call type Ⅱ errors[5]. Finally, appropriate use of biomarker results requires use of a Bayesian approach[6], i.e. integrating pretest probabilities with biomarker test results (expressed as sensitivity and specificity) to estimate the posttest probability of disease.

Prerequisites for the clinical use of biomarkers for NASH include the elucidation of specific indications, the standardization of analytical methods, the characterization of analytical features, the assessment of performance characteristics, the incremental yield of different markers for given clinical indications, and the demonstration of cost-effectiveness. Although the development of NASH biomarkers fulfilling these features is challenging, it should not discourage our quest, but remind us that we need to cognize the challenges ahead. Technological advances will likely facilitate the use of multimarker profiling[7] to identify patients with NASH in the near future.

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