Editorial Commentary

Clinical utility of non-invasive tests to predict clinical outcomes in non-alcoholic fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease, and the fastest-growing cause of hepatocellular carcinoma (HCC) worldwide (1,2). As the number of people with NAFLD is too great to perform surveillance in all, risk-stratification strategies are increasingly important to identify those at the highest risk of decompensation and HCC (3,4).

Cholankeril *et al.* conducted a retrospective cohort study of a large number [202,319] of people with NAFLD, and examined the association between temporal changes in the fibrosis-4 (FIB-4) score and the risk of progression to HCC or a composite endpoint of either cirrhosis or HCC. Results were analyzed after 3 and 5 years (5). Over 3 years, about one-fifth of patients with "low risk" FIB-4 scores at baseline progressed to either indeterminate or high risk, and close to half of those who had "indeterminate" FIB-4 scores at baseline progressed to high risk. The incidence rate (IR) of HCC development was 0.28 per 1,000 person-years. This study also found that the IR of HCC increased with an increase in FIB-4 values from baseline, with an IR of 0.05 per 1,000 person-years in patients who remained at low risk at baseline and after 3 years, compared to 0.76 per 1,000 person-years in patients who progressed from low risk to high risk. Furthermore, these patients also had a 17-fold higher risk of developing cirrhosis or HCC (composite outcome).

The FIB-4 test is a non-invasive, readily available blood-based biomarker of fibrosis that can be utilized in primary care or resource-limited settings. It also allows primary physicians and non-hepatologists to stratify NAFLD patients at a higher risk of developing cirrhosis or HCC. A large cross-sectional study showed that the FIB-4 score was a good predictor of advanced fibrosis in patients with NAFLD (c-statistic 0.8), as well as progression to advanced fibrosis over time (c-statistic 0.81) (6). The current study adds to the existing literature by demonstrating the clinical utility of monitoring longitudinal changes in FIB-4.

However, there are limitations to this approach. FIB-4 has been shown to have lower specificity in older age groups with type 2 diabetes mellitus (T2DM) (7) and interpretation of FIB-4 scores may be confounded by other comorbidities which affect the aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet values.

Besides that, as a significant proportion of patients included in the study by Cholankeril *et al.* were males (94%), it is unclear if these data are generalizable to females.

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Emerging data suggest that females with NAFLD are at a similar risk of decompensation and HCC, compared to males (8,9). The American Association for the Study of Liver Diseases (AASLD) recently published an updated algorithm (10) for the evaluation of patients at risk for or with NAFLD across the primary care and specialist settings, in concordant with the American Gastroenterology Association (AGA) clinical care pathway published in 2021 (11). The guidelines recommend performing a second non-invasive liver stiffness measurement, such as vibration-controlled transient elastography (VCTE), for select patients. These patients include those with a FIB-4 score of >1.3 or those with <1.3 but with metabolic risk factors or T2DM. A VCTE score of <8.0 kPa signifies low-risk patients, while patients with intermediate (8–12 kPa) or high-risk (>12 kPa) scores should be monitored annually with VCTE.

A recently published prospective study found that repeated liver stiffness measurements were useful in monitoring interval progression in non-advanced chronic liver disease patients with VCTE scores <10 kPa and were able to accurately predict clinical outcomes in people with both compensated (VCTE ≥10 kPa) and decompensated chronic liver disease. A 20% increase in LSM at any time was associated with an approximately 50% increased risk of hepatic decompensation and liver-related death in patients with compensated advanced chronic liver disease. It also showed that repeated liver stiffness measurements with VCTE were superior to FIB-4, model for end-stage liver disease (MELD), or single time-point liver stiffness measurements in predicting hepatic decompensation in 12 months, and provided higher accuracy (12). In another prospective study, the optimal baseline liver stiffness thresholds were ≥16.6 kPa for predicting progression to cirrhosis, and ≥30.7 kPa for predicting liver-related events (4). Thus, while the paper by Cholankeril *et al.* has demonstrated the value of using evolving FIB-4 scores to estimate the risk of cirrhosis or HCC, incorporating a change in VCTE values over time may provide greater granularity in predicting clinical outcomes of NAFLD patients.

As physicians, the ability to identify patients who will require closer monitoring and surveillance is paramount in delivering quality clinical care. The ability to use non-invasive tests to predict the progression of disease and risk of HCC may be a valuable tool that can be used in delivering personalized care for people with NAFLD.

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