

MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

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Prognostic Value of Liver Stiffness Measurement by VCTE in MASLD/MASH



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G&H What is the prognostic accuracy of vibration-controlled transient elastography–based liver stiffness measurement for predicting liver-related events in metabolic dysfunction-associated steatotic liver disease, compared with using other tools?

SG Vibration-controlled transient elastography (VCTE)-based liver stiffness measurement has excellent performance and an area under the receiver operating curve (AUROC) of over 80% for predicting future liver-related outcomes in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), including those with metabolic dysfunction-associated steatohepatitis (MASH). Such outcomes include the development of ascites, hepatic encephalopathy, variceal bleeding, liver cancer, need for liver transplant, and liver-related death. Liver biopsy also performs well for this purpose with an AUROC of 80% to 90%. The more fibrosis on biopsy, the higher the risk of the liver-related event. Noninvasive tests other than VCTE, such as composite liver stiffness measurement–based scores or blood-based tests like the Fibrosis-4 (FIB-4) Index or Nonalcoholic Fatty Liver Disease Fibrosis Score, also have excellent performance for predicting future liver-related events in patients with MASLD/MASH.

G&H Is there still a role for using liver biopsy, or is VCTE-based liver stiffness measurement appropriate for predicting liver-related events in all MASLD/MASH patients?

SG Practice patterns have dramatically shifted in recent years away from liver biopsy owing to its many limitations such as invasiveness and cost. Based on accumulating

evidence on the performance of noninvasive tests, including liver stiffness measurement, there has been a shift away from using liver biopsy in clinical practice. Clinicians rarely perform liver biopsy nowadays for patients with MASLD to diagnose or stage MASH. Nevertheless, liver biopsy may still be offered for patients who are interested in clinical trials, many of which require performance of liver biopsy. Thus, prognostication, staging, and clinical practice have shifted mostly to noninvasive tools, most commonly, VCTE-based liver stiffness measurement. However, there is still a use for other noninvasive tests, for example, in patients who have severe obesity. VCTE may not work in these patients, so magnetic resonance (MR) elastography may instead be used. In practices where neither MR-based elastography nor VCTE-based liver stiffness measurement is available, simple noninvasive tests such as FIB-4 or the Enhanced Liver Fibrosis score can be used to fulfill the purpose of staging the disease and predicting future events.

G&H What factors can affect prognostic reliability of liver stiffness measurement by VCTE?

SG One of the most important factors is the fasting requirement before the use of VCTE. Data support the idea that fasting for at least 3 hours improves the accuracy of measurement. It is common both in clinical practice as well as in studies to insist on a 3-hour fasting period to reduce the effects of the increase in hepatic blood flow that appears on liver stiffness after eating. Another factor that affects the reliability of liver stiffness measurement is the patient's anatomy, particularly their chest wall thickness. The thicker the chest wall, the more difficult the measurement, as seen in the setting of obesity or anatomic

variations. Lastly, operator experience is a major factor. Experienced operators are able to capture more accurate measurement of liver stiffness and do so reliably and repeatedly. When using VCTE to measure liver stiffness, it is important to capture at least 10 reliable measurements with low variability at an interquartile range below 30%.

G&H What are the most commonly used liver stiffness measurement thresholds in MASLD/MASH patients, and how do these cutoffs affect management?

SG Guidelines based on data that our group and others have generated have settled on three thresholds: 8, 12, and 20 kilopascals (kPa). Patients with MASH and a stiffness of 8 kPa or more likely have underlying clinically significant fibrosis (stage 2 or more). Essentially, anyone with a liver stiffness over 8 kPa should be referred to specialty or hepatology care. These are the prime patients who would benefit from treatment of MASH, so this threshold has an immediate implication for identifying at-risk patients. Because these are the patients who may progress, they should be offered treatment quickly. Twelve kPa is the threshold to identify advanced fibrosis (bridging fibrosis or cirrhosis). The implication is that these are the patients in whom clinicians are going to look for cirrhosis. Twenty kPa is when clinicians begin to look for not only cirrhosis but also portal hypertension and more advanced cirrhosis; start focusing on surveillance for liver disease complications such as liver cancer, varices, and decompensation of cirrhosis; and think about intervention to prevent progression, such as offering patients beta blockers like carvedilol. This 20 kPa threshold is also important because essentially only patients between 8 and 20 kPa may be eligible for the currently approved treatments for MASH.

G&H Could you compare the prognostic value of a single baseline VCTE liver stiffness measurement vs serial measurements over time?

SG Both are very useful. When I first see a patient, the baseline measurement of liver stiffness immediately gives me an idea of where the patient is. For example, do they have at-risk MASH with a liver stiffness of 8 kPa or more in which case I need to start thinking about treatment because the patient is at increased future risk of developing liver-related events? One of the recent studies our group performed with the Nonalcoholic Steatohepatitis Clinical Research Network prospective cohort found that patients with a baseline liver stiffness measurement below 10 kPa have a 1% to 2% 3- to 5-year risk of developing a liver-related event. The risk goes up to 5% in patients who have

a liver stiffness measurement of 10 to 15 kPa, and the risk is even higher at 10% to 12% over a 3-year period in patients who cross the 15 kPa threshold at baseline. Thus, baseline liver stiffness measurement helps clinicians prioritize which patients are higher risk and need intervention faster.

Follow-up liver stiffness measurement is equally valuable, as clinicians want to know the course of the liver disease in the patients they are managing. Those whose liver stiffness continues to deteriorate over time are in a much higher risk category than those who remain stable or who experience improvement in liver stiffness measurement. On the other hand, our study, as well as studies from other groups, also indicate that when liver stiffness decreases over time, the risk of liver-related events goes down accordingly. Thus, both baseline and follow-up liver stiffness values are very important in clinical management.

G&H Is a 15% decrease in liver stiffness over a year clinically meaningful?

SG It is possible that a 15% decrease could be real and clinically meaningful. However, it has been recognized that this tool like others has its own inherent measurement variability. Even liver biopsy, which is considered the gold standard, suffers from the issue of variability and repeatability. Therefore, a higher threshold of change would be considered more reliable and representative of true change in liver disease histology. The current consensus, based on data our group and others have generated, is that 30% change from baseline is a more reliable and meaningful change in liver stiffness both in research and clinical practice.

G&H What is the prognostic value of composite scores such as AGILE 3+ and 4, which include liver stiffness as one of their parameters?

SG These composite scores have prognostic value at baseline as well as in follow-up. In addition to liver stiffness measurement, the AGILE 3+ and 4 scores incorporate diabetes and sex plus widely available laboratory values such as aspartate aminotransferase, alanine aminotransferase, and platelet count. The AGILE 3+ score also includes age, which is not part of AGILE 4. Published data indicate that both baseline values of these scores as well as their longitudinal changes on follow-up can predict liver-related events.

In an attempt to improve performance, these scores include other variables in addition to liver stiffness measurement, but these additions have not resulted in significant improvement in the accuracy of prediction over simpler tools such as liver stiffness measurement alone.

Both liver stiffness measurement alone, and as part of a composite score such as AGILE 3+ and 4, produces an AUROC in the 80% range, essentially without significant differences. In a busy clinical practice, unless these scores are automatically calculated, most clinicians will not have time to plug in all of the variables to calculate the scores.

G&H Could you discuss other methods for measuring liver stiffness, such as shear wave elastography, Velacur, and MR elastography?

SG Both shear wave elastography and Velacur are promising ultrasound-based tools for measuring liver stiffness to noninvasively assess the severity of MASLD and MASH and indirectly estimate liver fibrosis. There are emerging data on their use in assessing fibrosis and disease severity, but the main limitation is that there are limited data on the usefulness of both tools for predicting clinical events in patients with MASLD and MASH.

As for MR elastography, more data are available both for assessing MASLD and MASH disease severity as well as for prognosis. This tool has its place in clinical practice, specifically for patients who have severe obesity in whom VCTE is not feasible or successful. However, MR elastography also comes with limitations. It is more expensive than VCTE and is limited to specialized places, usually tertiary centers, that have the required software. Overall, looking at noninvasive modalities, VCTE-measured liver stiffness has the most robust and extensive data both for assessing disease severity in patients with MASLD/MASH as well as prognosticating which patients are at higher risk for developing future liver-related events.

G&H Could you expand on the interest in using liver stiffness measurement change as a surrogate endpoint in MASH clinical trials?

SG Ultimately, both patients and the field want to move away from liver biopsy. As mentioned, not only is it invasive, but it is also very costly. However, the desired transition has to be made when there is sufficient rigorous evidence supporting the robustness of liver stiffness measurement and its changes as a reasonably likely surrogate endpoint for predicting outcomes. This leap cannot be made without rigorous supporting evidence. This is critical because if the surrogate is not robust, reproducible, and accurate over time, mistakes could occur. Liver stiffness measurement could overestimate the risk of a clinical event—whether it be histologic improvement or worsening or the occurrence of liver decompensation—or it could miss an event altogether. Based on data available

thus far, we can confidently say there are good data to support several notions. One is that the baseline value for VCTE-based liver stiffness measurement is a surrogate for future liver-related events. There are also robust data to indicate that changes in liver stiffness over time are associated with changes in liver-related event risk (both increase and decrease). Additionally, there are emerging robust data that changes in liver stiffness measurement correlate with response to effective therapies for MASH. However, more data are still needed to use liver stiffness measurement change as a surrogate endpoint in MASH clinical trials. This may be possible in the next 5 to 10 years but is largely dependent on whether ongoing phase 3 and 4 trials will be able to resolve some of the remaining important questions about liver stiffness measurement.

G&H What are the next steps in research in this area?

SG To resolve the remaining issues, more data are needed to determine the optimal magnitude of change of liver stiffness measurement that predicts improvement in fibrosis and histology. Additionally, more research is needed to understand factors involved in patients in whom improvement in liver stiffness is seen but their histology worsens and, vice versa, patients who have worsening liver stiffness but their histology improves. We need more research to provide guidance on this complex issue. I am optimistic that data generated from the ongoing phase 3 and 4 clinical trials will help us to find practical and robust answers to these remaining issues.

Disclosures

Dr Gawrieh has consulted for TransMedics, Novo Nordisk, Kowa, Spruce, and GSK. He has received grant support from Zydus.

Suggested Reading

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