Editorial Commentary

Can liver stiffness measurement accurately predict disease progression and clinical outcome in patients with metabolic dysfunction-associated steatotic liver disease and bridging fibrosis or cirrhosis?

Diederick J. van Doorn[1]^, Adriaan G. Holleboom[2]^, R. Bart Takkenberg[1]^, Joanne Verheij[3]^, Marten A. Lantinga[1]^

[1]Department of Gastroenterology and Hepatology, Amsterdam UMC, University of Amsterdam, Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, The Netherlands; [2]Department of Vascular Medicine, Internal Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, The Netherlands; [3]Department of Hepatopancreatobiliary Pathology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Correspondence to: Marten A. Lantinga, MD, PhD. Department of Gastroenterology and Hepatology, Amsterdam UMC, University of Amsterdam, Amsterdam Gastroenterology Endocrinology Metabolism, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands. Email: m.a.lantinga@amsterdamumc.nl.

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Metabolic dysfunction-associated steatotic liver disease (MASLD)—until recently termed non-alcoholic fatty liver disease (NAFLD)—is a rising cause of chronic liver disease with an estimated global prevalence of 30% (1). There is no evidence that the presence of steatosis or steatohepatitis alone in MASLD correlates with liver-related complications or mortality. However, there is a strong association between liver fibrosis stage and increased liver-related and all-cause mortality risk in MASLD (2). Therefore, there is a clear need to assess the accuracy of non-invasive tests in establishing the degree of fibrosis in MASLD and ultimately the risk of disease progression.

The goal of the meta-analysis by Loomba *et al.* was to substantiate that an increased liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) at baseline is associated with the risk of disease progression in MASLD (3). The authors state that previous studies (4-6) show an association between baseline LSM and risk of progression to cirrhosis and liver decompensation. Recently, the Baveno consortium proposed incremental LSM thresholds for prognostication of liver fibrosis and decompensation (7). Based on this proposition, the authors aimed to find optimal LSM thresholds that could predict the risk of specific clinical outcomes in patients with advanced fibrosis (F3–F4) due to MASLD. The secondary aim was to investigate whether LSM changes (≥5 kPa and ≥20%) impact outcomes and whether combination with clinical scores could improve this prediction: Agile 3+ and Agile 4, which both incorporate LSM (3).

The authors used data from four randomized controlled trials. Even though all trials failed to show treatment efficacy and were stopped prematurely, data of serial biopsies and LSM were available. Two studies (prematurely stopped at 48 weeks) investigated the effect of selonsertib in

^ ORCID: Diederick J. van Doorn, 0000-0003-3299-0654; Adriaan G. Holleboom, 0000-0002-2911-2917; R. Bart Takkenberg, 0000-0003-2179-1385; Joanne Verheij, 0000-0003-1283-630X; Marten A. Lantinga, 0000-0003-3137-901X.

patients with F3 and F4 due to MASLD (8). The primary outcome was ≥1 stage of improvement in fibrosis score at week 48. The two other studies (prematurely stopped at 96 weeks) looked into the effect of simtuzumab, also in F3 and F4 patients (9). The primary outcome for patients with F3 was a decrease in hepatic collagen and for F4 a decrease in hepatic venous pressure gradient (HVPG). This effect was evaluated at 48 and 96 weeks. All studies had a planned duration of 240 weeks. The authors divided the patients in two groups: F3 to predict the progression to F4, and F4 to predict the occurrence of liver-related clinical events.

The authors found that for 664 patients with bridging fibrosis (F3), the median LSM was 12.7 kPa and that 14% of patients had an increase in LSM of ≥5 kPa and ≥20%. During a median follow-up of 16.6 months, 16% (n=103) of patients progressed from F3 to F4 which was biopsy confirmed in 93.2%. After adjustment for multiple baseline characteristics, the adjusted hazard ratio (aHR) was 3.99 with every 3-kPa increase (P<0.0001). The optimal LSM threshold for predicting progression to F4 according to the authors was ≥16.6 kPa at baseline. In patients with F3 and LSM of ≥16.6, progression to F4 occurred in 31.1%, whilst progression to F4 occurred in only 9.1% of patients with LSM <16.6 kPa. Increase of LSM ≥5 kPa and ≥20% in comparison to baseline showed a significant increase in progression to cirrhosis compared to patients who did not have such an increase (22% *vs.* 14%). Lastly, the Agile 3+ score has been evaluated as predictor for progression to cirrhosis. With an aHR of 4.75 per 0.1 units, the optimal threshold was ≥0.90 (P<0.0001). When comparing LSM and Agile 3+, no significant difference in predictive value was observed.

For 734 patients with F4, median LSM was 21.1 kPa. During 16.2 months follow-up only 4% (n=27) of patients experienced liver-related complications (ascites, hepatic encephalopathy or bleeding). For these patients, the optimal LSM threshold at baseline was set at ≥30.7 kPa. The authors found an aHR of 10.13 per 5-kPa increase (P<0.0001). In the F4 group, LSM increase ≥5 kPa and ≥20% after baseline was not significantly associated with an increased risk of decompensation. Lastly, the Agile 4 score was evaluated. With an aHR of 11.84 per 0.1 units, the optimal threshold was ≥0.72 (P<0.0001). When comparing LSM and Agile 4, no significant difference in predictive value was observed.

Firstly, the study performed by Loomba *et al.* is of high quality and methodologically well-constructed. There is an unmet need in accurately diagnosing and staging of fibrosis to predict progression to cirrhosis or development of liver-related complications. The current reference standard of liver biopsy is not routinely performed due to its invasive nature. The authors showed once more that the use of LSM is a valuable non-invasive modality in the armamentarium of diagnosing and monitoring of patients with liver disease. The authors performed this study because they felt that there was a lack of prospective evidence in patients with F3/F4 at baseline.

When looking at the paper of Eddowes *et al.* which is seen as a landmark paper for LSM cut-off values in patients with MASLD, it is noteworthy that the corresponding values for each grade of fibrosis of F ≥ F2, F ≥ F3, and F = F4 were 8.2, 9.7, and 13.6 kPa, respectively (10). When looking at the proposed predictive threshold for progression from F3 to F4 in patients with MASLD in the study by Loomba *et al.*, the value is ≥16.6 kPa. This is technically already considered F4 based on the Eddowes criteria. On the other hand, one could argue that the correlation between LSM and biopsy is not as profound as it is made out to be, especially in the case of obese-MASLD. But that would only implicate that a biopsy is needed to prove or disprove the LSM value at baseline, which brings us back to square one: the need for non-invasive tools to accurately assess fibrosis grade in MASLD. Furthermore, in this study, still 9.1% of patients with a LSM <16.6 kPa progressed to F4, which in a clinical setting cannot safely be ignored when treating patients.

When looking at the data for patients with F4 and their risk for developing liver-related complications, a similar observation can be made as with F3. According to the newest Baveno guidelines, clinically significant portal hypertension (CSPH)—and thus a risk of developing liver-related complications—is assumed from a LSM of 25 kPa and above (7). Granted, this has not yet been validated in patients with obese-MASLD by the Baveno consortium, but it gives a precedent as to which level of LSM to expect when assessing the risk of decompensation. Loomba and colleagues proposed a LSM threshold of ≥30.7 kPa, which lies well above 25 kPa. This can possibly be explained by the relatively short follow-up time of around 16 months. This might not have been long enough to progress from F3 to F4, or F4 to complications. Resulting in only the 'worst cases' to meet the defined outcomes.

However, evidence suggests that the risk of liver-related complications due to CSPH can already manifest in an earlier stage of MASLD prior to cirrhosis. This might be due to a porto-sinusoidal component of MASLD, where

lipid accumulation and hepatocyte ballooning may cause stellate cell activation resulting in increased portal pressure (11,12). Involvement of the sinusoidal space might implicate that the portrayed LSM value is an underestimate of the portal pressure and thus the risk of complications. Selecting 30.7 kPa as a threshold seems eerily high considering.

Another limitation that is worth mentioning, also described by the authors, is that all biopsies were evaluated by a single pathologist. Furthermore, it is not clear from the methods section what criteria were used for the assessment of biopsy adequacy. For reliable staging, representative liver tissue of adequate size is needed. Within the categories F3–F4, there is also a lot of variety in the total amount of fibrosis, together with subsequent architectural changes (13). Nevertheless, the presence of bridging fibrosis is probably one of the features in MASLD that is less prone to interobserver variability and very relevant as crucial component of vascular alterations in advanced fibrosis, 'a bridge too far' (14).

Research into accurate, non-invasive tools is imperative to help identify MASLD patients at risk for disease-progression or complications. Data from the meta-analysis by Loomba *et al.* and also a recent large data meta-analysis by Mózes *et al.* (15) are highly promising. However, non-invasive tools available in daily practice lack the needed sensitivity and therefore cannot yet fully replace liver biopsy. To implement the proposed LSM thresholds would mean that ±10% of F4 patients would be missed, and ±70% would be incorrectly seen as F4. Indeed, the authors do not claim to have defined a clinically relevant cut-off value, yet carefully state that these values could be used in the setting of clinical trials to stratify for risk of complications. Further research and optimization of non-invasive tools for MALSD patients is needed. LSM is quickly gaining ground as diagnostic and monitoring tool for physicians. Refining cut-off values to applicability in daily practice is of high importance, with the ultimate goal to reduce both underdiagnoses of advanced fibrotic MASLD and over referral of metabolic dysfunction-associated steatotic liver (MASL)/metabolic dysfunction-associated steatohepatitis (MASH) without fibrosis.

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