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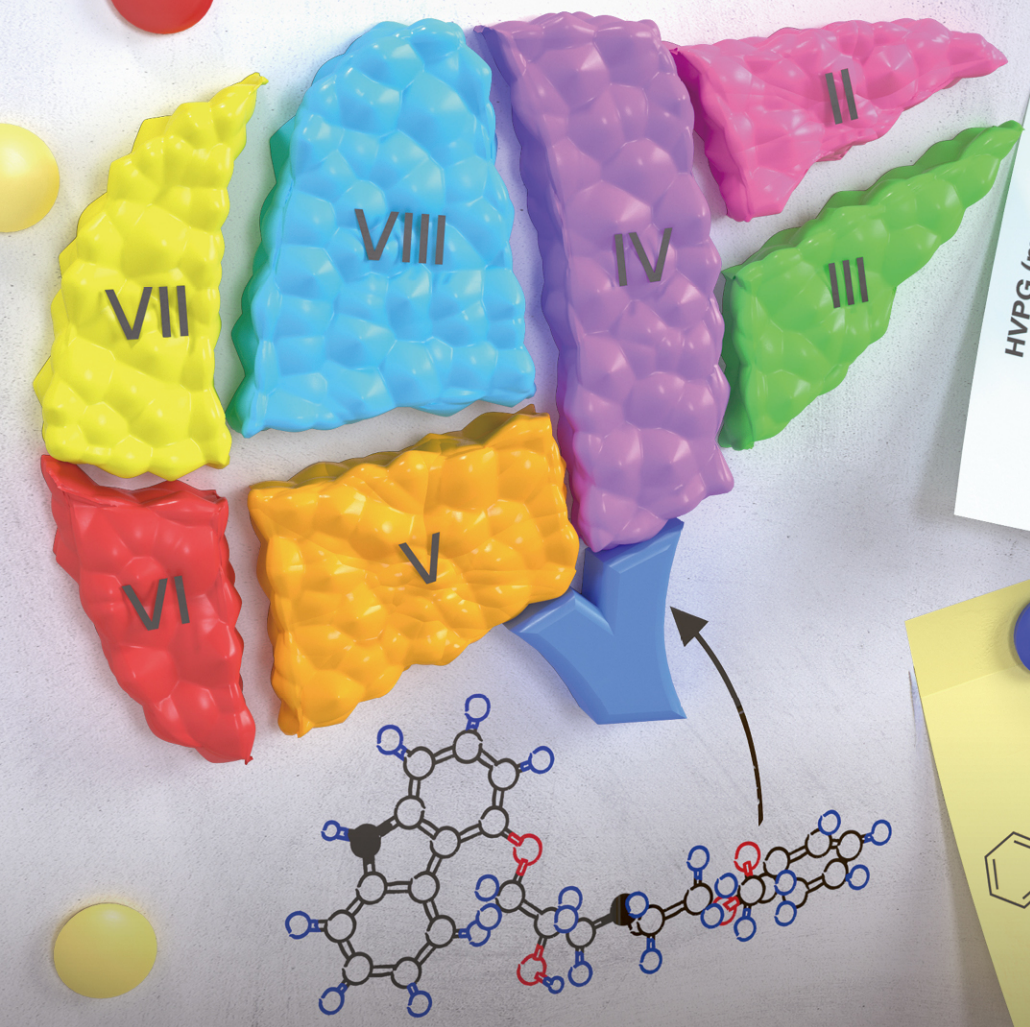

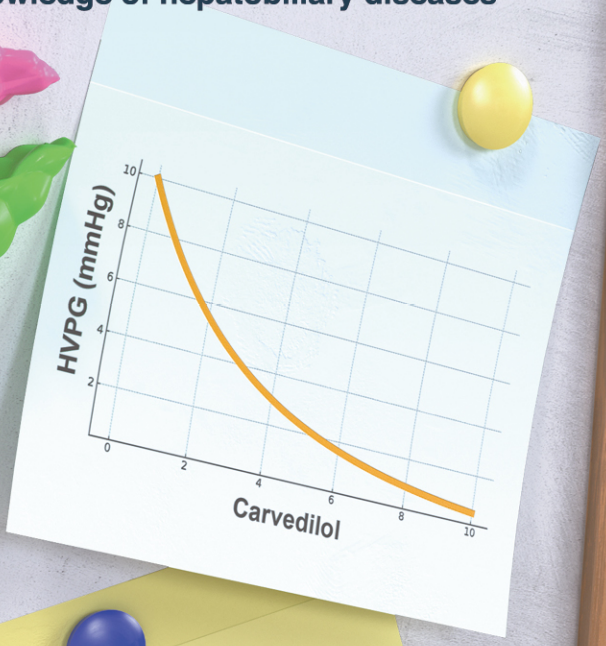

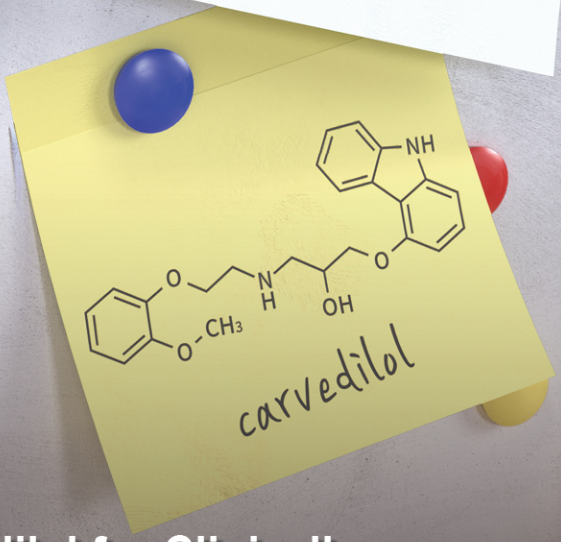

Non-invasive Model guiding Carvedilol for Clinically Significant Portal HTN

Intrapatient variability of tacrolimus on CKD in LT
HCV self-testing and disease burden reduction
MASLD and microbiota
Bariatric surgery for metabolic cirrhosis

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Editorial

Towards unification of liver stiffness measurement cutoffs: Editorial on "Optimal cut-offs of vibration-controlled transient elastography and magnetic resonance elastography in diagnosing advanced liver fibrosis in patients with nonalcoholic fatty liver disease: A systematic review and meta-analysis"

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Liver fibrosis is the natural response to liver injury from a variety of acute and chronic liver diseases. Although fibrous tissue has the function of dampening tissue injury in the short term, excessive deposition of fibrous tissue in case of chronic tissue injury becomes maladaptive. In the field of hepatology, cirrhosis is the stage where there is extensive fibrous tissue in the liver so much so that the scar starts to contract and distort the architecture of the liver. This is a critical point in the natural history of chronic liver disease. When a patient develops cirrhosis, he/she is at risk of portal hypertension, cirrhotic complications and hepatocellular carcinoma. Therefore, it is important to assess the degree of liver fibrosis, which reflects the prognosis, helps select patients for treatment and surveillance for liver complications, and indicates whether there is response to treatment.[1]

Because it is neither desirable nor feasible to perform liver biopsy routinely to assess and monitor patients with chronic liver disease, noninvasive tests are preferred. In large longitudinal studies, various noninvasive tests have already been shown to be as good as histological fibrosis stage in predicting major adverse liver outcomes.[2] In particular, vibration-controlled transient elastography (VCTE) is a point-of-care test that can estimate liver fibrosis (through liver stiffness measurement [LSM]) and steatosis (through controlled attenuation parameter) simultaneously and is well suited for the evaluation of metabolic dysfunc-

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tion-associated steatotic liver disease (MASLD), currently the most common chronic liver disease affecting over 30% of the general population.[3] Another key development in noninvasive tests is magnetic resonance imaging (MRI)-based techniques. MRI proton density fat fraction is already considered the gold standard for the quantification of hepatic steatosis, whereas magnetic resonance elastography (MRE) has been shown to be superior to VCTE in terms of both success rate and accuracy in head-to-head comparisons.[4] However, different studies have proposed different LSM cutoffs, in a way creating confusion among healthcare providers and impeding the application of these technologies in the wider community. In this issue of *Clinical and Molecular Hepatology*, Chon et al.[5] report the largest meta-analysis to date on the performance of VCTE and MRE in patients with MASLD, and attempt to suggest optimal LSM cutoffs.

The meta-analysis adhered to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy (PRISMA-DTA) Studies.[5] The literature search was performed across four databases: Medline, EMBASE, Cochrane Library, and KoreaMed. Two independent reviewers were responsible for article screening, data extraction, and assessing study quality, with a third reviewer involved in cases of disagreement. For the statistical analysis, the researchers applied a bivariate random-effects model, using the weighted mean of transformed diagnostic accuracy to calculate the pooled results. The overall diagnostic accuracy of VCTE and MRE was assessed by analyzing pooled sensitivity, specificity, and the area under the receiver operating characteristic curve (AUROC) at each stage of liver fibrosis, including F1, F2, F3 (advanced fibrosis), and F4 (cirrhosis). Additionally, the optimal cutoff values for advanced fibrosis for each diagnostic tool were determined by comparing AUROC values across various diagnostic ranges, as summarized from the primary studies.

The analysis included 63 studies for VCTE and 14 studies for MRE, with good quality across the included trials. Researchers found that for detecting mild fibrosis (≥F1), MRE may be a superior option. VCTE had an AUROC of 0.83 (95% confidence interval [CI], 0.80–0.86), with a sensitivity of 0.78 and specificity of 0.75. MRE showed a higher AUROC of 0.89 (95% CI, 0.86–0.92), with sensitivity and specificity of 0.78 and 0.87, respectively. The corresponding cutoff ranges for F1 were 5.0–9.6 kPa for VCTE and 2.5–3.14 kPa for MRE.

For moderate fibrosis (≥F2), similar findings were yielded, with MRE having an AUROC of 0.92 (95% CI, 0.89–0.94), sensitivity of 0.85, and specificity of 0.86. VCTE had an AUROC of 0.83 (95% CI, 0.80–0.86), sensitivity of 0.79, and specificity of 0.74. The cutoff ranges for F2 were 4.8–16.4 kPa for VCTE and 2.77–4.14 kPa for MRE.

For advanced fibrosis (≥F3), both methods demonstrated similar results. VCTE had an AUROC of 0.87 (95% CI, 0.84–0.90), sensitivity of 0.81, and specificity of 0.79, while a slightly higher AUROC was observed for MRE at 0.89 (95% CI, 0.86–0.92) with sensitivity and specificity of 0.85 and 0.89. The cutoff ranges for F3 were 7.1–14.1 kPa for VCTE and 2.3–4.8 kPa for MRE.

For cirrhosis (F4), the diagnostic performance of both VCTE and MRE was identical. Both tools demonstrated an AUROC of 0.94 (95% CI, 0.91–0.96), with the same sensitivity (0.88) and specificity (0.89). The cutoff values ranged from 6.9–20.1 kPa for VCTE and 3.35–6.7 kPa for MRE.

The researchers determined that the optimal cut-off value for diagnosing advanced fibrosis with VCTE was 7.1–7.9 kPa, with studies showing the highest AUROC of 0.90 (95% CI, 0.87–0.92) compared to other ranges, yielding a sensitivity of 0.89 and specificity of 0.67. For MRE, the optimal cut-off range was 3.62–3.8 kPa, yielding a higher AUROC of 0.94 (95% CI, 0.91–0.96) compared to the 3.9–4.8 kPa range, with a sensitivity of 0.88 and specificity of 0.91.

What can we learn from this meta-analysis?[5] Above all, it confirms the findings from smaller studies that MRE is somewhat but not substantially superior to VCTE for the diagnosis of liver fibrosis. The superiority is mainly observed for mild to moderate fibrosis but not advanced fibrosis or cirrhosis. Thus, if the target is advanced liver disease and the selection of patients for hepatocellular carcinoma and

Abbreviations:

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; PRISMA-DTA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy; VCTE, vibration-controlled transient elastography

varices surveillance, the less expensive option would suffice.

On the other hand, the method to determine the optimal LSM cutoffs in this study deserves discussion. The authors focused on advanced fibrosis and determined the AUROC of studies proposing different cutoffs. AUROC reflects the discriminatory performance of a continuous variable and is not affected by the cutoff. Thus, the varying AUROC in different studies is due to study factors such as patient composition, presence of potential confounding factors, and reliability of the histological reference standard. Rather, the best approach to determine optimal cutoffs is through an individual participant data meta-analysis. One example from the LITMUS group included 798 patients with MASLD from eight studies and determined optimal MRE cutoffs at 3.14 kPa for F2-F3, 3.53 kPa for F3-F4, and 4.45 kPa for F4 disease.[6]

In addition, by combining data from multiple studies, it would be important to answer a number of questions pertinent to the field. For example, previous studies from individual cohorts have proposed different LSM cutoffs for patients with different liver diseases. In particular, some studies suggested higher cutoffs for alcohol-related liver disease. This may make interpretation confusing, especially if our goal is to build clinical care pathways that involve primary care physicians in the initial assessment.[7] Confounding factors for LSM should also be studied in greater detail. Food intake prior to LSM, acute hepatic inflammation, congestive heart failure, biliary obstruction and amyloidosis are well-established causes of false-positive LSM and can be avoided by careful patient selection and instructions. The impact of obesity and hepatic steatosis on VCTE-LSM remains controversial. In a previous multicenter study, the same VCTE-LSM cutoffs appear to work similarly well when the M and XL probes were used in patients with body mass index <30 and ≥30 kg/m^2, respectively.[8]

In recent years, the publication of the Baveno VI and Baveno VII consensus documents has further streamlined the application of VCTE-LSM.[9] The famous “rule of 5” provides a simple and practical framework for the diagnosis and prediction of compensated advanced chronic liver disease, clinically significant portal hypertension, and high-risk varices. This allows evidence-based patient selection for hepatocellular carcinoma surveillance, initiation of non-selective beta-blockers for the prevention of variceal hemorrhage and hepatic decompensation, and endoscopic screening for varices in case beta-blockers are contraindicated. However, questions remain. The use of VCTE-LSM ≥25 kPa to rule in clinically significant portal hypertension does not apply to obese patients with MASLD. The introduction of spleen stiffness measurement as a biomarker of portal hypertension is a welcomed development, but again its performance in obese patients requires further evaluation. Finally, studies should determine if these algorithm-guided managements translate into improved clinical outcomes.

In conclusion, the study by Chon, Jin and colleagues provides high-quality data on the performance of LSM by VCTE and MRE and addresses the important question of cutoff determination and validation. This remains a fertile field for further research. At the end of the day, we should also ensure that the clinical knowledge is implemented in clinical practice to benefit the huge number of patients with chronic liver disease.[10]

Authors’ contribution

The authors contributed equally to the literature review and manuscript preparation. They approved the final version of the manuscript.

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Conflicts of Interest

Vincent Wong served as a consultant or advisory board member for AbbVie, AstraZeneca, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Inventiva, Merck, Novo Nordisk, Pfizer, Sagimet Biosciences, TARGET PharmaSolutions, and Visirna; and a speaker for Abbott, AbbVie, Echosens, Gilead Sciences, Novo Nordisk, and Unilab. He has received a research grant from Gilead Sciences, and is a co-founder of Illuminatio Medical Technology.

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