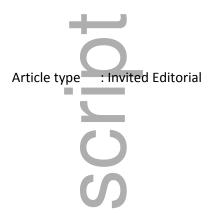
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Editorial: the impact of steatosis on liver stiffness quantification is minimal

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Nonalcoholic fatty liver disease (NAFLD) is a leading, growing cause of chronic liver disease. Histologically, NAFLD is a spectrum that ranges from steatosis to steatohepatitis and cirrhosis. However, longitudinal cohort studies have consistently shown that fibrosis stage alone governs long-term risk for adverse outcomes such as hepatocellular carcinoma and decompensated cirrhosis. Thus, efficient risk-stratification of patients with NAFLD is key to optimize both outcomes and resource utilization. Scoring systems such as FIB-4 can define low risk cohorts (e.g. FIB-4<1.3) but additional evaluation is needed for patients with intermediate and high-risk scores. For these patients, vibration-controlled transient elastography (VCTE) is powerful, low-cost, point-of-care tool.

The final frontier of VCTE research is defined by 3 principle questions. First, the majority of published experience with VCTE relates to M-probe use, yet 1 in 4 M-probe exams fail or are unreliable in NAFLD.⁷ The 'XL-probe' is now widely available but data are limited regarding test performance and cutoffs. Second, prospective intention-to-screen data are needed to define the optimal testing strategy by body mass index (BMI) in a setting with access to both VCTE and magnetic resonance elastography. Third, VCTE yields lower positive predictive values (PPV) than negative predictive values (NPV) owing to confounding factors affecting liver stiffness including inflammatory activity and hepatosteatosis, albeit controversially, best captured by controlled attenuation parameter (CAP).

Karlas et al. performed a patient-level meta-analysis of M-probe VCTE examinations to assess the impact of CAP and steatosis in 2,058 patients (18% NAFLD)⁸. The authors found no effect of hepatosteatosis and marginal effects of increasing CAP scores on liver stiffness. Though many patients with viral hepatitis were included, the most important data relates to NAFLD where cutoffs to achieve 90% sensitivity or specificity for F3-F4 fibrosis were 6.7 kPa or 11.9

kPa. Accounting for CAP, the NPV for F3-F4 only rose from 94.3% at CAP 200 dB/m to 95.5% at 350 dB/m. CAP adjustment also did not alter the 68% PPV for patients with F3-F4 fibrosis. The study limits include the lack of XL-probe data and ALT-based cutoffs for patients with NAFLD; conclusions from a cohort (mean BMI 27kg/m²) may not generalize to many clinical practices; and true correct-classification rates should derive from intention-to-screen data, accounting for screen failures.

VCTE's strength is its high NPV for advanced fibrosis. Weaker PPV is its limitation. Since PPV is dependent on test-characteristics and the prevalence of advanced fibrosis, efforts to improve VCTE's PPV have two strategic options: adjust for confounders or optimize patient selection. Karlas, improving on a prior report from this database by focusing on how results impact decision making, suggests no benefit for in adjusting VCTE cutoffs using fat-based metrics. While a study of ALT-adjusted liver stiffness cutoffs is welcome, to improve VCTE's PPV we have to help the test by selecting higher-risk patients. Building on these data, future studies should evaluate cohorts enriched with higher-risk patients (e.g. high FIB-4 scores), using XL-probe and intention-to-screen design.

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