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

Nonalcoholic fatty liver disease (NAFLD) is a leading, growing cause of chronic liver disease.[1] Histologically, NAFLD is a spectrum that ranges from steatosis to steatohepatitis and cirrhosis.[2] 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.[3,4] Thus, efficient risk-stratification of patients with NAFLD is key to optimise both outcomes and resource utilisation.[5] Scoring systems such as FIB-4 can define low risk cohorts (eg FIB-4 < 1.3) but additional evaluation is needed for patients with intermediate and high-risk scores.[6] 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 three principal 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, as 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 2058 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 27 kg/m^2) may not generalise 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 optimise patient selection. Karlas, improving on a prior report from this database by focusing on how results impact decision making,[9] suggests no benefit from 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 (eg high FIB-4 scores), using XL-probe and intention-to-screen design.

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Editorial: the impact of steatosis on liver stiffness quantification is minimal—Authors' reply

In their editorial, Drs Hassan and Tapper[1] discuss the potential role of vibration controlled transient elastography (VCTE) in the context of liver disease. Originally, VCTE was available with the M-probe, but more recently, the XL-probe was introduced in order to enable measurements among patients with higher body mass index (BMI). Hassan and Tapper raise a number of important points: (1) patients with non-alcoholic fatty liver disease (NAFLD) are of particular interest and their relevance will increase in the coming years, (2) XL-probe research is lacking, (3) negative predictive values (NPVs) for ruling out relevant fibrosis and cirrhosis are much higher than the corresponding positive predictive values (PPVs) and (4) prospective study designs and pre-selection with blood tests are needed in the screening setting to identify high-risk patients.

We agree wholeheartedly and would like to expand on these points with a few additional thoughts.[2,3] Both as clinicians and researchers, we are quite familiar with the technology and certainly see the need to conduct research on the XL-probe, but are confident that its basic properties will not differ greatly from those of the M-probe. However, the XL-probe is not yet part of the standard VCTE equipment and is associated with substantial cost. Research centres have access to these tools, but there is still a long way to go before they find their way into daily clinical practice—a prerequisite for screening. Alternatives for liver stiffness measurements (LSM) have become available that are incorporated in standard ultrasound devices, which require further evaluation, but could become important in the screening landscape.[4]

Despite its importance, the above considerations imply that LSM cannot be the primary screening tool for millions of NAFLD patients. As pointed out by Drs Hassan and Tapper, anthropometry and blood tests (eg the NAFLD fibrosis score or FIB-4) could become important as pre-selection instruments.[5] At the moment, awareness of such options and familiarity with the relevant guidelines is poor at best.[6,7] In addition, the transfer of screening algorithms proposed in practice guidelines[8] to daily routine is an unexpected challenge.[6,9]

Along the path to improved disease management, we will have to understand the progress of NAFLD better and explore how diagnostic technologies complement each other, keeping in mind that LSM is just a surrogate parameter.

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