DR ELLIOT B TAPPER (Orcid ID : 0000-0002-0839-1515)

Author Manuscript

Article type : Invited Editorial

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

Ammar Hassan MD and Elliot B. Tapper MD

Division of Gastroenterology and Hepatology, Department of Medicine, University of Michigan Hospitals, Ann Arbor, MI

Correspondence:

Elliot B. Tapper

3912 Taubman, SPC 5362

1500 E Medical Center Dr

Ann Arbor, MI 48109

T: (734) 647-9252

F: (734) 936-7392

e: etapper@umich.edu

Key words: cirrhosis, nonalcoholic fatty liver disease, hepatitis c, hepatitis b

Word count: 497

Tables/figures: none

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/apt.14584

This article is protected by copyright. All rights reserved

Disclosures: Ammar Hassan is responsible for the concept, data acquisition and writing. Elliot Tapper is the guarantor of this article and responsible for the concept, data acquisition and writing. Neither author conflicts of interest to disclose.

Financial support: No financial support was received by the authors

Author Manuscript

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 optimize both outcomes and resource utilization.[5] 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.[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 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

This article is protected by copyright. All rights reserved

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/m^2) 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,[9] 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.

Author Manuscript

References

1. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology* 2018;**67**(1):123-133.

2. Adams LA, Lymp JF, Sauver JS, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005;**129**(1):113-121.

3. Ekstedt M, Hagström H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology* 2015;**61**(5):1547-1554.

4. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver Fibrosis, but no Other Histologic Features, Associates with Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2015.

This article is protected by copyright. All rights reserved

5. Tapper EB, Sengupta N, Hunink MM, Afdhal NH, Lai M. Cost-effective evaluation of nonalcoholic fatty liver disease with NAFLD fibrosis score and vibration controlled transient elastography. *The American journal of gastroenterology* 2015;**110**(9):1298-1304.

6. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clinical Gastroenterology and Hepatology* 2009;**7**(10):1104-1112.

7. Tapper EB, Challies T, Nasser I, Afdhal NH, Lai M. The Performance of Vibration Controlled Transient Elastography in a US Cohort of Patients With Nonalcoholic Fatty Liver Disease. *The American journal of gastroenterology* 2016.

8. Karlas T, Petroff D, Sasso M, et al. Impact of controlled attenuation parameter on detecting fibrosis using liver stiffness measurement. Aliment Pharmacol Ther 2018; doi: 10.1111/apt.14529

9. Petta S, Wong VWS, Cammà C, et al. Improved noninvasive prediction of liver fibrosis by liver stiffness measurement in patients with nonalcoholic fatty liver disease accounting for controlled attenuation parameter values. *Hepatology* 2017;**65**(4):1145-1155.

Author Manuscript

This article is protected by copyright. All rights reserved