Variability of ultrasound-based methods to assess liver stiffness in NAFLD

Results of the Non-invasive Biomarkers of Metabolic Liver Disease (NIMBLE) study 1.1 on the reproducibility and repeatability of shear-wave and transient elastography in non-alcoholic fatty liver disease

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Introduction

- Regulatory qualification of non-invasive tests (NITs) to quantify liver fibrosis for drug development is a major unmet need in non-alcoholic fatty liver disease (NAFLD).
- Repeatability and reproducibility are key performance metrics that inform the context of use and support the regulatory qualification of quantitative imaging biomarkers.
- The repeatability and reproducibility of ultrasound shear-wave elastography (SWE) and vibration-controlled transient elastography (VCTE)-derived estimates of liver stiffness have not been characterized across device vendors and liver fibrosis stages.

Aim

- To establish the repeatability and reproducibility of ultrasound shear-wave elastography (SWE) and vibration-controlled transient elastography (VCTE)-derived estimates of liver stiffness across device vendors and liver fibrosis stages.

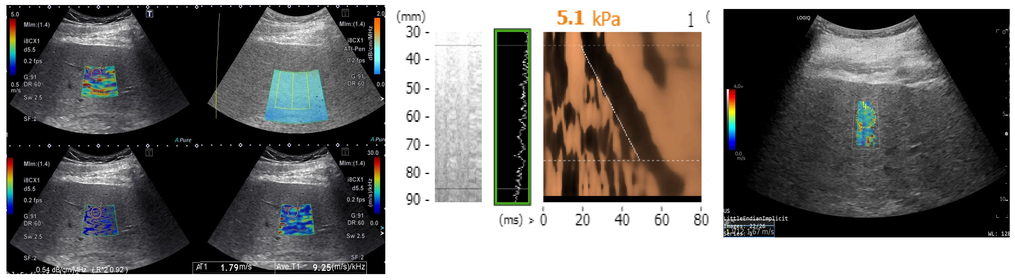
Method

- Adults with suspected or established NAFLD were prospectively recruited at 2 sites.
- Subjects were stratified by FIB-4 (<= 1.3, >1.3<2.67, >= 2.67). A prespecified number of subjects in each FIB-4 group were recruited to minimize spectrum bias.
- At visit 1, each subject underwent 6 examinations on different ultrasound systems (Figure 1) and VCTE performed by a single sonographer. At visit 2, held within 7 days of visit 1, a different sonographer performed 6 additional scans (Figure 2) following a prespecified device use plan matrix.
- Sonographers and clinical investigators were blinded to liver-related subject data. All imagery was subject to quality review and centrally read by an independent blinded Radiologist.
- To facilitate comparability, VCTE and SWE were analyzed in units of m/s by an independent statistician who was blinded to the clinical data.
- The primary end point was pooled different-day, different-operator reproducibility coefficient (RDC_{DDDO}).
- Secondary endpoints included scanner-specific RDC_{DDDO}, same-day/same-operator repeatability coefficient (RC_{SDSO}), and between-vendor RDC_{SDSO}.
- RC and RDC are QIBA-recommended metrics for assessment of repeatability and reproducibility, with lower values implying lower variability.
- The study was powered to detect a 95% RDC_{DDDO} upper bound ($UB_{95\%}$) of ≤ 35%.
- The study was not powered to compare different vendors' measurement variability.
- The $UB_{95\%}$ threshold of ≤ 35% was selected a priori as it was considered, based on expert opinion, to connote adequate repeatability and reproducibility for biomarker application in some contexts of use relevant to clinical trial execution such as diagnostic enrichment.

Results

- 40 participants (mean age 60 years, 60% female) with low (17), intermediate (15), and high (8) FIB-4 scores were recruited. Mean body mass index was 30.9 kg/m^2. RDC_{DDDO} was 30.7% ($UB_{95\%}$ 34.4%) for SWE and 35.6% ($UB_{95\%}$ 43.9%) for VCTE. SWE vendor-specific RDC_{DDDO} varied from 24.2%-34.3%. Pairwise differences between vendors were not significant, although the study was not powered to detect such differences. RC_{SDSO} was 21.0% for SWE (13.9%-35.0%, by scanner) and 19.6% for VCTE. Between-vendor RDC_{SDSO} was 52.7% ($UB_{95\%}$ 64.7%).

	Number of Observations	RDC_{DDDO}	Upper 95% Confidence Bound	RC_{SDSO}	Upper 95% Confidence Bound
Vendor 1	24	31.9%	42.0%	19.0%	25.0%
Vendor 2	24	24.2%	32.1%	13.9%	18.3%
Vendor 3	24	29.9%	39.4%	14.2%	18.7%
Vendor 4	24	32.3%	42.5%	14.9%	19.6%
Vendor 5	24	34.3%	45.2%	35.0%	46.1%
Pooled SWE	40	30.7%	34.4%	21.0%	23.5%
VCTE	39	35.6%	43.9%	19.6%	24.1%



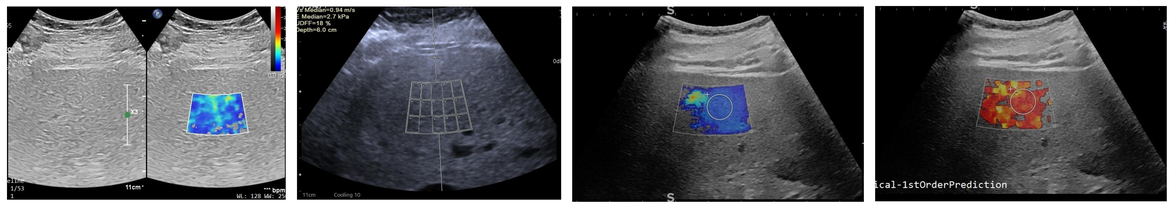


Figure 1: Example images from participating device manufacturers.

Conclusions

- SWE demonstrated good RDC_{DDDO} (30.7%[$UB_{95\%}$ 34.4%]). Slightly higher RDC_{DDDO} (35.6%[$UB_{95\%}$ 43.9%]) was observed for VCTE.
- Considerably higher SWE variability is observed when comparing measurements on different vendor platforms (between-vendor RDC_{SDSO} = 52.7% [$UB_{95\%}$ 64.7%]).
- These estimates are likely to inform ultrasound-based NIT qualification by (1) defining expected variability, (2) establishing that serial examination variability is lower when performed on the same vendor platform, and (3) informing future clinical trial design.

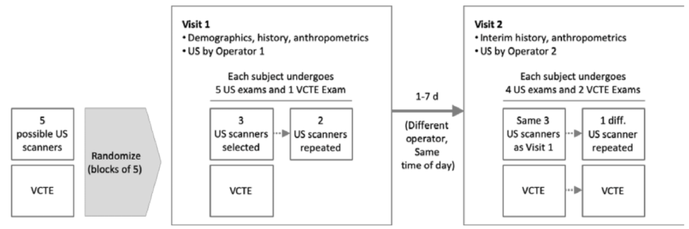


Figure 2: Study flow chart

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