Study Protocol and Statistical Analysis Plan

Study Title: Beyond Confounders: Addressing Source of Measurement Variability and Error in Shear Wave Elastography

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HYPOTHESIS: We hypothesize that variation using ultrasound elastography (UE) for the estimation of stage of liver fibrosis in patients with diffuse liver disease exists due to different methods of measurements, and/or different systems.

BACKGROUND: Liver disease and cirrhosis are important causes of morbidity and mortality in the United States and are a major public health problem with 40,000 deaths and more than 1.4 billion dollars spent on medical services. Hepatic fibrosis is the final common pathway for many different liver insults and is known to be a dynamic process, which is reversible if diagnosed early and treated. If untreated, fibrosis eventually progresses to cirrhosis, which is irreversible. The diagnosis of fibrosis relies on liver biopsy (the gold standard) however, is an invasive procedure with risks and sampling errors. Indirect biomarkers of fibrogenesis can measure some of these components to determine categories of fibrosis, with a sensitivity and specificity of 47% and 90% respectively.It is shown in the literature that, fat content of liver is related with fibrosis development. Biopsy is accepted as the most accurate technique to assess liver fat and fibrosis amount. Fibrotic livers demonstrate increased stiffness, a property that can be measured using technology named Ultrasound Elastography or sonoelastography (SWE). SWE is performed by insonating the patient with a low energy, amplitude, and frequency shear wave created by a vibrating probe. The propagated wave travels faster with increasing fibrosis: the stiffer the tissue, the faster the shear wave propagates. A pulse-echo ultrasound acquisition allows measurement of the wave velocity and the results are presented as kilopascals (kPa). Prior reports have described sensitivity and specificity for liver fibrosis detection of 80% and 97% respectively for SWE. The benefits of SWE are that it is inexpensive, reproducible, painless, rapid (< 10 min), easy to perform, and can be used for diagnosis, prognosis and monitoring disease progression.

SPECIFIC AIMS:
-Compare shear wave elastography (SWE) measurements from different ultrasound systems; using histopathology as reference standards.
-Assess intra-operator and inter-operator reliability by measuring variability in elastography values by two operators on a single system.
-Determine the effect of deviations from guidelines (less number of measurements and measurements during active breath)

The proposed investigation is a cross-sectional study using ultrasound elastography and fat quantification modalities. We enrolled 30 subjects 18 years old and older in whom diffuse liver disease was suspected, and who had undergone non-focal liver biopsy in the past 6 months or are scheduled to undergo biopsy within 3 months of enrollment, as part of their routine clinical care.

Inclusion criteria:
-   Adult patients (age 18 or older)
-   Men or women

- Suspected diffuse liver disease and have had a liver biopsy within the last 6 months or are scheduled for a liver biopsy in the next 3 months.
- Consent to participate in the study

Exclusion criteria:
- Pregnancy
- Acute illness/cognitive impairment resulting in inability to cooperate with ultrasound
- Patients that do not consent to ultrasound examination.

All subjects came for 2 study visits within 60 days of each other. In addition, subjects needed to fast for at least 4 hours prior to study visits. Sonoelastography was performed using four FDA-approved ultrasound units. 2 sonographers performed;

- Median Elastograpy (10 measurements) on regular and variable map at a depth(in the area between 2cm from capsule and 6.5cm from skin)
- Median SWE value with active/free breath(10measurements)
- Median SWE value with less number of acquisitions(3measurements)

STATISTICAL ANALYSIS PLAN:
Statistical analysis software to use: SPSS (Release 24, IBM, NY, USA) software.
Intra-operator agreement between each operators' median measurement was calculated using ICC (Intraclass correlation coefficient). 95% confidence intervals were computed for parameter estimates. All p-values were two sided. p values less than 0.05 were considered statistically significant.