RSNA/QIBA: Shear wave speed as a biomarker for liver fibrosis staging

Timothy J. Hall[1], Andy Milkowski[11], Brian Garra[18], Paul Carson[15], Mark Palmeri[2], Kathy Nightingale[2],
Ted Lynch[17] Abdullah Alturki[14], Michael Andre[14], Stéphane Audiere[3], Jeffery Bamber[10], Richard Barr[12],
Jeremy Bercoff[13], Jessica Bercoff[13], Miguel Bernal[5], Javier Brum[5], Huan Wee Chan[10], Shigao Chen[7],
Claude Cohen-Bacrie[13], Mathieu Couade[13], Allison Daniels[8], Ryan DeWall[1], Jonathan Dillman[15], Richard Ehman[7],
SF Franchi-Abella[4], Jeremie Fromageau[10], Jean-Luc Gennisson[5], Jean Pierre Henry[13], Nikolas Ivancevich[11],
Jan Kalin[11], Sarah Kohn[1], Jennifer Kugel[7], Ken Lee[1], NL Liu[4], Thanasis Loupas[13], Joan Mazernik[12],
Stephen McAleavey[16], Véronique Miette[3], Stephen Metz[8], BM Morel[4], Thomas Nelson[14], Eric Nordberg[1],
Jennifer Oudry[3], Monali Padwal[11], Ned Rouze[2], Anthony Samir[6], Laurent Sandrin[3],
Janet Schaccitti[12], Cedric Schmitt[9], Vijay Shamdasani[8], Pehngfei Song[7],
Pamela Switalski[8], Michael Wang[2], Keith Wear[18], Hua Xie[8], Heng Zhao[7]

[1]Medical Physics Department, University of Wisconsin, Madison, Wisconsin 53705
[2]Duke University, Durham, NC [3]Echosens, Paris, France [4]Hôpitaux universitaires Paris-Sud (APHP), Paris, France
[5]Institut Langevin, Paris, France [6]Massschusetts General Hospital, Boston, MA [7]Mayo Clinic, Rochester, MN
[8]Philips Ultrasound, Bothell, WA [9]Rheolution, Inc, Montreal, Canada [10]Royal Marsden Hospital, London, UK
[11]Siemens Ultrasound, Issaquah, WA [12]Southwoods Imaging Center, Youngstown, OH
[13]Supersonic Imagine (SSI), Aix-en-Provence, France [14]University of California at San Diego
[15]University of Michigan, Ann Arbor, MI [16]University of Rochester, Rochester, NY
[17] Computerized Imaging Reference Systems, Inc. (CIRS), Norfolk, VA [18]Food and Drug Administration, USA

Abstract—**An interlaboratory study of shear wave speed (SWS) estimation was performed. Commercial shear wave elastography systems from Fibroscan, Philips, Siemens and Supersonic Imagine, as well as several custom laboratory systems, were involved. Fifteen sites were included in the study. CIRS manufactured and donated 11 pairs of custom phantoms designed for the purposes of this investigation. Dynamic mechanical tests of equivalent phantom materials were also performed. The results of this study demonstrate that there is very good agreement among SWS estimation systems, but there are several sources of bias and variance that can be addressed to improve consistency of measurement results.**

I. INTRODUCTION

In 2008 the Radiological Society of North America (RSNA) created the Quantitative Imaging Biomarker Alliance (QIBA) with pharmaceutical companies, imaging system manufacturers, academics, clinicians and representatives from the USA federal government (e.g., FDA, NIH, NIST) to advance the concept of converting "imaging systems" to "measurement systems." The Alliance is organized by Modality Committees and within these committees are Technical Committees whose efforts involve specific classes of biomarkers. Each Technical Committee is supported by one or more Subcommittees organized for specific tasks. The goal is to create QIBA/UPICT (Uniform Protocol for Imaging in Clinical Trials) protocols that specify methods for data acquisition, analysis and interpretation as well as QIBA Profiles that will provide specific claims of what can be accomplished by following the QIBA Protocol. The intent is to validate the profile across imaging systems with phantoms and volunteers working with other organizations such as drug and instrument companies and clinical trials organizations.

The Ultrasound Modality Committee was formed in 2012. Our only Technical Committee (TC) is the Ultrasound Shear Wave Speed TC. We are developing a protocol and data analysis methods to allow direct comparison of shear wave speed (SWS) measurements in liver for staging fibrosis. Several systems that measure SWS in the liver are commercially available, and many articles are reporting the ability to differentiate among fibrosis stages. Existing literature suggests that different estimates of shear wave speed in the same liver are obtained with different measurement systems (see, for example, [1]). These differences can cause uncertainty and a lack of technology adoption in the clinical community. Given the need for serial assessment of liver fibrosis, and the impracticality of serial liver biopsy, providing a common SWS estimate among systems would make these studies more clinically viable and speed adoption of the technology.

The first step toward understanding sources of bias and variance in SWS estimates is to perform a study in relatively simple phantoms. Our intent was to measure SWS in a set of equivalent phantoms containing homogeneous, isotropic and nearly completely elastic material. The lack of a loss component in the complex modulus was expected to ease direct comparison among the various SWS estimation systems (for example, the frequency content of the shear wave wouldn't matter in such media). The methods, preliminary results and conclusions of our initial investigation are described below.

II. METHODS

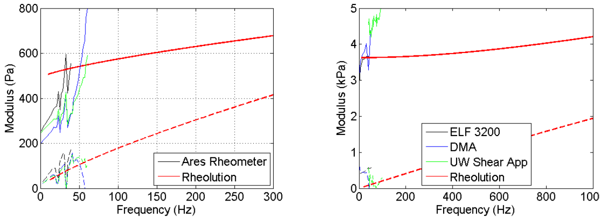
The first phase of our study was designed to estimate SWS in pairs of phantoms that are nearly completely elastic (little loss component). These phantoms are homogeneous cylinders (10cm diameter, 10cm deep; except for the MRI phantoms which are 20cm diameter) and one of each pair is relatively soft and one relatively stiff (compared to liver). The phantoms were distributed among 15 sites (12 included in the current analysis) for measurements on commercial clinical SWS-capable systems (Fibroscan, Philips, Siemens S2000, SSI Aixplorer) as well as experimental systems under development in some labs. Prior to distribution to those sites, all phantoms were measured in a single lab (Duke University) with a single system (Verasonics with a custom software implementation) to assess the between-phantom component of variance.

Before data acquisition at the various sties commenced, the SWS TC members agreed to have measurements performed at three depths relevant for liver evaluation (3.0, 4.5 and 7.0cm). Each site had at least three appraisers scan each phantom at least three times to estimate the bias and components of variance in SWS estimates among systems. The order of data acquisition was randomized for phantoms, appraisers, depths, and imaging systems (if more than one was used) to allow for detailed statistical investigation of results. Participants were all blinded to the intermediate results of others.

In addition, several test samples of the same phantom materials were manufactured for independent material property assessment with a dynamic mechanical analysis (DMA) equipment (Rheolution RheoSpectris, Ares shear rheometer, Enduratec ELF 3200, a custom dynamic mechanical tester in the polymer chemistry group at the University of Wisconsin and a custom shear apparatus in the Medical Physics Department at the University of Wisconsin). Each test machine required a unique sample geometry and the set of measurements represents a variety of different mechanical stimuli for material property assessment. All participants were blinded to the results of DMA until the conclusion of SWS data acquisition.

III. RESULTS

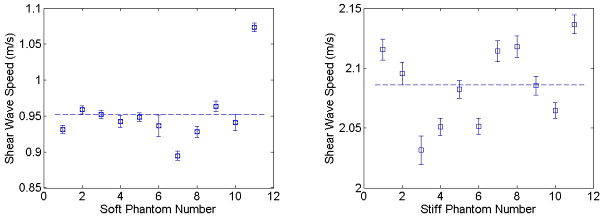
Figure 1 show plots of the results from independent dynamic mechanical testing of the phantom materials used in this study. Reasonable agreement was obtained among very different dynamic mechanical tests. The largest discrepancy is seen in storage modulus estimates for the softer material. The soft phantom materials were particularly difficult to measure on any of the dynamic mechanical testing devices. These materials were also more lossy than expected from previous studies with similar, but stiffer, materials. The relative mechanical loss is quantified by the dissipation factor, $\tan\delta$, which is the ratio of the loss component to the storage component of the complex shear modulus and is equal to the phase angle between the applied stress and resulting strain in harmonic loading. Measurements, with confident results, on the softer materials extended up to only 300Hz, and $\tan\delta = 0.6$ at 300Hz. The stiff phantom materials were easier to measure, measurements extended up to 1kHz, and $\tan\delta = 0.26$ at 500Hz (a nominal center frequency for shear waves produced with acoustic radiation force).



(a) Soft Material (b) Stiff Material

Fig. 1. Results of dynamic mechanical testing of separately manufactured samples of the phantom materials.The solid and dashed lines show the storage and loss components of the complex shear modulus, respectively.

Results from the single-site (Duke University) SWS measurement on all phantoms are shown in Fig. 2. Relatively small, but important, differences in SWS were found among phantoms (both soft and stiff phantoms). All following results are adjusted these differences (using Duke estimates as the standard for comparison) – a required approximation. The mean SWS estimates, converted to shear moduli, are in reasonable agreement with elastic modulus estimates from DMA (Fig. 1).



(a) Soft Material (b) Stiff Material

Fig. 2. SWS estimates (Duke University) at 40mm depth in all phantoms. The line corresponds to the group mean. Deviations from this value were used to adjust all results reported below.

Figure 3 shows SWS results reported by each site confounded by differences among phantoms (although adjusted for using Duke measurements) and the fact that some sites used systems from multiple vendors.

Figure 4 shows SWS estimates grouped according to the system used (combining data across sites) and demonstrate an apparent bias in SWS estimates depending on which system was used and how soft/lossy the phantom material was. There is still a fairly large variance among SWS estimates for a given system.

To better understand and characterize the sources of variance in SWS estimates, we further analyzed data from individual systems. Figure 5 shows SWS estimates obtained

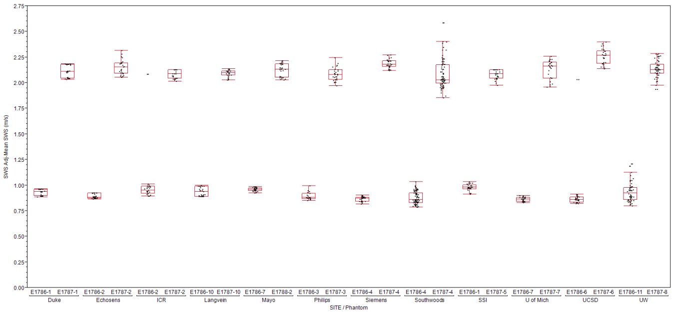
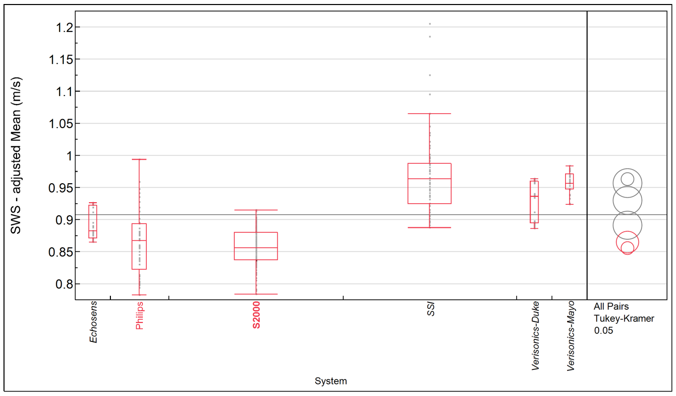
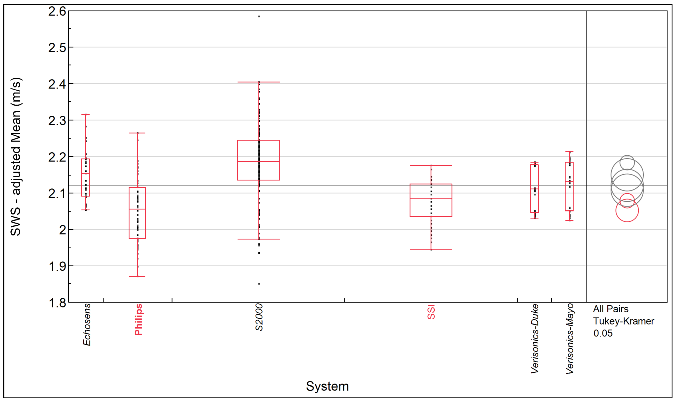


Fig. 3. Adjusted SWS estimates for both soft and stiff phantoms obtained by each group. Note that some groups used systems from different vendors which increased the variance in this plot.



(a) Soft Phantoms



(b) Stiff Phantoms

Fig. 4. Adjusted SWS estimates obtained at all sites group by the commercial system or research implementation used.

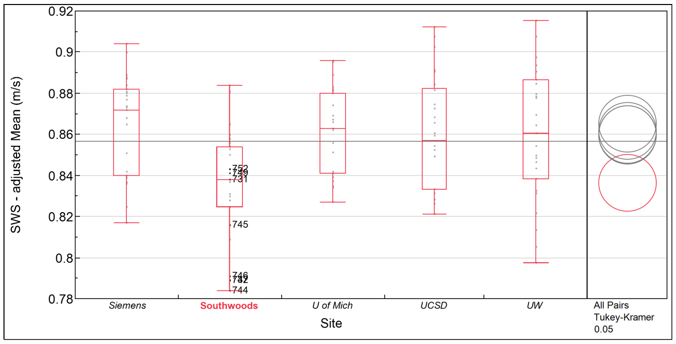


Fig. 5. Adjusted SWS estimates for the soft phantoms obtained by each site using Siemens S2000 systems. Note that Siemens and Southwoods used the same phantom pair, but Southwoods used a different transducer than the other sites.

from each site using a Siemens S2000. Data from Southwoods stands out as being different from the rest. Further investigation determined that a different transducer (4V1 phased array) was used at this site which was different from all other sites (4C1 curved linear array). These data suggest that there is a small component of variance attributed to the different (but equivalent) systems at the various sites.

Investigating this subset of data further, we examined results obtained by each appraiser using an S2000, shown in Fig. 6, and the results demonstrate that there is little difference among appraisers (noting the transducer-related bias for data from Southwoods). Appraisers appear to contribute equally to the variance.

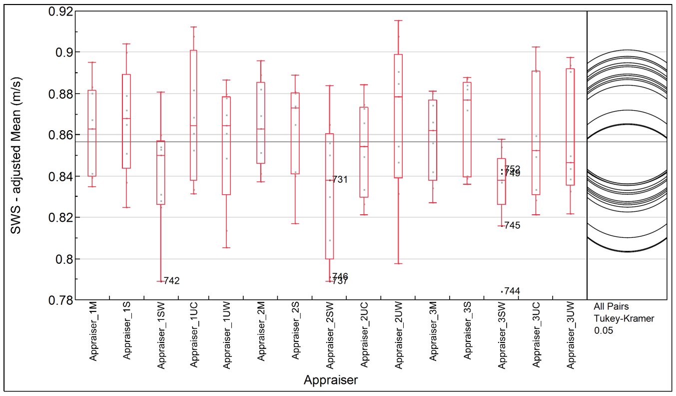


Fig. 6. Adjusted SWS estimates for the soft phantoms obtained by each appraiser using Siemens S2000 systems.

Investigating the sources of variance within each appraiser using the S2000, we found no significant temporal dependence in the data (randomized for acquisition order among appraisers, phantoms, acquisition depths and systems—if more than one was used). We did find a significant difference among measurements at each depth, as shown in Fig. 7. We don't know if this systematic error is due to the imaging system (for example, a difference in the frequency content of the shear wave with depth), a difference in phantom material properties with depth, or some other source.

Similar depth-dependent SWS estimates in the soft phantoms were found among nearly all systems for the soft phantoms, as shown in Fig. 8.

Combining data from all sites for the soft and stiff phantoms, there is strong evidence for a depth dependent bias in SWS among these systems and phantoms, shown in Fig. 9.

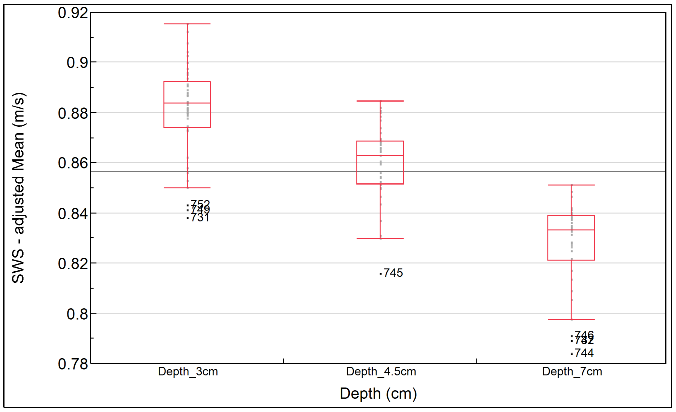


Fig. 7. Adjusted SWS estimates as a function of depth into the the soft phantoms obtained using Siemens S2000 systems (combined across sites).

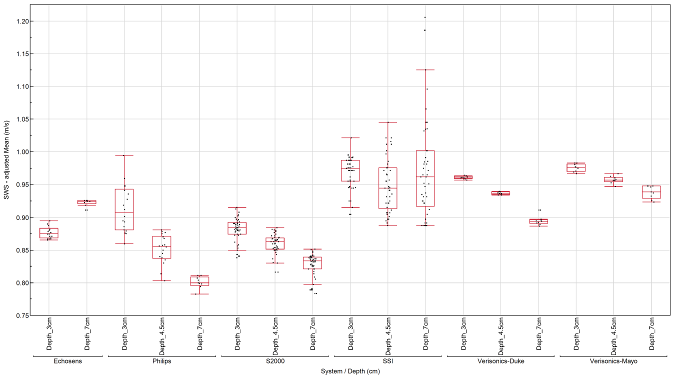
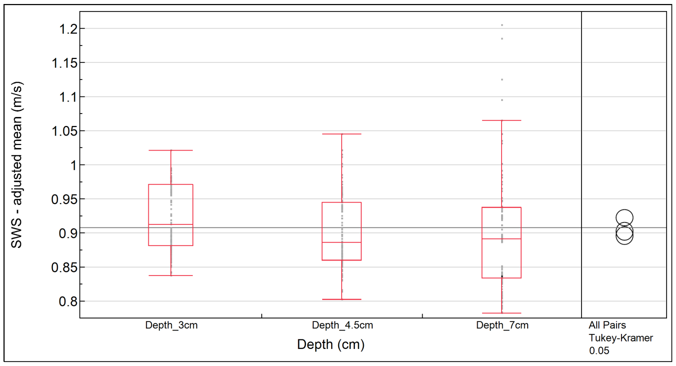


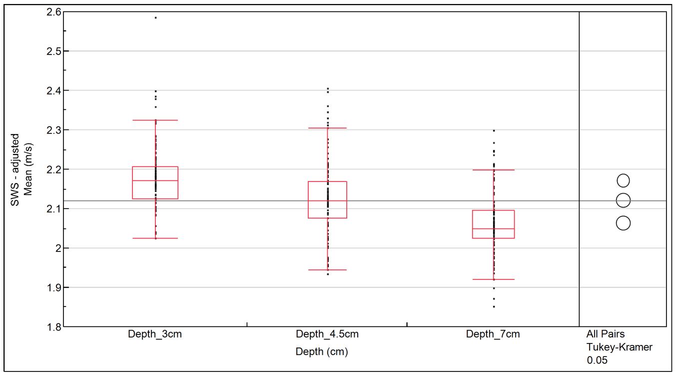
Fig. 8. Adjusted SWS estimates for the soft phantoms grouped by measurement depth and system used.

The source(s) of this bias requires further investigation, and that is the intent of the QIBA SWS TC effort.

The results of this study will allow us to greatly refine the plan for a Phase 2 interlaboratory study of SWS estimation. For example, our current plan is to change the phantom design to provide scanning windows on perpendicular surfaces. This will allow investigation of any potential depth-dependent material properties. A single phantom of each desired stiffness will be circulated among sites involved in the study. In that way, all sites will be measuring the same phantom. An identical phantom will be kept at the manufacturing site and its properties will be monitored during the serial measurements at contributing sites (to test for potential temporal change of phantom viscoelastic properties). A smaller number of sites and participants can be involved based on the findings of the current study. More suggestions for improvements on this study will likely result from further analysis of the existing data.



(a) Soft Phantoms



(b) Stiff Phantoms

Fig. 9. Adjusted SWS estimates obtained at all sites group by the commercial system or research implementation used.

IV. CONCLUSIONS

There is a statistically significant difference in SWS estimates among systems and with depth into the phantom (demonstrated with all imaging systems). No statistically significant differences were found among appraisers using the same (or equivalent) systems or sites using equivalent systems. These are very encouraging results in our quest for equivalent SWS estimates among commercial systems.

V. ACKNOWLEDGEMENTS

We gratefully acknowledge the support of CIRS, Inc. who provided the phantoms used in this study. We are also grateful to the RSNA for covering the costs of shipping the phantoms to the individual sites. The QIBA effort is funded in part by the RSNA and a contract with the NIBIB (HHSN268201000050C). The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the FDA.

REFERENCES

[1] I. Sporea, et al. "Acoustic Radiation Force Impulse Elastography for fibrosis evaluation in patients with chronic hepatitis C: An international multicenter study," *European Journal of Radiology* 81: 4112-4118, 2012.