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ON PATIENT RELATED FACTORS AND THEIR IMPACT ON ULTRASOUND-BASED SHEAR WAVE ELASTOGRAPHY OF THE LIVER

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Abstract—The aim of the study was to investigate patient-related factors associated with either reliable or poorly reliable measurement results of ultrasound-based shear wave elastography (SWE) of the liver. A total of 188 patients were analyzed prospectively with binary logistic regression using the interquartile range/median as cutoff to define two groups based on reliably and poorly reliable SWE results. SWE results correlated significantly with liver biopsy. Factors associated with reliable SWE results (i.e., no negative impact on measurements) were age, sex, cirrhosis, antiviral and/or cardiovascular medication, smoking habits and body mass index. Factors associated with poorly reliable SWE results were increased skin-to-liver capsule distance (odds ratio = 3.08, 95% confidence interval: 1.70–5.60) and steatosis (odds ratio = 2.89, 95% confidence interval: 1.33–6.28). These findings indicate that the interquartile range/median as a quality parameter is useful in avoiding poorly reliable SWE results. How best to examine patients with increased skin-to-liver capsule distance is a matter of some controversy, as the incidences of obesity, diabetes and metabolic syndrome are increasing worldwide; however, our results indicate that reliable SWE results can be obtained in this group of patients by using ultrasound-based SWE. (E-mail: marie.byenfeldt@umu.se, Marie.byenfeldt@aleris.se) © 2018 The Author(s). Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key Words: Shear wave elastography, Liver fibrosis, Skin-to-liver capsule distance, Interquartile range, Quality parameter, Reliability, Steatosis, Liver biopsy.

INTRODUCTION

Since the introduction of the non-invasive ultrasound-based method of shear wave elastography (SWE), the number of patients undergoing liver biopsy has declined dramatically. Nevertheless, standardized examination protocols for SWE have yet to be established, and uncertainties persist concerning how to perform reliable SWE examinations (Cosgrove et al. 2013); thus, there is a need to standardize these procedures. Several factors may affect SWE reliability (Dietrich et al. 2017), and little is known about how sex, body mass, patient positioning and examination technique influence the results.

Liver fibrosis is a progressive disease that can develop from chronic liver conditions, such as alcoholic steatohepatitis (ASH) (Canbay et al. 2016; Joshi-Barve et al. 2015) and non-alcoholic steatohepatitis (NASH) (Lee et al. 2017), as well as hepatitis B virus (HBV) (European Association for the Study of the Liver [EASL] 2017) and hepatitis C virus (HCV) (EASL 2014). Hepatitis may cause inflammation of the liver, which can lead to fibrosis, cirrhosis and, in the worst case, hepatocellular carcinoma (HCC) (EASL 2014, 2015, 2017). It is important to stage these patients so that treatment can be started when necessary because an estimated 22% of individuals with HCV progress to cirrhosis within 20 years (Freeman et al. 2001). Several classification systems are available for staging liver fibrosis based on histologic findings, and the most commonly used in Europe is the Metavir score table, where F0 represents normal liver tissue and F4 represents cirrhosis (Goodman 2007). Direct-acting antiviral agents (DAAs) are available that can leave patients virus free after successful treatment, and in Sweden, the consensus for treatment initiation is a cutoff Metavir ≥F2. Reliable liver fibrosis staging is critical to ensure that the right patients receive treatment, because the cost for DAA treatment is substantial (Lagging et al. 2017). In addition, repeated follow-up examinations for previously detected fibrosis are...
important, and both invasive and non-invasive methods are available (Srinivasa Babu et al. 2016).

The current gold standard for diagnosing liver fibrosis is liver biopsy; however, some authors have viewed liver biopsy as an imperfect option (Barr et al. 2016). It is also an invasive method that involves tissue sample variability (Bedossa et al. 2003), even when performed by experienced physicians. Likewise, when expert pathologists interpret biopsy findings, the error rate is as high as 20% (Castella et al. 2010) for staging fibrosis, failure to recognize cirrhosis occurs in 20% of cases (Abdi et al. 1979; Afdhal 2003) and sampling errors arise because biopsies represent only 1/50,000th of the total liver mass (Lee 1994, 1–21). Inter-observer variation between two pathologists is 6%–10% among all cases with respect to staging (Regev et al. 2002). One in 1000 liver biopsies carries a risk for severe complications (Piccinino et al. 1986), with a mortality rate of approximately 1/100,000 (Bravo et al. 2001).

It would thus be advantageous if non-invasive methods could replace liver biopsy because such methods could be repeated frequently and without the need for post-procedure hospitalization. Blood marker tests, although non-invasive, exhibit low accuracy in discriminating among intermediate stages of fibrosis, and several hepatic and extrahepatic conditions may influence them (Schiavon et al. 2014). Hence, great interest exists in establishing non-invasive methods to diagnose liver fibrosis, such as SWE (Barr 2014), which can also predict significant liver fibrosis stage ≥ 2 (Beland et al. 2014). These methods can also be repeated daily if necessary, and several options are available for detecting, monitoring and staging liver fibrosis.

Two such technologies are transient elastography (TE), using the FibroScan device, and ultrasound-based SWE. Both technologies involve the creation of shear waves in the tissue while the speed of their propagation is measured and quantified. The applied force that generates the shear waves differs between the two methods; for TE, forces are mechanically generated through the skin surface into the liver, whereas for the ultrasound-based method, the source is acoustic radiation force impulses (ARFIs), also known as push pulses (Dietrich et al. 2017). TE using the FibroScan device is well-established and was introduced in 2003. Results with this technology correlate well with the degree of fibrosis (Armstrong et al. 2013; Kettaneh et al. 2007). Although TE does not allow for B-mode imaging, it has been assumed to be less sensitive to boundary conditions, and the acquisition time is short and well adapted to mobile organs such as the liver (Sandrin et al. 2003). Using ultrasound-based SWE with push pulse, the B-mode imaging capacity allows for measurements of the region of interest (ROI) set by the operator either as a focused point (pSWE) or within a volume (2-D SWE), depending on the ultrasound device (Dietrich et al. 2017; Piscaglia et al. 2016). Ultrasound-based SWE thus has a clear advantage over TE because vessels and lesions can easily be avoided (Bamber et al. 2013; Barr 2014; Nightingale et al. 2002; Shiina et al. 2015). Results of SWE with push pulses correlate well with liver fibrosis. The mean diagnostic accuracy of ARFI, expressed as area under the receiver operating characteristic curve, is 0.87 for significant fibrosis (F ≥ 2), 0.91 for severe fibrosis (F ≥ 3) and 0.93 for cirrhosis (Friedrich-Rust et al. 2009, 2012; Lupsor et al. 2009). In addition, intra- and inter-operator reliability is good to excellent (Bota et al. 2012; Hudson et al. 2013). An international multicenter study including 10 centers and 5 countries reported a highly significant correlation between liver fibrosis and ultrasound-based SWE results (Sporea et al. 2012).

To maintain reliable and valid measurement for SWE in the liver when using TE technology with the FibroScan device, the manufacturer, Echosens, specifies that two parameters must be employed: the success rate (SR) and the reliability criteria for liver stiffness (Boursier et al. 2013). SR is met if a minimum of 60% of at least 10 measurements are performed successfully. The reliability criteria for liver stiffness require that measurement results be considered poorly reliable when the interquartile range (IQR)/median is >0.30 with a liver stiffness median of 27.1 kPa (Boursier et al. 2013; Castella et al. 2010; Sandrin et al. 2003). Because SWE measurements do not have a normal distribution, the median value should be used. The IQR (the difference between the 75th and the 25th percentiles) is used as a distribution measurement for the median and expresses the distribution around the median (Dietrich et al. 2017).

The relationship between shear wave speed and shear modulus is represented by the equation \( C_T = \sqrt{\mu/\rho} \), where \( C_T \) = speed of shear wave propagation, \( \mu \) = shear modulus and \( \rho \) = density. The equation is for linear, isotropic and elastic solids, and two challenges lie in the relationship of generating shear waves within tissues in vivo and reconstructing \( C_T \)-measured displacement fields. Common challenges with the two different techniques for applying the needed force can be (i) the ability to transmit enough energy through skin and subcutaneous fat to generate sufficient shear waves in the liver and (ii) the limitation of the distance between ribs for TE (Palmeri et al. 2008). Shear waves are transverse; the particle movements are across the direction of the waves and can be imagined as ripples on a water surface when disturbed. They are unlike ultrasound longitudinal waves, which are more rapidly attenuated in soft tissue and travel much more slowly (Bamber et al. 2013; Cosgrove et al. 2013). The positions or frictions at tissue boundaries are not known, and biological tissues are complicated and require assumptions of a linearly elastic, homogeneous, isotropic, infinite and continuous medium. In practice, the force-deformation
relationship is usually both non-linear and time dependent; elasticity varies spatially and with direction (anisotropy); tissue boundaries and structure change the relationship between shear elastic modulus and shear wave speed because of shear wave propagation and shear wave scattering; and finally, tissue content may vary with scars, fluid collections or tumor boundaries (Bamber et al. 2013). All of these factors together can result in artifacts and may contribute to effects on SWE measurement reliability. Various influences on measurement reliability have been evaluated, such as breath-holding technique, patient positioning, post-prandial state and system-specific factors (Barr et al. 2016). There is also a large measurement bias that is depth dependent (Zhao et al. 2011). It is important to identify factors that may be affected by tissue and boundaries, such as body mass index (BMI), skin-to-liver capsule distance (SCD) and the presence of cirrhosis and/or steatosis in the liver, so that they can be considered in a standardized examination protocol to increase the measurement reliability of ultrasound-based SWE.

Our aim was to investigate patient-related factors associated with either reliable or poorly reliable measurement results when performing ultrasound-based SWE of the liver, using the reliability criteria for liver stiffness (Boursier et al. 2013), which have not yet been applied in this context. The investigated factors were age, sex, smoking habits, BMI, presence of cirrhosis and/or steatosis in the liver, use of cardiovascular and/or antiviral mediation and SCD. Another aim was to see how body constitution, as expressed by either BMI or SCD, would best associate with poorly reliable SWE results.

METHODS

This prospective study was approved by the Research Ethical Review Board in Umeå (No. 2015/355-31). The research was performed in accordance with the World Medical Association Declaration of Helsinki, 2013. Between March 2014 and March 2017, we enrolled a total of 261 consecutive patients with hepatitis B and C, ASH, NASH, primary biliary cholangitis (PBC) or human immunodeficiency virus (HIV) or having follow-up for methotrexate treatment, all examined for the first time using ultrasound-based SWE of the liver. A total of 73 patients were excluded as follows: 11 examinations not in accordance with the method description, 3 deaths shortly after the examination, 27 no responses to the consent letter, 25 not giving approval and 7 with wrong addresses. Thus, 188 patients (66 women and 122 men) were included after giving their written informed consent. All patients were recruited from a single radiology department in northern Sweden (Fig. 1).

The reliability criteria for liver stiffness cutoff were IQR/median ≥0.30 and a liver stiffness median ≥7.1 kPa, defined as poorly reliable measurement results (Boursier et al. 2013). Applying this cutoff divided the 188 patients into two groups: those with poorly reliable and those with reliable measurement results.

To study the impact on ultrasound-based SWE of patient-related factors (age, sex, smoking habits, BMI, SCD, presence of steatosis and/or cirrhosis in the liver, use of antiviral and/or cardiovascular medication [ATC codes: J05 A (DAA), C01, C07, C08, C09]), we used binary univariate and multivariate logistic regression to investigate associations with either group.

For smoking habits, BMI and SCD, data for 59 patients were analyzed, with the main aim of determining how body constitution associates with poorly reliable results. All ultrasound-based SWE measurement results were compared with liver biopsy findings, when available (n = 48).

![Flowchart for inclusion of the 188 patients. IQR = interquartile range.](image-url)
**Point SWE liver examination**

The ultrasound device used in the study was a Philips iU22 (Philips Healthcare, Bothell, WA, USA), applying the ElastPQ technique, pSWE and a C5 convex probe. The ElastPQ program uses ARFI as the applied force, with a focused radiation force impulse at a certain depth to generate shear waves that propagate laterally from the focus point. In the image, a fixed ROI of 0.5 × 1.5 cm can be placed by moving a trackball, with the depth decided by the operator, and a single measurement can be performed by pressing a button. Tissue in the ROI is mechanically excited using short-duration pulses, which generate tissue displacements at the location. The displacements result in shear waves that propagate away laterally, and by tracking ultrasound beams at the time-to-peak displacement of each location, the speed of the shear waves can be measured and used as an indication of liver stiffness. The stiffer the liver, the faster the shear waves propagate through the tissue (Barr 2014; Palmeri et al. 2008; Shima et al. 2015; Srinivasa Babu et al. 2016).

The shear wave speed can then be presented in meters per second or in kilopascals using Young’s modulus $E = 3(\nu v_s^2 \rho)$, where $E$ is Young’s modulus, $\nu$ is the shear wave velocity and $\rho$ is the tissue density (Dietrich et al. 2017; Goertz et al. 2012; Ling et al. 2013). Thus, in this study, the shear wave speed is expressed in kilopascals through Young’s modulus.

All patients had been fasting for 5 h. Because the liver becomes stiffer during physical activity, patients were required to rest at least 10 min before the SWE examination (Gersak et al. 2016; Goertz et al. 2012; Popescu et al. 2013). The respiratory phase is also important, and during measurement, patients had to hold their breath in a relaxed phase (Ling et al. 2013).

Measurements were performed using an intercostal approach, at liver segment VII/VIII (Goertz et al. 2010; Liao et al. 2015), with the patient in supine position, the right arm elevated above the head (Barr et al. 2016). The measurements were performed at a depth of 3–5 cm below the liver capsule (Huang et al. 2014; Wang et al. 2014). Whenever possible, the angle of the beam was kept at 0°, and the probe was kept perpendicular to the liver (Karlas et al. 2011). At least 10 measurements were performed, and the median result was used (Dietrich et al. 2017). The median result was then entered into the Metavir score table, which is graded from F0 to F4, with F0 representing normal liver tissue and F4 representing cirrhosis. With progressing fibrosis, the liver becomes stiffer and thus warrants a higher Metavir score (Barr 2014; Goodman 2007).

The presence of ascites and/or steatosis in the liver was confirmed or ruled out by means of standard B-mode ultrasound examination, comparing brightness to the right kidney for steatosis. The SCD was measured in the same image used for the SWE measurements.

**Examination quality**

The same ultrasound device and probe were used for all SWE liver examinations. The probe was tested regularly by a technician at the radiology department using the onboard program check. The patients were examined while wearing light clothing, and all weight and length measurements were taken using the same equipment. All examinations were performed by the same operator (M.B.). Intrahepatic vessels were avoided with the help of power Doppler to identify fluid-filled vessels. The ultrasound device ElastPQ program displayed 00.00 for invalid measurements, and these were then not included in the examination. The median values for SWE liver measurement results from at least 10 measurements, expressed in kilopascals, were saved in a worksheet and printed as an image in the ultrasound device.

**Statistical analyses**

Statistical analysis was performed using SPSS Statistics Version 23 (IBM, Armonk, NY, USA). Continuous variables were summarized as the mean ± standard deviation or median (min–max) and categorical variables as the frequency (percentage). The Mann–Whitney test, Student’s t-test, $\chi^2$ test and Fisher’s exact test were used as appropriate. Correlations between variables as well as SWE and liver biopsy results were analyzed using Spearman’s $r$. The data for liver stiffness were expressed as the median (IQR). The reliability criteria for liver stiffness (Boursier et al. 2013) were used as the cutoff; the group with poorly reliable measurement results was coded as 1, and the group with reliable measurement results was coded as 0.

Binary logistic stepwise regression analyses were used to assess factors independently associated with poorly reliable measurement results. Significant factors from the univariate analyses were then analyzed in a multivariate logistic regression model. Nagelkerke, Cox and Snell and Hosmer–Lemeshow tests were used to evaluate the model. Ninety-five percent confidence intervals (CIs) were calculated for all statistical tests. A $p$ value < 0.05 was regarded as indicating statistical significance. All statistical tests were two-sided.

**RESULTS**

A total of 188 patients were included, and eight patient-related factors were tested for association with the reliable and poorly reliable measurement groups. The characteristics of all patients are provided in Table 1. Ascites was not present in the patients examined.

With the use of reliability criteria for liver stiffness (Boursier et al. 2013) as the cutoff, 52 of 188 patients (28%) were categorized into the poorly reliable measurement group and 136 of 188 (72%) were in the group with reliable measurement results.
On univariate regression analysis, among age, sex, presence of steatosis and/or cirrhosis in the liver, use of cardiovascular and/or antiviral medication and SCD, only sex and cirrhosis were not associated with poorly reliable results. Further analysis with the significant factors in the multivariate analysis revealed that the presence of steatosis in the liver and increased SCD were associated with poorly reliable results (odds ratio \[\text{OR} = 2.89\] and \[\text{OR} = 3.08\], respectively; see Table 2). For smoking habits, BMI and SCD, on multivariate analysis, only SCD was associated with poorly reliable results (\[n = 59, \text{OR} = 6.12\]; see Table 3). The ultrasound-based SWE measurements exhibited a significant positive correlation (\[n = 48, r = 0.476, p = 0.001\]) with coexisting liver biopsy results (Fig. 2).

**DISCUSSION**

In this prospective study, eight patient-related factors were tested with respect to their impact on ultrasound-based SWE liver measurement reliability with pSWE in

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### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Reliable measurement (n = 136)</th>
<th>Poorly reliable measurement (n = 52)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) 45.5 (18.0–83.0)*</td>
<td>54.5 (22.0–71.0)</td>
<td>0.010*</td>
<td></td>
</tr>
<tr>
<td>Sex Male 85 (62.5%)</td>
<td>37 (71.2%)</td>
<td>0.267†</td>
<td></td>
</tr>
<tr>
<td>Female 51 (37.5%)</td>
<td>15 (28.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin-to-liver capsule distance (cm) 1.8 (1.1–3.9)</td>
<td>2.3 (1.2–4.9)</td>
<td>&lt;0.001†</td>
<td></td>
</tr>
<tr>
<td>Smoking habits† (n = 97)</td>
<td></td>
<td>0.930†</td>
<td></td>
</tr>
<tr>
<td>Non-smoker, former smoker n (%) 40 (29.4%)</td>
<td>20 (38.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily smoker n (%) 25 (18.4%)</td>
<td>12 (23.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis Primary biliary cholangitis 2 (1.5%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C virus 72 (52.9%)</td>
<td>39 (75.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B virus 45 (33.1%)</td>
<td>6 (11.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic steatohepatitis 4 (2.6%)</td>
<td>3 (5.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-alcoholic steatohepatitis 3 (2.6%)</td>
<td>2 (3.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptogenic (of unknown cause) 9 (6.6%)</td>
<td>2 (3.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human immunodeficiency virus 1 (0.7%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (y)† (n = 136) 7.5 (0–58)</td>
<td>18.0 (0–54)</td>
<td>&lt;0.001†</td>
<td></td>
</tr>
<tr>
<td>Presence of steatosis No steatosis 97 (71.3%)</td>
<td>18 (34.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steatosis 39 (28.7%)</td>
<td>34 (65.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of cirrhosis No cirrhosis 130 (95.6%)</td>
<td>46 (88.4%)</td>
<td>0.095†</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis 6 (4.4%)</td>
<td>6 (11.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of medication No medication 104 (76.5%)</td>
<td>32 (61.5%)</td>
<td>&lt;0.001†</td>
<td></td>
</tr>
<tr>
<td>Antiviral 6 (4.4%)</td>
<td>1 (1.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular 26 (19.1%)</td>
<td>17 (32.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiviral + cardiovascular 0</td>
<td>2 (3.8%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Values are expressed as the median (min–max) or the number (%). P values < 0.05 indicate statistical significance and are in boldface.
† Mann–Whitney \(U\)-test.
‡ \(\chi^2\)-test.
§ Fisher’s exact test.
‖ Data missing for some patients.

### Table 2. Impact of patient-related factors on shear wave elastography (n = 188)

<table>
<thead>
<tr>
<th>Factor</th>
<th>(\beta)</th>
<th>p Value*</th>
<th>Wald</th>
<th>Crude OR</th>
<th>CI (95%)</th>
<th>(\beta)</th>
<th>p Value*</th>
<th>Wald</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>0.03</td>
<td><strong>0.01</strong></td>
<td>6.00</td>
<td>1.03</td>
<td>1.00–1.05</td>
<td>0.01</td>
<td>0.44</td>
<td>0.27</td>
<td>1.01</td>
<td>0.98–1.04</td>
</tr>
<tr>
<td>Sex</td>
<td>0.39</td>
<td>0.27</td>
<td>1.23</td>
<td>1.48</td>
<td>0.74–2.96</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steatosis</td>
<td>1.55</td>
<td><strong>&lt;0.001</strong></td>
<td>19.80</td>
<td>4.70</td>
<td>2.38–9.29</td>
<td>1.06</td>
<td><strong>0.01</strong></td>
<td>7.24</td>
<td>2.89</td>
<td>1.33–6.28</td>
</tr>
<tr>
<td>Medication†</td>
<td>0.44</td>
<td><strong>0.01</strong></td>
<td>6.18</td>
<td>1.55</td>
<td>1.10–2.19</td>
<td>0.70</td>
<td>1.41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1.04</td>
<td>0.08</td>
<td>2.98</td>
<td>2.83</td>
<td>0.87–9.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCD (cm)</td>
<td>1.31</td>
<td><strong>&lt;0.001</strong></td>
<td>22.04</td>
<td>3.70</td>
<td>2.14–6.37</td>
<td>1.12</td>
<td><strong>&lt;0.001</strong></td>
<td>13.65</td>
<td>3.08</td>
<td>1.70–5.60</td>
</tr>
</tbody>
</table>

\* CI = confidence interval; OR = odds ratio; SCD = skin-to-liver capsule distance.
† p Values < 0.05 indicate statistical significance and are in boldface.
† Antiviral, cardiovascular.
a total of 188 patients. The reliability criteria for liver stiffness (Boursier et al. 2013) were used as the cutoff in binary logistic regression analysis.

Ultrasound-based SWE exhibited a significant positive correlation with liver biopsy. In addition, on univariate analysis, sex, age, BMI, use of cardiovascular and/or antiviral medication, presence of cirrhosis in the liver and smoking habits were not associated with poorly reliable results. On multivariate analysis, presence of liver steatosis and increased SCD were associated with an increased likelihood of poorly reliable results. Body constitution appears to have been better measured with SCD than with BMI, as the latter exhibited no association with poorly reliable measurements. To our knowledge, this study is the first to use the reliability criteria for liver stiffness (Boursier et al. 2013) as a cutoff in binary logistic regression analysis of ultrasound-based SWE of the liver with push pulse as applied force.

The study results are relevant because obesity resulting in steatosis and an increased amount of subcutaneous fat between the probe and liver constitutes a risk for diagnostic error. Thus, establishing a reliable ultrasound-based SWE method to identify patients with significant fibrosis is warranted to initiate treatment in those with hepatitis, thus avoiding progression to hepatocellular carcinoma. Also, in non-alcoholic fatty liver disease (NAFLD), out-

<table>
<thead>
<tr>
<th>Factor</th>
<th>β</th>
<th>p Value*</th>
<th>Wald</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>−0.01</td>
<td>0.61</td>
<td>0.26</td>
<td>0.99</td>
<td>0.95–1.03</td>
</tr>
<tr>
<td>Sex</td>
<td>−0.86</td>
<td>0.30</td>
<td>1.07</td>
<td>0.42</td>
<td>0.08–2.16</td>
</tr>
<tr>
<td>Smoking habits†</td>
<td>0.87</td>
<td>0.24</td>
<td>1.38</td>
<td>2.39</td>
<td>0.56–10.26</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>−0.02</td>
<td>0.84</td>
<td>0.04</td>
<td>0.98</td>
<td>0.80–1.20</td>
</tr>
<tr>
<td>SCD (cm)</td>
<td>1.81</td>
<td><strong>0.01</strong></td>
<td>6.33</td>
<td>6.12</td>
<td>1.50–25.10</td>
</tr>
</tbody>
</table>

Nagelkerke $R^2 = 31.5\%$
Cox and Snell $R^2 = 22.8\%$
Hosmer–Lemeshow $p = 0.20$

BMI = body mass index; CI = confidence interval; OR = odds ratio; SCD = skin-to-liver capsule distance.

* p values < 0.05 indicate statistical significance and are in boldface.
† Daily and former smoker versus non-smoker.

Fig. 2. Correlation of shear wave elastography measurement results with liver biopsy results, in Metavir score. SWE = shear wave elastography.
comes can include inflammation, fibrosis, cirrhosis and, in the worst case, hepatocellular carcinoma (Augustin et al. 2017).

With ARFI, it is possible to measure liver tissue displacements. In addition, ARFI can be performed in complex media, without significant artifacts originating from nearby structures, and therefore can directly correlate with liver stiffness (Nightingale et al. 2001).

The current results diverge in part from previous findings. Most of the participants were men, and HCV was the dominant cause of liver disease (59% of patients). Sex was not associated with reliably results, although earlier studies had reported significantly higher values for men (Corpechot et al. 2006; Huang et al. 2014). The findings in general have been mixed. In one report on intra-class correlations for 186 patients, BMI, sex and age did not influence concordance (Fraquelli et al. 2016). Yet another analysis of data for 1031 participants found an association of older age, being male and BMI with a risk for failed and unreliable measurements (Bota et al. 2014).

To date, results with BMI also have varied. For example, in a study with 135 participants, BMI was significantly higher in the unreliable group (Maruyama et al. 2016), whereas it was not associated with less reliable results in another investigation (Huang et al. 2014). Furthermore, in a small study with healthy volunteers, BMI was not significantly correlated with liver elasticity (Fang et al. 2017). Why BMI did not associate with the poorly reliable measurement results in this study but SCD did is a somewhat confusing outcome that needs to be addressed in future studies. Few reports have compared the two while also including a larger number of participants. Recently published results for 55 patients, comparable to the 59 in the current work, indicated that SCD was more significant for increased measurement variability compared to BMI (Nadebaum et al. 2018). When using ultrasound-based SWE, SCD could therefore be a candidate for replacing BMI to achieve greater accuracy because an increased layer of subcutaneous fat can have a tremendous impact on ultrasound imaging, both in general and also for SWE.

Another little-studied factor that affects boundaries is increased waist circumference, which together with increased BMI has exhibited a significant correlation with the standard deviation-to-mean stiffness value ratio in a study of 605 patients (Varbobitis et al. 2016). Increased SCD is also a problem for TE performed with FibroScan; the manufacturer Echosens does not recommend measurements for SCD >3.5 cm with the XL probe. There is a broad consensus on not using the XL probe because measurements with it have been less reliable (Dietrich et al. 2017), which means that the M probe is the better choice with the limit of SCD <2.5 cm, according to Echosens.

In this study, the presence of steatosis in the liver was associated with poorly reliable results, which also was confirmed in a recent study using pSWE technology (Conti et al. 2017); thus, as for TE, there are problems with the accuracy of measurement results, with a risk for misclassification in the presence of obesity. Nevertheless, poorly reliable results from other studies using pSWE and 2-D SWE exhibited no correlation with steatosis (Ferraioli et al. 2014a; Samir et al. 2015), which means that liver steatosis has a somewhat doubtful impact on reliability. It could possibly reflect the difficulties involved in performing SWE in obese patients, which is paired with the increased SCD because of increased subcutaneous fat. Earlier studies confirmed that the rate of reliable measurements is significantly higher for more experienced operators when doing examinations in obese patients (Gradinaru-Tascau et al. 2013), indicating that training can help (Ferraioli et al. 2014b). Nevertheless, the presence of liver steatosis does give the operator an indication of concern with respect to reliability.

One limitation of this study is possibly the use of the reliability criteria for liver stiffness (Boursier et al. 2013) as a cutoff because other reports have indicated discriminant cutoff values of 21% (Lucidarme et al. 2009). Nevertheless, another study involving ultrasound-based SWE with push pulse revealed discordance with an IQR/median ≥30% (Bota et al. 2013). Therefore, even though TE and ultrasound-based SWE do not use the same applied force to create shear waves, we hypothesize that the reliability criteria for liver stiffness (Boursier et al. 2013) for TE are also valid for ultrasound-based SWE, which needs to be confirmed in future studies.

In a recent report, the standard deviation for the SWE mean was identified to be the strongest factor associated with the quality of shear wave propagation (Zhou et al. 2017). Studies have also found that technical failures are not machine dependent, and for high SWE reliability, ultrasound devices should not be used interchangeably (Woo et al. 2015). With the aid of reliability criteria for liver stiffness (Boursier et al. 2013), displayed on the ultrasound machine monitor during ultrasound-based SWE of the liver, poorly reliable measurement results can be avoided. However, no guidelines for ultrasound-based SWE are currently in place to describe how to achieve an IQR/median ≤30%. One way is for the operator to delete uncertain measurements, including outliers, while performing the examination to maintain the IQR/median ≤30%. The IQR/median values are available on the monitor for some ultrasound devices, although not displayed in real time for all of them (Piscaglia et al. 2016).

Future feasibility solutions

Using the reliability criteria for liver stiffness (Boursier et al. 2013) as a cutoff in this study resulted in
approximately 28% (52/188) of SWE results being poorly reliable, primarily because of the increasing distance between the probe and liver capsule with increasing subcutaneous fat. Reducing the distance by applying pressure with the probe would be of great value; however, the recommendation is to perform the examination with minimal scanning pressure (Dietrich et al. 2017) because probe pressure is thought to result in falsely high measurement values or greater measurement variance (Cui et al. 2013). Nevertheless, some authors have recommended applying force with the probe when necessary (Cosgrove et al. 2013), although this suggestion has not been confirmed in a controlled study. Another way of reducing the distance is to place the patient in a left decubitus position (Goertz et al. 2012), but one group has reported that SWE examinations performed in positions other than supine produce less accurate results (Liao et al. 2015). How to perform an accurate SWE examination in obese patients without negatively affecting measurement values will have to be determined in future studies.

CONCLUSIONS

Ultrasound-based SWE values exhibit a significant, positive correlation with liver biopsy results. When using the SWE method, application of the IQR/median as a quality parameter helps to avoid up to 28% of poor SWE results for patients with an increased layer of subcutaneous fat between the probe and liver capsule or with liver steatosis. These results also suggest that SCD should be used in preference to BMI to maintain a reliable SWE results. The patient-related factors of sex, age, smoking habits, use of antiviral and/or cardiovascular medication, BMI and presence of cirrhosis in the liver did not associate with poorly reliable SWE results.

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