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● *Original Contribution*

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 reliable 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)

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

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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% (Castera 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 ($F \geq 2$), 0.91 for severe fibrosis ($F \geq 3$) 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 ≥7.1 kPa (Boursier et al. 2013; Castera 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, μ = shear modulus and ρ = 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