Original papers

Med Ultrason 2020, Vol. 22, no. 1, 7-12
DOI: 10.11152/mu-2225

Are there different cut-off values for staging liver fibrosis using 2D-SWE implemented on different systems from the same manufacturer?

Ioan Sporea, Felix Bende, Alina Popescu, Raluca Lupușoru, Renata Fofiu, Roxana Șirli

Department of Gastroenterology and Hepatology, „Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania

Abstract

Aim: To evaluate the range of liver stiffness (LS) cut-off values for predicting different stages of liver fibrosis (LF) for 2D-SWE-GE implemented on three different systems from General Electric Healthcare (LOGIQ E9, LOGIQ S8, LOGIQ P9). **Material and method:** We performed a comparative study evaluating the performance of 2D-SWE-GE (LOGIQ E9, S8, P9) for predicting different stages of LF using Transient Elastography (TE) as the reference method. All patients (with or without chronic hepatopathies) were evaluated by TE, 331 patients were included in the LOGIQ E9 study, 179 in the LOGIQ S8 study and 234 in the LOGIQ P9 study. Reliable liver stiffness measurements (LSM) were defined for TE as the median value of 10 measurements with an interquartile range/median ratio (IQR/M)≤0.30 and for 2D-SWE-GE as the median value of 10 measurements and IQR/M≤0.30. **Results**: Reliable LSM was obtained by both methods in 91.5% subjects of the LOGIQ E9 group, in 95.5% subjects from the LOGIQ S8 group and in 87.6% subjects in the LOGIQ P9 group. The performance of 2D-SWE-GE for predicting F≥2 with LOGIQ E9, LOGIQ S8 and LOGIQ P9 systems were: cut-offs 6.7 kPa, 6.9 kPa and 6.8 kPa; AUCs 0.95, 0.92 and 0.93. For predicting F≥3, the performances were: cut-offs – 8.2 kPa, 8.2 kPa and 7.6 kPa; AUCs - 0.97, 0.93 and 0.94. For predicting F4, the performances were: cut-offs – 9.3 kPa, 9.3 kPa and 9.3 kPa; AUCs - 0.96, 0.91 and 0.91. **Conclusion:** The LS cut-off values for 2D-SWE-GE implemented on different systems for predicting F≥2, F≥3 and F=4 are not significantly different.

Keywords: liver fibrosis; bidimensional Shear Wave Elastography (2D-SWE); General Electric ultrasound machine

Introduction

Chronic liver diseases are quite frequent around the world, having different etiologies connected with the prevalence of chronic viral infections in a region, with the risk of metabolic syndrome and with alcohol consumption. No matter the etiology, liver disease severity assessment is important for prognosis and therapy.

Received 29.09.2019 Accepted 26.11.2019
Med Ultrason
2020, Vol. 22, No 1, 7-12
Corresponding author: Felix Bende
13-15/11 Claude Debussy street,
300779 Timisoara, Romania
E-mail: bendefelix@gmail.com
Phone: +40755353852

Classically, liver biopsy was considered to be the standard for liver diseases severity evaluation. However, this strategy has been greatly changed in the last 10-15 years, due to the development of new non-invasive modalities for liver assessment (biological tests or elastographic methods). These non-invasive methods are inexpensive, easy to perform and repeat and well accepted by patients. For some etiologies such as chronic viral hepatopathies, the liver biopsy can be avoided, because the aim of the treatment is to cure the virus, no matter the severity of the liver disease. Evaluation of fibrosis stage before treatment is important only in order to exclude liver cirrhosis (which needs a long-life screening for hepatocellular carcinoma by ultrasound) [1]. Regarding non-alcoholic fatty liver disease (NAFLD) or alcoholic

liver disease (ALD), screening for liver fibrosis severity by liver biopsy is unfeasible due to the large number of people affected.

Liver elastography using ultrasound (US) waves is a good and proven method for liver fibrosis evaluation that can be used in large cohorts. A great number of papers published on various types of liver elastography have shown good correlations with liver biopsy [2-4]. Also, important meta-analyses demonstrated good results for all shear wave elastographic methods for predicting liver fibrosis (LF) severity, in various chronic liver diseases [5-7]. The latest guidelines published on this topic by international professional societies [8,9] educate the users regarding the effectiveness of elastographic techniques and the cut-off values to be used for different systems. According to these guidelines, ultrasound-based elastography methods are divided into shear wave elastography (SWE) and strain elastography. Only SWE is recommended by these guidelines for liver fibrosis assessment. SWE methods are subdivided into Transient Elastography (TE), point SWE (pSWE) and 2D-SWE.

Published guidelines support the fact that different systems from different companies do not have the same cut-off values for the same level of fibrosis. Also, there is no information regarding the cut-off values for different US systems produced by the same company and no comparative studies.

Therefore, the aim of this study was to evaluate the range of liver stiffness (LS)cut-off values for predicting different stages of LF by 2D-SWE, implemented on three different systems from General Electric Healthcare (LOGIQ E9, LOGIQ S8, LOGIQ P9).

Material and method

Patients

We compared the results of three studies (a previously published study [10] and two other studies presented now) performed in our Department in different periods, evaluating the performance of 2D-SWE from General Electric manufacturer (LOGIQ E9, LOGIQ S8, LOGIQ P9) for predicting different stages of LF, using TE as the reference method.

The current study population comprised 744 adult subjects, with or without chronic liver disease, included in 3 different subgroups (LOGIQ E9, LOGIQ S8, LOGIQ P9), as shown in figure 1. All participants agreed to undergo elastographic measurements (signed informed consent). The study was approved by the local Ethics Committee and was performed in accordance with the last revised version of the Helsinki Declaration.

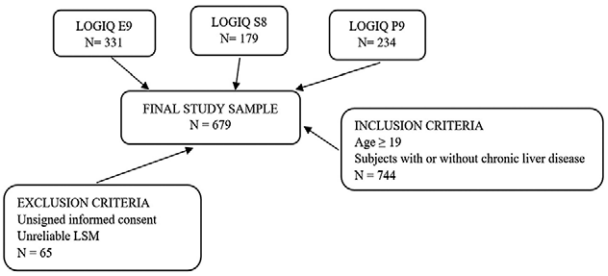

Fig 1. Study design

The general inclusion criteria for subjects with chronic liver disease were: chronic viral (B and C viruses) or non-viral hepatitis (alcoholic or non-alcoholic steatohepatitis, primary biliary cholangitis) or cirrhosis; aminotransferases levels <3x normal values. The general inclusion criteria for healthy liver subjects were: no history of liver disease or alcohol abuse, normal abdominal US examination and previously tested negative for hepatitis B/C virus. Patients undergoing antiviral treatment, patients with ascites (who cannot be evaluated by TE), patients with US signs of biliary obstruction and liver congestion secondary to heart failure and patients with focal liver lesions were excluded.

We obtained LS measurements from all subjects in the same session by means of TE and 2D-SWE-GE. We excluded 65 patients because LSM obtained by TE or/ and 2D-SWE-GE were unreliable; the remaining 679 patients were included in the final statistical analysis.

Elastographic measurements

TE was performed in all subjects with FibroScan® device (EchoSens, Paris, France) in fasting condition. In each subject, we aimed for 10 valid LS measurements. The examination was performed in supine position, by intercostal approach, with the right arm in maximum abduction, using the M probe (standard probe – transducer frequency 3.5 MHz) or the XL probe (transducer frequency 2.5 MHz). In all patients, the M probe was used first, and if the results were unreliable, we used the XL probe. A median value of 10 valid LS measurements was calculated and the results were expressed in kiloPascals (kPa). Reliable measurements were defined as: median value of 10 valid LS measurements with an interquartile range interval (IQR = the difference between the 75th and 25th percentile, essentially the range of the middle 50% of the data) ≤0.30.In all studies TE was used as the reference method using the following cut-off values from published meta-analysis (F≥2: 7.2 kPa; F≥3: 9.6 kPa; F=4 14.5 kPa) [11].

LS evaluation by 2D-SWE was performed using the LOGIQ E9 system - 2D-SWE-GE.E9, LOGIQ S8 system - 2D-SWE-GE.S8 and LOGIQ P9 system - 2D-SWE-GE.

P9 (GE Healthcare, Chalfont St Giles, United Kingdom). All measurements were performed in fasting condition, in supine position, with the right arm in maximum abduction, by intercostal approach, in the right liver lobe, in the best acquired acoustic window for liver evaluation. LS measurements using 2D-SWE-GE were performed using a C1-6-D convex probe (LOGIQ E9) and a C1-5-D convex probe (LOGIQ S8, LOGIQ P9). The SWE region-of-interest (ROI) was placed at least 1-2 cm below the liver capsule, in a region free of large vessels. Once a suitable image was found, the patient was asked to suspend breathing and afterward image acquisition was initiated. Usually two or three colored image frames were acquired during 5 seconds of suspended breathing. The process was repeated until at least 10 shear wave frames were acquired. Within each saved SWE image and frame a circular measurement region was placed and the measurement obtained. The average stiffness, expressed in terms of Young's Modulus within each measurement region, was automatically recorded by the system in a worksheet. The system automatically calculated the median value and IQR of the valid measurements. A valid LS assessment was considered as the median value of 10 measurements acquired in a homogenous area with an IQR≤0.30.

Statistical analysis

For continuous data with normal distribution, data were presented as mean±standard deviation (SD), for continuous data without normal distribution, data were presented as median and IQR, while for nominal variables data were presented as percentages. The normality was tested using the Kolmogorov-Smirnov test.

The differences between the groups were assessed using student t-test for continuous variables with normal distribution, by Mann-Whitney U test for continuous variables without normal distribution. Fisher test and Pearson chi-squared test for proportions. The influence of different dichotomous variables was tested using univariate and multivariate logistic regression models. The comparison between two medical methods was assessed using Spearman correlation coefficient, Bland-Altman plot analysis and Cohen inter-rater agreement (kappa). The performance of methods was tested using receiver operating characteristics analysis (AUC). For comparison between studies we used meta-analysis with the „Inverse variance method- I^2". We tested the homogeneity with homogeneity tests and in case of heterogeneity, we used the random and fixed effects model. In general, heterogeneity was classified in three categories: <25% (low heterogeneity), between 25 and 75% (medium heterogeneity) and >75% (high heterogeneity).

For the statistical analysis, we used R software version i386 3.6.1, MedCalc software version 19.8.7 and Microsoft Office 2019. A p-value< 0.05 was considered significant, at a level of 95% confidence level for intervals.

Results

The compared results of LSM obtained in 3 different cohorts evaluated at different moments in our department, as showed in Table I: 1) LOGIQ E9 study included 331 subjects; reliable LSM were obtained with TE and 2D-SWE-GE.E9 in 303/331(91.5%) subjects [10]; 2) LOGIQ S8 study included 179 subjects; reliable LSM were obtained with TE and 2D-SWE-GE.S8 in 171/179 (95.5%) subjects; 3) LOGIQ P9 study included 234 consecutive subjects; reliable LSM were obtained with both methods (TE and 2D-SWE-GE) in 205/234 (87.6%) subjects.

Table I. Main characteristics of the final study population.

Parameter	LOGIQ E9 N = 303	LOGIQ S8 N = 171	LOGIQ P9 N = 205	P-value
Age (years)	55(19-85)	55.4(26-84)	61(24-98)	<0.0001
BMI (kg/m2)	27.3±5.3	27.7±4.5	27.2±5.1	0.65
Gender				
Male	38.4	50.8	54.1	0.01
Female	61.6	49.2	45.9	0.01
Fibrosis stage				
F<2	30.1	29.8	30.5	<0.0001
F=2	10.2	24.4	18.3	0.0003
F=3	12.2	19.1	16.8	0.09
F=4	47.5	26.7	34.4	<0.0001
Mean TE (kPa)	16.7±13.4	12.8±1.04	13.5±2.4	0.0003
Mean 2D-SWE-GE (kPa)	10.1±4.2	8.7±0.31	9.7±1.3	<0.0001

The results are expressed as number (%) or mean±standard deviation; N = Number; BMI = Body Mass Index; F = Fibrosis; TE = Transient Elastography; 2D-SWE-GE = Bidimensional Shear Wave Elastography from General Electric.

The analysis of the three studies indicated that there was a significant heterogeneity regarding the LS values obtained using different GE machines: I^2 =84%, Q=12.29, p=0.002; for this reason, a random-effects model was used (fig 2).

The best cut-off values for 2D-SWE-GE in the previous studies for predicting F≥2, F≥3 and F=4 are presented in Tables II-IV.

For the performance comparison between the studies and to establish the best cut-off values, we evaluated their performance according to the AUROC's. Data was very homogenous for all the fibrosis stages; therefore, fixed-effects model was used (fig 3): for fibrosis stage F≥2, I^2 =0%, Q=0.35, p=0.83; in fixed-effects model (z=49.65, p<0.0001), the pooled AUC of 2D-SWE was 0.93 (95%CI: 0.89;0.96); for fibrosis stage F≥3, I^2 =0%, Q=0.65, p=0.72; in fixed-effects model (z=50, p<0.001), the pooled AUC of 2D-SWE was 0.94 (95%CI: 0.90;0.97);for liver cirrhosis F=4, I^2 =0%, Q=0.81, p=0.66; in fixed-effects model (z=42.4, p<0.01), the pooled AUC of 2D-SWE was 0.91 (95%CI: 0.90;0.97).

The LS cut-off values for 2D-SWE-GE implemented on different systems were: for F≥2 ranged from 6.7- 6.9 kPa, for F≥3 ranged from 7.6- 8.2 kPa and for F=4 was 9.3 kPa.

Table II. Performance of the LOGIQ E9 study

Fibrosis stage	Cut-off point (kPa)	Se (%)	Sp (%)	AUC
F≥2	>6.7	92.7	85.5	0.95
F≥3	>8.2	95	89.3	0.97
F=4	>9.3	91.7	92.5	0.96

F = Fibrosis; Se = Sensibility; Sp = Specificity; AUC = Area Under the Curve.

Table III. Performance of the LOGIQ S8 study

Fibrosis stage	Cut-off point (kPa)	Se (%)	Sp (%)	AUC
F≥2	>6.9	85.8	90.2	0.92
F≥3	>8.2	87.5	86.8	0.93
F=4	>9.3	85.7	81.2	0.91

F = Fibrosis; Se = Sensibility; Sp = Specificity; AUC = Area Under the Curve.

Table IV. Performance of the LOGIQ P9 study

Fibrosis stage	Cut-off point (kPa)	Se (%)	Sp (%)	AUC
F≥2	>6.8	83.5	91.2	0.93
F≥3	>7.6	86.5	92.7	0.94
F=4	>9.3	75.5	92.5	0.91

F = Fibrosis; Se = Sensibility; Sp = Specificity; AUC = Area Under the Curve

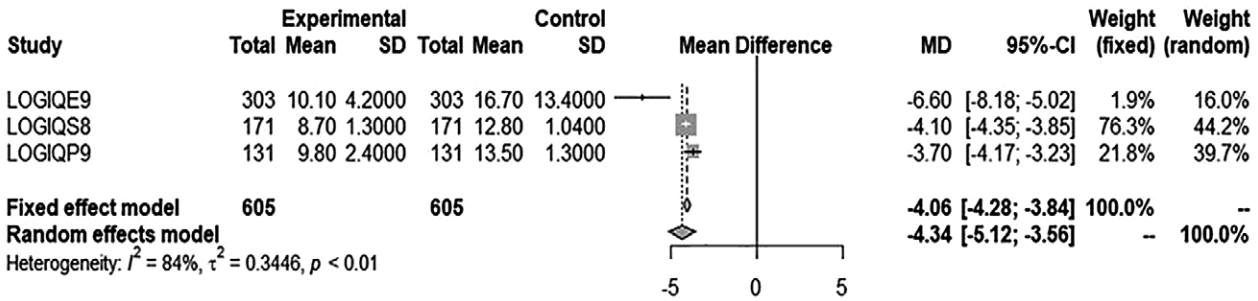

Fig 2. Graphic representation of liver stiffness measurement mean values by 2D-SWE-GE

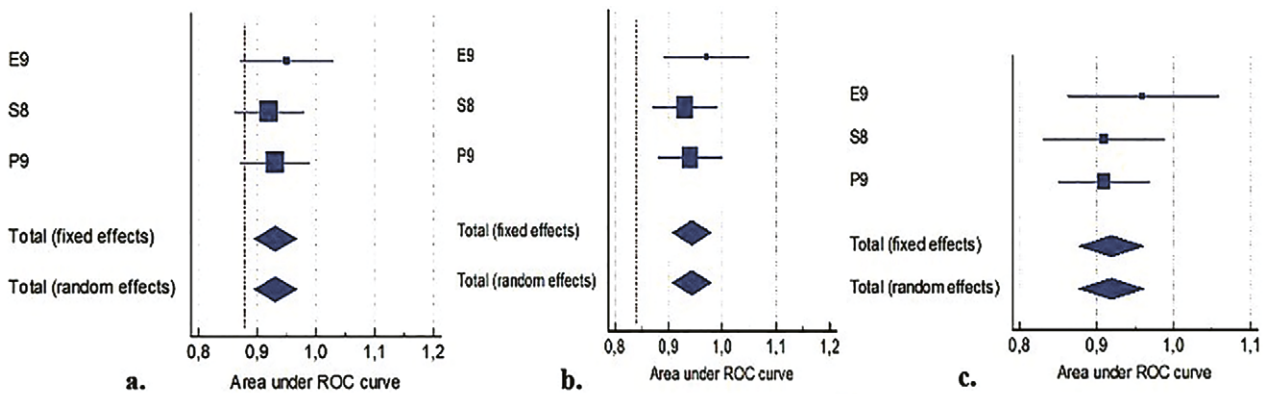

Fig 3. Meta-analysis of AUROCs' in detecting liver fibrosis stage F≥2 (a); liver fibrosis stage F≥3 (b); and liver cirrhosis F=4 (c).

Discussion

In our days, liver elastography became a standard modality for liver fibrosis assessment. The use of TE, or ARFI (Acoustic Radiation Force Impulse) elastographic methods (pSWE and 2D-SWE), dramatically decreased the number of liver biopsies. In HCV and HBV chronic infection, liver biopsy is now quite rarely performed. For other chronic hepatopathies, the decrease in number of liver biopsies was also spectacular due to the use of elastographic methods for liver fibrosis evaluation.

One point that is now well known is the fact that different US systems have different cut-off values for the same stage of fibrosis [5,10,11-14]. From this perspective, when an US system with elastographic module is launched on the market, the cut-off values for different stages of fibrosis must be recommended. On the other hand, because these cut-off values can differ according to etiology (HCV, HBV, NAFLD or ALD), it is better to recommend separately these cut-offs. Because of the very fast development of the new elastographics ystems, usually little information is available on each system, and a "white paper" gives limited information regarding the cut-off values (usually not regarding the etiologies).

In this paper, we tried to find if different machines from the same producer (General Electric) have the same cut-off values, for the same stage of fibrosis. The systems that we compared are of a different class of performance, from high to medium class.

Despite the fact that the three valuated studies were not homogeneous in terms of the number of patients, the gender and the distribution of fibrosis, we had similar diagnostic performances and therefore we could compare them.

Our study showed that all three systems from General Electric have resembling cut-off values, without significant differences among them. In these conditions, the results obtained with the systems from the General Electric are comparable and recommendations for the users can be given.

If for many years only TE existed and a lot of papers were published about this system, around 10 years ago Virtual Touch Quantification (VTQ) technology from Siemens was developed. Initially, it was known as ARFI, an incorrect name since ARFI is in fact, a technology used for tissue excitation both in pSWE and in 2D-SWE. There are many published papers that compare VTQ with liver biopsy [3,15] and also meta-analyses that confirm its value [6,16].

The new idea of more than one manufacturer is to introduce elastographic modules, not only in high-class machines (very expensive and thus not affordable for everyone) but also in middle-class US machines. In these conditions, the accessibility to liver elastography increases. Not very far into the future, screening of liver fibrosis in high-risk categories of patients will be possible using middle-class US machines accessible to many categories of medical specialties (including general practitioners).

To our knowledge, this study is the first that evaluated three systems from the same company in regard to LS cut-off values. The results show that the cut-off values are similar and can be used in daily practice.

Our paper has some limitations: the study was not a head to head comparison, data were not strictly homogenous and liver biopsy was not used as the gold standard method. However, the value of this paper is related to the demonstration of non-significant differences between the cut-off values for different stages of liver fibrosis when using various US machines from the same manufacturer.

In **conclusion,** liver stiffness cut-off values for 2D-SWE-GE implemented on different systems (E9, S8 and P9) for predicting F≥2, F≥3 and F=4 are similar and can be used in daily practice.

Conflict of interest: none

References

1. Bolondi L. Screening for hepatocellular carcinoma in cirrhosis. J Hepatol 2003;39:1076–1084.
2. Castéra L, Vergniol J, Foucher J, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343-350.
3. Sporea I, Sirli RL, Deleanu A, et al. Acoustic Radiation Force Impulse Elastography as Compared to Transient Elastography and Liver Biopsy in Patients with Chronic Hepatopathies. Ultraschall Med 2011;32:S46-S52.
4. Palmeri ML, Wang MH, Rouze NC, et al. Noninvasive evaluation of hepatic fibrosis using acoustic radiation force-based shear stiffness in patients with nonalcoholic fatty liver disease. J Hepatol 2011;55:666-672.
5. Herrmann E, de Lédinghen V, Cassinotto C, et al. Assessment of biopsy-proven liver fibrosis by two-dimensional shear wave elastography: An individual patient data-based meta-analysis. Hepatology 2018:67:260-272.
6. Bota S, Herkner H, Sporea I, et al. Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis. Liver Int 2013;33:1138-1147.
7. Li C, Zhang C, Li J, Huo H, Song D. Diagnostic Accuracy of Real-Time Shear Wave Elastography for Staging of Liver Fibrosis: A Meta-Analysis. Med Sci Monit 2016;22:1349-1359.
8. Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography, Update 2017 (Long Version). Ultraschall Med 2017;38:e48.

9. Ferraioli G, Filice C, Castera L, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 3: liver. Ultrasound Med Biol 2015;41:1161-1179.
10. Bende F, Sporea I, Sirli R, et al. Performance of 2D-SWE. GE for predicting different stages of liver fibrosis, using Transient Elastography as the reference method. Med Ultrason 2017;19:143-149.
11. Tsochatzis EA, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. J Hepatol 2011;54:650-659.
12. Mare R, Sporea I, Lupuşoru R, et al. The value of ElastPQ for the evaluation of liver stiffness in patients with B and C chronic hepatopathies. Ultrasonics 2017;77:144-151.
13. Cassinotto C, Boursier J, de Lédinghen V, et al. Liver stiffness in nonalcoholic fatty liver disease: A comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy. Hepatology 2016;63:1817–1827.
14. Cassinotto C, Lapuyade B, Mouries A, et al. Non-invasive assessment of liver fibrosis with impulse elastography: comparison of Supersonic Shear Imaging with ARFI and FibroScan®. J Hepatol 2014;61:550-557.
15. Ferraioli G, Tinelli C, Lissandrin R, et al. Point shear wave elastography method for assessing liver stiffness. World J Gastroenterol 2014;20:4787-4796.
16. Liu H, Fu J, Hong R, Liu L, Li F. Acoustic Radiation Force Impulse Elastography for the Non-Invasive Evaluation of Hepatic Fibrosis in Non-Alcoholic Fatty Liver Disease Patients: A Systematic Review & Meta-Analysis. PLoS One 2015;10:e0127782.