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Original paper

Biases of Shear Wave vs Transient Elastography in fibrosis assessment of patients with fatty liver disease

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Abstract

Background: The assessment of fibrosis in chronic liver diseases using non-invasive methods is an important topic in hepatology.

Aim: To compare Shear Wave and Transient elastography and in what the possible measurement biases and discordance factors are concerned.

Material and Methods: This study enrolled 139 patients with non-alcoholic fatty liver disease, who underwent assessment of hepatic fibrosis by Shear Wave and Transient elastography.

Results: The results obtained by the two methods were correlated in the most cases, but discordance in one or more degrees of fibrosis stage was also found. The multiple correlations analysis regarding the predictors of discordance indicated that a significant influence was exercised by the fibrosis degree, steatosis, BMI and necroinflammatory activity.

Conclusions: Shear Wave and Transient elastography appear as comparably reliable methods for assessment of liver fibrosis, but there are possible discrepancies in evaluating fibrosis stage.

Keywords

Non-alcoholic fatty liver disease, liver fibrosis, Transient elastography, Shear Wave elastography.

Abbreviations

SWE – *Shear Wave elastography*; TE – *Transient elastography*; NASH – Non-alcoholic fatty liver disease; ROI – region-of-interest; BMI – body mass index.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of a metabolic syndrome and is the first cause of chronic hepatic disease being recognized as a leading cause of liver-related morbidity and mortality in many developed countries worldwide (MARCHESINI & al [1]; ANSTEE & al [2]; MCPHERSON & al [3]; BELLENTANI & al [4]; MACHADO & al [5]; ARMSTRONG & al [6]).

Liver fibrosis is part of the structural and functional alterations in most chronic liver diseases. The presence and extent of fibrosis is one of the main prognostic factors regarding the evaluation of progression to cirrhosis and related complications, independent on the etiology of liver disease (EKSTEDT & al [7]; ANGULO & al [8]).

Consequently, using a noninvasive, affordable, reproducible and high sensitivity method in order to assess liver fibrosis in NAFLD patients is currently an important topic in hepatology (NIH CONSENSUS, [9]; CASTERA & al [10]).

Such non-invasive methods rely on two different approaches: a “biological” one based on the quantification of biomarkers in serum samples (FibroTest, FibroMeter, FibroSpectII, HepaScore, aspartate-to-platelet ratio index – APRI) and a physically – based one, relying on measuring liver stiffness, which are: transient elastography, an ultrasound-based technique (acoustic radiation force impulse imaging – ARFI, point shear wave elastography – pSWE, 2D-shear wave elastography – 2D-SWE) and 3-D magnetic resonance elastography. Despite the complementarity of these approaches, they rely on different rationales (RATZIU & al [11]; EASL-ALEH CLINICAL PRACTICE GUIDELINES, [12]).

Liver stiffness assessment methods based on serum biomarkers are well validated, have a good applicability, but have the disadvantage of being expensive and of using parameters that are not specific for liver disease and, therefore, may vary more in other pathological conditions (RATZIU & al [11]).

On the other hand, methods based on the evaluation of liver stiffness are easy to apply, they evaluate a physical parameter specific to the liver, the analytic method is simple and the cost is low (only if the device is available). Among the most validated non-invasive methods used to assess staging of liver fibrosis is transient elastography (TE), which is based on liver stiffness measurement and can be considered the non-invasive standard for the measurement of liver stiffness. There are several advantages of TE, including short procedure time (less than 5 minutes), immediate results, and the possibility to perform it either at patient’s bedside or in an outpatient clinic. This method has been well validated for viral hepatitis (B, C and in HIV-VHC coinfections) but is less well validated in other chronic liver diseases (SANDRIN, [13]; FRIEDRICH-RUST, [14]; MYERS, [15]; TAMANO & al [16]).

The method has the disadvantage that it has a lower applicability than serum biomarker (obesity, ascites, operator experience), region-of-interest (ROI) cannot be chosen and requires a dedicated device damage (CASTERA & al [17]; SIGRIST & al [18]).

SWE is a new and promising technique based on liver assessment which is studied. Current results show that this

technique is at least equivalent to TE for non-invasive staging of liver fibrosis. One advantage of SWE is its implementation on an ultrasound device and also the advantage that ROI can be adjusted in size and location and chosen by the operator (SIGRIST & al [18]; FERRAIOLI & al [19]; POYNARD & al [20]).

Considering the current NAFLD guidelines, there is the need to consider performing a liver biopsy in patients at high risk for advanced fibrosis or for NASH, and when there is not possible to exclude other etiologies for fatty liver or coexisting chronic liver disease, through non-invasive methods. However, many authors consider that first using a non-invasive method to rule out advanced fibrosis is preferable (CHALASANI & al [21]). The present study compares two non-invasive methods of fibrosis assessment (TE and SWE) in NAFLD. We examined the predictors of discordance between TE and SWE, defined as a difference of one or more stages between techniques. The aim was to compare the applicability (the measurement of reliable results) and performances of SWE for the diagnosis of fibrosis as compared with TE applying a methodology without gold standard (liver biopsy). The study protocol is not addressed to assess the sensibility/specificity of these methods.

Methods

Patients

We performed a prospective study, including 139 patients with NAFLD, evaluated in the Institute of Gastroenterology and Hepatology – Emergency Hospital “St. Spiridon” Iasi, between January 2017 and December 2017. According to the American Association for the Study of Liver Disease guidelines, NAFLD is confirmed when the following 4 criteria are simultaneously present: (1) fatty change of the liver; (2) no other factors causing chronic liver disease are present; (3) no other factors inducing fatty change of the liver are present; (4) no significant alcohol abuse is present (CHALASANI & al [21]).

All patients diagnosed with fattening of the liver detected by ultrasound examination (US) were included in the study. The exclusion criteria were the evidence of decompensated liver cirrhosis (Child-Pugh class B or C), other pathological conditions which may interfere with measurements results (biliary obstruction, primary biliary cirrhosis, autoimmune or viral hepatitis, metabolic or hereditary liver diseases, protein-calorie malnutrition, total parenteral nutrition, rapid weight loss, a history of intestinal resection, inflammatory bowel disease, thyroid disease, malignancy, drug use, chronic heart disease, or with vascular malformation or focal lesion detected on US, excessive alcohol consumption for more than 5 years, liver stiffness measurement failure, or unreliable Fibroscan (less than 10 valid measurements). The study was approved by the local Ethics Committee. Patients’ written informed consent was obtained before enrollment.

Clinical and laboratory data

Demographic details and BMI were collected. A complete blood count and blood chemistry tests were assessed. ALAT and ASAT values for liver enzymes and total cholesterol and triglycerides (TG) values for blood lipids were measured. Prothrombin activity, fibrinogen, alkaline phosphatase, gamma glutamyl transferase were also investigated at inclusion in study.

Ultrasound exam (U)

Ultrasonography examinations were performed by a single examiner. Patients were placed in supine position and examined using either subcostal or intercostal approach. The craniocaudal sizes of the left and right liver lobe were measured, on the midclavicular line, in the sagittal plane. Bipolar spleen diameter (BSD) and portal vein diameter were examined using ultrasonography. The degree of liver fattening was categorized as grade I steatosis when there was a slight increase in the diffusion of liver echogenicity and normal echogenicity of the diaphragm and intrahepatic vein walls. Patients with increased liver echogenicity, with minimal washout of intrahepatic vein walls and diaphragm echogenicity were classified as grade II steatosis. Patients with a definite increase in liver echogenicity with posterior segments of the liver not clearly visible and intrahepatic vein walls and diaphragm partly or fully obscured were evaluated as grade III steatosis.

Liver Stiffness Measurement by Shear Wave elastography (SWE)

A GE Healthcare LOGIQ E9 system with the R5 software version and the C1-6-D probe was used in order to acquire data on liver shear wave elastography. All measurements were performed by the same investigator, using the same device, during ultrasound examination.

The patients were placed in the left posterior oblique position, with the right arm over their head and the right liver lobe was assessed using intercostal approach, using the 7th or 8th intercostal spaces in the right anterior axillary line to perform measurements. The acquisition region-of-interest (ROI) was selected at least at 1 cm below the liver capsule, with no significant vessels (if possible). During end-expiration breath holds, 10 repeated SWE measurements were performed, with each SWE acquisition requiring about 1 to 2 seconds. Following acquisitions, the measurements were performed by placing 10 circular measurement regions over the saved SWE images, each circular region accounting for approximately 1 cm in diameter.

The median value was considered representative and the results were expressed in kilopascals (kPa). A SWE measurement was considered valid if the interquartile range was < 30% of the median value. An unsuccessful 2d-SWE acquisition was considered when the elasticity map was filled with colour on less than 50% of the area.

(FERRAIOLI & al [19]; SAMIR & al [22]).

Liver Stiffness Measurement by FibroScan- transient elastography (TE)

Measurements were performed by a single experienced evaluator, with the patient placed in dorsal decubitus, examining the right liver lobe, through intercostal spaces. Only procedures with ≥ 10 validated measurements were considered reliable. The success rate was calculated as a percent of the validated measurements from the total number of measurements. The median value was considered representative and the results were expressed in kilopascals (kPa). A Fibroscan was considered valid if the interquartile range was < 30% of the median value and the success rate was > 60% (BOURSIER & al [23]).

Statistical Analysis

Variables in the present study were assessed by frequencies and descriptive statistics (categorical variables) and descriptive statistics (qualitative variables).

Patient characteristics are reported as means and standard deviations, medians (ranges), or n (%) when appropriate. Continuous variables were compared with Mann-Whitney U tests. Spearman's analysis was used to investigate correlations between variables. Univariate and multivariate logistic regression analyses were performed to identify independent factors related to discordance between TE and SWE. Hazard ratios (HRs) and corresponding 95% confidence intervals are also indicated. A two-sided P value of <0.05/0.01 was considered significant. All statistical analyses were performed using the SPSS 20.0 software.

Results

Between January 2017 and December 2017, 139 patients met the inclusion criteria. Sixteen patients (11.51%) were excluded: twelve patients (8.63%) because of unreliable liver stiffness measurement by TE (IQR > 30% in 5 patients and no acquisitions in 7 patients) and four (2.87%) because of unreliable liver stiffness measurement by SW (IQR > 30%).

Baseline characteristics of the study population

A total of 123 patients were evaluated (49 men and 74 women), with a mean age of 53.56 years. Their clinical, laboratory and ultrasound descriptive parameters are summarized in Table 1.

Table 1. Baseline characteristics (biological and ultrasound parameters) of the study population

	Mean	Std dev.	Std.Err	Min	Max
Age (years)	53.56	12.532	1.911	26	76
BMI (kg/m ²)	31.5091	4.13852	0.62391	26	45
PLT	250795.45	57035.109	8598.366	130000	348000
PT %	98.25	8.887	1.34	72	120
Fibrinogen	351.52	72.536	10.935	165	486
AST	24.2	10.564	1.593	12	71
ALT	37.75	19.439	2.931	14	93
Alkaline phosphatase	75.59	19.795	2.984	30	122
Gamma glutamyl transferase	60.14	56.434	8.508	14	334
Total cholesterol (mg/dl)	225.3	49.943	7.529	126	356
Triglycerides (mg/dl)	193.2	119.927	18.08	42	485
RL (mm)	140.5	15.687	2.365	12	186
LL (mm)	89.5	14.742	2.222	53	121
PV (mm)	12.9636	1.83596	.27678	9.80	17.80
BSD (mm)	120.18	15.015	2.264	85	155

Abbreviations: RL: right lobe of the liver, LL=: left lobe of the liver, PV: portal vein diameter; BSD: bipolar spleen diameter

Regarding non-parametrical variables, patients in the working group were divided in: grade 1 steatosis (9 patients – 7.31%); grade 2 steatosis (63 patients – 51.21%) and grade 3 steatosis (51 patients – 4.46%). Liver stiffness assessment proved that TE and SWE results were correlated in 79 cases

(64.22%). Discordance in one degree of fibrosis stage was found in 16 patients (13.01%) and discordance in more than one degree of fibrosis stage in 28 patients (22.76%), as shown in Figure 1.

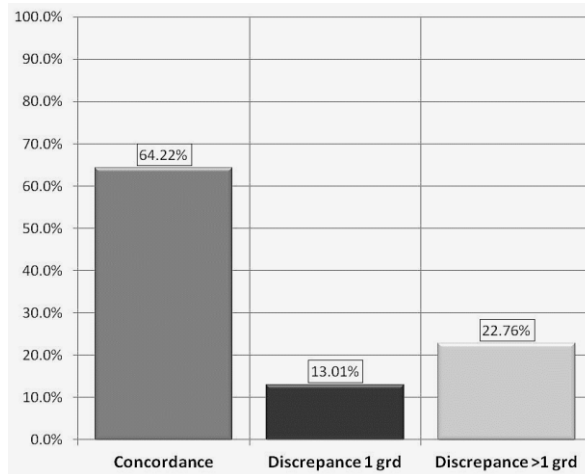


Figure 1. Overall fibrosis concordance and discordance levels in the patients included in the study.

Correlations between variables

As for the examined predictors of discordance between SWE and TE in patients with NAFLD, discordance is defined as a difference of at least 1 degree among observations performed by both methods. We analyzed demographic, clinical and biological parameters in patients with documented discrepancies for the pair of evaluation methods (TE and SWE); then we have compared those results with the parameters in concordant pairs. Statistically significant results for the up-mentioned parameters are correlated with a discordant pair of evaluation methods. We have used paired t-test and non-parametric Mann-Whitney U test

that does not require assumption of normal distributions.

In the next figures, the top and bottom of the boxes represent the first and third quartiles respectively. The length of the box thus represents the interquartile range within which 50% of the values were located. The line through the middle of each box represents the median. The error bars show the minimum and maximum values (range). In our study, the SWE and TE measurements showed a concordance in patients with higher liver stiffness values (Fig 2). Pearson correlation for liver stiffness values generated by TE vs SW shows a significant association, supported by correlation coefficient ($r = 0.60545$).

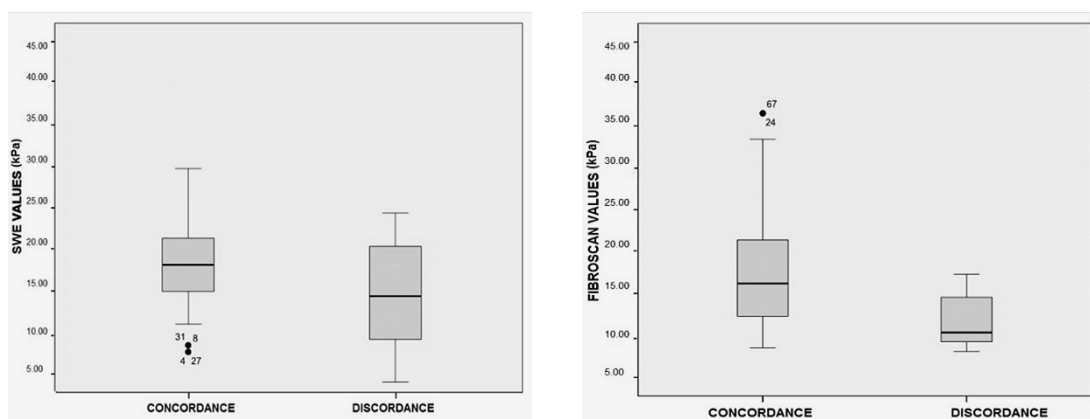


Figure 2. Concordance/discordance levels related to liver stiffness values: SWE and FibroScan measurements.

In the univariate analysis, discordance between SWE and TE in fibrosis staging (liver stiffness) was significantly influenced by: BMI, aspartate aminotransferase values and degree of liver steatosis. Results for multiple correlations

regarding the predictors of discordance on the first hand and coefficients of parameters influencing differences between TE and SWE values on the other hand, are shown in Tables 2 and 3.

Table 2. Multiple correlations in non-parametric test for predictive analysis

Multiple correlations	Estimated value
Multiple correlation coefficient r	0.703538
Multiple R ²	0.494965
F(6, 1161)	5.880368
P	0.000085
Std.Err. of Estimate	0.649850

Table 3. Correlation coefficients of parameters influencing differences between TE and SWE values

Partial correlation	Correlation coefficients (Beta)	Std.Err.	T	p 95% CI
Intercept			-2.89836	0.005939
Age	-0.020559	0.121224	-0.16959	0.866145
Sex	0.133840	0.118238	1.13195	0.264077
Platelets count	-0.178353	0.120928	-1.47487	0.147704
GGT	-0.088282	0.113211	-0.77980	0.439879
Steatosis	0.354682	0.120599	2.11180	0.040693
BMI	0.489139	0.118196	3.29232	0.002021
ASAT	0.502725	0.121724	3.30850	0.001930

The results of nonparametric test for predictive analysis shows that, in majority of the cases with discordance between TE and SWE values, the differences were influenced by age, BMI, level of liver enzymes (ALAT, ASAT), liver steatosis and platelets count. The analysis of the partial correlation coefficients indicated that a significant influence in discordance of fibrosis stage was exercised by the ASAT ($r_{\text{partial}} = 0.50$, $p < 0.01$), followed by the value of BMI ($r_{\text{partial}} = 0.48$, $p < 0.01$) and the last predictive factor – steatosis degree ($r_{\text{partial}} = 0.35$, $p < 0.05$) (Table 3).

Discussions

In our series SWE applicability was (97.13%) significantly higher than that TE (91.36%). SWE applicability was greater than TE applicability in obese patients and the rate of failure appears to be lower than for TE. These same results were reported by other authors (POYNARD & al [20], ELKRIEF & al [24]; WONG & al [25]; BOTA & al [26]).

The prevalence of significant discordance (more than 1 degree) in our study was higher (22.76%) than that in other studies (THIELE & al [27], GERBER & al [28]; KIM & al [29]).

It is possible that these results are due to the fact that SW elastography offers the possibility to choose the placement of ROI within the color stiffness box and also to include or exclude each single measurement when determining the final value. Furthermore, it is a greater potential for the operator to influence the final results than when using Fibroscan, where this variability is not applicable (LI & al [30], CASSINOTTO & al [31]; MULLER & al [32]).

Both methods are comparable in most cases for staging advanced liver fibrosis (F3) and diagnosing cirrhosis (F4). In our study, SWE values are well correlate with transient elastography values in cases of advanced fibrosis (F3-F4) but not as well at low levels of liver fibrosis (F0-F2) Related to this aspect, most previous reports noted the high degree of concordance for advanced fibrosis stages (F3-F4) (KIM & al [29], LI & al [30]; PISCAGLIA & al [33]).

High values of liver stiffness (>15 kPa) showed independent positive association with concordance between TE and SWE, fact that has been reported by other authors as well (GERBER & al [28]; JEONG & al [34]). Similarly to other studies, in the study we performed, high body mass index (BMI) was an important factor in predicting the discordance between TE and SWE (PISCAGLIA & al [33]; JEONG & al [34], YOON & al [35]; CHANG & al [36], PETTA & al [37]).

The second factor that may influence the concordance between the two methods is necroinflammatory activity, which is closely related to ALT/AST level. Our results show that the discordance in fibrosis staging was influenced by the ASAT values. Results from other studies have identified elevated liver enzymes as a predictor of discordance. No effect of the high level of liver enzymes was seen on liver stiffness measurements in other previously reported studies (ELKRIEF & al [24], PISCAGLIA & al [33]).

Impact of steatosis on discordance between TE and SWE was also evaluated in the present study, concluding- similarly to other studies – that the presence of steatosis influences conducting liver stiffness measurement, in order to assess fibrosis (GAIA & al [38], PETTA & al [39]). On the contrary, in the study performed by Deffieux et al elasticity measurements were not influenced by the degree of steatosis (DEFFIEUX & al [40]). In our study lot, liver stiffness degree did not correlate with platelet counts in either the univariate or multivariate analysis. This result is similar to those observed in other studies using shear wave or transient elastography techniques (OLIVARES-GAZCA & al [41]).

For liver stiffness measurements by TE, there was a possible overestimation, related to the necroinflammatory activity, while for estimated fibrosis using SWE, there was a possible underestimation, due to the high BMI and presence of liver steatosis. Our study has limitations: the study population had a high prevalence of obesity, which could be a technical limitation and the analysis was performed in a relatively small number of patients; thus, these results need to be validated in larger studies.

Conclusions

SWE and transient elastography appear as comparably reliable methods for non-invasive assessment of liver fibrosis. However, there are possible discrepancies in evaluating fibrosis stage using TE and SWE, such differences being significantly influenced by BMI, level of necroinflammatory activity and liver steatosis. Both methods show better reliability for the detection of advanced fibrosis and cirrhosis (F3-F4) when compared to the detection of incipient or significant fibrosis (F0-F2).

Although alternative SWE seem to overcome limitations of TE, their quality criteria for high sensitivity interpretation have not yet been well defined.

Given the socio-economic impact determined by the increased morbidity and mortality caused by chronic hepatic diseases, the development of non-invasive, accessible and precise methods is essential. These methods would prove helpful in establishing an early diagnostic, which in turn would lead to an efficient treatment.

In the future, formulas that combine methods of elastometry and biomarkers that identify hepatic fibrosis will completely replace hepatic biopsy in establishing the severity of hepatic illness, both in NAFLD and in other chronic hepatic diseases.

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