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Point shear wave elastography and vibration controlled transient elastography for estimating liver fibrosis in a cohort of liver transplant patients

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Abstract. – OBJECTIVE: Liver transplant (LT) patients need regular follow-up both by ultrasonography and elastography. Shear wave elastography is now available in high-end ultrasound systems that, however, may yield different values for any given liver, reflecting technological differences. The aim of this study was to establish whether the point shear wave elastography QElaXto® (QEpSWE), available on Esaote (Genoa, Italy) systems, is comparable to the standard Fibroscan® (vibration-controlled transient elastography, VCTE) in the real-life setting of liver transplant (LT) patients.

PATIENTS AND METHODS: We prospectively examined with QEpSWE 196 consecutive LT patients referred for VCTE and ultrasound examination. The agreement between QEpSWE and VCTE was assessed with Lin concordance correlation coefficient (CCC) and Bland-Altman analysis. The performance of QEpSWE was assessed with the ROC curves using the VCTE cut-offs of 7 and 12 kPa for F2-F3 and F4, respectively.

RESULTS: The two methods showed 100% of successful and reliable liver stiffness measurements (LSM), similar median LSM in the whole group and in the two subgroups F2-F3 and F4 of fibrosis, with a disagreement in categorization of liver fibrosis in only 2% of cases, and never more than 1 stage of fibrosis. Further, they presented the same degree of higher LSMs in clinically unstable LT patients and an excellent overall agreement (CCC=0.91, accuracy=0.95, precision=0.96), even if agreement was less satisfactory in the range of severe fibrosis. The optimal cutoffs of QEpSWE were 6.7 and 11.6 kPa for F2-F3 and F4, respectively.

CONCLUSIONS: The values of VCTE and QEpSWE showed a very high correlation in the staging of liver fibrosis. QEpSWE seems a promising method for staging liver fibrosis in LT patients.

Key Words:
Liver transplant, Ultrasound, Elastography, Diagnostic procedure, Liver fibrosis, Point shear wave elastography, Transient elastography, Liver stiffness.

Abbreviations

ASH, alcoholic steatohepatitis; BMI: body mass index; IQR: interquartile range; SD: standard deviation; IQR/M: interquartile range divided by the median liver stiffness value; kPa: kiloPascal; LSM: liver stiffness measurement LT: liver transplant; MMF: mycophenolate mofetil/sodium; mTOR: mammalian target of rapamycin; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatits; pSWE, point shear wave elastography; QEpSWE: QElaXto point shear wave elastography; SVR: sustained virological response; US: ultrasound; VCTE: vibration-controlled transient elastography.

Introduction

Liver transplant (LT) patients requires regular graft's follow-up due to their higher risk of developing complications, mainly for their immunosuppressed state[1,2]. Both periodic ultrasound (US) examination and evaluation of liver stiffness measurement (LSM) are surveillance tools useful in real-life clinical practice to periodically monitor LT patients[3]. Vibration-controlled transient elastography (VCTE; FibroScan®, Echosens, France) is the first and most validated elastographic method and is now considered the reference standard to indirectly assess liver fibrosis[4].

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The availability of several other ultrasound elastographic techniques that measure liver stiffness during the standard echography[4] is nowadays a reality, but the various elastography systems may yield different values for any given liver reflecting technological differences[5].

QElaXto® (implemented on MyLab™Eight Platform, Esaote, Italy) is a point shear wave elastography technique (QEpSWE) that has preliminarily been proven to be accurate in staging liver fibrosis in a population with 95% chronic hepatitis C[6]. The aim of this study was to correlate the results of LSM obtained by QEpSWE with those obtained by VCTE and the diagnostic performance for fibrosis of QEpSWE in a cohort of LT patients in follow-up at our institution, before its clinical routinary use.

Patients and Methods

This was a single center cross-sectional study. From June 2018 to February 2019, consecutive individuals, followed-up at our Institution after LT, were enrolled at the moment of the referral for LSM with the Fibroscan® device and US examination.

According to his/her active biochemical/clinical conditions each transplanted patient has been defined as clinically stable (no active problem and requiring only regular periodic protocol surveillance) or unstable (requiring active monitoring or intervention) at the moment of elastography. Diagnosis of NASH has been made on liver histology, while the term "cholestatic disease" refers to abnormalities of the entire biliary tract, including intrahepatic and extrahepatic bile ducts that may occur in LT patients. None of the patients in this series had ascites. The study was performed according to the 1976 Declaration of Helsinki and its later amendments and followed our Internal Review Board policies. All patients gave their informed consent to the study.

Transient Elastography

VCTE measurements were performed using the Fibroscan® 502 Touch device with M probe, following the standardized procedure2020/6/8 and the results are expressed in kilopascals (kPa). XL probe was used for LSM in those patients who, due to their obesity, had a skin-capsule distance of >2.5 cm or as suggested by manufacturer's software.

A stiffness measurement was defined reliable when the median value of 10 measurements was obtained with a success rate of more than 60% and an interquartile range/median ratio (IQR/M) less than 30%[8].

The physicians who undertook all the examinations had an experience of >1000 VCTE procedures.

The cut-offs in use to stage liver fibrosis vary according to the etiology of liver disease[9]. However, in order to organize in indicative categories of liver fibrosis severity the results of VCTE as reference method, the following cut-offs, outlined in a published meta-analysis on patients with chronic viral hepatitis[10], were used for all transplanted patients: <7 kPa defined the normal/mild fibrosis group (F0-F1), ≥7 kPa defined the group with significant fibrosis (F2-F3) and ≥12 kPa defined those with cirrhosis (F4).

Point Shear Wave Elastography

Point shear wave elastography is implemented on high-end commercial US machines. QElaXto is a pSWE technique available on the US scanner MyLab™ Eight Platform (Esaote, Genoa, Italy). QEpSWE can give a measure of the liver stiffness on a "single" point, based on estimation of shear wave propagation in transverse direction. Stiffness measurements were acquired following the standardized procedure as described elsewhere[9,11].

QElaXto contains the program "3D eWave shear wave quality graph" for immediate feedback about measurement quality (3D histogram qualitative display of the propagation of the perturbation Space-Time-Displacement) and an automatic "reliability tool" for performed measurements based on statistical analysis of acquired signals: no measurement is displayed if signal/to noise ratio is low. Ten valid LSMs, median value in kPa and the IQR/M were recorded in each patient. Reliable LSMs were defined as the median value of 10 measurements and an IQR/M less than 30%[8,11].

Statistical Analysis

Descriptive statistic was performed to describe baseline demographic, clinical and anthropometric characteristics. Kolmogorov-Smirnov test was used for assessing the normality of numerical variables: if the data followed a normal distribution, they were expressed as the mean value and standard deviation (SD), otherwise in cases of deviation from normality median and interquartile range (IQR: 25^{th}-75^{th} percentile) were used. Categorical variables were presented as counts

and percentages. Chi-square test was used to compare categorical variables, and differences between quantitative variables were analyzed by *t*-test or the Mann-Whitney test according to normal or non-normal distribution of the data. The diagnostic performance of QEpSWE for predicting significant fibrosis and liver cirrhosis compared to reference standard (VCTE) was assessed by calculating the area under the receiver operating characteristic curve (AUROC), choosing the optimal cut-off values corresponding with the maximum of the Youden index (sensitivity + specificity-1).

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-) and their corresponding 95% confidence intervals (95% CI) were calculated.

Lin's concordance correlation coefficient (CCC) was performed to assess the agreement between LSMs of QEpSWE and VCTE with calculation of r Pearson coefficient (measure of precision) and bias correction factor (measure of accuracy). Also, Bland and Altman's plot was used to compare the two measurement techniques. For each measure, the average of kPa for VTCE and QEpSWE were calculated and then plotted against the difference of the two measurements. The mean difference and the 95% limit of agreement (LOA) were added to the Bland-Altman plot. If the differences within mean ± 1.96 SD (LOA) are not clinically important, the two methods may be used interchangeably.

A p-value <0.05 was considered statistically significant. All tests were two-sided. Statistical analyses were performed using SPSS Software for Windows, Version 13.0 (SPSS Inc., Chicago, IL, USA), and MedCalc software, Version 12.7.0 (MedCalc Software, Mariakerke, Belgium).

Results

We prospectively studied 196 consecutive LT patients. The main demographic and clinical characteristics of the studied cohort are reported in Table I. Overall, our patients are composed of three-quarters of males, overweight in two cases out of three and observed more than 10 years after liver transplantation. One hundred thirty-eight patients, according to VCTE, had F0-F1 fibrosis, 39 F2-F3 and 19 F4 (12 with clinical signs of cirrhosis: 3 esophageal varices, 4 previous ascites, 5 portosystemic encephalopathy).

Reliable Liver Stiffness Measurements of QEpSWE and VCTE

The two methods showed excellent feasibility, being 100% the rate of successful LSMs for both VCTE and QEpSWE. Unsuccessful measurements of VCTE with M probe, in 9 obese patients (out of 27, 33%), were all obtained by the use of XL probe. The rates of reliable LSMs were also 100% for both VCTE and QEpSWE.

Agreement Between QEpSWE and VCTE

As shown in Table II, the median VCTE LSM and its corresponding QEpSWE LSM were similar in the whole group (p=0.90) and in the two stages of fibrosis (F2-F3 significant and F4 cirrhosis) defined according to standard VCTE.

The mean of IQR/M ratio was significantly higher in QEpSWE measurements than in VCTE, both in the whole group and in the subgroups according to VCTE-derived fibrosis stages.

There was excellent agreement between paired LSM from QEpSWE and VCTE (CCC=0.91, 95% CI 0.89-0.93, accuracy=0.95, precision=0.96, p<0.0001). The differences of the two measurements against their means were plotted using the Bland-Altman analysis (Figure 1). This graphic method reveals mean differences of 0.4 kPa with LOA from -4.1 kPa to +5.0 kPa, clearly indicating that the values of the two methods did not always overlap and the difference was wider for values in the severe stiffness range.

Diagnostic Performance of QEpSWE

The performance of QEpSWE in defining optimal cut-offs to diagnose fibrosis as clinically significant (F2-F3) and severe (F4) according to VCTE as the reference standard, was assessed by AUROC curves (Figure 2): cut-offs were 6.7 kPa (sensitivity: 94.8, specificity: 100.0) and 11.6 kPa (sensitivity: 100.0, specificity: 98.3); AUROC r values were identical: 0.99 (95% CI, 0.97-1.00) and 0.99 (95% CI 0.97-1.0), for F2-F3 and F4 fibrosis, respectively. The performance of QEpSWE is shown in Table III.

Clinical Applications

Four cases (2% of all patients), in significant fibrosis group by VCTE cutoffs, were classified in a different stage of liver fibrosis by QEpSWE stiffness measurement, with 3 patients shifting

Table I. Demographic and clinical data of liver transplant patients.

Characteristics	Overall (n = 196)
Age at follow-up, median years (IQR)	65 (58-70)
Gender: Males (%)/Females (%)	150 (76)/46 (24)
BMI, mean (SD)	26.4 (3.6)
Obesity (%)	27 (14)
Overweight (%)	99 (51)
Months of follow-up after LT, mean (SD)	134.3 (83)
Tacrolimus immunosuppression (%)	128 (65)
Cyclosporine immunosuppression (%)	48 (24)
MMF associated (%)	95 (48)
mTOR associated (%)	36 (18)
AST, U/L (IQR)	24 (17-32)
ALT, U/L (IQR)	20 (14-16)
GGT, U/L (IQR)	36 (18-110)
Total bilirubin, mg/dL (IQR)	0.8 (0.5-1.4)
Platelets count, 10^3/mm^3 (SD)	142 (62)
Serum albumin, g/dL (IQR)	4.4 (4.1-4.7)
INR (IQR)	1.03 (0.97-1.15)
Etiology of liver disease at LT	
Hepatitis C (%)	72 (37)
Hepatitis B (%)	77 (39)
HCV/HBV (%)	11 (6)
HCV/other non-HBV etiologies (%)	3 (2)
ETOH (%)	17 (9)
Other etiologies (%)	33 (17)
Pre-LT HCV treatment with SVR (%)	22 (26)
Post-LT HCV treatment with SVR (%)*	64 (74)
Arterial Hypertension (%)	51 (26)
Diabetes (%)	58 (30)
Dyslipidemia (%)	52 (27)
Chronic renal failure (%)	46 (23)

BMI: body mass index; IQR: interquartile range; SD: standard deviation; LT: liver transplant; MMF: mycophenolate mofetil/sodium; mTOR: mammalian target of rapamycin; PT: prothrombin time, INR: international normalized ratio, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phophatase, GGT: gamma-glutamyl transferase, SVR: sustained virological response. *No patient had still active replication (all HCV RNA negative).

Table II. Median or mean LSM and IQR/M values for each fibrosis stage of the transient elastography method and the point shear wave measurement method with their ability to categorize LT patients into the same stiffness class.

	Whole group	Not significant fibrosis (F0-F1)*	Significant fibrosis (F2-F3)*	Liver cirrhosis (F4)*
	Median values of LSM for each fibrosis stage			
VCTE, kPa median (IQR)	5.6 (4.8-7.8)	5.1 (4.5-5.7)	8.7 (7.8-10.2)	16.9 (13.9-26.1)
QEpSWE, kPa median (IQR)	5.6 (4.7-7.6)	5.05 (4.5-5.8)	8.9 (7.1- 9.8)	15.5 (14.3-17.5)
p	0.80	0.90	0.87	0.51
	Median IQR/M values of LSM for each fibrosis stage			
VCTE, IQR/M median (IQR)	12 (9-16)	13 (9-16)	13 (9-16.7)	10 (6.5-14)
QEpSWE, IQR/M median (IQR)	17 (13-22)	17 (13-21)	19 (14-23)	17.5 (10-24)
p	< 0.0001	< 0.0001	0.0009	0.004
	Ability to categorize LT patients into the same fibrosis stage			
VCTE, (number of patients) (%)	196	138 (70)	39 (20%)	19 (10%)
Reclassification according to QEpSWE (number of patients)	196	142 (73)	34 (17)	20 (10)
p		0.58	0.52	0.86

*Fibrosis stage assessed with VCTE as reference standard. IQR: interquartile range; IQR/M: interquartile/median; SD: standard deviation; kPa: kiloPascal; LSM: liver stiffness measurement; LT: liver transplant; QEpSWE: QElaXto point shear wave elastography; VCTE: vibration-controlled transient elastography.

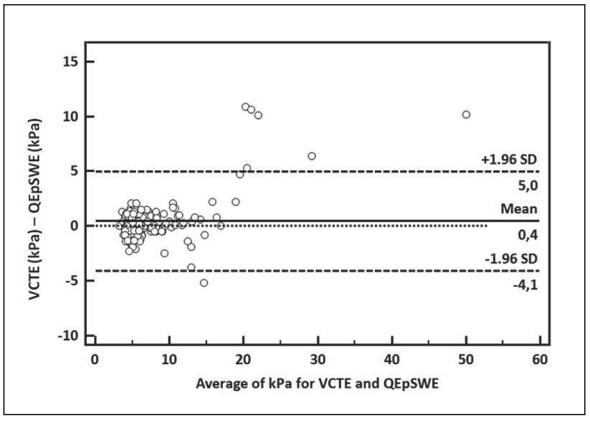

Figure 1. Bland-Altman plot of differences between the point shear wave measurement (QEpSWE) method and transient elastography (VCTE). In the scatter plot XY, Y-axis shows the difference between the two measurements and the X-axis represents the average of these measurements. Horizontal lines are tracked 1) at the mean difference of ratings (full line); 2) at line of all perfect average agreement (Y=0) (dotted line); 3) at the 95% limits of agreement (dashed lines), which are defined as the mean difference ±1.96 times the standard deviation of the differences.

to group mild fibrosis e 1 to severe fibrosis. In no case there was a discordance of more than 1 stage of fibrosis between the two methods.

LSM values with the two methods have been evaluated in the two different clinical conditions of stable and unstable LT patients (Table IV). One hundred seventy patients were clinically stable with no abnormal clinical-biochemical feature of liver disease (86 cured HCV, 88 suppressed HBV, 17 post-ethanol cirrhosis and 33 other etiology, with overlapping cases). Twenty-six patients had abnormal clinical-biochemical signs of their liver disease (4 NASH, 9 cholestatic disease, 5 HCV advanced functionally decompensated cirrhosis, 4 recurrent ASH, 3 chronic rejections). Both methods detected significantly higher LSMs in the pathological conditions, with values not statistically different between them.

Discussion

Our study, performed with paired examinations, shows that the LSM acquired by QEpSWE and VCTE have a very good correlation in the particular population of liver transplant patients. In the setting of liver transplant follow-up, VCTE is the most validated method because it was the first to be used thanks to the dedicated device Fibroscan®. VCTE for the staging of liver fibrosis has been accepted as an alternative to liver biopsy in patients with chronic hepatitis C recurrent after LT[1,4]. VCTE, moreover, showed its importance in predicting fibrosis progression both in HCV and non-HCV LT diseases[12] and in formulating prognosis on graft survival[13]. Few studies are available on use of different SWE techniques on LT patients, all with real time 2D SWE. A recent study[14] in patients with recurrent hepatitis C virus infection after LT showed its utility to differenti-

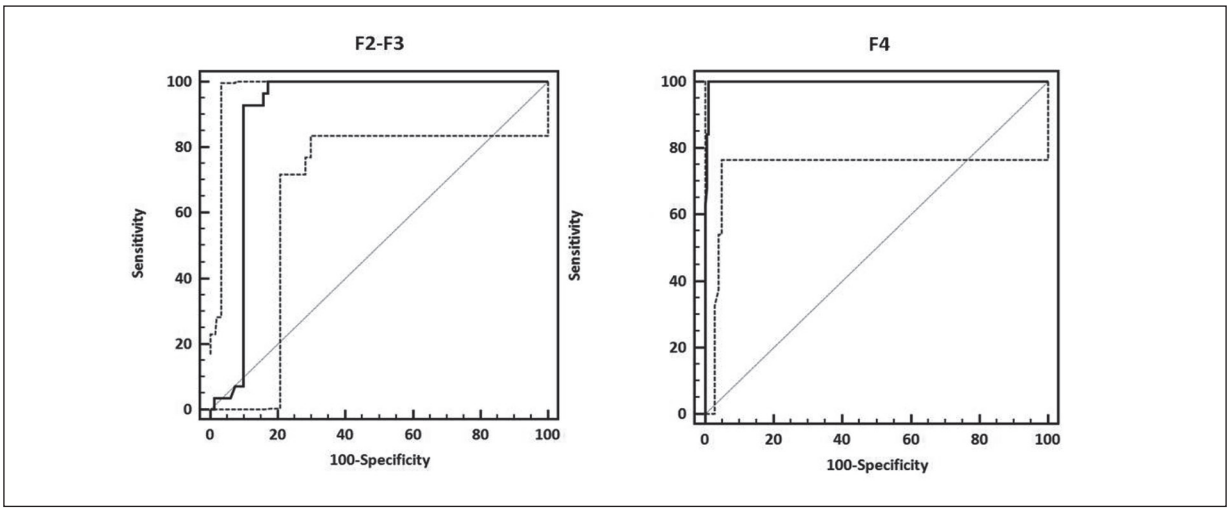

Figure 2. Area under the receiver operating characteristic curves (AUROCs) for point shear wave elastography (QEpSWE) in assessing significant (F2-F3) and severe (F4) liver fibrosis in patients with LT. Optimal cut-off values (criterion) corresponding with the maximum of the Youden index (sensitivity + specificity-1) are automatically generated.

Table III. Performance of QEpSWE in diagnosing significant fibrosis (F2-F3) and cirrhosis (F=4).

Parameter	F2-F3 (n = 39)	F4 (n = 19)
Area under the ROC curve (95% CI)	0.90 (0.83-0.95)	0.99 (0.97-1.00)
Cutoff value (kPa)	> 6.7	> 11.6
Sensitivity % (95% CI)	92.8 (76.5-99.1)	100.0 (82.4-100)
Specificity % (95% CI)	90.2 (81.7-95.7)	98.87 (96.0-99.9)
Positive likelihood ratio (95% CI)	9.52 (8.4-10.8)	88.5 (87.1-89.9)
Negative likelihood ratio (95% CI)	0.079 (0.02-0.4)	–
Positive predictive value % (95% CI)	76.5 (58.5-89.4)	90.5 (69.6-98.8)
Negative predictive value % (95% CI)	97.4 (90.7-99.7)	100.0 (97.9-100)

ate low from advanced liver fibrosis. Korda et al[15] used a SWE technique to monitor the beneficial therapeutic effects of direct-acting antivirals in hepatitis C recurrence following liver transplantation. According to Yoon et a[16] real-time 2D SWE has the potential to reliably detect rejection or recurrent hepatitis early after LT (4 weeks), both in HCV- and non HCV-patients.

Liver biopsy maintains a central role in evaluating post-transplant liver diseases, especially because rejection often remains to be detected[2]. However, once a histobioptic diagnosis has been made, LSM becomes a reference point and elastography plays a pivotal role in subsequent monitoring over time of liver transplanted patients[3,17,18]. It must be considered that in liver transplants management, having now solved the problem of recurrent hepatitis C[19], the classification of LSM in a correct stage of fibrosis still remains important, but it is equally essential to follow its variation over time.

A limitation of this study is that the cut-offs for fibrosis notoriously vary depending on the etiology of liver disease[9] and the two techniques were compared in a cohort of LT patients who have mixed etiology of their liver conditions. This

Table IV. Demographic and clinical data of stable and unstable liver transplant patients.

Characteristic	Stable LT patients (170)	Unstable LT patients (26)	p
Gender: Males (%)/Female (%)	127 (75)/43 (25)	23 (88)/3 (12)	0.22
BMI, mean (SD)27 (5.6)	26 (3.1)	0.15	
Obesity (%) 23 (13.5)	4 (15.4)	0.96	
Overweight (%)86 (50.6)	13 (50)	0.87	
Months of follow-up after LT, mean (SD)	131 (80)	157 (101)	0.14
AST, U/L (IQR)20 (16-25)	39 (25-47)	< 0.0001	
ALT, U/L (IQR)15 (13-21)	25 (20-50)	0.0001	
GGT, U/L (IQR)22 (16-40)	123 (72-286)	< 0.0001	
Total bilirubin, mg/dL (IQR)	0.65 (0.5-0.9)	1.4 (1-2.6)	< 0.0001
Platelets count, 103/mm3 (SD)	150 (65)	128 (55)	0.16
Serum albumin, g/dL (IQR)	4.5 (4.3-4.7)	4.3 (3.85-4.5)	0.01
INR (IQR) 1.02 (0.96-1.07)	1.08 (0.99-1.24)	0.06	
Liver diagnosis*:			
NAFLD (%) on ultrasound	41 (24)	0	
NASH (%) 0	4 (15)		
ASH (%) 0	3 (12)		
Chronic rejection (%)	0	4 (15)	
Cholestatic disease (%)	0	9 (35)	
Severe hepatic damage in the result of recurrence of primary disease after LT (%)	15 (9)	5 (19)	
Unclassified (%)4 (2)	1 (4)		
VCTE, kPa, median (IQR)	5.3 (4.6-6.4)	12.0 (9.5-22.7)	< 0.0001
QEpSWE, kPa, median (IQR)	5.3 (4.6-6,3)	11.7 (8.5-16.2)	< 0.0001

ALP: alkaline phosphatase; ALT: alanine aminotransferase; ASH: alcoholic steatohepatitis; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; INR: international normalized ratio; IQR: interquartile range; LT: liver transplant; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; SD: standard deviation. *Liver diagnosis indicate the main active post-transplant liver disease in the single patient.

heterogeneity, however, reflects the unselected characteristic of the real world of follow-up of liver transplant patients[20], as in many other centers in the world. In fact, our Liver Unit is located in a referral tertiary Hospital that is not a center of liver transplantation, but is a spoke of a hub/spoke network and has in charge patients who need local support for their long follow-up, wherever they have been transplanted: network spoke centers interface with the hub center (the regional Liver Transplant Unit) and with transplant centers located outside the region, as required.

On this assorted population both QEpSWE and VCTE showed 100% of successful LSMs, also with those criteria of reliability that in a similar pSWE system have been shown to offer the best quality[21]. The 100% rate of successful measurements of QEpSWE have been shown also with other pSWE methods, as reported in a meta-analysis of six studies in patients with NAFLD (99.2%)[22-23]. In our study VCTE with M probe had a slightly lower success rate of valid measurements than QEpSWE: this advantage of QEpSWE might have been due to its real-time B-mode imaging guidance, to the possibility of accepting only high quality single LSM and to its feasibility in obese patients without using the dedicated XL probe as in VCTE.

We found that the mean of IQR/M ratio was significantly higher in QEpSWE measurements than in VCTE. IQR/M is a marker of LSM accuracy acquired with VCTE in patients with hepatitis C[24]. The lower the IQR/M ratio, the more reliable the LSM is considered[8]

The graphic representation of agreement between the two SWE techniques by Bland-Altman plot clearly shows that the values of the two methods are not always overlapping and the difference is greater for severe stiffness values, where the widest divergences are found. It has been described that the reproducibility of various machines tends to worsen at higher stiffness values, both in stiff phantom targets and *in vivo*[25]. Even if in this range of stiffness, the clinical meaning does not change (cirrhosis), our results confirm that the two techniques are not completely interchangeable.

In the real world, during a years-long follow-up, repeated LSMs for monitoring could be performed with different devices: the limitation of not automatic interchangeability of two different elastographic equipment in defining stiffness thresholds should be kept in mind, maintaining caution on their clinical interpretation[11,26].

This type of study has other limits. First of all, it was not designed to compare QEpSWE with liver biopsy for staging liver fibrosis. However, it seems very unlikely that all new US elastography techniques could be compared to liver biopsy (LB) in a well-designed study because of the restricted indications in transplanted patients. VCTE has been accepted as a reliable substitute of LB by clinical guidelines[4] also because it shares with LB the limitations of a considerable overlap between early and intermediate fibrosis stages (F1-F3), with sensitivities and specificities of cut-offs generally <90% and, thus, both methods are not entirely perfect in diagnosing the exact stage of fibrosis[9,27]. So, by using VCTE as the reference standard, it was possible to apply the best quality criteria in order to check the performance of the new technique.

Second, our findings could be in part affected by the spectrum bias of the not uniform distribution of patients across all fibrosis stages, with a high percentage of patients in F0-F1 fibrosis stages (70%) and a relatively low percentage (30%) of enrolled patients in F2-F3 and F4 fibrosis stages.

Finally, the study has not been extended to evaluate reproducibility over time of repeated QEpSWE repetition in the follow-up of LT patients.

Conclusions

Liver stiffness measurements obtained with QEpSWE are both reliable and accurate for estimating liver fibrosis in practical context of the management of liver transplant recipients. These values substantially reproduced those obtained by standard VCTE, but there are some divergences in the range of advanced fibrosis. Although the two different methods of liver stiffness measure cannot be considered interchangeable, QEpSWE seems a promising method for staging liver fibrosis in LT patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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