Abdominal Radiology

Published online: 31 August 2018

Abdom Radiol (2019) 44:464–472
https://doi.org/10.1007/s00261-018-1732-8

Evaluation of acoustic radiation force impulse (ARFI) elastography as non-invasive diagnostic tool in living donor liver transplantation

Hanan Abdelhaleem,[1] Hadeel Gamal Eldeen,[1] Mohammed Mahmoud Nabeel,[1] Reham Abdelmoniem,[1] Wafaa Elakel,[1] Naglaa Zayed,[1] Zeinab Abdellatif,[1] Bahaa Monir,[2] Mohamed Said Abdelaziz,[1] Sherif Mogawer,[3] Mona Elamir,[3] Mostafa Elshazli,[4] Ayman Salah,[4] Adel Hosny,[4] and Ayman Yosry[1]

[1]Department of Endemic Medicine and Liver Unit, Faculty of Medicine, Kasr Al-Aini Hospital, Cairo University, Cairo 11562, Egypt
[2]Department of Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt
[3]Department of Internal Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt
[4]Department of Surgery and Liver Transplantation, Faculty of Medicine, Cairo University, Cairo, Egypt

Abstract

Background and aims: Role of acoustic radiation force impulse (ARFI) elastography, in transplant setting, is not well established. We aimed to define the normal mean values of the liver stiffness by ARFI Elastography in healthy liver donors and to evaluate ARFI elastography as predictor of graft fibrosis post living donor liver transplant (LDLT) in comparison to other non-invasive methods (transient elastography [TE], APRI and FIB4).
Patients and methods: A total of 100 subjects (70 recipients and 30 donors) were recruited. APRI and FIB4 scores were calculated for all recipients. TE and ARFI elastography (Siemens Acuson S2000 Ultrasound System, Germany) were performed to all subjects. All donors and only 30 recipients had liver biopsy. Significant fibrosis was defined as ≥ F2.
Results: The mean ARFI velocity among the donors was 1.05 ± 0.09 m/s. Regarding the recipients: mean age was 49.5 ± 8.49 years, 85.7% males, fibrosis stages < F2 were the most frequent stages by liver biopsy (86.7%) and TE (67.1%). ARFI median was significantly correlated with TE median, APRI and FIB-4 ($r = 0.888$, $p = 0.000$; $r = 0.62$, $p = 0.000$, and $r = 0.585$, $p = 0.000$, respectively). ARFI performed well in discriminating patients with ≥ F2 (AUROC = 0.93, 95% CI 0.86–0.99, $p < 0.01$) with best cutoff median value of 1.34 m/s (sensitivity 90%, specificity 82%).
Conclusion: ARFI can be used as a reliable method in assessment of significant fibrosis post-LDLT.

Key words: LDLT—Non-invasive—ARFI elastography—Graft fibrosis

Abbreviations

ARFI	Acoustic radiation force impulse
AUROC	Area under roc curve
LB	Liver biopsy
LSM	Liver stiffness measurement
LT	Liver transplantation
LDLT	Living donor liver transplantation
TE	Transient elastography

In living donor liver transplantation (LDLT), progressive liver fibrosis remains a major problem for patients with recurrent liver diseases. Fibrosis progression is accelerated in recurrent HCV with 20%–54% of LT recipients developing bridging fibrosis–cirrhosis within the first 5 years post LT. Chronic hepatitis C causes persistent low-level inflammation and an immune response that favors replacement of functional liver by scar tissue resulting in early advanced graft fibrosis and cirrhosis. Due to the accelerated nature of fibrosis progression in recurrent hepatitis C, frequent assessment of

Correspondence to: Hadeel Gamal Eldeen; *email:* hgamal@kasralainy.edu.eg

liver fibrosis is essential, particularly to indicate timely antiviral therapy [1].

The gold standard for assessment of hepatic fibrosis is liver biopsy; however, it is associated with potential risks of morbidity and mortality and is often not accepted by patients. Thus, non-invasive tools for assessment of hepatic fibrosis are warranted [2].

Transient elastography (TE) (Fibroscan) and acoustic radiation force impulse (ARFI) have been extensively investigated for the assessment of liver fibrosis in immune-competent patients [3, 4]. TE is the most widely used method for the assessment of liver fibrosis in liver-transplanted patients; however, the accuracy of ARFI in the transplant setting needs further evaluation [5].

ARFI elastography "Virtual Touch Tissue Quantification" by SIEMENS is a new non-invasive ultrasound elastographic imaging modality for assessment of hepatic fibrosis. It quantifies the mechanical properties of tissue by measuring the shear wave velocity induced by acoustic radiation and propagating in the tissue. ARFI elastography is coupled to conventional ultrasound equipment, so both B-mode information and the elastography measurement can be performed quickly in one setting. It can be freely moved to a maximum depth of 8 cm from the skin plane. The measurement is expressed in m/s, expressing shear wave speed, traveling perpendicular to the shear wave source. In addition, ARFI elastography does not need unnecessary manual compression and can be used in severely obese and in patients with ascites [6, 7].

In this study, we aimed to define the normal mean values of the liver stiffness by ARFI elastography in healthy liver donors and to evaluate accuracy of ARFI elastography as predictor of graft fibrosis post living donor liver transplant (LDLT) in comparison to other non-invasive methods (transient elastography [TE], APRI and FIB4).

Subjects and methods

Study design

This cross-sectional study was conducted on 100 subjects (70 LDLT recipients and 30 potential liver donors), who were presented to liver transplantation unit at Al-Manial Specialized Hospital, Faculty of Medicine, Cairo University, Egypt from January 2015 to December 2016. The study was in accordance with the Declaration of Helsinki. It was approved by the local Ethics Committee of Faculty of Medicine, Cairo University. An informed consent was obtained from all subjects prior to enrolment.

Study population

Post-LDLT recipients (n = 70)

Inclusion criteria were as follows: adults, both genders, and recipients of right lobe post LDLT were recruited irrespective of the primary liver disease presenting at least 6 months after LDLT during periodic follow-up visits. All included patients did not have any biliary or vascular surgical complications at the time of the scan.

Exclusion criteria were as follows: age < 18 years old, LDLT recipients who had received antiviral treatment for recurrent HCV post LT or those decompensated liver disease (graft failure).

Living liver donors (n = 30)

Potential and clinically fit donors for LDLT who met the following criteria:

Inclusion criteria were as follows: adults of both genders with normal laboratory tests and accepted imaging findings including conventional ultrasonography and CT volumetry to be eligible for liver biopsy (according to the policy of our center to have LB prior to donation). Exclusion criteria were as follows: donors having abnormal laboratory tests or unaccepted imaging findings for liver transplantation or pathological findings on liver biopsy.

Methodology in details

Evaluation of post-LDLT recipients and donors

Data concerning recipients' medical history since LDLT, primary liver disease, indication for liver transplantation, and current immunosuppression were retrieved from medical records. In addition, demographic data of the donors were obtained. All recipients were maintained in an immunosuppressive regimen that was either cyclosporine- or tacrolimus-based, associated with corticosteroids in the first few months. None of the patients considered in the study were on any drugs that can potentially increase the transaminases values. Some recipients underwent either per protocol (1 year post LT) or on demand liver biopsy for graft dysfunction based on the clinical decision.

Assessment of stage of liver fibrosis using the following non-invasive methods

Indirect serum markers (done in recipients only): calculation of

FIB4 score.

$$\text{Age [years]} \times \text{AST [U/L]}/\text{platelets}[10^9/\text{L}] \times \text{ALT[U/L]}.$$

A cutoff value for FIB-4 was used for categorizing the patients into three stages of fibrosis, according to Sterling et al. [8]: non-significant fibrosis ($<$ F2): $<$ 1.45, significant fibrosis ($\geq$ F2): 1.45 to $<$ 3.25, and cirrhosis (F4): $\geq$ 3.25 [8].

APRI score.

$$= [(\text{AST}/\text{ULN AST}) \times 100]/\text{platelets}\,(10^9/\text{L})]$$

Cutoff values were used for categorizing the patients into three stages of fibrosis, according to Lin et al. [9]: non-significant fibrosis ($<$ F2): $<$ 0.7, significant fibrosis ($\geq$ F2): 0.7 to $<$ 1, and cirrhosis: $\geq$ 1 [9].

Liver stiffness measurement (LSM) in both recipient and donors

Transient elastography. Transient elastography using a FibroScan® device (Echosens, Paris) was performed to measure liver stiffness (LS). TE was performed with a standard M probe, an XL probe (for obese patients). Measurements were performed, after overnight fasting, through the intercostal spaces, on patients lying in the dorsal decubitus position with the right arm in maximal abduction. Measurement depth was between 25 and 65 mm below the skin surface. The software determines whether each measurement is successful or not. Successful measurements were validated using the following criteria: number of shots $\geq$ 10, ratio of valid shots to the total number of shots $\geq$ 60% and interquartile range (IQR) is less than 30% of the median liver stiffness measurement (LSM) value (IQR/LSM $\leq$ 30%). The results were expressed in kilopascal (kPa). The cutoff value we used for differentiation of significant fibrosis ($\geq$ F2) is 8.5 kPa and for cirrhosis ($\geq$ F4) is 12.5 kPa according to Carrion et al. [10] and Kamphues et al. [11] who had performed the largest two studies on LT patients to assess diagnostic performance of TE [10, 11].

ARFI elastography. ARFI elastography was performed using a Siemens ACUSON S3000 Ultrasound System (Siemens AG, Erlangen, Germany) with a 6C1 HD transducer, by using Virtual Touch Tissue Quantification (VTTQ) application. A quadratic cursor, with a size of 10 $\times$ 5 mm representing the anatomic region of interest (ROI) to be measured, is placed in the requested area of the liver parenchyma. At the push of a button, a short-duration acoustic pulse is transmitted, which leads to localized tissue displacement and consecutive shear wave propagation away from the area of excitation. The location of the region of interest in the liver was 2 cm below the liver capsule [12]. The depth of measurements ranged between 2 and 8 cm. The shear wave propagation velocity (expressed in m/s) is proportional to the square root of tissue elasticity within the cursor [13] (Fig. 1).

The examination was performed in fasting conditions, with the patient lying in a dorsal decubitus position, with both arms above the head through an intercostal approach. In each patient, ten valid ARFI measurements were obtained, avoiding large vessels or bile ducts. Failed measurements were defined as zero valid shots (that display as "xxx m/s"). Unreliable measurements were defined as median of ten valid measurements with an IQR-to-median value ratio greater than 30% or a success rate (SR = ratio of the number of successful acquisitions divided by the total number of acquisitions) less than 60% [15, 16].

The time needed to perform all ARFI measurements was approximately 5–10 min. The ARFI LSM value is presented by shear wave velocity (SWV, m/s). The cutoff values used for the diagnosis of fibrosis stages were as follows: (F $\geq$ 2: 1.34 m/s), (F $\geq$ 3: 1.55 m/s), and (F4: 1.80 m/s) [17].

Liver biopsy (LB)

Liver biopsy was performed under ultrasonography guidance after checking the adequacy of the patients' coagulation profile. The Metavir scoring method was used [18]. Only liver biopsy samples with at least 10 mm long or had six portal tracts were examined to allow for adequate interpretation. Tissue specimens were analyzed by a single expert pathologist. The pathologist was blinded to the results of liver stiffness measured by both TE and ARFI elastography. Regarding the recipients, liver biopsy was performed whenever indicated (n = 30) either as protocol biopsy (1 year post LT) or in case of unexplained graft dysfunction. For all donors, It was done performed as a routine assessment after exclusion of liver disease by laboratory investigations and abdominal ultrasound. Any donor having fibrosis stage $>$ F0 was excluded.

Statistical analysis

Patients' data were described. Quantitative variables were presented by mean and standard deviation (SD) or by median and IQR for non-parametric data. Qualitative data were presented by number and percent. Patients were categorized into two groups according to fibrosis stages; non-significant ($<$ F2) and significant ($\geq$ F2).

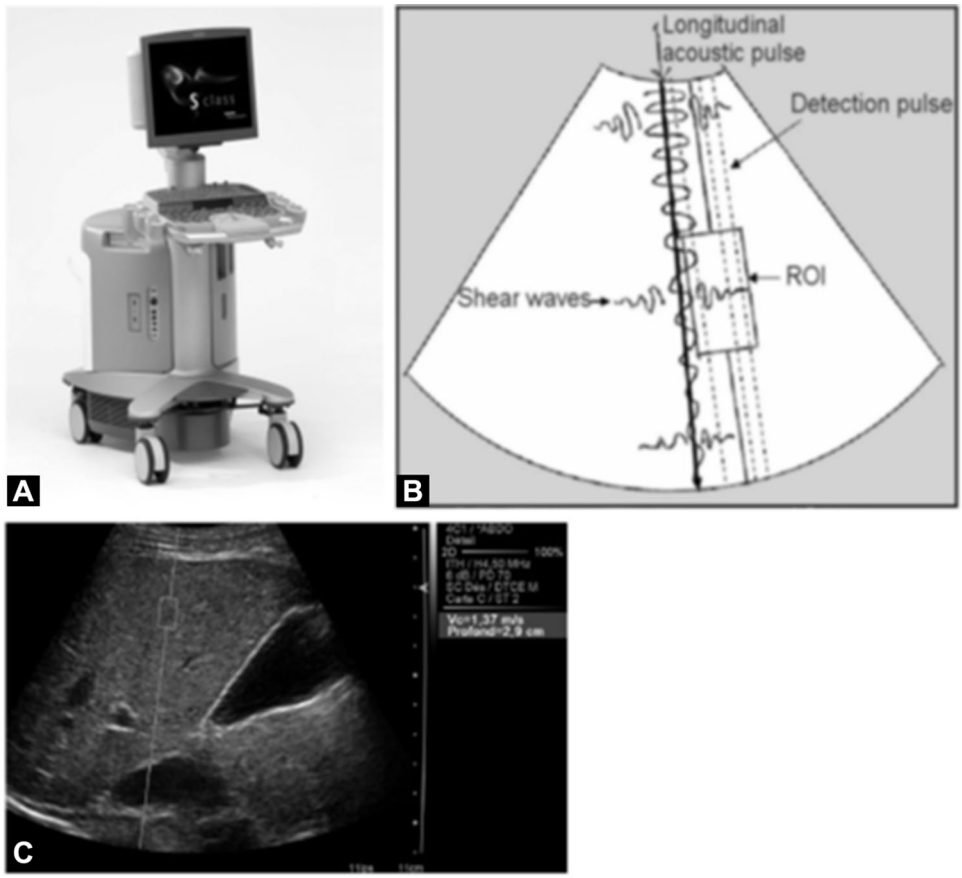

Fig. 1. ARFI: **A** ultrasound diagnostic imaging device onto which the ARFI® software has been implemented; **B** diagram summarizing the principle of a measurement with the "Virtual Touch Tissue Quantification Imaging" system; **C** example of result produced by the device. Quoted from Frulio and Trillaud [14].

Comparison between these two groups was done by Student's *t* test. ROC curve for performance of fibrosis indices in relation to TE was constructed to assess the performance and to detect the best cutoff values. Pearson and spearman correlations among the fibrosis indices were done. In all tests, *p* value was considered significant if less than 0.05.

Results

This study was conducted on 100 subjects: 70 LDLT recipients and 30 liver donors (Fig. 2).

Recipients

ARFI elastography was performed successfully in all 70 patients, while failed measurement of LS by means TE was evident in one patient (BMI $>$ 40).

The demographic features, laboratory, and fibrosis stages of the studied 70 LT recipients shown in (Table 1).

The mean ARFI value was 1.04 $\pm$ 0.11 for patients staged as F0; 1.24 $\pm$ 0.06 for F1; 1.40 $\pm$ 0.05 for F2; and 1.64 $\pm$ 0.08 for F3 and 2.32 $\pm$ 0.51 for F4.

The overall median ARFI velocity, fibroscan, FIB-4, and APRI among all recipients were as follows: 1.24 m/s (IQR: 0.7–3.27), 6.2 kPa (IQR: 3.1–34.4), 1.84 (IQR: 1.64–13.15) and 0.71 (IQR: 0.15–7.83), respectively.

ALT, AST, GGT, total bilirubin, and INR were directly correlated to median ARFI value while hemoglobin, platelets, and serum albumin were inversely correlated to ARFI median values. Age and BMI did not show correlation to ARFI median values (Table 2).

There was a significant positive correlation between median ARFI values and all non-invasive fibrosis modalities: TE, APRI, and FIB4 (TE: $r = 0.888$, $p = 0.000$; APRI: $r = 0.501$, $p = 0.000$; FIB4: $r = 0.447$, $p = 0.000$) (Table 3).

ROC curve was plotted to assess the performance of ARFI in discriminating significant fibrosis $\geq$ F2 from non-significant $<$ F2 using fibroscan as a reference of fibrosis stages (Fig. 3). ARFI performed well in discriminating fibrosis $<$ F2 and $\geq$ F2 with AUROC 0.93 ($p < 0.01$, 95% CI 0.86–0.99). Best cutoff value for significant fibrosis $\geq$ F2 was 1.34 m/s at which sensitivity was 90%, specificity 82%, PPV 65%, and NPV 95% and accuracy of 0.86.

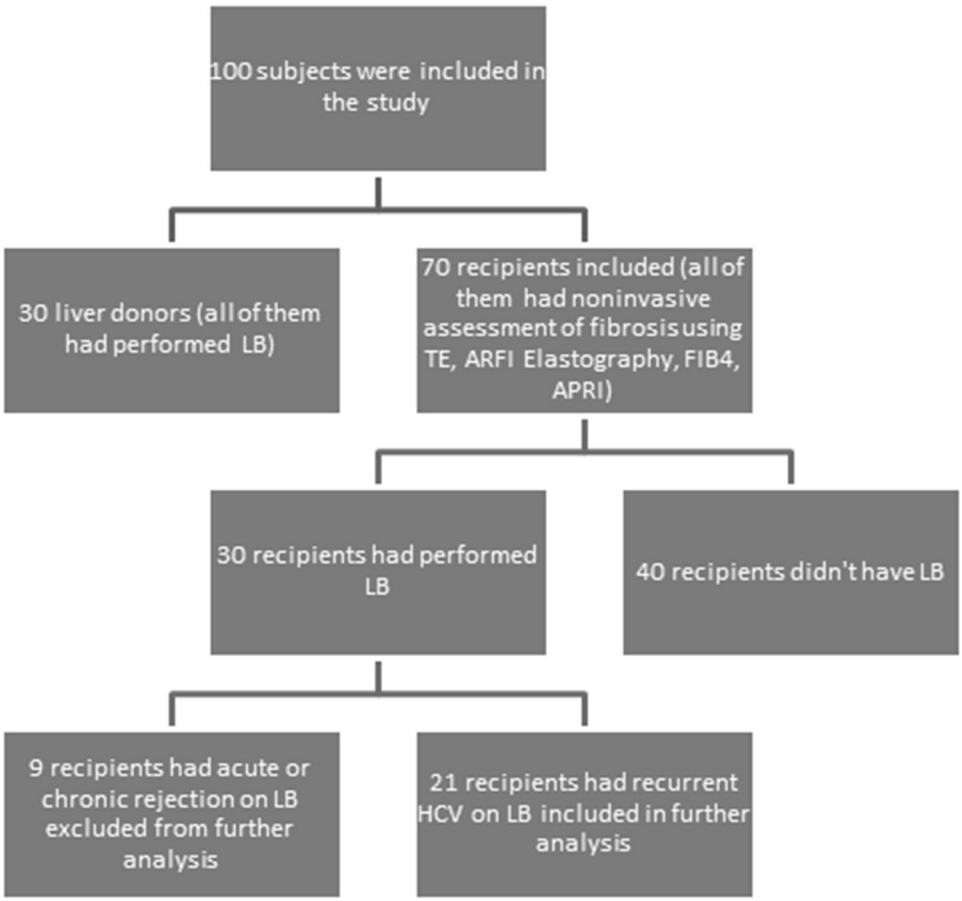

Fig. 2. Flow chart of all included subjects.

Regarding the group of recipients who had liver biopsies ($n = 30$):

The histopathological features of liver biopsy were acute cellular rejection ($n = 8$), chronic rejection ($n = 1$) and recurrent HCV post LT ($n = 21$).

We excluded nine patients with rejection on liver biopsy from further data analysis. Most of them had no or minimal evidence of fibrosis on LB while fibroscan, APRI and FIB4 tests' mean values were corresponding to fibrosis stage F3/F4. So, we were left with 21 liver biopsies of patients with recurrent HCV post LT (F0 in 4 patients; F1 in 14, F2 in 2, F3 in 1). Only three biopsies (14.3%) had fibrosis ≥ F2, which was considered as a limitation of the study to carry on further analysis in this group.

The mean value of fibroscan readings for patients with ≥ F2 on biopsy was significantly higher than those of patients with fibrosis: < F2 (9.53 ± 3.13 kPa vs. 5.77 ± 1.92 kPa, $p < 0.01$). Similarly, the mean value of ARFI readings was significantly higher in patients with fibrosis ≥ F2 than patients < F2 (1.69 ± 0.12 m/s vs. 1.14 ± 0.23 m/s, $p < 0.01$).

Regarding indirect serum markers, both APRI and FIB4 indices failed to discriminate between significant and non-significant fibrosis when compared to biopsy (1.35 ± 0.68 vs. 1.13 ± 1.44, $p = 0.79$; 2.57 ± 2.11 vs. 1.92 ± 0.83, $p = 0.67$, respectively).

Donors

The mean age of the studied individuals was 28.8 ± 4.93 years (range 20–42) with 73.3% males and mean BMI 24.7 ± 1.69 kg/m^2. The range of ARFI velocities of all subjects was (0.87–1.23 m/s). The mean ARFI velocity among the donors was 1.05 ± 0.09 m/s. There were no correlations between median ARFI velocities with age or BMI ($r = -0.028$, $= -0.060$; $p = 0.88$, 0.75, respectively). Also, no significant difference (p value = 0.12) between median ARFI velocities among males (1.07 ± 0.07 m/s) and females (0.99 ± 0.12 m/s).

Table 1. Demographic, laboratory, Doppler data, and stages of hepatic fibrosis encountered in the recipients

	Mean ± SD	Median and IQR
Demographics		
Age (years)	49.5 ± 8.49	50.5 (22–63)
BMI (kg/m^2)	26.28 ± 4.20	25.7 (16.73–45.43)
Duration post LT (months)	28.5 ± 27.6	18.5 (6–144)
	Number	Percent
Gender		
Male	60	85.7
Female	10	14.3
Causes of LT		
HCV	60	85.7
Cryptogenic	5	7.2
HCC	3	4.3
PBC	1	1.4
Alcoholic	1	1.4
Immunosuppression regimens		
Tacrolimus + MMF	42	60
Cyclosporin + MMF	11	15.7
Tacrolimus	10	14.3
Cyclosporin + Everolimus	3	4.3
Everolimus	2	2.9
Everolimus + MMF	1	1.4
Tacrolimus + Everolimus	1	1.4
	Mean ± SD	Median and IQR
Laboratory data		
ALT (U/L)	87.04 ± 87.62	57 (7–467)
AST (U/L)	86.37 ± 104.26	41.5 (13–462)
Total bilirubin (mg/dl)	2.31 ± 4.61	0.9 (0.2–27.2)
Albumin (g/L)	4.0 ± 0.55	4 (3.5–5)
INR	1.11 ± 0.15	1.07 (0.96–1.65)
Doppler findings		
PV velocity (cm/s)	49.78 ± 19.42	46.9 (18–128)
Hepatic artery resistivity index (RI)	0.67 ± 0.05	0.68 (0.51–0.78)
Fibrosis stages (LB)	LSM by TE Number (mean ± SD) (kPa)	LSM by ARFI Number (mean ± SD) (m/s)
Fibrosis stage		
F0	29 (4.72 ± 0.73)	29 (1.04 ± 0.11)
F1	16 (6.78 ± 0.79)	13 (1.24 ± 0.06)
F2	8 (8.35 ± 0.48)	7 (1.40 ± 0.05)
F3	6 (11.77 ± 0.88)	11 (1.64 ± 0.08)
F4	9 (23.19 ± 7.86)	10 (2.32 ± 0.51)
Total number of patients	69[a]	70

[a]One patient failed measurement of liver stiffness by TE as BMI was > 40

Discussion

The results of our study showed a clear correlation between ARFI values and other non-invasive methods of assessment of liver stiffness in post-LDLT patients. We also demonstrated that ARFI elastography has a very good performance in identifying patients with significant fibrosis when compared to the gold standard method (liver biopsy). Furthermore, we obtained the normal mean values of the liver stiffness by ARFI elastography in healthy Egyptian subjects (liver donors).

To reduce the number and risks of liver biopsies, the development of non-invasive tests to assess hepatic fibrosis has been an active area of research in recent years. Assessment of fibrosis can be done non-invasively and quickly for LT patients by fibroscan and there is an extensive amount of data published on this subject, especially among patients with recurrent HCV, which proved accuracy of fibroscan in assessment of liver fibrosis in these patients [19–21]. However, we have to put into consideration the limitations of fibroscan.

ARFI, a newly developed method to estimate liver stiffness, is included in a conventional ultrasound machine; so, both B-mode information and the elastography measurement can be performed quickly in one setting using a single device. Doppler studies, which is an important part of patients' follow up, can also be done [6, 7].

Table 2. Correlations between median ARFI values and both demographic and laboratory parameters

	Median ARFI
Age	
r	− 0.066
p value	0.585
BMI	
r	− 0.161
p value	0.182
Hb	
r	− 0.262
p value	0.029*
Plt	
r	− 0.290
p value	0.015*
INR	
r	0.364
p value	0.002*
ALT	
r	0.496
p value	0.000*
AST	
r	0.512
p value	0.000*
ALP	
r	0.204
p value	0.091
GGT	
r	0.360
p value	0.002*
T.Bil	
r	0.358
p value	0.002*
ALB	
r	− 0.508
p value	0.000*

Statistical significance (*p value < 0.05)

Table 3. Correlation between median ARFI velocity and other non-invasive fibrosis modalities

	ARFI	Fibroscan	APRI	FIB4
ARFI (*r*)		0.888	0.618	0.585
p value		0.000	0.000	0.000
Fibroscan (*r*)	0.888		0.501	0.447
p value	0.000		0.000	0.000

In this study, we aimed at evaluating the accuracy of ARFI as a non-invasive modality in assessment of fibrosis in recipients of LDLT compared to other non-invasive modalities mainly fibroscan and blood-based indices of fibrosis: APRI and FIB4 tests. In addition, we aimed to obtain the normal mean values of the liver elasticity/stiffness by ARFI elastography in healthy Egyptian subjects (liver donors) having normal histology on liver biopsies.

This study included 70 recipients and 30 donors. All recipients and donors were subjected to full history taking, physical examination, and laboratory tests. APRI and FIB4 scores were calculated for all recipients. TE and ARFI elastography were performed to all recipients and donors. Liver biopsy was performed to all donors and showed no fibrosis. While for recipients, only 30 patients had liver biopsy (either as a protocol biopsy or for graft dysfunction). Routine liver biopsy was not performed because most of the patients had recurrent HCV in their laboratory tests and they were scheduled to start directly acting antiviral therapy within 6 months after LT. Another issue is that the national committee of control of viral hepatitis (NCCVH) in Egypt adopted policy to treat all LT patients having recurrent HCV based on laboratory tests without the need to perform liver biopsy.

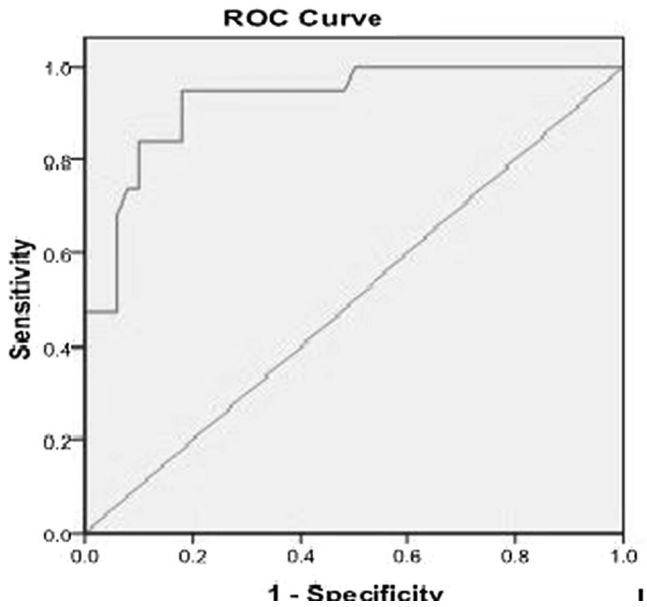

Fig. 3. AUROC curve for ARFI performance in discriminating fibrosis < F2 and ≥ F2 using fibroscan as reference.

Regarding LT recipients, the mean age of our cohort was 49.5 ± 8.49 years, 85.7% males, with mean BMI 26.2 ± 4.2 kg/m^2. Post hepatitis C cirrhosis was the commonest cause of LT (85.7%). The mean duration post LT was 28.5 ± 27.6 months (median 18.5, range 6–144 months). Fibrosis stages < F2 were the most frequent stages found in the recipients who had liver biopsy (86.7%) and in 69 recipients who had TE (65.2%).

There was no correlation between age or BMI and median ARFI values but we identified significant correlations between median ARFI values and laboratory tests (directly with ALT, AST, GGT, INR, and total bilirubin and inversely with albumin, Hb and platelets). Our results were in agreement with Wildner et al. [5] who found significant correlations between ARFI velocities and AST, ALT, GGT, ALP, and bilirubin [5].

In the current study, we found a significant correlation between median liver stiffness measured by fibroscan and median ARFI values ($r = 0.888$, $p = 0.00$).

The performance of ARFI in discriminating post LT patients with significant fibrosis from those without was assessed using fibroscan as reference (based on the extensive published studies and meta-analyses: Beckebaum et al. [19], Carrion et al. [20] and Adebajo et al. [21] confirming the very good ability of fibroscan in diagnosis of fibrosis in LT patients) [19–21].

ARFI performed well in discriminating patients with ≥ F2. Overall, ARFI showed an AUC of 0.93 (95% CI 0.86–0.99, $p < 0.01$) in discriminating patients with significant fibrosis. Using a cutoff of 1.34 m/s, ARFI possesses an NPV of 95% and a PPV of 65% in discriminating patients with significant fibrosis. Bingulin et al. also reported good performance of ARFI in LT setting with AUROC = 0.885 for discriminating fibrosis > F2 and ≥ F2 with sensitivity and NPV 100% but at a cutoff value of 1.36 m/s [2].

APRI and FIB4 scores also showed significant direct correlation with both ARFI and fibroscan median values. The results of our study were comparable to those reported by Wildner et al. [5] who found significant correlations between median ARFI velocities and APRI score in LT patients [5].

Among the 30 patients who had liver biopsies, nine recipients had evidence of cellular rejection and their laboratory tests showed marked elevation of serum transaminases. Those patients had advanced degree of fibrosis on all non-invasive fibrosis tests including fibroscan, ARFI, APRI, and FIB4, while there was no/mild fibrosis in most of their liver biopsies. This could be explained by the fact that liver stiffness measured in different studies using ARFI, TE or serum markers of fibrosis following LT correlated not only with the fibrosis stage, but also with necroinflammatory activity, cholestasis, and cellular rejection. This means that higher values of ARFI, TE and serum markers in case of recurrent active viral hepatitis, cholestasis or rejection may be misinterpreted as significant fibrosis [7, 22, 23]. Accordingly, liver stiffness assessed by non-invasive techniques is not the best way to evaluate a LT patient with suspected cellular rejection or severe graft inflammation.

We excluded those nine patients with rejection from further data analysis to avoid false positive results of significant fibrosis. Among the other 21 patients with liver biopsy, F0 and F1 stages on METAVIR score were the most frequent stages found in biopsies (85.7%) while no one had graft cirrhosis (F4, which is considered as one of study limitation). Indeed, many other studies that dealt with fibrosis in LT patients had also low proportion or absent cirrhotics [2, 7, 24].

Our liver biopsy results further confirming that both median fibroscan and ARFI values were significantly higher among patients with significant fibrosis.

If a normal range of ARFI velocities among the Egyptian population became available, it can serve as a reference for further studies on ARFI elastography in chronic liver diseases. We recruited 30 Egyptian liver donors; ARFI elastography was done to obtain the normal range of ARFI velocities. Several studies had evaluated the normal range of ARFI elastography in healthy volunteers; however, most of them depended on laboratory and imaging data only to ensure normal liver morphology and function in volunteers without data on liver histology which could not be obtained due to ethical issues [25–27].

The first study by Friedrich-Rust et al. evaluated the normal ARFI velocity in 20 healthy volunteers who did not perform laboratory tests. The mean velocity was 1.13 ± 0.23 m/s (0.85–1.42) [26]. Other studies recruiting healthy volunteers have reported a normal mean and SD of ARFI velocity as follows: 1.30 ± 0.49 m/s in 38 healthy volunteers by Sporea et al. [12], 1.08 ± 0.13 m/s ($n = 25$) by Takahashi et al. [25] and 1.56 ± 0.52 m/s ($n = 20$) by D'Onofrio et al. [28].

In our cohort, among the 30 donors with normal histology, the mean ARFI velocity was 1.05 ± 0.09 m/s (range 0.87–1.23 m/s). Our results are comparable to the results of healthy volunteers in Asian studies where the mean ARFI velocity ranged between 1.07 and 1.10 m/s [25, 29] but are lower than results from European studies which reported mean velocities ranged between 1.13 and 1.56 m/s [12, 28]. The reason for which the mean ARFI velocity of our study and Asian studies is different from European studies is unclear due to insufficient information about the normal healthy subjects involved in previous studies and because no data on liver histology were available in other studies.

Although many studies have demonstrated the effects of BMI, gender, and age on fibroscan [30, 31], no studies reported similar effect on ARFI elastography [32, 33]. Our study also did not show any effect of BMI, gender, or age on ARFI velocities among healthy liver donors. However, further large-scaled studies are needed for validation.

Conclusions

ARFI elastography performed well in discriminating patients with significant fibrosis (≥ F2). It can be used as an easy, reliable and non-invasive modality for assessment of graft fibrosis post LT.

Acknowledgments Very special thanks to Cairo University Center of Hepatic Fibrosis (CUC-HF) funded through Scientific Technology and development Fund (STDF fund: project ID 5274) where this work was accomplished.

Author contributions HAH, MD: study design, conception and manuscript revision. HGE, MD, MRCP: performed ARFI elastography, data analysis, manuscript writing. MMN, MD: study design and manuscript revision. RAE, MD: performed Fibroscan, data collection. WE, MD: performed statistics and statistical analysis. NZ, MD: study design and manuscript revision. ZA, MD: statistical analysis. BM, MD: histopathology reading. MSA, MD: data analysis. SM, MD: data analysis. ME, MD: manuscript writing. ME, MD: data analysis. AS, MD: manuscript writing. AH, MD: study design, conception and manuscript revision. AY, MD: study design, conception and manuscript revision.

Compliance with ethical standards

Funding Scientific Technology and development Fund (STDF Fund: Project ID 5274).

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical approval The current study was approved by the ethical committee of the institution. It was done in accordance with the 1964 Helsinki declaration and its later amendments.

References

1. Berenguer M, Schuppan D (2013) Progression of liver fibrosis in post-transplant hepatitis C: mechanisms, assessment and treatment. J Hepatol 58(5):1028–1041
2. Bignulin S, Falleti E, Cmet S, et al. (2016) Usefulness of acoustic radiation force impulse and fibrotest in liver fibrosis assessment after liver transplant. Ann Hepatol 15(2):200–206
3. Chung JH, Ahn HS, Kim SG, et al. (2013) The usefulness of transient elastography, acoustic-radiation-force impulse elastography, and real-time elastography for the evaluation of liver fibrosis. Clin Mol Hepatol 19:156–164
4. Cassinotto C, Lapuyade B, Mouries A, et al. (2014) Non-invasive assessment of liver fibrosis with impulse elastography: comparison of Super-sonic Shear Imaging with ARFI and FibroScan®. J Hepatol 61:550–557
5. Wildner D, Strobel D, Konturek PC, et al. (2014) Impact of acoustic radiation force impulse imaging in clinical practice of patients after orthotopic liver transplantation. Med Sci Monit 20:2027–2035
6. Bota S, Herkner H, Sporea I, et al. (2013) ARFI elastography versus transient elastography for the evaluation of liver fibrosis. Liver Int 33(8):1138–1147
7. Crespo G, Fernandez-Varo G, Marino Z, et al. (2012) ARFI, FibroScan, ELF, and their combinations in the assessment of liver fibrosis: a prospective study. J Hepatol 57(2):281–287
8. Sterling R, Lissen E, Clumeck N, et al. (2006) Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 43(6):1317–1325
9. Lin ZH, Xin YN, Dong QJ, et al. (2011) Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology 53:726–736
10. Carrión J, Navasa M, Bosch J, et al. (2009) Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. Liver Transpl 12:1791–1798
11. Kamphues C, Lotz K, Röcken C, et al. (2010) Chances and limitations of non-invasive tests in the assessment of liver fibrosis in liver transplant patients. Clin Transplant 24:652–659
12. Sporea I, Sirli RL, Deleanu A (2010) Acoustic radiation force impulse elastography as compared to transient elastography and liver biopsy in patients with chronic hepatopathies. Ultraschall Med 32:S46–S52
13. Nightingale K (2011) Acoustic radiation force impulse (ARFI) imaging: a review. Curr Med Imaging Rev 7(4):328–339
14. Frulio N, Trillaud H (2013) Ultrasound elastography in liver. Diagn Interv Imaging 94 (5):515-534
15. Castéra L, Foucher J, Bernard PH, et al. (2010) Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. Hepatology 51(3):828–835
16. Bota S, Sporea I, Sirli R, et al. (2011) Factors that influence the correlation of acoustic radiation force impulse (ARFI), elastography with liver fibrosis. Med Ultrason 13(2):135–140
17. Friedrich-Rust M, Romen D, Vermehren J, et al. (2012) Acoustic radiation force impulse-imaging and transient elastography for non-invasive assessment of liver fibrosis and steatosis in NAFLD. Eur J Radiol 81:e325–e331
18. Bedossa P, Poynard T (1996) An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 24(2):289–293
19. Beckebaum S, Iacob S, Klein C, et al. (2010) Assessment of allograft fibrosis by transient elastography and non-invasive biomarker scoring systems in liver transplant patients. Transplantation 89:983–993
20. Carrión J, Torres F, Crespo G, et al. (2010) Liver stiffness identifies two different patterns of fibrosis progression inpatients with hepatitis C virus recurrence after liver transplantation. Hepatology 51:23–34
21. Adebajo C, Talwalkar J, Poterucha J, Kim W, Charlton M (2012) Ultrasound based transient elastography for the detection of hepatic fibrosis in patients with recurrent hepatitis C virus after liver transplantation: a systematic review and meta-analysis. Liver Transpl 18:323–331
22. Rigamonti C, Fraquelli M, Bastiampillai A, et al. (2012) Transient elastography identifies liver recipients with nonviral graft disease after transplantation: a guide for liver biopsy. Liver Transpl 18(5):566–576
23. Yoon K, Lim S, Park J, et al. (2012) Liver stiffness measurement using acoustic radiation force impulse (ARFI) elastography and effect of necro-inflammation. Dig Dis Sci 57(6):1682–1691
24. Corradi F, Piscaglia F, Flori S, et al. (2009) Assessment of liver fibrosis in transplant recipients with recurrent HCV infection: usefulness of transient elastography. Dig Liver Dis 41(3):217–225
25. Takahashi H, Ono N, Eguchi Y, et al. (2010) Evaluation of acoustic radiation force impulse elastography for fibrosis staging of chronic liver disease: a pilot study. Liver Int 30:538–545
26. Friedrich-Rust M, Wunder K, Kriener S, et al. (2009) Liver fibrosis in viral hepatitis: noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. Radiology 252:595–604
27. Rizzo L, Calvaruso V, Cacopardo B, et al. (2011) Comparison of transient elastography and acoustic radiation force impulse for non-invasive staging of liver fibrosis in patients with chronic hepatitis C. Am J Gastroenterol 106:2112–2120
28. D'Onofrio M, Gallotti A, Mucelli R (2010) Tissue quantification with acoustic radiation force impulse imaging: measurement repeatability and normal values in the healthy liver. Am J Roentgenol 195:132–136
29. Kim J, Lee JY, Kim Y, et al. (2010) Acoustic radiation force impulse elastography for chronic liver disease: comparison with ultrasound-based scores of experienced radiologists, Child-Pugh scores and liver function tests. Ultrasound Med Biol 36:1637–1643
30. Corpechot C, El Naggar A, Poupon R (2006) Gender and liver: is the liver stiffness weaker in weaker sex? Hepatology 44:513–514
31. Colombo S, Buonocore M, Del Poggio A, et al. (2012) Head-to-head comparison of transient elastography (TE), real-time tissue elastography (RTE), and acoustic radiation force impulse (ARFI) imaging in the diagnosis of liver fibrosis. J Gastroenterol 47:461–469
32. Goertz R, Zopf Y, Jugl V, et al. (2010) Measurement of liver elasticity with acoustic radiation force impulse (ARFI) technology: an alternative noninvasive method for staging liver fibrosis in viral hepatitis. Ultraschall Med 31(2):151–155
33. Son C, Kim S, Han W, et al. (2012) Normal liver elasticity values using acoustic radiation force impulse imaging: a prospective study in healthy living liver and kidney donors. J Gastroenterol Hepatol 27(1):130–136