Liver Stiffness Measurements Using Acoustic Radiation Force Impulse in Recipients of Living-Donor and Deceased-Donor Orthotopic Liver Transplant

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Abstract

Objectives: The aim of this study was to evaluate the diagnostic efficiency of the acoustic radiation force impulse (Siemens Medical Solutions, Erlangen, Germany) elastography in assessment of fibrosis in orthotopic liver transplant patients.

Materials and Methods: We enrolled 28 orthotopic liver transplant patients (deceased and living donors), whose biopsy decision had been prospectively given clinically. Ten acoustic radiation force impulse elastographic measurements were applied before the biopsy or within 3 days after the biopsy by 2 radiologists. After the core tissue needle biopsy, specimens of all patients were analyzed according to the modified Ishak scoring system. Measurements of acoustic radiation force impulse elastography and pathology specimen results were compared.

Results: From 28 biopsies, fibrosis scores of 4 biopsies were evaluated as F0 (14.3%), 16 as F1 (57.1%), 4 as F2 (14.3%), and 4 as F3 (14.3%). Mean results of acoustic radiation force impulse measurements were calculated as 1.4 ± 0.07 in F0, 1.74 ± 0.57 in F1, 2.19 ± 0.7 in F2, and 2.18 ± 0.35 in F3. There were no significant correlations of mean acoustic radiation force impulse values between the F0 versus F1 (P = .956) and F0 versus F2 stages (P = .234). A statistically significant correlation of mean acoustic radiation force impulse values was found between the F0 and F3 fibrosis stages (P = .046).

Conclusions: Acoustic radiation force impulse imaging is a promising screening test for detecting significant liver fibrosis (≥ F3 in modified Ishak) in living-donor or deceased-donor orthotopic liver transplant recipients.

Key words: Liver biopsy, Liver fibrosis, Metavir, Transient elastography, Ultrasonography

Introduction

Liver transplant is the only treatment option for advanced liver disease. However, after liver transplant, acute complications (including primary dysfunction, hepatic artery thrombosis, portal vein thrombosis, hepatic venous obstruction, bile leak, and biliary stricture) or chronic complications (including chronic rejection, disease recurrence, and drug-induced complications) may occur. Post-transplant liver dysfunction can have various causes; evaluation of the causes, which can lead to diffuse parenchymal damage, including fibrosis, is of clinical importance.

Postoperative B-mode and Doppler ultrasonography (US) are standard procedures for the assessment of graft complications. From US findings, clinical symptoms, and abnormal laboratory findings, a liver biopsy may be required. Although liver biopsy is the standard method for the assessment of morphologic liver changes and fibrosis, it is an invasive procedure that may cause complications.

Transient elastography (TE) is currently the most widely used and endorsed method for the assessment of liver fibrosis in many conditions, such as chronic hepatitis B and C, nonalcoholic steatohepatitis, and nonalcoholic fatty liver disease, as well as in posttransplant patients. Insufficient performance in detecting mild fibrosis, failure to measure liver elasticity in patients with obesity, ascites, and narrow intercostal space, and inability to target liver parenchyma by direct visualization are problems that remain a considerable adversity of this tool.

Acoustic radiation force impulse (ARFI; Siemens Medical Solutions, Erlangen, Germany) elastography is a new technology to measure liver stiffness and...
evaluate liver fibrosis. This technology is included in conventional ultrasonographic devices, and it can be performed during a conventional B-mode examination with a single transducer. The principle of this method is based on the shearing of the examined tissue, which induces a smaller strain in hard tissues than in soft ones. The US probe produces an acoustic pulse, which generates shear waves that propagate into the tissue. The propagation speed (measured in meters per second) increases with the stage of the fibrosis.\textsuperscript{6} It has been shown that ARFI is a reliable technique for diagnosing or excluding liver cirrhosis\textsuperscript{9,10} and shows similar predictive value for significant fibrosis and cirrhosis compared with TE.\textsuperscript{6} However, the standard cut off value of the ARFI technique is not yet well established in the clinical care of liver transplant patients.

The aim of this study was to evaluate the diagnostic efficiency of the ARFI technology for the assessment of fibrosis in patients who received orthotopic liver transplant (OLT).

**Materials and Methods**

We enrolled 28 OLT patients (deceased and living donors), whose biopsy decision was made clinically because of posttransplant dysfunction, for prospective evaluation of cause and severity of fibrosis.

The ARFI elastographic measurements were applied before the biopsy or within 3 days after the biopsy, by 2 radiologists.

The local ethics committee approved the project, and written informed consent was obtained from all patients for the use of their data for research. For ARFI elastographic measurements, we used the Siemens Acuson S3000 ultrasonographic system with 6C1 transducer (Virtual Touch Tissue Quantification; Siemens Medical Solutions). For measurement, a quadratic cursor representing the anatomic region of interest to be measured is placed in the requested area of the liver parenchyma, and numerical values are obtained. Ten measurements in segments III to IV on the left lobe graft and segments VII to VIII on the right lobe graft could be obtained, avoiding large vessels or bile ducts. The measurements were performed about 2 to 3 cm in depth from the surface of the liver, with results expressed as meters per second.

For liver biopsy, our interventional radiology department used a US-guided procedure with a core tissue needle (18G; 2-cm sample notch). Biopsy specimens of all patients were analyzed by an experienced pathologist in our institution. The fibrosis stage was determined according to the modified Ishak scoring system. The fibrosis scores are defined as follows: 0, no fibrosis; 1, fibrous expansion of some portal areas, with or without short fibrous septa; 2, fibrous expansion of most portal areas, with or without short fibrous septa; 3, fibrous expansion of most portal areas with occasional portal to portal bridging; 4, fibrous expansion of most portal areas with marked bridging (portal to portal as well as portal to central); 5, marked bridging with occasional nodules (incomplete cirrhosis); and 6, cirrhosis, probable or definite.\textsuperscript{10} Mean ± standard deviation, median, minimum, and maximum values are used here to describe the quantitative variables. In addition, frequency and percentages are given for nominal data. Normality assumption was checked by Shapiro-Wilks test, and it was found that data did not conform to normal distribution. The distributions of ARFI measurements were compared among fibrosis groups with the nonparametric Kruskal-Wallis (with Conover-Dunn multiple comparison test) and Mann-Whitney U tests. For all analyses, SPSS version 21.0 software was used (SPSS: An IBM Company, IBM Corporation, Armonk, NY, USA), and statistical significance was set at $P < .05$.

**Results**

Our study included 28 patients who received living-donor or deceased-donor OLT (16 men [57.1%] and 12 women [42.9%]). Median age was 33.8 years (range, 4-66 y), and median time period from OLT to liver biopsy was 43.7 months (range, 1-120 mo). Causes for liver transplant were hepatitis B virus infection (9 patients), hepatitis C virus infection (4 patients), cryptogenic cirrhosis (4 patients), Wilson disease (3 patients), Budd-Chiari syndrome (2 patients), biliary atresia (2 patients), intoxication (1 patient), Alagille syndrome (1 patient), and fulminant hepatitis A (1 patient). Of 28 patients, 5 patients (17.9%) received deceased-donor grafts and 23 patients (82.1%) received living-donor grafts. The mean value of the depth of ARFI measurements was 3 ± 0.5 cm.

Of the 28 biopsies, 4 (14.3%) were evaluated as fibrosis score F0, 16 (57.1%) were evaluated as fibrosis score F1, 4 (14.3%) were evaluated as fibrosis
score F2, and 4 (14.3%) were evaluated as fibrosis score F3. There were no specimens with fibrosis scores evaluated as F4, F5, or F6. The mean ARFI measurements were 1.4 ± 0.07 m/s in F0, 1.74 ± 0.57 m/s in F1, 2.19 ± 0.7 m/s in F2, and 2.18 ± 0.35 m/s in F3.

We found that mean ARFI values between F0 and the other fibrosis stages (F1, F2, and F3) were significantly correlated (P = .042). When the correlation between F0 and the other fibrosis stages were analyzed separately, there were no significant correlation of mean ARFI values between the F0 versus F1 (P = .956) and F0 versus F2 (P = .234). A statistically significant correlation of mean ARFI values was found between the F0 and F3 fibrosis stages (P = .046) (Figures 1 and 2). Figure 3 shows box plots for ARFI measurements versus stages of fibrosis.

**Figure 1. Ultrasonography and Pathology Specimen Results of an Orthotopic Liver Transplant Patient With Fibrosis Stage (Modified Ishak) F3**

(A) Acoustic radiation force impulse (ARFI) elastography during real-time B-mode ultrasonography. Quadratic cursor was placed in the region-of-interest (white box), showing intercostal approach in the left liver lobe (segment IV). ARFI shear-wave-velocities (Vs) are displayed in m/s and the depth of measurement in centimeters. (B) Pathology specimen. Portal to portal bridging necrosis is observed (F3) (Masson trichrome ×200 magnification).

**Figure 2. Ultrasonography and Pathology Specimen Results of an Orthotopic Liver Transplant Patient With Fibrosis Stage (Modified Ishak) F1**

(A) Acoustic radiation force impulse (ARFI) elastography during real-time B-mode ultrasonography. Quadratic cursor was placed in the region-of-interest (white box), showing intercostal approach in the right liver lobe (segment VIII). ARFI shear-wave-velocities (Vs) are displayed in m/s and the depth of measurement in centimeters. (B) Pathology specimen. Fibrous expansion of a portal area, with short fibrous septa is seen (F1) (Masson trichrome at ×200 magnification).
Discussion

Our study revealed a significant correlation between ARFI values and liver fibrosis in post-OLT patients. The ARFI values increased in parallel with fibrosis staging but were not accurate enough to differentiate between F0 and F1 or F2 fibrosis stages in accordance with the modified Ishak scoring system.

The evaluation of liver parenchyma in terms of liver fibrosis in posttransplant liver grafts is a crucial issue. The detection of early stages of fibrosis in these patients is specifically important. In the literature, previous studies have evaluated post-OLT fibrosis with ARFI elastography, with pathologic evaluations done by the METAVIR, Batts-Ludwig, or Scheuer scoring systems. The METAVIR, Batts-Ludwig, and Scheuer scoring systems are almost similar, and they all have 4 categories. Modified Ishak and METAVIR scores are widely accepted scoring systems for assessment of fibrosis and necroinflammation. Modified Ishak and METAVIR are nearly identical systems. However, modified Ishak is a wider scale. Despite METAVIR, which determines the grade of the activity of interface hepatitis and lobular necrosis, the Ishak system detects portal infiltrate and confluent necrosis with the 2 previous parameters.\(^{12,13}\) Unlike other scoring systems, there are 6 categories in the modified Ishak scoring system. Compared with the METAVIR scoring system, in the modified Ishak scoring system, F1 and F2 are equal to F1, F3 is equal to F2, F4 and F5 are equal to F3, and F6 is equal to F4. The METAVIR system is more reproducible but is less effective for monitoring minor changes.\(^{13}\) Goodman and associates suggested application of METAVIR in routine work and the application of the modified Ishak score in clinical trials because of its higher sensitivity in fibrosis assessment.\(^{14}\) The major difference of our study from other studies in the literature is that we used the modified Ishak scoring system, which allows monitoring minor changes in fibrosis, and conducted ARFI elastographic evaluations in the early fibrosis stages.

Noninvasive methods such as ARFI or TE have gained increased importance in the follow-up of patients after OLT. Both techniques provide accurate diagnosis of significant fibrosis and cirrhosis.\(^{7,15,16}\) Assessment of fibrosis can be examined quickly and noninvasively in this group of patients by TE. However, TE has many limitations in measurement. The performance of TE may be limited in patients with a high body mass index, ascites, or narrow intercostal space.\(^{15,17}\)

Conventional US devices include ARFI; therefore, B mode information and the elastography measurement can be performed quickly using a single device, as in TE.\(^{11,18}\) The US-guided device makes it possible to identify the most appropriate place for the elastographic measurements, for instance avoiding nearby interfering structures, such as hepatic vessels and ascites.\(^{19}\) In nontransplant patients, regarding the accuracy of ARFI imaging in cirrhotic liver disease, several studies have reported that ARFI imaging provides good diagnostic performance and excellent accuracy, with ARFI values increasing in parallel with fibrosis stage.\(^{15,16,20}\) In their study, Sporea and associates\(^ {16}\) reported that ARFI was well-correlated with liver fibrosis caused by viral hepatitis; however, ARFI was not accurate enough to differentiate between F1 versus F2 due to the small proportion of F0 and F1 patients (by METAVIR scoring). Crespo and associates\(^ {18}\) indicated high accuracy only in advanced fibrosis stages (by Scheuer scoring) of liver fibrosis with ARFI imaging, in transplant and nontransplant patients with liver disease of various causes.

For fibrosis staging by ARFI elastography in post-OLT patients, only few experiences are published in the literature.\(^ {5,18,21-23}\) Liao and associates\(^ {21}\) reported a sensitivity ratio of 95.5% using a shear-wave velocity cutoff value of 1.058 m/s in the evaluation of posttransplant graft dysfunction in early fibrosis stages (≤ F1, by METAVIR scoring); which constituted a larger proportion of the study group (94.5%). The group indicated that there was a significant difference in F0 compared with F1. They also reported that ARFI measurements had a high specificity (92.9%) using a cutoff value of 1.8 m/s in the advanced fibrosis stages. However, Wildner and associates\(^ {4}\) reported that the areas under the receiver operating characteristic curves for patients with advanced fibrosis (F3) and cirrhosis (F4) (by Batts-Ludwig scoring) were 92.9% and 80% and had discretely higher cutoff values (≥ F1, 1.48 m/s). Pinto and associates\(^ {22}\) indicated a statistically significant difference in shear-wave velocities between the F0-F1 and F2-F4 groups (by Batts-Ludwig scoring), concluding that ARFI might serve as a potential method for assessing significant fibrosis in pediatric patients after liver transplant. Tomita and associates\(^ {23}\) reported that the ARFI measurements were significantly higher for patients...
with F1 and F2 portal fibrosis versus patients with F0 portal fibrosis (by METAVIR scoring).

In the present study, we found mean ARFI values of 2.18 ± 0.35 m/s for patients with F3 fibrosis (by modified Ishak scoring), whereas the shear-wave velocities in patients with F0 fibrosis were significantly lower (1.4 ± 0.07 m/s). The cutoff values that were reported by Wildner and associates seem to be closer to our ARFI measurements. When the lower cutoff values were considered, which were determined by Liao and associates, there was only 1 patient under the threshold with F1 (by modified Ishak scoring) fibrosis in our patient group. However, with regard to this threshold, specificity decreases prominently (reported 25.7% in F1 stage fibrosis by METAVIR scoring).

In our study, there was no significant correlation of mean ARFI values between F0 versus F1 and F2 (by modified Ishak scoring) stages that corresponded to F1 in METAVIR scoring, as opposed to that shown by Liao and associates and Tomita and associates. However, there was a statistically significant correlation of mean ARFI values, which was found between F0 and F3 (by modified Ishak scoring) fibrosis stages that corresponded to F2 in METAVIR scoring, unlike the studies of Sporea and associates and Crespo and associates, which indicated a significant correlation in higher fibrosis stages. In overall evaluations, it seems that a clear detection of fibrosis can be possible in more advanced fibrosis stages (≥ F2 in METAVIR and similar scoring systems; ≥ F3 in modified Ishak).

There were some limitations in our study. The most important limitation was the small sample size due to the small number of patients with significant fibrosis and, in particular, none with cirrhosis.

In conclusion, ARFI imaging is a promising screening test for detecting significant liver fibrosis (≥ F2 in METAVIR and similar scoring systems, ≥ F3 in modified Ishak) in patients after living-donor or deceased-donor OLT. Although similar results have been published indicating the accuracy of ARFI in advanced fibrosis stages, for detection of early fibrosis stages, further multicentric prospective studies with larger series of patients are needed. These studies could help obtain clear cutoff ARFI values, which may help to confirm the effectiveness of this method in diagnosing liver fibrosis in post-OLT patients.

References

