ELSEVIER

The Acoustic Radiation Force Impulse Elastography Evaluation of Liver Fibrosis in Posttransplantation Dysfunction of Living Donor Liver Transplantation

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ABSTRACT

Background. The acoustic radiation force impulse elastography (ARFI) is a new technology of elastography integrated into B-mode ultrasonography. It has been a reliable method to evaluate liver fibrosis of chronic liver disease in recent years, but less applied in the posttransplantation liver. The aim of the study was to evaluate liver fibrosis by the ARFI with correlation of pathological stages in living donor liver transplantation (LDLT).

Materials and Methods. From August 2010 to August 2012, there were 57 LDLT patients with liver biopsy (LB) due to posttransplantation dysfunction; all patients also received posttransplantation ARFI liver stiffness measurement (LSM) after transplantation for liver fibrosis staging. The ARFI elastography was performed using a Siemens Acuson S2000 ultrasound system with 4V1 transducers (Acusion, Siemens Medical Systems Co. Ltd. Erlangen, Germany). The ARFI LSM value was presented by shear wave velocity (SWV, m/s). The fibrosis staging as F0 to F4 was in accordance with the Metavir scoring system.

Results. A total of 57 patients had both posttransplantation LB and effective ARFI fibrosis staging for correlation. The ARFI LSM value increased with severity of liver fibrosis and had significant linear correlation with the results of histological fibrosis staging. The ARFI LSM sensitivities (Se), specificities (Sp), and cutoff values based on receiver-operator characteristic curve were F0: 0.75 m/s (Se: 93.8%, Sp: 4%), F1: 1.06 m/s (Se: 95.5%, Sp: 25.7%), F2: 1.81 m/s (Se: 50%, Sp: 83.6%) and F3: 2.33 m/s (Se: 100%, Sp: 92.9%). Predictive value of ARFI LSM reported a significant difference between early fibrosis stage (F0–F1) and advanced fibrosis stage (F $\geqq$ 2) ($P < .05$).

Conclusion. In this study, ARFI demonstrated a strong linear correlation and severity of liver fibrosis with LB pathologic staging. ARFI can be an alternative and compensatory method for frequent LB in the posttransplantation liver.

LIVER TRANSPLANTATION allograft dysfunction is the major posttransplantation problem of living donor liver transplantation (LDLT) [1,2]. Early allograft dysfunction may present by elevated liver function test results; the common etiologies of allograft include acute or chronic hepatitis, acute rejection, and malignancy [2]. Eventually, the prognosis of the posttransplantation dysfunction may lead to liver graft parenchyma stiffness change and fibrosis.

Liver biopsy (LB) remains the gold standard method for evaluating liver parenchyma change, and can well demonstrate fibrosis, portal infiltrate, and lobular necrosis [3]. However, biopsy is an invasive procedure that may cause major complications, such as bleeding. Additionally, a small

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biopsied sample size may lead to misdiagnosis of fibrosis stage [4]. Frequent biopsy in posttransplantation liver graft is not an ideal option; therefore, a noninvasive, repeatable, and reliable method is important. Recently, transient elastography (TE) has been found to be a noninvasive and quantitative way to measure liver stiffness change in chronic hepatitis or cirrhosis [5]; it has provided reliable correlation with fibrosis staging results. However, TE has many limitations, such as high body mass index and ascites; it may overestimate liver stiffness in acute hepatitis; additionally, it cannot measure the specific site of liver parenchyma [6,7]. Acoustic radiation force impulse (ARFI) imaging is a new elastography method for the evaluation of tissue stiffness. It is integrated into conventional B-mode ultrasound examination. ARFI can generate acoustic radiation force as a pressure wave that spreads through tissue, and can be measured as shear wave velocity (SWV) that presents the degree of tissue stiffness [8]. Using ARFI and TE for liver fibrosis evaluation has been adopted in patients with chronic hepatitis or cirrhotic liver, and they both reported a promising and reliable correlation with liver fibrosis change [7]. The ARFI examination seems to have more advantage in varied types of liver graft. Therefore, we designed this study of posttransplantation liver parenchyma fibrotic change measured by ARFI liver stiffness measurement (LSM) and correlated with biopsy pathological staging.

PATIENTS

From August 2010 to August 2012, a total of 57 patients with LDLT (43 men, 14 women, mean age 57 ± 7.62 years) received LB due to posttransplantation dysfunction. The liver function test, blood platelet count, prothrombin time, and viral titer were collected. The fibrosis staging was based on the Metavir scoring system. Indications for biopsy in these 57 patients were abnormal graft dysfunctions in posttransplantation follow-up, which were suspected rejection-related or recurrent hepatitis; the definition of posttransplantation dysfunction was AST and ALT >100 IU/dL or persistent hyperbilirubinemia. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by our institutional review boards. Written informed consent was obtained from all participants for the use of their data for research purposes.

ARFI LSM

Both B-mode standard ultrasonography scanning and LSM by ARFI were performed using the Siemens Acuson S2000 ultrasound system with 4V1 transducers (Acusion, Siemens Medical Systems Co. Ltd. Erlangen, Germany). Technically, ARFI LSM had focused on a specific segment of liver (the right lobe graft was accessed in S5-6, the left lobe graft in S3-4), avoiding motion artifacts and hepatic vessels as much as possible. The measurement was performed at a portion of the liver that was about 4 to 6 cm in depth from the skin surface. The values of LSM were presented by shear wave velocity (SWV = m/s) and calculated as the median ARFI value from 10 measurements. The procedures were performed by senior radiologists who were blinded to the clinical, serological, and histological data.

LB and Pathological Fibrosis Staging

LB was performed percutaneously with ultrasonography assistance by senior physicians, using 17- to 18-gauge modified Menghini needles (Biomol, Boca Raton, Florida). All specimens were sealed, fixed, and examined by pathologists in our facility. The scoring system of fibrosis stage was based on the Metavir scoring system, in which fibrosis was classified on a F0 to F4 scale as follows: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis and few septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis [9].

Statistical Analysis

The diagnostic performance of ARFI and the stage of liver fibrosis sensitivity and specificity were developed as area under the receiver-operator characteristic (ROC) curves. The areas under the curves and 95% confidence intervals (CI) used the Mann-Whitney statistic calculation. The optimal cutoff value was chosen to maximize the sum of the sensitivity and specificity on the Youden index. Differences were considered significant at $P < .05$. Correlation between ARFI LSM liver fibrosis staging and LB pathological fibrosis stage was analyzed using both the Kendall tau-b and the Spearman rho methods.

RESULTS

A total of 57 LDLT patients (43 men, 14 women, mean age 57 ± 7.62 years) were enrolled in our study and had effective ARFI LSM and valid LB due to posttransplantation dysfunction; 44 patients received right lobe liver graft, (n = 44 of 57, 77%) and 13 patients received left lobe liver graft (n = 13 of 57, 23%). Two major indications for LB in posttransplantation dysfunction were recurrent viral hepatitis (n = 44 of 57, 77.2%), and acute or chronic rejection (n = 28 of 57, 49.1%). The LB stages were 32 patients at F0 (56%), 22 patients at F1 (38.5%), 2 patients at F2 (3.5%), and 1 patient at F3. The calculated cutoff values of ARFI LSM were analyzed based on the ROC curve (Fig 1A). There were F0: 0.75 m/s (sensitivity [Se]: 93.8%, specificity [Sp]: 4%), F1: 1.06 m/s (Se: 95.5%, Sp: 25.7%), F2: 1.81 m/s (Se: 50%, Sp: 83.6%), and F3: 2.33 m/s (Se: 100%, Sp: 92.9%), but the F4 cutoff value was not available (Table 1). The values of ARFI LSM of liver fibrosis staging demonstrated linear correlation with the LB pathological fibrosis stage in either the Kendall tau-b or the Spearman rho method (Fig 1B). A significant difference between F0 (SWV cutoff value = 0.75 m/s) and F1 (SWV cutoff value = 1.06 m/s) was found in the early liver fibrosis stage ($P < .0001$). The advanced liver fibrosis stage (F ≧ 2) also had high specificity, with an SWV cutoff value of 1.8 m/s, which was statistically different in fibrosis stages between F0 and F ≧ 2 ($P < .05$).

DISCUSSION

TE and ARFI have been used as noninvasive methods in the evaluation of liver fibrosis, and they both provide diagnosis of significant fibrosis and cirrhosis accurately [7,10,11]. However, TE has many limitations in measurement; the