Journal of Pediatric Surgery 50 (2015) 559–564

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

# The degree of spleen stiffness measured on acoustic radiation force impulse elastography predicts the severity of portal hypertension in patients with biliary atresia after portoenterostomy ☆

Hajime Uchida [a,d,*], Seisuke Sakamoto [a], Megumi Kobayashi [a], Takanobu Shigeta [a], Masatoshi Matsunami [a], Kengo Sasaki [a,d], Hiroyuki Kanazawa [a], Akinari Fukuda [a], Yutaka Kanamori [b], Mikiko Miyasaka [c], Shunsuke Nosaka [c], Naoki Kawagishi [d], Mureo Kasahara [a]

[a] Organ Transplantation Center, National Center for Child Health and Development, Tokyo, Japan
[b] Department of Surgery, National Center for Child Health and Development, Tokyo, Japan
[c] Department of Radiology, National Center for Child Health and Development, Tokyo, Japan
[d] Division of Transplantation, Reconstruction and Endoscopic Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan

ARTICLE INFO

*Article history:*
Received 2 May 2014
Received in revised form 27 December 2014
Accepted 31 December 2014

*Key words:*
Acoustic radiation force impulse
Biliary atresia
Pediatric liver transplantation
Portal vein
Spleen stiffness

ABSTRACT

*Background/purpose:* Acoustic radiation focus impulse (ARFI) elastography is a new method for assessing the degree of tissue stiffness. We herein evaluated the degree of spleen stiffness (SS) using ARFI elastography in patients with biliary atresia (BA) after Kasai portoenterostomy (KPE).
*Methods:* We retrospectively collected the liver stiffness (LS) and SS values on ARFI elastography from 43 patients undergoing KPE between September 2010 and November 2013. We analyzed the correlations between these values and variables related to the severity of liver dysfunction and portal hypertension (PHT). The data were expressed as the standard deviation score (*z*-score) relative to the previously reported normal values for the patient's age.
*Results:* The SS value was significantly associated with the spleen diameter and development of collateral vessels, in comparison to the LS value. Interestingly, there was a significant correlation between SS value and the portal vein (PV) diameter. Thirty patients (69.8%) consequently underwent LT; these patients showed higher SS values and smaller PV diameters than the patients monitored without LT.
*Conclusions:* The degree of SS measured on ARFI elastography can be used to predict the severity of PHT in BA patients after KPE.



Biliary atresia (BA) is the most common cholestatic disease in infants, leading to liver cirrhosis. The first surgical option for BA consists of the procedure proposed by Kasai, Kasai portoenterostomy (KPE) [1]. Liver transplantation (LT) should be considered in patients with failed KPE [1]. Although reconstruction of bile drainage can be successfully obtained with KPE, the majority of patients with BA must continue to be closely monitored for the progression of liver fibrosis to cirrhosis complicated by portal hypertension (PHT) [2]. LT is most often indicated by 2 years of age for the following conditions: recurrent cholangitis, PHT complications, liver failure with hyperbilirubinemia, hepatopulmonary syndrome, and failure to thrive [2,3]. However, the optimal timing of LT in patients with BA remains controversial due to the difficulty in predicting the prognosis [4]. The Pediatric End-stage Liver Disease (PELD)/Model of End-stage Liver diseases (MELD) score is generally used as scoring system to select patients with liver dysfunction [5,6]. Nevertheless, because the PELD/MELD score does not necessarily reflect the severity of PHT, it is sometimes impossible to determine whether a patient with BA requires LT using only this scoring system [7].

Acoustic radiation force impulse (ARFI) imaging technology is a new noninvasive method with the capability to measure the degree of tissue stiffness with real-time B-mode imaging [8]. Measurements of liver stiffness (LS) obtained using ARFI elastography may be applied to diagnose liver fibrosis in both adults and children with liver disease, in place of liver biopsies [9,10]. In addition, recent reports in adults indicate that measurements of the spleen stiffness (SS) on ARFI elastography reflect the severity of PHT [11].

In the current report, we analyzed the correlations between the SS values measured using ARFI elastography and variables indicating the severity of liver dysfunction and PHT in BA children with a history of KPE and compared the parameters for the patients requiring LT to those for the patients observed without LT.

☆ Author Contributions: H.U.: study design, writing of the paper, S.S.: study design, critical revision of the article for clinical content, M.K., T.S., M.M., K.S., I.H., H.K., A.F., Y.K., N.K.: collection of the data, M.M., S.N.: critical revision of the article for radiological content, M.K.: study design, critical revision of the article for clinical content.

* Corresponding author at: Transplantation Center, National Center of Child Health and Development, 2-10-1 Okura, Setagaya, Tokyo, 157-8535, Japan. Tel.: +81 3 3416 0181; fax: +81 3 3416 2222.
*E-mail address:* uchida-h@ncchd.go.jp (H. Uchida).

http://dx.doi.org/10.1016/j.jpedsurg.2014.12.026
0022-3468/

## 1. Patients and methods

### 1.1. Patients

We obtained written informed consent from all subjects involved in this study. We retrospectively collected data on 46 patients with undergoing KPE between September 2010 and November 2013. Three patients were excluded from this study because of polysplenia (n = 2) and post-splenic artery embolization (n = 1). Therefore, we retrospectively collected data for ARFI examinations in 43 patients, including 14 males and 29 females. We analyzed the latest single measurement for each patient treated without LT as independent findings. Regarding LT patients, the most recent results obtained before LT were used in this analysis. According to the data related to BA, the type of extrahepatic bile duct structure was classified as type 3 in 40 patients, type 1 in two patients, and not assessed in one patient [2]. The patients underwent KPE at a median 74 days after birth, ranging from 27 to 183 days. Thirty patients (69.8%) with BA after KPE consequently underwent LT, including 29 recipients of living donor liver transplantation (LDLT) and one recipient of deceased donor liver transplantation. The subjects consisted of 12 males and 18 females, with a median age of 9 months (range, 5 months to 12.9 years) at LT. The indications for LT included jaundice (n = 22), growth retardation (n = 14), gastrointestinal bleeding (n = 9) and refractory cholangitis (n = 4). This study was conducted with the approval of the ethics committee of the National Center for Child Health and Development, Tokyo (No. 152).

### 1.2. ARFI examinations

The ARFI measurements were obtained using the virtual touch tissue quantification (VTTQ) mode on a Siemens Acuson S2000TM ultrasound system. The VTTQ software package (Siemens Medical Solutions) was used to measure the shear wave velocity in different regions of interest (ROIs) within the liver and spleen parenchyma. ROIs in the liver and spleen parenchyma, free of large blood vessels, were selected. The LS was measured in the right lobe of the liver, as the anatomical features of the left lobe of the liver may be influenced by respiratory fluctuations and the pulsation of the aorta [12]. The LS and SS values were measured 1 cm below the capsule, using the intercostal and/or subxiphoid approach. Five valid measurements were obtained at the same ROI depth (3–5 cm) in each patient during slow breathing and the mean values were calculated. These values were expressed as the standard deviation score (*z*-score) relative to the previously reported normal values for the patient's age [13]. All ARFI examinations were performed by experienced radiologists who were blinded to the patients' clinical information. The maximum spleen bipolar diameter and portal vein diameter were measured using ultrasonography (US) and expressed as the *z*-score relative to the previously reported normal values for the patient's body height [14,15].

### 1.3. Clinical parameters

Clinical parameters of PHT, such as the presence of ascites and development of collateral vessels, and laboratory data, including the platelet count, prothrombin time and aminotransferase, total bilirubin, albumin and cholinesterase levels, were collected at the time of the ARFI examination. The presence of ascites and development of collateral vessels were evaluated based on US or computed tomography (CT) findings. The aspartate aminotransferase to platelet ratio index (APRI), clinical prediction rule (CPR; calculated from platelet count, spleen size z-score, and albumin concentration) proposed by Gana et al., Child–Pugh score (CPS) and PELD score, if the patient's age was below 12 years, or MELD score, if the patient's age was above 12 years, were calculated as clinical parameters related to the severity of BA [16–18].

### 1.4. Statistical analysis

Correlations between variables were examined using Pearson's or Spearman's correlation coefficients. The chi-squared or Fisher's exact tests were used for comparisons of categorical variables. Differences between continuation variables were analyzed with the Mann–Whitney U test or Student's *t*-test. A receiver operating characteristic (ROC) curve was constructed, and the area under the ROC (AUROC) was calculated with the corresponding 95% confidence interval (CI). An AUROC of greater than 0.7 was considered to be indicative of a fair test, 0.8 was considered good and more than 0.9 was considered excellent. ROC curves were used to evaluate the ability of the LS and SS values to identify patients requiring LT. Optimal cutoff values were chosen so that the sum of the sensitivity and specificity was highest. The statistical analyses were performed using the SPSS version 22.0 software package (SPSS Inc., Chicago, IL). A *P* value of less than 0.05 was considered to be statistically significant in this study.

## 2. Results

The characteristics of the 43 patients who underwent ARFI examinations are shown in Table 1. The mean age was 2.51 ± 3.23 years. The mean alanine aminotransferase (ALT), asparate aminotransferase (AST) and cholinesterase levels were 114.9 ± 73.2, 156.1 ± 73.2 and 231.2 ± 95.6 IU/L, respectively. The development of collateral vessels and ascites was found on 32 (74.4%) and 13 (30.2%) patients, respectively, and the actual measured values expressed as the *z*-score for the LS and SS values ranged from 0.57 to 21.1 (median, 11.5) and −1.07 to 7.96 (median, 3.82), respectively.

### 2.1. Correlations between the LS and SS values and the other parameters

Table 2 shows the correlations between the LS and SS values and the other parameters. The LS and SS values were significantly associated with the CPS values (LS: $r = 0.716$, $P < .001$, SS: $r = 0.465$, $P = .003$) and PELD/MELD scores (LS: $r = 0.843$, $P < .001$, SS: $r = 0.468$, $P = .003$). On the other hand, the SS values were significantly associated with the development of collateral vessels ($P = .018$) in comparison to the LS values (Fig. 1). In addition, there were significant correlations

**Table 1**
Patients' characteristics at the time of ARFI examinations (n = 43).

| Variable | Value | Range |
|---|---|---|
| Age at US (y) | 2.51 ± 3.23 | 0.24–12.6 |
| Body weight (kg) | 11.8 ± 9.2 | 3.52–46.6 |
| Height (cm) | 80.9 ± 26.5 | 55.4–152.4 |
| Laboratory values | | |
| Platelet count ($10^4$/μL) | 20.3 ± 10.5 | 4.2–43 |
| PT (%) | 75.3 ± 24.3 | 23.4–128.4 |
| Total bilirubin (mg/dL) | 6.92 ± 9.42 | 0.37–37.8 |
| AST (IU/L) | 156.1 ± 73.2 | 20–586 |
| ALT (IU/L) | 114.9 ± 73.2 | 13–318 |
| Albumin (g/dL) | 3.55 ± 0.58 | 2.3–4.6 |
| Cholinesterase (IU/L) | 231.2 ± 95.6 | 104–474 |
| Development of collateral vessels, n (%) | 32 (74.4) | |
| Presence of ascites, n (%) | 13 (30.2) | |
| Child–Pugh score[a] | 8.11 ± 2.17 | 5–12 |
| Child–Pugh classification, A/B/C[a] | 12//20/11 | |
| PELD/MELD score[a] | 8.91 ± 12.3 | .–13–37 |
| LS (m/s) | 2.75 ± 0.88 | 1.28–4.31 |
| SS (m/s) | 3.27 ± 0.59 | 1.72–4.25 |
| Spleen diameter (mm) | 96.5 ± 27.3 | 58–163 |
| Spleen diameter z-score | 3.11 ± 2.33 | −1.25–8.33 |
| PV diameter (mm) | 4.97 ± 1.80 | 2–10.4 |
| PV diameter z-score | −0.79 ± 1.09 | −3.06–1.25 |

ALT, alanine aminotransferase; AST, asparate aminotransferase; LS, liver stiffness; MELD, Model for End-stage Liver Disease; PELD, Pediatric End-stage Liver Disease; PT, prothrombin time; PV, portal vein; SS, spleen stiffness; US, ultrasonography.
[a] N = 42.