Correlation of Transient Elastography and Biliary Cirrhosis in Longterm Survivors of Biliary Atresia

Witsanee Srisuwan, M.D.*, Wison Laochareonsuk, M.D.*, Panu Wetwittayakhlang, M.D., Supika Kritsaneepaiboon, M.D.***, Surasak Sangkhathat, M.D.***

**Department of Surgery, **Department of Internal Medicine and NKC Institute of Gastroenterology and Hepatology, ***Department of Radiology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.*

ABSTRACT

Objective: This study aimed to use transient elastography (TE) to evaluate the correlation between liver stiffness measure (LSM) and functional status of native liver in longterm follow-up of pediatric patients with biliary atresia (BA).

Methods: Twenty cases of BA who had undergone hepatic portoenterostomy and had good initial outcome (total bilirubin < 2 mg/dL) were enrolled for a transient elastography. The LSMs derived from the study were analyzed with clinical and radiological parameters and endoscopic findings of esophageal varices.

Results: The median age at enrollment of the 20 cases was 8.4 years. Of the 20 cases, 15 were diagnosed as cirrhosis by ultrasonography and 9 had esophageal varices detected by an endoscopy. Parameters that were significantly associated with LSM were history of cholangitis, splenomegaly, cirrhosis and esophageal varices. Significantly higher LSM was found to be correlated with hyperbilirubinemia, transaminitis, alkaline phosphatasemia, thrombocytopenia and prolonged INR. On linear regression, LSM was significantly correlated with pediatric end-stage liver disease score at the r^2 of 0.32 and correlated with the aspartate transaminase to platelet ratio index at the r^2 of 0.70. The area under the receiver operating characteristic curve that reflected the performance of LSM in predicting esophageal varices was 0.97. At the cut-off value of 10.2 kPa, the sensitivity and specificity of LSM in predicting esophageal varices were 100% and 72.7%, respectively.

Conclusion: TE can be useful as a non-invasive, point-of-care evaluation of liver fibrosis in long term follow-up of BA. A high LSM indicates surveillance for esophageal varices in these patients.

Keywords: Transient elastrography; biliary atresia; liver stiffness measurement (Siriraj Med J 2021; 73: 32-37)

INTRODUCTION

Biliary atresia (BA) is a progressive inflammatory cholangiopathy occurring during infancy period that can lead to liver cirrhosis and death within 2 years of life.[1] The incidence of BA is reported at approximately 1 in 10,000-20,000 live births with a higher incidence in Asians.[2,3] The etiology of BA remains unclear although some evidence suggests genetic involvement. Currently, hepatic portoenterostomy (HPE, also known as Kasai's operation) is the initial surgical treatment of choice and gives a good longterm outcome in 30%-50% of cases.[4] The procedure replaces a fibrotic extrahepatic bile duct with an intestinal conduit interposed between the hepatic portal plate and the jejunum.

Corresponding author: Surasak Sangkhathat
E-mail: surasak.sa@psu.ac.th
Received 17 August 2020 Revised 8 October 2020 Accepted 9 October 2020
ORCID ID: http://orcid.org/0000-0003-3622-3233
http://dx.doi.org/10.33192/Smj.2021.05

About 40% of BA cases who undergo HPE receive no benefit from the surgery. However, among the cases who achieve biliary drainage after the surgery, progression of cirrhosis continues at varying rates. About half of the patients who have long term survival after HPE later develop biliary cirrhosis, portal hypertension, esophageal varices and/or liver failure.[4] Long term follow-up of the liver functions and surveillance for esophageal varices and cirrhosis are mandatory in BA cases. Various laboratory tests are used as indices of liver function reserve in pediatric chronic liver diseases. The aspartate transaminase to platelet ratio index (APRI) has been proposed as an indicator for liver fibrosis in pediatric patients with chronic hepatitis C and also BA.[5,6] The Pediatric End-stage Liver Disease (PELD) score has been widely used to predict life-year benefit from a liver transplantation.[7] Imaging evaluation of cirrhosis is usually performed by an ultrasound study while evaluation of esophageal varices needs an esophagoscopy. In our institute, an esophagoscopy is usually considered when a child with BA reaches 2-3 years of age or when there are clinical signs of portal hypertension.

The recent development of transient elastometry (TE) provides a non-invasive technique to evaluate the extent of liver fibrosis.[8] TE emits a 50-MHz ultrasound wave from its probe and measures the velocity of the shear wave passing through the liver parenchyma. The shear wave velocity is then converted into a liver stiffness measurement (LSM), which is expressed in kilopascals (kPa).[9] TE has been widely used in various chronic liver diseases in adults including chronic hepatitis and fatty liver.[10,11] The scanning procedure can be performed on an out-patient basis and usually takes less than 10 minutes. Studies involving BA patients have shown a correlation between liver stiffness and degree of liver fibrosis in both before and after HPE.[12-15] In 2011, a study of liver stiffness in post-HPE patients suggested that the stiffness value was correlated well with the presence of esophageal varices. A more recent study of liver stiffness measurements performed at 3 months post-HPE significantly predicted the risk of liver cirrhosis and the need for a transplantation.[15] To our knowledge, to date there have been only a few studies of TE in longterm BA survivors and these have focused on the correlation between the liver stiffness and the risk of developing portal hypertension or esophageal varices. This study aimed to evaluate the correlation between liver stiffness measurement by Fibroscan and clinical/laboratory profiles of liver functions in cases of BA who had good outcome after HPE with more than 2 years of follow-up period.

MATERIALS AND METHODS

Patients

This cross-sectional study included 20 cases of BA who underwent HPE in our institute between 2001-2015 and had good initial outcome defined as having post-operative bilirubin level of less than 2 mg/dL. On enrolment under informed consent of the parents or other guardians, the patients were clinically examined for growth anthropometry and signs of portal hypertension by the attending surgeon. Additional evaluation consisted of liver function study (total bilirubin, direct bilirubin, total protein, albumin, alkaline phosphatase, aspartate aminotransferase (AST) and alanine aminotransferase), platelet count, hepatobiliary ultrasonography and upper gastrointestinal endoscopy. Clinically significant esophageal varix was defined as the varix grade 2 or more according to the Japanese Research Society for Portal Hypertension definition (1991).[16] The aspartate transaminase to platelet ratio index (APRI) was calculated as AST (×40) × 100/platelet count (109/L). A Fibroscan was then performed within 1 month of the laboratory and endoscopic tests. The study was approved by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University.

Transient elastography

The TE procedures were performed by trained internists using a Fibroscan 502 Touch system (Echosens, Paris, France). Two types of probe were used in this study: an S probe for thoracic diameters < 45 cm and an M probe for thoracic diameters > 45 cm. Scanning was performed in a supine position with maximal abduction of the right arm. For quality control, the median values of liver stiffness measurements from 10 validated measurements with interquartile range (IQR) < 25% and reliability measured as IQR/M < 25% were used.[17] All studies were performed without sedation and under non-fasting conditions.

Statistical analysis

Data are presented as arithmetic means with ranges when they have normal distribution and medians with interquartile ranges otherwise. LSMs from the Fibroscan studies were cross tabulated with various clinical and investigative factors that are indicators of cirrhosis and portal hypertension including the PELD scores. Association analysis used Student t-test or Mann Whitney U test as appropriate. Correlations between the LSMs and liver cirrhosis as diagnosed by an ultrasonography and also the presence of esophageal varices were analysed by using a receiver operating characteristic (ROC) curve. Correlations between LSMs and PELD scores were analysed

by linear regression analysis. A P-value of less than 0.05 was considered statistically significant.

RESULTS

The twenty BA patients enrolled in this study consisted of 10 male and 10 female patients in an age range from 2.3 years to 21.0 years. The median age at enrolment was 8.4 years (IQR 5.6 - 21.0 years). The mean age at HPE in these patients was 73 days (range 30-119 days) with 2 cases having their operation later than 90 days of age. Twelve cases had ever had at least 1 episode of cholangitis. Three patients had growth parameters of less than the tenth percentile of the normal growth curve of Thai children. Ultrasound diagnosed liver cirrhosis in 15 cases, splenomegaly in 11 cases and presence of ascites in 2 cases. Esophagogastroscopy detected esophageal/gastric varices in 9 cases.

The median LSM was 12.4 kPa (IQR 6.0-32.4 kPa). Clinical and radiologic parameters that were significantly associated with LSM were history of cholangitis, splenomegaly, cirrhosis and presence of esophageal varices (Table 1). When LSM was analysed with the liver function test, significant associations were found between the stiffness value and total bilirubin, direct bilirubin, serum albumin, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase (Table 2). Higher LSM values were also significantly associated with thrombocytopenia and high prothrombin time INR. On linear regression, LSM was significantly correlated with the PELD score at the p-value of 0.02 and r^2 at 0.32. In addition, there was significant correlation between LSM and APRI at the p-value of < 0.01 and r^2 at 0.70.

To determine the diagnostic performance of LSM and cirrhosis diagnosed by ultrasonography, an ROC curve was plotted between sensitivity and 1-specificity to predict esophagogastric varices by each LSM value. The area under the ROC curve was 0.97 and the cut-off value that best predicted the presence of esophageal varices was at 10.2 kPa (sensitivity 100.0 % and specificity 72.7%) (Fig 1). The area under the curve when analysed against APRI in predicting esophageal varices was 0.99.

DISCUSSION

Gradual deterioration of liver function is a natural history after surgery in BA patients. Even in cases that had achieved good bile flow after surgery, cirrhosis and portal hypertension were eventually occurred. Ascending cholangitis may accelerate the cirrhotic changes. Evaluation of the severity of cirrhosis usually relies on clinical evaluation and ultrasonography. In general, an esophagoscopy is indicated when there are clinical or radiological signs of portal hypertension. In this study, we evaluated the values of transient elastography in BA related cirrhosis by studying the association between LSM and liver profiles in good outcome BA cases who had been followed more than 2 years. The study demonstrated significant associations between LSM and both APRI and radiologic diagnosis of liver cirrhosis. In addition, LSM was significantly associated with other signs of liver decompensation and portal hypertension including hyperbilirubinemia and presence of esophageal varices.

In 2011, a study by Chongsrisawat and colleagues has reported that both LSM and APRI could equally predict the esophageal varices in BA cases with an acceptable accuracy.[12] Consistent with that report, our data showed good correlation between LSM and APRI and near perfect performance of both parameters in predicting significant esophageal varices. The data suggested that screening for esophageal varices during BA follow-up can be performed in particular cases and Fibroscan is the effective tool for case selection. Our study also suggests that an LSM of 10.2 kPa is a practical cut-off value for variceal prediction, a value which is similar to the value range of 9.7-12.5 kPa as suggested by the previous studies.[12,18,19]

One of limitations in this study was its cross-sectional design which meant that all variables analysed were measured at a single time-point during the wide range follow-up period. Chronological changes over time of the LSM might be more useful in following the rate of deterioration of the native liver function. The timing of scanning has varied among earlier reports. One study in pre-operative BA cases suggested that LSM was superior to APRI in predicting histologically confirmed high-grade fibrosis (F4 by the Metavir scoring system).[14] Another study performed at 3 months post HPE demonstrated good correlations between high LSMs and liver-related events such as ascites, variceal bleeding or death during the follow-up period which suggested the earlier need of transplantation.[13]

CONCLUSION

In conclusion, our study performed transient elastography during long term follow-up in BA patients who achieved good biliary drainage after HPE. As in other studies, we found correlations between LSMs and other clinical/radiological evidence of portal hypertension. Using a cut-off of 10.2 kPa, TE predicted esophageal varices with high sensitivity.

TABLE 1. Association between liver stiffness measure (LSM) by a transient electrography and clinical signs, esophagogastroscopic detection of varices and ultrasound findings.

	Cases (%)	LSM (kPa)	*P*-value*
History of cholangitis			
No	8 (40%)	8.12	0.03
Yes	12 (60%)	30.33	
Weight or height <10th percentile			
No	17 (85%)	21.75	0.31
Yes	3 (15%)	19.77	
Splenomegaly by examination			
No	12 (60%)	8.22	< 0.01
Yes	8 (40%)	41.29	
Esophageal varices			
Absent	11 (55%)	7.66	< 0.01
Present	9 (45%)	38.30	
Cirrhosis by ultrasound			
Absent	5 (25%)	5.18	< 0.01
Present	15 (75%)	26.87	
Splenomegaly by ultrasound			
Absent	9 (45%)	6.61	< 0.01
Present	11 (55%)	33.59	
Ascites by ultrasound			
Absent	18 (90%)	21.35	0.61
Present	2 (10%)	22.35	
Intrahepatic duct dilatation			
Absent	16 (80%)	17.76	0.32
Present	4 (20%)	36.22	
Fatty change			
Absent	19 (95%)	22.31	-
Present	1 (5%)	5.10	

*Mann Whitney U test

TABLE 2. Association between liver stiffness measure (LSM) by a transient electrography and liver function profiles, prothrombin time-INR and platelet count.

		Cases (%)	LSM (kPa)	*P*-value*
Total bilirubin (mg/dL)				
	TB < 2.0	16	12.45	< 0.01
	TB > 2.0	4	57.45	
Direct bilirubin (mg/dL)				
	DB < 2.0	17	16.13	0.02
	DB > 2.0	3	51.60	
Serum albumin (g/dL)				
	Alb < 3.5	2	75.00	0.02
	Alb > 3.5	18	15.50	
Aspartate aminotransferase (U/L)				
	AST < 35	15	7.30	0.04
	AST > 35	5	26.17	
Alanine aminotransferase (U/L)				
	ALT < 35	8	7.15	< 0.01
	ALT > 35	12	30.98	
Akaline phosphatase (U/L)				
	ALP < 200	3	5.77	0.04
	ALP > 200	17	24.21	
Prothrombin time-INR**				
	INR < 1.2	10	13.41	0.04
	INR > 1.2	9	32.06	
Platelet count (x 10^9 cells/L)**				
	< 150	9	27.8	0.047
	> 150	9	9.96	

*Mann Whitney U test, **presence of missing values

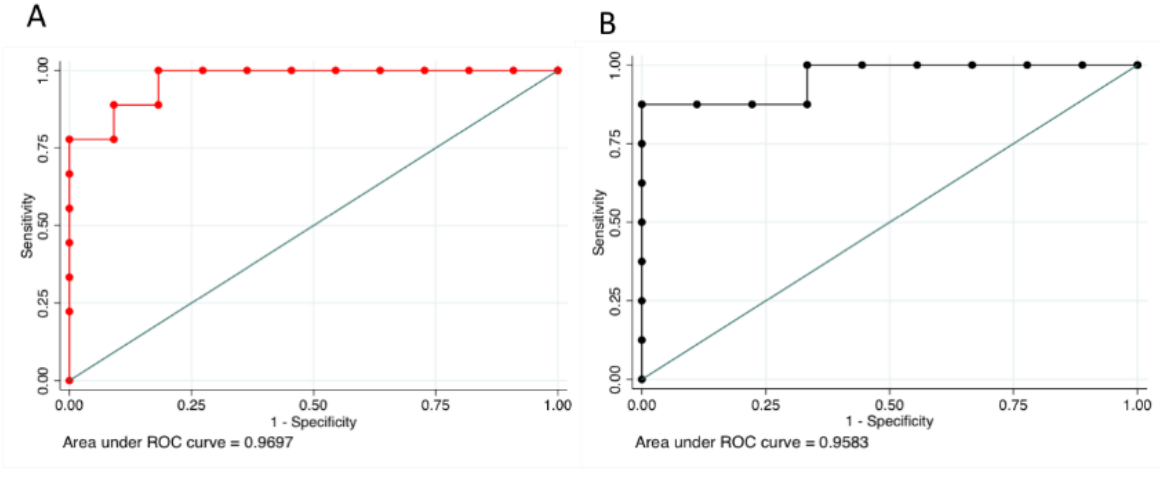

Fig 1. Diagnostic performance of (A) liver stiffness measure and (B) aspartate transaminase to platelet ratio index in predicting esophageal varices in biliary atresia patients.

ACKNOWLEDGEMENTS

The authors thank the nurses in the NKC Institute of Gastroenterology and Hepatology, Songklanagarind Hospital for their cooperation in performing the transient elastography. Dave Patterson edited the English Language in the manuscript.

REFERENCES

1. Hartley JL, Davenport M, Kelly DA. Biliary atresia. Lancet 2009;374:1704-13.
2. Lee KJ, Kim JW, Moon JS, Ko JS. Epidemiology of Biliary Atresia in Korea. J Korean Med Sci 2017;32:656-60.
3. Sanchez-Valle A, Kassira N, Varela VC, Radu SC, Paidas C, Kirby RS. Biliary Atresia: Epidemiology, Genetics, Clinical Update, and Public Health Perspective. Adv Pediatr 2017;64:285-305.
4. Sangkhathat S, Patrapinyokul S, Tadtayathikom K, Osatakul S. Peri-operative factors predicting the outcome of hepatic porto-enterostomy in infants with biliary atresia. J Med Assoc Thai 2003;86:224-31.
5. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-26.
6. Kim SY, Seok JY, Han SJ, Koh H. Assessment of liver fibrosis and cirrhosis by aspartate aminotransferase-to-platelet ratio index in children with biliary atresia. J Pediatr Gastroenterol Nutr 2010;51:198-202.
7. Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl 2001;7:567-80.
8. Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. Hepatology 2006;43:S113-20.
9. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003;29:1705-13.
10. Yoneda M, Yoneda M, Fujita K, Inamori M, Tamano M, Hiriishi H, et al. Transient elastography in patients with non-alcoholic fatty liver disease (NAFLD). Gut 2007;56:1330-1.
11. Castera L, Le Bail B, Roudot-Thoraval F, Bernard PH, Foucher J, Merrouche W, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. J Hepatol 2009;50:59-68.
12. Chongsrisawat V, Vejapipat P, Siripon N, Poovorawan Y. Transient elastography for predicting esophageal/gastric varices in children with biliary atresia. BMC Gastroenterol 2011;11:41.
13. Hahn SM, Kim S, Park KI, Han SJ, Koh H. Clinical benefit of liver stiffness measurement at 3 months after Kasai hepatoportoenterostomy to predict the liver related events in biliary atresia. PLoS One 2013;8:e80652.
14. Shen QL, Chen YJ, Wang ZM, Zhang TC, Pang WB, Shu J, et al. Assessment of liver fibrosis by Fibroscan as compared to liver biopsy in biliary atresia. World J Gastroenterol 2015;21:6931-6.
15. Wu JF, Lee CS, Lin WH, Jeng YM, Chen HL, Ni YH, et al. Transient elastography is useful in diagnosing biliary atresia and predicting prognosis after hepatoportoenterostomy. Hepatology 2018;68:616-24.
16. Idezuki Y. General rules for recording endoscopic findings of esophagogastric varices (1991). Japanese Society for Portal Hypertension. World J Surg 1995;19:420-2.
17. Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005;41:48-54.
18. Chang HK, Park YJ, Koh H, Kim SM, Chung KS, Oh JT, et al. Hepatic fibrosis scan for liver stiffness score measurement: a useful preendoscopic screening test for the detection of varices in postoperative patients with biliary atresia. J Pediatr Gastroenterol Nutr 2009;49:323-8.
19. Colecchia A, Festi D, di Biase AR. Noninvasive parameters for predicting esophageal varices in children: their sequential use provides the best accuracy. Gastroenterology. 2012;142:e32.