Original Article | Pediatric Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2020.0055
Korean J Radiol 2021;22(2):253-262

Korean Journal of Radiology
KJR

Diffusion-Weighted Imaging for Differentiation of Biliary Atresia and Grading of Hepatic Fibrosis in Infants with Cholestasis

Jisoo Kim, MD[1], Hyun Joo Shin, MD, PhD[1, 2], Haesung Yoon, MD, PhD[1, 2], Seok Joo Han, MD, PhD[2, 3], Hong Koh, MD, PhD[2, 4], Myung-Joon Kim, MD, PhD[1, 2], Mi-Jung Lee, MD, PhD[1, 2]

[1]Department of Radiology and Research Institute of Radiological Science, Yonsei University College of Medicine, Seoul, Korea; [2]Severance Pediatric Liver Disease Research Group, Yonsei University College of Medicine, Seoul, Korea; Departments of [3]Pediatric Surgery and [4]Pediatrics, Yonsei University College of Medicine, Seoul, Korea

Objective: To determine whether the values of hepatic apparent diffusion coefficient (ADC) can differentiate biliary atresia (BA) from non-BA or be correlated with the grade of hepatic fibrosis in infants with cholestasis.

Materials and Methods: This retrospective cohort study included infants who received liver MRI examinations to evaluate cholestasis from July 2009 to October 2017. Liver ADC, ADC ratio of liver/spleen, aspartate aminotransferase to platelet ratio index (APRI), and spleen size were compared between the BA and non-BA groups. The diagnostic performances of all parameters for significant fibrosis (F3–4) were obtained by receiver-operating characteristics (ROCs) curve analysis.

Results: Altogether, 227 infants (98 males and 129 females, mean age = 57.2 ± 36.3 days) including 125 BA patients were analyzed. The absolute ADC difference between two reviewers was 0.10 mm^2/s for both liver and spleen. Liver ADC value was specific (80.4%) and ADC ratio was sensitive (88.0%) for the diagnosis of BA with comparable performance. There were 33 patients with F0, 15 with F1, 71 with F2, 35 with F3, and 11 with F4. All four parameters of APRI (τ = 0.296), spleen size (τ = 0.312), liver ADC (τ = -0.206), and ADC ratio (τ = -0.288) showed significant correlation with fibrosis grade (all, $p < 0.001$). The cutoff values for significant fibrosis (F3–4) were 0.783 for APRI (area under the ROC curve [AUC], 0.721), 5.9 cm for spleen size (AUC, 0.719), 1.044 x 10^{-3} mm^2/s for liver ADC (AUC, 0.673), and 1.22 for ADC ratio (AUC, 0.651).

Conclusion: Liver ADC values and ADC ratio of liver/spleen showed limited additional diagnostic performance for differentiating BA from non-BA and predicting significant hepatic fibrosis in infants with cholestasis.

Keywords: *Biliary atresia; Diffusion magnetic resonance imaging; Liver cirrhosis*

INTRODUCTION

Infantile jaundice can arise through a variety of causes, with biliary atresia (BA) being one of them. BA leads to hepatic fibrosis without surgical correction, which may progress to hepatic failure and eventually require liver transplantation (1, 2); hence, early diagnosis of BA is of paramount importance in infants presenting jaundice. Various imaging modalities, including ultrasonography (US) and MRI, are commonly used to diagnose BA (3, 4). Associated findings include the triangular cord sign, invisible common bile duct, abnormal gallbladder morphology, enlarged hepatic artery, splenomegaly, increased liver stiffness through elastography, which can be seen both on US and MRI, and hepatic subcapsular flow (detected on Doppler US) (3-7). The combination of these imaging findings allows the diagnosis of BA before operation (3, 8). US is the most commonly used imaging technique; however, MRI is employed to differentiate the causes of hyperbilirubinemia because it is less affected by

Received: September 5, 2019 **Revised:** May 6, 2020
Accepted: May 11, 2020
Corresponding author: Mi-Jung Lee, MD, PhD, Department of Radiology and Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
• E-mail: mjl1213@yuhs.ac

the practitioner's skills and provides a larger field of view with a good spatial resolution (9, 10).

Another strength of hepatobiliary MRI is diffusion-weighted imaging (DWI), a type of quantitative imaging associated with hepatic fibrosis (11, 12). Many studies show that, in patients with chronic liver disease, as fibrosis progresses, hepatic apparent diffusion coefficient (ADC) values are lowered and can be used to evaluate liver fibrosis as similarly to other non-invasive methods of blood chemistry tests (13, 14). In previous studies, ADC values and clinical scores for assessing hepatic fibrosis showed a significant correlation in patients with BA (15, 16). However, only a few report the use of DWI in the diagnosis of BA and, in particular, on the relationship between the histologically diagnosed degree of hepatic fibrosis and DWI in pediatric patients (17).

Therefore, the purpose of this study was to investigate whether the values of hepatic ADC of liver MRI would differentiate BA from non-BA and correlate with the grade of hepatic fibrosis in infants with cholestasis.

MATERIALS AND METHODS

Subjects

This retrospective cohort study was approved by our Institutional Review Board, and the need for informed consent was waived. However, written informed consent for sedation and MRI was received before each examination as routine clinical practice. Infants who underwent liver MRI examinations to evaluate hyperbilirubinemia from July 2009 to October 2017 were included. Liver MRI was performed in all consecutive infants suspected of various hepatobiliary diseases including BA or choledochal cyst, presenting persistent hyperbilirubinemia even after conservative treatment. We excluded patients when DWI was not included in the MRI scan or when patients were older than 12 months at the time of diagnosis. Included subjects were divided into BA and non-BA groups according to the intraoperative cholangiography findings and pathologic results, or clinical follow up.

Demographic data assessed included age, sex, aspartate aminotransferase (AST, IU/L), alanine transaminase (ALT, IU/L), total bilirubin (mg/dL), direct bilirubin (mg/dL), alkaline phosphatase (ALP, IU/L), γ-glutamyl transferase (γGT, IU/L), and platelet count (10^3/μL) at the time of MRI examination. The AST to platelet ratio index (APRI), known as a clinical parameter of hepatic fibrosis (18), was calculated from the ratio of platelet count to AST. Additionally, histologic grades of hepatic fibrosis were obtained using the METAVIR grading system (F0 as no fibrosis, F1 as portal fibrosis without septal fibrosis, F2 as portal fibrosis with a few septal fibrosis, F3 as numerous septal fibrosis, and F4 as cirrhosis) if the patient underwent intraoperative or percutaneous liver biopsy within one-month following liver MRI.

MRI Acquisition

Liver MRI was performed using an 1.5T system (Intera Achieva; Philips Healthcare) with a cardiac coil. The MR examinations were performed under sedation offered by a trained pediatric sedation team, and the patients were in free-breathing status. The sequences of MRI included axial and coronal T2-weighted single-shot fast spin-echo, axial T1-weighted spin-echo, coronal respiratory-gated fast spin-echo three-dimensional MR cholangiopancreatography, and axial DWI. A transverse fat-suppressed single-shot spin echo-planar imaging was performed using the following parameters: repetition time/echo time, 2000 ms/64.1 ms; matrix size, 128 x 128; field of view, up to 240 mm; slice thickness, 7 mm; number of excitation, 2.0; flip angle, 90°; b-values of 0, 500, 1000 s/mm^2 or 0, 100, 150, 500, 1000 s/mm^2; and tridirectional diffusion gradients.

Image Analysis

Spleen size was measured on axial and coronal images and the larger value was determined as spleen size.

To obtain liver ADC values, circular regions-of-interest (ROIs) were drawn in the axial images of the right hepatic lobe avoiding the areas of respiratory motion, artifact, and major vessels (Fig. 1). Additional circular ROIs were also drawn at the central portion of the spleen avoiding gross vessels. The diameter of the ROI was about 12 mm on the liver and 8 mm on the spleen. These evaluations for ADC values were independently performed by two radiologists with 15 and 3 years of experience in liver MRI, respectively. The ADC value was calculated automatically from each ROI of DWI sequences using all available b-values from the mono-exponential fit. The ADC ratio of liver/spleen was also used for normalization (19, 20).

Statistical Analysis

Statistical analyses were performed using SPSS version 23 (IBM Corp.) and MedCalc version 19.1.3 (MedCalc software). Inter-observer agreement was evaluated for the data of ADC

https://doi.org/10.3348/kjr.2020.0055

Korean Journal of Radiology
KJR

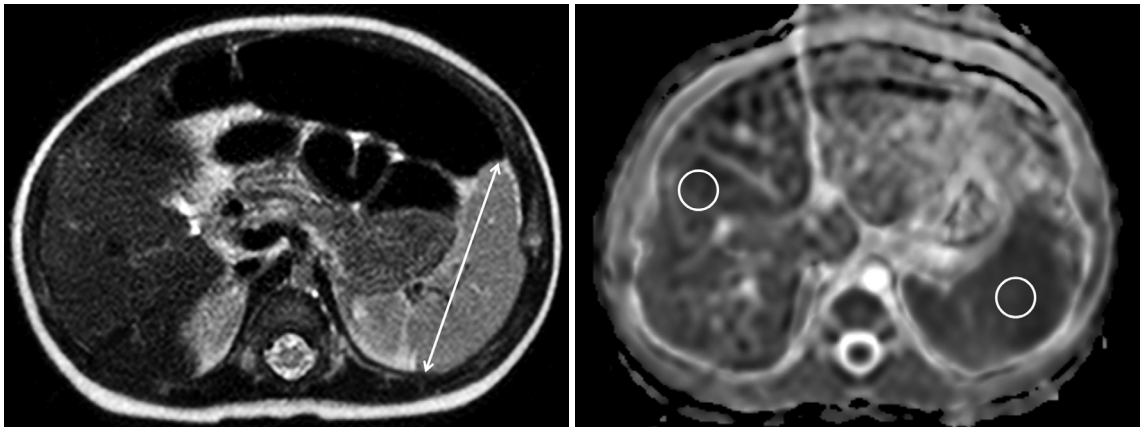

Fig. 1. A representative case for measurement of imaging parameters from a 43-day-old girl diagnosed as biliary atresia.
A. The spleen size was measured as the largest diameter among measurements on axial and coronal views as shown in this case of axial T2-weighted image. The spleen size was 6.0 cm. **B.** Circular regions-of-interest are drawn in the homogeneous parenchyma of liver and spleen avoiding major vessels on an axial image of ADC map. The ADC value was 0.975 x 10^{-3} mm^2/s from liver and 0.932 x 10^{-3} mm^2/s from spleen. The ADC ratio of liver and spleen was 1.0. ADC = apparent diffusion coefficient

values from the two reviewers using intraclass correlation analysis. The absolute difference was also checked for ADC from the two reviewers. The subsequent analysis used the ADC values from the first reviewer. Demographic data and ADC values were compared between BA and non-BA groups using the independent *t* test and chi-square test. Kendall's tau coefficient was used to evaluate the correlation between clinical parameters or ADC values and the histologic grade of hepatic fibrosis. The diagnostic performances for significant hepatic fibrosis (F3 and F4) were assessed and compared using the area under the receiver-operating characteristic curve (AUC) analysis. All data were presented as the mean and standard deviation. *P* values less than 0.05 were considered statistically significant.

RESULTS

Subjects and Baseline Characteristics

Altogether, 227 infants were included in the evaluation of cholestasis. Among them, 125 patients (55.1%, 44 males and 81 females) were diagnosed to have BA with operative and pathologic confirmation and the other 102 patients (44.9%, 54 males and 48 females) were assigned to the non-BA group, including diagnoses of choledochal cyst (n = 44), acute hepatitis (n = 18), genetic disorders (n = 9), metabolic disease (n = 5), paucity of intrahepatic bile duct (n = 2), biliary dyskinesia (n = 1), inspissated bile syndrome (n = 1), and idiopathic condition (n = 22).

The clinical and laboratory results of the two groups are shown in Table 1. The age at the time of MRI was not significantly different between the two groups ($p = 0.892$), but the gender distribution was significantly different, with more female patients included in the BA group ($p = 0.005$). Among the laboratory results, AST, ALT, direct bilirubin, ALP, and γGT were significantly higher in the BA group compared with the non-BA group (Table 1). However, the APRI calculated from the ratio of platelets and AST was not different between the two groups ($p = 0.149$).

Liver MRI Results

Spleen size, as measured on the liver MRI, was significantly larger in the BA group compared with the non-BA group (mean, 6.2 ± 1.1 vs. 5.5 ± 1.1 cm; $p < 0.001$).

For ADC evaluation, 3 b-values were used in 211 patients including 113 from BA and 98 from non-BA groups. In addition, 5 b-values were used in 16 patients as 12 from BA and 4 from non-BA groups. The distribution of the group members according to the different b-value numbers were not different ($p = 0.078$).

The ADC values from liver and spleen could be obtained in all included patients without failure or error. The mean size of the circular ROIs was 105.1 ± 15.2 mm^2 for the liver and 57.3 ± 15.7 mm^2 for the spleen. The intraclass correlation coefficients from the two reviewers' data were 0.875 for liver ADC values and 0.779 for spleen ADC values. The absolute difference for ADC was 0.101 ± 0.094 x 10^{-3} mm^2/s for liver and 0.103 ± 0.115 x 10^{-3} mm^2/s for spleen. Table 1 shows the ADC values of the BA and non-BA groups, including liver ADC, spleen ADC, and the ratio of liver to spleen ADC. Liver ADC values (mean, 1.098 vs. 1.171 x 10^{-3}

https://doi.org/10.3348/kjr.2020.0055

Table 1. Comparison of Clinical and Laboratory Results and Imaging Findings between the BA and Non-BA Groups

Parameters	BA (n = 125)	Non-BA (n = 102)	*P*
Demographics			
Age (days)	56.9 ± 30.2	57.6 ± 42.8	0.892
Sex (male:female)	44:81	54:48	0.005
Laboratory results			
AST (IU/L)	181.3 ± 160.3	121.5 ± 142.7	0.004
ALT (IU/L)	122.9 ± 112.3	85.0 ± 124.4	0.017
Total bilirubin (mg/dL)	7.6 ± 2.8	6.7 ± 4.4	0.076
Direct bilirubin (mg/dL)	5.8 ± 2.3	3.8 ± 3.3	< 0.001
ALP (IU/L)	473.5 ± 207.9	406.2 ± 276.5	0.038
γGT (IU/L)	466.2 ± 338.7	175.7 ± 201.4	< 0.001
Platelet (10^3/μL)	439.6 ± 151.4	427.9 ± 155.6	0.567
APRI	1.5 ± 1.6	1.1 ± 1.9	0.149
Imaging findings			
Spleen size (cm)	6.2 ± 1.1	5.5 ± 1.1	< 0.001
Liver ADC (x 10^{-3} mm^2/s)	1.098 ± 0.211	1.171 ± 0.220	0.011
Spleen ADC (x 10^{-3} mm^2/s)	0.880 ± 0.166	0.903 ± 0.206	0.338
Liver/spleen ADC	1.26 ± 0.19	1.33 ± 0.25	0.029

P values from independent *t* test except for sex from chi-square test. ADC = apparent diffusion coefficient, ALP = alkaline phosphatase, ALT = alanine transaminase, APRI = aspartate aminotransferase to platelet ratio index, AST = aspartate aminotransferase, BA = biliary atresia, γGT = γ-glutamyl transferase

mm^2/s; $p = 0.011$) and the ratio of liver and spleen ADC values (mean, 1.26 vs. 1.33; $p = 0.029$) were significantly lower in the BA group than in the non-BA group. However, spleen ADC values were not different between the two groups ($p = 0.338$).

Diagnosis of BA

Table 2 demonstrates the diagnostic performance to differentiate BA using the parameters from laboratory findings and MRI values. Among the laboratory parameters, γGT had the AUC value of 0.847 ($p < 0.001$), 87.2% sensitivity, and 71.7% specificity using the cutoff value of 183 IU/L. APRI had 80.0% sensitivity and 52.9% specificity for the diagnosis of BA with a cutoff value of 0.455 (AUC value of 0.669, $p < 0.001$). Among the MRI parameters, spleen size had 72.8% sensitivity and 61.8% specificity for the diagnosis of BA with a cutoff value of 5.6 cm (AUC value of 0.690, $p < 0.001$). The liver ADC showed the highest specificity of 80.4% for the diagnosis of BA when using the cutoff value of 1.044 x 10^{-3} mm^2/s (AUC value of 0.620, $p = 0.001$). The ADC ratio of liver and spleen showed the highest sensitivity of 88.0% among the imaging parameters with the cutoff value of 1.4.

The combined parameter of γGT and spleen size had an AUC value of 0.861 ($p < 0.001$) and the combined parameter of γGT, spleen size, and liver ADC had AUC value of 0.862 ($p < 0.001$) without significant differences. The AUC values of only γGT and the combined parameter of γGT, spleen size,

Table 2. Diagnostic Performance of Laboratory and Imaging Parameters for the Differentiation of BA

Parameters	AUC (95% Confidence Interval)	*P*	Cutoff Values	Sensitivity (%)	Specificity (%)
Laboratory results					
AST (IU/L)	0.698 (0.634–0.757)	< 0.001	> 70	82.4	57.8
ALT (IU/L)	0.693 (0.628–0.752)	< 0.001	> 31	90.4	49.0
Direct bilirubin (mg/dL)	0.710 (0.646–0.768)	< 0.001	> 3.2	89.6	48.5
ALP (IU/L)	0.619 (0.552–0.682)	0.002	> 301	82.4	45.1
γGT (IU/L)	0.847 (0.793–0.892)	< 0.001	> 183	87.2	71.7
APRI	0.669 (0.604–0.730)	< 0.001	> 0.455	80.0	52.9
Imaging findings					
Spleen size (cm)	0.690 (0.626–0.750)	< 0.001	> 5.6	72.8	61.8
Liver ADC (x 10^{-3} mm^2/s)	0.620 (0.553–0.683)	0.001	≤ 1.044	45.6	80.4
Liver/spleen ADC	0.589 (0.522–0.654)	0.019	≤ 1.4	88.0	27.5
Combined parameters					
γGT + spleen size	0.861 (0.812–0.910)	< 0.001			
γGT + liver ADC	0.852 (0.800–0.904)	< 0.001			
Spleen size + liver ADC	0.691 (0.622–0.761)	< 0.001			
γGT + spleen size + liver ADC	0.862 (0.813–0.911)	< 0.001			

AUC = area under the receiver-operating characteristic curve

https://doi.org/10.3348/kjr.2020.0055

Korean Journal of Radiology
KJR

and liver ADC were not different (p = 0.429).

Correlation between Histologic Grades of Hepatic Fibrosis and Parameters

The mean time interval between MRI examination and histologic evaluation was 4.5 ± 4.3 days (range, 0–27 days). Histologic grades of hepatic fibrosis according to the METAVIR grading system were obtained for 165 patients through intraoperative or percutaneous biopsy. There were 33 patients with F0 (BA:non-BA = 2:31), 15 with F1 (BA:non-BA = 8:7), 71 with F2 (BA:non-BA = 65:6), 35 with F3 (BA:non-BA = 34:1), and 11 with F4 (BA:non-BA = 11:0). The ADC values from the liver and spleen and the grades of hepatic fibrosis were not different between the groups using 3 b-values and 5 b-values (all, p > 0.05).

The correlations of fibrosis grades and the parameters are shown in Figure 2. There were significant correlations between hepatic fibrosis grades and all four parameters of APRI (τ = 0.296), spleen size (τ = 0.312), liver ADC (τ = -0.206), and ADC ratio (τ = -0.288) (all, p < 0.001). However, the spleen ADC value was not correlated with hepatic fibrosis grade (τ = 0.035, p = 0.550). Among the clinical and laboratory parameters, age (τ = 0.279) and γGT (τ = 0.352) also showed correlation with fibrosis grades (both, p < 0.001).

On the partial correlation analysis considering the BA group, age (τ = 0.383, p < 0.001), γGT (τ = 0.242, p = 0.002), spleen size (τ = 0.248, p = 0.001), liver ADC (τ = -0.224, p = 0.004), and ADC ratio (τ = -0.291, p < 0.001) also showed correlation with hepatic fibrosis grades. However, APRI (τ = 0.094, p = 0.232) and spleen ADC (τ = 0.026, p = 0.746) were not correlated with hepatic fibrosis grades.

Assessment and Comparison of Diagnostic Performances for Significant Hepatic Fibrosis

The diagnostic performances of the parameters for significant hepatic fibrosis (F3–4), including APRI, spleen

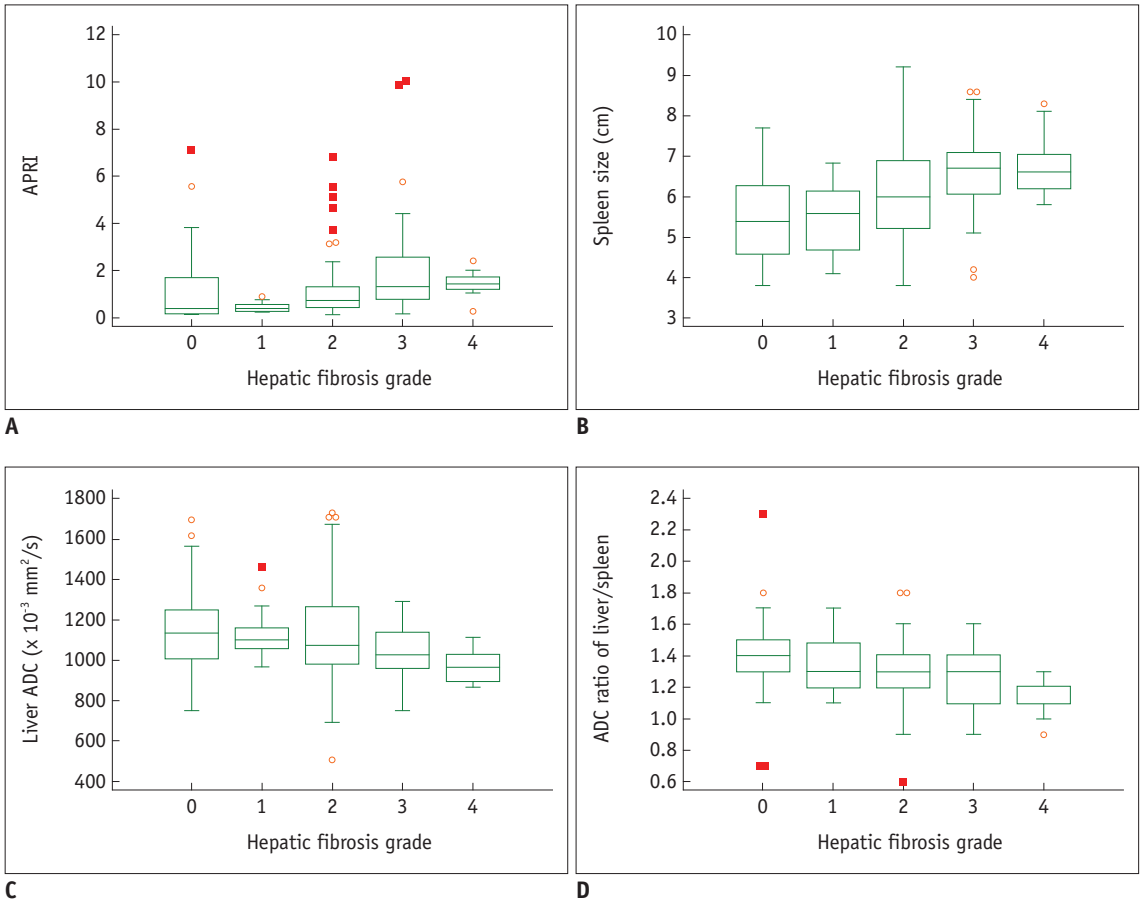

Fig. 2. Box plots for comparison of hepatic fibrosis grades and parameters.
Box plots show the values according to the hepatic fibrosis grade of APRI **(A)**, spleen size **(B)**, liver ADC **(C)**, and the ADC ratio of liver and spleen **(D)**. The values of APRI (τ = 0.296) and spleen size (τ = 0.312) showed positive correlation and the values of liver ADC (τ = -0.206) and ADC ratio (τ = -0.288) showed negative correlation with hepatic fibrosis grades (all, p < 0.001). APRI = aspartate aminotransferase to platelet ratio index

https://doi.org/10.3348/kjr.2020.0055

size, liver ADC, and ADC ratio are shown in Table 3 and Figure 3. The AUC value of APRI was 0.721, and the suggested cutoff value was 0.783. Spleen size of more than 5.9 cm showed 84.8% sensitivity and 56.3% specificity, and the AUC was 0.719. The liver ADC value ≤ 1.044 x 10^{-3} mm^2/s showed an AUC value of 0.673 (95% confidence interval [CI], 0.596–0.744), and the ADC ratio value ≤ 1.22 showed an AUC value of 0.651 (95% CI, 0.573–0.723). When the AUC of these four parameters were compared, none showed any significant difference for diagnosing significant hepatic fibrosis (all, $p > 0.2$).

When considering the BA group only (120 patients), the AUC value of age was 0.787 with 93.3% sensitivity and 53.3% specificity when using the cutoff value of 45 days for diagnosing significant hepatic fibrosis. When the parameters of age, APRI, spleen size, and liver ADC values were combined, as shown in Table 3, the highest AUC value was 0.796 (95% CI, 0.715–0.878) in combination of age, spleen size and liver ADC value. However, the AUC values were not statistically different.

DISCUSSION

It is important to differentiate BA from non-BA in neonatal cholestasis; it is also desirable to evaluate hepatic fibrosis grades non-invasively in these patients. Our study showed that spleen size measured on MRI, liver ADC value, and ADC ratio of liver/spleen could differentiate BA from non-BA patients. Liver ADC value was a specific (80.4%) and ADC ratio a sensitive (88.0%) parameter for

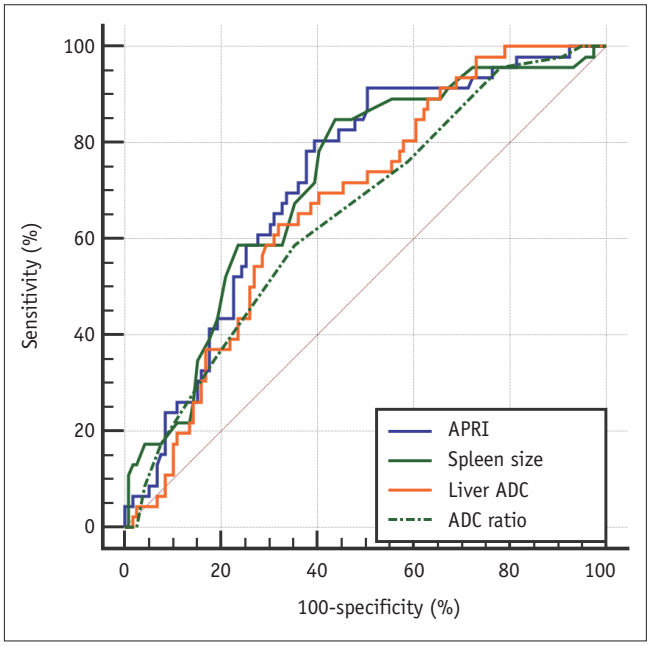

Fig. 3. Receiver-operating characteristics curves of the parameters including APRI, spleen size, liver ADC, and ADC ratio of liver and spleen for the diagnosis of significant hepatic fibrosis (F3–4). No significant differences were observed between the parameters (all, $p > 0.2$).

Table 3. Diagnostic Performances of Laboratory and Imaging Parameters for the Differentiation of Significant Fibrosis (F3–4)

Parameters	AUC (95% Confidence Interval)	*P*	Cutoff Values	Sensitivity (%)	Specificity (%)
All patients					
Laboratory results					
AST (IU/L)	0.755 (0.682–0.818)	< 0.001	> 146	73.9	72.3
ALT (IU/L)	0.761 (0.688–0.823)	< 0.001	> 74	80.4	66.4
Direct bilirubin (mg/dL)	0.732 (0.657–0.798)	< 0.001	> 5.3	78.3	63.9
ALP (IU/L)	0.668 (0.590–0.739)	< 0.001	> 298	95.7	33.6
γGT (IU/L)	0.708 (0.632–0.776)	< 0.001	> 382	67.4	71.4
APRI	0.721 (0.646–0.788)	< 0.001	> 0.783	80.4	60.5
Imaging findings					
Spleen size (cm)	0.719 (0.644–0.786)	< 0.001	> 5.9	84.8	56.3
Liver ADC (x 10^{-3} mm^2/s)	0.673 (0.596–0.744)	< 0.001	≤ 1.044	63.0	68.1
Liver/spleen ADC	0.651 (0.573–0.723)	0.001	≤ 1.22	58.7	64.7
Only BA group					
Combined parameters					
Age (days)	0.787 (0.703–0.856)	< 0.001	> 45	93.3	53.3
Age + APRI	0.790 (0.706–0.874)	< 0.001			
Age + spleen size	0.790 (0.706–0.875)	< 0.001			
APRI + spleen size	0.721 (0.629–0.813)	< 0.001			
Age + APRI + spleen size	0.795 (0.711–0.879)	< 0.001			
Age + spleen size + liver ADC	0.796 (0.715–0.878)	< 0.001			

https://doi.org/10.3348/kjr.2020.0055

Korean Journal of Radiology
KJR

the diagnosis of BA. Moreover, these parameters could be used to predict the histologic degree of hepatic fibrosis. Splenomegaly more than 5.9 cm, hepatic ADC values lower than 1.044 x 10^{-3} mm^2/s and ADC ratio lower than 1.22 were associated with significant hepatic fibrosis (F3–4), even though the diagnostic performance was not superior to APRI.

Our study also demonstrated good inter-observer agreement for the measurement of ADC in infantile liver MRI with free breathing. The intraclass correlation coefficients were 0.875 for the liver and 0.779 for the spleen. Moreover, the ADC ratio of the liver and spleen showed the same trend as the liver ADC value. There was no study using normalized ADC value taking the spleen as the reference organ, which could decrease variability in ADC measurement (20).

Previously, only a few studies suggested the utility of DWI parameters for diagnosing BA. Two studies reported lower hepatic ADC values in BA patients compared with the values in control subjects (15, 16). However, the number of BA patients was small (n = 32 or 33), and the age range was wide (0–13 years). Moreover, they showed the difference between BA patients and normal healthy subjects, but not with non-BA cholestasis patients. A recent study in 59 neonates and infants demonstrated the utility of diffusion tensor imaging in neonatal cholestasis for the differentiation of BA from non-BA (17). When using the b-values of 0 and 1000 s/mm^2, the ADC cutoff value of 1.317 x 10^{-3} mm^2/s showed 78% sensitivity and 81.5% specificity for diagnosing BA (17). However, there was no difference in fractional anisotropy values between the two groups. Although the study is meaningful, the number of included patients was still small. Our study included several times the number of patients in existing studies, all of which were neonates and infants with cholestasis. Our results were consistent with previous studies showing significantly lower ADC values in the BA group compared with the non-BA group. The suggested cutoff value of our study was 1.044 × 10^{-3} mm^2/s, which is lower than that of the previous report. This may be due to the use of different b-values and different levels of fibrosis in the patient population.

Not only conventional DWI with the mono-exponential model, but also advanced DWI techniques with bi- or stretched-exponential models can be used nowadays. In our study, we used both 3 and 5 b-values including the b-value of 0 s/mm^2, which can theoretically introduce perfusion effects into the diffusion data. In a previous study, there was no significant difference between diffusion parameters using mono-, bi-, and stretched-exponential models in differentiating BA from non-BA in infants with hyperbilirubinemia, even using only two b-values (21). Similarly, another study found that ADC derived from the mono-exponential model was the most valuable parameter among a variety of analytical methods including mono-, bi-, and stretched-exponential, and kurtosis models in renal cell carcinoma subtype analysis (22). Thus, ADC derived from the mono-exponential model, even with small b-values, could not be inferior to other novel DWI analytical models. Moreover, in pediatric patients, the use of multiple b-values leads to longer anesthesia, so if a small b-value number can achieve similar performance, the analysis using a mono-exponential model with fewer b-values is also meaningful.

Several studies have shown a correlation between hepatic fibrosis grades and hepatic ADC values in adults using variable DWI analysis (13, 23, 24). However, only three studies dealt with the correlation between the two in pediatric patients. The first study reported that the right liver ADC value showed a negative correlation with liver scores in 33 BA patients and 18 healthy subjects without pathologic evaluation (15). The second report showed that the right liver to psoas ADC ratios in 32 BA patients were negatively correlated with clinical or histological hepatic fibrosis grades (16). However, most patients were F4 (19/32, 59%) and no patients were F0 or F1. In the other study using diffusion tensor imaging for evaluating hepatic fibrosis grades of BA patients, the ADC value could not differentiate fibrosis grades (17). None of the studies compared the diagnostic performance of hepatic ADC value with APRI or spleen size.

The patients of our study were distributed relatively evenly among each fibrosis group, and this study showed that the degree of hepatic fibrosis in neonatal cholestasis and the diagnosis of BA were associated with liver ADC values. In addition, we compared the diagnostic performance of APRI and spleen size in determining significant fibrosis, which showed no significant difference from that of liver ADC values. Overall analysis in this large cohort study confirmed that diffusion parameters have the possibility of non-invasively monitoring hepatic fibrosis and of overcoming sampling error, which is a limitation of conventional biopsy.

In general, BA patients receive the Kasai operation first, but a large number of them develop end-stage liver disease resulting in liver transplantation (25, 26). Hepatic fibrosis is an independent predictor of survival in BA patients. Infants

 https://doi.org/10.3348/kjr.2020.0055

with severe fibrosis had a worse overall survival of the liver regardless of age at the time of the Kasai operation (2). In addition, a higher incidence of bowel perforation or biliary complications after liver transplantation has been reported in patients who have undergone prior Kasai operations (27, 28). A recent meta-analysis demonstrated that a portoenterostomy prior to liver transplantation had a higher risk of postoperative infection (29). Therefore, immediate liver transplantation instead of the Kasai operation as the bridge could lead to better prognosis in some selected patients (30, 31). Diagnosis of the hepatic fibrosis grade through imaging procedures, as performed in this study, can be helpful in predicting prognosis in BA patients and ultimately in determining the treatment plan, even though age was also a significant predictor. Further research is needed on the prognostic value of hepatic fibrosis grading through imaging studies.

Even though γGT alone showed high diagnostic performance for BA in our study, we cannot use this parameter alone in real-world situations. One of the most common causes of neonatal cholestasis is BA, but it accounts for about 25–40% (32). γGT value is generally elevated in neonatal cholestasis, not only in BA but also in Alagille syndrome, progressive familial intrahepatic cholestasis type 3, choledochal cyst with cholangitis, and some cases of alpha-1-antitrypsin deficiency. The primary test for diagnosing neonatal cholestasis is a laboratory test, which detects an increase in γGT following the identification of gross structural abnormalities by US. However, if structural abnormalities are not clear, liver biopsy or genetic study is recommended, rather than liver MRI. Although γGT appears to have a high diagnostic performance for BA in this study, as this study only included patients who underwent liver MRI in consideration of structural abnormalities, this will show different results if we applied it in general infantile jaundice patients.

There are several limitations to this study. Our study is a retrospective study only including patients with liver MRI, even though we considered all consecutive studies. We included patients not only with conjugated but also non-conjugated hyperbilirubinemia who underwent liver MRI. As liver MRI is not recommended for infants with hepatitis, who improve through conservative treatment or without any structural lesions on US at the initial evaluation, there could be selection bias. The second limitation is that we included both ADC values from 3 or 5 b-values, even though we demonstrated no remarkable difference in results between these two groups. There is also a measurement error problem for ADC, even though we demonstrated inter-observer variability and absolute inter-observer difference. Additional studies including intra-observer variability are needed. The third limitation is the lack of evaluation for additional effects on conventional US or MR based diagnoses. In clinical practice, the diagnosis is made through a combination of multiple findings, rather than just one imaging finding. We do not differentiate BA from the choledochal cyst based on DWI finding. However, the high specificity of liver ADC value for diagnosing BA could be one of the helpful findings. Therefore, for practical evaluation, it would be better to assess the diagnostic ability of diffusion parameters in addition to existing findings. In addition, the role of DWI can be interpreted as helping to predict the degree of hepatic fibrosis when the diagnosis is already possible by other findings.

In conclusion, liver ADC and ADC ratio of liver/spleen were significantly lower in BA patients compared with non-BA patients. All analyzed parameters, including APRI, spleen size, hepatic ADC, and the ratio of liver and spleen ADC values, showed a significant correlation with the histologic hepatic fibrosis grade, in spite of considerable overlaps. Especially, AUC values of the parameters ranged between 0.651–0.721 for diagnosing significant hepatic fibrosis (F3–F4). Thus, hepatic diffusion parameters may have limited diagnostic performance to differentiate BA from the non-BA and predict the histologic degree of hepatic fibrosis in neonatal cholestasis patients. The inter-observer variability should be considered and further study for the additional evaluation of these parameters is needed.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

ORCID iDs

Jisoo Kim
https://orcid.org/0000-0002-3481-127X
Hyun Joo Shin
https://orcid.org/0000-0002-7462-2609
Haesung Yoon
https://orcid.org/0000-0003-0581-8656
Seok Joo Han
https://orcid.org/0000-0001-5224-1437
Hong Koh
https://orcid.org/0000-0002-3660-7483

https://doi.org/10.3348/kjr.2020.0055

Myung-Joon Kim
https://orcid.org/0000-0002-4608-0275
Mi-Jung Lee
https://orcid.org/0000-0003-3244-9171

REFERENCES

1. Perlmutter DH, Shepherd RW. Extrahepatic biliary atresia: a disease or a phenotype? *Hepatology* 2002;35:1297-1304
2. Weerasooriya VS, White FV, Shepherd RW. Hepatic fibrosis and survival in biliary atresia. *J Pediatr* 2004;144:123-125
3. Humphrey TM, Stringer MD. Biliary atresia: US diagnosis. *Radiology* 2007;244:845-851
4. Kim YH, Kim MJ, Shin HJ, Yoon H, Han SJ, Koh H, et al. MRI-based decision tree model for diagnosis of biliary atresia. *Eur Radiol* 2018;28:3422-3431
5. Kim WS, Cheon JE, Youn BJ, Yoo SY, Kim WY, Kim IO, et al. Hepatic arterial diameter measured with US: adjunct for US diagnosis of biliary atresia. *Radiology* 2007;245:549-555
6. Lee MS, Kim MJ, Lee MJ, Yoon CS, Han SJ, Oh JT, et al. Biliary atresia: color doppler US findings in neonates and infants. *Radiology* 2009;252:282-289
7. Leschied JR, Dillman JR, Bilhartz J, Heider A, Smith EA, Lopez MJ. Shear wave elastography helps differentiate biliary atresia from other neonatal/infantile liver diseases. *Pediatr Radiol* 2015;45:366-375
8. Zhou L, Shan Q, Tian W, Wang Z, Liang J, Xie X. Ultrasound for the diagnosis of biliary atresia: a meta-analysis. *AJR Am J Roentgenol* 2016;206:W73-W82
9. Han SJ, Kim MJ, Han A, Chung KS, Yoon CS, Kim D, et al. Magnetic resonance cholangiography for the diagnosis of biliary atresia. *J Pediatr Surg* 2002;37:599-604
10. Liu B, Cai J, Xu Y, Peng X, Zheng H, Huang K, et al. Three-dimensional magnetic resonance cholangiopancreatography for the diagnosis of biliary atresia in infants and neonates. *PLoS One* 2014;9:e88268
11. Taouli B, Tolia AJ, Losada M, Babb JS, Chan ES, Bannan MA, et al. Diffusion-weighted MRI for quantification of liver fibrosis: preliminary experience. *AJR Am J Roentgenol* 2007;189:799-806
12. Taouli B, Chouli M, Martin AJ, Qayyum A, Coakley FV, Vilgrain V. Chronic hepatitis: role of diffusion-weighted imaging and diffusion tensor imaging for the diagnosis of liver fibrosis and inflammation. *J Magn Reson Imaging* 2008;28:89-95
13. Lewin M, Poujol-Robert A, Boëlle PY, Wendum D, Lasnier E, Viallon M, et al. Diffusion-weighted magnetic resonance imaging for the assessment of fibrosis in chronic hepatitis C. *Hepatology* 2007;46:658-665
14. Koinuma M, Ohashi I, Hanafusa K, Shibuya H. Apparent diffusion coefficient measurements with diffusion-weighted magnetic resonance imaging for evaluation of hepatic fibrosis. *J Magn Reson Imaging* 2005;22:80-85
15. Mo YH, Jaw FS, Ho MC, Wang YC, Peng SS. Hepatic ADC value correlates with cirrhotic severity of patients with biliary atresia. *Eur J Radiol* 2011;80:e253-e257
16. Peng SS, Jeng YM, Hsu WM, Yang JC, Ho MC. Hepatic ADC map as an adjunct to conventional abdominal MRI to evaluate hepatic fibrotic and clinical cirrhotic severity in biliary atresia patients. *Eur Radiol* 2015;25:2992-3002
17. Liu B, Cai J, Zhu J, Zheng H, Zhang Y, Wang L. Diffusion tensor imaging for evaluating biliary atresia in infants and neonates. *PLoS One* 2016;11:e0168477
18. Leung DH, Khan M, Minard CG, Guffey D, Ramm LE, Clouston AD, et al. Aspartate aminotransferase to platelet ratio and fibrosis-4 as biomarkers in biopsy-validated pediatric cystic fibrosis liver disease. *Hepatology* 2015;62:1576-1583
19. Do RK, Chandarana H, Felker E, Hajdu CH, Babb JS, Kim D, et al. Diagnosis of liver fibrosis and cirrhosis with diffusion-weighted imaging: value of normalized apparent diffusion coefficient using the spleen as reference organ. *AJR Am J Roentgenol* 2010;195:671-676
20. Kim BR, Song JS, Choi EJ, Hwang SB, Hwang HP. Diffusion-weighted imaging of upper abdominal organs acquired with multiple b-value combinations: value of normalization using spleen as the reference organ. *Korean J Radiol* 2018;19:389-396
21. Kim J, Yoon H, Lee MJ, Kim MJ, Han K, Han SJ, et al. Clinical utility of mono-exponential model diffusion weighted imaging using two b-values compared to the bi- or stretched exponential model for the diagnosis of biliary atresia in infant liver MRI. *PLoS One* 2019;14:e0226627
22. Zhang J, Suo S, Liu G, Zhang S, Zhao Z, Xu J, et al. Comparison of monoexponential, biexponential, stretched-exponential, and kurtosis models of diffusion-weighted imaging in differentiation of renal solid masses. *Korean J Radiol* 2019;20:791-800
23. Chow AM, Gao DS, Fan SJ, Qiao Z, Lee FY, Yang J, et al. Liver fibrosis: an intravoxel incoherent motion (IVIM) study. *J Magn Reson Imaging* 2012;36:159-167
24. Seo N, Chung YE, Park YN, Kim E, Hwang J, Kim MJ. Liver fibrosis: stretched exponential model outperforms mono-exponential and bi-exponential models of diffusion-weighted MRI. *Eur Radiol* 2018;28:2812-2822
25. McDiarmid SV, Anand R, Lindblad AS; The SPLIT Research Group. Studies of pediatric liver transplantation: 2002 update. An overview of demographics, indications, timing, and immunosuppressive practices in pediatric liver transplantation in the United States and Canada. *Pediatr Transplant* 2004;8:284-294
26. Shneider BL, Mazariegos GV. Biliary atresia: a transplant perspective. *Liver Transpl* 2007;13:1482-1495
27. Urahashi T, Ihara Y, Sanada Y, Wakiya T, Yamada N, Okada N, et al. Effect of repeat Kasai hepatic portoenterostomy on pediatric live-donor liver graft for biliary atresia. *Exp Clin Transplant* 2013;11:259-263
28. Neto JS, Feier FH, Bierrenbach AL, Toscano CM, Fonseca EA, Pugliese R, et al. Impact of Kasai portoenterostomy on liver

 https://doi.org/10.3348/kjr.2020.0055

transplantation outcomes: a retrospective cohort study of 347 children with biliary atresia. *Liver Transpl* 2015;21:922-927
29. Wang P, Xun P, He K, Cai W. Comparison of liver transplantation outcomes in biliary atresia patients with and without prior portoenterostomy: a meta-analysis. *Dig Liver Dis* 2016;48:347-352
30. Azarow KS, Phillips MJ, Sandler AD, Hagerstrand I, Superina RA. Biliary atresia: should all patients undergo a portoenterostomy? *J Pediatr Surg* 1997;32:168-172; discussion 172-174
31. Superina R. Biliary atresia and liver transplantation: results and thoughts for primary liver transplantation in select patients. *Pediatr Surg Int* 2017;33:1297-1304
32. Fawaz R, Baumann U, Ekong U, Fischler B, Hadzic N, Mack CL, et al. Guideline for the evaluation of cholestatic jaundice in infants: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2017;64:154-168

https://doi.org/10.3348/kjr.2020.0055