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Title Page:

Liver-spleen volume ratio as a predictor of native liver survival in patients with biliary atresia

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Abbreviations: ALT alanine aminotransferase, AUC area under the curve, AST aspartate aminotransferase, APRi aspartate aminotransferase–platelet ratio index, BA biliary atresia, ChE cholinesterase, CT computed tomography, GGT γ-glutamyl transferase, IQR interquartile range, KP Kasai portoenterostomy, LSR liver-spleen volume ratio, LT liver transplantation, LV liver volume, PH portal hypertension, PBC primary biliary cirrhosis, PT-INR prothrombin time–international normalized ratio, ROC receiver operating characteristic, SV spleen volume, SLV standard liver volume, SSV standard spleen, T-Bil total bilirubin, TC total cholesterol

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TRANSPLANTATION PROCEEDINGS

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Abstract

Purpose: The appropriate timing of liver transplantation (LT) in patients with BA who had survived with their native livers until adolescence remains controversial. Liver–spleen volume ratio (LSR) has been reported to be efficacious in predicting the prognosis of chronic liver disease. We studied whether LSR could predict long-term native liver prognosis and be one of the indications for LT in patients with BA.

Methods: Patients with BA who survived with their native liver until age 15 years were included. These patients were classified into two groups. The unfavorable prognosis group included patients who underwent or awaiting LT or developed complications such as refractory cholangitis, gastrointestinal bleeding due to esophagogastric or intestinal varices. The favorable prognosis group included patients who survived with their native liver without such complications. We compared the two groups in terms of LSR, hematological data, and histological data.

Results: Of 19 patients, 8 were in the unfavorable group and 11 were in the favorable prognosis group. LSR was significantly lower in the unfavorable prognosis group (p=0.009). Receiver operating characteristics (ROC) curve analysis showed the area under curve of LSR was 0.891, which was higher than those of liver fibrosis markers. The optimal LSR cut-off value for predicting poor native liver prognosis was 1.97 with a sensitivity of 75.0% and specificity of 87.5%.

Conclusions: LSR reflects splenomegaly and liver atrophy. LSR might be a reliable predictor of native liver prognosis and could guide decisions about LT in patients with BA.

Liver-spleen volume ratio as a predictor of native liver survival in patients with biliary atresia

1. Introduction

Patients with biliary atresia (BA) have progressive liver damage, even after successful Kasai portoenterostomy (KP) [1-3]. Approximately 40–50% of patients with BA can survive with their native liver until 10 years of age [4,5]. However, many of these patients have progressive liver insufficiency and severe complications of BA; they ultimately need liver transplantation (LT) in adolescence or adulthood [1,6-8]. Patients with BA who need LT usually living-donor LT because of the scarcity of deceased donors in Japan. Patients who undergo LT at the age of 12 years or higher have been reported to have worse prognosis than patients who undergo LT when they were younger than 12 years [4,9,10]. The appropriate timing of LT in patients with BA who have survived with their native liver until adolescence remains controversial [11,12].

Portal hypertension (PH) is a major complication in patients with BA [13]. PH is associated with progressive liver fibrosis [14]. Symptoms of PH include splenomegaly, thrombocytopenia, and ascites [15]. Recently, quantitative evaluation of liver and spleen size using abdominal computed tomography (CT) and volumetric analysis has become possible. In adult patients with liver diseases such as primary biliary cirrhosis (PBC) and chronic viral hepatitis, liver-spleen volume ratio (LSR) has been reported to be efficacious for predicting the severity and prognosis of liver failure [16,17]. LSR could be a predictor of native liver prognosis in patients with BA, but there have been no previous reports about this topic. We hypothesized that LSR could predict long-term native liver prognosis and could therefore guide decisions about LT in patients with BA. We studied patients with BA who have survived for more than 15 years with their native liver.

2. Methods

This study included 19 patients with BA who were born between 1989 and 2006 and survived with their native liver until 15 years of age. Their medical records and laboratory findings were retrospectively reviewed. They were classified into two groups: unfavorable prognosis and favorable prognosis. Patients who underwent LT, were awaiting LT, or developed complications such as refractory cholangitis, gastrointestinal bleeding due to esophagogastric or intestinal varices, hepatopulmonary syndrome, or portopulmonary hypertension up to December 2021 were classified into the unfavorable prognosis group. Patients who survived with their native liver and did not develop such complications up to December 2021 were classified into the favorable prognosis group. This study was approved by our hospital institutional review board (approval number 15252). The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. All patients or their guardians gave their informed consent prior to their inclusion in this study.

We examined the following laboratory data at 10 years of age: aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), total bilirubin (T-Bil), serum albumin, bile acid, total cholesterol (TC), cholinesterase (ChE), platelet count, and prothrombin time–international normalized ratio (PT-INR). We evaluated the aspartate aminotransferase–platelet ratio index (APRi) and FIB-4 index as markers of fibrosis. Child-Pugh score and liver fibrosis (METAVIR score) based on percutaneous liver biopsy findings around 10 years of age were also assessed.

Volumetric data for the liver and spleen from abdominal CT around 10 years of age were evaluated with the Synapse Vincent volume analyzer (Fujifilm Medical, Tokyo, Japan). Liver area was extracted automatically. However, in pediatric patients, the automatic extraction often contains surrounding organs such as the intestines and spleen, which needed to be corrected manually. Spleen area was traced manually. Liver volume (LV, mL) and spleen volume (SV, mL) were calculated based on the extracted areas. To eliminate the effect of body size, liver volume (LV)/standard liver volume (SLV), spleen volume (SV)/standard spleen volume (SSV), and liver-spleen volume ratio (SLR) were calculated. BSA was calculated using the following formula: BSA = (body weight [kg])$^{0.425}$×(height [cm])$^{0.725}$×0.007184 [18]. SLV was calculated using the Urata formula [19]: SLV = 706.2× BSA [m^2] + 2.4. SSV was calculated using the following formula: SSV = 0.7+(4.6× body weight [kg]) [20]. LSR was calculated as LV/SV.

Continuous variables were expressed as medians [interquartile range (IQR)] and analyzed using the nonparametric Wilcoxon test. Categorical variables were analyzed using Pearson's chi-square test. A difference was considered significant when $p < 0.05$. We used receiver operating characteristic (ROC) analysis to identify the cutoff point with the highest accuracy for predicting unfavorable outcome. We defined the cutoff value as the value with the highest Youden index or the value with the highest specificity if there were multiple values with the same highest Youden index. Statistical analyses were performed with JMP Pro 16 software (SAS Institute, Cary, NC, USA).

3. Results

Characteristics of the study patients

Demographic characteristics of the study patients are summarized in Table 1. Among the 19 patients, 11 patients were classified into the favorable prognosis group and 8 patients were classified into the unfavorable prognosis group. Details about complications of BA among patients in the unfavorable prognosis group are shown in Table 2.

Patient age, sex, and age at KP were similar between the groups. Laboratory data and histological findings from percutaneous biopsy at 10 years of age in each group are shown in Table 1. Platelet count, bile acid levels, and PT-INR were significantly different between the groups (*p*=0.039, 0.029, and 0.028, respectively). T-Bil, AST, ALT, GGT, TC, and ChE levels were similar between the groups. Regarding liver fibrosis markers, APRi and FIB-4 index were significantly higher in the unfavorable prognosis group (*p*=0.012 and 0.006, respectively). The groups had similar Child-Pugh score, METAVIR scores for liver fibrosis based on percutaneous liver biopsy findings of the two groups were similar.

Analysis of volumetric data

Fig. 1 shows the volumetric data for the liver and spleen by group. Abdominal CT was performed on 16 patients (8 in each group). Median age at CT was similar: 8.8 years [5.8–17.5 years] in the favorable prognosis group and 10.8 years [10.0 –11.8 years] in the unfavorable prognosis group. The two groups had similar LV/SLV (favorable prognosis group, 1.08 [0.94–1.15]; unfavorable prognosis group, 1.06 [0.97–1.20]). SV/SSV was significantly higher in the unfavorable prognosis group (favorable group, 1.44 [0.85–2.79]; unfavorable prognosis group, 4.01 [2.24–5.81]; *p*=0.016). LSR was significantly lower in the unfavorable group (favorable prognosis group, 4.13 [2.15–5.16]; unfavorable prognosis group, 1.57 [1.01–2.11]; *p*=0.009).

ROC analysis

The ROC curves for LSR, SV/SSV, APRi, and FIB-4 index in predicting poor native liver outcome are shown in Fig. 2. Area under the curve (AUC) for LSR, SV/SSV, APRi, and FIB-4 index was 0.891, 0.859, 0.847, and 0.875, respectively. The ROC curve for LSR had the highest AUC among these markers. The optimal cutoff LSR value for predicting unfavorable outcome was 1.97, with sensitivity of 75.0% and specificity of 87.5%. The positive predictive value was 85.7% and the negative predictive value was 77.8%. The cutoff value, sensitivity, and specificity of SV/SSV, APRi, and FIB-4 index are shown in Table 3.

4. Discussion

Deciding on the appropriate timing of LT and referral to a transplant center is difficult for patients with BA and long-term survival with their native liver because of the slow, latent progression of liver damage and complications [11,12]. Age at KPE, BA type, and presence of cholangitis have been reported as short-term prognostic factors in patients with BA after KPE [11]. Pediatric end-stage liver disease (PELD) score can be used as a severity index to predict the need for LT in patients with BA [21]. However, these short-term prognostic factors and PELD score cannot predict long-term native liver prognosis and future need for LT.

Splenomegaly is a common complication of BA. It reflects portal hypertension caused by liver fibrosis. The severity of splenomegaly reflects the progression of liver fibrosis. In patients with BA, hepatomegaly occurs first. However, it has been reported that patients in of their SLV calculated based on their height and weight [22,23]. LSR reflects splenomegaly and liver atrophy; it may guide decisions about LT in patients with BA.

To identify whether LSR could be a good predictor of native liver prognosis in patients with BA, we studied long-term outcomes of patients who had survived with their native liver for more than 15 years and underwent volumetric analysis of the liver and spleen. In this study, we found that the favorable and unfavorable prognosis groups had significantly different LSRs. LSR had higher AUC than SV/SSV, APRi, and FIB-4 index. LSR had good specificity at the cutoff value of 1.97. In a previous study, Murata et al. [16] reported that the high LSR group had a significantly higher survival rate among patients with PBC and that LSR could identify patients with asymptomatic PBC who subsequently develop symptoms. The LSR cutoff value in their study was 6.5. Huang et al. [24] studied adult patients who underwent partial hepatectomy for liver tumors. Most patients had chronic hepatitis B and hepatocellular carcinoma. They reported that LSR is negatively correlated with the degree of chronic liver disease and that low LSR is associated with post-hepatectomy complications and liver failure. The LSR cutoff value in their study was 3.22. In the current study, LSR values in patients with BA were lower than values in patients from previous reports; the optimal cutoff value in the current study was 1.97. Since LV was similar between the groups and this result was consistent with previous reports [16,17], splenomegaly in patients with BA might be more severe than in patients with PBC or chronic hepatitis.

In our analysis, there were significant differences in some hematological parameters such as platelet count, PT-INR, and bile acid levels between the groups. However, these hematological parameters tend to vary due to infection and other factors. We thought that these hematological data alone could not be indications for LT in patients with BA. Instead, more static and stable values parameters are needed. Since splenomegaly and liver atrophy progress gradually, LSR does not fluctuate. In this respect, LSR might be advantageous for predicting the long-term prognosis of the native liver.

This study has some limitations. This study was a retrospective, single-center analysis. Therefore, the number of patients in each group was small. The timing of CT differed among patients and might have been affected by their clinical condition. Furthermore, CT slice thickness and image quality might have been affected by the time period in which examinations were performed. Prospective multi-institutional studies are needed to confirm the true efficacy of LSR as a predictor of long-term native liver prognosis in patients with BA.

In conclusion, LSR is strongly correlated with native liver prognosis. LSR, which reflects splenomegaly and liver atrophy, might be an indication for LT in patients with BA.

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Tables

	Favorable prognosis group (n=11)	Unfavorable prognosis group (n=8)	*p* value
Age, years	24.2 (15.7-31.7)	23.2 (15.2-32.2)	0.804
Sex M/F	4/7	2/6	0.600
Age of KPE, days	69 [54-77]	59 [35-78]	0.591
Hematological data			
AST, U/l	41 [27-63]	59 [44-106]	0.173
ALT, U/l	51 [32-72]	71 [39-112]	0.341
GGTP, U/l	52 [17-221]	163 [104-305]	0.173
Total Bilirubin, g/dl	0.6 [0.5-0.8]	1.2 [0.5-1.9]	0.170
Platelet count, $10^3/\mu l$	163 [91-235]	86 [65-123]	0.039
Albumin, g/dl	4.3 [4.1-4.3]	4.0 [3.8-4.4]	0.104
Total Cholesterol, g/dl	178 [164-219]	164 [153-296]	0.680
Bile Acid, g/dl	17.2 [10.2-111.2]	58.3 [19.7-187.2]	0.029
ChE, IU/l	237 [217-339]	221 [150-276]	0.364
PT-INR	1.10 [1.09-1.15]	1.16 [1.13-1.21]	0.028
Fibrosis and liver failure marker			
APRI	0.88 [0.40-1.36]	1.84 [1.12-3.39]	0.012

FIB-4 index	0.52 [0.22-0.72]	0.97 [0.71-1.34]	0.006
Child-Pugh score	5 [5-5]	5 [5-5.75]	0.088
Histological findings			
METAVIR score number (%)			
F0	5 (45)	3 (38)	
F1	3 (27)	2 (25)	0.827
F2	1 (9)	1 (13)	
F3	1 (9)	1 (13)	
F4	0	1 (13)	

Data were expressed as median with ranges. M: male, F: female, KP: Kasai portoenterostomy, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ChE: cholinesterase, PT-INR: prothrombin time-international normalized ratio, APRI: AST-platelet ratio index

Table 1. Patient demographics and laboratory and histological data

Case	Sex	Age, years	Age of CT, years	LSR	Current condition
1	F	15.3	11.3	1.75	NLS, though suffering from esophageal varix requiring EIS
2	F	20.0	9.9	1.11	NLS, though suffering from esophageal varix requiring EVL
3	F	22.7	11	1.39	NLS, though suffering from refractory cholangitis and cirrhosis
4	M	22.8	7.8	1.97	NLS, though suffering from gastrointestinal bleeding and portal vein thrombosis
5	F	23.6	10.2	3.56	NLS, though suffering from refractory cholangitis, gastrointestinal bleeding, and cirrhosis
6	M	29.9	14.9	1.06	LDLT at age 20 with indication for refractory cholangitis

7	F	30.8	10.6	2.15	NLS, though suffering from refractory cholangitis and port-pulmonary hypertension
8	F	32.2	11.9	0.98	LDLT at age 18 with indication for liver failure

M: male, F: female, LSR: liver-spleen volume ratio, NLS: native liver survival, EIS: endoscopic injection sclerotherapy, EVL: endoscopic variceal ligation, LDLT: living-donor liver transplantation

Table 2. Patient characteristics and current complications in the unfavorable prognosis group

	Cut-off value	Specificity	Sensitivity	AUC
LSR	**1.97**	**0.875**	**0.75**	**0.891**
SV/SSV	1.72	0.625	1.00	0.859
APRi	1.73	1.00	0.625	0.847
FIB-4	0.52	0.636	1.00	0.875

Data were expressed as median with ranges. LSR: liver-spleen volume ratio, SV/SSV: spleen volume/ standard spleen volume, APRi: aspartate aminotransferase-platelet ratio index

Table 3. Volumetric analysis of liver and spleen

Figures

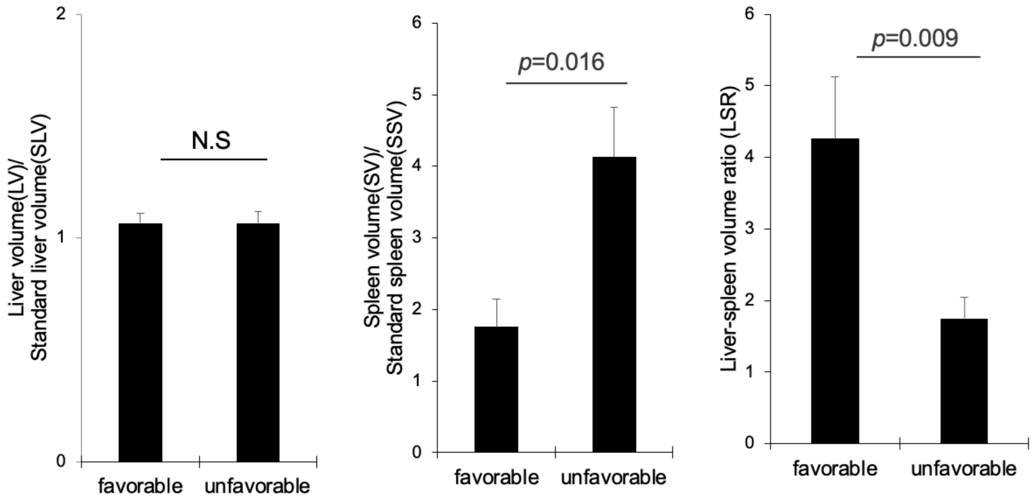

Figure 1. Liver volume/ standard liver volume (LV/SLV), spleen volume/ standard spleen volume (SV/SSV) and liver-spleen volume ratio (LSR) in each group

a: LV/SLV, b:S V/SSV, c: LSR. Data are shown by mean and standard error. N.S: not significant

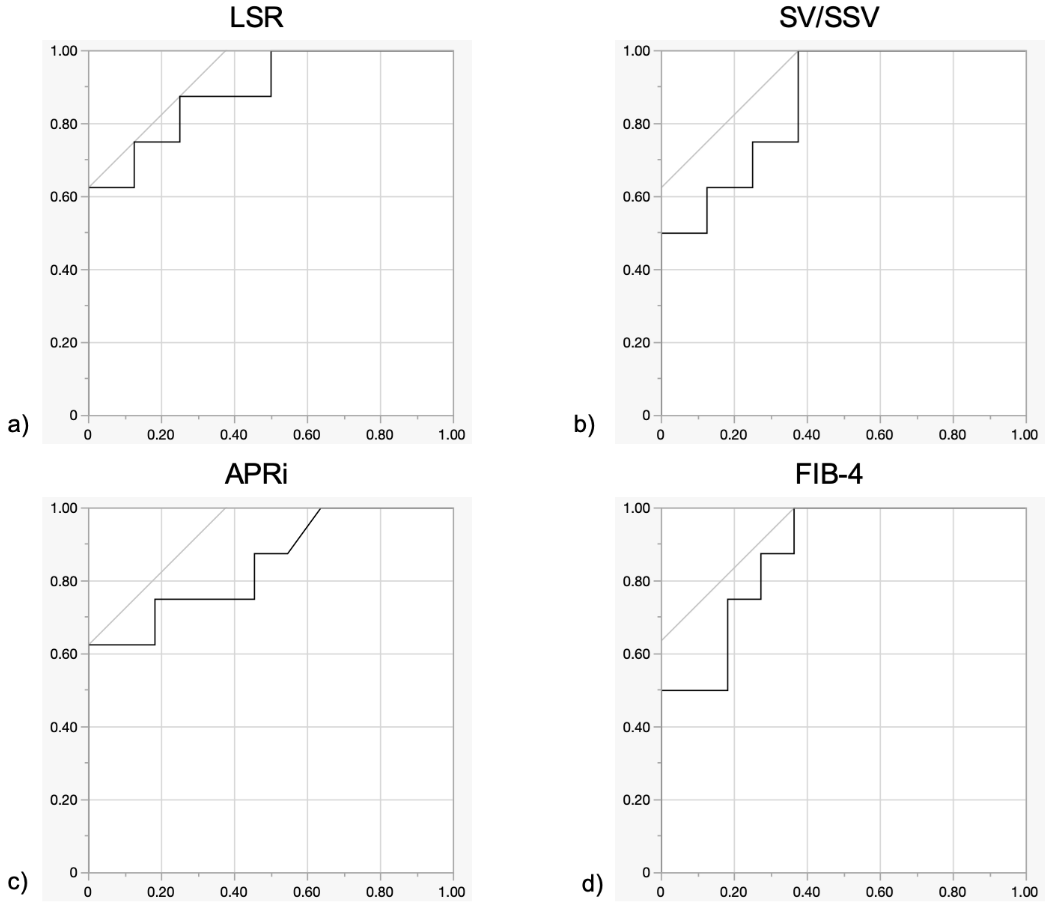

Figure 2. Receiver operating characteristic (ROC) curve of LSR, SV/SSV, aspartate aminotransferase- platelet ratio index (APRi) and FIB-4

a: LSR, b: SV/SSV, c: APRi, d: FIB-4. The unfavorable group was regarded as positive.