liver transplantation) was assessed using serial data collection. The prognosis at 1 year of age was investigated as either death before liver transplantation, receiving liver transplantation before 1 year of age, or surviving with their native liver. Among the patients surviving with their native liver at 1 year of age, the earliest blood test results after reaching 1 year of age were collected from the medical records; if transfusion had been performed or cholangitis had occurred before the blood test was performed, the data at >1 month after transfusion or cholangitis were selected. The BALF score that had been developed to predict liver fibrosis stage in BA patients aged ≥1 year was then used to evaluate the status of the native liver. The BALF score was calculated using the following equation:[4]

BALF score = $7.196+1.438\times \mathrm{Log_e}$ [TB (mg/dl)]$+0.434\times \mathrm{Log_e}$ [GGT (IU/l)] $- 3.491\times \mathrm{Log_e}$ [albumin (g/dl)]$-0.670\times \mathrm{Log_e}$ [age (years)].

Statistical analysis. The categorical and ordinal data are presented as frequencies and were statistically compared using the Fisher exact test. The continuous data are presented as medians (ranges) and were statistically compared using the Mann–Whitney *U*-test. Correlations between the ordinal and/or continuous data were assessed by the Spearman correlation coefficient (r). For logistic regression analyses, the P value of each independent variable was determined using the Wald χ^2-value (Wald), which was calculated by squaring the ratio of the regression coefficient divided by its standard error. For receiver-operating characteristic curve analyses, areas under the curve (AUCs) were calculated; an AUC of 1.0 indicates a test of perfect diagnostic power, whereas an AUC of 0.5 indicates no diagnostic power. Differences between AUCs were examined using the DeLong test. The cutoff values were determined as the points that showed high sensitivity and specificity in a balanced manner. P values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS 22.0 software (IBM SPSS, Chicago, IL, USA) and R 3.1.0 software (The R Foundation for Statistical Computing Vienna, Austria; http://www.R-project.org/).

RESULTS

Patient characteristics. We excluded two and three patients with BA splenic malformation syndrome from the development and validation cohorts, respectively. No patient had a history of splenectomy or partial splenic embolization before data collection. One histology examination using percutaneous needle biopsy obtained after the initial surgery from a development cohort patient was inappropriate for evaluation and was excluded from the study. After exclusions, the development cohort included 58 patients and 73 liver histology examinations, and the validation cohort included 92 patients and 117 liver histology examinations. The timing of the patients' participation and tissue sampling in the development and validation cohorts is summarized in Figure 1. Patient characteristics according to the development and validation cohorts are shown in Table 1. Significant differences between the development and validation cohorts were found in the frequencies of disease type ($P=0.02$) and initial bile drainage surgical procedure ($P=0.03$): the validation cohort included more patients with type 3 disease requiring hepatoportoenterostomy. Significant differences regarding liver transplantation before 1 year of age were also found: the validation cohort included fewer patients received primary liver transplantation, and more patients received liver transplantation after bile drainage surgery than in the development cohort ($P<0.001$). Days of age at the time of liver transplantation were significantly lower in the validation cohort than in the development cohort ($P=0.009$).

Liver histology and blood test results. In the development cohort, 10 (13.7%) histology examinations showed a liver fibrosis stage of F1, whereas 19 (26.0%) showed a stage of F2, 20 (27.4%) showed a stage of F3, and 24 (32.9%) showed a stage of F4. In the validation cohort, eight (6.8%) histology examinations showed a stage of F1, 23 (19.7%) showed a stage of F2, 27 (23.1%) showed a stage of F3, and 59 (50.4%) showed a stage of F4. Liver histology examinations and the corresponding blood test results from the development and validation cohorts according to the biopsy examination or liver transplantation are presented in Table 2. At the time of biopsy examinations, serum direct bilirubin levels were significantly lower and serum albumin levels were significantly higher in the development cohort than in the validation cohort ($P=0.03$ and $P<0.001$, respectively), because the development cohort involved a greater number of needle biopsy examinations, which were performed for patients with a better surgical response than the validation cohort ($P=0.002$). At the time of liver transplantation, blood test results were significantly worse in the development cohort than in the validation cohort, indicating different timing of liver transplant surgery between the cohorts.

Determination of the iBALF score equation. The results of the ordered logistic regression analyses in the development cohort are shown in Table 3. In the univariate analyses, natural logarithms of the blood platelet counts provided the highest significance (Wald = 31.461, $P<0.001$). In the multivariate analysis, the second significant independent variable was identified as natural logarithms of the serum TB levels using a forward selection method. As the third independent variable, natural logarithms of the prothrombin time-international normalized ratios and days of age were significant; we selected the days of age, because the distribution of the iBALF score approached the distribution of the previously reported BALF score. Finally, natural logarithms of the serum TB levels, blood platelet counts, and days of age at examination were selected as significant independent variables. The iBALF score equation was determined as:

iBALF score = $8+1.185\times \mathrm{Log_e}$ [TB (mg/dl)] $- 1.882\times \mathrm{Log_e}$ [platelet count (10^9/l)]$+1.093\times \mathrm{Log_e}$ [age (days)].

iBALF scores according to the liver fibrosis stages. Figure 2 shows the boxplots for the iBALF score and APRI vs. the histological fibrosis stages in the development and validation cohorts. The iBALF score was more strongly correlated with the histological fibrosis stage than the APRI in both cohorts ($r=0.80$ and 0.73 in the development and validation cohorts, respectively; $P<0.001$). Between the

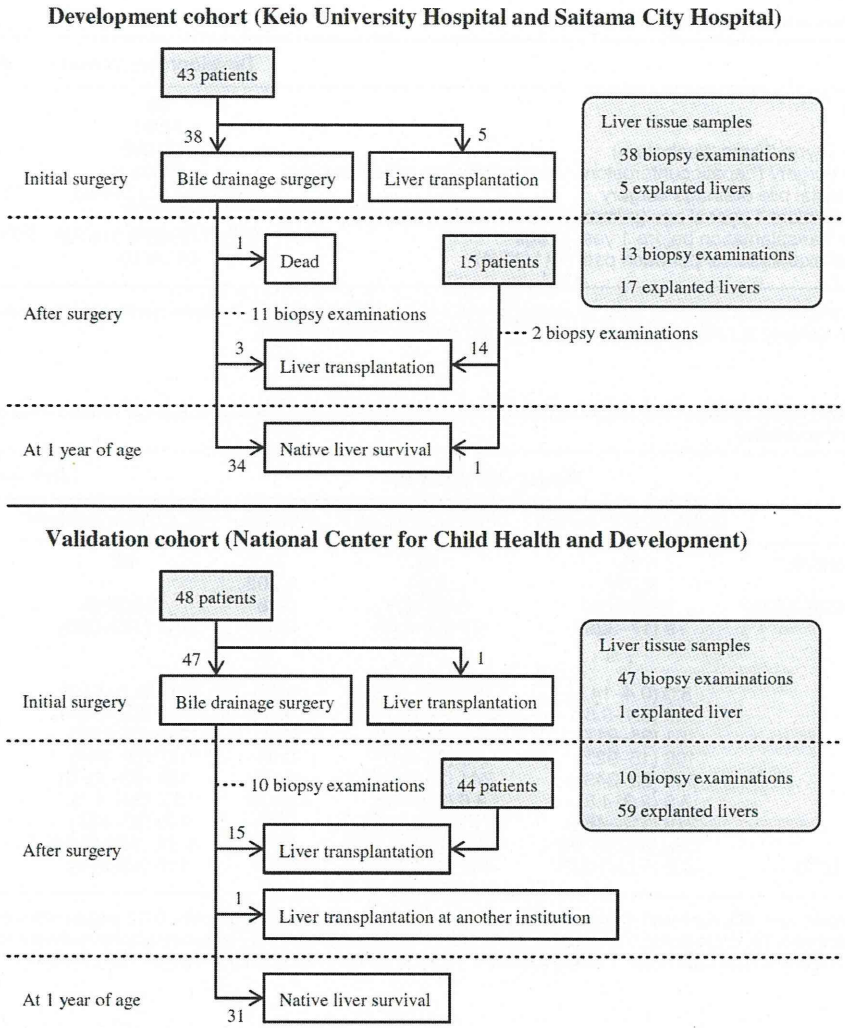

Figure 1 Timing of the patients' participation and tissue sampling in the development and validation cohorts. The number was counted after excluding two and three patients with biliary atresia splenic malformation syndrome from the development and validation cohorts, respectively.

cohorts, the iBALF score in the histology examinations displaying F4 showed a significant difference ($P=0.006$); the median iBALF score values were 8.08 (range, 4.75–10.71) in the development cohort and 6.84 (range, 2.88–9.69) in the validation cohort. No significant difference was found in the other histological fibrosis stage groups.

Diagnostic power of the iBALF score. Figure 3 shows the receiver-operating characteristic curves of the iBALF score for diagnosing each fibrosis stage, compared with the APRI. In the development cohort, the AUCs of the iBALF score were 0.84 for a fibrosis stage ≥F2, 0.91 for ≥F3, and 0.96 for F4 ($P<0.001$). In the validation cohort, the AUCs of the iBALF score were 0.86 for ≥F2, 0.90 for ≥F3, and 0.89 for F4 ($P<0.001$); the diagnostic power for F4 fibrosis appeared to be worse than in the development cohort. The AUCs of the iBALF score were significantly greater than those of the APRI in diagnosing ≥F2 ($P=0.03$) and F4 ($P=0.01$) in the development cohort, indicating more favorable diagnostic power than the APRI; no significant difference was found in diagnosing ≥F3 in the development cohort and in diagnosing ≥F2, ≥F3, and F4 in the validation cohort.

Cutoff value and diagnostic accuracy of the iBALF score. The cutoff values and diagnostic accuracies of the iBALF score for predicting histological fibrosis stages are shown in Table 4. The cutoff values of the development cohort were 3.00 for a fibrosis stage ≥F2, 3.99 for ≥F3, and 5.75 for F4, which were brought close to the previously reported cutoff values of the BALF score by adjusting the constant of the iBALF score equation. The diagnostic accuracies of the iBALF score for each fibrosis stage were acceptable: 78.1–93.2% in the development cohort and 80.3–82.9% in the validation cohort. The validation cohort appeared to have lower diagnostic accuracy for F4 diagnosis than the development cohort (82.0% vs. 93.2%, respectively).

Table 1 Patient characteristics of the development and validation cohorts

	Development cohort	Validation cohort	*P*-value
Number of patients	58	92	
Sex (male/female)	25/33	28/64	0.12
Disease type (type 1/type 2/type 3/unknown)	9/2/45/2	6/0/85/1	0.02
Initial bile drainage surgery (hepaticoenterostomy/hepatoportoenterostomy/none)	3/50/5	2/89/1	0.03
Days of age at the initial bile drainage surgery	74 (17–151) ($n=53$)	73 (27–195) ($n=91$)	0.28
Liver transplantation before 1 year of age (primary/after bile drainage surgery/none)	5/17/36	1/60/31	<0.001
Days of age at liver transplantation before 1 year of age	290 (179–356) ($n=22$)	233 (126–346) ($n=61$)	0.009
Number of histology examinations per each patient (1/2/3/4)	46/10/1/1	69/21/2/0	0.59

The categorical and ordinal data are presented as the number of patients and were statistically compared using the Fisher exact test. The continuous data are presented as medians (ranges) and were statistically compared using the Mann–Whitney *U*-test.

Table 2 Comparisons of the liver histology examinations and corresponding blood test results between the development and validation cohorts according to the biopsy examination or liver transplantation

	Biopsy examination			Liver transplantation		
	Development cohort	Validation cohort	*P*-value	Development cohort	Validation cohort	*P*-value
Number of examinations	51	57		22	60	
Wedge/needle	41/10	56/1	0.002			
Fibrosis stage (F1/F2/F3/F4)	10/19/18/4	8/23/19/7	0.78	0/0/2/20	0/0/8/52	0.72
Days of age	79 (17–328)	77 (27–345)	0.96	290 (179–356)	232 (126–346)	0.01
Blood test results						
TB (mg/dl)	8.0 (0.4–14.5)	8.3 (0.6–25.8)	0.06	20.6 (5.5–47.7)	12.1 (1.2–33.9)	<0.001
DB (mg/dl)	4.9 (0.1–9.5)	5.6 (0.3–17.6)	0.03	14.5 (3.2–34.4)	8.7 (0.6–22.1)	0.001
AST (IU/l)	161 (35–917)	150 (44–473)	0.77	269 (55–560)	162 (61–659)	0.007
ALT (IU/l)	109 (15–922)	110 (24–447)	0.98	127 (30–240)	110 (29–426)	0.44
GGT (IU/l)	582 (62–3434)	741 (36–2610)	0.15	124 (50–1010)	253 (20–1452)	0.28
Albumin (g/dl)	3.9 (2.3–4.8)	3.6 (2.6–4.3)	<0.001	3.2 (2.2–4.1)	3.0 (1.9–4.2)	0.72
ChE (IU/l)	279 (116–461)	270 (128–395)	0.86	140 (53–334)	143 (57–367)	0.73
PT-INR	1.03 (0.84–1.48)	1.00 (0.81–1.91)	0.19	1.41 (0.95–2.54)	1.28 (0.95–2.18)	0.047
Platelet count ($\times 10^9$/l)	448 (172–1092)	444 (111–982)	0.93	118 (48–276)	196 (34–760)	0.02

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ChE, cholinesterase; DB, direct bilirubin; GGT, γ-glutamyltransferase; PT-INR, prothrombin time-international normalized ratio; TB, total bilirubin. The categorical and ordinal data are presented as the number of examinations and were statistically compared using the Fisher exact test. The continuous data are presented as medians (ranges) and were statistically compared using the Mann–Whitney *U*-test.

Prognosis at 1 year of age according to the iBALF score at the initial surgery. Figure 4 shows the relationships between the iBALF score at the initial surgery and outcomes. The outcomes are presented as the need for liver transplantation before 1 year of age or as the BALF score at 1 year of age as a noninvasive liver fibrosis marker. None of the nine patients with an iBALF score >6 survived with their native liver: five patients in the development cohort underwent liver transplantation as the initial surgery, and four patients in the validation cohort required liver transplantation before 1 year of age. Among the patients who survived with their native liver at 1 year of age, the correlations between the iBALF score at the initial surgery and the BALF score at 1 year of age were not significant in the development ($n=34$, $r=0.19$, $P=0.29$) or validation ($n=31$, $r=0.04$, $P=0.81$) cohorts.

DISCUSSION

The BALF score was the first noninvasive fibrosis marker developed specifically for postsurgical BA patients aged ≥1 year; herein, the iBALF score was additionally developed for BA patients aged <1 year. Although the BALF score calculated for patients aged <1 year was previously reported to show apparently high values regardless of the liver fibrosis stages,[4] the iBALF score showed strong correlations with the histological liver fibrosis stages and good diagnostic powers for each fibrosis stage in the development and validation cohorts. The differences between the BALF and iBALF scores in patients aged <1 year were mainly derived from serum GGT level (included in the BALF score) and age (included in both scores), both of which had reverse coefficients in the logistic regression analyses for predicting liver fibrosis stages. Serum GGT elevation was reported to be associated with advanced fibrosis in patients aged ≥1 year,[4] but the current study indicated that serum GGT elevation was associated with less-advanced fibrosis in patients aged <1 year. The effects of age on liver fibrosis progression were positive in patients aged <1 year and negative in patients aged ≥1 year.[4] Although different equations were needed, we adjusted the iBALF score to have similar values for each fibrosis stage as the previously reported BALF score values in patients aged ≥1 year, this will aid in more easily understanding the iBALF scores in comparison with BALF scores, regardless of the age of the child. We suggest that the iBALF and BALF scores can monitor liver fibrosis in a similar manner before and after 1 year of age, respectively.

Table 3 Ordered logistic regression analyses for predicting liver fibrosis stages in the development cohort

Variable	Coefficient (95% confidence interval)	Standard error	Wald	*P*-value
Univariate analysis				
Log_e (platelet count ($\times 10^9$/l))	−2.859 (−3.858 to −1.860)	0.510	31.461	<0.001
Log_e (age (days))	1.812 (1.119–2.506)	0.354	26.213	<0.001
Log_e (TB (mg/dl))	1.517 (0.891–2.142)	0.319	22.565	<0.001
Log_e (albumin (g/dl))	−7.950 (−11.270 to −4.631)	1.694	22.038	<0.001
Log_e (PT-INR)	7.126 (4.125–10.127)	1.531	21.662	<0.001
Log_e (ChE (IU/l))	−2.841 (−4.078 to −1.604)	0.631	20.272	<0.001
Log_e (DB (mg/dl))	1.269 (0.706–1.832)	0.287	19.534	<0.001
Log_e (GGT (IU/l))	−0.926 (−1.398 to −0.454)	0.241	14.772	<0.001
Log_e (AST (IU/l))	0.924 (0.235–1.612)	0.351	6.920	0.009
Log_e (ALT (IU/l))	0.278 (−0.312–0.868)	0.301	0.852	0.36
Multivariate analysis				
Log_e (TB (mg/dl))	1.185 (0.574–1.796)	0.312	14.452	<0.001
Log_e (platelet count ($\times 10^9$/l))	−1.882 (−3.052 to −0.712)	0.597	9.935	0.002
Log_e (age (days))	1.093 (0.232–1.955)	0.439	6.190	0.01

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ChE, cholinesterase; DB, direct bilirubin; GGT, γ-glutamyltransferase; PT-INR, prothrombin time-international normalized ratio; TB, total bilirubin.

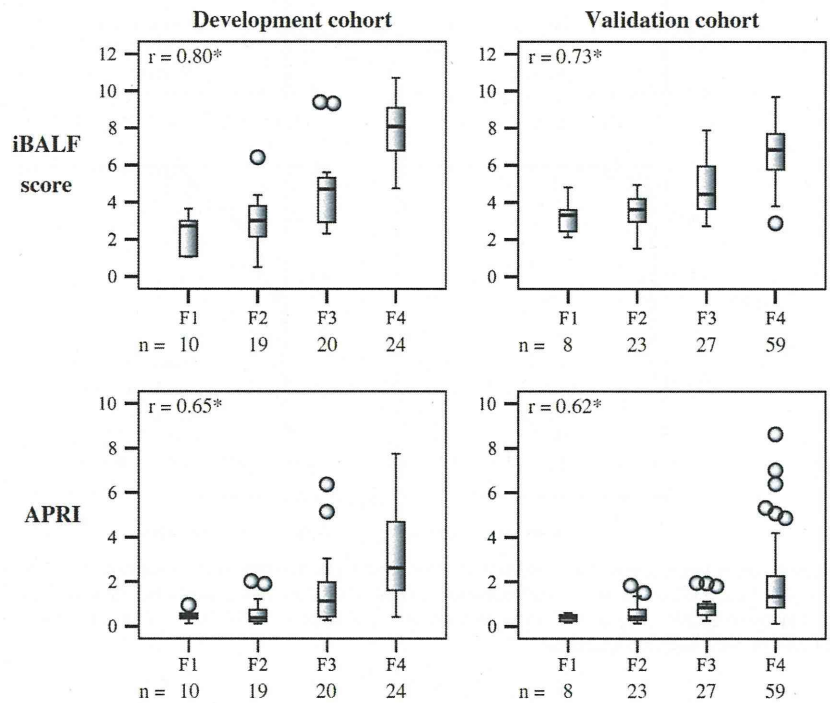

Figure 2 Values of the infant biliary atresia liver fibrosis (iBALF) score and aspartate aminotransferase-to-platelet ratio index (APRI) according to the histological fibrosis stages. Boxplots show the median values with the interquartile ranges, and error bars indicate the smallest and the largest values within 1.5 box-lengths of the upper and the lower quartiles. Circles represent the individual points for outliers. Correlations between the markers and the fibrosis stages were evaluated using the Spearman correlation coefficient (*r*); **P*<0.001.

For infants with BA at presentation, two types of surgical procedure could be chosen—bile drainage surgery or liver transplantation. There were two reports regarding effects on outcomes after liver transplantation comparing early failure of hepatoportoenterostomy, which was defined as the need for liver transplantation within the first year of life, and primary liver transplantation. Alexopoulos *et al.*[10] described that early failure of hepatoportoenterostomy adversely affected patient and graft survival rates. Neto *et al.*[11] reported that early failure of hepatoportoenterostomy had no effect on patient and graft survival, that late failure of hepatoportoenterostomy had a protective effect compared with primary liver transplantation, and that previous hepatoportoenterostomy increased biliary complications and bowel perforations after liver transplantation. Thus, it is important to know which patients can benefit from bile drainage surgery at presentation. In this study, we attempted to reveal the association between the iBALF score at the initial surgery and prognosis using the BALF score at

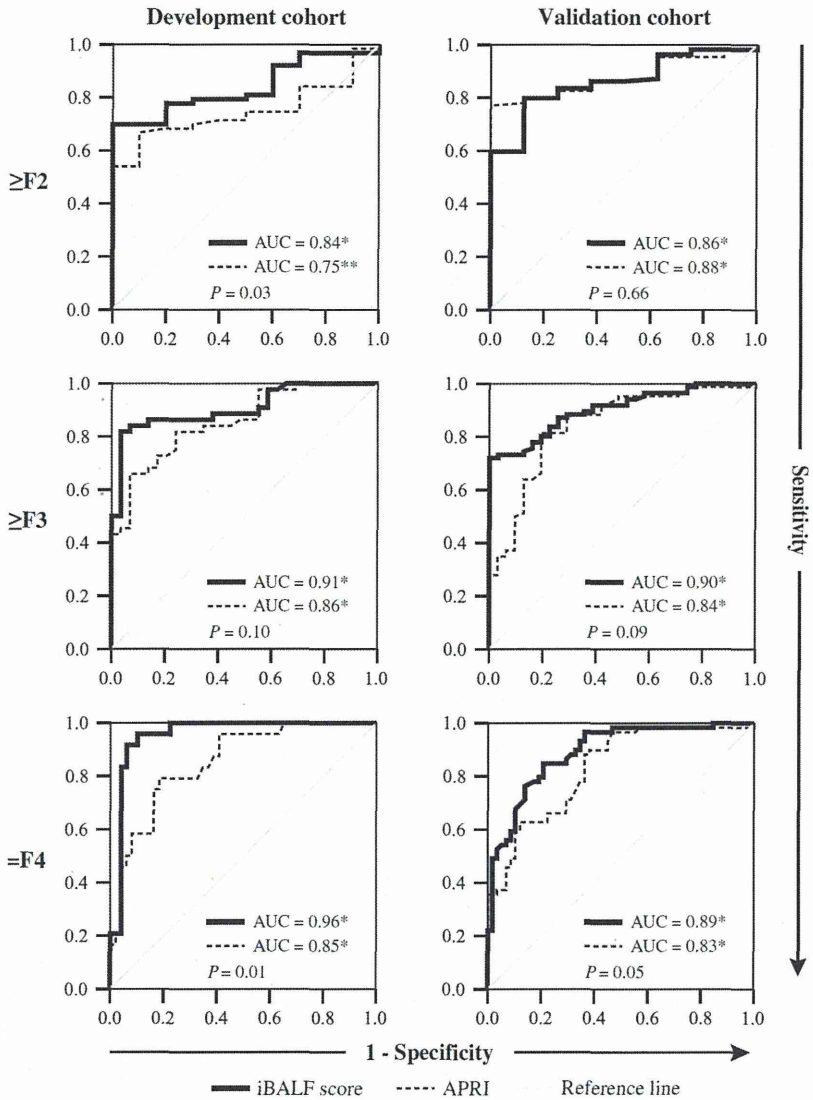

Figure 3 Receiver-operating characteristic curves of two fibrosis markers for diagnosing each fibrosis stage. Evaluated noninvasive markers included the infant biliary atresia liver fibrosis (iBALF) score (thick lines) and the aspartate aminotransferase-to-platelet ratio index (APRI, dashed lines). Gray lines indicate the reference lines. The diagnostic power of each marker was assessed by calculating the area under the curve (AUC); $^{*}P<0.001$, $^{**}P=0.01$. The *P* values in the panels represent the differences between AUCs of the iBALF score and the APRI using the DeLong test.

1 year of age. The results (Figure 4) suggest that BA patients with an iBALF score >6 at presentation might require liver transplantation rather than bile drainage surgery. However, the number of these severely affected patients was small in both cohorts. Except for these severely affected patients, the iBALF score at the initial surgery did not seem to be associated with native liver survival at 1 year of age. There was no correlation between the iBALF score at the initial surgery and the BALF score at 1 year of age among the patients with native liver survival, suggesting that liver fibrosis at the initial surgery had a limited effect on liver fibrosis progression or remission. We previously reported similar data on the actual fibrosis stages in 15 patients aged ≥2 years who underwent serial histological examinations at the time of initial surgery and after surgery and who were included in the development cohort of the current study: seven of these 15 patients showed remission of fibrosis, five showed the same fibrosis stage, and three showed progression of fibrosis.[4] We believe that effective postsurgical antifibrotic therapy for BA patients is needed and that noninvasive fibrosis monitoring would be highly valuable in clinical practice and study.

In addition to our previous report, several other studies have proposed noninvasive markers to assess liver fibrosis in BA patients. The APRI, which was originally developed to predict cirrhosis in hepatitis C patients,[8] has been widely investigated in BA patients. Kim *et al.*[12] described that the correlation coefficient between the APRI and Metavir fibrosis score from 35 patients at the time of hepatoportoenterostomy was

0.77 ($P<0.001$) and that the AUCs of the APRI for ≥ F3 and F4 fibrosis were 0.92 and 0.91, respectively. By contrast, Lind *et al.*[13] reported that the APRI was not significantly different according to the fibrosis stage in 31 patients at the time of hepatoportoenterostomy. In 23 patients after successful hepatoportoenterostomy (median, 4.2 years; range, 1.6–18.9 years after surgery), Lampela *et al.*[14] described a significant correlation between the APRI and Metavir fibrosis score ($r=0.63$, $P<0.001$) and a good diagnostic accuracy of the APRI for ≥ F3 with 93% sensitivity and 67% specificity. Another noninvasive fibrosis marker, transient elastography (Fibroscan), was more recently investigated to assess liver

Table 4 Cutoff values and diagnostic accuracies of the infant biliary atresia liver fibrosis (iBALF) score for predicting histological fibrosis stages

	n (%)	Cutoff	Sensitivity	Specificity	Accuracy
Development cohort (n = 73)					
≥ F2	63 (86.3%)	3.00	77.8%	80.0%	78.1%
≥ F3	44 (60.3%)	3.99	86.4%	86.2%	86.3%
= F4	24 (32.9%)	5.75	91.7%	93.9%	93.2%
Validation cohort (n = 117)					
≥ F2	109 (93.2%)	3.56	83.5%	75.0%	82.9%
≥ F3	86 (73.5%)	4.34	80.2%	80.6%	80.3%
= F4	59 (50.4%)	5.12	84.7%	79.3%	82.0%

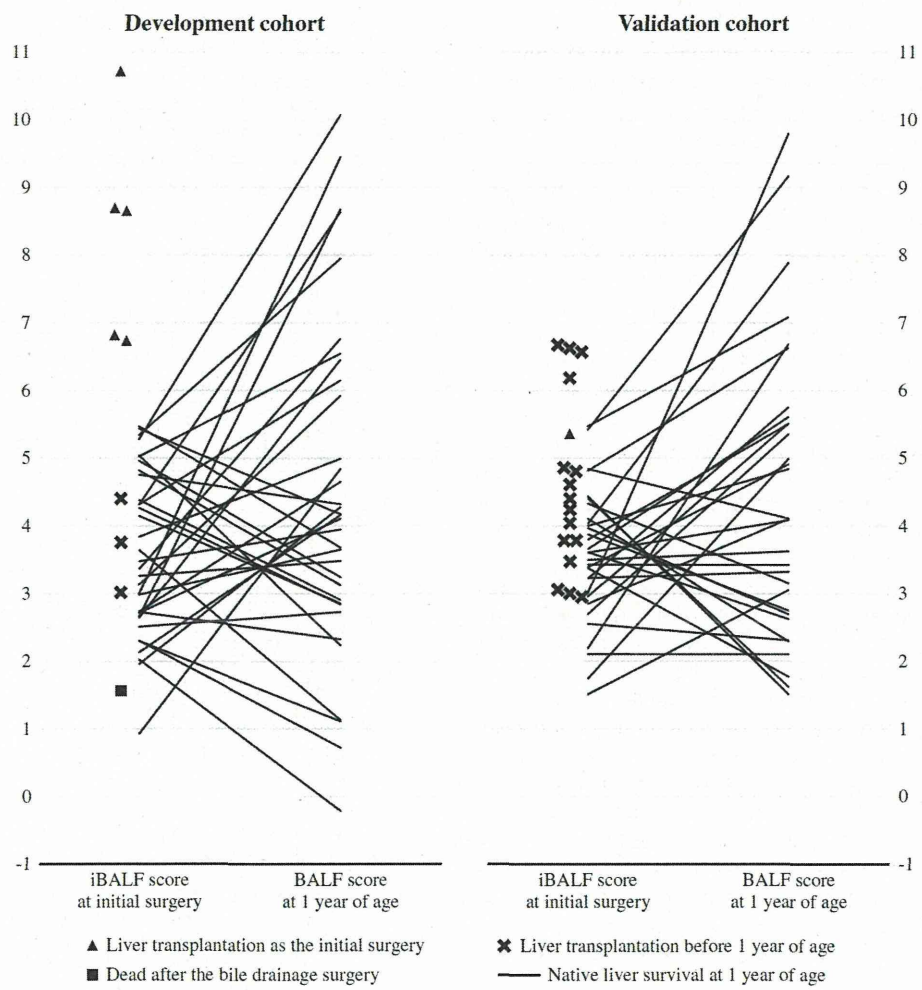

Figure 4 Relationships between the infant biliary atresia liver fibrosis (iBALF) score at the initial surgery and prognosis. Triangles indicate the patients receiving liver transplantation as the initial surgery. Crosses represent the patients requiring liver transplantation after bile drainage surgery before 1 year of age. The square indicates the patient who died after bile drainage surgery. The patients who survived with their native liver at 1 year of age are expressed by lines between the iBALF score at the bile drainage surgery and the biliary atresia liver fibrosis (BALF) score at 1 year of age.

stiffness using the ultrasound technique; Shin *et al.*[15] described that liver stiffness measurements obtained via transient elastography significantly correlated with Metavir fibrosis stages ($r=0.63$, $P<0.001$) and had good diagnostic powers for predicting severe fibrosis (≥F3; AUC = 0.86) and cirrhosis (F4; AUC = 0.96) in 47 BA patients aged <1 year at the time of hepatoportoenterostomy with liver biopsy or liver transplantation. Moreover, the APRI and transient elastography had already been investigated for associations with esophageal varices, an important consequence of liver fibrosis and portal hypertension, in postsurgical BA patients.[14,16–18] The current study suggests the advantages of the iBALF score over the APRI: stronger correlation with the fibrosis stages and more favorable diagnostic power than the APRI. Unlike the elastography methods, the iBALF score has good accessibilities, such as no need for a special device and simple equation components that allow retrospective calculation.

Although the current study indicated that the iBALF was a good noninvasive fibrosis marker even in the validation cohort, it has several limitations. First, patients were selected from three institutions, two of which were assigned to the development cohort and one to the validation cohort, resulting in significant differences in patient characteristics and blood test results between the cohorts. BA patients aged <1 year can be divided into three situations: patients before surgery, patients with a good postsurgical course, and patients requiring liver transplantation after bile drainage surgery. Although we intended that the iBALF-scoring system could apply in all situations, needle biopsy examinations for postsurgical patients with good bile drainage were performed at only one of the three participating institutions, thus the sample size was too small. To reflect the data from patients with a good postsurgical course in the iBALF score composition, we assigned the small number of these patients to the development cohort rather than randomly assigning them to the development cohort or the validation cohort. Thus, the relationships between liver fibrosis stage and the iBALF score of patients with a good postsurgical course could not be validated. In addition, there was a probable difference in the timing of liver transplantation between the institutions. Because of serious deceased donor organ shortages in Japan,[19] the timing of liver transplantation using liver allografts from living donors probably reflected the transplantation policy of each institution, resulting in significantly different ranges of the iBALF score in F4 patients between the cohorts and wide overlap in the ranges of the F3 and F4 groups in the validation cohort. The second limitation was general problems in prior studies of noninvasive fibrosis markers using the biopsy examinations as a reference standard: namely, biopsy sampling errors,[20] and observer variability.[21] Subcapsular wedge biopsy examination, which was used in most subjects in the current study, would tend to overestimate liver fibrosis. Thus, the fibrosis stages evaluated based on liver biopsy examinations might have false-positive and false-negative results.

In this study, we developed the iBALF score as a noninvasive surrogate fibrosis marker for BA patients aged <1 year, in addition to the previously developed BALF-scoring system for BA patients aged ≥1 year. Although some concerns remain, the iBALF score was validated to strongly correlate with liver fibrosis stage and to have good diagnostic powers for predicting liver fibrosis. The iBALF and BALF scores may be useful in future clinical studies as surrogate fibrosis markers.

CONFLICT OF INTEREST

Guarantor of the article: Tatsuo Kuroda, MD, PhD.
Specific author contributions: Hirofumi Tomita designed the study, collected and interpreted the data, performed the statistical analysis, and drafted the manuscript; Yasushi Fuchimoto designed the study, collected the data, and critically reviewed the manuscript. A. Fujino and T. Kuroda designed the study, interpreted the data, and critically reviewed the manuscript. K. Hoshino, M. Sakamoto, M. Kasahara, Y. Kanamori, and M. Nakano designed the study and critically reviewed the manuscript. Y. Masugi, A. Nakazawa, and S. Akatsuka participated in the histological evaluations and critically reviewed the manuscript. Y. Yamada and F. Yoshida collected the data and critically reviewed the manuscript. All authors have seen and approved the final version of the manuscript.
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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Although liver fibrosis is a prominent feature of biliary atresia (BA) patients, noninvasive liver fibrosis markers in BA patients have been limited.
- ✓ We previously developed a BA liver fibrosis (BALF) score as the first specific liver fibrosis marker for BA patients aged ≥1 year.

WHAT IS NEW HERE

- ✓ We developed a novel noninvasive fibrosis marker for BA patients aged <1 year—the infant BALF (iBALF) score.
- ✓ The iBALF score was validated to be a good noninvasive marker of native liver fibrosis for BA patients during infancy.
- ✓ The iBALF and BALF scores can monitor liver fibrosis in a similar manner before and after 1 year of age, respectively.
- ✓ The BA patients with an iBALF score >6 at presentation had poor outcome on native liver survival at 1 year of age.

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Living donor domino liver transplantation using a maple syrup urine disease donor: A case series of three children – The first report from Japan

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Abstract: As the priority of LD-Domino LT is the safety of the first recipient, limitations and technical difficulties in the second recipient often occur. The most technically challenging part of LD-Domino LT is the reconstruction of the vessels. For the reconstruction of HVs, the native HVs were exteriorized as far as possible using a CUSA because longer extensive HVs are essential for facilitating the reconstruction. At the back table, the HVs of the domino graft were sutured together, and the single cuff of the HVs was anastomosed to the IVC by joining the orifices. The HAs, the presence of insufficient length, and multiple vessels in the whole liver rendered the reconstruction more difficult. We determined the dividing sites of the vessels according to the preoperative 3D-CT findings obtained in two institutions. This is the first case series using grafts in DLT obtained from LDLT for patients with MSUD between two institutions. In conclusion, LD-Domino LT is a safe and feasible therapeutic option to expand the donor pool by technical refinement in the reconstruction of the second recipient. Further studies with a greater accumulation of patients and a longer follow-up will be necessary to establish LD-Domino LT using an MSUD donor.

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Key words: biliary atresia – domino liver transplantation – familial hypercholesterolemia – maple syrup urine disease – protein C deficiency

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LD-Domino LT was developed to expand the donor pool especially in countries where there is limited DDLT for patients such as in Japan. There are only approximately 40–50 DDLT donors each year, with just three donors under six yr of age so far. Therefore, there are few opportunities to receive a whole liver from an age-matched, similarly sized donor. The possibility of amyloidosis as a late complication of DLT using a FAP donor is also a worrisome issue for

Abbreviations: 3D-CT, three-dimensional computerized tomography; BA, biliary atresia; BCAA, branched-chain amino acid; CHA, common hepatic artery; CIT, cold ischemic time; CUSA, cavitron ultrasonic surgical aspirator; DDLT, deceased donor liver transplantation; DLT, domino liver transplantation; FAP, familial amyloidotic polyneuropathy; FFP, fresh frozen plasma; FH, familial hypercholesterolemia; GDA, gastroduodenal artery; GRWR, graft-to-recipient weight ratio; HAs, hepatic arteries; HDL-C, high-density lipoprotein cholesterol; HVs, hepatic veins; IVC, inferior vena cava; LD-Domino LT, living donor domino liver transplantation; LDL-C, low-density lipoprotein cholesterol; LDL-R, low-density lipoprotein receptor; LDLT, living donor liver transplantation; LHA, left hepatic artery; LHV, left hepatic vein; LLS, left lateral segment; LT, liver transplantation; MHV, middle hepatic vein; MSUD, maple syrup urine disease; ND, not detected; PC, protein C; PV, portal vein; RHA, right hepatic artery; RHV, right hepatic vein; SMA, superior mesenteric artery; TC, total cholesterol; TG, triglyceride; WIT, warm ischemic time.

pediatric patients (1, 2). However, for pediatric patients with metabolic liver diseases, such as MSUD, who are undergoing LDLT, DLT is often performed with similarly sized pediatric patients.

MSUD is an autosomal recessive disorder caused by an impaired activity of the branched-chain alpha-keto acid dehydrogenase. MSUD exerts a risk of serious neurologic disability and untimely death, despite recent progress in nutritional and medical management. Ketoacidosis causes cerebral edema that can culminate in brain herniation and cardiorespiratory arrest (3). LT has been performed for satisfactory correction of the enzymatic disorder and the prevention of long-term neurologic consequences (4). Furthermore, a recent report has described the safe use of explanted livers for DLT grafts in 11 cases with an excellent outcome (5). In most cases, however, an excellent outcome is generally obtained only after performing DDLT for MSUD. The most major differences in LD-Domino LT compared with deceased donor lie in the multiple vascular pedicles of insufficient length in the graft for second recipient. The main concern for LD-Domino LT is the safety of the first recipient; native hepatectomy is performed while carefully preserving the retrohepatic IVC, the portal trunk, and the peripheral HAs. The explanted MSUD liver has multiple and insufficient length vascular pedicles, and successful hepatic vascular reconstruction is essential for the second recipient.

In 2014, we presented a case of pediatric PC deficiency that was successfully treated by LD-Domino LT from a pediatric patient with MSUD (5). We applied our experience to three patients who underwent LD-Domino LT using whole liver and evaluated the feasibility and efficacy of the technique. To the best of our knowledge, this is the first case series using grafts in DLT obtained from LDLT for patients with MSUD between two institutions.

Patients and methods

Between November 2005 and May 2015, 330 children underwent LT in our institution, the National Center for Child Health and Development in Tokyo, Japan, with an overall survival rate of 92.2%. Three patients each with PC deficiency, BA, and FH, respectively, were indicated for LD-Domino LT because for two of them (PC deficiency and FH), both parents had heterozygous mutations, while the other (BA) patient was considered to be a low priority on the DDLT waiting list. Analyses of blood amino acids and urine organic acid were performed to exclude the presence of MSUD in the second recipients.

Each patient with MSUD and the first donor of the LLS for the corresponding patient with MSUD underwent 3D-CT for the evaluation of the anatomy of their HAs, PV, and HVs. All three patients with MSUD received an LLS from one of their parents, and all parents of the patients with MSUD agreed to donate their liver.

LD-Domino LT was performed between two institutions. At our department, the immunosuppression regimen consisted of tacrolimus and low-dose steroids. During the follow-up period, the assessments of blood amino acids and urine organic acids were continuously made. The endocrine function was evaluated by determining specific parameters such as serum leucine, isoleucine, valine, and alloisoleucine levels.

This study was approved by the review board of each institution and the Japan Society for Transplantation.

Results

The characteristics of the first donors, together with the first and second recipients, are summarized in Table 1. LD-Domino LT was performed in three cases (cases 1, 2, and 3). Cholesterol-level changes in the FH patient (case 3) are summarized in Table 2. Table 3 shows that BCAA homeostasis was maintained with an unrestricted protein diet in all three cases.

Case 1

A one-yr and 11-month-old girl presented with multiple cerebral bleeding and subcutaneous bleeding on her lower limbs. The patient was found to have a serum PC activity of less than 5%. A genetic mutational analysis confirmed the diagnosis of PC deficiency. The patient had started receiving FFP and activated PC concentrate treatments since one yr and two months of age. She underwent ophthalmectomy due to bilateral vitreous hemorrhages at one month of age. Despite the maximal medical therapy, she had repeated purpura fulminans and was listed for LT. Both her parents had heterozygous mutations in the PC genes and were excluded as living donors; therefore, she was placed on the DDLT waiting list. This patient was selected to receive LD-Domino LT because of physical size matching to the first recipient on our waiting list. We selected the dividing site of the vessels according to the preoperative 3D-CT findings of the first donor and recipient. Because the LHA of the first donor was branched from the right gastric artery, along with having a sufficient length, the GDA was ligated and the CHA was dissected in the first recipient. The RHV, MHV, LHV, and superficial vein were sutured together by venoplasty at the back table, and the single cuff of the HVs was anastomosed to the IVC by joining the orifices. PV anastomosis was performed with the branch patch technique. Roux-en-Y anastomosis was employed for biliary reconstruction. Immunosuppressive treatment was initiated with tacrolimus and low-dose steroids. The patient's