ゲンとLithostathineが胆道内へ逆流すると機序は不明だがトリプシンが活性化し不溶性Lithostathineが生じて蛋白栓が形成されると報告している[17-19]．またAndoら[20]によると膵内胆管の遺残があると分流手術をしても10%に蛋白栓の再形成が生じ，逆に手術により膵内胆管を完全に切除すれば，術後に蛋白栓が再形成されることはないとしている．我々の経験した症例6，7は膵内胆管が完全に切除されていたにも関わらず拡張膵管の通過障害にて膵炎を発症した．理論上，遺残胆管のない分流手術後に蛋白栓が再形成されないとすると，初回手術時の共通管内の蛋白栓が完全に除去されていなかった可能性がある．特に，症例7は術後21日目に膵炎を発症しており，共通管内の蛋白栓の遺残がその原因であることは容易に想像できる．2例（症例6，7）は，どちらも新古味分類Ibであり，共通管の拡張とその内部の蛋白栓を術中造影で認めた．このような下部胆管が非常に細く共通管内にアプローチしにくい形態の場合は，術中胆道造影を繰り返し，確実に蛋白栓を洗い流すことが重要と考えられた．

残りの1例（症例8）は，不完全型の膵管癒合不全が原因の膵炎と考えられた．根治術前の発症時に，CTで膵周囲に液体貯留を伴う真の膵炎所見を呈していた．基本的に膵・胆管合流異常での高アミラーゼ血症は，共通管の通過障害による膵液のcholangio venous reflaxが原因と考えられており[21]，CT上膵炎所見（膵周囲の浮腫など）を呈することは希である．おそらく発症時の症状（高アミラーゼ血症を伴う腹痛）は膵・胆管合流異常によるものではなく，膵管癒合不全による症状であると推測される．Teruiら[22]は自験例の検討より先天性胆道拡張症の膵管癒合不全合併は1.4%であると報告しており，頻度の高いものではない．根治術前の発症時にCT上真の膵炎所見を呈している例は，膵管癒合不全を併存している可能性があるため，画像検査を慎重に行い診断を付ける必要がある．また，膵管癒合不全を認めたときは術後に膵炎を起こす可能性があるため慎重にフォローする必要がある．

先天性胆道拡張症術後の胆管系・膵管系合併症について自験例をまとめた．以前から指摘されているとおり肝内結石は，左右肝管起始部の相対的狭窄と肝内胆管拡張を伴った例に発症しており，肝門部胆管を形成し大きな吻合口を作成することが重要であることが再認識された．膵管系の合併症に関し，新古味分類Ibのような非常に細くなった下部胆管が拡張した共通管に合流するような症例の場合，共通管内の蛋白栓の遺残のリスクがある．そのため術中胆道造影を繰り返し蛋白栓の遺残のないことを確認する必要があると思われた．また，CT上膵炎所見を呈するような膵・胆管合流異常症の場合，膵管癒合不全などの膵管の奇形を合併している可能性があるため，画像検査を慎重に行い評価する必要がある．

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Complications Related to Bile Duct or Pancreatic Duct After Congenital Choledochal Cyst Excision

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Recently, some complications involving the bile duct or pancreatic duct have been reported in patients with choledochal cyst. In this series, complications involving the bile duct or pancreatic duct in patients with choledochal cyst treated in our institution from April 1995 to December 2013 were investigated. Moreover, the shapes of the bile duct or pancreatic duct in these patients were evaluated. Five cases of bile duct complications and 3 cases of pancreatic duct complications were identified. Three cases of bile duct complications were associated with intrahepatic bile duct stones. In these 3 cases, intrahepatic bile duct dilation and intrahepatic bile duct stricture were found during a definitive operation. In 2 cases of pancreatic duct complications, a protein plug was identified in a common channel in the patients who pancreatitis after a definitive operation. Regarding the shape of the connection of their bile duct and pancreatic duct examined during a definitive operation, a very narrow distal bile duct was connected to a dilated common channel, and a protein plug was observed in that common channel. Another case of pancreatic duct complication was caused by incomplete pancreas divisum, and endoscopic sphincterotomy of the minor duodenal papilla was performed. Patients having a dilated common channel containing a protein plug detected during the definitive operation may have a risk of pancreatitis after operation and should be monitored closely.

Key words: choledochal cyst, pancreaticobiliary maljunction, stone, pancreatitis, complication

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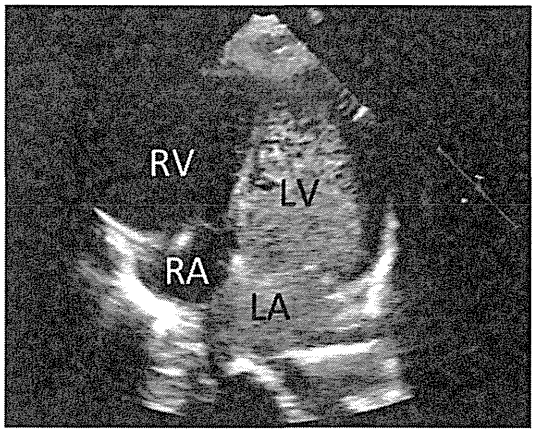

Fig. 1 Transthoracic contrast echocardiography showing microbubbles from the pulmonary artery returning directly to the left atrium (LA). LV, left ventricle; RA, right atrium; RV, right ventricle.

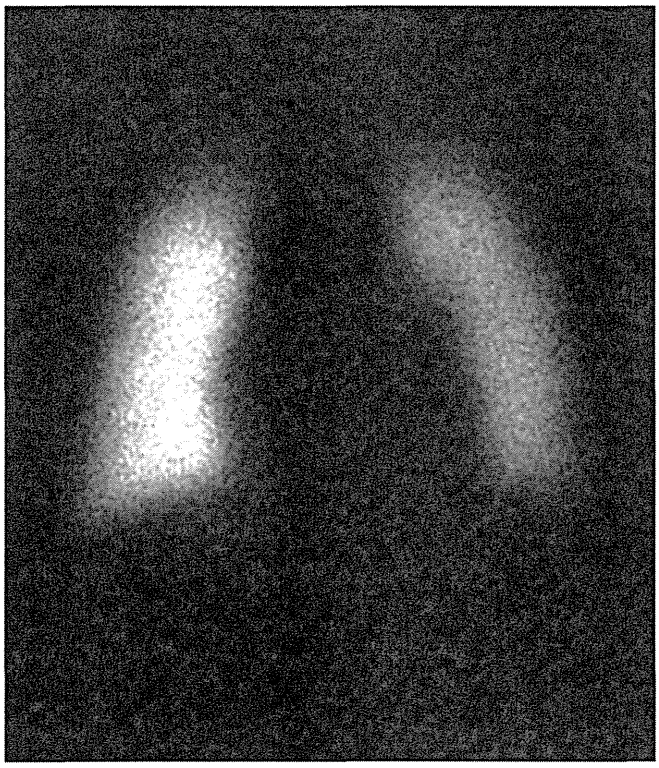

Fig. 2 Lung scanning with ^{99m}Tc-labeled macroaggregated albumin showing cold areas in the peripheral lung fields. The rate of right-to-left shunting is 35%.

accepted as the first-choice therapy for BA, and 38–62% of patients will achieve initial biliary drainage after hepatoportoenterostomy.[1] But, given that intrahepatic inflammatory processes continue for at least 6 months after hepatoportoenterostomy, even patients with successful hepatoportoenterostomy will have some progressive hepatic fibrosis and cirrhosis.[2] Consequently, various complications, such as portal hypertension and HPS, may occur in the long term.

Hepatopulmonary syndrome is a disorder of altered gas exchange induced by abnormal intrapulmonary vascular dilatations and/or arteriovenous fistulae associated with hepatic disease.[3] This condition allows the passage of mixed venous blood rapidly or even directly into the pulmonary vein, and an arterial oxygenation defect will occur.[3] In the present case, arterial deoxygenation was severe, and transthoracic contrast echocardiography and lung scanning with ^{99m}Tc-labeled macroaggregated albumin indicated prominent right-to-left shunting. There is no accepted effective medical therapy for HPS, and liver transplantation is the only successful treatment.[3] The median survival of patients with severe HPS without liver transplantation is <12 months.[4] Because of the severe mortality of HPS, partial pressure of oxygen <60 mmHg is considered to be an indication for liver transplantation.[5] The present patient was suitable for liver transplantation, and the preparations for transplantation proceeded. Given that the patient had a brain abscess, which delayed liver transplantation, further immunosuppression after the procedure will complicate management because recurrence of the infection must be taken into consideration.

To the best of our knowledge, brain abscess in HPS has been reported in three patients in the English-language literature.[6–8] Only one of them was a pediatric patient, and he had HPS associated with BA, as in the present case.[6] The mechanism by which HPS caused brain abscess in the past reports is not clear. In our view, the presumed mechanism is right-to-left bacterial transit through intrapulmonary vascular dilatations and/or arteriovenous fistulae. This is supported indirectly by the following two facts. First, the most common predisposing factor for brain abscess in children is cyanotic congenital heart disease: 30–34% of patients diagnosed with brain abscess have underlying cyanotic congenital heart disease.[9] This suggests that right-to-left shunting increases the risk of brain abscess. Furthermore, other common predisposing factors for brain abscess in children, such as hematogenous dissemination from a distant infection focus, spread of contiguous infection, penetrating cranial injury, or past neurological procedures,[9] were not found in the present case. Second, brain abscess has been reported in other diseases that cause intrapulmonary right-to-left shunting and which resemble HPS, such as hereditary hemorrhagic telangiectasia.[10] Hereditary hemorrhagic telangiectasia is a vascular disorder that causes recurrent epistaxis, mucocutaneous telangiectasia, and arteriovenous malformations in various viscera. It has been found that pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia often connect a pulmonary artery to a pulmonary vein, bypassing the normal pulmonary capillary bed and forming intrapulmonary right-to-left shunting.[10] Furthermore, decreased immune defenses due to cirrhosis and an arterial oxygenation defect probably contributed to the development of the brain abscess in the present case.

In conclusion, brain abscess in HPS associated with BA is uncommon, but it can cause serious neurological deficits and complicate subsequent liver transplantation. Brain abscess must be considered as a possible complication of HPS with BA.

Acknowledgment

All authors have no conflicts of interest to disclose.

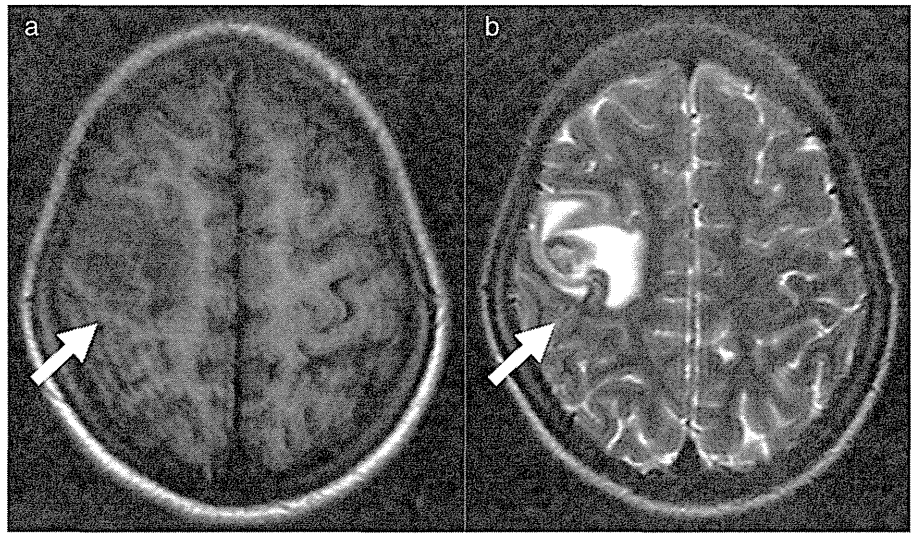

Fig. 3 Brain magnetic resonance imaging showing a right parietal brain abscess (arrows) that appears (a) slightly hypointense on T1-weighted imaging and (b) hyperintense on T2-weighted imaging.

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First Japanese case of Zellweger syndrome with a mutation in *PEX14*

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Abstract Zellweger syndrome, one of the peroxisome biogenesis disorders, is an autosomal recessive disease caused by mutations in *PEX* genes. It is characterized by severe hypotonia, failure to thrive, psychomotor retardation, liver dysfunction, and sensorineural hearing impairment. Most of the patients with this disease die before the age of 1 year. *PEX14* is the 13th *PEX* gene responsible for peroxisome biogenesis disorders. Thus far, only two patients with *PEX14* deficiency have been reported. Here, we report the first case of a Japanese patient with a *PEX14* mutation who showed severe hypotonia, psychomotor retardation, demyelination, and developed rickets at the age of 5 months. An increased excretion of 3,6-epoxydicarboxylic acids leads to the diagnosis of Zellweger syndrome and a mutation analysis of *PEX14* revealed a homozygous mutation of c.538C>T (p.Q180X). The patient survived for a prolonged period of time but died of liver failure at the age of 46 months.

Key words 3,6-epoxydicarboxylic acid, demyelination, peroxisome biogenesis disorders, *PEX14*, Zellweger syndrome.

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Peroxisomes are single-membrane organelles that contain many of the enzymes necessary for β-oxidation of fatty acids and synthesis of bile acids.[1] *PEX* genes encode peroxins necessary for peroxisome biogenesis and peroxisomal protein import. Mutations in *PEX* genes lead to peroxisome biogenesis

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Original Article

Scoring system for the prediction of severe acute pancreatitis in children

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Abstract ***Background***: The lack of an accurate scoring system for pediatric acute pancreatitis could cause delays in appropriate clinical management and increase the risk of progressive life-threatening complications. We investigated a modified Ministry of Health, Labour and Welfare of Japan (JPN) scoring system that uses pediatric systemic inflammatory response syndrome (SIRS) score, age, and weight to establish a more useful scoring system for children.

Methods: A retrospective chart review was conducted of pediatric patients with acute pancreatitis who were admitted to Juntendo University Hospital between 1985 and 2011. The sensitivity, specificity, and positive and negative predictive values of the pediatric JPN scoring system were calculated and then compared with those of previously developed scoring systems.

Results: The patient group consisted of 145 patients (88 girls, 57 boys). The pediatric JPN score had greater sensitivity (80%) than the Ranson (60%), modified Glasgow (50%), and DeBanto (60%) scores. The specificity was 96% for the pediatric JPN score, 94% for the Ranson score, 99% for the modified Glasgow score, and 86% for the DeBanto score.

Conclusion: The pediatric JPN score can be used to predict severe acute pancreatitis during the initial medical assessment.

Key words guideline, Ministry of Health, Labour and Welfare of Japan (JPN) scoring system, pediatrics, severe acute pancreatitis, severity assessment.

In 2002, DeBanto *et al.* were the first to suggest a scoring system for predicting the severity of acute pancreatitis (AP) in children.[1] This system was modified from the Ranson[2,3] and Glasgow systems[4] and consists of the following eight parameters: age (<7 years old); weight (<23 kg); white blood cell count at admission (>18 500 cells/μL); lactate dehydrogenase (LDH) at admission (>2000 U/L); 48 h trough Ca^{2+} (<8.3 mg/dL); 48 h trough albumin (<2.6 g/dL); 48 h fluid sequestration (>75 mL/kg per 48 h); and 48 h rise in blood urea nitrogen (BUN; >5 mg/dL). Patients who met three or more of these criteria were predicted to have a severe outcome (Table 1). This scoring system, however, is not exact for Asian children.[6] Recently, Lautz *et al.* reported that the Ranson, modified Glasgow, and DeBanto pediatric scores have limited ability to predict AP severity in children and adolescents in the USA.[7] Assessment of severity at the initial medical examination plays an important role in providing adequate early treatment and transferring patients to a medical facility equipped to treat severe AP. The lack of an accurate scoring system for pediatric AP, however, could cause delays in appropriate clinical management and increase the risk of progressive life-threatening complications.

In 1990, the AP severity scoring system of the Ministry of Health, Labour and Welfare of Japan (JPN score) was developed.[8] The scoring system was partially revised in 1999 and revised again to the current version in 2008 (Table 1).[5,8] The current criteria consist of nine prognostic factors and/or computed tomography (CT) grades based on contrast-enhanced CT. This system, however, does not reflect the characteristics of children and adolescents. The JPN score criteria (2008 version) include two parameters, systemic inflammatory response syndrome (SIRS) score and age ≥70 years, that make the system inappropriate for use in children.[5] Similarly, the Ranson and modified Glasgow scores contain a parameter concerning age (≥55 years) that is not appropriate for pediatric patients.[3,4] In the present study, we investigated a modified JPN score that reflects pediatric SIRS score, age, and weight to establish a more useful scoring system for children.

Methods

The current study was a retrospective chart review of all children and adolescents (<18 years of age) with an ICD-9 code of 577.0 or an ICD-10 code of K85 who were admitted to the Pediatric or Pediatric Surgery Department of Juntendo University Hospital

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Table 1 Comparison of parameters of three scoring systems

Parameter	Pediatric JPN scoring system	JPN scoring system (2008 version)[5]	Parameter	DeBanto score[1]
1	BE ≤ −3 mEq or shock (Table 2 lists SBP depending on age)	BE ≤ −3 mEq or shock (SBP ≤80 mmHg)		
2	PaO_2 ≤60 mmHg (room air) or pulmonary insufficiency (ventilation required)	PaO_2 ≤60 mmHg (room air) or pulmonary insufficiency (ventilation required)		
3	BUN ≥40 mg/dL (or Cr ≥2 mg/dL) or urine volume <0.5 mL/kg/h even after fluid resuscitation	BUN ≥40 mg/dL (or Cr ≥2 mg/dL) or urine volume <400 mL/day even after fluid resuscitation	1 2	48 h rise in BUN >5 mg/dL 48 h fluid sequestration <75 mL/kg/48 h
4	LDH ≥2 × above upper limit (Age-adjusted value)	LDH ≥2 × above upper limit	3	Admission LDH >2000 U/L
5	Platelet count ≤1 × 10^5/mm^3	Platelet count ≤1 × 10^5/mm^3		
6	Ca ≤7.5 mg/dL	Ca ≤7.5 mg/dL	4	48 h trough Ca <8.3 mg/dL
7	CRP ≥15 mg/dL	CRP ≥15 mg/dL		
8	Pediatric SIRS score ≥3	SIRS score ≥3	5	Admission white blood cell count >18 500 cell/μL
9	Age <7 years and/or weight <23 kg	Age ≥70 years	6 7 8	Age <7 years Weight <23 kg 48 h trough albumin <2.6 g/dL

BE, base excess; BUN, blood urea nitrogen; Ca, calcium; Cr, creatinine; CRP, C-reactive protein; JPN, Ministry of Health, Labour and Welfare of Japan; LDH, lactate dehydrogenase; PaO_2, partial pressure of arterial oxygen; SBP, systolic blood pressure; SIRS, systemic inflammatory response syndrome.

between 1985 and 2011. This study was approved by the Juntendo University Institutional Review Board. The diagnosis of AP was confirmed on elevation of serum amylase or lipase more than twofold the upper limit of normal, clinical signs and symptoms, and/or imaging.

Based on the JPN scoring system (2008 version), the pediatric JPN scoring system was developed using pediatric SIRS score (Tables 2,3)[9] and the parameters of age <7 years old and/or weight <23 kg, as reported by DeBanto *et al.*[1] The parameters of the pediatric JPN score were as follows: (i) base excess (BE) ≤−3 mEq or shock (systolic blood pressure cut-offs according to age group; Table 3); (ii) PaO_2 ≤60 mmHg (room air) or respiratory failure; (iii) BUN ≥40 mg/dL (or creatinine [Cr] ≥2.0 mg/dL) or oliguria (<0.5 mL/kg per h); (iv) LDH ≥2 × upper limit; (v) platelet count ≤1 × 10^5/mm^3; (vi) calcium (Ca) ≤7.5 mg/dL; (vii) C-reactive protein (CRP) ≥15 mg/dL; (viii) number of positive measures in pediatric SIRS score ≥3; and (ix) age <7 years old or/and weight <23 kg. The cut-off for predicting a severe outcome was set at three criteria. A comparison of the parameters of the present system, the JPN scoring system (2008 version), and the DeBanto system is shown in Table 1. To identify the severe patients who were initially diagnosed as having mild pancreatitis, the severity was determined using data from 72 h after the onset of pancreatitis.

Table 2 Pediatric SIRS score[9]

- Core temperature >38.5°C or 36.0°C
- Tachycardia, defined as mean heart rate >2 SD above normal for age; or for children <1 year old, bradycardia, defined as mean heart rate in the <10th percentile for age.
- Mean respiratory rate >2 SD above normal for age.
- Leukocyte count elevated or decreased for age or >10% immature neutrophils.

SIRS, systemic inflammatory response syndrome.

An episode of pancreatitis was considered to be clinically severe if the patient died; had pancreatic surgery; developed a pseudocyst, abscess, or infected necrosis; or met the Atlanta criteria (1992 version) for organ dysfunction (systolic blood pressure, 90 mmHg; PaO_2, 60 mmHg; creatinine, 2 mg/dL; or gastrointestinal bleeding, 500 mL/24 h).[1,10] The clinical and laboratory

Table 3 Age-specific vital signs and laboratory variables[9]

Age group	Tachycardia (beats/min)	Bradycardia (beats/min)	Respiratory rate (breaths/min)	Leukocyte count (×10^3/mm^3)	Systolic blood pressure (mmHg)
0 day–1 week	>180	<100	>50	>34	<65
1 week–1 month	>180	<100	>40	>19.5 or <5	<75
1 month–1 year	>180	<90	>34	>17.5 or <5	<100
2–5 years	>140	NA	>22	>15.5 or <6	<94
6–12 years	>130	NA	>18	>13.5 or <4.5	<105
13–18 years	>110	NA	>14	>11 or <4.5	<117

Lower values for heart rate, leukocyte count, and systolic blood pressure are for the 5th percentile, and upper values for the heart rate, respiration rate, or leukocyte count are for the 95th percentile. NA, not available.

Table 4 Demographic characteristics and etiology

	Mild AP	Severe AP
N	135	10
Age (years), mean ± SE (range)	7.38 ± 0.03 (0.8–17)	6.40 ± 0.42 (2–13)
M : F	51:84	6:4
Etiology		
1. Congenital anomalies of the pancreaticobiliary system		
• Choledochal cyst and/or abnormal union of the pancreaticobiliary junction	46 (34.1)	1 (10.0)
• Pancreas divisum	9 (6.7)	1 (10.0)
• Gallstones	9 (6.7)	0
• Others	13 (9.6)	0
2. Drugs	16 (11.9)	3 (30.0)
3. Trauma	14 (10.3)	0
4. Multisystem disease	8 (5.9)	5 (50.0)
5. Infections	5 (3.7)	0
6. Familial	3 (2.2)	0
7. Others	12 (8.9)	0

AP, acute pancreatitis.

factors used in the Ranson, modified Glasgow, DeBanto, and pediatric JPN scores were compared between patients with mild and severe AP. Finally, using a score of three or more positive parameters as a positive result, the sensitivity, specificity, and positive and negative predictive values were calculated.

Statistical analysis

The results are expressed as mean ± SE. Unpaired Mann–Whitney *U*-test and Fisher's exact test were used to identify significant changes, as appropriate. Receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) was calculated to compare the overall accuracy of the different scoring systems. The AUC ± SE was calculated under non-parametric assumptions. All *P*-values were two-tailed, and $P < 0.05$ was considered statistically significant. Statistical analysis was done using SPSS version 18.0 (IBM, Tokyo, Japan).

Results

Patient demographics and AP etiology

The patient group consisted of 145 patients (88 girls, 57 boys) aged 0.8–17 years (mean age, 7.3 years). Of the 145 AP patients, 79 (54.5%) had congenital anomalies of the pancreaticobiliary system. Of these 79 children, common bile duct dilatation and/or abnormal union of the pancreaticobiliary junction was present in 47 children. Nineteen children had drug-induced AP (13.1%), and 14 children had trauma-induced AP (9.7%). Thirteen children had multisystem disease (9.0%), five had infections (3.4%), and 12 had AP of unknown etiology (8.3%). The demographic data for both the mild and severe groups according to the Atlanta criteria are given in Table 4.

Criteria for severity by Atlanta criteria

According to the Atlanta criteria, 10 children had severe pancreatitis, including two who died. The total number of criteria met was 27, because four patients met one criterion, two patients met two criteria, two patients met three criteria, one patient met four criteria, and one patient met nine criteria (Table 5).

Clinical and laboratory parameters of pediatric JPN score

The results of the statistical analysis between mild and severe cases of AP for 12 individual clinical and laboratory parameters are listed in Table 6. The parameters of BE ($P \leq 0.05$), BUN ($P \leq 0.01$), LDH ($P \leq 0.01$), and CRP ($P \leq 0.01$) achieved a statistically significant difference between mild and severe AP, while no significant difference was found for platelet count, serum calcium level, age or weight. The incidence of shock ($P \leq 0.01$), pulmonary insufficiency ($P \leq 0.01$), oliguria ($P \leq 0.01$), and pediatric SIRS score ≥3 ($P \leq 0.01$) was significantly higher in severe AP than mild AP.

Outcome: Pediatric JPN score compared to Atlanta criteria

The consistency between pediatric JPN score and Atlanta criteria was examined. Severe outcome occurred in 1.5% (2/132) of patients with 0–2 points, 50.0% (5/10) of patients with 3–4 points, 100% (2/2) of patients with 5–6 points, and 100% (1/1) in the patient with 7–8 points. The mortality of severe AP identified using the Atlanta criteria was 20% (2/10); the pediatric JPN scores of these patients were 5 and 7 points.

Table 5 Criteria for severity on Atlanta criteria

Criteria for severity	No. patients (%)
1. Death	2 (20)
2. Surgery on pancreas	1 (10)
3. Shock	8 (80)
4. Pulmonary insufficiency	4 (40)
5. Renal failure	6 (60)
6. Gastrointestinal bleeding	2 (20)
7. Pseudocyst	2 (20)
8. Abscess	1 (10)
9. Infected necrosis	1 (10)

Table 6 Clinical and laboratory parameters

		Mild AP (n = 135)			Severe AP (n = 10)			
		Mean ± SE	n	Range	Mean ± SE	n	Range	P
		Patient criteria met			Patient criteria met			
1	BE ≤ −3 mEq	−2.6 ± 2.7	8	−6.1–1.9	−9.5 ± 2.5	9	−1.3—25	<0.05
	or shock	0	135		6	10		<0.01
2	PaO_2 ≤60 mmHg (room air)	NA			NA			
	or pulmonary insufficiency	0	135		4	10		<0.01
3	BUN ≥40 mg/dL	10.6 ± 0.45	135	2–26	28.9 ± 5.60	10	6–61	<0.01
	or oliguria (<0.5 mL/kg/h)	0	135		2	10		<0.01
4	LDH ≥2 × above upper limit	1.13 ± 0.05	119	0.32–3.56	2.12 ± 0.12	8	0.74–3.84	<0.01
5	Platelet count ≤1 × 10^5/mm^3	29.9 ± 1.0	135	2.3–67.7	12.4 ± 2.94	10	1.2–33.0	NS
6	Ca ≤7.5 mg/dL	9.53 ± 0.07	126	7.2–10.8	8.24 ± 0.21	10	7.4–9.6	NS
7	CRP ≥15 mg/dL	2.36 ± 0.29	135	0.1–15.5	12.7 ± 1.96	10	4.8–22.6	<0.01
8	Pediatric SIRS score ≥3	2	135	0–3	6	10	1–4	<0.01
9	Age <7 years and/or weight <23 kg	7.38 ± 0.03	135	0.8–17	6.40 ± 0.42	10	2–13	NS
		26.3 ± 1.3	135	7.3–64.1	20.9 ± 3.7	10	10.5–47.0	NS

AP, acute pancreatitis; BE, base excess; BUN, blood urea nitrogen; Ca, calcium; CRP, C-reactive protein; LDH, lactate dehydrogenase; PaO_2, partial pressure of arterial oxygen; SIRS, systemic inflammatory response syndrome.

Comparison of four scoring systems in predicting severity of AP

The means of the Ranson (1.15 ± 0.07 vs. 3.20 ± 0.49, $P \leq 0.01$), modified Glasgow (0.50 ± 0.06 vs. 2.76 ± 0.42, $P \leq 0.01$), DeBanto (1.41 ± 0.10 vs. 2.70 ± 0.47, $P \leq 0.01$), and pediatric JPN (0.82 ± 0.06 vs. 3.80 ± 0.49, $P \leq 0.01$) scores varied significantly between the mild and severe groups (Table 7). ROC curves were produced for each scoring system to compare the overall predictive value, without confining the analysis to any arbitrary cut-off (Fig. 1). On ROC analysis the AUC (mean ± SE) for the pediatric JPN score (0.980 ± 0.012) was superior to the Ranson (0.886 ± 0.056), modified Glasgow (0.935 ± 0.034), and DeBanto (0.754 ± 0.074) scoring systems (Fig. 1).

Using the cut-off of 3 points, pediatric JPN score had better sensitivity (80.0%) as compared to the Ranson (60.0%), modified Glasgow (50.0%), and DeBanto (60.0%) scores. The specificity was 96.3% for the pediatric JPN score, 93.6% for the Ranson score, 98.5% for the modified Glasgow score, and 86.0% for the DeBanto score. The positive predictive value of the modified Glasgow score (71.4%) was superior to the other scoring systems (pediatric JPN, 61.5%; Ranson, 42.8%; and DeBanto, 24.0%). The negative predictive value of the four systems was almost identical (pediatric JPN, 98.4%; Ranson, 96.7%; modified Glasgow, 96.4%; and DeBanto, 96.7%; Table 7).

Discussion

Alcohol and gallstones are the main etiologies of AP in adults.[11,12] The etiology in children, however, is often drugs, infection, trauma, or anatomic anomalies such as choledochal cyst and abnormal union of the pancreatobiliary junction.[1,7,13] Because the basic pathogenesis of AP does not greatly differ between adults and children, the current approach to pediatric AP relies on experience and knowledge gained from treating adult AP.[13] There are no data, however, on the mortality rate of severe AP in childhood. The mortality rate in Japanese adults decreased from 27% in 1996 to 8% in 2011 due to the development of new diagnostic and therapeutic methods.[14] Providing intensive care unit (ICU) management, specialized therapies such as continuous regional arterial infusion of protease inhibitor and antibiotics, enteral nutrition via nasojejunal feeding, and continuous hemodiafiltration have improved the outcome of severe AP by reducing infection and averting pancreatic surgery, even in children.[15–17] To reduce the mortality rate, it is important for patients with severe AP to be transferred to a medical facility with adequate monitoring and intensive care. Several scoring systems are used in adults to identify severe AP, but there is no universally accepted scoring system for predicting the severity of childhood AP.[1,6,7]

The JPN scoring system (2008 version), which is based on clinical signs, blood test data, and imaging, is widely used in Japan to determine treatment strategies.[5] The effectiveness of

Table 7 Prediction of severity of AP

System	Mild (mean ± SE)	Severe (mean ± SE)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Ranson score (maximum, 11 points)	1.15 ± 0.07	3.20 ± 0.49	84.8	60.0	93.6	42.8	96.7
Modified Glasgow score (maximum, 8 points)	0.50 ± 0.06	2.76 ± 0.42	95.2	50.0	98.5	71.4	96.4
DeBanto score (maximum, 8 points)	1.41 ± 0.10	2.70 ± 0.47	84.1	60.0	86.0	24.0	96.7
Pediatric JPN score (maximum, 9 points)	0.82 ± 0.06	3.80 ± 0.49	95.2	80.0	96.3	61.5	98.4

AP, acute pancreatitis; JPN, Ministry of Health, Labour and Welfare of Japan; NPV, negative predictive value; PPV, positive predictive value.

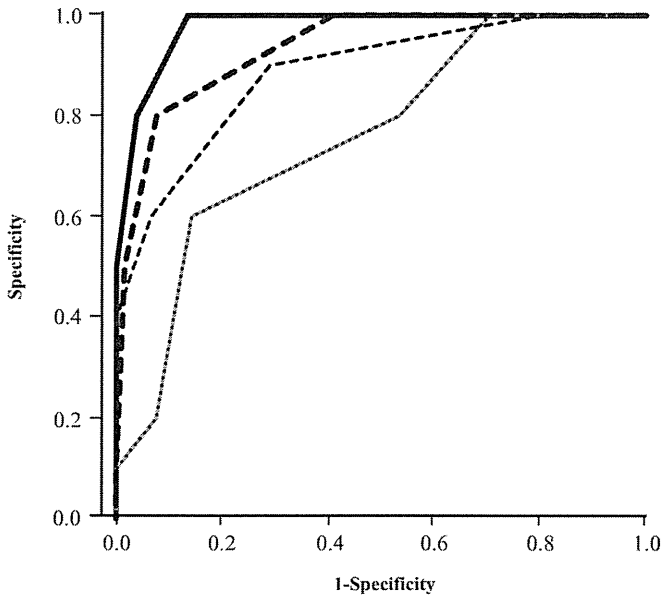

Fig. 1 Receiver operating characteristic curve of the discrimination of the (—) modified Ministry of Health, Labour and Welfare of Japan (pediatric JPN) score, (----) Ranson, (-----) modified Glasgow, and (·····) DeBanto scores for predicting major complications in pediatric acute pancreatitis. The area under the curve (AUC) was greater for the pediatric JPN score (0.980) than for the Ranson (0.886), modified Glasgow (0.935), and DeBanto (0.754) prognostic scores.

CRP, which is a criterion in the JPN system, as a single marker for the prediction of severity has been reported,[18,19] but CRP is not a criterion in the Ranson, modified Glasgow or DeBanto scores. The cut-off for predicting severe outcome at CRP ≥15 mg/dL after 48 h from onset of AP was recommended at the Santorini consensus conference (1999),[20] in the World Congress of Gastroenterology guidelines (2002),[21] and in the UK guidelines (2005).[22] Unfortunately, the JPN scoring system lacks the predictive value needed to guide confident clinical decision-making in children. When the JPN system (2008 version) was used in the present patients, the specificity was 100% but the sensitivity was only 50%. In the present study, we modified only two parameters of the JPN scoring system to produce the pediatric JPN scoring system.

The AUC of the ROC curve provides a global assessment of test performance, without applying any arbitrary cut-off. In this analysis, the pediatric JPN score had the best overall discrimination. Using the cut-off of 3 points in each system, this new system had equal or better clinical accuracy (95.2%) as compared to the Ranson (84.8%), modified Glasgow (95.2%), and DeBanto systems (84.1%). The present study, however, has several limitations that are inherent to any retrospective study. Because mean platelets, serum Ca, BUN, and CRP did not reach the cut-off in the severe AP group, reconstruction of new suitable cut-offs for pediatric patients is needed to examine an increased number of severe AP cases. Additionally, the usefulness of the pediatric JPN score should be examined in Western children, because there are etiological differences in AP between Asian and Western children.[23,24]

The international consensus conference on pediatric sepsis and organ dysfunction was held in February 2002 in San Antonio, Texas, where the criteria for adult SIRS were modified for pediatric use, and the definitions of sepsis, severe sepsis, and septic shock for pediatric patients were revised.[9] It was determined that at least two of four criteria, one of which must be abnormal temperature or leukocyte count, are required to confirm SIRS in a pediatric patient. Age-specific normal values for vital signs and laboratory data were incorporated into the definitions of SIRS and sepsis in children. Because SIRS criteria were derived from the adult respiratory distress syndrome criteria, there was much discussion that this criteria contained higher sensitivity and lack of specificity. A literature review by Carvalho *et al.* cited one study reporting a 68% prevalence of SIRS in the pediatric ICU.[25] In adults, 68% of patients admitted to the ICU met at least two criteria for SIRS.[26] In Japan, the prevalence of SIRS reached 84% among all adult ICU patients.[27] These data are not fully comparable to the present ones due to differing patient age groups and cut-off criteria.

In many clinical settings, the very old and the very young are at the highest risk of poor outcome. Persons in these age groups often have lower physiological reserves than do otherwise healthy adults in the prime of life. In the present study, although there were no significant differences in age and weight among patients with mild or severe AP, the age (6.40 ± 0.42 years) and weight (20.9 ± 3.7 kg) in the severe group were similar to those in the first pediatric report on AP by DeBanto *et al.*[1] In contrast, in the second report by Lautz *et al.* patients younger than 7 years were more likely to have mild (29%) than severe AP (12.5%, $P < 0.05$).[7] Further examination is necessary to verify the cut-offs for age and weight in a validation group.

The CT severity index (CTSI) has proven to be very useful in adults.[5,28] Recently, Lautz *et al.* reported that CTSI was superior to a clinical scoring system for identifying children with AP at heightened risk for developing serious complications.[29] Although 42 of 145 patients received plain and/or contrast-enhanced CT, in the present study it was not possible to evaluate the performance of the CTSI because only three patients with severe AP received CT. Most patients received non-invasive abdominal echosonography instead of CT. Clinical trials assessing the usefulness of the CT scoring system in Japanese children and adolescents with AP are needed.

Conclusion

Pediatric JPN score, although not perfect, is sufficient for the prediction of outcome in the initial period in order to identify pediatric patients with severe AP. The use of this scoring system at admission may help to improve treatment outcome in pediatric patients.

Acknowledgments

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膵炎を発症した PCDH19遺伝子異常症の1例

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薬剤性膵炎は、薬剤が原因で生じた膵炎で、急性膵炎の臨床像を呈する。臭化カリウム（KBr）あるいはクロバザム（CLB）使用中に薬剤性膵炎を発症した症例の報告はない。今回群発するけいれんの治療として使用したKBr、CLBによって薬剤性膵炎を発症したPCDH19遺伝子異常症の1女児例を経験したのでその臨床経過を報告する。症例はPCDH19遺伝子異常症の5歳女児。発熱上昇に伴いけいれんが群発し、CLB開始、PB、KBrを増量したが効果なし。チオペンタールNaの投与を開始し止痙した。その後、血液検査で膵酵素の上昇を認めるようになった。薬剤性膵炎を考え、チオペンタールNa、PBを中止したが変化ないため、CLB、KBrを中止したところ、中止後より膵酵素の減少を認め、膵酵素は正常化した。KBrやCLB使用中に薬剤性膵炎をきたす可能性があり、注意を要する。

Keywords：薬剤性膵炎、PCDH19遺伝子異常症、DLST、臭化カリウム、クロバザム

緒　言

臭化カリウム（KBr）は古典的な抗てんかん薬（AED）であるが、種々のAEDの開発に伴い使用頻度は激減した。しかし、近年Dravet症候群、乳児移動性部分発作けいれんなど、難治なてんかん症候群に一定の発作抑制効果があり使用されている[1)]。クロバザム（CLB）は、従来は抗不安剤として使用されていたがGastautがてんかん発作にも有効であることを報告して以来、抗てんかん薬としても使用されるようになり、2000年5月本邦で市販承認された[2)]。KBrの副作用として、眠気、

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嘔吐、下痢、皮膚症状が[3]、CLBの副作用として眠気、ふらつきなどが報告されている[2]。

薬剤性膵炎は、薬剤が原因で生じた膵炎で、急性膵炎の臨床像を呈する。多くは軽症で予後良好な疾患であるが、重症化し死亡する例もあり注意を要する[4]。AED投与中に膵炎を発症した報告はバルプロ酸（VPA）に多く、他にカルバマゼピン、フェニトインなどが報告されているが[5]、KBrあるいはCLB使用中に薬剤性膵炎を発症した症例の報告はない。

PCDH19遺伝子は接着分子プロトカドヘドリン19をコードするX染色体上の遺伝子で、その異常により、女性はてんかんや様々な程度の知的障害を発症する。発作は乳幼児期に発熱に誘引される焦点発作や全般発作が出現し、群発することが特徴である。発作出現の予防にはKBr、CLBあるいはフェニトインが有効とされ、発作の出現時にはミダゾラム（MDZ）が有効である。神経細胞のPCDH19遺伝子異常がモザイクに存在することにより正常なネットワーク構造を保持できなくなることがその病態ではないかと推定されている[6]。

今回、群発するけいれん治療として使用したKBrとCLBによって薬剤性膵炎を発症したと診断したPCDH19遺伝子異常症の1女児例を経験したので報告する。

症　例

【症例】5歳　女児

【主訴】けいれん群発

【既往歴】1歳11カ月から発熱時に群発するけいれんを認めた。精神発達遅滞があり、遺伝子検査でPCDH19遺伝子異常症の診断に至っている。けいれんに対してVPAは無効で中止。その後、フェノバルビタール（PB）とCLBの併用で発作が減少、その後KBrが追加投与され、けいれんは抑制。外来担当医はCLBを無効と判断し、入院10日前から中止していた。

【家族歴】兄に自閉症

【現病歴】X年6月16日、37℃台の発熱に伴い数十秒間持続する全身性間代性けいれんが約1時間間隔で群発したため当院を受診。けいれんのコントロール目的に入院となった。

【身体所見】身長95cm、体重18kg、体温37.7℃、心拍80回/分、呼吸数23回/分、血圧96/55mmHg、診察所見では、咽頭；軽度発赤、心音；整、呼吸音；清、腹部聴診・触診所見；異常なし。発作間歇期の意識レベルは清明。

【臨床検査所見】血液生化学検査（表1）では、異常なし。

【治療経過】治療経過を図1に示す。けいれん群発に対して、MDZ 0.15mg/kg/hrの持続投与を開始した。また、けいれんの群発にはCLBを中止したことが関係していると考えられたため、PB（1.5mg/kg/day）、KBr（30mg/kg/day）の内服に加えCLB 0.1mg/kg/dayを再開した。発熱とけいれん群発の影響もあり、入院当初は内服が困難でありPBは坐剤を投与した。その後、発熱は持続するもののけいれんの出現はなく経過し、AEDの内服が可能となったことを確認し、第5病日にMDZ 0.1mg/

表1　血液検査所見

①入院時血液検査所見

血算		生化学			
WBC	12080/μl	TP	7.1 g/dl	CK	120 U/L
Neut	67.6%	ALB	4.5 g/dl	Na	138 mEq/l
Lym	22.5%	AST	32 U/L	K	3.6 mEq/l
RBC	481X10⁶/μl	ALT	14 U/L	Cl	112 mEq/l
Hb	13.5/μl	LDH	287 U/L	Glu	134 mg/dl
Hct	41.8%	BUN	12 mg/dl	CRP	0.08 mg/dl
PLT	28.3X10⁴/μl	Cre	0.31 mg/dl	NH3	60 μg/dl

②DLST

薬剤名	測定値	S.I.(%)
control	124	
potassium bromide	265	213
phenobarbital	213	171
clobazam	255	205
thiopental Na	88	70

判定 S.I.（%）：181%以上で陽性

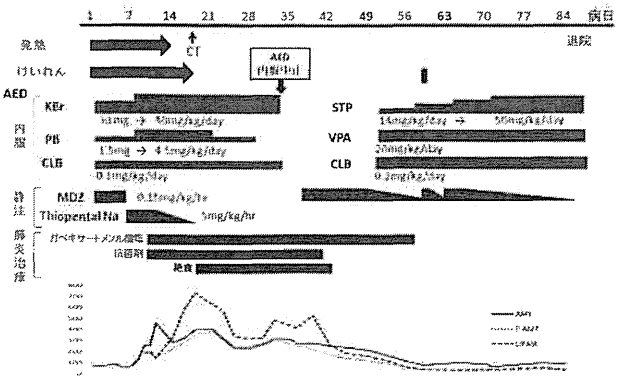

図1　臨床経過
AED; 抗けいれん薬, AMY; アミラーゼ, CLB; クロバザム, KBr; 臭化カリウム, MDZ; ミダゾラム, P-AMY; 膵アミラーゼ, PB; フェノバルビタール, STP; スチリペントール, VPA; バルプロ酸

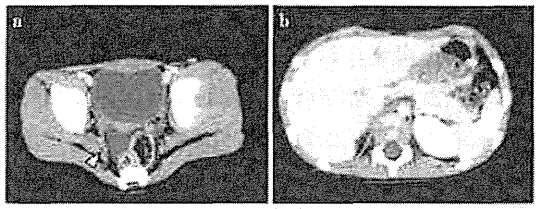

図2　腹部CT画像
a: 軽度腹水を認める（△）, b: 明らかな異常所見はなし

kg/hrに減量した。しかし、第6病日に再度、けいれんの群発がみられたため、MDZ 0.15mg/kg/hrの持続投与を再開し、同時にKBr 40mg/kg/day、PB 4.5mg/kg/dayの増量を行ったが、けいれんの群発が続いた。MDZを中止しチオペンタールNa（Thio）5mg/kg/hrの投与を開始し、けいれん群発は消失した。継続してThioを使用していたが、第10病日より血液検査にて膵酵素の上昇（アミラーゼ（AMY）256 U/L（正常値33-120U/L）, 膵由来アミラーゼ（P-AMY）187U/L（正常値14-41U/L）, リパーゼ192U/L（正常値130-400U/L））がみられた。重度知的障害のため腹痛の有無については評価困難であったが、膵酵素が正常値の3倍以上上昇していたため急性膵炎を発症したと診断し、ガベキサートメシル酸塩40mg/kg/day、抗菌剤（セフォゾプラン塩酸塩）80mg/kg/dayの投与を開始した。しかし効果がみられず、第18病日膵酵素はさらに上昇した（AMY 322 U/L, P-AMY 285U/L, リパーゼ582U/L）。同日施行した腹部造影CTでは少量の腹水を認める以外には、胆石などの胆管系疾患を含め画像上異常所見は認めなかった（図2）。Thioの投与を開始後膵酵素が上昇したため、Thioによる薬剤性膵炎が除外できず、同日より絶食を開始し、Thio投与も中止した。しかし中止後も膵酵素の上昇が持続（AMY 399U/L, P-AMY 357U/L, リパーゼ734U/L）するため、その他の薬剤性膵炎を考慮し、第20病日よりPBを減量し第29病日に中止した。またPB中止後も膵酵素の低下がみられないため（第33病日; AMY 320U/L, P-AMY 305U/L, LIPASE 491U/L）、第33病日よりKBrとCLBも同時に中止し、全てのAEDを中止した。Thio投与開始からすべてのAEDを中止していく経過で、けいれんはなかったが、すべての薬剤を中止した後よりけいれんが再発。第36病日にMDZ 0.1mg/kg/hrの持続投与を再開した。一方で、KBr、CLB中止後約1週間経過した第43病日頃より膵酵素が低下（AMY 257U/L, P-AMY 174U/L, リパーゼ268U/L）してきた。退院に向けMDZを中止し、AED内服の再開が必要であったが、膵炎を発症した経緯がありKBrやCLBは投与が懸念されたため、過去の報告からトピラマート（TPM）に有効性を示す症例が多いことを説明し[6]、投与に承諾を得ようと試みたが未

使用な薬剤に対して効果・副作用が不明なことが不安という理由でTPMの使用に承諾が得られなかった。そこでDravet症候群とPCDH19異常症が幼児期に熱誘発性のけいれんを発症するという類似点があることからスチリペントール（STP）の使用についてお話ししたところ両親から投与に承諾がえられ、第51病日よりスチリペントール（STP）14mg/kg/dayを開始した。投与開始に際しては、再度併用薬としてVPA 20mg/kg/dayとCLB 0.2mg/kg/dayを併用しなければいけないこと、CLBの投与により薬剤性膵炎が再燃する可能性を両親に十分説明し承諾を得た。第60病日、62病日にけいれん群発を認めたが、STPを50mg/kgまで増量して以降、発作症状が消失した。第86病日にMDZは中止できた。退院後、STPの副作用と考えられる眠気の症状がみられるようになったため、現在は家族の希望でSTPを15mg/kg/dayまで減量している。膵酵素は第85病日にすべて正常化し（AMY 93U/L, P-AMY 36U/L, リパーゼ241U/L）、以降現在まで上昇を認めていない。退院後、AED各薬剤についてDLSTの結果が得られ、KBr、CLBが陽性であった（表1）。

考　案

群発するけいれん治療の経過中に膵酵素の上昇をきたし、AEDの中止により膵酵素が正常化し、AEDによる薬剤性膵炎と診断されたPCDH19遺伝子異常症の1女児例を経験した。また、KBrとCLBの使用が薬剤性膵炎の原因と考えられた。

急性膵炎の診断においては、①腹痛、②血清アミラーゼあるいはリパーゼの正常値の3倍以上の上昇、③画像上の変化（腹水を伴う膵腫大あるいは膵周囲の脂肪織の炎症所見あるいは壊死）のうち2項目がみられることとされるが[7]、本症例は重度知的障害を合併していて腹痛の評価が困難であるが、血清アミラーゼとリパーゼの正常値の3倍以上の上昇があり、画像でも腹水貯留をみとめていることから、急性膵炎を発症していたと診断した。

小児における急性膵炎の原因としては、胆石などの胆管系疾患（10-30%）、外傷（10-40%）、全身性疾患に伴うもの（33%）、薬剤性（25%>）、特発性（13-34%）が多く、続いて感染（10%>）、代謝性疾患（2-7%）、遺伝性（5-8%）と報告されている[7]。Malloryは薬剤性膵炎の診断根拠として①薬剤投与中に出現すること、②投与中止によって寛解すること、③再投与によって再発することの3点が必要であるとしているが[5]、本症例では、KBr, CLBの投与中に膵酵素の上昇とこれらの中止による速やかな膵酵素の低下がみられ、高ビリルビン血症、胆道系酵素の上昇、画像検査に肝臓、胆のうの形態的な異常がなく、外傷既往や全身性疾患・代謝性疾患を疑う経過ではなく、調べ得た限りの抗体検査から感染症が原因と考えにくく、家族歴もみられなかったことから、本症例の膵酵素の上昇は、薬剤性膵炎としてよいと考えた。

薬剤性膵炎の発症機序においては、①Oddi括約筋の収縮による膵酵素の流出障害、②薬物あるいはその代謝物による直接障害、③アレルギーあるいは過剰反応があげられる[4]。アレルギー反応が発症機序と診断した症例ではDLSTを診断に用いている報告が散見されている[8]。本症例でもKBrおよびCLBのDLSTが陽性であったことから（表1）、これらの薬剤のアレルギー反応が薬剤性膵炎の発症機序ではないかと推定された。

小児では、VPA、L-アスパラギナーゼ、プレドニゾン、6-メルカプトプリンなどが薬剤性膵炎を起こしうる薬剤として報告されており[7]、またAEDではVPAのほかにカルバマゼピンやフェニトイン内服中に膵炎を発症した報告があるが[5]、チャレンジテスト陽性で他の膵炎の原因が除外されたものはVPAのみにとどまる[4]。KBrにおいては、イヌにおいてKBrとPBの併用時に膵炎を発症し、薬剤性膵炎と診断された報告がある[9]。発症機序は不明であるが、PB単独使用と比較しPBとKBrの併用時に膵炎の発症率が上昇すると述べられている[9]。したがってKBrとCLBの併用が膵炎発症に関与する可能性はある。またCLBは膵炎発症前に断続的に投与されていた薬剤であり、再投与後に膵炎の再発がみられないことから、KBrだけが膵炎発症に関与したとも考えられる。CLBの内服中やKBrとCLBの併用中の薬剤性膵炎は成人例も含めて報告がなく、今後の症例の蓄積が必要である。また因果関係が明確でなくともこれらの薬剤の使用時には薬剤性膵炎の発症

に注意を払う必要がある。

PCDH19異常症は乳児期よりけいれんを発症し、発作抑制に難渋する場合がある。KBrやCLBは有効な薬剤として知られており、PCDH19異常症において使用頻度が高い[6]。したがって本疾患の診療においては、KBrやCLBの使用が薬剤性膵炎を発症する可能性があることに留意すべきと思われた。

まとめ

けいれん群発の治療中に薬剤性膵炎を発症したPCDH19異常症の1女児例を経験した。KBrとCLBの使用が原因薬剤ではないかと推定され、発症には本剤に対するアレルギーが考えられた。

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Development and Validation of a Novel Fibrosis Marker in Biliary Atresia during Infancy

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OBJECTIVES: Most biliary atresia (BA) patients suffer from liver fibrosis and often require liver transplantation. The aim of this study was to develop and validate a novel fibrosis marker for BA patients aged <1 year—the infant BA liver fibrosis (iBALF) score—subsequent to the previously reported fibrosis marker for BA patients aged ≥1 year.

METHODS: From three institutions for pediatric surgery, BA patients and their native liver histology examinations performed at the age of <1 year were retrospectively identified and assigned to a development cohort (58 patients and 73 examinations) or validation cohort (92 patients and 117 examinations) according to their institutions. Histological fibrosis stages (F0–F4), blood test results, and clinical information at the time of liver histology examination were reviewed. The iBALF score was determined using multivariate ordered logistic regression analysis and was assessed for its associations with histological fibrosis stages.

RESULTS: The iBALF score equation was composed of natural logarithms, including serum total bilirubin level, blood platelet counts, and days of age. The score revealed a strong correlation with fibrosis stage ($r = 0.80$ and 0.73 in the development and validation cohorts, respectively; $P < 0.001$). The areas under the receiver-operating characteristic curves for diagnosing each fibrosis stage were 0.86–0.94 in the development cohort and 0.86–0.90 in the validation cohort ($P < 0.001$), indicating good diagnostic power. In addition, no patient with an iBALF score >6 (equivalent to F4) at the initial surgery survived with their native liver at 1 year of age ($n = 9$).

CONCLUSIONS: The iBALF score that was developed was a good noninvasive marker of native liver fibrosis for BA patients aged <1 year.

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INTRODUCTION

Biliary atresia (BA) is a common cause of pediatric cholestasis due to obliterative cholangiopathy that develops in 1/5,000–1/19,000 newborns and is the most common indication for pediatric liver transplantation.[1] Because rapid progression of liver fibrosis is a prominent feature of BA patients, early diagnosis and timely surgical correction of cholestasis are needed.[1,2] In general, hepatoportoenterostomy is initially attempted to achieve initial bile drainage for most patients in whom the disease involves the bile duct at the porta hepatis (type 3 disease) and for whom a surgical anastomosis between the bile duct and the gastrointestinal tract cannot be created.[1] Although hepatoportoenterostomy can achieve initial bile drainage in 50–60% of cases, advanced liver fibrosis and possible progression of liver fibrosis after surgery lead to portal hypertension and cirrhosis.[1,2] Liver transplantation is performed secondarily when bile drainage is not achieved or when cirrhotic complications affect patients.[3] Thus, liver fibrosis is thought to be an important predictor of outcome for BA patients, for whom long-term survival with the native liver is only achieved in ~20%.[2,3]

Although assessment of liver fibrosis is considered to be useful in BA patients, liver histology examinations are generally performed only at the same time as surgical procedures; liver tissue is obtained via surgical wedge biopsy during laparotomy or total hepatectomy during liver transplant surgery; postsurgical liver biopsy examinations for monitoring fibrosis progression are not generally performed.[2] However, we have performed postsurgical liver biopsy examinations to more precisely evaluate native liver status and to determine the optimal timing for liver transplantation, mostly from living donors in Japan, in clinical practice. Because reliable, surrogate, noninvasive liver fibrosis markers in BA patients have been limited,[2] we previously developed a BA liver fibrosis (BALF) score using a retrospective analysis of postsurgical native liver histology examinations.[4] The BALF score was calculated using standard liver test results and age and is a potential liver fibrosis marker in BA patients aged ≥1 year; however, the score was unable to predict liver fibrosis in

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patients aged <1 year.[4] Because some patients require primary or early liver transplantation owing to rapid progression of liver fibrosis, we considered that an available, reliable and noninvasive liver fibrosis marker during infancy would be of great worth. In the current study, we developed a novel noninvasive fibrosis marker for BA patients aged <1 year, subsequent to the previously reported BALF score. This novel fibrosis marker was delineated as the infant BALF (iBALF) score and was validated in an independent population of BA patients.

METHODS

Study population and ethical considerations. The medical records of BA patients at three institutions for pediatric surgery were retrospectively reviewed, and 155 patients from whom native liver specimens had been obtained at <1 year of age between March 1993 and April 2014 were identified. The patients were assigned to either the development cohort ($n=60$) or the validation cohort ($n=95$), according to the participating institutions: the development cohort derived from Keio University Hospital and Saitama City Hospital, and the validation cohort derived from the National Center for Child Health and Development. We confirmed that the development and validation cohorts did not share the same patient. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethical committees of all three participating institutions. All of the biopsies and surgeries were performed after obtaining written informed consent.

Liver tissue sampling and histology examinations. During the initial bile drainage surgery, wedge biopsy examinations were performed using surgical resection from the edge of the liver. Postsurgical liver histology examinations were performed in several patients from wedge biopsy specimens during re-laparotomy and from percutaneous liver biopsy specimens of ≥1.0 cm in length using an 18-gauge suction needle under ultrasonographic guidance. Explanted livers were obtained during liver transplant surgery and were histologically examined. Histological liver fibrosis stages were based on the documented findings by experienced pathologists at the time liver tissue samples were obtained; if needed, re-evaluation by an experienced pathologist participating in the current study was performed at each institution. For liver fibrosis grading, the Metavir scoring system[5] or the new Inuyama classification[6] was used with the following classifications: F0, no portal fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa or lobular distortion without cirrhosis; and F4, cirrhosis.

Data collection and data exclusion. The patients' clinical information and blood test results were collected from the medical records in association with liver histology examinations. The collected clinical information included sex, disease type, history of surgical procedure, age at the time of surgery, age at tissue sampling, and method of tissue sampling. Patients who had a history of splenectomy or partial splenic embolization and those with BA splenic malformation syndrome were excluded. The disease type was determined according to the classification of the Japanese Biliary Atresia Society:[7] atresia at the level of the most proximal part of the common bile duct (type 1), hepatic duct (type 2), and porta hepatis (type 3). The collected blood test results included serum total bilirubin (TB), direct bilirubin, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase (GGT), albumin, and cholinesterase levels; prothrombin time-international normalized ratios; and platelet counts, which had been examined within a few days before liver tissue sampling. The impact of transfusion, cholangitis, and vitamin K deficiency on the blood test results was excluded to the greatest extent possible; if transfusion had been performed or cholangitis had occurred before liver tissue sampling, data preceding transfusion or cholangitis up to 1 month were used, whereas in cases of vitamin K deficiency at the time of initial surgery, data after correction of vitamin K deficiency were used. Cholangitis was defined as fever and serum TB elevation without any other apparent cause, and vitamin K deficiency was defined as coagulopathy that improved soon after vitamin K administration.

Development of the iBALF score. Development of the iBALF score was accomplished using a similar method to BALF score development.[4] To predict the histological fibrosis stage, ordered logistic regression analyses were performed, using the semiquantitative histological fibrosis grading as ordinal data (from F0 to F4) for the dependent variable; the logarithmic values of the collected blood test results and days of age at the time of corresponding histological examination served as the independent variables. To determine the iBALF score equation, significant independent variables and the regression coefficients from the multivariate analysis were used. The constant of the score equation was determined by bringing the cutoff values of the iBALF score for fibrosis prediction close to the previously reported BALF score cutoff values in patients aged ≥1 year (2.42 for ≥F2, 4.12 for ≥F3, and 5.64 for F4).[4]

Assessment of the iBALF score. After determination of the iBALF score equation from the development cohort, the scores were calculated from the development and validation cohort data; the values of the iBALF score were obtained along with the corresponding histological examination results. The diagnostic power of the iBALF score for predicting each fibrosis stage was assessed using a receiver-operating characteristic curve comparing the blood platelet counts and the aspartate aminotransferase-to-platelet ratio index (APRI), which has been the most widely investigated fibrosis marker in BA patients. The APRI was calculated using the following equation:[8]

APRI = (aspartate aminotransferase/upper normal limit/platelet counts (10^9/l)) × 100.

The upper normal limit of aspartate aminotransferase was determined according to the age-specific reference intervals for Japan.[9]

Assessment of the prognosis at 1 year of age. The prognosis of the patients who participated in the study from the initial surgery (initial bile drainage surgery or primary

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 = $7.196+1.438\times\text{Log}_e$ [TB (mg/dl)]$+0.434\times\text{Log}_e$ [GGT (IU/l)] $- 3.491\times\text{Log}_e$ [albumin (g/dl)]$-0.670\times\text{Log}_e$ [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 = $8+1.185\times\text{Log}_e$ [TB (mg/dl)] $- 1.882\times\text{Log}_e$ [platelet count (10^9/l)]$+1.093\times\text{Log}_e$ [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

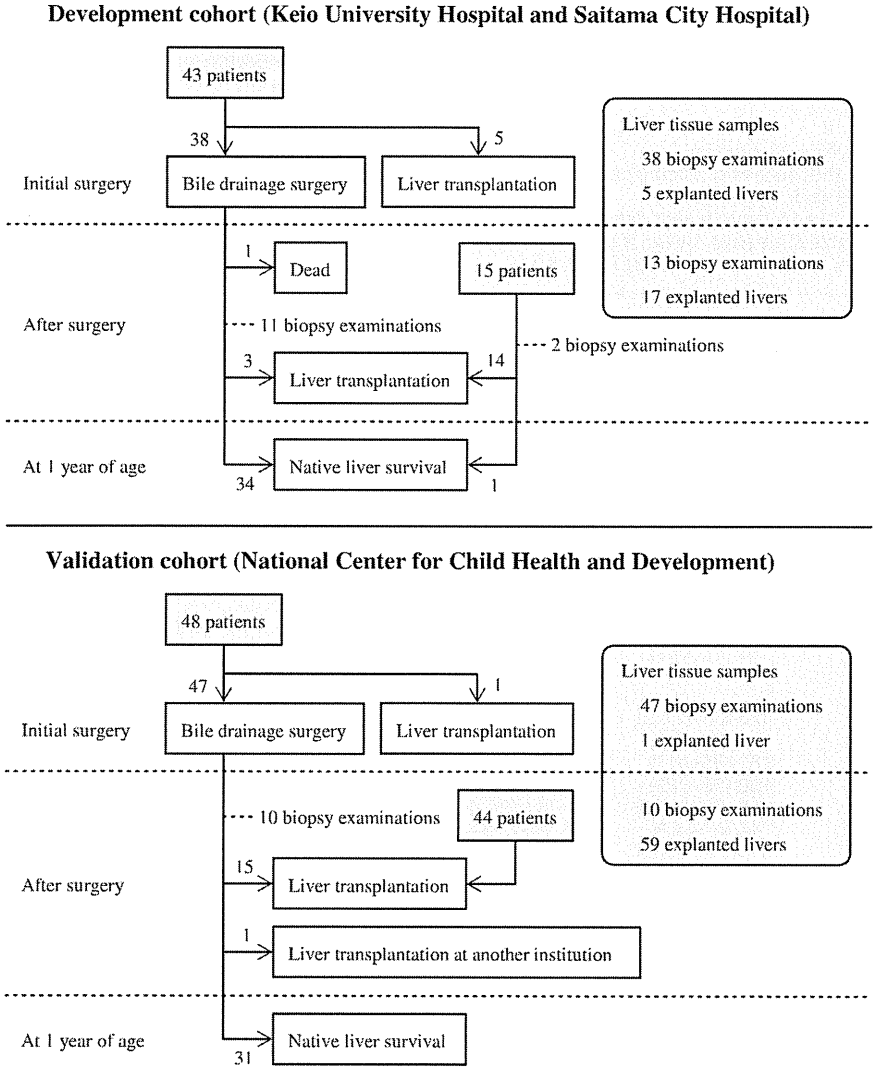

Figure 1 Timing of the patients' participation and tissue sampling in the development and validation cohorts. The number was counted after excluding two and three patients with biliary atresia splenic malformation syndrome from the development and validation cohorts, respectively.

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.