Factors Related to the Clinical Outcomes of the Kasai Procedure in Infants with Biliary Atresia

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ABSTRACT

Objective: The Kasai portoenterostomy has been accepted as the primary therapeutic treatment for biliary atresia. However, successful bile drainage does not always promise a long-term native liver survival. Several clinical factors were evaluated to discover associations with the outcomes.

Methods: A retrospective chart review was conducted of infants with biliary atresia who underwent the conventional Kasai portoenterostomy at Siriraj Hospital, January 2006-August 2018. The patient demographics, perioperative clinical and laboratory data, adjuvant therapies, complications, and interventions were analyzed in correlation to the short- and long-term outcomes. The short-term outcome evaluated was the resolution of jaundice, while the long-term outcome was remaining jaundice-free with the native liver.

Results: The complete medical records of 80 patients were retrospectively reviewed. Their mean age at the time of the Kasai portoenterostomies was 97 days. Overall, 66.3% achieved jaundice clearance. The mean follow-up duration was 50.5 months, with 51.3% of the patients remaining jaundice-free with their native liver. A prolonged duration of a prophylactic antibiotic was significantly related to the jaundice clearance, with a p-value of 0.002. Moreover, a lower number of episodes of cholangitis was significantly related to a good long-term outcome (p-value, 0.024).

Conclusion: The prolonged provision of a prophylactic antibiotic as adjuvant therapy after the Kasai portoenterostomy was associated with jaundice clearance. An increased incidence of cholangitis episodes was associated with poor long-term outcomes. Postoperative adjuvant therapy should be standardized and maintained for the care of biliary atresia patients to improve their outcomes.

Keywords: Adjuvant therapy; biliary atresia; cholangitis; Kasai portoenterostomy outcome; prophylactic antibiotic
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INTRODUCTION

Biliary atresia is an idiopathic inflammatory cholangiopathy of infancy. It is characterized by progressive fibrosing obliteration at varying levels of the intrahepatic and extrahepatic bile ducts, and inevitable cirrhosis.[1,2] It is the most common cause of neonatal direct hyperbilirubinemia and cirrhosis in children, and the most common indication for pediatric liver transplantation worldwide.[2,3] The Kasai portoenterostomy[4] has been accepted as the primary therapeutic treatment for the restoration of bile flow and the preservation of the liver. However, the procedure produces variable outcomes. Successful drainage does not always predict a long-term, jaundice-free native liver survival as progressive irreversible liver injury and complications of cirrhosis (mainly portal hypertension) can occur despite adequate bile drainage

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being achieved.[3,5-8] Previous studies from large-scale institutions have demonstrated various pathological, clinical, and surgical factors associated with successful bile drainage and long-term, transplant-free survival.[1,3,7-10]

Unfortunately, the majority of infants in developing countries reach tertiary-care centers when they are older than the maximum recommended age of 2 months for the performance of a Kasai portoenterostomy. As well, liver transplantation is not always suitable for every family. Faced with limitations in financial support, transportation, and the provision of continuing care for the immunosuppressed children, a number of biliary atresia children die of end-stage liver disease. We therefore conducted this study to identify any clinical factors that are associated with improved outcomes for Kasai portoenterostomy.

MATERIALS AND METHODS

A retrospective chart review was conducted of infants with biliary atresia who underwent the conventional Kasai portoenterostomy procedure at Siriraj Hospital, January 2006 - August 2018. Patients who were operated on at another hospital or who developed complications unrelated to biliary atresia or the Kasai operation were excluded. An analysis was made of the patient demographics and laboratory data with respect to the short- and long-term outcomes. The laboratory tests comprised the gamma-glutamyl transpeptidase (GGT) levels prior to, and at specific times after, the operation, as well as the full range of liver function tests (total bilirubin, direct bilirubin, aspartate transaminase, alanine transaminase, and alkaline phosphatase). Also analyzed were the perioperative clinical data (postoperative steroid administration; the duration of the steroid; and intravenous and prophylactic antibiotic administration) to ascertain their impact on the short- and long-term outcomes. The short-term outcome evaluated was the achievement of jaundice clearance, which was defined as a serum total bilirubin level of ≤ 1.2 mg/dL at any time point after the procedure. Patients who did not achieve normalized bilirubin levels were considered to have the poor short-term outcome of no jaundice clearance. The long-term outcomes were categorized as “good” and “poor”. A good long-term outcome was defined as a patient being jaundice-free with the native liver for more than 6 months after the Kasai portoenterostomy, with regular monitoring up to the last follow-up appointment. On the other hand, the poor long-term outcomes comprised patients who remained clinically jaundiced or developed cirrhosis with the native liver, patients who underwent a liver transplantation, and disease-related deaths. In cases of patients who achieved jaundice clearance, the durations until the total bilirubin reached normal levels were evaluated. Details of the overall levels of complications that were suspected to affect the long-term outcomes (such as the development of cholangitis, the duration until the first episode of cholangitis, and the number of episodes of cholangitis) were correlated to both the short- and long-term outcomes. The diagnosis of cholangitis after the portoenterostomy procedure was based on clinical symptoms of either progressive jaundice, with or without fever and acholic stool. These were proven by increase bilirubin and GGT levels from baseline in association with leukocytosis and increase C-reactive protein level. The number of salvage interventions (namely, redo-portoenterostomies and percutaneous biliary drainage) were reviewed to establish any associations with the long-term outcomes.

Statistical analyses

Data were prepared and analyzed using PASW (Predictive Analytics Software) Statistics 18.0 (IBM SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean and standard deviation for normally distributed data, or as median with range in the case of the non-normally distributed data. For both the short- and long-term comparison groups, the independent sample t-test was used to compare the normally distributed data related to the good and poor outcomes, while the Mann–Whitney U test was employed for the non-normally distributed data. Categorical data were analyzed using Pearson’s chi-squared test, Yates’s continuity correction, or Fisher’s exact test to compare the proportional data of the two groups. A receiver operating characteristic curve was employed to identify the optimal cut-off points of age at operation to classify the patients with good outcomes. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy (all with the corresponding 95% confidence interval [95% CI]) were calculated for each cut-off point. Statistical significance was determined to be a p-value of < 0.05. The statistically significant factors identified in a univariate analysis were subsequently tested in a multivariate analysis. The latter model used multiple binary logistic regression and adjusted odds ratio (OR) in order to adjust for confounding factors and demonstrate the magnitude of any associations between the independent factors and the outcomes.

Ethics approval

The protocol for this study was approved by the Institutional Review Board of Siriraj Hospital (Si 641/2018).

RESULTS

A total of 85 cases with biliary atresia were identified as having been treated at Siriraj Hospital from January 2006 to August 2018. Complete medical records of 80 of those patients were available and formed the basis of the study. There was a slight female predominance (a 3:2 female-to-male ratio), as demonstrated in Table 1. The mean age at Kasai portoenterostomy was 97 days, ranging from 21-204 days. Approximately 94% of the cases received an adjuvant steroid for an average duration of 4 weeks. All cases received intravenous empirical antibiotics, mostly for durations of 2-3 weeks. A prophylactic antibiotic was provided to 97.5% of cases and maintained for durations of 12-24 months after the operation. Altogether, 66.3% of the patients achieved jaundice clearance while the remainder (33.7%) never attained normal bilirubin levels. The mean duration until jaundice clearance was 4 months, ranging from 4-72 weeks after the operation. The incidence of postoperative cholangitis was 87.5%, occurring in 70 out of the total of 80 cases. The average duration to the development of cholangitis was approximately 2 months after the operation, with cases arising as early as within the first week and as late as 12 months. The overall mean number of cholangitis events was 3 episodes throughout the follow-up period. The incidences of the salvage procedures-redo-Kasai operation and percutaneous transhepatic biliary drainage-were 7.5% and 15%, respectively. The mean follow-up duration was 50.5 months, with 51.3% of the patients remaining jaundice-free with their native liver for more than 6 months after the Kasai portoenterostomy.

By using a receiver operating characteristic curve to classify patients with reference to the short-term outcome, the optimal cut-off point for the age at operation was determined to be 90 days. In fact, the accuracy in predicting the long-term outcome was higher for the cut-off point of 80 days. However, as the majority of patients in this study were older, we elected to use the cut-off point of 90 days in the multivariate analysis (Tables 2 and 3). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy (all with the corresponding 95% CI) of each age group in predicting the outcomes are detailed in Tables 2 and 3.

The univariate analysis of the potential factors related to the good short-term outcome (the achievement of jaundice clearance) is presented in Table 4. The clinical factors significantly associated with jaundice clearance were an age at operation of less than 90 days, a prolonged duration of use of a prophylactic antibiotic, and the absence of postoperative cholangitis. The laboratory factors which were significantly lower among patients with jaundice clearance were the total and direct bilirubin levels, and the hepatic enzymes (aspartate transaminase and alanine transaminase). The only laboratory factor significantly higher among patients with jaundice clearance was the serum GGT level on postoperative day 1. The subsequent multivariate analysis of all of the significant factors associated with jaundice clearance revealed that the only independent factor was the duration of the prophylactic antibiotic, with an adjusted OR of 1.128 (95% CI, 1.045–1.217) and a p-value of 0.002 (Table 5).

The univariate analysis of the potential factors related to the good long-term outcome (remaining jaundice-free with the native liver for more than 6 months after the operation) is demonstrated in Table 6. Approximately half of the study population (41 out of the 80 patients) remained jaundice-free with their native livers, all of which (100%) originally achieved jaundice clearance after the Kasai portoenterostomy. Twelve out of the 53 patients who initially achieved jaundice clearance later became jaundiced or progressed to cirrhosis, accounting for 30.8% of the poor long-term outcome group. The clinical factors found to be significantly associated with the good long-term outcome were the initial achievement of jaundice clearance, an age at operation of less than 80 days, a prolonged duration of use of a prophylactic antibiotic, a shorter duration until the attainment of jaundice clearance, the absence of postoperative cholangitis, and a lower number of episodes of cholangitis.

As previously mentioned, the cut-off point for the age at operation of 80 days more accurately predicted the long-term outcome than the cut-off point for the age of 90 days. Consequently, the age at operation of less than 90 days did not demonstrate any significant correlation to the good long-term outcome in the univariate analysis. As detailed in Table 6, the median age at operation of 77 days for the patients with a good long-term outcome was considerably lower than the median of 99 days for those with a poor long-term outcome (p-value, 0.021). The multivariate analysis of all of the significant factors associated with the good long-term outcome established that the only independent factor was the lower number of episodes of cholangitis, with an adjusted OR of 0.678 (95% CI, 0.484-0.949) and a p-value of 0.024 (Table 7).

As indicated in Tables 5 and 7, the multivariate analyses were not applied to certain factors. This was because those factors were involved in all, or none, of the measuring outcomes. Specifically, jaundice clearance was achieved in 100% of the cases with a good long-term outcome, while postoperative cholangitis occurred in 100% of the cases with poor short- and long-term outcomes. Therefore, the ORs, 95% CIs, and p-values of those factors could not be calculated in the logistic regression analyses.

TABLE 1. Patient demographics and clinical data (n = 80).

Factors	Incidence/mean ± SD	Percentage/range
Gender		
Female	49	61.3%
Male	31	38.7%
Age at Kasai operation (days)	96.7 ± 39.8	21–204
Body weight at operation (kilograms)	5.2 ± 0.9	2.8–6.9
Postop steroid administration		
No	5	6.2%
Within 7 days	55	68.8%
After 7 days	20	25%
Duration of steroid administration (days)	26 ± 9.5	0–60
Duration of intravenous antibiotics (days)	19.8 ± 10.1	6–63
Prophylactic antibiotic		
Yes	78	97.5%
No	2	2.5%
Duration of prophylactic antibiotic (months)	21.8 ± 22.8	0–144
Jaundice clearance		
Yes	53	66.25%
No	27	33.75%
Duration till jaundice clearance (weeks; n = 53)	16.4 ± 13.8	4–72
Postoperative cholangitis		
Yes	70	87.5%
No	10	12.5%
Duration till cholangitis (weeks; n = 70)	9.2 ± 18.5	1–144
Cholangitis episodes (n = 70)	3 ± 2.6	0–12
Redo-Kasai operation	6	7.5%
PTBD	12	15%
Liver transplantation (LT)	6	7.5%
Follow up duration (months)	50.5 ± 45.8	1–153
Status (follow-up > 6 months)		
Jaundice-free (NL)	41	51.3%
Deceased/cirrhosis/LT	39	48.7%

Abbreviations: PTBD, percutaneous transhepatic biliary drainage; LT, liver transplantation; NL, native liver; SD, standard deviation

TABLE 2. Accuracy of ages at different cut-off points in predicting short-term outcome.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
Age < 80 days	0.547	0.704	0.784	0.442	0.600
n = 37	(0.415–0.673)	(0.515–0.841)	(0.628–0.886)	(0.304–0.589)	(0.490–0.700)
Age < 90 days	0.642	0.667	0.791	0.486	0.650
n = 43	(0.507–0.757)	(0.478–0.814)	(0.648–0.886)	(0.334–0.641)	(0.541–0.745)

Abbreviations: PPV, positive predictive value; NPV, negative predictive value

TABLE 3. Accuracy of ages at different cut-off points in predicting long-term outcome.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
Age < 80 days	0.585	0.667	0.649	0.605	0.625
n = 37	(0.434–0.722)	(0.510–0.794)	(0.488–0.782)	(0.456–0.736)	(0.515–0.723)
Age < 90 days	0.634	0.564	0.605	0.595	0.600
n = 43	(0.481–0.764)	(0.410–0.707)	(0.456–0.736)	(0.435–0.737)	(0.490–0.700)

Abbreviations: PPV, positive predictive value; NPV, negative predictive value

DISCUSSION

The current research is a continuation of an earlier study at the same single center[11], but it included more participants and monitored them for a longer period. Previous studies have reported the impact of patient age at the time of surgery on the outcomes of the Kasai portoenterostomy.[7,12,13] Our review obtained a finding consistent with that of many other studies, which is that a younger age at surgery improves the rates of jaundice clearance and transplant-free survival with the native liver.[3,7,9,10,12,13] In more detail, this study found that a patient age of less than 90 days was significantly associated with the good short-term outcome of the achievement of jaundice clearance. Moreover, those aged less than 80 days were significantly associated with the good long-term outcome (maintaining the jaundice-free status with the native liver for more than 6 months after the operation). In Thailand, the majority of patients receive a Kasai portoenterostomy later than the maximum recommended age of 2 months. Concerned about the burdensome need to provide constant care to those patients, the authors were motivated to find any significant controllable factors impacting on the improvement of their care and the achievement of better outcomes. Despite the present study's findings, it is not our hospital's policy to withdraw salvage surgery when infants with biliary atresia present at an age over 90 days. On the contrary, the hospital encourages the Kasai portoenterostomy in children presenting as late as 4 or 5 months of age with less than a hard liver consistency. The aim is to provide the opportunity-no matter how limited-for the children to grow, and for their families to appreciate the children's requirements and understand the long-term care needed prior to the imminent liver transplantation. The Kasai portoenterostomy procedure may provide more time for those patients and their families for whom a liver transplantation may not be feasible in the future for a range of reasons.

TABLE 4. Univariate analysis of laboratory and clinical factors related to good short-term outcome (jaundice clearance).

Factor	Jaundice clearance		*P*-value
	Yes (n = 53)	No (n = 27)	
Gender, n (%)			0.985
Female	33 (62.3%)	16 (59.3%)	
Male	20 (37.7%)	11 (40.7%)	
Age at Kasai operation (days)			
Mean ± SD	87.2 ± 35.8	115.3 ± 41.3	
Age < 90, n (%)	34 (64.2%)	9 (33.3%)	**0.002**
Age ≥ 90, n (%)	19 (35.8%)	18 (66.7%)	**0.017**
Body weight at operation (kg)			0.503
Mean ± SD	5.3 ± 0.94	5.2 ± 0.98	
Liver function test, median (min-max)			
Total bilirubin (TB)	9.1 (4.3–17.5)	10.6 (6.85–31.3)	**0.003**
Direct bilirubin (DB)	8.0 (3.2–14.4)	9.1 (5–26.1)	**0.015**
Aspartate transaminase (AST)	205 (3–1101)	286 (114–843)	**0.001**
Alanine transaminase (ALT)	129 (10–505)	193 (42–554)	**0.023**
Alkaline phosphatase (ALP)	492 (270–871)	487 (383–846)	0.171
Gamma-glutamyl transpeptidase (GGT)	705 (121–2491)	450 (84–2184)	0.132
GGT on postoperative day 1	n = 49	n = 23	**0.014**
Median (min-max)	913 (114–3031)	478 (79–3062)	
GGT at 3 months after operation	n = 34	n = 18	0.397
Median (min-max)	650.5 (15–1796)	524 (34–1990)	
GGT at 4 months after operation	n = 32	n = 13	0.764
Median (min-max)	435.5 (20–2752)	316 (27–2302)	
GGT at 5 months after operation	n = 27	n = 9	0.144
Median (min-max)	315 (20–2480)	784 (136–1311)	
GGT at 6 months after operation	n = 26	n = 8	0.239
Median (min-max)	212 (18–1990)	369 (70–1280)	
Postoperative steroid administration			0.671
None, n (%)	4 (7.5%)	1 (3.7%)	
Within 7 days, n (%)	37 (69.8%)	18 (66.7%)	
After 7 days, n (%)	12 (22.7%)	8 (29.6%)	
Duration of steroid (days), median (min-max)	28 (0–60)	28 (0–38)	0.724
Duration of intravenous antibiotic (days)			
Median (min-max)	18 (7–42)	14 (6–63)	0.477
Prophylactic ATB (n = 78), n (%)	52 (98.1%)	26 (96.3%)	1.000
Duration of prophylactic antibiotic (months)			**< 0.001**
Median (min-max)	24 (0–144)	5 (0–60)	
Postoperative cholangitis, n (%)	43 (81.1%)	27 (100%)	**0.014**
Duration till cholangitis (weeks)	n = 43	n = 27	
Median (min, max)	5 (1–144)	4 (1–28)	0.666
Episodes of cholangitis, median (min, max)	2 (0–12)	2 (1–8)	0.124

Abbreviations: ATB, antibiotic; SD, standard deviation

TABLE 5. Univariate and multivariate analyses adjusted for significant factors associated with jaundice clearance, plus postoperative cholangitis.

Factor	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age < 90 days	3.579 (1.347–9.512)	0.011	2.817 (0.630–12.592)	0.175
TB	0.803 (0.680–0.949)	0.010	0.581 (0.245–1.380)	0.219
DB	0.795 (0.653–0.968)	0.022	1.893 (0.680–5.264)	0.222
AST	0.997 (0.994–0.999)	0.013	1.001 (0.995–1.007)	0.822
ALT	0.994 (0.989–1.000)	0.034	0.991 (0.976–1.005)	0.217
Postop GGT	1.001 (1.000–1.002)	0.048	1.000 (0.999–1.002)	0.528
Duration of prophylactic ATB	1.118 (1.051–1.189)	< 0.001	1.128 (1.045–1.217)	0.002
Postoperative cholangitis	Not applicable		Not applicable	

Abbreviations: TB, total bilirubin; DB, direct bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; Postop GGT, postoperative gamma-glutamyl transpeptidase; ATB, antibiotic

The study identified several probable factors associated with jaundice resolution after a Kasai portoenterostomy. Significant laboratory results were found with the good-short-term-outcome group, with lower levels of bilirubin and liver enzymes being found with earlier, rather than later, ages at diagnosis and at operation. For that reason, the multivariate analysis did not find those factors to be significant independent correlates of the short-term outcome. The only independent factor associated with the achievement of jaundice clearance was the prolonged provision of a prophylactic antibiotic. Nevertheless, a conclusion could not be made that the administration of a prophylactic antibiotic secured a better short-term outcome. This is because a number of individuals with poor outcomes expired prior to the scheduled discontinuation of the prophylactic antibiotic at 18-24 months after the operation, resulting in an overall shorter duration of prophylactic antibiotic usage for the poor-outcome group.

Postoperative cholangitis, a common and serious complication following the Kasai portoenterostomy, has been varyingly reported to occur in between 40% and 93% of cases.[5,10,14-17] Moreover, its occurrence has been found to significantly reduce the survival rate of patients with either good or inadequate bile flow[7,16,17], and repeated episodes-especially within the first 2 years of surgery-have been associated with a decrease in native liver survival and, ultimately, with the need for liver transplantation.[18-21] In the current study, the overall incidence of cholangitis was 87.5%, and perioperative intravenous antibiotics were universally provided (usually for 1-2 weeks, but even longer if the cholangitis worsened). The majority of the antibiotics were combinations of third generation cephalosporins and metronidazole. A postoperative, adjuvant, prophylactic antibiotic was subsequently provided to prevent recurrence of the cholangitis, most episodes of which typically occur within 12 months of the Kasai procedure.[16,21,22] Nevertheless, recent trials and systematic reviews have yielded inconclusive results for determining the effectiveness of prophylactic antibiotics for the prevention of cholangitis after the Kasai portoenterostomy.[19,22–24] In addition, there is no strong evidence that the prolonged use of oral prophylactic antibiotics beyond the early postoperative period offers any greater protection against cholangitis.[5,19,23] Still, most experienced institutions provide oral prophylactic antibiotics for periods of 6 months or longer, similar to the requirements of our hospital's protocol. A randomized control trial by Bu et al.[22] found that there was a significantly lower rate of recurrent cholangitis among patients provided with prophylactic antibiotics than that for a historical control group who did not receive antibiotics. Although a Dutch national cohort by deVries et al.[24] did not identify any reduction in the cholangitis rate of the prophylactic antibiotic group, it did demonstrate that the prophylactic usage was associated with a higher, 4-year, transplant-free

TABLE 6. Univariate analyses of laboratory and clinical factors related to good long-term outcome (remaining jaundice-free with native liver).

Factor	Jaundice-free with native liver		*P*-value
	Yes (n = 41)	No (n = 39)	
Jaundice clearance (n = 53), n (%)	41 (100%)	12 (30.8%)	**< 0.001**
Age at operation (days), median (min-max)	77 (31–162)	99 (21–204)	**0.021**
< 90 days, n (%)	26 (63.4%)	17 (43.6%)	0.116
≥ 90 days, n (%)	15 (36.6%)	22 (56.4%)	
< 80 days, n (%)	24 (58.5%)	13 (33.3%)	**0.027**
≥ 80 days, n (%)	17 (41.5%)	26 (66.7%)	
Preoperative GGT	n = 35	n = 36	0.765
Median (min-max)	705 (121–2335)	596 (84–2491)	
Postoperative GGT	n = 38	n = 34	0.250
Median (min-max)	874.5 (114–2345)	732 (79–3062)	
GGT at 3 months after operation	n = 26	n = 26	0.985
Median (min-max)	581 (15–1796)	578 (34–1990)	
GGT at 4 months after operation	n = 27	n = 18	0.926
Median (min-max)	439 (20–2752)	305.5 (27–2302)	
GGT at 5 months after operation	n = 21	n = 15	0.067
Median (min-max)	282 (20–2480)	624 (100–1311)	
GGT at 6 months after operation	n = 20	n = 14	0.069
Median (min-max)	198.5 (18–1990)	383.5 (70–1280)	
Postoperative steroid administration			0.495
No, n (%)	3 (7.3%)	2 (5.1%)	
Within 7 days, n (%)	30 (73.2%)	25 (64.1%)	
After 7 days, n (%)	8 (19.5%)	12 (30.8%)	
Duration of steroid (days), median (min-max)	28 (0–60)	28 (0–38)	0.074
Duration of intravenous antibiotics (days)			0.674
Median (min-max)	17 (7–42)	18 (6–63)	
Prophylactic antibiotic (n = 78), n (%)	40 (97.6%)	38 (97.4%)	1.000
Duration of prophylactic antibiotic (months)			**0.006**
Median (min-max)	21 (0–88)	11 (0–144)	
Duration till jaundice clearance (weeks)	n = 41	n = 12	**0.006**
Median (min-max)	9 (4–72)	20.5 (9–60)	
Postoperative cholangitis, n (%)	31 (75.6%)	39 (100%)	0.001
Duration till cholangitis (weeks)			0.368
Median (min-max)	3 (1–29)	4 (1–144)	
Episodes of cholangitis, median (min-max)	1 (0–12)	3 (1–11)	**< 0.001**
Redo-Kasai operation, n (%)	2 (4.9%)	4 (10.3%)	0.426
PTBD, n (%)	4 (9.8%)	8 (20.5%)	0.301

Abbreviations: GGT, gamma-glutamyl transpeptidase; PTBD, percutaneous transhepatic biliary drainage

TABLE 7. Univariate and multivariate analyses of all significant factors associated with good long-term outcome, plus jaundice clearance and postoperative cholangitis.

Factor	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Jaundice clearance	Not applicable		Not applicable	
Age < 90 days	2.243 (0.915–5.500)	0.077	0.700 (0.139–3.536)	0.666
Duration of prophylaxis antibiotic	1.009 (0.988–1.030)	0.391	0.982 (0.950–1.016)	0.304
Duration till jaundice clearance	0.962 (0.920–1.005)	0.085	1.000 (0.941–0.062)	0.998
Postoperative cholangitis	Not applicable		Not applicable	
Episodes of cholangitis	0.703 (0.562–0.880)	0.002	0.678 (0.484–0.949)	0.024

survival rate of 54% compared to 34% for the control group. Our protocol of providing a prophylactic antibiotic for 18-24 months after the Kasai operation is based on several lines of evidence. Firstly, recurrent cholangitis frequently occurs during the first 2 years of the Kasai procedure. In addition, the auto-anastomosis of the internal fistula between the bile ductules in the portal plate and the intestinal mucosa matures within 6 weeks of the operation.[15] Finally, wound maturation takes 18-24 months in general. Another reasonable approach would be to provide protection during the immunosuppression phase of concomitant steroids and discontinue their use after 1 year, i.e., once the cholangitis risk is significantly decreased.[19] In the present study, the multivariate analysis of the factors associated with jaundice clearance was not able to be applied to postoperative cholangitis due to the 100% involvement of the postoperative cholangitis in the group of patients without jaundice clearance (Table 4).

In the analysis of the factors associated with a good long-term outcome (remaining jaundice-free with the native liver for more than 6 months after the operation), the only independent factor that was found was the lower number of episodes of cholangitis. Interestingly, the episodes were not a significant factor related to the short-term outcome of jaundice clearance. This is because the incidences of cholangitis occurred for a median of 2 episodes in the group with jaundice resolution as well as in the group without jaundice resolution. On the other hand, the patients who remained jaundice-free with their native liver developed cholangitis for a median of 1 episode, while those who had a poor long-term outcome had a median of 3 episodes of cholangitis throughout their follow-up period (adjusted OR, 0.678; 95% CI, 0.484–0.949; p-value, 0.024). These findings are consistent with previous studies which reported that, firstly, an increased number of cholangitis episodes negatively affected the native liver survival, and secondly, having episodes more than 2 years after the Kasai portoenterostomy appeared to be a prognostic marker for a future liver transplantation.[18,20,21]

In addition to cholangitis, the univariate analysis demonstrated other significant factors affecting the long-term outcome, namely, an age at operation of less than 80 days, the achievement of jaundice clearance, a prolonged provision of a prophylactic antibiotic, and a shorter duration to attain jaundice clearance. In a long-term study of native liver patients who had survived for more than 20 years after the Kasai operation, Nio et al.[25] concluded that the age at operation, the early development of cholangitis, and the time to jaundice resolution were prognostic factors influencing long-term native liver survival. In contrast, the multivariate analysis performed for the current study found that the number of cholangitis episodes was the only independent, significant factor affecting the long-term outcomes. Jaundice clearance was present in 100% of the patients who achieved a good long-term outcome, while the development of cholangitis was present in 100% of the patients who had poor long-term outcomes. Therefore, a logistic regression analysis could not be performed for the 2 variables, jaundice clearance and the development of cholangitis.

Consistent with other studies[26,27], it is evident from the present study that jaundice clearance following the Kasai portoenterostomy was essential for long-term native liver survival. If the age at the operation is the first controllable factor in the management of biliary atresia, surgical technical standardization would be the second factor impacting on the resolution of jaundice. To maintain a jaundice-free, native liver survival, postoperative adjuvant therapy would be the third key factor. Our surgical technique was based on the original Kasai operation.[4] It was modified in accordance with the Tohoku University standardization protocol, which entails a moderate dissection when transecting the fibrous remnants of the porta hepatis in the same plane as the liver capsule.[26]

Another important adjuvant therapy is the provision of corticosteroids during the postoperative care period following a Kasai portoenterostomy. The results of randomized controlled trials[3,28,29] and meta-analyses[30,31] have indicated that the administration of moderate- to high-dose steroids is beneficial by increasing the rate of jaundice clearance during the first 6 months after the operation. The majority of those trials found that the elevated rate of jaundice clearance occurred only in patients operated on at a younger age. Even so, those patients did not demonstrate any improvement in their long-term, native liver survival rates. The meta-analysis by Chen et al.[31] also revealed that a longer duration of steroid therapy following the Kasai portoenterostomy failed to elicit any further beneficial outcomes. Our postoperative steroid regimen typically consisted of a low dose of oral prednisolone (2 mg/kg/day), which was tapered by half each week for 4 consecutive weeks; that dosage was provided to 94% of the patients in the current study. No differences were evident in either the short- or long-term outcomes of the steroid and non-steroid groups; however, this was most likely the result of the very low number of participants in the non-steroid group. Furthermore, variations in the timing of the initiation of the steroids did not produce any significant differences in the outcomes of the no-steroid, early-steroid, and late-steroid groups. Nevertheless, at our institution, the use of steroids is deemed to be an important adjuvant therapy during the postoperative care period. They are also used for the treatment of cholangitis after a portoenterostomy, given the evident inflammatory process presented and the very rare incidence of side effects associated with the steroids.

The incidences of the salvage procedures (redo-portoenterostomy and percutaneous biliary drainage) were quite low. The redo-portoenterostomy would be provided for patients with a history of biliary drainage or jaundice clearance after the first portoenterostomy, which later developed recurrent jaundice. The percutaneous biliary drainage was the intervention for those with recurrent jaundice or cholangitis, which imaging proved biliary collection or biloma. The analysis of their correlation to the long-term outcomes did not demonstrate any statistical significance.

Finally, the analysis of GGT activity was included in the present study to discover any correlation the activity might have with bile drainage or any prognostic value that would facilitate the prediction of portoenterostomy outcomes. Serum GGT has been utilized to indicate cholestasis, and an elevated level has been reported to be highly accurate in differentiating biliary atresia from other causes of neonatal cholestasis.[32,33] Interestingly, the present study found that the median serum GGT level on postoperative day 1 was significantly higher for the patients with jaundice resolution than for those without (913 and 478 IU/L, respectively; p-value, 0.014). Furthermore, in our comparison of the good and poor long-term outcomes, the median serum GGT levels on postoperative day 1 were 874.5 vs. 732 IU/L, respectively, although with no statistical significance. Despite several drop-out variables at each time point, the serum GGT activity of the patients with jaundice clearance tended to peak on day 1 before gradually decreasing below the serum GGT levels for the patients who had persistent jaundice during months 5 and 6 post-surgery, albeit without statistical significance. By contrast, the GGT activity of the patients with persistent jaundice tended to start in the high 300-500s IU/L and either persist at that level or climb to a peak in month 5 after surgery. Having examined the correlation between GGT activity and the outcomes after the Kasai portoenterostomy, Ihn et al.[34] reported that a concentration exceeding 550 IU/L at month 5 was one of the independent risk factors for decreased native liver survival. Our review of the serum GGT level did not elicit any statistical significance in both the short- and long-term outcome analysis. Nevertheless, given appropriate long-term care, a decreasing serum GGT level is expected in month 5 for the patients, especially in the case of those who achieved a normalized bilirubin level within 4 months of the operation. Thus, it is highly desirable to collect a larger and more complete set of data to analyze the GGT activity in patients with long-term native liver survival, even though the results would be mainly of prognostic value.

With the inherent limitations of a retrospective review, this is another descriptive study on the outcomes of the treatment of biliary atresia. It is difficult for a single center with a limited number of patients to reach statistical significance in the analysis of the listed factors. Still, the study demonstrated comparable outcomes to research by other large-scale centers, with its 66.3%

jaundice clearance rate; a 51.3% jaundice-free, native liver survival within a mean follow-up duration of 50 months; and an essentially acceptable treatment regimen. Further clarification and collaboration with other centers may help standardize the treatment protocol for this rare disease.

CONCLUSION

The prolonged provision of a prophylactic antibiotic as adjuvant therapy during the postoperative care of biliary atresia patients after the Kasai portoenterostomy was associated with a good short-term outcome (the achievement of jaundice clearance). The increased number of cholangitis episodes was associated with poor long-term outcomes, including poor native liver survival. Postoperative adjuvant therapy should be standardized and maintained for the care of biliary atresia patients to improve their outcomes.

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REFERENCES

1. Sokol RJ, Mack C, Narkewicz MR, Karrer FM. Pathogenesis and outcome of biliary atresia: current concepts. J Pediatr Gastroenterol Nutr 2003;37:4-21.
2. Davenport M. Biliary atresia. Semin Pediatr Surg 2005;14:42-8.
3. Superina R, Magee JC, Brandt ML, Healey PJ, Tiao G, Ryckman F, et al. The anatomic pattern of biliary atresia identified at time of Kasai hepatoportoenterostomy and early postoperative clearance of jaundice are significant predictors of transplant-free survival. Ann Surg 2011;254:577-85.
4. Kasai M, Kimura S, Asakura Y, Suzuki H, Taira Y, Ohashi E. Surgical treatment of biliary atresia. J Pediatr Surg 1968;3:665-75.
5. Wong ZH and Davenport M. What happens after Kasai for biliary atresia? A European multicenter survey. Eur J Pediatr Surg 2019;29:1-6.
6. Shinkai M, Ohhama Y, Take H, Kitagawa N, Kudo H, Mochizuki K, et al. Long-term outcome of children with biliary atresia who were not transplanted after the Kasai operation: > 20-year experience at a children's hospital. J Pediatr Gastroenterol Nutr 2009;48:443-50.
7. Altman RP, Lilly JR, Greenfeld J, Weinberg A, Leeuwen KV, Flanigan L. A multivariable risk factor analysis of the portoenterostomy (Kasai) procedure for biliary atresia: twenty-five years of experience from two centers. Ann Surg 1997;226: 348-55.
8. Nio M, Ohi R, Miyano T, Saeki M, Shiraki K, Tanaka K, et al. Five- and 10-year survival rates after surgery for biliary atresia: a report from the Japanese Biliary Atresia Registry. J Pediatr Surg 2003;38:997-1000.
9. Davenport M, Kerkar N, Mieli-Vergani G, Mowat AP, Howard ER. Biliary atresia: the King's College Hospital experience (1974–1995). J Pediatr Surg. 1997;32:479-485.
10. Chardot C, Carton M, Spire-Bendelac N, Le Pommelet C, Golmard JL, Auvert B, et al. Prognosis of biliary atresia in the era of liver transplantation: French national study from 1986 to 1996. Hepatology 1999;30:606-11.
11. Laohapensang M and Srikuancharoen P. The relationship between clinical outcomes after Kasai operation and related factors in infants with biliary atresia. J Med Assoc Thai 2017;100(Suppl4): S99–104.
12. Serinet MO, Wildhaber BE, Broue P, Lachaux A, Sarles J, Jacquemin E, et al. Impact of age at Kasai operation on its results in late childhood and adolescence: a rational basis for biliary atresia screening. Pediatrics 2009;123:1280-6.
13. Nio M, Wada M, Sasaki H, Tanaka H. Effects of age at Kasai portoenterostomy on the surgical outcome: a review of the literature. Surg Today 2015;45:813-8.
14. Ernest van Heurn LW, Saing H, Tam PK. Cholangitis after hepatic portoenterostomy for biliary atresia: a multivariate analysis of risk factors. J Pediatr 2003;142:566-71.
15. Luo Y, Zheng S. Current concept about postoperative cholangitis in biliary atresia. World J Pediatr 2008;4:14-9.
16. Wu ET, Chen HL, Ni YH, Lee PI, Hsu HY, Lai HS, et al. Bacterial cholangitis in patients with biliary atresia: impact on short-term outcome. Pediatr Surg Int 2001;17:390-5.
17. Nio M, Sano N, Ishii T, Sasaki H, Hayashi Y, Ohi R. Cholangitis as a late complication in long-term survivors after surgery for biliary atresia. J Pediatr Surg 2004;39:1797-9.
18. Lunzmann K, Schweizer P. The influence of cholangitis on the prognosis of extrahepatic biliary atresia. Eur J Pediatr Surg 1999;9:19-23.
19. Davenport M. Adjuvant therapy in biliary atresia: hopelessly optimistic or potential for change? Pediatr Surg Int 2017;33:1263-73.
20. Koga H, Wada M, Nakamura H, Miyano G, Okawada M, Lane GJ, et al. Factors influencing jaundice-free survival with the native liver in post-portoenterostomy biliary atresia patients: results from a single institution. J Pediatr Surg 2013;48:2368-72.
21. Chen SY, Lin CC, Tsan YT, Chan WC, Wang JD, Chou YJ, Lin CH. Number of cholangitis episodes as a prognostic marker to predict timing of liver transplantation in biliary atresia patients after Kasai portoenterostomy. BMC Pediatr 2018;18:119.
22. Bu LN, Chen HL, Chang CJ, Ni YH, Hsu HY, Lai HS, et al. Prophylactic oral antibiotics in prevention of recurrent cholangitis after the Kasai portoenterostomy. J Pediatr Surg 2003;38: 590-93.
23. Decharun K, Leys CM, West KW, Finnell SME. Prophylactic antibiotics for prevention of cholangitis in patients with biliary atresia status post-Kasai portoenterostomy: a systematic review. Clin Pediatr (Phila) 2016;55:66-72.
24. De Vries W, de Langen ZJ, Groen H, Scheenstra R, Peeters PM, Hulscher JB, et al. Biliary atresia in the Netherlands: outcome of patients diagnosed between 1987 and 2008. J Pediatr 2012;160:638-44.
25. Nio M, Wada M, Sasaki H, Tanaka H, Okamura A. Risk factors affecting late-presenting liver failure in adult patients with

biliary atresia. J Pediatr Surg 2012;47:2179-83.

26. Sasaki H, Tanaka H, Nio M. Current management of long-term survivors of biliary atresia: over 40 years of experience in a single center and review of the literature. Pediatr Surg Int 2017;33: 1327-33.

27. Nio M, Wada M, Sasaki H, Kazama T, Tanaka H, Kudo H. Technical standardization of Kasai portoenterostomy for biliary atresia. J Pediatr Surg 2016;51:2105-8.

28. Davenport M, Parsons C, Tizzard S, Hadzic N. Steroids in biliary atresia: single surgeon, single centre, prospective study. J Hepatol 2013;59:1054-8.

29. Bezerra JA, Spino C, Magee JC, Shneider BL, Rosenthal P, Wang KS, et al. Use of corticosteroids after hepatoportoenterostomy for bile drainage in infants with biliary atresia: the START randomized clinical trial. JAMA 2014;311:1750-9.

30. Zhang D, Yang HY, Jia J, Zhao G, Yue M, Wang JX. Postoperative steroids after Kasai portoenterostomy for biliary atresia: a meta-analysis. Int J Surg 2014;12:1203-9.

31. Chen Y, Nah SA, Chiang L, Krishnaswamy G, Low Y. Postoperative steroid therapy for biliary atresia: Systematic review and meta-analysis. J Pediatr Surg 2015;50:1590-4.

32. Robie DK, Overfelt SR, Xie L. Differentiating biliary atresia from other causes of cholestatic jaundice. Am Surg 2014;80: 827-31.

33. Chen X, Dong R, Shen Z, Yan W, Zheng S. Value of Gamma-Glutamyl Transpeptidase for Diagnosis of Biliary Atresia by Correlation With Age. J Pediatr Gastroenterol Nutr 2016;63: 370-3.

34. Ihn K, Ho IG, Chang EY, Han SJ. Correlation between gamma-glutamyl transpeptidase activity and outcomes after Kasai portoenterostomy for biliary atresia. J Pediatr Surg 2018;53:461-7.