Title page

Multicenter, retrospective, comparative study of laparoscopic and open Kasai portoenterostomy in children with biliary atresia from Japanese high-volume centers

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Abstract

Purpose: Multicenter study was undertaken to analyze the results of laparoscopic and open Kasai portoenterostomy.

Methods: Subjects were infants with type III biliary atresia who underwent open operation (n=106) or laparoscopic operation (n=21) between January 2012 and December 2015. Clinical data were compared between open and laparoscopic operations (2016-0534). Propensity score matching was performed to reduce the effect of treatment selection bias. Multivariate analyses were used to estimate the effect of the surgical approach on the jaundice clearance rate and the native liver survival rate.

Results: The postoperative jaundice clearance rate and the 1-year native liver survival rate were not significantly different between open and laparoscopic operations. Rates of cholangitis and major complications of laparoscopic operation were comparable to those of open operation. Blood loss, time to resume oral intake, time to drain removal, and duration of analgesic usage of laparoscopic operation were significantly superior to those of open operation. Similar results were observed when analysis was adjusted based on propensity score. Multivariate analyses demonstrated that only age at operation was a poor prognostic factor.

Conclusion: Laparoscopic Kasai portoenterostomy was associated with several favorable perioperative outcomes compared with open Kasai portoenterostomy. The difference of surgical approach was not a significant independent predictor.

Key words: biliary atresia, Kasai, portoenterostomy, laparoscopy, multicenter study, prognostic factor

Text

Introduction

Laparoscopic Kasai portoenterostomy (Lap-Kasai) for treating biliary atresia is still a controversial topic [1,2]. Although the outcomes of Lap-Kasai have been reported as unfavorable compared to those of open Kasai portoenterostomy (Open-Kasai) in western countries, Japanese results of Lap-Kasai previously reported from a few centers were encouraging [3-5]. However, a single-center study is not sufficient to assess the efficacy and safety of Lap-Kasai. Therefore, a multicenter, retrospective study was undertaken to analyze the results of a large cohort of patients who underwent Lap-Kasai and Open-Kasai for type III biliary atresia. In order to ensure the quality of research, the institutions were limited to Japanese high-volume centers that have expertise in the management of children with biliary atresia. The short-term outcomes in terms of the jaundice clearance rate and native liver survival rate at 1 year, and the rate of adverse events were mainly compared between the two procedures.

Methods

Institutions

This study was a multicenter study in Japan, and the head office of this study was the Department of Pediatric Surgery, Nagoya University Graduate School of Medicine. This study received approval at the board meeting of the Japanese Biliary Atresia Society, and the Japanese Biliary Atresia Society Registry (JBAR) data was used for selecting the participating institutions. A facility inclusion criterion was that more than 11 patients underwent surgery for biliary atresia between January 2012 and December 2015. According to JBAR data, only 8 institutions met the facility inclusion criterion, and all 8 institutions participated in this study. Board members were chosen from the participating facilities, and they determined the protocol for this study.

Study subjects

Subjects were infants with type III biliary atresia who underwent Open-Kasai or Lap-Kasai between January 2012 and December 2015. The medical records of 144 patients with biliary atresia from 8 institutions were collected. According to JBAR data, 432 patients underwent the operation for biliary atresia in this period, and our data accounted for 33% (144/432) of the total Japanese cases. We excluded 15 patients with type I biliary atresia (Open-Kasai: 14, Lap-Kasai: 1) and 2 patients with type II biliary atresia (Open-Kasai: 1, Lap-Kasai: 1). Finally, 127 patients were included in this study.

One hundred six patients underwent Open-Kasai at 8 facilities, and 21 patients underwent Lap-Kasai at 3 facilities.

Study design

Data were retrieved from each institutional database and were retrospectively reviewed. The observation period was 1 year after initial Kasai portoenterostomy. The clinical data regarding patients' characteristics and surgical results were compared between the Open-Kasai and Lap-Kasai groups. These paired comparisons were performed in both all patients and the propensity-matched patients as described later herein. Jaundice clearance was defined as a total bilirubin concentration lower than the upper limit value of normal range, as determined by each facility. A major postoperative complication was defined as Clavien-Dindo grade ≥III. Operative and perioperative treatment, including steroid and antibiotic usage, was provided in accordance based on each institutional protocol.

Statistical analyses

Categorical variables are presented as absolute numbers and percentages. Continuous variables are described as medians and ranges. Statistical analyses were performed using the Fisher exact test for categorical variables and the Mann-Whitney U test for continuous variables. The Kaplan-Meier method was used to estimate the native liver survival, and the differences between survival curves were evaluated using the log-rank test. Case matching was performed between the two groups to reduce the effect of treatment selection bias and potential confounding factors in this retrospective study. We set the possible confounders as biliary atresia splenic malformation syndrome (BASM), the age at operation, and serum total bilirubin (Tbil) concentration preoperatively. BASM and the age at operation were prevsiously reported as the potential preoperative prognostic factors of biliary atresia [6-11]. The Tbil concentration preoperatively reflects the degree of preoperative cholestasis. At first, we excluded 6 patients with BASM (only in the open-Kasai group). Then, the predicted probability of laparoscopic surgery was calculated by fitting a logistic regression model using the other variables. We used the receiver operating characteristic (ROC) and area under the curve (AUC) to measure the goodness of fit statistics. AUC was 0.64 (95% confidence interval: 0.532-0.757) calculated from the ROC curve. We performed adjustment for the differences with propensity score matching using the following algorithm: 1:1 optimal match with no caliper and no replacement. We used the standardized difference to measure covariate balance. Imbalance was defined as an absolute value greater than

0.20 (small size effect).

Multivariate analyses were used to estimate the effect of the surgical approach on the jaundice clearance rate and the native liver survival rate. Logistic regression analysis was used to estimate the effect of the surgical approach on the jaundice clearance rate, and we controlled for selected confounding variables that have been reported as potential prognostic factors of Kasai portoenterostomy in other studies: BASM, the age at operation, and cholangitis [6-13]. In addition, a Cox proportional hazard model was used to verify independent predictive parameters of the native liver survival rate.

All statistic analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statical Computing, Vienna, Austria) [14]. Values of $p < 0.05$ were considered statistically significant.

Ethical statement

This study protocol was approved by the Nagoya University Hospital Institutional Review Board (no. 2016-0534) and the ethics committee of each facility.

Results

Patients' baseline characteristics

The patients' baseline characteristics are presented in Table 1. After one-to-one propensity score matching, all patients in the Lap-Kasai group were matched to similar patients in the Open-Kasai group (n=21 in each group). The covariate balance in the matched patients improved in regard to the potential confounders, i.e., BASM, the age at operation, and serum Tbil concentration preoperatively. As shown in Table 1, the two groups were comparable in terms of patients' baseline characteristics.

Surgical results

Surgical results are shown in Table 2. The median blood loss was significantly less in the Lap-Kasai group compared with the Open-Kasai group, and the number of patients who required blood transfusion in the perioperative period was less in the Lap-Kasai group compared with the Open-Kasai group. The time to resume oral intake, time to drain removal, and duration of postoperative analgesic usage were significantly shorter in the Lap-Kasai group than in the Open-Kasai group. The rates of jaundice clearance after Open-Kasai and Lap-Kasai were 64% (68/106) and 71% (15/21) of patients, respectively. There were no significant differences between the two groups (p=0.62). The rate of adverse events were also not significantly different between the two groups.

Similar results were observed when the analysis was adjusted based on the propensity score.

The native liver survival rate at 1 year after Open-Kasai and Lap-Kasai were 63% and 67%, respectively. The Kaplan-Meier curves for the native liver survival are shown in all study patients and the propensity-matched patients (Figure 1). The intergroup comparison of the native liver survival showed no significant difference between the Open-Kasai and Lap-Kasai groups.

The revison Kasai portoenterostomy was performed in 15 patients after the initial Kasai procedure owing to repeated cholangitis (n=2) and reccurent jaundice after initial operation failure (n=6), or achieving transiently jaundice free status following initial operation (n=7). The revision was conducted via laparotomy if the initial Kasai procedure was done via laparotomy (n=8). Conversely, patients whose initial Kasai procedure was done laparoscopically underwent the revision laparoscopically (n=7).

The rates of reccurent jaundice after achieving transiently jaundice free status following initial Open-Kasai and initial Lap-Kasai were 25% (17/68) and 33% (5/15) of patients, respectively. There were no significant differences between the two groups (p=0.53).

The revision for reccurent jaundice was perforemed for 3 of 17 patients, who were transiently jaundice free after initial Open-Kasai. The rates of jaundice clearance after the revision of Open-Kasai was 67% (2/3) and the native liver survival rate at 1 year after initial operation was 100% (3/3). The revision was performed in 4 of 38 patients in whom initial Open-Kasai failed. Both the rates of jaundice clearance after revision and the native liver survival rate at 1 year after initial operation were 0% (0/4). One revision for repeated cholangitis after initial Open-Kasai achieved native liver survival at 1 year-old. The revision for reccurent jaundice was perforemed for 4 of 5 patients, who were transiently jaundice free after initial Lap-Kasai. The rates of jaundice clearance after the revision was 75% (3/4) and the native liver survival rate at 1 year after initial operation was 75% (3/4). The revision was performed in 2 of 6 patients in whom initial Lap-Kasai failed. The rates of jaundice clearance after revision was 100% (2/2) and the native liver survival rate at 1 year after initial operation was 50% (1/2). One revision case for repeated cholangitis after initial Lap-Kasai underwent liver transplantation within 1 year after initial operation.

Multivariate analyses

In logistic regression analysis, the jaundice clearance rate was significantly affected only by the age at operation (odds ratio=0.44, 95% confidence interval 0.19-0.99, *p*=0.046). The difference of surgical approach was not significantly relevant to the jaundice clearance rate (odds ratio=1.08, 95% confidence interval 0.37-3.13, *p*=0.88) (Table 4). Additionally, in multivariate Cox proportional hazard analysis, only the age at operation was a significant independent predictor of the native liver survival rate (hazard ratio=2.09, 95% confidence interval 1.15-3.82, *p*=0.016). The difference of surgical approach had no significant association with the native liver survival rate (hazard ratio = 0.98, 95% confidence interval 0.43-2.24, *p*=0.96) (Table 5).

Discussion

Minimally invasiveness should be considered in pediatric surgery. Increasing numbers of pediatric procedures are being performed laparoscopically. Many pediatric patients receive benefits, including a smaller wound, faster recovery, and less pain, after the introduction of minimally invasive surgery. In particular, Lap-Kasai has several postulated advantages over Open-Kasai. During Lap-Kasai, the magnifications produced by a 30°, 10-mm scope at a focal length of 5 cm are ×38 and ×100 when zooming, enabling more micro bile ducts to be identified in the biliary remnant than with the naked eye [15]. Transection of the biliary remnant with excellent visibility might lead to an improvement in surgical results of Kasai portoenterostomy. In addition, biliary atresia occasionally requires repeated abdominal procedures, such as revision or liver transplantation. The reduced severity of adhesion following Lap-Kasai might lead to a decrease of surgical risks during subsequent procedures [4].

Since the first case of Lap-Kasai was reported by Esteves et al. in 2002 [16], many cases have been described in literatures, and systematic reviews of these comparative studies concluded that Lap-Kasai is feasible but the outcomes appear unfavorable compared to Open-Kasai [1,2]. In these reviews, the jaundice clearance rate after Lap-Kasai was reportrd as 58% [1], and the native liver survival rates were reported as 57% at 6 months and 47% at 2 years [2]. The reasons for the poor outcomes were assumed to be due to the learning curve associated with the operation and the prolonged use of pneumoperitoneum [2]. Alternatively, the studies from Japanese centers suggested that Lap-Kasai could be performed successfully [3-5]. We believe that this is because Lap-Kasai in Japan has been performed according to the original concepts of Kasai, including shallow transection of the biliary remnant and preservation of the fibrotic connective tissues [5]. In addition, Lap-Kasai in Japan has been performed under meticulous postoperative cares in the same manner as Open-Kasai. In this Japanese multicenter study, the short-term outcomes of Lap-Kasai for type III biliary atresia were that the jaundice clearance rate after Lap-Kasai was 71% and the native liver survival rate was 67% at 1 year. These results were almost identical to those of Open-Kasai. Moreover, our findings showed the superiority of Lap-Kasai to Open-Kasai in operative blood loss, the time to resume oral intake, time to drain removal, and duration of postoperative analgesic usage. The each institutional postoperative treatment protocol could have caused the signicant differences in the time to resume oral intake, but the other outcomes were not effected by the postoperative protocol. These results might suggest that Lap-Kasai has equivalent effectiveness and less invasiveness compared to Open-Kasai.

Previous studies have reported the prognostic factors in patients with biliary atresia. Needless to say, the type of biliary atresia was recognized as a significant prognostic factor [6,10,17]. According to JBAR data, the jaundice clearance rate was the best in type I cyst (78%), and the worst in type III (59%) [17]. In our study, the subjects were limited to infants with type III biliary atresia. The age at operation is also known to be an important prognostic factor, and many studies have tended to show advantages of early Kasai portoenterostomy [6-10]. In addition, infants with syndromic BASM were reported to respond less well to Kasai portoenterostomy and have a poor overall outcome [6,9,11]. Regarding the postoperative factor, cholangitis, especially early chlangitis, has been reported to be a poor prognostic predictor [7,12,13]. We used multivariate analyses to estimate the effect of the surgical approach on the jaundice clearance rate and native liver survival rate after controlling for these reported potential confounders. We found that only age at operation (>70 days) was a poor prognostic factor, and the difference of surgical approach was not a significant independent predictor.

This study has some limitations. First, this was a retrospective study, and the patients were not randomized. To reduce the effect of treatment selection bias and potential confounding factors, propensity score matching was performed. In this matching, we narrowed down the covariates to the potential confounders which have the possible association with the outcome of interest for the small sample size. In consequence, the covariate balance in the matched patients improved in regard to the potential confounders. However, the absolute standardized differnce in weight at operation was more than 0.20 after maching. Second, this study lacked a standardized postoperative treatment protocol because each institution that participated in this study had its own treatment regimen for maximizing the restoration of bile flow. Particularly, it remains very controversial whether the revision should be undergone. The revision has tended to be negatively viewed by some institutions because repeated abdominal procedures are thought to promote adhesion and increase the surgical risks during future liver transplantation, while others suggest that the revision could delay the need for liver transplantation and contribute to improved native liver survival [18]. In this study, the reasons for the revision following initial Open-Kasai and initial Lap-Kasai were the same; the insufficient biliary drainage after initial operation and the repeated cholangitis. However, whether or not to perform the revision depended on each institutinal operative strategy. Although there were no significant differences between the rates of recurrent jaundice after achieving sufficient bile drainage following initial Open-Kasai and initial Lap-Kasai, the revision for reccurent jaundice was performed for only 18% (3/17) of the patients who were transiently jaundice free after initial Open-Kasai, but for 80% (4/5) after initial Lap-Kasai. The institutions, which underwent Lap-Kasai, aggresively underwent the revision. The revision for initial operation failure was also performed for 11% (4/38) of the patients in whom initial Open-Kasai failed and for 33% (2/6) of the patients in whom initial Lap-Kasai failed. The reason for this difference of the revision rates might be that the adhesion following the laparoscopic procedure was considered to be less dense than open procedure, and the surgeons, who performed Lap-Kasai, did not hesitate to do the revision and believed that the patients with biliary atresia could benefit from the revision. Although the efficacy of the revision is controversial, this difference might have some influence on the outcome.

Lastly, the number of patients was not sufficient to prove the non-inferiority of Lap-Kasai compared with Open-Kasai statistically.

In conclusion, this Japanese multicenter study suggest that Lap-Kasai was associated with several favorable perioperative outcomes such as operative blood loss, time to drain removal, and duration of postoperative analgesic usage. Only age at operation is a poor prognostic factor and the difference of surgical approach was not a significant independent predictor. A larger randomized, controlled trial with a longer follow-up time is needed to confirm this conclusion.

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Conflict of Interest

The authors declare that they have no conflict of interest or financial ties to disclose.

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Figure legend

Figure.1 Kaplan-Meier curves for survival with and without a native liver.

A. All patients: open Kasai portoenterostomy group (n=106) and laparascopic Kasai portoenterostomy group (n=21). B. Propensity-matched patients: open Kasai portoenterostomy group (n=21) and laparoscopic Kasai portoenterostomy group (n=21).

TABLE 1. Comparison of patients' baseline characteristics between the Open-Kasai and Lap-Kasai groups

	All patients				Propensity-matched patients			
	Open-Kasai $n = 106$	Lap-Kasai $n = 21$	p-value	Absolute standardized difference	Open-Kasai $n = 21$	Lap-Kasai $n = 21$	p-value	Absolute standardized difference
Sex (male), n (%)	38 (36%)	7 (33%)	1	0.053	7 (33%)	7 (33%)	1	0
Birth weight (g)	2884 (940-4272)	2888 (2310-4006)	0.96	0.076	2865 (1436-3548)	2888 (2310-4006)	0.9	0.15
BASM, n (%)	6 (5.7%)	0	0.59	0.35†	0	0	1	-
Age at operation (days)	57 (13-174)	53 (38-89)	0.45	0.33†	53 (18-98)	53 (38-89)	0.86	0.14
Weight at operation (g)	4226 (2164-7000)	4236 (3110-5942)	0.99	0.057	3965 (2164-5580)	4236 (3110-5942)	0.37	0.36†
Serum Tbil concentration before operation (mg/dl)	8.4 (3.6-31.4)	7 (4.7-11)	0.051	0.52†	7.3 (4.5-10.5)	7 (4.7-11)	0.77	0.023

Values are presented as the n (%) or median (range).
BASM: biliary atresia splenic malformation syndrome; Tbil: total bilirubin; Open-Kasai: open Kasai portoenterostomy; Lap-Kasai: laparoscopic Kasai portoenterostomy.
† Absolute standerdized difference >0.20 (small size effect).

TABLE 2. Comparison of surgical results between the Open-Kasai and Lap-Kasai groups

	All patients			Propensity-matched patients		
	Open-Kasai $n = 106$	Lap-Kasai $n = 21$	p-value	Open-Kasai $n = 21$	Lap-Kasai $n = 21$	p-value
Surgical data						
Operative time (min)	318 (163-627)	366 (253-590)	0.11	296 (167-470)	366 (253-590)	0.1
Blood loss (ml)	41 (0-260)	17 (3-80)	0.0026*	52 (0-125)	17 (3-80)	<0.001*
Blood transfusion in the perioperative period, n (%)	54 (51%)	1 (4.8%)	<0.001*	11 (52%)	1 (4.8%)	0.0014*
C-reactive protein level at POD 1 (mg/dl)	3.2 (0.4-8.6)	3.6 (2.2-6.2)	0.3	3.8 (1.4-7.6)	3.6 (2.2-6.2)	0.76
Time to resume oral intake (POD)	6 (2-54)	3 (3-6)	<0.001*	5 (2-14)	3 (3-6)	0.0093*
Time to drain removal (POD)	10 (5-22)	5 (4-13)	<0.001*	10 (5-22)	5 (4-13)	<0.001*
Duration of postopetive analgesic usage (POD)	1 (0-11)	0 (0-2)	0.010*	1 (0-4)	0 (0-2)	0.021*
Postoperative hospital stay (POD)	51 (22-228)	34 (22-223)	0.0079*	41 (22-228)	34 (22-223)	0.25
Outcome for cholestasis						
Jaundice clearance after the initial Kasai procedure, *n* (%)	68 (64%)	15 (71%)	0.62	13 (62%)	15 (71%)	0.74
Time required for jaundice clearance, (POD)	52 (11-216)	34 (21-182)	0.27	48 (17-216)	34 (21-182)	0.78
Postoperative steroid therapy, n (%)	105 (99%)	21 (100%)	1	21 (100%)	21 (100%)	1
Revision Kasai portoenterostomy, *n* (%)	8 (7.5%)	7 (33%)	0.0035*	1 (4.8%)	7 (33%)	0.045*
Status at 6 months after the initial Kasai procedure, *n* (%)						
Survival with a native liver	85 (80%)	18 (86%)		16 (76%)	18 (86%)	
Jaundice-free survival with a native liver	60 (57%)	13 (62%)		13 (62%)	13 (62%)	
Survival with liver transplantation	21 (20%)	3 (14%)		5 (24%)	3 (14%)	
Died	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Status at 1 year after the initial Kasai procedure, *n* (%)						
Survival with a native liver	67 (63%)	14 (67%)		14 (67%)	14 (67%)	
Jaundice-free survival with a native liver	59 (56%)	14 (67%)		13 (62%)	14 (67%)	
Survival with liver transplantation	37 (35%)	7 (33%)		7 (33%)	7 (33%)	
Died	2 (1.9%)	0 (0%)		0 (0%)	0 (0%)	
Adverse event						
Cholangitis within 1 year, *n* (%)	40 (38%)	12 (57%)	0.14	9 (43%)	12 (57%)	0.54
Early cholangitis within 1 month, *n* (%)	19 (18%)	3 (14%)	1	3 (14%)	3 (14%)	1
Complications (Clavien-Dindo grade ≥III), *n* (%)	10 (9.4%)	2 (9.5%)	1	3 (14%)	2 (9.5%)	1
SSI, n (%)	2 (1.9%)	0 (0%)	1	0 (0%)	0 (0%)	1

Values are presented as the *n* (%) or median (range).
POD: postoperative day; SSI: surgical site infection; Open-Kasai: open Kasai portoenterostomy; Lap-Kasai: laparoscopic Kasai portoenterostomy.
* $p < 0.05$

TABLE 3. Logistic regression analysis of factors affecting jaundice clearance

	Jaundice clearance rate	Multivariate analysis		
	n (%)	Odds ratio	95% CI	*p*-value
BASM (positive vs. negative)	2/6 (33%) vs. 81/121 (67%)	0.26	0.04-1.54	0.14
Age at operation (>70 days vs ≤70 days)	19/38 (50%) vs. 64/89 (72%)	0.44	0.19-0.99	0.046*
Early cholangitis within 1 month (positive vs. negative)	12/22 (55%) vs. 71/105 (68%)	0.61	0.23-1.61	0.32
Surgical approach (laparoscopic vs. open)	15/21 (71%) vs. 68/106 (64%)	1.08	0.37-3.13	0.88

* $p < 0.05$
BASM: biliary atresia splenic malformation syndrome; CI: confidence interval.

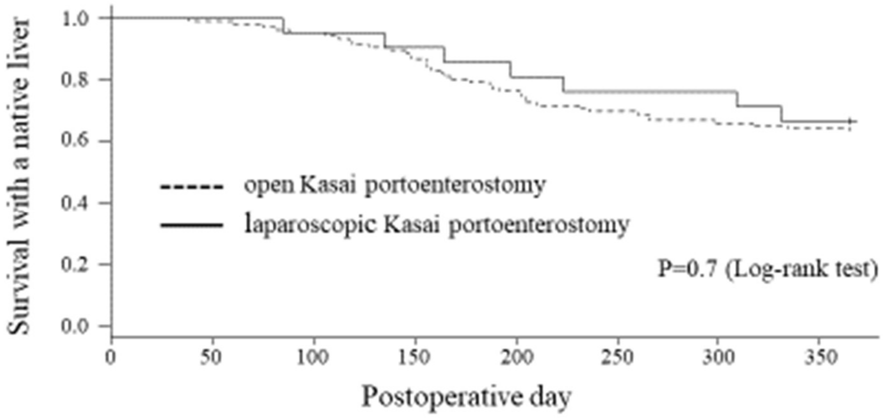
TABLE 4. Cox proportional hazard analysis of factors affecting native liver survival

	1-year native liver survival rate	Multivariate analysis		
	n (%)	Hazard ratio	95% CI	*p*-value
BASM (positive vs. negative)	3/6 (50%) vs. 78/121 (64%)	1.21	0.37-3.98	0.76
Age at operation (>70 days vs. ≤70 days)	18/38 (47%) vs. 63/89 (71%)	2.09	1.15-3.82	0.016*
Cholangitis within 1 year (positive vs. negative)	31/52 (60%) vs. 50/75 (67%)	1.19	0.66-2.15	0.56
Surgical approach (laparoscopic vs. open)	14/21 (67%) vs. 67/106 (63%)	0.98	0.43-2.24	0.96

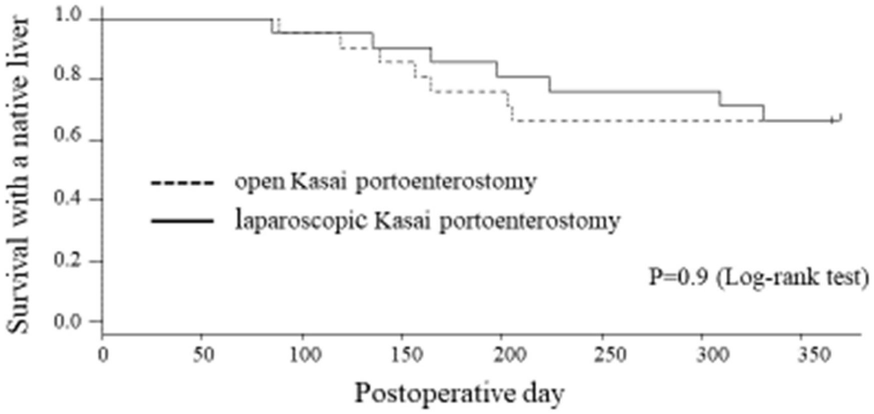
* $p < 0.05$

BASM: biliary atresia splenic malformation syndrome; CI: confidence interval.

A.


Survival with a native liver
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
300
350
Postoperative day
open Kasai portoenterostomy
laparoscopic Kasai portoenterostomy
P=0.7 (Log-rank test)

B.


Survival with a native liver
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
300
350
Postoperative day
open Kasai portoenterostomy
laparoscopic Kasai portoenterostomy
P=0.9 (Log-rank test)