

Impacts of Early Kasai Portoenterostomy on Short-Term and Long-Term Outcomes of Biliary Atresia

Ryuji Okubo ^{1,2}, Masaki Nio ^{1,2}, Hideyuki Sasaki ^{1,2} and the Japanese Biliary Atresia Society²

There are discrepancies regarding the clinical impact of age at Kasai portoenterostomy (KP) on surgical outcomes. Hence, we re-assessed the clinical significance of age at KP. We analyzed 224 patients with type III (atresia of bile duct at the porta hepatis) biliary atresia at Tohoku University Hospital. We classified patients into two groups: KP at ≤ 60 days of age (group TE) and >60 days of age (group TL). Group TE was subdivided into three groups (TE1, TE2, and TE3) according to age at time of surgery. Subsequently, 2,643 patients in the Japanese Biliary Atresia Registry were classified similarly. Background and surgical outcomes were compared. Of the 2,643 cases, 323 patients who underwent revision KP were analyzed separately. The jaundice clearance rates (JCRs) were 81.4%, 100%, 64.7%, 83.0%, and 65.2% of patients in the TE, TE1, TE2, TE3, and TL groups, respectively. The 15-year native liver survival rates of patients in the TE, TE1, TE2, TE3, and TL groups were 62.2%, 88.9%, 33.9%, 64.4%, and 42.9%, respectively. The 30-year native liver survival rates of patients in the TE, TE1, TE2, TE3, and TL groups were 38.6%, 74.1%, 25.4%, 35.8%, and 31.7%, respectively. The JCRs were 66.2%, 69.4%, 64.1%, 66.7%, and 59.7% for patients in groups JE, JE1, JE2, JE3, and JL, respectively. The 15-year native liver survival rates were 48.1%, 56.7%, 43.9%, 48.9%, and 37.2% for patients in groups JE, JE1, JE2, JE3, and JL, respectively. The JCRs following revision KP were higher in the JE1 group than in the other groups. *Conclusion:* Early KP was associated with favorable outcomes except in patients aged 31–45 days. (*Hepatology Communications* 2021;5:234–243).

Biliary atresia (BA) is a rare disease of the liver and bile ducts that develops during the perinatal period or early infancy. The pathogenesis of BA is unknown, and patients with BA can only survive with successful surgical treatment. Although the prognosis of BA has greatly improved due to the introduction of Kasai portoenterostomy (KP), BA is responsible for most liver transplantations (LTx) in children.

Even in an era of LTx, KP is currently the first-line treatment modality for patients with BA. The first requirement for long-term native liver survival following KP is good bile drainage and jaundice clearance. Several prognostic indicators in patients with BA after KP have been reported, including the association of congenital anomalies (especially splenic malformations⁽¹⁾), degree of hepatic fibrosis,⁽²⁾ type of obstruction,^(3,4) number and size of bile ducts in the fibrous

Abbreviations: BA, biliary atresia; BASM, biliary atresia splenic malformation; JBAR, Japanese Biliary Atresia Registry; JCR, jaundice clearance rate; KP, Kasai portoenterostomy; LTx, liver transplantation; NLSR, native liver survival rate; TUH, Tohoku University Hospital.

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remnant at the porta hepatis,⁽⁵⁾ bile drainage during the early phase following KP,⁽⁶⁾ association of cholangitis,⁽⁷⁾ and so on. Among them, the age at which KP was performed has been focused on several times.⁽⁸⁾ According to many reports, early age at KP, specifically an age of 60 days or less, is generally associated with good bile drainage through the bile ducts.^(8,9) However, some studies report that the age at KP is not associated with the efficiency of bile drainage following KP.^(4,7,10,11) Thus, there is a discrepancy in the literature regarding the clinical impact of age at the time of KP on the outcome. In this study, we aimed to clarify this discrepancy by retrospectively evaluating the clinical significance of the age at KP as a prognostic indicator, with a focus on jaundice clearance in patients whose operative age was 60 days or younger using data from Tohoku University Hospital (TUH) and the Japanese Biliary Atresia Registry (JBAR).

Patients and Methods

TUH

In this retrospective study, between 1972 and 2018, we treated 224 patients with type III BA at the porta hepatis of the liver at the TUH. We divided the patients into two groups based on the age at which they underwent KP. Eighty-six patients underwent KP at the age of 60 days or younger and were categorized into the early group (group TE), while the other 138 underwent KP at the age of 61 days or older and comprised the late group (group TL). Group TE was further subdivided into three groups according to the operative age: group TE1, ≤ 30 days ($n = 10$); TE2, 31-45 days ($n = 17$); and TE3, 46-60 days ($n = 59$).

JBAR

JBAR, a nationwide registry of patients with BA, was launched in 1989 by the Japanese Biliary Atresia Society, which consisted of 101 member hospitals caring for patients with BA. JBAR used an initial questionnaire, a questionnaire for LTx, and a follow-up questionnaire. Each patient was followed up for 30 years.⁽³⁾ Between 1989 and 2018, 3,483 patients entered the initial registration of JBAR. Among them, we selected 2,643 cases according to the flowcharts (Fig. 1). We then divided patients in the same manner: group JE, ≤ 60 days ($n = 1,208$); JL, > 60 days ($n = 1,435$); JE1, ≤ 30 days ($n = 139$); JE2, 31-45 days ($n = 406$); and JE3, 46-60 days ($n = 663$). Of the 2,643 cases, 323 patients who underwent revision KP were analyzed separately.

MEASURES

We examined sex, gestational age, birth weight, age at surgery, associated anomaly, direct bilirubin level at surgery, cholangitis, revision KP, jaundice clearance rates (JCRs), total bilirubin level at 6 months after KP, and 15-year and 30-year native liver survival rates (15NLSRs and 30NLSRs). Associated anomalies included polysplenia, asplenia, preduodenal portal vein, absence of inferior vena cava, malrotation, situs inversus, and congenital heart disease. Cholangitis was defined as a case with fever and inflammatory findings, as well as elevated liver function and biliary enzymes. The revision KP was indicated for cases that decreased once under normal range for each hospital and then re-elevated, or when good bile excretion was confirmed once and then was suddenly interrupted. The surgical method used was to re-dissect the fibrous tissue formed in the hilum, and then perform the

ARTICLE INFORMATION:

From the ¹Department of Pediatric Surgery, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan; ²The Japanese Biliary Atresia Society, Office of the Japanese Biliary Atresia Society, Department of Pediatric Surgery, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Masaki Nio, M.D., Ph.D., F.A.C.S.
Department of Pediatric Surgery
Tohoku University Graduate School of Medicine
1-1, Seiryu-machi, Aoba-ku

Sendai, Miyagi, 980-8574 Japan
E-mail: mnio@ped-surg.med.tohoku.ac.jp
Tel.: +81-2-2717-7235

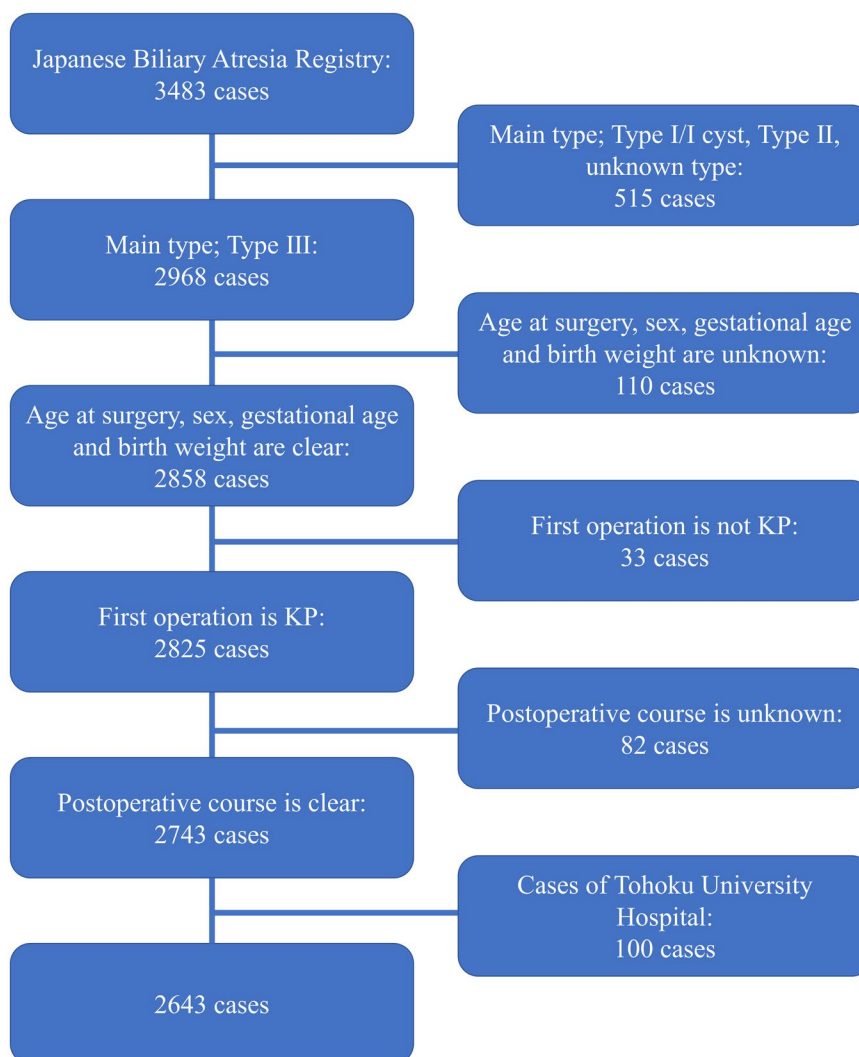


FIG. 1. Selection of patients in JBAR.

hepatic portojejunostomy again. We excluded cases with only hepatic hiatus curettage. The JCRs were defined as a blood level of total bilirubin <2.0 mg/dL and were examined after the initial KP at the TUH. At the JBAR, they were defined as a blood level of total bilirubin within normal range of each hospital and were examined after the initial KP and after revision KP, respectively.

ETHICAL APPROVAL

The study protocol was approved by the Clinical Research Ethics Board of the Tohoku University Graduate School of Medicine (2016-1-809). Parents/guardians of all study participants provided “opt-out”

informed consent according to the requirements of the Clinical Research Ethics Board.

STATISTICAL ANALYSES

Descriptive data were summarized as number (percentages) for categorical variables and as the mean \pm SD for continuous variables. Fisher’s exact test and Mann-Whitney U test were used to compare the two groups. A P value < 0.05 was considered statistically significant. In contrast, the Fisher’s exact test and Kruskal-Wallis test were used to compare the four groups. The Bonferroni test was performed as a *post hoc* test, and a P value < 0.008 was considered statistically significant among the groups.

Survival rates were analyzed using the Kaplan-Meier method, and the log-rank test was used to compare the long-term survival distributions among the groups. The Holm test was performed as a *post hoc* test.

Statistical analysis was performed using the commercially available software JMP Pro 14.2 (SAS Institute Japan Ltd., Tokyo, Japan).

Results

STUDY RESULTS OF TUH

Patient Background for TUH

There were no differences in sex between groups. The associated anomaly in group TE2 was significantly higher than in the other groups. Direct bilirubin level at surgery was directly proportional to age at surgery (Table 1).

JCRs in TUH

The JCRs were achieved in 81.4% and 65.2% of patients in groups TE and TL, respectively, and there

was a significant difference in the clearance between the groups ($P = 0.0099$). The JCRs were achieved in 100%, 64.7%, and 83.0% of patients in groups TE1, TE2, and TE3, respectively. The JCRs in group TE2 were significantly lower than in group TE1 and similar to that in group TL (Table 1).

Incidence of Cholangitis and Need for Revision KP in TUH

The frequency of cholangitis was similar among all groups. Revision KP was higher in group TE2 than in other groups; however, the difference was not statistically significant (Table 1).

Long-Term Survival at TUH

The long-term survival rate was significantly better in group TE than in group TL (log rank, $P = 0.0374$; Fig. 2), and the 15NLSRs were 62.2% and 42.9% in groups TE and TL, respectively. The 15NLSRs were 88.9%, 33.9%, and 64.4% in groups TE1, TE2, and TE3, respectively, (Table 1); however, there were no

TABLE 1. PATIENT BACKGROUND AND CLINICAL OUTCOMES IN TUH

Group	Group TE (n = 86)			Group TL (n = 138)	P Value (TE:TL)
	TE1: n = 10	TE2: n = 17	TE3: n = 59		
Number of patients					
Female, n (%)	58 (67.4)			83 (60.1)	0.3199
	4 (40.0)	9 (52.9)	45 (76.3)		
Age at surgery (days), mean, SD	46.9, 11.8			78.5, 18.3	<0.0001
	19.8, 7.5	40.9, 3.6	53.3, 3.7		
Associated anomaly, n (%)	7 (8.1)			9 (6.5)	0.7905
	1 (10)	5 (29.4)*	1 (1.7)*		
Direct bilirubin (mg/dL), mean, SD	6.8, 3.1			7.6, 2.5 ^{‡,}	0.0037
	5.1, 3.7 ^{†,‡}	5.3, 1.6 ^{§,}	7.3, 3.1 ^{†,§}		
JCR, n (%)	70 (81.4)			90 (65.2)	0.0099
	10 (100)	11 (64.7)	49 (83.0)		
Cholangitis, n (%)	44 (51.2)			63 (46.7)	0.5812
	5 (50.0)	8 (47.0)	31 (52.5)		
Revision KP, n (%)	22 (25.6)			25 (18.1)	0.2373
	1 (10)	6 (35.3)	15 (25.4)		
15NLSR, %	62.2			42.9	0.0374
	88.9	33.9	64.4		
30NLSR, %	38.6			31.7	0.0374
	74.1	25.4	35.8		

Note: P value < 0.008 is considered statistically significant among the four groups.

* $P = 0.0017$.

† $P = 0.0074$.

‡ $P = 0.0005$.

§ $P = 0.0061$.

|| $P = 0.0001$.

statistically significant differences in the long-term survival rates among the groups (log rank, $P = 0.0284$; Fig. 3). The 30NLSRs were 38.6%, 74.1%, 25.4%, 35.8%, and 31.7% of patients in the TE, TE1, TE2, TE3, and TL groups, respectively. The NLSRs were maintained between 15-year and 30-year in TE1; however, it decreased extremely in TE3 at about 30 years of age.

STUDY RESULTS OF THE JBAR

Patient Background of the JBAR

The frequency of females was slightly higher in group JE2 than both in group JE3 and group JL. Gestational age was highest in group JE1 than in the other groups. Birth weight was higher in the early group than in the late group; however, no differences were observed among the three early groups. The associated anomaly in the JBAR was similar among all groups, unlike the TUH. Direct bilirubin level at surgery increased in proportion to age at surgery (Table 2).

JCRs in the JBAR

JCRs were achieved in 66.2% and 59.7% of patients in groups JE and JL, respectively, and there was a significant difference in the clearance between the groups

($P = 0.0009$). JCRs were achieved in 69.4%, 64.1%, and 66.7% of patients in groups JE1, JE2, and JE3, respectively. The JCRs were the lowest in group JE2 in the early group; however, the difference was not statistically significant (Table 2). The ratios in which a total bilirubin level of 1.2 mg/dL was used as a cutoff value were 68.0%, 72.6%, 65.1%, 68.8%, and 64.4% of the patients in groups JE, JE1, JE2, JE3, and JL, respectively.

Incidence of Cholangitis and Need for Revision KP in the JBAR

The frequency of cholangitis was almost similar among the four groups. Revision KP was higher in group JE1 than in the other groups; however, there were no statistically significant differences (Table 2).

Long-Term Survival in the JBAR

The long-term survival rate was significantly better in group JE than in group JL (log rank, $P = < 0.0001$; Fig. 4), and the 15NLSRs were 48.1% and 37.2% in groups JE and JL, respectively. The 15NLSRs were almost the same in the early group (group JE1, 56.7%; group JE2, 43.9%; and group JE3, 48.9%, respectively), and there were no statistically significant differences in the long-term survival rates among the early groups (Table 2 and Fig. 5).

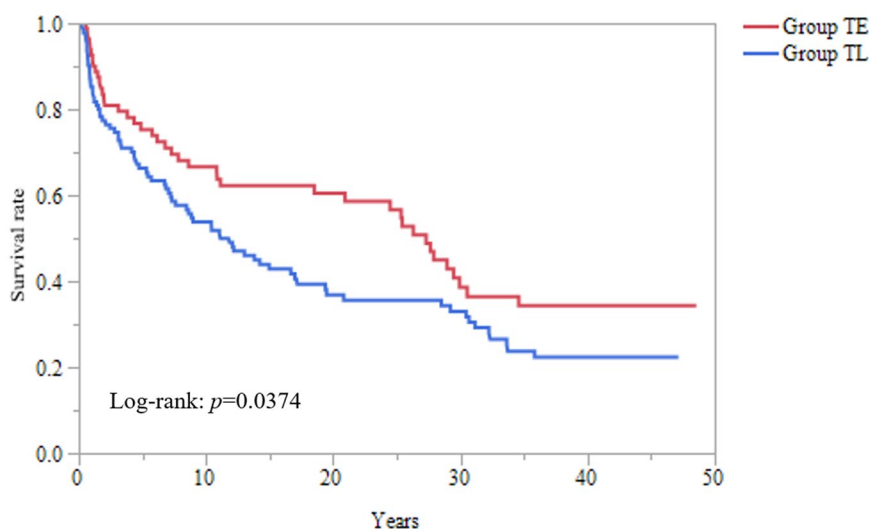


FIG. 2. Kaplan-Meier survival curves for groups TE and TL in TUH. Long-term survival was significantly better in group TE than in group TL (log rank, $P = 0.0374$). The 15NLSRs were 62.2% and 42.9% in groups TE and TL, respectively. The 30NLSRs were 38.6% and 31.7% in groups TE and TL, respectively.

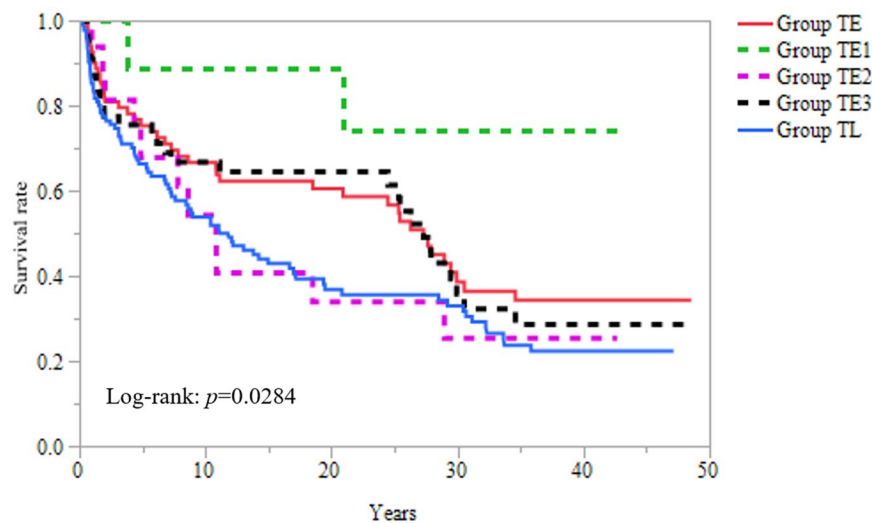


FIG. 3. Kaplan-Meier survival curves for all groups in TUH. The 15NLSRs were 88.9%, 33.9%, and 64.4% in groups TE1, TE2, and TE3, respectively. The 30NLSRs were 74.1%, 25.4%, and 35.8% in groups TE1, TE2, and TE3, respectively.

Patient Background and Clinical Outcomes in Patients Who Underwent Revision KP at the JBAR

The associated anomaly was slightly higher in group JE3. The direct bilirubin level at initial surgery increased in proportion to the age at surgery. The frequency of cholangitis following initial surgery increased in proportion to age at surgery in the early group, but it was lower in the late group than in the early group. The JCRs after initial KP were almost similar in all groups; however, JCRs following revision KP were higher in group JE1 than in the other groups; however, there were no statistically significant differences (Table 3).

Discussion

Since the development of KP in late the 1950s, many efforts, including refinement of surgical techniques and postoperative management, have been made to achieve good outcomes. Several prognostic indicators of KP have also been presented, and age at KP is the most frequently studied among them. Morio Kasai reported that early KP performed before 60 days of birth was associated with better bile drainage.⁽⁹⁾ Since then, many researchers have also reported that favorable outcomes are achieved

following early KP. However, other studies^(4,7,11) reported conflicting results, indicating that there were no obvious advantages of early KP. The timing of KP as a significant prognostic indicator is still controversial, and there are currently no explanations for this discrepancy regarding the effect of age at KP on the outcome.

In the current study, better bile drainage was confirmed in the early group aged ≤ 60 days compared with the late group aged >60 days. However, within the early group, although the best results were achieved in the youngest patients who underwent KP during the neonatal period, the group of patients aged 46–60 days achieved better outcomes than the group aged 31–45 days at KP, especially in the TUH study. Therefore, the rule “the earlier the procedure is performed, the better the prognosis” could not be applied to this special subset of patients as far as the experience with a limited number of cases in a single institution was concerned. Thus, we further evaluated this concern using the JBAR data, and similar results were obtained.

Considering the relationship between the age at surgery and the outcome, two possibilities would be raised (i.e., the age at surgery was too late in group E2 compared with group E1; the age at surgery in group E2 was too early compared with group E3); apparently conflicting these two speculations might hold together, if the timing of establishment of biliary

TABLE 2. PATIENT BACKGROUND AND CLINICAL OUTCOMES IN THE JBAR

Group	Group JE: n = 1,208				P Value (JE:JL)
	JE1: n = 139	JE2: n = 406	JE3: n = 663	Group JL: n = 1,435	
Number of patients					
Female, n (%)	775 (64.2)			853 (59.4) [‡]	0.0143
Gestational age (weeks), mean, SD	38.8, 1.6			38.5, 1.9 ^{§,}	0.0008
	39.0, 1.6 [§]	38.8, 1.6	38.7, 1.6		
Birth weight (g), mean, SD	2,927, 434			2,882, 462	0.0144
	2,979, 418	2,951, 409	2,902, 450		
Age at surgery (days), mean, SD	45.3, 10.8			85.6, 25.3	<0.0001
	24.8, 4.7	38.9, 4.2	53.4, 4.2		
Associated anomaly, n (%)	71 (5.8)			60 (4.2)	0.0480
	4 (2.9)	26 (6.4)	41 (6.2)		
Direct bilirubin (mg/dL), mean, SD	5.5 (2.2)			7.1 (2.6) [#]	<0.0001
	4.6, 1.8 ^{¶,#}	5.1, 2.0 ^{¶,#}	6.0, 2.3 [#]		
JCR, n (%)	762 (66.2)			806 (59.7) ^{**}	0.0009
	93 (69.4)	248 (64.1)	421 (66.7) ^{**}		
Total bilirubin (<1.2 mg/dL) at 6 months after KP, n (%) [*]	464 (68.0)			445 (64.4)	0.1709
	69 (72.6)	153 (65.1)	242 (68.8)		
Cholangitis, n (%)	496 (43.1)			609 (44.3)	0.8235
	55 (41.7)	161 (41.8)	280 (44.6)		
Revision KP, n (%)	152 (12.6)			171 (11.9)	0.6335
	25 (18.0)	53 (13.1)	74 (11.2)		
15NLSR, %	48.1			37.2 ^{††,‡‡}	<0.0001
	56.7 ^{‡‡}	43.9	48.9 ^{‡‡}		

Note: *P* value < 0.008 is considered statistically significant among the four groups.

Missing values (n) were 44, 171, 311, and 744 of patients in groups JE1, JE2, JE3, and JL, respectively.*

[†]*P* = 0.0060.

[‡]*P* = 0.0007.

[§]*P* = 0.0016.

^{||}*P* = 0.0050.

[¶]*P* = 0.0009.

[#]*P* = < 0.0001.

^{**}*P* = 0.0029.

^{††}*P* = 0.0038.

^{‡‡}*P* = 0.0001.

obstruction and/or the severity of liver pathology would change case by case.

From the stool color data, there were more meconium abnormalities in group E1 followed by group E2; there might be some members of the population in whom the bile discharge stopped early in group E1, and some might also be included in group E2 (Supporting Information). In this population, the operative age of 1 to 1.5 months might be too late. Considering whether there would be any relationship between the timing of the stoppage of bile excretion and the developmental immaturity of the liver, we examined gestational age and birth weight in each group; however, no particular trends were seen

in groups E1-E3. Furthermore, it was obvious that the cholestasis tended to become more severe with age, based on the data of direct bilirubin level at KP. Alternatively stated, the disease condition might have been completed in group E1 at an early stage, but the liver condition itself was not severe yet. However, there might be a selection bias with many cases of meconium abnormalities in group E1.

In contrast, if the group JE2 included many cases in whom the timing of KP was too early, it was expected that the results of revision KP of the group JE2 would be better than those of the other groups; however, the JCRs after revision KP were lowest in group JE2. The JCR following revision KP was highest in group JE1,

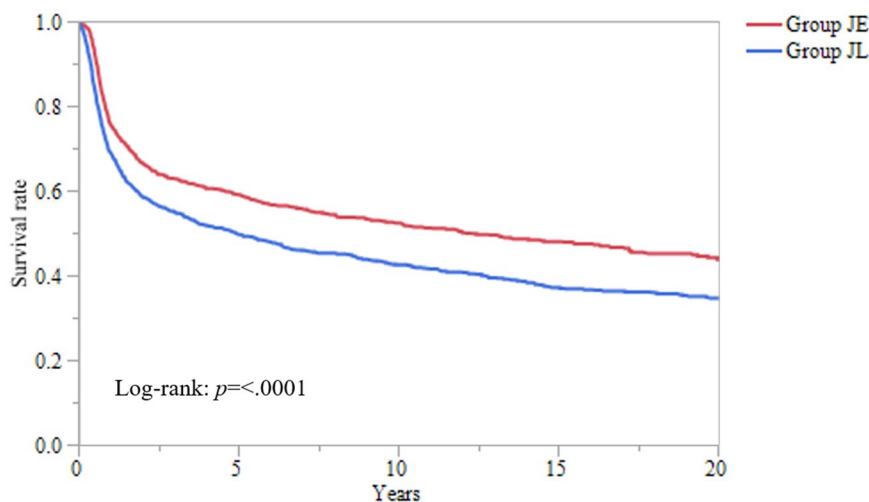


FIG. 4. Kaplan-Meier survival curves for group JE and JL in the JBAR. Long-term survival was significantly better in group JE than in group JL (log rank, $P = < 0.0001$). The 15NLSRs were 48.1% and 37.2% in groups JE and JL, respectively.

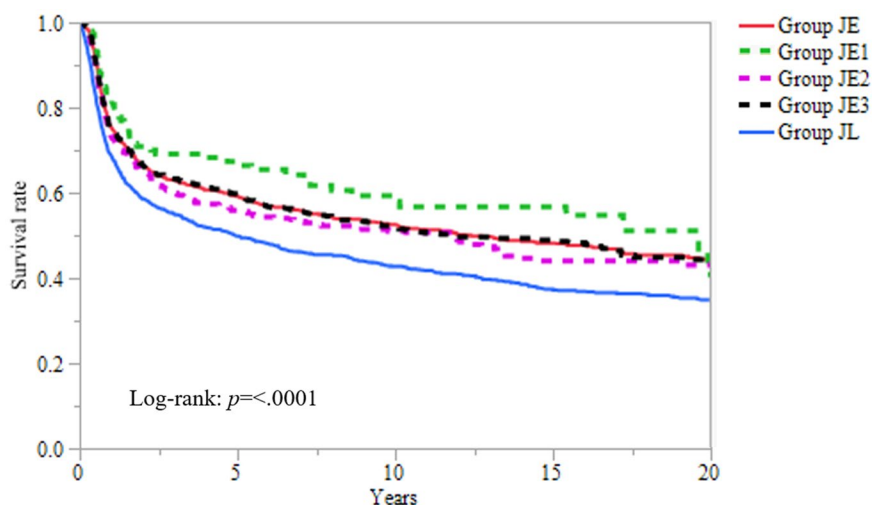


FIG. 5. Kaplan-Meier survival curves for all groups in the JBAR. The 15NLSRs were 56.7%, 43.9%, and 48.9% in groups JE1, JE2, and JE3, respectively.

suggesting that more patients, in whom the timing of KP was too early, were included in group E1 than in other groups.

From the differences in surgical results depending on the facilities or age, few results pointed out why group E2 had the worst performance (Supporting Information).

Although the reason for the reduction in the JCRs in the group aged 31–45 days at KP was still unclear with these current study results, another possibility was that a severe type of BA was included in this subgroup. The frequency of the associated anomaly was

significantly higher in group E2 than in group E3 in the TUH study. This result might have a direct or indirect effect on the patient outcome; the poor outcome of associated anomalies themselves and/or the severe liver pathology in BA that was associated with major anomalies might have a certain impact on the patient outcome. Regarding associated anomalies of BA, the biliary atresia splenic malformation (BASM) was reported as a certain subset with poor prognosis. The incidence of BASM was much lower in Asian countries, including Japan, than in Western countries,^(1,3)

TABLE 3. PATIENT BACKGROUND AND CLINICAL OUTCOMES IN THE JBAR (REVISION KP)

Group	Group JE: n = 152			Group JL: n = 171	P Value (JE:JL)
	JE1: n = 25	JE2: n = 53	JE3: n = 74		
Number of patients					
Age at initial surgery (days), mean, SD	43.5, 11.6			83.3, 25.9	<0.0001
	24.8, 4.8	38.5, 4.1	53.4, 4.4		
Associated anomaly, n (%)	7 (4.6)			6 (3.5)	0.7783
	0 (0)	2 (3.8)	5 (6.8)		
Direct bilirubin at initial surgery (mg/dL), mean, SD	5.9, 2.4			7.2, 2.5 [†]	<0.0001
	4.6, 1.4*, [†]	5.7, 1.9 [†]	6.6, 2.7*		
JCR by initial KP, n (%)	28 (21.2)			29 (22.0)	1.0000
	6 (26.1)	9 (19.2)	13 (21.0)		
Cholangitis following the initial surgery, n (%)	61 (42.1)			63 (34.0)	0.4873
	7 (28.0)	20 (38.5)	34 (50.0)		
Age at revision surgery (days), mean, SD	101.3, 54.0			142.9, 75.5	<0.0001
	99.3, 95.5	97.8, 43.3	104.5, 41.0		
JCR following revision KP, n (%)	57 (37.5)			55 (32.2)	0.3494
	13 (52.0)	15 (28.3)	29 (39.2)		

Note: *P* value < 0.008 is considered statistically significant among the four groups.

**P* = 0.0002.

[†]*P* = < 0.0001.

and BASM itself was not an independent risk factor in short-term and long-term prognosis in our own series.⁽¹²⁾ However, we still assumed that there were some patients with severe BA in group E2, in whom favorable outcomes could not be expected regardless of the age at KP.

We did not arrive at a reasonable explanation for the clinical outcome of group E2, which was poor or equal to that of group E3. In some reports, no favorable effect of early KP on the outcome was found: They treated patients whose operative age was primarily around 30–60 days,^(10,11) and the number of patients whose age was <30 days and >60 days appeared to be limited and the age range was not wide enough for the analysis. The current study showed that age at the time of KP had a significant effect on most patients with BA. However, the impact of this variable might be less significant in a certain subset that included a number of patients with inherent severe liver pathology, and this might provide an additional explanation for the discrepancy in the significance of the age at KP.

Our current policy regarding the timing of KP is as follows: We perform KP at 3 or 4 weeks of age for patients with a prenatal or perinatal diagnosis of BA, because we believe the first or second week of life is too early to perform the procedure, based on our institutional experience.⁽¹³⁾ However, we never postponed

KP until 30 days of age or later. In patients diagnosed with BA after the neonatal period, including the period between 31 and 45 days of age, we performed KP as early as possible. In cases in which the timing at KP is believed to be too early from the pathological analysis of liver biopsy specimen taken at KP and/or diagnostic imaging analysis including ^{99m}Tc-DTPA galactosyl human serum albumin liver scintigraphy,⁽¹⁴⁾ we would perform revision KP 4 to 5 weeks after the initial KP.

Our experience of revision KP under this policy was quite limited; thus, we cannot justify this indication of the revision KP yet. However, we will potentially find cases that undergo KP with inappropriate timing, and following accumulation and evaluation of these cases, we will be able to decide the optimal timing of KP for each case.

This study has limitations related to the retrospective nature of data collection for a longitudinal clinical study and the limited number of materials, especially in TUH study. Prospective studies analyzing patients with early KP are essential in determining the real role of the age at KP as a prognostic indicator as well as the optimal timing of KP.

In conclusion, this study analyzed the effect of age at KP on prognostic outcomes in patients with BA. Outcomes that were more favorable were associated with a younger age, specifically 60 days or younger,

except in the group of patients aged 31–45 days at KP. This result might clarify the discrepancy that exists in the literature regarding age at KP as a prognostic indicator. Further studies are necessary, but these results may help to clarify the significance of age as a prognostic indicator for bile drainage after KP.

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Author names in bold designate shared co-first authorship.

Supporting Information

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