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ORIGINAL ARTICLE

# A periodic comparison of the survival and prognostic factors of biliary atresia after Kasai portoenterostomy: a single-center study in Korea

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## Abstract

**Purpose** We explored the chronologic changes in prognostic factors and clinical outcomes of Kasai portoenterostomy (KPE) for biliary atresia (BA).

**Methods** Patients undergoing KPE between 1997 and 2016 were analyzed retrospectively. Ninety-two consecutive patients who underwent KPE from 1997 to 2006 (Era 1) were compared with 150 patients who underwent KPE from 2007 to 2016 (Era 2) for clinical outcomes and prognostic factors.

**Results** The jaundice clearance rate increased by 8.8% (66.7% vs. 75.5% for Eras 1 and 2, respectively, $p = 0.180$), and the 5-year native liver survival (NLS) rate improved slightly (62.5% vs. 64.0% for Eras 1 and 2, respectively, $p = 0.617$) in Era 2. The hazard ratio for age at KPE ($\geq 90$ days) with regard to 5-year NLS and the odds ratio for age at KPE ($< 90$ days) with regard to jaundice clearance were both lower in Era 2 than in Era 1 (1.95 vs. 2.25 and 2.67 vs. 5.21, respectively).

**Conclusion** The clinical outcomes improved over a period in a single surgeon's practice. We demonstrated that the impact of age at the time of KPE on operative outcomes became less significant over time with the increase in the single surgeon's experience and improvement in medical treatment for BA.

**Keywords** Biliary atresia · Kasai portoenterostomy · Prognosis · Liver fibrosis · Native liver survival

## Introduction

Biliary atresia (BA), the most common cause of neonatal cholestasis, predisposes the patient to progressive liver fibrosis and is the most frequent indication for pediatric liver transplantation (LTx). BA has changed from being uncorrectable disease to correctable with the application of Kasai portoenterostomy (KPE). The number of long-term survivors with native livers has therefore increased. The Health Insurance Review and Assessment Service database (based on the Korean universal health insurance system) has revealed that the incidence of BA is higher in Korea (1.06 per 10,000 live births) than in Western countries (0.42–0.71 per 10,000) [1–4]. Despite this high prevalence, there are few published studies on the long-term outcomes of these patients [5].

Over the past decades, various pathologic, surgical, and medical factors have been investigated to determine the predictors of a successful KPE and long-term native liver survival (NLS). The severity of hepatic fibrosis at the time of KPE, syndromic BA, and anatomic variance of biliary remnants are well established, nonmodifiable prognostic

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factors of long-term prognosis, whereas the experience of the medical center in BA management and age at the time of KPE are important modifiable factors [6]. Because there is little data regarding time-related risk factors of prognosis in patients with BA, we compared the outcomes of patients with BA by dividing a 20-year period into two eras [7]. Furthermore, we explored the impact of age at the time of operation and the other above-mentioned prognostic factors on NLS after KPE.

## Methods

### Study population

All consecutive patients with BA who underwent KPE between June 1, 1997 and September 30, 2016 at Severance Children's Hospital (Seoul, Korea) were included in this study. We excluded patients who underwent redo KPE after undergoing failed KPE at other medical centers. The patients were divided into two groups, with 92 patients in Era 1, who underwent KPE during the first period from 1997 to 2006 and 150 patients in Era 2, who underwent KPE during the second period from 2007 to 2016. The study period was divided evenly between groups into 10 years. During the study period, all baseline characteristic, radiologic, and laboratory data were entered into a computerized database and retrospectively reviewed. The patients' records were anonymized before analysis. The study was approved by the institutional review board of Severance Hospital (approval number: 4-2017-1101). The need to obtain informed consent was waived owing to the study's retrospective nature.

### Data collection

The data collected at the time of KPE included the baseline demographic and clinical characteristic data: age at the time of KPE, laboratory values, serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin (TB), direct bilirubin, and gamma-glutamyl transpeptidase. Syndromic BA was defined as BA that was associated with unusual anomalies, including one or more of the following: poly- or asplenia, intestinal malrotation, preduodenal portal vein, interrupted inferior vena cava, situs inversus, and cardiac anomalies. BA associated with an extrahepatic bile duct cyst was confirmed via intraoperative cholangiography using fluoroscopy. Early cholangitis was defined as fever (> 38.0 °C) accompanied by elevated serum TB levels, leukocytosis with a left shift, and normal to acholic stools after KPE.

### Operative methods and postoperative care

The surgical technique was consistent throughout the study period. All procedures were performed by a single surgeon (S.J. Han). Extended portoenterostomy was the treatment of choice, regardless of the type of BA. Dissection of the porta hepatis involved extended dissection of the proximal part of the fibrotic biliary remnant, with ligation of the small vessels that drained into the caudate lobe. A Roux-en Y limb of about 60 cm was passed retrocolically to the hilum, and portoenterostomy was performed using anastomosis with interrupted 5-0 or 6-0 multifilament absorbable sutures.

Postoperative care was provided by multidisciplinary teams of experts, including pediatric hepatologists, gastroenterologists, nurses, social workers, pharmacists, and dieticians. The addition of high-dose corticosteroids after KPE was selectively determined when the patients showed insufficient bile flow with grey-pigmented stool, without any surgery-related complications or accompanied CMV hepatitis. Steroid protocol consisted of parenteral methylprednisolone (gradual tapering of dose everyday from 10, 8, 6, 5, 4, 3, to 2 mg/kg/day) followed by less than 8 weeks of oral prednisone (2 mg/kg/day). Intravenous immunoglobulin was used in a rare number of patients with intractable cholangitis who did not respond to conventional treatment. All patients' postoperative care included continuous enteral administration of ursodeoxycholic acid (30 mg/kg/day, every 8 h), probiotics, and fat-soluble vitamin supplementation. Prophylactic intravenous antibiotics with a combination of third-generation cephalosporins (usually cefoperazone/sulbactam) for 28 days, metronidazole for 7 days, and amikacin for 5 days following KPE were continued throughout the perioperative period. Routine follow-up tests included ultrasonography and hepatic elastography (Fibroscan®). Endoscopic surveillance for esophageal and gastric varices included an endoscopic screening examination for patients whose post-KPE transient elastography score was over 9.6 kPa since April 2007 [8, 9]. We also attempted to prevent esophageal variceal bleeding by administering β-blockers, such as propranolol, to patients with a high bleeding risk or history of bleeding, after observing esophageal varices. In addition, annual or biannual contrast echocardiography was performed to screen for hepatopulmonary syndrome or pulmonary arterial hypertension [10, 11].

### Outcome measures

The endpoints of this study were native liver and overall survival. NLS was calculated as the time from birth to

loss of the native liver; the loss of native liver was defined as LTx or death. Overall survival was calculated as the time from birth to death for many reasons, regardless of whether transplantation was performed. If a patient had not lost their native liver or died, the patient was censored from the analysis on April 3, 2017. Complete patient information regarding vital status was available up to the last follow-up date.

### Statistical analysis

The data were analyzed using SPSS, ver. 23.0 for Windows (IBM, Armonk, NY) and R software version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). The Kolmogorov–Smirnov test was used to test for normality. To compare independent continuous variables between groups, Student's *t* test or Mann–Whitney's *U* test was used, as appropriate. Categorical variables were compared using Fisher's exact test. Qualitative variables are described as numbers (percentages) and quantitative variables as a mean and standard deviation (SD). Frequencies of jaundice clearance and 5-year NLS are visualized using grouped bar charts. Survival analysis was performed with the Kaplan–Meier method, and survival curves were compared using a log-rank method. Logistic regression analysis was used to identify the predictive factors of jaundice clearance at 6 months after KPE (total bilirubin < 2.0 mg/dL). Univariate analyses with Cox regression analyses were performed to determine the risk factors associated with the loss of native liver. Two-tailed *P* values < 0.05 were considered statistically significant.

## Results

### Clinical characteristics and outcomes

A total of 242 patients with BA were identified over the entire study period, of which 92 patients were in Era 1 and 150 in Era 2. Table 1 shows the clinical characteristics of and comparison between patients in the Era 1 and Era 2 groups. The interval from KPE to LTx in the Era 2 group was significantly shorter than that in the Era 1 group (9.1 vs. 12.8 months, respectively, $P = 0.027$). Regarding the BA phenotype, most patients had isolated BA: nine had syndromic BA and 18 had extrahepatic, cystic BA. The proportion of each phenotype showed no statistical difference over time. The jaundice clearance rate (JCR) was higher in the Era 2 group than in the Era 1 group, but did not reach statistical significance (67.4% vs. 75.3% for the Era 1 and Era 2 groups, respectively, $P = 0.180$). The overall mean age of the study patients at last follow-up was 6.0 years; the median age was 12.8 years in the Era 1 group and 4.4 years in the Era 2 group. The details of the outcome of the recruited patients are given in Fig. 1 as a flowchart.

### Trends in the jaundice clearance rate and 5-year native liver survival rate according to each age group

The 242 patients were divided into four groups according to age at the time of KPE and period: Group 1, younger than 31 days; Group 2, 31–60 days; Group 3, 61–90 days; and Group 4, older than 90 days. Figure 2 shows that the JCR for Group 4 (> 90 days) increased with time (Era 1: 35.3%, Era 2: 56.5%). The 5-year NLS rate in Group 4 increased

**Table 1** The baseline characteristics of patients with BA during Eras 1 and 2

| | Total ($n = 242$) | Era 1 ($n = 92$, 1997–2006) | Era 2 ($n = 150$, 2007–2016) | *P* value |
|---|---|---|---|---|
| Age at KPE, days (SD) | 64.7 (31.7) | 66.4 (27.7) | 63.6 (33.0) | 0.509 |
| Age at KPE, days (median, range) | 63 (8–182) | 65 (13–182) | 61 (8–174) | 0.374 |
| Age at KPE, < 90 days (SD) | 201 (83.1) | 75 (81.5) | 126 (84.0) | 0.618 |
| Sex, male (%) | 94 (38.8) | 39 (42.4) | 55 (36.7) | 0.375 |
| Extrahepatic, cystic BA (%) | 18 (7.4) | 6 (6.5) | 12 (8.0) | 0.671 |
| Syndromic BA (%) | 9 (3.7) | 4 (4.4) | 5 (3.3) | 0.673 |
| Early cholangitis (%) | 107 (44.2%) | 43 (46.7%) | 64 (42.7%) | 0.508 |
| Follow-up, years (IQR) | 6 (2.6–11.0) | 11.9 (10.4–13.8) | 4.4 (2.2–6.8) | < 0.001 |
| Interval from KPE to LTx, months (IQR, Era1:Era2 = 30:42) | 9.8 (6.1–26.1) | 12.8 (7.9–80.6) | 9.1 (5.7–17.7) | 0.027 |
| Jaundice clearance rate | 72.3% | 67.4% | 75.3% | 0.180 |
| 5-year native liver survival rate | 63.4% | 62.5% | 64.0% | 0.617 |
| 5-year overall survival rate | 88.1% | 85.7% | 89.6% | 0.303 |

*SD* standard deviation, *IQR* interquartile range, *KPE* Kasai portoenterostomy, *BA* biliary atresia, *LTx* liver transplantation

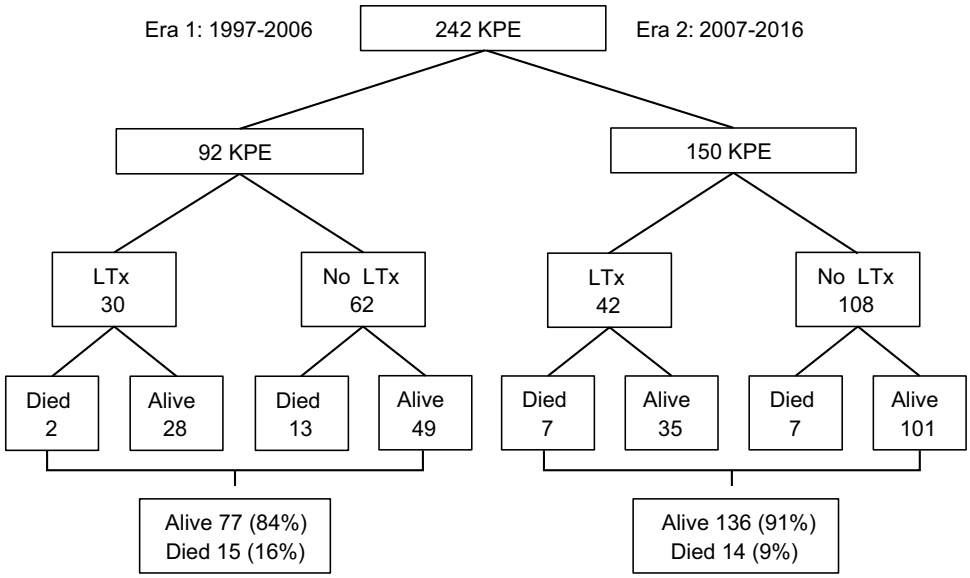


**Fig. 1** A flow diagram of the management and outcomes of patients in Era 1 and Era 2. *KPE* Kasai portoenterostomy, *LTx* liver transplantation

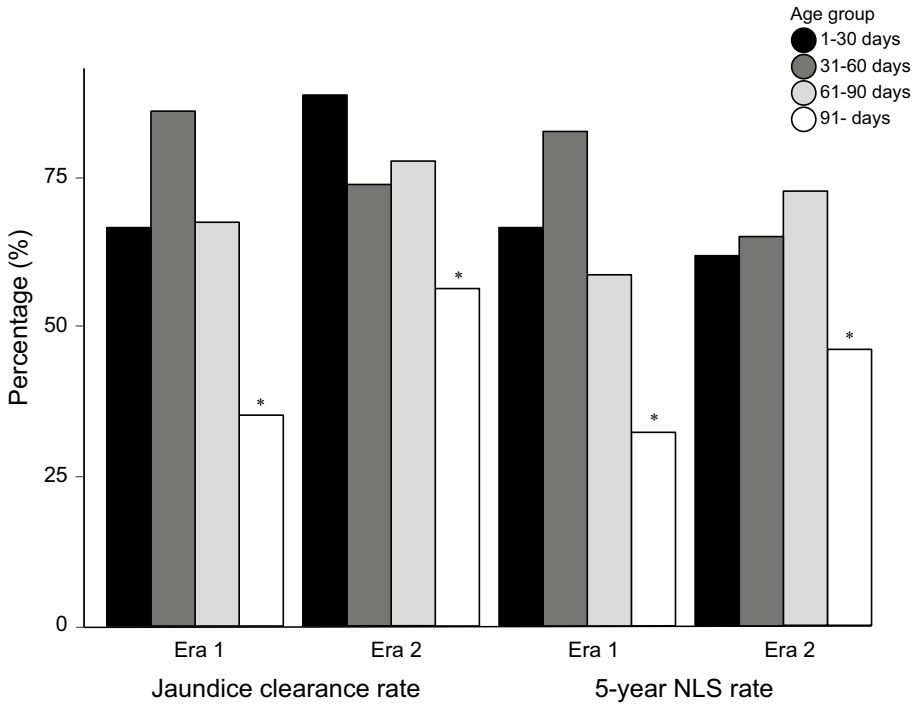


**Fig. 2** Grouped bar graph showing the 5-year NLS rate and jaundice clearance rate by each era. *The asterisks indicate age group 4 (> 90 days)

with time (Era 1: 32.4%, Era 2: 46.2%). Although Group 4 showed a lower JCR and 5-year NLS than other age groups, a tendency toward increased JCR and 5-year NLS was noted in Group 4 over time.

## Native liver and overall patient survival

Comparing Era 1 and Era 2 in the total population, we found that the 5-year NLS rates were nearly identical in both groups (62.5% vs. 64.0%, respectively, $P = 0.617$, Fig. 3a). Although the difference between Era 1 and Era 2 groups did not appear to be statistically significant, Era 2 conferred a 3.9% survival benefit in the 5-year overall survival compared with Era 1 (85.7% vs. 89.6%, respectively, $P = 0.303$, Fig. 3b). At the end of the study period, 213 of the 242 patients (88%) were alive, and 29 patients (12%) had died (Fig. 1). A total of 20 patients (13 vs. 7 for Era 1 and Era 2, respectively) without LTx died during the study period. The most common cause of death was a combination of liver failure with multi-organ failure in 9, followed by variceal bleeding in 7 and sepsis in 4.

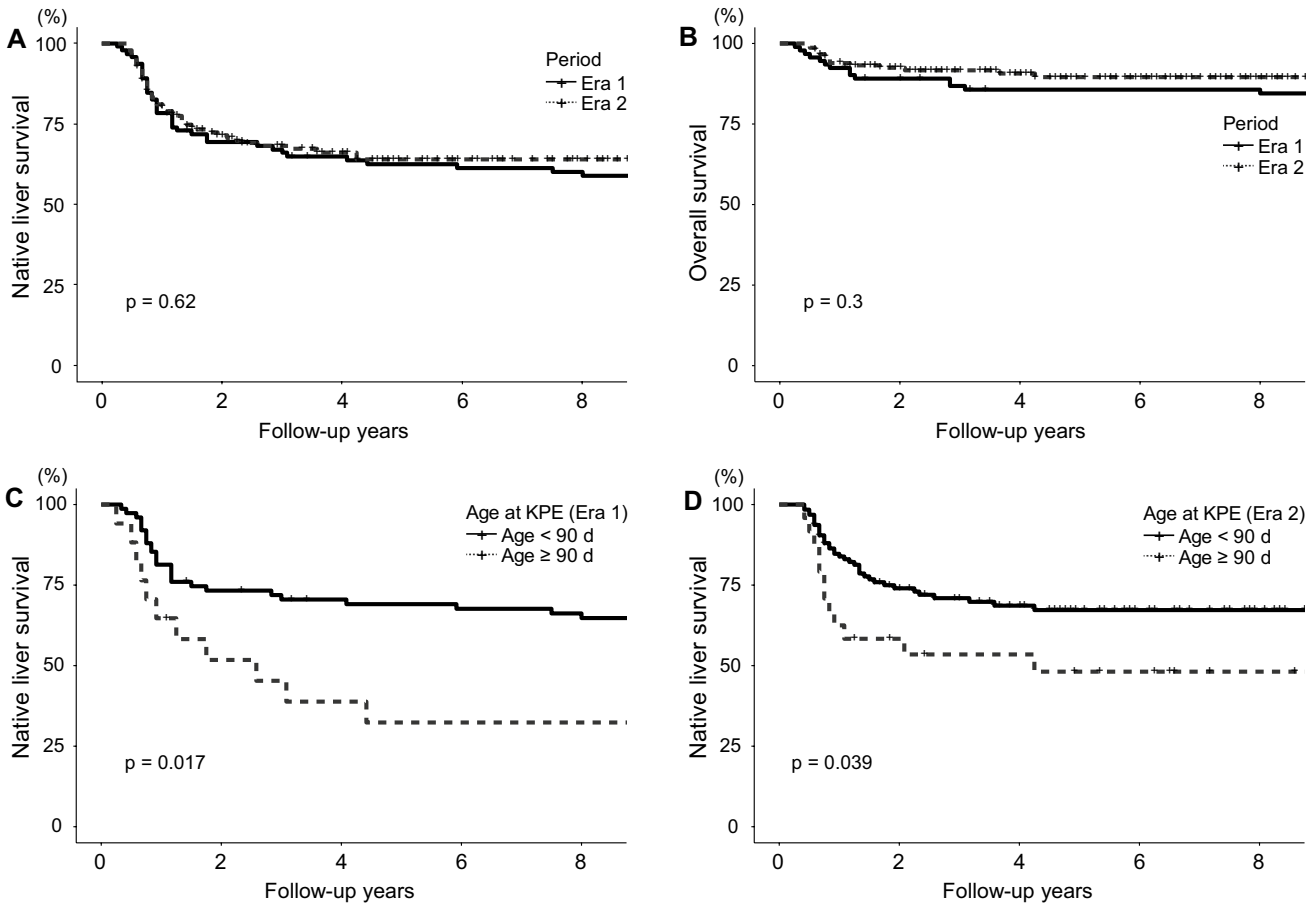


**Fig. 3** The 5-year native liver survival curves of **a** patients who underwent KPE in Era 1 and in Era 2; **b** 5-year overall survival curves of patients who underwent KPE in Era 1 and in Era 2; **c** patients older than 90 days who underwent KPE and those younger than 90 days in Era 1; **d** patients older than 90 days who underwent KPE and those younger than 90 days in Era 2. *KPE* Kasai portoenterostomy

The NLS curves for patients undergoing KPE in Era 1 and Era 2 were plotted according to their age categorization at the time of KPE (≤ 90 or > 90 days). In a comparison of patients older than 90 days with those younger than 90 days, we found that the 5-year NLS rate was significantly superior for the younger group than for the older group, both in Era 1 (69.1% vs. 32.4%, respectively, $P = 0.017$, Fig. 3c) and Era 2 (67.2% vs. 46.2%, respectively, $P = 0.039$, Fig. 3d).

## Periodic comparison of risk factors affecting outcomes

Logistic regression analyses were performed to identify the chronological changes in factors that affected jaundice clearance. Jaundice clearance was significantly associated with age at the time of KPE when categorized as a dichotomous variable (≤ 90 or > 90 days). The odds ratio of age at the time of KPE was smaller in Era 2 than in Era 1 [2.67 (95% CI 1.07–6.68, $P = 0.035$) vs. 5.21 (95% CI 1.69–16.03, $P = 0.004$), respectively, Fig. 4a].

As shown in Fig. 4b, univariate Cox regression analysis found that age at the time of KPE and TB at 6 months after KPE were the only statistically significant risk factors for native liver failure after KPE in both periods. The hazard ratio of age at the time of KPE became less significant in Era 2 than in Era 1 [1.95 (95% CI 1.01–3.74, $P = 0.045$) vs. 2.25 (95% CI 1.13–4.52, $P = 0.022$), respectively], whereas the hazard ratio of TB at 6 months after KPE became more significant in Era 2 than in Era 1 [1.35 (95% CI 1.25–1.46, $P < 0.001$) vs. 1.19 (95% CI 1.13–1.25, $P < 0.001$), respectively]. However, we were unable to perform a subgroup multivariate Cox regression analysis for each period owing to the small number of patients with syndromic BA and cystic BA.

## Discussion

Although collaborative efforts have aimed to analyze the prognostic factors affecting NLS to improve the initial therapeutic response of KPE in BA patients, determining accurate

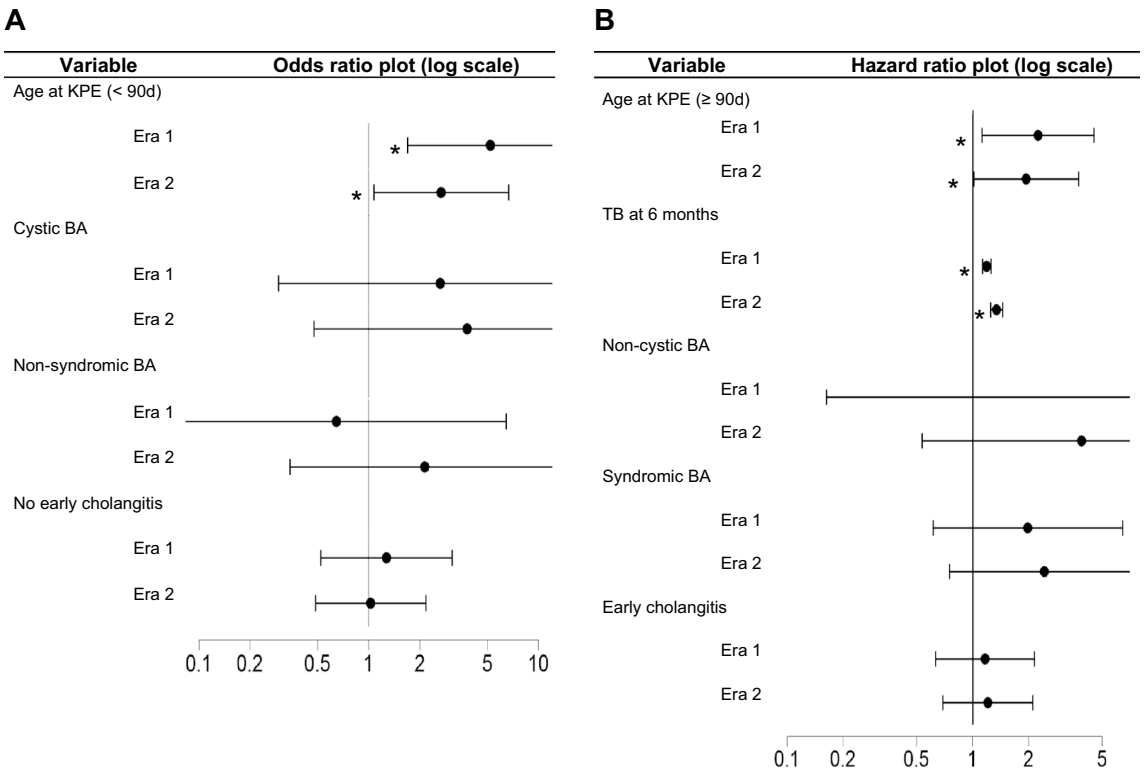


**Fig. 4** A forest plot depicting the independent predictors of **a** the factors of jaundice clearance in the univariate logistic regression analysis and **b** the factors of native liver failure after KPE in the univariate Cox regression analysis. *The asterisks indicate statistically significant variables. *KPE* Kasai portoenterostomy, *BA* biliary atresia

prognosis for BA patients remains challenging because of heterogeneity from both an etiologic and pathophysiologic standpoint. In patients with complex heterogeneity, published data regarding major prognostic factors support that a younger age at the initial surgery, postoperative jaundice clearance, and classification of the BA phenotype may play important roles in patient outcomes [5, 12].

In this study, we reported the largest outcome series of Korean children with BA and the changes in short- and long-term KPE outcomes over the last 20 years. The underlying goal was to analyze variance in the aforementioned prognostic factors over time. To maintain homogeneity with regard to the surgeon-related factors, type of operation, and ethnicity, we included only Korean patients undergoing KPE under a single experienced pediatric surgeon. Although the clinical outcome cannot be determined from a national registry, experiences with surgical BA management at a high-volume center in an area with a relatively high prevalence of this condition can provide meaningful information on the management of these patients.

The results of the current study are consistent with those of earlier studies demonstrating that early KPE is associated with favorable short- and long-term outcomes of patients with BA [13, 14]. However, when we compared the impact of age at the time of KPE over time, the odds ratio and hazard ratio decreased in Era 2 compared to those in Era 1, both with respect to the JCR and 5-year NLS rate. The statistical power also decreased. Presumably, various factors that are difficult to quantify, such as the proficiency of surgery, increased center experiences, and the improvement of care for chronic liver disease after KPE, have relatively weakened the influence of age at the time of KPE. Our BA programs routinely monitor the degree of liver cirrhosis via hepatic elastography and further decrease the risk of variceal bleeding since the beginning of Era 2 [15]. These findings support that the clinical decision concerning the optimal timing of primary LTx should be made based on the individualization of various conditions, such as increased risk of hepatic decompensation and uncontrolled systemic symptoms, and not solely on the operative age [16, 17].

Centralization of surgical treatment for BA in a high-volume center allowed for standardized care and significantly improved patient outcomes in the UK and Finland [12, 18, 19]. In several studies, the caseload was considered high if a single center treated more than five cases per year [19, 20]. In Korea, where no centralized policy has been implemented, a domestic, nationwide, retrospective study demonstrated that the top five high-caseload institutions tended

to have better outcomes than those with lower caseloads, although no statistically significant differences were found [21]. In our institution, 161 KPE procedures have been performed over the past decade, which accounts for approximately 37% of all KPEs performed in Korea. Extended portoenterostomy is an important procedure to ensure maximum drainage of fine bile ductules to maintain high JCR at our center. Intraoperative accidental hepatic arterial ligation or portal vein injury did not occur during the time frame. Above-mentioned surgical technique and adjuvant therapy regimens might be associated with improved outcomes. Our study showed that surgical outcomes, with respect to both JCR and the 5-year NLS rates, tended to improve in patients in Era 2 in comparison to those in Era 1. By adopting a centralized BA care policy, we expect that the survival rate and the level of qualitative postoperative care can be maximized.

In this study, 18 patients (7.4%) with cystic BA and 9 patients with syndromic BA (3.7%) were included. Many studies have suggested that the presence of an extrahepatic cyst or the syndromic BA phenotype may affect the prognosis of BA patients [22–24]. The impact of cystic BA and syndromic BA phenotypes on jaundice clearance and NLS was insignificant in univariate analysis for each era, but the impact of syndromic BA on NLS was identified in the multivariate Cox regression analysis (data not shown). However, as the proportion of syndromic BA and cystic BA is very small compared with that of isolated BA, it is difficult to interpret the impact on the prognosis by directly comparing these types of BA with isolated BA. Because of the unique pathophysiologic nature of cystic BA, prenatal diagnosis tends to occur earlier in cystic BA than in isolated BA, and cystic BA patients tend to undergo KPE at an early age. Therefore, a more detailed comparison can be obtained through subsequent studies, including a subgroup analysis or age-matched analysis.

The shortened interval from KPE to LTx in Era 2 may reflect not only increased organ availability for LTx, but also an advanced operative technique [25]. We assume that the more widespread use of living donor LTx and earlier referral to transplant surgeons allowed patients to undergo LTx with a shorter waiting time. The surgical outcomes for 20 years, beginning in 1997, were divided symmetrically into two periods of 10 years. Furthermore, we actively began to perform pediatric LTx for patients with BA at our hospital in 2006. The percentage of LTx for BA in this institution was only 16.7% (5/30) of total LTx in Era 1, and it increased to 47.6% (20/42) in Era 2 (Fig. 1). Collaboration between the pediatric surgeon and transplant surgeon became active, and the accessibility to living donor LTx was improved. Thus, the shorter waiting time for LTx in patients with failed KPE in Era 2 than in Era 1 can be explained.

This study has some potential limitations. This longitudinal clinical study was retrospective in design and was based on data that were extracted from medical records. Our study involved the experience of only a single surgeon; nonetheless, this might also be an advantage considering that the surgical technique was consistent in all cases. It is however likely that there have been minor modifications in the surgical techniques, postoperative adjuvant regimens, and other risk factors that could not be controlled for over this long spanning period. This study did not include patients with rare conditions who had poor hepatic function at presentation and underwent primary LTx. However, we focused on the clinical outcomes after KPE, rather than the overall prognosis after LTx, and on determining the impact of prognostic factors over a long follow-up period. Despite rigorous data quality control, there were missing and incomplete data in cases such as migration to other countries or transfer to other pediatric transplantation centers.

In conclusion, the JCR, NLS rate, and overall survival rate slightly improved in Era 2 in comparison to Era 1. The impact of age at the time of operation on both jaundice clearance and NLS became less significant over time, primarily owing to the increase in the center's experience and advancement of optimal medical treatment for chronic liver disease. Although this report is the largest Korean BA study, with the establishment of a national registry, a collaboration among pediatric surgeons, hepatologists, and transplantation surgeons is anticipated to support and improve the standards of care.

## Compliance with ethical standards

**Conflict of interest** The authors have no conflicts of interest or financial relationships relevant to this article to disclose.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the institutional review board of Severance Hospital (approval number: 4-2017-1101).

**Informed consent** A waiver of informed consent was granted because the study was determined to be minimal risk and because data are de-identified.

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