Postoperative course and indications for liver transplantation in biliary atresia: 20 years of experience in our hospital

Wataru Sumida (wsumida@med.nagoya-u.ac.jp)
Nagoya University Graduate School of Medicine

Chiyoe Shirota
Nagoya University Graduate School of Medicine

Takahisa Tainaka
Nagoya University Graduate School of Medicine

Satoshi Makita
Nagoya University Graduate School of Medicine

Aitaro Takimoto
Nagoya University Graduate School of Medicine

Shunya Takada
Nagoya University Graduate School of Medicine

Yoichi Nakagawa
Nagoya University Graduate School of Medicine

Takuya Maeda
Nagoya University Graduate School of Medicine

Yosuke Goda
Nagoya University Graduate School of Medicine

Guo Yaohui
Nagoya University Graduate School of Medicine

Liu Jiahui
Nagoya University Graduate School of Medicine

Akinari Hinoki
Nagoya University Graduate School of Medicine

Hiroo Uchida
Nagoya University Graduate School of Medicine

Hizuru Amano
Nagoya University Graduate School of Medicine

Article
Abstract

Undergoing a Kasai portoenterostomy (KP) to enable the clearing of jaundice (COJ) is the only way for patients with biliary atresia (BA) to achieve native liver survival (NLS). However, COJ does not always guarantee NLS. We retrospectively reviewed the clinical course and indications for liver transplantation (LT) of BA cases in our hospital. We reviewed the clinical course of patients who underwent KP for BA at our hospital from January 2003 to June 2022 and who were followed up until December 2022. In all, we reviewed 129 cases of which 32 failed to achieve COJ, and 31 underwent LT. COJ was achieved in 97 cases. The median time to the first KP was 58 days, which was significantly earlier than the median time of 69 days of the cases who failed COJ. Of the 97 cases who achieved COJ, 25 required LT. The indications for LT included recurrent jaundice (9 cases), cholangitis (8 cases), gastrointestinal bleeding (4 cases), hepatopulmonary syndrome (3 cases), and the other (1 case). Of all cases reviewed, 55% of cases were able to live with their native liver, and 26% of cases who achieved COJ required LT.

Introduction

Biliary atresia (BA) is a congenital disease characterized by progressive fibrosis and obstruction of the biliary tree caused by inflammation of unknown etiology. Failure to treat BA properly results in cholestasis, which causes progressive cirrhosis and hepatic failure, with few patients surviving for more than 2 years\(^1\).

Kasai portoenterostomy (KP) is an operation that facilitates bile drainage by dissecting the tissue of the porta hepatis, exposing residual microscopic bile ductules, and performing a Roux-en-Y anastomosis between the jejunum and porta hepatis to drain the exuding bile juice\(^2\). The clearance of jaundice (COJ) by KP is the only way for patients with BA to survive with their own liver. When COJ is not achieved, the liver cirrhosis progresses, and the patients will require liver transplantation (LT) to survive.

However, even if COJ has been achieved with KP, some patients with BA require LT. We retrospectively examined the indications for liver transplantation and its timing and investigated the characteristics of patients who underwent this surgery for BA at our hospital, in particular, regarding their relationship with the indications for LT.

Methods

Patients who underwent open or laparoscopic KP for BA at our hospital from January 2003 to June 2022 were followed up until December 2022. Their background, laboratory data, complications, and postoperative course (including LT) were retrospectively reviewed. This study was approved by the institutional ethics board of Nagoya University Hospital (approval number: 2022 – 0341). Since this was a retrospective observational study and the data analyzed were anonymized, informed consent from participants or their parents/guardians was obtained through an opt-out method on our hospital website.
in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

The cases were divided into groups according to whether they achieved COJ. This was defined as the level of total bilirubin (TB) reaching the normal range for our hospital after KP. This was less than 1.2 mg/dl until December 2017 and less than 1.5 mg/dl from January 2018. The duration of COJ was defined as the time from the first KP to the date the TB first reached the normal range on the laboratory test. Each group was compared in terms of the patients' backgrounds and laboratory tests.

Further analysis was done for the patients who required LT, according to the indications. The patients were divided into 6 categories: (1) Failure to achieve clearance: i.e., the TB never reached the normal range after KP. (2) Recurrence of jaundice: the TB became elevated again after it had reached the normal range. (3) Cholangitis: the cholangitis was uncontrollable. (4) Gastrointestinal bleeding: the gastrointestinal bleeding was uncontrollable. (5) Hepatopulmonary syndrome: the pulmonary arteriovenous shunt was uncontrollable. (6) Others.

Statistical analysis was performed with Fisher’s exact test for categorical variables. For continuous variables, the Mann–Whitney U test was used to compare data between each group. A $p$ value $< 0.05$ was considered statistically significant. Receiver operating characteristic (ROC) analysis was performed for the items in which statistically significant differences were detected. The thresholds, and their sensitivity, specificity, and area under the curve (AUC) were determined.

### Results

A total of 129 KPs were performed (male 44, female 85) during the study period. The median age at KP was 61 days old (range 19–138). The cases were followed up for a median of 3176 (range 199–7235) days by December 2022.

The KP was redone in 35 cases. Of these, 29 cases were done before COJ, and 6 cases underwent redo KP once COJ had been achieved. Of the 29 cases who underwent redo KP before COJ, 15 (53%) cases achieved COJ afterwards, whereas 14 cases failed.

Of the 129 cases, 32 (25%) failed to achieve COJ. Except for 1 case who died from liver failure 485 postoperative days after refusing LT, the remaining 31 cases underwent LT with the indication of failure to achieve clearance at a median of 141 (range, 54–539) days after the first surgery. After LT, 2 cases died from postoperative complications (Table 1).
Table 1
Cases of native liver survival and indications for liver transplantation (LT)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Cases</th>
<th>Alive</th>
<th>Age at first KP (days)</th>
<th>Time between first KP and LT (days)</th>
<th>Time between COJ and irreversible recurrence of jaundice (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native liver survival</td>
<td>71 (55%)</td>
<td>71</td>
<td>58 (19–138)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Failure to resolve</td>
<td>31 (24%)</td>
<td>29</td>
<td>69 (36–133)</td>
<td>141 (54–539)</td>
<td>-</td>
</tr>
<tr>
<td>Recurrence of jaundice</td>
<td>9 (7%)</td>
<td>9</td>
<td>55 (29–80)</td>
<td>331 (224–2429)</td>
<td>76 (9–1884)</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>8 (6%)</td>
<td>8</td>
<td>57 (46–104)</td>
<td>460 (366–1438)</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>4 (3%)</td>
<td>4</td>
<td>54 (34–66)</td>
<td>1261 (485–2486)</td>
<td>-</td>
</tr>
<tr>
<td>Hepatopulmonary syndrome</td>
<td>3 (2%)</td>
<td>3</td>
<td>53 (39–77)</td>
<td>1686 (981–2095)</td>
<td>-</td>
</tr>
<tr>
<td>Others</td>
<td>1 (1%)</td>
<td>1</td>
<td>75</td>
<td>5736</td>
<td>-</td>
</tr>
</tbody>
</table>

KP: Kasai portoenterostomy, COJ: clearance of jaundice

The remaining 97 (75%) cases finally achieved COJ. After COJ, 1 case died due to a coexisting congenital anomaly at 1109 days postoperatively. Cases with COJ underwent the first KP at a median of 58 (range 19–138) days old, whereas the cases without COJ underwent the procedure at a median of 69 (range 36–133) days old. The difference was statistically significant ($p < 0.001$) (Fig. 1a). The ROC analysis of the relationship between the date of the first KP and COJ showed that the prognosis was worse if the first KP was performed after 65 days. The sensitivity and specificity were 0.67 and 0.75, respectively, and the AUC was 0.73 (Fig. 1b). Of the 97 cases with COJ, 71 patients achieved native liver survival (NLS) at the end of the observation period, whereas 25 (26%) cases underwent LT after COJ.

A total of 56 cases had undergone LT by the end of the follow-up. The cases of NLS underwent their first KP at a median of 59 (range 19–138) days old, whereas the cases with LT underwent it at a median of 66 (range 29–133) days old. The difference was statistically significant ($p = 0.02$) (Fig. 2a). The ROC analysis of the relationship between the date of the first KP and NLS showed that the prognosis was worse if the first KP was performed after 65 days. The sensitivity and specificity were 0.66 and 0.67, respectively, and the AUC was 0.69 (Fig. 2b). The possibility of NLS was also plotted using the Kaplan–Meier method. (Fig. 3).

Of the 25 patients who underwent LT after COJ, 9 cases had recurrent jaundice, 8 cases had cholangitis, 4 cases had gastrointestinal bleeding, and 3 cases had hepatopulmonary syndrome. One case was classified as ‘other’ (Table 1). The median postoperative days for COJ in cases with LT was 46 (range...
11–135) days, which was not significantly different from that in the cases with NLS of 39 (range 1–267) days ($p = 0.31$) (Fig. 4). The characteristics of each indication for LT are described below.

**Recurrence of jaundice**

Nine cases underwent LT for recurrent jaundice. They underwent their first KP at a median of 55 (range 29–80) days old. This was not significantly different from that of the NLS cases. They achieved COJ at a median of 78 (range 29–135) days after the first KP. Irreversible recurrence of jaundice occurred after a median of 76 days (range, 9–1884 days) after the first COJ. They underwent LT at a median of 331 (range 224–2429) days after the first KP.

In 1 case, the recurrence of jaundice occurred with an evident trigger: the surgery for intestinal obstruction 593 days after the KP. Afterwards, the case underwent LT at 752 days after KP. In the remaining 8 cases, we could not identify any trigger. In 5 of them, their direct bilirubin (DB) never reached the normal range ($\leq 0.2$ mg/dl) even though their TB reached the normal range. These cases had a particularly short time from COJ to recurrence of jaundice and from KP to LT, a median of 14 days (range 9–76 days) and 266 days (range 224–331 days), respectively. In contrast, the remaining 3 cases had a median of 1372 days (range 771–1884 days) and 1665 days (range 1479–2429 days), from COJ to recurrence of jaundice and from KP to LT, respectively.

Furthermore, DB reached the normal range in all other cases who achieved COJ except for one case. This patient survived with their native liver to the end of the follow-up period, but already had recurrent jaundice and was expected to require LT.

**Cholangitis**

Cholangitis was the indication for LT in 8 cases. They underwent their first KP at a median of 57 (range 46–104) days old and achieved COJ at a median of 31 (range 11–128) days after the first KP. They underwent LT at a median of 460 (range 366–1438) days after the first KP. Although 43 of the 95 COJ cases had at least 1 episode of cholangitis, most were successfully treated. However, 8 cases had uncontrolled cholangitis, with bile lakes, and required LT.

Bile lakes were observed in 16 of the 95 cases. All cases had multiple episodes of cholangitis, except 1 with a solitary bile lake who had no episodes. Among the cases of cholangitis, those with only 1 or 2 bile lakes were controlled each time. However, the cases with diffuse multiple bile lakes were refractory to treatment.

Five cases with bile lakes underwent the Roux-en-Y anastomosis, and 3 underwent percutaneous drainage of the bile lake. Although 5 cases finally required LT, 3 cases who had undergone anastomosis overcame recurrent cholangitis, of which 2 achieved NLS. The residual case underwent LT because of hepatopulmonary syndrome.
Gastrointestinal bleeding

Four cases underwent LT for the indication of gastrointestinal bleeding. They underwent their first KP at a median of 54 (range 34–66) days old and achieved COJ at a median of 35 (range 24–87) days after the first KP. They underwent LT at a median of 1261 (range 485–2486) days after the first KP.

Of the 95 cases with COJ, 18 cases had at least 1 episode of gastrointestinal bleeding. All of them underwent gastrointestinal fibroscopy (GIF) or colonic fibroscopy in each episode. However, the origin of bleeding could not be identified for some of them. They underwent LT at a median of 1686 (range 981–2486) days after the first KP.

GIF was also done to evaluate the esophageal or gastric varices. When the red color sign was positive, endoscopic variceal ligation (EVL) or endoscopic injection sclerotherapy (EIS) was performed. We performed 170 GIF examinations in 49 patients and 81 EVL or EIS procedures were performed in 23 patients. As a result, almost all varices were kept under control. However, in the 4 cases who underwent LT, the source of the repetitive gastrointestinal bleeding could not be identified or controlled.

Hepatopulmonary syndrome

Three patients underwent LT having developed hepatopulmonary syndrome. They underwent the first KP at a median of 53 (range 39–77) days old and achieved COJ at a median of 85 (range 38–87) days after the first KP.

After low percutaneous oxygen saturation was noted at follow-up, pulmonary perfusion scintigraphy was performed. The shunt rates were high, ranging from 29–34%. Two of the patients underwent LT about 3 months after their intrapulmonary shunts became obvious, and the third underwent LT about 1 year after, because he was awaiting a cadaveric donor. They underwent LT at a median of 981 (range 485–2486) days after the first KP.

Others

One case underwent LT due to decreased hepatic synthetic capacity caused by poor portal vein blood flow 15 years after the first KP.

Discussion

BA is a liver disease developing in neonates and early infancy. It is rare with a reported incidence of between 1 in 5000–20,000 live births. It ranges widely among countries reporting population-based data. Although its definite etiology is unclear, KP is the only treatment option for BA patients to survive with their native liver.
Currently, when KP does not resolve the jaundice, LT is the widely performed treatment of choice. The survival rate of patients with BA in Japan is approximately 90%\(^4\). However, the results of KP have not changed significantly over the years. According to data from The Japanese national registry, the probability of COJ after KP was approximately 60% in the 1990s\(^5\), and has not changed recently\(^4\). This analysis shows that we were able to achieve COJ in 75% of patients.

Past reports revealed that KP performed earlier, especially within 30 days, achieved a higher rate of COJ\(^4\). A recently published systematic review reported that KP performed after 90 days old achieved a lower rate of COJ than that of groups that had it done earlier. However, no significant differences were found among groups in which KP was performed before 30 days old, between 31 and 45 days old, and between 46 and 60 days old\(^6\). In our cases, as in previous reports, early KP achieved good results. In fact, all children who underwent KP before 30 days old achieved COJ. However, there was little difference in the rate of COJ between the group that received the first KP at 31–45 days old and at 46–60 days old. And, among the cases who underwent the first KP before 60 days of age, 89% of them achieved COJ. Among the cases in which KP was performed after 90 days old, 36% of cases achieved COJ, and 33% of cases survived with their native liver; therefore, it is worthwhile to attempt KP even in cases with a late diagnosis.

Pediatric surgeons have often struggled to achieve COJ for patients with BA. Redo KP had been a strategy; however, since the global spread of LT, few reports about redo KP have been published outside Japan\(^1,7−11\). These reports indicate that redo KP has achieved a certain level of efficacy. In our case, 52% of patients were able to achieve COJ with redo KP.

However, COJ does not always guarantee NLS for BA patients. In fact, some patients require LT even after their jaundice has resolved. Reports from East Asia such as Japan, China, and Korea indicate about 10–20% discrepancy between the jaundice clearance rate and long-term NLS rate\(^12\). This discrepancy can be attributed to patients who still require LT after COJ. Among our patients, 25 (19%) cases required LT after COJ. According to our Kaplan–Meier analysis, the chance of NLS seemed to be stable at approximately 50% about 7 years after KP.

Reports have shown that LT is more often required in the group of cases taking longer to achieve COJ after KP\(^13\). In our experience, there was no significant difference in the duration of COJ between patients who had NLS and those who required LT.

Indications for LT in patients with post-Kasai BA include liver cirrhosis, liver failure, gastrointestinal bleeding, growth retardation, pruritus, hepatopulmonary syndrome, and repeated cholangitis\(^14\). However, few papers present accurate proportions for each indication. One paper reported that 83% of LT cases were due to jaundice, and in nonjaundice cases, 55% were due to hepatopulmonary syndrome, 27% to cholangitis, and 9% cases to gastrointestinal bleeding\(^15\). Another paper reported indications for LT among cases without jaundice as 44% due to cholangitis, 30% to portal hypertension, and 23% to gastrointestinal bleeding\(^16\). These studies did not report the cases whose jaundice never resolved separately from those
in whom it resolved but recurred. We considered these two indications separately and focused on cases who required LT despite the achievement of COJ. Therefore, as the indications for LT, we focused on recurrent jaundice, repeated cholangitis, gastrointestinal bleeding, and hepatopulmonary syndrome. No cases underwent LT for growth retardation or pruritus.

In the group of recurrent jaundice, one patient’s jaundice recurred just after bowel obstruction. One earlier study reported that the onset of bowel obstruction suggested a poor prognosis\textsuperscript{17}. In 5 of the cases without an evident trigger, the DB had never reached a normal range. Additionally, of the other cases with COJ, the only case whose DB had not reached the normal range had recurrent jaundice at the end of the follow-up period. Although the case had not undergone LT at the end of the follow-up period, the case was predicted to require the procedure eventually. It is noteworthy because this phenomenon was never seen in cases with NLS or other indications for LT in our cases and we could not find any reports about the relationship between normalization of DB and NLS after COJ in the literature. DB reflected the true ability of bile excretion. Therefore, even though TB has reached the normal range, if DB does not, LT may not be avoidable. The cases in which DB did not reach the normal range had recurrent jaundice very early, and LT was required within a year after KP. Therefore, such cases may be treated like the cases who could not achieve COJ.

In our experience, the key factor in the requirement of LT due to uncontrollable cholangitis was the bile lake. In general, patients with BA frequently encounter cholangitis, but most cases are controllable with appropriate treatment. However, if the bile lakes were evident, the cholangitis occurred more frequently and induced a worse prognosis\textsuperscript{18}. Some of them with solitary bile lakes were successfully treated\textsuperscript{18,19}; however, the cases with diffuse bile lakes required liver transplantation because of uncontrollable cholangitis. In other words, if the bile lake could be controlled by, for example, jejunal anastomosis, the frequency of cholangitis could be reduced and the chance of NLS might be increased.

Some indications for LT were related to portal hypertension, i.e., gastrointestinal bleeding and hepatopulmonary syndrome. In our experience, LT was performed for gastrointestinal bleeding in 4 cases and hepatopulmonary syndrome in 3 cases. In addition, the case classified as ‘other’ also appeared to be due to portal hypertension. Although gastrointestinal bleeding was observed in several cases with BA, esophageal or gastric varices were controlled with endoscopic treatment, such as EVL or EIS. We routinely measured the stiffness of the spleen by ultrasonography to predict the presence of esophageal or gastric varices and perform EVL or EIS if necessary\textsuperscript{20}. This treatment prevented most gastrointestinal bleeding. However, recurrent bleeding from an unknown source was uncontrollable and required LT. It has been reported that about 30% of cases with end-stage liver disease had hepatopulmonary syndrome. Although its standard treatment is LT, severe hypoxemia is a relative contraindication. Therefore, early detection and intervention are required\textsuperscript{21}. For this indication, it appeared that LT was inevitable. For following up the BA cases after surgery, we routinely check their percutaneous oxygen saturation, and our case was referred for LT with appropriate timing because of a low percutaneous oxygen saturation.
Conclusion
We reported our experience of treating BA for 20 years, focusing on COJ and LT. About 75% of patients achieved COJ, but 26% of these cases required LT and 55% of patients survived with their native liver. Some patients with BA required LT even after COJ. The BA cases with recurrent jaundice, cholangitis, and gastrointestinal bleeding often required LT, although in some cases, LT could be avoided with specific treatment.

Declarations
Author contributions
W.S. and U.H. conceptualized and designed the study, collected data, drafted the initial manuscript, and reviewed and revised the manuscript. C.S., T.T., S.M., H.A., A.T., S.T., Y. N., T.M., Y.G., G.Y., L.J., and A.H. collected data, carried out the initial analyses, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

No funding was secured for this study.

Competing interests

The authors declare no competing interests.

References


**Figures**

Figure 1

The relationship between age at first KP and COJ in our cases.

a) Histogram of age at first KP for cases with achieved and failed COJ.

b) ROC curve for the relationship between the date of first KP and COJ.
Figure 2

The relationship between age at first KP and NLS.

a) Histogram of age at first KP for cases surviving with their native liver.

b) ROC curve for the relationship between date of first KP and NLS.

Figure 3
Kaplan–Meier curve of our cases with NLS.

**Figure 4**

Plot of postoperative days at the clearance of jaundice and cumulative jaundice clearance ratio. The jaundice clearance ratio eventually reached 75%. Patients who survived with their native liver are plotted with white circles. Patients who eventually underwent LT despite of clearance of jaundice were plotted with black diamonds.