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REVIEW ARTICLE

# Effects of age at Kasai portoenterostomy on the surgical outcome: a review of the literature

**Masaki Nio · Motoshi Wada · Hideyuki Sasaki · Hiromu Tanaka**

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**Abstract** The efficacy of early Kasai portoenterostomy has been repeatedly reported. However, the optimal age for performing this procedure remains controversial. This article reviews the literature on the age of patients at the time of Kasai portoenterostomy and its utility as a prognostic indicator. The age at the time of surgery is a known predictor of outcome; however, its exact predictive value in this context is unclear. Multicenter studies involving large volumes of data have tended to show advantages of early Kasai portoenterostomy, and there is no clear evidence to recommend any delay in the timing of surgery. At present, a reasonable strategy would be to perform a Kasai portoenterostomy as early as possible. The stool color card system has recently been implemented in Japan as part of a nationwide screening program, and it is expected to work well based on the early reports. However, efforts to identify an optimal screening system for ensuring the earliest diagnosis of biliary atresia should continue. An early diagnosis of biliary atresia is difficult, and global efforts are required to improve the early diagnosis rates.

**Keywords** Biliary atresia · Kasai portoenterostomy · Early diagnosis · Liver transplantation

## Introduction

Kasai portoenterostomy was developed in the 1950s and was a significant milestone in the treatment of biliary atresia. The procedure has offered the chance of survival to patients with an uncorrectable type of biliary atresia that was previously considered to be fatal. Morio Kasai had expected to cure 80 % of patients with biliary atresia with this surgery. However, according to a recent report from the Japanese Biliary Atresia Registry (JBAR), the jaundice-free native liver survival rate unfortunately remains at approximately 60 % between six and 18 months after Kasai portoenterostomy.

Many studies have been performed to determine the factors that may influence the surgical outcomes, and much attention has been paid to the age at the time of the operation, which was reported as a significant risk factor by Kasai [1]. He reported a better surgical outcome in patients younger than 60 days old at the time of surgery. Since then, the efficacy of early surgery has been reported by numerous studies [2–8]. However, the optimal timing of Kasai portoenterostomy remains controversial [9–15]. Although the prognosis for patients aged ≥3 months is generally poor, there is no consensus whether 2 months is a critical age that can impact the prognosis. The role of neonatal surgery is also a matter of debate. This review discusses the literature on the significance of the age at Kasai portoenterostomy as a risk factor for a poor prognostic outcome.

## The age at Kasai portoenterostomy and the jaundice clearance rate

Many papers have supported the effectiveness of early surgery. In Japan, more than 2,600 cases of biliary atresia had been registered in the JBAR by 2012. The highest jaundice clearance rate (JCR) achieved among patients who underwent neonatal surgery and whose data were recorded in the JBAR was 71 %. The JCR worsened as the age at surgery

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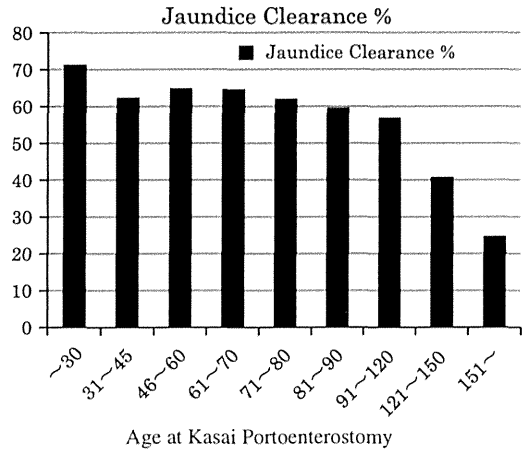


**Fig. 1** The age at Kasai portoenterostomy and the jaundice clearance rate among the patients in the Japanese Biliary Atresia Registry. The best jaundice clearance rate (JCR), 71 %, was achieved by patients who underwent neonatal surgery. The JCR was worse among patients with an age at the time of the procedure >3 months, but it was essentially the same among those aged between 1 and 3 months old

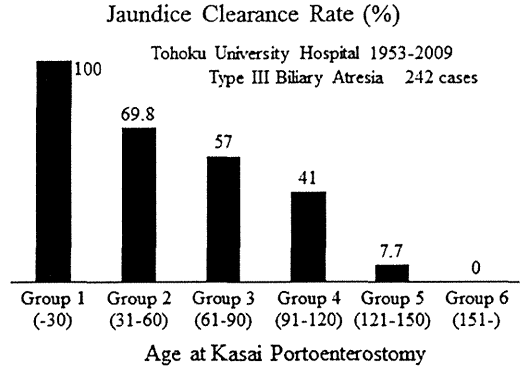


**Fig. 2** The age at Kasai portoenterostomy and the jaundice clearance rate among the patients at Tohoku University Hospital. A total of 242 patients with type III biliary atresia were assessed to identify the relationships between their age at Kasai portoenterostomy and the jaundice clearance rate (JCR). The patients were classified into six groups based on their age at Kasai portoenterostomy. The age at portoenterostomy and the JCR were significantly inversely correlated ($p < 0.0001$)

increased past 3 months old, but was essentially the same among patients aged 1–3 months old [16] (Fig. 1).

Among 242 patients with Type III biliary atresia (atresia at the porta hepatis, the most common type) at Tohoku University Hospital (TUH), the correlation between the age at portoenterostomy and the JCR was assessed using a Chi squared test. They were found to be significantly inversely correlated (Fig. 2).

Numerous multicenter studies have been performed in countries other than Japan. One Canadian group reported a 10-year native liver survival rate of 49 % among patients who underwent neonatal surgery, but the rate was 15 % among those with an age of >3 months old at the time of the operation [17]. Better outcomes following early surgery have also been reported from France [18], Switzerland [19] and Brazil [20] (Table 1).

On the other hand, some authors, including McKiernan [10], Wildhaber [12] and Shneider [14], have reported no significant relationship between the age at Kasai portoenterostomy and postoperative jaundice clearance. In the German registry, no significant advantage of early surgery was found [21]. Davenport et al. [22] reported the potential for reasonable medium-term survival in approximately one-third of infants aged ≥100 days undergoing portoenterostomy. At TUH, while some patients had an unfavorable postoperative course even after early portoenterostomy (before they were 2 months old), others achieved excellent bile drainage even after late surgery at ≥3 months of age. A 33-year-old female patient who underwent Kasai portoenterostomy at TUH at the age of 148 days is now a healthy mother of two children.

The reasons for these different outcomes among countries and institutions remain unclear. Although differences in surgical techniques and postoperative management may have some impact on the outcome, the severity of the pathological involvement of the hepatobiliary system, which is partly associated with the age at the operation, is believed to be a more important factor influencing the prognosis.

If the timing of disease onset varies greatly between cases due to various mostly unknown etiologies, then the age at the operation would be less significant as a predictive factor. On the other hand, if patients with similar disease characteristics, including the etiology and timing of disease onset, are treated using the same therapeutic strategy, including surgical techniques and postoperative management, then the age may be a significant risk factor.

The age at the operation is known to be an important predictive factor, but its predictive value is unclear at present. Therefore, the selection of Kasai portoenterostomy versus primary liver transplantation should not be decided based on a patient's age [15].

## The age at Kasai portoenterostomy and the long-term outcome

As the number of long-term survivors following Kasai portoenterostomy has grown, the relationship between the age at the operation and the long-term prognosis has also been studied; however, the relationship has not been fully elucidated. Lykavieris et al. reported that the 20-year native liver survival rate was significantly better in patients whose age was ≤90 days at the time of the operation, even though <18 %

**Table 1** The age at Kasai portoenterostomy and the native liver survival rate in various countries

| | | | | | | |
|---|---|---|---|---|---|---|
| Canada | Number of centers | 12 | Age at Kasai operation | <30 days | >91 days | |
| | Years of native liver survival | >10 years | Native liver survival % | 49 % | 15 % | |
| France | Number of centers | 45 | Age at Kasai operation | ≤45 days | >45 days | |
| | Years of native liver survival | 4 years | Native liver survival % | 51 % | 40 % | |
| Swiss | Number of centers | 7 | Age at Kasai operation | ≤45 days | 46–75 days | >75 days |
| | Years of native liver survival | 2 years | Native liver survival % | 75 % | 43.7 % | 11.3 % |
| Brazil | Number of centers | 6 | Age at Kasai operation | <60 days | 61–90 days | >90 days |
| | Years of native liver survival | 4 years | Native liver survival % | 54 % | 33.3 % | 26.6 % |
| Netherland | Number of centers | 6 | Age at Kasai operation | ≤60 days | >60 days | |
| | Years of native liver survival | 4 years | Native liver survival % | 56 % | 34 % | |

of patients in their long-term series who were treated with Kasai portoenterostomy avoided liver transplantation [23]. In contrast, Shinkai et al. [24] reported that the age at the operation had no significant effect on either the short-term or long-term prognosis following Kasai portoenterostomy.

According to findings from the TUH study of Type III biliary atresia patients who became jaundice-free following Kasai portoenterostomy, while the long-term outcome was influenced by the age at the time of the operation until the patients were 30 years old, the difference was smaller thereafter, and the native liver survival rate of each age group eventually tended to be concentrated at approximately 30 % [25]. The 40-year life expectancy may therefore be approximately 30 % even in patients who become jaundice-free following Kasai portoenterostomy, regardless of their age at the time of the procedure. This would be due to the existing liver pathology, which is determined very early in life in the majority of cases.

However, we still believe that better long-term results can be expected in more recent cases because the surgical outcomes improved remarkably during the 1970 s. Besides the age at the time of Kasai portoenterostomy, the time required for jaundice to disappear and an association between early cholangitis and portal hypertension have also been suggested as potential predictors of the prognosis after >20 years [26]. However, no reliable indicator for predicting very long-term prognosis (>30 years) has been identified so far. Further investigations are required to identify definitive factors that can determine the ultimate outcome of biliary atresia. Follow-up JBAR registration is ongoing, and the current status of 20-year survivors is gradually becoming apparent. After another 10 years, we should be able to determine 30-year outcomes using the JBAR data.

## Repeat Kasai portoenterostomy

After the initial Kasai portoenterostomy, a second Kasai portoenterostomy may be required in some cases. The main indications for the repeat procedure are insufficient bile drainage after the first surgery, or a cessation of bile drainage due to cholangitis or another cause. I hypothesize that the optimal timing of the initial and repeat Kasai portoenterostomy would be as follows: In the early phase of biliary atresia, the bile flow in the intrahepatic bile duct may be severely decreased due to the original pathology. If early surgery can be performed during this phase, good bile drainage cannot be achieved because there is insufficient bile reaching the porta hepatis, and thus, this area will rapidly be replaced by another fibrous mass before an enterobiliary anastomosis is established. In such cases, the drainage route of the bile in the liver may recover after a certain period due to the regeneration of the intrahepatic biliary network, and good bile drainage may be achieved after a timely repeat Kasai portoenterostomy.

If this hypothesis proves to be correct, then there is certainly an optimal time for Kasai portoenterostomy, and we should refrain from performing early surgery for this select subset of patients. However, neonatal surgery currently yields the best JCR, and it is difficult to confirm the above hypothesis clinically.

At TUH, jaundice was resolved in three quarters of the patients who achieved good bile drainage, but was not resolved at all in patients with poor or no bile drainage following initial Kasai portoenterostomy. Thus, the patients who develop sudden cessation of bile flow after achieving sufficient bile drainage following the initial Kasai portoenterostomy are currently the best candidates for repeat Kasai portoenterostomy, which should be employed only once for this select subset of patients. This is the widely accepted indication for repeat Kasai portoenterostomy [27].

The JBAR data indicate that the incidence of repeat Kasai portoenterostomy declined from 28 % between 1989 and 1999 to 15 % between 2000 and 2011 ($p < 0.0001$). The JCR after repeat surgery (34 vs. 36 %) and the jaundice-free native liver survival rates (57 vs. 55 %) were essentially the same between the two groups (Table 2).

**Table 2** Redo Kasai portoenterostomies recorded in the Japanese Biliary Atresia Registry

| Period | 1989–211 | 1989–1999 | 2000–2011 | *p* |
|---|---|---|---|---|
| *N* | 2,630 | 1,423 | 1,207 | |
| JCR % after the initial Kasai surgery | 61 | 63 | 61 | ns |
| Redo % | 21 | 28 | 15 | *<0.0001* |
| JCR % after Redo | 35 | 34 | 36 | ns |

*JCR* jaundice clearance rate

The incidence of repeat Kasai surgery was significantly reduced, but the overall survival rate was significantly higher in the later period (90 vs. 95 %, $p < 0.0001$). These results may be attributed to the improved availability of early liver transplantation and the limited number of patients selected for repeat surgery in the latter period [28].

Regarding the efficacy of repeat surgery among all patients, a further analysis of patients who have undergone repeat surgery may provide important information for determining more precise indications for repeat surgery. Even in the JBAR data, the number of neonatal cases remains limited, and the efficacy of repeat surgery for early neonatal cases is uncertain. Accumulated experience with repeat surgery for neonates would enable the elucidation of the disease process of biliary atresia and the optimal timing of Kasai portoenterostomy.

## Trends regarding the age at Kasai portoenterostomy

The relationship between the age at Kasai portoenterostomy and the surgical outcome is not straightforward. While the prognosis is poor in some patients even after early surgery, it is excellent in some patients who undergo late Kasai portoenterostomy at an age ≥4 months. Multicenter studies with a large volume of data have tended to show that early Kasai portoenterostomy is advantageous, and there is no clear evidence to recommend a delay in the timing of surgery as yet. At this stage, a reasonable strategy would be to make every effort to ensure that Kasai portoenterostomy is performed as early as possible, and to select patients for repeat Kasai surgery or liver transplantation on a case-by-case basis according to their condition and the extent of liver damage after a failed initial Kasai portoenterostomy.

Despite the importance of early Kasai portoenterostomy having been advocated for a long time, the age of the patients at the time of surgery has not significantly decreased since the JBAR was initiated. The age has also remained unchanged in the TUH series over the past 40 years.

The outcomes of medical treatment have improved markedly among small children in Japan, including those with biliary atresia. This is primarily due to a high standard of public health care, careful monitoring and management of expectant and nursing mothers, the development of new medical equipment, technical advances and free infant medical checks. However, earlier Kasai portoenterostomy has not been realized. The main reason for this may be that in Japan, the health checks of newborn babies are mainly performed by obstetricians who have no experience with biliary atresia. A prenatal diagnosis of biliary atresia remains difficult, because the condition does not present with any detectable signs during the prenatal period except for cystic structures at the porta hepatis in a minor subset of cystic types, such as Type I and Type IIId cysts according to Kasai's classification. Most patients develop no conspicuous symptoms except for jaundice, which is a common symptom in healthy neonates during the first month of life. The color of the meconium is normal in the majority of patients with biliary atresia. Whitish or clay-colored stools are passed early in life by only a quarter of patients, and direct bilirubin is rarely assessed for neonatal jaundice even by neonatologists. Thus, an early diagnosis of biliary atresia is very difficult.

## Approaches to the early diagnosis of biliary atresia

The need to establish a screening system has been remarked upon for a long time [29]. Currently, the stool color card is regarded as the most promising approach. The stool color card was originally developed by Matsui et al. and has been utilized in several areas of Japan since the early 1990s. Comparing the sample color shown in the card with the stool passed by the baby, the family member or another caregiver may be able to notice an abnormality of the stool color, and the baby can be taken to a specialist hospital for treatment [30]. In Taiwan, a similar card system was introduced nationwide early this century, and a successful outcome in terms of an early diagnosis was reported [31]. A pilot study of this system was introduced in Switzerland in 2009 [32].

In 2012, a nationwide stool color card system was introduced in Japan. The stool color card is inserted in the maternal and child health handbook, and the instructions indicate that it should be checked at least twice: once at the 1-month regular health check and again at a later date. The stool color card is based on a subjective color assessment, and it has the advantages of simplicity and low cost. On the other hand, color decisions made primarily by mothers may be incorrect, partly because mothers tend to have difficulties recognizing severe illness in their children due to the so-called normalcy bias.

It is important that mothers and caregivers are aware that patients with biliary atresia usually pass yellowish stools in the early neonatal period, and that the stool color then becomes pale yellow or whitish. The color card screening system was introduced to help increase the rate of early diagnosis of biliary atresia by double-checking the stool color, and more importantly, this system is expected to highlight the existence of biliary atresia, which is a very rare disease, and increase the awareness of the condition by mothers, physicians, and public health nurses.

In some areas in Japan, urinary sulfated bile acid (USBA) is used for the early diagnosis of biliary atresia [33]. Compared with the stool color card system, this method is quantitative, and thus, more objective. The method may be promising, but it has numerous disadvantages related to cost effectiveness, the proper handling of urine samples, and control of the false-positive rate, which all need to be resolved before it can be adopted as a nationwide screening system. An appropriate combination of USBA and the stool color card system may be a practical solution for overcoming the disadvantages of using each method individually.

Direct bilirubin [34] and serum bile acid [35, 36] measurements have previously been evaluated for screening for biliary atresia. However, these approaches were associated with problems related to the timing of sampling and the setting of appropriate cut-off levels that could not be resolved. Thus, no screening system was established. A trial of a new protein biomarker has also been reported [37].

The stool color card system has just begun nationally in Japan, and the system is expected to work well based on the initial results and the findings in other countries. However, we should continue to pursue an optimal screening system for ensuring the earliest possible diagnosis of biliary atresia.

## Future prospects

Every effort has been made to achieve better outcomes following Kasai portoenterostomy since its development half a century ago. Currently, the 1- and 10-year native liver survival rates are approximately 60 and 50 %, respectively (Fig. 3). However, 30–40 % of patients require a liver transplantation several years after a Kasai portoenterostomy. Some patients have undergone a liver transplantation after surviving >40 years due to advanced liver cirrhosis or severe complications.

Several reports have been published regarding hepatic regeneration using iPS cells, and this is a promising area for future therapies [38]. Biliary atresia may be treated using this technology in the near future.

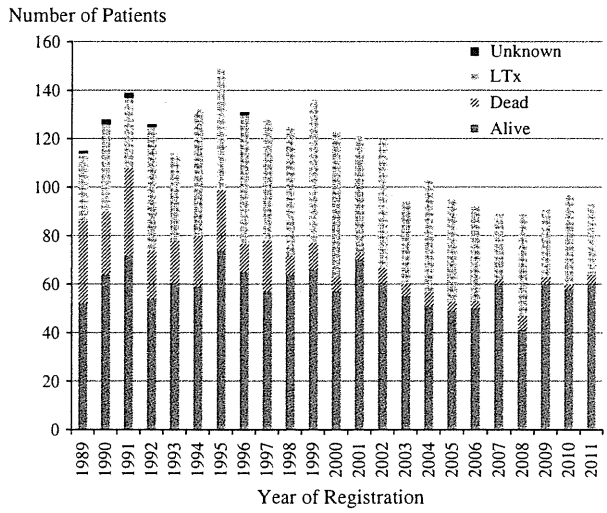


**Fig. 3** The current status of the patients in the Japanese Biliary Atresia Registry. The current status has been recorded for most patients included in the registry. While the short-term native liver survival rate is approximately 60 %, approximately 40 % of patients have required a liver transplantation within several years of a Kasai portoenterostomy

Great advances in the treatment of biliary atresia can be achieved by elucidating its etiology. Our ultimate goal is the prevention of biliary atresia. Until such a time, everything possible should be done to improve the outcomes following Kasai portoenterostomy, including finding ways to ensure an earlier diagnosis and the implementation of appropriate surgical techniques and postoperative care, including the management of long-term survivors.

Difficulties related to the early diagnosis of biliary atresia are not a problem limited to Japan [39], and efforts must be focused on improving the rates of the early diagnosis of biliary atresia worldwide.

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ORIGINAL ARTICLE

# Liver transplantation following the Kasai procedure in treatment of biliary atresia: a single institution analysis

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**Abstract**
*Purpose* This study aimed to assess outcomes of liver transplantation (LTx) in patients with biliary atresia (BA).
*Methods* The Kasai procedure was performed for 358 patients at Tohoku University Hospital between January 1955 and December 2013; 64 (17.9 %) required LTx. These 64 patients were divided into 4 groups according to their age at the time of transplantation: Group 1, aged <2 years ($n = 27$); Group 2, aged 2–9 years ($n = 16$); Group 3, aged 10–19 years ($n = 11$); and Group 4, aged ≥20 years ($n = 10$). Clinical parameters were evaluated retrospectively.
*Results* Both living-donor ($n = 57$) and deceased-donor ($n = 7$) LTx were performed. Indications were irreversible jaundice ($n = 53$), intractable cholangitis ($n = 3$), hepatopulmonary syndrome ($n = 6$), portopulmonary hypertension ($n = 1$), and intestinal bleeding ($n = 1$). Jaundice occurred more frequently in Groups 1 and 2 than in Groups 3 and 4 ($p = 0.031$). Survival rates were 81.5, 100, 90.9, and 80 % in Groups 1, 2, 3, and 4, respectively.
*Conclusion* Although the overall LTx survival rate was satisfactory, some adult recipients experienced LTx-related difficulty. Close follow-up, meticulous assessment of physical and social conditions, presence of a multidisciplinary support system, and appropriate time course for LTx are all essential factors in the treatment of BA.

**Keywords** Biliary atresia · Liver transplantation · Long-term follow-up · Donor

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## Introduction

Outcomes for patients with biliary atresia (BA) have greatly improved since the introduction of the Kasai procedure in the mid-1900s. According to data from the Japanese Biliary Atresia Registry, 55 % of patients with BA have a >10 year survival without liver transplantation (LTx) [1]. However, Shinkai et al. [2] reported a 20-year native liver survival rate of 44 % and various severe complications among patients showing native liver survival of more than 20 years. Therefore, a substantial number of patients eventually required LTx. The settings of LTx in Japan are different from those in Western countries. Particularly, living donors are widely available, whereas deceased donors are rare [3]. Therefore, patients requiring LTx are confronted with various difficulties, such as obtaining a suitable donor and psychological conflict related to donations from relatives. We hypothesized that these problems could be characterized according to the age of the patient at time of LTx. In this study, we compared the clinical course following the Kasai procedure and the outcomes of LTx among patients in different age groups.

## Methods

Between January 1955 and December 2013, 358 patients underwent the Kasai procedure at Tohoku University

Hospital in Japan. Of these, 258 patients received the Kasai procedure before 1990. Of the 258 patients, 189 died without LTx. However, only seven patients died without LTx after 1990. Finally, 64 patients (17.9 %) required postoperative LTx for various reasons such as persistent jaundice and sever portal hypertension. The transplantations were performed in six hospitals, in Japan and overseas, including Tohoku University Hospital. The patients were divided into four groups according to their age at the time of LTx: Group 1, aged <2 years ($n = 27$); Group 2, 2–9 years ($n = 16$); Group 3, 10–19 years ($n = 11$); and Group 4, ≥20 years ($n = 10$). Patient characteristics are shown in Table 1. The type of obstruction varied: 6 patients had type I BA (atresia of the common bile duct), 4 had type II BA [atresia of the hepatic duct(s)], and 54 had type III BA (atresia of the porta hepatis) (Table 1). We retrospectively reviewed the clinical course after the Kasai procedure and compared them between the groups. Variables measured were postoperative jaundice clearance, preoperative treatment of portal hypertension, indications for LTx, donor and graft types, outcomes after LTx, and psychosocial problems encountered. Statistical analysis was performed using Fisher's exact test or the Chi square test, and a $p$ value <0.05 was used to determine statistical significance. The Ethics Committee of Tohoku University approved this retrospective study.

## Results

### Jaundice clearance after the Kasai procedure

In Group 1, 22 patients experienced persistent jaundice, whereas 5 developed recurrent jaundice after postoperative resolution of jaundice. Of the 37 patients in the other groups, 35 achieved jaundice clearance after the Kasai procedure before developing a recurrence and/or other severe complications such as irritable cholangitis and secondary pulmonary perfusion disorder necessitating LTx.

**Table 1** Patient characteristics

| | Group 1 | Group 2 | Group 3 | Group 4 | $p$ |
|---|---|---|---|---|---|
| Number | 27 | 16 | 11 | 10 | |
| Male:female | 12:15 | 4:12 | 3:8 | 4:6 | .55 |
| Median age at LTx (years) | 1.1 | 6.1 | 14.5 | 32.3 | |
| Type of obstruction | | | | | |
| I | 0 | 2 | 1 | 3 | .19 |
| II | 1 | 1 | 1 | 1 | |
| III | 26 | 13 | 9 | 6 | |
| Treatment for portal hypertension | | | | | |
| Only EIS | 1 | 2 | 0 | 0 | .0411 |
| Only intervention for hypersplenism | 0 | 2 | 2 | 2 | |
| Both treatments | 0 | 3 | 3 | 2 | |

*EIS* endoscopic injection sclerotherapy

### Treatment of portal hypertension before LTx

Fourteen patients developed severe portal hypertension and underwent treatment such as endoscopic injection sclerotherapy (EIS) and partial splenic embolization (PSE) after the Kasai operation; these patients subsequently underwent LTx. One, five, three, and two patients in Groups 1, 2, 3, and 4, respectively, underwent EIS. Five, four, and one patient in Groups 2, 3, and 4, respectively, underwent PSE. One and four patients in Groups 3 and 4, respectively, underwent splenectomy. Three, three, and two patients in Groups 2, 3, and 4, respectively, underwent EIS and intervention for hypersplenism including splenectomy and PSE (Table 1). The patients who underwent EIS, PSE, and splenectomy did not always have persistent jaundice. Esophageal varices and hypersplenism in patients who had relatively preserved hepatic function were well controlled by EIS and/or intervention for hypersplenism such as splenectomy and PSE. None of the patients had portal hypertension that required LTx.

### Indications for transplantation

Persistent or recurrent jaundice was the primary indication for LTx in 38 patients (90.4 %) aged ≤9 years (Groups 1 and 2) and 14 patients (66.7 %) aged ≥10 years (Groups 3 and 4) ($p = 0.031$) (Fig. 1). In Group 1, jaundice led to liver failure in 26 patients and intractable cholangitis in 1 patient. In Group 2, 13 patients experienced jaundice, intractable intestinal bleeding occurred in 1 patient, and hepatopulmonary syndrome (HPS) occurred in 2. In Group 3, jaundice occurred in six patients, intractable cholangitis associated with intrahepatic biliary dilatations occurred in one, and HPS occurred in four. In Group 4, jaundice occurred in eight patients, intractable cholangitis associated with intrahepatic biliary dilatations in one, and portopulmonary hypertension (PPH) in one (Table 2).

### Donor types

Fifty-seven (89.0 %) and seven patients (11.0 %) underwent living- and deceased-donor LTx, respectively. Living-donor LTx was predominant in each group (Table 3). For the 48 patients in Groups 1, 2, and 3, the donor was a mother or father of the recipient. In Group 4, six relatives other than the parents (2 siblings and 1 spouse) were the donors. One (3.8 %), four (25 %), one (10 %), and one (10 %) patient in Groups 1, 2, 3, and 4, respectively,

**Table 2** Primary indication for liver transplantation

| | Group 1 | Group 2 | Group 3 | Group 4 |
|---|---|---|---|---|
| Jaundice | 26 | 13 | 6 | 8 |
| IC | 1 | 0 | 1 | 1 |
| HPS | 0 | 2 | 4 | 0 |
| PPH | 0 | 0 | 0 | 1 |
| IB | 0 | 1 | 0 | 0 |

*IC* intractable cholangitis, *HPS* hepato-pulmonary syndrome, *PPH* porto-pulmonary hypertension, *IB* intestinal bleeding

**Table 3** Status of liver transplantation

| | Group 1 | Group 2 | Group 3 | Group 4 | *p* |
|---|---|---|---|---|---|
| Donor | | | | | |
| Deceased | 1 | 4 | 1 | 1 | .19 |
| Living | 26 | 12 | 10 | 9 | |
| Lobes/segments of living graft | | | | | |
| Lateral segment | 23 | 6 | 0 | 0 | <.0001 |
| Left lobe | 3 | 3 | 2 | 0 | |
| Right lobe | 0 | 0 | 5 | 9 | |
| Unknown | 0 | 3 | 3 | 0 | |
| ABO-incompatible | 2 | 3 | 1 | 0 | .27 |
| Outcome | | | | | |
| Survival | 22 | 16 | 10 | 8 | .28 |
| Death | 5 | 0 | 1 | 2 | |

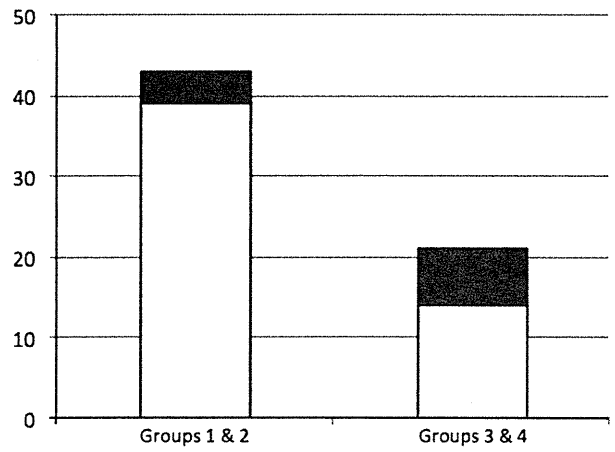


**Fig. 1** Differences in primary indications for liver transplantation in biliary atresia in younger and older age groups, $p = 0.031$ (*open bar* jaundice, *closed bar* not jaundice)

underwent deceased-donor LTx. Six of the deceased-donor transplantations were performed in hospitals in four countries (USA, France, Australia, and Taiwan) prior to 2004; the seventh was performed at our institution in 2008.

ABO-incompatible grafts were used in 2, 3, and 1 patients in Groups 1, 2, and 3, respectively. The oldest patient who received LTx with an ABO-incompatible graft was aged 11 years.

## Grafted lobes and segments

Fifty-seven patients received living-donor LTx; 37 received left-sided hepatic lobes, including lateral lobes; 14 received right lobes; and six received unnamed lobes. Twenty-six patients in Group 1 received living-donor grafts; 23 (88.5 %) were lateral segments and three were left lobes. Of the patients aged ≤9 years (Groups 1 and 2), none required the right lobe. In the older age groups (Group 3 and 4), 12 patients (70.6 %, excluding the patients for whom data could not be retrieved) required the right lobe because of their larger body size (Table 3, $p < 0.0001$). In Group 4, the nine patients who received living grafts all received right lobes.

## Transplantation outcomes

The follow-up period after transplantation was between 0.4 and 24 years (average 13.6 years). Fifty-six recipients (87.5 %), including six ABO-incompatible recipients, survived; eight recipients, including one who received a deceased-donor LTx, died (Table 3). Five patients died of postoperative complications such as vascular problems and graft failure during the early postoperative course.

A 39-year-old man had advanced hepatic failure with poor general condition at the time of LTx. He developed severe complications, including portal thrombosis, and eventually died of graft failure on postoperative day 20. A 21-year-old woman died of deteriorated PPH associated with postoperative pneumonia 1 month after transplantation. An 11-year-old boy died of an unrelated event 1 year after undergoing a successful deceased-donor LTx. All living donors survived without significant morbidity following donor operation.

## Psychosocial problems

The six patients who underwent deceased-donor LTx in overseas hospitals faced financial difficulty because of increased medical costs compared to those in domestic hospitals, where medical insurance is available. Most of these patients had their expenses covered through public donations. However, the fund-raising campaigns were associated with stress for the patients and their families. In Group 4, two recipients who were on the waiting list for a deceased-donor LTx did not choose living-donor LTx for a prolonged time because they felt guilty about receiving a graft from a family member. After being persuaded by their

families, both agreed to living-donor LTx. The 39-year-old man mentioned above had already developed severely advanced hepatic failure by the time of transplantation and died of postoperative complications. Two patients who received living-donor transplantations had difficulties finding appropriate living donors and obtaining donor consent.

## Discussion

The outcomes of the Kasai procedure have greatly improved over the past five decades. LTx is performed for approximately 30–40 % of infants and small children with BA in Japan [1, 4]. The number of adult long-term survivors has been increasing recently. Most younger patients received liver donations from their parents, as living-donor LTx is common in Japan. LTx using a left or right living lobe is initially considered in adult patients.

The unique donor situation in Japan is attributed to difficulties in obtaining deceased-donor grafts. Sensitive factors, such as religious sentiments and ethics of the Japanese, are thought to be obstacles for acceptance of the concept of brain death. In Japan, deceased-donor LTx has been legally approved, and the Japan Organ Transplant Network, which is similar to the United Network for Organ Sharing (UNOS), was created in 1997. Before that time, a deceased-donor LTx was practically impossible. This circumstance explains the overseas deceased-donor transplantations observed in our patient population.

From 1997, LTx has been dependent on living donors in Japan [3]. According to the UNOS report, 113,889 deceased-donor LTxs (96 % of all transplantations) were performed between 1988 and 2012 in the USA. According to the registry of the Japanese Liver Transplantation Society, 139 deceased-donor LTxs (2.1 % of all transplantations) were performed between October 1997 and December 2011, whereas 6,642 LTxs were performed between January 1964 and December 2011 in Japan. The widespread adoption of LTx is still slow in Japan, even after revision of the Japan Organ Transplant Law in 2010, prompted by the Istanbul Declaration restricting transplant travel [5].

According to Japanese Biliary Atresia Registry, the incidence of types I, II, and III BAs is 12, 2, and 86 %, respectively [1]. Type III BA is believed to be the most severe with the worst prognosis. In fact, all 24 patients in Group 1 had type III BA. However, patients with types I and II BAs were present in the other groups. Group 4 included three patients (30 %) with type I BA and included the most patients with a correctable type of BA. For patients with type I BA, a better jaundice clearance rate correlated with a longer native liver survival time. These patients, however, tended to develop long-term morbidities, including intractable cholangitis associated with intrahepatic biliary dilatation and/or stone formation, as mentioned in our previous research [6]. Some of these patients required LTx in their clinical course. Further investigation into the differences among the types of BA is necessary to improve survival in patients with long-term retention of their native liver.

The primary indication for LTx was predominantly persistent or recurrent jaundice in the younger age groups. In the older age groups, there was an increased incidence of another pathology including pulmonary perfusion abnormalities secondary to liver cirrhosis (e.g., HPS) [7]. PPH was a secondary pulmonary perfusion abnormality [8]. PPH can progress subclinically; therefore, it can be severely advanced at the time of diagnosis, as observed in our 21-year-old female patient who died of severe PPH after LTx.

Esophageal varices and hypersplenism were the most common symptoms of portal hypertension following the Kasai procedure; these affected the quality of life for the long-term survivors. Esophageal variceal rupture associated with a severe bleeding tendency from hypersplenism necessitates LTx in some cases. In our experience, esophageal varices and hypersplenism did not require LTx, because these pathologies were well managed by EIS and PSE, respectively [4, 9]. Therefore, to provide an appropriate disease management protocol and to avoid missing the optimal time for LTx in long-term survivors of BA, close follow-up according to a systematically designed program, including esophageal fiberscopy and diagnostic imaging focusing on the hepatic pathology and pulmonary circulation, is strongly recommended.

Other issues with living-donor LTx include size-matching and the health status of aged donors as well as ethical problems. Size-matching is problematic for adult recipients with a large physique; therefore, right lobes were primarily used for these recipients. However, utilization of the right lobe as a graft may be hazardous for the donors because right lobe donation is associated with a higher complication rate than left lobe donation [10]. That, however, was unavoidable in our society, where obtaining a deceased-donor graft is extremely difficult. Marginal grafts, which have a risk of initial poor function or primary non-function, from aged and ABO-incompatible donors were also utilized often for the same reason. Recent advances in immunosuppressive regimens can control acute rejections in young recipients after ABO-incompatible LTx [11]. Our study included four patients aged $\leq$11 years who underwent ABO-incompatible LTx; all these patients survived without episodes of severe rejection. However, because of the absence of ABO-compatible donors, adult patients with deteriorated hepatic function

had to wait on the deceased-donor liver transplant list for a long time.

Psychosocial problems are serious issues in patients with advanced cirrhosis [12], and most patients and their families were subjected to a great deal of stress because of the necessity for LTx. Difficulties in decision-making regarding receiving living-donor grafts and obtaining consent were major problems. One patient in this study was confronted with these problems. This patient was in poor general condition at the time of LTx and died of multiple complications. However, this patient may have been saved with earlier transplantation. To resolve the problems experienced by long-term survivors who require LTx, it is essential to use a multidisciplinary support team that includes pediatric and transplant surgeons, psychiatrists, clinical psychologists, transplant coordinators, skillful nursing staff, and social workers.

One limitation of our current study is that it is a retrospective case series. Our hypothesis is that a multidisciplinary support team can be useful, especially for long-term native liver survivors with BA. It is important to evaluate this hypothesis with a prospective controlled study.

Another limitation of this study is insufficient assessment of adult patients requiring LTx and their relatives. Quantitative analysis using a psychological questionnaire can be useful to address this limitation.

In conclusion, while there was satisfactory overall survival after transplantation, many difficulties were encountered, such as donor selection and psychosocial problems, particularly in adult recipients. The number of adult native liver survivors who experienced such problems will increase if the number of deceased donors does not increase. Close follow-up, meticulous assessment of physical and social conditions, presence of a multidisciplinary support system, and appropriate time course for LTx are all essential factors in the treatment of BA.

**Conflict of interest** The authors declare that they have no conflict of interest.

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# 重症肝肺症候群を合併した胆道閉鎖症に対し生体肝移植を施行した1例

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**要　旨**

今回我々は重症肝肺症候群を合併した胆道閉鎖症に生体肝移植を施行し，良好な結果を得た1例を経験したので報告する．症例は14歳女児．胆道閉鎖症に対し65生日に肝門部空腸吻合術を施行．11歳時より次第に黄疸・低酸素血症が進行．移植前はroom airで$PaO_2$ 39 mmHg，$SpO_2$ 80%前後，肺内シャント率41%と重症肝肺症候群を来していた．父親をドナーとする拡大左葉グラフトを用いた生体肝移植を施行．術後早期に2度の消化管穿孔を来した．術後1か月目にシャント率59.9%と一過性に増悪を認めたが，術後6か月時にはroom airで$SpO_2$ 100%，$PaO_2$ 90.0 mmHg，シャント率11.9%と著明な改善を認めた．重症肝肺症候群を合併した胆道閉鎖症に対する生体肝移植は術後合併症に注意を要するが，移植禁忌とはならない．しかし，長期予後についての十分なエビデンスは少なく，慎重な経過観察が必要である．

**索引用語：胆道閉鎖症，肝肺症候群，肝移植**

## I　はじめに

肝肺症候群（hepatopulmonary syndrome: HPS）は，進行した肝疾患患者でみられ，低酸素血症を呈する予後不良な疾患である[1)-4)]．HPSに対する根本的な治療は肝移植であり，酸素化の改善や生存期間の延長が認められている[2)]．しかし，重症例では移植後1年生存率48%と成績が悪いことから[2)5)6)]，その適応については依然議論の多いところである．

今回我々は重症HPSを合併した胆道閉鎖症に対して生体肝移植を施行し，著明な酸素化の改善が得られた1例を経験したので報告する．

## II　症　　例

患者：14歳女児．

既往歴・家族歴：特記事項なし．

現病歴：胆道閉鎖症（III-b1-v）に対し65生日に前医にて肝門部空腸吻合術を施行．術後黄疸は消失したものの，しばしば胆管炎を起こしていた．

3年前より爪のチアノーゼを認め，階段昇降で息切れを自覚．次第に黄疸，低酸素血症が進行したため肝移植目的に当院紹介となった．

入院時現症：身長147.5 cm，体重63 kg．皮膚・眼球結膜の黄染著明．呼吸音，心音に異常は認めず．日常生活動作での息切れがあり，口唇・爪のチアノーゼ，ばち指を認めた．Room airで酸素飽和度80%前後．腹水貯留なく，四肢浮腫を認めた．

移植前検査所見：血算で血小板減少を認めた．生化学検査では低アルブミン血症，肝機能障害，高アンモニア血症を認め，血液凝固能は延長していた．MELD scoreは27であった．動脈血ガス分析では$PaO_2$ 39 mmHgと著明な低酸素血症を認めた（表1）．

胸部単純X線検査：両下肺野で血管陰影の増強を認めた（図1a）．

腹部CT検査：肝右葉が萎縮，左葉内側区域が腫大し，肝表面は不整で肝硬変の所見を呈していた．肝内胆管左葉枝の数珠状の拡張，肝内結石を認めた．中等度の脾腫と，脾腎シャント，胃食道静脈瘤，上腸間膜静脈-右卵巣静脈シャントの発達を認めた．腹水は認めなかった（図1b）．

肺換気血流シンチ：両肺の換気・血流分布に明らかな異常は認めなかったが，肺外臓器の描出が見られ，右→左シャントの所見でシャント率は41.9%であった．動脈血ガス分析と併せ，肝肺症候群の最重症型と診断した

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**表1　移植前検査所見**

| 血算 | |
|---|---|
| 白血球数 | 6,240/μl |
| 赤血球数 | 341万/μl |
| ヘモグロビン量 | 12.0 g/dl |
| ヘマトクリット値 | 36.8% |
| 血小板数 | 6万/μl |

| 凝固能 | |
|---|---|
| PT-Time | 20.4 sec |
| PT-% | 42% |
| PT-INR | 1.75 |
| APTT | 53 sec |

| 生化学 | | | |
|---|---|---|---|
| 総蛋白 | 7.8 g/dl | グルコース | 125 mg/dl |
| アルブミン | 3.6 g/dl | ナトリウム | 141 mmol/l |
| 尿素窒素 | 6 mg/dl | カリウム | 3.3 mmol/l |
| クレアチニン | 0.35 mg/dl | クロール | 102 mmol/l |
| 総ビリルビン | 44.9 mg/dl | カルシウム | 8.8 mg/dl |
| 直接ビリルビン | 31.4 mg/dl | CRP | 2.53 mg/dl |
| AST | 173 U/l | アンモニア | 99 μg/dl |
| ALT | 56 U/l | | |
| LDH | 368 U/l | | |
| ALP | 554 U/l | | |
| γ-GTP | 42 U/l | | |
| 総胆汁酸 | 253.9 μmol/l | | |

| 動脈血ガス分析 | |
|---|---|
| pH | 7.44 |
| $PaO_2$ | 39.0 mmHg |
| $PaCO_2$ | 35.6 mmHg |
| $SaO_2$ | 76.0% |
| $HCO_3^-$ | 24.0 mmol/l |
| BE | 0 mmol/l |

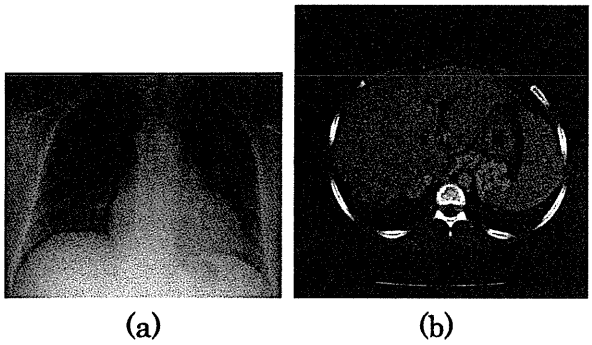


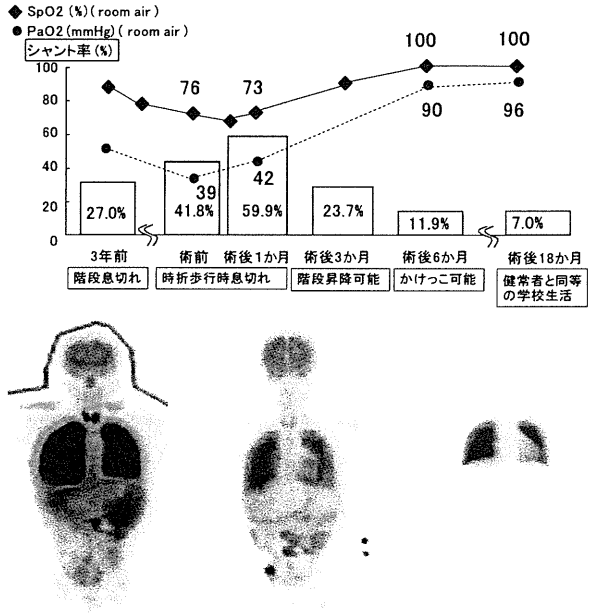

**図1　入院時画像検査**

［胸部単純X線検査］両下肺野に血管陰影の増強を認める（a）.
［腹部造影CT］肝内胆管左葉枝の数珠状の拡張，中等度の脾腫と，脾腎シャント，胃食道静脈瘤の発達を認めた（b）.

（図2a）.

心エコー：右心への圧負荷所見なく，TR-PG 11.0 mmHgと肺高血圧は認めなかった.

手術：生体肝移植，脾臓摘出術，人工肛門造設術を行った．ドナーは45歳の父親で，血液型は一致．術前評価では拡大左葉グラフトを用いた場合，グラフト重量／標準肝容量比36%，グラフト重量／レシピエント体重比0.62%と過小グラフトが予想された．右葉グラフトを用いた場合，ドナー残肝容量33%と不足（当科適応基準35%）であり，他のドナー候補がなく，レシピエントの状態が悪いことから，ドナーの安全性を優先し，拡大左葉グラフトを選択した．実際に得られた拡大左葉グラフトの重量は330 gであり，グラフト重量／標準肝容量比30.1%，グラフト重量／レシピエント体重比0.52%と過小グラフトになった．レシピエントは逆






a. 術前　　b. 術後1か月　　c. 術後半年

**図2　肺換気血流シンチの経時変化**

(a)：術前．両肺の換気・血流分布に異常は認めなかったが，肺外臓器の描出が見られシャント率は41.9%であった．(b)：術後1か月．シャント率59.9%と一過性の増悪を認めた．(c)：術後6か月．room airで$SpO_2$ 100%，$PaO_2$ 90.0 mmHg，シャント率11.9%と著明な改善を認めた.

T字切開にて開腹を行ったが，肝臓及び腸管の癒着が非常に高度であり開腹に困難を極めた．癒着剥離に際し，小腸部分切除を余儀なくされ，数か所の腸管漿膜損傷に対し修復を行った．脾機能亢進が強かったこと，過小グラフト症候群が予測されたことから脾摘を行った．摘出肝は1,450 gであった．また，脾腎シャント及び，卵巣

静脈に向かうシャント血管は結紮した．レシピエント肝静脈は一穴にして長径35 mmとし，グラフトはバックテーブルで静脈形成し，長径38 mmとして吻合した．門脈はグラフト門脈左枝（径15 mm）とレシピエント門脈本幹（径10 mm）を端々吻合した．温虚血時間41分，冷虚血時間は57分であった．動脈はレシピエントは固有肝動脈まで硬化が強く，胃十二指腸動脈から分岐する上前膵十二指腸動脈（径2 mm）とグラフト左肝動脈（径2 mm）を顕微鏡下に端々吻合した．胆道再建は外瘻ステントとして2 mm RTBDチューブを挿入し，Roux-en-Y法にて挙上した空腸と胆管空腸吻合を行った．閉腹前の門脈血流は680 ml/minであった．癒着剥離による腸管漿膜の損傷が多数に及んだことを踏まえ，小腸部分切除—端々縫合を行った部位よりも口側にloop ileostomyをおき手術を終了した．手術時間は19時間8分，出血量は3,270 mlであった．

術後経過：移植後も$SpO_2$は70％前後，$PaO_2$は30.0 mmHg以下となることもたびたびあった．術後早期に2度の消化管穿孔を来した．1回目は術後6日目に，回盲部より15 cm口側の回腸が穿孔しており腸管切除端々吻合を施行．2回目は術後9日目にloop ileostomyの口側20 cm及び肛門側30 cmで穿孔しており，計50 cmの小腸切除と2連銃式の人工肛門再造設を行った．以後も低酸素血症は持続していたが，術前状態と同等に維持されていたため術後13日で人工呼吸器から離脱した．術後17日目にドレーン排液の性状が変化し，再度消化管穿孔が疑われたため試験開腹を施行したが，新たな穿孔部位は認めなかった．幸いsmall-for-size graft syndromeは生じず，腹水量は1日300 mlを超えることはなかった．胆管炎を起こすことはあったが，術後の肝機能は良好で，血漿交換等要さず黄疸は順調に改善した（図3）．術後1か月目にシャント率59.9％と術前より悪化したが，酸素投与のみで呼吸状態は安定しており，以後は順調に経過し術後54日で退院した．術後3か月時点でシャント率23.7％，room airで$SpO_2$ 90％以上となり，6か月時にはroom airで$SpO_2$ 100％，$PaO_2$ 90.0 mmHg，シャント率11.9％，18か月時にはシャント率7.0％，$PaO_2$ 96.2 mmHgと劇的な改善を認め，現在健常者と同等の学校生活を送り，著明なQOLの改善を認めている（図2）．なお，ドナーは術後経過問題なく，術後10日で退院した．

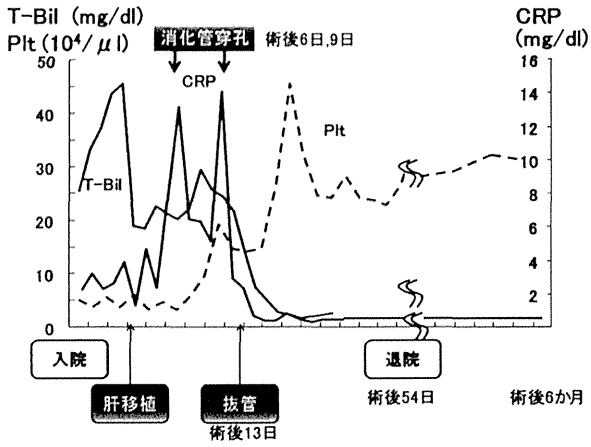



図3 術後臨床経過

移植後6日目，9日目に消化管穿孔をおこし，腸管切除と人工肛門再造設を行った．移植後も低酸素血症は持続していたが，術前状態と同等に維持されていたため術後13日で人工呼吸器から離脱した．消化管穿孔により一時的に黄疸が増悪したものの，グラフト機能は良好で，術後1か月頃にはビリルビン値は正常化した．呼吸状態は安定し，術後54日で退院した．

## III 考 察

HPSは，肝疾患あるいは門脈圧亢進症に合併し，肺内血管の拡張に起因する低酸素血症を呈する疾患である[1)-4)]．成人では肝疾患患者の13～47％に合併するとの報告があり[3)4)]，小児においては8～19％，胆道閉鎖症に限っては9～20％との報告がある[7)8)]．診断に際しては次の3要件を満たす必要がある[1)-3)]．①肝機能異常：多くは門脈圧亢進症を伴うが，急性肝炎等においても発症する．②低酸素血症：room airで$PaO_2$<80 mmHgまたはA-aDO2≧15 mmHg（64歳以上では$PaO_2$≦70 mmHgまたはA-aDO2≧20 mmHg）③肺内血管拡張による機能的な右左シャントが存在する．HPSの重症度は，A-aDO2≧15 mmHg（64歳以上では≧20 mmHg）の症例において①軽症：$PaO_2$≧80 mmHg，②中等症：60≦$PaO_2$<80 mmHg，③重症：50≦$PaO_2$<60 mmHg，④最重症：$PaO_2$<50 mmHg（100％酸素吸入時$PaO_2$<300 mmHg）とされており[1)]，本症例は最重症型の症例であった．HPSの重症度はChild-Pugh分類やMELD scoreとは相関せず，独立した予後不良因子とされており，なかでも$PaO_2$<50 mmHgの症例は予後が悪く，肝移植を施行しない場合での5年生存率は，$PaO_2$≧50 mmHgでは23％であるのに対し，$PaO_2$<50 mmHgでは10％である[2)6)]．

治療は，種々の薬物療法が拡張した肺内血管を収縮させたり，血管拡張を抑制する目的で投与され有効であったとの報告はあるが，確立されたものはなく[9)]，現時点で唯一有効なのは，現疾患の治療にもなる肝移植である[2)3)5)6)]．肝移植を施行しない場合の5年生存率は23％であるのに対し，移植を施行したものでは76％と著明な予後の向上が得られ[2)]，また，移植によるHPSの

改善率は82％で再発は稀であると報告されている[3]．ただし，肝移植後の短期成績はHPS非合併例と比較すると，移植後6か月の死亡率でHPS合併症例33％ vs HPS非合併例9.2％と有意に悪い[10]．これは，HPS合併症例では低酸素血症に起因する術後合併症が多いためで，創傷治癒遷延，創感染，敗血症，胆管吻合不全，血栓症などの術後合併症のリスクが高いことが報告されている[10)-13)]．Guptaらの報告では[13]，術後早期に23.8％で低酸素性呼吸不全が見られ，29％で出血や血管合併症，40％に胆道合併症がみられた．これらの合併症を防ぐため，肝移植術後管理では組織への十分な酸素供給が必要であり，$PaO_2$やHbを維持することが推奨される[13]．Schillerらは術後の低酸素血症に対しNOが有効であったと報告しており[14]，Flemingらは体外式膜型人工肺（ECMO: extracorporeal membrane oxygenation）が有効であったことを報告している[15]．本症例のような最重症例においては，かつて肝移植は禁忌とする施設が多かったが[16)17)]，近年では最重症例においても良い成績が報告され，他の合併症がなくHPSが予後規定因子となるような症例では肝移植の適応とする意見がある[2)13)]．

胆道閉鎖症に合併したHPSに対する肝移植についてのまとまった報告は少ないが，Egawaらは術前シャント率によって予後を検討している[12]．この報告では，1年生存率は軽症（シャント率<20％）80％，中等症（シャント率20％-40％）66.7％，重症（シャント率>40％）48％であり，生存例においては全例HPSの改善が見られている．しかし，術前シャント率が高いほどHPSの治癒に時間を要していた．また，重症例において創感染80％，胆汁漏40％，門脈血栓20％，脳血管合併症20％と高率に術後合併症を認めた．Urahashiらの報告では3例中2例で胆管吻合部狭窄，1例で門脈血栓が見られたが，全例生存している[18]．一方，Tumgorらの報告では[8]，特に合併症を認めていない．Uemotoらは，術後合併症や感染症が高率であることを報告し，心肺腎機能が維持されている限りは過度な酸素化は図らず，低酸素血症を許容する一方で，手術合併症や感染症のリスク軽減のため，3週間以上の十分な期間酸素化の維持に努めることを提言している[19]．

当科では2012年9月までに肝移植を行った胆道閉鎖症62例中4例にHPSの合併を認めた（表2）．平均年齢は14歳（10～18歳），重症度は中等症2例，重症1例，最重症1例で平均術前シャント率は33.1％，平均術前$PaO_2$ 58.8 mmHgであった．生体肝移植により，いずれの症例でも酸素化の改善が得られているが，術後合併症は消化管穿孔2例，胆管空腸吻合部縫合不全・吻合部狭窄1例，術後出血1例，門脈血栓1例と高率に認め，低酸素血症による組織の脆弱性が関与していると考えられた．移植前に脾臓摘出術を行った症例3では，脾摘術後2回の消化管穿孔を認めたが，同様に低酸素血症に起因すると考えられた．全例生存中であるが，長期経過にて，症例1は胆管狭窄により繰り返す胆管炎，門脈血栓を来し，移植後13年でグラフト機能不全となり肝肺症候群・肺高血圧を合併している．症例2は初回移植時にシャント結紮は行っておらず，移植後シャント率の再上昇は認めなかった．しかし，移植術後8年で原因不明のグラフト肝硬変で再移植を余儀なくされた．症例3は，

**表2**　当科におけるHPSを合併した胆道閉鎖症に対する生体肝移植症例

| 症例 | HPS診断時年齢（歳） | 移植時年齢（歳） | 術前シャント率（％） | 術前$PaO_2$（mmHg） | 術後シャント率（％） | 術後$PaO_2$（mmHg） | 移植術後合併症 | 転帰 |
|---|---|---|---|---|---|---|---|---|
| 1 | 14 | 14 | 44 | 69 | 24.5 | 48 | 術後出血（術後3日目）<br>胆管空腸吻合部縫合不全（術後22日目）<br>胆管空腸吻合部狭窄 | 15年生存中<br>グラフト機能不全，肺高血圧症合併のため再移植待機 |
| 2 | 10 | 10 | 32.8 | 68 | 4.4 | 104.8 | なし | 移植後8年<br>移植肝硬変のため再移植 |
| 3 | 18 | 18 | 13.9 | 59 | 8.9（術後1か月）<br>19.7（術後2年半） | 148<br>59.1 | 門脈血栓（移植前脾摘時，消化管穿孔2回） | 2年生存中<br>門脈血栓によるシャント率の再上昇 |
| 4（本例） | 10 | 14 | 41.8 | 39 | 7 | 96.2 | 消化管穿孔（術後6日目，9日目） | 2年生存中 |

一旦低酸素血症は改善したものの，結紮したシャント血管より門脈本幹へ血栓が波及．側副血行路が発達し，術後2年半の経過でシャント率19.7%，$PaO_2$ 59.1 mmHgと再度低酸素血症を来している．胆道閉鎖症における肝移植では，先に葛西手術が行われていることや，繰り返す胆管炎による炎症のため，血管合併症や消化管穿孔が多いと言われている[20][21]．胆道閉鎖症におけるHPS合併例では，低酸素血症も相まってさらに高率にこれら術後合併症が起こることが考えられる．したがって，胆道閉鎖症におけるHPSを合併した生体肝移植において重要なことは，重症HPSが禁忌とはならないが，重症度が高いほど術後管理に難渋するため，HPS合併症例では早期の肝移植の検討に努めること．術後合併症に対する対策と周術期の呼吸管理に十分注意すること．さらに，長期経過においては，残存シャントによるHPSの再発が懸念されるため，術前術中のシャント血管の評価を十分に行い，長期的な観察が必要であると考えられた．

今回我々はHPS最重症型を合併した胆道閉鎖症に対し生体肝移植を施行し，良好な結果を得た．HPSは肝移植により可逆的であるため，最重症型であっても他に予後不良因子がない場合では肝移植を考慮することが推奨される．しかし，低酸素血症に起因する術後合併症が高率に見られるため，胆道閉鎖症においてはより慎重な管理が求められる．

本論文において申告すべき利益相反状態はない．

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# Case Report of Living Donor Liver Transplantation for Biliary Atresia With Severe Hepatopulmonary Syndrome

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Here, we report a case of successful resolution of severe hepatopulmonary syndrome (HPS) in biliary atresia by living donor liver transplantation (LDLT). A 14-year-old girl diagnosed as having biliary atresia (BA) with HPS was referred to our hospital for LDLT. She underwent Kasai portoenterostomy 65 days after birth. Her jaundice and hypoxia worsened from 11 days after birth. On admission, her data on oxygenation were as follows: $SpO_2$ in room air was approximately 80%, arterial blood gas analyses showed $PaO_2$ of 39 mmHg, and perfusion scintigraphy showed a shunt ratio of 41%. From these findings, this patient was determined to have severe HPS. LDLT was performed using an extended left lobe graft from her father. She underwent relaparotomy and ileostomy twice owing to bowel perforation 6 and 9 days after LDLT. One month after LDLT, the shunt ratio increased to 59.9% transiently, but her respiratory condition improved gradually. Six months after LDLT, her data on oxygenation significantly improved as follows: $SpO_2$ in room air, 100%; $PaO_2$, 90.0 mmHg; and shunt ratio, 11.9%. We recommend that although the complication rate after LDLT for BA with severe HPS is relatively high, LDLT should be performed with utmost care. However, there is no significant evidence for the long-term prognosis after LDLT; therefore, it is necessary to closely monitor such a patient for a long period of time.

Key words: biliary atresia, hepatopulmonary syndrome, liver transplantation

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■ 原 著

# 生体肝移植後の学童後期・思春期の小児の療養生活の実態と生活の満足度

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# Daily-life situations and subjective-life satisfaction of living liver-transplanted adolescent children

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**【Summary】**

**【Objective】** This study examines the daily-life situation and the subjective-life satisfaction of living liver-transplanted preadolescent and adolescent children.
**【Design】** Cross-sectional survey
**【Methods】** Our study sample consists of 9 preadolescent and adolescent children who had undergone liver transplantation. Data were collected through semistructured interviews and questionnaires about their daily-life experiences. Descriptive statistics and qualitative descriptive research methods were used for the data analyse.
**【Results】** Our survey showed how elementary school children (fourth to sixth grades) could manage their health by themselves with parental support. They did know that they experienced an operation in their childhood period, but did not sufficiently understand the "transplantation" itself. Self-management of high-school children differs according to their transplantation period or their perception about the transplantation. In regard to subjective-life satisfaction, all the elementary school children had scores higher than the standard value; however, half of the high school children showed scores lower than that value. In particular, the subjective-life satisfaction did not always correspond with their physical situations.
**【Conclusion】** Preadolescent children could manage their health with parental support. Their satisfaction score was higher than the standard value. However, they did not sufficiently understand the "transplantation" itself. Self-management of adolescent children differs according to their transplantation period or their perception about the transplantation. The satisfaction score did not necessarily correspond to their physical situation. Medical staffs should support children with due consideration of their past experiences and understanding of the disease, the treatment, and the transplantation itself.

**Keywords:** liver transplantation , children, quality of life

## I. 緒 言

小児に対する肝移植の生存率は，成人の肝移植に比して良好である[1)]。小児の肝移植患者は，成人の肝炎や肝癌のような移植後に再発する可能性のある疾患は少なく，長期生存が期待される。

末期肝不全患者に対する有効な根治的治療は，肝移植であるが，移植医療を受けた患者家族の術後の長期的な見通しは，情報が少なく，不確定な部分が多い。肝移植を必要とする小児は，移植を受けるまでの間，対症療法をしながら慢性疾患患者としての生活が続

[1] 九州大学大学院医学研究院保健学部門，[2] 九州大学大学院医学研究院小児外科学分野
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く[2]。移植後は，免疫抑制剤の内服や感染予防のための自己管理，移植後長期において起こりうる合併症への不安等，種々の問題を抱えながら生活していかなければならない。

小児肝移植後の長期的問題は，医学的見地から各移植施設において調査されているが[3-6]，心理社会的問題に関しては，明らかになっていない部分が多い。学童から思春期の小児は，生活の主体が家庭から学校へと移行し，家族中心の健康管理から小児主体の健康管理に移行する重要な時期にある。特に，慢性疾患をもつ思春期の小児は，自己同一性の確立という発達課題の中，病気をもつ自分を見つめなおし新たな自己像を形成していく段階にある。また，思春期は，思春期特有の思考や，疾患・治療に対する否認などの情緒面の問題，友達など周囲との関係性の影響を受けやすく，不適切なセルフケア行動といったセルフケアの逸脱が生じやすい時期である[7]。そのため，医療者は，思春期の小児の病気とともに生活していく自分としてのアイデンティティを確立していく過程で経験する葛藤や混乱に一緒に向き合い，小児のもつ力を最大限に引き出し，困難に対処できるように支援する必要がある。しかし，個々の病状によって移植時期は異なり，成長発達過程で身体・精神・社会面において，患児・家族がどのような問題に直面し，どのように対処しているのかは明らかにされていない。そこで，本研究では，学童後期・思春期の小児への支援を検討するために，肝移植後の学童後期・思春期の小児の療養生活の実態および生活の満足度を明らかにすることを目的とした。

## II. 方　法

### 1. 対　象

現在A病院に外来通院中の10～18歳の肝移植後の小児で，本人の承認および保護者の同意が得られ，病名・病気についての説明を受けている者とした。また，質問紙調査および面接を行うため，識字可能で自分の体験を自由に語ることのできる者とした。

### 2. 調査期間

調査期間は，2011年10月～2012年3月であった。

### 3. 調査方法

対象者への依頼は，担当医が基準を満たすことを確認した者に対し，外来受診時に行った。面接は，診察室で対象者と研究者の1対1（本人が希望する場合，親の同伴も可とした）で行った。面接内容は，同意を得た上でICレコーダーに録音した。基本的属性および療養生活，病気に対する捉えや体験については，質問紙（自作）調査および半構造化面接を行い，生活の満足度については，既存の質問紙を用いた。質問紙は，診察の待合中に記載してもらい，面接の際に回収した。面接は，質問紙の結果を基に行った。また，外来診察時は診察に同席するとともに，検査データの情報を得た。

### 4. 調査内容

基本的属性として，性別，現在の年齢，就学状況，原疾患，移植時期，移植時年齢，身長・体重，家族構成について尋ねた。原疾患・移植時期等，子どもが分からない場合は，保護者に確認した。また，肝機能データについては，診察時に確認した。

療養生活については，日常生活（起床・就寝時間，食事，活動等），療養行動（日常注意していること，免疫抑制剤の内服，困っていること等），学校生活（出席状況，体育やクラブ活動・行事への参加，学校生活をどう感じているか，放課後の活動，友達関係，周囲の人の理解等），病気に対する捉えや体験について尋ねた。

生活の満足度は，中村ら[8,9]の開発した，疾患とは直接関係のない一般の日常生活に関する満足度（包括的なQOL）を調べる調査票（小学校高学年から中学生用と，高校生以上用の2種類）を用いた。小・中学生用は，「不安や悩み」「家と家族の満足」「友達の満足」「学校と先生の満足」「全体的な健康の満足」「体力と勤勉性，自尊感情」の6因子・37項目（総得点：185点），高校生用は，「友達の満足」「学校生活の満足」「精神面の満足」「親と経済の満足」「異性との関係性・自尊感情」「身体的活力」「進学や就職の悩み」「きょうだい関係の満足」の8因子・40項目（総得点：200点）から構成される。得点が高いほど，生活の満足度が高い。各質問紙は，信頼性・妥当性が確認されている。

### 5. 分析方法

1）事例ごとの個別分析

療養生活に関しては，質問紙の結果より実態を整理した。面接内容は，得られた録音データから逐語録を作成し，療養生活における子どもの認識や実際，子どもの体験や直面した困難・問題とそれに対する対処に

ついて，類似性のある内容を整理し，まとまりの意味を表す簡潔な一文で表した。生活の満足度質問紙は，点数を小学生の男子/女子，高校生の男子/女子の標準値における標準偏差よりデータを基準化（基準値平均を0，標準偏差を1）し，基準値と比較した。

2）全体分析

個別の質問紙と面接結果より，療養生活の実態について類似性のある内容を整理し，意味内容が損なわれないよう抽象度を高め，カテゴリーを抽出した。分析は，小児看護学の研究者2名のスーパーバイズを受けながら行い，分析結果の真実性を確保した。

### 6. 倫理的配慮

対象者およびその保護者に対して，研究参加の自由，途中中断の権利，プライバシーの保護，研究結果の公表などについて口頭・書面にて説明し，同意を得て実施した。なお，本研究は，研究者所属機関の倫理審査委員会の承認（承認番号：23-51）を得て実施した。

### 7. 用語の定義

療養行動：肝移植後の子どもに必要な内服管理や感染予防，情報獲得などの疾患管理に伴う行動

## III. 結　果

### 1. 対象者属性

対象者は，男子3名，女子6名だった。現在の年齢は，平均年齢14.2±3.0（SD）［10～17］歳で，小学生3名，高校生6名であった。移植時の平均年齢は，8.2±5.4［2～17］歳で，移植後経過期間は，7カ月から12年1カ月［平均5.7±3.6年］だった。すべての症例は，免疫抑制剤の内服治療中であったが，うち1名のみ脳死肝移植登録中で，外来でアルブミン製剤の点滴治療を要していた。身長のSDスコア平均は，−1.11±0.9［−2.46−−0.07］SDで，−2SD以下は，1名のみだった。肥満度の平均は，10.2±0.22［−9.5−61.5］%で，軽度肥満が1名，高度肥満が1名でいずれも女子であった（**表1**）。

### 2. 肝移植後の学童後期・思春期の小児の療養生活の実態

全症例結果より，療養生活の実態は，小学生3名と高校生6名では発達段階を反映した相違がみられたため，小学生と高校生に分けて，日常生活・学校生活・疾患管理に対する認識と実際，病気に対する捉えや体験および生活の満足度（QOL）の特徴を示す。療養

**表1　対象者の概要**

| 症例 | 年齢（歳）/性別/学校 | 移植後経過期間 | 原疾患 | 家族構成 | 肝機能（U）AST/ALT/γGTP | 身長SD/肥満度（%） |
|---|---|---|---|---|---|---|
| A | 10/男/小学校 | 5年9カ月 | 先天性門脈欠損症<br>高ガラクトース血症 | 2人（母） | 33/14/15 | −0.4/−6.8 |
| B | 10/女/小学校 | 7年3カ月 | 先天性門脈欠損症<br>高ガラクトース血症<br>声門下狭窄 | 5人<br>（母，兄，祖母，伯母） | 29/20/18 | −1.2/−7.9 |
| C | 11/女/小学校 | 8年2カ月 | 胆道閉鎖症 | 4人<br>（母，姉，兄） | 21/15/16 | 0.4/15.7 |
| D | 15/男/高校 | 2年11カ月 | 胆道閉鎖症 | 5人<br>（両親，兄，妹） | 24/21/19 | −1.7/−9.5 |
| E | 17/女/高校 | 7カ月 | 胆道閉鎖症 | 4人（両親，妹） | 14/10/14 | 2.46/28.1 |
| F | 15/女/高校 | 1年11カ月 | 胆道閉鎖症<br>肝肺症候群 | 7人<br>（両親，弟4人） | 34/36/77 | 1.6/61.5 |
| G | 17/女/高校 | 7年 | 劇症肝炎 | 3人（母，姉） | 27/24/62 | 2.1/7.1 |
| H | 17/男/高校 | 7年4カ月 | 胆道閉鎖症<br>（脳死肝移植登録中） | 7人<br>（両親，妹3人，弟1人） | 177/164/21 | 0.07/1.5 |
| I | 16/女/高校 | 12年1カ月 | 胆道閉鎖症 | 3人（母，弟） | 24/14/22 | 0.1/2.1 |