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Surgical outcome and etiologic heterogeneity of infants with biliary atresia who received Kasai operation less than 60 days after birth

A retrospective study

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Abstract

This study aimed to analyze the impact of etiologic heterogeneity and operation age on prognosis of infants with biliary atresia (BA) who received Kasai operation prior to 60 days of age.

From 2004 to 2010, 158 infants received Kasai operation before turning 60 days old. According to Davenport 2012 classifications, 4 groups of BA were defined: cystic BA, syndrome BA, and associated malformation, cytomegalovirus (CMV)-associated BA, and isolated BA. Native (autologous) liver survival rates and incidence of cholangitis 2 years after operation, as well as jaundice clearance rates 3 months after operation, were recorded.

Although infants who received the operation between 51 and 60 days of age had a better jaundice clearance 3 months after operation and lower incidence of cholangitis as compared with those under 40 or between 41 and 50 days of age, there was no significant difference in survival rates. Among types of BA, infants with cystic BA had the best prognosis. In the syndrome BA and associated malformations group, as well as CMV-associated group, infants who received the operation early (<40 days of age) had a worse outcome as compared with those who received the operation between 41 and 50 days or 51 and 60 days of age.

Both clinical etiologic heterogeneity and operation age may influence BA prognosis.

Abbreviations: BA = biliary atresia, CMV = cytomegalovirus.

Keywords: biliary atresia, etiologic heterogeneity, operation age, prognosis

1. Introduction

Biliary atresia (BA) is characterized by portal tract inflammation, inflammatory cell infiltration, and bile duct plugging and proliferation, thus resulting in biliary cirrhosis and ultimately liver function failure.[1–3] The incidence of BA is higher in Asia (including China) than in Western countries.[2,4–6] Despite advances in drug development, hepatoportoenterostomy (HPE) remains the main therapy for BA since its introduction in the 1950s. A majority of patients with BA undergo the Kasai operation following diagnosis. Despite these efforts, up to 50% of children who receive the Kasai operation will ultimately require liver transplantation; therefore, there remains an unmet medical need for improvement of the Kasai operation.[2,5]

Age at initial Kasai operation of infants with BA is a well-recognized factor affecting survival; however, whether younger age at surgery results in a higher survival rate is still controversial.[7–9] One study examining 103 BA cases showed that there was no significant difference in 1-year survival rates of autologous liver in children less than 60 days old versus in children more than 60 days old at the time of operation.[9] Another study, however, showed that operation at a very young age (less than 30 days) resulted in a worse prognosis.[10] In 2012, Chen et al[11] found that children aged more than 90 days who received the operation exhibited a better prognosis. In recent years, increasing evidences show that BA is caused by a variety of different bile duct injuries (ie, atresias), thus resulting in numerous, but common, clinical manifestations of the disease.[12–15] Determining the cause of BA in specific patient cases can potentially improve their prognosis and outcome. Due to medical advances and emerging popularity of early diagnosis, the age at BA diagnosis, treatment, and operation has decreased in recent years. Surgery in children less than 60 days old has gradually increased, but there is little knowledge regarding prognosis at this age. Given the importance of age at surgery and disease characterization in determining eligibility for the Kasai

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Table 1

Overall operation age and surgical outcome.

Age, d	n	Survival rate, %
<60	158	56.3 (89/158)
61–90	224	52.2 (117/224)
>90	94	41.4 (39/94)

operation, we sought to investigate etiology type classification, summarize liver survival factors in children less than 60 days old who received surgery, and contribute to the development of treatment programs for younger children with BA in order to allow for early treatment plans.

2. Materials and methods

2.1. Study population

Between January 2004 and December 2010, a total of 476 cases of BA were treated by Kasai surgery at the Children's Hospital of Fudan University. We retrospectively analyzed these data, so ethics approval and patient written informed consent were not necessary for our study. Among 476 cases of BA, 158 patients who underwent surgery were younger than 60 days old at the time of Kasai operation. Clinical information including surgery age and the 2-year autologous liver survival rate were recorded.

Patients who underwent surgery at less than 60 days of age were divided into 3 groups: less than 40 days old, 41 to 50 days old, and 51 to 60 days old. These 3 groups of patients were followed and 2-year autologous liver survival rates were compared.

2.2. BA classification

The intraoperative finding and radiographic evaluation before operation were analyzed. According to Davenport BA classification, BA infants who underwent surgery at less than 60 days of age were divided into 4 types of BA (15): syndromic BA and associated malformations, cystic BA, cytomegalovirus (CMV)-associated BA, and isolated BA. Specific classification criteria are as follows:

(1) Syndromic BA and associated malformations. This class can be further divided into 2 subtypes: congenital malformation syndrome BA (eg, multi-spleen syndrome and cat eye syndrome), or malformations just as isolated sporadic deformities BA (eg, esophageal atresia and intestinal atresia).
(2) Cystic BA: extrahepatic biliary obstruction cyst structure replaced normal structure.
(3) CMV-associated BA: in children with this type of BA, there is a significant percentage of serum positive for the CMV antibody, suggesting perinatal CMV infection as a potential cause of BA.
(4) Isolated BA: this is the most common type of BA; however, its etiology and disease onset are currently poorly understood. The degrees of inflammation and biliary obstruction vary. We predominantly compared and analyzed cases of isolated BA and investigated 2-year autologous liver survival rates.

2.3. Statistical analysis

All data were analyzed using IBM SPSS 11.0. The chi-square test was used for comparison of groups. $P < .05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

In 476 cases of BA, 158 cases were of children aged less than 60 days at the time of Kasai operation, where 28 patients were less than 40 days old, 56 patients were between 41 and 50 days old, and 74 patients were between 51 and 60 days old. According to the aforementioned etiological classification criteria, of 158 cases 19 cases were cystic BA, 35 cases were CMV-associate BA, 36 cases were syndromic BA and associated malformations, and 68 cases were isolated BA. All of the patients were finished by single chief surgeon in our institution.

3.2. Impact of surgery age on 2-year survival of autologous liver

The 2-year survival rate of autologous liver in all patients was 51.5% (245/476 cases). For patients less than 60 days old, between 61 and 90 days old, or older than 90 days, 2-year survival rates were 56.3% (89/158 cases), 52.2% (117/224 cases), or 41.4% (39/94 cases), respectively (Table 1). Comparing children less than 60 days old and 61 to 90 days old demonstrated no significant difference between the groups ($P = .113$). Comparing children less than 60 days old to children older than 90 days, however, demonstrated a significant difference in 2-year survival rates ($P = .028$).

We further explored the impact of surgery age on 2-year survival rates of autologous liver in 158 cases of infants younger than 60 days old. As shown in Table 2, 2-year survival rates of autologous liver when surgery is at an age less than 40 days old was 42.8% (12/28 cases), while survival rates when surgery occurred between 41 and 50 days of age or 51 and 60 days of age were 55.4% (31/56 cases) or 62.1% (46/74 cases), respectively.

Comparing these 3 groups demonstrated that surgery at less than 40 days old had the lowest 2-year autologous liver survival rates as compared with surgery at 41 to 50 days of age or 51 to 60 days of age (<40 vs 41–50, $P = .018$; <40 vs 51–60, $P = .029$). Surgery age at 51 to 60 days old exhibited the highest 2-year autologous liver survival rates (51–60 vs <40, $P = .029$; 51–60 vs

Table 2

Operation age and surgical outcome.

Age, d	n	Survival rate, %	Jaundice clearance, %	Cholangitis incidence, %
<40	28	42.8 (12/28)	46.4 (13/28)	46.4 (13/28)
41–50	56	55.4 (21/56)	58.9 (33/56)	41.1 (23/56)
51–60	74	62.1 (46/74)*	75.7 (56/74)†	33.8 (25/74)‡

* Operation age and survival rates ($P = .065$).
† Operation age and clearance of jaundice 3 months after operation ($P = .024$).
‡ Operation age and incidence of cholangitis ($P = .041$).

Table 3

Two-year autologous liver survival rates vary depending on etiologic heterogeneity and age at Kasai operation.

BA type	Cystic BA		Cytomegalovirus-associated		Syndromic BA and associated malformation		Isolated		Total	
Age, d	n	Rate (cases/total)	n	Rate (cases/total)	n	Rate (cases/total)	n	Rate (cases/total)	n	Rate (cases/total)
<40	4	75% (3/4)	4	25% (1/4)	4	0% (0/4)	16	50% (8/16)	28	46.4% (12/28)
41–50	11	63.6% (7/11)	10	50% (5/10)	14	50% (7/14)	21	57.1% (12/21)	56	55.4% (31/56)
51–60	4	75% (3/4)	21	66.7% (14/21)*	18	66.7% (12/18)†	31	54.8% (17/31)	74	62.1% (46/74)
Total	19	68.4% (13/19)‡	35	57.1% (20/35)	36	52.7% (19/36)	68	54.4% (37/68)	158	56.3% (89/158)

BA = biliary atresia.

* Different operation age and survival rates in cytomegalovirus-associated group ($P = .041$).

† Different operation age and survival rates in syndromic BA and associated malformation group ($P = .029$).

‡ Survival rate among different etiologic heterogeneity groups ($P = .033$).

41–50, $P = .043$). These results suggest that surgery age between 51 and 60 days of age may have an improved survival of autologous liver in BA infants.

3.3. Impact of etiologic heterogeneity on 2-year survival of autologous liver

Among the 158 cases of infants who underwent surgery at less than 60 days old, cystic BA had the smallest incidence (19 cases). The 2-year survival rate of autologous liver (68.4%, 13/19 cases), however, was significantly higher than other etiologic groups ($P = .033$). The 2-year survival rates of autologous liver of other etiologic groups are as follows: CMV-associated BA (57.1%), syndromic BA and associated malformations (52.7%), and isolated BA (54.4%) (Table 3). No significant differences were identified between these 3 groups ($P = .177$). These results suggest that cystic BA has the highest 2-year survival rate of autologous liver in BA infants.

3.4. Impact of etiologic heterogeneity on jaundice clearance

We further explored the impact of etiologic heterogeneity on jaundice clearance. As shown in Table 4, cystic BA had the highest jaundice clearance rate (78.9%) as compared to the other 3 BA groups ($P = .044$). Next, we investigated the impact of surgery age. Interestingly, infants with CMV-associated BA who had surgery between 51 and 60 days of age exhibited the highest rate of jaundice clearance (76.2%), as compared to infants who had surgery at less than 40 days of age (25%) or between 41 and 50 days of age (50%) ($P = .036$). A similar trend was observed in syndromic BA and associated malformations. Infants who had surgery between 51 and 60 days of age exhibited the highest rate of jaundice clearance (77.8%), as compared to infants who had surgery at less than 40 days of age (25%) or between 41 and 50 days of age (50%) ($P = .017$).

These results suggest that cystic BA has the highest jaundice clearance rate in BA infants. Infants undergoing surgery between 51 and 60 days of age exhibited the highest jaundice clearance rate both in CMV-associated BA, and syndromic BA and associated malformations.

3.5. Impact of etiologic heterogeneity on incidence of cholangitis

We also explored the impact of etiologic heterogeneity on incidence of cholangitis. As shown in Table 4, cystic BA had the lowest incidence of cholangitis (15.8%) as compared to the other three BA groups ($P = .011$). Next, we investigated the impact of surgery age. Interestingly, infants with CMV-associated BA who underwent surgery between 51 and 60 days of age exhibited the lowest incidence of cholangitis (33.3%), as compared with infants who underwent surgery at less than 40 days of age (50% incidence) or between 41 and 50 days of age (40% incidence) ($P = .045$). A similar trend was observed in infants with syndromic BA and associated malformations. Infants who underwent surgery between 51 and 60 days of age exhibited the lowest incidence of cholangitis (33.4%), as compared with infants who underwent surgery at less than 40 days of age (50% incidence) or between 41 and 50 days of age (42.9% incidence) ($P = .027$).

These results suggest that cystic BA has lowest incidence of cholangitis in BA infants. Infants undergoing surgery between 51 and 60 days of age exhibited the lowest incidence of cholangitis both in CMV-associated BA, and syndromic BA and associated malformations.

Table 4

Jaundice clearance rates vary depending on etiologic heterogeneity and age.

BA type	Cystic BA		Cytomegalovirus-associated		Syndromic BA and associated malformation		Isolated		Total	
Age, d	n	Rate (cases/total)	n	Rate (cases/total)	n	Rate (cases/total)	n	Rate (cases/total)	n	Rate (cases/total)
<40 d	4	75% (3/4)	4	25% (1/4)	4	25% (1/4)	16	50% (8/16)	28	46.4% (13/28)
41–50 d	11	72.7% (8/11)	10	50% (5/10)	14	50% (7/14)	21	61.9% (13/21)	56	58.9% (33/56)
51–60 d	4	100% (4/4)	21	76.2% (16/21)*	18	77.8% (14/18)†	31	70.9% (22/31)	74	75.7% (56/74)
Total	19	78.9% (15/19)‡	35	62.9% (22/35)	36	61.1% (22/36)	68	63.2 (43/68)	158	64.5% (102/158)

BA = biliary atresia.

* Different operation age and jaundice clearance rates in cytomegalovirus-associated group ($P = .036$).

† Different operation age and jaundice clearance rates in syndromic BA and associated malformation group ($P = .017$).

‡ Jaundice clearance rates of different etiologic heterogeneity groups ($P = .044$).

4. Discussion

Previous studies have suggested that age at surgery is an important factor affecting the prognosis of BA. Generally, the greater the age at surgery, the worse the prognosis. In recent years, however, studies have found age did not impose a significant influence on the outcome of Kasai operation in infants who underwent surgery between 60 and 100 days old, whereas some older children still have better survival rates and jaundice clearance.[6,7,11] In the 476 cases of BA examined in this study, the 2-year survival rate of autologous liver was 51.5%. The survival rate in children who underwent surgery at less than 60 days old was significantly higher than those who underwent surgery at more than 90 days of age. There was no significant difference, however, when compared to infants who underwent surgery between 60 and 90 days of age. Although the majority of infants with BA who undergo the Kasai operation will receive increased autologous liver survival time and jaundice clearance, determination of optimal age at surgery will be important to achieve the best outcome. Based on our results and clinical practices, we suggest that surgery around 60 days of age would be optimal for Kasai operation.

Interestingly, we found that surgery between 51 and 60 days of age showed the highest 2-year survival rate of autologous liver within the less than 60-days-old group. Most importantly, surgery at less than 40 days of age displayed the lowest 2-year survival rate of autologous liver. This is inconsistent with the traditional view that earlier surgery age could achieve the best outcomes. More recent studies showed that BA is caused by a variety of different factors, such as bile duct injury and atresia, resulting in a range of common clinical manifestations of the disease. Due to the variety of disease etiologies, the time when bile duct damage occurs may be different (may happen at the embryo and various stages of the perinatal period).[1–3,16–18] In most cases of extrahepatic BA, the bile ducts are normal at birth, but something causes them to be damaged (independently or with the help of an activated immune system) and replaced with fibrous tissue (sclerosis). Along with the growth of the age, the bile ducts were damaged increasingly and had a worse prognosis. Thus, we have reason to believe that the etiological classification and operation age of BA influences prognosis.[15,19,20]

Previous study has suggested that CMV infection in children with BA yielded the worst prognosis among known types.[21] Previous study showed that the outcome of CMV infected BA exhibited similar with other BA types.[22] These 2 studies included patients of varying ages who were diagnosed with BA. The average age was 73 and 65 days, respectively. In the present study, we explored the 2-year survival rate of autologous liver in infants who underwent surgery at less than 60 days of age. Two-year survival rates of autologous liver in CMV-associated BA were significantly lower than in cystic BA, however, there was no significant difference when compared with syndromic BA and associated malformations. Thus, the impact of etiologic heterogeneity on 2-year survival rates of autologous liver may differ between infants who undergo surgery at less than 60 days of age as compared with those who undergo surgery at greater than 60 days of age.

Cystic BA is recognized as a special kind of BA.[23,24] In the past, this type of clinical BA was often easily confused with the common bile duct cyst.[23–25] Abnormal hilar cyst-like structures could be found in the liver during prenatal ultrasound examination as early as 17 to 22 weeks of pregnancy. Based on this, some scholars have speculated that the development of cystic BA may occur in the 1st trimester or during early embryonic development.[19,26] Alternatively, there are some normal extrahepatic biliary structure in this BA type of, and thus with a better prognosis.[23,25] In this study, 19 cases of cystic BA received early diagnosis, typically in the 50 days before surgery (4 cases within 40 days, 11 cases between 41 and 50 days, 4 cases in 51–60 days). The overall 2-year survival of autologous liver was the highest (68.4%) as compared to other etiologic heterogeneity groups. Clinical outcomes, including incidence of cholangitis and jaundice clearance, were also better than in other etiologic heterogeneity groups. Additionally, there were promising outcomes among the different groups when surgery occurred before 60 days of age. Thus, very early surgical intervention (at less than 40 days of age) may not be necessary for Kasai operation in cystic BA.

Two-year survival rates of autologous liver in infants who underwent surgery at less than 40 days old were significantly lower than in infants who underwent surgery between 41 and 50 days of age or 51 and 60 days of age in CMV-associated BA, and syndromic BA and associated malformations. The exact cause for this discrepancy is unclear, however, these results indeed suggest a better surgery window time of 41 to 60 days old in CMV-associated BA, and syndromic BA and associated malformations.

Isolated BA represents the most common of the BA etiologic heterogeneity groups, representing 68 (43%) of 158 cases of infants who underwent surgery at less than 60 days of age. Two-year survival rates of autologous liver exhibited no significant differences among infants who underwent surgery at less than 40, between 41 and 50, or 51 to 60 days of age. Although there may be differences in disease onset, severity of inflammation, and degree of bile duct obstruction,[27,28] surgery at less than 60 days old can achieve similar outcomes among patients with isolated BA.

Some other factors, such as liver fibrosis, to some extent have influence on the prognosis of the patients with BA. However, in this research, we mainly focus on the age operation age and etiologic heterogeneity which presented before operation. So, this will make some limitations in this paper.

Nevertheless, our study found that surgery age has important impact on the 2-year survival of autologous liver following Kasai operation. Except cystic BA, our results also find that 51 to 60 days of age may serve as the best time for Kasai operation. Operation age, combined with clinical classification, can impact the prognosis of BA. To make this conclusion more clearly, it needs a long-term follow-up study.

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