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# Infants with extrahepatic biliary atresia: Effect of follow-up on the survival rate at Ege University Medical School transplantation center

*Miray Karakoyun[1], Maşallah Baran[2], Caner Turan[3], Murat Kılıç[4], Orkan Ergun[5], Sema Aydoğdu[6]*

[1]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Tepecik Training and Research Hospital, İzmir, Turkey
[2]Department of Pediatric Gastroenterology, Hepatology and Nutrition, İzmir Katip Çelebi University School of Medicine, İzmir, Turkey
[3]Department of Pediatric Emergency, Ege University School of Medicine, İzmir, Turkey
[4]Department of Transplantation, Kent Hospital, İzmir, Turkey
[5]Department of Pediatric Surgery, Ege University School of Medicine, İzmir, Turkey
[6]Department of Pediatric Gastoenterology, Hepatology and Nutrition, Ege University School of Medicine, İzmir, Turkey

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Original Article

## ABSTRACT

**Background/Aims:** Biliary atresia (BA) is the main cause of neonatal cholestasis and the primary reason for infant liver transplants worldwide. It is an obliterative cholangiopathy observed only in children and caused by progressive inflammation and fibrosis of the bile duct. We collaborated with a liver transplantation center to investigate the effects of follow-up in patients with BA.

**Materials and Methods:** Medical records of 99 patients who were diagnosed with BA and monitored at our center from 1990 to 2002 (27 patients) and from 2003 to 2015 (72 patients) were analyzed retrospectively. Patients were evaluated for birth weight; age at jaundice onset; age at alcoholic stool detection; age at the time of Kasai portoenterostomy (KPE), if performed; age at admission to our center; age at liver transplantation; duration between KPE and transplantation; pediatric end-stage liver disease (PELD) scores during transplantation; and growth and developmental status. The periods 1990-2002 and 2003-2015 were defined as phases I and II, respectively.

**Results:** The median age of the patients at presentation to our hospital was 149 (range: 20-730) days during phase I and 61 (range: 28-720) days during phase II. The median age at jaundice onset was 7 days, and the median age at alcoholic stool detection was 15 days. There was no significant difference between phases I and II in terms of age at jaundice onset, age at alcoholic stool detection, or birth weight. Twenty-five (92.5%) of the 27 patients in the phase I group were admitted to our center after undergoing KPE. Forty-four (61.1%) of the 72 patients in the phase II group (median age at the time of KPE: 47 days) were operated at our center. Median ages of the patients at the time of KPE at our center were 67.5 (range: 25-220) and 47 (range: 28-139) days during phases I and II, respectively. The median age of the 28 patients who were transferred from another center was 70 (range: 45-105) days during phase II. Liver transplantation was performed in 55 of 99 patients (55.5%). Significant differences were observed in the age at transplantation, duration between KPE and transplantation, and PELD scores between patients with BA who underwent KPE at our center and who underwent KPE at other institutes from other institutes.

**Conclusion:** These findings demonstrate the importance of a timely diagnosis of BA and undergoing KPE before malnutrition and/or cirrhosis deteriorate the patient's health. Furthermore, follow-up of patients with BA at a liver transplantation center increased the success of KPE and improved survival rates.

**Keywords:** Biliary atresia, follow-up, liver transplantation

## INTRODUCTION

Extrahepatic biliary atresia (BA) is the leading hepatobiliary disease worldwide, and it progresses with cholestasis at childhood and requires palliative or radical surgery (liver transplantation) (1). BA is primarily an obliterative cholangiopathy caused by progressive inflammation and fibrosis of the bile duct that is only observed in childhood. The frequency of BA is 1 in 15000 in the Far East and 5-7 in 100,000 in the USA and Europe. If progressive fibrosis of bile ducts occurs in addition to BA, secondary biliary

**Address for Correspondence:** Miray Karakoyun E-mail: miraykarakoyun@hotmail.com
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cirrhosis can be caused in a short period of 2 months and the prognosis becomes even more serious. BA is lethal without treatment, and the average life expectancy is 8-9 months. Therefore, it is the leading cause of neonatal cholestasis and the primary cause of infant liver transplantation worldwide (2-4).

Childhood hepatobiliary disease that is accompanied by cholestasis and leads to liver transplantation accounts for 40%-60% of the liver transplantation programs (LTPs) for children (5-7). BA accounts for approximately 30% and 70% of liver transplantations in Western countries and Japan, respectively, and for 24% of pediatric liver transplants performed at our transplantation center (3-5,8).

Approximately 10% of the patients with BA also suffer from anomalies in other organs such as the heart, esophagus, intestine, spleen, venous veins, and central nervous systems (8-10). BA treatment typically consists of two steps. The first step is a Kasai portoenterostomy (KPE), which facilitates neonatal bile flow and gives the infant valuable time to develop, thus buying time prior to a full liver transplantation, which is often the second step. Transplantation is performed if the success of KPE is inadequate or if complications such as secondary biliary cirrhosis arise (11,12). KPE performed during the early stage helps in reducing complications during a liver transplantation (13-15). Following liver transplantation, the 2-year survival rate is approximately 80%. In this study, we aimed to compare data between patients with BA who were transferred from other centers and those who were diagnosed, treated, and monitored at our center.

## MATERIALS AND METHODS

This retrospective study included 99 patients diagnosed with BA who were monitored at our center. Twenty-seven patients (13 male) were monitored between 1990 and 2002 and 72 (38 male) were monitored from2003 to 2015. The former period was defined as phase I and the latter as phase II.

Patients with BA during both phases were evaluated for birth weight; age of jaundice onset; age at first alcoholic stool detection; age at the time of KPE, if performed; and age at presentation to our center. The patients who underwent KPE at our center during phase II were compared with those who were transferred from other centers with respect to the age at liver transplantation, duration between KPE and transplantation, pediatric end-stage liver disease (PELD) scores during transplantation, and growth and development status. LTP, which was established in March 1997, evaluated patients diagnosed with BA until December 2015. Our study was made in accordance with the declaration of Helsinki. Informed consent could not be obtained due to retrospective design of the study.

### Statistical Analysis

Descriptive statistics were used to describe continuous variables (mean, standard deviation, minimum, maximum, and median values). Comparison of two variables was performed by the Student's t test. Comparison of two independent and abnormally distributed continuous variables was performed by The Mann-Whitney U test.

The $\chi^2$ test was used for categorical variables and expressed as observation counts (and percentages). The Kaplan-Meier method was used to calculate survival rates for the overall population. Statistical significance was accepted when p=OR<0.05.

Statistical analyses were performed using the MedCalc Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium).

## RESULTS

The median time of onset of jaundice was 7 (min-max: 1-30) days, and the median time of detection of alcoholic stool, according to the information provided by the patients' families, was 15 (min-max: 1-75) days.

The median birth weight of the patients in this series was 3190 g (range: 1500-4300 g). There was no significant difference between phases I and II in terms of the age at jaundice onset, age at the first alcoholic stool detected, or birth weight. The median age of the patients at presentation to our hospital during phases I and II was 149 (range: 20-730) and 61 (range: 28-720) days, respectively. With respect to the weight of the patients at presentation, 14 patients were <3$^{rd}$ weight percentile, 7 patients were in the 3$^{th}$-10$^{th}$ weight percentiles, and 6 patients were in the 10$^{th}$-25$^{th}$ weight percentiles during phase I, whereas 29 (40.2%) of the 72 patients were below the 3rd weight percentile, 22 (30.5%) patients were in the 3$^{th}$-10$^{th}$ weight percentile, 12 (16.7%) patients were in the 10$^{th}$-25$^{th}$ weight percentile, and 9 (12.6%) patients were above the 25$^{th}$ weight percentile during phase II.

During phase I, the median age at the time of KPE was 67.5 (range 25-120) days among 27 patients who underwent KPE at our center and 71.5 (range 30-138) days among patients who underwent KPE at another center. On the other hand, during phase II, the median age at the time of KPE operation was 47 days (range28,139) among patients who underwent KPE at our center and 70 days (range: 45-105) among 28 patients who underwent KPE at another center.

Liver transplantation was performed in 50 of 99 (8 patients from phase I and 42 from phase II) patients with BA during the pediatric LTP. There were significant differences in the age at transplantation, time between KPE and transplantation, and PELD scores between patients with BA who underwent KPE at our center and those patients from other institutes (p<0.05). The survival times of patients with BA who did not receive a transplant are shown in Table 1, 2.

In phase I, none of the patients diagnosed and treated at our hospital underwent liver transplantation, whereas 28 patients

**Table 1.** The status of patients from our center and other institutes during the transplantation phase

| Institutes | Our center (n=28) | Other institutes (n=22) | p |
|---|---|---|---|
| Transplantation time (months) | 34±25.9 | 16.5±12 | <.05 |
| Duration between referral to the hospital and transplantation (months) | 23.1±27 | 6.5±9.1 | <.05 |
| PELD score during transplantation | 21 (15-36) | 29 (21-45) | <.05 |
| Growth rate during transplantation | | | |
| Below 3rd percentile | 4 | 10 | |
| Between 3rd and 10th percentiles | 7 | 10 | |
| Between 10th and 25th percentiles | 8 | 2 | |
| Over 25th percentile | 9 | - | |

PELD: pediatric end-stage liver disease

**Table 2.** Survival without transplantation in patients with biliary atresia

| Years | % Survival |
|---|---|
| 1st year | 53.3 |
| 2nd year | 40 |
| 3rd year | 40 |
| 5th year | 26 |

**Table 3.** Pediatric LTP and survival rate in patients with BA

| Years | % Survival (n=50) |
|---|---|
| 1st year | 76.5 |
| 2nd year | 72 |
| 5th year | 68.5 |
| 10th year | 66.6 |

LTP: liver transplantation program; BA: biliary atresia

in phase II underwent liver transplantation. Liver transplantation was performed in 8 and 14 patients coming from another center in phases I and II, respectively. Data from the patients at our center and those from other institutes who underwent transplantation are shown in Table 1, 2. Data of the pediatric LTP and survival rates of patients with BA are shown in Table 3.

Table 4 shows the survival rates after liver transplantation because of BA during phases I and II. Statistical analysis could not be performed because of the low number of patients, but there was a statistically significant difference in survival rates between phases I and II. The comparison of survival rates in patients who underwent liver transplantation between phases I and II is shown in Table 4.

In our pediatric LTP, the fastest growth and development were observed in patients with BA after transplantation. Patients with BA, who were below the 3rd weight percentile, reached

**Table 4.** Comparison of survival in patients who underwent liver transplantation during phases I and II

| Survival | Before year 2002 (n=8) % | After year 2002 (n=42) % |
|---|---|---|
| 1st year | 62.2 | 86.3 |
| 2nd year | 50 | 81 |
| 5th year | 37.5 | 81 |
| 10th year | 37.5 | 78.5 |

**Table 5.** Growth performance of patients with BA before transplantation and after the 1st year of transplantation

| Growth status | Before transplantation (%) | After transplantation (%) |
|---|---|---|
| Below 3rd percentile | 14 (28%) | - |
| 3rd to 10th percentile | 17 (34%) | - |
| 10th to 25th percentile | 10 (20%) | - |
| 25th to 50th percentile | 9 (18%) | 14 (28.5%) |
| 50th to 75th percentile | - | 24 (47.5%) |
| Above 75th percentile | - | 12 (24%) |

BA: biliary atresia

the 25th-50th weight percentiles in the first 6-month follow-up. After transplantation, the 1st year growth rate changed between 10-16 cm. All patients had organomegaly and acid before liver transplantation. The weight percentile was below 50 and 62% of the patients were below the 10th weight percentile. After transplantation, none of the patients were below the 25th weight percentile and those of 71.5% were above the 50th weight percentile. The growth performance of patients with BA before transplantation and after the 1st year of transplantation is shown in Table 5.

## DISCUSSION

Kasai portoenterostomy, ideally before 3 months of age, is the first recommended treatment for managing BA. KPE may preclude the need for LT in approximately 15% children (16,17). In children who do require LT after KPE, KPE allows the child to develop further before performing LT (18,19). The present study aimed to evaluate the management of patients with BA before and after 2002 in our pediatric LTP, one of the top pediatric liver transplantation centers in our country, and to compare our results with those in the literature. Comparing the two study phases in terms of age at the time of KPE showed that the optimal time to perform KPE was not different for patients who were transferred from other centers, whereas the duration between admission and the time of KPE was significantly shorter in our center. This clearly indicates that BA is not being diagnosed early enough in our country; practitioners and pediatricians must be vigilant and knowledgeable about the symptoms of BA to en-

sure early diagnosis Since the first study on KPE was published in 1959, the 2-year survival rate of patients with BA has increased from 10% to 53%, whereas the 5-year survival rate is currently 60% and the 10-year survival rate is 50% (3). A study conducted by Altman et al. (17) in 1997 determined a 5- and 10-year survival rates of 45% and 35%, respectively. The Japan Biliary Atresia Group reported the most favorable rates thus far as a 5-year survival rate of 59.7% and a 10-year survival rate of 52.8% (9).

According to the literature, nearly half of the patients with BA survive the 1st year, but by the 5th year only one fourth survive without a liver transplantation. Transplantation is essential for long-term survival and these patients should be followed up at transplantation centers (20,21).

According to data collected at our transplantation center, patients with BA who received a transplant gained a 76.5% survival advantage in the 1st year and 68.5% in the 5th year. These data show that the survival rate for patients with BA is higher following prompt diagnosis and a good preparation program.

### Survival Rate after 2002

According to a study performed in Japan, the 5- and 10-year survival rates of the patients with BA after liver transplantation were 75.8% and 66.7%, respectively (9). In a study of 440 patients between 1986 and 1996 in France, 226 of whom underwent a liver transplantation after KPE, 5- and 10-year survival rates were 70% and 68%, respectively (8,22). As shown in Table 5, the survival rate of patients diagnosed with BA at our center after 2002 was similar to that reported in the literature (5,8,14). Clinicians can help in increasing survival rates by being aware of the symptoms of BA to facilitate early diagnosis. Additionally, they should be knowledgeable about the improvements in prognosis following both types of surgery. Good management of latent and overt infection and complete preoperative preparation are also essential; internists and pediatricians should collaborate closely to manage these patients as effectively as possible.

As shown in Table 1, the patients who were transferred from other clinics were younger with higher body weights and tended to undergo liver transplantation at an earlier age (average of 6.5 months) than other patients (average of 23 months). Malnutrition often necessitates earlier liver transplantation. In addition to the medical management of cholangitis, portal hypertension, and metabolic acidosis, many patients require parenteral nutrition with a special diet and fat-soluble vitamin supplements. These measures help reduce the incidence of infection after transplantation (22). Growth rates of patients who undergo liver transplantation because of BA improve rapidly following surgery. In our study, before transplantation, only 18% patients were in the 25-50th weight percentile, whereas 82% were below the 25th percentile; 1 year following transplantation, all patients were above the 25th weight percentile. The studies performed by Fouquet et al. (23) and Burdelski et al. (24) corroborated these findings.

Biliary atresia in infants is asymptomatic for the first 15 days of life because alcoholic stools and icterus often go unnoticed by parents and physicians; this condition is not recognized until malnutrition slows the growth rate of the patient.

When practitioners and pediatricians detect hyperbilirubinemia, which does not develop until after 15 days of age, they should check not only the total bilirubin level but also the direct and indirect bilirubin levels. If these are concerning, the patient should be transferred immediately to a pediatric gastroenterology department or preferably to a liver transplantation center, and the color of the stool should be monitored. Our data demonstrate the importance of prompt diagnosis and timely KPE for patients with BA. Ideally, for the best prognosis, KPE should be performed before malnutrition and complications, such as cirrhosis, develop. If necessary, liver transplantation should then be performed following excellent preoperative preparation and management to further facilitate healthy growth and development, thereby improving the prognosis considerably.

**Ethics Committee Approval:** Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

**Informed Consent:** Informed consent is not necessary due to the retrospective nature of this study.

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Original Article

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