Strategies to improve the outcome of biliary atresia

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Mortality of biliary atresia in children not undergoing liver transplantation in the Netherlands

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Chapter 2

ABSTRACT

In order to further improve the outcome of BA, we characterized the mortality of biliary atresia (BA) patients who did not undergo liver transplantation (OLT) in The Netherlands, and compared our results to international data. For this purpose, we analyzed the causes of mortality of non-transplanted BA patients before the age of five years, using the Netherlands Study group of Biliary Atresia Registry (NeSBAR) database. To evaluate trends in mortality, we compared the cohort 1987-1996 (n=99) with 1997-2008 (n=111). We compared clinical condition at OLT assessment with available international data, using the Pediatric End-stage Liver Disease (PELD)-score. Mortality of non-transplanted BA children was 26% (26/99) in 1987-1996 and 16% (18/111) in 1997-2008 (p=0.09). Sepsis was the prevailing direct cause of death (30%;13/44). PELD-scores at the time of assessment were higher in non-transplanted BA patients (median 20.5; range 13-40) compared to international data (mean/median between 11.7 and 13.3). Based on our national data, we conclude that pre-transplant mortality of BA patients is still considerable, and that sepsis is a predominant contributor. Our results strongly indicate that the prognosis of patients with BA in The Netherlands can be improved by earlier listing of patients for OLT and by improving pre-transplant care.

INTRODUCTION

Biliary atresia (BA) is an obstructive cholangiopathy of unknown aetiology, occurring in the perinatal period. The incidence varies from 1:15.000 to 1:19.000 live births in Western Europe.[60,111,151] The initial treatment consists of the Kasai portoenterostomy, which aims to restore bile flow from liver to intestine.[82] Nevertheless, in the majority of cases, orthotopic liver transplantation (OLT) will be needed eventually, either within years after surgical correction or after prolonged follow-up.[103,128,159,184] OLT is indicated early when surgical correction fails to clear jaundice, or when complications of end-stage liver disease develop due to biliary cirrhosis, which might be accelerated by repeated episodes of cholangitis.[11,163] Worldwide, BA is responsible for 50-70% of the indications for OLT under the age of 2 years (data from United Network for Organ Sharing and Eurotransplant).[60,74,133]

The postnatal age at which the Kasai procedure is performed has been negatively related to both successful clearance of jaundice and to postponement of OLT.[21,81,128,152,163] Another important factor that might determine outcome is experience of the treatment center in the management of BA patients.[32,110] Long-term overall outcome is influenced by accessibility to OLT.[128]

Despite the availability of OLT in West-European countries, epidemiological studies on the prognosis of BA still report mortality in non-transplanted BA patients.[110,147,151,159] The aim of this retrospective study is to assess whether improvement in the prognosis of BA patients is possible. For this purpose, we aimed to gain insight in the causes of mortality in BA patients, who had not had a transplant at their time of death, and to identify clinical or demographic risk factors for pre-transplant mortality. To assess whether our national findings might be applicable for other countries as well, we set out to compare our findings with available data from other developed countries. We used the prospective NeSBAR (Netherlands Study group of Biliary Atresia and Registry) database from 1987-2008. Because there were many developments in surgical, anesthesiological and pediatric disciplines within this period, we also assessed whether this has affected treatment outcome by comparing the cohort 1987-1996 to the cohort 1997-2008.

PATIENTS AND METHODS

The database of NeSBAR is based on an ongoing joint effort of the Dutch Society for Pediatrics and the Dutch Society for Pediatric Surgeons. The prospective NeSBAR registry contains the patient data of all BA patients treated in the six specialised academic centers in which primary treatment (portoenterostomy according to Kasai or one of its variants) has been performed from January 1st 1987 onwards. Follow-up also takes place in one of the six specialised academic centres.

Within these centers, one pediatric gastroenterologist and one pediatric surgeon guarantee proper data collection. Data entry is yearly checked on site by one researcher using the pediatric and surgical patient files. Pediatric OLT has been concentrated in one national center. The Dutch pediatric OLT program started in 1982, and the living related liver transplantation program in 2004. The definitive diagnosis of BA was based on laparotomy and intraoperative cholangiography, and confirmed by the pathology of the resection specimen.

For the present study, we included all BA patients born between January 1st 1987 and 31st of December 2008 who underwent surgical correction for BA. Subsequently, we selected the BA patients who died under the age of five years without OLT. This limit is arbitrarily chosen, however the vast majority of patients in whom restoration of bile flow fails do not survive beyond five years with native liver.[21,81,110,163] Follow-up ended the 31st of December 2008.

Original patient files, operative reports and office notes were reviewed on site by one

researcher (WdV) to obtain relevant demographic data and clinical characteristics. This study was performed according to the guidelines of The Medical Ethical Committee of the University Medical Center Groningen.

The following data were extracted from the database: date of birth, associated congenital anomalies, age at Kasai, age at assessment for OLT, Pediatric End-stage Liver Disease-score (PELD-score)[108,155,201] at date of OLT assessment, and cause and age of death. PELD-scores were calculated to assess the clinical severity of end-stage liver disease, using the PELD scoring system and Dutch growth charts.[51,108]

Sepsis was defined as a systemic inflammatory response in combination with a positive blood culture.[14] Cases in which fever (>37.5°C), leukocytosis (>12·10^9 cells/L) and no proven non-infectious cause of a systemic inflammatory response were present, were also considered as having sepsis. Patients were designated as having end-stage liver disease when a combination of complications of portal hypertension or compromised hepatic synthetic function was present, such as (variceal) hemorrhage with compromised clotting, hepatorenal or hepatopulmonary syndrome and encephalopathy.

Statistical analysis

The incidence of BA in The Netherlands was determined by calculating the number of diagnosed cases per number of live births, obtained from the Statistics Netherlands website (http://www.cbs.nl). Analysis of categorical variables was performed by Fisher's exact test or Mann-Whitney U-test, and of continuous variables with Student's t-test or Mann-Whitney U-test as appropriate. Native liver survival rates of both cohorts were calculated with the Kaplan-Meier method with time between birth and pre-transplant mortality or OLT, and overall survival rates for all patients assessed for OLT with time between birth and death. Survival data were compared using the log-rank test. Two-tailed p-values below 0.05 were considered statistically significant.

RESULTS

Patients

In the Netherlands, between January 1, 1987 and December 31, 2008, 211 BA patients underwent surgical correction. Kasai portoenterostomy was carried out in 202 patients, 5 patients underwent a hepaticojejunostomy and 4 patients a choledochojejunostomy. One patient was lost to follow-up due to emigration before reaching the age of five, and had to be excluded from the study.

Of 210 patients, 119 (57%) either died or were transplanted before five years of age. Forty-four patients (21%) died with their native liver before reaching the age of five years. Biliary Atresia Splenic Malformation syndrome (BASM), defined as the presence of malformations including polysplenia or asplenia in conjunction with BA[31], was present in 2/44 deceased patients (5%), compared to 4/75 (5%) in the transplanted group and 12/210 (6%) in the whole study group. Mortality of BA patients without OLT above the age of 5 was only 2% (4/210). The causes of death of these patients were: car accident, pericarditis, hepatopulmonary syndrome, and end-stage liver disease with sepsis.

The numbers and specific causes of death of all 44 non-transplanted BA patients are depicted in Table 1. Sepsis was the major cause of death occurring in 13/44 (30%) of the patients. Progressive liver failure was the cause in 7/44 (16%) of the cases, congenital anomalies in 6/44 (14%), absence of parental consent for OLT and gastro-intestinal bleeding each in 4/44 (9%) of the cases

Table 1: Causes of mortality in 44 non-transplanted BA patients in the Netherlands between 1987-2008.

Sepsis	30% (13/44)
Progressive liver failure	16% (7/44)
Congenital anomalies	14% (6/44)
Gastro-intestinal bleeding	9% (4/44)
No parental consent	9% (4/44)
Complications of Kasai	7% (3/44)
Miscellaneous	16% (7/44)

and 3/44 (7%) died from complications related to the Kasai portoenterostomy procedure. In Table 2, the causes of death are listed separately for the two cohorts and phase of care. Eighteen of the 44 (41%) non-transplanted patients had not been assessed for OLT. Four of these 18 not-assessed patients (22%) died due to sepsis. During assessment, six patients (14%) died, of whom four (67%) due to sepsis. After assessment, OLT was refused by parents in 2 cases, and 5 patients were not listed on medical grounds (together 16%). Finally, thirteen patients (30%) died while on the waiting list for OLT. An important cause of death was, again, sepsis (5/13; 38%). In all these cases, sepsis was superimposed on a certain degree of liver failure but was nevertheless considered the major direct cause of death. The source of the infection could be proven in 8 cases, namely: spontaneous bacterial peritonitis in three cases, cholangitis in two cases, and urinary tract infection, throat infection and intra-venous central line infection in one case, respectively. In five other cases, the source of the infection remained obscure. Only one patient succumbed to sepsis caused by a micro-organism for which a vaccine became available thereafter (Haemophilus influenzae type B).

Two of the 44 non-transplanted BA patients showed initial clearance of jaundice (total bilirubin < 17 µmol/L within 6 months post-surgery). The cause of death in these patients was not directly related to BA (namely, cardiomyopathy and cerebral herniation).

Demographic and clinical factors

Table 3 shows the demographic and clinical characteristics of patients who died without transplantation during the two cohorts. The mean gestational age was shorter in the cohort 1997-2008 compared to the cohort 1987-1996 (39.2±1.5 weeks vs. 36.9±3.3; p=0.006).

About one quarter of the patients had associated anomalies. Ages at Kasai were not significantly different between the cohorts. The time elapsed between Kasai portoenterostomy and death was shorter in the cohort 1997-2008 compared to 1987-1996 (median 237 vs. 173 days, p=0.04). Three patients died within a month post-surgery, one patient in the cohort 1987-1996 at day 22 post-surgery (cause of death, sepsis) and two patients in the cohort 1997-2008 at days 2 and 3 post-surgery (causes of death, necrotic liver lobe, and abdominal compartment syndrome, respectively). On average, patients died at a younger age in the cohort 1997-2008, at a median age of 256 days versus 355 days in the cohort 1987-1996 (p=0.03). This difference is mainly attributable to the two patients dying very soon after Kasai portoenterostomy. The median time between assessment for OLT and death was 79 days (range: 15-358) in the non-transplanted group. For comparison, median time between assessment and OLT was 125 days in BA patients of the same age who had been transplanted in our center (range: 16-585).

Table 2: Causes of mortality in 44 non-transplanted BA patients according to cohort and phase of treatment.

		1987 - 1996	1997 - 2008
Causes of not being assessed for OLT (n= 18)	No parental consent	2	-
	Severe congenital anomalies[a]	2	1
	Sepsis	4	-
	Progressive liver failure	2	-
	Death by other causes[b]	1	3
	Complications of Kasai	-	3
Causes of death during assessment for OLT (n = 6)	Progressive liver failure	-	1
	Sepsis	1	3
	Gastro-intestinal bleeding	1	-
Causes of refutation for OLT after assessment (n = 7)	No parental consent	2	-
	Severe malnutrition	1	1
	Cardiomyopathy	2	-
	Renal dysfunction	1	-
Causes of death during being listed for OLT (n = 13)	Progressive liver failure	2	2
	Sepsis	2	3
	Gastro-intestinal Bleeding	1	2
	Acute on chronic encephalopathy	1	-

[a] patient 1: combination of pulmonal dysplasia, cardiomyopathy, and an unspecified metabolic disorder; patient 2: Pierre Robin sequence, situs inversus and cardiac malformation; patient 3: a condition interpreted as 'caudal regression syndrome'.

[b] patient 1: lethal hemorrhage in a hepatoblastoma tumor; patient 2: cerebral herniation coinciding with status epilepticus of unknown cause; patient 3: cardiac failure; patient 4: congenital anomalies with unclarified deterioration of clinical condition.

PELD-scores

To determine whether the clinical condition of BA patients at the time of assessment differed from international data, we calculated PELD-scores retrospectively. The PELD-scores of non-transplanted patients were not different between cohorts 1987-1996 and 1997-2008 (median 16.0 (range -7-37) vs. 20.5 (13-40); see Table 4). For comparison, the PELD-scores of transplanted BA patients were 18.3 (0-38) in cohort 1987-1996 and 13.4 (-2-32) in cohort 1997-2008. The PELD-scores of the non-transplanted patients were higher compared to transplanted BA patients in the cohort 1997-2008 (p=0.01). The PELD-scores of the non-transplanted BA patients were markedly higher than those of comparable BA patients in the available international literature (mean/median between 11.7 and 13.3).[7,15,184] The 5-year overall survival of patients with PELD-scores at assessment ≤15 was 71%, and survival of patients with PELD-scores > 15 was 41% (p=0.001).

Table 3: Demographic and clinical data of 44 non-transplanted BA patients in the cohorts 1987-1996 and 1997-2008.

		1987-1996 n=26	1997-2008 n=18	p-value
Average birth weight±SD (grams)		3178±691	2903±905	n.s.
Average gestational age±SD (weeks)		39.2±1.5	36.9±3.3	0.006
Male		10 (39%)	8 (44%)	n.s.
Congenital anomalies	None	20 (77%)	13 (72%)	n.s.
	Cardiac	1 (4%)	2 (11%)	
	Malrotation	2 (8%)	2 (11%)	
	Polysplenia/asplenia	1 (4%)	1 (6%)	
	Situs inversus	-	2 (11%)	
	Intestinal Atresia	1 (4%)	-	
Average age at Kasai±SD (days)		65±16	68±27	n.s.
Median time between Kasai and death (days)		237 (22-699)	173 (2-442)	0.04
Median age of death (days)		355 (121-739)	256 (41-752)	0.03
Median time between assessment for OLT and death (days)		88 (range: 16-358)	50 (range: 15-158)	n.s.
Death<5 yrs without OLT		26/99 (26%)	18/111 (16%)	0.09
OLT<5 yrs		25/99 (25%)	49/111 (44%)	0.004

Table 4: PELD-scores at time of OLT assessment according to outcome

	Death<5 yrs without OLT 1987-1996	Death<5 yrs without OLT 1997-2008	OLT 1987-1996	OLT 1997-2008	England [7] 2001-2005	Belgium [15] 1994-2002	USA [184] 1995-2003
BA diagnoses	100%	100%	100%	100%	100%	64%	100%
Median age (months)	8.6	5	7.7	6.5	8	1.4	86.6%<5 years
Bilirubin (mg/dL)	12.7 (1.6-28.0)	25.8 (18.3-28.8)	17.3 (3.5-32.7)	14.0 (1.5-34.2)			
Albumin (g/dL)	3.1 (2.4-3.6)	2.6 (1.8-3.6)	3.3 (1.6-3.8)	2.7 (1.9-3.9)			
INR (ratio)	1.4 (1.1-4.2)	1.5 (1.2-3.3)	1.8 (0.9-3.5)	1.3 (1.0-3.3)			
PELD-score	16.0 (-7-37)[b,d]	20.5 (13-40)[a,b]	18.3 (0-38)[c,d]	13.4 (-2-32)[a,c]	12.9	13.3±9.7*	11.7*

Values expressed as median (range); [a] p=0.01; [b] p=0.11; [c] p=0.08; [d] p=0.58
*mean±SD

Evolution in treatment outcome

Theoretically, the timing of referral of BA patients for OLT could have changed over time as the technique became more accepted as a treatment option in young children. We compared non-transplant mortality in the cohort of patients born between 1987 and 1996, with the cohort born between 1997 and 2008. The overall incidence of BA in the cohort 1987-1996 was 1:17,679 live births, the incidence in cohort 1997-2008 was 1:19,804 live births.

Figure 1 shows the mortality rate of non-transplanted BA patients treated with Kasai in both cohorts. In 1987-1996, 26 out of 99 cases (26%) died with their native liver (2.6 cases/year). In 1997-2008, 18 out of 111 cases (16%) died with their native liver (1.5 cases/year, p=0.09). In cohort 1997-2008, fewer patients died without OLT assessment (7/111, 6%), compared with cohort 1987-1996 (11/99, 11%). Also, fewer cases were refuted for OLT in the last cohort (1/111, 1%), compared to the first cohort (6/99, 6%). The combined percentage of either "not assessed" or "not accepted" significantly decreased by more than 50% over time (from 17/99 to 8/111 patients; p=0.03). The mortality during assessment or while listed for OLT was similar in the two cohorts. In cohort 1997-2008 a limited number of patients were referred for assessment and eventual liver transplantation to Belgium (n=12), partly because of the earlier availability of living-related OLT in Belgium. In 1987-1996, 25 of 99 patients underwent OLT before the age of 5 (25%), this number increased to 49 of 111 patients (44%) in 1997-2008 (p=0.004).

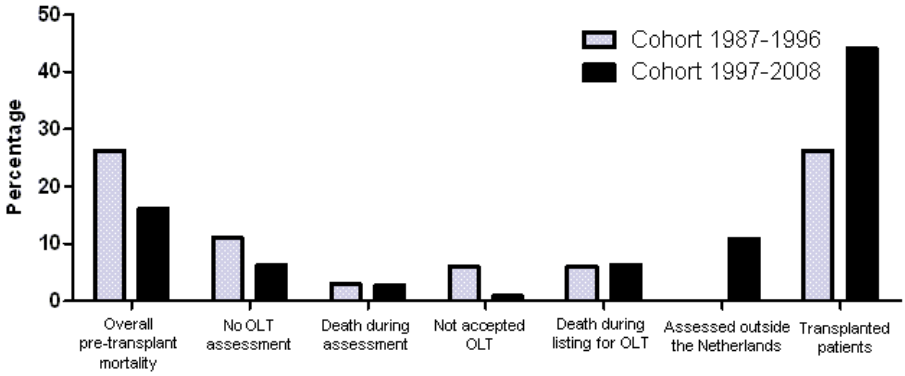

Figure 1: Pre-transplant mortality in the different clinical stages prior to OLT: comparison between the cohorts 1987-1996 and 1997-2008. Overall pre-transplant mortality, p=0.09. Combined 'No OLT assessment' and 'Not accepted OLT' p=0.03. Transplanted patients, p=0.04.

In Figure 2, the percentages of pre-transplant mortality and OLT are depicted in survival curves. Pre-transplant mortality occurred mainly in the first 2 years of life, and the age distribution of mortality was not different between the cohorts.

DISCUSSION

We aimed to assess whether improvement in the prognosis of BA patients is possible. For this purpose, we quantified and analyzed the mortality of all Dutch BA patients who had not undergone OLT. Although the rate of OLT in the BA patients has increased during the past 2 decades, the pre-transplant mortality has not decreased significantly and is relatively high when compared

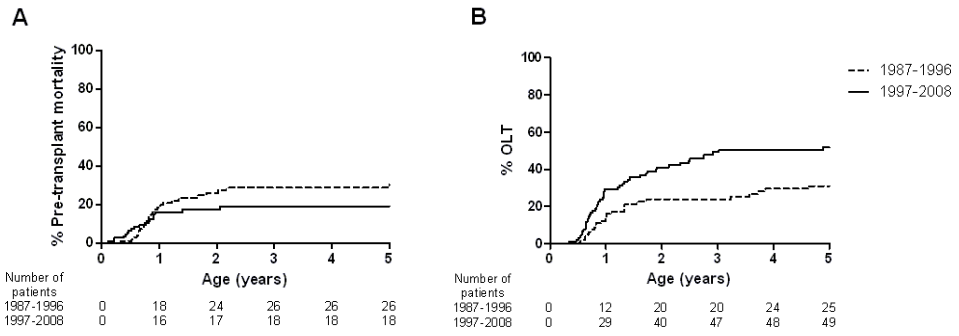

Figure 2: Kaplan Meier curves showing the percentage of pre-transplant mortality (**panel A**) and OLT (**panel B**) at five-year follow-up for the cohorts 1987-1996 (continuous line) and 1997-2008 (dashed line). Panel A, p=0.09; panel B, p=0.004)

to published international data. The most prevalent cause of death was sepsis. Comparison of retrospectively calculated PELD-scores reveals that the patients with pre-transplant mortality were already in a more advanced state of disease when they were assessed for OLT when compared to international data.

Although the percentage of patients dying without OLT tended to decrease from 26% between 1987-1996 to 16% between 1997-2008, this difference is not significant. In the period 1997-2008 the percentage of all BA patients below five years of age who had undergone OLT had significantly increased to 44%, from 26% in 1987-1996. Thus, despite an increase of the fraction of patients transplanted before five years of age, the pre-transplant mortality failed to decrease. Moreover, the pre-transplant mortality is at least twice as high as national data from France (7.5%; cohort 1997-2002)[7,151] and from England and Wales (4.2%; cohort 1999-2002).[32] Pre-transplant mortality was very limited above the age of five (in our data 2%).

Present data show that in the majority of non-transplanted BA patients who died (59%), the cause of death was directly or indirectly related to end-stage liver disease such as sepsis, liver failure, gastro-intestinal bleeding or severe malnutrition. The prevalence of BASM reported from England and Wales is higher than the prevalence we found (10.2% vs 6%, respectively).[32] The prevalence of BASM in the non-transplanted group reported in the current study was not different compared to the rate in the transplanted patients or in our whole BA population. We cannot exclude structural under detection of splenic abnormalities, particularly in the beginning of the study period. Congenital heart disease had been reported previously as an important contributor to pre-transplant mortality.[31] In contrast, heart disease was the major contributor in 7% of deaths, another 7% died because of severe other congenital anomalies combined with heart disease in our series.

Sepsis was the most important direct cause of death (13/44 patients; 30%). Theoretically, sepsis could be related to post-operative cholangitis. However, the median age of death was considerably higher than the age at Kasai surgery, and therefore variation in the immediate post-operative antibiotic treatment is not likely to exert a dominant effect on this parameter. Recently it was shown that infections are common in the month before OLT, especially when biliary problems are the cause of end-stage liver disease.[18] Currently, there is no nationwide consensus about antibiotic

prophylaxis post-Kasai or in case of liver failure in The Netherlands. Based on the identified causative agents in this study, it is not likely that recent expansions of the National Vaccination Program are to prevent those life threatening infections.

The reasons why patients with BA did not undergo OLT changed over time. In the period 1987-1996, when OLT for small children was still relatively new, 42% of the patients who died without OLT, had not been evaluated for OLT. Especially in the beginning of the cohort, both specialists and parents were probably still relatively hesitative to refer a child for OLT assessment. In the most recent cohort the numbers of patients assessed for OLT and the fraction of patients that were transplanted had considerably increased. With six specialized centers involved in the treatment of BA patients in The Netherlands, it is obvious that the case-load per center is low in our country. Some deaths early after Kasai may relate to surgical technique, and centralization is likely to overcome this problem.

The condition in which BA patients are referred for OLT likely contributes to the mortality. The Pediatric End-stage Liver Disease-score (PELD-score) has come into use to identify pediatric end-stage liver disease patients with the highest risk of mortality.[48,109,155,184] An increase in PELD-score is associated with an increased mortality, and with a worse outcome after OLT.[25,109,184] Indeed, we showed that PELD-scores of the non-transplanted children in our study were markedly higher than those of the transplanted BA patients, and higher than PELD-scores from international reports with similar patients groups, where means and medians of 11.7-13.3 are reported.[7,15,184] This supports the presumption that a subset of BA patients under five years of age in The Netherlands was assessed for OLT in an already too advanced state of disease, contributing to pre-transplant mortality. Furthermore, we showed a significantly worse overall survival of children assessed with a PELD-score > 15.

Throughout the studied period, referral for OLT assessment was based on each doctor's individual judgement rather than objective clinical parameters such as the PELD-score. This might explain the late referral for a therapy which has in itself a good outcome in our country, around 90% 1-year survival nowadays. Despite the utilisation of the split-liver technique in ~20% of pediatric OLT's in our country, lack of a suitable donor organ may demand a long waiting list time in some cases. The prioritization of donor livers has been based on objective clinical parameters: until 2006 the Child-Pugh score was used. From 2007 onwards the 'pediatric MELD-score' was instituted, a system in which every child below 12 years of age receives a MELD of 28, or more when the calculated MELD is higher. We expect that the increasing utilisation of living donors (program running since 2004) will help to relieve the problem of suitable donor organ shortage. Our data thus indicate that the relatively high mortality without OLT in The Netherlands is mainly due to late consideration and subsequent listing for OLT in our patients.

Collectively, our results offer several possibilities to improve the prognosis of patients with BA. First, an increased awareness of the susceptibility of (end-stage) BA patients for infections and sepsis should be advocated in a national protocol combined with a more aggressive preventive and therapeutic antibiotic strategy for these patients. Second, the survival of BA patients is expected to increase when they are referred early to the national transplant center, especially when it has become apparent that there is no clearance of jaundice. Close monitoring of post-surgical bilirubin levels, growth and the PELD-score should be helpful in this respect and these parameters are now included in a guideline offered by the national transplant center. Furthermore the transplant center started a 'reach-out' program, in which potential OLT candidates from the BA treatment centers are discussed at regular intervals. Third, patients listed for OLT should be transplanted within a reaso-

nable timeframe. Therefore, efforts should be made to increase the availability of donor organs and the utilisation of living donors, as the amount of patients surviving until OLT will increase. Overall, centralization of care for BA may be the most important factor in reducing pre-transplant mortality. The outcome of the Kasai procedure can be maximized in this way, which reduces the need for OLT. Second, post-surgical care and referral for OLT are optimized more easily.[32]

Our present study underlines that the prognosis of a disease with a very low prevalence can be analyzed to provide targets for improvement. Only scrutinous database efforts could reveal that even in a Western country, substantial preventable mortality exists. We feel that it is rather likely that the important lesson we learned from BA in The Netherlands bears significance for other countries where collaborations exist between (regional) pediatricians, pediatric surgeons, and a centralized care for rare diseases. Therefore, the results in this report show the importance of nationwide databases in gaining insight in possibilities to (further) increase the prognosis of patients with rare diseases. The national character and long time span largely exclude chance and regional variation. Concentration on a specific subgroup of treatment failures unveils specific characteristics of this group, what otherwise would have remained obscure.

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