Strategies to improve the outcome of biliary atresia

Vries, Willemien de

Biliary atresia in the Netherlands: outcome of 231 patients diagnosed between 1987-2008

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Willemien de Vries
Zacharias J de Langen
Henk Groen
Rene Scheenstra
Paul MJG Peeters
Jan BF Hulscher
Henkjan J Verkade
also on behalf of NeSBAR

Chapter 4

ABSTRACT

Objective

To determine the outcome of biliary atresia, and to identify prognostic factors, using a national database.

Study design

All children born between January 1987 and December 2008 who underwent Kasai surgery for biliary atresia were retrieved from the NeSBAR (Netherlands Study group on Biliary Atresia Registry) database. Outcomes were measured in terms of clearance of jaundice (bilirubin <1.17 g/dL (20 µmol/L) within 6 months post-surgery) and 4-year transplant-free survival. The cohorts 1987-1997 and 1998-2008 were compared. Survival rates were determined using Kaplan Meier, and prognostic factors using univariate and multivariate analyses.

Results

Since 1987, 214 patients underwent Kasai surgery for biliary atresia. Four-year transplant-free survival has been 46±4%, and 4-year overall survival 73±3%. Clearance of jaundice, surgery ≤60 days and post-operative antibiotic prophylaxis use were independently associated with increased transplant-free survival. The yearly case-load per center (range 0.5-2.1) was not correlated with transplant-free survival (r=0.024, p=0.73).

Conclusions

During the past 2 decades, outcome parameters have remained constant and
were comparable to those reported from other Western countries, despite a relatively low annual case-load per center. Timely surgical correction and postoperative antibiotic therapy were associated with a higher transplant-free survival rate.

INTRODUCTION

Biliary atresia is an important cause of cholestasis in infancy. It is the consequence of a destructive inflammatory process that results in fibrosis and obliteration of the biliary tract. When untreated it leads to cirrhosis-related death within one year in 50 to 80% of the patients.[163] Three types of biliary atresia can be distinguished, depending on the anatomical site of obstruction. In type I, the common bile duct is obstructed, whereas in type II, the obstruction is located at the level of the common hepatic duct. In type III, the most prevalent subtype (~90% of all cases), the entire biliary tree is obstructed including the porta hepatis.[84] Also, a syndromic form of biliary atresia has been characterized termed biliary atresia splenic malformation syndrome (BASM). In this variant, biliary atresia is associated with polysplenia or asplenia. Heterotaxy, cardiac and venous anomalies, and intestinal malrotation are also often found in BASM. The prognosis is considered worse compared to non-syndromic biliary atresia.[29,31,60]

Treatment for biliary atresia is primarily surgical, and consists of Kasai porto-enterostomy in type III, or its variants, choledochojejunostomy in type I, and hepaticojejunostomy in type II.[82] Liver transplantation (OLT) is the only therapeutic option when bile flow is not adequately restored, and liver fibrosis and cirrhosis progress with subsequent decompensation. Even when bile flow is sufficient, an ongoing inflammatory process may cause progressive fibrosis eventually necessitating liver transplantation.[127] Biliary atresia constitutes 50-75% of pediatric OLT indications throughout the Western world.[60,126,143]

Centralization of surgical treatment has been shown to increase the outcomes in England/Wales and France.[32,151] A few studies have investigated whether post-surgical administration of medicaments such as antibiotic prophylaxis, immunosuppressants and ursodeoxycholic acid (UDCA) could improve the post-surgical outcome of biliary atresia, but until now the effects have remained a matter of controversy.[17,30,135,189,204]

The outcome of biliary atresia was analyzed for the last time in The Netherlands in 1989.[68] The first aim of this study was to determine the short-term outcome of biliary atresia in The Netherlands, a country in which, as yet, treatment has not been centralized. We compared our results to those of other national studies. Secondly, we aimed to identify pre- and post-surgical prognostic factors for clearance of jaundice and transplant-free survival at the age of 4 years, including post-surgical administration of antibiotics, UDCA and high-dose prednisolone. Furthermore, we examined pre-OLT prognostic factors for the 4-year post-transplant survival, as data about biliary atresia specific prognostic factors are scarce.[25,184]

PATIENTS AND METHODS

The Netherlands Study group on Biliary Atresia Registry (NeSBAR) database is based on an ongoing joint effort of the Dutch Society for Pediatrics and the Dutch Society for Pediatric Surgeons. The registry contains the patient data of all biliary atresia patients treated in the six specialized academic centers in the Netherlands. Each center is independent and offers extensive diagnostic work-up for neonatal cholestasis, primary surgical treatment (classical portoenterostomy according to Kasai or one of its variants) and subsequent follow-up. The Kasai procedure is exclusively performed by pediatric surgeons, and in each center one senior pediatric surgeon is appointed who supervises all procedures. Pediatric OLT is concentrated in one national center, in Groningen. Within these centers, one pediatric gastroenterologist and one pediatric surgeon guarantee proper patient inclusion.

Data entry is checked annually by one researcher by reviewing patient files, surgical reports and office notes on-site.

Collected data include date of birth, sex, congenital anomalies, date of referral to a treatment center, imaging studies done, results of biopsies, preoperative laboratory values, date of surgical correction, operative report, post-operative medications, laboratory values and medication use at follow-up, date of OLT, date of last follow-up and final outcome. In each patient, the diagnosis of biliary atresia was confirmed by intraoperative cholangiography (or by impossibility to perform cholangiography due to atretic gallbladder and/or bile ducts) and by pathology of the resection specimen.

For the present study, we retrieved all biliary atresia patients born between January 1st 1987 and December 31st 2008 from the NeSBAR database. The study was performed according to the guidelines of the Medical Ethical Committee of the University Medical Center Groningen.

Medication

During the study period, a wide variety of antibiotic regimens were applied. To allow analyzing the contribution of antibiotics in general, we simplified the analysis by categorizing patients according to whether they had received postoperative antibiotic prophylaxis of any kind and duration or not. When UDCA was administered after Kasai surgery, the dosage was 20 mg/kg/day. In case of insufficient bile drainage (defined as a less than 50 percent decrease in bilirubin levels), UDCA was discontinued after 1 month to avoid potential toxic effects. When corticosteroids were administered, the following dosage regimen was used: starting with 20 mg/kg/day prednisolone at the first post-surgical day and every subsequent day a reduction of 2.5 mg/kg/day. On day 6 the dosage was tapered to 2 mg/kg/day for 5 consecutive days, then 1.5 mg/kg/day for 5 days, 1.0 mg/kg/day for 5 days and 0.5 mg/kg/day for 5 days. Corticosteroids were not administered to patients with signs of an active viral infection in the liver biopsy specimen.

Outcome parameters

The outcome was analyzed in terms of clearance of jaundice, defined as bilirubin levels below 1.17 mg/dL (or 20 µmol/L) within 6 months after surgical correction; transplant-free survival, defined as the time between birth and OLT, death or last follow-up; and overall survival. Of the transplanted patients, the 4-year post-transplant survival rates were analyzed. Pediatric End-stage Liver Disease (PELD) scores were calculated retrospectively using Dutch growth charts.[108] In order to study basic patient characteristics and evolution of treatment outcome in time, we compared the cohort 1987-1997 (Cohort A) to the cohort 1998-2008 (Cohort B). Results are presented for the study group as a whole. In case of significant differences between the 2 cohorts, these results are mentioned in the text.

Statistical analysis

The incidence of biliary atresia 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). Patient characteristics of cohort A and B were compared using Mann-Whitney U-test for continuous data, and Fisher's exact test for categorical variables. Four-year survival rates were calculated using Kaplan Meier survival analysis and expressed as calculated survival rate with 95% confidence interval. Univariate analyses were done using $\chi 2$-tests and log rank tests, multivariate

analyses were done using logistic regression analysis for clearance of jaundice and Cox's regression analyses for transplant-free survival and post-transplant survival. The proportional hazards assumption was verified graphically. The variables used in the respective multivariate models were chosen based on literature findings and on univariate analyses.[17,30,31,33,108,128,151,189,204] All variables used in the univariate analyses were subsequently used in a multivariate model. The relationship between case-load and transplant-free survival was examined using Pearson's correlation analysis.[32,146] All significance tests were 2-tailed, p-values <0.05 were considered statistically significant. Statistics was performed using PASW 18.0.

RESULTS

Patients

From January 1st 1987 until December 31st 2008, 231 infants (114 females, 49.4%) were diagnosed with biliary atresia in the Netherlands. Three patients from overseas (Dutch Antilles) had been operated on in the 'continental' Netherlands, but excluded from further analysis because the first presentation and follow-up were beyond close accessibility for analysis. The overall incidence of biliary atresia in the Netherlands was 1:18.619 live births. No patients were lost to follow-up and the median follow-up of all patients was 6.9 years (range: 0.1-21.9), of survivors 9.7 years (range: 0.5-21.9).

Four patients did not undergo surgery, in two cases because curative surgery was contraindicated as a consequence of severe cardiac anomalies, one patient died because of a severe intracranial hemorrhage due to vitamin K deficiency and one late presenting (133 days of age) patient underwent OLT without prior exploration. Ten patients underwent an explorative laparotomy without corrective surgery. In six patients corrective surgery was not performed, because in the beginning of the study period, it was presumed that OLT without prior corrective surgery might result in a better outcome.[206] Corrective surgery was not performed in two patients because the neurological outcome of a severe intracranial hemorrhage was awaited, in one case because an anomalous portal vein branched into the porta hepatis, and in one case because exploration revealed a completely cirrhotic porta hepatis. All these ten patients were subsequently assessed for OLT and primary OLT was performed in six patients.

A total of 214/231 (93%) patients underwent surgical correction and were included for further analysis. The patient characteristics of these patients are summarized in Table 1. The age at surgical correction was not significantly different in cohort A and B: 120/214 (56%) of the patients were operated on ≤60 days of age. Late surgery (≥90 days of age) was performed in 8% (18/214) of the patients. Type I biliary atresia was diagnosed less frequently in cohort B (3/104 cases) compared to cohort A (11/109, p=0.05). The case load of the treatment centers for Kasai surgery for biliary atresia ranged from 0.5 to 2.1 cases per center per year.

The transplantation rate of biliary atresia patients before the age of four increased significantly from 28/110 (27%) in cohort A to 41/104 (39%) in cohort B (p=0.04). Six patients were referred to neighboring countries for assessment and eventual OLT in cohort B, partly because of the earlier availability of living-related OLT there. These six patients were excluded from overall survival and post-transplant survival analyses. Median age at OLT in the Netherlands was 1.7 (range 0.5-4.0) years in cohort A and 0.9 (range 0.3-4.0) years in cohort B (p=0.04). In cohort B, corticosteroids were given more frequently as a postsurgical therapy compared to cohort A, 27/104 (26%) vs. 12/110 (11%;

Table 1: Characteristics of patients undergoing surgical correction for biliary atresia (BA)

		Period 1987-2008 n (%)
Number of BA patients		214
Female		104 (48.6%)
Type BA	Type I	14 (6.5%)
	Type II	27 (12.6%)
	Type III	172 (80.4%)
	Undetermined	1 (0.9%)
Anomalies	No anomalies	170 (79.4%)
	BASM	10 (4.7%)
	Other	34 (15.9%)
Median age referral		47.0 (range 1-165)
Median age surgery		59.0 (range 20-210)
Age at surgery	≤ 45 days	41 (19.1%)
	46-60 days	79 (36.9%)
	61-89 days	76 (35.5%)
	≥ 90 days	18 (8.4%)
OLT < 4 yrs		69 (32.2%)
4 year post OLT survival, OLT < 4 yrs	1987-1997	79% [95% CI 63-95]
	1998-2008	78% [95% CI 63-93]
Corticosteroids		39 (18.2%)
UDCA		67 (31.3%)
Antibiotics	All	127 (59.3%)
	Neomycin/colistin/nystatin	20 (16.0%)
	Ciprofloxacin	19 (15.2%)
	Co-trimoxazole	55 (44.8%)
	Other	31 (24.8%)

p=0.005). The number of patients receiving UDCA and/or antibiotics did not change significantly in the two cohorts. The type of antibiotics used was unknown in two patients. In the group treated with antibiotic prophylaxis, 77 out of 124 patients had at least one episode of cholangitis, whereas in the non-antibiotic prophylaxis group, 41 out of 80 patients experienced cholangitis (p=0.15). The median duration of UDCA treatment was 702 days (range: 41 days-22 years). Outcome after surgical correction Four-year transplant-free survival has been 46±4%, and 4-year overall survival 73±3%. The outcome parameters in terms of clearance of jaundice, transplant-free survival and overall survival did not change significantly between cohort A and cohort B (Table 2).

Because the outcomes did not change significantly over the two time periods, univariate analyses were performed over the whole study period.

Table 2: International data available on the outcome of biliary atresia

Country	Period	Number of patients	Median Age Kasai	Overall survival (4 year) Percentage [95% CI]	Transplant-free survival (4 year) Percentage [95% CI]	Clearance of jaundice#
England [32]	1999-2002	148	54	89% [82-94]	51% [42-59]	57%
France [151]	1997-2002	271	57	87.1% [82.6-91.6]	42.7% [35.6-49.8]	39.5%
Canada [146]	1996-2002	150	55	82% [75-88]	39% [30-47]	n.r.
Switzerland [203]	1994-2004	48	68	91.5±4.1%	37.4±7.9%	39.5%
Japan [128]	1989-1999	1381		75.3%*	59.7%*	62%**
The Netherlands	1998-2008	104	59	76% [68-85]	42% [32-52]	38%
(present study)	1987-1997	110	59.5	69% [60-78]	49% [40-59]	33%

bilirubin <20 µmol/L within 6 months post-surgery

* 5-year survival values

** defined as bilirubin <2 mg/dL (equivalent to 34.2 µmol/L)

Clearance of jaundice

Type I and II biliary atresia, postoperative administration of UDCA and administration of antibiotics were each significantly associated with a higher clearance of jaundice rate in the univariate analysis. None of the investigated variables was significantly associated with clearance of jaundice in the multivariate logistic regression model (see Table 3). Neither was clearance of jaundice associated to annual case-load (r=-0.002, p=0.97).

Transplant-free survival

The performance of surgery ≤60 days, subtype I/II biliary atresia, clearance of jaundice, and administration of antibiotics were each significantly associated with higher four-year transplant-free survival rates (univariate analysis, Table 4). Surgery performed before 45 days of life did not show further benefit on the 4-year transplant-free survival compared to surgery performed between 45 and 60 days (54±8% vs. 56±6% respectively; p=0.99, see Figure 1). The transplant-free survival of type I/II biliary atresia was significantly lower in cohort B (44±12%) compared to cohort A (71±9%; p=0.04). In cohort A, 8/24 (33%) patients with these subtypes underwent hepaticojejunostomy or choledochojejunostomy and 16 patients classical Kasai portoenterostomy. In cohort B, only 2/17 (12%) underwent hepaticojejunostomy or choledochojejunostomy and the other 15 patients classical Kasai portoenterostomy (p=0.2). The transplant-free survival of the BASM patients was not significantly different. BASM patient characteristics are shown in Table 5. The annual caseload of the treatment centers was not correlated to the transplant-free survival (r=0.024, p=0.73).

Table 3: Univariate and multivariate analysis of clearance of jaundice of biliary atresia (BA) patients born between 1987-2008

	Univariate analysis			Logistic regression analysis*		
	n	Clearance of jaundice	p-value	n	Odds ratio [95%CI]	p-value
Age at surgery						
≤ 60 days	117	39%	0.31	199	1	0.23
> 60 days	94	31%			0.7 [0.4-1.3]	
Subtype BA						
Type I/II	39	51%	0.03		1	0.19
Type III	171	32%			0.6 [0.3-1.3]	
BASM						
Yes	10	40%	0.75		1	0.99
No	198	36%			1.0 [0.3-3.9]	
Cohort						
1987-1997	108	39%	0.39		1	0.66
1998-2008	103	33%			0.9 [0.5-1.6]	
Cholangitis						
Yes	86	35%	0.56		1	0.74
No	116	40%			1.1 [0.6-2.0]	
Corticosteroids						
Yes	39	39%	0.72		1	0.11
No	172	36%			0.4 [0.1-1.2]	
Antibiotics						
Yes	125	43%	0.009		1	0.10
No	86	26%			1.8 [0.9-3.6]	
UDCA						
Yes	67	46%	0.045		1	0.09
No	144	31%			2.2 [0.9-5.4]	

n reflects the number of complete datasets available for analysis

*Odds ratio's express the likelyhood that clearance of jaundice is achieved compared to the reference category

Table 4: Univariate and multivariate analysis of transplant-free survival of biliary atresia (BA) patients born between 1987-2008

	Univariate analysis			Cox's regression analysis		
	n	4-year survival Mean [95% CI]	p-value	n	Hazard ratio [95%CI]	p-value
Age at surgery						
≤ 60 days	119	56% [46-65]	0.003	199	1	0.001
> 60 days	95	34% [25-44]			2.1 [1.4-3.1]	
Subtype BA						
Type I/II	41	60% [44-76]	0.049		1	0.23
Type III	172	42% [34-50]			0.7 [0.4-1.3]	
BASM						
Yes	10	40% [6-75]	0.57		1	0.15
No	200	46% [39-53]			0.5 [0.2-1.3]	
Cohort						
1987-1997	110	49% [40-59]	0.20		1	0.13
1998-2008	104	42% [32-52]			0.7 [0.5-1.1]	
Clearance of jaundice						
Yes	76	92% [85-98]	<0.0001		1	<0.0001
No	135	18% [12-25]			0.05 [0.02-1.2]	
Cholangitis						
Yes	118	49% [40-58]	0.46		1	0.48
No	86	47% [36-58]			1.2 [0.8-1.8]	
Corticosteroids						
Yes	39	45% [28-62]	0.88		1	0.25
No	175	46% [38-54]			0.6 [0.3-1.4]	
Antibiotics						
Yes	127	54% [45-63]	0.001		1	0.04
No	87	34% [24-44]			1.6 [1.0 -2.6]	
UDCA						
Yes	67	52% [39-65]	0.08		1	0.44
No	147	43% [35-51]			1.3 [0.7-2.6]	

n reflects the number of complete datasets available for analysis

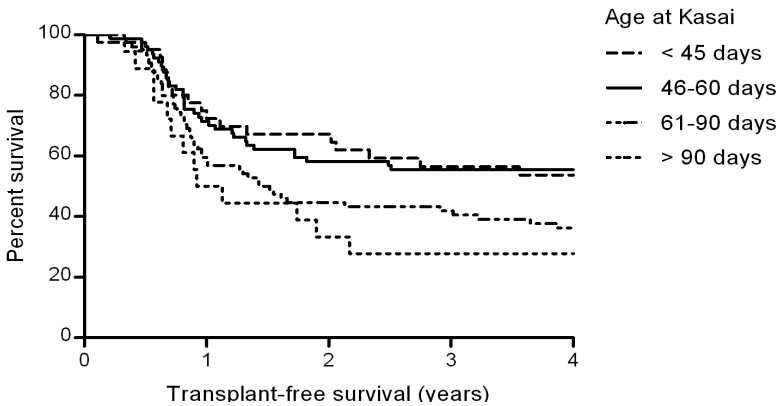

Figure 1: Transplant-free survival of biliary atresia patients according to age at Kasai surgery

The performance of surgery ≤60 days, clearance of jaundice and administration of antibi otics appeared to be associated independently with 4-year transplant-free survival in the Cox's regression analysis (Table 4).

Post-transplant survival

Full size OLT was performed in 15% (9/62) of biliary atresia patients, reduced grafts were utilized in 45% (28/62), split grafts in 21% (13/62) and living donor grafts in 5% (3/62) of biliary atresia patients. Fifteen percent (9/62) of the patients underwent early re-transplantation (within one week) because of graft dysfunction, vascular thrombosis or acute rejection, often with different graft types.

A PELD-score ≤15 at assessment was significantly associated with a better 4-year post-transplant survival of transplanted patients, whereas age ≤1 year and cohort B were not (univariate analysis, Table 6). In the multivariate model, however, none of the variables was significantly associated with 4-year survival (Table 6).

Table 5: Characteristics Biliary Atresia Splenic Malformation syndrome patients

Patient	Sex		Birth weight (gram)	Gestational age (weeks)	Age surgery (days)	Type BA	OLT	Age OLT (years)	Status (4 years follow-up)	Age death (years)
1	m	polysplenia	unknown	unknown	34	III	yes (abroad)	2.2	alive	
2	m	polysplenia, situs inversus	3200	40	46	III	yes (abroad)	2.8	alive	
3	f	asplenia, left isomerism, situs inversus, mono-atrial heart	3405	38+6	47	III			died	0.2
4	m	polysplenia, severe stenosis of pulmonary artery	3960	39+2	49	III			died	1.8
5	f	polysplenia, intestinal malrotation, Meckel's diverticulum	3450	40	54	III	yes	1.3	alive	
6	m	polysplenia, intestinal malrotation	3560	38	59	III		2.2	alive	
7	f	asplenia, intestinal malrotation, annular pancreas, Meckel's diverticulum	3420	39+3	60	III			died	0.9
8	m	polysplenia	2740	unknown	66	III		4.0	alive	
9	m	polysplenia, intestinal malrotation, anomalous hepatic vein	unknown	unknown	89	III	yes	0.5	died	0.6
10	m	polysplenia	2500	38+2	102	III	yes	0.9	died	1

Table 6: Univariate and multivariate analysis of 4-year post-OLT survival of biliary atresia patients transplanted between 1987-2008

	Univariate analysis			Cox's regression analysis		
	n	4-year survival mean [95% CI]	p-value	n	Hazard ratio [95%CI]	p-value
Age at OLT						
≤ 1 year	36	71% [56-87]	0.10	59	1	0.38
> 1 year	27	89% [76-101]			1.8 [0.5-7.1]	
PELD-score at assessment						
≤15	24	90% [78-102]	0.04		1	0.07
>15	35	69% [52-87]			0.3 [0.07-1.1]	
Cohort OLT						
1987-1997	22	77% [59-96]	0.87		1	0.52
1998-2008	41	80% [67-93]			1.5 [0.4-5.2]	

n reflects the number of complete datasets available for analysis

DISCUSSION

We analyzed the outcome of a national cohort of biliary atresia patients, with the aim to identify prognostic and potentially modifiable factors for survival. Our national results of the Netherlands are comparable to those of other Western countries (France, England and Wales) and remarkably constant over time: the transplant-free survival was similar to the previous Dutch cohort analysis.[68] It is striking that, although general health care underwent many developments, the transplant-free survival has remained that constant over the past three decades. The overall survival has increased slightly, which, most likely, can be attributed to an increased transplantation rate. This illustrates that effort needs to be put forward to improve the outcome.

The age at the time of Kasai surgery is a potentially modifiable factor which has been shown in multiple studies to correlate negatively with transplant-free survival. The current study confirms this finding with respect to surgery before or at 60 days of age in the multivariate model. We could not find an additional benefit of very early surgery (<45 days) compared to surgery between 45 and 60 days, in contrast to reports by others.[147,152] It is possible that this can be attributed to power limitations. The exact optimal timing of surgery remains to be determined, but our report indicates that all efforts should be directed to perform surgery at least before 60 days of age. Infant health care in the Netherlands is rather strictly organized, including several visits to health care professionals during the first months of life. Nevertheless, 44% of the patients is operated on after the age of 60 days which suggests that many biliary atresia patients are not recognized early. We cannot completely exclude that these late operated children had a later onset of disease, rather than a doctor's delay. However, their worse survival would rather suggest that it is mostly due to insufficient recognition of the early symptoms of neonatal cholestasis. Therefore, we argue that better information towards both infant health care professionals and parents should attempt to

increase their awareness. An updated guideline on jaundice in infants has recently been adopted in the Netherlands, which includes that the conjugated serum bilirubin fraction should be measured in any infant who is (still) jaundiced at the age of 3 weeks. An effective and discriminative approach would be the stool color card as used in Taiwan.[71,98] Furthermore, minimizing the delay between median age at referral and at surgery (now 12 days) may contribute to earlier surgery and improved transplant-free survival rates.

In the univariate analysis we found higher survival rates for those patients having biliary atresia type I or II, which has been reported by others.[31,128,151] More detailed analysis showed that the "beneficial" effect associated with these subtypes disappeared in cohort B, coinciding with a decreased utilization of the appropriate variants of Kasai's portoenterostomy. The patient numbers in the presented cohort are very small. Due to the retrospective design of the study, we cannot completely exclude incorrect subtype diagnosis or inappropriate surgical procedures. Thus, this matter should be assessed further in order to establish whether adaptation of the mode of surgery according to the subtype has an effect on the survival rates.

We did not find a significant worse survival of BASM patients, as has been demonstrated before, other studies have shown that the survival is decreased compared to isolated biliary atresia.[31,80,192] Our study contains only 10 BASM patients, producing a very large 95% confidence interval for survival. Therefore we do not draw conclusions about the survival of the BASM patient group. However, our data do demonstrate that individual BASM patients might have a favorable outcome.

Age at surgery, clearance of jaundice and antibiotic administration were each independently associated with 4-year transplant-free survival in the multivariate model. Antibiotic prophylaxis and UDCA use were the only factors significantly associated with clearance of jaundice in a univariate model. Both antibiotics and UDCA are used on a wide scale in biliary atresia patients, but the effects on postoperative outcome parameters are barely studied in biliary atresia. The beneficial effect of UDCA on biochemical parameters in biliary atresia has been shown in a prospective case-control study in 16 patients, but these were all patients with resolution of jaundice after surgery (defined as conjugated bilirubin ≤34 μmol/L), and long-term outcome measures were not studied.[204] In a randomized, double blind trial with primary biliary cirrhosis patients, a decreased risk of death or OLT requirement was observed in patients using UDCA, when compared to those using placebo.[99] Contrary effects of high-dose UDCA were found in a randomized, double blind trial with primary sclerosing cholangitis patients, where patients on UDCA had an increased development of oesophageal/gastric varices and OLT requirement compared to those using placebo.[101] In a small, double blind, randomized, placebo-controlled trial in 23 biliary atresia patients, no effect of UDCA administration was found on transplantation rate at ~14 months of age.[1] As disease mechanisms of the mentioned cholestatic diseases are poorly understood, as well as the mechanisms of action of UDCA, it is very difficult to predict whether UDCA might have beneficial or detrimental effects in biliary atresia. Since UDCA is currently used in biliary atresia patients, this matter deserves further study.

In a previous study, the post-operative administration of neomycin was shown to increase the survival. However, the control group in this study consisted solely of patients with cholangitis.[17] Comparison of a neomycin treated group to a group of biliary atresia patients regardless of cholangitis status might offer more insight in the effects of neomycin on biliary atresia patients in

general. Antibiotic prophylaxis might have a beneficial effect by reducing episodes of overt cholangitis, which are associated with a decrease in transplant-free survival.[17,189] In the presented study, the incidence of cholangitis was not lower in the patients on antibiotic prophylaxis. We speculate that low-grade infection of bile ducts, which might be a trigger for fibrosis formation, might be reduced by prophylactic antibiotic use. On the other hand, the development of microbial resistance or overgrowth of insensitive species might cause an increase of cholangitis episodes. The discrepancy with a previous study, where no effects of antibiotic prophylaxis were found, might be explained by the types of antibiotics used, the prevalence of microbial resistance in the general population and the definition of a good outcome (bilirubin <6.0 mg/dL at 2 years, vs. 4-year transplant-free survival).[159] In the present study, median treatment durations could not be analyzed, and an analysis on specific antibiotic subtypes could not be performed. Therefore, we want to emphasize that the set-up of the study does not allow drawing firm conclusions regarding the most favorable post-surgical medicamental regimen. It may be that other (unknown) factors had an effect on survival rather than the antibiotics itself. Side-effects of frequently used antibiotics include nausea, diarrhea and anorexia, which may aggravate malnutrition in biliary atresia patients. Nevertheless, the results show an interesting tendency and should evoke initiatives towards more prospective and randomized clinical research.

The regimen of high-dose prednisolone used in a subset of the patients did not show any effect on clearance of jaundice or transplant-free survival. A randomized, double-blind, placebo-controlled trial in 73 patients using low-dose prednisolone (starting dose in that study was 2 mg/kg/day, in contrast to the 20 mg/kg/day used in patients in the present study) demonstrated a reduction in bilirubin levels within the first two months post-surgery, but not in the need for OLT within six and 12 months.[30] An open labeled pilot study on 49 biliary atresia patients using methylprednisolone (starting dose of 10 mg/kg/day) failed to show beneficial effects of corticosteroids on the transplant-free survival after six months and two years. Notably, in the latter study, patients received methylprednisolone, and patients in the study and control group received UDCA (dosage 25 mg/kg/day) and antibiotic prophylaxis as well.[135] The results of a presently ongoing large trial in the United States using prednisolone in a dosage of 4 mg/kg/day for three weeks, which is subsequently tapered over 13 weeks, are awaited (www.clinicaltrials.gov).

It is not clear, to what extent pre-OLT factors such as the PELD-score can serve as prognostic factors for biliary atresia patients specifically.[25,184] The univariate analysis on 4-year post-transplant survival revealed that a PELD-score ≤15 at assessment for OLT is significantly associated with a better post-transplant survival. In the multivariate analysis, however, this was not significant. It should be realized, however, that this multivariate analysis is limited by the low number of patients that could be included. In another study, the PELD-score was not a prognostic factor for post-transplant survival in biliary atresia patients.[184] Knowledge of the pre- and post-transplant prognostic value of (among others) the PELD-score is important for OLT policies. Based on the present data we feel that proper timing of OLT is important to increase post-transplant survival, possibly including specialized post-Kasai follow-up. Recently we demonstrated that late referral to a transplant center contributed to pre-transplant mortality in biliary atresia patients.[33] In our present analysis we observed the discrepancy between relatively good transplant-free survival rates, but less favorable overall survival rates (in the low range compared to other Western countries). Much emphasis in biliary atresia literature has been rightfully placed upon the timing of Kasai surgery and short-term post-surgical variables. Our present data indicate that the importance of the medical post-Kasai

follow-up should not be underestimated with respect to overall prognosis, particularly when the follow-up is not provided by professionals involved in OLT-programmes.

Our results were achieved without efforts to centralize treatment. Case-load per centre is very low for Kasai portoenterostomy in our country. However, we do not think it can be concluded from our data that surgical caseload has no effect on transplant-free survival. Schreiber et al. found no significant effects of center size on transplant-free survival in Canada.[146] However, the largest treatment center in the latter study has still a moderate case-load (78 portoenterostomies in 10 years) compared to the large centers in France, and England and Wales. The largest center in Canada tends to perform surgery later (38% ≤60 days) than the smaller centers (48% operated on ≤60 days), which may interfere with the center-size effect. In a German study, the 2-year transplant-free survival of patients operated on in larger (≥ 5 cases) was 26.4% compared to 7.7% in the centers treating less than 5 patients annually (p=0.015).[135] The OLT rates were high in that study, 60-70% of biliary atresia patients had been transplanted after 2 years. In small countries, or large countries with a low population density, the maximum achievable caseload per center is limited. It is therefore important that the minimum caseload volumes beneficial in biliary atresia treatment are determined.

The presented results should encourage efforts to diagnose and refer biliary atresia patients in a timely manner. A beneficial effect for post-operative antibiotics and UDCA administration is suggested by retrospective analysis, but prospective data are needed for substantiation of this observation. Surgical Kasai treatment centers with a small case-load do not necessarily produce unfavorable transplant-free survival rates. Centralization of post-surgery care and follow-up may be important to improve the overall prognosis, for example by appropriate timing of the screening and listing of patients for OLT. However, the minimum beneficial case-load remains to be determined.

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