TITLE PAGE

Title:

Native liver survivors of portoenterostomy for biliary atresia with excellent outcome. Redefining "successful" portoenterostomy.

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ABSTRACT

Purpose:

Native liver survivors (NLS) after portoenterostomy (PE) for biliary atresia (BA) with normal biomarkers defined as total bilirubin (T-Bil), aspartate aminotransferase (AST)/alanine aminotransferase (ALT) for liver function (LF), cholinesterase (ChE), platelet count (PC), and absence of portal hypertension (PHT) were reviewed to redefine "successful" PE.

Methods:

92 post-PE BA patients were classified as NLS-1: normal biomarkers, PHT (-); NLS-2: at least one abnormal biomarker, PHT (-); NLS-3: normal biomarkers, PHT (+); NLS-4: abnormal biomarkers, PHT (+) and reviewed for a maximum 32 years.

Results:

As of June 2022, 55/92 (59.8%) had received liver transplants and 37/92 (40.2%) were NLS. NLS patients were classified as excellent outcome (EO): NLS-1 (n=10; 27.0%) or non-EO: NLS-2: (n=8; 21.6%), NLS-3: (n=6; 16.2%), and NLS-4: (n=13; 35.1%). Compared with non-EO, EO had PE earlier (50.5 versus 65 days; not significant; p=0.08), significantly earlier onset of symptoms (13 days versus 32 days; p=0.01) and significantly shorter jaundice-clearance (JC; 34.5 days versus 56.0 days; p<0.001). Durations of follow-up were similar: 13 years in EO, 18.5 years in NLS-2, 20 years in NLS-3, and 15 years in NLS-4.

Conclusions:

Incidence of "successful" PE or EO is low and correlated with early onset of symptoms and quicker JC.

KEYWORDS: Biliary atresia, portoenterostomy, native liver, survival, liver transplantation, excellent outcome, portal hypertension, classification

Introduction

Biliary atresia (BA) is a rare congenital disease with a reported incidence of 1 in 8,000 to 22,000 live births. Its etiology is unknown and involves progressive obliteration of extrahepatic bile ducts and cholangiopathy [1, 2]. If BA is untreated, progressive jaundice, hepatic inflammation, and fibrosis can cause cirrhosis, that is ultimately life-threatening. However, portoenterostomy (PE), first performed in Japan in 1955 [3], but not reported in English until 1968 [4] by Morio Kasai, the surgeon who developed it, gained international acceptance enabling BA patients to achieve native liver survival (NLS; defined as a BA patient surviving with their own liver after PE) for the first time. However, despite various technical refinements, enhanced pre-, intra-, and post-operative management [5, 6], use of cholagogues, steroids [7], and prophylactic antibiotics [8], that improved mid- to long-term NLS rates after PE, approximately 50% of BA patients require liver transplantation (LTx) within two years of PE [9, 10].

Most pediatric surgeons around the world would agree that a "successful" PE implies achieving jaundice clearance (JC) after PE and NLS [11, 12]. However, a considerable proportion of post-PE NLS BA patients suffer from liver dysfunction, cholangitis, thrombocytopenia, portal hypertension (PHT), and impaired quality of life (QOL) [13-17]. This apparent contradiction, where "success" is associated with morbidity, so concerned one of the co-authors (AY) that he started investigating a more practical relevant definition of success. While doing so, he noticed that there were no reports in the literature classifying NLS according to type, severity, or number of post-PE morbidities, and very few papers that focused specifically on BA patients who had done well post-PE with NLS.

In this study, "biomarkers", defined as total bilirubin (T-Bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT) to represent liver function (LF), cholinesterase (ChE), and platelet count (PC), and absence of portal hypertension (PHT) were used to classify post-PE NLS BA patients. Patients with normal biomarkers and no PHT were classified as having excellent outcome (EO). The aim of this study was to investigate the incidence of NLS BA patients after PE with EO to establish factors prognostic for EO in NLS and redefine "successful" PE.

Methods

Patient selection, perioperative management, and data collection

The medical records of 125 BA patients treated by PE at three pediatric surgical centers affiliated with Juntendo University Faculty of Medicine between January 1989 and June 2022 were reviewed retrospectively. To focus on mid- and long-term NLS, 23 patients with less than 6 years follow-up, 1 case who died from a cause unrelated to BA, and 9 patients who were lost-to-follow-up were excluded, leaving 92 patients as subjects for this study (Figure 1).

PE techniques, pre-operative management, and post-operative protocols were consistent throughout the study period from 1989-2022 in all patients, although laparoscopic PE became the preferred procedure of choice after 2009 [18]. Standard postoperative management protocols for antibiotics, choleretics, and corticosteroid administration have been published previously [19, 20].

Demographic, clinical, and laboratory data included gender, birth weight, type of BA, symptoms such as acholic stools, persistent neonatal jaundice, age at onset of symptoms, duration of symptoms, and type of PE (open or laparoscopic). Duration of symptoms was defined as the number of days from the onset of symptoms to the day of PE. Postoperative data included time taken to achieve jaundice clearance (JC; T-Bil<1.6 mg/dL), incidence of cholangitis, presence of PHT, and Pediatric End-stage Liver Disease score (PELD; for patients<12 years old) [21] or Model for End-stage Liver Disease (MELD) score (for patients≥12 years old) [22] at the latest outpatient visit.

Clinical status was evaluated using biomarkers. Normal range for each biomarker was defined as: T-Bil<1.6 mg/dL, AST <34U/L, ALT <43U/L, ChE 185-435U/L, and PC>150 $x10^3/\mu L$. Abnormal LF was defined as both AST and ALT being above normal. PHT was defined as splenomegaly and/or esophageal varices (EV) detected by diagnostic imaging using ultrasonography (US) [23], computed tomography (CT) or magnetic resonance imaging (MRI). The Spleen Index reference [24] was used. EV were evaluated endoscopically by gastroenterologists or pediatricians, and treated by endoscopic variceal ligation (EVL) when indicated.

NLS categories

Subjects were classified into 4 groups (NLS-1, NLS-2, NLS-3, and NLS-4) according to their clinical status at the last outpatient follow-up visit or within one year of data collection (June 2022). Inclusion definitions were: NLS-1; normal biomarkers, no PHT; NLS-2; at least one abnormal biomarker, no PHT; NLS-3; normal biomarkers, PHT; NLS-4; abnormal biomarkers, PHT. Only NLS-1 was considered to have excellent outcome (EO), a status equivalent to good health and well-being experienced by people in general. NLS-2, NLS-3, and NLS-4 were designated as non-EO.

Statistical analysis

Categorical variables (such as gender) were expressed as numbers and percentages, and were compared using Fisher's exact test). Continuous variables (such as age) were expressed as median and interquartile range (IQR) and were compared using the Wilcoxon rank sum test. Long-term NLS rates were analyzed with Cox regression analysis. All statistical tests were two-sided, and a $p<.05$ was considered significant. Statistical analyses were performed using GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, California USA).

Ethical approval

Since this study was conducted as a retrospective review, no informed consent was required from subjects. Institutional review board or research ethic board approval was obtained from each of the three institutes participating in this study. This study complies with the Helsinki Declaration of 1975 (revised 1983).

Results

At the time of data collection for the 92 mid- to long-term post-PE patients studied, 55/92 (59.8%) had received LTx after PE; median age at LTx was 0.8 years (range: 0.2-21.2 years, [IQR: 0.6-1.7]) and 37/92 (40.2%) were NLS. Figure 2 shows the Kaplan-Meier curve for NLS rate for all living post-PE patients who could be contacted (n=115 after excluding 9 patients lost-to follow-up and 1 death unrelated to BA). The curve declines rapidly in the first 2 years but slows down later on, with NLS rates of 52.1%, and 46.0% at 10, and 20 years after PE, respectively.

Table 1 summarizes the 37 NLS patients; 13 were male (35.1%) and 24 were female (65.9%). NLS patients by group were: NLS-1 (EO): 10/37 (27.0%), NLS-2: 8/37 (21.6%), NLS-3: 6/37 (16.2%), and NLS-4: 13/37 (35.1%). Note the incidence of EO in this series of 92 was 10/92 or 10.9%. Median follow-up duration (years) was 13.0 years (range: 6.0-32.0) for NLS-1 (EO), 18.5 years (range: 8.0-32.0) for NLS-2, 20.0 years (range: 11.0-26.0) for NLS-3, and 15.0 years (range: 6.0-24.0) for NLS-4 (p=NS, respectively). Birth weights were comparable for all NLS groups. Types of BA in this study were: Type I: (n=4; 10.8%), Type II: (n=2; 5.4%), and Type III: (n=31; 83.8%). There were no syndromic BA including BA with splenic malformation (BASM) cases in NLS indicating that all NLS were non-syndromic BA [25]. Incidence of comorbidity in NLS patients was single ventricle in NLS-2 (n=1) and

ileal atresia in NLS-3 (n=1) who had BA diagnosed incidentally during surgery for ileal atresia and had PE 4 weeks later. Presenting symptoms in NLS patients were acholic stool in 25/37 (67.6%) and persistent jaundice in the rest. Median age at onset of symptoms according to groups was: EO: 13.0 days (IQR: 6.5-21.0), NLS-2: 30.5 days (IQR: 18.5-52.8), NLS-3: 31.5 days (IQR: 17.3-45.0), and NLS-4: 41.0 days (IQR: 20.0-60.0). Despite earlier onset of symptoms in EO, differences between other NLS groups were not statistically significant (p=NS, respectively). Median age at PE was earliest in EO (50.5 days), 81.0 days in NLS-2, 54.5 days in NLS-3, and 63.0 days in NLS-4. Again, despite EO being younger at PE, differences were not statistically significant (p=NS, respectively). Mean durations of symptoms prior to PE were similar: EO (36.0 days), NLS-2 (33.5 days), NLS-3 (24.5 days) and NLS-4 (24.0 days) (p=NS, respectively). Note that duration of symptoms between EO and non-EO were similar (p=0.10). The percentage of laparoscopic PE performed in each group was similar.

The overall incidence of PHT was 51.4% (19/37) in this study, which is comparable to previous reports in the literature (33-81%, Table 5). Specifically, in NLS-3 (n=6), 5 (83.3%) had splenomegaly alone and 1 (16.7%) had splenomegaly and EV and in NLS-4 (n=13) more than half (53.8%) had both splenomegaly and EV. Despite this higher incidence, differences were not statistically significant (p=0.18). Outcome (EO versus non-EO) was compared with respect to PHT to determine if PHT may be prognostic. Median onset of symptoms of BA was significantly earlier in EO than non-EO; 13 days (IQR: 6.5-21.0) versus 32.0 days (IQR: 17.0-58.0) (p=0.01). Median time taken for JC in EO was significantly shorter than in non-EO; 34.5 days (IQR: 22.3-37.5) versus 56.0 days (IQR: 41.0-77.0) (p<0.001). JC was also achieved significantly earlier in PHT (-) compared with PHT (+); 35.5 days (IQR: 23.8-38.8) versus 57.0 days (IQR: 52.5-90.0) (p<0.001). Median age at PE was earlier in EO compared with non-EO; 50.5 days (IQR: 45.5-61.3) versus 65.0 days (IQR: 54.0-82.5). This difference was not statistically significant (p=0.08). See Table 2, Table 3. Both PELD (-9.0 versus -6.5, p=0.12) and MELD scores (6.0 versus 6.0, p=0.96) were similar for EO versus non-EO implying they are unlikely to be practical indicators when liver dysfunction is not severe. In PHT (+), all 19 patients were type III BA, however, in PHT (-), types of BA were type I (n=4), type II (n=2), and type III (n=12). As shown in Table 3, BA type was significanly different bewtween PHT (-) and PHT (+): type I and II BA was only seen in PHT(-) group, suggesting that type of BA could be etiologic for EO. Differences in PHT according to type of BA were statistically signficiant (p=0.02). In this study, 2/4 (50.0%) type I BA achieved EO, 1/2 (50.0%) of type II achieved EO, and 7/31 type III (22.6%) achieved EO. When EO was

compared with non-EO with respect to type of BA, differences were not statistically significant (p=0.54). There were no statistically significant differences between EO and non-EO for type of BA.

EO patients (n=10) are summarized in Table 4. At the time of data collection, 4 patients were over the age of 20. BA type was I in cases 5 and 10, II in case 8, and III in the cases 1, 2, 3, 4, 6, 7, and 9. All had early onset of symptoms starting within 30 days of birth. In case 9, although an acholic stool was noticed around 2 weeks after birth, the patient was only referred for assessment when jaundice and an enlarged liver were noticed during a scheduled immunization around 80 days of age. PE was performed at 95 days of age. All EO patients had good growth curves throughout their follow-up. Two were attending counselling for reasons that could not be determined from medical records but were most likely unrelated to BA or chronic illness. Case 3 had 3 episodes of post-operative cholangitis. Case 1 and case 10 had cholangitis within one year of data collection; both recovered fully with antibiotics. Only 4/10 EO patients (cases 2, 7, 8, and 9) met EO criteria for their entire postoperative course. The other 6 patients (cases 1, 3, 4, 5, 6, 10) were EO at the time of data collection. Specifically, cases 1, 4, 5, 6, and 10 changed groups for the first 7 years postoperatively because of fluctuating T-Bil, AST, and ALT levels due to cholangitis or other complications, which made them NLS-2 at times. Case 3, was diagnosed with EV, had EVL at 16 months of age with persistent mild EV on follow-up endoscopy that resolved spontaneously when 7 years old, without recurence. Thus, case 3 converted from NLS-3 to EO. All 10 EO patients have been clinically stable with only temporary setbacks.

Discussion

Many reports describe NLS in post-PE BA patients in terms of negative criteria, such as impaired liver function, presence of PHT, thrombocytopenia, or other associated morbidities [13, 15, 26], hardly ever describing NLS patients in terms of normal liver function, or absence of PHT. So, such reports merely describe NSL post-PE patients who are doing well as patients with fewer complications and less negative clinical findings. From extensive review of the literature, there would appear to be only 6 papers referring to NLS patients with EO and its incidence, although the criteria for EO varies with each paper [27-32]. Table 5 compares these 6 papers (1 to 6) with the present study. EO rates in NLS patients varied from 2%-30%. Paper 4 was the only one to calculate EO as a percentage of the total cohort during the observation period. EO rates were not mentioned in the other papers but could be calculated in all except paper 6, and varied from 1.8-11.5% which is in keeping with the 10.9

% result of this study (Table 5). Papers 2, 3, and 4 defined EO as normal liver function (T-Bil, AST, ALT, Albumin (Alb), total serum bile acid, ChE, alkaline phosphatase, prothrombin time, PC) as well as excluding complications, but either did not define PHT (paper 4) or did not mention if PHT was included specifically as a complication (papers 2 and 3). The remaining three papers, 1, 5, and 6 defined EO specifically as normal liver biochemistry with absence of PHT. Paper 1 used similar criteria to this study but did not include PC and their overall incidence of EO (EO as a percentage of total cohort) was 11/40 (27.5%) which was similar to the overall incidence in this study (27.0%) although their duration of follow-up was shorter, at 10-19 years. Paper 5 included "no late cholangitis" in addition to normal liver function and absence of PHT as criteria for EO, which were stricter than the definition for EO used in this study. Their duration of follow-up was also longer, and as a result, had 5/51 (9.8%) EO patients. The largest cohort was paper 6 with 219 NLS patients followed-up for 5-18 years. Their EO criteria, included "no medications for liver disease" and "normal health related quality of life" in addition to normal liver function, absence of PHT, and no complications, were the strictest of all, and their incidence of EO was only 4/219 (1.8%) NLS patients. The categories used in this study were chosen based on extensive evaluation of positive and negative clinical findings to best represent the clinical status of NLS patients. From these papers and the current study, EO is low, and would appear to be readily influenced by different durations of follow-up and divergent definitions that prevent direct comparison and discussion. The categories used in this study were chosen based on extensive evaluation of positive and negative clinical findings

A separate topic of interest when researching EO patients for this study was factors contributing to EO. In this study, EO was compared with non-EO. None of the other papers reported this. In this study, it was clear that early onset of symptoms and quicker JC were correlated with EO and these data were different to non-EO group results. There are several reports on correlation between early onset and prognosis, however, their implications are opposite; early onset induced worse outcomes [33-37]. The reason for this is, embryonic BA, BASM, and/or syndromic BA were included in their analyses. In the present study, these types of BA were not represented and results of this study showed that age at onset was significantly earlier. Of note is that embryonic BA, BASM, and syndromic BA have worse prognosis after PE and the 4 cases of syndromic BA identified in this study with situs inversus, polysplenia, and/or intestinal malrotation were in the LTx group and not included in NLS. In fact, it could even be suggested that there may be a subtype of non-syndromic BA who have early clinical onset after birth and achieve EO in the mid- to long-term.

Often, a concern when investigating onset of symptoms or duration of symptoms in a retrospective study is the reliability of medical records and human memory. Because the Japanese Biliary Atresia Registry (JBAR) [38] established in 1989 to collect data nationwide including onset, BA type, and age at PE, well known to pediatric surgeons, neonatologists, obstetricians, and pediatricians, and each baby's health handbook with infant stool color card screening for BA and other conditions recorded, well known to all pregnant women and mothers, were referred to when required to confirm timing and onset of symptoms and medical records in Japan are detailed, so medical records are considered to be highly reliable. In addition, at the 3 centers involved in this study, there are policies to ensure that basic data is recorded thoroughly for research purposes facilitating retrospective analysis [20]. Nevertheless, where possible, data were double checked and/or confirmed.

Quicker JC is now widely accepted as being predictive for NLS. Koga et al. [39] previously reported that when JC was achieved within 60 days of PE, NLS was as high as 80% compared with patients who acieved JC after 60 days of PE. Median time taken for JC in EO, 34.5 days was significantly shorter than 56.0 days in non-EO (p<0.001) (Table 2). So, data from the present study provides strong evidence that time taken for JC could be prognostic for NLS with EO. JC was also achieved significantly earlier in PHT (-) than PHT (+); 35.5 days versus 57.0 days (p<0.001). Note that median time taken for JC in PHT (-) for NLS-2 (36.0 days) was similar to NLS-1 (34.5 days), see Table 1. Therefore, while JC within 60 days is predictive for NLS, even quicker JC, around 35 days, may be predictive for NLS without PHT on mid- to long-term follow-up.

While reviewing NLS patients for this study, patients were noted to fluctuate between NLS-1 and NLS-2 depending on clinical cirumstances, but once classified as NLS-3 or NLS-4, there was little expectation for returning to NLS-1 or NLS-2 because PHT is essentially irreversible and once diagnosed, is unlikely to improve, especually if it has persisted for several years, although one EO case did just this after spontaneous resolution of EV. Hadžić et al. [30] reported 3/16 patients who underwent post-PE liver biopsy during a median period of 36 months (range: 36-72 months; no IQR reported) and showed no evidence of fibrosis. Another report from Finland [40] showed 36% of post PE patients had disappearance of collagen and alpha-smooth muscle actin at examination, a median of 3 years after surgery associated with reduced progression of fibrosis, collagen accumulation, and platelet-derived growth factor RNA expression. Taken together, liver fibrosis does appear to undergo postoperative remodelling in selected cases with spontaneous resolution of PHT. As demonstrated by case 3 in this study, further research on such patients is required to establish facors contributing to resolution of PHT.

In conclusion, the systematic classification developed for this study revealed that the incidence of EO patients in BA patients after PE was 10.9% and 27.0% in NLS patients. Early onset of symptoms and early JC would seem to be associated with EO. EO should be considered as "successful" PE.

Figure Legends

Fig. 1 Patient selection

125 BA patients who had PE from January 1989 to June 2022 were identified for this study. 92 patients were enrolled as the study cohort as mid- to long-term post-PE patients. At the time of data collection (June, 2022) 55 patients had been transplanted and 37 were NLS.

BA: biliary atresia, PE: portoenterostomy, NLS: native liver survival.

Fig. 2 Kaplan-Meier analysis of native liver survival

The survival curve includes 23 patients followed-up for less than 6 years, totaling 115 post-PE patients; only 9 patients lost to follow-up and 1 death unrelated to BA were excluded. The curve declines rapidly in the first 2 years. NLS survival rates were 52.1% at 10 years and 46.0% at 20 years after PE.

PE: portoenterostomy, BA: biliary atresia, NLS: native liver survival.

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Fig. 1 Patient selection

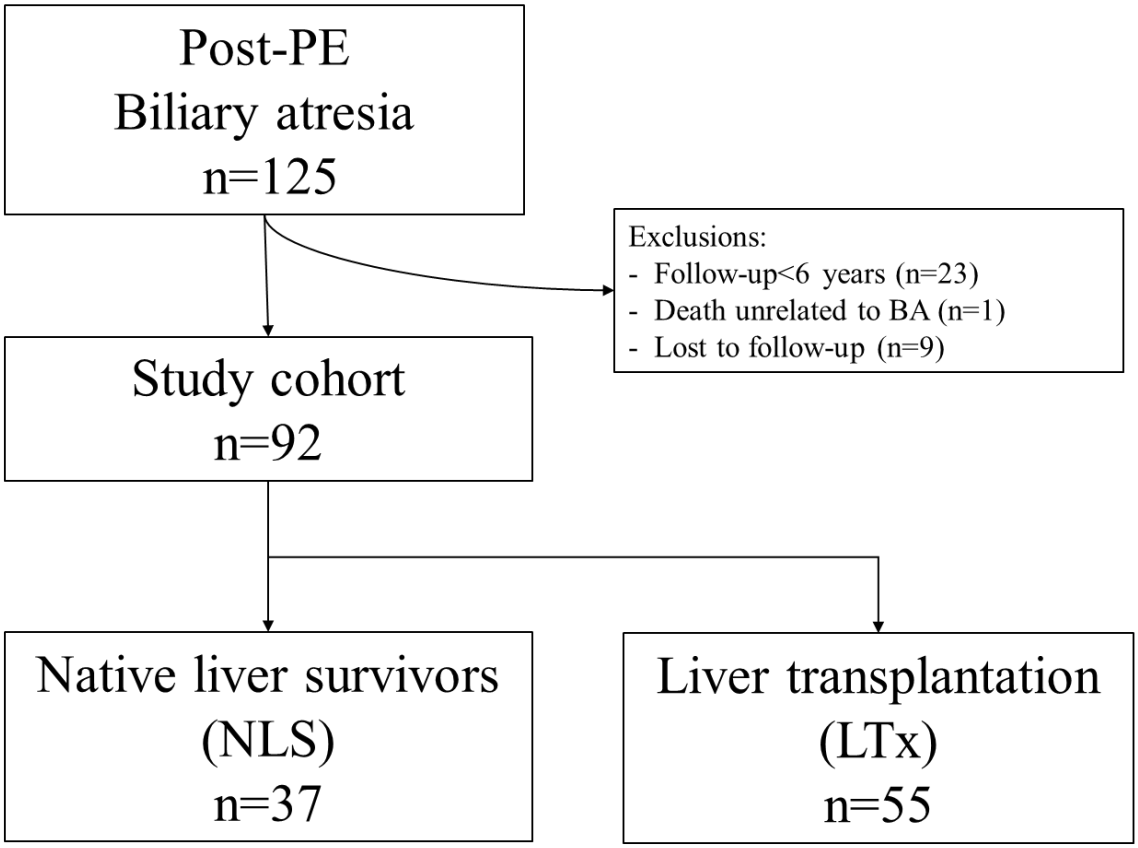

Fig. 2 Kaplan-Meier analysis of native liver survival

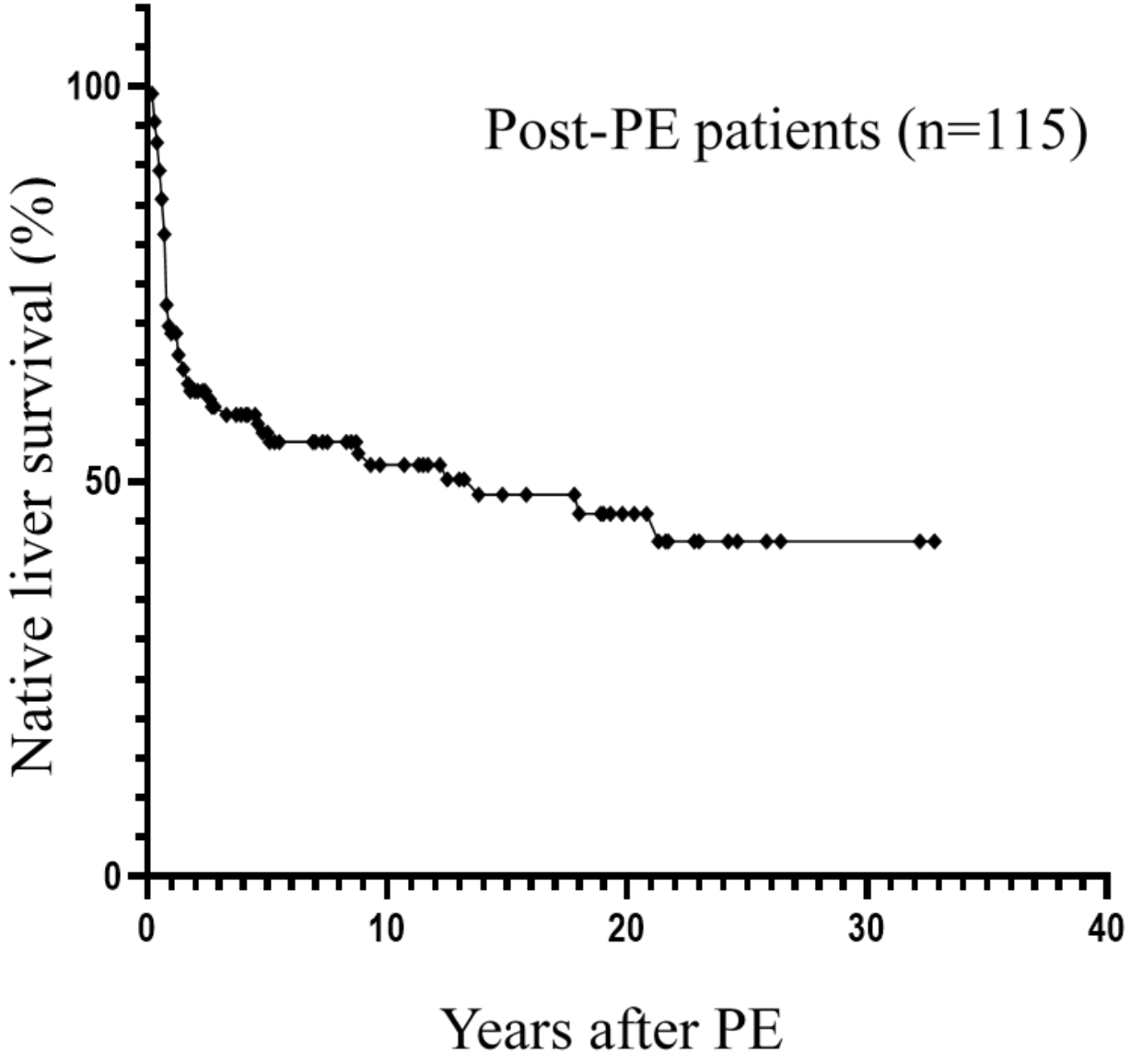

Table 1 Summary of native liver survivors (NLS; n=37)

	Total	EO	non-EO		
		NLS-1	NLS-2	NLS-3	NLS-4
NLS patients, n (%)	37 (100.0)	10 (27.0)	8 (21.6)	6 (16.2)	13 (35.1)
NLS in total cohort (%) (n=92)	40.2% (37/92)	10.9% (10/92)	8.7% (8/92)	6.5% (6/92)	14.1% (13/92)
Median duration of follow-up, years [range]	17.0 [6.0-32.0]	13.0 [6.0-32.0]	18.5 [8.0-32.0]	20.0 [11.0-26.0]	15.0 [6.0-24.0]
Age at the time of data collection, n (%)					
6-10	8 (21.6)	3	3	0	2
11-15	10 (27.0)	3	0	2	5
16-20	7 (18.9)	1	3	1	2
21-25	9 (24.3)	2	1	2	4
>26	3 (8.1)	1	1	1	0
Gender, n (%)					
Male	13 (35.1)	2	4	2	5
Female	24 (64.9)	8	4	4	8
Type of biliary atresia, n (%)					
I	4 (10.8)	2	2	0	0
II	2 (5.4)	1	1	0	0
III	31 (83.8)	7	5	6	13
Comorbidity, n (%)					
Yes	2 (5.4)	0	1[a]	1[b]	0
No	35 (94.6)	10	7	5	13
Median birth weight, grams [IQR]	2910 [2530-3170]	2940 [2700-3170]	2920 [2490-3190]	2730 [2500-3060]	2950 [2690-3140]
Initial symptoms, n (%)					
Pale stool	25 (67.6)	8	5	3	9
Jaundice	10 (27.0)	2	3	2	3
Other	2 (5.4)	0	0	1[b]	1[c]
Median onset of symptoms, days [IQR]	27.0 [13.0-48.0]	13.0 [6.5-21.0]	30.5 [18.5-52.8]	31.5 [17.3-45.0]	41.0 [20.0-60.0]
Median age at portoenterostomy, days [IQR]	62.0 [50.0-82.0]	50.5 [45.5-61.3]	81.0 [68.8-87.8]	54.5 [47.3-61.8]	63.0 [54.0-82.0]
Median duration of symptoms, days [IQR]	28.0 [23.0-41.0]	36.0 [29.0-51.0]	33.5 [7.0-62.3]	24.5 [19.3-27.5]	24.0 [15.0-32.0]
Surgical technique, n (%)					
Open portoenterostomy	29 (78.4)	7	7	5	10
Laparoscopic portoenterostomy	8 (21.6)	3	1	1	3
Median time taken for JC, days [IQR]	45.0 [35.0-61.0]	34.5 [22.3-37.5]	36.0 [28.0-41.0]	59.0 [50.0-89.0]	57.0 [53.0-82.0]
Portal hypertension, n (%)					
Splenomegaly	11 (29.7)	-	-	5	6
EV	0 (0)	-	-	0	0
Splenomegaly+EV	8 (36.3)	-	-	1	7
Cholangitis within one year, n (%)					
Yes	4 (10.8)	2	0	1	1
No	33 (89.2)	8	8	5	12

a: single ventricle b: ileal atresia c: hemorrhage

EO excellent outcome, *NLS* native liver survival, *BASM* biliary atresia associated splenic malformation, *IQR* interquartile range, *JC* jaundice clearance, *EV* esophageal varices

Table 2 Summary of EO versus non-EO patients

	EO	non-EO	
	NLS-1	NLS-2, NLS-3, NLS-4	*p*
Number of cases, n (%)	10 (27.0)	27 (73.0)	-
Duration of follow-up, years [range]	13.0 [6.0-32.0]	18.0 [6-32.0]	0.45
Male, n (%)	2 (20.0)	11 (40.7)	0.44
Type of biliary atresia, n (%)			0.54
I	2 (20.0)	2 (7.4)	
II	1 (10.0)	1 (3.7)	
III	7 (70.0)	24 (88.9)	
Comorbidity, n (%)	0 (0.0)	2 (7.4) Single ventricle Ileal atresia	1.00
Median birth weight, grams [IQR]	2940 [2700-3170]	2910 [2530-3170]	0.51
Median onset of symptoms, days [IQR]	13.0 [6.5-21.0]	32.0 [17.0-58.0]	0.01
Median age at PE, days [IQR]	50.5 [45.5-61.3]	65.0 [54.0-82.5]	0.08
Median duration of symptoms, days [IQR]	36.0 [29.0-51.0]	26.0 [18.0-36.0]	0.10
Laparoscopic PE, n (%)	3 (30.0)	5 (18.5)	0.66
Median time taken for JC, days [IQR]	34.5 [22.3-37.5]	56.0 [41.0-77.0]	<0.001
Cholangitis within one year, n (%)	2 (20.0)	2 (7.4)	0.29
PELD score (<12 years old) [IQR]	-9.0 [-9.3 - -1.8]	-6.5 [-9.0 - -3.5]	0.12
MELD score (≧12 years old) [IQR]	6.0 [6.0-7.5]	6.0 [6.0-7.0]	0.96

EO excellent outcome, *NLS* native liver survivors, *IQR* interquartile range, *PE* portoenterostomy, *JC* jaundice clearance, *PELD* Pediatric End-stage Liver Disease, *MELD* Model for End-stage Liver Disease

Table 3 Summary of patients according to portal hypertension. PHT (-) (NLS-1=EO, NLS-2) versus PHT (+) (NLS-3, NLS-4)

	PHT-	PHT+	
	NLS-1=EO, NLS-2	**NLS-3, NLS-4**	***p***
Number of cases, n (%)	18 (48.6)	19 (51.3)	-
Duration of follow-up, years [range]	16.0 [6.0-32.0]	17.0 [6.0-26.0]	0.62
Male, n (%)	6 (33.3)	7 (36.8)	0.99
Type of biliary atresia, n (%)			0.02
I	4 (22.2)	0 (0.0)	
II	2 (11.1)	0 (0.0)	
III	12 (66.7)	19 (100.0)	
Median birth weight, grams [IQR]	2920 [2570-3170]	2850 [2610-3140]	0.59
Median onset of symptoms, days [IQR]	19.0 [9.0-30.0]	36.0 [17.0- 58.0]	0.10
Median age at portoenterostomy, days [IQR]	63.5 [48.5-82.8]	57.0 [53.0-76.0]	0.83
Median time taken for JC, days [IQR]	35.5 [23.8-38.8]	57.0 [52.5-90.0]	<0.001

PHT portal hypertension, *EO* excellent outcome, *NLS* native liver survivor, *IQR* interquartile range, *JC* jaundice clearance

Table 4 Summary of excellent outcome (EO) cases (n=10)

Case	Gender	Follow-up years	Type of BA	Prenatal diagnosis	Symptom onset (days)	Age at PE (days)	JC (days)	Growth failure	Post-op cholangitis	Schooling Employment	Biomarker data					NOTES
											T-Bil (mg/dL)	PC (10^3/μL)	AST (U/L)	ALT (U/L)	ChE (U/L)	
1	Female	32	III	None	8	26	36	None	1	College graduate Employed full-time	0.56	317	34	23	360	AST/ALT occasionally high (NLS-2).
2	Female	22	III	None	11	50	14	None	0	Employed full-time	0.91	269	14	13	322	NLS-1 throughout the study period.
3	Female	21	III	None	30	62	26	None	4	Full-time student	1.55	207	19	13	384	EVL at 16 months, followed-up until 7 years old Latest endoscopy shows no EV. At least 4 episodes of cholangitis until 6 years old
4	Male	20	III	None	22	45	39	None	NA	Full-time student	0.26	187	32	16	286	Stable throughout the study period.
5	Female	14	I	CBD	6	51	38	None	1	Full-time student	0.30	369	18	8	343	Cholangitis 1 month after PE.
6	Female	12	III	None	6	59	42	None	2	Occasional truancy	0.48	213	23	24	314	Psychological counseling. 2 episodes of cholangitis before 5 years old
7	Male	11	III	None	30	87	21	None	0	Occasional truancy	0.94	213	51	31	266	Admitted on day 83 of life PE on day 87 of life. Psychological counseling.
8	Female	8	II	CBD	4	37	33	None	0	Full-time student	0.40	276	28	24	362	Original prenatal diagnosis was ovarian cyst. No jaundice/acholic stools until day 20 of life.
9	Female	7	III	None	15	95	36	None	0	Full-time student	0.35	332	39	24	484	Parents noted acholic stools from 2nd week of life. Massive liver and jaundice diagnosed on day 80 of life.
10	Female	6	I	CBD	18	46	19	None	1	Full-time student	0.82	375	42	36	388	Fluctuated between NLS-1 and NLS-2 for first 2 years.

EO excellent outcome, *BA* biliary atresia, *PE* portoenterostomy, *Post-op* postoperative, *T-Bil* total bilirubin, *PC* platelet count, *ChE* cholinesterase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *NLS* native liver survival, *EVL* endoscopic variceal ligation, *EV* esophageal varices, *NA* not applicable, *CBD* congenital biliary dilatation

Table 5 Papers about post-PE native liver survivor BA patients with excellent outcome (including the present study)

Paper	Year Author Country	Duration of follow-up (years)	NLS cases (n)	EO in NLS%	EO in total cohort%	Biomarkers	PHT definition	PHT in NLS%	Reported complications	Definition of EO	Reported prognostic factors for EO
1	1990 Laurent France	10-19	40	27.5% (11/40)	9.0% (11/122)	T-Bil, AST, ALT, ALP, γGTP, Alb, PT	Hepatomegaly, Splenomegaly, EV	72.5%	GI bleeding	"Normal liver function tests and absence of PHT"	None
2	1993 Toyosaka Japan	11-29	20	30.0% (6/20)	7.9% (6/76)	T-Bil, AST, ALT, Alb, TBA, ChE, ALP	Low WBC and/or PC Presence of EV	47.6%	Intestinal ulcer (bleeding) Biliary re-obstruction Pulmonary arteriovenous shunt	"Normal liver function without complications"	None
3	1997 Shimizu Japan	21-26	6	16.7% (1/6)	2.6% (1/39)	T-Bil, ALT	Low WBC and/or PC Splenomegaly, EV	33.3%	Cholangitis Hypersplenism, EV	"No sequelae, normal liver function"	None
4	2003 Hadžić UK	10-22	NA	NA	11.5% (28/244)	T-Bil, AST, Alb, PT, PC	Not clearly defined	NA	Cholangitis GI bleeding	"Absence of surgical complications, unremarkable clinical examination"	None
5	2005 Lykavieris France	20-35	51	9.8% (5/51)	1.8% (5/271)	T-Bil, AST, ALT, γGTP	Splenomegaly, EV	69.8%	Cholangitis Gall stones	"Normal biomarkers, no PHT, and no late cholangitis"	None
6	2014 Ng USA Canada	5-18	219	1.8% (4/219)	NA	T-Bil, AST, ALT, Alb, γGTP, PT, PC	Low PC Clinical splenomegaly Ascites and/or EV Hepatopulmonary syndrome	81.3%	Cholangitis Bone fracture Ascites Variceal hemorrhage	“Ideal outcomes defined as the presence of: (1) normal liver biochemical tests (2) absence of complications of CLD (3) not receiving medications for liver disease (4) normal health related quality of life"	None
Present study	2022 Tsuboi Japan	6-32	37	27.0% (10/37)	10.9% (10/92)	T-Bil, AST, ALT, ChE, PC	Splenomegaly and/or EV	51.3%	Cholangitis	Normal liver biomarkers and no PHT	Early onset Quicker JC

NLS native liver survival, *EO* excellent outcome, *PHT* portal hypertension, *T-bil* total bilirubin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *γGTP* gamma-glutamyl transferase, *Alb* albumin, *PT* prothrombin time, *EV* esophageal varices, *GI* gastrointestinal, *TBA* total serum bile acid, *ChE* cholinesterase, *WBC* white blood cell count, *PC* platelet count, *UK* United Kingdom, *NA* not applicable, *USA* United States of America, *CLD* chronic liver disease, *JC* jaundice clearance