

Long-term effects of Kasai portoenterostomy for biliary atresia

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Abstract

The prospective study enrolled 144 patients after surgical treatment of biliary atresia in early infancy. We analyze the immediate effectiveness of the surgery and the age-related structure of complications in the up to 16-year follow-up. The immediate 2-year survival rate after the surgery constituted 49.5%. At the time of this writing, 17 of the patients have celebrated their 10th birthdays with good quality of life and no indications for LT. The obtained results underscore the critical importance of surgical correction of BA by Kasai surgery during the first 60 days of life and subsequent dynamic follow-up of the patients for the purpose of the early detection and timely correction of possible complications.

Key words: biliary atresia, Kasai portoenterostomy, cholangitis, portal hypertension, bile ducts dilatations, native liver survival.

Introduction

Till the mid 20th century biliary atresia (BA) was lethal [1, 2]. Surgical correction of this defect by portoenterostomy was introduced in 1952 by Prof. Morio Kasai. The operation includes resection of fibrotic lesions in the portal area and re-establishment of the physical connection of the liver with the intestine by a Roux loop anastomosis resulting in restoration of the bile flow to the intestine [3]. This operation is considered as a maintenance treatment for the majority of BA cases. It prolongs the native liver survival in preparation for the liver transplantation (LT). Current estimations of 5-year survival rates for BA patients with native

liver are 30–70% [4-Error! Reference source not found.. In most cases, Kasai surgery is a palliative treatment for children with BA that prolongs life with the native liver and it is an important step in preparing for liver transplantation. Notably, in some patients, the Kasai procedure alone can provide a good functional state of the liver for more than 20 years, and the longest to date follow-up of a native liver survivor with minimal liver symptoms is over 60 years [6]. At the same time, direct connection of intrahepatic bile ducts with the intestine greatly increases the risks of cholangitis, which is observed in 45–87% of the patients [4]. Other complications arising in the follow-up include portal hypertension, biliary cysts, and hepatopulmonary syndrome [1, 4, 7].

BA is the most common indication for LT in children. According to a multi-center study involving 1911 patients at 39 clinics in North America in 2011–2018, BA patients constitute 38.5% of the liver transplant recipients under the age of 18 [8].

The study is aimed at evaluation of functional condition of the liver, rates of survival as a function of the age at surgery, and the age-related structure of complications in the follow-up of Kasai surgery.

Materials and methods

144 infants diagnosed with BA, including 61 boys (42.4%) and 83 girls (57.6%), weighing 3.24 ± 0.53 kg at birth [min 1.50; max 4.25] were enrolled in the prospective study; 13 of the patients were born prematurely (at 34–36 wGA). The patients underwent Kasai surgery in 2000–2020 at the age of 79.4 ± 21.5 days of life [min 27; max 138]. The in-patient treatment started under the age of 3 months for all patients. Upon the admission, all patients manifested jaundice, colorless stools, and the increased hepatic and splenic volumes. The BA diagnosis was confirmed by a standard complex examination for all cases [8].

The open Kasai procedure with anti-reflux was performed for 34 (23.6%) of the patients, whereas 63 (43.8%) of the patients were operated laparoscopically and 47 (32.6%) of the patients were operated through a minilaparotomy incision.

During the postoperative period, all patients received multimodal analgesia, infusion therapy with partial parenteral nutrition, ursodeoxycholic acid, antibacterial and symptomatic therapies, and glucocorticoid therapy in accordance with the established guidelines [9][10].

The postoperative in-patient care lasted 24.8 ± 11 days [min 9; max 69].

The immediate effectiveness of the surgery was determined by coloration of stools, jaundice reduction and decreased bilirubin levels.

The follow-up encompassed:

1. Evaluation of functional condition of the liver (cholestatic syndrome manifestations, increased transaminase levels, and indicators of synthetic activity of the liver) with relation to age;
2. Analysis of immediate or delayed complications (postoperative complications, bacterial cholangitis, bile ducts dilatation, portal hypertension, hepatopulmonary syndrome) with relation to age;
3. Survival study.

Cholangitis was diagnosed on the basis of febrile fever symptoms, elevated serum levels for the markers of systemic inflammation (C-reactive protein, procalcitonin), alterations in ESR, WBC counts and WBC differential, in combination with varying degree of clinical and biochemical manifestations of cholestatic syndrome, increased transaminases, and reduced synthetic function of the liver.

Portal hypertension was determined on the basis of impaired blood flow in the portal system (umbilical vein recanalization, ascites, enlarged spleen, and the altered volume rate of portal blood flow) as revealed by Doppler ultrasound examination, esophageal varices, and hematological indicators of hypersplenism (thrombocytopenia, anemia, leukopenia).

The follow-up duration varied from 6 months to 16 years.

The data were processed in StatSoftStatistica 10 (StatSoft Inc., Tulsa, OK, USA) and Microsoft Excel 2016 software. Numerical variables were described by mean and standard deviation values (mean \pm SD). Categorical variables were described by absolute numbers and frequencies of the events. Univariate comparisons for two dependent groups were made by non-parametric Wilcoxon test. Bilateral Fisher's exact test was applied for the comparison of frequencies between the groups. The survival was described by Kaplan-Meier curves. The differences were considered statistically significant at $p < 0.05$.

The study protocol was reviewed and approved by the Local Ethics Committee of the Pirogov Russian State Medical University (Protocol No.2002/18 from Sept 02 2002); the study was conducted in accordance with the Declaration of Helsinki. All participants (children's parents) provided written informed consent.

Results

1. Restoration of the liver function

Age of the patients at Kasai surgery constituted 79.4 ± 21.5 days. The majority of patients (77, corresponding to 53%) were operated at the age of 61–90 days. Of the rest, 32 infants (22%)

were operated at younger age (< 60 days of life) and 36 infants (25%) were operated at > 90 days of life.

During the postoperative in-patient care, serious complications were developed by 7 patients (4.9%). One patient had duodenal perforation on day 4 post-operation (p/o), and two patients had colon perforations on days 3 and 7 p/o; these patients were re-operated for the management. One patient had adhesive intestinal obstruction treated surgically on day 15 p/o. Gastrointestinal bleedings in three other patients were treated conservatively. One patient died of colon perforation on day 12 p/o.

The effectiveness of surgical intervention (as assessed by coloration of stools, jaundice reduction, and a decrease in bilirubin levels in the early postoperative period) constituted 89.5% (128 patients). For 16 patients (11.1%) the operation was ineffective.

In the patients with ineffective surgery (n = 16), the stools remained acholic, the jaundice persisted, the biochemical markers of cholestasis and transaminase increased, and the indicators of synthetic function of the liver decreased. The situation eventually led to biliary cirrhosis with lethal outcomes for 2 patients (1.7%) at the age of 5 and 7 months. Twelve patients with ineffective Kasai surgery received liver transplants at the age of 7.8 ± 2.5 months.

In 128 patients who benefited from the surgery (89.5% of the total sample), the coloration of stools occurred on day 4.36 ± 4.32 p/o. Although for the majority of patients in this group the colored stools were primarily observed on days 3–4 p/o, in few cases the coloration occurred on day 1 p/o. In 2 patients, the coloration primarily occurred on days 30 and 34 p/o. During the postoperative in-patient care, the jaundice was attenuated in 90 patients and totally suppressed in 28 patients.

Furthermore, in 122 patients (95.3% of 128 patients who benefited from the surgery) bilirubin levels were reduced from 172.62 ± 63.7 to 93.6 ± 63.2 $\mu\text{mol/L}$, while in 6 patients both total and direct bilirubin levels were reduced to normal values (Table 1). A rapid reduction in GGT activity to normal levels was observed in 16 patients, while the majority experienced an increase in the GGT activity during postoperative period, despite the reduction in bilirubin levels, coloration of stools, and mitigation of jaundice. These changes were statistically significant (Table 1). A transient increase in the activity of transaminases observed in the majority of patients (92.5%) during the early postoperative period (Table 1) may be considered as a physiological response to inhalational anesthetics, somnoleptics, myorelaxants, and antibacterials (as the liver is basically involved in their metabolization) and is definitely not a poor prognostic factor. No significant changes in the plasma cholesterol levels of the patients were observed during the postoperative in-patient care (Table 1).

Table 1. Blood test indicators before and after the surgery (only the patients with effective surgical correction of BA included, $n = 128$).

Indicators	Before surgery $\bar{x} \pm s$ [min; max]	After surgery $\bar{x} \pm s$ [min; max]	Wilcoxon test results
GGT U/L	634±347 [398; 1805]	989±496 [96; 2134]	p < 0.05
ALT U/L	137±94 [70; 286]	266±179 [81; 663]	p > 0.05
AST U/L	236±99 [142; 339]	253±118 [74; 447]	p > 0.05
Bilirubin total μmol/L	211±67 [123; 418]	93±58 [5; 342]	p < 0.05
Bilirubin direct μmol/L	108±46 [77; 244]	58±42 [1; 202]	p < 0.05
Cholesterol mmol/L	5.5±1.6 [1.4; 11.6]	5.5±2.2 [1.7; 15.1]	p > 0.05
Fibrinogen, g/L	2.5±0.6 [1.3; 4.2]	2.3±0.7 [1.3; 4.7]	p > 0.05
PI, %	90±12 [77; 120]	96±18 [50; 140]	p < 0.05
Albumin g/L	38±5 [28; 47]	37±5 [27; 51]	p > 0.05
Cholinesterase U/L	6262±1989 [2509; 11776]	5123±1634 [2391; 11129]	p > 0.05

In the early postoperative period, plasma indicators of synthetic function of the liver (albumin, fibrinogen, and cholinesterase) remained within the reference range for all patients. A moderately but significantly decreased prothrombin index (PI) observed in 18 patients as a consequence of vitamin K deficiency was corrected by menadione sodium bisulfite administration.

No significant alterations in the size of liver or spleen in the early postoperative period were revealed by ultrasound examination ($p > 0.05$). Minor signs of portal hypertension manifested as moderate ascites and umbilical vein recanalization were revealed in 8 patients and resolved on their own.

Upon the leave from the hospital and by the end of the first year of life, the positive effect was maintained in 98 patients. The remaining 30 patients with the pronounced positive effect in the early postoperative period eventually developed colorless stools and the signs of liver cirrhosis. The age-related dynamics of the liver function indicators evaluated with the exclusion of liver transplant recipients is given in Table 2.

By the age of 1 year, total bilirubin was reduced to normal levels in 25 patients with effective Kasai surgery (constituting $11.8 \pm 2.3 \mu\text{mol/L}$). In 73 patients, bilirubin was still elevated ($98.4 \pm 33.6 \mu\text{mol/L}$) but significantly and stably reduced as compared with the initial levels before the surgery. By the age of 2–3 years, bilirubin levels were reduced to normal values in all patients with effective Kasai procedure (Table 2).

Table 2. Age-dependent dynamics of the native liver function indicators in the follow-up of Kasai surgery (the values are given as $\bar{x} \pm s$ [min; max]).

Age, years	n	GGT U/L	ALT U/L	AST U/L	Bilirubin total $\mu\text{mol/L}$	Bilirubin direct $\mu\text{mol/L}$
1	98	148 ± 95 [36; 327]	136 ± 99 [16; 381]	107 ± 62 [39; 376]	58 ± 99 [9; 381]	33 ± 65 [1; 251]
2	61	166 ± 175 [8; 1275]	131 ± 101 [15; 371]	111 ± 66 [39; 377]	61 ± 114 [6; 401]	35 ± 49 [1; 229]
3	51	121 ± 88 [8; 288]	82 ± 68 [18; 239]	94 ± 57 [33; 198]	20 ± 11 [7; 45]	9 ± 12 [2; 39]
5	31	93 ± 99 [9; 388]	45 ± 43 [17; 152]	51 ± 36 [4; 144]	14 ± 7 [5; 31]	4 ± 2 [1; 11]
10	19	139 ± 120 [15; 398]	46 ± 36 [20; 97]	55 ± 31 [22; 233]	14 ± 8 [6; 38]	5 ± 3 [2; 13]
>10	17	74 ± 86 [16; 147]	22 ± 4 [19; 25]	35 ± 6 [30; 45]	19 ± 6 [14; 28]	8 ± 1 [3; 10]

By the age of 1 year, the activity of GGT was reduced to normal values in 22 patients. In 76 patients, it was still elevated but reduced significantly as compared with the initial level. By the age of 3 years, 86% of the patients had normal GGT levels. Several cases of persistence of the elevated GGT levels should be noted (up to 412.3 U/mL, Table 2), although such patients had normal levels of bilirubin and other cholestasis markers, and showed no indications for LT.

By the age of 1 year, the activity of ALT was reduced to a normal value (17 U/L) in 1 patient only. For the rest, it constituted 109.12 ± 84.65 U/L. The activity of AST was elevated in all 1-year old patients (105.17 ± 59.2 U/L, Table 2). By the age of 4 years, 65% of the patients had normal levels of transaminase activity. However, the moderate elevation of ALT/AST activity persisted in 14% of the patients for at least 3–5 years after the surgery.

Thus, the majority of BA patients with effective Kasai surgery showed normal bilirubin levels by the age of 1 year, while the reduction in the activity of GGT, ALT and AST took much longer, and the elevated blood plasma levels for these enzymes typically persisted (for > 5 years in some patients).

2. Complications

The age-related structure of complications is shown in Figure 1.

Bacterial cholangitides and portal hypertension occurred most typically. Cystic dilatation of intrahepatic bile ducts was less common. One patient developed hepatopulmonary syndrome used as an indication for LT at the age of 3 years.

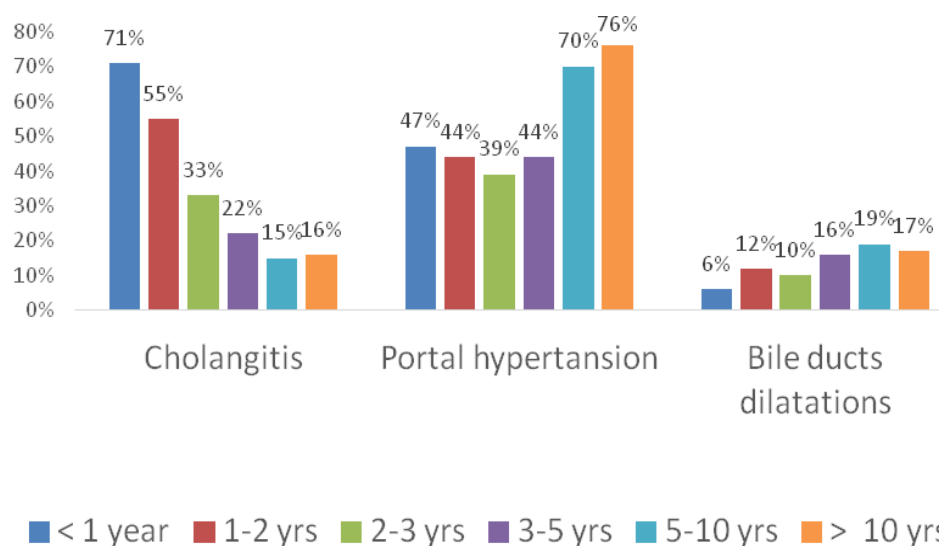


Figure 1. Age-related structure of complications observed in BA patients after Kasai surgery (percent values reflect the proportion of patients affected by the condition, not the number of episodes).

2.1. Cholangitides

During the 1st year after surgery, 102 of 143 patients (71%), regardless of the effectiveness of the surgical intervention, had at least a single episode of cholangitis which required the in-patient treatment with intravenous administration of antibacterials (Figure 1). Seven patients with recurrent cholangitides were re-operated for the antireflux valve insertion, which was effective. In 19 patients with effective Kasai surgery, the recurrent cholangitides promoted the onset of liver cirrhosis, which served as an indication for LT performed at the age of 9–14 months.

During the 2nd year of life, 54 of 98 patients (55%) had episode(s) of cholangitis requiring the in-patient antibacterial therapy (Figure 1). Two of the patients underwent the antireflux valve

insertion at the age of 18 and 19 months. In 24 patients, cholangitis led to biliary cirrhosis; these patients received liver transplants at the age of 18–28 months.

During the 3rd year of life, acute cholangitis was diagnosed in 20 patients (33%, Figure 1). Three of those developed weak signs of systemic inflammatory reaction, but acholic stools were observed in none of the cases. The episodes were successfully resolved by oral administration of antibacterials on the out-patient basis.

During the 4th and 5th years of life, cholangitis was diagnosed in 11 patients (22%, Figure 1). For the age groups of 5–10 and >10 years, the occurrence constituted 15% and 16%, respectively. In the latter group, only 2 patients had single episodes of hepatocellular dysfunction with portal hypertension at the age of 12 and 14 years (despite the ongoing observation and maintenance therapy), which served as indications for LT.

2.2. Portal hypertension

During the 1st year after surgery, 67 of 143 patients (47%) were diagnosed with portal hypertension (PH, Figure 1). Of those, 26 patients (38.8%) showed minimal signs of umbilical vein recanalization and 20 patients (29.9%) developed ascites. It should be noted that recanalization of umbilical vein frequently clears on its own during infancy — in 24 patients it was transient and cleared by the age of 1.5 years. Esophageal varices (EV) were identified in 22 patients (32.8% of PH cases, including 10 cases of EV grade I, 8 cases of EV grade II, 3 cases of EV grade III, and 1 case of EV grade IV). Seven patients underwent EV sclerotherapy and 6 patients had EV bleeding episodes during the first year. Hypersplenism with thrombocytopenia was identified in 7 cases (10.4%), one of them also with the signs of anemia. One patient with well-preserved liver function developed a therapy-resistant ascites and received LT at the age of 11 months. One patient had gastrointestinal bleeding with lethal outcome at the age of 7.5 months.

During the 2nd year of life, 43 patients (44%, Figure 1) manifested the signs of PH including recanalized umbilical vein (rUV, 5 cases, 11.6% of PH cases), ascites (4 cases, 9.3%), and/or EV (14 cases, 32.6%, including 2 cases of EV grade I, 7 cases of EV grade II, and 1 case of EV grade III). Three patients had EV bleedings and received sclerotherapy. Hypersplenism was observed in 18 cases (41.9% of PH cases), with the related splenic thrombocytopenia in 14 cases and a combination of thrombocytopenia and anemia in 5 cases.

Two patients, 1.5 and 2.5 year old, diagnosed with EV grade III–IV with high risks of bleeding, received a small-diameter splenorenal shunt, which ensured partial drainage of the blood from portal circulation into the vena cava inferior. This intervention mitigated the severity of EV to grade I–II.

During the 3rd year of life, 24 patients (39%, Figure 1) manifested the signs of PH including rUV (5 cases, 20.8% of PH cases), ascites (2 cases, 8.3%), and/or EV grade I–III (15 cases, 62.5%, including 7 cases of EV grade I, 6 cases of EV grade II, and 2 cases of EV grade III). Three EV patients received sclerotherapy. Two patients had esophageal bleedings, the conservative treatment of which was successful. The signs of hypersplenism were observed in 7 cases (29.2%), the related splenic thrombocytopenia was identified in 8 cases (33.3%) and splenic thrombocytopenia combined with anemia was identified in 2 cases of PH (8.3%).

During the 4th and 5th years of life, 20 patients (44%, Figure 1) manifested the signs of PH including rUV (11 cases, 55% of PH cases), EV (16 cases, 80%, including 8 cases of EV grade I, 5 cases of EV grade II, and 3 cases of EV grade III) and/or thrombocytopenia (9 cases, 45%).

Among the 5–10 year olds, 22 patients (70%, Figure 1) manifested signs of PH including both EV (22 cases, 100% of PH cases, including 8 cases of EV grade I, 8 cases of EV grade II, and 4 cases of EV grade III) and rUV (22 cases, 100%). Three of the patients had EV bleedings, and one patient received sclerotherapy. The majority of patients also had hypersplenism with thrombocytopenia (20 cases, 91%).

At the age of > 10 years, 13 of 17 patients (76%, Figure 1) manifested signs of PH including rUV in 12 cases (92.3% of PH cases), EV in 13 cases (100%, including EV grade I in 5 cases, EV grade II in 5 cases, and EV grade III in 3 cases), hypersplenism with thrombocytopenia in 13 cases (100%), and hypersplenism with thrombocytopenia combined with anemia in 10 cases (76.9%). Two of the patients had EV bleedings, and one patient received sclerotherapy.

2.3. Intrahepatic bile duct dilatations

Intrahepatic bile duct (iHBD) dilatations were revealed in 9 patients during the 1st year after surgery (6.2%), in 10 patients during the 2nd year of life (12.2%), and in 6 patients during the 3rd year of life (9.8%, Figure 1). The majority of cases represented moderate iHBD dilatations (0.5–4.5 mm), and no signs of biliary obstruction were observed. Three patients with iHBD dilatations of 30–40 mm and highly recurrent cholangitides were re-operated for applying cystoenteroanastomosis on the basis of the existing Roux loop. The interventions were successful and prevented further growth of the iHBD cysts as revealed by dynamic ultrasound examinations.

In patients aged > 3 years, moderate iHBD dilatations (1.5–2 mm) were observed with no signs of biliary obstruction or any other indications for the surgery (Figure 1). The dilatations were revealed in 8 patients aged 3–5 years (15.7%), 6 patients aged 5–10 years (19.4%), and 3 patients aged > 10 years (17.6%). It should be noted that, by contrast with biliary cirrhosis, none of the observed iHBD dilatations interfered with synthetic function of the liver, and this

condition can be generally interpreted as a consequence of the partial biliary obstruction prior to the portoenterostomy and in association with it.

3. Survival study

Of all participants, 89.5% survived till the age of 5 months. In the native liver (non-LT) subgroup, survival rates for 1-, 2-, 3-, 5-, 10-, and over 13-year period constituted, respectively, 72.9, 49.5, 45.5, 40.6, 34.6, and 28.7% (Figure 2).

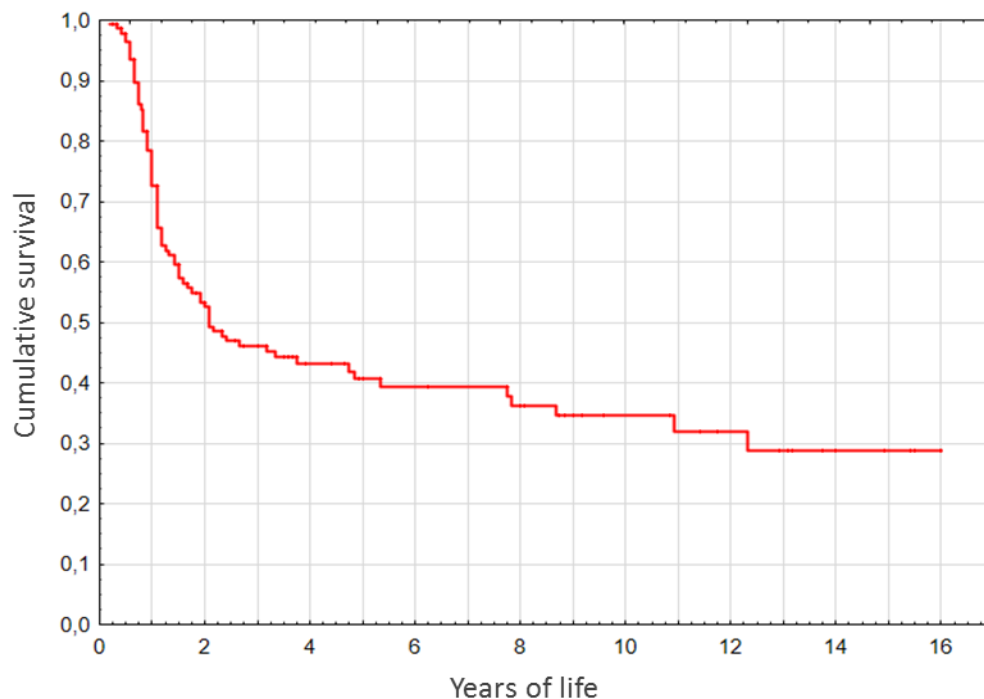


Figure 2. Survival with native liver (non-LT subgroup) after Kasai surgery.

For the native liver (non-LT) subgroup stratified by the age at Kasai surgery, survival rates for the patients operated at the age under 60 days were higher. Of those differences, however, only the difference in 2-year survival rates was significant ($p < 0.05$, Figure 3). It should be noted that survival rates for the < 1 year-olds showed no correlation with the age at Kasai surgery (Figure 3).

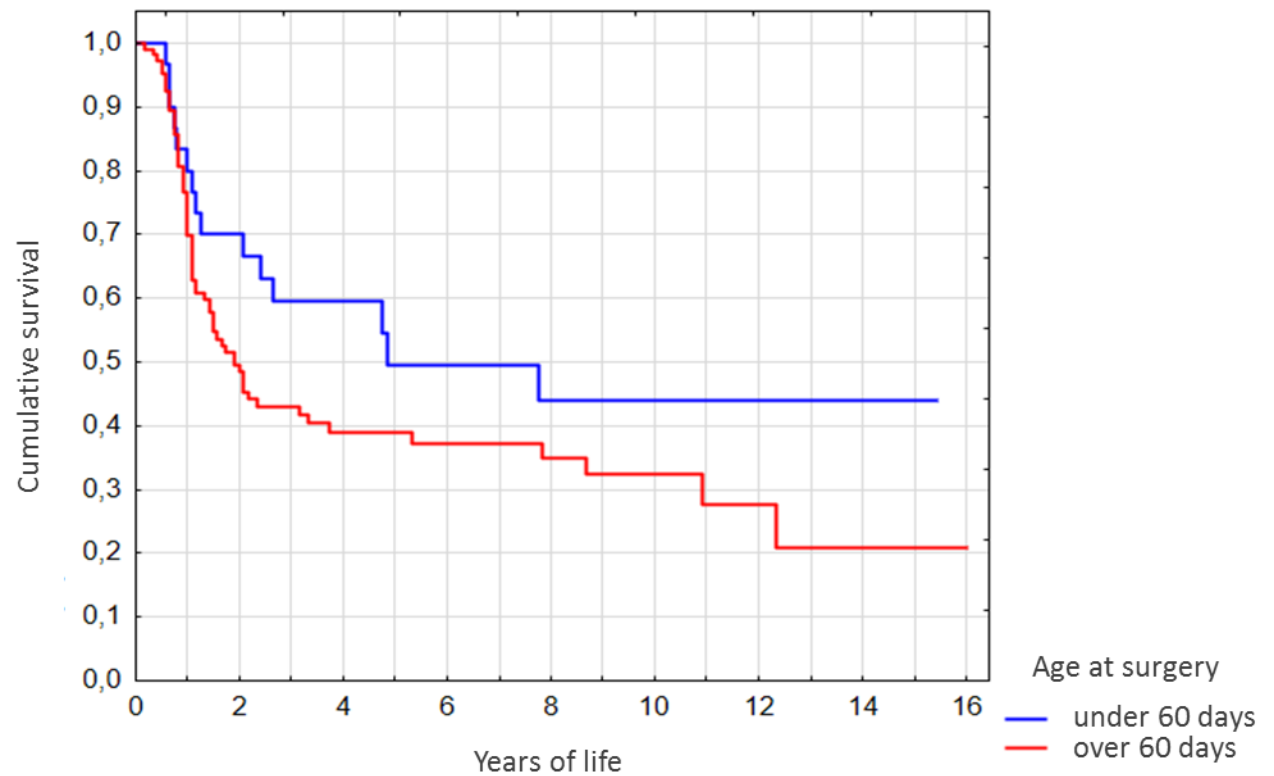


Figure 3. Survival curves for the non-LT subgroup stratified by the age at Kasai surgery.

Advanced stratification of the sample by the age at Kasai surgery (Figure 4) revealed a similar pattern. By years 2 and 3 after the surgery, survival among the patients operated at the age under 60 days was significantly higher as compared with the patients operated at 60–90 days of life ($p = 0.03$ and $p = 0.04$, respectively, Figure 4), and no significant differences were observed for other age groups.

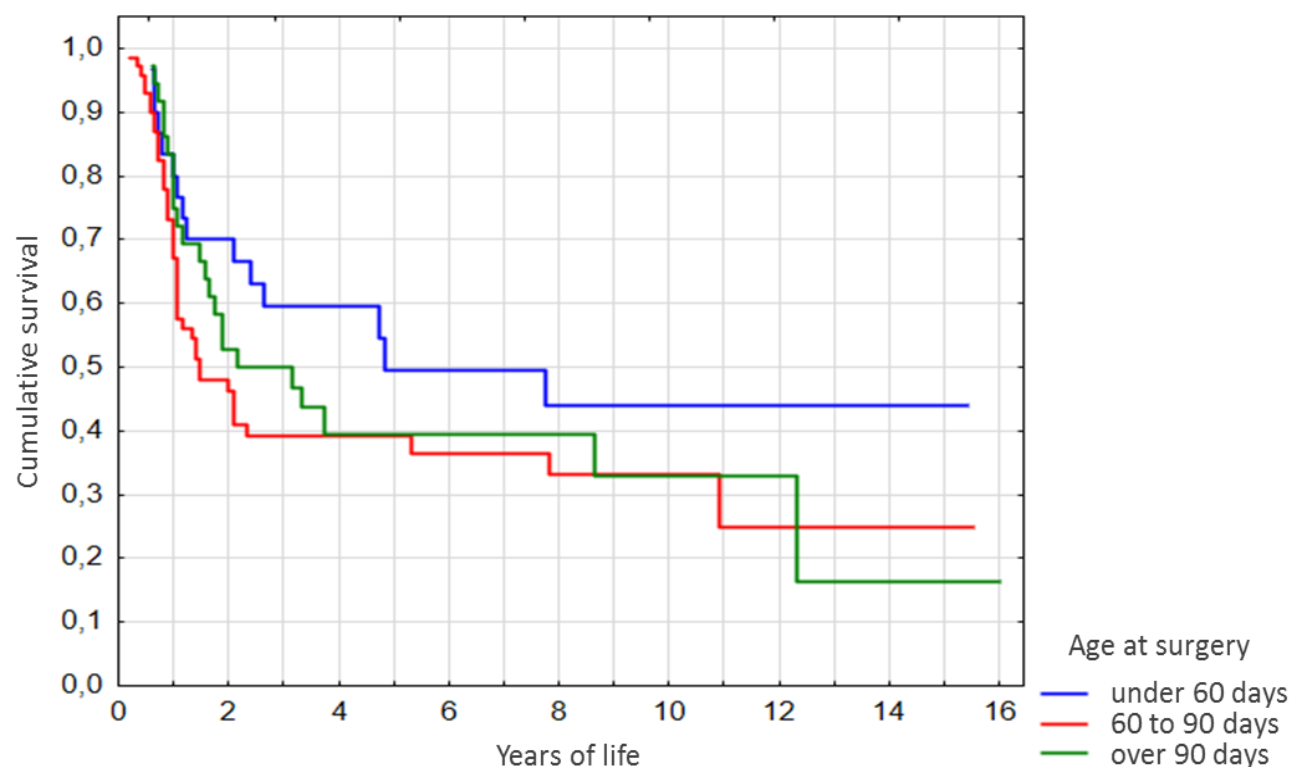


Figure 4. Survival curves for the non-LT subgroup with advanced stratification by the age at Kasai surgery.

Discussion

We investigated the effectiveness of Kasai surgery as revealed by postoperative resolution of BA symptoms, age-related complications, and survival rates. The effectiveness of Kasai surgery assessed in the early postoperative period was 89.5%. According to several representative studies, the effectiveness of Kasai surgery generally varies within the range of 50–95% **Error! Reference source not found.** In some studies, the effectiveness is assessed by a decrease of bilirubin levels to 2 mg/dL (34.2 μ mol/L), which renders the effectiveness of 40% on average **Error! Reference source not found.**

In our experience, Kasai surgery, when effective, caused coloration of the stools within 4–8 days p/o. Mitigation of the jaundice and reduction in bilirubin levels progressed gradually and took much longer. The increased activity of GGT and transaminases in the early postoperative period was observed in the majority of patients with effective Kasai surgery (as compared to the values before the surgery). In our opinion, this may reflect the compensatory reaction of the body to the surgical intervention *per se*, as well as to the use of potentially hepatotoxic pharmaceuticals (anesthetics, antibacterials, etc.). In the follow-up, the GGT/ALT/AST activities gradually decreased. Their long-term dynamics may be relevant. As demonstrated by Ihn *et al.*,

high plasma levels of GGT (above 500 U/L, persisting for at least 5 months and accompanied by jaundice) represent a poor prognostic factor which significantly shortens the native liver life expectancy **Error! Reference source not found.** At the same time, Noor *et al.* revealed no correlation of the total bilirubin levels and GGT/ALT activities in postoperative period with the native liver life expectancy [18]. According to our experience, in 86% of the patients with effective Kasai surgery, GGT levels decreased slowly and reached the reference range by the age of 3 years only. At the same time, in 89% of the patients, the majority of them having elevated GGT levels, bilirubin decreased to normal levels by the end of the first year. In the remaining 11% of the patients, bilirubin decreased to normal levels by the age of 2–3 years. In a longer follow-up, none of the > 4 year-olds had bilirubin levels > 58 $\mu\text{mol/L}$ even during the episodes of cholangitis. By contrast with bilirubin, transaminase levels were reduced to normal values in only 65% of the 4 year-old patients, while 14% of the patients showed moderate elevation of transaminase levels for up to 5 years (and in few cases even longer). It should be noted that in such cases transaminase levels show no age-related dynamics and apparently have no prognostic significance.

The observed correlation of the native liver survival rates with the age at surgery is consistent with the literary data on this subject [11, 13, 16, 19]. For instance, Wang *et al.* have demonstrated that Kasai surgery at the age under 81 days significantly increases the native liver life expectancy as compared with the patients operated at later age [13]. In a large-scale multicenter study carried out in France with the enrollment of 1044 patients during 1986–2009 period, the 5-, 10-, and 20-year native liver survival rates constituted 40%, 36%, and 30%, respectively **Error! Reference source not found.** In a study by Liu *et al.* (2017) the survival constituted 84% and 71% for 1 year and 2 years of life, respectively **Error! Reference source not found.** Nio *et al.* (2012) reported a 20-year survival of 33% **Error! Reference source not found.** Some published observations of the native liver survival encompass 26 years [21] and 40 years [6], and most remarkably over 60 years **Error! Reference source not found. Error! Reference source not found.** after Kasai surgery.

The predominant complications in the follow-up were recurrent cholangitides and portal hypertension. Of the total sample of operated BA patients (independently of the surgery effectiveness), 71% suffered at least a single episode of cholangitis during the first year after surgery. The observed age-related decrease in the frequency and severity of cholangitides is consistent with the literary data. As shown by Lee *et al.*, 51.5% of the episodes arise during the initial 180 days p/o, followed by 21.6% between days 180–365 p/o, 11.3% between months 12 and 18 p/o, and 15.5% between months 18 and 24 p/o. Despite the diversity of possible mechanisms, the most common cause of cholangitis in the follow-up of Kasai surgery is the

ascending infection from small intestine via the portoenteroanastomosis [22, 23]. It is believed that the expanding bacterial flora suppresses the albumin synthesis and promotes the accumulation of ammonia which additionally facilitates the bacterial expansion. Cystic dilatations of intrahepatic bile ducts are also favorable for the inflammation. Besides, retention of bile in the dilated ducts and small cysts favors the formation of microconcrements which may damage the biliary tree and trigger the dormant inflammatory reaction. High intraluminal pressure of the small intestine may also contribute to cholestasis, growth of pathogenic microflora, and, ultimately, the ascending cholangitis **Error! Reference source not found.** Plausible contribution of direct surgical side effects e.g. ischemic lesions in the stitching area and inflammatory response from the biliary tract **Error! Reference source not found.** should be mentioned as well, especially since we observed the cholangitides in the early postoperative period not only in the cases of effective Kasai surgery, but also in the cases of ineffective surgery when the persistent paleness of stools in the postoperative period indicated the lack of communication between the biliary system and the intestine. As reported by Selvalingam *et al.*, the probability of cholangitides in the early postoperative period also depends on the diameter of bile ducts within the operative field: smaller diameters (< 150 µm) correlate with higher frequencies of cholangitides **Error! Reference source not found.**

Portal hypertension (PH) of diverse pathophysiology (from the moderate splenomegaly and umbilical vein recanalization, which minimally affected the life quality, to the ascites and severe esophageal varices) was manifested by 47% of the patients during their first year after the surgery. Later on, the occurrence of PH increased, reaching 76% after the age of 10 years. The primary cause of PH is hepatic fibrosis, which develops before the operation and subsequently becomes aggravated by recurrent cholangitides. According to the reported evidence, portal hypertension in the follow-up of Kasai surgery occurs in 37–70% of the patients **Error! Reference source not found.** **Error! Reference source not found.** Importantly, for the patients with effective Kasai surgery, even the clinically evident PH was not considered as an indication for the emergency liver transplantation, as the varices were subject to scheduled surgical correction, thrombocytopenia was not accompanied by hemorrhages, and no indications for blood transfusion were encountered. Apparently, PH is a primary consequence of the fibrotic alteration of hepatic tissues within the portal area. Therefore, PH episodes are inherent for BA, and can only be mitigated (not completely resolved) by a successful Kasai surgery. Strictly speaking, PH should be considered as an echo of deteriorating changes that would rapidly progress in the absence of timely surgical intervention (and this point is consistent with our observations for the cases of ineffective surgery). However, a detailed discussion of this issue is beyond the scope of this study.

Conclusion

The results of this study support the view of Kasai surgery as a crucial maintenance measure for BA patients, which is also the essential precondition of native liver survival. The immediate 2-year survival rate after the surgery constituted 49.5%. At the time of this writing, 17 of the patients have celebrated their 10th birthdays with good quality of life and no indications for LT. For less successful outcomes, the Kasai procedure still allows to delay LT for at least few months, considering that LT effectiveness largely depends on the age and satisfactory physiological condition of the patient.

The most common complications in the follow-up are recurrent cholangitides ultimately leading to liver cirrhosis. The risks of developing cholangitides are high during the first 3 years of life and decrease with the patient's age. The risks of portal hypertension, by contrast, increase with the patient's age; however, in the majority of cases this complication has no critical influence on the functional condition of the liver, and it is not an indication for LT.

The obtained results underscore the critical importance of surgical correction of BA by Kasai surgery during the first 60 days of life and subsequent dynamic follow-up of the patients for the purpose of the early detection and timely correction of possible complications.

Declarations

Ethics approval and consent to participate: The study protocol was reviewed and approved by the Ethics Committee of the Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology; the study was conducted in accordance with the Declaration of Helsinki (Protocol No.2002/18 from Sept 02 2002). All participants (children's parents) provided written informed consent.

Consent for publication: Not applicable.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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