Short- and long-term outcomes after Kasai operation for type III biliary atresia: Twenty years of experience in a single tertiary Egyptian center-A retrospective cohort study

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ABSTRACT

Objectives: Kasai portoenterostomy (KPE) is the treatment of choice for the fatal devastating infantile type III biliary atresia (BA). The study aimed to analyze short- and long-term outcomes after this procedure and their predictors in a tertiary center. Methods: We retrospectively analyzed 410 infants who underwent KPE for type III BA in the period from February 2000 to December 2019. The overall male/female ratio was 186/224. Results: The early (>6 months) complications involved 187 (45.6%) of our infants with a higher incidence of early cholangitis that affected 108 (26.3%) of them. The jaundice clearance at the 6th post-operative month that reached 138 (33.7%) of them had an independent correlation with mild portal tract ductal and/or ductular proliferation, using postoperative steroids therapy, and absence of early postoperative cholangitis. The early infant mortality that affected 70 (17.1%) of our patients was mostly from sepsis. On the other hand, late (<6 months) patients complications and mortalities affected 256 (62.4%) and 240 (58.5%) of patients respectively; moreover, liver failure and sepsis were the most frequent causes of late mortalities in non-transplanted and transplanted cases respectively. Lastly, the long-term (20-year) native liver survival (NLS) that reached 91 (22.2%) of patients had an independent correlation with age at operation ≤90 days, higher preoperative mean serum Alb, portal tract fibrosis grades F0 and F1, absence of intraoperative bleeding, absence of post-operative cholangitis, the occurrence of jaundice clearance at the 6th postoperative month and absence of post-operative portal hypertension (PHN). Conclusions: Sepsis had a direct effect on early and late patient mortalities after Kasai operation for type III BA; moreover, patient age at operation <90 days, higher fibrosis grades, the occurrence of postoperative cholangitis and PHN, and persistence of post-operative jaundice had negative insult on long-term postoperative outcome. So, it is crucial to modulate these factors for a better outcome.

1. Introduction

Biliary atresia (BA) is a neonatal progressive destructive fibroobliterative cholangiopathy of extra- and intra-hepatic biliary system with fatal outcome in the 1st 2 years of life if left untreated due to the resulting liver cirrhosis, portal hypertension (PHN), end-stage liver disease (ESLD) and liver failure [1-5]. Despite being a disease of unknown origin; viral infection, ductal plate malformations, genetic predisposition, and abnormal bile acid metabolism are possible causes [6]; while, immunologic, inflammatory, infectious, and obstructive pathways are possible theories of pathogenesis [7]. Moreover, type III BA that is characterized by biliary obstruction at the level of the porta hepatitis is the most common type (<90%) with the worst prognosis [8,9].

However, early detection of this serious disease is fundamental for early surgery and better prognosis [10]. Timely Kasai portoenterostomy (KPE) by resecting the whole atretic part of the extrahepatic biliary tree and creating an anastomosis between a Roux-en-Y limb of the jejunum and the portal plate at porta hepatitis remains the gold standard, first and the mainline of treatment of this devastating disease aiming to facilitate bile flow, clear jaundice and delay liver consequences leading to improved outcome [1,2].
Despite their improvement in the recent decades; jaundice clearance and long-term (20-year) native liver survival (NLS) after KPE are still in the wide ranges of 29–82% [8,11–17] and 14–44% [2,13,18–21] of patients respectively, while the remaining patients with the poor outcome will need liver transplantation (LT) despite its associated limited donor availability, difficulties, morbidity, and mortality or they will die from liver failure [16,17,22–25]; so it is crucial to modulate factors affecting those early and/or late outcomes after KPE to improve them aiming to delay or reduce the need for LT [13].

These factors can be classified into pre-/intra-operative factors (i.e. age at surgery, surgical center and surgeon experience, liver fibrosis degree, presence and size of bile ductules at the portal plate, associated anomalies, anatomical type of BA, international normalization ratio (INR), etc) as well as postoperative parameters (i.e. using a steroid, antibiotic and/or ursodeoxycholic acid (UDCA), jaundice clearance, the occurrence of cholangitis/PHN, intrahepatic biliary cyst formation, etc) [8–10,26–28]. Finally, as there is scanty literature on the long-term (20-year) outcome and its predictors after KPE for type III BA, our work aimed to analyze this important issue besides analyzing short-term outcome and its predictors in a tertiary Egyptian hepatopancreato-biliary (HPB) center.

1.1. Patients and methods

Four hundred fifty patients underwent KPE for type III BA in the period from February 2000 to the end of 2019 in the department of HPB surgery and pediatric hepatology departments where written informed consents regarding surgeries and researches were obtained from the parents/guardians. Our work has been reported in line with the STROCSS criteria.

The recorded data included pediatric patients demographics, type of BA (Non-cystic III or cystic III), associated congenital anomalies (biliary atresia splenic malformation (BASM), cardiac or other anomalies), the onset of neonatal jaundice (since or after birth), preoperative labs (i.e. LFTs, INR, CBC, etc), preoperative abdominal US findings (hepatomegaly, splenomegaly, abnormal gallbladder (atrophic, non-contrastive or absent), hepatic subcapsular flow, and the presence or absence of triangular cord (TC) sign). Preoperative PHN was identified by the presence of thrombocytopenia (platelets >150 K/μL) associated with splenomegaly on US ± gastroesophageal (GO) varices [32]. Intra-operative liver biopsy and biopsy of the excised atretic biliary tree findings, operative bleeding, blood, and plasma transfusion, operative time and postoperative hospital stay, post-operative medications, patient short- and long-term outcomes, and lastly follow up data. BA was diagnosed clinically (persistent jaundice, dark urine, clay stool, etc), biochemically (liver function tests (LFT), etc), by imaging (the abdominal ultrasonography (US), hepatobiliary iminodiacetic acid (HIDA) scan, etc), by duodenal intubation and measurement of intraluminal bile, pathologically (preoperative liver biopsy findings) and confirmed by operative exploration, intra-operative cholangiography (IOC) that was done whenever possible; Fig. 1(a,b,c) and by operative liver biopsy and biliary remnant pathologic findings. The macroscopic classification of BA was based on the Japanese society of pediatric surgeons (JSPS) classification where Non-cystic type III BA and cystic type III meant occlusion at the level of the porta-hepatis without and with the presence of cyst at the liver hilum respectively; Figs. 1(b), 2 and Fig. 1(c)
respectively [8,20,33] (see Fig. 3).

The surgical technique: Under general anesthesia by the anesthetic author of the manuscript, it was induced by inhalation of 100% oxygen and 8% sevoflurane until loss of consciousness occurred, then concentration of sevoflurane was decreased to 4%, then fentanyl 1 µg/kg and rocuronium 0.9 mg/kg were administered to facilitate oral tracheal intubation, then anesthesia was maintained by 50% oxygen/air and sevoflurane. Surgery was performed by qualified HPB surgeons who used identical techniques. In brief; a small incision in the right upper abdomen was done, then after its entry; the abdomen was grossly inspected to identify any associated anomalies. In many cases, the diagnosis of BA was confirmed by visual inspection of the liver that appeared cholestatic or fibrotic with absent, fibrotic, or atrophic gallbladder; figure [3]. However, if a normal gallbladder or hilar cyst appeared, cholangiography was performed through them to confirm the diagnosis; figure [1]. Once BA was confirmed and without liver mobilization; the gallbladder remnant was dissected from the liver bed and followed to the junction with the common hepatic duct(CHD), then the fibrous cord representing the distal common bile duct(CBD) remnant was dissected, isolated, and divided, allowing further dissection of the biliary remnant up to the portal vein (PV) bifurcation, then the dissected tissue was transected at this level of the portal plate with either a knife or sharp micro-scissor; Fig. 4, then KPE reconstruction was completed between the transected fibrous portal plate at the liver hilum and 35–50 cm Roux-en-Y jejunal limb using 5–0 or 6–0 polydioxanone(PDS) sutures, allowing drainage of bile from the small ductules located within the portal plate; Fig. 5. Lastly, a tube drain was put in the right upper quadrant (RUQ) and a wedge liver biopsy was taken before abdominal closure [2,34].

The histopathology of the liver biopsy and the biliary remnants included the followings: 1- Portal tract ductal and/or ductular proliferation that was classified according to a semi-quantitative scoring system [35] into mild (presence of 5–9 bile ducts per portal tract), moderate (≥10 bile ducts per portal tract) and marked proliferation (≥10 bile ducts per portal tract with elongated, attenuated and angulated ducts) 2- Portal tract fibrosis that was graded according to Metavero fibrosis score [36] into F0 (no fibrosis), F1 (fibrous portal expansion), F2 (few bridges or septa) F3 (numerous bridges or septa) and F4 (cirrhosis) 3- Presence of macrophages or giant cells in portal tracts 4- The presence of remnant ducts at the porta-hepatis and their size(< or > 150 µm).

Our protocol of postoperative medical and nutritional management of all patients was nearly the same during the study period and included: 1- Prophylactic antibiotics in the form of I.V. 3rd generation cephalosporin + metronidazole till the 6th postoperative day then oral cotrimoxazole for 6 months 2- Ursodeoxycholic acid (10–15 mg/kg divided into 3 doses); a choleretic drug that was given with the beginning of oral...
intake for 3 months 3- Lipid, and lipid-soluble vitamins given for 3 months 0.4- According to the treating physician’s preference, some patients were given post operative steroids (oral prednisolone 2 mg/kg/day from day 5 to day 21, then 1 mg/kg/day from day 22 to day 28) [37]. Liver biopsy result, The post-KPE outcome of patients: It was classified into 1- Short-term (<6 months) morbidities and mortalities (N.

B cholangitis was known by fever accompanied by elevated serum bilirubin (<2.5 mg/dL), leukocytosis, and stool color change [38], however, PHN was identified as mentioned before [32], 2- Jaundice clearance at the 6th-month post-operatively and its predictors, as well as the overall survival, a P-value of <0.05 was significant [29, 30].

The Kaplan-Meier method was used for survival analysis to assess the long-term NLS and its predictors as well as the overall survival, a P-value of <0.05 was significant [29, 30].

2. Results

2.1. The characteristics of infants

They were categorized into 186(45.4%) males, and 224(54.6%) females; their median age at operation was 65 (range, 30–135) days, moreover, ages <60 days (A), 60–90 days (B) and >90 days (C) were 90 (22%), 225(54.9%), and 95 (23.2%) of our infants respectively. Their median weight and height reached 4.5 (range, 3–7.5) Kg, and 56 (range, 49–66) cm respectively. Type III and type III cystic BA affected 390(95.1%) and 20(4.9%) of cases respectively. BA splenic malformation (BASM), cardiac anomalies (i.e. Ventricular septal defect (VSD), atrial septal defect (ASD), patent foramen oval (PFO), and patent ductus arteriosus (PDA)) and other anomalies (i.e. Situs inversus totals, preduodenal portal vein, etc) were present in 13(3.2%), 7(1.7%), and 9 (2.2%) of them respectively. The jaundice was observed since and during the 1st week after birth in 268(65.4%) and 142(34.6%) of patients respectively. Preoperative laboratory values are shown in Table 1; moreover, preoperative PHN reached 7.3% of patients. According to preoperative US findings; hepatomegaly, splenomegaly, abnormal gallbladder, hepatic subcapsular flow, and positive TC sign were seen in 190 (46.3%), 164(40%), 336(82%), 391(95.4%), and 142(34.6%) of our patients respectively. Table 1.

The histopathology of the intra-operative liver biopsy and the excised extrahepatic biliary tree showed the followings: 1- Mild, moderately, and marked portal tract ductal and/or ductular proliferation in 212(51.7%), 136(33.2%), and 62(15.1%) of patients respectively, 2- Portal tracts fibrosis grades F0, F1, F2, F3, and F4 in 17(4.1%), 190(46.3%) 144(35.1%), 40(9.8%), and 19(4.6%) of them respectively, 3- Portal tracts macrophages and giant cells in 230(56.1%), and 75(18.3%) of them respectively, 4- Portal hepatitis remnant duct size >150μm, 150μm and no ducts in 210(51.2%), 108(26.3%), and 92 (22.4%) of our cases respectively. Operative bleeding affected 24(5.9%) of patients where blood and plasma were transfused to 6(1.5%) and 23 (5.6%) of them respectively. The median operative time and post-operative hospital stay were 4 (range, 2.5–7.5) hours and 8 (range, 5–70) days respectively. Lastly, postoperative steroid therapy was used in 116(28.3%) of patients according to the treating physician preference. Table 1.

2.2. Short-term outcome

The early (<6 months post-Kasai) complications involved 187 (45.6%) of our pediatric patients where the single patient was affected by single or multiple complications; they were classified regarding Clavien Dindo system (CDS) as 112 (27.3%), 71(1.7%), and 68(16.6%) grades II, III, and V respectively (we recorded the highest CDS in patients with multiple complications). Table 2.

The early infection affected 172(42%) of infants in the form of cholangitis, urinary tract infection (UTI), chest infection, and wound infection that affected 108(26.3%), 26(6.3%), 85(20.7%), and 54 (13.2%) of patients respectively. Cholangitis occurred in single or multiple episodes that were managed conservatively by hydration, steroids, and antibiotics with improvement in some patients and mortality from sepsis in the others (Clavien II, V). However, all cases with UTI improved after antibiotic therapy (Clavien II). On the other hand, some cases with chest infection improved after medical treatment; however, the other cases progressed to pneumonia and died from sepsis (Clavien II, V). Lastly, wound infection improved after treatment with antibiotics, wound care, and/or 2ry sutures for burst abdomen (Clavien II, III). Table 2.

Sixty-four (15.6%) of our infants were complicated with early abdominal collection in the form of ascites, intestinal and biliary leaks...
Regarding ascites; it improved after diuretic therapy except for some cases that died from liver failure and others that underwent LT (Clavien that affected 49 (12%), 8(2%), and 7(1.7%) of them respectively. Lastly, bile leak was treated conservatively or surgically with success in some cases and mortality from sepsis in the others (Clavien III, V). Table 2.

The early intestinal obstruction that involved 5(1.2%) of infants was due to sepsis, liver failure, GIT bleeding, aspiration pneumonia, and multi-organ failure (MOF) that involved 34(8.3%), 25 (6.1%), 8(2%), 1(0.2%), and 1(0.2%) of them respectively. Lastly, the early (6 months) NLS and mortality in all cases from massive GIT bleeding (Clavien V). Table 2.

To be continued.

**Table 1**
The characteristics of infants.

| Category                        | No (%)           | Median(range) |
|---------------------------------|-----------------|---------------|
| Age at operation(days)          | 65(30–135)      |               |
| A (<60 days)                    | 90 (22%)        |               |
| B (60–90 days)                  | 225 (54.9%)     |               |
| C (>90 days)                    | 95 (22.2%)      |               |
| Gender                          | 186 (45.4%)     |               |
| Males                           | 224 (54.6%)     |               |
| Females                         | 7 (1.7%)        |               |
| Weight(KG) (Median(range))      | 4.5(3.7-7.5)    |               |
| Height(Cm) (Median(range))      | 56(49-66)       |               |
| Type of BA                      | 390 (95.1%)     |               |
| Non-cystic III                  | 20 (4.9%)       |               |
| Cystic III                      |                 |               |
| Associated anomalies            |                 |               |
| BASM                            | 13 (3.2%)       |               |
| Cardiac                         | 7 (1.7%)        |               |
| Others                          | 9 (2.2%)        |               |
| Onset of jaundice               | 268 (65.4%)     |               |
| Since birth                     | 142 (34.6%)     |               |
| After birth                     |                 |               |
| Preoperative labs (Median(range))| 11.9(4.3–32)   |               |
| TB(mg/dL)                       | 8.5(3–23)       |               |
| DB(mg/dL)                       | 170(51–955)     |               |
| AST(U/L)                        | 130(19–4940)    |               |
| ALT(U/L)                        | 130(131–2175)   |               |
| ALP(U/L)                        | 828.5(104–3310) |               |
| GGT(U/L)                        | 3.6(2.4–4.6)    |               |
| Alb(g/dL)                       | 10.8(1–13)      |               |
| INR                             | 387(121–1123)   |               |
| Platelets (K/ul)                |                 |               |
| Preoperative PHN                | 30 (7.3%)       |               |
| Findings in the preoperative US | 190 (46.3%)     |               |
| Hepatomegaly                    | 164 (40%)       |               |
| Splenomegaly                    | 336 (82%)       |               |
| Abnormal gallbladder            | 391 (95.4%)     |               |
| Hepatic subcapsular flow        | 142 (34.6%)     |               |
| Positive TC sign                |                 |               |
| Liver portal tracts biopsy findings | 212 (51.7%)  |               |
| Ductal and/or ductular proliferation | 136 (33.2%)  |               |
| Mild                            | 62 (15.1%)      |               |
| Moderate                        | 17 (4.1%)       |               |
| Marked                          | 190 (46.3%)     |               |
| Fibrosis                        | 144 (35.1%)     |               |
| F0                              | 40 (9.8%)       |               |
| F1                              | 19 (4.6%)       |               |
| F2                              | 230 (56.1%)     |               |
| F3                              | 75 (18.3%)      |               |
| F4                              | 210 (51.2%)     |               |
| Presence of macrophages         | 108 (26.3%)     |               |
| Presence of giant cells         | 92 (22.4%)      |               |
| Porta hepatis remnant duct size |                 |               |
| > 150 μm                        |                 |               |
| < 150 μm                        |                 |               |
| BA: Biliary atresia, BASM: Biliary atresia splenic malformation, TB: Total bilirubin, DB: Direct bilirubin, AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, GGT: Gamma glutamate transferase, Alb: Albumin, INR: International normalization ratio, PHN: Portal hypertension, TC: Triangular cord.

in some patients and failure in others (Clavien II, III, V).

The early intestinal obstruction that involved 5(1.2%) of infants was managed conservatively or by surgical exploration with improvement in some of them and death from sepsis in the others (Clavien II, V). On the other hand, S4 (13.2%) of our cases had early PHN with bleeding GO varices in 8 of them; these bleeding varices were managed by endoscopic injection sclerotherapy after resuscitation with unfortunate failure and mortality in all cases from massive GIT bleeding (Clavien V). Lastly, encephalopathy affected 30(7.3%) of patients who were given anti-coma measures with success in some patients and LT or mortality from liver failure in the others (Clavien II, III, V).

Table 2.

The median total and direct bilirubin at1,3, and 6 post operative months were 8 mg/dL (0.6–19) and 5.5 mg/dL (0.3–16), 7 mg/dL (0.4–19.1) and 5.05 mg/dL (0.2–15), and 6 mg/dL (range, 0.3–17.7), and 4.5 mg/dL (range, 0.1–16), respectively. However, jaundice clearance at the 6th post operative month reached 138(33.7%) of our infants.

Table 2.

The early patient mortality that affected 70(17.1%) of our patients was due to sepsis, liver failure, GIT bleeding, aspiration pneumonia, adult respiratory distress syndrome (ARDS), and multi-organ failure (MOF) that involved 34(8.3%), 25 (6.1%), 8(2%), 10(2.0%), 1(0.2%), and 1(0.2%) of them respectively. Lastly, the early (6 months) NLS and
overall survival were 339(82.7%), and 340(82.9%) respectively. Table 2.

Predictors of jaundice clearance at the 6th post-operative month:

On univariate analysis; all studied variables except patient gender, and mean preoperative direct bilirubin (DB) of 7.8 ± 2.6 mg/dL, mean Aspartate transaminasae (AST) of 160.6 ± 68.3 U/L, mild portal tracts ductal and/or ductular proliferation, using postoperative steroids therapy and absence of early cholangitis post-operatively were the independent predictors of it, moreover, cystic type III BA and shorter operative time had a trend towards independent correlation with it. Table 3.

2.3. Long-term outcome

Two hundred fifty six (62.4%) of our patients had late (>6months) complications; moreover, CDS grades II, III, and V involved 7(1.7%), 19 (4.6%), and 230(56.1%) of them respectively.

The post-Kasai cholangitis (early and/or late), Late cholangitis, and cholangitis within 2 years of operation affected 175(42.7%), 99(24.1%), and 230(56.1%) of them respectively with late GO varices (47.1%) of our patients respectively with late GO varices were managed by endoscopic injection sclerotherapy and/or by band ligation in elder children with success in some patients and mortality from sepsis in the others (Clavien II, V). Table 4.

PHN (early and/or late) and late PHN affected 239(58.3%) and 193(47.1%) of our patients respectively; those varices were managed by endoscopic injection sclerotherapy and/or by band ligation in elder children with success in most cases and failure in the remaining patients that died from massive GIT bleeding despite adequate resuscitation and management (Clavien II, III, V). On the other hand, hepatopulmonary syndrome (HPS) was diagnosed in 34(8.3%) of patients with mortality in 14 of them despite aggressive support and management. (Clavien II, V) Table 4.

The postoperative late incisional hernia and intestinal obstruction complicated 3 (0.7%), and 7 (1.7%) of our studied patients respectively; they were managed surgically with successful treatment in all hernia cases and failure of treatment with mortality from sepsis in some of the intestinal obstruction cases (Clavien III, V). Table 4.

Lastly, late encephalopathy and ascites affected 43(10.5%), and 186 (45.4%) of patients respectively; they were managed with liver supportive treatment, anti-coma measures for encephalopathy, and diuretics for ascites with success in some patients and LT or mortality from liver failure in the others (Clavien II, III, V). Table 4.

Nineteen (4.6%) of our patients underwent LT at a median of 21.5 (range, 5–118) months where post-transplant survival reached 9/19 (47.4%) of cases. Table 4.

The late (>6 months) patient mortality reached 220(58.5%) of our patients where mortality in non-transplanted cases affected 230(56.1%) of them due to liver failure, sepsis, GIT bleeding, and HPS that involved 149(36.3%), 49(12%), 19(4.4%), and 14(3.4%) of them respectively. On the other hand, post-transplant mortality was 10/19(52.6%) and 10/ 410(2.4%) of transplanted and all patients respectively due to post-transplant sepsis, chronic rejection, portal vein thrombosis (PVT) and hepatic artery thrombosis (HAT) in 5(1.2%), 3(0.7%), 10(0.2%), and 1 (0.2%) of them respectively. Table 4.

Lastly, the 1-year, 3-year, 5-year, 10-year, 15-year, and 20-year NLS reached 315(76.8%), 236(57.6%), 204(49.8%), 152(37.1%), 101 (24.6%), and 91(22.2%) of them respectively. However, the 1-year, 3-

Table 3

Predictors of jaundice clearance at the 6th postoperative month.

| Character | Jaundice clearance No = 138 | No clearance No = 272 | P-value Univariate analysis | P-value Multivariate analysis |
|-----------|-----------------------------|-----------------------|-----------------------------|-----------------------------|
| Age (days) (Mean ± SD) | 63.1 ± 14.2 | 73.5 ± 18.1 | 0.000 | >0.05 |
| Age category | A (<60 days) 84 (60.9%) | 43 (34.1%) | 0.000 | >0.05 |
| C (≥90 days) 7 (5.1%) | 181 (141%) | 88 (68.3%) | 0.000 | >0.05 |
| Gender | Male 75 (54.3%) | 123 (100%) | <0.05 | <0.05 |
| F | 149 (54.8%) | 123 (100%) | <0.05 | <0.05 |
| Type of BA | III 123 (89.1%) | 267 (100%) | 0.000 | 0.1 |
| III, cystic | 15 (10.9%) | 5 (1.8%) | 0.000 | >0.05 |
| Associated anomalies | BASM 1 (0.7%) | 12 (4.4%) | 0.034 | >0.05 |
| Preoperative labs | AST (Mean ± SD) 7.8 ± 2.6 | 9.9 ± 3.3 | 0.000 | 0.003 |
| TB (mg/dL) | 160.6 ± 236.2 | 0.000 | >0.05 |
| DB (mg/dL) | 68.3 ± 142.4 | <0.05 | >0.05 |
| ALIT (U/L) | 137.8 ± 162.2 | 0.1 | >0.05 |
| ALT (U/L) | 74.6 ± 305.1 | <0.05 | >0.05 |
| Alka phosph (U/L) | 588.9 ± 635.9 | 0.000 | >0.05 |
| GGT (U/L) | 288.7 ± 273.2 | 0.000 | >0.05 |
| ALB (g/dL) | 1078.8 ± 960.7 | 0.05 | >0.05 |
| INR | 799.1 ± 731.8 | >0.05 | >0.05 |
| Platelets (K/µL) | 3.8 ± 0.5 | 3.4 ± 0.6 | 0.000 | >0.05 |
| Portal tracts ductal and/or ductular proliferation | 18 (12.3%) | 119 (43.8%) | >0.05 | >0.05 |
| Portal tract fibrosis | 11 (8%) | 6 (2.2%) | >0.05 | >0.05 |
| F0 | 103 (33%) | 87 (32%) | >0.05 | >0.05 |
| F1 | 74.6% | 125 (39%) | >0.05 | >0.05 |
| F2 | 19 (13.8%) | 46 (15%) | >0.05 | >0.05 |
| F3 | 5 (3.6%) | 15 (5%) | >0.05 | >0.05 |
| F4 | 0 (0%) | 19 (7%) | >0.05 | >0.05 |
| Presence of portal tracts macrophages | 44 (31.9%) | 186 (68.4%) | >0.05 | >0.05 |
| Presence of portal tracts giant cells | 7 (5.1%) | 68 (25%) | >0.05 | >0.05 |
| Remnant duct size at porta hepatitis > 150 μm | 110 (79.7%) | 100 (36%) | >0.05 | >0.05 |
| ≤ 150 μm | 19 (13.8%) | 89 (32.7%) | >0.05 | >0.05 |
| No ducts | 9 (6.5%) | 83 (30.5%) | >0.05 | >0.05 |
| Operative bleeding | 0 (0%) | 24 (8.8%) | >0.05 | >0.05 |
| Operative time (hours) (Mean ± SD) | 3.8 ± 4.4 | 1.1 | >0.05 | >0.05 |
| Postoperative steroids | 94 (68.1%) | 22 (8.1%) | 0.000 | 0.000 |
| Early cholangitis | 10 (7.2%) | 98 (36%) | 0.000 | 0.001 |
| Early PHN | 1 (0.7%) | 53 (19.5%) | >0.05 | >0.05 |

BA: Biliary atresia, BASM: Biliary atresia splenic malformation, TB: Total bilirubin, DB: Direct bilirubin, AST: Aspartate transaminase, Alb: Albumin, INR: International normalization ratio, PHN: Portal hypertension.
time, as well as mild portal tracts ductal and/or ductular proliferation were independent predictors of it, furthermore, lower mean INR and operative bleeding, the occurrence of jaundice clearance at the 6th postoperative month, absence of post-operative cholangitis, and PHN were the independent predictors of it, furthermore, lower mean INR and operative time, as well as mild portal tracts ductal and/or ductular proliferation and using postoperative steroids therapy, had a trend towards independent correlation with it. Table 5, Fig. 7.

3. Discussion

KPE for type III BA aims to form an internal fistula with the intrahepatic biliary tree through porta hepatis residual ductules [16] resulting in improving bile flow, clearing jaundice, restoring synthetic and excretory liver functions, and providing healthy growth [2,8] however, its better outcome occurs when performed early at the experienced center by experienced surgeons in the presence of appropriate support facilities with good postoperative care and medication [5]. Similarly, we did our best for the early detection and management of BA cases throughout the whole study period; moreover, our pediatric department designed and validated a scoring system in 2014 for achieving this goal [39].

Jaundice clearance at the 6th-month post KPE occurred in 33.7% of our patients that was comparable to the previous retrospective literature studies of different sample sizes (range; 29–82%) [8,11-17]; this wide variation of jaundice clearance in the literature came from different definitions of it, different periods of its occurrence as well as different postoperative medications (i.e. steroids) in those literature studies. On the other hand, it was only 27.1% in our previous study due to the difference in jaundice resolution time (3 months), patient NO, and study period [40].

Cholangitis is the most catastrophic complication after KPE occurring in 30–93% of patients [11,22,41–43] and is mostly ascending in nature due to the biliointeretic reconstruction; moreover, most of its attacks start within the 1st 2 years after the operation [44,45]. Similarly, and despite doing our best to prevent their occurrence by prophylactic AB for 6 months after the operation; Cholangitis (early and/or late), early cholangitis, and cholangitis within 2 years after KPE affected 42.7%, 26.3%, and 39.3% of our patients respectively, also, early cholangitis ranged from 13.2 to 48% in Suzuki et al., 2010 [16], Nightingale et al., 2017 [46] and Nio et al., 2015 [47] retrospective studies. However, late-onset cholangitis develops due to several causes (i.e. the presence of intrahepatic biliary stones, dilatations, and/or lakes) [21,44,48]; it was 24.1% and 22% in our, and Nio et al., 2004 [45] retrospective studies respectively.

PHN affects 30–70% of patients after KPE [11,49,50]; moreover, it results from the progression of liver fibrosis stimulating portosystemic shunting with fatal varices formation [44]. Similarly, PHN (early and/or late), early and late PHN affected 58.3%, 13.2%, and 47.1% of our patients respectively, however, early PHN was found in 23% of Chung et al., 2015 [51] infants, and late PHN affected 70% and 37% of patients in Lykavieris et al., 2005 [52] and Nio et al., 1997 [53] long-term follow up retrospective studies respectively.

PHN: Portal hypertension, GO: Gastro-esophageal, GIT: Gastrointestinal system, HPS: Hepatopulmonary syndrome, CDS: Calvien Dindo system, LT: Liver transplantation, PVT: Portal vein thrombosis, HAT: Hepatic artery thrombosis, NLS: Native liver survival.

year, 5-year, 10-year, 15-year, and 20-year overall survival was 318 (77.6%), 244 (59.5%), 211 (51.5%), 161 (39.3%), 110 (26.8%), and 100 (24.4%) of them respectively. Table 4, Fig. 6.

2.4. Predictors of long-term (20-year) NLS

On univariate analysis; all studied variables were significant predictors of long-term NLS except patient gender, BASM anomaly, and mean preoperative (ALT, GGT, and platelets). However, on multivariate analysis; patient age ≤90 days, higher preoperative mean serum alb, portal tract fibrosis grades F0 and F1, absence of intraoperative bleeding, the occurrence of jaundice clearance at the 6th postoperative month, absence of post-operative cholangitis, and PHN were the independent predictors of it, furthermore, lower mean INR and operative time, as well as mild portal tracts ductal and/or ductular proliferation year, 5-year, 10-year, 15-year, and 20-year overall survival was 318 (77.6%), 244 (59.5%), 211 (51.5%), 161 (39.3%), 110 (26.8%), and 100 (24.4%) of them respectively. Table 4, Fig. 6.

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low availability of living donor grafts, refusal of LT by most parents/guardians and low No of pediatric LT centers in Egypt, 2. High post-transplant mortality that reached 52.6% of transplanted cases. So, it is fundamental to do our best in the future to improve NLS post-KPE in Egypt to avoid or delay LT; moreover, our discussion aimed mainly to study the factors affecting jaundice clearance and 20-year NLS after KPE to modulate them for getting the best long-term NLS. (NB. Transplant free survival (TFS) means survival without LT and it includes the survival of a patient with his native liver (SNL) and survival of the native liver itself (NLS), so, in our discussion; we will consider SNL and NLS in the literature as TFS, also, short-, mid- and long-term TFS will mean ≤3-year, 4-year, and ≥5-year TFS respectively).

The effect of age at KPE that is affected by many factors (i.e. access to medical care, diagnosis efficiency, surgery scheduling, etc) on post-operative jaundice resolution, short-, mid- and long-term both NLS and overall survivals has been a matter of debate for years in the literature as some reports have been against its benefit, while most others have ensured its importance [60]; those ensuring studies have documented that the operation has had better outcomes when has been performed before 90 days of life due to the presence of an association between younger age at KPE and both increased porta-hepatis remnant ducts NO and decreased fibrosis grade [8,61,62]; therefore, performing it before 90 days has been the goal of most centers. Similarly, despite the need for more improvement, only 23% of our infants underwent the operation after 90 days of life as we did our best for early detection of the disease, moreover, age<90 days at KPE was a significant predictor of postoperative jaundice resolution and independent predictor of long-term NLS in our study, also, younger age at KPE was a significant predictor of jaundice resolution in Chardot et al., 2013 [13], Pakarinen et al., 2018 [20], Parolini et al., 2019 [22], Hanalioglu et al., 2019 [27], and Ihn et al., 2018 [63] retrospective studies. Moreover, it was an independent predictor of 4- and 5-year TFS in de Vries et al., 2012 [15] and Qiao et al., 2015 [64] retrospective studies respectively. Furthermore, it had a significant association with short- and long-term TFS outcomes in Zhen et al., 2015 [9], Chardot et al., 2013 [13], Pakarinen et al., 2018 [20], Hanalioglu et al., 2019 [27], and Nightingale et al., 2017 [46] studies. On the other hand, it was not a predictor of jaundice resolution in Webb et al., 2017 [11], Sookpotaram et al., 2006 [59] or Yassin et al., 2020 [65] retrospective studies, also, it was not associated with short- or long-term TFS outcomes in Webb et al., 2017 [11], Jain et al., 2019 [21], Koga et al., 2013 [38], Chung et al., 2015 [51], Ramos-Gonzalez et al., 2019 [58], Ihn et al., 2018 [63], Nio et al., 2010 [66], Sasaki et al., 2016 [67], Chiang et al., 2017 [68], Nio et al., 2018 [69] or Wildhaber et al., 2003 [70] retrospective or prospective studies.

Cystic BA that is seen in 5–10% of cases has a good prognosis after KPE [71]. Similarly, cystic type III BA that affected 5% of our infants had a trend towards being an independent predictor of post-KPE jaundice resolution; moreover, it had a significant correlation with 20-year NLS, also, cystic BA was a significant predictor of good NLS in Davenport et al., 2011 [17] study and Toyosaka et al., 1993 [72] documented good NLS after successful KPE that was done for elder infant with type III cystic BA.

BA associated anomalies were a significant predictor of less both jaundice clearance and NLS in our study, similarly, it was a significant predictor of less jaundice resolution and independent predictor of poor short-term SNL in Davenport et al., 2011 [17] and Chung et al., 2015 [51] studies respectively, however it was not associated with jaundice resolution in Pakarinen et al., 2018 [20] retrospective multicenter study, moreover, it was not correlated with long-term TFS outcomes in Pakarinen et al., 2018 [20], Ramos-Gonzalez et al., 2019 [58] or Chiang et al., 2017 [68] retrospective studies. Despite being a predictor of less jaundice clearance; BASM anomaly was not associated with NLS in our work; similarly, it was not a predictor of TFS outcomes in de Vries et al., 2012 [15], Pakarinen et al., 2018 [20], or Nio et al., 2018 [69] studies. Conversely, it was a predictor of poor SNL in Shneider et al., 2006 [12] and Chardot et al., 2013 [13] studies.

Preoperative lower mean DB and AST were independent predictors of Post KPE jaundice clearance and significant predictors of good NLS in our work; similarly, lower preoperative median AST had a significant correlation with jaundice resolution in Yassin et al., 2020 [65] retrospective study, also, Preoperative lower mean DB and AST had a trend towards significant correlation with SNL in Goda et al., 2013 [73] retrospective study. The preoperative INR value reflects the secretory-synthetic liver function affecting the long-term postoperative outcomes [27]. Similarly, preoperative INR was a predictor of both jaundice clearance and long-term NLS in our work. Conversely, it was not a predictor of jaundice clearance in Yassin et al., 2020 [65] retrospective study.

The Portal tracts ductal and/or ductular proliferation seen in BA occurs as a response to chronic cholestasis and/or comes from the ductular transformation of the periportal hepatocytes [74]. In our series; the mild form of portal tracts ductal and/or ductular proliferation was an independent predictor of jaundice resolution besides having a trend towards being an independent predictor of good NLS, similarly, Santos et al., 2009 [57] and Muthukangarajan et al., 2016 [75] found better short-term NLS with a lesser degree of biliary proliferation.

Advanced fibrosis was a significant predictor of jaundice persistence and independent predictor of poor NLS in our series, in similar, it was an independent predictor of poor long-term TFS in Hanalioglu et al., 2019 [27] and Wildhaber et al., 2003 [70] studies. Moreover, it was a significant predictor of poor short- and long-term NLS in Webb et al., 2017 [11] and Nightingale et al., 2017 [46] retrospective studies. However, the presence of liver fibrosis or its increased grade at surgery was not associated with postoperative jaundice resolution in Hanalioglu et al.,

Fig. 6. A-KM long-term NLS curve B-KM long-term overall survival curve.
Table 5

Predictors of long-term NLS.

| Category | NLS | No NLS | P-value | P-value |
|----------|-----|--------|---------|---------|
|          | No (%) | No (%) | Univariate analysis | Multivariate analysis |
| Age(days) (Mean ± SD) | 64 ± 12.7 | 71.8 ± 18.4 | 0.000 | > 0.05 |
| Age category | 29 (31.9%) | 61 (19.1%) | 0.000 | 0.000 |
| A (<60 days) | 59 (64.8%) | 166 (52%) | 0.000 | 0.000 |
| B (60-90 days) | 3 (3.3%) | 92 (28.8%) | 0.000 | 0.000 |
| C (>90 days) | 11 (12.1%) | 71 (23.1%) | 0.000 | 0.000 |
| Gender | Male | 53 (58.2%) | (46.4%) | 0.000 |
|          | Female | 171 | (53.6%) | |
| Type of BA | 80 (87.9%) | 310 | 0.001 | > 0.05 |
| Preoperative labs | 11 (12.1%) | (97.2%) | |
| Associated anomalies | 2 (2.2%) | 27 (8.5%) | 0.038 | > 0.05 |
| BASM | 1 (1.1%) | 12 (3.8%) | > 0.05 | |
| TR (mg/dL) | 11.6 ± 3.3 | 12.4 ± 3.7 | 0.047 | < 0.05 |
| ALT (U/L) | 8.4 ± 2.7 | 9.4 ± 3.4 | 0.012 | > 0.05 |
| GGT (U/L) | 171 ± 93.3 | 222 ± 1.1 | 0.001 | < 0.05 |
| Alk phos (U/L) | 3.9 ± 0.5 | 970.7 ± 0.9 | > 0.05 | > 0.05 |
| AST (U/L) | 543.6 ± 15.6 | 159.6 ± 3.7 | 0.004 | 0.02 |
| ALT (U/L) | 282.8 ± 282.4 | 0.05 | 0.09 |
| Alk phos (U/L) | 1104.8 ± 641.9 | 0.000 |
| GGT (U/L) | 733.2 ± 274.5 | |
| Alk phos (U/L) | 3.9 ± 0.5 | 970.7 ± 0.9 | > 0.05 | > 0.05 |
| INR | 1 ± 0.4 | 761.1 |
| Platelets (K/ul) | 438.5 ± 158.7 | 3.5 ± 0.6 | 0.043 | 0.01 |
| Portal tract ductal and/or ductular proliferation | 75 (82.4%) | 137 | 0.000 | 0.1 |
| Mild | 16 (17.6%) | (42.9%) |
| Moderate | 0 | (37.6%) |
| Portal tract fibrosis | 6 (6.6%) | 11 (3.4%) | 0.000 | 0.000 |
| F0 | 68 (74.7%) | 122 |
| F1 | 17 (18.7%) | (38.2%) |
| F2 | 0 | 127 |
| F3 | 0 | (39.8%) |
| F4 | 0 | 40 (12.5%) |
| Presence of portal tract macrophages | 28 (30.8%) | 202 | 0.000 | > 0.05 |
| Remnant duct size at porta hepatitis > 150 µm | 73 (80.2%) | 137 | 0.000 | > 0.05 |
| < 150 µm | 2 (2.2%) | 92 (28.8%) | 0.000 | > 0.05 |
| No ducts | 0 | 90 (28.2%) |
| Operative bleeding time (hours) (Mean ± SD) | 3.6 ± 1 | 4.4 ± 1.1 | 0.004 | 0.000 |
| Postoperative steroids | 63 (69.2%) | 53 (16.6%) | 0.000 | 0.1 |
| Jaundice clearance at 6 months | 84 (92.3%) | 54 (16.9%) | 0.000 | 0.000 |
| Cholangitis | 6 (6.6%) | 169 (53%) | 0.000 | 0.000 |
| PHN | 11 (12.1%) | 228 | (71.5%) |

NLS: Native liver survival, BA: Biliary atresia, BASM: Biliary atresia splenic malformation, TB: Total bilirubin, DB: Direct bilirubin, AST: Aspartate transaminase, ALT: Alanine transaminase, ALK: Alkaline phosphatase, GGT: Gamma glutamate transferase, Alb: Albumin, INR: International normalization ratio, PHN: Portal hypertension.
injection sclerotherapy (EIS) was an independent predictor of poor long-term NLS in Sasaki et al., 2016 [67] study. On the other hand, post-KPE PHN was not a predictor of short- or long-term TFS in Webb et al., 2017 [11] or Chung et al., 2015 [51] studies.

The annual center volume/caseload, as well as the surgeon and center experiences, improve post-KPE outcome [8,81], similarly, our center is one of the biggest centers in Egypt performing such procedures with a mean annual caseload of 20.5 ± 10.1 cases (median 17 (range; 5–53) cases) where there was a significant correlation between annual caseload >15 cases and NLS (P = 0.008); also, mid- and long-term TFS was correlated with the higher annual caseload in Serinet et al., 2006 [14], Pakarinen et al., 2018 [20] and Davenport et al., 2004(363) [82] studies; in the same line, the center experience was a predictor of short- and long-term TFS in Nightingale et al., 2017 [46], Lampela et al., 2012 [83] and Kvist and Davenport, 2011 [84] studies. Conversely, annual caseload was not a predictor of TFS outcomes in de Vries et al., 2012 [15] or Schreiber et al., 2010 [85] studies.

Fig. 7. KM analysis long-term NLS curves: A: Age at operation and long-term NLS (Log rank = 0.000) B: Liver fibrosis and long-term NLS (Log rank = 0.000) C: Jaundice clearance at the 6th post-operative month and long-term NLS (Log rank = 0.000) D: Post-operative cholangitis and long-term NLS (Log rank = 0.000) E: Post-operative PHN and long-term NLS (Log rank = 0.006).

To the best of our knowledge; this is one of the unique studies documenting the followings: 1- The significant correlation between post-operative sepsis from different causes (i.e. cholangitis, pneumonia, bile leak, intestinal leak, and intestinal obstruction) and mortalities (P = 0.000); so it is fundamental to prevent and manage sepsis post KPE aggressively to improve outcome, 2- The significant correlation between intra-operative bleeding (N.B associated significantly with preoperative PHN (P < 0.05) and postoperative jaundice persistence, as well as its independent correlation with less long-term NLS and we think this came from the significant correlation between bleeding and both older age(P < 0.05) and higher fibrosis grade(P < 0.05) that were related to poor
outcome; so, it is crucial to decrease and properly manage intraoperative bleeding for better outcome, 3- The significant association between higher preoperative mean serum alb and postoperative jaundice resolution, as well as its independent correlation with long-term NLS; so it is a must to improve the preoperative nutritional status of the infant for getting better outcome.

In conclusion: Sepsis had a direct effect on early and late patient mortalities after KPE; moreover, patient age at operation, >90 days, higher fibrosis grades, the occurrence of postoperative cholangitis and PHN, and persistence of post-operative jaundice had a negative insult on the long-term postoperative outcome. So, it is crucial to modulate these factors for a better outcome.

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Declaration of competing interest

No conflict of interest to declare.

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The main limitation of the study is being retrospective, done at a single center where multiple factors were studied, so, it is advisable to do further randomized multicenter prospective studies of the effect of a single factor (i.e. Sepsis, age, fibrosis, cholangitis, PHN, etc) on the outcome of KPE for type III BA.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.01.052.

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Author contribution

Emad Hamdy Gad: Surgical procedures, study design, data collection, writing, statistical analysis and publication.

Yasmin Kamel: Data collection, writing and statistical analysis.

Tahany Abdel-Hameed Salem: Data collection, analysis and writing.

Mohammed Abdel-Hafez Ali: Data collection, analysis and writing.

Ahmed Nabil Sallam: Surgical procedures, data collection, analysis and writing.

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All the authors of this paper accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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