Stretching the Limit of Native Liver Survival in Biliary Atresia After Kasai Portoenterostomy – a 37-year Territory-wide Study

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Abstract

Objective

We present a 37 years' experience in the management of biliary atresia (BA) and discuss long-term complications after Kasai portoenterostomy (KPE).

Methods

A retrospective territory-wide study from 1980 to 2017 on 231 patients with open KPE from three tertiary paediatric surgical centres was performed. The jaundice clearance (JC) rate, native liver survival (NLS) rate and complications were analyzed.

Results

The mean follow up period was 15.4 +/- 6.2 years. Over 60% of patients remained JC within 2 years after KPE. Seventy patients (30.3%) received liver transplant (LT) at a median age of 6.2 years (range: 0.5 to 25 years). The NLS rates at 10, 20 and 30 years were 70.7%, 61.5% and 53.0% respectively with no significant change over the study period. The median bilirubin level among all native liver survivors (n=153) was 24 μmol/L (2 to 162 μmol/L). Portal hypertension (PHT) and recurrent cholangitis were found in 51.6% and 27.5% of them respectively.

Conclusion

With a vigilant follow up program, more than 60% of BA patients could remain stable with the disease and achieve long term survival without LT. Although portal hypertension and recurrent cholangitis are common, they do not need to be the indications for LT if managed properly.

Introduction

Biliary atresia (BA) is a progressive fibrosclerosing disease of the biliary tract and affects all ethnicities with a noticeably higher incidence in the Asia-Pacific region (1). Kasai portoenterostomy (KPE) is by far the most widely accepted primary treatment with a variable outcome. Liver transplant (LT) is regarded as the salvage treatment when KPE fails to restore biliary drainage. KPE is also labelled as failure when patients develop complications related to recurrent cholangitis, portal hypertension (PHT) and hepatic dysfunction which could happen in 60% of BA patients (2). These complications are often indications for LT. Literatures from various studies have reported that early drainage rate is in the range of 50–60% and only less than half of the patients could remain transplant-free after KPE (1, 3–5). In addition, it was estimated that around half of the LT will be performed before the age of 2 (6). Although LT is a potential treatment for these complications, transplant recipients need to face the problems associated with an ultra-major operation and the life-long use of immunosuppressants. This could impair the immune system, leading to recurrent infection and most severely, haematological malignancy (7). Even worse, this notorious side-effect is more pronounced in children. In some countries, another major hurdle to LT is the

low organ donation rate. Thus, eliminating or deferring the need of LT for as long as possible is a legitimate goal for BA treatment. The main purposes of this study were 1) to describe our territory-wide experience in managing BA and report the treatment outcomes of KPE based on 37 years' follow up data; and 2) to present the long-term problems encountered by native liver survivors and elucidate alternative treatment other than LT.

Methods

Study design and patients

This was a retrospective regional-based study conducted in the only three tertiary paediatric surgical centres performing KPE in Hong Kong. A list of BA patients receiving treatment between 1980 to 2017 was retrieved and their medical records were reviewed. This study has been approved by the University of Hong Kong/Hospital Authority Hong Kong West Cluster Institutional Review Board (HKU/HA HKW IRB number: UW20-156) and was performed in accordance with the ethical standards in the Declaration of Helsinki. Informed consent from parents and/or legal guardians for study participation have been obtained.

The management strategy of BA in Hong Kong

In Hong Kong, the three centres broadly adopted a common approach for BA over the years. The diagnosis of BA was established by surgical exploration +/- cholangiogram and liver biopsy. KPE remained the preferred primary treatment option for BA, except when the patients presented late and/or surgical exploration revealed a grossly cirrhotic liver. In those situations, the chief surgeons decided to not proceed with KPE and the patients were referred for primary LT. The operations were performed by or with the attendance of an experienced surgeon who had completed training for more than 5 years. KPE was performed by conventional open approach according to the original principle with minor technical variations except 16 laparoscopic KPEs performed by a single surgeon in one of the centres in 2002 to 2006. Since 2004, 169 patients have received oral steroid as a routine adjuvant therapy after KPE with some variations in the duration and dosage. Similarly, ursodeoxycholic acid and antibiotics were given post-operatively but the exact protocol varied among centres. Fat-soluble vitamin supplements were given in the early post-operative period. Patients and their care-takers were well informed about the potential complications and their manifestations. Life-long follow up were conducted the primary surgical team from every three to six months. A more frequent visit would be scheduled if the liver function was abnormal or in the presence of complications necessitating a close monitoring. There was no specific protocol regarding the medications for portal hypertension but PHT was actively screened. Splenomegaly were measured by ultrasonography and esophageal varices were managed by endoscopic sclerotherapy or banding. All cholangitic episodes were promptly diagnosed and treated rigorously with at least two weeks of intravenous antibiotics after full septic work up. Radiological investigations were performed to look for liver abscesses/cysts or other structural anomalies in resistant cases. A central venous catheter would be inserted if more than 4 weeks of antibiotics was expected. Patients with BA-complications

admitted to district hospitals other than these three paediatric surgical centres would be transferred back to the parent team for management. The paediatric LT programme started in 1993 and both living as well as deceased donor LT were performed. The decision of LT was jointly reviewed by the paediatric surgical and the LT teams.

Registered data and outcome measurements

The medical records were retrieved using ICD-9 coding ‘751.61: Biliary atresia’; ’51.37: Kasai portoenterostomy’ and ’50.59: Transplant of liver’. Demographic information, peri-operative details, clinical and laboratory data including serum bilirubin and albumin level; international normalized ratio (INR) and platelet count were extracted. In all patients, the outcome measurements were native liver survival (NLS) and JC rate (total serum bilirubin level </= 20 μmol/L) after KPE. NLS was defined as survival with own liver and has not been listed for LT at the time of writing. For native liver survivors, additional analysis included the assessment of synthetic liver function and the following complications: (i) hypersplenism which was defined by a clinically palpable spleen/spleen length above age-specific value in abdominal ultrasound and platelet count < 150 X 10^9/L; (ii) oesophago-gastric varices (OGV) of any grade detected during surveillance or emergency endoscopy; and (iii) recurrent (> 1 episode) cholangitis. An episode of cholangitis was defined by the presence of fever (core body temperature > 38.5 degree Celsius) and elevated bilirubin level above 20 μmol/L on two consecutive blood samples requiring intravenous antibiotics treatment. An episode that required more than 2 weeks of antibiotics or intervention was regarded as severe cholangitis. In this study, the exclusion criteria for outcome analysis were (i) incomplete medical record or laboratory data; (ii) loss of follow up data for more than 3 consecutive years; (iii) KPE performed by laparoscopic approach and iv) LT as the primary procedure.

Statistical analysis

Scientific analysis was performed with a standard statistical package (Windows, version 26.0; SPSS Inc., Armonk, NY, USA). Continuous variables were reported as medians (ranges) or mean (+/- SD) when appropriate. NLS was estimated with Kaplan-Meier analysis.

Results

Study population

During the study period, there was a total of 289 BA patients identified. There were more female than male (F:M = 168:121). Between 1996 to 2017, the annual incidence of BA ranged from 1.18 to 1.86 per 10,000 live births (Fig. 1). Fifty-eight patients were excluded from the outcome analysis because of i) incomplete medical record (n = 12); ii) follow up visit defaulted (n = 18); iii) laparoscopic KPE (n = 16) and iv) LT as the primary procedure (n = 7). Furthermore, 5 patients who died of liver failure without surgical treatment were also excluded. As a result, 231 patients with conventional open KPE as the primary surgical procedure were included (Fig. 2). The median age at operation was day 59 (day 19 to 135). In

this study, all patients were followed up at their respective centres and the mean follow up period was 15.4 +/- 6.2 years. The demographic data were summarized in Table 1

Table 1
Demographic data and clinical outcomes of 231 BA patients with open KPE performed in Hong Kong between 1980 to 2017

Patient characteristics	Number (%) or mean +/- SD
Sex	
- Male	97 (42.0%)
- Female	134 (58.0%)
Associated major anomalies	
- Yes	17 (7.4%)
- No	214 (92.6%)
Age of KPE (days)	59 (19–135)
Age of KPE	
- < 50 days	60 (25.9%)
- 51 to 60 days	63 (27.3%)
- 61 to 70 days	57 (24.7%)
- > 70 days	51 (22.1%)
Use of adjuvant steroid since 2004	
- Yes	169 (73.2%)
- No	62 (26.8%)
Mean follow up duration (years)	15.4 +/- 6.2
Jaundice clearance*	
- 6 months	143 (61.9%)
- 12 months	154 (66.7%)
- 24 months	149 (64.5%)
*Failure of jaundice clearance is defined as serum bilirubin ≥ 20μmol/L or transplanted	

Post-KPE outcomes (n = 231)

Jaundice clearance

JC was defined as serum total bilirubin level </= 20μmol/L. Patient who have received LT were considered as failure of JC. The JC rates at 6,12 and 24 months after KPE were 61.9%, 66.6% and 64.5% respectively.

Native liver survival (Fig. 3a and b)

Until the last follow up, 153 patients (66.2%) were still surviving with their own liver (Table 1). Forty-three of them (28.1%) have reached adulthood (> 18 years). Seventy-patients (30.3%) received LT at a median age of 6.2 years (range: 0.5 to 25 years) and 8 patients (3.4%) were recorded death after KPE without transplant. The indications for LT included: liver failure with median Paediatric End-Staged Liver Disease/Model for End-Staged Liver Disease score being 15.4 (range 9–33) (n = 59); severe portal hypertension (n = 7) and recurrent cholangitis (n = 4). Kaplan-Meier analysis estimated the 10-, 20- and 30-year NLS rate were approximately 70.7%,61.5%, 53.0% respectively (Fig. 3a). When we divided the study period into 1980–1999 and 2000–2017, there was no statistical significance difference in the native liver survival between these two study periods (p = 0.324).

Major morbidities among native liver survivors (n = 153) (Table 2)

Liver function

Among 153 native liver survivors, 99 patients (64.7%) were jaundice-freed at the most recent follow up and the median bilirubin level of them was 24 μmol/L (2 to 162 μmol/L). Concerning the synthetic liver function, 94.8% and 91.5% of patients had a normal INR and albumin level for age.

Hypersplenism

All native liver survivors underwent ultrasound scan during follow up visit. Hypersplenism was found in 79 patients (51.6%). The median platelet count was 145x 10^9/L (range 34-550x 10^9/L). Two patients have undergone image-guided partial splenic embolization for the management of hypersplenism. Their platelet counts have risen from 45 and 36x 10^9/L (pre-embolization) to 89 and 121x 10^9/L (post-embolization) respectively.

Oesophago-gastric varices (OGV)

At least one upper endoscopy was performed in 53 native liver survivors (34.6%). The median age for the first endoscopy to be performed was 7 years old (range: 0.5 to 24 years old). Overall, 31 of them were found to have OGV and the youngest patient was a 3 year old boy. Twelve patients experienced at least one bleeding episode requiring emergency endoscopic intervention.

Recurrent cholangitis

Forty-two native liver survivors (27.5%) suffered from more than one episode of cholangitis until the last follow up and 13 patients developed a severe attack requiring an intravenous antibiotics for more than two weeks (range: 18 to 443 days). Three patients required external biliary drainage. After the removal of

PTBD catheter, the three of them continued to survive without LT. Liver abscess were identified in 5 patients and 2 of them required image-guided drainage. Otherwise, the abscess responded well to antibiotics therapy and they remained transplant-free. The median age to experience the first episode of cholangitis was 2 years old (range: 0.5 to 23 years). Five patients had their first cholangitic attack after adulthood.

Table 2
Latest clinical condition of 153 native liver survivors as documented in the most recent follow up

Clinical condition / Blood parameter	Number (%) or median value (range)
Jaundice clearance*	99 (64.7%)
Bilirubin level (μmol/L)	24 (2-162)
Albumin (g/L)	37 (19–54)
INR	1.1 (0.9–2.3)
Platelet* (x10^9)	145 (34–550)
Hypersplenism*	79 (51.6%)
OGV^	31 (58.4%)
Recurrent cholangitis*	42 (27.5%)
*Percentage calculated based on 153 native liver survivors	
^Percentage calculated based on 53 patients who have received upper endoscopy	

Discussion

The incidence of BA in our locality is close to other Eastern countries and is slightly higher than the Caucasian population (8–11). We observed a higher incidence between 2006 and 2015 and this could be due to the transient immigration policy that allowed eligible women from Mainland China, one of the countries with the highest incidence of BA, to deliver their babies in Hong Kong during that period. Interestingly, although our incidence is higher than Western countries, we are not regarded as high-volume centres due to the small actual case number annually. To overcome the problem of limited patient volume, all BA patients in our public health care system are treated in the three centres in this study and the KPE always involved the experienced surgeons. In this cohort, despite multiple surgeons were involved, results were relatively consistent across different eras and centres due to the adherence to the same overarching surgical principle, the same peri-operative management and regular sharing of clinical experience among the three centres. The concentration of expertise in a small number of centres also enhanced our surgical outcomes with a JC up to 66.6% at one year after KPE. Herein, we included open KPE only because the results of laparoscopic KPE performed for a short period in one local centre were shown to be inferior to open KPE, a finding which corroborated with other international publications (12–14)

In recent years, BA has transformed from a condition that is incompatible with life to a disease with long-term complications (15). Patients and their care-takers should be given adequate information about the complications and any non-specific but alarming symptoms should be explained in order to facilitate an early medical attention when complication arises. Among these, PHT is of upmost importance because there is still no effective therapy except LT to alleviate this problem. Nevertheless, in our series, only a minority of patients were transplanted for PHT. More than half of our survivors had hypersplenism but this may not always be symptomatic. In some patients, pancytopenia can develop despite their liver function being preserved. While splenectomy would be considered in these cases, splenic embolization is a less invasive alternative treatment. This has been performed in two patients with satisfactory outcome. The procedure was well tolerated and their platelet count increased to a reasonably safe level. We could not prove the usefulness of this treatment scientifically due to the small sample size but this has opened a new treatment avenue for hypersplenism in post-KPE patients. While hypersplenism maybe silent, OGV are prone to bleed. As there is no international consensus regarding surveillant endoscopy after KPE, there are variations in the policy among our centres. Only one third of our BA survivors (n = 53) have received endoscopic examination but there were already 31 (58%) cases of OGV detected; with 12 patients required emergency procedure for haemostasis. We postulate the actual number would be higher if all patients were surveyed. This finding also concurs with other studies that revealed a high incidence of OGV detected by surveillance endoscopy (16, 17). Although PHT takes time to develop, our data suggested that it OGC could be found as early as 3 years old. Hence, in contrary to the belief of ‘on-demand’ endoscopy, we recommend that upper endoscopy should be performed in every BA patient to screen for OGV, preferably within a few years after KPE. This policy should continue when the patient is transited to adult care as OGV can continue to develop after adolescence. Even though PHT is considered as a predictor for future LT in a recent study by Jain et al (18), proper management of its complications could potentially keep them from LT. Recently, non-invasive measurement of liver fibrosis is available for clinical use and this should be incorporated in the follow up visit of BA patient as an indirect monitoring of PHT (19). Medical treatment for PHT are available but the potency and side effect remains unknown due to the lack of large-scale clinical trials (20).

Cholangitis is another potentially lethal complication after KPE and is postulated to be responsible for the worsening of cholestasis. In a study by Jain et al, a 4-fold increase in the risk of future LT is found in patients with late onset of cholangitis (18). Our data revealed that 27.5% of our patients developed recurrent cholangitis, a figure lower than a recent study by a Korean group reporting 76.2% of cholangitis would recur (21). Notably, only a minority of patients in our series (n = 4) necessitated a liver transplant due to the indication of recurrent cholangitis. All patients with clinical suspicion of cholangitis will undergo full work-up and confirmed cases would be given broad-spectrum intravenous antibiotics for at least 2 weeks to ensure adequate coverage. Liver abscess and biliary stasis, though uncommon, were actively sought out and external drainage was performed if necessary. We believe an aggressive management to cholangitis is necessary to prevent it becoming intractable that ultimately worsens the prognosis (22). Even though most cholangitis occurred shortly after KPE, it can happen at any time and the first presentation can be at adulthood. Follow-up providers should therefore retain a high index of

suspicion in any BA survivors with fever and deranged liver function. BA-related cholangitis is different from usual gallstone induced cholangitis in adult. It could happen without an identifiable anatomical obstruction. Knowledge in this could expedite the treatment process without unnecessary investigations. Occasionally, long term prophylactic antibiotic is necessary to prevent recurrence. Home intravenous antibiotics administration has been reported with success especially in compact city where home-hospital distance is short (23).

The value of KPE as the primary treatment has been challenged by the high post-Kasai LT rate (24). While it is still true that BA is the most common indication for paediatric LT, our survival analysis revealed that more than 60% of our patients could remain transplant-free as far as 20 years after KPE with no significant difference observed between the historical and recent patients. This survival rate is comparable to the results reported by some high-volume centres (24, 25). Furthermore, the median bilirubin level among those long term native liver survivors was 24 μmol/L and liver synthetic function was preserved in most of them. This finding, together with the conclusion from the previous study by Wong et al on the quality of life among BA survivors (26), has indicated that most post-KPE patients with mild cholestasis but preserved synthetic function do not require LT if their complications are well managed and many can indeed survive with the disease. We believe KPE should still be regarded as the primary treatment in experienced centres and LT should be regarded as a salvage treatment. In our previous study focusing on all transplant recipients, we concluded that LT should be considered only when PELD/MELD score was greater than 15, taking into account the risk-benefit ratio (27). The involvement of the paediatric surgical team in the long term management of these patients also facilitates the practice of personalized medicine due to a better knowledge in the patient's history. For in-patient care, thanks to the geographical advantage in our city, patients could be easily transferred back to the parent hospital within a couple of hours for further management of disease-related complications. Under this management strategy, in addition to enhancing native liver survival, the timing of LT could also be prolonged to beyond 4 years, the median LT time for BA patients previously reported by a multicentre study in the US. (28).

A major strength of our study is the relatively large sample size for a rare congenital disease as well as the availability and completeness of long-term data. However, we acknowledge there are several limitations to our study. First, the data of 30 patients (12.9%) could not be used. Second, the peri-operative management protocol including the endoscopic policy was not consistent amongst centres and had undergone some changes over the study period. This could have affected the true incidence of OGV in this series Last, some important clinical information was not recorded due to the inherent retrospective nature of the study.

In summary, the native liver survival of BA patients treated in a low- to mid- volume centre can be excellent by centralization of surgical care and a comprehensive follow up programme. With a meticulous attention to potential complications, it is possible to avoid or defer LT. Specifically, native liver survivors should be monitored closely for the development of PHT and cholangitis. OGV are common and early surveillance is therefore recommended to avoid life threatening bleeding. The participation of the

paediatric surgical team in the long term management of BA patients enhances the delivery of precision care. In places with shortage of organ donor, avoiding LT brings a remarkable benefit to the patients and the society. At patient level, children could be spared from a high risk ultra-major operation at young age and the use of immunosuppressants is delayed. To the society, the liver grafts which are valuable social resources, can be allocated to other liver failure patients and more lives will be saved.

Abbreviations

BA: Biliary atresia; JC: Jaundice clearance; KPE: Kasai portoenterostomy; NLS: Native liver survival; LT: Liver transplant; MELD: Model for End-Stage Liver Disease; PELD: Pediatric end-stage liver disease; PHT: Portal hypertension

Declarations

Contributors' Statement Page

Patrick Chung, Edwin Chan and Kenneth Wong conceptualized and designed the study, collected data, drafted the initial manuscript, and reviewed and revised the manuscript.

Fanny Yeung, Jennifer Mou and Judy Hung designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Albert Chan, Michael Leung, Kim Hung Lee, Paul Tam coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of Interest Disclosures (includes financial disclosures):

All the authors have no conflicts of interest to disclose

Human transplantation research declaration:

NO organs/tissues were procured from prisoners. Organ procurement for liver transplantation in this study was performed by the Division of Liver Transplantation, Department of Surgery, Queen Mary Hospital, The University of Hong Kong

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What's Known on This Subject:

Residual problems are common in biliary atresia patients after Kasai portoenterostomy and many of whom are subjected to liver transplant as the salvage treatment. Overall, only less than half of the patients can achieve long-term native liver survival.

What This Study Adds:

This study reported the long term outcome of biliary atresia in a local territory.The complication encountered by native liver survivors were reported. With a dedicated follow up programme, many of the post-Kasai sequelae do not require liver transplantation and could be managed by alternative therapies. More than 60% of our patients can survive with the disease-related problems even not managed in high volume centre.

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Figures

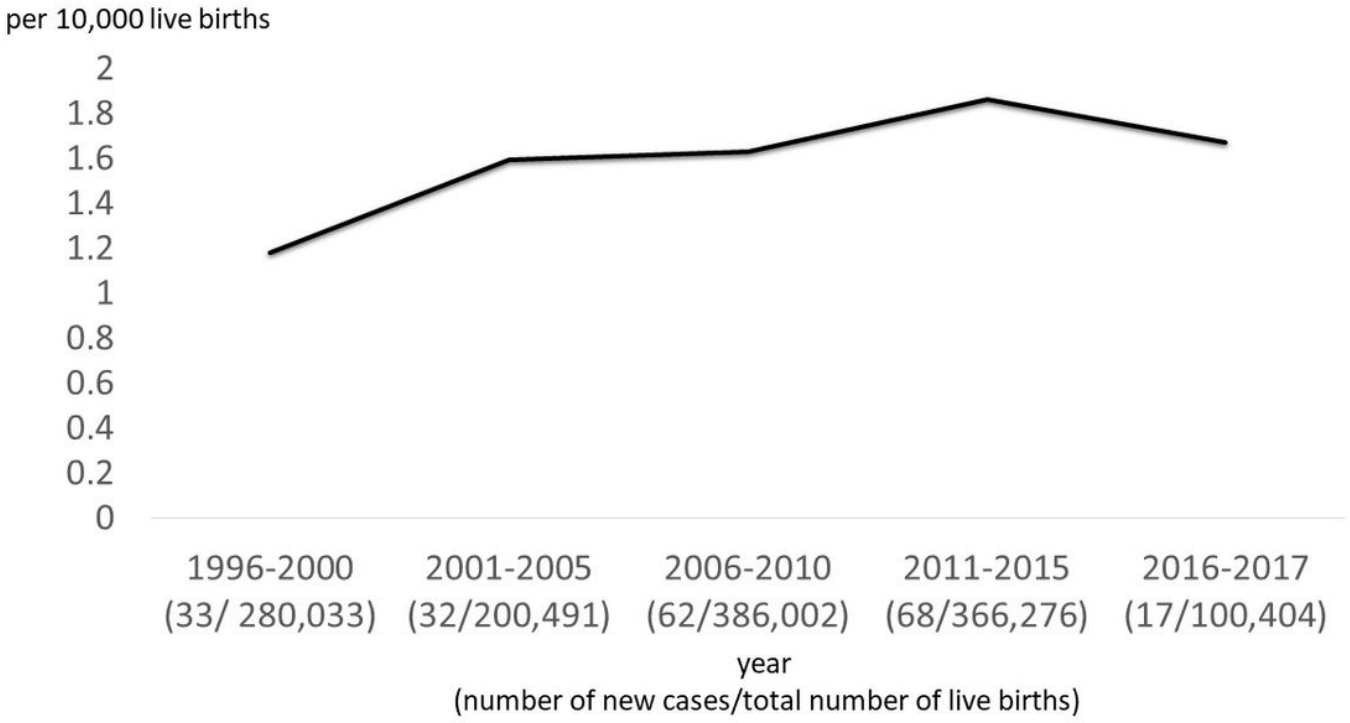

Figure 1

The incidence of BA (per 10,000 live birth) in Hong Kong from 1996 to 2017

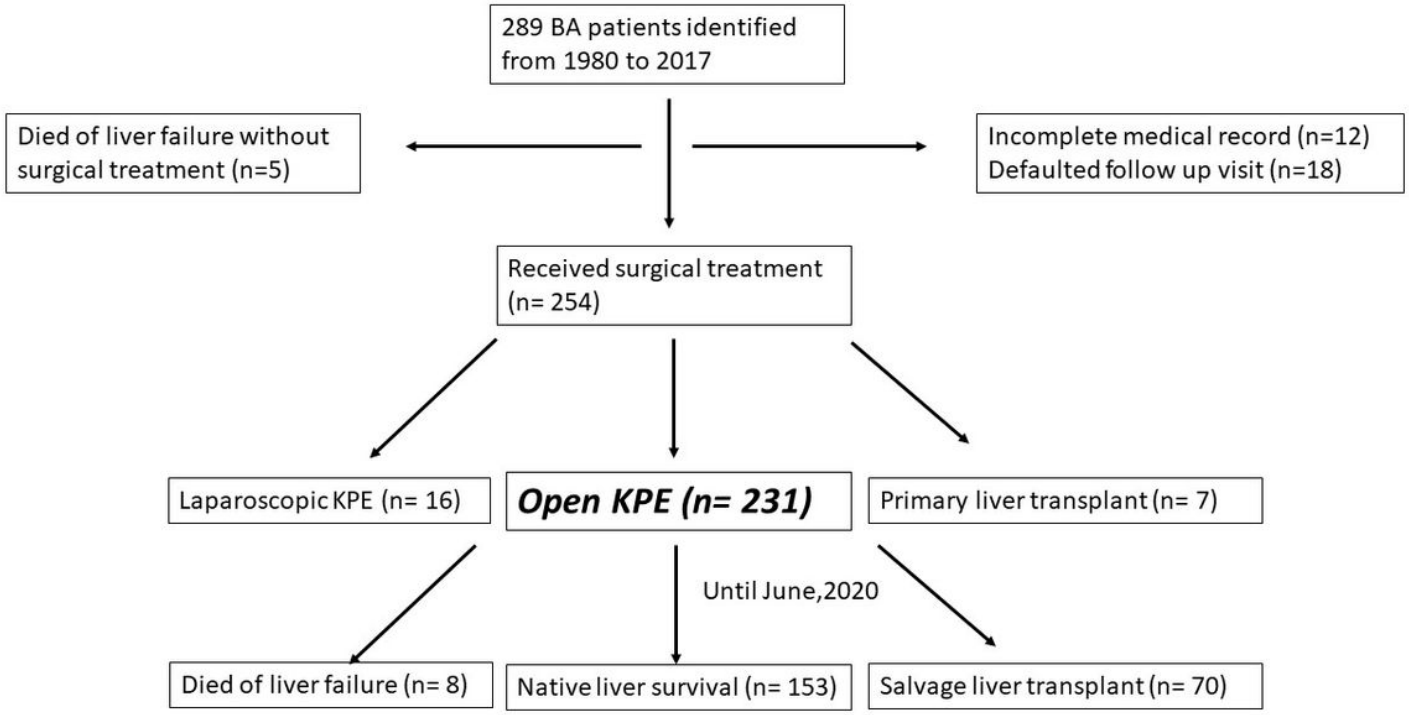

Figure 2

Flowchart of patient recruitment in this study. Ultimately, 231 BA patients with open KPE were analyzed for their clinical outcomes.

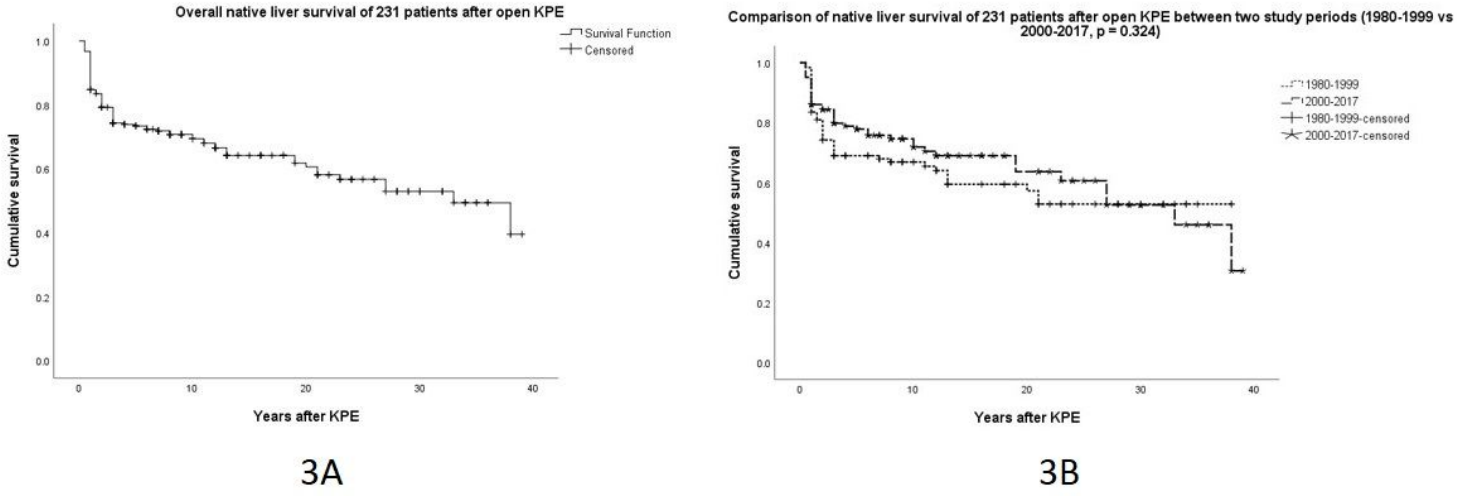

Figure 3

a) Kaplan Meier curve showing overall NLS for 231 BA patients after open KPE. The estimated survival rate at 10, 20, and 30 years were approximately 70.7%,61.5%, 53.0% respectively. b) There was no significant difference in the native liver survival between 1980 – 1999 and 2000 – 2017 (p=0.324)