

A Retrospective Review of the Outcome of Children Presenting to Tygerberg Children's Hospital with Biliary Atresia

By

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Declaration

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Abbreviations and acronyms

BA	biliary atresia
EHBA	extra hepatic BA
HPE	hepaticportoenterostomy
KPE	Kasai portoenterostomy
K P	Kasai procedure
LTx	liver transplantation
BARC	BA Research Consortium
TCH	Tygerberg Children's Hospital
RCCH	Red Cross Children's Hospital
UK	United Kingdom
USA	United States of America
BASM	BA splenic Malformations
UDCA	UrsodeoxyCholic Acid
SA	South Africa

Abstract

Background

Biliary atresia (BA) is the end result of an inflammatory process leading to fibrosis and obliteration of the biliary tract with the development of biliary cirrhosis. It is a leading cause of end-stage liver disease in children. It accounts for more than 50% of pediatric liver transplantations (LTx). Surgical treatment with Kasai portoenterostomy (PE) has improved the prognosis for patients with BA, even if most eventually need LTx. A key determinant for the post- Kasai PE patient survival is patient age at surgery as well as peri and post-operative management.

Objectives

This study reviews the short and long-term outcome and identifies prognostic factors of children with BA

Study design

A retrospective descriptive study

Methods

Folder review of all children born between May 1997 and May 2011 with biliary atresia as extracted from Tygerberg Children Hospital records database. Data collected included demographic details, clinical characteristics, liver biochemistry and liver biopsy results and outcome post Kasai PE.

Results

Thirty seven patients with confirmed extra hepatic BA (EHBA) , 23 females and 14 males, mean age 89 days (12.7 weeks), range 7 - 227 days, were identified. Twenty three patients underwent

Kasai PE. Two of these underwent both Kasai PE and cystenterostomy or cholecystojejunostomy. In 15 of 23 patients, a good short term surgical outcome was achieved as supported by the establishment of bile flow, pigmented stools, resolution of jaundice and improvements in liver biochemistry. Recurrent episodes of cholangitis were experienced in 9 cases (39%) during the first 3-12 months postoperatively. Seven of these patients had a progressive deterioration in clinical symptoms and liver function. Four patients died during postoperative follow up and 4 others were lost to follow up. Of the 14 patients who were not operated on, 6 died, 3 were lost to follow up and their outcome is unknown, and 5 were still alive at last date of follow up (one underwent LTx, one is on the inactive waiting list for LTx and 3 have not yet been referred for LTx).

Conclusion

Our study demonstrates that of the 23 patients in whom surgery was performed, 15(65.2%) were documented still alive (range 14 months to 14 years) of whom 4 are eligible for LTx; 4(17.4%) died during the post-operative period, and 4 (17.4%) were lost to follow up. Of the 23 children operated on, 13(56.5%) underwent surgery between 60 and 90 days of age (9 were still alive at the last follow up date, 2 were lost to follow up and 2 died), 4 (17.4%) operated before or at 60 days 2 survived, 1 is lost to follow up and 1 died). Of the 6(26.1%) BA patients who underwent Kasai PE after 90 days of life 4 were alive, 1 lost to follow up and 1 died). There was no significant difference in outcome for those who underwent early (< 60 days) and late surgery (60 to 90 days). However, timely referral and surgical correction before 90 days and post-operative antibiotic as well as nutritional therapy were associated with a higher post Kasai surgery survival rate.

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Literature review

Biliary atresia (BA) is a serious but relatively rare congenital disease of the bile ducts and liver of unknown aetiology. It is an important cause of severe cholestatic jaundice in infancy¹ and is also the most common indication for liver transplantation in South African children². It is associated with severe complications and is consistently fatal if a Kasai portoenterostomy (KPE) is not performed in the first weeks of life³. The reported incidence of biliary atresia varies from 5/100000 births per year in Holland to 32/ 100000 in French Polynesia⁴. Individual studies suggest an overall incidence in the United States of 1 per 10,000-15,000 live births. The incidence of BA is highest in Asian populations. The incidence and outcome of biliary atresia in South Africa is unknown as well as in African and developing countries in general.

No single unifying hypothesis has explained the varying presentations of BA indicating that BA is probably not a single disease entity. In 1885, BA was reported as an autopsy finding and, despite various studies since then, its aetiopathogenesis has not been fully determined⁵. It is a condition unique to infancy that is characterized by progressive fibrotic obliteration and obstruction of the extra-hepatic biliary tree ultimately leading to liver cirrhosis and liver failure.

Two forms of biliary atresia occur: a syndromic form that is associated with congenital abnormalities such as situs inversus, polysplenia, and severe congenital malformations of the heart; and a more common non-syndromic form that is not associated with other congenital abnormalities. The latter form accounts for approximately 80% of all cases of biliary atresia. It is postulated that the syndromic form (also known as embryonic type) results from an insult during the differentiation of the hepatic diverticulum from the foregut of the embryo. The non-syndromic form is thought to result from an insult late in gestation⁶.

The pathology of the extra hepatic biliary system widely varies in these patients, and the following classification is based on the predominant site of atresia: Type I involves obliteration of the common duct, the proximal ducts are patent; Type II is characterized by atresia of the hepatic duct, with cystic structures found in the porta hepatis; Type III (>90% of patients) involves atresia of the right and left hepatic ducts to the level of the porta hepatis. These variants should not be confused with intrahepatic biliary hypoplasia, which comprises a group of distinct and surgically non correctable disorders.

Various aetiologies have been suggested. These include intrauterine or early postnatal viral infections, metabolic insults, abnormalities in bile duct morphogenesis or pancreaticobiliary ductal malformation, genetic factors, vascular insults, and immunological factors. No single unifying hypothesis has explained the varying presentations of biliary atresia indicating that BA is probably not a single disease entity. Several studies have identified elevated antibody titers to reovirus type 3 in patients with biliary atresia when compared with controls. They reported a high prevalence of positive serologic results for reovirus in patients with atresia, but this finding was not replicated in a subsequent study⁷. Some other studies failed to demonstrate evidence of viral (reovirus) infection in infants with cholestasis⁸. Other viruses, including rotavirus and cytomegalovirus (CMV), have also been implicated. No single agent has been identified as causative for biliary atresia. With regard to CMV, Tarr et al, assessed 23 patients with BA using liver histology, serology and culture and found five (24%) CMV positive patients⁹. Fischler reported CMV infection in almost 25% of affected infants using immunoglobulin M (IgM) serology¹⁰. They also detected CMV DNA in the liver of 50% of children with atresia whose mothers were CMV-positive. Similarly, a Brazilian study identified positive IgM for CMV in 28.5% of patients with BA or a choledochal cyst. Interestingly, an even higher frequency of

CMV infection has been found in cases of idiopathic neonatal hepatitis, providing support to the concept that both disorders are ends of the same pathological spectrum, originally described by Landing as infantile obstructive cholangiopathy¹¹. The role of immune dysfunction has been considered. Sokol et al, suggested that, from the molecular position, viral antigens may cross-react with biliary antigens, activating an immune response against the virus, and also against biliary antigens. Therefore, persistence of immune injury to bile duct cells may lead to disease progression. Several researchers have studied the potential effects of other aetiological agents, including teratogens and immunological factors. Again, no clear correlations with BA have been established.

Most children present within four to six weeks after birth with conjugated jaundice, acholic stools and dark urine. If BA is diagnosed within the first two to three months after birth, a KPE can successfully restore bile flow into the intestinal tract in up to 90% of patients leading to improvement of jaundice and delayed progression of liver disease¹². However, if untreated, liver cirrhosis develops within the first months of life and the majority of children will die before the age of two years in the absence of liver transplantation. In addition, children who have had an unsuccessful portoenterostomy also require liver transplantation, usually before 2-5 years¹³.

In 1959, Kasai and Suzuki¹⁴ introduced hepatic portoenterostomy to reestablish bile flow in BA and it was the first breakthrough in the treatment of BA. It is now accepted that early diagnosis and timely surgery have a significant impact on long-term prognosis. While an early KPE improves the outcome of infants with BA, complications are still common. These include ascending cholangitis, portal hypertension, pruritis, malnutrition and chronic liver failure.

The most frequent early complication is ascending cholangitis, and its treatment is key for the preservation of bile flow and to improve the prognosis of the patient. Ascending cholangitis

occurs in 40 to 90% of surgically treated children¹⁵ and recurrent post-operative cholangitis is associated with obliteration of the intra-hepatic bile ducts and progression to liver cirrhosis.

Portal hypertension is the second most frequent complication of atresia. Its presence depends on the degree of liver fibrosis at KPE.

Longer term complications include fat malabsorption, malnutrition and fat soluble vitamin deficiency. Vitamin K dependent coagulopathy may occur as may vitamin D deficiency, which leads to a reduction in bone density and rickets. Clinical deficiencies of vitamin A and E are unusual with suitable supplementation, but peripheral neuropathy secondary to vitamin E deficiency in cholestasis is well recognized. Close follow-up after surgery is therefore required. Delayed psychomotor development is observed in patients who present with progressive chronic liver disease, apparently associated with malnutrition.

The most important long-term prognostic factors in predicting outcome after the Kasai procedure appear to be age at time of surgery, achievement of biliary drainage, experience of the centre, occurrence of ascending cholangitis, as well as pre-operative needle liver biopsy results such as the degree of liver fibrosis and of intrahepatic bile duct injury¹⁶.

Age at the time of the Kasai procedure is perhaps the most important prognostic indicator. Most reports state that the best outcomes, in both initial success and long-term survival, occur in patients younger than 60–70 days at the time of operation (68% 10 year survival). The Japanese Biliary Atresia Registry records favourable outcomes up to 90 days of age, with a rapid drop in success after that point. Many other series report that performance of a Kasai procedure in infants after 70 days of age is a risk factor for a poor outcome; however, some do not agree with this. Hanmin et al proved that Kasai may be performed successfully in all infants presenting up

to 120 days of age¹⁷.

Even if it is a very important postoperative prognostic factor, primary biliary drainage is not a guarantee of the long-term success after a KPE. However, patients who do not achieve primary biliary drainage after a KPE will never do so. Surgical treatment via a second (redo) Kasai procedure for patients who did not achieve primary drainage as well as for those who had initial drainage but subsequent cessation, was met with initial interest following case reports and a small series that demonstrated successful bile drainage. Recent reports, however, suggest that redo KPE is not a useful strategy in the vast majority of patients¹⁸.

If KPE is not performed, fibrosis will progress to end-stage cirrhosis and death in the first year of life in 50 to 80% of children and in 90 to 100% of patients by the third year of life.

The survival of infants born with BA has improved over the last 30 past years. Of eleven infants born with BA in one region in England during the period 1971-73 only one child survived to 10 years¹⁹. In contrast about 90% of children in England and Wales with BA are presently surviving as a result of KPE and liver transplantation²⁰. There was a similar improvement in the USA.

Prior to the introduction of the Kasai procedure the mean survival time in the USA was approximately 19 months²¹. A later multi-centre retrospective study of 104 infants with BA, diagnosed between 1997 and 2000²², showed that at age 24 months 56% of children were alive with native livers, 40% had undergone liver transplantation and 4% had died without undergoing liver transplantation (attributable to congenital heart diseases). These data led to a UK Department of Health directive indicating that all infants with suspected biliary atresia should be referred to one of three designated centres (St James Hospital in Leeds, Birmingham Children's

Hospital and King's College Hospital, London) where both the Kasai operation and, if necessary, liver transplantation could be offered.

The impact of the centralisation of biliary atresia surgery in the UK has recently been assessed. A total of 148 infants with biliary atresia were treated between January 1999 and June 2002. A Kasai PE was carried out in 142 and primary liver transplant in five (3%). Early clearance of jaundice after KPE was achieved in 57% of infants, compared to 55% in an earlier series. Of 135 children who survived, 62% still had their native liver and 38% had received transplants compared to 40% in the earlier series. The overall 4year estimated survival was 89% (95% CI 82% to 94%) compared to 85% (95% CI 77% to 92%) in the pre-centralised era, suggesting that centralisation of surgery did not lead to improved survival.

In a **Canadian** study²³, 230 patients with BA were identified. The median age at KPE was 64 days. The overall 4 year post-Kasai PE native liver survival was 39%.

Tohoku University, a Japanese centre with the world's longest running series of portoenterostomies performed between 1951 and 1998 analysed the development in long-term survival patterns²⁴. It included a comparison of hematologic and biochemical data as well as quality of life analysis in a group of Japanese patients. Long-term survival rate in the Japanese BA patients increased dramatically from 1 to 17 years after 1975. The quality of life of survivors was comparable in Japan and England²⁵. The best outcomes were achieved when HPE was performed before three months of age.

In developed countries, the outlook for patients with BA has improved remarkably owing to early referral, good diagnostic facilities and access to surgery and liver transplantation. In the UK, USA, Taiwan, Thailand and Argentine the use of a cheap, non-invasive screening method for cholestatic infants has proven that an infant stool colour card is helpful for parents and primary

caregivers; it increases early referrals of BA infants to specialised centres and early surgery with an increased chance of success and a good outcome. In Japan parents receive written advice on the serious implications of pale stools and dark urine associated with jaundice in early age. This advice is reinforced with posters in infant welfare clinics as well as the 'well baby' review at 4 weeks of age²⁶.

In developing countries, especially in Sub-Saharan Africa, there is little information on the current outlook for these children. In Nigeria²⁷, a study of 14 patients with BA managed from 1991 to 2004 at Ahmadou University Hospital, Zaria, with a median age of 16 weeks (between 6 and 24 weeks) showed that 11 patients at presentation already had liver cirrhosis and raised LFTs and could not have corrective surgery. Three had a Kasai PE but of these three patients, one died from acute gastroenteritis at 2 years, one from cholangitis after 8 weeks, and the third one died from anaesthetic complications. Of the 11 patients who did not have surgery, 10 were lost to follow up and their outcome is unknown. The remaining patient had a laparotomy and liver biopsy and subsequently died from peritonitis.

Mabogunje (1987) reported 36 histologically confirmed cases of BA in infants and children aged 2-20 months from one of the tertiary health centres in Nigeria within a 13 year study period, where almost half of them died, 19 were lost to follow-up and 2 survived with persistent jaundice. In this same report, a KPE was performed on four of the children, however bile flow was not established in any of the children.

In South Africa, a study of 71 infants with BA (from 1993 to 1998) was performed at Baragwanah Hospital, Soweto²⁸. The findings appear to confirm a high incidence and poorer outcome of BA in Black infants from Soweto; of the 71, only 10(14%) were jaundice free.

In Egypt, Ahmad (2009) found that 15 of 30 cases (50%) had a successful Kasai, one died 3

weeks after surgery from fulminant hepatic necrosis and multiorgan failure, 4 were lost to follow up, 2 were transplanted, 8 were awaiting LTx²⁹.

In South Africa no recent studies have evaluated the long-term outcome of biliary atresia. This study describes the outcome of infants and children with biliary atresia who have been treated at our tertiary hospital. In this study we describe factors that potentially influence prognosis (e.g. age of referral, nutrition, and post-operative cholangitis), the frequency of complications (e.g. intestinal hemorrhage, spontaneous bacterial peritonitis, and liver failure) and the survival of children with biliary atresia. These data are necessary to improve the management of biliary atresia in this setting. The study will unfortunately not be able to assess the incidence of biliary atresia in South Africa.

Patients and Methods

Study Site

Tygerberg Children's Hospital (TCH), Cape Town is a large tertiary centre that accepts referrals from the Eastern, Northern and Western Cape Provinces in South Africa. Facilities for Kasai surgery (porto/ hepatico enterostomy) are available.

Patients were enrolled in the study if they met the following criteria:

Inclusion Criteria

1. Admitted to TCH between January 1997 and December 2011.
2. Presenting to TCH with cholestatic liver disease:

Diagnosis of BA based on:

- a. Clinical features (persistent acholic stools and no other aetiology for the cholestasis),

- b. Biochemical (pronounced elevation of the GGT, greater than ALT)
- c. Compatible histology
- d. Ultrasound compatible with biliary atresia
- e. Operative cholangiogram (where available)
- f. Hepatobiliary scintiscanning (where available)

Exclusion Criteria

Where the diagnosis of BA could not confidently be confirmed (as described in the inclusion criteria), patients were excluded from the study.

Ultrasonography was used to exclude specific anomalies of the extrahepatic biliary system such as choledocal cyst. BASM (BA splenic malformations) was defined as the presence of malformations (polyplenia, asplenia) including situs inversus and cardiac anomalies in conjunction with BA.

The study was performed according to the guidelines of the Medical Ethical Committee of the University of Stellenbosch.

Data collected included birth date, date of presentation to health centre with first symptoms, whether the Kasai operation was performed or not, date of Kasai operation, biochemical evaluation of liver function (total/ conjugated serum bilirubin, prothrombin time and transaminases) also bile duct enzymes before and after Kasai operation, abdominal ultrasound to assess cirrhosis, oesophagoscopy to assess oesophageal varices and portal hypertension, medication used at follow-up, date of last follow-up and final outcome, date and cause of death and reasons why Kasai operation was not performed. Due to the retrospective nature of the study, data collection in some cases was incomplete.

Early success of the Kasai operation was defined by complete clearance of jaundice and with

conjugated bilirubin level normal or less than 20mmoles per liter within six months post-surgery. The bile flow was evaluated on the basis of stool colour. Patients had good bile drainage if they had pigmented stools and their jaundice resolved; patients with partial bile clearance had pigmented stools but persistent jaundice; and those with failed bile drainage had persistent acholic stools and jaundice. Portal hypertension was considered present when at least one of the following physical signs was present: splenomegaly, ascites and collateral veins or esophageal varices at oesophagoscopy. Cholangitis was diagnosed if the patient suffered from high fever, with worsening jaundice, acholic stools, or deranged LFTs and bilirubin as well as positive blood culture.

In terms of post-operative management, the aim of antibiotic therapy was for the prevention or treatment of ascending cholangitis. Ursodeoxycholic acid (UDCA) for the promotion of choleresis and prevention of fibrosis and progression of the liver disease was seldom used. The most common therapeutic options to treat pruritis included Rifampicin, Phenobarbital and anti histaminic drugs. Maintaining the nutritional status was essential to a good outcome.

Macronutrient, micronutrient and fat-soluble vitamins were given to prevent deficiencies especially vitamin A, D, E and K deficiencies. Breastfeeding was acceptable after KPE. Infant formula with medium-chain triglycerides was given to all non-breastfed infants.

All patients were assessed for other causes of cholestatic liver disease. This included looking at clinical features (for Alagille syndrome), laboratory investigations (TORCHES screen for some congenital infections), urine reducing substances for galactosaemia, alpha 1 antitrypsin level for alpha1 antitrypsin deficiency), sepsis screen, as well as an ultrasound to exclude a choledocal cyst.

The date of diagnosis was the first date that the diagnosis of BA was recorded for the patients.

On the statistical analysis, survival rates were analyzed with the Kaplan-Meier method and compared using the log-rank test. A p value of less than 0.05 was considered statistically significant. Analyses were performed using SPSS and Stata software.

Results

We found 37 cases of BA from 1997 to 2011 at our Children's Hospital. The median age of the study patients at age of presentation was 10.4 weeks. The diagnosis of BA was based on the clinical features (persistent acholic stools and jaundice), biochemical, and radiological data and was confirmed by hepatobiliary scintiscanning, operative cholangiogram findings, and histological examination of liver biopsy and resected biliary remnants.

Thirty two cases were isolated BA, 4 cases were BA associated with a choledocal/ liver cyst, and 1 case had BASM. Of the 37 patients, 7(18.9%) were lost to follow-up with their native liver in situ. Of these 7 patients, Kasai surgery was performed on 4, the remaining 3 had no surgery. A Kasai procedure was carried out in 23 patients (62.2%); The early and late postoperative complications were evaluated retrospectively. Referrals for LTx for those who did not improve after Kasai procedure or those who did not have Kasai were documented. One patient who did not have a Kasai PE underwent LTx and three are on the waiting list for LTx. All patients were followed up by our paediatric gastroenterology service.

Demography of patients

Table 1

Variables	Overall cohort
Number of patients	37
Male: female	1:1.6
Median age on admission at TCH(weeks)	9.96
Median age at Kasai operation(weeks)	10.85
Percentage of patients who underwent Kasai operation	62.2%
<60 days	17.4%
61-90 days	56.5%
>90 days	26.1%
BASM	3%
BA with choledocal or intrahepatic bile cyst	10.8%

Two patients file's data were incomplete. There were more females than males, the female-to-male ratio was 1.6: 1.

Gender

Table 2

Gender	Frequency	Percent
female	23	62.2
male	14	37.8
Total	37	100.0

Ethnic group

In terms of ethnicity, the study group included 75.6% Coloured, 18.9% Black and 5.4% Whites.

Among the Blacks, two were immigrants from Zimbabwe, the remainder were South Africans.

Table 3

Ethnic Group	Frequency	Percentage
Black	7	18.9
Coloured	28	75.6
White	2	5.4
Total	37	100.0

Referral age, delay to Kasai before and after admission to TCH

The mean age at presentation to the primary health services was 10.9 weeks (76.8 days), standard deviation 6.7 weeks (47 days). The mean patient age at presentation to our centre (TCH) was 12.9 weeks (90.5 days), standard deviation 7.7 weeks (54.3 days).

Age of presentation by Urban/Rural origin

Table 4

Origin	Age presentation to TBH mean	Age presentation to TBH - Std.Dev	Age presentation to TBH - 95.00%	Age presentation to TBH +95.00%	N
Rural	100.6000	67.38567	63.28306	107.3773	15
Urban	81.2727	44.28391	61.63834	100.9071	22

P value 0.0797

The majority of referrals 22(59.40%) were from urban and suburban areas while 15(40.6%) were from rural areas. We defined rural and urban areas based on the clinic / primary health care centre of the area of origin where the patient has presented for the first onset of his illness.

Of the 15 patients from rural areas, only 7 were eligible for surgery of whom 4 underwent surgery between 8 and 12 weeks, and 3 after 12 weeks of age. Of the 22 patients from urban and suburban areas, 16 were eligible for Kasai surgery of whom 4 underwent surgery at/ before 8 weeks, 9 between 8 and 12 weeks and 3 after 12 weeks of age. Compared to urban patients, rural patients presented to TCH 19 days later. The age at presentation to TCH for rural patients was 100.60 while it was 81.27 days for urban patients ($P= 0.079$). Of the 23 patients, 15(65.2%) were diagnosed before 12 weeks of age and 8 (34.8%) diagnosed after 12 weeks. There were several reasons for delayed presentation to TCH. In 10 of 15 patients, parents did not realize their child was unwell until failure to thrive and abdominal distension were identified. Several children were misdiagnosed (breast milk jaundice, physiological neonatal jaundice) and parents were repeatedly reassured at referring health care centres that jaundice was physiological. Three patients presented timeously but had a delay in surgery- the reason for this delay was not determined. There were no delays due to parental reluctance to accept the diagnosis of serious liver disease or urgent surgery. Another reason for delayed presentation of rural infants was geographical (far from TCH) and poor infrastructure in terms of patient transport. The mean time to surgery from admission to our centre was 21.6 days with standard deviation 14.620 days.

Clinical features

Jaundice, pale stools and dark urine were present in all 37 patients, with hepatomegaly in 27 (72.9%), hepatosplenomegaly in 10 (27%) and abdominal distension in 6 patients (16.2%). Three patients had choledocal cysts and one a liver cyst. The BASM phenotype (associated anomalies

such as cardiac anomalies) was diagnosed in one patient (2.7%). Three had galactosuria but no galactosemia. Two were CMV IgM or pp65 positive.

Kasai Portoenterostomy and age at surgery

Of the 37 cases, 23(62.2%) were eligible for Kasai surgery. The median patient age at surgery was 10.85 weeks (range 5.5 and 19 weeks). Of the 23 patients, 15(65.2%) were diagnosed before 12 weeks of age and 8(34.8%) diagnosed after 12 weeks. Most of the cases were clinically diagnosed in primary or secondary health services (district hospital and clinics), and diagnosis was confirmed at TCH. Fourteen (37.8%) other patients did not undergo a Kasai PE or any of its variants (hepatico jejunostomy) because they had advanced liver disease with signs of liver cirrhosis, chronic liver failure or severe failure to thrive. Two of these patients, with multiple liver or choledocal cysts, underwent a cystenterostomy and drainage by pigtail catheter at 24 and 43 weeks of age respectively (no Kasai performed). Seventeen (73.9%) of the Kasai PE were performed before or at age of 12 weeks while the remaining 6 (26.1 %) were operated after 12 weeks of age.

Management post Kasai

Of the 23 Kasai PEs performed, 2 patients (with a choledochal cyst and intrahepatic bile cyst respectively required a cystenterostomy or cholecystojejunostomy. After surgery, antibiotics e.g. Bactrim or IV Ampicillin and IV Gentamycin (in 82% of patients) were prescribed; steroids (IV Methylprednisolone or oral Prednisone) were given for 10 to 14 days after surgery (in 43.5% of patients). Rifampicin was given to most of the patients for variable duration after surgery. All patients received Vitamin A, D and E supplements from admission. Nutritional support was given to provide a diet rich in medium chain fatty acids and increased caloric and protein content.

Early post-operative complications (occurring within 3 to 6 months after surgery)

Confirmed cholangitis occurred in 9 (39.1%) out of 23 patients, most commonly in the first three to six months post Kasai PE. The risk was less in those patients with good bile flow compared to those with partial bile drainage (Table 6). Cholangitis was difficult to differentiate from a generalized viral illness in which a similar exacerbation in jaundice and deranged LFTs may occur. In our patients, blood cultures were obtained prior to starting antibiotics. A number of organisms were cultured: E. Coli, Staph epidermidis, Proteus, Klebsiella pneumonia, H. influenza, Serratia morascens. The patients were treated with intravenous broad spectrum antibiotics- first line Cefotaxime/Gentamycin + Ampicillin and the third line Meropenem, Vancomycin or Ciprofloxacin. The treatment duration was 7-14 days. Cases of abdominal wall surgical wound sepsis were noted in 2 patients, umbilical hernia in 2 patients, and umbilical sepsis in one. A bowel obstruction in one patient due to adhesions required adhesiolysis and a case of anastomosis breakdown needed a repair. Two patients developed pneumomediastinum and right lower lobe collapse requiring PICU admission. Three patients developed sepsis which was treated adequately with broad spectrum antibiotics (Table 5).

Table 5

Main post-operative complications	No of patients
Cholangitis	9(39%)
GI bleeding	10(43.4%)
Portal hypertension	11(47.8%)
Sepsis	6(26%)
Hepatic encephalopathy	2(8.6%)
Liver cirrhosis	12(52.1%)
Infections (CMV, HSV, Mumps)	6(26%)
Vitamin Deficiencies	5(21.7%)
Pruritus	8(34.8%)

Late post-operative complications (occurring after 6 months of surgery)

Portal hypertension was detected in 11 patients (47.8%) in the late post-operative period. The age of onset of portal hypertension was not documented.

Gastrointestinal bleeding occurred in 10 patients (43.4%) in the postoperative period early bleeds in 4 months and later bleeds at 12 months. An endoscopic examination was performed for all of them. Two had both oesophageal and rectal bleeds. Four underwent injection sclerotherapy and were started on Octreotide.

Cases of liver cirrhosis (characterized by hard liver), splenomegaly, abdominal distention, histological and /or ultrasonography signs, were present in 11(47.8%) patients, 5 of whom presented as such prior to surgery.

There were 5 cases of chronic liver failure, and one of hepatic encephalopathy. Eight (34.8%)

patients complained of pruritus. Five of these patients had worsening jaundice and deranged LFTs.. In the remainder, the bilirubin and LFTs were normal. Almost all the children with pruritus were started on Rifampicin and in a few patients, Phenobarbital and UDCA were added.

Nutritional complications

Cases of avitaminosis (A, D, E, and K) were established in five patients. Three cases of malnutrition were identified. Malnutrition may have been secondary to fat soluble vitamins malabsorption caused by the absence of bile salts or to chronic infection/ illness. Two cases of peripheral neuropathy were documented and may have been related to vitamin E deficiency. Most patients received Multivitaminsm Folate and elemental iron were added depending on the patient's clinical status. Baseline fat soluble vitamin levels were performed in our laboratory (vitamin A, D, E) before or after surgery. Apart from two, all the patients tested had normal blood vitamin levels within the normal ages. Patients with vitamin D deficiency corrected rapidly with supplements while those with vitamin E deficiency did not respond well to supplements.

Infections

Congenital infection (TORCHES), viral hepatitis (A, B, C) and septic screens were performed in most of the patients. HIV screening was done in all patients and all were HIV negative. Three of them were HIV exposed but PCR negative. A few patients developed nosocomial infections. There were two confirmed cases of CMV and one of HSV infection. One patient developed mumps. Three had sepsis and severe adinoviral infection (adenovirus) which required treatment in PICU. Two had pulmonary tuberculosis and two developed acute gastroenteritis.

Success

Kasai procedure was performed in 23 patients; it was successful in most of the operations (19

cases) but failed in 4 cases. Surgery was considered successful if bile flow was established with pigmented stools and resolution of jaundice. Thirteen of our patients had successful bile drainage within 3 months of surgery. Six had only partial success with pigmented stools but persistent jaundice. Four procedures failed to establish bile flow with secondary persistent pale stools and jaundice.

Table 6 showing correlation between patient's age (days) and grading of biliary drainage after Kasai PE (%) and numbers ().

Table 6

Patient's age (days)	Grading of biliary drainage after Kasai PE (%) and number of patients involved ().		
	Good	Partial	Failed
<60	50%(2)	25%(1)	25%(1)
60-90	42.8%(6)	28.5%(4)	28.5%(4)
>90	60%(3)	20%(1)	20%(1)

Of the patients in whom partial bile drainage was initially achieved, most improved and their jaundice cleared at 6 to 12 months. Those with failed bile drainage developed complications such as portal hypertension, liver cirrhosis, progressive chronic liver failure, malnutrition and end-stage liver disease.

Liver biochemistry

Success of surgery was evaluated performing liver biochemistry. Total serum bilirubin levels returned to normal limits (below 20mmol/l) in 16 patients; 12 of these patients also normalised their serum GGT and ALP. Four patients initially normalised their total serum bilirubin levels but then deteriorated again. Eight patients had deterioration in liver function with rising bilirubin

levels and deranged liver biochemistry. Cirrhosis and portal hypertension were accompanied with raised liver enzymes (GGT, ALP) and prolonged INR, while bleeding complications were associated with prolonged INR, PTT and low platelets.

Serum alpha-fetoprotein levels were normal in all 18 (48.6%) patients studied.

Liver biopsy and other investigations

Liver histology was used to assess eligibility for KPE. Liver biopsies were performed on 36 patients (either prior or during Kasai surgery) while in one patient, the histology results could not be traced but HIDA and operative cholangiogram were conclusive for BA. In all 36 patients, the diagnosis of BA was confirmed. The portal plate showed atretic, fibrosed bile ducts, bile duct proliferation and bridging fibrosis in those patients (23) who had KPE. Liver biopsies (wedge or core needle) results in 36 patients were consistent with features of BA such as bile duct proliferation, supportive of extrahepatic bile duct obstruction. Six biopsies showed features of liver cirrhosis. Operative cholangiogram was performed on 22 patients. The surgeon was unable to canalise the bile duct in the remainder of the patients who had a KPE. The cholangiogram helped to confirm the diagnosis of BA as well as of choledochal and liver cysts in 4 cases. HIDA scan performed in 24 babies demonstrated the absence of excretion of bile into the gut with dilated gall bladders which are in keeping with BA.

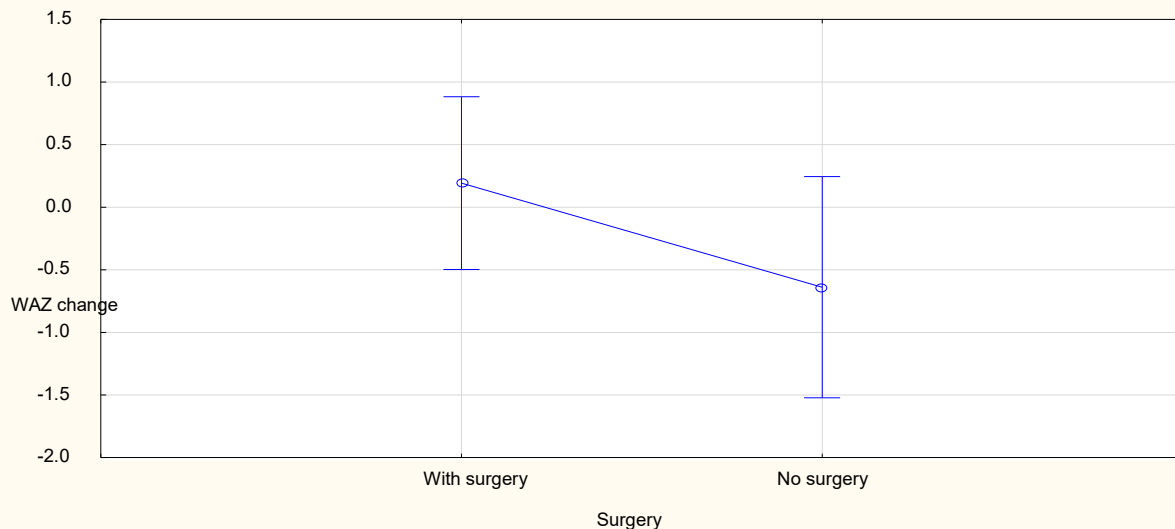
Growth parameters

Growth parameters were assessed on admission date, before and after Kasai PE at monthly to 2 monthly follow up visits. The mean weight on admission was 4.7kg (95% CI 4-4.5) and the median 4.6kg (standard deviation 0.95), the mean Z-score at admission was 0 to -2 Z-score.

Using the Weight for Age Z-score, we compared good and poor outcome patients. Of the 37 cases with BA 21(56.7%) had good weight gain, 12(32.4%) poor weight gain, 2(5.4%) weight loss and 2(5.4%) had missing data. With respect to length, 23(65.7%) grew well, 5(14.3%) had faltering growth and in 7(20%) no data was available. Below is the z-score graphics expressing the weight of these patients.

Comparison of change in Z score (last weight vs admission WAZ)

Figure 1



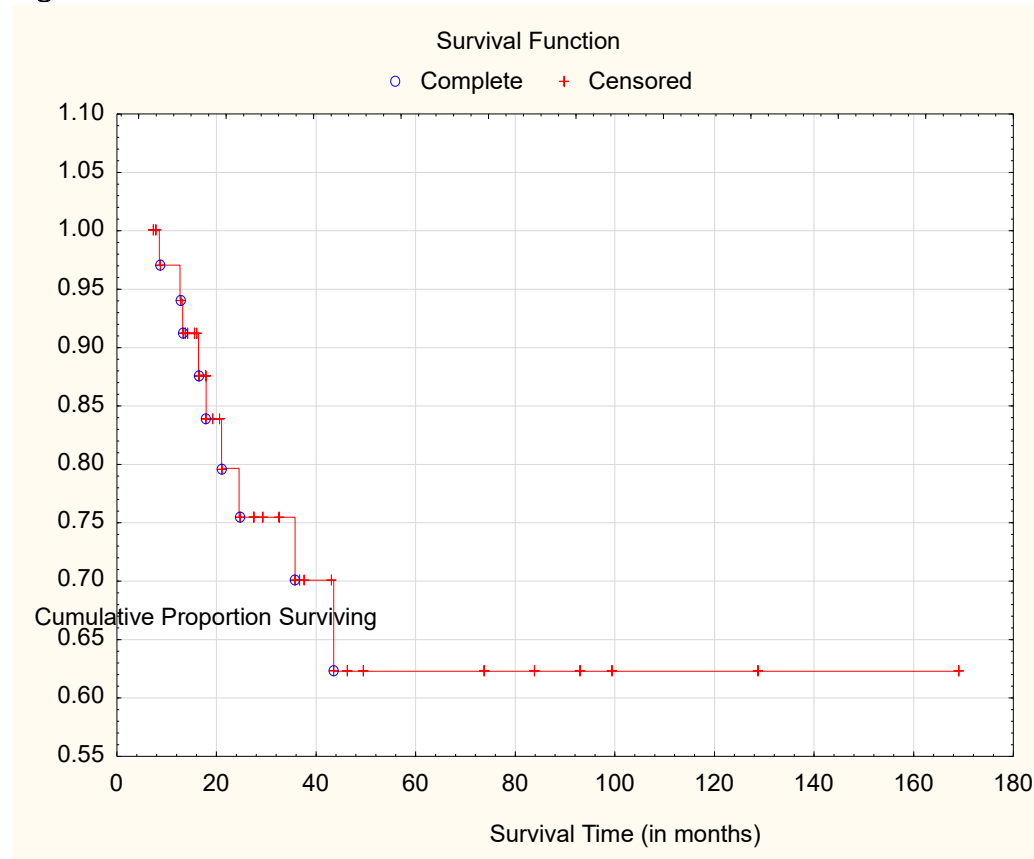
Survival and outcome of patients with biliary atresia

Patient survival was defined as the time period between date of birth and the censoring date (last date known alive) or patient death. Mean follow-up in survivors was 3.15 years, standard deviation 3.02 with median 2.16 years (range 0.5-14) for all the patients.

Survival to all patients.

Censored on loss to follow-up and survival with last follow-up .Survival for full sample

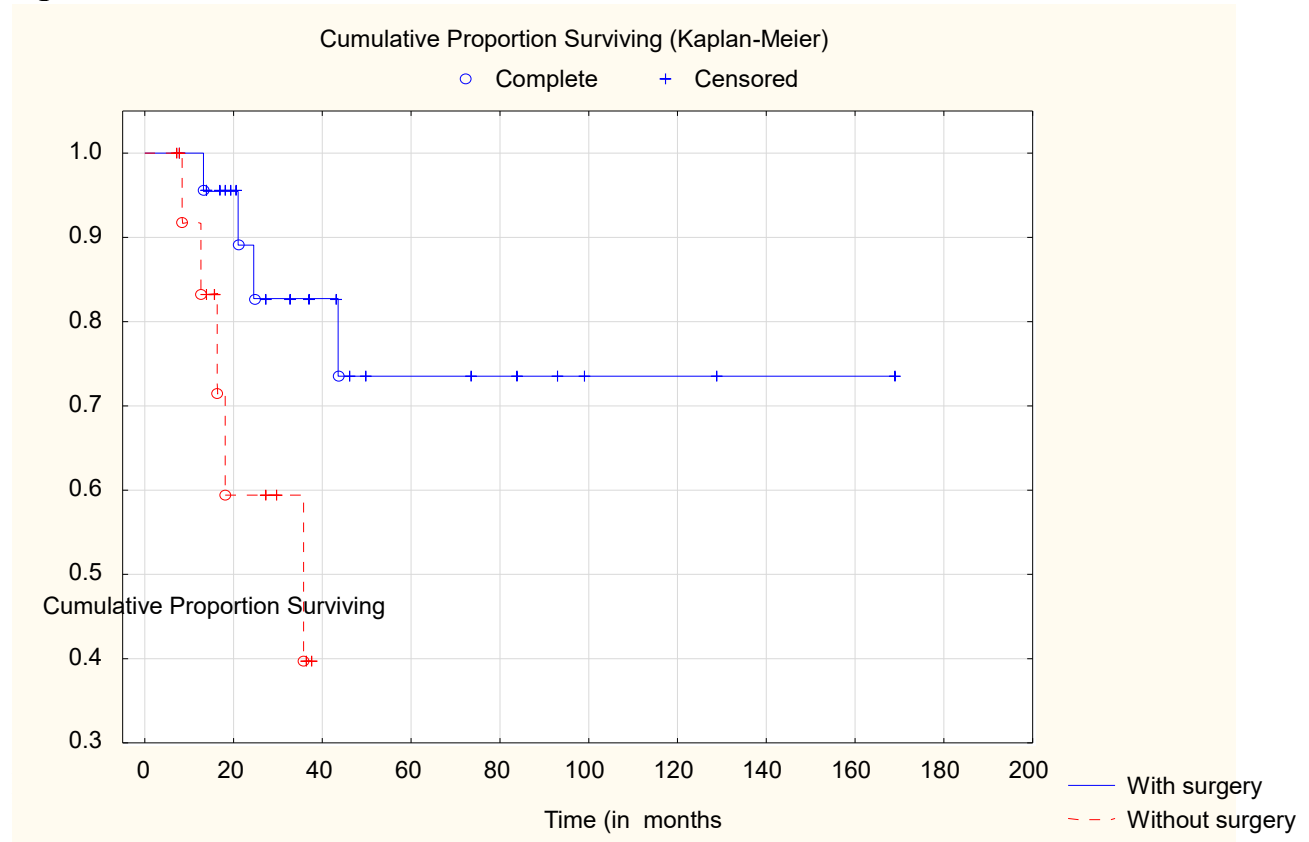
Figure 2



For cases who were not operated on, the two years survival with native liver was 58 %. The mean age at last follow of these patients was 1.68 year, median 1.3, standard deviation 0.9. The mean age of follow up in this group was 4.1 year (median 2.88, standard deviation 3.5). Better survival with native liver was associated with early KPE, good bile flow in the postoperative period, good pre and postoperative management as well as aggressive nutritional management^{30, 31}

Survival comparing the KPE/non-KPE groups.

Figure 3



The Log Rank test did not reach statistical significance possibly due to the small sample size

Patients who underwent Kasai surgery had a longer survival time compared to those who were not operated on. Most of the non-operated patients died at an early age. The mean age at time of death for the 10 deceased was 25.3 months, median 19.5, standard deviation 16.2 (range 8.5 to 59) months.

In those who had Kasai surgery, deaths were due to sepsis in 3 patients and to an unknown cause in one (who deceased at home). For those who did not undergo surgery, hepatic encephalopathy

in one, end stage liver disease and severe failure to thrive in three patients were the cause of death (2 died at home - one had KPE and one not). Four were not referred for LTx. Six patients were lost to follow up and their outcome is unknown.

Causes of death in all patients irrespective whether KPE was done

Table 7

Main causes of death	No of patients
Sepsis	3
Hepatic encephalopathy	1
End-stage liver disease	3
Excessive esophageal bleeding	1
Unknown cause(died at home)	2

The median survival time in patients who underwent KPE surgery was longer (4.1 years) compared to the survival time in patients without KPE which was much shorter (1.68 year).

Outcome of patients who underwent Kasai surgery

Table 8

Age (days) at surgery	Alive	Lost to follow up	Died
<60	2	1	1
60-90	9	2	2
>90	4	1	1

Of the 23 patients in whom surgery was performed, 15 were documented still alive at last follow up date, 4 were lost to follow up and their outcome is unknown since last seen at 8, 21 and 37 months of age respectively. Four were dead at 12, 13, 21 months and 4 year of age. Of the 15 still

alive, 4 are on the active/inactive waiting list for LTx. Of the 14 patients who did not have KPE, 6 died, 3 are lost to follow up and 4 are documented alive (one of whom underwent LTx, one is on the inactive waiting list for LTx and 3 are being investigated for referral for LTx).

Results after Kasai PE

Table 9

Result	Number	Percentage
Successful KPE	19	82.6%
Known alive at last follow up	15	65.2%
Lost to follow up	4	17.4%
Death	4	17.4%
Candidates on Liver transplant waiting list (included in the 15 alive patients)	4	17.4%

Results without Kasai PE

Table 10

Result	Number	Percentage
Patients who did not have KPE	14	37.8%(of the 37)
Death	6	42.8%(of the 14)
Lost to follow up	3	21.4%(of the 14)
Alive after Liver transplant	1	7%
Awaiting Liver transplant	1	7%
Alive not yet referred for LTx	3	21.4%

Patients lost to follow up

In our study, 7 patients were lost to follow up. Of the 7 patients, 6(85.7%) were from rural areas. Attempts to trace patients by means of the hospital information system (clinicom), telephonic calls to children's parents or relatives, and contact with RXH liver transplant unit have been tried several times. Of the 7 patients, 3 patients were traced of whom 2 died (the information was abstained from the relatives of the deceased children) and one patient, 14 years old is on the inactive waiting list for liver transplant at RXH. In the 4 remaining patients the outcome is unknown, but they are more likely deceased than alive.

Discussion

BA is a rare but important and potentially treatable disorder as shown initially by Kasai and later by other medical workers. For decades, the Kasai portoenterostomy (KPE) has been the regular surgical procedure for BA worldwide. We analysed the presentation and outcome of BA patients treated in our centre from 1997 to 2011, with the aim of identifying prognostic factors in these patients. Many previous studies have analysed the prognostic factors associated with the Kasai PE and it is controversial as to which factors will predict a successful or failed KPE. The age at time of Kasai surgery is a potential factor that has been shown in multiple studies to correlate negatively with survival after KPE. The issue is whether the Kasai procedure is done within 60 or 90 days of life. In our study the survival and outcome of patients was not significantly impacted by the age at time of surgery. We believe that the numbers were too small to show a statistically significant difference. There was early jaundice clearance and drainage of bile in 50% of patients who underwent Kasai before or at 60 days of age, in 43.8% of those with surgery between 60 and 90 days; and in 60% of those in whom surgery was performed after 90 days of life. Of the 23 patients in whom surgery was performed, 15 were documented still alive (range 14 months to 14 years) at the last follow up date, 4 were lost to follow up and their outcome is unknown and 4 died. Of the 15 children still alive, 9 underwent surgery between 60 and 90 days (of whom 2 were lost to follow up and 2 died); 2 had surgery before or at 60 days (of whom one was lost to follow up and 1 died) and 4 had a KPE after 90 days of life (one was lost to follow up and 1 died). There was no significant difference in outcome for those who presented early at 60 days or late at 90 days of life. A factor which impacts time of surgery is timing of presentation of patients to the referral centre. In our study, we found that 32% were referred late with consequent

delay in surgery to after 90 days. The reasons for delayed referral were parents' ignorance of their child's clinical condition and awareness of need to seek health care as well as failure to appreciate the importance of jaundice in a young infant by medical staff. In a survey done by Howard ER et al, the reasons for late referral for effective surgery were almost identical to those found in our study³². The introduction of a newborn screening programme for BA in Western (UK, France), Asian (Japan, Taiwan) and American (Argentina) countries contributed to diagnosis within the first weeks of life with Kasai surgery subsequently performed at an early age 30-60 days of life. In the UK and Japan, a yellow alert educational programme was initiated to expedite the referral of the infants with BA to specialized centres. In Asia (Thailand and Taiwan), a stool colour card has been introduced to identify jaundiced infants with BA. It may be beneficial to introduce such health care policies in SA to improve the timing of referral for patients with BA.

In a review by Tan (Tan C, 1994), it is stated that the time of onset, rate of progression, and the severity of the disease process in BA varies from case to case and the author argues against determining prognosis purely on age at surgery.

Several recent studies have suggested that the expertise of the site and the experience of the surgeon performing the Kasai surgery are major prognostic factors; centers with greater case experience show evidence of better survival rates. In the UK where they register annually around 2000 to 3000 cases of BA, a centralisation policy was implemented in 1999 restricting the referral and management of all BA patients throughout the country to 3 skilled pediatric hepatology units. In France, a decentralisation policy was maintained with efforts to promote collaboration and ensure high standards of care among all the treatment centers. These different policies led to an increase in 4-year patient survival rates from 85 to 89% (UK) and 74% to 87%

(France) between 1997 and 2002.

In SA KPE surgery is mostly restricted to tertiary university hospitals and LTx are only done in two centres- Red Cross Children's Hospital in Cape Town and Donald Gordon Hospital in Gauteng. Within TCH, only senior paediatric surgeons perform KPE surgery, and the post-operative care is similar to that of other institutions.

Other factors which influence survival include postoperative complications. We were unable to report on the number of episodes of post-operative cholangitis as consistent diagnostic criteria were not used.

The effect of steroids (introduced after 2007 as part of post-operative treatment) on the outcome post-surgery could not be assessed due to the limited sample and lack of a uniform dosing regimen for all post-operative patients. In fact, these liver diseases trigger fat soluble vitamins (A, D, E and K) deficiency and consequently a malabsorption of the nutrients.

Our study unfortunately was not able to assess the incidence of BA in our tertiary centre. Our BA patients were mostly born in the drainage areas of our tertiary centre with the problem of obstructive jaundice. It was not possible to establish the total number of babies born at various clinics, day and district hospitals over the same period as our study.

The few studies from developing countries which assessed outcome differ from those from developed countries. In Nigeria, one report³³ of 36 histologically confirmed cases of BA in infants (range 2-20 months) over a 13 year study period, found that almost half of the patients died, 19 were lost to follow up and 2 survived with persistent jaundice. An Egyptian study showed that of 30 patients who underwent Kasai PE, 15 (50%) had a successful Kasai, one died 3 weeks after surgery from fulminant hepatic necrosis and multiorgan failure, 4 were lost to

follow up and 8 were candidates for LTx.

During our study period, 23 patients underwent Kasai surgery of whom 19 had a successful outcome. The study showed that 15 (65.2%) patients were still alive at the time of conclusion of the study, four (17.4%) died during the postoperative period from sepsis, end-stage liver disease, hepatic encephalopathy and multiorgan failure and 4 (17.4%) were lost to follow up. Of the 15 patients (out of the 23) still alive (range 1-14years), 4 are eligible for LTx and are on the active or inactive waiting lists for LTx and 11 are still followed up in our clinic.

Based on our data, we believe the KPE is a useful initial step even for those who present at an older age, but without established liver cirrhosis. Our results are encouraging but still not as good as those of Western countries (UK, USA, France) and Asian countries (Japan, Taiwan). It is remarkable that general health care underwent many developments in SA especially with public health systems with which all the South Africans with low income, adult and children, have access to health care. The Kasai patient's survival rate has increased over the ten years.

Conclusion

In the last five decades, BA has gone from a fatal disease to one that is treatable for most children. The Kasai PE is the optimal initial management for patients with BA, even for selected cases presenting after 90 days. Early PE is more likely to result in improved outcomes. Surgery performed by an experienced paediatric surgeon could result in a better outcome (and prevent a number of failed PE performed at any age). Long-term survival for patients with BA may exceed 90% if some conditions are fulfilled. Policies to ensure timely diagnosis and intervention, therapeutic surgery and good nutrition are all needed to enhance the outcome of patients with BA. Patients who had successful KPE surgery grow and develop better and are ultimately better liver transplant candidates than malnourished children. Early identification and referral of babies with obstructive jaundice is essential to offer Kasai PE at the most favourable time. Based on the literature, the introduction of the newborn screening programme for BA patients helped to diagnose patients within the first weeks of life with earlier Kasai surgery (at 30-60 days of life) and with subsequent outcome and survival rate. Health care policies to improve the timing of referral for patients with BA should be introduced in SA to achieve this.

This study is one of the first to document the outcomes of children with BA in SA. Further studies are needed to analyse incidence and long-term outcomes of children with BA in the Western Cape and in SA.

Despite all improvements in terms of early diagnosis and treatment made in the past 50 years, BA remains a poorly understood disease. Its cause remains unknown, yet if found it may hold the key to advancement in the treatment and possible prevention of the disease. Knowledge gained in understanding the role of the immune system in the aetiology of BA may provide new and

promising therapeutic strategies. This will allow more significant data to guide additional potential improvements in the care and hopefully look for much needed light on this dark chapter of paediatrics.

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Appendices

Appendix 1: Protocol

A Retrospective Review of the Outcome of Children Presenting to Tygerberg Children's Hospital with Biliary Atresia

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Introduction

Biliary atresia (BA) is a serious but relatively rare congenital disease of the bile ducts and liver and frequently has fatal complications. The reported incidence varies from 5/100000 births per year in Holland to 6/100000 in UK to 32/100000 in French Polynesia (Christophe et al, 2001). The incidence in South Africa is unknown. The precise mechanism underlying the pathogenesis of the BA remains unclear. It is characterized by progressive fibrotic obliteration and obstruction of the extra hepatic biliary tree ultimately leading to liver cirrhosis and liver failure. Most children present within four to six weeks with conjugated jaundice, pale, acholic stools and dark urine.

If BA is diagnosed within the first two to three months after birth, a Kasai portoenterostomy (KPE) which connects the bile drainage from the liver to the intestinal tract, can successfully restore bile flow into the intestinal tract in 50% to 90% of patients. In some infants jaundice resolves and the progression of liver disease is delayed. However, if untreated, liver cirrhosis gradually develops within the first months of life and the majority of children die before the age of two years. After a KPE, complications such as ascending cholangitis (bacterial), poor growth and malnutrition, portal hypertension and liver failure may develop. Children who have not had a KPE performed within the first 3 months of life or who have had an unsuccessful KPE require liver transplantation (LTx), usually before 2-5 years of life.

The survival of infants born with BA has improved over the last 30 past years. Of eleven infants born with BA in one region in England during the period 1971-73 only one child survived to 10 years (Purricelli et al, 2004). In contrast to this, at present, in England and in Wales about 90% of children with BA are surviving, at least in the short-term through KPE and LTx. (Davenport et al, 2006

In South Africa (SA), the incidence of extra hepatic biliary atresia (EHBA) is still unknown and few studies have evaluated the long-term outcome after surgery. It is the most frequent indication for LTx in children in SA (Spearman et al, 2006). The outcome of all children with BA is however not well documented. This study will describe the outcome of infants and children with BA who have been treated at Tygerberg Children's Hospital (TCH). We will describe the parameters that influence prognosis (e.g. age of referral, nutrition and postoperative cholangitis); the frequency of complications (e.g. intestinal hemorrhage, spontaneous bacterial peritonitis, and liver failure) and the survival of children with BA in our institution. These data are necessary to identify factors leading to the delayed diagnosis of BA; to improve the management of biliary atresia and to optimize the selection of children for LTx.

Aim

The aim of this study is to review the presentation and long-term outcome of the infants with BA presenting to Tygerberg Children's Hospital.

Objectives

The objectives of the study are to describe the following features of children with BA who present to TCH:

1. Demographic details.
2. Clinical features at presentation.
3. Causes of delayed presentation.
4. Short term complications after surgery.
5. Long-term outcome

Research methodology

Study design

A retrospective descriptive study will be performed using data sourced from patient records.

Sample

Patients will be traced from a database of outpatients and inpatients seen at the Paediatric Gastroenterology outpatient clinic and Pediatric Gastroenterology inpatient service. The data will be collected from the clinical records of children identified. Information regarding outcome of referral for liver transplant will be requested from the paediatric liver transplant unit at Red Cross Children's Hospital.

Inclusion criteria

The following inclusion criteria will be used:

1. Children who presented to Tygerberg Hospital 1997 to 2011
2. Children with a diagnosis of biliary atresia as confirmed by clinical and biochemical findings and liver histology. When performed an operative cholangiogram will serve as further confirmation of the diagnosis.

Sample Size

It is estimated that the sample size will be 37 children.

Methodology

A datasheet will be used to record the applicable information from TCH file, folders, and clinical pathology results database. (Appendix 7). All the information will be analyzed using standard statistical methods.

Variables

The following variables will be recorded:

3. The demographic characteristics of the patients (gender, ethnicity, residential address). (Appendix 2)
4. The date of birth and age of presentation,
5. The delay from presentation to the health service and delay at Tygerberg Hospital to confirmation of the diagnosis, and causes of delayed presentation and confirmation.
6. Complications of surgery. (Appendix 6)
 - a. Cholangitis in the post-operative period.
 - b. Surgical complications.
 - c. Bile flow after surgery (determined by the presence of bile stained stool).
7. Histology of preoperative and/or intra-operative liver biopsies.
8. Measures of morbidity occurring after diagnosis:
 - a. Growth (weight and length). (Appendix 3)
 - b. Presence of fat soluble vitamin deficiencies (clinical and biochemical signs).
 - c. Liver biochemistry. (Appendix 4)
 - d. The presence of signs of portal hypertension.(Appendix 5)
 - e. Intestinal hemorrhage. (Appendix 5)
 - i. Age of first hemorrhage.
 - ii. Etiology of hemorrhage.
9. Number of admissions required
10. Therapy given (all drugs, vitamin supplements, nutritional support, surgical treatment, sclerotherapy)
11. Death and cause of death.
12. The following aspects regarding liver transplantation will be recorded:
 - a. Date referred for transplantation.
 - b. Date accepted for transplantation.
 - c. Date and outcome of liver transplant performed.

Statistical Methods

All the informations will be analyzed using standard statistical methods:

1. Variables will be summarized as medians and interquartile ranges.
2. Outcome data (survival, time to first variceal bleed, time to transplantation) will be described by survival curves (Kaplan Meier Curve).

Ethical considerations

Importance of this study to the community

There is no recent data available describing the outcome of children with BA in the Western Cape, South Africa . This data aims to identify areas where the management of children can potentially be improved (e.g. causes of late presentation, quality of nutritional support, and the effective management of complications such as variceal hemorrhage).

Anonymity

Patients will be assigned a study number in the database. The names and hospital numbers of the patients linked to the study numbers will be held in a separate database once data entry has been completed. This database will be kept secure in an alternative area. Patients who have been lost to follow-up will be recalled for review. The consent of the legal guardians will not be sought.

Budget

All costs will be wholly carried by the Department of Paediatrics and the principal researcher himself.

Biochemistry data

Patient ID	
Date	
Tprot	
Alb	
Glob	
Br tot	
Br conj	
Cholesterol	

AST	
ALT	
LDH	
ALP	
GGT	
Ca	
Phosphate	
INR	
PTT	
WBC	
Hb	
MCV	
Platelets	
RBC	

Complications

Patient Number

*Complication
date*

*Complication
description*

- Cholangitis*
- Portal hypertension*
- Wound sepsis*
- Bleeding*
- Long term complica*
- Malnutrition*
- avitaminosis*
- fat malabsorption*

Follow-up data

<i>Patient number</i>	<input type="text"/>
<i>Date of visit</i>	<input type="text"/>
<i>Jaundice</i>	<input type="checkbox"/>
<i>Splenomegaly</i>	<input type="checkbox"/>
<i>Hepatomegaly</i>	<input type="checkbox"/>
<i>Size of spleen</i>	<input type="text"/>
<i>Size of liver</i>	<input type="text"/>
<i>Varice bleeding</i>	<input type="checkbox"/>
<i>Ascites</i>	<input type="checkbox"/>
<i>Cholangitis</i>	<input type="checkbox"/>
<i>Other infections</i>	<input type="checkbox"/>
<i>Description of infections</i>	<input type="text"/>
<i>Pruritis</i>	<input type="checkbox"/>
<i>Non-varice bleedin</i>	<input type="checkbox"/>
<i>Notes</i>	<input type="text"/>