# Outcomes of Paediatric Liver Transplant for Biliary Atresia

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine

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## DECLARATION

I, Yentl Gamiet declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in Surgery at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any other degree or examination at any other University.

_____17th_____day of ____November_____2020 in Johannesburg

## DEDICATION

To Germaine

May our future be filled with more sleep and sunshine.

## PRESENTATIONS ARISING FROM THIS STUDY

- Protocol and provisional findings presented at Hepatobiliary and Transplant Congress, Johannesburg, November 2017
- Completed study presented at South African Transplant Society Congress, Cape Town, September 2019
- Completed study presented at Hepatobiliary and Transplant Congress, Johannesburg, November 2019

# ABSTRACT

Background

Despite the widespread use of Kasai Portoenterostomy (KPE) for biliary atresia, more than two thirds of these patients require liver transplant. Liver transplantation is not widely available in South Africa, and Wits Donald Gordon Medical Centre is one of two centres performing paediatric liver transplantation in the country, and the only centre performing living related donor transplants. The study aims to outline the experience with liver transplant for biliary atresia in terms of the post-operative complications and one-year survival outcomes, with the goal to ascertain the factors which govern those outcomes

Methods

A retrospective review was performed at the centre. Demographic data was collected, and tabulated. Survival analysis was performed using Kaplan Meier curves. Complication rates were categorised into biliary, vascular and enteric complications, and classified as early and late. Mortality was analysed according to cause and timing which was categorised as early and late.

Results

Sixty-seven first time liver transplants were performed for biliary atresia, at WDGMC from 2005 to 2017. Sixty-nine percent were female patients and thirty-one percent were male patients. Forty-eight percent of patients under the age of 5 years, had a z-score of -2 or worse for mid upper arm circumference (MUAC). The rates of biliary complications, enteric complications and vascular complications were 34%, 12% and 12%, respectively. One-year

overall survival of the cohort is 84.5%, and overall graft survival is 82.9%. Overall mortality was 22% but cause of death was difficult to corroborate.

Conclusion

Complication rates and survival outcomes are comparable to international single centre studies despite the high rates of malnutrition in our study cohort. Early referral of all patients with biliary atresia to a paediatric liver transplant centre is essential for early detection of indications, and medical and nutritional optimisation of patients.

Keywords:

Biliary atresia, liver transplant, paediatric

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## LIST OF ABBREVIATIONS

BA - Biliary Atresia

WDGMC - Wits Donald Gordon Medical Centre

KPE - Kasai Portoenterostomy

MUAC - Mid Upper Arm Circumference

LDLT - Living Donor Liver Transplant

SNL - Survival with Native Liver

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# CHAPTER 1: INTRODUCTION

## 1.1 Literature Review

Biliary Atresia (BA) is the most common indication for liver transplantation in children worldwide [1,2]. It is a progressive fibrosing cholangiopathy with an incidence of 1 in 5000-20000 live births, depending on geographical location [3]. Most centres subscribe to the surgical standard of an initial procedure to establish bile drainage, followed by liver transplant if indicated. After diagnosis of BA, the ideal management is expedient resection of the biliary remnant in the portal plate, with reconstructive hepaticojejenostomy (Kasai Portoenterostomy [KPE]), within 60 days of age and about 86-95% of patients with BA undergo KPE [4,5,6,7,8,9]. Despite surgical mastery of the KPE, and advances in post-operative medical care, the majority of patients with biliary atresia will ultimately still require a liver transplant [4-9].

The magnitude of the need for paediatric liver transplant, is underscored by the actuality that non-drainage of the KPE is not the only indication for transplant, and complications such as portal hypertension with variceal bleeding, recurrent cholangitis, hepatic fibrosis, hepatopulmonary syndrome and growth failure – may occur before evidence of non-drainage is confirmed [6,10]. For most patients, even a timely KPE is simply a bridge to liver transplantation, therefore improved access to liver transplantation is a significant step toward improved long-term outcomes for children with biliary atresia. Primary transplant is reserved for patients who present after a significant delay rendering them a "missed biliary atresia" and therefore disqualified as a candidate for a KPE [9,11,12]

The incidence of so-called syndromic biliary atresia is reported as 5-10% [9,10,11,13]. This finding is associated with poor surgical outcomes for KPE [4]. This type of BA is thought to be a field defect, occurring early in gestation, and associated with abnormalities in other organ

systems. These abnormalities are polysplenia, asplenia, preduodenal portal vein, malrotation and situs inversus.

Before the innovation of KPE, the outcomes for biliary atresia were dismal, with death occurring by three years of age in 90 to 100% of patients [5,13]. KPE was introduced in 1959 by Morio Kasai, [15] but has undergone relatively little progression and evolution in surgical technique. In the post KPE era, the reported five-year survival with native liver (SNL) is 42-59% in the developed world and the percentage of BA patients that ultimately require liver transplant has been recorded as ranging between 53-78% [4,16]. In South Africa, studies in Johannesburg and Cape Town report two-year SNL of 32.6% and 41.2% respectively [17,18]. In the study performed in Johannesburg, South Africa, only 11 out of 70 patients diagnosed with biliary atresia were alive with their native liver at 24 months of age. Factors that may contribute to these poor outcomes include delay in diagnosis and subsequent referral, non-centralisation of care, poor post-operative management and inadequate treatment of cholangitis. The centralisation of care for patients with BA has been studied and found to lead to formidable improvements in outcomes [4]. Currently, KPE are performed at numerous centres in South Africa, whilst liver transplantation is centralised at the Wits Transplant Programme based at the WDGMC and the Red Cross Children's Hospital in Cape Town.

The patient with biliary atresia undergoing liver transplantation is usually younger and of smaller stature than the patient transplanted for other indications [19,20]. This is thought to be due to the early onset of liver fibrosis and cirrhosis, and subsequent nutritional depletion, as evidenced by objectively higher PELD scores [21]. Most studies report a female preponderance [6,11,19].

Operative morbidity related to liver transplantation is consistently affected by the so-called "learning curve". This phenomenon is measured in terms of the era of transplantation and

other technical considerations. Although previous surgery is speculated to be a risk factor for intra-operative complications, particularly related to breeching the integrity of the gastrointestinal tract, it does not translate into a significant effect on overall survival [5]. It is purported that the effect of previous surgery is not related to the KPE, but subsequent relooks to manipulate a non-draining KPE – in the hopes of it draining. The overall rate of enteric complications is reported as being between 6-14% [22,23].

Hepatic artery thrombosis, portal vein thrombosis and haemorrhage constitute most of the vascular complications. In the literature, the vascular complication rate is estimated to be between 4 and 22% [2,8]. The incidence of hepatic vein thrombosis is illusive. The rate of post-operative thrombosis related to hepatic inflow and outflow, does not translate into a significant influence on overall survival [8]. The occurrence of vascular complications is comparable between patients transplanted for BA, and patients transplanted for other indications [3,20].

As with vascular complications, the rate of biliary complications for patients transplanted for BA, are on par with liver transplants for other indications, at 15-25% [2,4,24]. Almost half of these, present as a late complication, and only strictures that are symptomatic, present acutely [5].

Single centre studies of paediatric liver transplant in general, has shown to have one-year overall survival and graft survival of 73-89% and 81-88%, respectively [2,20,25]. In patients transplanted for BA, these results correspond with one-year overall survival and graft survival reported as 83-91% and 77-91%, respectively [5,6, 11,12,19, 21,25-,30].

There is no conformity amongst centers regarding the timing of deaths. In a previous study at

the Wits Donald Gordon Medical Centre (WDGMC), more than half of paediatric post-transplant deaths occurred in the early post-operative period [1]. In another South African study, describing the experience of paediatric liver transplant in the other centre in Cape Town – Red Cross Children's Hospital, most of the deaths occurred more than six months after the initial transplant [20].

It was difficult to compare the causes of death, as there are no consensus definitions regarding this. Some studies cite infective causes as the inciting event and capture that as the cause of death while other studies tabulate multi-organ failure as the cause of death without mention of the inciting event.

The factors that contributed to outcomes for overall survival were UNOS status [5] graft type [5,25,26], pretransplant serum bilirubin [5], pretransplant weight [25], transplant era [25] and age at KPE [8]. The factors that worsened graft survival were growth failure [28], graft type [12,25, 28] and whether the transplant was performed in a high-volume centre [12].

The relationship between MUAC and risk of death has been studied and published results have prompted the institution of a policy to withhold liver transplant until the MUAC z-score is above -2. The hazard ratio for death in these patients was 5. As a result, the policy was changed to admitting severely malnourished patients for aggressive nutritional rehabilitation prior to offering liver transplantation [31].

The WDGMC is one of two centres performing paediatric liver transplants in South Africa. It is a private academic hospital, affiliated to the University of the Witwatersrand, and a sub-specialist training and referral centre. The centre has a collaboration with the public sector, to provide liver transplantation to state sector patients. Consequently, all patients listed are offered transplantation on a 'sickest first' basis, regardless of payer status, and the number of public sector transplants has increased steadily. The referral area extends well beyond

Johannesburg, and numerous patients are referred from multiple centres throughout South Africa and Sub-Saharan Africa. WDGMC is currently the only centre offering living donor liver transplantation (LDLT) within the region.

Deceased donors' organ retrievals are performed according to the standard "rapid" multivisceral harvest technique described by Starzl et al [32]. All splits and reductions are performed on the back table [32]. Cadaveric graft types utilised are whole livers, split liver grafts and occasionally reduced size grafts.

The predominant grafts utilized for LDLT and split liver transplant is a left lateral segment graft, occasionally including segment IV for larger children. Two implantation techniques are utilised – the classic bi-caval technique for whole liver grafts, and the piggyback technique with preservation of the native inferior vena cava, when reduced, split and LDLT grafts are used [32].

This descriptive study aims to define the profile of patients undergoing liver transplantation for biliary atresia in the Transplant Programme at the Wits Donald Gordon Medical Centre (WDGMC). The study further aims to present one-year survival outcomes, post-operative morbidity in this group of patients, as well as factors that may affect these outcomes.

## 1.2 Objectives

The objectives for this retrospective study are:

1. To describe the demographic characteristics of paediatric patients undergoing liver transplant for biliary atresia at WDGMC.
2. To evaluate post-operative complications for paediatric patients undergoing liver transplant for biliary atresia
3. To assess one-year survival outcomes for paediatric patients undergoing liver transplant for biliary atresia.
4. To determine the factors affecting these outcomes.

# CHAPTER 2: METHODS

## 2.1 Patient selection

A retrospective study of the initial 67 first-time liver transplants performed in children for BA, dating from the unit's inception in 2005 to December 2017, was performed. A paediatric patient is defined as a patient between the ages of 0 and 18 years on the day of transplant. Institutional permission from the ethics committee of the University of the Witwatersrand (Ethics clearance number: M170752) was obtained.

## 2.2 Sources of Data

The data was extracted from an existing Redcap database titled "Paediatric Liver Transplant Practice Audit at WDGMC" [33]. Extracted data included recipient demographics, date of transplant, recipient weight at transplant, z-scores for weight, height, mid-upper-arm-circumference (MUAC), donor type, graft type, history of previous KPE, Paediatric end-stage liver disease (PELD) score, associated anomalies, surgical complications, patient survival, liver graft survival data and cause of death. Only the z-scores for patients under the age of five years were used, as several factors have been reported to affect the consistency of the z-score beyond this age [34]. The z-score for MUAC has also been shown to be as reliable as the Body Mass Index (BMI) and z-score for weight seems to account for other nutritional factors in patients with BA, such as hypoalbuminemia, hepatosplenomegaly and ascites [35]. With regards to nutritional status and readiness for transplant – the policy was changed during the study period – to one of aggressive nutritional rehabilitation for patients with a z-score for MUAC of -2 or less. This may affect the study in terms of earlier results.

### 2.3 Data Analysis

Descriptive statistics were tabulated and presented as frequency and percentage for categorical variables. For continuous variables, the statistics were presented as mean, standard deviation, median and histograms.

Overall survival estimates were determined by the Kaplan-Meier method. Actuarial survival is defined as the time from transplant to the time of death, and graft survival is defined as the time from transplant to the time of re-transplantation or death – whichever occurred first.

Complications were tabulated as biliary, vascular, enteric and other, and were also categorised as early and late. Within the biliary complications, early complications were defined as those that occurred before 90 days, and late complications, after 90 days post transplantation. Biliary complications were further categorized as bile leaks, cut surface leaks, biliary strictures, retained stents and blind ending ductal systems. A blind ending ductal system occurs when the outflow end of the blind donor cystic duct remnant is included in the suture line of a biliary anastomosis.

Mortality was classified as early and late, with 90 days being the defining time period. Data was analysed using SAS 94.0

## CHAPTER 3: RESULTS

One hundred and forty-two first time liver transplants were performed at the WDGMC during the study period – sixty-seven for biliary atresia. The trend in transplant volume over time is shown in figure 1 and demonstrates the initial increase from inception in 2005, followed by cessation of the programme, and then resumption in 2013, with steadily increasing numbers annually. (Figure 1)

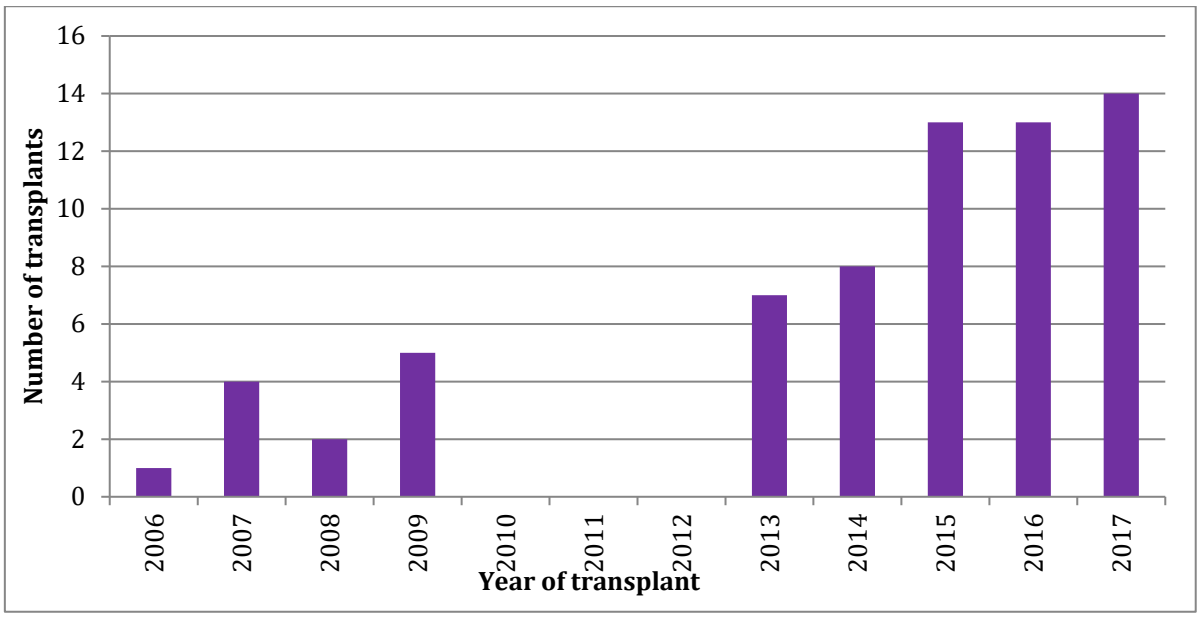


*Figure 1: Trend in Liver Transplant for Biliary Atresia over Time*

Of these 46 (69%), were female and 21 (31%) were male. Thirty-three patients (49%) received a LDLT and thirty-four (51%) from deceased donors. (Figure 2) Within the latter group 13 whole (19%), 13 split (19%), and 8 reduced size grafts (12%) were transplanted. Patient characteristics and parameters are shown in table 1.The median PELD score was 18 (IQR: 14-23) and the median albumin was 29g/L (IQR: 26-33g/L) (Table 1)

*Table 1: Patient and Blood Parameters*

| **Characteristics** | Mean | Median |
|---|---|---|
| **Recipient age at transplant (n=67/67)** | 30m (SD: 33.6m) | 21.6m (IQR: 13.2-1-28.8m) |
| **Recipient weight at transplant (n=67/67)** | 11.2kg (SD:6.09kg) | 9.4kg (7.4-13kg) |
| **Transplant PELD score (n=67/67)** | 18.06 (SD: 9.23) | 18 (IQR: 15-21.75) |
| **Serum albumin at Transplant (n=59/67)** | 29.24g/L (SD: 6.47g/L) | 29g/L (IQR: 26-33.5g/L) |

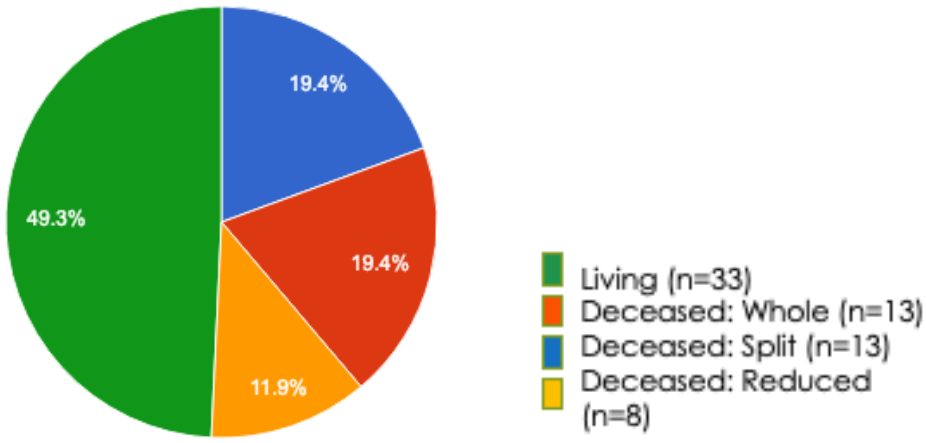


*Figure 2: Pie chart of graft type utilised*

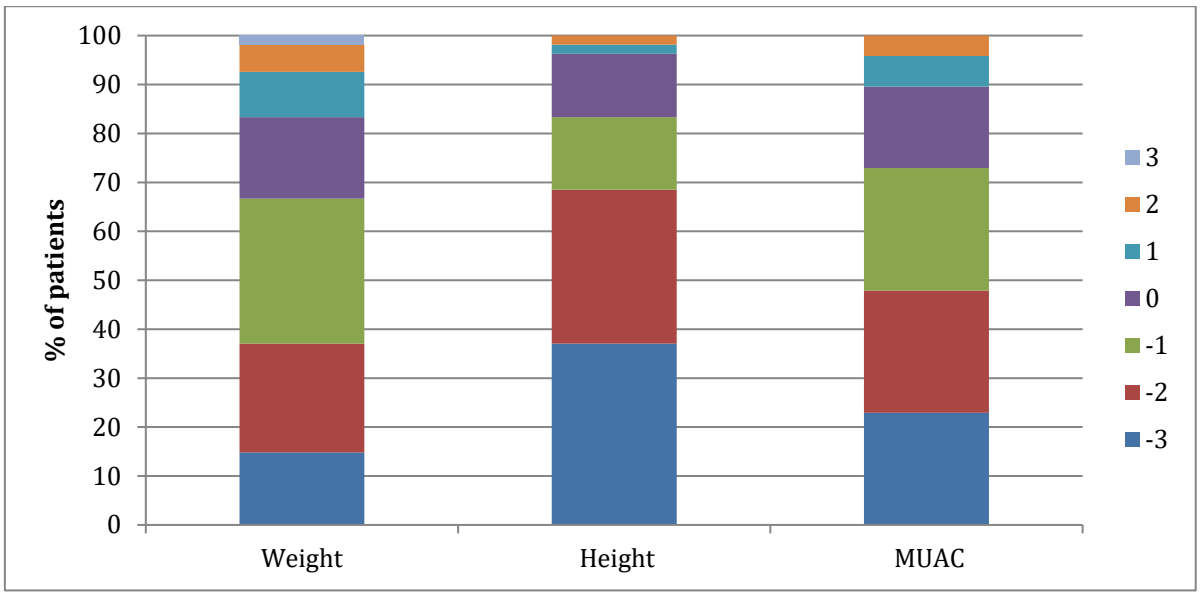


*Figure 3: Nutritional characteristics in the form of z-scores for the 61 recipients under 5 years of age*

Fifty percent of patients under the age of five years had a pre-transplant z-score for weight of -1 or better, while only 33% of these patients had a pre-transplant z-score for height of -1 or better. Fifty-two percent of patients under the age of five years had a pre-transplant z-score for MUAC of -2 or worse. (Figure 3) (Table 2)

*Table 2: Patient nutritional characteristics in the form of Z-scores for the 61 recipients under 5 years of age*

| **wt for age (n=54/61)** | n (%) |
|---|---|
| -3 | 8 (15%) |
| -2 | 12 (22%) |
| -1 (or better) | 34 (62%) |
| **ht for age (n= 54/61)** | |
| -3 | 19 (35%) |
| -2 | 17 (32%) |
| -1 (or better) | 18 (33%) |
| **MUAC for age (n= 48/61)** | |
| -3 | 11 (23%) |
| -2 | 12 (25%) |
| -1 (or better) | 25 (52%) |

Forty-three patients (64%) had a history of previous KPE. We could determine the age at KPE for twenty-five of these patients, and the median age at KPE was 80 days (IQR: 60-100 days).

Six patients met the criteria for BASM, with all other associated anatomical abnormalities occurring in this group. The specific abnormalities encountered were polysplenia, interrupted IVC, malrotation, preduodenal portal vein and situs inversus. None of these patients died during the transplant period and none were retransplanted.

Twenty-six relook laparotomies were performed in twenty-four patients. One patient had a relook for a biliary leak, and then required another relook for an enteric injury. A second patient required a relook for abdominal compartment syndrome, and then needed a relook for a colonic perforation. Seven laparotomies were done for bile leaks, six for enteric

complications, one for portal vein thrombosis, one for hepatic artery thrombosis and one for hepatic venous obstruction, two for haemorrhage, one for primary non-function, two for biliary strictures, one cause of death was undocumented. There were eight documented enteric complications (12%). Seven out of the eight patients who suffered enteric breaches had a history of previous KPE. Eight patients (12%) sustained vascular complications - six developed portal vein thrombosis and 2 sustained hepatic artery thrombosis. Both patients who developed hepatic artery thrombosis had relook laparotomies with redo of the anastomosis, but one of these patients succumbed to an early death, during the acute post-operative period.

Twenty-four biliary complications developed in twenty-three patients (34%). One patient experienced two biliary complications namely a cut surface leak and had a blind ending ductal system. Eleven patients developed biliary strictures, seven of these were early biliary strictures and four were late. The remaining biliary complications were anastomotic leaks (7), cut surface leaks (3), blind ending ductal system (2), and a retained stent (1).

The one year overall patient survival is 84.5%, (C.I. 73-91%) (Figure 4), and the one-year graft survival is 82.9% (C.I. 71-90%). The median follow-up is 1.7y (IQR:0.4-3.8) (Figure 5)..

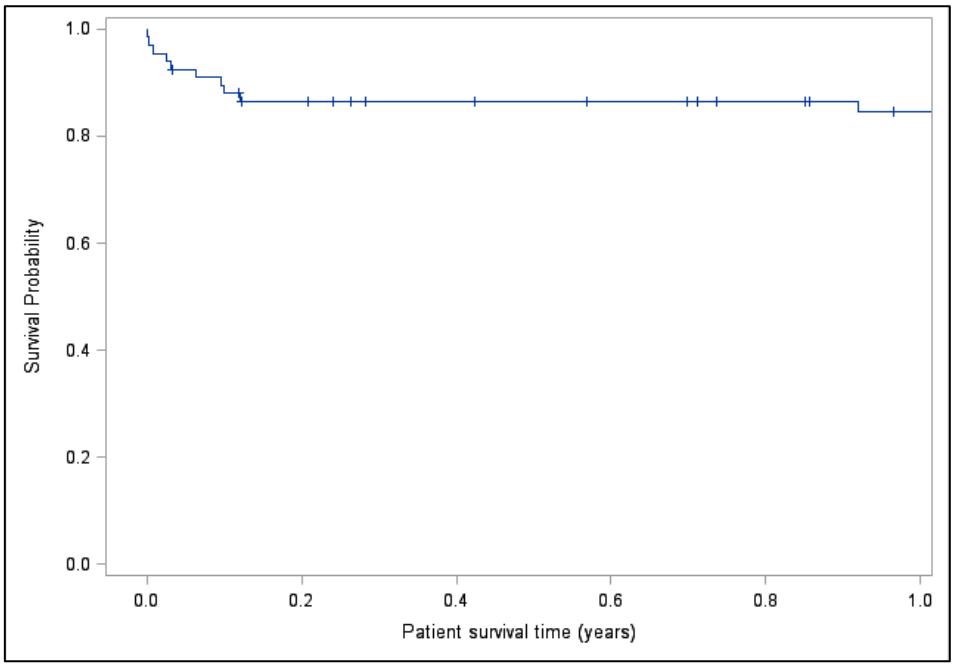


*Figure 4: Kaplan-Meier Graph of One Year Patient Survival*

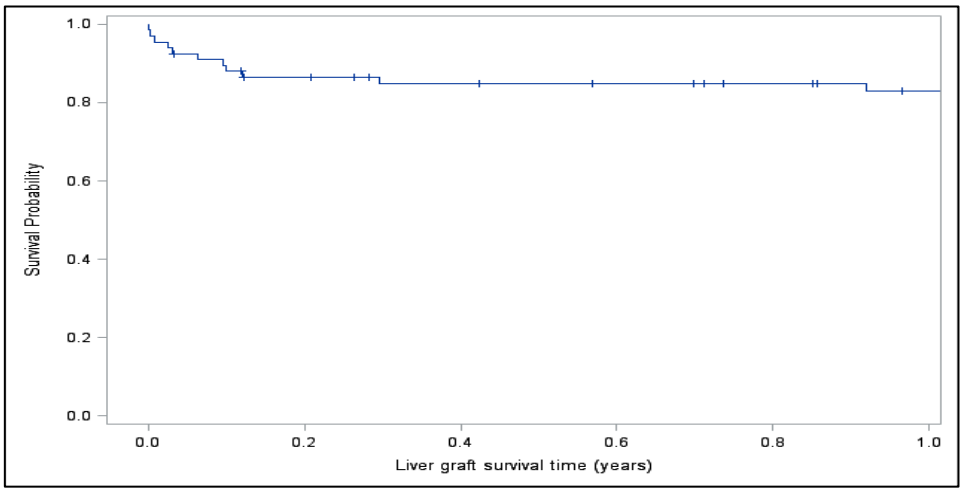


*Figure 5: Kaplan-Meier Graph of One Year Graft Survival*

Fifteen patients demised during the study period, reaching a mortality of twenty-two percent (22%). Nine out of fifteen patients suffered early deaths, and ten out of fifteen patients had infectious causes cited as the cause of death. The other deaths were caused by acute venous outflow obstruction, primary non-function, intractable pulmonary hypertension and chronic graft rejection. Eleven of the fifteen patients who demised had a

pre-transplant z-score for MUAC of -2 or worse which is not an accurate representation of the current status, but a reflection of the previous policies regarding nutritional rehabilitation.

# CHAPTER 4: DISCUSSION

## 4.1 Comparative Outcomes

Liver transplantation is integral to the management of patients with biliary atresia. It should be performed at a centre which meets the criteria for an excellent multidisciplinary approach. The one-year overall survival of 84,5%, and one-year graft survival of 82,9%, are on par with reports in single centre studies, which publishes these as 83-92% and 77 to 98% respectively [5,6, 11,12,19,25-30].

In contrast, the published outcomes for KPE in South Africa are far below the accepted standard, with the rate of successfully draining KPE reported between 19 and 27% [17,18] compared to 45-55% in larger series [4]. Currently, KPE are performed at numerous centres in Johannesburg and surrounds, and only referred to the Wits Transplant Programme for transplantation. This discrepancy is presumed to be the result of technical and institutional inconsistency. The data regarding previous KPE, was incomplete and the numbers were too small to analyse whether previous KPE affected survival.

The median age for transplant in our group of patients is 21,6 months corresponds to the median age at transplant in other single centres studies [11,30]. When compared to the median age for transplant for other indications – it is clear that patients with biliary atresia are transplanted at a younger age and have a lower median weight [21]. All the living donors were related, and the PELD scores and serum albumin reflect the early onset of liver failure, and delay in referral which is characteristic of this patient population. The incidence of syndromic BA is the same as international reported.

The rates of biliary, vascular and enteric complications fall within the reported range. The mortality rate of this study falls within the reported range of most single centre reviews [11,26,28].

The rate of enteric complications is within the reported range of 2.4-20% [22,23,36,37]. There is discordance in the literature whether enteric complications are higher in patients transplanted for biliary atresia versus those patients transplanted for other indications [19,22].Within our institution, it is a subjective and untested observation that patients who have had previous KPE, have more difficult and longer transplant surgeries, with the potential for more complications. Unfortunately, we were not able analyse whether survival outcomes or complications were affected by previous KPE, as much of the data is missing.

The study numbers were too small to perform a statistically sound regression analysis, and therefore the factors contributing to poor outcomes were not calculated. The only valid conclusions that were found were those regarding the pretransplant nutritional status which is discussed under the next heading.

The causes of death were not captured as single entities but rather as contributing factors to the deaths such as multi-organ failure or infection. This did not allow comparison with causes of the death in similar studies

## 4.2 Nutritional Assessment

Assessment of nutritional status in patients with biliary atresia is complex. This group of patients fulfill the WHO definitions of protein energy malnutrition, by being underweight for height with muscle wasting. About half the patients in this study satisfy the criteria of moderate to severe malnutrition with a weight for height z-score of -2 or worse, and two

thirds of this groups of patients meet the criteria for chronic malnutrition and stunting, with a height for age z-score of -2 or worse. Mid upper arm circumference should be included as part of a detailed anthropometrical assessment, as it corrects for hepatosplenomegaly and ascites [34,35].

Delayed referral results in progressive malnutrition for multiple reasons including; poor oral intake, increased energy expenditure, malabsorption, chronic enteropathy, deterioration in hepatic synthetic function, infective complications and immunosuppression [35]. Nutritional rehabilitation is of utmost importance, as the nutritional status has a recognised effect on pre- and post-transplant mortality. [38,39].

It follows that if the management of biliary atresia were centralised – patients would be managed by an experienced team resulting in early identification of the need for liver transplant, comprehensive work-up and nutritional resuscitation, and expedient surgery.

## 4.3 Limitations of the study

Despite the valuable conclusions achieved in this study, the limitations include the retrospective nature, and resultant inconsistencies in the data available, as well as the short median follow-up of 1.7 years. This allows for assessment of one-year outcomes but falls short of accurate reflection of long-term postoperative complications and mortality. The study sample was too small to perform statistically sound univariate or multivariate analysis - a larger sample would enable the study of factors contributing to these outcomes, and it is an, area of future study.

# CHAPTER 5: CONCLUSION

The Kasai operation has one of the highest failure rates in its stated objective in paediatric surgery. In South Africa, the failure rate is over 60% highlighting the need for readily available access to liver transplantation. This report of liver transplantation for children with BA in South Africa demonstrates that good outcomes can be achieved across disparate health care systems, such as private sector and state sector. Living related donor liver transplants are becoming more accessible, and although these patients have unpropitious characteristics - the survival outcomes are shown to be favourable. Complication rates are within international norms.

Despite having inadequate patient numbers – the effect of malnutrition has profound consequences, and accurate nutritional assessment and aggressive nutritional rehabilitation is crucial. It is hoped that this experience will continue to yield improved care for children with BA, early referral for transplantation might spare some infants needless surgery, and quite possibly result in diminished morbidity and mortality following liver transplant.

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# APPENDIX 1: APPROVED PROTOCOL

**Outcomes of Paediatric Liver Transplant for Biliary Atresia**


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Supervisors: Dr Andrew Grieve

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Paediatric Surgical Consultant and HOD

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## Literature Review

Biliary Atresia is the most common indication for liver transplant in the paediatric population, despite the worldwide utilisation and mastery of the Kasai portoentorostomy.[1] Two thirds of patients require liver transplant despite porto-enterostomy although the timing of transplant is still controversial. According to projections based on data from our local hepatobiliary clinic – 10-20 children would be listed for transplantation annually, in the greater Johannesburg area. [2]

The natural course of untreated biliary atresia is dismal, with the median survival between 8 and 14 months. The Kasai porto-enterostomy has ushered in a new era of hope for children with biliary atresia. Despite cure rates for about a third of these patients, primary or delayed failure of the KPE remains the principle indication for liver transplant. About 86-95% of patients with biliary atresia undergo KPE before transplant.[3,4,5]

Patients with biliary atresia tend to undergo liver transplant earlier than the rest of the paediatric population, due to the early establishment of the fibrosis and cirrhosis, and consequentially earlier symptoms of liver failure.[6] Paradoxically, these patients have a more severe grade of liver dysfunction at transplantation.[7]

Hepatotropic viruses such as CMV, EBV and Reo virus have frequently been isolated in the livers of these patients, and a relatively strong linear relationship exists between the recording of these findings and poor outcomes. These factors, combined with a history of previous surgery would lead one to conclude that this group of patients would demonstrate poorer outcomes and higher rates of morbidity.

There are conflicting reports in the literature regarding the rate of complications between the two groups.

The overall rate of enteric complications is as high as 14%. [8]There is an unequivocal increase in the rate of enteric complications in the group transplanted for biliary atresia. This is thought to be due to the factors mentioned above.[9] Although previous surgery is speculated to be a risk factor for intra-operative complications – this does not translate into an effect on the overall survival. It is speculated that the effect of previous surgery is not related to the Kasai-portoenterostomy but to subsequent relooks to manipulate a non-draining Kasai, in the hopes of it draining.

The rate of vascular complications range between 4 and 22%[1,4] These complications are subdivided into hepatic artery thrombosis, portal vein thrombosis and haemorrhage. The rate of hepatic artery thrombosis is a significant morbidity, as the result is inevitably retransplantation.[3] A learning curve has consistently been demonstrated in multiple studies and the rate of hepatic artery thrombosis decreases with improved technical competency in reconstructing the hepatic artery.[3,5] Intra- and post-operative haemorrhage or rupture of a vessel, is a technical factor that not only affects the immediate post-operative course but has effect on long term survival outcomes, as it results in blood transfusion. Blood transfusion has been assessed as predictor of poor long-term outcome.

Biliary complications are found to be around 15-25% for liver transplant overall and is comparable to biliary complications in patients transplanted for biliary atresia.[1,3,12] Almost half of these present as a late complication, and only strictures that are symptomatic, present acutely.[3] The risk factors associated with the development of biliary complications are the utilisation of reduced size liver transplants, hepatico-jejeunostomy as opposed to choledochocholedochostomy, higher risk for arterial thrombosis, and susceptibility to CMV infection. CMV infection is the only factor which is more prevalent in the biliary atresia

cohort but this finding does not seem to translate into a statistically significant difference in the incidence of biliary complications.

The one year overall survival and graft survival for paediatric liver transplant is 85 -92% and 63 – 84% in most experienced centres.[1,] In patients who have been transplanted for biliary atresia, one year overall survival and graft survival is reported as 67 – 83% [3,7] and 66-81%.[3,7] There seems to be a difference in the overall survival, but not necessarily the graft survival.

There is no conformity amongst centers regarding the timing of deaths. In a previous study at the Wits Donald Gordon Paediatric Liver Transplant Unit(WDGPLTU), more than half of post-transplant deaths occurred in the early post-operative period.[1] In another South African study, describing the experience of paediatric liver transplant in the other centre in Cape Town – Red Cross Hospital, most of the deaths occurred more than six months after the initial transplant.[11]

One of the most consistent factors predicting poor outcome, is the degree of liver failure at the time of transplant. There are several ways that this is expressed – two of the most common, are the PELD score (Paediatric-End-Stage-Liver Disease) Score and total serum bilirubin.

The PELD score utilises the following factors: the age of the patient, the weight and height of the patient, serum albumin and INR as a measure of the synthetic function of the liver, as well as serum bilirubin. The PELD score therefore encompasses some of the factors that independently affect the outcome.

The difficulty in extrapolating these measurements to patients with biliary atresia is that the score does not account for, the other relevant variables, such as the presence of varices, portal hypertension, hepatopulmonary syndrome and pruritis, or any of the other indications

for performing a liver transplant in patients with biliary atresia.

The effect of the disease on serum albumin and INR might be delayed as synthetic functions might be relatively preserved. The serum bilirubin concentration does not seem to be an accurate depiction of the degree of cholestasis or fibrosis. The weight of the patient might be falsely elevated due to the presence of ascites or splenomegaly.

The patient's weight is understood to be a reflection of the patient's nutritional status. The mid upper arm circumference has been shown to be a much more accurate representation of the state of nutrition and is not yet routinely used in these protocols.

The era of transplantation has been cited in many studies as having an impact on the outcome of these patients. Intuitively, the more experience the centre has in paediatric liver transplant, the better the co-ordination and team work, as well as the technical competencies. These advances result in less complications and adverse effects, as well as more efficient follow-up which would then lead to better outcomes.

It has also been shown that the factors that predict poor success rates after Kasai portoenterostomy have effects on the outcome of liver transplant too. These factors are the finding of polysplenia (representing syndromic biliary atresia), as well as the presence of CMV.

It has been traditionally thought that outcomes for biliary atresia are worse due to the issues mentioned in the preceding paragraphs, but no other disease shows more shockingly poor outcomes than acute fulminant hepatitis.

The Wits Donald Gordon Paediatric Liver Transplant Unit was founded in 2005, and since its inception – one hundred and nineteen liver transplants (*increased to 142 after study period had been extended) have* been performed. The unit is one of two paediatric liver transplant units in South Africa. The history of the unit can be divided into two eras – November 2005 to October 2012, and November 2012 to the present. The differences in successes and outcomes between the two eras, are due to strategic improvements in staffing, and expertise, as well as the introduction of a living donor programme. The impact of these changes is evident in the growing impetus of the programme. The cohort of patients from November 2005 and December 2016, provides an opportunity to analyse the outcomes.

## 3. Research Question, Aims and Objectives

### Research Questions

Are survival outcomes for patients being transplanted for biliary atresia at our centre, comparable to other centres?

### Overall Aim

To determine if there is a difference between outcomes in patients who have undergone liver transplant for biliary atresia, in our centre, compared to other centres.

### Secondary Aims

To ascertain the factors which determine these differences in outcomes.

### Objectives

1. To describe the demographic characteristics of paediatric patients undergoing liver transplant for biliary atresia at WDGMC.
2. To evaluate post-operative complications for paediatric patients undergoing liver transplant for biliary atresia

3. To assess one-year survival outcomes for paediatric patients undergoing liver transplant for biliary atresia.
4. To determine the factors affecting these outcomes.

## 4. Research Methodology

### Population and study sample

The Wits-Donald Gordon paediatric liver transplant unit (WDGPLTU) has been in existence since November 2005. There have been 142 first time liver transplants performed at the centre – 67 of these for biliary atresia – between 2005 and end of 2017. Patients were referred from different hospitals in Johannesburg, but their assessment, selection, work-up and medical treatment were managed by the WDGMC.

Paediatric patients are defined as those younger than 18 years at the time of the transplant. All retransplants were excluded. Patients received the following grafts whole livers, reduced size grafts, split grafts, living donor grafts and multi organ (liver and kidney).

Early post-operative period was defined as the period from operation to discharge from hospital. Post-operative complications, time of death, and cause of death will be tabulated.

### Sources of Data

Hospital patient records will be reviewed, including operative notes, serology and histology results. The records from transplant to last follow up date have been placed into a transplant database by the transplant team. I will interrogate this database base for this research project with the permission of Professor Loveland (Supervisor).

### Data Analysis

Retrospective data will be reviewed and captured in an excel spreadsheet. Cox univariate

analysis will be used, and a positive correlation will be marked by a p-value of <0.02. Multivariate analysis will be used to determine the prognostic factors governing patient and graft survival. One-year overall survival outcomes and graft survival will be assessed using Kaplan-Meier Survival Curves and compared between the groups.

## 5. Ethics and Human Subjects Issues

Application has been made to the University of Witwatersrand Human Research Ethics Committee.

## 6. Timeframes

Data from November 2005 to 31 December 2017 will be reviewed.

## 7. Funding

No funding will be required.

## 8. Appendices

8.1 Record Review

8.2 Timeframes

8.3 References

**Yentl L. Van Heerden**

**M.med: Outcomes of Paediatric Liver Transplant for Biliary Atresia**

**Record Review Information Sheet**

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1. Age
2. Gender
3. Race
4. Diagnosis
5. PELD score
6. Previous surgical history (KPE)
7. Age at transplant
8. Weight at transplant
9. Type of graft
10. Latest blood results – LFT
11. Complications and treatment of complications

**Dr Yentl van Heerden**

**Department of Paediatric Surgery**

**M.Med: Outcomes of Paediatric Liver transplant for Biliary Atresia**

| | Feb | Mar | April | May | June | July | Aug | Sept | Oct | Nov | Dec |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Project Idea | X | | | | | | | | | | |
| Literature Review | | X | X | X | X | | | | | | |
| Preparing Protocol | | | | X | X | X | | | | | |
| Protocol Deadline | | | | | | | 16/8 | | | | |
| Protocol Assessment | | | | | | | | | | | |
| Ethics Application | | | | | | 7/7 | | | | | |
| Collecting Data | | | | | | X | X | X | | | |
| Data Analysis | | | | | | | | X | | | |
| Writing up Report | | | | | | | | X | X | X | |
| Report Submission | | | | | | | | | | | X |
| | | | | | | | | | | | |

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registry of the Japanese Liver Transplantation Society. Am J Transplant. 2018 Mar;18(3):659–68. [http://dx.doi.org/10.1111/ajt.14489] [PMID: 28889651]

# APPENDIX 2: ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Yentl van Heerden

## HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

## CLEARANCE CERTIFICATE NO. M170752

| | |
|---|---|
| **NAME: (Principal Investigator)** | Dr Yentl van Heerden |
| **DEPARTMENT:** | Paediatric Surgery<br>Wits Donald Gordon Medical Centre |
| **PROJECT TITLE:** | Outcomes of Liver Transplant for Biliary Atresia:<br>A 13 Year Cohort |
| **DATE CONSIDERED:** | 28/07/2017 |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | |
| **SUPERVISOR:** | Dr Andrew Grieve |
| **APPROVED BY:** | Professor CB. Penny Co-Chairperson, HREC (Medical) |
| **DATE OF APPROVAL:** | 07/09/2017 |

UNIVERSITY OF THE WITWATERSRAND
PROF CLEMENT PENNY
HREC (MEDICAL) AND BEC
- 7 SEP 2017
JOHANNESBURG

**This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.**

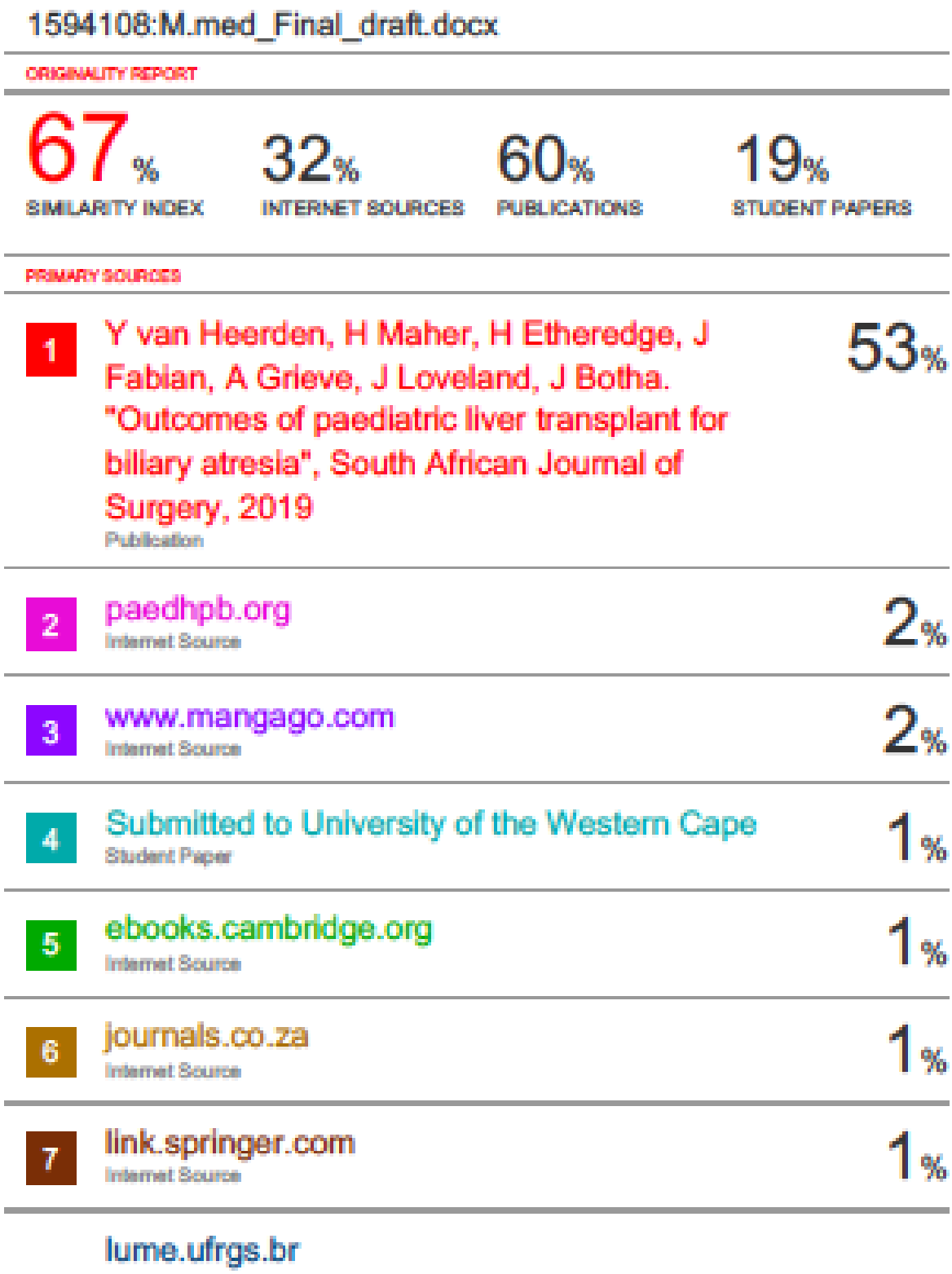
**DECLARATION OF INVESTIGATORS**

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review July and will therefore be due in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

**PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES**

## APPENDIX 3: TURNITIN CERTIFICATE



1594108:M.med_Final_draft.docx

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# APPENDIX 4: PUBLISHED ARTICLE



# Outcomes of paediatric liver transplant for biliary atresia

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**Background:** Despite the widespread use of Kasai Portoenterostomy (KPE) for biliary atresia, more than two thirds of these patients require liver transplant. Liver transplantation is not widely available in South Africa, and Wits Donald Gordon Medical Centre is one of two centres performing paediatric liver transplantation in the country, and the only centre performing living related donor transplants.
**Methods:** A retrospective review was performed at the centre. Demographic data were collected, and tabulated. Survival analysis was performed using the Kaplan Meier method. Complication rates were categorised into biliary, vascular and enteric, and classified as early and late.
**Results:** Sixty-seven first time liver transplants were performed for biliary atresia at WDGMC from 2005 to 2017. Sixty-nine percent were female patients and thirty-one percent were male patients. Forty-eight percent of patients under the age of 5 years had a z-score of -2 or worse for mid upper arm circumference (MUAC). One year overall survival of the cohort is 84.5%, and overall graft survival is 82.9%. Overall mortality was 22%, with infection being the most common cause of death.
**Conclusion:** Early referral of all patients with biliary atresia to a paediatric liver transplant centre is essential for early assessment of indications, and medical and nutritional optimisation of patients. Primary liver transplant should be considered for a select group of patients with unique clinical indications.
**Keywords:** Biliary atresia, liver transplant, paediatric
**Abbreviations:** BA, Biliary Atresia; WDGMC, Wits Donald Gordon Medical Centre; KPE, Kasai Portoenterostomy; MUAC, Mid Upper Arm Circumference; LDLT, Living Donor Liver Transplant; SNL, Survival with Native Liver

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## Introduction

Biliary Atresia (BA) is the most common indication for liver transplantation in children worldwide.[1,2] Most centres subscribe to the surgical standard of an initial procedure to establish bile drainage, followed by liver transplant if indicated. After diagnosis of BA, the ideal management is expedient resection of the biliary remnant in the portal plate, with reconstructive hepaticojejenostomy (Kasai Portoenterostomy [KPE]), within 60 days of age.[3,4] Despite advances in postoperative medical care, the majority of patients with BA will ultimately still require a liver transplant.[5-7] Transplantation should be available as soon as it is indicated to optimise patient survival.

BA is a progressive fibrosing cholangiopathy with an incidence of 1 in 5-20000 live births, depending on geographical location.[8] It is heterogeneous in terms of anatomy and aetiology.[8,9] The disease is broadly classified according to whether the insult causing the obliteration, occurred early or later in gestation. Subtypes include isolated BA, syndromic (Biliary Atresia Splenic Malformation [BASM]) and cystic (CBA) variant. The most common subtype is isolated BA, which makes up 80% of the overall incidence, and is believed to develop later in gestation or even as a post-natal event.[3] Isolated BA is thought to evolve as a secondary autoimmune and inflammatory response to a perinatal viral insult.[8] The syndromic sub-type is thought to develop as a field defect at 10 to 12 weeks gestational age – this on account of its associated abnormalities, including situs inversus, interrupted inferior vena cava, pre-duodenal portal vein, malrotation and splenic anomalies.[8,10] Similarly, CBA is also thought to occur earlier in gestation as it is the only subtype that has been successfully detected on antenatal ultrasound. It is characterised by cystic dilatation in an otherwise obliterated extra-hepatic biliary tree. Each of these two subtypes account

for 10% of the overall incidence of BA.[11] The prognostic implications differ between the three groups and, patients with BASM have a worse prognosis overall while those with CBA have significantly better outcomes.[3,10,11]

BA is also classified morphologically according to the level of obliteration of the extrahepatic biliary tree. Type I represents obliteration at the level of the common bile duct (CBD), and accounts for 5%; Type II at the level of the common hepatic duct and accounts for 3%; and Type III represents obliteration at the level of the porta hepatis (with no distal patency) and accounts for more than 90%. The Ohi classification expands on the traditional classification by further categorising BA according to the morphology of the common bile duct signified by letters a to d, and according to the morphology of the hepatic ducts. The distal subtypes are "a", signifying a patent CBD; subtype "b", a fibrous CBD; subtype "c", an aplastic CBD; and subtype "d", representing the miscellaneous subset. The proximal subtypes are annotated by Greek letters, α, β, γ, μ, ν and ο, and these represent a dilated, hypoplastic, bile lake, fibrous, fibrous mass and aplastic proximal extrahepatic biliary system, respectively.[12] It has been shown that Ohi subtypes II and III are less likely to be associated with successful drainage when compared with subtype I.[13] Subtypes b, c, d are less likely to result in successful drainage when compared to subtype a[13] (Figure 1).

Before the innovation of KPE, the outcomes for BA were dismal, with death occurring by three years of age in 90–100% of patients.[6,14] KPE was introduced in 1959 by Kasai,[15] but has undergone relatively little progression and evolution in surgical technique. In the post KPE era, the reported five-year survival with native liver (SNL) is 42–59% in the developed world.[3,16] In South Africa, studies in Johannesburg and Cape Town report two-year SNL of 32.6% and 41.2% respectively.[7,17] In the study performed in Johannesburg, South Africa, only 11 out of 70 patients diagnosed with BA were alive with their native liver at 24 months of age. Factors that may contribute to these poor outcomes include delay in diagnosis and subsequent referral, non-centralisation of care, poor postoperative management and inadequate treatment of cholangitis. Internationally, the percentage of patients that ultimately require liver transplant ranges between 53–78% of all patients with BA.[5,6] For most patients, even a timely KPE is simply a bridge to liver transplantation, therefore improved access to liver transplantation is a significant step toward improved long term outcomes for children with BA.

This descriptive study aims to define the profile of patients undergoing liver transplantation for BA in the Transplant Programme at the Wits Donald Gordon Medical Centre (WDGMC). The study further aims to present one year survival outcomes, as well as postoperative morbidity in this group of patients.

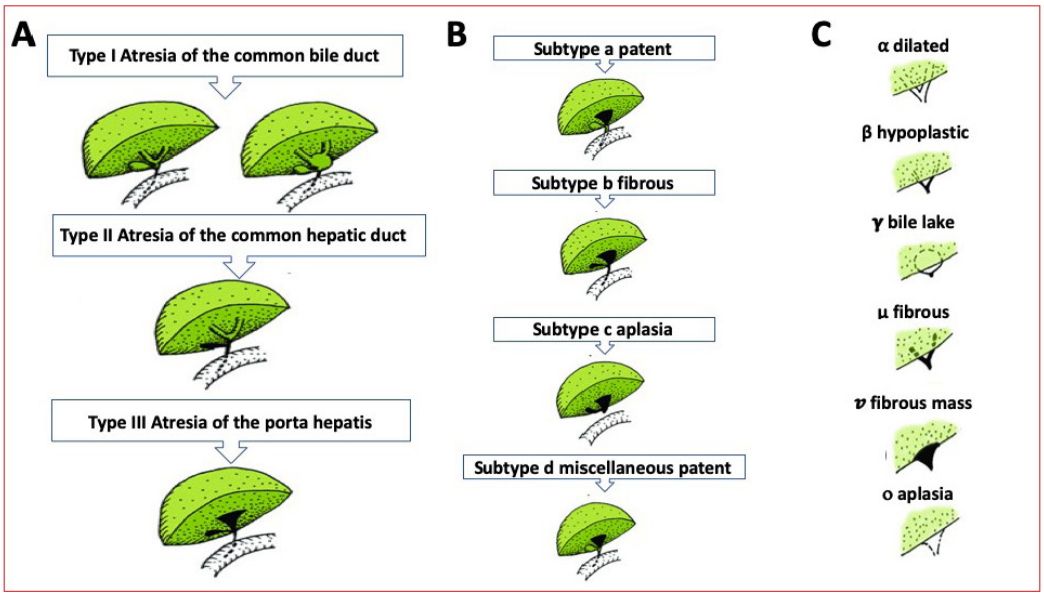


*Figure 1: Schematic representation of the Ohi Classification of Biliary Atresia based on the anatomical site, extrahepatic and intrahepatic subtypes (modified from Superina et al.)*[12]

## Patients and methods

### *Background*

The WDGMC is one of two centres performing paediatric liver transplants in South Africa. It is a private academic hospital, affiliated to the University of the Witwatersrand, and a sub-specialist training and referral centre. The centre has a collaboration with the public sector to provide liver transplantation to state sector patients. Consequently, all patients listed are offered transplantation on a 'sickest first' basis, regardless of payer status, and the number of public sector transplants has increased steadily. The referral area extends well beyond Johannesburg, and numerous patients are referred from multiple centres throughout South Africa and Sub-Saharan Africa. WDGMC is currently the only centre offering living donor liver transplantation (LDLT) within the region.

Deceased donor organ retrievals are performed according to the standard "rapid" multivisceral harvest technique described by Starzl et al.[18] All splits and reductions are performed on the back table.[18] Deceased donor graft types utilised are whole livers, split liver grafts and occasionally reduced size grafts.

The predominant grafts utilised for LDLT and split liver transplant is a left lateral segment graft, occasionally including segment IV for larger children.

Two implantation techniques are utilised – the classic bi-caval technique for whole liver grafts, and the piggyback technique with preservation of the native inferior vena cava, when reduced, split and LDLT grafts are used.[19]

### *Data management*

The initial 67 first-time liver transplants performed in children for BA, dating from the unit's inception in 2005 to December 2017, were analysed. A paediatric patient is defined as a patient between the ages of 0 and 18 years on the day of transplant. The data were extracted from an existing REDcap database titled "Paediatric Liver Transplant Practice Audit at WDGMC".[20] Extracted data included recipient demographics, date of transplant, duration between listing and transplant, recipient weight at transplant, graft weight at transplant, graft weight/recipient weight ratio (GWRW), z-scores for weight, height, mid-upper-arm-circumference (MUAC), donor type, graft type, length of hospital stay, history of previous KPE, paediatric end-stage liver disease (PELD) score, associated anomalies, immunosuppression, surgical complications, patient survival, liver graft survival data and cause of death. Only the z-scores for patients under the age of five years were used, as several factors have been reported to affect the consistency of the z-score beyond this age.[21] The z-score for MUAC has also been shown to be as reliable as the Body Mass Index (BMI) and z-score for weight seems to account for other nutritional factors in patients with BA, such as hypoalbuminemia, hepatosplenomegaly and ascites.[22]

### *Data analysis*

Descriptive statistics were tabulated and presented as frequency and percentage for categorical variables. For continuous variables, the statistics were presented as mean, standard deviation, median and histograms.

Overall survival estimates were determined by the Kaplan-Meier method. Actuarial survival is defined as the time from transplant to the time of death, and graft survival is defined as the time from transplant to the time of re-transplantation or death – whichever occurred first.

Complications were tabulated as biliary, vascular, enteric and other, and were also categorised as early and late. Within the biliary complications, early complications are defined as those that occurred before 90 days, and late complications, after 90 days post transplantation. Among those who sustained vascular complications – early complications were defined as those that occurred before 30 days, and late complications, those that occurred after 30 days.

The cause of death was classified as early and late, with 90 days being the defining time period. Data was analysed using SAS 94.0.

## Results

One hundred and forty-two first time liver transplants were performed at the WDGMC during the study period – 67 for BA. The trend in transplant volume over time is shown in Figure 2 and demonstrates the initial increase from inception

**Table 1: Patient characteristics**

| | Mean | Median |
|---|---|---|
| **Recipient age at transplant (n=67/67)** | 30m (SD: 33.6m) | 21.6m (IQR: 13.2-1-28.8m) |
| **Recipient weight at transplant (n=67/67)** | 11.2kg (SD:6.09kg) | 9.4kg (7.4-13kg) |
| **Implant graft weight (n=60/67)** | 0.46kg (SD:0.35kg) | 0.31kg (IQR: 0.27-0.48kg) |
| **Graft weight Recipient Weight Ratio (n=60/67)** | 4.4 (SD:3.0) | 3.5 (IQR:2.7-4.9) |
| **Time from listing to transplant (n=65/67)** | 5.4 months (SD: 4.2months) | 3.9 Months (IQR:2.8-6.4 months) |
| **Number of days patient hospitalised (n=59/67)** | 40.1 days (SD:25.1days) | 36 days (IQR:23-54 days) |
| **Number of days patient in ICU (n=40/67)** | 19.3days (SD: 18.7d) | 11 days (IQR: 7-30 days) |
| **Number of days patient in high care (n=31/67)** | 6.7days (SD:9.6days) | 4 days (IQE: 2-7days) |
| **Transplant PELD score (n=67/67)** | 18.06 (SD: 9.23) | 18 (IQR: 15-21.75) |
| **Serum Albumin at Transplant (n=59/67)** | 29.24g/L (SD: 6.47g/L) | 29g/L (IQR: 26-33.5g/L) |

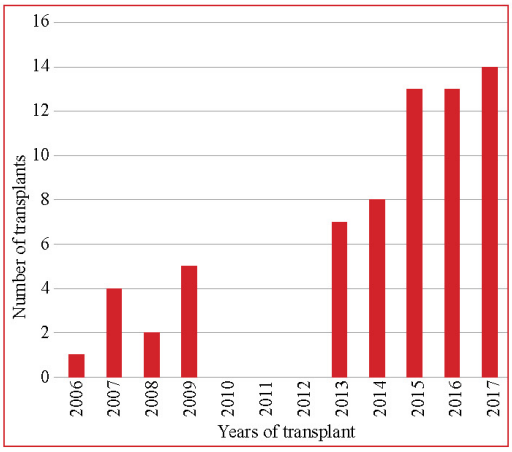


*Figure 2: Figure of transplant volume over time*

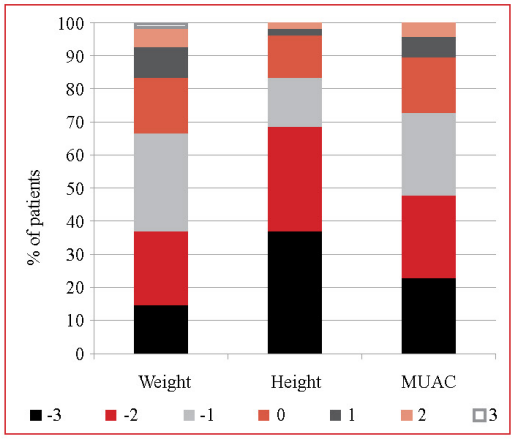


*Figure 3: Bar graph of nutritional assessment (z-scores for patients under the age of 5 years)*

in 2005, followed by cessation of the programme, and then resumption in 2013, with steadily increasing numbers annually (Figure 2).

Of these 46 (69%), were female and 21 (31%) were male. Thirty-three patients (49%) received a LDLT and thirty-four (51%) from deceased donors. Within the latter group, 13 whole (19%), 13 split (19%), and 8 reduced size grafts (12%) were transplanted. The median PELD score was 18 (IQR: 14–23) and the median albumin was 29g/L (IQR: 26–33 g/L) (Table 1).

Fifty percent of patients under the age of five years had a pre-transplant z-score for weight of -1 or better, while only 33% of these patients had a pre-transplant z-score for height of -1 or better. Fifty-two percent of patients under the age of five years had a pre-transplant z-score for MUAC of -2 or worse (Figure 3).

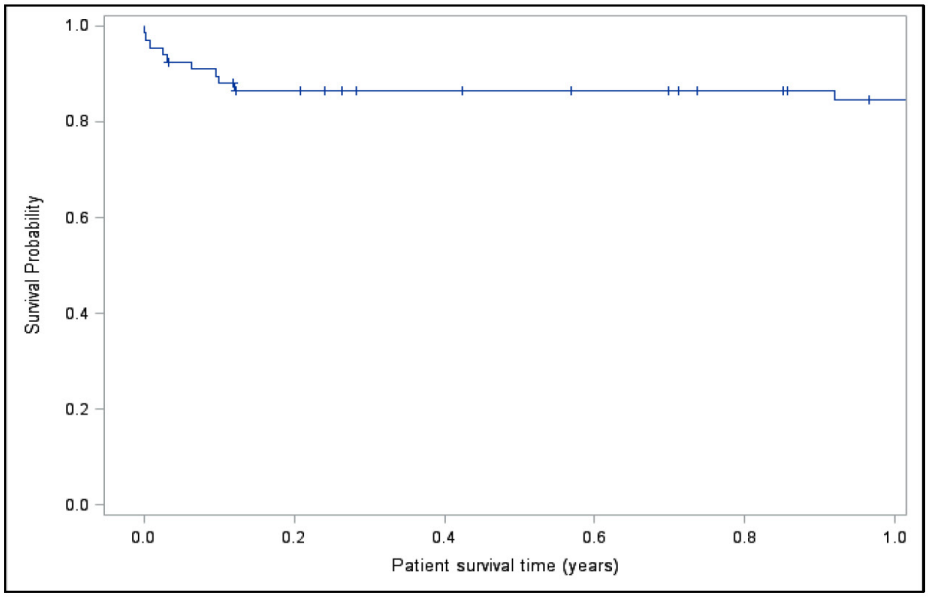


*Figure 4: Kaplan-Meier graph of one year patient survival*

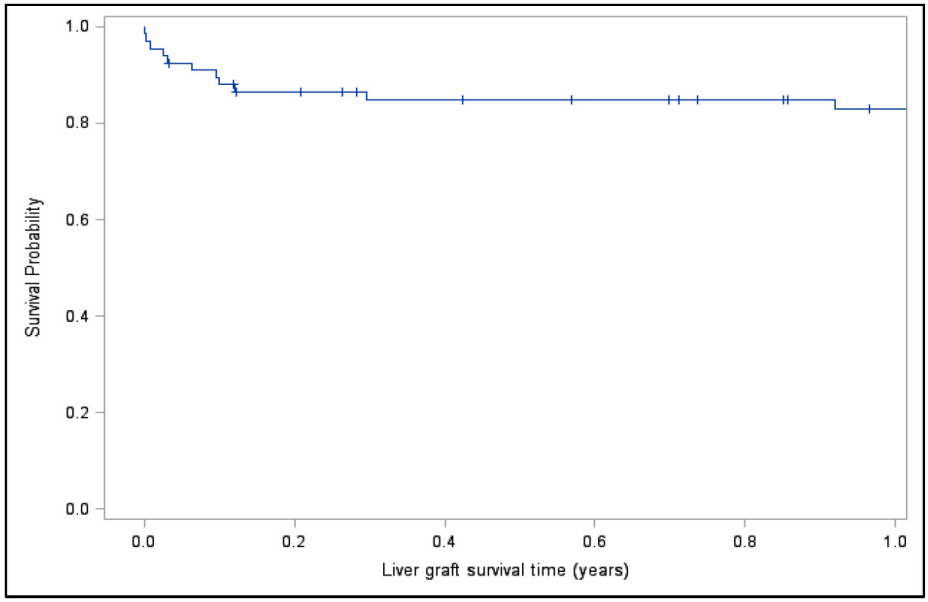


*Figure 5: Kaplan-Meier graph of one year graft survival*

Forty-three patients (64%) had a history of previous KPE. We could determine the age at KPE for twenty-five of these patients, and the median age at KPE was 80 days (IQR: 60–100 days).

Five patients met the criteria for BASM, with all other associated anatomical abnormalities occurring in this group. The specific abnormalities encountered were polysplenia, interrupted IVC, malrotation, preduodenal portal vein and situs inversus. Three patients had pre-transplant portal vein thrombosis.

The one year overall patient survival is 84.5%, (C.I. 73–91%) (Figure 4), and the one year graft survival is 82.9% (C.I. 71–90%). The median follow up is 1.7 years (IQR:0.4–3.8) (Figure 5).

Fifteen patients in this cohort died by the end of the study period. The leading cause of death was infection in ten patients (67%) and nine patients (60%) suffered early deaths.

Twenty-six relook laparotomies were performed in twenty-four patients. There were ten documented enteric complications (13%). Eight patients (12%) sustained vascular complications – six developed portal vein thrombosis and 2 sustained hepatic artery thrombosis. Both patients who developed hepatic artery thrombosis had relook laparotomies with redo of the anastomosis, but one of these patients demised during the acute postoperative period.

Twenty-four biliary complications developed in twenty-three patients (32%). One patient experienced two biliary complications namely a cut surface leak, and had a blind ending ductal system. Eleven patients developed biliary strictures, seven of these were early biliary strictures and four were late. The remaining biliary complications were anastomotic leaks (7), cut surface leaks (3), blind ending ductal system (2), and a retained stent (1).

## Discussion

Currently, KPE is performed at numerous centres in South Africa, and only referred to the Wits Transplant Programme for transplantation. The published outcomes for KPE in South Africa are far below the international standard, with the rate of successfully draining KPE reported between 19 and 27%[7,17] compared to 45–55% in larger series.[23] Liver transplantation is integral to the management of patients with BA. It should be performed at a centre which meets the criteria for an excellent multidisciplinary approach. The survival outcomes in this study are on par with most centres with comparable patient loads. The mortality rate of this study falls within the reported range of most single centre reviews.[24-27]

Despite the valuable conclusions achieved in this study, the limitations include the retrospective nature, and resultant inconsistencies in the data available, as well as the short median follow-up of 1.7 years. This allows for assessment of one year outcomes but falls short of accurate reflection of long term postoperative complications and mortality. A larger sample would enable the study of factors contributing to these outcomes, and it is an area of future study.

Assessment of nutritional status in patients with BA is complex. This group of patients fulfills the WHO definitions of protein energy malnutrition, by being underweight for height with muscle wasting. About half the patients in this

study satisfy the criteria of moderate to severe malnutrition with a weight for height z-score of -2 or worse, and two thirds of this group of patients meets the criteria for chronic malnutrition and stunting, with a height for age z-score of -2 or worse. Mid upper arm circumference should be included as part of a detailed anthropometrical assessment, as it corrects for hepatosplenomegaly and ascites.[22,28]

Delayed referral results in progressive malnutrition for multiple reasons including: poor oral intake, increased energy expenditure, malabsorption, chronic enteropathy, deterioration in hepatic synthetic function, infective complications and immunosuppression.[23] Nutritional rehabilitation is of utmost importance, as the nutritional status has a recognised effect on pre- and post-transplant mortality.[29,30]

The relationship between MUAC and risk of death is currently being studied and unpublished results have prompted the implementation of a policy at the WDGMC transplant unit to delay liver transplant until the MUAC z score is above -2. Eleven of the fifteen patients who died had a pre-transplant z-score for MUAC of -2 or worse. This result may incorrectly reflect the current reality, as upon evaluation of the study population during the study period, a significantly higher mortality rate was observed in patients with a MUAC z-score of -2 or worse. The hazard ratio for death in these patients was 5. As a result, the policy was changed to admitting severely malnourished patients for aggressive nutritional rehabilitation prior to offering liver transplantation.

It follows that if the management of BA were centralised, patients would be managed by an experienced team resulting in early identification of the need for liver transplant, comprehensive work-up and nutritional resuscitation, and expedient surgery.

The rate of enteric complications is within the reported range of 2.4–20%.[31-34] There is discordance in the literature as to whether enteric complications are higher in patients transplanted for BA versus those patients transplanted for other indications.[32,34]

Primary liver transplant may be a logical choice for selected patients. There is little evidence for liver transplant as the primary surgery from the outset, as it is not the current standard, but results are promising.[14] Most research describing patients who have had a primary liver transplant alludes to patients who have a delayed diagnosis, and have been referred "too late" for a KPE.[34,36] The selected patients would be those with proven risk factors for an unsuccessful KPE, would include patients beyond 100 days as an indication on its own, and those older than seventy days, who fall into other risk groups such as those with BASM, Ohi Type II or III, those with ductal plate abnormalities, and those with established cirrhosis.[14,29]

## Conclusion

This report of liver transplantation for children with BA in South Africa demonstrates that good outcomes can be achieved across disparate health care systems. It is hoped that this experience will continue to yield improved care for children with BA, early referral for transplantation might spare some infants needless surgery, and quite possibly result in diminished morbidity and mortality following liver transplant.

### *Ethics approval*

Ethics approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (Ethics clearance number: M170752).


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