The paediatric liver transplant experience in Johannesburg, South Africa: A broad overview and update

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Background. The Wits Transplant Unit in Johannesburg, South Africa (SA), performed its first paediatric liver transplant in 2005. Initial experiences from the unit were published in 2012 and 2014. Since then, significant progress has been made in building the capacity of the unit, improving outcomes and enhancing service delivery.
Objectives. To present a broad overview and update of the unit's 17-year experience.
Methods. We conducted a retrospective review of all paediatric liver transplants performed in Johannesburg from 1 January 2005 to 31 December 2021 with a minimum 1-year follow-up. Data were accessed from the Wits Donald Gordon Medical Centre Paediatric Liver Transplant Research Database (University of the Witwatersrand human research ethics approval ref. no. M190749). The following data were collected: donor and recipient sociodemographic and clinical characteristics, details of transplant procedures, and donor graft and recipient outcomes (postoperative complications, and graft and recipient survival).
Results. A total of 270 transplants were performed during the review period. Two-thirds of the recipients (n=180; 66.7%) were aged <5 years at time of the transplant, and half (n=135; 50.0%) received a living-donor graft. The most common indication for liver transplant was biliary atresia, followed by acute liver failure. Unadjusted recipient survival was 80.1% (95% confidence interval (CI) 75 - 85) at 1 year and 68.2% (95% CI 59 - 75) at 5 years. Waiting-list mortality decreased from 27.3% in 2017 to 5.9% in 2021. One hundred and fifty-four recipients (57.0%) experienced at least one type of surgical complication that required intervention, the most common being biliary in nature (n=91; 33.7%).
Conclusion. Over the past 17 years, a sustainable paediatric liver transplantation service has been established in Johannesburg. Living-donor, split and ABO-incompatible liver transplants have been incorporated in response to the severe organ shortage in SA. However, our outcomes can be improved. Additionally, a national transplant initiative to co-ordinate timeous referrals and expand access to liver transplantation for children with severe acute and chronic liver failure is advised.

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Since its inception in 1963,[1-3] paediatric liver transplantation has evolved significantly. Globally, liver transplantation is accepted as the standard of care for children with end-stage liver disease and acute liver failure unresponsive to supportive care.[4-6] Improvements in surgical techniques, hepatology, immunosuppression and critical care have made this possible.[5-7] In many centres around the world, waiting-list mortality currently approaches zero.[4]

In South Africa (SA), there have been advances in the scope and depth of liver transplant services available for children.[8-12] Initially pioneered by colleagues in Western Cape Province, liver transplantation services subsequently expanded to Gauteng.[8-12] Despite this progress, access to liver transplantation for many children in SA remains severely restricted because resource-intensive transplant services are difficult to sustain outside of large urban metropoles.[9,10,13] Additionally, there are currently no published national guidelines to assist referral of children with advanced liver disease, and healthcare worker as well as public education regarding the availability of such services is inadequate.[9,10,13,14]

When paediatric liver transplantation was established in Johannesburg in 2005, the programme relied solely on deceased-donor grafts.[8-12] In response to persistent deceased-donor organ shortages and an ever-increasing need, services have evolved to include various iterations of liver transplants.[8-12] The initial experiences of the Wits Transplant Unit were published in 2012 and 2014,[7,8] and since then an enormous amount has evolved.[9-12] This article provides a broad overview and update of our experience with paediatric liver transplantation in Johannesburg over the past 17 years.

Methods

We conducted a retrospective review of all paediatric liver transplants performed in Johannesburg from 1 January 2005 to 31 December 2021. Data were accessed from the Wits Donald Gordon Medical Centre Paediatric Liver Transplant Research Database (University of the Witwatersrand human research ethics approval ref. no. M190749). Data collected at the time of the transplant included recipient age, sex, primary disease necessitating transplant, Model for End-stage Liver Disease (MELD)/Pediatric End-stage Liver Disease (PELD) score, time on waiting list prior to transplant, nutritional status (mid-upper arm circumference in children aged ≤5 years or body mass index in those aged >5 years), donor type (deceased or living), donor-recipient ABO blood group compatibility, graft type (whole or partial), graft-to-recipient weight ratio (GRWR), additional organs transplanted, recipient and graft 1- and 5-year survival, postoperative surgical complications (biliary, vascular and/or enteric), surgical re-explorations prior to discharge, hospital length of stay (LoS), and annual waiting-list outcomes. Paediatric patients were defined as those <18 years of age on the day of transplantation. LoS was defined as the number of days from transplant to discharge from Wits Donald Gordon Medical Centre or death, whichever came first. Patient and graft survival estimates were determined by the Kaplan-Meier method. All survival data were unadjusted. The relationship between recipient/donor characteristics (study variables) and recipient survival was assessed by Cox proportional hazards regression. Categories with $n<15$ were not included in the analysis. Study variables that were significant on univariable analysis ($p<0.20$) were combined into a multivariable model after examining each pair of variables for possible confounding using the χ^2 test (or Fisher's exact test for 2 × 2 tables). Non-significant variables were sequentially removed from the multivariable model. Data analysis was carried out using SAS version 9.4 for Windows (SAS Institute, USA). A p-value <0.05 was considered statistically significant.

Results

Recipient and donor characteristics

Two hundred and seventy paediatric liver transplants were performed during the review period. Fig. 1 shows the number of transplants performed per year and Fig. 2 the distribution of different graft types used

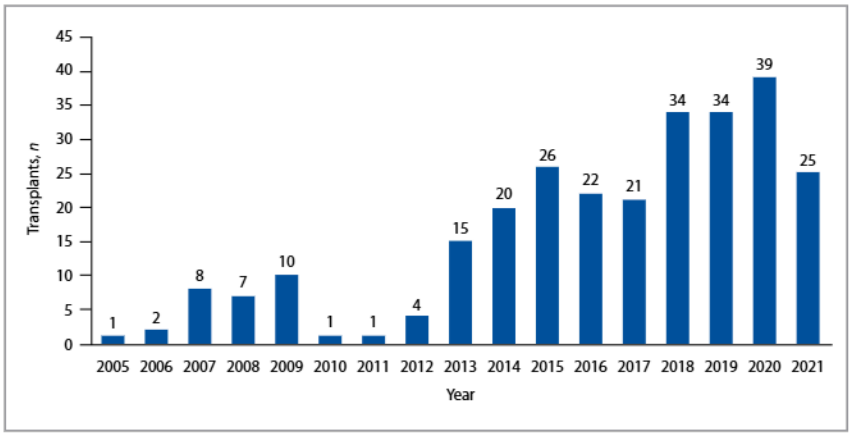

Fig. 1. Number of paediatric liver transplants performed per year in Johannesburg, South Africa, 2005 - 2021 (N=270).

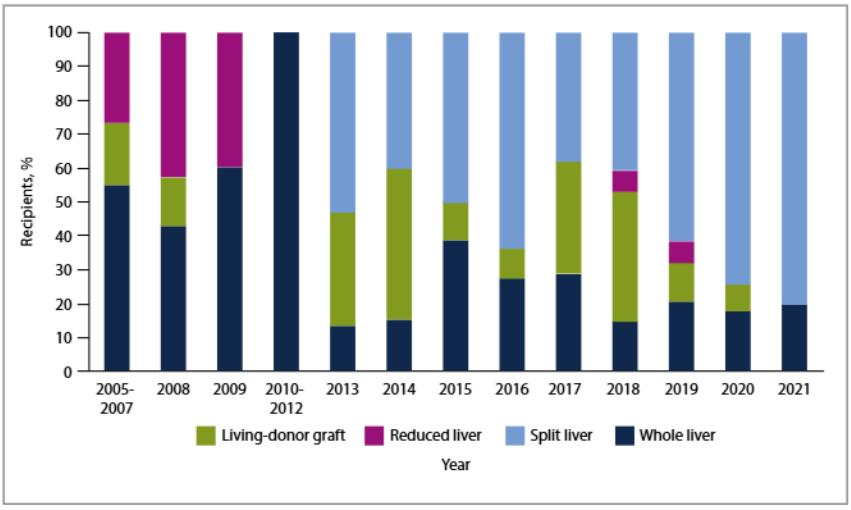

Fig. 2. Proportion of different graft types used per year in Johannesburg, South Africa, 2005 - 2021 (N=270).

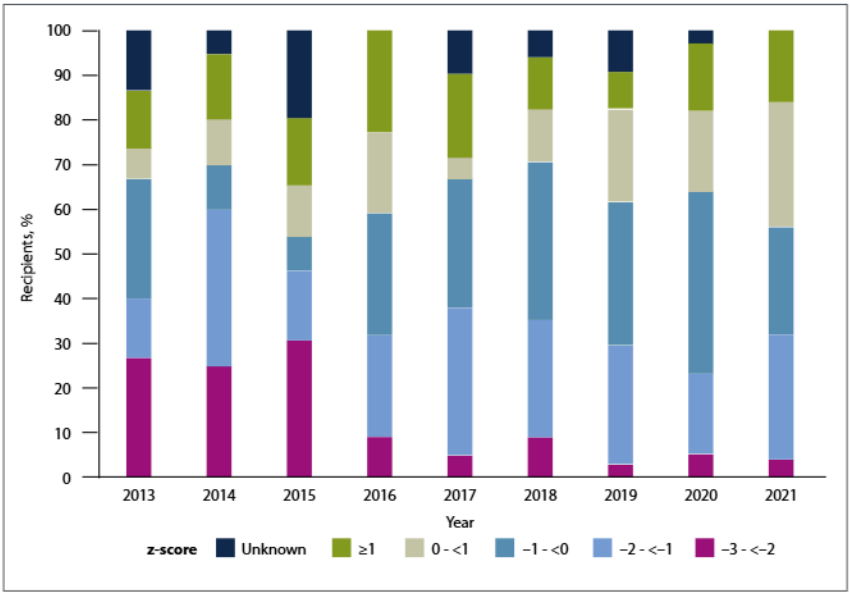

Fig. 3. Distribution of malnutrition scores per year of paediatric liver transplant recipients in Johannesburg, South Africa, 2013 - 2021 (N=236).

Table 1. Characteristics of paediatric liver transplant recipients in Johannesburg, South Africa, 2005 - 2021 (*N*=270)

Characteristic	*n* (%)*
Age (years)	
< 1	30 (11.1)
1 - 5	150 (55.6)
> 5	90 (33.3)
Sex	
Male	112 (41.5)
Female	158 (58.5)
Aetiology	
Acute liver failure	45 (16.7)
Cholestatic disease	
Biliary atresia	126 (46.7)
Other cholestastic diseases†	16 (5.9)
Metabolic diseases‡	48 (17.8)
Neoplastic§	7 (2.6)
Veno-occlusive disease	11 (4.1)
Other¶	17 (6.3)
Medical urgency	
Status 1	45 (16.7)
MELD/PELD score	
≥35	9 (3.3)
30 - 34	3 (1.1)
15 - 29	105 (38.9)
<5	100 (37.0)
Unknown	8 (3.0)
Nutritional status	
Malnourished	
Severe	27 (10.0)
Moderate	57 (21.1)
Mild	65 (24.1)
Well nourished	71 (26.3)
Unknown	50 (18.5)
Time on waiting list	
Days	
<31	97 (35.9)
31 - 60	21 (7.8)
Characteristic	***n*** **(%)***
61 - 90	31 (11.5)
Months	
3 - <6	62 (23.0)
6 - <12	34 (12.6)
>12	25 (9.3)
Transplant history	
First	254 (94.1)
Retransplant‖	16 (5.9)
Procedure type	
Liver only	254 (94.1)
Liver and another organ	16 (5.9)
Graft type	
Whole	72 (26.7)
Partial	
Split	49 (18.1)
Reduced	14 (5.2)
Living donor	135 (50.0)
GTWR, mean (IQR)	2.7 (1.9 - 3.8)
LoS (days), median (IQR)**	24 (15 - 44)

MELD/PELD = Model for End-stage Liver Disease/Pediatric End-stage Liver Disease; GTWR = graft-to-recipient weight ratio; IQR = interquartile range; LoS = length of hospital stay; AIH = autoimmune hepatitis; PSC = primary sclerosing cholangitis.

*Except where otherwise indicated.

†Other cholestatic diseases: Alagille syndrome n=12/270 (4.4%); progressive familial intrahepatic cholestasis *n*=4/270 (1.5%).

‡Metabolic diseases: AIH *n*=15/270 (5.6%); oxalosis *n*=13/270 (4.8%); alpha-1 antitrypsin deficiency *n*=7/270 (2.6%); PSC *n*=4/270 (1.5%); haemolytic uraemic syndrome *n*=2/270 (0.7%); citrullinaemia *n*=2/270 (0.7%); AIH/PSC overlap syndrome *n*=2/270 (0.7%); familial hypercholesterolaemia *n*=1/270 (0.4%); maple syrup urine disease *n*=1/270 (0.4%); Wilson's disease *n*=1/270 (0.4%).

§Neoplastic: hepatoblastoma *n*=5/270 (1.9%); hepatocellular carcinoma *n*=2/270 (0.7%).

¶Other: chronic rejection of liver graft *n*=4/270 (1.5%); cystic fibrosis *n*=3/270 (1.1%); polycystic kidney disease and hepatic fibrosis *n*=3/270 (1.1%); Benty syndrome (non-cirrhotic portal hypertension) *n*=1/270 (0.4%); Caroli's syndrome *n*=1/270 (0.4%); cryptogenic *n*=1/270 (0.4%); hepatitis B *n*=1/270 (0.4%); idiopathic *n*=1/270 (0.4%); neonatal sclerosing cholangitis *n*=1/270 (0.4%); secondary biliary cirrhosis *n*=1/270 (0.4%).

‖Retransplants: hepatic artery thrombosis *n*=8/16 (50.0%); primary graft non-function *n*=2/16 (12.5%); small for size *n*=1/16 (7.3%); chronic rejection of liver graft *n*=4/16 (25.0%); secondary biliary cirrhosis *n*=1/16 (7.3%).

**Liver-only recipients discharged home from Wits Donald Gordan Medical Centre (*n*=209).

Table 2. Characteristics of paediatric liver transplant donors in Johannesburg, South Africa, 2005 - 2021 (*N*=270)

Characteristic	*n* (%)
Donor type	
Deceased	135 (50.0)
Living	
Maternal	80 (29.6)
Non-maternal	55 (20.4)
ABO compatibility	
Identical	210 (77.8)
Incompatible	
Minor	46 (17.0)
Major	14 (5.2)

Table 3. Complications of paediatric liver transplant recipients in Johannesburg, South Africa, 2005 - 2021 (*N*=270)

Complication	*n* (%)
Any complication (biliary/enteric/vascular)	154 (57.0)
Biliary complications*	91 (33.7)
Stricture	45 (16.7)
Leak	
Anastomotic	27 (10.0)
Cut surface	29 (10.7)
Blind-ending ductal system	2 (0.7)
Retained stent	2 (0.7)
Enteric complications	27 (10.0)
Vascular complications†	40 (14.8)
Hepatic artery	
Thrombosis	13 (4.8)
Rupture	2 (0.7)
Portal vein	
Thrombosis	9 (3.3)
Stenosis	7 (2.6)
Hepatic vein	
Thrombosis	2 (0.7)
Stenosis	7 (2.6)
Inferior vena cava	
Thrombosis	0 (0.0)
Stenosis	2 (0.7)
Other	5 (1.9)

*Paediatric liver transplant recipients who had at least one biliary complication.
†Paediatric liver transplant recipients who had at least one vascular complication.

over time. Table 1 summarises paediatric recipient and transplant characteristics, while Table 2 summarises the donor characteristics. Of note, 66.7% (*n*=180/270) of recipients were aged <5 years at time of the transplant. Seventy recipients (25.9%) weighed <10 kg. Additionally, data collected since 2013 on nutritional status of recipients reflected that 11.4% of recipients (*n*=27/236) were severely malnourished. Fig. 3 shows the decreasing trend towards transplanting moderately and severely malnourished recipients (*z*-score <–2).

Forty-five (16.7%) of the 270 recipients received a liver transplant for acute liver failure. Of the remaining recipients, most were transplanted for biliary atresia (*n*=126/270; 46.5%). The most frequent PELD/MELD scores were between 15 and 29 (*n*=105/270; 38.9%) and <15 (*n*=100/270; 37.0%).

Half of the recipients (*n*=135/270; 50.0%) received living-donor liver transplants, with a median GRWR of 2.3. The remaining recipients received deceased-donor livers: 72/270 (26.7%) whole grafts, 49/270 (18.1%) split grafts and 14/270 (5.2%) reduced grafts. Sixty recipients in the cohort (22.2%) received ABO-incompatible (ABOi) livers, of which 14 had a major incompatibility. These represented 5.2% of all paediatric liver transplants performed. Sixteen (5.9%) of all the recipients received a multiorgan transplant including a liver, and 16 procedures (5.9%) were retransplants.

Outcomes

Recipient and graft survival characteristics were determined for first transplants only (*n*=254/270); the survival curves are shown in Fig. 4. The median follow-up time was 2.3 years. The 1- and 5-year unadjusted recipient survival estimates were 80.1% (95% confidence interval (CI) 75 - 85) and 68.2% (95% CI 59 - 75), respectively, while the 1- and 5-year unadjusted graft survival estimates mirrored recipient survival and were 78.9% (95% CI 74 - 84) and 66.7% (95% CI 58 - 74), respectively.

Recipient and donor characteristics were analysed to determine which characteristics contributed to poorer recipient survival. In the initial univariable analysis, the following factors were significantly associated with an increased risk of recipient death: moderate and severe malnutrition (*z*-scores <–2), retransplant, surgical re-exploration and vascular complications. Of note, the cause of liver failure (acute v. chronic) was not significantly associated with an increased risk of recipient death. In the final multivariable analysis, however, the only characteristics that remained significant were surgical re-exploration (relative risk (RR) 2.20; 95% CI 1.43 - 3.40) and retransplant (RR 3.93; 95% CI 2.02 - 7.66).

One hundred and fifty-four (57.0%) of all recipients experienced at least one type of surgical complication that required intervention. The most common complications were biliary (*n*=91/270; 33.7%). Biliary complications were more prevalent in partial grafts (41.4%) compared with whole grafts (12.5%) ($p<0.0001$). Donor type and ABO compatibility were not associated with an increased incidence of biliary complications. Thirteen recipients (4.8%) developed hepatic artery thrombosis. Hepatic artery-associated complications were not significantly associated with donor type, graft type or ABO incompatibility. Table 3 shows the complications experienced by paediatric liver transplant recipients.

With regard to pretransplant outcomes (previously known as waiting-list outcomes), data were available from 2017. As of 2021, the percentage of candidates who died while waiting for a transplant (waiting-list mortalities) per year from 2017 onwards was as follows: 27.3% (2017), 18.1% (2018), 20.0% (2019), 11.5% (2020) and 5.9% (2021). The percentage of waiting-list candidates transplanted (list-to-transplant percentages) were as follows: 40.9% (2017), 48.6% (2018), 71.4% (2019), 67.3% (2020) and 67.6% (2021). These trends are shown in Fig. 5. Additionally, 55.2% of recipients (*n*=149/270) were transplanted within 90 days, and only 9.3% (*n*=25/270) were on the transplant waiting list for longer than a year.

Discussion

Paediatric liver transplantation is undoubtedly the most significant advance in the treatment of acute and end-stage liver disease in children over the past 50 years.[1,2] Although it is a resource-intensive endeavour,[7,8] the role of liver transplantation in SA remains significant. In our unit, biliary atresia remains the most common indication for paediatric liver transplantation, something that has not changed in our unit over the past 17 years.[7,8] Significantly, however, transplantation for acute liver failure has emerged as the second most common indication for liver transplant,[11] probably driven by some of the programme's advances.

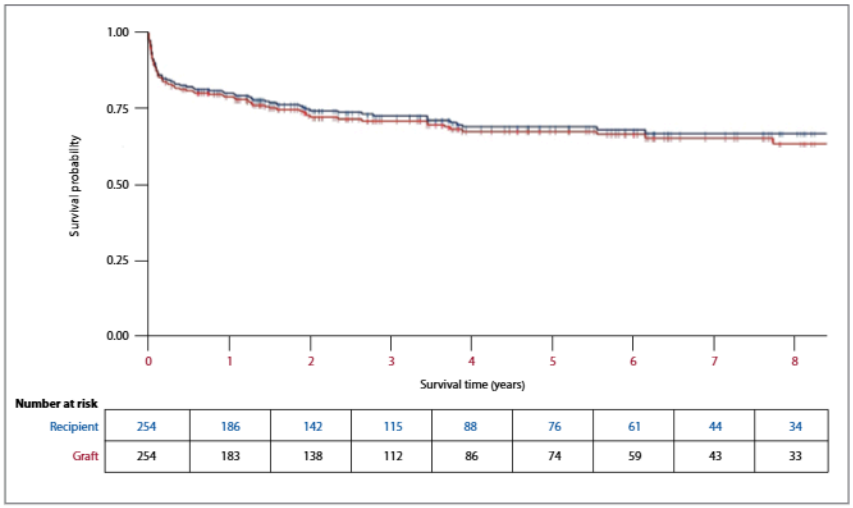

Fig. 4. Kaplan-Meier plots for recipient and graft survival of paediatric liver transplant recipients in Johannesburg, South Africa.

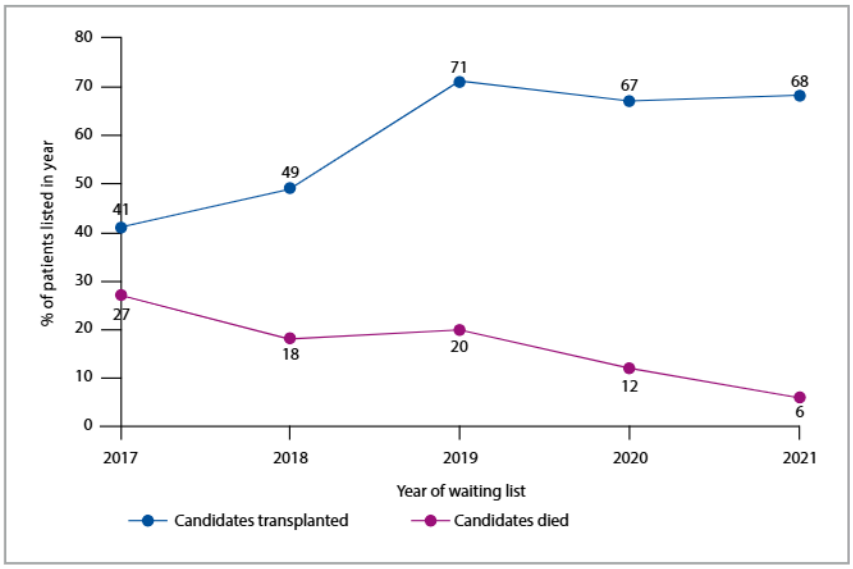

Fig. 5. Status 1 year after listing of transplant candidates on the Wits Transplant Unit waiting list in Johannesburg, South Africa.

Programme milestones

The addition of various components to the unit over the years has enabled programme growth. These have included but not been limited to: (*i*) the co-operation of dedicated medical, allied and nursing caregivers, resulting in more comprehensive patient management; (*ii*) improved transplant-related co-ordination and management; (*iii*) improved patient selection/listing (in particular, nutrition optimisation and psychosocial evaluation); (*iv*) innovative graft procurement and utilisation (expansion of the living-donor, split-liver and ABOi liver transplant programmes); (*v*) human resource development (recruitment of full-time non-medical paediatric staff, recruitment of full-time paediatric transplant hepatologists, recruitment of paediatric transplant intensivists, addition of a transplant microbiologist, and establishment of a transplant-specific employment model); (*vi*) infrastructure development (the construction of a dedicated transplant intensive care unit, a paediatric transplant ward and laminar-flow operating theatres large enough to accommodate the entire liver transplant process); (*vii*) commitment to continued university-linked medical education, training and research; and (*viii*) nurturing of a private-public sector arrangement with the Gauteng Department of Health.[8,10-12] These components have made the outcomes as discussed below possible.

Outcomes

The European Liver Transplantation Registry reported 1-year and 10-year paediatric liver transplant recipient survival rates of 83% and 75%, respectively, based on a review of 5 895 paediatric patients who received liver transplants between 1988 and 2005.[4] Additionally, the United Network for Organ Sharing (UNOS) reported 1-year and 5-year recipient survival rates for just over 9 000 paediatric liver transplants of 90% and 81%, respectively. Other centres have similarly reported 1-year survival rates ranging between 70% and 90%.[1,4] Our 1-year and 5-year recipient survival rates are 80% and 68%, which compare reasonably with the international literature. Moreover, our 1-year and 5-year graft survival rates of 79% and 68% are equally comparable with the UNOS-reported 1-year and 5-year graft survival rates of 83% and 68%, respectively.[1,4] Factors associated with an increased risk of poor survival in our cohort included surgical re-exploration and retransplant. This is in keeping with the international literature, where survival after retransplant is poor.[13,14] Surgical re-exploration is a surrogate for severity of disease; the more surgically compromised patient is generally more likely to receive a re-exploration and may have a poorer outcome.[15,16] Surprisingly, and unlike international data where nutritional status has been shown to influence paediatric liver transplant recipient outcomes,[17-20] our cohort did not demonstrate a statistically significant association between risk of mortality and nutritional status, perhaps because of the decreasing trend towards transplanting moderately and severely malnourished recipients (*z*-scores <–2).

Despite the internationally comparable graft and patient survival rates, our surgical complication rate remains ~60%. The most common complications were biliary in nature. Biliary complications were more common in partial grafts than in whole grafts, probably reflecting the complexity of partial liver graft transplantation.[19,20] Despite the complications noted, the lower overall mortality does perhaps demonstrate that the unit has a capacity to rescue such that surgical morbidity does not necessarily result in mortality. Irrespectively, we acknowledge that liver transplantation is associated with significant surgical morbidity, and therefore remaining cognisant of our outcomes will allow us to continue working towards lowering our surgical complication rate.

The reduction of the waiting-list mortality from nearly 30% in 2017 to just over 5% in 2021, improvement of the list-to-transplant percentage from 40.9% to 67.6%, and the transplanting of 55.2% of our candidates within 90 days highlight additional success of the programme. These waiting-list outcomes are comparable to the 2021 Organ

Procurement and Transplantation Network/Scientific Registry of Transplant Recipients reported waiting-list mortality, list-to-transplant percentage and time to transplant <90 days figures of 3%, 76.7% and 46.4%, respectively.[21]

Partial liver grafts

In our previous publications, we highlighted that the worldwide shortage of deceased-donor organs remains the biggest barrier to organ transplantation.[7-11] Similar shortages in SA have contributed and continue to contribute significantly to waiting-list mortality.[7-11] Implementing a partial-graft programme that includes the use of reduced grafts, split grafts and living-donor grafts has significantly increased organ availability.[10,11] Consequently, we have seen a steady increase in the number of transplants performed from <10 per annum in the mid-2000s to nearly 40 in 2020. The introduction of the living-donor liver programme was a sentinel step forward in our programme,[10,11] with half of the recipients in our entire cohort having received a living-donor graft. In terms of deceased-donor transplantation, split grafts provide the additional advantage of utilising one organ for two recipients, thus increasing organ utility. Partial grafts have therefore become a vital component of our programme.[8]

ABO-incompatible transplants

It is well accepted that children aged <2 years receiving ABOi liver grafts have similar outcomes to those receiving ABO-compatible grafts.[22] The performance of ABOi liver transplants in our programme has been most beneficial.[11] To date we have performed 60 ABOi paediatric liver transplants. Fourteen (23.3%) of these have been transplants with major incompatibility. Over the years, not only has the total number of ABOi transplants increased, but so has the proportion of transplants with major incompatibility. Despite the initial caution and trials of creating a standardised ABOi transplant protocol, we have grown more comfortable with these more complex patients, further increasing our donor pool, and delivering acceptable results.[11] We anticipate further growth in this innovative form of transplantation, facilitating expansion of the donor pool and improved organ utility.

National transplant framework

Chapter 8 of the South African National Health Act 2003 legislates the framework within which human blood, blood products, tissues and gametes from both living and deceased persons may be used.[23,24] It gives a broad overview of and directives pertaining to procurement and utilisation of human organs,[23,24] an important step forward in comparison with the Human Tissues Act of 1983.[25] Despite this legal framework, transmission and implementation on the ground has not always been congruent with the spirit of the law.[24,26] Regulatory guidelines from national to hospital level are still underdeveloped.[9,12,26] As the incidence of end-stage liver disease continues to grow in sub-Saharan Africa,[26,27] the need for transplantation is growing.[7-12] This situation is best represented by the growing national organ waiting list in the context of a decreasing proportion of transplant organ recipients.[26] Although many factors have contributed to the slow growth of transplantation as a national agenda, it is beneficial to have a carefully controlled, monitored and expansive transplant system to ensure timeous referrals, co-ordinate organ allocation and expand access to liver transplantation for children with severe acute and chronic liver failure.[26]

Conclusion

The Wits Transplant Unit remains one of two centres offering paediatric liver transplantation in SA. As such, we desire to offer world-class service to our population. We have striven hard to overcome the numerous challenges related to providing a comprehensive paediatric liver transplant service, and through collaborative hard work, improved techniques and care have created a programme that offers a unique and wide-reaching service. After 17 years of paediatric liver transplantation, we recognise that while much has been achieved, our outcomes can be improved. Additionally, implementation of a more in-depth national transplant framework is advisable.

Declaration. None.

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