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Carolyn Bouter; Russell Britz; Bernd Strobele; Sharan Rambarran; F Van Der Schyff ...

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Research Article

Adult and Paediatric Liver Transplantation: Wits Transplant Data 2020

Bouter C[1], Britz R[1], Strobele B[1], Rambarran S[1], van der Schyff F[1], Brannigan L[1], Demopoulos D[1], Beretta M[1], Berkenfeld S[1], Parbhoo D[1], Bobat B[1,2], Mahomed A[1,2], Reynders M[1], Maher H[1], Gaylard P[3], Etheredge H[1,2], J Botha[1,4], Fabian J[1,2]*

[1]Wits Donald Gordon Medical Centre, Johannesburg, South Africa
[2]Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[3]Data Management and Statistical Analysis (DMSA), Johannesburg, South Africa
[4]Department of Surgery, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
**Correspondence to: June Fabian, june.fabian@mweb.co.za; or june.fabian@wits.*

INTRODUCTION

The Wits Transplant Unit is housed within the Wits Donald Gordon Medical Centre, which is part of the University of Witwatersrand's Academic Teaching Hospital Complex within the Faculty of Health Sciences, Johannesburg, South Africa. From the programme's inception in 2004 to the end of 2020, the transplant unit performed 491 adult and 247 paediatric liver transplants for acute or chronic end-stage liver disease (ESLD). The ongoing shortage of deceased donor organs, which worsened during the COVID-19 pandemic, mandates routine splitting of suitable deceased donor organs, as far as possible, to produce two usable grafts. Introducing the living donor liver transplant (LDLT) programme for children in 2012, followed by an adult LDLT programme, and increasing the number of ABO-incompatible transplants helps mitigate the impact of pervasive deceased donor organ shortages in South Africa.(1,2) These initiatives have increased the number of transplants performed annually. However, each year, waitlisted adults and children are lost due to organ shortages. In the absence of an annual liver transplant registry in South Africa, publishing this annual report for paediatric and adult liver transplantation for 2020, we commit to making our data publicly accessible for citizens and fellow healthcare professionals.

Methods

Using REDcap,(3,4) the Transplant Unit established prospective databases for the paediatric and adult liver transplant programmes with approval from the Wits Human Research Ethics Committee for both databases. While most data were previously collected and are available for year-on-year comparison, some additional variables were collected for the first time in 2018. These comprise the baseline comparators for this report.

Paediatric and adult data collected

Recipient variables at the time of transplant: age, sex, self-reported ethnicity, the primary cause of ESLD, transplant history (first or re-transplant), blood type (ABO), referring health sector, height, weight, body mass index, mid-upper arm circumference (MUAC) z-scores (children <5 years), medical urgency: *status one score, paediatric ESLD (PELD) score, model for ESLD (MELD) score (adults), presence or absence of diabetes mellitus (adults), time on the waitlist, transplant type (liver alone, liver and another organ), graft type (whole liver, split liver and reduced- size graft), length of hospital stay at time of transplant, biopsy-proven graft rejection within 90 days of transplant (paediatric programme), one month, one year, and three year recipient and graft survival.

*A status one score is given to high urgency patients with seven days or less life expectancy if not transplanted. This score is most applicable to acute liver failure patients.

Donor variables: blood type (ABO), vital status (living or deceased donor) and donor risk index (DRI) (5) for deceased donors (adults).

Potential liver transplant recipients on the waitlist: numbers at the start and end of every year, removal from the

waitlist, age, sex, self-reported ethnicity, primary disease, medical urgency (PELD score), wait time, and outcomes one year after listing.

Outcomes

All survival estimates are for first transplants and all causes of ESLD. One month and one year patient and graft survival estimates, respectively, are based on transplants carried out in the 2.5 years before the last 12 months of follow-up, i.e. patients transplanted between 1 July 2017 and 31 December 2019. Three year patient and graft survival estimates are based on transplants carried out in the 2.5 years before the last three years of follow-up, i.e. patients transplanted between 1 July 2015 and 31 December 2017. Risk-adjusted estimates are based on the observed vs estimated deaths (or graft failures) using a model based on transplant number, chronic vs acute liver failure, recipient age and sex.

Results

Section A: Paediatric Liver Transplant Annual Report for 2020

Table A1 summarises the clinical and demographic characteristics of children undergoing liver transplantation. In 2020, we observed a slight male preponderance (56%) with 67% of transplants in children under five years of age. When comparing 2020 to prior years, there were reduced referrals from state sector hospitals and fewer national referrals for children with acute liver failure.

Of the 247 children transplanted since 2004, 61.5% (152/247) occurred in the last five years (**Supplementary Figure A1**), and of these, 56.6% (86/152) were grafted from living donors, reflecting the year-on-year increase in living donation (**Supplementary Table A1**). Of the deceased donor transplants (N=66), 32 were whole liver, 30 were split-liver, and four were reduced-size grafts.

Overall, the pretransplant nutritional status of our paediatric liver transplant recipients improved from 2016 (**Supplementary Table A2**). Since most transplants occurred under five years of age, we included a graphical representation of the primary nutritional index for this age group, namely the mid-upper arm circumference (MUAC), to demonstrate progress towards achieving target z-scores of –1 to 0 (**Figure A1**).

We determined medical urgency for transplantation using the PELD score, with a trend towards transplanting children with lower PELD scores, reflecting the increase in LDLT and fewer referrals for those with acute liver failure. For 2020, all transplant procedures were liver alone, with no additional other solid organs transplanted (**Supplementary Table A3**).

Outcomes defined as the incidence of biopsy-proven rejection within 90 days of liver transplant, and one month, one and three year graft and recipient survival are represented in **Table A2** and **Supplementary Figures A2-A3**. Unadjusted one month, one year, and five year recipient survival (as a percent with the 95% confidence interval for the percent) was 86% (76–92), 75% (64–84), and 73% (60–82), respectively. The median length of hospital stay at the time of transplant decreased from 31 days in 2016 to 17 days in 2020 (**Supplementary Table A3**).

Characteristics of children waitlisted for liver transplant and their outcomes after one year on the waitlist are summarised in **Supplementary Tables A4 and A5**. While most children undergo liver transplantation within six months of being waitlisted, 20% still died while awaiting transplantation in 2019.

Section B: Adult Liver Transplant Annual Report for 2020

Table B1 summarises the clinical and demographic characteristics of adults undergoing liver transplantation, with 50% of transplants performed for cholestatic liver failure. Chronic viral infections, notably hepatitis B (3%) and hepatitis C (3%) were the least common indications for liver transplantation. Overall, in 2020 fewer transplants were performed than in prior years (**Supplementary Figure B1**), with reduced referrals for acute liver failure. Living donors 20.6% (7/34) increased in 2020 but remained relatively small in proportion to the reliance on deceased donor grafts 79.4% (27/34) and the frequency of ABO-incompatible transplants decreased (9%) compared to previous years - likely reflecting the reduced referrals for acute liver failure (**Table B2**).

The high rates of endemic CMV infection in South Africa are reflected in donor and recipient serological testing with no donor "negative" and recipient "negative" pairs at the time of transplantation. Most donors and recipients were non-immune to hepatitis B infection, possibly due to the absence of a widespread vaccination before 1994 in South Africa. Despite high national prevalence rates for HIV infection, only 3% of liver transplant recipients were HIV positive (**Supplementary Table B1**).

Outcomes defined as one month, one and three year graft and recipient survival are represented in **Table B3**, **Supplementary Figure B2**. Unadjusted one month, one year, and three year recipient survival (as a percent with the 95% confidence interval for the percent) was 89% (81–94), 80% (71–86), and 77% (67–84), respectively.

Characteristics of adults waitlisted for liver transplant and their outcomes after one year on the waitlist are summarised in **Supplementary Tables B2 and B3**. 72% of adults received a liver graft within one year of waitlisting, and 11% died while awaiting transplantation in 2019.

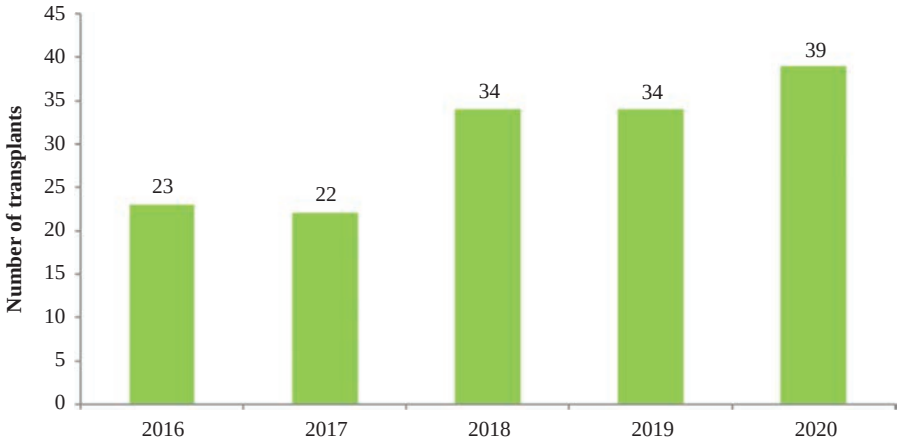
DISCUSSION

The Wits Liver Transplant Programme is the most extensive programme in South Africa and the only programme offering living donor liver transplantation. Despite introducing a living donor liver transplant programme for

PAEDIATRIC LIVER TRANSPLANTATION ANNUAL REPORT 2020

Table A1: Clinical and demographic characteristics for paediatric liver transplant recipients

	2016	2017	2018	2019	2020
Number of transplants	*23*	*22*	*34*	*34*	*39*
Age (%)					
<1 year	13	9	9	9	21
1–5 years	57	68	62	59	46
6–10 years	17	9	3	20	10
11–17 years	13	14	26	12	23
Sex (%)					
Female	74	55	56	62	44
Self-reported race (%)					
Black	57	68	73	73	46
White	39	18	3	18	28
Indian	4	0	6	3	16
Mixed	0	14	18	6	10
Primary Disease (%)					
Acute liver failure	9	14	26	24	13
Cholestatic disease	57	64	50	50	56
Budd-Chiari - Veno-occlusive disease	4	9	3	3	0
Metabolic disease	9	14	9	12	8
Malignancy	0	0	0	3	5
Other	22	0	12	9	18
Previous Kasai procedure in recipients with biliary atresia (%)					
Yes	54	50	47	75	50
Transplant history (%)					
First	91	95	94	94	95
Re-transplant	9	5	6	6	5
Blood type (%)					
A	48	45	29	26	31
B	9	9	29	21	13
AB	9	5	3	9	5
O	35	41	38	44	51
Health Care Sector (%)					
Funded	65	41	53	41	69
State	35	59	47	59	31
Wait time (%)					
<31 days	18	27	44	38	36
31–60 days	4	5	12	3	20
61–90 days	13	14	6	6	0
3–<6 months	39	27	20	21	23
6–<12 months	13	18	3	23	8
1–<2 years	13	9	6	6	13
2-<3 years	0	0	6	3	0
3 years or longer	0	0	3	0	0



Supplementary Figure A1: Number of paediatric liver transplants per year

Supplementary Table A1: Donor characteristics for paediatric liver transplants

	2016	2017	2018	2019	2020
Number of transplants	*23*	*22*	*34*	*34*	*39*
Blood type (%)					
A	35	36	35	29	23
B	4	9	18	18	13
AB	9	5	3	6	5
O	52	50	44	47	59
Living donors	*14*	*8*	*14*	*21*	*29*
Donor relationship to the recipient (%)					
Maternal	36	63	79	57	66
Non-maternal	64	37	21	43	34

children and adults, splitting donor grafts where possible to increase utility, and increasing the relative proportions of ABO-incompatible liver transplants, there are still children and adults who die on the waitlist each year. While strides have been made to reduce the reliance on deceased donor organs for paediatric transplantation, the adult liver transplant programme is still heavily reliant on deceased donation, thus limiting the capacity for increasing transplantation rates.

Transplantation for any South African with ESLD is available through the Wits Liver Transplant Programme and referrals are accepted from any health facility in South Africa. Reduced referrals for acute liver failure and the decreased numbers of adult liver transplants in 2020 are likely reflections of the impact of the COVID 19 pandemic. During the COVID 19 pandemic, the South African Transplant Society (SATS) published a position statement regarding solid organ transplantation.(6) While supporting the ongoing provision of transplant-related care, SATS advised that individual transplant centres should decide upon levels of transplant activity based on organ availability and available resources. Globally, poor pandemic preparedness has adversely affected the capacity for overwhelmed health systems to maintain critical services unrelated to COVID-19 care. Solid-organ transplantation is a case in point.(7) The argument against solid organ transplantation relates to the perioperative risk of COVID 19 infection during transplantation, the risk of transmission of COVID 19 infection from deceased and living donors, and diverting healthcare staff and infrastructure (like ICU beds) to non-COVID related care. Protagonists argue a more rational approach to balancing resources - pointing out that more patients would die on the waitlist or from complications related to ESLD.(8) Additional pandemic-related factors that curtailed liver transplant services include termination of organ procurement services and the cessation of services for evaluating and listing patients with end-stage liver failure for transplantation.(9)

Benchmarking outcomes for the Wits Transplant Unit is restricted by the absence of national and regional data. One year survival (unadjusted) differs among international transplant centres with discrepancies by country income

Supplementary Table A2: Pretransplant nutritional characteristics for paediatric liver transplant recipients

	2016	2017	2018	2019	2020
Recipients aged <=5y	*16*	*17*	*23*	*21*	*26*
Height z-score (%)					
-3 to <-2	31	41	44	24	39
-2 to <-1	25	18	26	33	19
-1 to <0	38	29	17	14	15
0 to <1	6	0	0	10	19
1 or more	0	0	4	5	8
Unknown	0	12	9	14	0
Weight z-score (%)					
-3 to <-2	25	6	4	10	12
-2 to <-1	19	35	18	29	35
-1 to <0	25	47	61	28	27
0 to <1	12	6	13	14	11
1 or more	19	6	4	14	15
Unknown	0	0	0	5	0
Mid Upper Arm Circumference z-score (%)					
-3 to <-2	12	6	0	0	0
-2 to <-1	25	35	26	43	19
-1 to <0	19	6	35	14	50
0 to <1	6	0	4	14	12
1 or more	13	6	9	5	8
Unknown	25	47	26	24	11
Recipients aged >5y	*7*	*5*	*11*	*13*	*13*
BMI z-score (%)					
-3 to <-2	0	0	18	8	8
-2 to <-1	0	20	27	0	23
-1 to <0	29	40	28	54	15
0 to <1	43	20	27	23	31
1 or more	28	20	0	15	15
Unknown	0	0	0	0	8
All recipients	*23*	*22*	*34*	*34*	*39*
Malnutrition z-score (%)					
-3 to <-2	9	4	9	3	5
-2 to <-1	22	32	26	26	21
-1 to <0	30	27	35	33	38
0 to <1	17	5	12	20	18
1 or more	22	23	12	9	15
Unknown	0	9	6	9	3

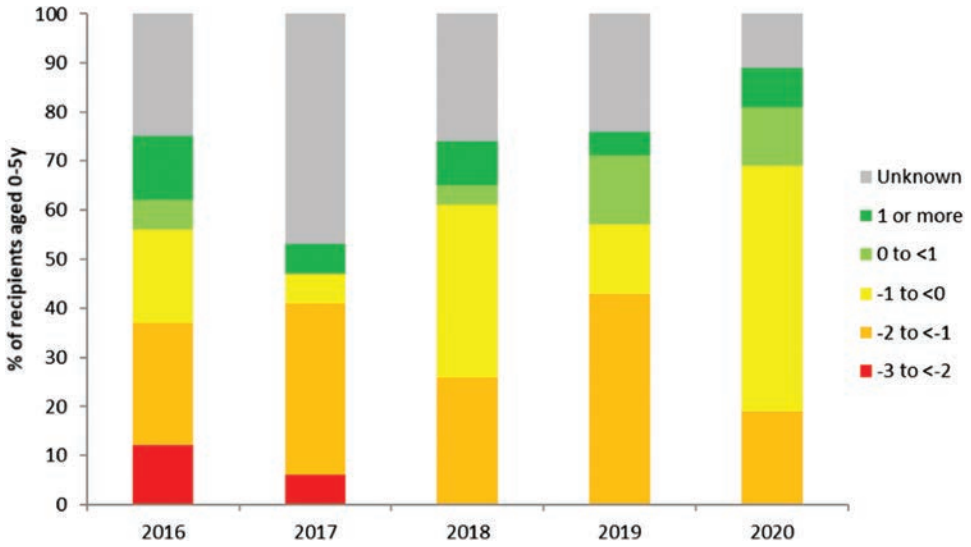


Figure A1: Pretransplant distribution of mid-upper arm circumference (MUAC) z-scores for liver transplant recipients younger than five years

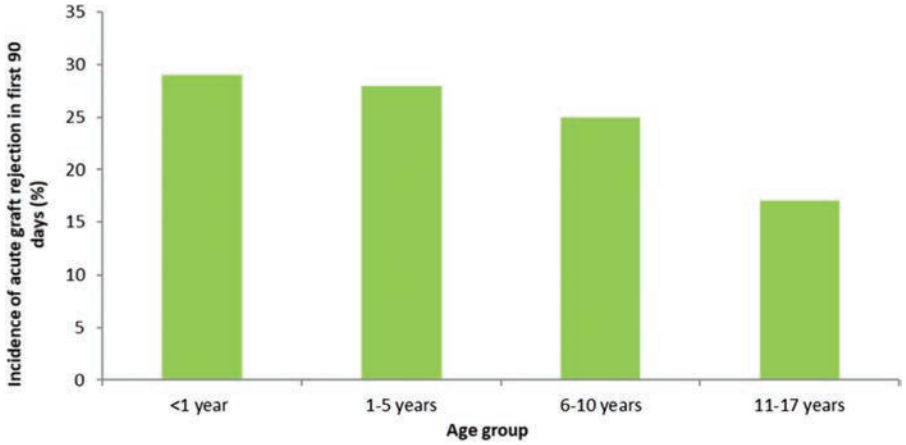
Supplementary Table A3: Paediatric liver transplant recipient medical urgency and procedure type

	2016	2017	2018	2019	2020
Medical urgency (%)					
Status one			29	24	13
MELD/PELD ≥ 35	13	14	0	3	0
MELD/PELD 30–34	4	0	0	0	3
MELD/PELD 15–29	52	50	35	26	41
MELD/PELD < 15	26	36	35	44	44
Unknown	5	0	0	3	0
Procedure Type (%)					
Number of transplants	*23*	*22*	*34*	*34*	*39*
Liver alone	96	91	94	97	100
Liver and another organ	4	9	6	3	0
Median days in hospital after transplant (Liver alone transplants)	31	24	22	20	17

Table A2: Paediatric recipient and graft survival

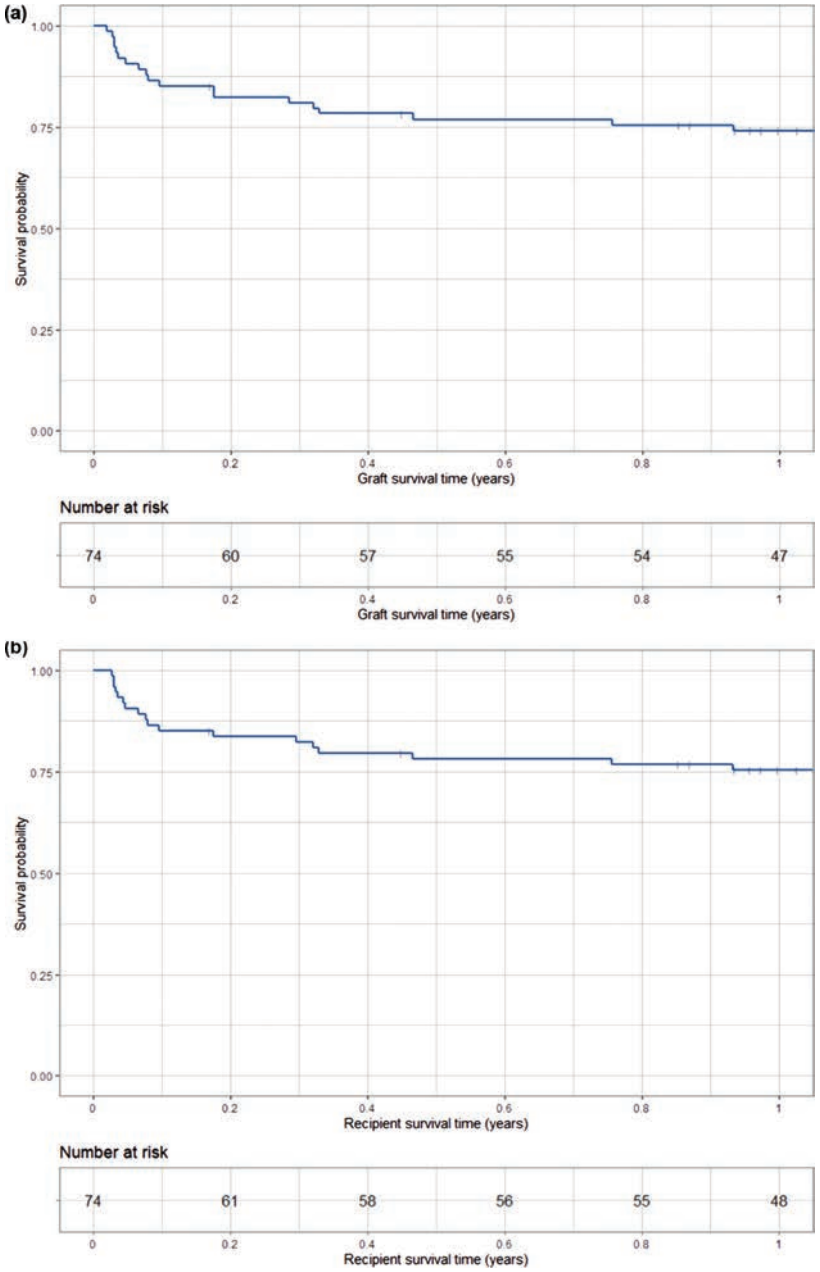
	Recipient		Graft	
	Unadjusted	**Risk-adjusted**	**Unadjusted**	**Risk-adjusted**
One month survival				
Number of transplants	*74*		*74*	
Survival estimate (%) (95% CI)	86 (76–92)	86 (76–92)	86 (76–92)	89 (78–95)
One year survival				
Number of transplants	*74*		*74*	
Survival estimate (%) (95% CI)	75 (64–84)	73 (62–82)	74 (62–83)	73 (61–82)
Three year survival:				
Number of transplants	*62*		*62*	
Survival estimate (%) (95% CI)	73 (60–82)	77 (63–86)	71 (58–81)	76 (62–86)

All survival estimates are for first transplants and all causes of end-stage liver disease. One-month and one-year patient and graft survival estimates are based on transplants carried out in the 2.5 years prior to the last 12 months of follow-up, i.e. patients transplanted between 1 Jul 2017 and 31 Dec 2019. Three-year patient and graft survival estimates are based on transplants carried out in the 2.5 years prior to the last 3 years of follow-up, i.e. patients transplanted between 1 Jul 2015 and 31 Dec 2017. Risk-adjusted estimates are based on the observed vs estimated deaths (or graft failures) using a model based on transplant number, chronic vs acute liver failure, recipient age and gender.



Supplementary Figure A2: Incidence of biopsy-proven acute graft rejection in the first 90 days after paediatric liver transplant

These data include paediatric liver transplants in the 2.5 years before the last 12 months of follow-up, i.e. those transplanted between 1 July 2017 and 31 December 2019.



Supplementary Figure A3: One year paediatric liver transplant recipient (a) and graft (b) survival

Supplementary Table A4: Characteristics of paediatric liver transplant candidates on the waitlist (as of 31st December for each year)

	2017	2018	2019	2020
Number of patients	*24*	*40*	*22*	*28*
Age (%)				
<1 year	17	30	32	18
1–5 years	63	45	41	57
6–10 years	12	20	9	7
11–17 years	8	5	18	18
Gender (%)				
Male	42	48	50	43
Female	58	52	50	57
Ethnicity (%)				
Black	96	85	95	86
White	0	3	0	4
Indian	4	10	5	7
Mixed	0	2	0	3
Diagnosis of liver failure (%)				
Acute liver failure	4	5	5	7
Cholestatic disease	71	85	64	61
Budd-Chiari - Veno-occlusive disease	4	0	0	0
Metabolic disease	0	0	13	8
Malignancy	4	0	0	0
Other	17	10	18	24
Medical urgency (%)				
MELD/PELD ≥ 35	0	0	13	11
MELD/PELD 30–34	0	2	5	3
MELD/PELD 15–29	37	40	41	25
MELD/PELD < 15	63	58	41	61
Wait time (%)				
< 1 year	71	83	32	61
1–< 2 years	13	12	50	7
2–< 3 years	12	5	14	18
3–< 4 years	4	0	4	11
4–<5 years	0	0	0	3

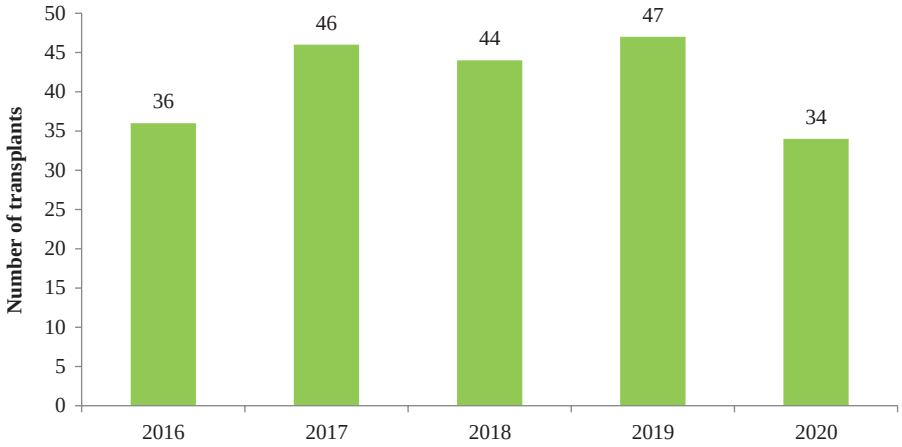
Supplementary Table A5: Outcomes of potential paediatric transplant recipients one year after listing

	2017	2018	2019
Patients listed during year	*44*	*72*	*35*
Status at 1 year after listing (%)			
Transplanted	41	49	71
Patient died	27	18	20
Removed from list (for reasons other than death or transplant)	14	8	14
Still waiting for transplant	18	25	6

SECTION B: ADULT LIVER TRANSPLANTATION ANNUAL REPORT 2020

Table B1: Clinical and demographic characteristics for adult liver transplant recipients

	2016	2017	2018	2019	2020
Number of transplants	*36*	*46*	*44*	*47*	*34*
Age (%)					
18–34 years	22	22	16	28	21
35–49 years	28	19	21	19	35
50–64 years	36	48	52	42	32
65 years or older	14	11	11	11	12
Sex (%)					
Female	36	37	43	55	41
Self-reported race (%)					
Black	25	29	14	23	18
White	69	61	73	55	67
Indian	6	4	9	20	6
Mixed	0	4	4	2	9
Unknown	0	2	0	0	0
Primary Disease (%)					
Acute liver failure	8	9	16	13	9
ASH/NASH	28	26	25	21	15
Cholestatic	25	31	25	36	50
Hepatitis B	3	4	5	0	3
Hepatitis C	3	4	0	5	3
Metabolic	5	13	4	4	0
Malignancy	25	2	9	6	11
Other	3	11	16	15	9
Transplant history (%)					
First	94	93	98	93	97
Re-transplant	6	7	2	9	3
Blood type (%)					
A	56	39	32	26	23
B	8	15	25	15	21
AB	6	4	7	4	9
O	30	41	36	55	47
Health Care Sector (%)					
Funded	84	89	89	94	91
State	14	11	11	6	9
Wait time (%)					
< 31 days	33	35	45	45	35
31–60 days	11	13	21	21	12
61–90 days	11	15	11	6	3
3–<6 months	25	22	9	13	29
6–<12 months	14	9	7	4	18
1–<2 years	6	6	7	11	3



Supplementary Figure B1: Number of adult liver transplants per year

Table B2: Procedure and donor type and donor risk index for adult liver transplants

	2016	2017	2018	2019	2020
Number of transplants	*36*	*46*	*44*	*47*	*34*
Procedure Type (%)					
Liver alone	94	98	100	98	97
Liver and another organ	6	2	-	2	3
Median days in hospital after transplant (Liver alone transplants)	15	13	13	15	13
Donor type (n)					
Living donor transplants	1	0	0	1	7
Deceased donor transplants	35	46	44	46	27
Whole liver	*33*	*40*	*43*	*44*	*26*
Split liver	*2*	*6*	*1*	*2*	*1*
Donor Risk Index (cadaver donors) (%)					
<=1.00	0	4	0	0	0
1.01–1.40	26	11	23	28	26
1.41–1.60	17	24	20	11	18
1.61–1.80	14	17	14	22	15
1.81–2.00	17	11	14	11	11
>2.00	23	33	27	22	11
Unknown	3	-	2	6	19
Donor-recipient blood group compatibility (%)					
ABO incompatibility-major[1]	8	2	16	23	9

[1] A or B or AB to O; AB to A or B; A to B; B to A

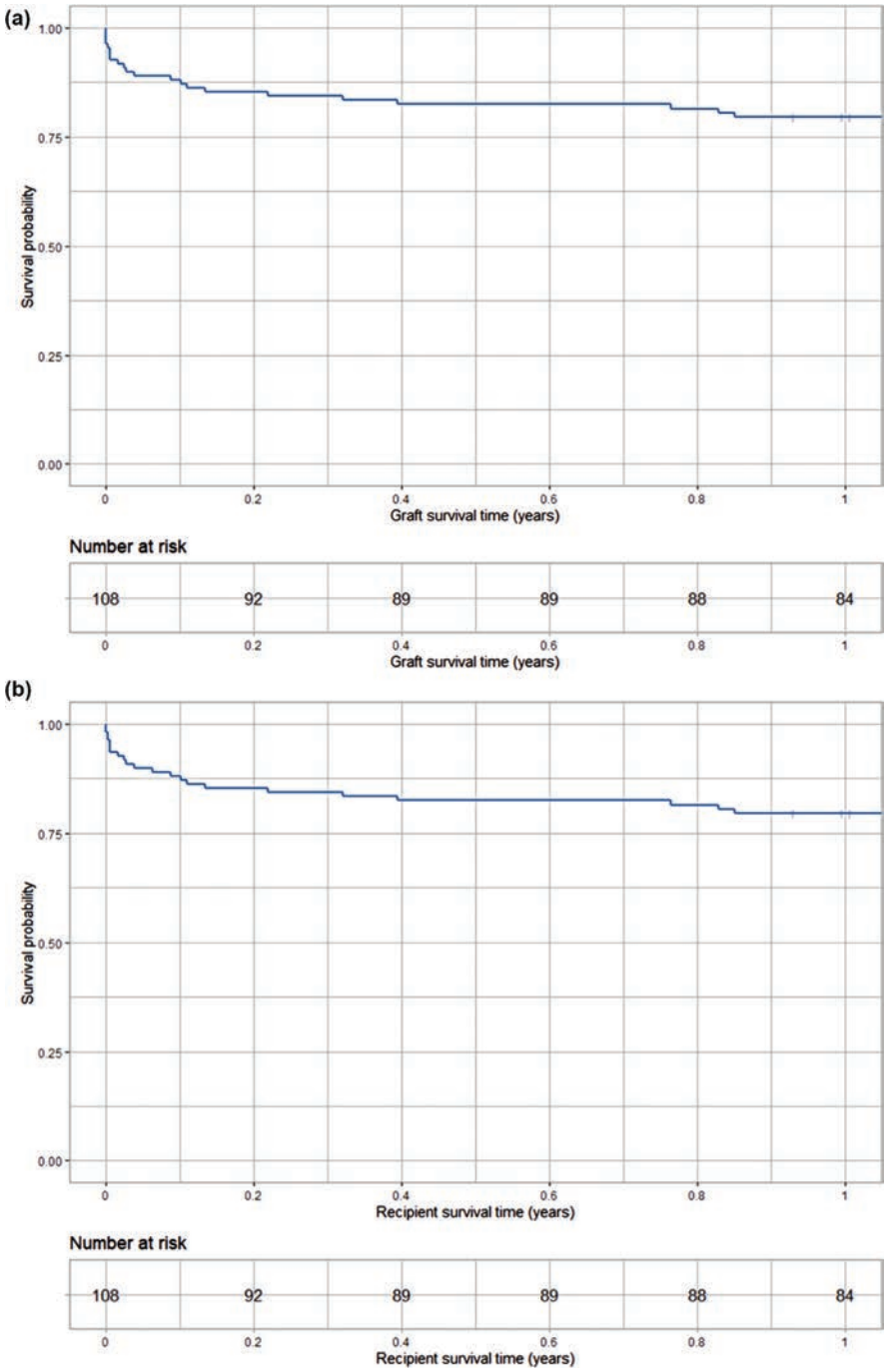
Supplementary Table B1: Donor-recipient serology matching for 2020 reported as percent (%)

Donor/Recipient	CMV	Hep B core	Hep B surf. ant.	Hep C	HIV
D–/R-	-	53	50	97	97
D–/R+	26	15	12	-	3
D–/R unknown	3	3	3	-	-
D+/R–	12	6	20	3	-
D+/R+	56	3	9	-	-
D+/R unknown	-	-	-	-	-
D unknown/R-	-	20	3	-	-
D unknown/R+	3	-	3	-	-
D unknown/R unknown	-	-	-	-	-

Table B3: Adult recipient and graft survival

	Recipient		Graft	
	Unadjusted	Risk-adjusted	Unadjusted	Risk-adjusted
One month survival				
Number of transplants	*108*		*108*	
Survival estimate (%) (95% CI)	89 (81–94)	91 (83–96)	89 (81–94)	92 (84–97)
One year survival				
Number of transplants	*108*		*108*	
Survival estimate (%) (95% CI)	80 (71–86)	83 (73–89)	80 (71–86)	84 (74–90)
Three year survival				
Number of transplants	*100*		*100*	
Survival estimate (%) (95% CI)	77 (67–84)	80 (70–87)	76 (66–83)	80 (69–87)

All survival estimates are for first transplants and all causes of end-stage liver disease. One-month and one-year patient and graft survival estimates are based on transplants carried out in the 2.5 years prior to the last 12 months of follow-up, i.e. patients transplanted between 1 Jul 2017 and 31 Dec 2019. Three-year patient and graft survival estimates are based on transplants carried out in the 2.5 years prior to the last 3 years of follow-up, i.e. patients transplanted between 1 Jul 2015 and 31 Dec 2017. Risk-adjusted estimates are based on the observed vs estimated deaths (or graft failures) using a model based on transplant number, chronic vs acute liver failure, recipient age and gender.



Supplementary Figure B2: One year adult liver transplant recipient (a) and graft (b) survival

Supplementary Table B2: Characteristics of adult liver transplant candidates on the waitlist (as of 31st December for each year)

	2017	2018	2019	2020
Number of patients	*26*	*27*	*32*	*28*
Age (%)				
18–34 years	31	15	28	11
35–49 years	27	33	28	25
50–64 years	34	41	38	43
65 years or older	8	11	6	21
Gender (%)				
Male	38	48	59	43
Female	62	52	41	57
Ethnicity (%)				
Black	35	33	28	36
White	46	45	47	50
Indian	12	22	13	14
Mixed	4	-	9	-
Unknown	3	-	3	-
Diagnosis of liver failure (%)				
Acute liver failure	4	4	-	7
ASH/NASH	15	33	22	39
Cholestatic	58	41	50	39
Hepatitis B	-	-	3	-
Hepatitis C	4	4	-	-
Metabolic	4	3	3	4
Malignancy	8	4	6	4
Other	7	11	13	7
Unknown chronic	-	-	3	-
Medical urgency (%)				
Status 1	nd	nd	19	0
MELD ≥ 35	-	-	-	-
MELD 30–34	-	-	-	-
MELD 15–29	-	-	-	-
MELD < 15	100	100	81	100
Wait time (%)				
<1 year	85	67	72	57
1–<2 years	15	26	19	21
2–<3 years	-	7	6	18
3–<4 years	-	-	3	4
4–<5 years	-	-	-	-
≥5 years	-	-	-	-

Supplementry Table B3: Outcomes of potential adult transplant recipients one year after listing

	2017	2018	2019
Patients listed during year	*70*	*61*	*66*
Status at 1 year after listing (%)			
Transplanted	66	62	73
Patient died	10	13	11
Removed from list (for reasons other than death or transplant)	11	10	11
Still waiting for transplant	13	15	9

status. In high-income settings, one year paediatric liver transplant recipient survival rates are 97% in Australia and New Zealand (10) and 95% in the USA.(11) Low and middle income countries report lower one year paediatric survival rates similar to our program, such as Malaysia (79%).(12) Similar trends have been reported in adult liver transplant recipients in the USA where one year survival is 94% (11) compared with 71% reported from a collective of transplant centres in Latin America.(13)

CONCLUSION

The Wits Transplant Unit transplanted 39 children with liver failure in 2020, most of whom were under the age of five years. Overall, one month, one year, and five year recipient survival was 86%, 75%, and 73%, respectively, and 20% of waitlisted children died while awaiting a graft. For adults, 34 received a liver transplant in 2020, and overall one month, one year, and five year recipient survival was 89%, 80%, and 77%, respectively, with fewer adults (11%) demising while on the waitlist. Despite continued reliance on deceased organs and ongoing deaths on the waitlist, efforts to increase living liver donation, utilise split donor grafts, and perform more ABO-incompatible transplants will help to address organ shortages for those with end-stage liver disease.

ACKNOWLEDGEMENT

Wits Donald Gordon Medical Centre funded the data collection and analysis.

CONFLICTS OF INTEREST

The authors have none to declare.

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