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ABO-incompatible liver transplantation – exploring utilitarian solutions to restricted access and organ shortages: A single-centre experience from Johannesburg, South Africa

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Background. Liver transplantation is the definitive management for severe acute liver failure refractory to supportive management, and end-stage chronic liver failure. Owing to a shortage of deceased liver donors, South Africa requires innovative techniques to broaden the donor pool.
Objectives. This study evaluated the outcomes of the Wits Transplant Unit ABO-incompatible liver transplant (ABOi-LT) programme.
Methods. This retrospective record review compared all adult and paediatric patients receiving ABO-compatible (ABOc) and ABO-incompatible (ABOi) liver transplants from January 2014 to December 2021 with a minimum one-year follow-up. Primary outcomes were recipient and graft survival and secondary outcomes included vascular, enteric and biliary complications, relook surgery, acute cellular rejection (ACR) and lenghth of hospital stay. Cox proportional hazards regression was performed to examine the effect of ABO-compatibility group on recipient and graft survival. The relationship between the ABO-compatibility group and categorical outcomes was assessed by binomial regression.
Results. During the study period, 532 liver transplants were performed; 44/532 (8%) were ABOi of which 14/44 (32%) were paediatric and 30/44 (68%) adult recipients. Within the pediatric group, the proportion of transplants performed for acute liver failure was significantly higher in the ABOi group (7/14; 50%) compared with the ABOc group (33/207; 16%) (p=0.005). Comparable recipient and graft survival estimates were noted: one-, three- and five-year recipient survival in the ABOi group was 77% (95% confidence interval (CI) 44 - 92), 58% (95% CI 17 - 84) and 58% (95% CI 17 - 84) respectively. There were significantly increased relative risks of relook surgery for the ABOi group compared with the ABOc group, both overall (relative risk (RR) 1.74; 95% CI 1.10 - 2.75) and at 90 days (RR 2.28; 95% CI 1.27 - 4.11); and also, for pre-discharge bloodstream infection (BSI), (RR 1.84; 95% CI 1.11 - 3.06). In adults, there were significantly more acute indications for liver transplantation in the ABOi (10/30; 33%) compared with the ABOc group (26/281; 9%) (p=0.0007) with the most common cause being drug or toxin ingestion (16/36; 44%). For the ABOi group, recipient survival estimates (95% CI) at 1, 3 and 5 years were 71% (50 - 84), 63% (41 - 78) and 58% (37 - 75) which, as noted with complication rates, were similar between ABO groups.
Conclusion. This study confirms ABOi-LT as a feasible option to increase the liver donor pool in this organ-depleted setting as recipient survival and complication rates were similar between ABO-compatibility groups.

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Liver transplantation remains the definitive management for children and adults with both severe acute liver failure refractory to supportive management, and end-stage chronic liver failure. Globally, liver transplant waiting lists exceed the growth of the donor pool, creating significant shortages of viable donor grafts.[1]

The United States of America, United Kingdom, Canada, Australia and the Nordic countries source most of their grafts from deceased donors and rarely use living donors.[2] These countries may rely on ABO-incompatible liver grafts in acute liver failure, or those waitlisted with chronic liver failure who become acutely decompensated, or when a living donor graft is not available.[3,4] Owing to cultural beliefs which limit deceased donation, some Asian countries such as Japan and South Korea rely primarily on living donors to source viable grafts. In this setting, living donor ABO blood group incompatible

liver transplantation (ABOi-LT) has been successfully pioneered, achieving recipient and graft outcomes comparable to living donor ABO-compatible liver transplantation (ABOc-LT).[5] Equivalent outcomes are likely due to advances in immunosuppression that reduce the risk of antibody-mediated rejection (AMR) with consequent graft loss such as rituximab, tacrolimus, mycophenolate mofetil, and antibody reduction strategies that include plasmapheresis and immuno-adsorption.[5] Use of rituximab precludes the need for splenectomy, which would previously have placed patients at higher risk of sepsis.[6] Traditionally, plasmapheresis has been used to deplete antibodies prior to, and following, ABOi-LT. In recent years, the advent of selective ABO immuno-adsorption columns avoids depletion of non-ABO antibodies, further lowering the risk of infection compared with plasmapheresis.[7] Despite these advances in immunosuppression which aim to minimise AMR, ABOi-LT still incurs higher risks for hepatic artery thrombosis (HAT) and sepsis – more from fungal than bacterial pathogens. Given these risks, ABOi-LT requires tailoring of appropriate immunosuppression, early detection and treatment of AMR, vigilant monitoring of hepatic artery blood flow, strict infection control measures, early detection of hospital-acquired infection, and antimicrobial stewardship to ensure appropriate antimicrobial use. Since fungal sepsis is hard to diagnose, transplant clinicians need to consider endoscopic tissue biopsy as far as possible for accurate and early diagnosis. Furthermore, within the context of already described risks associated with ABOi-LT, surgical risk also pertains to graft variants. Compared with whole, deceased donor grafts, living donor grafts have an increased risk of biliary complications owing to smaller bile duct size and the cut surface of the liver parenchyma.[8]

In South America and Africa, access to liver transplantation is limited. Barriers to transplantation in these countries include poor health systems infrastructure and limited human resources, organ transplant legislation that limits access to deceased donor organs, fiscal demands on stretched healthcare budgets that preferentially fund healthcare other than transplantation, and insufficient public and healthcare worker education regarding organ donation.[9] Within Africa, few countries offer liver transplantation and, within these, a large donor-to-waiting-list-candidate disparity remains.[10]

South Africa has a severe shortage of deceased donor organs which has worsened since the COVID-19 pandemic. The country also has diverse population groups with different cultural backgrounds and beliefs, and a high burden of infectious and non-communicable diseases. The country has two liver transplant centres, one in Johannesburg and the other in Cape Town.[11] The high demand for solid-organ transplantation combined with the low availability of deceased donors has necessitated the development of an ABOi-LT programme in the Wits Transplant Unit in Johannesburg following international best practice for desensitisation. The present study evaluates the outcomes of this programme.

Methods

Study design

This retrospective record review compared the outcomes of adults and children undergoing deceased and living donor ABOi-LT with the corresponding group who received ABOc-LT. All transplants performed between 1 January 2014 and 31 December 2021 at the Wits Transplant Unit were included in the analysis, allowing for a minimum one-year follow-up. Data were accessed from two longitudinal Research Electronic Data Capture (REDCap) databases.[12,13] Approval was granted from the University of the Witwatersrand Human Research Ethics Committee (Medical) (M190723 and M190749).

ABOi-LT desentitisation protocol used at Wits Transplant Unit

The Wits Transplant Unit developed an ABOi-LT protocol based on a comprehensive review of existing literature to determine international best practice, inputs from local subject matter experts, and pragmatic modifications based on available technology and logistical capabilities. Regarding the procedures followed in the unit, once a potential recipient is identified as eligible for liver transplantation, they are placed on the deceased donor waiting list as per the standard listing procedure. While on the deceased donor list, every effort is made to identify possible living liver donors. Should there be no available ABOc living donor, ABOi living donors are considered on a case-to-case basis by a multidisciplinary team. If no living donors are available (compatible or incompatible), the candidate remains on the waiting list until a deceased donor liver graft becomes available. In emergency cases (status 1), an ABOi deceased donor or living donor graft might be considered for a recipient. Thus, each ABOi-LT performed by the Wits Transplant Unit requires extensive input and review from a multidisciplinary team relating to the urgency of the case, the age of the recipient, availability of compatible grafts, and balancing risk v. benefit. In emergency cases – for example, children presenting with fulminant acute liver failure – anti-ABO antibodies are only measured postoperatively (as there is no time for intervention preoperatively) and plasmapheresis or immuno-adsorption columns are used as needed to keep the antibody titre below 1:64. In a non-emergency case, antibodies are measured 21 days prior to the planned date of transplant. If the antibody titre is below 1:64, then no pre-operative management is needed. If the titre is more than 1:64, then a single dose of rituximab 375 mg/m^2 intravenous infusion (IVI) is administered. At 14 days before transplant, antibody titres are measured again and, if the titre remains above 1:64, plasmapheresis or immuno-adsorption is initiated on alternate days until antibody levels drop below 1:64, at which point transplantation is performed. In both emergency and planned transplants, on day one post-transplant, a single dose of rituximab 375 mg/m^2 IVI is administered and the oral backbone of the immunosuppressive regimen is started which includes tacrolimus, mycophenolate mofetil and corticosteroids, with weaning of the latter within three months. An additional dose of rituximab may be considered on day 7 post-transplant, depending on antibody titres.

For more details, please see Appendix A: Wits Transplant Unit ABOi-LT protocol (https://www.samedical.org/file/2126). It is relevant to note that, for this study period, only rituximab and plasmapheresis were used as immuno-adsorption columns were not available.

Sample size calculation

Given that the ABOi groups comprised 6% (paediatrics) and 9% (adults) of the total sample, accrual and final follow-up periods of 8 and 1 year respectively, at 80% power and the 5% significance level, with the sample size available, significant hazard ratios (HRs) of 2.7 for paediatrics and 2.0 for adults could be detected, which was adequate for the purposes of this study.

Data collection

Data were reviewed for ABOi and ABOc (comprising ABO-identical and ABO-compatible) liver transplant recipients in adults and paediatrics to compare primary and secondary outcomes. Paediatric recipients were defined as younger than 18 years of age at the time of transplant. Primary outcomes were recipient and graft survival at one, three and five years. Graft failure was defined as recipient demise or re-transplantation. Secondary outcomes were:

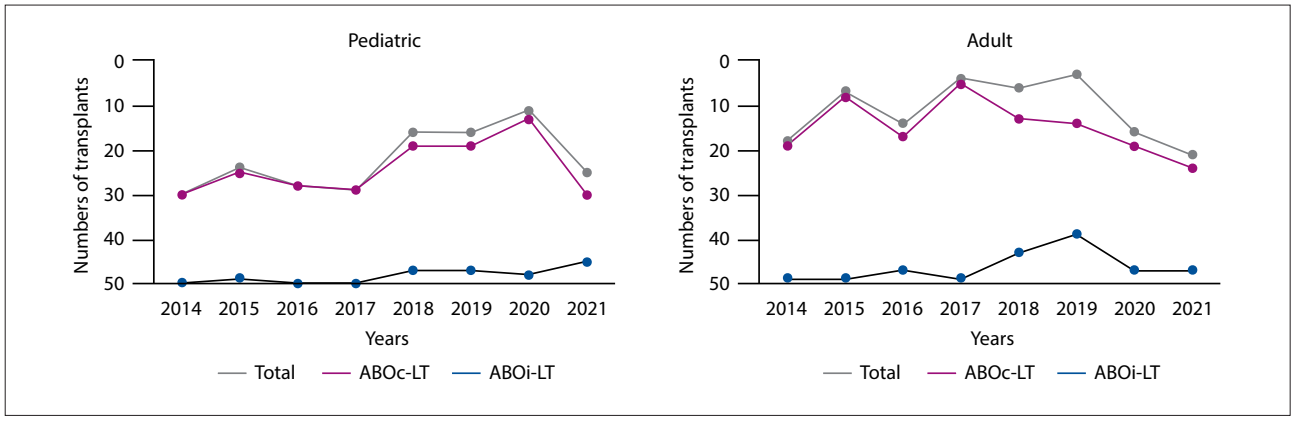


Fig. 1. Number of ABO-compatible and ABO-incompatible liver transplants in the Wits Transplant Unit from 2014 to 2021 in paediatrics and adults.

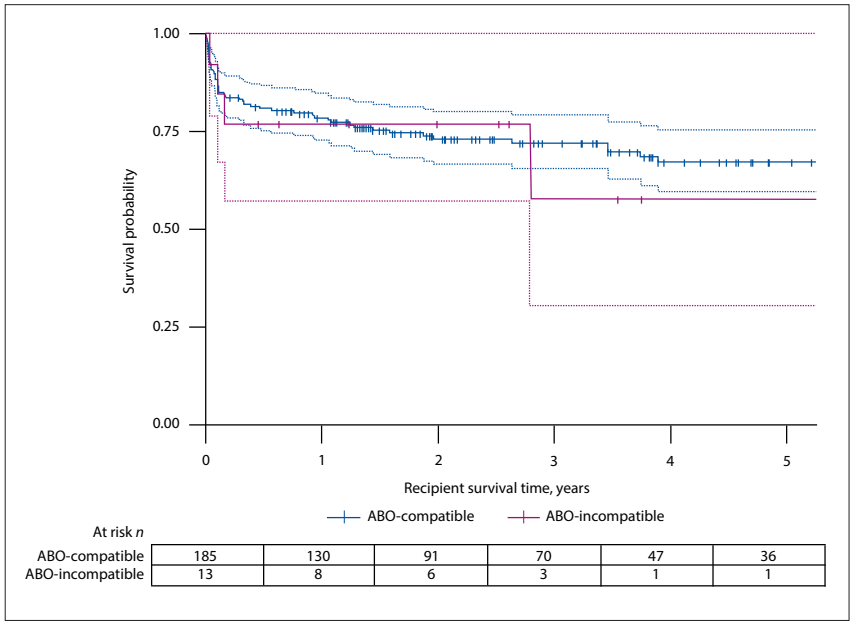


Fig. 2. Paediatric recipient survival estimates.

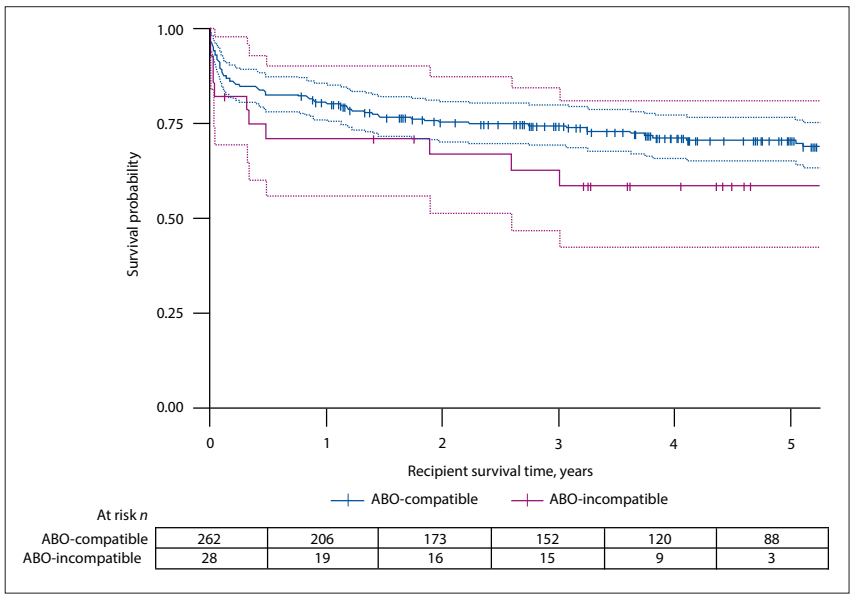


Fig. 3. Adult recipient survival estimates.

(*i*) relook surgery prior to discharge, and (*ii*) vascular, (*iii*) enteric and (*iv*) biliary complications that required intervention (radiological or surgical) assessed at 90 days and overall, (*v*) length of hospital stay (LOS) and (*vi*) acute cellular rejection (ACR). Vascular complications were anatomically differentiated as portal vein, inferior vena cava, hepatic artery and hepatic vein and further classified as thrombosis, stenosis, rupture and pseudo-aneurysm. Enteric complications were classified as duodenal, jejunal, ileal or colonic, and then defined as perforation, obstruction, and herniation or fistula either at or away from the anastomotic site. Biliary complications were noted as strictures or leaks. A secondary outcome specific to paediatric recipients was the incidence of post-transplant bloodstream infection (BSI) occurring before discharge, or after discharge requiring readmission within the first year of transplant, recorded from January 2018 onwards.

Clinical data comprised: year of transplant; recipient age at time of transplant; recipient sex; aetiology of liver failure; donor type: deceased (causes of death include anoxia, cerebrovascular accident, trauma or other) or living; ABO compatibility between donor and recipient defined as identical, compatible and incompatible; graft type: whole, split, reduced or living donor grafts; graft-recipient-weight-ratio (GRWR); transplant number; simultaneous liver-kidney transplant; and recipient paediatric end-stage liver disease (PELD)/model for end-stage liver disease (MELD) score at time of transplant. The donor risk index (DRI) was calculated for the adult group.[14]

Data analysis

Comparison of categorical study variables between ABO-compatibility groups was performed with the χ^2 test (Fisher's exact

Table 1. Paediatric liver transplant recipients: demographics and clinical characteristics

Recipient characteristics	Category	ABOc-LT (*n*=207) *n* (%)	ABOi-LT (*n*=14) *n* (%)
Age (years): Median (IQR)		2.8 (1.4 - 8.2)	5.8 (4.3 - 12.5)
Sex	Male	89 (43)	5 (36)
	Female	118 (57)	9 (64)
Aetiology	Acute	33 (16)	7 (50)
	Chronic	174 (84)	7 (50)
Acute aetiology	Viral infection	(8)	3 (43)
	Hepatitis A	9 (56)	2 (67)
	Enterovirus	2 (13)	0 (0)
	Parvovirus	1 (6)	0 (0)
	Adenovirus	2 (13)	0 (0)
	EBV	1 (6)	0 (0)
	Other	1 (6)	1 (33)
	Failed transplant*	8 (24)	1 (14)
	Wilson's disease	2 (6)	1 (14)
	Drug/toxin	2 (6)	0 (0)
	Other	3 (9)	1 (14)
	Unknown	2 (6)	1 (14)
Chronic aetiology	Cholestatic	114 (66)	4 (57)
	Metabolic	20 (11)	2 (29)
	BC-VOD	10 (6)	0 (0)
	Malignancy	5 (3)	1 (14)
	Other	25 (14)	0 (0)
Priority 1 listing		34 (16)	7 (50)
PELD/MELD: Mean (SD)†		17 (13)	26 (11)
Donor type	Deceased	88 (43)	6 (43)
	Living	119 (57)	8 (57)
ABO compatibility	Identical	174 (79)	0 (0)
	Compatible	33 (15)	0 (0)
	Incompatible	0 (0)	14 (6)
Graft type	Whole	45 (22)	4 (29)
	Split/reduced	43 (21)	2 (14)
	Living	119 (57)	8 (57)
Extended criteria organ		3 (1)	14 (100)
GRWR ratio: median‡ (IQR)		2.7 (1.8 - 3.9)	2.1 (1.5 - 2.6)
Transplant number	1	193 (93)	13 (93)
	2	14 (7)	1 (7)
Simultaneous kidney transplant		8 (4)	0 (0)

ABOc-LT = ABO-compatible liver transplant; ABOi-TL = ABO-incompatible liver transplant; IQR = interquartile range; EBV = Epstein-Barr virus; BC-VOD = Budd Chiari – veno-occlusive disease; PELD = paediatric end-stage liver disease; MELD = model for end-stage liver disease.
*Of the 9 cases of graft failure, 2 were for primary graft non-function, 6 for hepatic artery thrombosis and 1 for hepatic artery thrombosis and portal vein thrombosis.
†PELD/MELD score available for 216/221 (98%) of paediatric liver transplant recipients.
‡Graft-recipient weight ratio available for 215/221 (97%) of paediatric liver transplant recipients.

test was used for 2x2 tables or where the requirements for the χ^2 test were not met). Continuous variables were compared by the independent samples *t*-test, or by the Wilcoxon rank sum test if the assumptions of the *t*-test were not met. The relationship between the ABO-compatibility group and categorical outcomes (surgical re-exploration, biliary complications, enteric complications, vascular complications, infections pre-discharge, occurrence of acute cellular rejection (ACR)) was assessed by binomial regression. Hospital length of stay was compared between the ABO-compatibility groups using a general linear model (GLM). Cox proportional hazards regression was performed to examine the effect of ABO-compatibility group on recipient and graft survival. All comparisons were made unadjusted, and adjusted for age, cause of end-stage liver disease (ESLD) (acute/chronic), PELD/MELD score and GRWR (for the paediatric cohort); and adjusted for aetiology (adult cohort). Adjustment was achieved by including the additional variables in the regression model as covariates. Data analysis was carried out using SAS version 9.4 for Windows. A 5% significance level was used.

Results

From 1 January 2014 to 31 December 2021, 532 liver transplants were performed at the Wits Transplant Unit comprising 221/532 (42%) paediatric and 311/532 (58%) adult recipients. Of these transplants, 44/532 (8%) were ABOi, of which 14/44 (32%) were paediatric and 30/44 (68%) adult recipients. The number of transplants performed per year during the study period is depicted in Fig. 1.

Paediatric liver transplant recipients

The demographic and clinical characteristics of the paediatric liver transplant recipients are detailed in Table 1. Children were

Table 2. Paediatric outcomes

Outcomes*		Category	ABOc-LT (*n*=207)	ABOi-LT (*n*=14)	Unadjusted estimate	Adjusted estimate†
Primary			**% (95% CI)**	**% (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Recipient	Overall survival‡				1.24 (0.45 - 3.44)	0.60 (0.17 - 2.10)
	Survival estimates	1 year	78 (72 - 84)	77 (44 - 92)	*p*=0.99	
		3 years	72 (65 - 78)	58 (17 - 84)	*p*=0.91	
		5 years	67 (59 - 74)	58 (17 - 84)	*p*=0.95	
Graft	Overall survival				1.16 (0.42 - 3.20)	0.93 (0.32 - 2.74)
	Survival estimates	1 year	77 (70 - 82)	77 (44 - 92)	*p*>0.99	
		3 years	70 (63 - 77)	66 (32 - 86)	*p*=0.98	
		5 years	66 (57 - 73)	66 (32 - 86)	*p*>0.99	
Secondary			***n* (%)**	***n* (%)**	**RR (95% CI)**	**RR (95% CI)**
Relook§		90 days	51 (28)	7 (58)	2.22 (1.34 - 3.68)	2.28 (1.27 - 4.11)
		All	83 (40)	9 (64)	1.74 (1.16 - 2.60)	1.74 (1.10 - 2.75)
Complications	biliary	90 days	56 (27)	5 (36)	1.51 (0.73 - 3.12)	1.45 (0.71 - 2.94)
		All	73 (35)	5 (36)	1.13 (0.55 - 2.30)	1.13 (0.56 - 2.27)
	Enteric	90 days	16 (8)	2 (14)	2.32 (0.58 - 9.21)	2.61 (0.61 - 11.2)
		All	19 (9)	3 (21)	2.83 (0.94 - 8.48)	3.04 (0.96 - 9.57)
	Vascular	90 days	24 (12)	3 (21)	1.96 (0.68 - 5.67)	2.16 (0.68 - 6.86)
		All	32 (16)	4 (29)	1.93 (0.81 - 4.65)	2.08 (0.81 - 8.57)
ACR¶		90 days	27 (21)	1 (13)	0.57 (0.09 - 3.70)	1.25 (0.18 - 8.57)
		All	41 (31)	1 (13)	0.38 (0.06 - 2.41)	0.52 (0.08 - 3.47)
Clinical					**RR (95% CI)**	**RR (95% CI)**
BSI‖			44 (37)	8 (62)	1.79 (1.13 - 2.86)	1.84 (1.11. - 3.06)
					***p*-value**	***p*-value**
Days in hospital: Median (IQR)**			22 (15 - 41)	24 (20 - 44)	0.19	0.18

HR = hazard ratio; RR = relative risk; CI = confidence interval; ACR = acute cellular rejection; BSI = blood stream infection; IQR = interquartile range.
*Median follow-up 1.9 years.
†Adjusted for age, cause of end-stage liver disease (acute/chronic), PELD/MELD score and graft-recipient weight ratio.
‡Calculated for first transplant and liver-alone transplants (198/221; 90%): unadjusted.
§Relook rate available for 191/221 (86%) of paediatric liver transplant recipients.
¶Acute cellular rejection available outcomes available for 139/221 (63%).
‖Data were captured from January 2018 onwards; thus available for 132/221 (60%) of paediatric liver transplant recipients.
**Calculated from day of transplantation for liver-alone transplants and excludes deaths before discharge (172/221; 78%).

significantly older at the time of transplant in the ABOi group (median 5.8 years) compared with the ABOc (median 2.8 years) (*p*=0.016). The proportion of transplants performed for acute liver failure was significantly higher (7/14; 50%) in the ABOi group compared with the ABOc group (33/207; 16%) (*p*=0.005). This proportion is reflected by the significantly higher mean PELD/MELD score of 26 (SD 11) for the ABOi group compared with 17 (SD 13) for the ABOc group (*p*=0.017). Hepatitis A (11/19; 58%) was the most common overall cause of acute liver failure.

Comparable recipient and graft survival estimates were found between the two groups of recipients (Table 2). Recipient survival at one, three and five years in the ABOi group was 77% (95% confidence interval (CI) 44 - 92), 58% (95% CI 17 - 84) and 58% (95% CI 17 - 84), and 78% (95% CI 72 - 84), 72% (95% CI 65 - 78) and 67% (95% CI 59 - 74) in the ABOc group which showed no significant difference (Fig. 2). Considering the secondary outcomes, there were significantly increased relative risks of relook surgery for the ABOi group compared with the ABOc group, both overall (RR 1.74; 95% CI 1.10 - 2.75) and at 90 days (RR 2.28; 95% CI 1.27 - 4.11); and also, for pre-discharge BSI (RR 1.84; 95% CI 1.11 - 3.06). However, the relative risks of complications were comparable between ABO groups.

Adult liver transplant recipients

Adult donor and recipient demographic and clinical characteristics are compared in Table 3. As with the paediatric recipients, there was a significantly higher proportion of recipients with acute causes of liver failure in the ABOi group (10/30; 33%) compared with the ABOc group (26/281; 9%) (*p*=0.0007). The most common cause of acute liver failure in adult recipients was drug or toxin ingestion (16/36; 44%). Of those with drug or toxin-induced acute liver failure, all were female and 10/16 (63%) were related to antiretroviral therapy for the treatment of HIV. Cholestatic causes of chronic end-stage liver disease were higher in the ABOc group (99/255; 39%) compared with the ABOi group (3/20; 15%). Conversely, malignancy was a more common indication for transplant in the ABOi group (7/20; 35%) compared with the ABOc group (21/255; 8%). There were no significant differences in recipient survival estimates (95% CI) at one, three and five years for the ABOi group 71% (50 - 84), 63% (41 - 78) and 58% (37 - 75), and 81% (71 - 81), 74% (68 - 79) and 71% (64 - 76) for the ABOc group (Table 4 and Fig. 3). A significantly longer median length of stay in hospital was noted in the ABOi group of 20 (interquartile range (IQR) 10 - 38) days, compared with 14 (IQR 11 - 22) days in the ABOc group (*p*=0.024). However, complication rates between the ABO groups were not significantly different (Table 4).

Discussion

Given the pervasive organ shortages in South Africa, this study confirms the utility of ABOi-LT for paediatric and adult recipients. While ABOc-LT remains the transplant procedure of choice in the Wits Transplant Unit, the capacity to perform ABOi-LT allows a viable therapeutic alternative in cases that would otherwise not be offered liver transplantation – as seen in the paediatric group where more than half of the ABOi-LT grafts were obtained from living donors. Overall, despite comparable survival outcomes when comparing

Table 3. Adult liver transplant recipients: demographics and clinical characteristics

Recipient characteristics	Category	ABOc-LT (*n*=281) *n* (%)	ABOi-LT (*n*=30) *n* (%)
Age (years): Median (IQR)		51 (40 - 61)	53 (41 - 61)
Sex	Male	170 (60)	16 (53)
	Female	111 (40)	14 (47)
Aetiology	Acute	26 (9)	10 (33)
	Chronic	255 (91)	20 (67)
Acute aetiology	Drug/toxin	11 (42)	5 (50)
	Infection	4 (15)	3 (30)
	Failed transplant	5 (19)	1 (10)
	AIH	3 (12)	0 (0)
	Vascular	2 (8)	0 (0)
	Pregnancy	1 (4)	1 (4)
	Wilson's disease	1 (4)	0 (0)
Chronic aetiology	Cholestatic	99 (39)	3 (15)
	ASH/NASH	76 (30)	6 (30)
	Malignancy	21 (8)	7 (35)
	Metabolic	13 (5)	2 (10)
	Hepatitis B	10 (4)	0 (0)
	Hepatitis C	9 (4)	1 (5)
	Other	27 (11)	1 (5)
Priority 1 listing*		22 (8)	10 (33)
MELD: Mean (SD)		19 (8)	20 (10)
BMI: Mean (SD)		26.2 (5.1)	26.8 (4.8)
Donor type	Deceased	261 (93)	29 (97)
	Living	20 (7)	1 (3)
ABO compatibility	Identical	251 (81)	0 (0)
	Compatible	30 (10)	0 (0)
	Incompatible	0 (0)	30 (10)
Graft type	Whole	241 (86)	29 (97)
	Split/reduced	20 (7)	0 (0)
	Living	20 (7)	1 (3)
Extended criteria organ		8 (3)	29 (97)
GRWR ratio: Median (IQR)†		2.0 (0.7)	2.1 (0.5)
Transplant number	1	268 (95)	29 (97)
	2	13 (5)	1 (3)
Simultaneous kidney transplant		7 (2)	1 (3)
DRI	≤1.00	5 (2)	0 (0)
	1.01 - 1.40	96 (38)	13 (46)
	1.41 - 1.60	53 (21)	5 (18)
	1.61 - 1.80	35 (14)	5 (18)
	1.81 - 2.00	32 (13)	2 (7)
	>2.00	29 (12)	3 (11)

AIH = autoimmune hepatitis; ASH = alcoholic steatohepatitis; NASH = non-alcoholic steatohepatitis; BMI = body mass index (weight (kg)/(height) (m^2)); MELD = model for end-stage liver disease; IQR = interquartile range; DRI = donor risk index (was calculated for the deceased donors 273/290 (94%)).
*Listing status available for 307/311 (99%).
†Graft-recipient weight ratio was calculated for 215/311 (69%) of adult liver transplant recipients.

ABO-compatible with incompatible transplants, we observed higher rates of relook surgery and bloodstream infection with paediatric ABOi-LT recipients, and longer hospital length of stay in adult ABOi-LT recipients. Overall, while this study highlights the utility of ABOi-LT in our setting, desensitisation, and the potential for increased complications and longer hospital stays, makes this procedure more costly compared with ABOc-LT. Higher relook rates in the paediatric group compared with adults are likely due to the increased use of split grafts. Split grafts have smaller vessels and biliary ducts, and the cut surface of liver parenchyma increases risks for bleeding and bile leaks, all of which make the surgery technically more difficult.

Similar to a study in Taiwan, our results show comparable outcomes between ABO groups. However, recipient survival for adult ABOi-LT in our study was lower compared with the one-, three- and five-year survival rates of the Taiwan study which were 82%, 76% and 71%, respectively. In the Japanese transplant registry, adult ABOi-LT was 74% at five years in the rituximab era and, in a Swedish study with emergency deceased donor ABOi-LT, five-year recipient survival was 81%.[8,16,17] Lower survival rates observed in the present study might be from the use of both living and deceased donors, relatively small sample size, the high levels of acute liver failure resulting in critically ill recipients entering the system, or the learning curve associated

Table 4. Adult outcomes

Outcomes		Category	ABOc-LT (*n*=281)	ABOi-LT (*n*=30)	Unadjusted estimate	Adjusted estimate*
Primary†			% (95% CI)	% (95% CI)	HR (95% CI)	HR (95% CI)
Recipient	Overall survival‡				1.53 (0.81 - 2.88)	1.06 (0.54 - 2.06)
	Survival estimates	1 year	81 (71 - 81)	71 (50 - 84)	p=0.21	
		3 years	74 (68 - 79)	63 (41 - 78)	p=0.21	
		5 years	71 (64 - 76)	58 (37 - 75)	p=0.16	
Graft	Overall survival				1.60 (0.87 - 2.94)	1.16 (0.61 - 2.20)
	Survival estimates	1 year	80 (74 - 84)	67 (46 - 81)	p=0.11	
		3 years	73 (67 - 78)	59 (38 - 75)	p=0.12	
		5 years	69 (63 - 74)	55 (34 - 71)	p=0.13	
Secondary			n (%)	n (%)	RR (95% CI)	RR (95% CI)
Relook§		90 days	58 (22)	8 (27)	1.23 (0.65 - 2.33)	0.95 (0.50 - 1.82)
		All	71 (25)	8 (27)	1.05 (0.56 - 1.97)	0.78 (0.41 - 1.46)
Complications	Biliary	90 days	57 (20)	8 (27)	1.31 (0.70 - 2.49)	1.33 (0.69 - 2.56)
		All	73 (26)	10 (33)	1.28 (0.75 - 2.21)	1.32 (0.75 - 2.32)
	Enteric¶	90 days	8 (3)	1 (3)	1.14 (0.15 - 8.82)	0.83 (0.10 - 6.90)
		All	11 (4)	2 (7)	1.67 (0.39 - 7.14)	1.37 (0.30 - 6.32)
	Vascular	90 days	29 (10)	1 (3)	0.32 (0.05 - 2.29)	0.27 (0.04 - 1.97)
		All	36 (13)	1 (3)	0.26 (0.04 - 1.83)	0.22 (0.03 - 1.59)
ACR		90 days	25 (9)	2 (7)	0.75 (0.19 - 3.00)	0.84 (0.20 - 3.56)
		All	70 (25)	6 (20)	0.80 (0.38 - 1.70)	1.02 (0.48 - 2.18)
Clinical					p-value	p-value
Days in hospital‖: Median (IQR)			14 (11 – 22)	20 (10 – 38)	0.021	0.024

*Adjusted for age, cause of end-stage liver disease (acute/chronic), MELD score and aetiology.
†Median follow-up 3.6 years.
‡Calculated for first transplant and liver-alone transplants (198/311; 64%).
§The relook rates were assessed in 298/311 (96%) of adult liver transplant recipients.
¶Enteric complications were assessed in 304/331 (98%) of adult liver transplant recipients.
‖Calculated from day of transplant for liver-alone transplants and excludes death before discharge 262/311 (84%)

with developing a new service offered by the liver transplant programme. The Wits Transplant Unit also ran a programme for patients with isolated colorectal liver metastasis, where extended criteria liver grafts were used for liver transplantation, decreasing liver organ wastage.[18] While the unit routinely uses rituximab as part of the desensitisation protocol, only plasmapheresis was available for removal of circulating ABO-antibodies during the study period. Extensive efforts were made to procure immuno-adsorption columns in the country with limited success, but more recently this therapeutic option has become available. The high rates of acute liver failure from hepatitis A in the paediatric group deserve mention as hepatitis A vaccines are not freely available in the public sector as part of the national extended programme of immunisation schedule.[19]

South Africa relies heavily on deceased donors, with an opt-in donation process. Multifactorial barriers to deceased donor organ procurement include the lack of national transplantation regulations, low community awareness and education, and religious or cultural beliefs.[20] Living donor solid organ transplantation is one alternative with superior outcomes to deceased organ donation and widens the donor pool with donors who would not otherwise have donated. The Wits Transplant Unit offers living liver donation as a service, but this procedure is resource-intensive and may not be feasible in all South African transplant units. The use of ABOi (deceased and living) donors offers another option for local transplant centres informed by the results of this study, with the potential to establish a national protocol to guide centres that might wish to establish such a programme. To this end, a detailed desensitisation protocol has been shared as an appendix to the publication as an initial step. Deceased ABOi liver grafts, even used in non-urgent cases, do not decrease the donor pool, they just redirect liver grafts to the next candidate on the waiting list.

Many lessons were learned while establishing an ABOi-LT service in the Wits Transplant Unit. First, in the absence of a national desensitisation protocol, consensus was needed for devising a unit protocol. Ideally, the protocol needed to be informed by international best practice but also modified by what was available for use in the country, and what was feasible for the unit in terms of cost and available services. As an example, while emerging data supports the use of immuno-adsorption columns in preference to plasmapheresis,[7] there was no access to immuno-adsorption columns locally, despite efforts to source them. Recently, these have become available and will be used going forward. Second, relating to the higher rates of BSI in the paediatric ABOi-LT group, high rates of BSI in the paediatric liver transplant programme were previously identified and these data were published.[15] In response to the results of that study, the unit implemented (*i*) active surveillance of hospital-acquired infections post-transplant, (*ii*) inclusion of a medical microbiologist on daily ward rounds as part of the transplant team, (*iii*) strict oversight of antimicrobial prescribing practice as part of a comprehensive antimicrobial stewardship programme, (*iv*) monitoring of adherence to protocols for insertion and changing of intravenous access catheters, (*v*) active surveillance for cytomegalovirus infection, and (*vi*) six-

weekly multidisciplinary reviews of all laboratory-confirmed infections in paediatric liver transplant recipients for the first year of transplant. Despite these efforts, infection rates remain high, as seen in this study. As biomarkers of fungal sepsis are non-specific, it has been identified that the unit needs to shift to a more aggressive approach to making tissue-based diagnosis using gastrointestinal and bronchial endoscopy, and this is one area flagged for improvement. Third, surgical complications are reviewed for discussion on a case-by-case basis at monthly morbidity and mortality meetings where every effort is made to minimise such complications. As all these factors impact recipient survival, the unit has reflected on the lower survival reported in this study when compared with international centres. Aside from those already mentioned, improving pre-transplant nutritional status has been a major focus, especially in children. Overall, although nutritional status has improved, the pre-transplant status of many of our recipients remains less than ideal and will remain an ongoing challenge: many children have poor socioeconomic circumstances, are referred late for transplant listing with severe disease, and the heavy reliance on deceased donation impairs capacity to transplant earlier with better PELD scores.[21]

There are a number of limitations to this study: the retrospective design, single-centre experience, small sample size (the ABOi group comprised 6% of the paediatric and 9% of the adult liver transplantations performed), absence of BSI data in adults, and limited economic data to conduct a cost analysis of ABOi v. ABOc transplantation. Further studies with larger numbers are needed to validate these results.

Conclusion

This study confirms the utility of ABOi-LT as a viable option in South Africa to increase the potential liver donor pool as survival and complication rates between ABO-compatible and -incompatible groups were similar. Despite comparable survival, the study showed higher BSI rates in paediatric ABOi recipients and longer hospital stay in adult ABOi recipients. While this study demonstrates that ABOi liver transplantation is feasible, there are ongoing challenges to national scalability that need to be addressed, including use of standardised desensitisation protocols, capacitating resources in transplant centres to enable ABOi-LT, and ongoing efforts to improve graft and recipient survival.

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