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TITLE PAGE:

34 YEARS OF PAEDIATRIC LIVER TRANSPLANTATION IN AUSTRALIA AND NEW ZEALAND

Review Article

Keywords: paediatric, liver transplantation, Australia, New Zealand

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All authors have contributed to this review article and report no conflict of interest in its publication.

Ethical approval was sought from the Australia and New Zealand, Liver and Intestinal Transplant Registry.

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PAEDIATRIC LIVER TRANSPLANTATION IN AUSTRALIA AND NEW ZEALAND

Abstract:

Liver transplantation has become the standard of care for children with end stage liver disease. In Australia and New Zealand there are four paediatric liver transplant units, in Sydney, Melbourne, Brisbane and Auckland. Over the past 30 years there have been significant changes to indications for transplant, as well as medical and surgical advances. In this paper, using retrospective data from the Australia and New Zealand Liver Transplant Registry (ANZLTR), we review 977 children (less than 16 years of age) who underwent liver transplant from 1985-2018. The most common indication was biliary atresia (54%), although there has been an increase in other indications including inborn errors of metabolism, fulminant hepatic failure and malignant liver tumours. Over the past 3 decades, areas of change and innovation include: the use of "split grafts" to enable an adult and a child to receive the same donor liver; live donation; improvements in immunosuppressive regimens and infectious prophylaxis protocols; and innovative surgical techniques allowing transplantation in smaller infants. The outcomes for children who undergo liver transplant in ANZ are excellent, with current 10 year patient survival rates of 95%, comparable to other larger centres around the world.

Keywords:
Paediatric
Liver transplantation
Australia and New Zealand

Introduction:

Liver transplantation is standard of care for children with end stage liver disease. This was not always the case: in the early 1980's there was vehement opposition to establishing liver transplantation, both from within and outside the medical profession. Australia and New Zealand have four paediatric liver transplant units, established in Brisbane and Sydney in 1985, in Melbourne in 1988 and Auckland in 1998.[1, 2] Children from other Australian states and territories are sent interstate for liver transplantation, whilst the Auckland unit services all of New Zealand. Over the last 30 years there have been significant medical and surgical advances. These include advances in immunosuppression regimens, infection prophylaxis protocols and innovative surgical techniques which allow transplantation in smaller infants. Changes to organ allocation policies reflect both evolving community ethical standards and the unique topography of our region. We review paediatric liver transplantation in Australia and New Zealand (ANZ) from 1985 to 2018 inclusive.

Methods:

We obtained retrospective data regarding outcomes from the Australia and New Zealand Liver Transplant Registry (ANZLTR). Children are defined as <16 years of

age at the time of transplant. In this study, we arbitrarily divide the patients into 3 historical cohorts to demonstrate the changing experience over the past 3 decades: Groups A: 1985-1996, B: 1997-2007, and C: 2008-2018.

Organ allocation policy

Children listed for liver transplant are prioritised primarily on clinical status. The Paediatric End Stage Liver Disease (PELD) score,[3] based on bilirubin, international normalised ratio (INR), serum albumin and growth is a validated objective measurement of the likelihood that a child will die from their liver disease within 3 months used to prioritise children on the waiting list.

Waiting lists are based on the local state unit, unless a child requires urgent transplantation, when national priority occurs. Indications for transplant are based on patient and donor factors. Patient factors include PELD score/degree of illness, blood group and weight, while donor characteristics include weight, age, type of illness causing death and blood group. Unlike renal transplantation, HLA matching is not required; liver transplantation is based primarily on compatible blood grouping. Recent evidence and local experience have shown that for children <12-18 months it is safe to perform ABO incompatible liver (and heart) transplants, because children this age have low levels of naturally occurring antibodies to blood group antigens.[4-6]

Types of liver "grafts"

Poor organ donation rates in ANZ limit paediatric liver transplantation. The increasing demand for donor livers, particularly for adult patients (Figure 1), is not matched by increased organ donation rates. There are few whole-size, matched paediatric donor grafts available, necessitating the use of adult grafts either cut-down to the size of the child, or more commonly split to yield grafts for both an adult and a child. Live donor liver transplantation (LDLT), where an adult (usually a parent) donates part of their liver, is increasingly utilised to address donor shortages.

Results:

From 1985 to 2018 inclusive, 977 children <16 years received 1110 liver transplants (17.7% of the 6259 liver transplants performed over this period). Fifty-three NZ children were transplanted in Australia, primarily Brisbane, until the Auckland unit commenced paediatric transplants in 2002. The median age of the 977 children was 2.3y (range 24d to 15.9y); over 60% were <3y (Figure 2) and 52% female compared to 34% female in the adult transplant population.

Biliary atresia was the indication for transplantation in 54% (Figure 3). Metabolic diseases (15%) are detailed in Table 1, the commonest being α-1-antitrypsin deficiency. An increasing indication is rare inborn errors of metabolism (IEM),

usually with minimal or absent liver disease but a missing or defective enzyme cured by liver transplantation. The urea cycle disorders are the commonest IEM, but other rare IEM are being increasingly transplanted (Table 1). Different uncommon cholestatic disorders constituted 13% (Table 2). Fulminant hepatic failure (FHF), where previously well children go rapidly into liver failure, comprised 11%. Malignancy, mainly hepatoblastoma, was responsible for 4%. Unlike adults, children virtually never receive liver transplants for chronic viral hepatitis with cirrhosis, hepatocellular carcinoma or paracetamol hepatotoxicity. Figure 4 and Table 3 demonstrate changing indications, particularly over the past decade. Melbourne now performs combined liver-small bowel transplant for children with short bowel syndrome and end-stage liver disease dependent on total parenteral nutrition.

Graft types have changed reflecting smaller numbers of whole organ donors, earlier use of reduced size grafts, and increase in split and live donor grafts (Figure 5, Table 3). Split grafts accounted for 32% overall, but 47% in the most recent decade (Table 3). Donation after cardiac death (DCD) is primarily used in adult patients, but also several children. There has been one unsuccessful hepatocyte cell transplant.

The number of transplants has increased (Table 3), with 204 more transplants performed from 2008-18, compared with 1997-2007. The median recipient age and weight decreased slightly, while median donor age and weights rose. Paediatric mortality on the waiting list is low, especially recently, due mainly to splitting organs and to live donation. Australian adult waiting list mortality fell from 12.5% in 2008 to 3% in 2018 due to improved donation rate.

Overall patient actuarial 34-year survival is 73% for children, compared to 37% for adults. Factors influencing patient survival include the era of transplantation, weight at transplant, graft type and underlying disease. Survival has improved successively (Figure 6); recent one-year paediatric survival is 97%. Outcomes are worse with reduced size grafts compared with whole, split and live donor grafts, $p<0.001$ (Figure 7). The patient outcome according to graft type is, however, confounded by an era effect: most reduced size grafts were done earlier, when results were not as favourable (Figure 6). Patient survival according to disease type is similar except for malignancy (20-year survival 24%) and FHF (53%), though outcome of these has improved over time.

Nearly 12% of children received a second liver transplant, while 15% of these underwent a third procedure during childhood (Table 3). The rate of re-transplantation has fallen (Table 3). Regarding indications for re-transplant, rejection is rarer, biliary complications more common, while vascular problems (hepatic artery, portal vein, hepatic vein) persist. Primary non-function (PNF) remains a small but important cause of graft loss (early failure of liver function despite no obvious vascular or other cause).

Overall 169 children (17.3%) died following liver transplant, 60% in the first 12 months post-transplant. The commonest cause of death was graft failure (27%), largely due to vascular thrombosis, PNF or rejection. A further 20% died due to sepsis. Other causes of death included cerebrovascular complications (13%) and malignancy (9%) either *de novo* or as disease recurrence (Figure 8).

Discussion:

The excellent outcomes of ANZ children who undergo liver transplantation are comparable to other world centres.[7-9] ANZ has historically had one of the lowest organ donation rates in the world, limiting access of children to liver transplantation. From 2009, when the Australian Federal Government established an Organ and Tissue Authority, to 2018, rates rose from 11.4 to 22.2 donors per million population.[10]

This study demonstrates increasing paediatric liver transplantation in ANZ and improved outcomes over 34 years. Younger, smaller children with more severe disease are being successfully transplanted. This success is attributable to several factors: the "learning curve" of improved surgical technique, anaesthetic and post-operative care, medical, nursing and allied health care; better immunosuppression; improved prophylaxis against opportunistic infections such as cytomegalovirus (CMV) and *Pneumocystis jirovecii*; and aggressive management of post-transplant sepsis.

The ANZ paediatric waiting list mortality is low despite the poor organ donation rate. In contrast, the waiting list mortality for US children <2 years old was 12.4%,[11] and early post-transplant mortality 8%.[11, 12] A likely reason is the reluctance to split livers in the US, despite a superior organ donation rate. From 2010-15 only 6.3% of eligible livers were split; the number of potentially "split-able" livers was larger than the number of children who died on the waiting list.[13] In ANZ all grafts are designated to be split unless the graft is deemed unsuitable (anatomical variants, donor age >40-50y, graft steatosis), an adult patient is deemed "too sick" to receive a split graft, or due to surgical manpower issues.

Live donor grafts are increasingly used: benefits include good quality grafts from a healthy young donor and elective surgery scheduled during the "cold light of day" when the surgical team is fresh and ready. Concerns include risks to the donor, with a possible mortality of 0.2% in the US and Europe,[14] although the risks are generally lower when transplanting from an adult donor to a child than from adult to adult. There have been no donor deaths in ANZ. Reported donor morbidity is 20% for left lobectomies, and 40% for right.[15] The large Toronto live donor program recently reported their outcomes for adult patients undergoing right lobe donation: no donor deaths, and 24% of 587 donors had a complication.[16]

Graft types differ around the world. Whole grafts were used in 75% of 852 children transplanted at the University of California Los Angeles (UCLA) from 1984-2006, [7] and 65% of 196 at Wisconsin. [17] In our study, 29% were whole grafts (23.7 % from 2008-2018). This could suggest better survival with live donor than other graft types (Figure 7), although this could be an effect of era of transplant. [7, 18] Historic reports showed worse outcomes for split grafts compared with LDLT or whole grafts.[19-21] More recent studies, however, show equivalent patient and graft survival for children receiving split liver transplants, reflecting our experience in ANZ.[22-24]

The indications for liver transplant are similar worldwide: biliary atresia remains the commonest, despite attempts to diagnose and treat early with Kasai portoenterostomy. Our outcomes for transplantation for biliary atresia and other cholestatic diseases are very good, like others. [7, 25, 26]

Children with inborn errors of metabolism but minimal or no underlying liver disease present a challenge regarding waiting list priority for transplantation, particularly where the underlying defect is not completely corrected and extrahepatic manifestations persist or are exacerbated by transplantation and subsequent immunosuppression.

Transplantation for malignancy was 3.9% of all paediatric liver transplants, but 6% from 2008-18. Management of hepatoblastoma is challenging[7, 27] and, like others,[7, 27] we had relatively poor long term outcomes. However, markedly improved outcomes in ANZ (96% survival for 2008-18) reflect the evolving model of care for hepatoblastoma where the role of liver transplantation has become better defined, including primary transplant in certain tumour scenarios.[28]

Although 20-year survival for Fulminant Hepatic Failure was 53%, in keeping with other reports, [7, 19, 29] it was 80% from 2008-18, due to the use of live donors and improvements in recipient selection and intensive care management. [30, 31]

Our finding that size and age did not affect long-term outcome is consistent with the changing trend for better results in younger and smaller children. Historically these children did worse after transplant,[7, 25, 26] but recent reports show improved if not equivalent outcomes in all age groups. [32, 33]

The proportion of ANZ children requiring liver re-transplantation is consistent with 5-22% in other studies. [34-37] Encouragingly, our rate fell from >15% in 1985-1996 to 8.3% from 2008-18 (Table 3). Historically outcomes of re-transplantation were inferior: survival in a SPLIT analysis of a large multicentre US cohort (1995-2004), was 67% and 59 % at 1 and 4 years respectively. [34] Rates of survival were worse if re-transplantation occurred within one month of primary transplant, while whole organ re-transplants did significantly better. [34] Paediatric re-transplantation in ANZ showed similar outcomes from 1986-2000, but a pronounced improvement from 2001-17 with

patient survival of 89%, 87%, 87% and 71% at 1, 5, 10 and 15 years, respectively (paper under review). This era effect is more striking considering 42% of grafts used for re-transplant in ANZ are split grafts, again highlighting the importance of optimising donor liver utilisation.

Significant challenges remain for children undergoing liver transplantation.[38, 39] Protocol biopsies have revealed chronic graft dysfunction, even with normal liver function tests,[40] but also children with normal biopsies who might be considered for complete immunosuppression withdrawal.[41] Possible antibody-mediated graft dysfunction is being increasingly identified with HLA donor specific antibody measurement.[42] Other well-known complications include renal dysfunction and risks of malignancy and/or post-transplant lymphoproliferative disease. Neurodevelopmental and quality of life issues are also being addressed.[43-45] Organ donation remains a challenge, especially in a competing environment of increasing donor age and donor obesity, along with the exponential rise in adult liver transplant listings.

In summary, this study represents an important review of the successful implementation and development of paediatric liver transplantation in Australia and New Zealand. The results support the importance of liver transplantation for children in enabling the majority of them to survive and prosper, vindicating the controversial introduction of this therapy 35 years ago.

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TABLES

TABLE 1

Metabolic disorders undergoing paediatric liver transplantation in Australia and New Zealand

Metabolic Disorders	Paediatric
Alpha-1 antitrypsin deficiency	40
Urea cycle disorder	26
Ornithine transcarbamylase deficiency	*14*
Argininosuccinate lyase deficiency	*4*
Citrullinaemia [argininosuccinate synthetase deficiency]	*4*
Carbamyl phosphate synthetase 1 deficiency	*2*
Unspecified	*1*
Crigler-Najjar	12
Primary hyperoxaluria	10
Maple syrup urine disease	8
Wilson's disease	8
Homozygous hypercholesterolaemia	7
Propionic acidaemia	7
Tyrosinaemia	6
Glycogen storage disease	4
Bile acid synthesis / transport disorder	3
Haemochromatosis	3
Methyl malonic acidaemia	2
Niemann-Pick Type C	1
Familial immunodeficiency syndrome	1
Indian childhood cirrhosis	1
Methylmalonic acidaemia	1
Mitochondrial disease	1
Protein C Deficiency	1
Pyridoxamine 5 - phosphate oxidase deficiency	1
Total	**142**

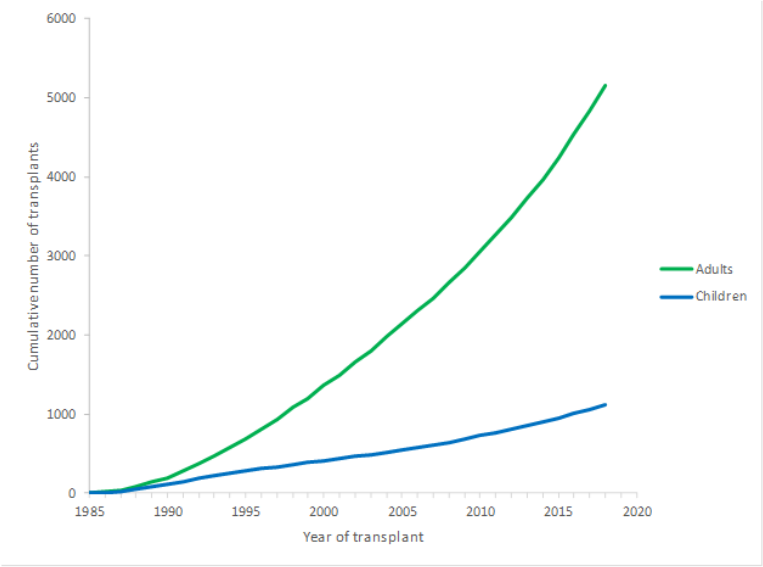
TABLE 2
"Other" diagnoses resulting in paediatric liver transplantation in Australia and New Zealand

"Other" Primary diagnosis	N
Alagille syndrome	39
Progressive familial intrahepatic cholestasis	28
Cystic fibrosis	15
Neonatal hepatitis	6
Histiocytosis X	5
Caroli's disease	4
Choledocal cyst	3
Ductopenia	3
Intestinal failure associated liver disease	3
Secondary biliary cirrhosis	3
Chronic Budd Chiari	2
Common variable immune deficiency	2
Polycystic liver and kidney disease	2
Autoimmune sclerosing cholangitis	1
Bile salt synthetic defect	1
Congenital Intrahepatic portosystemic shunt	1
Cornelia de Lange syndrome	1
Enterovirus hepatitis	1
Established cirrhosis with marked cholestasis	1
Gestational alloimmune liver disease	1
Hepatic fibrosis/polycystic kidney disease	1
Hepatic lymphangiomatosis	1
Idiopathic copper toxicosis	1
Ischaemic sclerosing cholangitis	1
Parvovirus	1

TABLE 3

	A: 1985-1996	B: 1997-2007	C:2008-2018	Total
No. paediatric patients	**271**	**260**	**446**	**977**
Recipient age (median yrs)	2.5	2.4	2.0	**2.3**
Recipient weight (median kg)	12.4	13.0	12.0	**12.4**
No. patients *(excludes 2 pts who had first graft OS)*	**271**	**259**	**445**	**975**
Malignancy indication	4	7	27	**38**
FHF indication	19	36	49	**104**
Number of transplants	**310**	**298**	**502**	**1110**
Deceased donor age (median yrs)	18.9	22.7	24.2	**22.6**
Deceased donor weight (median kg)	60	65	68	**65**
Living donor age (median yrs)	28.0	36.5	34.1	**34.7**
Split graft %	5.5	32.6	47.2	**31.6**
Whole graft %	40.0	26.8	23.7	**29.1**
Live donor graft %	1.9	6.0	12.5	**7.8**
Reduced %	52.6	34.2	16.5	**31.4**
Retransplant %				
- 1st graft	15.5	13.9	8.3	**11.8**
- 2nd graft	14.7	24	10	**15.4**

Deaths post LT %	36.2	16.2	6.5	**17.3**



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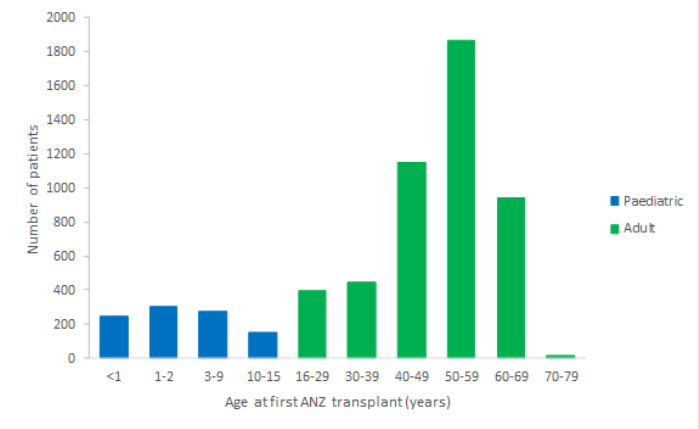

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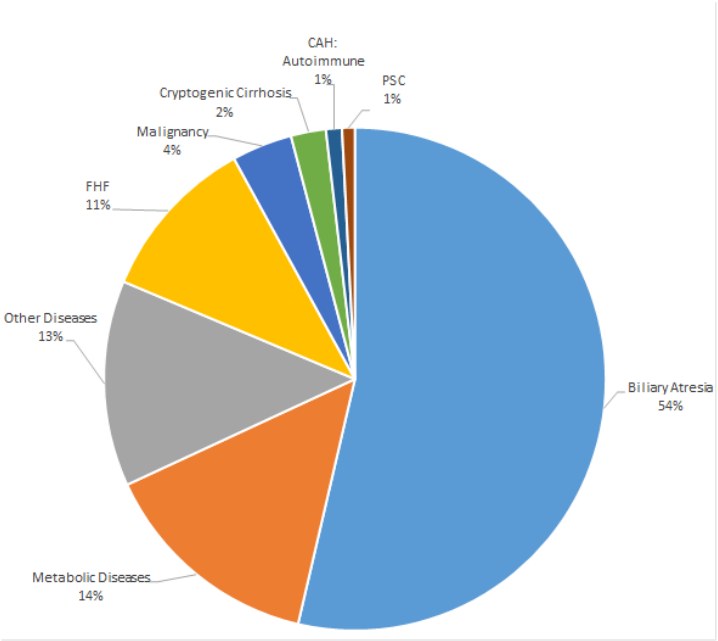
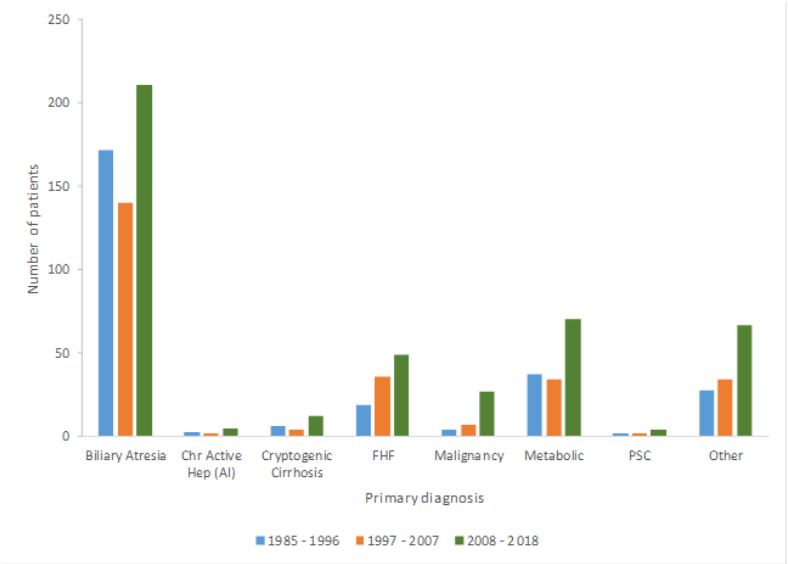
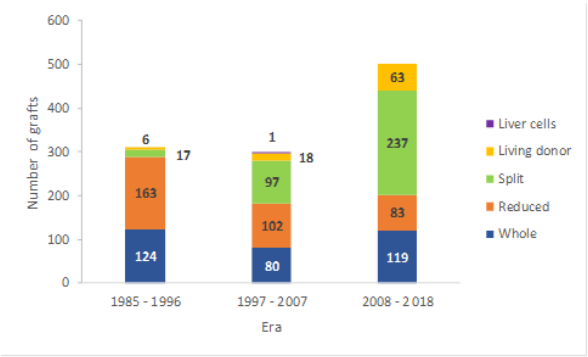


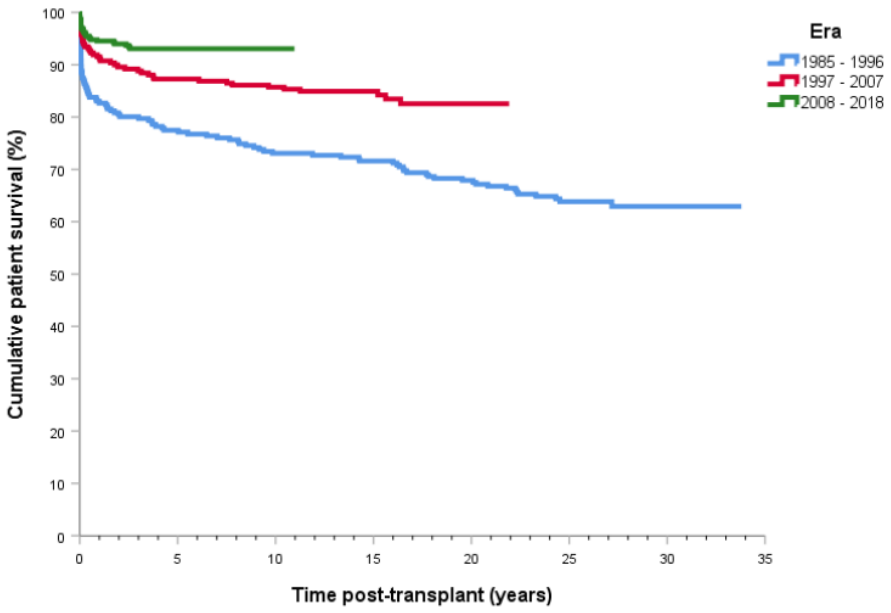
JPC_14969_Figure 3.tif



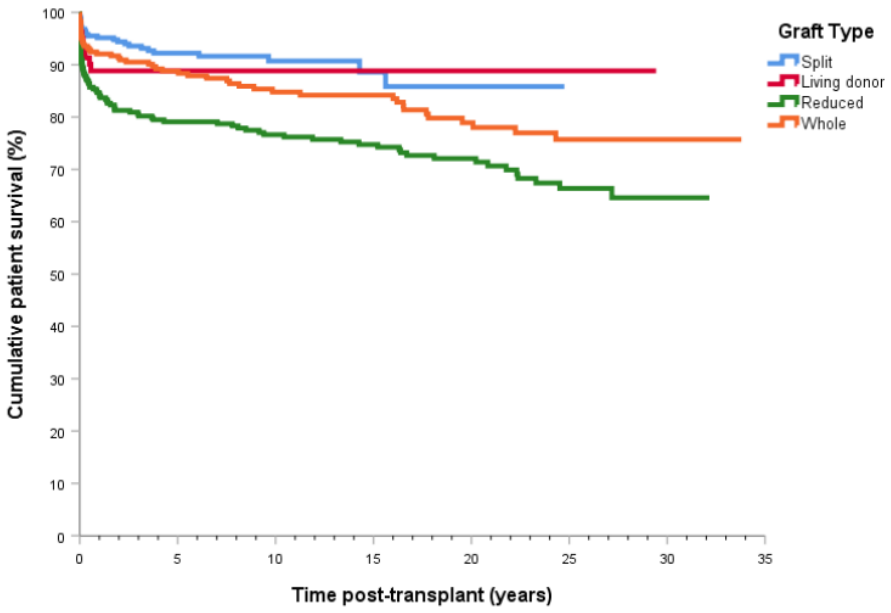
JPC_14969_Figure 4.tif



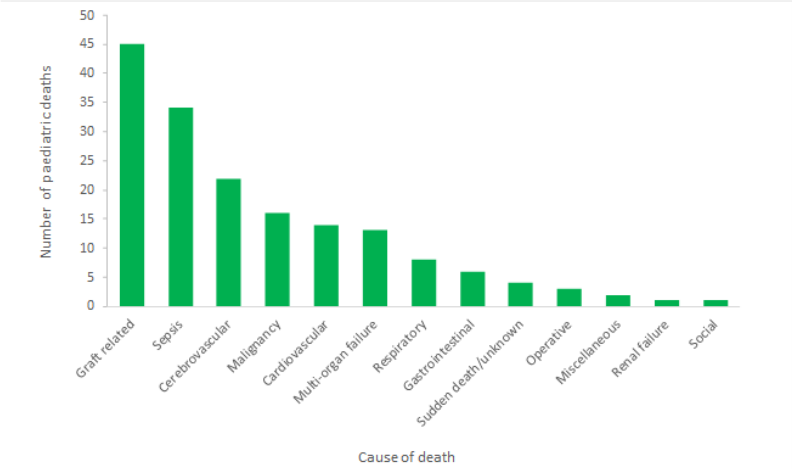
JPC_14969_Figure 5.tif



JPC_14969_Figure 6.tif



JPC_14969_Figure 7.tif



JPC_14969_Figure 8.tif