



LONG TERM OUTCOMES OF RENAL TRANSPLANTATION IN CHILDREN AT TRIPOLI CHILDREN HOSPITAL

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Abstract

Background: Kidney transplantation is the optimal treatment for end-stage renal disease in children. However, long-term graft survival has not significantly improved among paediatric patients. **Objective:** To investigate the determinants of long-term graft survival among Libyan paediatric recipients of kidney transplantation. **Methods:** In a single-centre cohort study, we studied 31 paediatric kidney transplantations performed from 2000-2019, follow up with nephrology clinic at Tripoli Children Hospital, Tripoli, Libya. Different variables were collected for each patient and graft survival rates were calculated. **Results:** After a follow-up period of 15.8 (± 4.0) years, the graft survival rate was 14.5 (± 0.5) years; the 1-, 5-, 10-, and 20-year mean graft survival rates were 90%, 81%, 62%, and 62%, respectively. The corresponding patient survival rates were 100%, 99.4%, 97.8%, and 96.5%, respectively. Pre-emptive transplantation ($p=0.006$) and living graft donation ($p=0.002$) led to higher graft survival, while primary disease of primary hyperoxaluria ($p=0.001$) led to lower graft survival. Chronic rejection was the most frequent cause of graft loss. **Conclusion:** Short-term graft survival still outpaces the long-term outcome. Modifying the mentioned determinants, with more intense immunosuppression for greater prevention of acute and chronic rejection, and increased rate of pre-emptive transplantation and living donor transplantation, long-term graft survival may significantly improve in future.

Keywords: Graft survival, Libya, Kidney transplantation.

INTRODUCTION

Chronic kidney diseases (CKD) are a major health problem world wide^[1]. According to The Kidney Diseases Improving Global Outcomes (KDIGO) guideline, CKD was defined by Presence of kidney damage either structural or Functional, or by a decline in glomerular filtration rate (GFR) below 60 ml / min/1.73m² of body surface area for more than 3months. ^[2] There for the term CKD define renal dysfunction as continuum rather than discrete change in renal Function, either in children or in adult^[3]. Children with CKD are at risk of developing end stage renal diseases ESRD which require renal replacement therapy (RRT)^[4]. RRT is the process of supporting the renal function through the application of intermittent or continuous extracorporeal (haemodialysis) or para corporeal (Peritoneal dialysis). Methods or ultimately by renal transplantation^[5]. The Majority of paediatric patients with ESRD who require dialysis can be managed with PD (Peritoneal dialysis) ^[6]. The choice of dialysis modality is most often based on patient and family Preference, centre philosophy, and availability of desired modality^[7]. Kidney transplantation is now considered the treatment of choice for ESRD in children because it is associated with better quality of life, Productivity and growth of children and long patient survival than what can be achieved by any modality of long-term dialysis^[8]. There are many risk factors for the long term out comes in children post renal transplantation, which related to many objectives including age of patient at time of renal transplantation has a significant impact on transplantation results. Two specific age groups potentially are impacting graft Survival for very different result. One group is that of recipient's underage of 2 years old, these patients are more likely to have high incidence of graft rejection.

The other group, which is Less well known, is that of adolescent recipients, when graft Loss percentages are higher, because of lack of therapeutic compliance and this age coincides with a transition period between paediatric and adult nephrology units. ⁽⁹⁾⁻⁽¹⁰⁾ Kidney transplantation is a surgical procedure to place a healthy kidney from donor into person whose has ESRD. The donor could be either live donor (related live donor and living un related donor) and Cadaveric graft which from deceased donor. The main issue remains kidney transplantation suppression of allograft rejection^[11]. Thus, the development of immunosuppressive drugs has been the key to successful allograft function.^[12] The increased immunosuppressive efficiency obtained in the last two decades in kidney transplantation dramatically reduced the incidence of allograft rejection. There are Many regimes of drugs used Post transplantation^[13].

1. Cyclosporine + MMF + Steroid
2. Cyclosporine + Myfortic + Steroid
3. Prograf + MMF + Steroid
4. Prograf + Myfortic + Steroid
5. Sirolimus + myofortic + steroid

Prograf=Tacrolimus MMF=Mycophenolate Mofetil, myofortic = Mycophenolic acid, Sirolimus=Rapimmune.

Children post renal transplantation May Suffer from various complications from the disease itself or as a side effect of Medication. There are many reported complications. (Anemia, infection, HTN, DM, epilepsy, gum hypertrophy). Infection: while Modern immunosuppression regimens have reduced the rate of acute rejection, infections complication have become more frequent especially virus-related infection (RSV, influenza CMV)^[14]. Hypertension is common in children post-

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transplant its likely due to a combination of primary disease, medical side effect^[15]. Anemia in renal transplant patient. is a known complication of renal patient as part of complications of ESRD and post transplantation drugs^[16]. Hyperglycemia and new-onset diabetes after transplant (NODAT) are serious and increasingly following kidney transplantation^[17]. Graft rejection as a deterioration in allograft function associated with specific pathological changes can be discovered by renal biopsy^[18]. The estimated incidence of CKD and RRT in children varies throughout the world, it has been reported to be as high as 15 cases per millions child in USA and as low as 4 cases per millions child below age 19 in Japan^[19]. The incidence of RRT varies greatly among Countries with a reported average, incidence based on population-based Studies of 6 cases per million children aged 0-14 years, and 8 cases per millions in aged 0-19 years^[19].

MATERIALS AND METHODS

Subjects

This study was a case Series observational study covered the period between (2000 -2019). 31 children aged between 3 and 20 years, who have followed up at transplantation clinic in nephrology unit at Tripoli children Hospital.

Study design

The study carried by reviewing the medical records of all patients who have done renal transplantation and followed up at nephrology clinic. Data was collected in a case sheet including the age seven age at transplantation place, donor information, primary diseases. pre transplantation RRT, drugs regimes, Complication post transplantation & graft rejection, patient outcomes graft and patient survival at 5, 10 years. Definition of graft rejection as a deterioration in allograft function associated with specific pathological changes can be discovered by renal biopsy.^[18] graft rejection can classify into Acute graft rejection which appears within the 1st 6 month after renal transplant and numbers of the attacks^[18]. Chronic graft rejection which accrues after 1 year post renal transplantation^[20]. Estimation of renal graft function by calculation of GFR (glomerular Filtration rate) GFR by original Schwartz equation^[19].

$GFR = K \times \text{Height cm} / \text{serum creatinine}$

Statistical analysis

Data of the questionnaire and results of blood tests were analyzed using software program statistical SPSS (version,24). N (31), the percentages were performed to investigate the significance in the association of the different variables such as age, sex haemodialysis with graft survival and graft survival at for the transplanted recipients. Our findings were given in tables as arithmetic mean and standard deviation. Difference between groups were assessed with ANOVA and Correlations between variables were assessed using Pearson's coefficient of correlation. In all cases, $p < 0.05$ was considered significant.

RESULTS

A total of 31 kidney transplant at was followed up at Tripoli children Hospital in Tripoli Libya, during 2000-2019. The

mean SD follow-up period was $9.68 (\pm 3.850)$ and it was found that 54.8% of participants were aged between 10-20 years and 29.0% were 5-10 years and 16.1% were 1-5 years. According to statistical analysis, there were 64.5% was male and 35.5% was female. Although the mean SD graft survival was higher among recipient's male aged 7-10 years, and also among female (35%) as shown in table (1).

From analysis the graft of donor was 77.4% who are live (related) it is higher than the patients who transplanted the kidney with not related was 22.6% shown in table (1). 64.5% of cases had congenital diseases which lead to renal transplantation, as shown in table 1

Table 1. Socio-demographic characteristics of paediatric kidney transplantation in Libya

Character	Frequency	%
Sex		
Male	20	64.5
Female	11	35.5
Age (year)		
1 - 5	5	16.1
5-10	9	29.0
10-20	17	54.8
Date of transplantation		
<2010	6	19.3
2011-2015	15	48.7
2016-2019	10	32.3
Place of transplantation		
Turkey	14	45.2
Jordon	5	16.1
China	4	12.9
Pakistan	4	12.9
UK	2	6.5
Egypt	1	3.2
Libya	1	3.2
Type of donor		
Living related	24	77.4
Living non relating	7	22.6
Pre-transplantation RRT		
Pre-emptive transplant	4	12.9
Haemodialysis	18	58.1
Peritoneal dialysis	9	29.0
Primary renal disease		
Congenital	20	64.5
Acquired	3	9.7
Unknown cause	8	25.8

From data analysis we found that, minimum percent from transplanted patients 3.2% was in Egypt and Libya and the maximum percent (45.2%) in Turkey (12.9%) in China and Pakistan respectively and only 8.5% in UK (Figure 1)

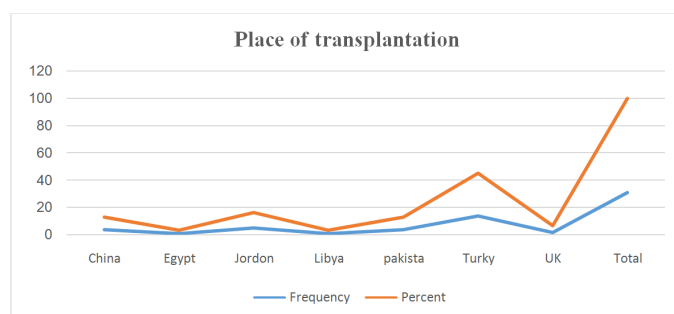


Figure 1. Illustrate the percentage of patients according to the place of plantation

According to data analysis the drug regimens was higher percentage who undertaken (Prograf+MMF+steroid) than the others who take another drugs which accounted 41.91% as (Table 2)

Table 2. The percentage of drug regimens among kidney transplantation recipients

Drug regimens	Frequency	Percent
cyclosporine+MMF+steroid	7	22.6
Cyclosporine-myforic-steriod	7	22.6
Prograf+MMF+steroid	13	41.9
Prograf+myforic-steriod	3	9.7
Sirolimus+myforic+steroid	1	3.2
Total	31	100.0

The post transplantation complications were 67.7% have anemia, 93.5% have infection it was a high percentage than others, 51.6 % have hypertension (HTN) (Table 3)

Table 3. Percentage of transplantation complication among kidney transplantation recipients

Complications	No (%)	yes(%)	total(%)
Anaemia	10 (32.3)	21(67.7)	31(100)
Infection	2 (6.5)	29 (93.5)	31(100)
H T N	15 (48.4)	16(51.6)	31(100)
D M	27 (87.1)	4(12.9)	31(100)
Epilepsy	29(93.5)	2(6.5)	31(100)
Gingival hyperplasia	30 (96.8)	1(3.2)	31(100)

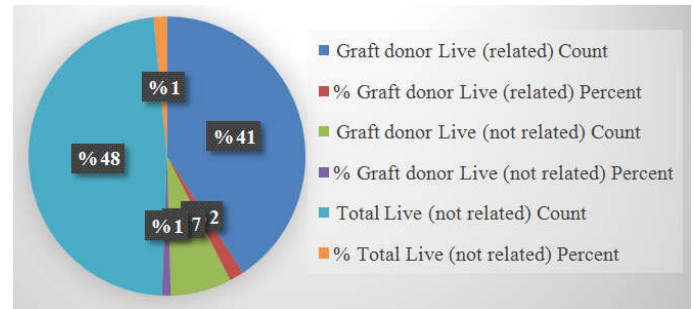
Related to data analysis graft rejection was 0% who have acute rejection and 9.7% who have chronic allograft nephropathy. The clinical outcomes were 21(67.7%) still follow up in nephrology unit one (3.2 %) of our patient died because of car accident and 9 (29.0%) transfer to adult nephrologist to complete follow up. The graft survival was significantly higher (90.3%) among for the patients who underwent transplantation at 5 years when comparing with patients who underwent the transplantation at 10 years (9.7%) and the patient survival was (87.1%) at 5 years and it was significantly higher than patient survival (12.9%) at 10 years (Table 4).

Table 4. Graft and patient survival among kidney transplantation recipient

Graft survival	Frequency	Percent
5 Years	28	90.3
10 Years	3	9.7
Total	31	100.0
Patient survival	Frequency	Percent
5 Years	27	87.1
10 Years	4	12.9
Total	31	100.0

The graft survival was significantly higher ($p=0.030$) among those who underwent pre-emptive transplantation; 95% CI: (7-10 years) than those who underwent haemodialysis (95% CI: 3-6 years) or peritoneal dialysis 95% CI) pre- transplantation. Moreover, graft survival was significantly higher ($p=0.030$) among recipients who underwent the dialysis for 3-6 years; 95% CI:) than those who underwent dialysis for shorter periods. The graft survival was higher among recipients of living donor grafts had 93.3%. Graft survival after 5 years that was significantly (p value=0.019) higher than that other groups. Although recipients of grafts from male donors and donors aged 7-10 years had a higher graft survival rate. The difference was statistically significant (0.030, 0.001) respectively. (Figure 2)

Although the mean±SD graft survival was higher among recipient's male aged 7–10 years (64.5%) and (35%) was female and the patients who transplanted the kidney were higher percentage in 2014 and 2015 (16.1%).

**Figure 2.**

DISCUSSION

Successful kidney transplantation is still the Gold standard method as a renal replacement therapy for children with end stage renal disease worldwide. The incidence of ESRD in the developed countries are 6.9 and 21.8 per million populations in the 0–4-year-old age group and 15–19-year-old age group, respectively [21]. To improve the long-term graft survival in paediatric kidney transplantation necessary to identify the factors that may influence the graft outcomes. There were many different sources for the donor which based on religious, cultural, and ethnical variations, However, the graft source in developing countries is usually from living donors. In this study, most of the grafts were from living donors, which was compatible with previous reports from Libya [22]. In Gupta et al 79.7% of transplanted kidneys were deceased donors. [23] In Current study confirmed that, using living donors lead to better graft survival with survival rate accounted, 100% after 10 years same as reported by some of other previous study. [24] Regarding the donor age and sex, we did not find any significant differences in graft survival, though some previous studies demonstrate that graft survival is worse with older-aged donors. In comparison, the findings of this study report excellent patient and graft survival findings (of 90% and 93.2%, respectively. [25] The overall one-year graft survival was 96%, three-year survival was 95%, and the five-year survival was 88%. [21] in one study from Iran the 1-, 5-, 10-, and 20-year mean graft survival rates were 90%, 81%, 62%, and 62%, respectively [26]. Our patients received the drug combinations based on the availability and applicability at the time of transplantation. They used Prograf+MMF+steroid, However, the combination of these three agents led to the best graft survival among our recipients. In our study the graft rejection was 9.7% which is chronic allograft nephropathy. Children are at increased risk for developing many complications following kidney transplantation compared with adults. A previous study in Iran reported the post-transplantation malignancies occur in only 0.6% of paediatric recipients [26]. This rate is 2.36% and 7.3% among children of the USA and France, respectively. In our study we found 93.5% had infection 67.7% had anaemia and 51.6 % have hypertension (HTN). In one Libyan study done by Austa et al, 2008 they found delayed graft function was observed in 3 (2.2%) patients, acute rejection in 6 (4.4%) patients, and post-transplantation infections in 8 (5.9%). Postsurgical complications included ureteric kink in 2 patients (1.5%) and an anastomotic urine leak in 4 (3.0%) [22]. Many studies report various predicting factors of graft survival including recipient age, sex, and race, donor age and type, dialysis history before the transplantation, previous transplant history, acute rejection, delayed graft function and GFR. However, in our study we found only graft rejection, dialysis history, and donor type are independent predictors of the graft survival.

Conclusion

Kidney transplantation is the preferred treatment for end-stage renal disease (ESRD) in children. Long-term graft survival may significantly improve by many factors like using more intense immunosuppression for greater prevention of acute and chronic rejection, increased rate of pre-emptive transplantation and using living donor transplantation. Kidney transplantation in children with ESRD results in 10-year patient survival exceeding 90%. Therefore, the long-term management of these patients is focused on maintaining quality of life and minimizing long-term side effects of immunosuppression. Supporting normal growth and development, and managing a smooth transition into adulthood.

REFERENCES

- Lysaght, M.J., *Maintenance dialysis population dynamics: current trends and long-term implications*. J Am Soc Nephrol, 2002. 13 Suppl 1: p. S37-40.
- Uhlir, K., et al., *Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO)*. Kidney Int, 2006. 70(12): p. 2058-65.
- Radhakrishnan, J. and D.C. Catran, *The KDIGO practice guideline on glomerulonephritis: reading between the (guide)lines--application to the individual patient*. Kidney Int, 2012. 82(8): p. 840-56.
- Schaefer, B. and E. Wuhl, *Educational paper: Progression in chronic kidney disease and prevention strategies*. Eur J Pediatr, 2012. 171(11): p. 1579-88.
- Karkar, A. and C. Ronco, *Prescription of CRRT: a pathway to optimize therapy*. Ann Intensive Care, 2020. 10(1): p. 32.
- Warady, B.A., et al., *Optimal care of the pediatric end-stage renal disease patient on dialysis*. Am J Kidney Dis, 1999. 33(3): p. 567-83.
- Covic, A., et al., *Educating end-stage renal disease patients on dialysis modality selection: clinical advice from the European Renal Best Practice (ERBP) Advisory Board*. Nephrol Dial Transplant, 2010. 25(6): p. 1757-9.
- Mir, S., et al., *Pediatric renal transplantation: single center experience*. Pediatr Transplant, 2005. 9(1): p. 56-61.
- Foster, B.J., *Heightened graft failure risk during emerging adulthood and transition to adult care*. Pediatr Nephrol, 2015. 30(4): p. 567-76.
- Harden, P.N., et al., *Bridging the gap: an integrated paediatric to adult clinical service for young adults with kidney failure*. BMJ, 2012. 344: p. e3718.
- Dobbels, F., et al., *Adherence to the immunosuppressive regimen in pediatric kidney transplant recipients: a systematic review*. Pediatr Transplant, 2010. 14(5): p. 603-13.
- Shapiro, R., *Living donor kidney transplantation in pediatric recipients*. Pediatr Transplant, 2006. 10(7): p. 844-50.
- Murray, J.E., et al., *Prolonged survival of human-kidney homografts by immunosuppressive drug therapy*. N Engl J Med, 1963. 268: p. 1315-23.
- Hogan, J., et al., *Infection-related hospitalizations after kidney transplantation in children: incidence, risk factors, and cost*. Pediatr Nephrol, 2017. 32(12): p. 2331-2341.
- Hooper, D.K., et al., *The quality of cardiovascular disease care for adolescents with kidney disease: a Midwest Pediatric Nephrology Consortium study*. Pediatr Nephrol, 2013. 28(6): p. 939-49.
- Drueke, T.B. and P.S. Parfrey, *Summary of the KDIGO guideline on anemia and comment: reading between the (guide)line(s)*. Kidney Int, 2012. 82(9): p. 952-60.
- Mehrnia, A., et al., *Effects of acute rejection vs new-onset diabetes after transplant on transplant outcomes in pediatric kidney recipients: analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) database*. Pediatr Transplant, 2016. 20(7): p. 952-957.
- Nankivell, B.J. and S.I. Alexander, *Rejection of the kidney allograft*. N Engl J Med, 2010. 363(15): p. 1451-62.
- Harambat, J., et al., *Epidemiology of chronic kidney disease in children*. Pediatr Nephrol, 2012. 27(3): p. 363-73.
- Solez, K., et al., *Banff '05 Meeting Report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ("CAN")*. Am J Transplant, 2007. 7(3): p. 518-26.
- Hazza, I., R. Al-Mardini, and G. Salaita, *Pediatric renal transplantation: Jordan's experience*. Saudi J Kidney Dis Transpl, 2013. 24(1): p. 157-61.
- Elusta, A., et al., *Living related donor kidney transplantation in Libya: a single center experience*. Saudi J Kidney Dis Transpl, 2008. 19(5): p. 831-7.
- Otukesh, H., et al., *Outcome of renal transplantation in children: a multi-center national report from Iran*. Pediatr Transplant, 2011. 15(5): p. 533-8.
- Hardy, B.E., et al., *Kidney transplantation in children and adolescents: an analysis of United Network for Organ Sharing Database*. Transplant Proc, 2009. 41(5): p. 1533-5.
- Sert, I., et al., *A retrospective analysis of long-term graft survival in 61 pediatric renal transplant recipients: a single-center experience*. Ann Transplant, 2013. 18: p. 497-504.
- Naderi, G., et al., *The Long-term Outcome of Pediatric Kidney Transplantation in Iran: Results of a 25-year Single-Center Cohort Study*. Int J Organ Transplant Med, 2017. 8(2): p. 85-96.
