The Influence of Dialysis Modality on Post-Transplant Outcomes

Reece Boosi

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine.

Johannesburg, 2020

I. Declaration

I, Dr Reece Boosi, declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

_____ (Signature of candidate)

12th day of June 2020 in Johannesburg

II. Dedication

For Kirti and my parents.

III. Presentations originating from this research

Oral presentation at the 2018 South African Renal Congress, Johannesburg, South Africa on the 18th October 2019.

IV. Abstract

Introduction: Renal transplantation is the therapy of choice for end stage kidney disease, offering mortality risk reduction and improved morbidity over dialytic therapies. Limited data is available evaluating the effect of pre-engraftment dialysis modality on transplant outcomes.

Methods: A retrospective review was conducted of all adult patients undergoing renal transplantation at Charlotte Maxeke Johannesburg Academic Hospital for the period 01/01/2006 – 31/12/2011 (n=103). Transplant outcomes were assessed by dialysis modality. χ^2 testing was used to compare dialysis modalities; Cox proportional hazard modelling was used to assess effect on graft outcomes. A $p < 0.05$ was deemed statistically significant.

Results: Antecedent dialytic modality was as follows: 55 patients (53.4%) received haemodialysis (HD), 35 (34%) received peritoneal dialysis (PD), and 13 (12.6%) received a combination of both (HD+PD, defined as either modality for > 3 months). Acute rejection (AR) was documented in 43.7% of patients; 54.3% of PD patients developed AR compared to 38.2% of HD patients and 38.5% of HD+PD patients (p=0.29). No significant difference in the number of episodes of AR was detected between modality groups (p=0.44). Chronic rejection (CR) developed in 22.3% of patients overall; 21.8% of HD patients, 25.8% of PD and 15.9% of HD+PD patients (p=0.74). PD was associated with an increased risk of developing any rejection (HR=2.4, 95% CI 0.9–6.4, p=0.02). Whereas dialysis modality did not affect graft survival (for HD β= 0.57, SE=0.5, Wald=1.2, 95% CI -0.4-1.6, p=0.27; for PD β=0.58, SE=0.5, Wald = 1.4, 95% CI -0.4-1.6, p=0.24), AR was found to be associated with future graft loss (β=1.29, SE=0.3, Wald = 18.1, 95% CI 0.7-1.9, p<0.001).

Conclusions: Antecedent PD is associated with an increased risk of graft rejection. Although AR is associated with graft loss, antecedent dialysis modality does not directly predict graft survival, likely reflecting the multifactorial nature of cumulative allograft injury.

V. Acknowledgements

I would like to show my appreciation to Dr Malcolm Davies and Dr Fatima Khan for their assistance and guidance in the completion of this research project.

V. List of Tables

VI. List of Figures

VII. Nomenclature

HD	Haemodialysis
PD	Peritoneal dialysis
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
ESRD	End-stage renal disease
KDIGO	Kidney Disease Improving Global Outcomes
GFR	Glomerular filtration rate
CKD	Chronic kidney disease
RRT	Renal replacement therapy
USRDS	United States Renal Data System
PPY	Patients per year
LDL	Low density lipid
VLDL	Very low-density lipid
DGF	Delayed graft function
RRF	Residual renal function
HLA	Human leukocyte antigen
PRA	Panel reactive antibodies
CyA/AZA	Cyclosporin A/Azathioprine
CyA/MMF	Cyclosporin A/Mycophenolate Mofetil
FK/MMF	Tacrolimus/Mycophenolate Mofetil

HIV	Human Immunodeficiency Virus
NHLS	National Health Laboratory Services
MDRD	Modification of Diet in Renal Disease
IQR	Inter-quartile range
SARR	South African Renal Registry

Contents

Chapter 1 – Protocol and extended Literature Review

1.1 Introduction

Kidney transplantation is the preferred renal replacement therapy, offering improved morbidity and mortality rates for patients diagnosed with end stage kidney disease (1). The scarcity of donor organs, however, necessitates that such patients require bridging with dialytic therapies until a transplant becomes available (2,3).

The effect of dialysis modality (haemodialysis, HD, or peritoneal dialysis, PD) on post-transplant outcomes has been studied in various developed populations with conflicting results regarding graft function, graft and patient survival, acute rejection as well as delayed graft function; no such data is available in the South African context. Charlotte Maxeke Johannesburg Academic Hospital is a public sector hospital, and the Transplant Unit of this institute serves the greater Johannesburg and surrounding areas. This study was undertaken to evaluate the effect of pre-transplant dialysis modality on post-transplant outcomes in the local setting.

1.2 End-stage Renal Disease in South Africa

End-stage renal disease (ESRD) is a significant contributor to morbidity and mortality in South Africa. The Kidney Disease Improving Global Outcomes (KDIGO) 2012 statement

defined ESRD as irreversible kidney damage resulting in decreased glomerular filtration rate (GFR) below 15 ml/min/1.73m^2(4,5). In South Africa, chronic kidney disease (CKD) and ESRD mainly affects individuals between 20 and 50 years of age, and is primarily attributable to hypertension and primary glomerular disease. This is in contrast to more developed nations where the disease generally affects middle aged to elderly patients and is predominantly caused by hypertension and diabetes mellitus (6). ESRD represents a significant burden on the South African Health sector; the significant cost of renal replacement therapy (RRT) and shortage of skilled professionals contribute to high rates of morbidity and mortality amongst patients with this disease in the local context (6).

1.3 Renal Replacement Therapies

Available RRTs include PD, HD and kidney transplantation. The most recent report of the South African Renal Registry found 6882 patients on HD and 1295 patients on PD; with only 219 kidney transplants (2.67% of all patients on RRT) having been performed in 2016 (2). Of these 219 kidney transplants, only 98 were from living donors (related and unrelated donor), with cadaveric donors being the dominant source of renal allografts(2). The South African Organ Donor Foundation has reported a decline in the number of renal transplants occurring in the Gauteng public sector, with 25 transplants in 2012, 23 in 2013 and 19 in 2014(1).

1.3.1 Peritoneal Dialysis (PD)

PD is an effective therapy in the treatment of ESRD. This modality makes use of a tunnelled peritoneal catheter (also known as a Tenckhoff catheter) usually made of silicone to instil 1.5 – 3 litres of a dextrose-containing solution into the peritoneal cavity for a determined period of time, usually 2 – 4 hours. Uraemic retention molecules are thus removed by a combination of convective clearance generated by ultrafiltration and diffusive clearance down a concentration gradient. Various forms of PD exist, such as continuous ambulatory PD and continuous cycler PD. The major advantage of PD over HD is the ability to perform PD in a setting outside the hospital, improving patient productivity and quality of life (7).

1.3.2 Hemodialysis (HD)

HD is the most commonly employed RRT in South Africa (8) . HD is based on the principle of solute diffusion down a concentration gradient across a semipermeable membrane. This mechanism, known as diffusive clearance, allows for the movement of toxic waste products from the circulation into the dialysate. This may be coupled with convective clearance, where waste products move from circulation to dialysate as a result of ultrafiltration. HD is typically performed in sessions 3 – 4 times per week, lasting 2 – 4 hours and almost exclusively within a hospital setting (7).

1.3.3 Kidney Transplantation

Kidney transplantation is performed in a limited number of specialised transplant centres in South Africa. There are 6 transplant centres within the state health sector (8); Charlotte Maxeke Johannesburg Academic Hospital provides kidney transplant services to the population of southern Gauteng and surrounding districts. Donor kidneys are harvested from living patients, and from donors declared to have suffered brainstem death, and are categorised as cadaveric, living related, living unrelated and living nonrelated donor transplants.

Kidney transplantation is the therapy of choice for patients with ESRD, as it is superior in terms of quality of life and long-term mortality risk. Comparisons of mortality, between transplant recipients and patients on dialysis awaiting transplantation, show a 66% reduction in mortality risk in the former group. In addition to a reduced mortality risk, transplant recipients have an increased projected life span, living up to 10 years longer than patients remaining on dialysis (9). The one and five year survival rates for living donor transplant recipients are 97.1% and 84.6% respectively. Cadaver donor transplant recipients have one and five year survival rates of 92.3% and 75.7% respectively. This is significantly higher than the one and five year survival rates of HD and PD patients which are 77.4% and 41.5% for HD, and 87.8% and 51.4% respectively (10). Furthermore, transplant recipients demonstrate lower hospital admission rates than those on dialysis, indicative of reduced morbidity. Hospitalisation of patients with ESRD represents a societal and financial burden, and accounts for approximately 40% of Medicare expenditure for RRT patients in the USA. Data analysed over the period 2005 – 2014 showed a decrease in hospital admissions in all ESRD

patients on RRT, attributed to targeted interventions reducing infection rates. Transplant recipients had the lowest admission rates at 0.8 hospitalisations per patient year (PPY) in 2014, compared to 1.6 hospitalisations PPY for patients on PD, and 1.7 hospitalisations PPY for patients on HD (10).

1.4 Pre-transplant Characteristics by Dialysis Modality

Analysis of 684 426 patients in the USRDS database by Mehrotra et al has revealed differences in patients receiving PD and those receiving HD. PD patients tend to be younger, White and less likely to have co-morbidities such as hypertension, diabetes mellitus or glomerulonephritis (11). This may have an influence on future kidney transplantation as recipient age forms a predictive factor for both patient and graft survival. Each year of life has been shown to increase the risk of graft failure by 1% (HR 1.01; $P < 0.001$) and increase the risk of recipient death by 4% (HR 1.04; $P < 0.001$) (12). Haemoglobin levels were found to be significantly higher in HD patients (10.3 g/dl; SD 1.8; $P < 0.01$) compared to PD (9.7 g/dl; SD 1.8; $P < 0.01$) (11); dyslipidaemia was observed to be more common in PD patients, with 20 – 50% of patients on PD having elevated total cholesterol and low density lipid (LDL) levels, resulting in a more atherogenic lipid profile when compared to patients on HD (13). This characteristic seems to continue into the post-transplant period as López-Oliva et al confirmed in 2011, with significantly elevated serum total cholesterol levels in PD patients at 12 months post-transplant (14).

1.5 Delayed Graft Function by Dialysis Modality

Several definitions for delayed graft function (DGF) exist, however, the most widely used defines DGF as the requirement of dialysis in the first post-operative week after transplantation (15). DGF is a common complication post-transplantation with an incidence as high as 27% depending on cold ischaemia time (16). As a result, DGF has significant financial implications not only related to the required dialysis but also to the prolongation of post engraftment hospital stay (17). The negative influence of DGF on long term graft function has been well described; grafts with delayed function, when compared to those without, have a 10 – 15% lower 1 year graft survival rates (18,19); other studies have shown a link between DGF and progressive graft failure over time (18,20–22).

DGF has been shown to exert a significant influence on recipient and graft outcomes in a number of studies (23–32). Molnar et al (n = 14 508) and Snyder et al (n = 22 736), have reported that PD, when compared to HD, is associated with a 36% and 26% decrease in the risk of DGF respectively (24,33). This finding has been confirmed in several other lower powered studies, in which PD reduced the risk of DGF by 11% – 37.5% compared to HD (23,26–28,30,31,34). A meta-analysis by Joachim et al showed a decrease risk for DGF in patients who received pre-transplant PD as opposed to HD with a pooled odds ratio of 0.5 (32). It has been suggested that the presence of residual renal function (RRF) may account for the differences in DGF observed between PD and HD patients; PD is associated with better preserved RRF (35), with complete disappearance of RRF taking on average over 3 – 4 years (36). Thus the native kidney urine output in recipients on PD may contribute to a reduced requirement for dialysis in the early post-transplant period.

1.6 Graft Function by Dialysis Modality

Estimated glomerular filtration rate is used as a marker of graft function over time. A number of studies have failed to show any effect for pre-transplant dialysis modality on graft function post-transplantation (28,30,37,38). Other factors, such as donor characteristics (age, gender, co-morbidities) (39), alloantigen-dependent factors (episodes of acute rejection, human leukocyte antigen (HLA) matching) and alloantigen-independent factors (infection, immunosuppression non-compliance, DGF) have instead been suggested to be more potent determinants of post-engraftment GFR (40–42). It is important to note that whilst DGF is a significant risk factor for the development of deteriorating graft function over time (hazards ratio of 1.47 as described by Prommool et al) (42), and the close link between HD and DGF as described above – a direct effect for pre-transplant dialysis modality and graft function post-transplantation has not been established. This may indicate the multifactorial nature of DGF and/or the multifactorial determinants of post-transplant graft function.

1.7 Graft Survival and/or Loss by Dialysis Modality

The effect of dialysis modality on post-transplant graft survival is controversial. Goldfarb-Rumyantzev et al and Kramer et al have found PD to result in better graft survival rates at 1 and 5 years post-transplant (HR 0.97, $p < 0.05$ and HR 0.83, $p < 0.05$ respectively) (12,26,28,43). Snyder et al have however shown benefit for HD; in this study the adjusted risk for death-censored graft failure was 1.15 times higher in the PD cohort when compared

to the HD cohort. This effect was even more apparent in the first 3 months post engraftment, when PD resulted in a 1.23 times increased risk for graft failure compared to HD. The majority of studies however, including Molnar et al (n = 14 508), and Schwenger at al (n = 57 315), dispute these findings, having shown no statistically significant difference in graft survival by dialysis modality (14,24,28,30,31,34,37,44,45). A meta-analysis by Joachim et al also failed to show any significant difference in graft survival by pre-transplant PD and HD (32).

1.8 Patient Survival and/or Loss by Dialysis Modality

Patient survival post-transplant is dependent upon a complex interplay of patient and transplant factors. Prolonged dialysis duration (greater than 3 years), independent of mode, is associated with higher patient mortality (19,46). This association maybe explained by the higher incidence of cardiovascular disease (including left ventricular hypertrophy and myocardial ischaemia) in patients with a longer duration of pre-transplant dialysis (19). Many studies have shown that PD patients are younger with shorter dialysis vintage prior to transplantation when compared to their HD counterparts (12,14,24,45). The effect of pretransplant dialysis modality on patient survival after engraftment is controversial. A number of studies have failed to show a significant difference in patient survival post-transplantation at 1, 3 and 5 years, including the large cohorts reported by Snyder et al and Schwenger et al (19,26,30,31,33,37,38,45). In comparison, Goldfarb-Rumyantzev et al (n = 92 844), have shown a protective effect of PD over HD with regards to patient survival (12,14,24,43), a finding confirmed in meta-analysis demonstrating a lower 5 year mortality rate in PD patients compared to HD (hazards ratio of 0.89; 95% CI 0.82 – 0.97). It has been

suggested that the apparent benefit of PD in terms of patient survival may reflect selection bias, with younger patients with lower incidences of co-morbidities such as cardiovascular disease being selected for PD, resulting in improved post-transplant survival.

1.9 Acute Rejection by Dialysis Modality

Despite a reduction in the incidence of acute rejection episodes over the past 3 decades as a result of significant improvements in immunosuppressive therapy, acute rejection is an important factor in graft survival (47). Whilst some episodes of aggressive acute rejection may result in short-term graft loss, other episodes may contribute to shortening long-term graft survival (28,30,44). The effect of an episode on long-term graft survival is influenced by a number of factors, including the number of rejection episodes, the timing of the rejection episode and severity thereof, as well as the recovery of renal function after rejection treatment(28,44). Dialysis is known to exert a substantial effect on immune function through the induction a chronic pro-inflammatory state (48). When analysing the impact of pre-transplant dialysis modality, most studies find no difference in the rate of acute rejection episodes between HD and PD groups (28,37,38,44). Vanholder et al have however, found an increased incidence of acute rejection in the PD cohort (30).

1.10 Aims

This study aims to evaluate the effect of pre-engraftment dialysis modality on post-transplant outcomes in kidney transplant recipients at the Charlotte Maxeke Johannesburg Academic Hospital Transplant Unit.

1.11 Objectives

The primary objective of this study was to assess post transplantation graft function and survival between patients who received HD and those who received PD pre-transplantation groups as evidenced by:

Graft renal function at 3, 6, 12 and 60 months.

The development and number of acute rejection episodes retrospectively diagnosed by allograft biopsy findings and/or therapy prescribed for rejection.

The presence of delayed graft function and duration thereof.

Secondary objectives of this study were:

1. To assess patient survival post transplantation between those receiving HD and those receiving PD prior to transplant.

2. To review and compare differences in baseline characteristics between HD and PD groups, including:

a) Age

b) Gender

c) Race

d) Human Immunodeficiency Virus (HIV) status

e) Donor graft source ie Living vs Cadaver

f) Cause of ESRD

g) Duration of dialysis pre transplant

h) Panel Reactive Antibodies (PRA)

i) Haemoglobin

j) Albumin

k) Phosphate

l) Lipid profile

m) Co-morbidities including hypertension, diabetes mellitus and dyslipidaemia

1.12 Methods

1.12.1 Study Design

A retrospective analysis of all patients receiving a first renal transplant at Charlotte Maxeke Johannesburg Academic Hospital during the period 1/1/2006 to 31/12/2011 was undertaken.

Patients were considered for inclusion when the following criteria were met:

- Age 18 years or older
- No previous renal transplant
- Documented duration of HD and/or PD prior to transplantation

The following exclusion criteria were applied:

- Death due to surgical complications

1.12.5 Methodology

Data Collection

Data was extracted from patient clinical records and summarised on a data collection sheet (Appendix I) which was used to capture demographic information, dialysis duration pre-transplantation, donor type, nature and number of episodes of acute rejection, and laboratory parameters pertaining to graft function in an anonymous fashion. Data collection sheets were then used to populate an Excel® datasheet which was imported into Statistica v13 (Tibco) for analysis.

Data Analysis

Patients included in this study were assigned to modality groups PD or HD through retrospective review of dialysis history. Patients who received both modalities were included in a separate group (PD +HD), defined as both dialysis modalities utilised for a minimum of 3 months each.

Baseline characteristics (gender, ethnicity, cause of ESRD, presence of diabetes mellitus, hypertension, dyslipidaemia, or HIV infection; age, haemoglobin, albumin, and phosphate serum concentration at transplantation) were determined for the series as a whole as well as

for dialysis modality subgroups. Continuous variables were subjected to the Shapiro Wilk W test, normality of distribution was confirmed through visual inspection of the histogram plot; the Central Limit Theorem was further applied in determining appropriate statistical testing. Categorical variables were compared between modality groups using the Fisher Exact test, the Chi-square test was substituted in multinomial analyses. Continuous variables were compared using the Mann Whitney U test for non-parametric data; variables showing Gaussian distribution were compared using the Student t-test.

Outcomes selected for analysis in this study were:

1. Delayed graft function
2. Development of acute rejection
3. Graft function at follow-up
4. Graft loss
5. Combined patient and graft loss.

The contribution of pre-transplant dialysis modality to each of these outcomes was assessed in two ways. Firstly, association between dialysis modality and outcome was assessed using Fisher exact or Chi-square testing as appropriate. Secondly, in order to mitigate against the effect of confounding variables and the effect over time, a multivariate Cox proportional hazards regression model was fitted for dialysis modality and other probable factors for the outcomes development of acute rejection, graft loss, and combined patient and graft loss. Linear regression modelling was also employed in analysing the effect of relevant factors including dialysis modality on time to development of acute rejection, as well as on graft

function at serial follow-up. Multivariate logistic regression was used to determine the effect of dialysis modality and other relevant factors on the diagnosis of delayed graft function.

1.13 Ethics

Ethics approval was obtained from the Human Resource Ethics Committee (Clearance Certificate No. M170954). Consent for the use of patient's records was received from the Academic Head of Internal Medicine and CEO/Superintendent of Charlotte Maxeke Johannesburg Academic Hospital. Due to the retrospective nature of the study, the need for consent from individual patients did not arise. Consent for the use of files from the CMJAH Renal Transplant clinic was obtained from the head of Nephrology, the head of Department of Internal Medicine and the superintendent of CMJAH.

1.14 Funding

This study was self-funded by the author.

1.15 Potential Limitations

This retrospective study included 144 patients who met the inclusion criteria, 41 of these patients had to be excluded as a result of inadequate data and/or loss to follow up. As a result our sample size was significantly reduced, however still exceeded the 100 patients required

for significance. Outcomes cannot be generalised for the overall population, as this is a single centre study at one tertiary academic centre.

1.17 References – Extended Literature Review

1. Muller E. Organ donation and transplantation in South Africa-an update: more about... general surgery. CME. 2013;31(6):220–2.
2. Davids MR, Jardine T, Marais N, Jacobs JC. South African Renal Registry annual report 2016. African J Nephrol. 2018;21(1):61–72.
3. Muller E, Thomson D, McCurdie F. Transplantation in South Africa. Transplantation. 2015;99(4):643–5.
4. Levey AS, Inker LA. Definition and staging of chronic kidney disease in adults. In: UpToDate. 2017.
5. KDIGO. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Vol. 3, Kidney International Supplements. 2013. p. 4–4.
6. Naicker S. Burden of end-stage renal disease in sub-Saharan Africa. Clin Nephrol. 2010;74 Suppl 1:S13–6.
7. Liu KD, Chertow GM. Dialysis in the treatment of Renal Failure. In: Harrison's Principles of Internal Medicine. 19th ed. 2015. p. 1822–6.
8. MR Davids, GK Balbir Singh NM and JJ. South Africa Renal Registry 2014. 2016.
9. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LYC, et al. Comparison of Mortality in All Patients on Dialysis, Patients on Dialysis Awaiting Transplantation, and Recipients of a First Cadaveric Transplant. N Engl J Med. 1999;341(23):1725–30.
10. USRDS Annual Data Report. Volume 2: ESRD in the United States. 2016;2(2):119–

38.

11. Mehrotra R, Chiu YW, Kalantar-Zadeh K, Bargman J, Vonesh E. Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease. Arch Intern Med. 2011;171(2):110–8.

12. Goldfarb-Rumyantzev AS, Hurdle JF, Scandling JD, Baird BC, Cheung AK. The role of pretransplantation renal replacement therapy modality in kidney allograft and recipient survival. Am J Kidney Dis. 2005;46(3):537–49.

13. Prichard SS. Impact of Dyslipidemia in End-Stage Renal Disease. J Am Soc Nephrol. 2004;14(90004):315S – 320.

14. López-Oliva MO, Rivas B, Pérez-Fernández E, Ossorio M, Ros S, Chica C, et al. Pretransplant peritoneal dialysis relative to hemodialysis improves long-term survival of kidney transplant patients: A single-center observational study. Int Urol Nephrol. 2014;46(4):825–32.

15. Mallon DH, Summers DM, Bradley JA, Pettigrew GJ. Defining delayed graft function after renal transplantation: Simplest is best. Transplantation. 2013;96(10):885–9.

16. Troppmann C, Gillingham KJ, Benedetti E, Stephen Almond P, Gruessner RWG, Najarian JS, et al. Delayed graft function, acute rejection, and outcome after cadaver renal transplantation: A multivariate analysis. Transplantation. 1995;59(7):962–8.

17. Samaniego M, Baldwin WM, Sanfilippo F. Delayed graft function: immediate and late impact. Curr Opin Nephrol Hypertens. 1997 Nov;6(6):533–7.

18. Ojo AO, Wolfe RA, Held PJ, Port FK, Schmouder RL. Delayed Graft Function: Risk Factors And Implications For Renal Allograft Survival. Transplantation. 1997 Apr;63(7):968–74.

19. Cosio FG, Alamir A, Yim S, Pesavento TE, Falkenhain ME, Henry ML, et al. Patient survival after renal transplantation: I. The impact of dialysis pre-transplant. Kidney Int.

1998;53(3):767–72.

20. Boom H, Mallat MJ, de Fijter JW, Zwinderman a H, Paul LC. Delayed graft function influences renal function but not survival. Transplant Proc. 2000;33(1–2):1291.

21. Quiroga I, McShane P, Koo DDH, Gray D, Friend PJ, Fuggle S, et al. Major effects of delayed graft function and cold ischaemia time on renal allograft survival. Nephrol Dial Transplant. 2006 Jun 1;21(6):1689–96.

22. Yarlagadda SG, Coca SG, Formica RN, Poggio ED, Parikh CR. Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis. Nephrol Dial Transplant. 2008 Oct 8;24(3):1039–47.

23. Van Biesen W, Vanholder R, Van Loo A, Van Der Vennet M, Lameire N. Peritoneal dialysis favorably influences early graft function after renal transplantation compared to hemodialysis. Transplantation. 2000;69(4):508–14.

24. Molnar MZ, Mehrotra R, Duong U, Bunnapradist S, Lukowsky LR, Krishnan M, et al. Dialysis modality and outcomes in kidney transplant recipients. Clin J Am Soc Nephrol. 2012;7(2):332–41.

25. Snyder JJ, Kasiske BL, Gilbertson DT, Collins AJ. A comparison of transplant outcomes in peritoneal and hemodialysis patients. Kidney Int. 2002;

26. Sezer S, Karakan S, Özdemir Acar FN, Haberal M. Dialysis as a bridge therapy to renal transplantation: Comparison of graft outcomes according to mode of dialysis treatment. Transplant Proc. 2011;43(2):485–7.

27. Binaut R, Hazzan M, Pruvot FR, Dracon M, Lelièvre G, Noël C. Comparative study of chronic ambulatory peritoneal dialysis versus hemodialysis patients after kidney transplantation: Clinical and financial assessment. Transplant Proc. 1997;29(5):2428.

28. Freitas C, Fructuoso M, Martins LS, Almeida M, Pedroso S, Dias L, et al. Posttransplant outcomes of peritoneal dialysis versus hemodialysis patients. Transplant

Proc. 2011;43(1):113–6.

29. Bleyer AJ, Burkart JM, Russell GB, Adams PL. Dialysis modality and delayed graft function after cadaveric renal transplantation. J Am Soc Nephrol. 1999;10(1):154–9.

30. Vanholder R, Heering P, Van Loo A, Van Biesen W, Lambert MC, Hesse U, et al. Reduced incidence of acute renal graft failure in patients treated with peritoneal dialysis compared with hemodialysis. Am J Kidney Dis. 1999;33(5):934–40.

31. Joseph JT, Jindal RM. Influence of dialysis on post-transplant events. Clin Transplant. 2002;16(1):18–23.

32. Joachim E, Gardezi AI, Chan MR, Shin JI, Astor BC, Waheed S. Association of pre-transplant dialysis modality and post-transplant outcomes: A meta-analysis. Perit Dial Int. 2017;37(3):259–65.

33. Snyder JJ, Kasiske BL, Gilbertson DT, Collins AJ. A comparison of transplant outcomes in peritoneal and hemodialysis patients. Kidney Int. 2002;62(4):1423–30.

34. Bleyer AJ, Burkart JM, Russell GB, Adams PL. Dialysis modality and delayed graft function after cadaveric renal transplantation. J Am Soc Nephrol. 1999;10(1):154–9.

35. Lang SM, Bergner A, Marcel Töpfer, Schiffl H. Preservation of Residual Renal Function in Dialysis Patients: Effects of Dialysis-Technique–Related Factors. Perit Dial Int. 2001;21(January 2001):52–7.

36. Rottembourg J. Residual renal function and recovery of renal function in patients treated by CAPD. Kidney Int Suppl. 1993;40(43):S106–10.

37. Cacciarelli T V., Sumrani NB, Dibenedetto A, Hong JH, Sommer BG. The Influence of Mode of Dialysis Pretransplantation on Long-Term Renal Allograft Outcome. Ren Fail. 1993 Jan 7;15(4):545–50.

38. Helal I, Abderrahim E, Ben Hamida F, Zouaghi K, Ounissi M, Barbouche S, et al. Impact of Dialysis Modality on Posttransplantation Results in Kidney Transplantation.

Transplant Proc. 2007;39(8):2547–9.

39. Auglienė R, Dalinkevičienė E, Kuzminskis V, Jievaltas M, Peleckaitė L, Gryguc A, et al. Factors influencing renal graft survival: 7-Year experience of a single center. Med. 2017;53(4):224–32.

40. Butler JA, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. Transplantation. 2004;77(5):769–76.

41. Smith AY, Van Buren CT, Lewis RM, Kerman RH, Kahan BD. Factors determining renal transplant outcome at the University of Texas at Houston. Clin Transpl. 1987;155–66.

42. Prommool S, Jhangri GS, Cockfield SM, Halloran PF. Time dependency of factors affecting renal allograft survival. J Am Soc Nephrol. 2000;11(3):565–73.

43. Kramer A, Jager KJ, Fogarty DG, Ravani P, Finne P, Pérez-Panadés J, et al. Association between pre-transplant dialysis modality and patient and graft survival after kidney transplantation. Nephrol Dial Transplant. 2012;27(12):4473–80.

44. Caliskan Y, Yazici H, Gorgulu N, Yelken B, Emre T, Turkmen A, et al. Effect of pre-transplant dialysis modality on kidney transplantation outcome. Perit Dial Int. 2009;29(SUPPL. 2):S117–22.

45. Schwenger V, Döhler B, Morath C, Zeier M, Opelz G. The role of pretransplant dialysis modality on renal allograft outcome. Nephrol Dial Transplant. 2011;26(11):3761–6.

46. Slizien A, Macuk A, Wolyniec W, Chamienia A, Niemierko M, Moszkowska G, et al. Influence of Dialysis Duration and Modality on Kidney Transplant Outcomes. Transplant Proc. 2009;29(3):S117–22.

47. Hart A, Smith JM, Skeans MA, Gustafson SK, Stewart DE, Cherikh WS, et al.

OPTN/SRTR 2015 Annual Data Report: Kidney. Am J Transplant. 2017;17:21–116.

48. Cohen G, Hörl W. Immune Dysfunction in Uremia—An Update. Toxins (Basel). 2012 Oct 24;4(11):962–90.

49. Haggerty S, Roth S, Walsh D, Stefanidis D, Price R, Robert D, et al. Guidelines for Laparascopic Peritoneal Access Surgery. 2013;(May 2010):1–34.

50. Klug EQ. South African Dyslipidaemia Guideline Consensus Statement. South African Med J. 2012 Feb 23;102(3):178.

51. Yeun JY, Kaysen GA. Factors Influencing Serum Albumin in Dialysis Patients. Am J Kidney Dis. 1998;32(6):118–25.

52. Piperi C, Kalofoutis C, Tzivras M, Troupis T, Skenderis A, Kalofoutis A. Effects of hemodialysis on serum lipids and phospholipids of end-stage renal failure patients. Mol Cell Biochem. 2004 Oct;265(1/2):57–61.

53. Van Biesen W, Vanholder R, Van Loo A, Van Der Vennet M, Lameire N. Peritoneal dialysis favorably influences early graft function after renal transplantation compared to hemodialysis. Transplantation. 2000;69(4):508–14.

54. Legendre C, Canaud G, Martinez F. Factors influencing long-term outcome after kidney transplantation. Transpl Int. 2014;27(1):19–27.

55. Guillou PJ, Will EJ, Davison AM, Giles GR. CAPD—a risk factor in renal transplantation? Br J Surg. 1984;71(11):878–80.

56. Lan H, Yang N, Brown F, Isbel N. Macrophage Migration Inhibitory Factor Expression In Human Renal Allograft Rejection. Transplantation. 1998;66(11):1465–71.

57. Aldar N, Unce M, Orris P, Elsh K. Donor Cytokine Genotype Influences The Development Of Acute Rejection After Renal Transplantation. Transplantation. 2001;71(3):469–76.

58. Matas AJ, Gillingham KJ, Payne WD, Najarian JS. The Impact of an Acute Rejection Epsiode on Long-Term Renal Allograft Survival. Transplantation. 1994;57(6):857–9.

59. County H. Graft Function Reduces Kidney Allograft Survival. Transplantation. 2001;74(10):1400–4.

60. Incenti FL V, Ensik STCJ, Ilo ROSF, Iller JOM. A Long-Term Comparison Of Tacrolimus (FK506) And Cyclosporine In Kidney Transplantation : Evidence For Improved Allograft Survival At Five Years 1. Transplantation. 2002;73(5):775–82.

Chapter 2 – Manuscript

Title:

The Influence Of Dialysis Modality On Post-Transplant Outcomes.

Authors:

Reece Boosi

Malcolm Davies

Fatima Khan

Affiliations:

Division of Nephrology, Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa.

Conflict Of Interest:

None

Corresponding Authors

Dr Reece Boosi

184 Oxford Rd, Illovo, Johannesburg 2196; reeceb001@gmail.com

Word Count:

Total: 3547 words

Abstract:

296 words

Introduction

Renal transplantation is the preferred treatment for end stage renal disease (ESRD), demonstrating improved mortality and morbidity outcomes, and carrying less long-term cost than dialytic therapies (2,3). However, limitations in donor graft availability result in most patients diagnosed with ESRD receiving prolonged courses of dialysis prior to engraftment(2).

In this regard, the effect of the type of dialysis modality prescribed during wait-listing for transplant on outcomes after engraftment remain uncertain, despite extensive study(2-14). Delayed graft function (DGF) has been reported to be more common in patients receiving haemodialysis (HD) compared to those receiving peritoneal dialysis (PD) (24,26–28,30,31,33,34). Graft function, graft survival and combined patient and graft survival has often been suggested in some studies to be independent of dialysis modality (14,24,28,30,31,34,37,45), although some show improved survival with antecedent HD (33), and others showing a beneficial effect for PD on these outcomes (12,43).

This study seeks to describe the effect of pre-engraftment dialysis modality on transplant outcomes in the local setting.

Methodology

Study Design

A retrospective review of all patients receiving a first renal transplant at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) during the time 01/01/2006 - 31/12/2011 was undertaken. Of a total of 144 patients undergoing renal transplant during this period - 103 were included, with 41 patients excluded from analysis due to loss to follow up or transfer out of the CMJAH Transplant Unit prior to the start of data collection on 1/10/2017, or duration of follow up of less than 5 years.

Data Collection

Data was extracted from patient clinical records and used to populate a Microsoft Excel database in an anonymous fashion.

Demographic data (age at transplantation, race and gender), co-morbidities (hypertension, diabetes mellitus and dyslipidaemia), cause of ESRD, HIV status, donor type (cadaveric or related living donor), panel reactive antibodies (PRA), and dialysis modality (namely PD, HD or a combination thereof, designated as PD and HD) were recorded. The combination group was defined as patients who received both dialysis modalities, with the time period for the lesser used modality being at least three months. This period was chosen to account for those

patients on PD requiring temporary HD due to peritonitis or during the peri-PD initiation period (49).

Graft outcomes were assessed across a number of measurements including: development of delayed graft function (DGF, defined as the need for dialysis within the first week after engraftment), graft function as evidenced by estimated GFR calculated using the Modification of Diet in Renal Disease (MDRD) equation at specified time periods (three, six, twelve and and sixty months post-transplantation), development of histologically-proven rejection, graft survival, and combination patient and graft survival.

Statistical analysis

Statistical analysis was undertaken using STATISTICA v13 (StatSoft). Categorical variables were described in terms of frequency and percentages. The central tendency of continuous variables was described using the mean or median, and the dispersion measurement by the standard deviation and interquartile range as appropriate. The Student t-test and the Mann Whitney U test were used for comparative analysis of parametric and non-parametric data, respectively. The Fisher Exact and Chi-square tests were used to compare categorical data. Regression analysis and Cox proportional hazards modelling was used to analyse factors influencing:

DGF (pre-transplant dialysis modality, haemoglobin and phosphate levels, gender and donor type)

Graft function (pre-transplant dialysis modality, age, DGF, donor type, co-morbidities, acute and chronic rejection)

The development of rejection (pre-transplant dialysis modality, DGF, donor type)

Graft loss (pre-transplant dialysis modality, time to first documented episode of rejection, DGF, donor type, graft function at 3 months)

Combined patient and graft loss (pre-transplant dialysis modality, DGF, acute rejection, graft function at 3 months, donor type)

A p-value of < 0.05 was considered to be statistically significant with a confidence interval of 95%.

Ethics

This study was approved by the Human Research ethics Committee of the University of the Witwatersrand (Clearance Certificate No. M170954).

Results

Descriptive Statistics

A total of 144 patients underwent first renal transplant during the period 01/01/2006 - 31/12/2011(Table 1). 41 Patients were excluded due to a variety of reasons, including

insufficient data (n = 21), loss to follow up (n = 6), and transfer out of CMJAH facility (n = 4); a total of 103 patients were included in analysis. Of these 103 patients, 66 were male (64.07%) and 37 were female (35.92%). 55 patients (53.39%) were on HD prior to transplantation, 35 patients were on PD (33.98%) and 13 patients received combined therapy (12.62%). For statistical clarity, the combined group were excluded from some analyses. The mean age of included patients was 40.5 years (SD 10.3 years). Patients were predominantly black African (n = 80; 77.7%) . Two patients were HIV positive at transplantation. The most common ascribed cause of ESRD in this series was hypertension (n = 59; 57.3%), 9 patients (8.7%) had ESRD due to glomerular disease of various types, 8 patients (7.8%) were diagnosed with abnormalities of the urogenital tract; 7 patients were diagnosed with diabetes mellitus (6.8%). Hypertension was the most common co-morbidity amongst patients (n = 39; 37.9%), although primary and secondary hypertension was not differentiated. In total, 88 renal grafts were from cadaveric donors (85.4%) and 15 were from living donors (14.6%).

Comparison of Baseline Characteristics at Transplantation by Dialysis Modality

The mean age of patients receiving HD (38.6 years) prior to transplant was non-significantly lower than those receiving PD (42.5 years, p = 0.66). There was no statistical difference in haemoglobin concentration (HD 11.9 g/dl, and PD 11.8g/dl) or phosphate levels (HD 1.4 mmol/l, PD 1.6 mmol/l) between dialysis modalities (p = 0.68 and p = 0.19 respectively); however, albumin levels were lower in PD (37.2 g/l) patients compared to HD (41.3 g/l) patients (Figure 1) (p = 0.002). Of the 55 patients who received HD as dialytic modality, 43 were of Black South African origin, whilst 12 were non-black (White, Indian or Coloured), and 34 were male and 21 female. Of the 35 who received PD, 27 were of Black South

African origin and 8 were non-black, 22 were male and 13 female. There was no statistical difference between dialysis modality by racial background or gender (p = 0.91 and p = 0.92 respectively). When the combined dialysis group is excluded for statistical clarity due to low numbers, 76 patients received kidneys from cadaveric donors (HD 43, PD 33), and 14 kidneys were from living donors (HD 12, PD 2). There is a statistical significant difference in the frequency of donor types (cadaveric donor vs living donor) by dialysis modality (p = 0.039). There was no significant statistical difference in the prevalence of either hypertension (HD 94.55% n = 52, PD 94.29% n = 33; p = 0.95) or diabetes mellitus (HD 3.64% n = 2, PD 11.43% n = 4; p = 0.14) by dialysis modality. Dyslipidaemia was defined, as per South African guidelines from 2018, as total cholesterol levels greater than 4mmol/l and/or LDL levels less than 1.8 mmol/l in very high risk patients (CKD KDIGO G2 and beyond being a very high risk criteria) (50). The prevalence of dyslipidaemia was higher in PD (22.86%, n = 8) patients than in HD (7.41%, n = 4) patients with a p-value that trended towards significance (Figure 2) (0.055).

Outcomes

DGF was more common amongst HD (65.45%) patients with 36 documented cases compared to 12 cases in those receiving PD (34.29%) (Figure 3) (p = 0.0049). Male gender (OR 1.84, p = 0.004), deceased donor (OR 2.99; p = 0.005) and HD (OR 2.22; p = 0.006) were all associated with an increased risk for the development of DGF (Table 2). Pre-transplant peritoneal dialysis did not affect risk of DGF (p = 0.12).

Multivariate analysis of variance using the Wilks lambda test showed no difference in graft function as indicated by eGFR at 3, 6, 12 and 60 months post engraftment between the various dialysis modalities (Figure 4) ($p = 0.33$). The mean eGFR for HD, PD and the combined group at 3, 6, 12 and 60 months is noted in Table 3. Multiple linear regression modelling revealed a negative effect for older age ($\beta = -0.38$, $p < 0.001$) and the development of DGF ($\beta = -0.35$, $p < 0.001$) on graft function at 3 months. Comparison of eGFR at 3 months post engraftment restricted to the PD and HD groups showed no statistically significant difference (Student t-test $p = 0.785$). Linear regression modelling for graft function at 60 months post-transplant indicated an effect for graft function at 3 months ($R^2 = 0.14$, $p = 0.001$), total number of rejection episodes ($R^2 = 0.11$, $p = 0.004$) and the development of chronic rejection ($R^2 = 0.16$, $p < 0.001$).

Acute rejection was more frequent in patients receiving PD (54.29%) than in those receiving HD (38.18%), although this did not reach statistical significance ($p = 0.19$). The frequency of patients developing chronic rejection was similar between patients receiving PD and HD (25.71% and 21.82% respectively, $p = 0.79$). There was no significant difference in number of rejection episodes by dialysis modality ($p = 0.222$). The above findings are summarised in Table 4. Patients receiving PD demonstrated poorer rejection-free survival than those receiving HD with a trend to statistical significance (Cox F-test $F = 1.633$, $p = 0.064$); rejection-free survival for the first 5 years after engraftment was significantly poorer in those receiving PD compared to those on HD (Cox F test $F = 1.863$, $p = 0.028$). Univariate Cox proportional hazards modelling suggested a shortened time to first rejection for patients receiving PD compared to those on HD (HR for PD 1.840, $p = 0.091$); restriction of the model to the first 5 years of engraftment demonstrated a significant role for PD as dialysis

modality in reducing time to first rejection episode (Figure 5) (HR 2.396, 95% CI 0.891 – 6.444, p = 0.024).

Multivariate Cox proportional hazards modelling was used to evaluate potential contributors to graft loss over time. Progressive refinement of the model identified time to first rejection (β 0.594 ± 0.242, p = 0.022) as a significant determinant of time to graft loss. Visual inspection of the correlation matrix for time to first rejection and time to graft loss (Figure 6) suggested, however, that the observed association was significantly affected by outlier effect. Although not achieving statistical significance in multivariate modelling (HR 2.194, p = 0.065), the presence of DGF in univariate survival analysis was associated with poorer allograft survival (Figure 9) (Cox Mantel test C = 2.335, p = 0.010). Progressive refinement of a logistic regression model was used to identify factors associated with the outcome of graft loss; in this analysis, only preceding diagnosis of acute rejection was found to be statistically significant (Wald's β 1.29, 95% CI 0.698 – 1.893, p < 0.0001). Consistent with this finding, Cox-Mantel testing failed to show a statistically significant difference in graft survival by dialysis modality (Figure 9) (C = -0.3844, p = 0.701).

Using a similar approach, Cox proportional hazards modelling was used to progressively identify factors influencing combined patient and graft outcomes. In this analysis, delayed graft function (Figure 9) and antecedent acute graft rejection contributed to increased risk of recipient death and / or graft loss (for DGF, HR = 3.118, 95% CI 1.716 – 5.662, p = 0.001; for acute rejection HR = 2.867, 95% CI 1.605 – 5.116, p = 0.001). Dialysis modality was not shown to affect the combined outcome of patient death and / or graft loss using Cox Mantel testing (Figures 7 & 8) (C = 0.336, p = 0.737).

Discussion

In 103 kidney transplant recipients with a comprehensive data set and follow-up of least 5 years after transplantation, antecedent haemodialysis increased the risk of delayed graft function, whereas antecedent peritoneal dialysis shortened the time (in months) to first documented episode of rejection. Although DGF and antecedent rejection were shown to affect a number of analysed outcomes (graft function at 3 months, time to first rejection, graft loss, and combined graft and patient loss), no direct effect for antecedent dialysis modality on any of these outcomes.

HD was the most commonly prescribed dialysis modality in this cohort (n = 55, 53.39%), with most recipients being male (n = 66, 64.07%) and of black African descent (n = 80, 77.67%). This is generally in keeping with data reported by the South African Renal Registry (SARR) in 2016, although the Registry has noted a slight preponderance of female patients (51%) receiving RRT in South Africa (2). Hypertension was the most common cause of ESRD in the present cohort in keeping with SARR data (2,8). The average age of recipients in this study was 40.5 years, consistent with the average age of recipients in the public sector reported by the SARR data of 41.5 years (2). Recipient age has been shown to be an important factor in predicting graft and patient survival; Goldfarb-Rumyantzev et al have demonstrated that each year of life adds 1% risk of graft failure and 4% risk of recipient death (12), however, analysis of the CMJAH data did not support these findings

Analysis of albumin levels at time of transplant demonstrated significantly lower levels in the PD group compared to the HD group (Figure 1) (37.24 vs 41.32, p = 0.002). This is common finding and is likely due to a combination of factors including chronic inflammatory states, increased albumin loss observed in PD and differences between artificial and physiological dialysis membranes(51). Living donors appeared to be more common amongst patients receiving HD (HD 13.33% vs PD 2.22%). The factors underlying this disparity are not clear from the available data. It is possible that analysis of this data was skewed by the relatively small number of living donor transplants undertaken; alternatively, the observed trend may reflect actual patterns in the larger recipient population. In the case of the latter, one might speculate that, since most state dialysis units preferably offer PD over HD, it is likely that patients receiving HD are those who have failed PD due to dialysis vintage or access loss. If this is the case, then deteriorating prognosis with respect to the perpetuation of dialytic therapy and/or patient fatigue with dialytic therapy may prompt relatives to pursue workup for donation.

Dyslipidaemia appeared to be more common amongst PD patients with a p-value tending towards significance (Figure 2) (p = 0.055). This may reflect increased total cholesterol and low-density lipid (LDL) levels in PD due to higher hepatic production of very low-density lipid (VLDL) and / or increased lipid clearance via the HD dialysis membrane (13,52).

Antecedent dialysis via HD, male gender, and transplantation with a cadaveric donor kidney increased the likelihood of DGF after engraftment. The increased risk of DGF in recipients receiving HD (Figure 3) has been reported in a number of studies comparing dialysis modalities (26–28,30,31,34,53) and has generally been attributed to better preservation of

native kidney residual renal function in PD patients (35). Other factors which are known to influence the development of DGF include cold and warm ischaemia time, HLA match and immunosuppression regimen (18).The former may underlie the association between cadaveric donor status and DGF in the present study; allograft retrieval from a cadaveric donor is more likely to be associated with an increased cold ischaemia time. In addition, significant cytokine release in such donors may result in allograft vasoconstriction, increasing the likelihood of DGF in this setting (20,30). Gender has not been traditionally identified as a risk factor for the development of DGF with the majority of studies finding no differences between males and females (16,22,46). A potential difference in underlying co-morbidities and/or transplantation related factors may account for the difference observed in this study. Of note, and consistent with other studies, in the CMJAH cohort DGF was observed to negatively influence graft survival (Figure 9). Poorer long-term graft outcomes in recipients experiencing DGF have been attributed to the chronic sequalae of acute kidney injury, as well as the immunological consequences of upregulated donor HLA antigen expression during allograft injury (54).

No significant effect for pre-transplant dialysis modality on graft function was observed in the present study (Figure 4), in keeping with the findings of other investigators (28,30,37,38). Early follow-up period graft function (at 3 months) was significantly dependent upon recipient age and the presence of DGF. Since delayed graft function represents acute kidney injury, graft function in the early post-engraftment period is likely to be strongly related to the extent of recovery from this injury and / or the severity of permanent fibrotic damage engendered during the injury process. The mechanisms underlying the negative association between recipient age and graft function at 3 months are less clear; potential mechanisms include a more potent immune response increasing the risk of undiagnosed rejection, poorer

compliance with immunosuppression, and increased rate of generation of urea and creatinine by virtue of better preserved muscle mass (28,37,38). Graft function at 60 months was found to be influenced by early graft function and the development of rejection – both total number of acute episodes and chronic rejection. It is noted that not all episodes of rejection will influence long term graft function, however, cumulative episodes, a lack of recovery of renal function with treatment and chronic rejection itself can influence graft function over time (47,48).

Whilst the incidence of acute and chronic rejection was similar between dialysis modality groups, the time to first rejection episode was noted to be shorter in the PD group (Figure 5). Previous studies have similarly found no difference in rejection episodes between dialysis modalities (28,34,37,38,44), however, Vanholder et al reported more rejection episodes in the PD cohort and suggested that the PD population is more immunocompetent (30). Chronic HD has been shown to impair the cellular immune response and studies of T-cell subsets have shown differences in allograft survival rates between HD and PD patients partly attributable to the persistence of immune integrity in the PD group (55). Data on the effect of dialysis modality on the time to development of rejection is limited with small studies investigating the influence of donor cytokine genotypes and donor macrophage activity (56,57). Whilst the mechanism underlying this observation in this study is unclear, a potential explanation may involve relative preservation of immune function in preserved and/or PD patients resulting in a shorter time to rejection as well as the higher frequency of living donors in the HD group.(living donors resulting in a reduced risk of rejection).

Time to first rejection episode in this cohort may predict graft survival after engraftment. Earlier development of rejection may limit long-term graft survival through the mechanism of progressive allograft injury due to compensatory mechanisms deployed by the injured graft in response to the rejection episode (58,59). Other factors, such as increased exposure to nephrotoxic calcineurin inhibitors in an attempt to control the recipient immune response may also contribute to this finding (60). However, visual inspection of the correlation matrix (Figure 9) suggests that selection bias may underlie the observed phenomenon. In this regard, the poorer survival of allografts diagnosed with DGF is of note. Whilst it may be that allograft injury during DGF shortens graft survival through the activation of compensatory mechanisms as outlined above, the possibility of DGF stimulating subclinical and hence unrecognised rejection cannot be fully excluded. Indeed, analysis of the CMJAH data indicates that preceding rejection is an important predictor of graft loss. Consistent with this finding, rejection and DGF were both found to be predictive of the combined outcome of graft and patient loss. This finding may indicate the interplay between DGF and rejection suggested above. In addition, the effect of these parameters on patient loss may hint at the effect of augmented immunosuppression in response to a diagnosis of rejection increasing the risk of patient death resulting from infection or accelerated cardiovascular disease.

Kaplan-Meier survival analysis showed no difference in graft survival or combined patient and graft survival by dialysis modality (Figures 7 & 8). This is in keeping with the majority of previously reported studies, including a large meta-analysis by Joachim et al (32). This is despite the observation that PD shortens time to first rejection episode, and the relationship between earlier rejection and graft loss. It is likely that the lack of a direct effect of dialysis modality on graft and/or patient outcomes in this study reflects the contribution of other confounding factors. Relevant factors which may not have been accounted for in the current

study as demonstrated by Legendre et al (54) include, HLA match, cardiovascular disease profile and time on dialysis.

Limitations

This study has several limitations. Restriction of the analysed cohort to a single transplant centre within Johannesburg precludes extrapolation to the national scale. Record keeping was a significant limiting factor; of the 144 patients that were transplanted in the determined time period, 41 were excluded on the basis of exclusion criteria, loss to follow up, inadequate data or transfer out of district. Some specifics of data collection were not available, namely duration of pre-transplant dialysis and duration of DGF, whilst other parameters were recorded but not in full detail. Underlying causes of ESRD were not always recorded, and in cases of ESRD ascribed to hypertension the distinction between hypertension as a cause or consequence of ESRD was not always clear.

Conclusion

Analysis of the CMJAH cohort suggests that HD confers a greater risk for the development of DGF, whilst PD shortens time to development of first rejection. The development of rejection, and the time to first documented episode thereof, negatively influence graft outcomes. The effect of rejection on later graft outcomes probably arises through multiple mechanisms, including accelerated graft senescence due to established damage with subsequent activation of systems which initially preserve GFR at the expense of further

fibrosis, ongoing subclinical rejection following partial treatment, and the potential nephrotoxic effect of immunosuppressants (such as the calcineurin inhibitors) used at higher dose following a rejection episode.. DGF was also shown to result in poorer graft survival; this may allude to interplay between DGF and subclinical or undiagnosed rejection in the early post-transplant period and its effect on long term graft survival. Pre-engraftment dialysis modality does not appear to directly affect graft outcomes in univariate analysis and could be attributed to other confounding factors such as time on dialysis, HLA matching and cardiovascular disease profiles not directly investigated in this study.

Tables

Table 1. Summary of Descriptive Data

	HD	PD	PD+HD	Total
Number	55	35	13	103
Black	43	27	10	80
Non-Black	12	8	3	23
Male	34	22	10	66
Female	21	13	3	37
Mean Age	38,55	42,51	0	40,51
Mean Haemoglobin Pre-Tx (g/dl)	11,93	11,78	0	11,7
Mean Albumin Pre-Tx (g/l)	41,32	37,24	0	40,35
Mean Phosphate Pre-Tx (mmol/l)	1,42	1,57	0	1,45
Cadaveric Donor	43	33	12	88
Living Donor	12	2	1	15
Hypertension	52	33	13	98
Diabetes Mellitus	53	31	10	94
Dyslipidaemia	50	27	10	87
HIV	0	1	1	2
DGF	36	12	5	53

Table 2. Factors influencing development of DGF

	OR	p
Male gender	1.84	0.004
Pre-transplant HD	2.22	0.006
Pre-transplant PD	0.61	0.12
Cadaveric Donor	2.99	0.005

Table 3. Summary of Graft Function by eGFR

Graft Function (ml/min/1.73m^2)	HD	PD	PD and HD
3 months	69,3	67,34	66,61
6 month	65,61	74,16	77,97
12 months	69,42	74,34	70,6
60 months	78,07	64,12	67,51

Table 4. Summary of Rejection (acute, number if episodes and chronic)

	HD (n=55)	PD (n=35)	p
Acute Rejection	21 (54.29%)	19 (38.18%)	0.19
Number of episodes			0.22
0	36	18	
1	9	7	
2	7	6	
≥ 3	3	4	
Chronic Rejection	12	9	0.79

Figures

Figure1. Pre-Transplant Albumin by Dialysis Modality

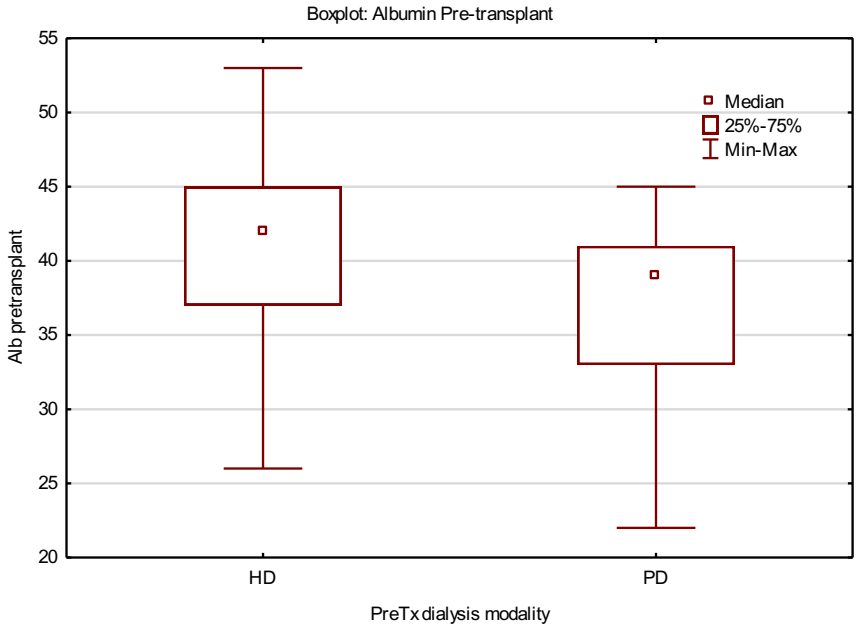


Figure 2. Prevalence of Dyslipidaemia by Dialysis Modality

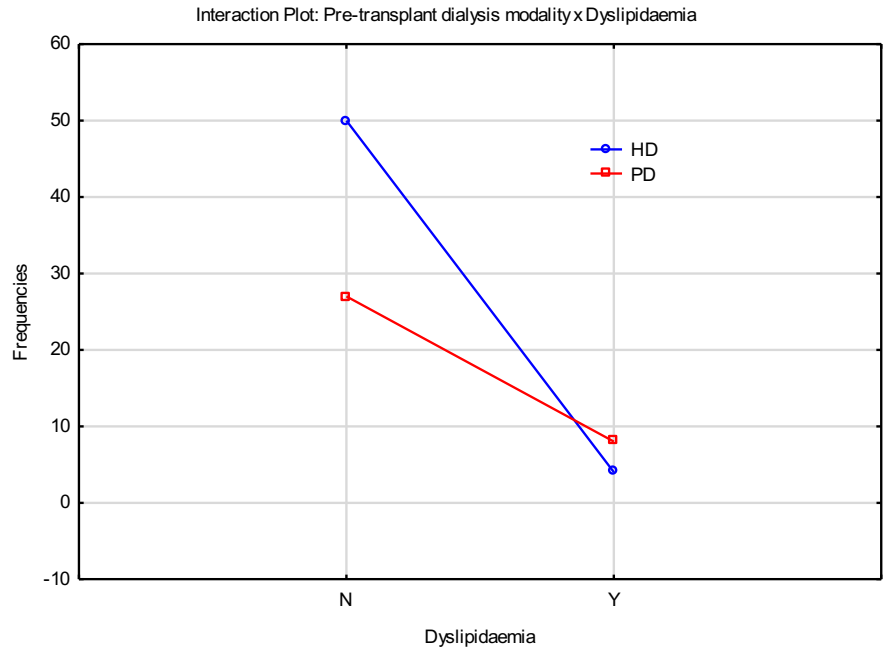


Figure 3. DGF by Dialysis Modality

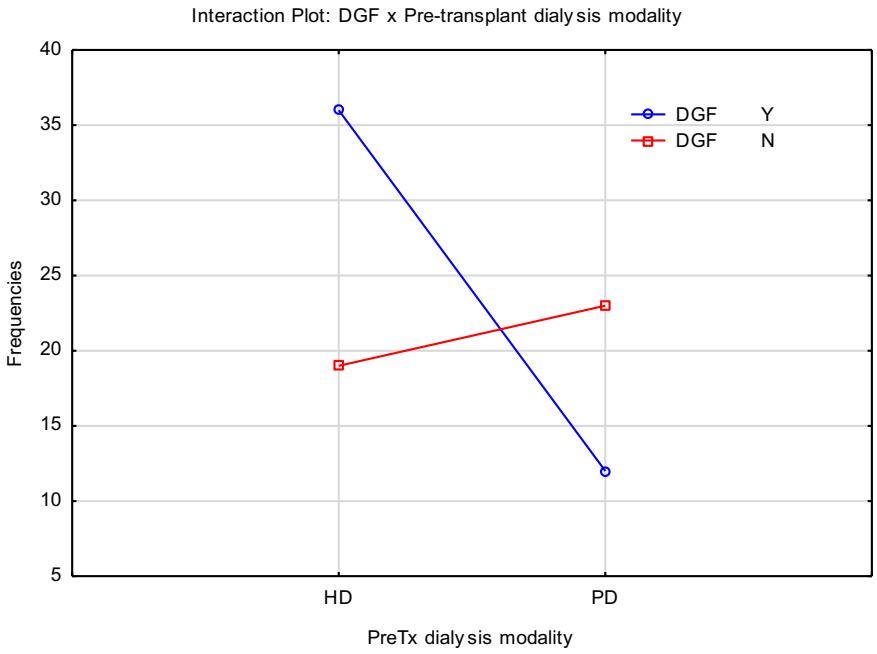


Figure 4. Graft Function by Dialysis Modality

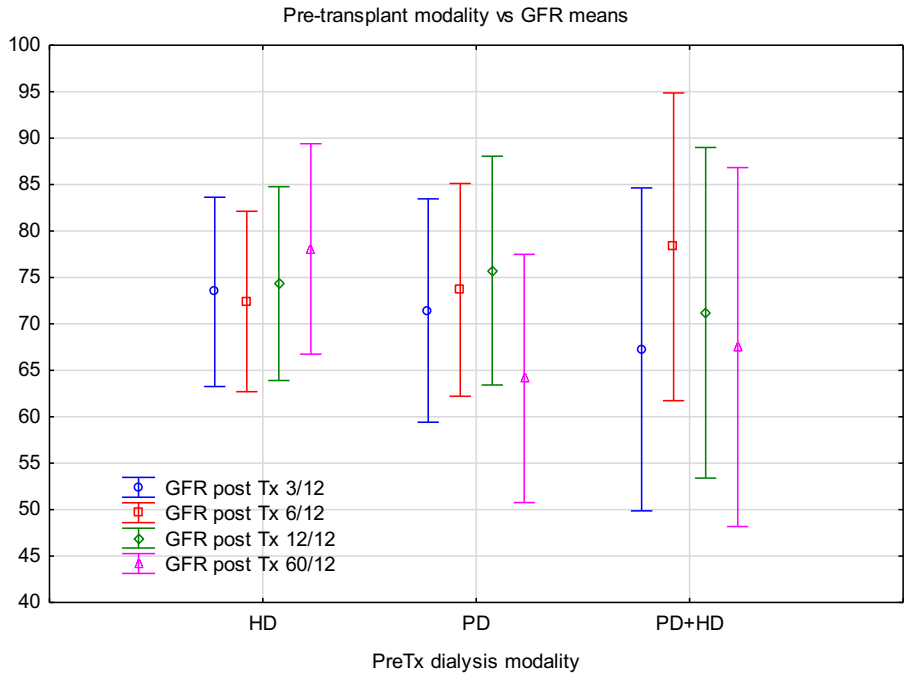


Figure 5. Kaplan-Meier survival graph demonstrating development of rejection by dialysis modality

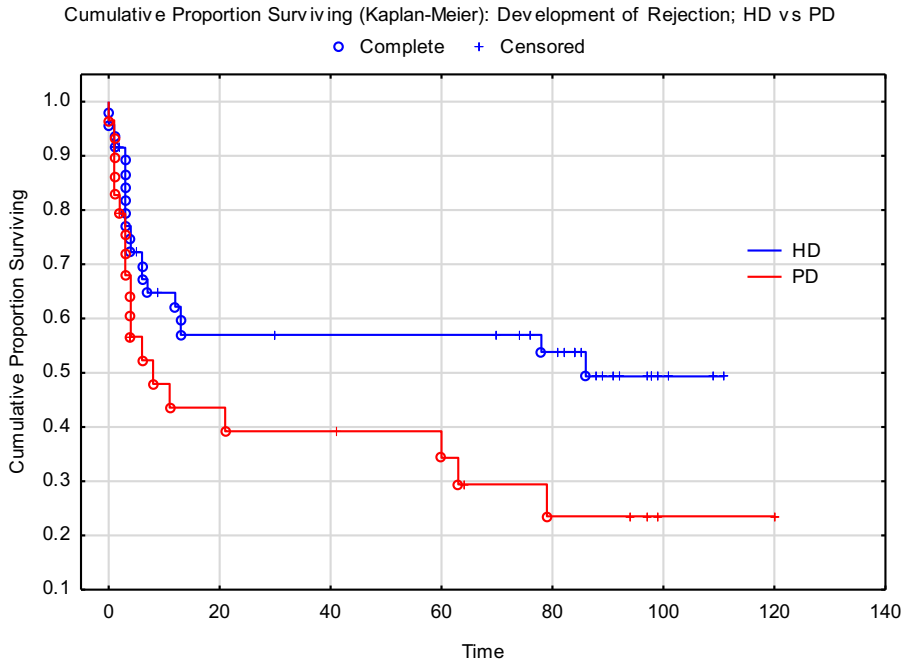


Figure 6. Correlation Matrix Plot for time to first documented rejection and graft loss

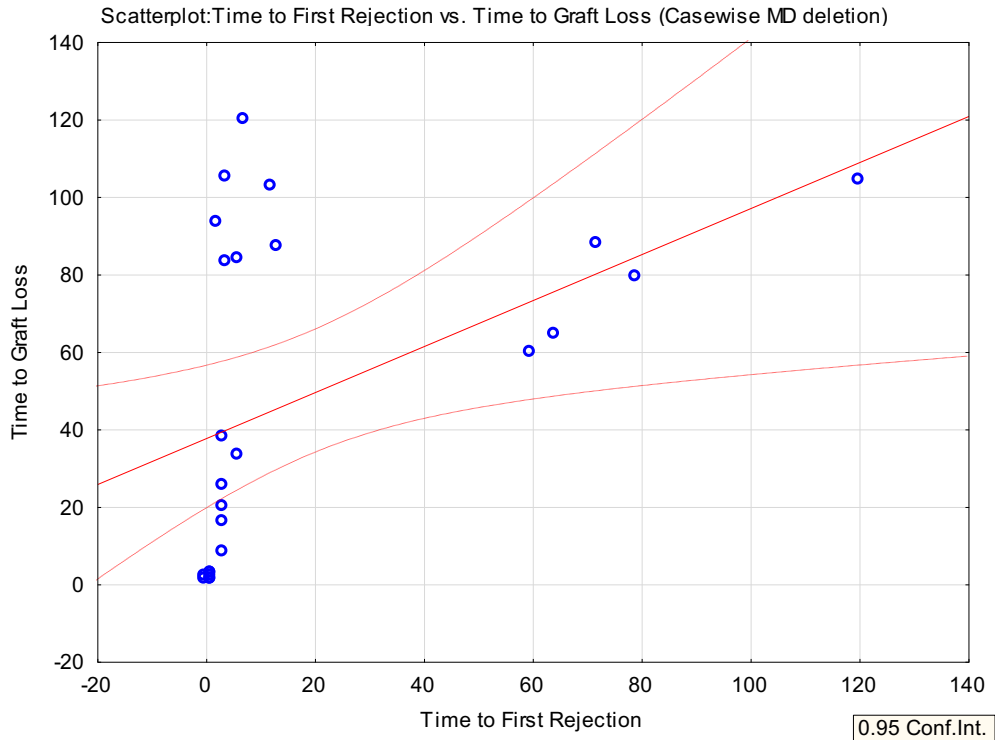


Figure 7. Kaplan-Meier survival graph comparing DGF and Graft Survival

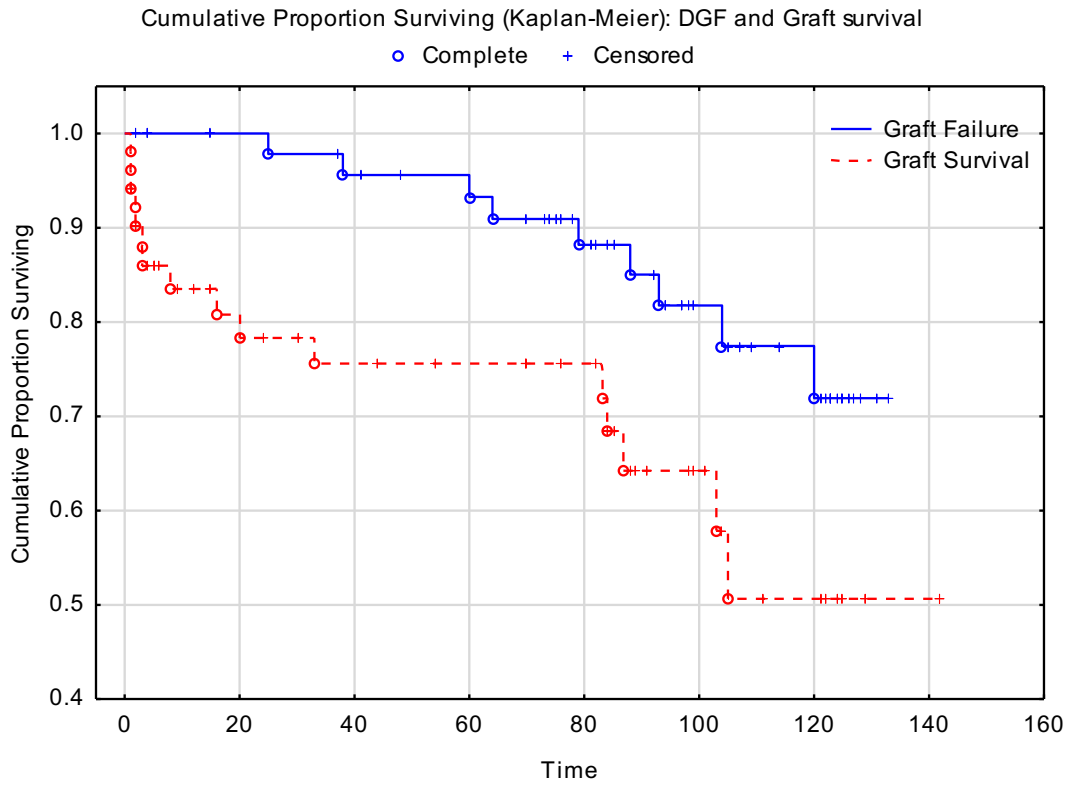


Figure 8. Kaplan-Meier graph demonstrating dialysis modalities effect on graft survival

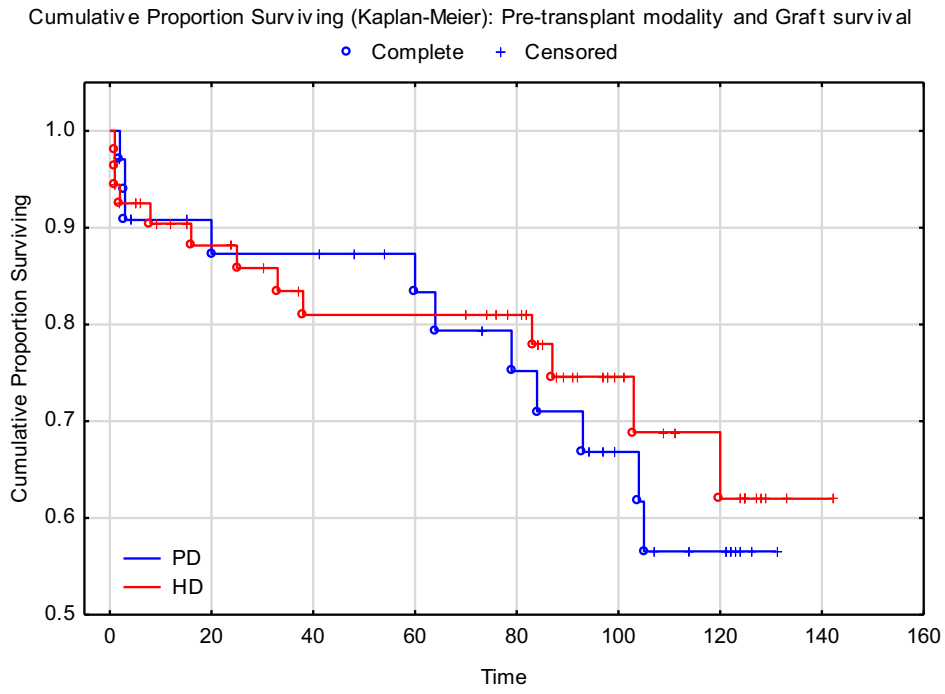
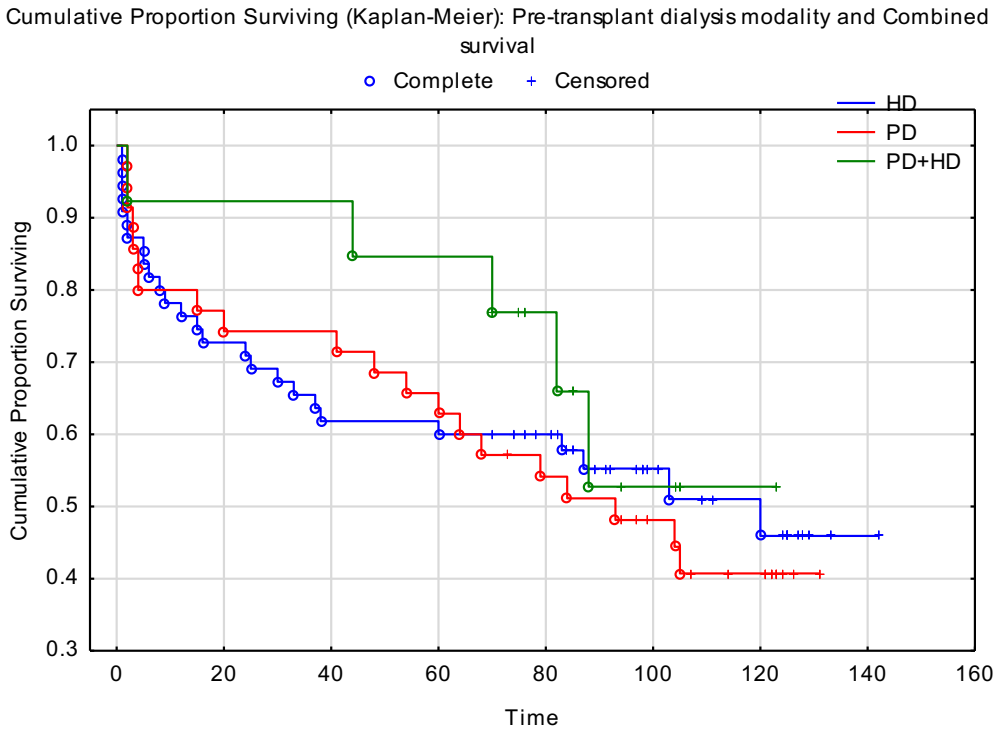


Figure 9. Kaplan-Meier graph demonstrating dialysis modalities effect on combined patient and graft survival



Reference – Manuscript

1. Muller E. Organ donation and transplantation in South Africa-an update: more about... general surgery. CME. 2013;31(6):220–2.
2. Davids MR, Jardine T, Marais N, Jacobs JC. South African Renal Registry annual report 2016. African J Nephrol. 2018;21(1):61–72.
3. Muller E, Thomson D, McCurdie F. Transplantation in South Africa. Transplantation. 2015;99(4):643–5.
4. Levey AS, Inker LA. Definition and staging of chronic kidney disease in adults. In: UpToDate. 2017.
5. KDIGO. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Vol. 3, Kidney International Supplements. 2013. p. 4–4.
6. Naicker S. Burden of end-stage renal disease in sub-Saharan Africa. Clin Nephrol. 2010;74 Suppl 1:S13–6.
7. Liu KD, Chertow GM. Dialysis in the treatment of Renal Failure. In: Harrison's Principles of Internal Medicine. 19th ed. 2015. p. 1822–6.
8. MR Davids, GK Balbir Singh NM and JJ. South Africa Renal Registry 2014. 2016.
9. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LYC, et al. Comparison of Mortality in All Patients on Dialysis, Patients on Dialysis Awaiting Transplantation, and Recipients of a First Cadaveric Transplant. N Engl J Med. 1999;341(23):1725–30.
10. USRDS Annual Data Report. Volume 2: ESRD in the United States. 2016;2(2):119–38.
11. Mehrotra R, Chiu YW, Kalantar-Zadeh K, Bargman J, Vonesh E. Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease.

Arch Intern Med. 2011;171(2):110–8.

12. Goldfarb-Rumyantzev AS, Hurdle JF, Scandling JD, Baird BC, Cheung AK. The role of pretransplantation renal replacement therapy modality in kidney allograft and recipient survival. Am J Kidney Dis. 2005;46(3):537–49.

13. Prichard SS. Impact of Dyslipidemia in End-Stage Renal Disease. J Am Soc Nephrol. 2004;14(90004):315S – 320.

14. López-Oliva MO, Rivas B, Pérez-Fernández E, Ossorio M, Ros S, Chica C, et al. Pretransplant peritoneal dialysis relative to hemodialysis improves long-term survival of kidney transplant patients: A single-center observational study. Int Urol Nephrol. 2014;46(4):825–32.

15. Mallon DH, Summers DM, Bradley JA, Pettigrew GJ. Defining delayed graft function after renal transplantation: Simplest is best. Transplantation. 2013;96(10):885–9.

16. Troppmann C, Gillingham KJ, Benedetti E, Stephen Almond P, Gruessner RWG, Najarian JS, et al. Delayed graft function, acute rejection, and outcome after cadaver renal transplantation: A multivariate analysis. Transplantation. 1995;59(7):962–8.

17. Samaniego M, Baldwin WM, Sanfilippo F. Delayed graft function: immediate and late impact. Curr Opin Nephrol Hypertens. 1997 Nov;6(6):533–7.

18. Ojo AO, Wolfe RA, Held PJ, Port FK, Schmouder RL. Delayed Graft Function: Risk Factors And Implications For Renal Allograft Survival. Transplantation. 1997 Apr;63(7):968–74.

19. Cosio FG, Alamir A, Yim S, Pesavento TE, Falkenhain ME, Henry ML, et al. Patient survival after renal transplantation: I. The impact of dialysis pre-transplant. Kidney Int. 1998;53(3):767–72.

20. Boom H, Mallat MJ, de Fijter JW, Zwinderman a H, Paul LC. Delayed graft function influences renal function but not survival. Transplant Proc. 2000;33(1–2):1291.

21. Quiroga I, McShane P, Koo DDH, Gray D, Friend PJ, Fuggle S, et al. Major effects of delayed graft function and cold ischaemia time on renal allograft survival. Nephrol Dial Transplant. 2006 Jun 1;21(6):1689–96.

22. Yarlagadda SG, Coca SG, Formica RN, Poggio ED, Parikh CR. Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis. Nephrol Dial Transplant. 2008 Oct 8;24(3):1039–47.

23. Van Biesen W, Vanholder R, Van Loo A, Van Der Vennet M, Lameire N. Peritoneal dialysis favorably influences early graft function after renal transplantation compared to hemodialysis. Transplantation. 2000;69(4):508–14.

24. Molnar MZ, Mehrotra R, Duong U, Bunnapradist S, Lukowsky LR, Krishnan M, et al. Dialysis modality and outcomes in kidney transplant recipients. Clin J Am Soc Nephrol. 2012;7(2):332–41.

25. Snyder JJ, Kasiske BL, Gilbertson DT, Collins AJ. A comparison of transplant outcomes in peritoneal and hemodialysis patients. Kidney Int. 2002;

26. Sezer S, Karakan S, Özdemir Acar FN, Haberal M. Dialysis as a bridge therapy to renal transplantation: Comparison of graft outcomes according to mode of dialysis treatment. Transplant Proc. 2011;43(2):485–7.

27. Binaut R, Hazzan M, Pruvot FR, Dracon M, Lelièvre G, Noël C. Comparative study of chronic ambulatory peritoneal dialysis versus hemodialysis patients after kidney transplantation: Clinical and financial assessment. Transplant Proc. 1997;29(5):2428.

28. Freitas C, Fructuoso M, Martins LS, Almeida M, Pedroso S, Dias L, et al. Posttransplant outcomes of peritoneal dialysis versus hemodialysis patients. Transplant Proc. 2011;43(1):113–6.

29. Bleyer AJ, Burkart JM, Russell GB, Adams PL. Dialysis modality and delayed graft function after cadaveric renal transplantation. J Am Soc Nephrol. 1999;10(1):154–9.

30. Vanholder R, Heering P, Van Loo A, Van Biesen W, Lambert MC, Hesse U, et al. Reduced incidence of acute renal graft failure in patients treated with peritoneal dialysis compared with hemodialysis. Am J Kidney Dis. 1999;33(5):934–40.

31. Joseph JT, Jindal RM. Influence of dialysis on post-transplant events. Clin Transplant. 2002;16(1):18–23.

32. Joachim E, Gardezi AI, Chan MR, Shin JI, Astor BC, Waheed S. Association of pre-transplant dialysis modality and post-transplant outcomes: A meta-analysis. Perit Dial Int. 2017;37(3):259–65.

33. Snyder JJ, Kasiske BL, Gilbertson DT, Collins AJ. A comparison of transplant outcomes in peritoneal and hemodialysis patients. Kidney Int. 2002;62(4):1423–30.

34. Bleyer AJ, Burkart JM, Russell GB, Adams PL. Dialysis modality and delayed graft function after cadaveric renal transplantation. J Am Soc Nephrol. 1999;10(1):154–9.

35. Lang SM, Bergner A, Marcel Töpfer, Schiffl H. Preservation of Residual Renal Function in Dialysis Patients: Effects of Dialysis-Technique–Related Factors. Perit Dial Int. 2001;21(January 2001):52–7.

36. Rottembourg J. Residual renal function and recovery of renal function in patients treated by CAPD. Kidney Int Suppl. 1993;40(43):S106–10.

37. Cacciarelli T V., Sumrani NB, Dibenedetto A, Hong JH, Sommer BG. The Influence of Mode of Dialysis Pretransplantation on Long-Term Renal Allograft Outcome. Ren Fail. 1993 Jan 7;15(4):545–50.

38. Helal I, Abderrahim E, Ben Hamida F, Zouaghi K, Ounissi M, Barbouche S, et al. Impact of Dialysis Modality on Posttransplantation Results in Kidney Transplantation. Transplant Proc. 2007;39(8):2547–9.

39. Auglienė R, Dalinkevičienė E, Kuzminskis V, Jievaltas M, Peleckaitė L, Gryguc A, et al. Factors influencing renal graft survival: 7-Year experience of a single center. Med.

2017;53(4):224–32.

40. Butler JA, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. Transplantation. 2004;77(5):769–76.

41. Smith AY, Van Buren CT, Lewis RM, Kerman RH, Kahan BD. Factors determining renal transplant outcome at the University of Texas at Houston. Clin Transpl. 1987;155–66.

42. Prommool S, Jhangri GS, Cockfield SM, Halloran PF. Time dependency of factors affecting renal allograft survival. J Am Soc Nephrol. 2000;11(3):565–73.

43. Kramer A, Jager KJ, Fogarty DG, Ravani P, Finne P, Pérez-Panadés J, et al. Association between pre-transplant dialysis modality and patient and graft survival after kidney transplantation. Nephrol Dial Transplant. 2012;27(12):4473–80.

44. Caliskan Y, Yazici H, Gorgulu N, Yelken B, Emre T, Turkmen A, et al. Effect of pre-transplant dialysis modality on kidney transplantation outcome. Perit Dial Int. 2009;29(SUPPL. 2):S117–22.

45. Schwenger V, Döhler B, Morath C, Zeier M, Opelz G. The role of pretransplant dialysis modality on renal allograft outcome. Nephrol Dial Transplant. 2011;26(11):3761–6.

46. Slizien A, Macuk A, Wolyniec W, Chamienia A, Niemierko M, Moszkowska G, et al. Influence of Dialysis Duration and Modality on Kidney Transplant Outcomes. Transplant Proc. 2009;29(3):S117–22.

47. Hart A, Smith JM, Skeans MA, Gustafson SK, Stewart DE, Cherikh WS, et al. OPTN/SRTR 2015 Annual Data Report: Kidney. Am J Transplant. 2017;17:21–116.

48. Cohen G, Hörl W. Immune Dysfunction in Uremia—An Update. Toxins (Basel). 2012 Oct 24;4(11):962–90.

49. Haggerty S, Roth S, Walsh D, Stefanidis D, Price R, Robert D, et al. Guidelines for Laparascopic Peritoneal Access Surgery. 2013;(May 2010):1–34.

50. Klug EQ. South African Dyslipidaemia Guideline Consensus Statement. South African Med J. 2012 Feb 23;102(3):178.

51. Yeun JY, Kaysen GA. Factors Influencing Serum Albumin in Dialysis Patients. Am J Kidney Dis. 1998;32(6):118–25.

52. Piperi C, Kalofoutis C, Tzivras M, Troupis T, Skenderis A, Kalofoutis A. Effects of hemodialysis on serum lipids and phospholipids of end-stage renal failure patients. Mol Cell Biochem. 2004 Oct;265(1/2):57–61.

53. Van Biesen W, Vanholder R, Van Loo A, Van Der Vennet M, Lameire N. Peritoneal dialysis favorably influences early graft function after renal transplantation compared to hemodialysis. Transplantation. 2000;69(4):508–14.

54. Legendre C, Canaud G, Martinez F. Factors influencing long-term outcome after kidney transplantation. Transpl Int. 2014;27(1):19–27.

55. Guillou PJ, Will EJ, Davison AM, Giles GR. CAPD—a risk factor in renal transplantation? Br J Surg. 1984;71(11):878–80.

56. Lan H, Yang N, Brown F, Isbel N. Macrophage Migration Inhibitory Factor Expression In Human Renal Allograft Rejection. Transplantation. 1998;66(11):1465–71.

57. Aldar N, Unce M, Orris P, Elsh K. Donor Cytokine Genotype Influences The Development Of Acute Rejection After Renal Transplantation. Transplantation. 2001;71(3):469–76.

58. Matas AJ, Gillingham KJ, Payne WD, Najarian JS. The Impact of an Acute Rejection Epsiode on Long-Term Renal Allograft Survival. Transplantation. 1994;57(6):857–9.

59. County H. Graft Function Reduces Kidney Allograft Survival. Transplantation.

2001;74(10):1400–4.

60. Incenti FL V, Ensik STCJ, Ilo ROSF, Iller JOM. A Long-Term Comparison Of Tacrolimus (FK506) And Cyclosporine In Kidney Transplantation : Evidence For Improved Allograft Survival At Five Years 1. Transplantation. 2002;73(5):775–82.

Appendix I - Data Collection Sheet

Patient study number:
_____
Age: _____
Gender: M F
Race: Black White
Coloured Indian
Donor: Cadaver Related
Living
PRA: _____
Cause of ESRD:
_____

HIV: Pos Neg Unknown
Pre-Transplant Dialysis Modality:

PD HD
PD+HD
Co-Morbidities:
HPT DM
Dyslipidaemia

RENAL FUNCTION

Time post transplant (months)	GFR (ml/min/1.73m2)
3	
6	
12	
60	

ALBUMIN

Time post transplant (months)	Albumin (g/l)
0 – At transplant	
3	
6	
12	
60	

HAEMOGLOBIN

Time post transplant (months)	Haemoglobin (g/dl)
0 – At transplant	
3	
6	
12	
60	

PHOSPHATE

Time post transplant (months)	Phosphate (mmol/l)
0 – At transplant	
3	
6	
12	
60	

ACUTE REJECTION EPISODES
Time to first rejection episode (months): _____
Total number of rejection episodes: _____

GRAFT FAILURE (Y/N)

Time post transplant (months)	Y/N
3	
6	
12	
60	

LIPID PROFILE

Total Cholesterol	
Triglyceride	
HDL	
LDL	

Appendix II – TurnItIn Report

Plagiarism software, TurnItIn, was used to review this dissertation. A similarity index of 38% was reported. This relates mostly to the use of standard definitions and referencing. All other similarities have been appropriately referenced.

TO WHOM IT MAY CONCERN

Re: TurnItIn Report: Dr Reece Boosi MMed: "The Influence of Dialysis Modalities on Post-Transplant Outcomes"

I have reviewed the TurnItIn report of Dr R Boosi's dissertation. The report identifies a similarity index of 38%. This mostly relates to the use of standard definitions and references. All other information that bears similarity has been appropriately referenced.

Yours sincerely.

Dr Malcolm Davies

HOD Nephrology

Internal Medicine

Helen Joseph Hospital

Supervisor

Appendix III – Ethics clearance certificate

R14/49 Dr Reece Boosi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170954

NAME: (Principal Investigator)	Dr Reece Boosi
DEPARTMENT:	Internal Medicine Renal Transplant Clinic Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	The Influence of Dialysis Modality on Post-Transplant Outcomes
DATE CONSIDERED:	29/09/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Malcom Davies
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	06/12/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review September and will therefore be due in the month of September each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES