University of Alberta

Impact of Donor and Recipient BMI Incompatibility on Graft Function after Kidney Transplantation

by

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Abstract: Renal transplant is the treatment of choice for people with end stage renal disease (ESRD) and long term survival, quality of life, and healthcare utilization after kidney transplantation is critically dependant on maintaining allograft function. One factor that may be an important predictor of post-transplant kidney function is the size match between donor and recipient, as it may represent the relationship between donor nephron mass and recipient demand. There have been a number of studies evaluating this, however the sum of the evidence is inconclusive. The overarching goal of this project is to define the importance of donor and recipient body size matching (specifically body mass index (BMI) matching) in renal transplant for graft function. **Methods:** This was a retrospective single-center cohort study, using an established renal transplant database which included all renal allograft recipients at the University of Alberta Hospital who received a transplant between January 2, 1990, and August 31, 2005. Data was collected at the time of transplant, monthly until 24 months post-transplant, and then every 6 months until death, graft loss, or loss to follow-up. Data included donor, recipient and transplantation characteristics previously reported to predict renal graft function and/or survival and with potential to confound or modify the effect of donor to recipient BMI ratio (D/RBMIR). In addition, creatinine was measured at each of the above time points. Multiple linear regression was used to determine the association between D/RBMIR and estimated glomerular filtration rate (eGFR) at 1 year, 3 years, and 5 years post-transplant, as well as annualized change in GFR. **Results:** eGFR at 1, 3, and 5 years after transplant increases as D/RBMIR decreases, however, the effect of D/RBMIR on eGFR is no longer statistically significant when the effect of recipient BMI is taken into account. D/RBMIR is not associated with annualized change in eGFR. Patients with higher BMI have higher eGFR at 1, 3 and 5 years post-transplant and have slower loss of eGFR over time, even after adjusting for eGFR at 1 year post-transplant (which did not predict slope). **Conclusions:** In summary, this project has demonstrated that recipient BMI is an important predictor of graft function after renal transplantation, and likely leads to hyperfiltration that can result in glomerulosclerosis and chronic allograft nephropathy, consistent with previously published data. A novel finding is that this effect is independent of the match between donor and recipient BMI, suggesting that the latter is not as important as previously suggested. Contrary to popular thought, D/RBMIR at transplant only predicts graft function when recipient BMI is not considered.

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1. CHAPTER ONE: INTRODUCTION

Renal transplant is the treatment of choice for people with end stage renal disease (ESRD) and long term survival after kidney transplantation is critically dependant on maintaining allograft function. Not only is survival affected by graft function but also quality of life and health care utilization. Renal allograft failure is one of the most common causes of ESRD, accounting for 25% to 30% of patients awaiting renal transplantation, and over 20% of kidney transplants performed go to patients who have failed one or more renal allografts. One of the primary goals in the care of people post-transplantation is the maximization and stabilization of long-term graft function. There has been a dramatic reduction in the rate of early allograft failure in the recent decade; further improvement in transplant outcomes has significant dependence on our ability to improve long-term graft function.

There have been numerous studies, both small observational studies and large database studies, evaluating the various factors predictive of long term graft outcome. These studies have provided useful data not only to predict long term graft outcomes but also influence decisions related to both pre- and post-transplant medical management of the recipient. Many of these variables are characteristics of the donor and recipient which cannot be manipulated but there is increasing thought that matching donor and recipient characteristics may be important. Donor-recipient matching is something that clinicians and administrators in renal transplant organizations have control over, even in deceased donor transplant; the acceptance of an organ for a particular recipient is decided by algorithms that take into account an understanding of the balance of risk factors for both graft function and graft and patient survival. Decisions related to donor and recipient matching also have very large implications for organ allocation and hence the time people must wait for a renal transplant. The more that is understood about the complex interplay between donor and recipient factors, the better equipped decision makers will be to positively influence not just patient and graft outcomes but also organizational matching processes.

The overarching goal of this project is to define the importance of donor and recipient body size matching (specifically body mass index (BMI) matching) in renal transplant for long term graft function. Outcome studies in renal transplantation are complex as they

must take into account the multitude of potential confounders for the primary relationship being assessed as well as measure outcomes over a meaningful duration of time. In addition, assessment of graft function over the long term is variable both in the clinical and research setting and valid outcome measurement is critical for meaningful associations to be determined. This project will assess the importance of donor to recipient BMI matching in light of these complexities.

There is a current theory that the size of the donor relative to the recipient influences how well a renal graft works post-transplant. The ratio of body sizes is thought to be a surrogate for the amount of nephrons donated relative to the size of the recipient and that if there is not adequate graft mass for the size of the recipient, the function of the transplanted organ is negatively affected.

In order to develop specific research questions and associated analytical methodology to address this theory and achieve the above stated goal of this project, a large body of background information needs to be understood. This includes the measurement of renal graft function, the etiology of long-term renal graft failure, the potential relationship between known predictors of graft function with body size, body size match between donor and recipient, and the theory of nephron dosing. Lastly, the current evidence related to body size matching at transplant and renal graft outcome needs to be reviewed. Chapters 2 and 3 that follow will provide this background information.

2. CHAPTER TWO: BACKGROUND

2.1 Measurement and epidemiology of long-term renal allograft function

The Assessment of Lescol in Renal Transplantation (ALERT) trial was a prospective randomized controlled interventional clinical trial which followed 2000 renal transplant recipients for 6 years post-transplant [1]. The allograft was lost in 14%, with the predominant identified etiology being an incompletely understood clinicopathological entity variously called chronic rejection, transplant nephropathy, chronic renal allograft dysfunction, transplant glomerulopathy, chronic allograft injury, or chronic renal allograft nephropathy, discussed below.

Although graft failure as an outcome in renal transplantation is an important one, it is important to evaluate other measures of outcome that have important clinical and quality of life implications. Two such measures are overall graft function and change in function over time. Inulin clearance is considered the gold standard to determine glomerular filtration rate (GFR) however its measurement is cumbersome and time consuming. Several radiopharmaceutical isotopes are useful tools for measurement of GFR and have been used as reference methods in a large number of studies [2]. They are not however used routinely clinically. Current methods to assess allograft function in a clinical setting are often limited to measurements of proxies for GFR such as serum creatinine (Cr), inverse serum Cr, slopes, and mathematically estimated GFR. Serum Cr is a commonly used measure of native kidney and graft function, however on its own is relatively imprecise. There are a number of estimation equations that have been developed to improve the precision of renal functional assessment using serum Cr [3, 4]. The 2 most common equations used clinically are the Modification of Diet in Renal Disease-2 (MDRD2) and Cockcroft-Gault (C-G). Assessment of graft function by estimation equations is considered a relevant end point in clinical trials and in routine follow-up of renal transplant patients [5]. These equations were however derived from other populations, which brings to question the validity of using them in the renal transplant population.

Raju et al. have detailed the precision, bias, and accuracy of various prediction equations in renal transplant, both in the total population and also in various subgroups [4]. Diethylene triamine pentaacetic acid (DTPA) isotope determined GFR was used as the reference standard. MDRD2 and C-G had similar precision (between subject variability) in

the transplant population as a whole and also in subgroups defined by estimated glomerular filtration rate (eGFR) (≥ 50 ml/min vs. < 50 ml/min) and BMI (≥ 25 kg/m^2 vs. < 25 kg/m^2). C-G had less bias (portrays the degree to which predicted values, on an average, differ from observed values) and more accuracy (degree to which variable represents what it is supposed to represent) than MDRD2. Analysis of the above subgroups also demonstrated that C-G performed better in terms of bias and accuracy in all with the exception of those with a eGFR <50ml/min). In general, C-G showed a tendency to overestimate GFR at all accuracy ranges and MDRD2 tended to underestimate GFR. In the subgroup analysis, the C–G overestimated and underestimated GFR by 10% and 14%, respectively, in patients with a BMI <25 kg/m^2. In patients with a BMI of 25–30 kg/m^2 the C–G equation over- and underestimated GFR by 22% and 6% respectively. In patients with BMI above 30 kg/m^2, the C–G over- and underestimated GFR by 34% and 11% respectively.

Analysis of pooled data from large transplant databases evaluating the long-term deterioration of kidney allograft function have found no difference in magnitude or significance of associations between tested predictive factors and rate of change of eGFR when C-G estimation was used in place of MDRD as the proxy measure of GFR [6]. However, several studies have evaluated the performance of C-G estimated slopes relative to rates of change determined by radio-isotope determined GFR in the renal transplant population and have demonstrated low precision and accuracy of eGFR slopes [7, 8]. Results from a recent study have demonstrated significantly better performance of estimated slopes after normalization of C-G eGFR 1.73 m^2 to body surface area (BSA). After normalization, the estimated variability in annual changes from C-G eGFR for the whole data set was not significantly different from isotope determined GFR annual change; i.e., the slope from isotope determined GFR was not significantly different that the C-G slope in the overall population [9]. There was no evidence of a difference in the performance of MDRD estimated slope or C-G estimated slope. Rostoker and colleagues sought to validate the improvement by adjustment for BSA of the accuracy of the original C-G equation to estimate GFR in a prospective study of 269 patients with chronic kidney disease (CKD) [10]. They demonstrated that inulin clearance differed significantly from the standard C-G method (and from MDRD2 eGFR) but not for the BSA-modified C-G formula. Inulin clearance correlated better with BSA-adjusted C-G eGFR than with standard C-G eGFR and in concordance studies, bias was far smaller with the BSA-

modified formula than with standard C-G eGFR; the bias of the MDRD2 was larger. Hence adjustment for 1.73 m^2 BSA appears to improve the accuracy of the original C-G estimation for GFR [10].

Monitoring changes in GFR is the recommended method for assessing the progression of CKD [11]. In native kidney disease the rate of change in eGFR over time has been used to predict those who will reach renal failure and also as an outcome measure for evaluating the effect of intervention [11-13]. Progressive CKD in native kidney disease is represented by a change in eGFR over time that ranges between 0 and 13 mls/min per year [14-16]. Clinical guidelines have characterized kidney transplant recipients as high risk of progressive loss of kidney function [11]. Several large retrospective studies within the current immunosuppressive era have described the epidemiology of long-term graft dysfunction [6, 17, 18]. Gill et al. described the annualized change in eGFR in over 40,000 renal transplant recipients [17]. Using data from the United States Renal Data System (USRDS), they studied all adult first, kidney-only transplant recipients between 1987 and 1996 with at least 2 years of allograft survival. Patients were followed for a mean of 5.7 (SD 2.3) years post-transplantation. Thirteen percent returned to dialysis or received repeat transplants and 11% died with allograft function. Annualized change in eGFR for each person was determined by applying linear least squares regression to all available eGFR estimates (by MDRD; median number of estimates 5) beginning 6 months post-transplant. Six months post-transplant, mean eGFR was 49.6 (SD 15.4) ml/min per 1.73 m^2. Annualized change in eGFR was -1.66 (SD) 6.51 ml/min per 1.73 m^2 per year. Thirty percent of patients had improvement in eGFR, 20% had no change, and 50% had a decline in eGFR. As a methodological note, results from goodness of fit tests demonstrated that the performance of more complex piece-wise linear regression (using the annualized change in GFR before and 2 years post-transplant) was similar to that from the linear least squares regression.

Analysis of pooled data (5 North American transplant centers) from a large number of kidney only transplants between 1984 and 2002 also evaluated trends in long-term kidney allograft function using annualized change in eGFR. Annualized change was determined as the slope from simple linear regression applied to eGFR measurements at months 1, 3, 6, 9, 12 and annually until failure or loss to follow-up. Both MDRD and C-G were used as estimation equations. Three different slopes were determined, starting at month 1,

month 6 and month 12. Mean number of eGFR used for slope calculation after 1 month, 6 months, and 12 months respectively were 9.3, 7.1, and 6.2. There was little change in the means of eGFR at different times after transplant. Slopes were significantly steeper among patients who required re-transplantation or returned to dialysis. For patients surviving more than 6 months post-transplant, mean annualized change in eGFR (standard deviation (SD)) was -0.5 (11.5) ml/min/1.73m^2/year (n=5495), -0.5 (14.2) ml/min/1.73m^2/year (n=1424), and -11.2 (25.4) ml/min/1.73m^2/year (n=1762) for those who remained alive, died, or required re-transplantation or return to dialysis, respectively [6].

2.2 Etiology of long-term graft dysfunction and failure

Chronic allograft nephropathy (CAN) is well recognized as the most common cause of graft failure after the first year post-transplant within the current immunosuppressive era. It clinically presents as a gradual deterioration in graft function, manifested by a slowly rising Cr concentration, as well as increased proteinuria and blood pressure. Histopathologic evidence of chronic nephropathy correlates with adverse long-term outcomes, including elevated concentrations of serum Cr and lower rates of graft survival. For example, Grinyo et al. demonstrated that early evidence of CAN by protocol biopsy in people with stable graft function (as defined by serum Cr concentration) is associated with long-term graft survival; at 10 years after surgery, allograft survival was 95%, 82%, and 41% among those without CAN, with CAN but without vasculopathy, and with both CAN and vasculopathy, respectively [19]. Overall, it is a poorly understood process but has diagnostic features on biopsy which involve all parts of the renal parenchyma including the blood vessels, glomeruli, interstitium, and tubules [20-22], and ends in accelerated glomerulovascular sclerosis.

2.2.1 Glomerular hyperfiltration and hypertrophy

The glomeruli hypertrophy and increase their filtration rate after transplantation, since the graft contains only about one-half the number of nephrons as two normal native kidneys. There is an attractive non-immunological hypothesis linking the decline in graft function and survival to hyperfiltration due to nephron under-dosing relatively pervasive in the literature [23]. This hypothesis is that the imbalance between nephron mass and

recipient size triggers glomerular enlargement, glomerulosclerosis and progressive renal failure. In some patients, the glomeruli in the transplant show areas of focal segmental glomerulosclerosis, predominantly in larger glomeruli, suggesting that the hypertrophic response to too few nephrons and the associated intraglomerular hypertension eventually injure the glomerular capillary wall [23-26].

The hypothesis has been supported by a number of studies both in animals and in humans. In rats, diminished grafted nephron mass is associated with higher levels of single nephron GFR and progressive proteinuria as well as structural injury; these effects are virtually absent in rats with increased kidney mass [26]. In humans, it has been shown that glomeruli enlarge during the first 4 months after transplant in renal allografts, with glomerular volume increasing on average by 20% [27], and glomerular size in early protocol biopsies has been associated with graft outcome [28]. Alperovich and colleagues have shown that Cr clearance (CrCl) at the time of protocol biopsy was associated with glomerular volume; between 4 and 6 months post-transplant, higher glomerular volume was associated with higher CrCl [29]. They postulated that this reflected an appropriate and beneficial adaptation in the renal allograft. However, they did not consider the long term impact of such "adaptation".

A small study (n=82) in live donor transplant confirmed the potential maladaptive effect of a small kidney weight to recipient weight ratio, demonstrating an increased incidence of proteinuria as the ratio decreased [30]; proteinuria is considered a marker of hyperfiltration and generally considered as a predictor of poor renal outcome. In a later study of living donor transplants, urine protein excretion was shown not to directly correlate with the graft weight but rather correlate with the ratios of graft weight to the parameters of recipient's metabolic demands (body weight, height, BSA, lean body weight, and BMI), associations which persisted after multivariate analysis [31]. The magnitude of the kidney weight to recipient weight incompatibility may be significantly associated not only with sustained hyperfiltration and early proteinuria but also with an increased risk for hypertension, a higher risk of glomerulosclerosis, and a significantly poorer long-term transplant survival [32]. It is possible that sustained "adaptive"

hyperfiltration, which may be more marked with incompatibility in size between the graft and the recipient, results in significantly poorer long-term graft outcome.

Hyperfiltration theory alone does not likely explain all of the relationship between relative nephron-underdosing and graft function and outcome. After uni-nephrectomy, glomerular volume increases by a factor of two-fold, but glomeruli usually do not develop sclerosis. In biopsies after the second year post-transplant, glomerulosclerosis is associated with glomerular volume enlargement of 250%, and the glomerular volume threshold for glomerulosclerosis after transplant is smaller than in native kidneys [24]. That the critical volume threshold for glomerulosclerosis is lower in transplanted than native kidneys suggests that there is an interaction with other factors not present in the native state.

There is likely a critical nephron mass needed to meet the metabolic demand of an individual, which depends on body size. It is clear that various clinical risk factors predispose to a more rapid rate of chronic graft loss and that these are likely to be additive with a final pathway of accelerated glomerulovascular sclerosis initiated when a critically low level of functioning nephrons is reached. The following discussion will outline some of the important known predictors of graft function and highlight their potential relationships with body size, body size match between donor and recipient, or the theory of nephron dosing.

2.3 Factors associated with long-term renal allograft function and survival

2.3.1 Immunological factors – HLA matching and sensitization

It is evident that immunological factors including acute rejection episodes have a role in long-term graft outcome. Long-term graft survival is generally measured in terms of the half life, which is defined as the time beyond the first year post-transplant at which 50% of grafts are no longer functioning. The half-life of better-matched renal allografts is longer than those for less well matched deceased donor grafts. In randomly human leukocyte antigen (HLA) matched grafts, the course is an exponential loss of functioning grafts, with a half-life of 7 to 8 years. Matching for HLA antigens has a major impact on this process, with half-lives of 20 years with deceased donors matched to recipient by

HLA-A, HLA-B, and HLA-DR [33]. Antibodies against HLA are found in subjects before transplantation who have been immunized to these glycoproteins by sensitization events such as pregnancy, blood transfusion, or a prior transplant. Panel reactive antibody (PRA) measures this degree of sensitization to lymphocyte antigens. As the PRA increases, there is an incremental increase in the risk of graft loss, and the presence of PRA against HLA antigens before transplantation is associated with early loss of grafts from deceased donors [34]. Transplants from HLA-identical sibling donors do not provide a target for antibodies to HLA antigens and therefore should not be affected by PRA. However, it is now evident that non-HLA immunity also appears to have an independent role in chronic graft loss. Evidence for this comes from a study of over 4000 recipients of HLA-identical sibling transplants in which patients with no PRA had significantly higher 10 year survival (72%) versus those with either 1% to 50% PRA (63%) or greater than 50% PRA (56%) [35]. This effect became apparent after the first post-transplant year and was, therefore, different from the early decline in graft survival associated with PRA in recipients of deceased donor kidneys. Further evidence for the importance of non-HLA immunity was further supported by a large, prospective study of 2231 patients with 2 years of follow-up which demonstrated that the presence of non-HLA antibodies correlates with decreased graft survival [36]. Multivariate analysis of United Network for Organ Sharing (UNOS) data demonstrates that matching at the rhesus (Rh) blood group antigen, a non-HLA antigen, is significantly related to better graft outcome (risk ratio 0.43) [37]. The above observations support that both HLA matching and PRA have both independent and interactive roles in determining longer-term graft function.

2.3.2 Immunological factors – rejection

Studies have documented the prognostic importance of acute rejection episodes in the development of CAN and late allograft loss. Patients with a history of acute rejection episodes are more likely to have late allograft failure [38-42]. Since the introduction of newer immunosuppressive agents over the last 2 decades (e.g., mycophenolate mofetil (MMF), tacrolimus and cyclosporin) acute rejection rates have decreased, however, the incidence of long-term failure has not decreased as dramatically. This suggests that the impact of rejection on graft function and survival is changing. It has been shown, using 63,045 primary renal transplant recipients reported to the USRDS from 1988 to 1997, that the impact of acute rejection on chronic allograft failure has significantly increased

over time, independently of known confounding variables [39]. The incidence of CAN is less than 1% in patients who have had no episodes of acute rejection [41]. By comparison, in live donor transplant, the incidence of CAN in patients with a history of acute rejection is 20% if rejection occurs within 60 days of transplant or 43% if rejection occurs after 60 days post-transplant. In deceased donor transplant these incidence rates increase further to 36% and 60%, respectively. This increased incidence of CAN is associated with a worse long-term renal outcome in grafts surviving for more than one year. When compared to patients with no acute rejection, those with episodes of acute rejection have a significant reduction in CrCl 1 to 5 years after transplantation (45 to 47 ml/min versus 54 to 60 ml/min) and a significant reduction in the estimated half-life of graft survival (6.6 versus 12.5 years) [43].

Immunological clinical correlates of a more rapid decline of graft function over time are similar to those of graft failure; the number of HLA mismatches, presence of panel reactive antibodies, and occurrence of acute rejection all significantly predict a more negative slope for annualized change in eGFR [6, 17].

2.3.3 Graft mass and the immune system

Although hyperfiltration theory has been postulated as a possible mechanism to explain the effect of grafted mass on outcomes, there may also be an interaction between nephron mass and immune system. Quantity of relative renal mass may be not only an important independent determinant of the tempo and intensity of chronic renal allograft failure, but also an effect modifier in relation to immunological factors. Findings of several studies point to a greater rejection rate in patients transplanted with reduced kidney mass, such as those from elderly donors, single pediatric grafts, and in female donors to male recipients [44-48]. The ratio of donor kidney weight to recipient BMI has been shown to have a significant association with incidence of acute rejection within the first year after transplantation [49]. In addition, when data is stratified according to surrogate indices of nephronal mass (e.g., pediatric on block donors vs. young donor (5 to 40 yrs) vs. old donors (>55years), it appears that the greater the mass, the lower the incidence of both acute and chronic rejection [50]. Donor gender, which may be a surrogate for nephron mass, has not been shown to influence graft outcome when the recipient is HLA

identical or when there is a combined 0 or 1 antigen mismatch at the HLA-B and HLA-DR loci [51]. These observations have led to the hypothesis that a large mass of transplanted tissue relative to recipient mass may dampen the immune response.

Experimental renal transplant animal models show that renal mass has a direct and independent effect on cellular and molecular determinants of antigen dependant injury. Azuma and colleagues examined the effect of manipulating nephron mass on antigen dependant injury in a rat model and correlated functional alterations with cellular and molecular events in the graft, focusing on macrophages, their chemo-attractants, and macrophage products (cell population thought to be critical in "chronic rejection") [52]. They observed that the intensity profiles of macrophage infiltration were modulated by renal mass; the more renal mass supplied, the more the onset of significant cell infiltration was postponed and its incremental progression reduced. Increase grafted mass also reduced T-cell infiltration and expression of major histocompatibility complex (MHC) class II, intercellular adhesion molecule (ICAM), and a variety of macrophage associated cytokines and growth factors. At early time points in the progression of chronic rejection, before the development of proteinuria and other indices of injury, increased renal mass had a profound attenuating effect on macrophage chemoattractants, intracellular adhesion molecules and endothelin expression. Loss of renal mass resulted in the opposite effect. It is postulated that hyperfiltration/hypertrophy associated with reduced grafted nephron mass leads to glomerular capillary hypertension and hyperperfusion with resulting endothelial cell expression of adhesion molecules and endothelin production. Endothelin promotes mesangial cell proliferation and is a prothrombotic agent, which can lead to further increased glomerular pressure and stimulation of endothelial and mesangial production of cytokines (tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6)). A cytokine gradient adjacent to vessel wall promotes mono cell adherence and infiltration into the glomerulus, vessels and interstitium and increased expression of MHC II antigen. An additional observation from the rat model is that MMF is able to decrease the progressive injury which occurs after nephron loss in the rat [53]. This may result from the ability of MMF to inhibit endothelial adhesion molecule expression and thus the inflammatory response to injury. These mechanisms could be seen as the interface between antigen-dependant and antigen-independent injury mechanisms.

2.3.4 Living versus deceased donor

Living donor kidney transplants have a greater long-term graft survival rate than deceased donor kidneys. Recent data from the Scientific Registry of Transplant Recipients shows 5-year graft survival rates for living donor, non-extended criteria deceased donor, and extended criteria deceased donor kidneys of 81%, 71%, and 55%, respectively [54]. A number of large studies have also evaluated the relationship between donor source and rate of change in allograft function over time and demonstrate a more rapid decline in patients who have received a deceased donor kidney [17].

The difference likely reflects the optimal circumstances surrounding living-related donation compared with higher potential for tissue injury during deceased donor transplant. Patients with significant tissue injury at the time of transplant (induced by brain death, cold ischemia time (CIT), or ischemia and/or reperfusion as examples) are at significantly higher risk of developing CAN and late allograft loss [55]. Brain death is associated massive release of catecholamines which causes profound vasoconstriction and endothelial injury coupled with a procoagulant state resulting from endothelial activation, release of cytokines, complement activation, and depletion of tissue plasminogen activator [56-58]. Cardiac arrhythmias and rapid fluctuations in blood pressure are common in the setting of brain death. Such factors may obviously adversely affect the function and integrity of the kidney. Ischemia and/or reperfusion injury is thought to be a critical risk factor for both early and late graft dysfunction; the incidence of this complication is highest when the CIT exceeds 18 hours, particularly with older donor kidneys [59, 60]. Circumstances surrounding organ removal, storage, and engraftment may also increase graft immunogenicity [58, 61-63]. The effects of early tissue injury on graft outcomes are felt to be mediated in large part by the increased risk of organ rejection that occurs due to upregulation of the immune system from injury-induced inflammation [58]. As shown in some [64-66] but not all [67] studies , injury alone may not influence graft survival in the absence of rejection; in over 9000 transplants analyzed from the United Kingdom national transplant database, damage recognized at organ retrieval or placement was not significantly associated with survival at three years [67].

2.3.5 Donor and recipient gender

It has been noted for a considerable time that renal grafts have better functional prognosis in female than male recipients and single center studies have documented inferior short-term and long-term graft survival when kidneys from female donors are transplanted into male recipients [68-70]. The idea of nephron underdosing has been proposed to explain these observations; with the postulate that female kidneys contain fewer nephrons thereby increasing the workload on the individual nephrons. There is however good evidence that organ-unrelated effects of donor gender on immune recognition and/or immune effector mechanisms are an alternate explanation. In a multicenter study of 100,000 solid organ transplant recipients it was observed that a dependence of graft outcome on donor gender was found for non-renal grafts as well[71], suggesting that alternate mechanisms must play a role.

2.3.6 Metabolic syndrome and recipient BMI

There have been a number of studies evaluating the relation between anthropometric characteristics of donors and recipients with the graft function and recipient survival. Meier-Kriesche et al. demonstrated that recipient BMI showed a very strong association with outcomes after renal transplantation [72, 73]. Extremes of very high and very low BMI were associated with a significantly worse patient and graft survival. Additional studies using data collected by UNOS have shown that graft survival is generally reduced in recipients with greater body weight, BMI, or BSA [74, 75].

There are a number of potential mechanisms by which recipient body size may influence the development of chronic allograft nephropathy and renal allograft outcomes. Clinical observations and experimental evidence suggest that non-immunological recipient characteristics which are associated with increased BMI are important in independently predicting long-term renal allograft function and survival, including metabolic syndrome, hypertension and hyperlipidemia [76-81]. These risk factors are also risk factors for

cardiovascular disease and like atherosclerosis, CAN is thought to result from a continuous response to injury; CAN is characterized by vascular lesions that have pathologic similarities to atherosclerosis. Furthermore, hyperfiltration is well recognized as a maladaptive process leading to glomerulosclerosis and overweight/obese individuals have larger kidneys and proportionally greater GFR [82-85]. It has been demonstrated that both the GFR (by inulin clearance) and renal plasma flow (by *p*-aminohippuric acid clearance) of obese, non-diabetic, patients are increased, the GFR being relatively more elevated than the renal plasma flow, resulting in an increased filtration fraction [83]. This hyperfiltration is mainly or solely due to an increased transcapillary hydraulic pressure difference, which is postulated to be the consequence of resistance of the glomerular microcirculation to insulin action. Elevated filtration fraction measured at 1 year post-transplant is independently associated with subsequent graft loss [85].

It is clear that various clinical risk factors predispose to a more rapid rate of chronic graft loss. These are likely to be additive with a final pathway of accelerated glomerulovascular sclerosis initiated when a critically low level of functioning nephrons is reached. Hence the relative size of the donor kidney may be an important determinant of the time to reach this critical low level and threshold for accelerated graft injury and loss.

3. CHAPTER THREE: LITERATURE REVIEW

3.1 Systematic review of donor nephron dosing relative to recipient demands

This review was undertaken to summarize the current state of the clinical epidemiological evidence related to the relationship between proxies of nephron dosing relative to parameters of renal transplant recipients' metabolic demands (body weight, height, BSA, lean body weight, and BMI) and renal graft outcomes (specifically function and survival).

3.2 Search strategy

A comprehensive search was conducted to identify all relevant studies. MEDLINE (1950 to March 2009) and EMBASE (1988 to March 2009) were searched using relevant search terms relating to renal transplant and matching of donor and recipient parameters of body weight, height, BSA, lean body weight, and BMI. PubMed was searched for in-process records and other non-indexed citations. The citations of included studies were reviewed to identify pertinent studies and articles citing the retrieved trials were identified by PubMed and via Web of Science. The strategy for searching MEDLINE follows as an example:

#1 kidney transplantation/
#2 ((kidney or renal) adj (transplant$ or recipient$)).tw
#3 #1 or #2
#4 obesity/
#5 overweight/
#6 body mass index/
#7 (overweight$ or over weight$).tw,ct
#8 (body mass ind$).tw,ct
#9 body surface area/
#10 (body surface area).tw,ct,
#11 (height).tw,ct
#12 (weight).tw,ct
#13($graft mass).tw,ct
#14 (nephron dos$).tw,ct
#15 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 (ratio$).tw,ct
#17 (donor to recipient).tw,ct
#18 (recipient to donor).tw,ct
#19 (match$).t,ct
#20 #16 or #17 or #18 or #19
#21 #3 and #15 and #20

3.3 Selection of studies for inclusion in the review

Studies in all languages were included. Studies were included in the review if they met 3 criteria. First, only studies examining kidney transplant recipients (vs. multi-organ recipients) in isolation were included. Second, studies had to test the relationship between a measure of donor nephron supply and recipient metabolic demand as a predictive variable for graft function and/or survival. Lastly, studies had to have used standardized and well accepted measures of graft function/survival.

3.4 Description of studies

Of the 701 titles and abstracts found, 29 studies were identified as potentially suitable and the full text retrieved. Of these, 23 studies were included in the review and 6 of these potential studies were excluded; 1 was excluded as it was a review article, 1 was excluded as age-matching was used as a surrogate for size matching (pediatric study), and 4 were excluded as they were earlier descriptions of the same cohort included in subsequent studies [86-89]. All of the included studies were obtained as a result of the database searches.

3.5 Results

A summary of the eligible studies is presented in **Table 1**. The table describes the study population's demographics, the predictor variable evaluated, the outcome measure(s) used, and the statistical methodology for hypothesis testing. The table also provides a summary of the results of the analysis.

Table 1: Summary of Studies Examining the Associations Between Matching "Nephron Dose" and "Metabolic Demand" and Graft Outcome

Author **Publication Date**	**Study Subjects** **Demographics** **Follow-up**	**Predictor Evaluated** **Outcomes(s) Measured**	**Statistical Analysis**	**Results**
Saxena **2004**	Eligible: 56 Analyzed: 56 All LUD and LRD Mean age not given Tacrolimus-based IS[a] M/F not given Body size demographics not given Follow-up not given	KV/RBWR[b] (categorical) "low" (<2.2 cm^3/kg) "medium" (2.2 to 2.84 cm^3/kg) "high" (>2.84 cm^3/kg) Outcome(s): eGFR at 6 and 12 months (by MDRD1)	1-way ANOVA, Kruskal-Wallis test, simple chi-squared analysis, or Fisher's exact test depending on data Linear regression for comparisons between KV/RBWR and eGFR Bivariable analysis; no adjustment for confounders	eGFR correlated with KV/RBWR at 6 and 12 months (r=0.46; p=0.0005 and r=0.41; p=0.003) 6 months – mean (SEM) GFRs in the low, medium, and high groups were 52.4 (2.8), 64.5 (6.2), and 82.0 (4.4) ml/min, respectively (p < 0.0005) 12 months - mean (SEM) GFRs in the low, medium, and high groups were 51.6 (3.6), 63.3 (3.8), and 83.9 (5.4) ml/min, respectively (p < 0.0001)
Miles **1996**	Eligible: 227 Analyzed: 169 All DD Mean age not given *(excluded pediatric recipients)* Cyclosporin-based IS[c] M/F 104/65 Body size demographics not given Follow-up not given	KV/RBSAR[d] (categorical) 11-38 ml/m^2 (n=31) 39-55 ml/m^2 (n=52) 56-77 ml/m^2 (n=59) 78-153 ml/m^2 (n=27) Outcome(s): 1 and 5 year graft survival (failure included death with a functional graft) Cr & proteinuria(>=3+) at 3, 6,12,36,60 months	Graft survival: Cox's proportional hazards and Kaplan-Meier analysis; Adjusted for baseline Cr, rejection, donor age, and cold ischemic time. Proteinuria and Cr: Chi-square analysis Smaller ratios had more pediatric donors (minimum age 3 years)	Serum Cr and presence of proteinuria were not significantly different between groups No association between KV/RBSAR and Cr or proteinuria No difference in adjusted graft survival between groups

Author Publication Date	Study Subjects Demographics Follow-up	Predictor Evaluated Outcomes(s) Measured	Statistical Analysis	Results
De Petris **2002**	Eligible: ? Analyzed: 43 Pediatric Recipient All pediatric DD Mean age 13 years (range 7.4-20.5) Cyclosporin-based IS[g] M/F Body size demographics not given Follow-up 3.2 yrs (range 1-6.8)	KV/RBSAR[e] (categorical) 14–29ml/m2 (n=13) 30–39 ml/m2 (n=16) 40–110 ml/m2 (n=14) Outcome(s): eGFR at the end of follow-up (by Schwartz)[j]	Student's t-test and Mann-Whitney Different follow-up times were not accounted for	eGFR was not significantly different between groups
Nicholson **2000**	Eligible: ? Analyzed: 100 All DD Mean age 36 years (SD -) Cyclosporin-based IS[g] M/F 59/41 Mean weight 66.8 kg (SD 11.3) Follow-up mean 8 years	TXSA/RBWR[f] (categorical) "high">0.45cm^2/kg "medium" 0.3 to 0.45 cm^2/kg "low"<0.3cm^2/kg Outcome(s): Radioisotope determine GFR at 1,6, and 12 months post-transplant 5 year graft survival	Student's t-test, Mann-Whitney U, Fisher's exact tests as appropriate. Log rank/Kaplan Meier survival curves Analysis not adjusted for covariates	Isotope GFR measurements were higher in the groups with a high or medium TXSA/RBWR but not statistically significant 5 year graft survival was not different Recipient body weight was significantly lower in the high TXSA/RBWR group than in the low TXSA/RBWR group
Taherimahmoudi **2007**	Eligible: 1000 Analyzed: 217 All LUD and LRD Mean age 36 years (SD -)	KW/RBMIR (continuous) Outcome(s): Serum Cr(limited details)	Logistic regression Correlation(Pearson) Only bivariable analysis	KW/RBMIR did not have a significant association with serum Cr

Author Publication Date	Study Subjects Demographics Follow-up	Predictor Evaluated Outcomes(s) Measured	Statistical Analysis	Results
...Taherimahmoudi (continued)	Cyclosporin-based IS[g] M/F not reported Mean weight 52 kg (range 24 to 82) Mean height 158 cm (range 100 to 190) Mean BMI 19.2 kg/m^2 (range 14 to 33) Follow-up mean 8 years (range 1 to 8)			
Kim **2002**	Eligible: ? Analyzed: 259 All LUD or LRD Excluded pediatric recipient, CNI toxicity on biopsy Mean age 36.0 years (SD?) Cyclosporin-based IS[g] M/F 173/86 Mean weight 57.5 kg (SD 9.5) Follow-up not reported	KW/RBWR (continuous) Outcome(s): Serum Cr and 24 hour CrCl (urine) at 1,2, and 3 years post-transplant Graft survival (Kaplan-Meier)	Multivariate survival analysis. Adjusted for: Age of donor and recipient, HLA match, use of antibody, ABO compatibility, acute rejection. Did not adjust for sex	KW/RBWR was not a significant independent predictor of graft survival KW/RBWR was significantly and independently correlated with Cr and CrCl at 1, 2, and 3 years (positive correlation)
Catena **2010**	Eligible: 86 Analyzed: 81 All DD Mean age 51 years (SD 11) Cyclosporin-based IS[g] or Tacrolimus-based IS[a] M/F not reported Mean weight 66 kg (SD 12)	KW/RBWR (continuous) Outcome(s): eGFR at 1 year post-transplant (by C-G)	Multiple linear regression Adjusted for: Recipient age DGF CIT Type of dialysis Etiology of ESRD Recipient sex Donor sex	eGFR at 1 year positively correlated with KW/RBWR Remained significant in multiple regression

Author Publication Date	Study Subjects Demographics Follow-up	Predictor Evaluated Outcomes(s) Measured	Statistical Analysis	Results
...Catena (continued)	Mean height 160 cm (SD 16) Mean BMI 21.3 kg/m^2 (SD 4.0) Follow-up not reported			
Giral **2010** **(included historical cohort originally published in 2005)**	Eligible: 1189 Analyzed: 1060 DD/LUD/LRD Kidney only Mean age 45.6years (SD 13.1) Cyclosporin-based IS[g] or Tacrolimus-based IS[a] M/F 659/401 Body size demographics not given Follow-up Mean 6.2 years Range 8 to 13 years	KW/RBWR (categorical) <2.3g/kg "small" or > 2.3 g/kg Outcome(s): eGFR over time (by MDRD measured at 3,6,12 months and then yearly) Graft survival	eGFR over time: Multivariate mixed-effect linear regression/Wald test Graft Survival: Kaplan-Meier survival curves Log-rank method for to test for differences in survival distributions (bivariable) Cox regression (with extension of semiparametric modeling*)- takes into account possible nonproportionality of covariates* Adjusted for: Acute rejection Recipient age DGF Donor Cr Retransplantation CIT	Patients with a small KW/RBWR increase their eGFR (5.7 mls/min1.73m^2) between 3 and 6 months ($p<0.0001$) and then plateau; no change in eGFR between 6 months and 7 years; after 7 years eGFR decreased by 3.13 ml/min/1.73m^2/year ($p<0.0001$) Larger ratio – increased at a slower rate between 3 and 6 months and decreased at a slower rate after 7 years (statistically significant for comparison between groups) Small KW/RBWR was an independent risk factor for transplant failure after 2 years of follow-up

Author Publication Date	Study Subjects Demographics Follow-up	Predictor Evaluated Outcomes(s) Measured	Statistical Analysis	Results
Douverny **2007**	Eligible: 178 Analyzed: 123 LRD or LUD Mean age 35 years (SD 13) Cyclosporin-based IS[g] M/F 43/80 Mean weight 61 kg (SD 17) Mean height 161 cm (SD 10) Mean BMI 23.2 kg/m^2 (SD 5.0) Follow-up not reported	KW/RBWR (continuous) Outcome(s): eGFR at 1 year post-transplant (by MDRD2)	Multiple linear regression Adjusted for: Donor age Recipient age Recipient weight Recipient BMI Rejection DGF Native kidney disease ACE inhibitors "etc." All in one model	KW/RBWR was independently associated with eGFR at 1 year ; as ratio increased, eGFR increased Statistically significant
Amante **2008**	Eligible: ? Analyzed: 53 LUD Excluded post-operative complications and rejection Mean age 39.8 years (range 6-74) Cyclosporin-based IS[g] or Tacrolimus-based IS[a] M/F 31/22 Mean weight 62.8 kg (SD 20) Mean height 160 cm (SD 16) Mean BMI 24 kg/m^2 (SD 5.8) Mean BSA 1.63m^2 (SD 0.39) Follow-up not reported	KW/RBWR KW/RBSAR KW/RBMIR (all continuous) Outcome(s): eGFR at 6 months post-transplant (by C-G and MDRD2)	Correlation (Pearsons)	KW/RBSAR was not associated with eGFR when calculated by either MDRD or C-G KW/RBWR and KW/RBMIR showed a statistically significant positive correlation with eGFR (MDRD only)

Author Publication Date	Study Subjects Demographics Follow-up	Predictor Evaluated Outcomes(s) Measured	Statistical Analysis	Results
OH **2008**	Eligible: ? Analyzed: 195 All LUD or LRD Excluded DGF, rejection, any post-operative complications Mean age 38.7 years (SD 10.3) Cyclosporin-based IS[g] (76%) Tacrolimus-based IS[a] (24%) M/F not reported Mean weight 57.0 kg (SD 9.8) Mean height 166.8 cm (SD 8.8) Mean BMI 20.4 kg/m^2 (SD 2.7) Mean BSA 1.6m^2 (SD 0.2) Mean lean body weight 46.4 kg (SD 7.7) Follow-up not reported	KW/RBWR KW/RBSAR KW/RBMIR KW/RLBWR D/RBMIR D/RBSAR Outcome(s): Serum Cr, urine Cr, urine protein in first month post-transplant Baseline CrCl (24 hr urine collection) in first month post-transplant	Multiple linear regression Not clear what variables were adjusted for in models Did not adjust for sex	KW/RBWR, KW/RBSAR, and KW/RBMIR independently predicted serum Cr at 6 months post-transplant (inverse correlation for the later 2 predictors) D/RBSAR independently predicted 24 hr CrCl (positive correlation)
Andres **2004**	Eligible: 1054 Analyzed: 424 (212 pairs) DD (only pairs recipients with same donor evaluated) Mean age 46.6 years (SD 12.6) Cyclosporin-based IS[g] M/F 323/101 Body size demographics not given Follow-up not reported	D/RBWR (categorical) *(Weight was categorized into <50, 50-75, and >75 kg)* "high"=>1 n=133 "equal"=1 n=255 "low"=<1 n=80	Paired analysis Graft survival – multiple Cox regression Cr at 3 months – mixed linear model Adjusted for: Donor age (ref <60) Recipient age (" ") Immunosuppression Rejection Time on dialysis	Relationship between donor and recipient weight had a significant effect on graft survival; the risk for graft loss was higher when donor weight was lower than the recipient weight There was no relationship between donor and recipient weight and Cr at 3 months Measurement error may have been a problem

Author Publication Date	Study Subjects Demographics Follow-up	Predictor Evaluated Outcomes(s) Measured	Statistical Analysis	Results
...Andres (continued)		Outcome(s): Graft survival (death-censored) Cr at 3 month post-transplant		
El-Agroudy **2003**	Eligible: 856 Analyzed: 776 LRD and LUD Excluded pediatric recipients and BMI>35 kg/m^2 Mean age 34 years (SD 8) Cyclosporin-based IS[g] or M/F 706/70 Body size demographics not given Follow-up "all achieved a minimum of 1 year"	D/RBWR (categorical) "Low" <0.9 (n=110) "medium"0.91 - 1.2 (n=355) "high" >1.2 (n=311) Outcome(s): Graft survival (by Kaplan-Meier survival curves censored for death with a functioning graft)	ANOVA Kruskal-Wallis Chi-squared No adjustment for co-variates	Recipient body weight significantly different between groups (decreases as D/RBWR increases) Significant difference in 5 and 10 year survival curves (highest in the "high" group) At one year, no difference in graft survival
Shaheen **1998**	Eligible: 462 Analyzed: 406 All LRD Mean age 34.3 yrs (range 5 to 63) Cyclosporin-based IS[g] M/F 278/128 Mean weight 56 kg Follow-up 4.6 yrs (mean)	D/RBWR (categorical) "high"=>1 n=177 "low"=<1 n=79 Outcome(s): Cumulative graft survival	Chi-square test (unadjusted two-way comparisons)	Overall patient survival 92.4%. Overall graft survival 84.5%. "high" 84.7% "low" 87.0% *(not significant)*

Author Publication Date	Study Subjects Demographics Follow-up	Predictor Evaluated Outcomes(s) Measured	Statistical Analysis	Results
Ghafari **2008**	Eligible: 232 Analyzed: 217 All LUD Mean age 41.6 years (SD 6.1) Cyclosporin-based IS[g] M/F 91/126 Mean weight 53 kg Follow-up 5 yrs (inclusion criteria)	D/RBWR (categorical) "high"=>1.1 n=34 "medium"=0.8-1.1 n=130 "low"=<0.8 n=52 Outcomes: 1,3, & 5 yr graft survival	Kaplan Meier curves Survival analysis	1 yr graft survival "high" 90.2% "medium" 91.4% "low" 92.6% 3 yr graft survival "high" 79.2% "medium" 80.3% "low" 81.2% 5 yr graft survival "high" 70.2% "medium" 66.9% "low" 69.5% *(not significant)*
Halldorson **2010**	Eligible: ? Analyzed: 17 All pediatric en-bloc[i] into adult Mean age 44.2 years (range, 25-58) Tacrolimus-based IS[a] M/F 9/11 Mean weight 59 kg (range, 47-79) Follow-up 3.4 yrs(SD 1.8)	D/RBWR (continuous) ***Note – all were<0.3 as child/adult*** Combined kidney length Outcomes: 1 and 12 month Cr Delta CrCl[h]	Simple linear regression (unadjusted bivariable relationship)	Lower D/RBWR was associated with higher Cr at 1 month *(significant)* ***See note range of ratio*** D/RBWR had no association with Cr at 12 months "smallest kidneys… have the greatest increase in CrCl over time" (*not significant)*
Massarweh **2005**	Eligible: ? Analyzed: 193 LRD(n=35) LUD(n=17) DD (n=141)	D/RBMIR (categorical) "high"=≥1 n=80 "low"=<1 n=108	Kaplan-Meier and Cox proportional hazards regression (multivariate analysis)	If donor BMI ≥ recipient BMI, trend toward longer graft survival *(not significant)*

Author Publication Date	Study Subjects Demographics Follow-up	Predictor Evaluated Outcomes(s) Measured	Statistical Analysis	Results
... Massarweh (continued)	Mean age 47.1 years (SD 1.0) Tacrolimus-based IS[a] M/F 115/78 BMI≥30kg/m^2 n=59 BMI<30kg/m^2 n=124 Follow-up 2 yrs (mean)	<u>Outcome(s):</u> Graft survival (failure defined as return to dialysis or death with a functioning graft)		
McGee **2010**	Eligible: 863 Analyzed: 668 DD, LUD, and LRD No exclusions Mean age 33 years (SD 15) Cyclosporin-based IS[g] Tacrolimus-based IS[a] M/F 392/277 Mean BMI 27 kg/m^2 (SD 7) Follow-up range 3-7.5 years	D/RBMIR (categorical) "matched" Donor BMI within 2 units of recipient BMI "large donor" Donor BMI > 2 units above recipient BMI "large recipient" Donor BMI < 2 units above recipient BMI <u>Outcome(s):</u> Graft survival (Kaplan Meier)	Multivariate Cox proportional hazards model Adjusted for: Donor age Recipient age Race Hypertension DM HLA mismatch CIT PRA Previous transplant Early rejection Gender match	No difference between different donor-recipient BMI combinations
Gaston **1996**	Eligible: 436 (218 pairs) Analyzed: 378 (189 pairs) DD Excluded donors<10years Mean age 41 years (SD 11) Cyclosporin-based IS[g] (all got OKT3 or ATG) M/F 230/148 Mean BSA 1.83m^2 (SD 0.23)	D/RBSAR (paired) (categorical) "high"=≥1.2 n=51 "medium"=0.81-1.19 n=255 "low"=≤0.8 n=39	Survivorship and hazard function by parametric model of Blackstone, Naftel, & Turner Adjusted for: Age Gender PRA HLA mismatch Donor age	D/RBSAR alone was not significant risk factors for graft loss Height was missing in 34% of donors and 14% of recipients so BSA was extrapolated using a different formula (possibility of measurement error)

Author Publication Date	Study Subjects Demographics Follow-up	Predictor Evaluated Outcomes(s) Measured	Statistical Analysis	Results
... Gaston (continued)	Follow-up range 3-7.5 years	Outcome(s): Graft survival (Kaplan-Meier) Failure included death with a functioning graft.	Donor race CIT DGF Discharge Cr Recipient BSA Donor BSA	
Giuliani **2009**	Eligible: 232 Analyzed: 156 Pediatric donors All DD Single kidney Pediatric recipients Mean age 12.7 years (SD 4.2) Tacrolimus-based IS[a] M/F 94/62 Mean weight 38.7 kg (SD 18.1) Mean BSA 1.21m^2 (SD 0.41) Follow-up 5 yrs (inclusion criteria)	D/RBSAR (categorical) "high"=≥1.2 n=69 "medium"=0.81-1.19 n=59 "low"=≤0.8 n=28 Outcome(s): 1 month, 1 yr, & 5 yr graft survival (cumulative) 1 months, 1 yr & 5 yr graft function (eGFR by Schwartz)[j] categorized as: "preserved" – <5% decrease in eGFR relative to time point before or "deteriorated" >5% decrease in eGFR relative to time point before	Logistic regression and Mantel-Haenszel method Association between D/RBSAR and outcomes unadjusted	In bivariable analysis, D/RBSAR significant associate with graft function at 1 and 5 years Smaller ratios had higher risk of deterioration in function at both 1 and 5 years (Note: results recorded incorrectly in table) 5 year graft survival significantly lower in group with a lower ratio
Kasiske **2002**	Eligible: 32083 Analyzed: 32093 (UNOS and USRDS) All first DD, single organ Mean age not given	D/RBSAR (categorical) Recipient BSA <1.6 m^2 and: donor BSA <1.6 m^2 donor BSA 1.6 to 2.2 m^2	Interval Poisson analysis Adjusted analysis for multiple patient and transplant characteristics	For those surviving at least 4 months with a functioning graft, adjusted RR for subsequent graft failure was increased 43% for large recipients of kidneys from small donors. For medium sized

Author Publication Date	Study Subjects Demographics Follow-up	Predictor Evaluated Outcomes(s) Measured	Statistical Analysis	Results
… Kasiske (continued)	*(database included all age recipients and donors)* Cyclosporin-based IS[g] *(not specified but likely given time frame)* M/F not given Follow-up not given	donor BSA >2.2 m^2 Recipient BSA 1.6 to 2.2m^2 and: donor BSA <1.6 m^2 donor BSA 1.6 to 2.2 m^2 donor BSA >2.2 m^2 Recipient BSA >2.2 m^2 and: donor BSA <1.6 m^2 donor BSA 1.6 to 2.2 m^2 donor BSA >2.2 m^2 Outcome(s): Graft survival (death censored) during first 4 months Graft survival (death censored) after first 4 months	Adjusted Poisson RRs compared with the reference group of median donor and medium recipient (Recipient BSA 1.6 to 2.2m^2 and donor BSA 1.6 to 2.2 m^2)	recipients of kidneys from small donors, adjusted RR was also increased (both statistically significant)
Lee **1997**	Eligible: ? Analyzed: 22837 All DD UNOS data set Mean age 41.3 years (SD 13.6) Cyclosporin-based IS[g] M/F not reported Body size demographics not reported Follow-up not reported	D/RBSAR (categorical) "high"=≥1.2 n=51 "medium"=0.81-1.19 n=255 "low"=≤0.8 n=39 Outcome(s): 5 year graft survival (Kalplan Meier)	Logistic and Cox regression Multivariate analyses (covariates: donor and recipient sex, age, and race, early rejection, creatinine at discharge)	Smaller D/RBSA ratio was a risk factor for lower 5-year graft survival rates

Author Publication Date	Study Subjects Demographics Follow-up	Predictor Evaluated Outcomes(s) Measured	Statistical Analysis	Results
Cho **1997**	Eligible: ? Analyzed: 12077 All DD Excluded < 6 years old Mean age not reported Immunosuppression not reported M/F not reported Body size demographics not given Follow-up not reported	D/RBWR D/RBSAR D/RBMIR D/RHR All categorical Outcome(s): Graft survival at 1 year (estimated by the product limit method considering death as graft failure)	Log rank test to compare survival curves Not adjusted for co-variates	Statistically significant inferior graft survival in the following groups when compared with the reference group: - recipient 40 kg heavier than the donor; - recipient more than twice as heavy as the donor; - recipient 40 cm taller than donor; - recipient 25% taller than the donor; - recipient more than two times the BMI of the donor; - recipient more than twice the BSA of the donor.

[a] Tacrolimus-based immunosuppression (IS) tacrolimus, MMF (or azathioprine), and prednisone/prednisolone

[b] renal volume by magnetic resonance imaging

[c] cyclosporine plus prednisone; imuran only given if worsening function; no MMF

[d] renal volume by length X width X thickness in the operating room

[e] renal volume by ultrasound using the formula for a prolate ellipsoid

[f] hilar cross-sectional area calculated from ultrasound determined renal capsule outline

[g] Cyclosporin-based immunosuppression (IS) cyclosporine, MMF (or azathioprine), and prednisone/prednisolone

[h] Delta CrCl change in CrCl (estimated by Cockcroft-Gault) between month 12 and month 1

[i] en-bloc=transplantation of both kidneys

[j] eGFR estimated glomerular filtration rate by Schwartz [90]

There is conflicting evidence related to the association between kidney size by direct measurement relative to recipient body size and graft survival. Eleven studies evaluated a direct measure of kidney size (volume in 3, cross-sectional area in 1, and weight in 7) relative to a body size parameter (with recipient body weight being the most common) [91-101]. Four of these studies looked at graft survival as an outcome and 3 found no association between the ratio of donor kidney size and recipient body size and this outcome (graft survival compared at 5 years in 2 studies and undefined in the other) [92, 94, 96]. One study reported a graft survival advantage with large KW/RBWR after 2 years of follow-up [98]. This study was significantly larger than those studies showing no association, which likely had inadequate statistical power to test the hypothesis rigorously. Three of the 4 studies adjusted for covariates (including the one demonstrating a survival advantage), although they were not consistent between studies and no study adjusted for gender match or the effect of recipient BMI [92, 96, 98].

There is also conflicting evidence related to the association between kidney size by direct measurement relative to recipient body size and GFR after transplant. Four of 5 studies which evaluated GFR 1 year after transplant demonstrated that a larger ratio was associated with higher eGFR [91, 96, 97, 99]; only 1 study adjusted for recipient BMI [99]. In contrast to these 4 studies, which all used creatinine based estimates of GFR, 1 of the 5 studies utilized isotope determined GFR (which would be considered the gold standard) and demonstrated no association between the size of the graft relative to the recipient and renal outcome [94]. An additional study demonstrated no significant association between KV/RBSAR and eGFR post-transplant, however the study was very small, the outcome was measured at variable time points, there was no adjustment for covariates, and only pediatric recipients of pediatric donors were studied [93]. Giral et al. demonstrated that a larger KW/RBWR was actually associated with a lower eGFR at 6 months, a slower rate of increase in eGFR between 3 and 6 months after transplant, and a slower rate of decline in eGFR (not seen until 7 years after transplant) [98]. This later study would support the hypothesis related to nephron dosing and hyperfiltration, although, their analysis was not adjusted for the body size of the recipient. This study by Giral was the largest in this group of studies (n=1060), with the remainder ranging from 43 to 259 participants.

Evidence related to the association between relative size of the donor in relation to the size of the recipient and graft survival is not conclusive. Thirteen studies evaluated the size of the donor relative to the size of the recipient. Six out of 11 studies reporting graft survival demonstrated a significant decrease in survival with smaller ratios (D/RBSAR in 3 studies and D/RBWR in 2 studies) [27, 28, 102-105]. The majority of these studies did not adjust for covariates in the analyses. Five out of 10 studies reporting graft survival demonstrated no survival advantage based on the ratio of donor and recipient size (D/RBSAR, D/RBMIR, and D/RBWR in 2 studies each). Relative to studies demonstrating a survival advantage, there appeared to be no difference in study size however a greater proportion of studies showing no survival advantage were adjusted for confounding variables. Of the 3 large database studies (n=12077, n=32083, n=22837) [27, 28, 104] all demonstrated a graft survival advantage with larger ratios (D/RBSAR in 3 and D/RBMIR in 1). However, all 3 analyzed deceased donor transplants in heterogeneous populations (which included pediatric to adult and adult to pediatric transplants) and 1 study demonstrated statistically inferior graft survival only at extremely small ratios (i.e. recipient more than twice the BSA or BMI than the donor).

Studies evaluating the association between relative size of the donor in relation to the size of the recipient and the change in eGFR over time in long-term follow-up after transplant are extremely limited. Change in eGFR over time was evaluated in 2 studies. The first was the change in eGFR in a population at the small extreme of donor to recipient matching (pediatric donor into adult recipient) [106]; they found no significant association between D/RBWR and change in eGFR between 6 and 12 months post-transplant in this population. The second study evaluated pediatric recipients of pediatric donors and smaller ratio of donor to recipient BSA had a higher risk of deterioration in eGFR between 3 and 5 years post-transplant [103].

Whether the potential effect of body size matching is simply due to an effect of recipient BMI or is due to effects of size mismatching that are independent of recipient BMI has not been adequately evaluated. Many studies included in this review failed to analyze potential confounding variables. Only 8 out of 22 studies included covariates in the statistical models, and although previously identified predictors of graft outcome were included as covariates in the majority of these studies, some important variables were left out of modeling including gender match (in all studies) and recipient

BMI in most. Given the association between recipient BMI and graft outcome previously discussed, it was important to review if studies evaluating the effect of size matching considered the confounding effect of recipient BMI; overweight and obese recipients are more likely to have a smaller donor to recipient match ratio than normal weight recipients [94]. Only 2 studies explicitly adjusted their analysis for recipient BMI. Kasiske et al. investigated whether the effect of size matching was simply due to an effect of obesity in the recipient or whether it could have been due to the effects of size mismatching that were independent of obesity [104]. They found that the increased risk of graft failure with smaller D/RBSAR persisted even after adjustment for obesity. Although they adjusted for obesity in their models, they did not consider the effect of the continuum of BMI. BMI has been shown to have a strong association with outcomes after renal transplant; both high and low are associated with significantly worse patient and graft survival [72, 73]. Although Oh et al. report adjustment for BMI, it is not clear how it is utilized in their models and what predictor variables were adjusted for BMI [101]. They also looked at eGFR only 1 month after transplant.

Overall limitations to the current body of evidence include predominantly small studies, failure to use multivariable analysis to eliminate possible confounding from the effects of other variables, and failure to evaluate long-term graft function and survival. Late graft loss remains a major problem in transplantation and we do not yet have a clear understanding of all of the important risk factors for this loss. Based on the above data, avoiding major kidney/recipient inadequacy could have a significant influence on long-term transplant function and it has been suggested that during donor and recipient matching both the potential sizes of the donor kidney and the recipient should be considered. The sum of studies done thus far evaluating graft/body size matching has not had the necessary impact to change clinical transplant practice. The deficiencies and incongruence of the previous studies and the importance of kidney/recipient inadequacy as a possible predictor of graft outcomes highlight the need for further research into this area.

Although donor kidney weight may be a reasonable surrogate index for nephron number, routine weighing of donor kidneys at the time of transplantation is not normal practice and if used as part of the matching process would have considerable consequences including potentially prolonging CIT. For the purposes of clinical decisions that can

potentially positively alter graft outcome, body size discrepancies as possible surrogates of nephron mass are perhaps more important to evaluate, as these are measures that can guide decisions regarding organ matching without negatively influencing peri-operative risks for poor graft outcome. In addition, the population most likely to be effected by size mismatching, if hyperfiltration is the proposed etiology, are those whose grafts survive in the short term and therefore the follow-up period for the true impact on graft survival of this predictor needs to be longer-term than what exists in the current literature. In fact, renal failure has been described up to 10 years after nephron reduction [75, 107, 108]. Given the difficulties inherent in performing longer-term follow-up studies, particularly related to loss to follow-up and loss of data, it is appropriate to consider the use of alternate outcome measures, for example slope analysis as discussed in Chapter 1.

Before proceeding with inclusion of surrogates of nephron dose to size matching, we need to be sure that they are important independent predictors of graft outcome, as it will have substantial impact on matching algorithms and transplant wait list times for individuals (with a bias towards larger people waiting longer).

4. CHAPTER FOUR: STUDY DESIGN AND METHODS

4.1 Research objectives and hypotheses

General Research Objective:

Although there is accumulating evidence in the literature related to surrogate measures of nephron dosing relative to recipient demands, questions still remain about the association between ratios of donor and recipient body size, as potential modifiable variable, and longer-term graft outcomes. The overarching goal of this project is to define the importance of donor and recipient body size matching (specifically BMI matching) in renal transplant for long term graft function.

Specific Research Questions:

1. In adults with a first time renal transplant, is the ratio of donor BMI to recipient BMI an independent predictor of estimated GFR at 1 year post-transplant?
2. In adults with a first time renal transplant, is the ratio of donor BMI to recipient BMI an independent predictor of estimated GFR at 3 years post-transplant?
3. In adults with a first time renal transplant, is the ratio of donor BMI to recipient BMI an independent predictor of estimated GFR at 5 years post-transplant?
4. In adults with a first time renal transplant, is the ratio of donor BMI to recipient BMI an independent predictor of annualized change in estimated GFR over time.
5. In adults with first time renal transplant, is the effect of body size matching simply due to an effect of recipient BMI or is it due to effects of size mismatching that are independent of recipient BMI.

4.2 Methods

4.2.1 Study design and data source

This was a retrospective single-center cohort study, using an established renal transplant database. This database includes all renal allograft recipients at the University of Alberta Hospital who received a transplant between January 2, 1990, and August 31, 2005. The last date of data collection (study end date) was November 30, 2006. Patients were followed from transplant date until graft loss, death, or the study end date, with data

collection monthly until 24 months post-transplant and then every 6 months until, death, graft loss, or loss to follow-up.

4.2.2 Study population

All adult (age > 18 yr), first, kidney-only transplant recipients at the University of Alberta Hospital who received a transplant between January 2, 1990 and August 31, 2005 were studied. Patients with a graft survival of less than 6 months were excluded. Recipients of a kidney from an extended criteria donor were also excluded (defined as age ≥ 60 yr or age ≥ 50 yr and < 60 yr and two of the following: hypertension, last Cr > 13 umol/liter or cerebrovascular cause of death). Patients were followed from transplant date until graft loss, death, or the study end date (last date of data collection, November 30, 2006). Post-transplant, patients received the standard immunosuppressive regimen of a calcineurin inhibitor (CNI), prednisone, and either azathioprine (before 1995; 20.2%), or MMF (1995 and after; 79.8%). Antilymphocyte globulin or OKT3 therapy was not routinely used as induction therapy unless the recipient had high immunological risk.

4.2.3 Description of outcomes and predictor variables

Outcomes: Four outcomes were used in separate analytical models:

1. Estimated GFR at 1 year post-transplant
2. Estimated GFR at 3 years post-transplant
3. Estimated GFR at 5 years post-transplant
4. Annualized change in eGFR over time

Estimated GFR (ml/min/1.73m^2) was determined by the C-G estimation equation which was then normalized to 1.73m^2 of recipient BSA as follows:

$$\text{eGFR} = \frac{(140 - \text{age}) \times \text{weight in kg} \times \text{constant}}{\text{serum Cr in umol/L}} \times \frac{1.73}{\text{BSA}}$$

(where *constant* is *1.23* for men and *1.04* for women)

Annualized change in eGFR was defined for each patient as the regression coefficient derived from simple linear regression applied to all available eGFRs beginning 6 months post-transplant (mls/min/1.73m^2/year). Estimated GFR was calculated from Cr measured at post-transplant month 6, monthly from month 12 to 24, and then every 6 months until graft failure or loss to follow-up. The mean (SD) and median number of eGFR measurements used to calculate the annualized change in eGFR was 18.2 (7.9) and 18, respectively. The minimum number of measurements was 2 (1% of total slopes calculated) and the maximum number was 40. Six percent of patients had slopes calculated with 5 or fewer measurements while 86% had 10 or more observations and 41% had 20 or more observations. The R^2 values for each slope were calculated. The mean (SD) for the R^2 for the regression relationships yielding the slope were 0.30 (0.27). Thus the average regression equation was a reasonable fit.

Exposure of interest: The ratio of donor to recipient BMI was the main predictor variable. D/RBMIR was computed as:

$$\text{D/RBMIR} = \frac{\text{donor BMI in kg/m}^2}{\text{recipient BMI in kg/m}^2} \quad \text{where BMI} = \frac{\text{weight in kilograms}}{(\text{height in meters})^2}$$

Recipient BMI was calculated using recipient weight at day 7 post-transplant. Although previous studies for the most part have used the ratio of donor to recipient size as a categorical variable, D/RBMIR was considered continuous for hypothesis testing in this study. The rationale for this was that if nephron dosing is the postulated mechanism underlying the effect of body size matching, there is no current evidence to suggest that there are thresholds of effect. Categorizing this variable would be arbitrary, as there is not yet a good understanding of its relationship with the outcomes, and would potentially lead to the loss of important information.

Confounding or effect modifying variables: Data was collected on donor, recipient and transplantation characteristics previously reported to predict renal graft function and/or survival and with potential to confound or modify the effect of D/RBMIR on graft function. Details of the variables used in analysis are summarized in **Table 2**.

Table 2: Description of Variables Included in Analysis

	Variable (Data type[a])	Variable Short- Hand	Definition
OUTCOME VARIABLES	eGFR at year 1[b] (C)	crcl_y1_adj	CrCl (as an estimation of GFR) in mls/min determined by C-G[c] estimation equation and then adjusted for 1.73 m^2 of BSA
	eGFR at year 3[b] (C)	crcl_y2_adj	
	eGFR at year 5[b] (C)	crcl_y3_adj	
	Annualized change in eGFR (C)	SLOPE_eGFR	Determined by simple linear regression to all available eGFRs[d] beginning 6 months post-transplant (ml/min/1.73 m^2/year)
PREDICTOR INVESTIGATED	Donor to recipient BMI ratio (C)	bmi_ratio	Recipient BMI calculated using recipient weight at day 7
COVARIATES	Recipient BMI (G)[e]	r_BMIcat	0=normal: BMI ≥ 18.5 to 24.9 kg/m^2 (reference category) 1=underweight: BMI < 18.5 kg/m^2 2=overweight:BMI ≥ 25.0 to 29.9 kg/m^2 3=obese: BMI ≥ 30.0 kg/m^2
	Recipient sex (G)	r_sex	0=female (reference category) 1=male
	Recipient age (C)	r_age	Years
	Recipient race (G)	r_race_cat	0=aboriginal (reference category) 1=caucasian 2=asian 3=black 4=other
	Donor BMI (G)	d_BMIcat	0=normal: BMI ≥ 18.5 to 24.9 kg/m^2 (reference category) 1=underweight: BMI < 18.5 kg/m^2 2=overweight:BMI ≥ 25.0 to 29.9 kg/m^2 3=obese: BMI ≥3 0.0 kg/m^2
	Donor sex (G)	d_sex	0=female (reference category) 1=male
	Donor age (C)	d_age	years

	Variable (Data type[a])	Variable Short- Hand	Definition
...COVARIATES (continued)	Donor race (G)	d_race_cat	0=aboriginal (reference category) 1=caucasian 2=asian 3=other
	Donor source (G)	dd_ld	0=deceased donor (reference category) 1=living donor
	Peak PRA (G)	pra_cat	0=0-9% 1=10-79% 2=>79%
	Number of HLA mismatches (G)	hla_ab_mm	0=none (reference) 1=1 mismatch 2=2 mismatches 3=3 mismatches 4=4 mismatches
	Acute rejection (G)	any_rej	0=no treatment for rejection(reference) 1=treatment for rejection with or without biopsy confirmation
	Treatment with ACEI or ARB (G)	ace_arb	0=No (reference) 1=Yes (on ACEI or ARB at 6 months post-transplant)
	Gender match between donor and recipient (G)	g_match	0=female donor to female recipient (reference category) 1=female donor to male recipient 2=male donor to female recipient 3=male donor to male recipient

[a] data type C continuous; data type G categorical

[b] post-transplant years

[c] see **Section 4.2.3** for detailed equation

[d] eGFR was calculated post-transplant at month 6, monthly from month 12 to 24, and then every 6 months until graft failure or loss to follow-up

[e] World Health Organization classification of BMI

Regression diagnostics (residual vs. fitted, residual vs. predictor, and normal probability plots) were performed on simple linear regression models of each explanatory variable (one at a time) with each respective outcome measure to ensure that the assumptions of linear regression were upheld. Peak PRA was initially considered as a continuous variable but changed to categorical after regression diagnostics suggested its functional form did not fit the assumptions of linear regression. Categories of peak PRA as shown in **Table 2**

were picked as they have been shown to incrementally augment the risk of graft loss [109].

Variables considered in statistical modeling as potential confounders of the association between D/RBMIR and annualized change in eGFR are shown in **Table 2**. Although donor and recipient sex may be important clinical variables and may predict outcome, particularly recipient sex, these variables were not evaluated in the main models; donor to recipient gender match, as defined in **Table 2**, was used in modeling as a representation of donor and recipient sex as well as the interaction between the 2 variables. This interaction may be an important confounder in prediction of graft outcome, particularly in relation to the hypothesis of nephron dosing. Inclusion of gender match along with recipient sex and/or donor sex in the same models would result in co-linearity as one predictor variable would be a linear combination of the other. PRA and HLA matching were entered into the model as interaction terms. Other donor, recipient, and transplantation characteristics that have previously been reported to influence allograft function over time and may have an additive effect in relation to body size matching in this model include donor type (deceased donor vs. live donor) and treatment with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). These factors were fit into the regression model as interaction terms.

4.3 Descriptive/analytical methods and model building

Characteristics of the donor and recipient populations were described as means (SD) or proportions. Distribution of D/RBMIR as the primary exposure of interest was graphically evaluated by histogram. Summary statistics were determined for each outcome measure and the variable distribution evaluated graphically by histograms. For all 4 outcomes as well as D/RBMIR, boxplots were evaluated to identify outliers (extreme value limit is computed as the upper quartile range + 1.5 x interquartile range (IQR) and the lower extreme value limit as the lower quartile range + 1.5 x IQR); these data points were reviewed and a decision made regarding removal or inclusion of the data in further analysis.

The bivariable relationship between D/RBMIR and other potential predictors of graft function was evaluated. For continuous variables, Pearson's correlation was used. Simple linear regression with multiple partial F-tests was used to compare mean D/RBMI between groups for categorical variables. Simple linear regression was used to evaluate the association between D/RBMIR and each of the 4 outcome measures (eGFR at 1, 3, and 5 years respectively and annualized change in eGFR), one at a time. The ability of various donor, patient, and transplant characteristics to predict eGFR at 1, 3, and 5 years respectively and annualized change in eGFR (one at a time) was also tested using simple linear regression; multiple partial F-tests were used to compare means between groups for categorical variables. Scatter plots and boxplots were used to graphically depict these relationships when predictors were continuous or categorical, respectively.

In order to determine the independent association between D/RBMIR and the outcomes specified, a multiple linear regression model was built. Estimated GFR at 1 year, 3 years, and 5 years post-transplant, as well as annualized change in GFR were considered as dependant variables in separate statistical models. Purposeful selection was the model building strategy used. All independent variables significant at the $p \leq 0.2$ level of significance in simple linear regression and all biologically important variables were included as potential explanatory variables in a multiple linear regression model. All potential explanatory variables were assessed for co-linearity using calculation of the variance inflation factor. Variables which were not significant at $p < 0.05$ in the multiple linear regression model were dropped, one at a time, from the model after assessment of their confounding effects; if confounding was observed, the variable was retained in the model. The significance of previously described first order interactions (see **Section 4.2.2**) were analyzed using multiple partial F-tests. The final multiple linear regression model was fit with statistically significant variables, confounding variables, and biologically significant variables.

As there are very few strong studies which have considered recipient BMI as an explanatory/causative factor for the effect of size ratios (either kidney to recipient or donor to recipient) on graft outcomes, one of the specific aims of this study was to evaluate the relationship between recipient BMI, donor to recipient BMI ratio, and post-transplant graft outcome. In particular, BMI of the recipient may be an explanatory

variable in the relationship. In order to evaluate this, separate models were built with and without recipient BMI as a predictor and the models compared.

The distribution and normal probability plot of Jackknife residuals were used to check the normality assumption of the linear regression models. Plots of leverage values and Jackknife residuals against predictor variables were used to detect outliers in independent variables and check equal variance assumption respectively. Cook's distance was used to identify points of influence of individual observations on regression coefficients and the tolerance statistic was used to detect co-linearity between independent variables considered in the multiple regression analysis.

Statistical analysis was performed using STATA software [110]. Statistical significance was defined as $p<0.05$.

5. CHAPTER FIVE: RESULTS

5.1 Descriptive characteristics of study population

There were 719 patients in the data set with first time kidney only transplant from a non-extended criteria donor. Ninety eight of these patients were excluded as D/RBMIR could not be calculated (50 patients had missing donor BMI and 55 patients had missing recipient BMI). The donor, transplant, and patient characteristics of the included and excluded sample are summarized in **Table 3**. Characteristics of the excluded population did not differ from those included in further analysis, with the exception of use of an ACEI or ARB (which was lower in the excluded population) and PRA category (with the excluded group appearing to be more sensitized). In addition, there was no difference (by 2 independent sample t-test) in time of follow-up, mean eGFR at 1, 3, or 5 years or annualized change in eGFR between those excluded and those included for further analysis. Patients were followed for a mean (SD) of 6.0 (3.7) years (median 5.5 years, minimum 1 year, maximum 15.5).

Table 3: Characteristics of the Recipient and Donor Population

	Included Population		Excluded Population	
VARIABLE	**RECIPIENTS**	**DONORS**	**RECIPIENTS**	**DONORS**
Age in year (mean(SD))	45.7 (13.5)	38.9 (11.2)	46.01 (14.8)	40.2 (10.9)
Sex (% male)	65.1	49.1	63.3	43.0
Race (%)				
Aboriginal	7.5	6.4	6.2	5.2
Caucasian	79.9	90.6	81.3	91.7
Asian	10.5	3.0	10.4	3.1
Black	1.1	-	1.0	-
Other	1.0	-	1.0	-
Donor source (% living donor)	46.2		48.9	
BMI kg/m^2 (mean(SD))	26.4 (5.5)	26.2 (5.5)		
BMI (WHO category (%))				
Underweight	2.4	2.7		
Normal weight	43.2	43.2		
Overweight	32.4	34.7		
Obese	22.0	19.4		
D/RBMIR (mean(SD))	1.02 (0.28)		Missing	
Female recipient of female donor (%)	18.8		25.5	
Female recipient of male donor (%)	16.1		11.2	
Male recipient of female donor (%)	32.1		30.6	
Male recipient of male donor (%)	33.0		32.7	
Number of HLA mismatches (%)				
0	11.2		9.4	
1	12.9		15.6	
2	32.4		31.3	
3	26.0		29.2	
4	17.5		14.5	
PRA (%)[‡]				
0-9%	72.7		57.1	
10-79%	24.5		38.5	
>80%	2.9		4.4	
Acute Rejection (%)	36.4		42.3	
On an ACEI or ARB (%)[‡‡]	29.1		12.5	

[‡] Significant difference between groups (chi-square with 2 degrees of freedom=12.7, p=0.002)
[‡‡]Significant difference between groups (chi-square with 1 degree of freedom=9.4, p=0.002)

The majority of recipients were Caucasian, with an even higher proportion of donors being Caucasian. Approximately half of the recipients received a deceased donor kidney. There were an equal number of male and female donors however more male recipients were represented by the data. In comparison to larger national databases, donor source, sex distribution, and PRA distribution were similar however this data set had a greater proportion of recipients with fewer HLA mismatches [34].

5.2 Descriptive characteristics of outcome measures

Graphical evaluation of all outcome variable distributions is illustrated in **Figure 6** (**Appendix 1**). The outcomes of estimated GFR at 1, 3 and 5 years post-transplant were normally distributed. A few outliers were identified for each outcome and these data points were reviewed with the decision to retain them in the dataset for further analysis. The distribution of annualized change in eGFR was slightly negatively skewed and significantly peaked (positive kurtosis). There were a number of outliers in annualized change in eGFR identified and these were reviewed but ultimately retained in the analysis. Summary statistics for each of the 4 outcome measures are reported in **Table 4**.

Table 4: Characteristics of Outcome Measures

	Estimated GFR at 1, 3, and 5 years Post-transplant			**Annualized Change in eGFR**
Statistic	**1 year** (ml/min/1.73m^2)	**3 years** (ml/min/1.73m^2)	**5 years** (ml/min/1.73m^2)	Mean follow-up (SD) 6.0 (3.7) yrs (ml/min/1.73m^2/yr)
Mean (SD)	65.8 (19.3)	66.3 (21.2)	64.5 (21.3)	-0.979 (7.12)
Median	64.7	64.6	63.2	-0.39
Minimum	10.1	17.3	11.9	-50.92
Maximum	133.8	151.4	132.9	31.38
Sample size (n)	605	471	351	609

Evaluation of the sample size at various time points post-transplant demonstrated a progressive decline in the number of measurements available for analysis. As seen in **Table 4**, the sample size was largest at 1 year post-transplant and decreased by approximately 42% by 5 years of follow-up. At 10, 12, and 14 years post-transplant the sample size was 101, 54, and 17 respectively.

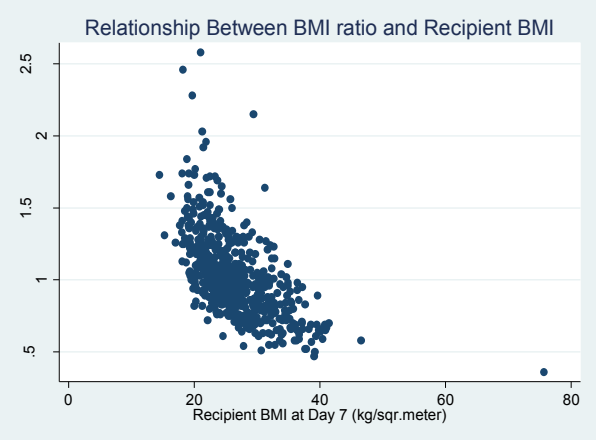
There did not appear to be a large change in eGFR between 1, 3 and 5 years after transplant and mean annualized change in eGFR demonstrated only a small negative slope. In order to further describe the characteristics of annualized change in eGFR, the proportion of patients with an increase, decrease, or no change in slope was determined. The proportion of transplant recipients who showed decline (change in GFR $\geq$-1.0 ml/min per 1.73m^2 per year), no change (change in GFR between -1.0 and 1.0 ml/min per 1.73m^2 per year), and improvement in GFR (increase in GFR $\geq$1.0 ml/min per 1.73m^2 per year) was 30% (n=178), 29% (n=173), and 41% (n=244), respectively. In those that declined, mean annualized change in eGFR (SD) was – 5.44 (6.77) ml/min per 1.73m^2 per year. Median (interquartile rage) was -3.19 (-3.84) ml/min per 1.73m^2 per year. In those that improved, mean (SD) annualized change in eGFR was 4.85 (4.75) ml/min per 1.73m^2 per year. Median (interquartile rage) was -3.04 (-3.86) ml/min per 1.73m^2 per year.

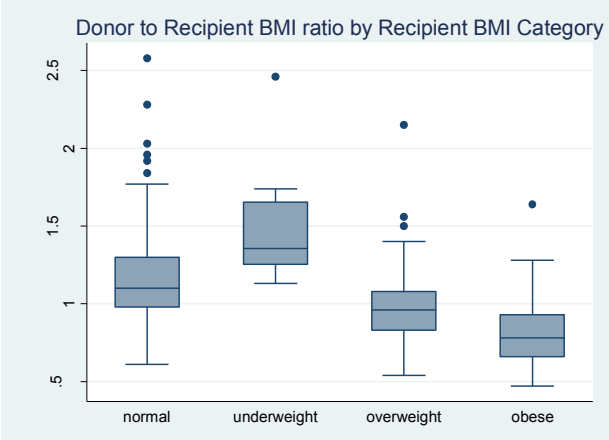
Although the average eGFR at the 3 time points and the average slope of eGFR over time suggest little change in the group as a whole, it is evident that a substantial proportion of patients have a clinically significant decrease in graft function over time. These findings are in keeping with previous observations in similar study populations and support that identifying predictors of graft function or change in function after transplant is of value in the current study population.

5.3 Association between D/RBMIR and recipient BMI

As reviewed in **Section 2.3.6**, recipient BMI is associated with a number of graft and patient outcomes and systematic review of the current literature shows that it has not been adequately evaluated whether the potential effect of body size matching is simply due to an effect of recipient BMI or is due to effects of size mismatching that are independent of recipient BMI. This led to the *a priori* hypothesis (reflected by Research Question #5, **Section 4.1**) that recipient BMI may have an explanatory role in the potential association between D/RBMIR and graft outcome. The following results support further evaluation of this hypothesis as they demonstrate that D/RBMIR is associated with recipient BMI.

Recipient BMI correlated significantly with D/RBMIR (Pearson's Correlation -0.59 $p<0.0001$); as recipient BMI increased, D/RBMIR decreased. A scatterplot illustrating this relationship is shown in **Figure 1**. When analyzed according to whether the recipient had a WHO classified BMI as normal, underweight, overweight, or obese, BMI category had a significant association with D/RBMIR (F statistic for overall effect (d.f. 3, 616)=89.15; $p<0.0001$). Mean (SD) D/RBMIR were 1.41 (0.37) in underweight, 1.16 (0.26) in normal, 0.96 (0.21) in overweight, and 0.80 (0.19) in obese. Comparisons of means demonstrated that underweight recipients had significantly higher D/RBMIR than normal weight recipients ($p<0.001$) and both overweight and obese recipients had significantly lower D/RBMIR than normal weight recipients ($p<0.001$ for both). Obese recipients had a significantly lower D/RBMIR than overweight recipients ($p<0.0001$). A boxplot illustrating these relationships is shown in **Figure 1**.





(normal BMI ≥18.5 to 24.9 kg/m^2; underweight BMI < 18.5 kg/m^2 ; overweight BMI ≥ 25.0 to 29.9 kg/m^2; obese BMI ≥ 30.0 kg/m^2)

Figure 1: Relationship Between D/RBMIR and Recipient BMI

The association between D/RBMIR and recipient BMI demonstrated here is important as it confirms that recipient BMI may be an explanatory variable in the potential relationship between D/RBMI and graft outcomes.

The results that follow demonstrate that the match between donor and recipient BMI is associated with graft function after transplant, when recipient BMI is not considered as a confounding variable. In models in which BMI is not adjusted for, eGFR at 1, 3, and 5 years after transplant increases as the ratio of donor to recipient BMI decreases. The effect of D/RBMIR on eGFR is no longer statistically significant when the effect of recipient BMI is taken into account, suggesting that much of the adverse effects of a mismatch between donor and recipient BMI previously reported may in fact be due to the effect of recipient BMI. Sections 5.4 to 5.6 that follow provide detailed results of these analyses.

5.4 Association between D/RBMIR and eGFR at 1 year post-transplant.

Figure 2 shows the relationship between D/RBMIR and the eGFR attained 1 year after transplantation. Simple linear regression showed a slightly lower eGFR of borderline significance among recipients with a higher D/RBMIR (for each 0.1 unit of increase in D/RBMIR, eGFR at 1 year post-transplant decreased by 0.6; p=0.056). The results of this analysis are summarized in **Table 5**.

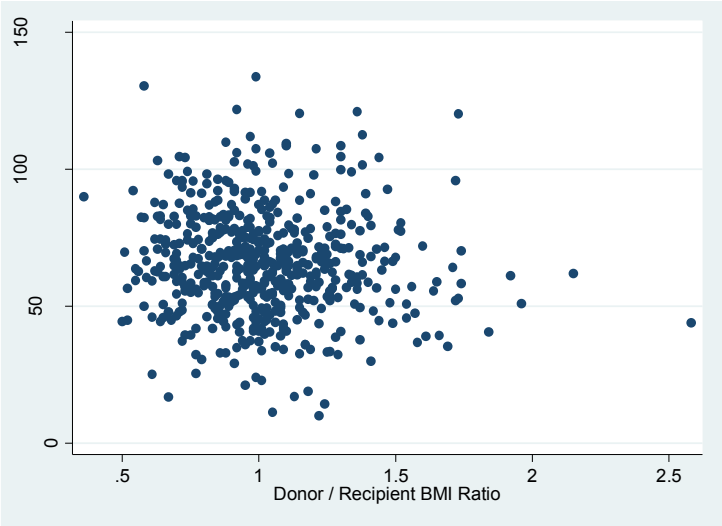


Figure 2: Relationship Between D/RBMIR and eGFR 1 Year After Transplant

Other variables found to have statistically significant association (p<0.05) with eGFR at 1 year post-transplant in unadjusted analysis were recipient BMI, donor age, donor sex, recipient sex, recipient age, gender match, number of HLA mismatches, use of an ACEI or ARB, occurrence of rejection, and donor source. The results of the regression analysis are summarized in **Table 5**.

In order to verify the association between D/RBMIR and eGFR at 1 year when controlling for the other explanatory variables, multivariable regression analysis was performed. Variables significant in bivariable analysis at p≤0.2 that were included in the initial

modeling were: D/RBMIR, recipient BMI category, donor age, donor race, recipient age, recipient race, gender match, number of HLA antibody mismatches, occurrence of any rejection, ACE-I or ARB use, and donor source (deceased vs. living donor). Donor race, recipient race, and number of HLA mismatches all had $p>0.5$ in multiple linear regression (see **Appendix 2-i**) and were removed after assessment of confounding. None of the pre-specified interactions (see **Section 4.2.2**) tested were significant. Results for multiple linear regression from the final model are included in **Appendix 2-ii**. The coefficient of multiple determination (R^2) was 0.30. **Table 5** shows the final model for adjusted eGFR 1 year after transplant from multiple linear regression and its relationship with the predictors evaluated. Regression diagnostics (see **Appendix 2-iii**) were performed on the final model as previously described (see **Section 4.3**). A number of influential observations on regression coefficients were identified, as well as a number of outliers in independent variables with high leverage. To demonstrate robustness of the results, the analyses were repeated after exclusion of these points (n=26), with results from the final regression model included in **Appendix 2-iv**. The only regression coefficient that was changed substantially (>15%) by elimination of these observations was that for ACEI or ARB use, however it remained a statistically significant independent predictor of eGFR at 1 year post-transplant. The model fit improved slightly; the coefficient of multiple determination (R^2) was 0.35.

After adjusting for recipient BMI category, donor age, recipient age, gender match, occurrence of acute rejection, donor source, and use of an ACEI or ARB, D/RBMIR is not independently associated with eGFR 1 year post-transplant. Removal of outliers and high leverage observations identified by regression diagnostics from the analysis did not change this association.

Table 5: Bivariable Analysis and Multiple Linear Regression: Outcome eGFR 1 Year After Transplant

	Bivariable analysis	Multiple Linear Regression -Final Model
Variables	**Coefficient (SE) (95% CI) p value**	**Coefficient (SE) (95% CI) p value**
D/RBMIR	-5.7 (3.0) (-11.6 to -0.2) 0.056	-5.7 (3.2) (-6.8 to 5.6) 0.86
Recipient BMI: Recipient underweight vs. normal	12.9 (5.3) (2.6 to 23.3) 0.01	5.0 (5.3) (-5.5 to 15.5) 0.346
Recipient overweight vs. normal	3.1 (1.8) (-0.5 to 6.7) 0.09	6.3 (1.7) (2.8 to 9.6) <0.001
Recipient obese vs. normal	3.9 (2.1) (-0.1 to 7.9) 0.06	9.5 (2.2) (5.2 to 13.9) <0.001
Recipient male vs. female	-3.7 (1.6) (-6.9 to -0.5) 0.02	Not entered
Recipient age	-0.5 (0.1) (-0.6 to -0.4) <0.0001	-0.5 (0.1) (0.6 to -0.4) <0.001
Recipient race Caucasian vs. Aboriginal	-4.6 (3.0) (-10.5 to 1.5) 0.1	
Asian vs. Aboriginal	-1.2 (3.8) (-8.7 to 6.3) 0.8	
Black vs. Aboriginal	-9.1 (7.8) (-24.4 to 6.1) 0.24	
Other vs. Aboriginal	8.1 (8.3) (-8.3 to 24.5) 0.3	
Donor BMI: Donor underweight vs. normal	1.4 (4.9) (-8.3 to 11.5) 0.77	Not entered
Donor overweight vs. normal	1.1 (1.9) (-2.5 to 4.7) 0.56	
Donor obese vs. normal	2.0 (2.2) (-2.4 to 6.3) 0.37	
Donor male vs. female	4.9 (1.6) (1.8 to 7.9) 0.002	Not entered
Donor age	-0.6 (0.1) (-0.7 to -0.4) <0.0001	-0.4 (0.1) (-0.5 to -0.3) <0.001
Donor race Caucasian vs. Aboriginal	-6.1 (3.1) (-12.2 to 0.04) 0.05	
Asian vs. Aboriginal	-4.1 (5.3) (-14.5 to 6.4) 0.45	
Other vs. Aboriginal	Dropped[a]	
Gender match: Female donor to male recipient vs. female donor to female recipient	-2.9 (2.3) (-7.4 to 1.5) 0.19	-3.1 (2.1) (-7.2 to 0.9) 0.13
Male donor to female recipient vs. female donor to female recipient	6.3 (2.6) (1.2 to 11.5) 0.017	6.0 (2.4) (1.3 to 10.7) 0.013
Male donor to male recipient vs. female donor to female recipient	1.4 (2.3) (-3.0 to 5.8) 0.53	2.7 (2.1) (-1.4 to 6.8) 0.19

	Bivariable analysis	Multiple Linear Regression -Final Model
Variables	**Coefficient (SE) (95% CI) p value**	**Coefficient (SE) (95% CI) p value**
Living vs. deceased	6.5 (1.6) (3.5 to 9.6) <0.001	4.7 (1.5) (1.8 to 7.6) 0.002
Peak PRA: 10 to 79% vs. 0 to 9%	0.05 (1.86) (-3.6 to 3.7) 0.98	Not entered
>79% vs. 0 to 9%	2.5 (4.6) (-6.8 to 11.9) 0.59	
Number of HLA mismatches: 1 vs. 0	-3.3 (3.2) (-9.5 to 2.8) 0.29	
2 vs. 0	-7.2 (2.7) (-12.5 to -1.9) 0.008	
3 vs. 0	-9.3 (2.8) (-14.8 to -3.8) 0.001	
4 vs. 0	-12.0 (3.0) (-17.9 to -6.1) <0.0001	
Rejection vs. none	-7.0 (1.6) (-10.1 to -3.8) <0.001	-7.8 (1.5) (-10.7 to -4.9) <0.001
Treatment with ACEI of ARB vs. no treatment	3.7 (1.7) (0.3 to 7.1) 0.04	3.8 (1.5) (0.8 to 6.8) 0.01
Regression Constant	-	98.5

[a] all donor race categories within the data set were Aboriginal, Caucasian or Asian

In order to evaluate recipient BMI as an explanatory variable in the relationship between D/RBMIR and eGFR 1 year after transplant, recipient BMI was dropped from the final multiple regression model and its impact on regression coefficients and significance of other variables observed. The results of this analysis are included in **Appendix 2-v**.

In the multiple regression model without recipient BMI category entered, D/RBMIR demonstrated a significant association with eGFR 1 year after transplant (regression coefficient=-8.1; 95% CI=-13.5 to -2.8; p=0.003). For every increase of 0.1 in D/RBMIR, eGFR at 1 year decreased by 0.8 mls/min/1.73m^2.

5.5 Association between D/RBMIR and eGFR at 3 years post-transplant.

Figure 3 shows the relationship between D/RBMIR and the eGFR attained 3 years after transplantation. Simple linear regression showed a lower eGFR among recipients with a higher D/RBMIR (for each increase of 1 in D/RBMIR, eGFR at 3 year post-transplant decreased by 9.8; p=0.008). The results of this analysis are summarized in **Table 6**.

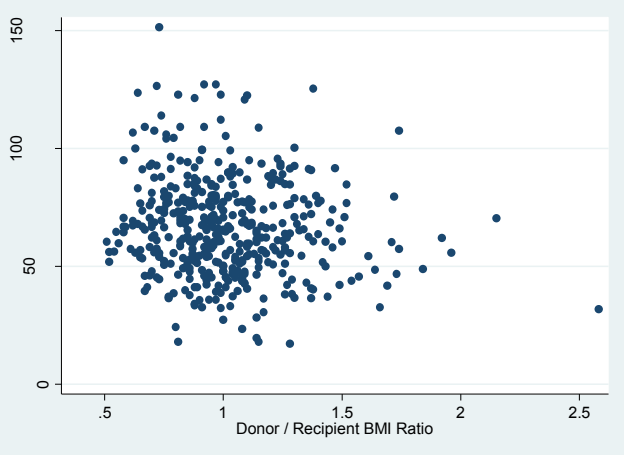


Figure 3: Relationship Between D/RBMIR and eGFR 3 Years After Transplant

Other variables found to have statistically significant association (p<0.05) with eGFR at 3 years post-transplant in unadjusted analysis were recipient BMI, donor age, donor sex, donor race, recipient sex, recipient age, recipient race, gender match, number of HLA mismatches, PRA category, use of an ACEI or ARB, occurrence of rejection, and donor source. The results of regression analysis are summarized in **Table 6**.

Multiple linear regression analysis was performed; variables significant in bivariable analysis at p≤0.2 that were included in the initial modeling were: D/RBMIR, recipient BMI category, donor age, donor race, recipient age, recipient race, gender match, number of HLA antibody mismatches, PRA category, occurrence of any rejection, ACE-I or ARB use, and donor source (deceased vs. living donor). Donor race, recipient race, number of HLA

mismatches, and PRA category all had p>0.5 in multiple linear regression (see **Appendix 3-i**) and were removed after assessment of confounding. For donor source, statistical significance was borderline (p=0.058) and, given that it was a significant independent predictor of eGFR 1 year after transplant, it was retained in the model. None of the pre-specified interactions (see **Section 4.2.2**) tested were significant. Results for multiple linear regression from the final model are included in **Appendix 3-ii**. The coefficient of multiple determination (R^2) was 0.26. **Table 6** shows the final model for adjusted eGFR 3 years after transplant from multiple linear regression and its relationship with the predictors evaluated. Regression diagnostics (see **Appendix 3-iii**) were performed on the final model as previously described (see **Section 4.3**). A number of influential observations on regression coefficients were identified, as well as a number of outliers in independent variables with high leverage. To demonstrate robustness of the results, the analyses were repeated after exclusion of these points (n=29), with results from the final regression model included in **Appendix 3-iv**. The regression coefficients for gender match were substantially changed (>15%) however it remained a significant independent predictor of eGFR at 3 years post-transplant. The model fit improved slightly; the coefficient of multiple determination (R^2) was 0.30.

After adjusting for recipient BMI category, donor age, recipient age, gender match, occurrence of acute rejection, donor source, and use of an ACEI or ARB, D/RBMIR was not independently associated with eGFR 3 years post-transplant. Removal of outliers and high leverage observations identified by regression diagnostics from the analysis did not change this association.

Table 6: Bivariable Analysis and Multiple Linear Regression: Outcome eGFR 3 Years After Transplant

	Bivariable analysis	Multiple Linear Regression -Final Model
Variables	**Coefficient (SE) (95% CI) p value**	**Coefficient (SE) (95% CI) p value**
D/RBMIR	-9.9 (3.7) (-17.2 to -2.6) 0.008	-2.4 (4.0) (-10.2 to 5.5) 0.55
Recipient BMI: Recipient underweight vs. normal	9.5 (6.8) (-3.7 to 22.9) 0.2	1.2 (7.6) (-13.8 to 16.2) 0.87
Recipient overweight vs. normal	4.9 (2.2) (0.5 to 9.2) 0.029	7.5 (2.2) (3.2 to 11.8) 0.001
Recipient obese vs. normal	6.3 (2.6) (1.2 to 11.5) 0.015	9.3 (2.8) (3.8 to 14.7) 0.001
Recipient male vs. female	-1.7 (2.0) (-5.8 to 2.3) 0.39	Not entered
Recipient age	-0.4 (0.1) (-0.5 to -0.2) <0.001	-0.4 (0.08) (-0.5 to -0.3) <0.001
Recipient race Caucasian vs. Aboriginal	-9.2 (4.1) (-17.4 to -1.1) 0.027	
Asian vs. Aboriginal	-5.5 (5.0) (-15.3 to 4.4) 0.3	
Black vs. Aboriginal	-8.5 (10.3) (-28.7 to 11.7) 0.4	
Other vs. Aboriginal	3.9 (12.9) (-21.4 to 29.2) 0.8	
Donor BMI: Donor underweight vs. normal	-2.9 (6.5) (-15.7 to 9.9) 0.66	Not entered
Donor overweight vs. normal	-0.4 (2.3) (-4.9 to 4.1) 0.87	
Donor obese vs. normal	2.5 (2.8) (-3.2 to 8.1) 0.39	
Donor male vs. female	4.9 (1.6) (1.8 to 7.9) 0.002	Not entered
Donor age	-0.6 (0.1) (-0.7 to -0.4) <0.0001	-0.5 (0.09) (-0.6 to -0.3) <0.001
Donor race Caucasian vs. Aboriginal	-8.2 (3.8) (-15.7 to -0.7) 0.03	
Asian vs. Aboriginal	-2.7 (6.5) (-15.5 to 10.2) 0.68	
Other vs. Aboriginal	Dropped[a]	
Gender match: Female donor to male recipient vs. female donor to female recipient	-0.4 (2.8) (-5.1 to 5.9) 0.88	-0.2 (2.6) (-5.4 to 5.0) 0.94
Male donor to female recipient vs. female donor to female recipient	8.5 (3.2) (2.1 to 15.0) 0.01	7.4 (3.1) (1.4 to 13.5) 0.02
Male donor to male recipient vs. female donor to female recipient	3.4 (2.7) (-2.0 to 8.7) 0.22	4.2 (2.6) (-1.0 to 9.4) 0.11

	Bivariable analysis	Multiple Linear Regression -Final Model
Variables	**Coefficient (SE) (95% CI) p value**	**Coefficient (SE) (95% CI) p value**
Living vs. deceased	6.0 (2.0) (2.2 to 9.8) 0.002	5.4 (1.9) (1.6 to 9.1) 0.005
Peak PRA: 10 to 79% vs. 0 to 9%	-4.5 (2.3) (-8.9 to -0.2) 0.042	
>79% vs. 0 to 9%	2.5 (5.6) (-8.6 to 13.5) 0.66	
Number of HLA mismatches: 1 vs. 0	-5.9 (3.9) (-13.6 to 1.7) 0.13	
2 vs. 0	-8.4 (3.4) (-15.0 to -1.8) 0.012	
3 vs. 0	-9.7 (3.5) (-16.6 to -2.9) 0.005	
4 vs. 0	-12.1 (3.7) (-19.5 to -4.8) 0.001	
Rejection vs. none	-7.7 (2.0) (-11.6 to -3.8) <0.0001	-8.8 (1.9) (-12.5 to -5.1) <0.001
Treatment with ACEI of ARB vs. no treatment	5.1 (2.2) (0.7 to 9.5) 0.022	4.0 (2.0) (-0.05 to 7.9) 0.053
Cons		99.3

[a] all donor race categories within the data set were Aboriginal, Caucasian or Asian

In order to evaluate recipient BMI as an explanatory variable in the relationship between D/RBMIR and eGFR 3 years after transplant, recipient BMI was dropped from the final multiple regression model and its impact on regression coefficients and significance of other variables observed. **In the multiple regression model without recipient BMI category entered, D/RBMIR demonstrated a significant negative association with eGFR 3 years after transplant** (regression coefficient=-9.9; 95% CI=-16.5 to -3.0; p=0.005). The results of this analysis are included in **Appendix 3-v**. For every increase of 0.1 in D/RBMIR, eGFR at 3 years decreased by 1 ml/min/1.73m^2.

5.6 Association between D/RBMIR and eGFR at 5 years post-transplant

Figure 4 shows the relationship between D/RBMIR and the eGFR attained 5 years after transplantation. Simple linear regression showed a lower eGFR among recipients with a

higher D/RBMIR (for each increase of 0.1 in D/RBMIR, eGFR at 5 years post-transplant decreased by 1ml/min/1.73m^2; p=0.01). The results of this analysis are summarized in **Table 7**.

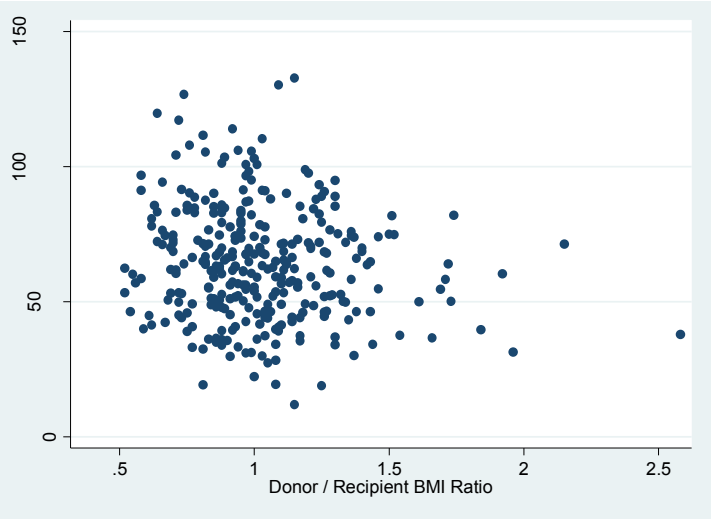


Figure 4: Relationship Between D/RBMIR and eGFR 5 Years After Transplant

Other variables found to have statistically significant association (p<0.05) with eGFR at 5 years post-transplant in unadjusted analysis were recipient BMI, donor age, donor sex, donor race, recipient age, use of an ACEI or ARB, occurrence of rejection, and donor source. The results of regression analysis are summarized in **Table 7**.

Multiple linear regression analysis was performed; variables significant in bivariable analysis at p≤0.2 that were included in the initial modeling were: D/RBMIR, recipient BMI category, donor age, donor race, recipient age, gender match, number of HLA antibody mismatches, occurrence of any rejection, ACE-I or ARB use, donor source (deceased vs. living donor). Although recipient race was not significant in bivariable analysis at p≤0.2, it was included in the multiple regression model as it had been significant at 1 year and 3 years post-transplant. Donor race, recipient race, and number of HLA mismatches all had p>0.5 in multiple linear regression (see **Appendix 4-i**) and were removed after

assessment of confounding. For donor source, statistical significance was not reached (p=0.08), however, given that it was a significant independent predictor of eGFR 1 year after transplant and is clinically important, it was retained in the model. Gender match was also not significant in multiple linear regression but was retained in the final model, as it significantly changed the regression coefficients for donor age and ACEI/ARB use when removed. None of the pre-specified interactions (see **Section 4.2.2**) tested were significant. Results for multiple linear regression from the final model are included in **Appendix 4-ii**. The coefficient of multiple determination (R^2) was 0.24. **Table 7** shows the final model for adjusted eGFR 5 years after transplant from multiple linear regression and its relationship with the predictors evaluated. Regression diagnostics (see **Appendix 4-iii**) were performed on the final model as previously described (see **Section 4.3**). A number of influential observations on regression coefficients were identified, as well as a number of outliers in independent variables with high leverage. To demonstrate robustness of the results, the analyses were repeated after exclusion of these points (n=20), with results from the final regression model included in **Appendix 4-iv**. Like the outcome of eGFR at 3 yrs post-transplant, removal of these outliers and high leverage observations changed the regression coefficients substantially for gender match. The regression coefficient for donor source was also changed. The model fit improved; the coefficient of multiple determination (R^2) was 0.31.

After adjusting for recipient BMI category, donor age, recipient age, gender match, occurrence of acute rejection, donor source, and use of an ACEI or ARB, D/RBMIR was not independently associated with eGFR 5 years post-transplant. Removal of outliers and high leverage observations identified by regression diagnostics from the analysis did not change this association.

Table 7: Bivariable Analysis and Multiple Linear Regression: Outcome eGFR 5 Years After Transplant

	Bivariable analysis	Multiple Linear Regression -Final Model
Variables	**Coefficient (SE) (95% CI) p value**	**Coefficient (SE) (95% CI) p value**
D/RBMIR	-10.9 (4.3) (-19.4 to -2.6) 0.01	-2.6 (4.6) (-11.7 to 6.4) 0.56
Recipient BMI: Recipient underweight vs. normal	21.6 (8.6) (4.7 to 38.6) 0.01	7.0 (11.1) (-14.8 to 28.8) 0.53
Recipient overweight vs. normal	6.8 (2.6) (1.8 to 11.9) 0.008	8.8 (2.6) (3.7 to 13.9) 0.001
Recipient obese vs. normal	7.2 (3.0) (1.3 to 13.2) 0.018	9.5 (3.4) (2.8 to 16.2) 0.006
Recipient male vs. female	-0.4 (2.3) (-5.1 to 4.2) 0.85	Not entered
Recipient age	-0.4 (0.1) (-0.5 to -0.2) <0.001	-0.4 (0.09) (-0.6 to -0.2) <0.001
Recipient race Caucasian vs. Aboriginal	-6.8 (4.1) (-15.7 to 2.1) 0.13	
Asian vs. Aboriginal	-2.3 (5.5) (-13.1 to 8.5) 0.67	
Black vs. Aboriginal	-19.9 (11.5) (-42.5 to 2.6) 0.08	
Other vs. Aboriginal	0.9 (13.0) (-24.7 to 26.5) 0.94	
Donor BMI: Donor underweight vs. normal	0.9 (7.3) (-13.5 to 15.4) 0.89	Not entered
Donor overweight vs. normal	-0.3 (2.8) (-5.2 to 5.8) 0.91	
Donor obese vs. normal	-1.9 (3.3) (-8.5 to 4.6) 0.56	
Donor male vs. female	5.8 (2.3) (1.4 to 10.3) 0.01	Not entered
Donor age	-0.6 (0.1) (-0.8 to -0.4) <0.001	-0.5 (0.1) (-0.7 to -0.2) <0.001
Donor race Caucasian vs. Aboriginal	-8.2 (3.8) (-15.7 to -0.7) 0.03	
Asian vs. Aboriginal	-2.7 (6.5) (-15.5 to 10.2) 0.68	
Other vs. Aboriginal	Dropped[a]	
Gender match: Female donor to male recipient vs. female donor to female recipient	0.06 (3.2) (-6.3 to 6.4) 0.98	-2.4 (3.1) (-8.5 to 3.8) 0.45
Male donor to female recipient vs. female donor to female recipient	7.5 (3.7) (0.04 to 15.0) 0.05	5.2 (3.7) (-2.1 to 12.5) 0.16
Male donor to male recipient vs. female donor to female recipient	5.1 (3.1) (-1.1 to 11.3) 0.11	4.0 (3.2) (-2.2 to 10.2) 0.21

	Bivariable analysis	Multiple Linear Regression -Final Model
Variables	**Coefficient (SE) (95% CI) p value**	**Coefficient (SE) (95% CI) p value**
Living vs. deceased	5.6 (2.2) (1.2 to 10.1) 0.01	4.7 (2.3) (0.1 to 9.2) 0.043
Peak PRA: 10 to 79% vs. 0 to 9%	-4.3 (2.6) (-9.3 to 0.8) 0.10	Not entered
>79% vs. 0 to 9%	0.6 (6.8) (-12.8 to 13.9) 0.93	
Number of HLA mismatches: 1 vs. 0	-3.7 (4.7) (-12.9 to 5.4) 0.42	
2 vs. 0	-5.7 (3.9) (-13.5 to 1.9) 0.14	
3 vs. 0	-11.2 (4.0) (19.1 to -3.2) 0.01	
4 vs. 0	-8.2 (4.3) (-16.7 to 0.3) 0.06	
Rejection vs. none	-5.7 (2.3) (-10.2 to -1.2) 0.01	-6.5 (2.2) (-10.8 to -2.1) <0.004
Treatment with ACEI of ARB vs. no treatment	6.9 (2.7) (1.6 to 12.3) 0.01	5.6 (2.6) (0.5 to 10.7) 0.03
Regression constant		94.7

[a] all donor race categories within the data set were Aboriginal, Caucasian or Asian

In order to evaluate recipient BMI as an explanatory variable in the relationship between D/RBMIR and eGFR 5 years after transplant, recipient BMI was dropped from the final multiple regression model and its impact on regression coefficients and significance of other variables observed. **In the multiple regression model without recipient BMI category entered, D/RBMIR demonstrated a significant association with eGFR 5 years after transplant** (regression coefficient=-10.3; 95% CI=-18.2 to -2.3; p=0.01). The results of this analysis are included in **Appendix 4-v**. For every increase of 0.1 in D/RBMIR, eGFR at 5 years decreased by 1 ml/min/1.73m^2.

The results described thus far have addressed the first 3 research questions outlined in Section 4.1. In adults with a first time renal transplant, the ratio of donor BMI to recipient BMI is an independent predictor of estimated GFR at 1, 3, and 5 years post-transplant when adjusting for multiple known predictors of

graft outcome. However, these associations are largely explained by the effect of recipient BMI on graft function (see Research Question #5, Section 4.1). Although each outcome (eGFR at 1, 3 and 5 years respectively) was modeled separately, the multiple linear regression models generated to test the significance of D/RBMIR demonstrated consistency in predictors selected for the final models. A comparison of the models is given below in Table 8. In addition to recipient BMI category, recipient age, donor age, gender match, the occurrence of rejection, treatment with ACEI or ARB, and donor source were significant predictors of eGFR. Donor BMI had no significant association with any outcome studied in bivariable analysis and therefore was not included in any subsequent modeling.

Table 8: Comparison of Final Models for Outcomes of eGFR at 1, 3, and 5 Years Post-Transplant

	Outcome eGFR 1 year	**Outcome eGFR 3 years**	**Outcome eGFR 5 years**
Variables	**Coefficient (SE) (95% CI) p value**	**Coefficient (SE) (95% CI) p value**	**Coefficient (SE) (95% CI) p value**
D/RBMIR	-5.7 (3.2) (-6.8 to 5.6) 0.86	-2.4 (4.0) (-10.2 to 5.5) 0.55	-2.6 (4.6) (-11.7 to 6.4) 0.56
Recipient BMI: Recipient underweight vs. normal	5.0 (5.3) (-5.5 to 15.5) 0.346	1.2 (7.6) (-13.8 to 16.2) 0.87	7.0 (11.1) (-14.8 to 28.8) 0.53
Recipient overweight vs. normal	6.3 (1.7) (2.8 to 9.6) <0.001	7.5 (2.2) (3.2 to 11.8) 0.001	8.8 (2.6) (3.7 to 13.9) 0.001
Recipient obese vs. normal	9.5 (2.2) (5.2 to 13.9) <0.001	9.3 (2.8) (3.8 to 14.7) 0.001	9.5 (3.4) (2.8 to 16.2) 0.006
Recipient male vs. female	Not entered	Not entered	Not entered
Recipient age	-0.5 (0.1) (0.6 to -0.4) <0.001	-0.4 (0.08) (-0.5 to -0.3) <0.001	-0.4 (0.09) (-0.6 to -0.2) <0.001
Recipient race Caucasian vs. Aboriginal			
Asian vs. Aboriginal			
Black vs. Aboriginal			
Other vs. Aboriginal			
Donor BMI: Donor underweight vs. normal	Not entered	Not entered	Not entered
Donor overweight vs. normal			
Donor obese vs. normal			
Donor male vs. female	Not entered	Not entered	Not entered
Donor age	-0.4 (0.1) (-0.5 to -0.3) <0.001	-0.5 (0.09) (-0.6 to -0.3) <0.001	-0.5 (0.1) (-0.7 to -0.2) <0.001
Donor race Caucasian vs. Aboriginal			
Asian vs. Aboriginal			
Other vs. Aboriginal			
Gender match: Female donor to male recipient vs. female donor to female recipient	-3.1 (2.1) (-7.2 to 0.9) 0.13	-0.2 (2.6) (-5.4 to 5.0) 0.94	-2.4 (3.1) (-8.5 to 3.8) 0.45

	Outcome eGFR 1 year	Outcome eGFR 3 years	Outcome eGFR 5 years
Variables	**Coefficient (SE) (95% CI) p value**	**Coefficient (SE) (95% CI) p value**	**Coefficient (SE) (95% CI) p value**
Male donor to female recipient vs. female donor to female recipient	6.0 (2.4) (1.3 to 10.7) 0.013	7.4 (3.1) (1.4 to 13.5) 0.02	5.2 (3.7) (-2.1 to 12.5) 0.16
Male donor to male recipient vs. female donor to female recipient	2.7 (2.1) (-1.4 to 6.8) 0.19	4.2 (2.6) (-1.0 to 9.4) 0.11	4.0 (3.2) (-2.2 to 10.2) 0.21
Living vs. deceased	4.7 (1.5) (1.8 to 7.6) 0.002	5.4 (1.9) (1.6 to 9.1) 0.005	4.7 (2.3) (0.1 to 9.2) 0.043
Peak PRA: 10 to 79% vs. 0 to 9%	Not entered		Not entered
>79% vs. 0 to 9%			
Number of HLA mismatches: 1 vs. 0			
2 vs. 0			
3 vs. 0			
4 vs. 0			
Rejection vs. none	-7.8 (1.5) (-10.7 to -4.9) <0.001	-8.8 (1.9) (-12.5 to -5.1) <0.001	-6.5 (2.2) (-10.8 to -2.1) <0.004
Treatment with ACEI or ARB vs. no treatment	3.8 (1.5) (0.8 to 6.8) 0.01	4.0 (2.0) (-0.05 to 7.9) 0.053	5.6 (2.6) (0.5 to 10.7) 0.03
Regression Constant	98.5	99.3	94.7

5.7 Association between D/RBMIR and annualized change in eGFR

In order to further define the importance of donor and recipient body size matching in renal transplant for long term graft function and specifically address if D/RBMIR is an independent predictor of annualized change in estimated GFR over time (see **Section 4.1**, Research Question #4), the following analyses were performed.

Figure 5 shows the relationship between D/RBMIR and the annualized change in eGFR. Simple linear regression demonstrated no relationship between these 2 variables. The results of this analysis are summarized in **Table 9**.

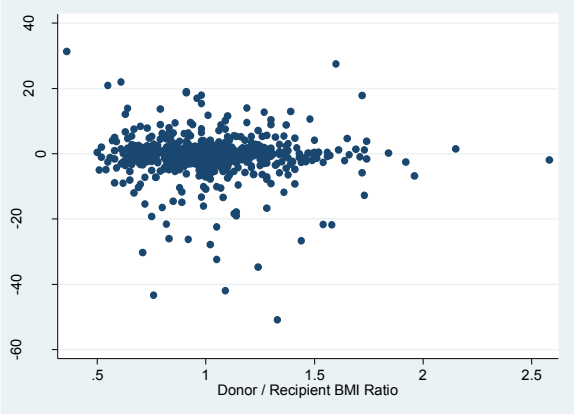


Figure 5: Relationship Between D/RBMIR and Annualized Change in eGFR

Variables found to have statistically significant association ($p<0.05$) with annualized change in eGFR in unadjusted analysis were recipient BMI, recipient sex, PRA, use of an ACEI or ARB, occurrence of rejection, and donor source. The results of regression analysis are summarized in **Table 9**.

Multiple linear regression analysis was performed. D/RBMIR was included in an initial model with all variables significant in bivariable analysis at $p\leq0.2$ (recipient BMI, recipient

age, gender match, PRA, use of an ACEI or ARB, occurrence of rejection, and donor source). Recipient age, PRA, and use of ACEI or ARB all had $p>0.5$ in multiple linear regression (see **Appendix 5-i**) and were removed after assessment of confounding. None of the pre-specified interactions (see **Section 4.2.2**) tested were significant. Results for multiple linear regression from the final model are included in **Appendix 5-ii**. The coefficient of multiple determination (R^2) was 0.12. **Table 9** shows the final model for adjusted annualized change in eGFR from multiple linear regression and its relationship with the predictors evaluated. Regression diagnostics (see **Appendix 5-iii**) were performed on the final model as described (see **Section 4.3**). A number of influential observations on regression coefficients were identified, as well as a number of outliers in independent variables with high leverage. To demonstrate robustness of the results, the analyses were repeated after exclusion of these points (n=43), with results from the final regression model included in **Appendix 5-iv**. Removal of these outliers and high leverage observations changed the regression coefficients substantially for recipient BMI, gender match, and occurrence of rejection. The model fit remained relatively unchanged (R^2=0.11).

After adjusting for recipient BMI category, gender match, occurrence of acute rejection and donor source, D/RBMIR was not independently associated with annualized change in eGFR. Removal of outliers and high leverage observations identified by regression diagnostics from the analysis did not change this association.

Table 9: Bivariable Analysis and Multiple Linear Regression: Outcome Annualized Change in eGFR

	Bivariable analysis	Multiple Linear Regression -Final Model
Variables	**Coefficient (SE) (95% CI) p value**	**Coefficient (SE) (95% CI) p value**
D/RBMIR	-0.8 (1.2) (-3.2 to -1.6) 0.53	1.6 (1.3) (-0.9 to 4.2) 0.20
Recipient BMI: Recipient underweight vs. normal	-5.9 (2.0) (-9.9 to -1.8) 0.005	-8.0 (2.2) (-12.4 to -3.6) <0.001
Recipient overweight vs. normal	1.0 (0.7) (-0.4 to 2.4) 0.18	1.2 (0.7) (-0.1 to 2.7) 0.07
Recipient obese vs. normal	1.7 (0.8) (0.1 to 3.3) 0.03	2.6 (0.9) (0.9 to 4.3) 0.003
Recipient male vs. female	1.6 (0.6) (0.3 to 2.9) 0.01	Not entered
Recipient age	0.03 (0.02) (-0.01 to -0.08) 0.13	
Recipient race Caucasian vs. Aboriginal	0.2 (1.2) (-2.1 to 2.6) 0.85	Not entered
Asian vs. Aboriginal	0.8 (1.5) (-2.1 to 2.6) 0.58	
Black vs. Aboriginal	-0.1 (3.1) (-6.1 to 5.8) 0.96	
Other vs. Aboriginal	-3.3 (3.3) (-9.7 to 3.1) 0.31	
Donor BMI: Donor underweight vs. normal	-1.9 (1.9) (-5.7 to 1.9) 0.33	Not entered
Donor overweight vs. normal	0.37 (0.7) (-1.1 to 1.8) 0.61	
Donor obese vs. normal	1.3 (0.8) (-0.2 to 2.8) 0.10	
Donor male vs. female	-0.3 (0.6) (-1.5 to 0.9) 0.64	Not entered
Donor age	0.02 (0.03) (-0.03 to 0.07) 0.39	Not entered
Donor race Caucasian vs. Aboriginal	0.2 (1.3) (-2.3 to 2.6) 0.90	Not entered
Asian vs. Aboriginal	-0.3 (6.5) (-4.5 to 3.8) 0.89	
Other vs. Aboriginal	Dropped[a]	
Gender match: Female donor to male recipient vs. female donor to female recipient	2.0 (0.9) (0.2 to 3.7) 0.03	1.5 (0.9) (-0.2 to 3.2) 0.09
Male donor to female recipient vs. female donor to female recipient	0.1 (1.0) (-1.0 to 2.1) 0.90	0.5 (1.0) (-1.5 to 2.5) 0.6
Male donor to male recipient vs. female donor to female recipient	1.4 (0.9) (-0.4 to 3.1) 0.12	2.0 (0.9) (0.3 to 3.9) 0.02

	Bivariable analysis	Multiple Linear Regression -Final Model
Variables	**Coefficient (SE) (95% CI) p value**	**Coefficient (SE) (95% CI) p value**
Living vs. deceased	1.5 (0.6) (0.3 to 2.7) 0.01	1.5 (0.6) (0.3 to 2.7) 0.01
Peak PRA: 10 to 79% vs. 0 to 9%	-1.8 (0.7) (-3.1 to -0.4) 0.01	
>79% vs. 0 to 9%	-1.8 (1.8) (-5.3 to 1.7) 0.31	
Number of HLA mismatches: 1 vs. 0	-0.8 (1.3) (-3.3 to 1.7) 0.52	
2 vs. 0	-1.2 (1.1) (-3.3 to 0.9) 0.26	
3 vs. 0	-1.8 (1.1) (-4.0 to 0.4) 0.11	
4 vs. 0	-2.6 (1.2) (-5.0 to 0.3) 0.03	
Rejection vs. none	-3.7 (0.6) (04.9 to -2.5) <0.001	-3.4 (0.6) (-4.6 to -2.2) <0.001
Treatment with ACEI or ARB vs. no treatment	1.4 (0.7) (0.2 to 2.7) 0.02	
Regression constant		-4.1

[a] all donor race categories within the data set were Aboriginal, Caucasian or Asian

In order to evaluate recipient BMI as an explanatory variable in the relationship between D/RBMIR and annualized change in eGFR, recipient BMI was dropped from the final multiple regression model and its impact on regression coefficients and significance of other variables observed. **In the multiple regression model without recipient BMI category entered, the association between D/RBMIR and annualized change in eGFR remained non-significant**, however the regression coefficient was significantly changed (regression coefficient=1.6; 95% CI=-0.9 to 4.2; p=0.20). The results of this analysis are included in **Appendix 5-v**.

5.8 Exploratory analysis

Estimated GFR at 1 year after transplant was added into the final models as a predictor for eGFR at 3 and 5 years post-transplant, respectively (see **Appendix 3-vi** and **4-vi**).

After adjusting for D/RBMIR, recipient BMI category, donor age, recipient age, gender match, occurrence of acute rejection, donor source, and use of an ACEI or ARB, estimated GFR at 1 year post-transplant was a significant independent predictor for both eGFR at 3 yrs (regression coefficient=0.8; 95% CI=0.7 to 0.9; p<0.001) **and at 5 years** (regression coefficient=0.7; 95% CI=0.6 to 0.8; p<0.001). When recipient BMI was dropped from each of these models which include eGFR 1 year post-transplant as a predictor variable, the previously demonstrated significant association between D/RBMIR with eGFR at 3 and 5 years, respectively, disappeared. There was no significant independent association demonstrated between eGFR at 1 year post-transplantation and annualized change in eGFR (see **Appendix 5-iv**).

Given the previous literature analyzing D/RBSAR as a surrogate measure of nephron dosing, D/RBSAR was substituted for D/RBMIR as the primary predictor of interest in the final multiple linear regression models for eGFR at 1, 3, and 5 years, as well as annualized change in eGFR. A higher D/RBSAR was associated with significantly higher eGFR at 1 year after transplant but not at 3 or 5 years. D/RBSAR was not associated with rate of decline in eGFR as assessed by annualized change in eGFR. The association with eGFR at 1 year post-transplant persisted after adjusting for recipient BMI. Multiple linear regression showed a higher eGFR among overweight and obese recipients 1 year relative to normal weight recipients (with obese being the highest), which was statistically significant even after adjusting for D/RBSAR. Recipient BMI was also predictive of annualized change in eGFR over time independent of the potential discrepancy between the size of the donor and recipient.

In order to evaluate the possible contribution of follow-up time to the precision of outcome measurements, this variable was included in the final model evaluating the role

of D/RBMIR in predicting change in eGFR over time. Time of follow-up (measured as the time between creatinine measured at 6 months and last measured creatinine) was not a significant predictor of annualized change in eGFR (data not included).

5.9 Summary of results

- Recipient BMI correlated significantly with D/RBMIR (Pearson's Correlation -0.59 $p<0.0001$), confirming that recipient BMI may be an explanatory variable in the potential relationship between D/RBMI and graft outcomes.
- The match between donor and recipient BMI is associated with graft function after transplant, when recipient BMI is not considered as a confounding variable; eGFR at 1, 3, and 5 years after transplant increases as the ratio of donor to recipient BMI decreases.
- The effect of D/RBMIR on eGFR is no longer statistically significant when the effect of recipient BMI is taken into account, suggesting that the effects of a mismatch between donor and recipient BMI may in fact be due to the effect of recipient BMI.
- D/RBMIR is not associated with annualized change in eGFR.
- Patients with higher BMI have higher eGFR at 1 year post-transplant, as well as at 3 and 5 years post-transplant.
- Patients with higher BMI have less negative slopes of change in eGFR over time, even after adjusting for eGFR at 1 year post-transplant (which did not predict slope).
- Increased eGFR and less negative slope in eGFR post-transplant in patients with higher BMI was also observed when an alternate surrogate of donor to recipient body size matching was used (D/RBSAR) as a covariate.
- Using an alternate surrogate of body size matching (D/RBSAR), an association with eGFR at 1 year after transplant, but not rate of decline in eGFR, was demonstrated.

6. CHAPTER SIX: DISCUSSION AND FUTURE RESEARCH

6.1 Discussion

There is a significant amount of epidemiological as well as basic science research related to factors which predict and mediate the way a renal allograft works and survives after transplant. The need for this knowledge is driven by a number of factors, both economic and patient centered. Ultimately, the longer a renal graft works well, the less the economic burden on health care systems, the greater the patient's quality of life, and the higher the morbidity-free survival. About 50% of renal grafts are lost by 10 years post-transplant, highlighting the need for better understanding of how to modify risks of poor outcome. It is reasonable to think that it is not just characteristics of the recipient or donor graft in isolation that may impact graft function and outcome, but there may be some combined effect that is more than just the sum of each component.

Given the hyperfiltration hypothesis that is pervasive in renal literature, one such variable may be the relative sizes of donor and recipient. The glomeruli hypertrophy and increase their filtration rate after transplant, since the graft contains only 50% of the nephron number in 2 normal kidneys. Glomerulosclerosis is a typical biopsy finding in chronic allograft nephropathy. These lesions are more likely to occur in maximally hypertrophied glomeruli, suggesting a mechanism of injury which could explain the reduced renal graft survival in settings where the graft is too "small" for the recipient, for example child to adult and female to male. A small donor to recipient body size ratio has also been used as a surrogate for such "nephron dosing", although the data currently does not confirm the importance of nephron number on transplant survival.

Similar to the evidence related to the association between kidney size by direct measurement relative to recipient body size and graft function or survival after transplant, the evidence related to the association between relative size of the donor in relation to the size of the recipient and graft survival is not conclusive. Studies evaluating the association between relative size of the donor in relation to the size of the recipient and the change in eGFR over time in long-term follow-up after transplant are extremely limited. Overall limitations to the current body of evidence include predominantly small studies, failure to evaluate long-term graft function, and failure to eliminate possible confounding from the effects of other variables. Importantly, whether the potential effect of body size matching is simply due to an effect of recipient BMI or is due to effects of size mismatching that are independent of recipient BMI has not been adequately evaluated. Transplant waitlist times for individuals who have increased BMI are already longer, so understanding the true effect of matching a donor by size has very large implications; the donor pool would be reduced for such an individual if donors of "smaller" size were eliminated.

From the current study, it is evident the match between donor and recipient BMI is associated with graft function after transplant, when recipient BMI is not considered as a confounding variable. In models in which BMI was not adjusted for, eGFR at 1, 3, and 5 years after transplant increased as the ratio of donor to recipient BMI decreased. Although this may appear to be evidence in opposition to some of the body of current literature and also in opposition to the current theory that inadequate nephron mass contributes to late graft failure (i.e. graft function looks better), it could be interpreted as congruent. Giral et al. demonstrated that individuals with a smaller ratio of donor kidney weight to recipient size increased their eGFR more rapidly in the early period post-transplant and then maintained the eGFR at a higher level with no significant change over

time until 7 years after transplant, when the eGFR declined at a faster rate than those with a larger ratio [98]. In the current study, when models evaluating eGFR at 3 and 5 years were adjusted for eGFR at 1 year, the results suggest that the effect of D/RBMIR on eGFR post-transplant occurs predominantly in the early post-transplant period (i.e. within the first year). Like the observations by Giral et al., Haldorson et al. also observed that recipients with the smallest ratios had the largest increase in eGFR over the first year after transplant [106]. If the hypothesis that hyperfiltration post-transplant leads to progressive and accelerated sclerosis, this can be extrapolated to postulate that those with an increased eGFR post-transplant (as a sign of hyperfiltration) may ultimately have reduced graft survival. Analysis of large data-sets has shown a more rapid decline in GFR among patients with higher levels of GFR at 1 year post-transplant [6, 17].

Change in renal allograft function over time has been established as a surrogate estimate of long-term allograft survival. In this study, several classical independent predictors for the rate of change in graft function over time were identified by multiple linear regression; deceased donor source and occurrence of rejection were risk factors for a more rapid decline. There was no evidence of a statistically significant association between D/RBMIR and annualized change in eGFR in either bivariable analysis or after adjustment for potential confounders. Giral et al. demonstrated in a similar population that the ratio of donor kidney weight to recipient weight did not predict a change in eGFR between 1 and 7 years post-transplant; the change in eGFR plateaued during this time period which is consistent with the findings from the current study, showing that the magnitude of the average decline in eGFR over the follow-up period was clinically very small [98]. Giral's study went on to show that there was an eventual decline in eGFR after 7 years and a more rapid decline was associated with a small ratio of donor kidney weight to recipient body weight. The average follow-up time in the current study was 6 years, the sample

size decreased progressively after that point, and annualized change in eGFR was considered to be continually linear over the follow-up period, based on previous literature but perhaps not representative of the optimal modeling of eGFR evolution. These factors may have limited the ability to detect an impact of D/RBMIR on a later annualized change in eGFR.

Importantly, the effects of mismatch between donor and recipient BMI on eGFR observed in this study were no longer statistically significant when the effect of recipient BMI was taken into account, suggesting that much of the adverse effects of a mismatch between donor and recipient BMI previously reported may in fact be due to the effect of recipient BMI. The finding in this study that overweight and obese recipients are more likely to have a smaller donor to recipient match ratio than normal weight recipients is supported in the literature and unlikely to be unique to just this current study sample [94]. Donor BMI had no association with any of the outcomes evaluated in this study.

Recipients with a higher BMI (i.e. overweight or obese) had elevated eGFR at 1, 3 and 5 years post-transplant, independent of the relative size of the donor. Recipient BMI also predicted annualized change in eGFR after adjustment for multiple covariates; low recipient BMI was associated with a significantly steeper GFR decline relative to normal weight recipients and obese recipients appeared to have a slower rate of decline than normal weight recipients, independent of donor and recipient size match. It is important to realize that weight gain or loss in a subject of a given body size could potentially bias any analysis of the relationship between change in eGFR over time and recipient BMI (as the estimation equation and indexing to BSA involve measures of weight). Therefore, the analysis was also performed adjusting for change in recipient BMI over time and these relationships persisted (data not shown). The current finding that low recipient BMI was

associated with a steeper eGFR decline is consistent with previously published data [18]. The more positive slope seen in recipients with elevated BMI may reflect hyperfiltration that is independent of the size match between donor and recipient. The data presented here suggests that overweight/obese individuals are more likely to have small D/RBMIRs but recipient BMI itself contributes more to the process of hyperfiltration than the "dose" of nephrons per se.

Animal data indicates that increased BMI is associated with intra-glomerular hypertension and hyperfiltration resembling glomerular microcirculation changes which occur after renal ablation, and elevated GFR in obese animals precedes glomerulosclerosis [111]. Bosma et al. have shown in non-obese subjects that filtration fraction is higher in subjects with a higher BMI (independent of age, gender, blood pressure or the way renal function is indexed), and that as BMI increases, radio-labeled tracer determined GFR also increases [112]. It has also been shown in renal transplant that higher BMI is independently associated with higher GFR (measured by radiotracer) and filtration fraction 1 year post-transplant, suggesting glomerular hyperfiltration with altered glomerular microcirculation dynamics; these effects were not explained by the presence of overt diabetes [85]. In this later study, data on donor BMI was missing and the investigators acknowledged the potential confounding effects of donor BMI on renal hyperfiltration. The data presented in this thesis suggests that higher BMI induces glomerular hyperfiltration independent of the donor BMI.

Of previous studies that showed an association between a measure of "nephron dosing", which is a term used to reflect the theory of hyperfiltration in the context of low nephron supply, and graft function/survival, only one study evaluated whether the effect of size matching was simply due to an effect of obesity in the recipient or whether it could have

been due to the effects of size mismatching that were independent of obesity [104]. They found that the increased risk of graft failure with smaller donor to recipient BSA ratio persisted even after adjustment for obesity. They also found that the effect of recipient obesity on late graft survival was no longer statistically significant after adjusting for the relative size of the donor and recipient. Although survival was not analyzed in the current study, a persistent effect of recipient BMI on eGFR as well as change in eGFR over time was observed after adjusting for potential size discrepancies.

It is apparent that there were differences in both the population studied and the measurement of body size mismatch in Kasiske's study and the current study. These differences may provide some insight into the potential circumstances associated with adverse effects of donor-recipient size disparities. All of the donors in Kasiske's study were deceased [104]. These grafts are likely to sustain more perioperative injury and therefore may have an exaggerated response to further discrepancies in "nephron dosing". The present study did not demonstrate any effect of donor source on the relationship between D/RBMIR or recipient BMI alone and graft function after transplant. In addition, Kasiske used donors and recipients of all ages, and hence was a fairly heterogeneous population which included transplants from children to adults, as well as adults to children, and extended criteria donors [104]. These matching situations have the potential to introduce confounding effects that may be independent of simply age of the donor and recipient (and hence may not be accounted for by including age in modeling).

Kasiske et al. evaluated the relationship between donor BSA relative to recipient BSA and graft outcomes [104]. When the data presented in the current project was re-analyzed using D/RBSAR as the primary predictor of interest, a higher ratio was associated with

significantly higher eGFR at 1 year after transplant, but not at 3 or 5 years. D/RBSAR was also not associated with rate of decline in eGFR as assessed by annualized change in eGFR. The association with eGFR at 1 year post-transplant, which was in the opposite direction of the effect of D/RBMIR, persisted after adjusting for recipient BMI. Overweight and obese recipients demonstrated an increased eGFR at 1 year relative to normal weight recipients (with obese being the highest), which was statistically significant even after adjusting for D/RBSAR. Recipient BMI again appeared to be predictive of annualized change in eGFR over time independent of the potential discrepancy between the size of the donor and recipient.

One of the best tests of the hyperfiltration hypothesis may be to determine if placing a small kidney into a large recipient is associated with an increased risk of graft failure. However, measurement of nephron number, functional capacity, and functional demand is highly complex, even more so in the setting of a renal graft. Furthermore, we need to be able to measure it in a way that is clinically applicable. The observations from this study in light of previous literature brings to the forefront the complexities of this very issue and the question of what exactly is being measured by these surrogates of "nephron dosing". A lot of the hypotheses regarding nephron dosing and hyperfiltration are based on the assumption that large individuals have a greater renal functional capacity than smaller individuals and that body size matching is really a surrogate for nephron dosing to metabolic demand. This may be too big a step to make and it is important to think about other possible explanations for what is observed.

There is discussion in the literature about the influence of gender matching on graft function post-transplant and it has been postulated that the ratio of donor kidney size to recipient body size is the explanatory variable in this pathway. However, reasons

underpinning the effect of gender match in transplant are not well understood and there is some evidence to suggest that there may be an effect of the "hormonal milieu" and differential immune phenomenon [71]. Analysis of data from a very large multicenter registry (more that 100,000 kidney transplants) has demonstrated inferior graft outcome when kidneys of female donors were transplanted into male recipients compared with kidneys from male donors transplanted into female or male recipients. The effect of donor gender was also evident when graft function was considered. After 1, 3, and 10 years after transplantation, the proportion of patients with a lower creatinine was higher if the graft was received from a male donor. In the current study, it was observed that male recipients of male donors had the slowest rate of decline in annualized change in eGFR (which was significantly different than female recipients of female donors). Also, both female recipients of male donors and male recipients of male donors had a higher eGFR at 3 and 5 years than recipients of female organs (observed in models where influential and high leverage statistics were excluded). These observations persisted even after adjustment for body size match of the donor and recipient (whether by D/RBMIR or D/RBSAR). This observation is of interest as a predominant hypothesis as to why gender differences occur in graft function and survival is that of "nephron underdosing"; data presented here suggests that other mechanisms may play a role.

Many of the previous database studies related to size matching in transplants have been representative of a heterogeneous population including pediatric to adult transplants, adult to pediatric transplants, inclusion of extended criteria donors, multi-organ and repeat transplant. The current study represents a relatively more homogenous population. Not all individuals in the database who met inclusion criteria could be analyzed; in order to determine if the sample analyzed was representative of the transplant population the characteristics of the excluded patients were compared to those

analyzed. Characteristics of the excluded population did not differ from those included in further analysis, with the exception of use of an ACEI or ARB (which was lower in the excluded population) and PRA category (with the excluded group appearing to be more sensitized). Given the small proportion of patients that make up the excluded population (13%) these differences are unlikely to affect the results of this study, particularly in light of the observation that there was no difference in the outcomes analyzed. Of note is that the majority of recipients were Caucasian and an even higher percentage of donors were Caucasian. An effect of race on the outcomes evaluated was not observed however this may relate to the lack of variability, particularly with donor race. Although there is no obvious reason why the results of this study could not be extrapolated to races not represented by the current population, this should be done with caution.

In summary, this project has demonstrated that recipient BMI is an important predictor of graft function post renal transplantation, and likely leads to hyperfiltration that can result in glomerulosclerosis and chronic allograft nephropathy, consistent with previously published data. A novel finding is that this effect is independent of the match between donor and recipient BMI, suggesting that the later is not as important as previously suggested. As BMI increases the ratio between donor and recipient BMI decreases, as recipients are not matched currently based on body size. Contrary to popular thought, D/RBMIR (as a surrogate for nephron dosing) at transplant only predicts graft function when recipient BMI is not considered. A previous understanding of donor and recipient gender matching in transplant as nephron underdosing affecting graft functional outcomes has been challenged with an alternate explanation. This project presents a similar challenge to the paradigm that matching donor and recipient BMI is important.

6.2 Limitations

One of the recurring themes in the literature related to the concept of nephron dosing in transplant and the match between donor and recipient anthropometrics is how to best measure the "exposure" of nephron dosing. The BMI ratio between donor and recipient is likely to encompass a lot more information than just the size of the donor kidney relative to the demands of the recipient. The results of this study therefore must be interpreted in light of this. If the ratio is considered purely as a surrogate of nephron dosing then this study would suggest that nephron dosing is not important and previous observations suggesting it is have been confounded by the recipient BMI. This conclusion however would not be definitively supported by the literature and indeed has some evidence in direct opposition. It is the differences in these studies that need to be sorted out in order to more fully understand the role of body size matching. It can, however, be concluded from this study that matching at transplant by BMI does not predict graft function after transplant independent of recipient BMI, and hence may not be a good parameter to incorporate into organ allocation algorithms, although how this reflects nephron dosing is not clear.

Interpreting data from studies utilizing a surrogate outcome of true GFR that is dependent in multiple ways on the body composition of the recipient is complex, particularly if the exposure or predictive variable of interest is a measure of body size. Muscle mass decreases over time in renal transplant patients [113] and therefore, as creatinine production is dependent on muscle mass, the use of serum creatinine-based equations may be subject to systematic error over time. As a result, serum creatinine-based equations may overestimate GFR progressively over time in transplant populations (26,27). Measurement error introduced by this might have reduced the ability of this

analysis to detect an association between D/RBMIR and annualized change in eGFR over time.

The precision of the estimated change in eGFR over time is also limited by a number of other factors. Although factors associated with systematic differences between estimated and measured GFR in cross-sectional comparisons may not affect the accuracy of determinations of trends in renal function (given that the later analysis depends on change in GFR over time and not absolute values) it has been shown that transplant GFR slope prediction is affected by degree of renal dysfunction; errors in slope prediction are much higher in those with better function and thus add a limitation for eGFR use in longitudinal studies on progressive graft dysfunction [9]. As the outcome is occurring over time, it is also dependent on the number of measurements of GFR and the duration of patient follow-up. Only 6% of the total slopes were calculated with 5 or fewer measurements, with only 1% based on 2 measurements. Eighty-six percent had 10 or more observations and 41% had 20 or more observations, hence the number of measurements is not likely to reduce precision. Furthermore, exploratory analysis demonstrated that duration of follow-up was not a significant predictor of annualized change in eGFR, either in bivariable analysis or in multiple linear regression.

6.3 Future research

Although the outcomes used in this study are clinically meaningful independent of graft survival, they may be considered to be surrogate measures of graft survival. Although this database provided a significant number of patients to evaluate, graft survival differences may be evident only many years after transplant, and as demonstrated the

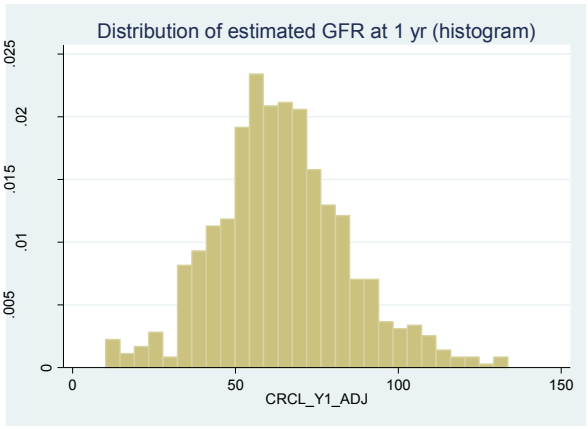
sample size significantly falls off in this study as time of follow-up gets longer. This study has not directly answered questions about graft survival. Additional data from this transplant population, including evolution of proteinuria, histological findings on biopsy, and ultimate graft survival in relation to body size matching, needs evaluation. Furthermore, it is evident that different parameters of recipient body size in relation to donor body size have varying associations with graft function and potentially graft survival. In order to gain greater insight into parameters that would be clinically useful in the matching process, differences in the prediction of outcomes need to be explored.

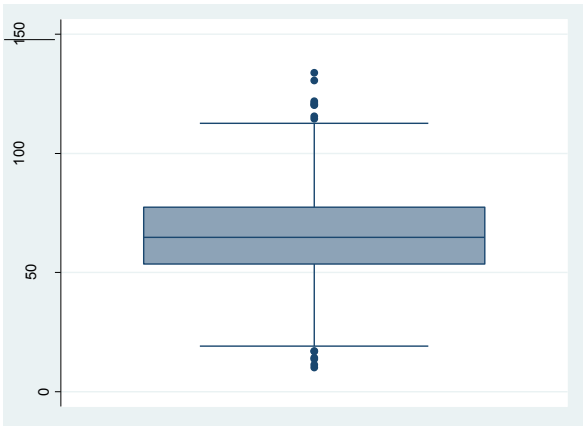
Despite the limitations, the methodology used in this analysis for generating a slope by simple linear regression is a commonly used approach, which is the rationale for using it here. There is little doubt that sequential measurement of GFR must form the basis for the study of chronic allograft dysfunction. In most observational studies and clinical trials, constant slopes over time are assumed and a linear relationship is constructed from GFR estimated at multiple time points; mean slopes are compared between groups of interest to evaluate the effect of interventions on, or the association of risk factors with, the rate of GFR decline. It is important to question whether this approach for measuring GFR slope, as applied in this study, is valid. Data from this transplant population needs to be evaluated using alternate methods of assessing the change in graft function over time with resulting observations about how potential predictive relationships may change.

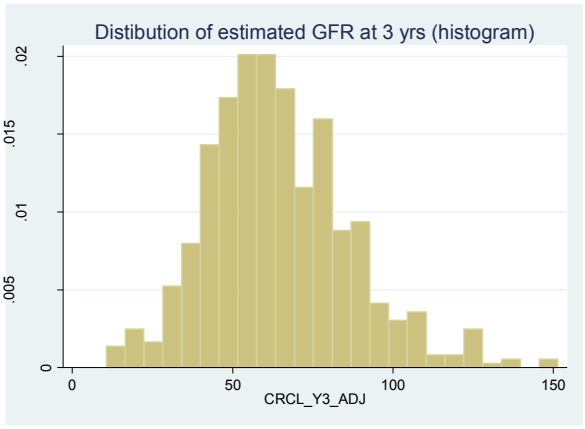
Lastly, there is not a consensus in the literature about what the best method is to estimate GFR in the transplant population and it is even less clear how to truly evaluate GFR when trying to evaluate the role of body size matching in transplant in the context of changing anthropometrics post-transplant. It is clear that large prospective studies need to be carried out evaluating graft function by radioisotope determined GFR with the goal

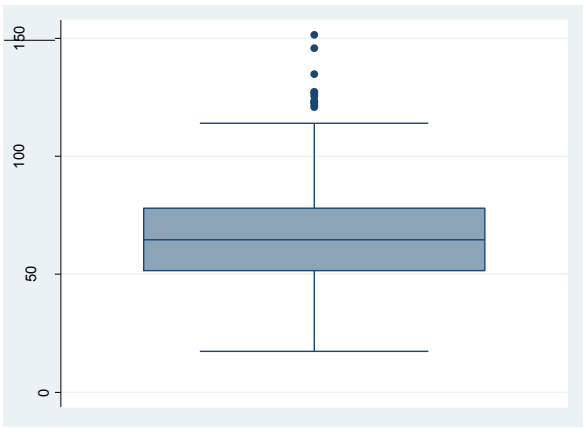
of addressing some of the methodological limitations of using surrogate markers in this complex population.

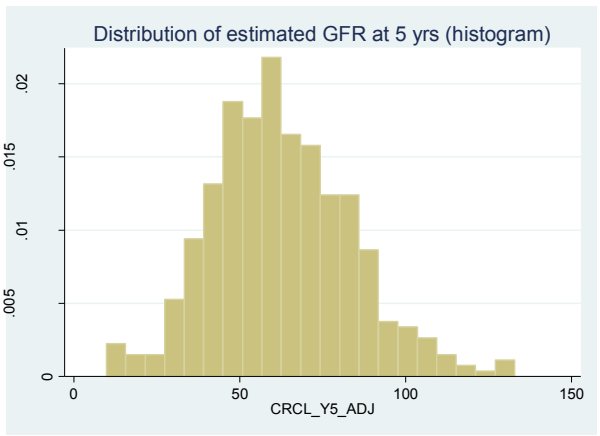
Figure 6: Distribution of Outcome Measures

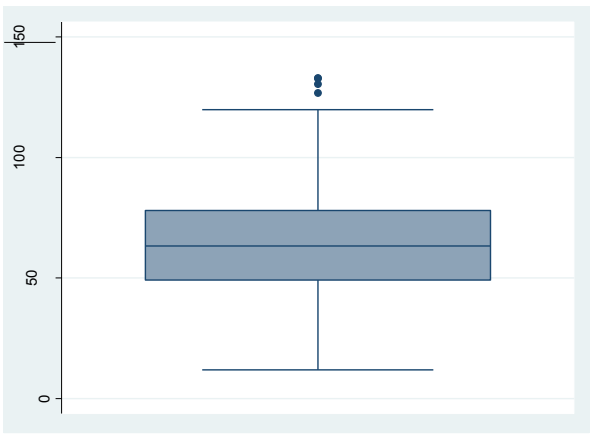


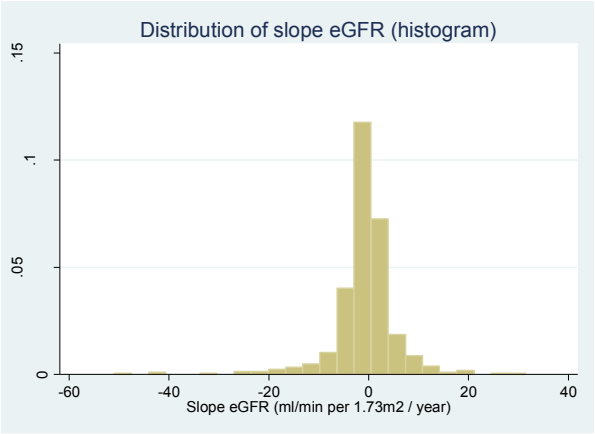


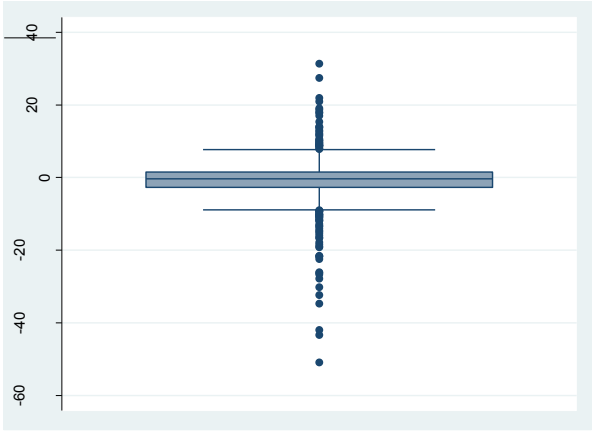









Distribution of slope eGFR (histogram)
0
.05
.1
.15
-60
-40
-20
0
20
40
Slope eGFR (ml/min per 1.73m2 / year)


-60
-40
-20
0
20
40

APPENDIX TWO: Model Building and Analysis of D/R BMI Ratio as an Independent Predictor of CrCl at 1 Year Post-transplant

i. Multiple linear regression model with all variables significant at p≤0.2:

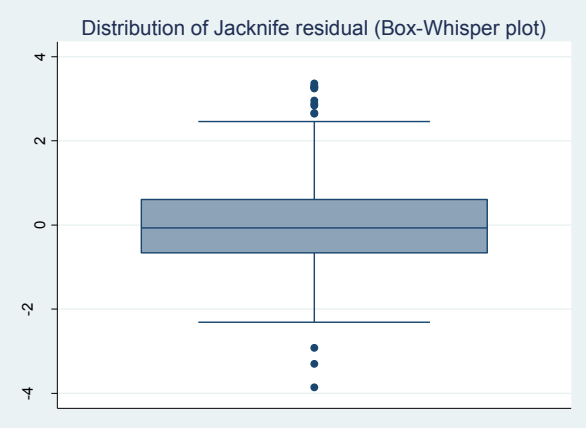
```
xi: regress  crcl_y1_adj bmi_ratio i.r_BMIcat d_age i.d_race_cat r_age
i.r_race_cat i.g_match i.hla_ab_mm any_rej ace_arb dd_ld if index_k==1 &
ecd_10==0 & tx_num==1

i.r_BMIcat      _Ir_BMIcat_0-3  (naturally coded; _Ir_BMIcat_0 omitted)
i.d_race_cat    _Id_race_ca_0-3 (naturally coded; _Id_race_ca_0omitted)
i.r_race_cat    _Ir_race_ca_0-4 (naturally coded; _Ir_race_ca_0omitted)
i.g_match       _Ig_match_0-3   (naturally coded; _Ig_match_0 omitted)
i.hla_ab_mm  _Ihla_ab_mm_0-4    (naturally coded; _Ihla_ab_mm_0omitted)

Source |       SS       df       MS              Number of obs =     537
-------------+------------------------------   F( 22,   514) =   10.35
       Model |  59788.9839    22  2717.68109   Prob > F      =  0.0000
    Residual |   135012.43   514  262.670096   R-squared     =  0.3069
-------------+------------------------------   Adj R-squared =  0.2773
       Total |  194801.413   536  363.435473   Root MSE      =  16.207
------------------------------------------------------------------------------
 crcl_y1_adj |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
   bmi_ratio |  -.5352622   3.246735    -0.16   0.869  -6.913    5.843
_Ir_BMIcat_1 |   4.351405   5.370886     0.81   0.418  -6.200   14.902
_Ir_BMIcat_2 |   5.797645   1.777135     3.26   0.001   2.306    9.288
_Ir_BMIcat_3 |   9.642231   2.261281     4.26   0.000   5.199   14.084
       d_age |  -.4039479   .0675655    -5.98   0.000   -.536   -.271
_Id_race_c~1 |  -1.554555   3.556083    -0.44   0.662  -8.540    5.431
_Id_race_c~2 |  -1.267046   5.427328    -0.23   0.815 -11.929    9.395
_Id_race_c~3 |  (dropped)
       r_age |  -.4834199   .0599146    -8.07   0.000   -.6011   -.365
_Ir_race_c~1 |    -2.7264   3.447153    -0.79   0.429  -9.498    4.045
_Ir_race_c~2 |   1.849565   3.972915     0.47   0.642  -5.955    9.654
_Ir_race_c~3 |   1.593671   7.462273     0.21   0.831 -13.066   16.253
_Ir_race_c~4 |   8.915472   7.367177     1.21   0.227  -5.558   23.388
 _Ig_match_1 |  -2.037203   2.148039    -0.95   0.343  -6.257    2.182
 _Ig_match_2 |   7.271204   2.467854     2.95   0.003   2.422   12.119
 _Ig_match_3 |   3.860876    2.18354     1.77   0.078   -.428    8.150
_Ihla_ab_m~1 |   .6246166   2.978491     0.21   0.834  -5.226    6.476
_Ihla_ab_m~2 |  -2.250529   2.609706    -0.86   0.389  -7.377    2.876
_Ihla_ab_m~3 |  -2.183448   2.888645    -0.76   0.450  -7.858    3.491
_Ihla_ab_m~4 |    -3.2102   3.153743    -1.02   0.309  -9.406    2.985
     any_rej |  -7.053872   1.530667    -4.61   0.000 -10.061   -4.046
     ace_arb |   4.073183   1.565285     2.60   0.010    .998    7.148
       dd_ld |   4.204782    1.79928     2.34   0.020    .669    7.739
       _cons |   102.3802   6.275054    16.32   0.000  90.052  114.708
------------------------------------------------------------------------------
```

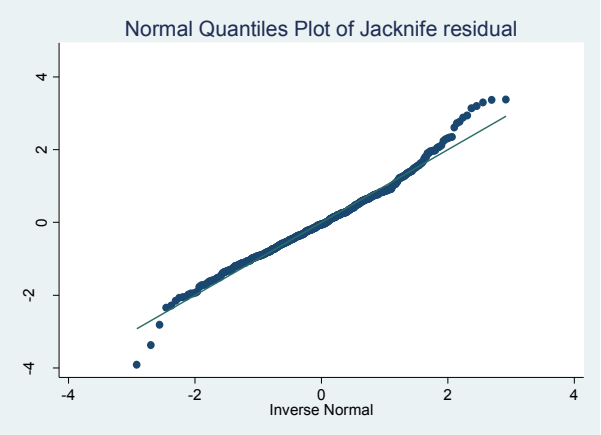
ii. Final multiple linear regression model:

```
xi: regress  crcl_y1_adj bmi_ratio i.r_BMIcat d_age r_age i.g_match any_rej
ace_arb dd_ld if index_k==1 & ecd_10==0 & tx_num==1

i.r_BMIcat     _Ir_BMIcat_0-3   (naturally coded; _Ir_BMIcat_0 omitted)
i.g_match      _Ig_match_0-3    (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     550
-------------+------------------------------   F( 12,   537) =   18.92
       Model |  59752.8554    12  4979.40462   Prob > F      =  0.0000
    Residual |  141312.607   537  263.151968   R-squared     =  0.2972
-------------+------------------------------   Adj R-squared =  0.2815
       Total |  201065.462   549  366.239458   Root MSE      =  16.222
------------------------------------------------------------------------------
 crcl_y1_adj |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
   bmi_ratio |  -.5764926   3.155628    -0.18   0.855  -6.775    5.622
_Ir_BMIcat_1 |   5.038163   5.344787     0.94   0.346  -5.461   15.537
_Ir_BMIcat_2 |   6.257936   1.744639     3.59   0.000   2.830    9.685
_Ir_BMIcat_3 |   9.596666     2.2054     4.35   0.000   5.264   13.928
       d_age |  -.4068858   .0662229    -6.14   0.000   -.536    -.276
       r_age |  -.4908815   .0577111    -8.51   0.000   -.604    -.377
 _Ig_match_1 |  -3.145691   2.072006    -1.52   0.130  -7.215    .924
 _Ig_match_2 |   5.987177   2.397104     2.50   0.013   1.278   10.696
 _Ig_match_3 |   2.720668   2.112959     1.29   0.198  -1.430    6.871
     any_rej |  -7.796817   1.469791    -5.30   0.000  -10.684  -4.909
     ace_arb |   3.778668   1.533687     2.46   0.014   .765    6.791
       dd_ld |   4.718937     1.4909     3.17   0.002  1.790    7.647
       _cons |   98.49778   5.049983    19.50   0.000  88.577   108.419
------------------------------------------------------------------------------
```

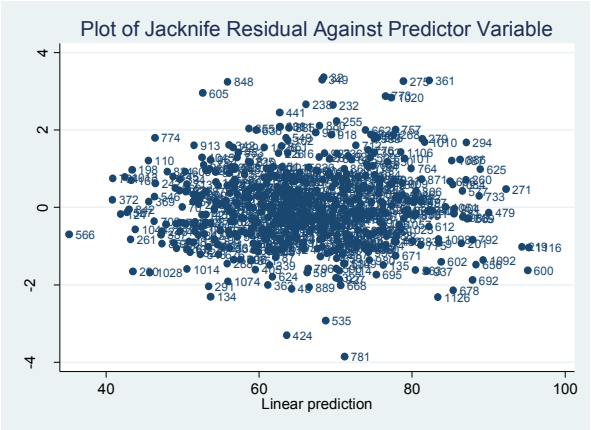
iii. Regression diagnostics for final model:

Verifying normality:

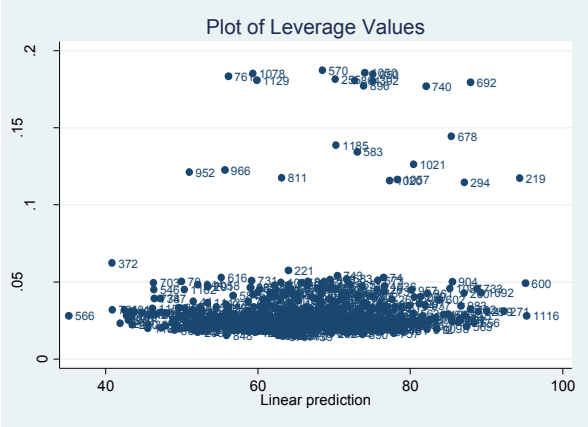




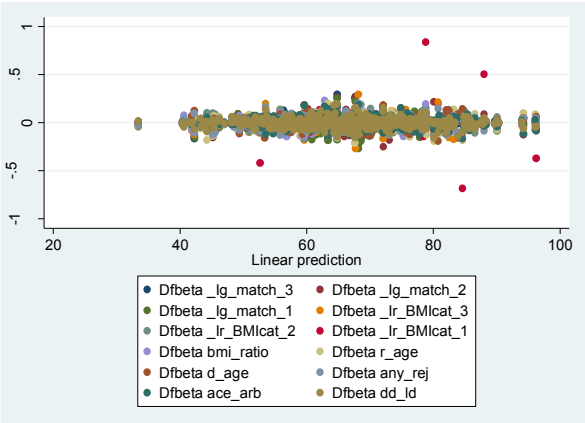
Verifying equal variance:

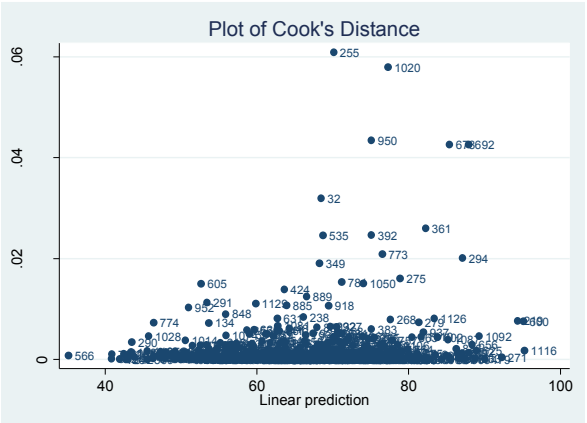


Detecting outliers in independent variables:



To measure influence of individual observations on regression coefficients:





iv. Final regression model – influential and high leverage excluded:

```
xi: regress  crcl_y1_adj bmi_ratio i.r_BMIcat d_age r_age i.g_match any_rej
ace_arb dd_ld if index_k==1 & ecd_10==0 & tx_num==1 & h<0.05
& cook<0.01

i.r_BMIcat    _Ir_BMIcat_0-3   (naturally coded; _Ir_BMIcat_0 omitted)
i.g_match     _Ig_match_0-3    (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     524
-------------+------------------------------   F( 11,   512) =   24.83
       Model |  56722.0509    11  5156.55008   Prob > F      =  0.0000
    Residual |  106330.414   512  207.676589   R-squared     =  0.3479
-------------+------------------------------   Adj R-squared =  0.3339
       Total |  163052.464   523  311.763794   Root MSE      =  14.411
------------------------------------------------------------------------------
 crcl_y1_adj |      Coef.   Std. Err.      t    P>|t|   [95% Conf.Int]
-------------+----------------------------------------------------------------
   bmi_ratio |  -2.810643   3.090915    -0.91   0.364   -8.883   3.261
_Ir_BMIcat_1 |  (dropped)*
_Ir_BMIcat_2 |   6.430731   1.580377     4.07   0.000    3.325   9.535
_Ir_BMIcat_3 |    8.52286   2.026478     4.21   0.000    4.541  12.504
       d_age |  -.4375193    .060556    -7.23   0.000    -.556   -.318
       r_age |  -.4741558   .0529735    -8.95   0.000    -.578   -.370
 _Ig_match_1 |  -3.313398   1.886229    -1.76   0.080   -7.019    .392
 _Ig_match_2 |   4.618089   2.224542     2.08   0.038     .247   8.988
 _Ig_match_3 |   2.086351   1.930734     1.08   0.280   -1.706   5.879
     any_rej |  -8.913121   1.339111    -6.66   0.000  -11.543  -6.282
     ace_arb |   2.993108   1.395888     2.14   0.032     .250   5.735
       dd_ld |   4.381395   1.366319     3.21   0.001    1.697   7.065
       _cons |   102.1656   4.792001    21.32   0.000   92.751 111.580
```

* coefficient dropped as no underweight subjects in this data-set

v. Multiple linear regression- final model with recipient BMI category removed

```
xi: regress  crcl_y1_adj bmi_ratio d_age r_age i.g_match any_rej ace_arb
dd_ld if index_k==1 & ecd_10==0 & tx_num==1
i.g_match   _Ig_match_0-3       (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     551
-------------+------------------------------   F(  9,   541) =   21.66
       Model |  53424.1702     9  5936.01891   Prob > F      =  0.0000
    Residual |   148233.97   541  273.999944   R-squared     =  0.2649
-------------+------------------------------   Adj R-squared =  0.2527
       Total |   201658.14   550  366.651164   Root MSE      =  16.553
------------------------------------------------------------------------------
 crcl_y1_adj |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
   bmi_ratio |  -8.142746   2.715711    -3.00   0.003  -13.477  -2.808
       d_age |  -.3745595   .0671001    -5.58   0.000    -.506   -.242
       r_age |  -.4353461   .0570383    -7.63   0.000    -.547   -.323
 _Ig_match_1 |  -2.277643   2.091692    -1.09   0.277   -6.386   1.831
 _Ig_match_2 |    6.35655   2.429654     2.62   0.009    1.583  11.129
 _Ig_match_3 |    3.17136   2.148551     1.48   0.141   -1.049   7.391
     any_rej |  -7.420721   1.492524    -4.97   0.000  -10.352  -4.488
     ace_arb |   4.252271   1.556443     2.73   0.006    1.194   7.309
       dd_ld |      5.126   1.516154     3.38   0.001    2.147   8.104
       _cons |   105.8127   4.912605    21.54   0.000   96.162 115.462
------------------------------------------------------------------------------
```

vi. Exploratory analysis:

Final model fit with D/RBSAR as a predictor

```
xi: regress  crcl_y1_adj  BSA_ratio i.r_BMIcat d_age r_age i.g_match any_rej
ace_arb dd_ld if index_k==1 & ecd_10==0 & tx_num==1
i.r_BMIcat      _Ir_BMIcat_0-3      (naturally coded; _Ir_BMIcat_0 omitted)
i.g_match       _Ig_match_0-3       (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS            Number of obs =     550
-------------+------------------------------         F( 12,   537) =   19.43
       Model |  60880.5803    12   5073.3817         Prob > F      =  0.0000
    Residual |  140184.882   537  261.051922         R-squared     =  0.3028
-------------+------------------------------         Adj R-squared =  0.2872
       Total |  201065.462   549  366.239458         Root MSE      =  16.157
------------------------------------------------------------------------------
 crcl_y1_adj |      Coef.   Std. Err.      t    P>|t|   [95% Conf. Interval]
-------------+----------------------------------------------------------------
   BSA_ratio |   11.00405   5.273873     2.09   0.037     .644      21.364
_Ir_BMIcat_1 |   3.105856   5.347672     0.58   0.562   -7.399      13.610
_Ir_BMIcat_2 |   7.411288   1.715104     4.32   0.000    4.042      10.780
_Ir_BMIcat_3 |   11.76884     2.1193     5.55   0.000    7.605      15.931
       d_age |  -.4272002   .0651815    -6.55   0.000    -.555       -.299
       r_age |  -.4854475   .0575361    -8.44   0.000    -.598       -.372
```

```
 _Ig_match_1 |  -1.810311    2.15973    -0.84   0.402   -6.052       2.432
 _Ig_match_2 |   4.640211   2.473858     1.88   0.061    -.219       9.499
 _Ig_match_3 |   2.980241    2.10767     1.41   0.158   -1.160       7.120
     any_rej |  -7.499931   1.469483    -5.10   0.000  -10.386      -4.613
     ace_arb |   3.698239   1.527823     2.42   0.016     .696       6.699
       dd_ld |     4.8562   1.478351     3.28   0.001    1.952       7.760
       _cons |   85.95896   6.963808    12.34   0.000   72.279      99.638
------------------------------------------------------------------------------
```

APPENDIX THREE: Model Building and Analysis of D/R BMI Ratio as an Independent Predictor of CrCl at 3 Years Post-transplant

i. Multiple linear regression model with all variables significant at p≤0.2:

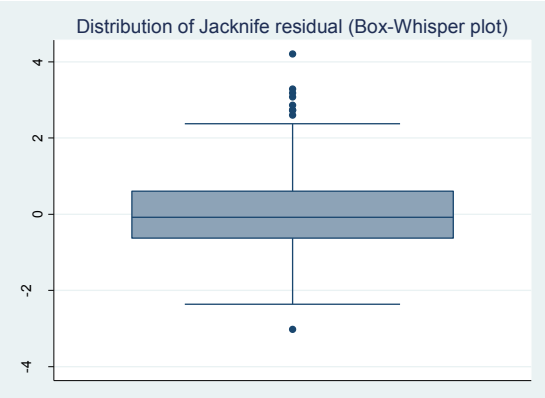
```
xi: regress  crcl_y3_adj bmi_ratio i.r_BMIcat d_age i.d_race_cat r_age
i.r_race_cat i.g_match i.pra_cat i.hla_ab_mm any_rej ace_arb dd_ld if
index_k==1 & ecd_10==0 & tx_num==1
i.r_BMIcat    _Ir_BMIcat_0-3   naturally coded; _Ir_BMIcat_0 omitted)
i.d_race_cat  _Id_race_ca_0-3 (naturally coded; _Id_race_ca_0 omitted)
i.r_race_cat  _Ir_race_ca_0-4 (naturally coded; _Ir_race_ca_0 omitted)
i.g_match     _Ig_match_0-3   (naturally coded; _Ig_match_0 omitted)
i.pra_cat     _Ipra_cat_0-2   (naturally coded; _Ipra_cat_0 omitted)
i.hla_ab_mm   _Ihla_ab_mm_0-4 (naturally coded; _Ihla_ab_mm_0 omitted)

      Source |       SS       df       MS      Number of obs =     408
-------------+------------------------------   F( 24,   383) =    6.08
       Model |   47816.551    24  1992.35629   Prob > F      =  0.0000
    Residual |  125452.287   383  327.551664   R-squared     =  0.2760
-------------+------------------------------   Adj R-squared =  0.2306
       Total |  173268.838   407  425.721961   Root MSE      =  18.098
------------------------------------------------------------------------------
 crcl_y3_adj |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
   bmi_ratio |  -1.793374   4.110111    -0.44   0.663   -9.874   6.287
_Ir_BMIcat_1 |   1.276801   8.385022     0.15   0.879  -15.209  17.763
_Ir_BMIcat_2 |   6.766933   2.273902     2.98   0.003    2.296  11.237
_Ir_BMIcat_3 |   9.329351   2.882472     3.24   0.001    3.661  14.996
       d_age |  -.4547937   .0875354    -5.20   0.000    -.626   -.282
_Id_race_c~1 |  -.6205707   4.544432    -0.14   0.891   -9.555   8.314
_Id_race_c~2 |   1.957125   6.747182     0.29   0.772  -11.309  15.223
_Id_race_c~3 |  (dropped)
       r_age |  -.4516564   .0813935    -5.55   0.000    -.611   -.291
_Ir_race_c~1 |  -5.195442   4.839126    -1.07   0.284  -14.710   4.319
_Ir_race_c~2 |   .5691166   5.281814     0.11   0.914   -9.815  10.954
_Ir_race_c~3 |   1.446075   10.24319     0.14   0.888  -18.693  21.586
_Ir_race_c~4 |   3.809062    11.5103     0.33   0.741  -18.822  26.440
 _Ig_match_1 |   1.227789   2.768693     0.44   0.658   -4.215   6.671
 _Ig_match_2 |    8.08908   3.146153     2.57   0.011    1.903  14.274
 _Ig_match_3 |   4.823385   2.771945     1.74   0.083  -.626    10.273
 _Ipra_cat_1 |  -2.625805   2.182481    -1.20   0.230   -6.916   1.665
 _Ipra_cat_2 |    9.02641   5.770749     1.56   0.119   -2.319  20.372
_Ihla_ab_m~1 |   -1.66996   3.858717    -0.43   0.665   -9.256   5.916
_Ihla_ab_m~2 |   -1.71278   3.377883    -0.51   0.612   -8.354   4.928
_Ihla_ab_m~3 |  -.8710043   3.662305    -0.24   0.812   -8.071   6.329
_Ihla_ab_m~4 |  -3.661572   4.021717    -0.91   0.363  -11.568   4.245
     any_rej |  -7.927762   1.986983    -3.99   0.000  -11.834  -4.021
     ace_arb |   5.072828   2.098928     2.42   0.016     .945   9.199
       dd_ld |   4.392148   2.308109     1.90   0.058    -.146   8.930
       _cons |   104.6739   7.991443    13.10   0.000   88.961 120.386
------------------------------------------------------------------------------
```

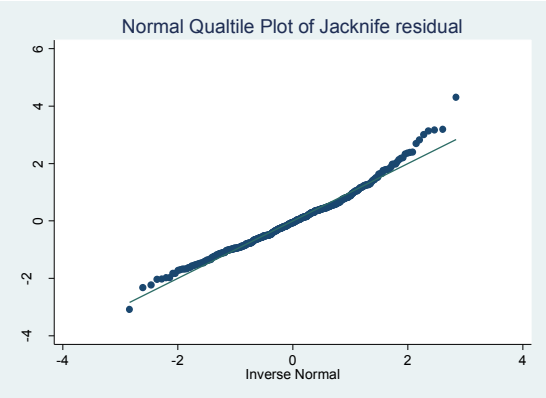
ii. Final multiple linear regression model:

```
xi: regress  crcl_y3_adj bmi_ratio i.r_BMIcat d_age  r_age  i.g_match
any_rej ace_arb dd_ld if index_k==1 & ecd_10==0 & tx_num==1
i.r_BMIcat      _Ir_BMIcat_0-3 (naturally coded; _Ir_BMIcat_0 omitted)
i.g_match       _Ig_match_0-3  (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     425
-------------+------------------------------   F( 12,   412) =   12.09
       Model |  48336.9947    12   4028.0829   Prob > F      =  0.0000
    Residual |  137303.654   412  333.261297   R-squared     =  0.2604
-------------+------------------------------   Adj R-squared =  0.2388
       Total |  185640.649   424   437.83172   Root MSE      =  18.255
------------------------------------------------------------------------------
 crcl_y3_adj |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
   bmi_ratio |  -2.359842   3.976616    -0.59   0.553  -10.176   5.457
_Ir_BMIcat_1 |   1.209009   7.643969     0.16   0.874  -13.817  16.235
_Ir_BMIcat_2 |   7.541561   2.208618     3.41   0.001    3.199  11.883
_Ir_BMIcat_3 |   9.315002   2.822449     3.30   0.001    3.766  14.863
       d_age |  -.4634913   .0851325    -5.44   0.000    -.630   -.296
       r_age |  -.4432665   .0773241    -5.73   0.000    -.595   -.291
 _Ig_match_1 |  -.1991352   2.640797    -0.08   0.940   -5.390   4.991
 _Ig_match_2 |   7.475721   3.071901     2.43   0.015    1.437  13.514
 _Ig_match_3 |   4.178779   2.636963     1.58   0.114   -1.004   9.362
     any_rej |  -8.826725    1.89079    -4.67   0.000  -12.543  -5.109
     ace_arb |   3.950093   2.033352     1.94   0.053    -.046   7.947
       dd_ld |    5.36564   1.907973     2.81   0.005    1.615   9.116
       _cons |   99.32352   6.445057    15.41   0.000   86.654 111.993
------------------------------------------------------------------------------
```

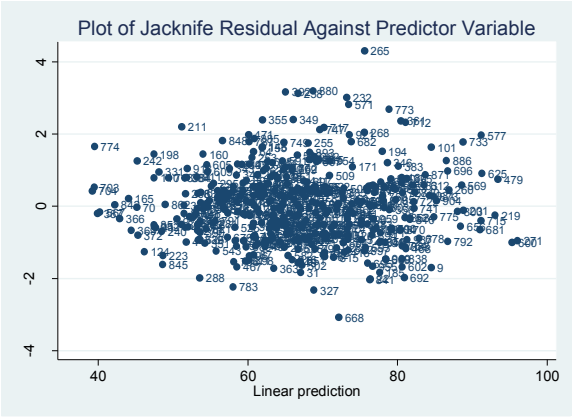
iii. Regression diagnostics for final model:

Verifying normality:

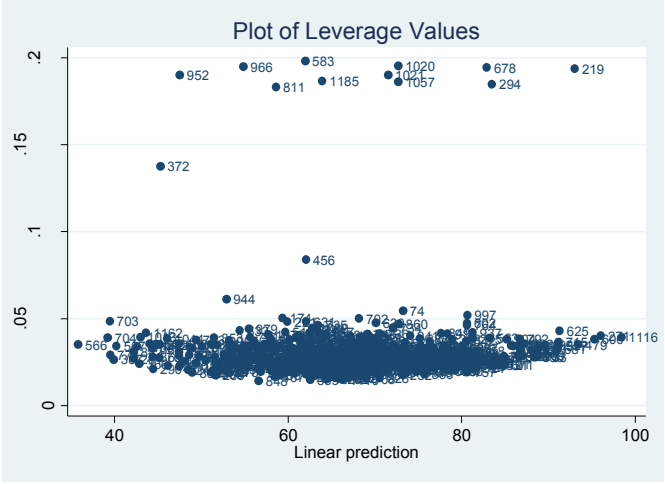




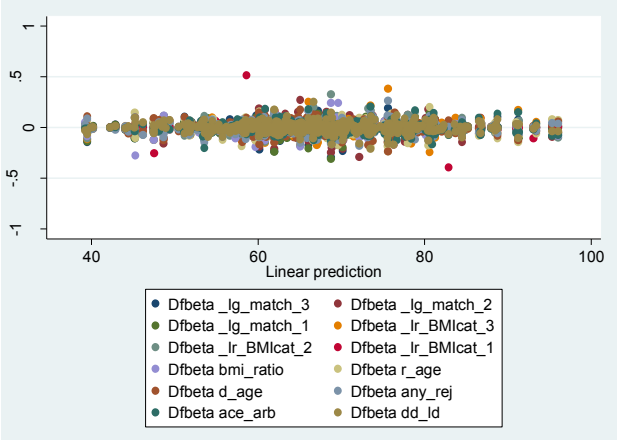
For checking equal variance assumption:

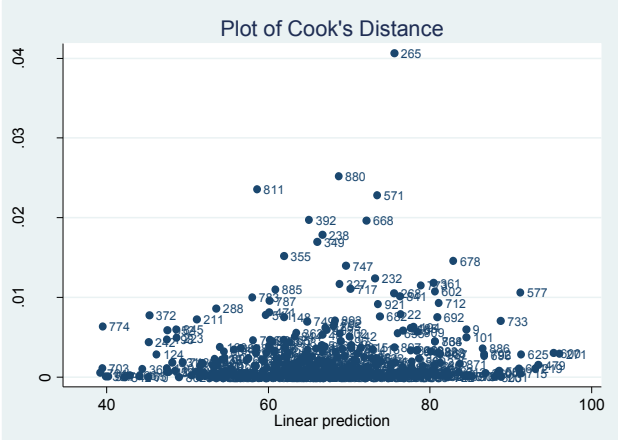


To detect outliers in independent variables:



To measure influence of individual observations on regression coefficients:





iv. Final regression model – influencial and high leverage excluded:

```
xi: regress  crcl_y3_adj bmi_ratio i.r_BMIcat d_age  r_age  i.g_match
any_rej ace_arb dd_ld if index_k==1 & ecd_10==0 & tx_num==1 & h<0.0
> 6 & cook<0.01
i.r_BMIcat   _Ir_BMIcat_0-3    (naturally coded; _Ir_BMIcat_0 omitted)
i.g_matc     _Ig_match_0-3     (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     396
-------------+------------------------------   F( 11,   384) =   15.28
       Model |  39766.3909    11  3615.12644   Prob > F      =  0.0000
    Residual |  90829.4155   384  236.534936   R-squared     =  0.3045
-------------+------------------------------   Adj R-squared =  0.2846
       Total |  130595.806   395  330.622295   Root MSE      =   15.38
------------------------------------------------------------------------------
 crcl_y3_adj |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
   bmi_ratio |  -1.694753    3.89887    -0.43   0.664   -9.360   5.971
_Ir_BMIcat_1 |  (dropped)*
_Ir_BMIcat_2 |   6.199955   1.942995     3.19   0.002    2.379  10.020
_Ir_BMIcat_3 |   8.038302   2.562466     3.14   0.002    3.000  13.076
       d_age |    -.43651   .0746657    -5.85   0.000    -.583   -.289
       r_age |  -.3462064   .0692638    -5.00   0.000    -.482   -.210
 _Ig_match_1 |   1.942388   2.318981     0.84   0.403   -2.617   6.501
 _Ig_match_2 |   11.02912   2.726481     4.05   0.000    5.668  16.389
 _Ig_match_3 |   5.605766   2.304077     2.43   0.015    1.075  10.136
     any_rej |  -7.960298   1.656299    -4.81   0.000  -11.216  -4.703
     ace_arb |   3.372522    1.76913     1.91   0.057    -.105   6.850
       dd_ld |   6.781939   1.676251     4.05   0.000    3.486  10.077
       _cons |   90.19679   6.005907    15.02   0.000   78.388 102.005
------------------------------------------------------------------------------
```

* coefficient dropped as no underweight subjects in this data-set

v. Multiple linear regression- final model with recipient BMI category removed

```
xi: regress  crcl_y3_adj bmi_ratio d_age  r_age  i.g_match  any_rej ace_arb
dd_ld if index_k==1 & ecd_10==0 & tx_num==1

i.g_match    _Ig_match_0-3    (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     425
-------------+------------------------------   F(  9,   415) =   14.01
       Model |  43262.2213     9  4806.91347   Prob > F      =  0.0000
    Residual |  142378.428   415  343.080549   R-squared     =  0.2330
-------------+------------------------------   Adj R-squared =  0.2164
       Total |  185640.649   424   437.83172   Root MSE      =  18.522
------------------------------------------------------------------------------
 crcl_y3_adj |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
   bmi_ratio |   -9.79239   3.438943    -2.85   0.005  -16.552  -3.032
       d_age |  -.4399665   .0860706    -5.11   0.000    -.609   -.270
       r_age |  -.3803575   .0765222    -4.97   0.000    -.530   -.229
 _Ig_match_1 |   .2542787   2.661186     0.10   0.924   -4.976   5.485
 _Ig_match_2 |   7.236847   3.104302     2.33   0.020    1.134  13.338
 _Ig_match_3 |    4.54658   2.668768     1.70   0.089    -.699   9.792
     any_rej |  -8.292756   1.908484    -4.35   0.000  -12.044  -4.541
     ace_arb |   4.336056   2.059274     2.11   0.036     .288   8.383
       dd_ld |   5.689779   1.932085     2.94   0.003    1.891   9.487
       _cons |    106.849   6.213546    17.20   0.000   94.635 119.063
------------------------------------------------------------------------------
```

vi. Exploratory analysis:

Final model fit with eGFR at 1 yr as a predictor

```
xi: regress  crcl_y3_adj  crcl_y1_adj bmi_ratio i.r_BMIcat d_age  r_age
i.g_match  any_rej ace_arb dd_ld if index_k==1 & ecd_10==0 & tx
> _num==1
i.r_BMIcat      _Ir_BMIcat_0-3  (naturally coded; _Ir_BMIcat_0 omitted)
i.g_match       _Ig_match_0-3   (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     423
-------------+------------------------------   F( 13,   409) =   50.02
       Model |  113814.234    13  8754.94108   Prob > F      =  0.0000
    Residual |  71586.0667   409  175.027058   R-squared     =  0.6139
-------------+------------------------------   Adj R-squared =  0.6016
       Total |  185400.301   422  439.337205   Root MSE      =   13.23
------------------------------------------------------------------------------
 crcl_y3_adj |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
 crcl_y1_adj |   .7999622   .0414374    19.31   0.000    .718     .881
   bmi_ratio |  -.1286224   2.887821    -0.04   0.964  -5.805    5.548
_Ir_BMIcat_1 |   6.002921   5.545147     1.08   0.280  -4.897   16.903
_Ir_BMIcat_2 |   3.265052   1.620949     2.01   0.045    .078    6.451
_Ir_BMIcat_3 |   2.753706   2.086914     1.32   0.188  -1.348    6.856
       d_age |  -.1492696   .0640097    -2.33   0.020   -.275  -.023
       r_age |  -.0956693   .0590148    -1.62   0.106   -.211    .020
 _Ig_match_1 |   1.451212   1.921753     0.76   0.451  -2.326    5.228
 _Ig_match_2 |    .144451    2.25952     0.06   0.949  -4.297    4.586
 _Ig_match_3 |    1.49153   1.916994     0.78   0.437  -2.276    5.259
     any_rej |  -3.650657   1.397947    -2.61   0.009  -6.398    -.902
     ace_arb |   1.149791   1.483483     0.78   0.439  -1.766    4.065
       dd_ld |   2.207812   1.396055     1.58   0.115   -.536    4.952
       _cons |   20.69626   6.198916     3.34   0.001   8.510   32.881
------------------------------------------------------------------------------
```

Final model fit with D/RBSAR as a predictor

```
xi: regress  crcl_y3_adj  BSA_ratio i.r_BMIcat d_age  r_age  i.g_match
any_rej ace_arb dd_ld if index_k==1 & ecd_10==0 & tx_num==1
i.r_BMIcat      _Ir_BMIcat_0-3      (naturally coded; _Ir_BMIcat_0 omitted)
i.g_match       _Ig_match_0-3       (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS              Number of obs =     425
-------------+------------------------------           F( 12,   412) =   12.21
       Model |   48685.642    12  4057.13684            Prob > F      =  0.0000
    Residual |  136955.007   412  332.415066            R-squared     =  0.2623
-------------+------------------------------           Adj R-squared =  0.2408
       Total |  185640.649   424   437.83172            Root MSE      =  18.232
------------------------------------------------------------------------------
 crcl_y3_adj |      Coef.   Std. Err.      t    P>|t|   [95% Conf. Interval]
-------------+----------------------------------------------------------------
   BSA_ratio |   8.194338   6.920818     1.18   0.237  -5.410182    21.79886
```

```
_Ir_BMIcat_1 |  -.2995862   7.630393    -0.04   0.969  -15.29894    14.69977
_Ir_BMIcat_2 |   8.793215   2.185464     4.02   0.000   4.497164    13.08927
_Ir_BMIcat_3 |   11.61419   2.747326     4.23   0.000    6.21367    17.01472
       d_age |  -.4901319   .0843658    -5.81   0.000  -.6559731   -.3242907
       r_age |  -.4400535   .0772864    -5.69   0.000  -.5919783   -.2881288
 _Ig_match_1 |   .9346641   2.782035     0.34   0.737  -4.53409    6.403419
 _Ig_match_2 |   6.550347   3.177945     2.06   0.040   .3033373    12.79736
 _Ig_match_3 |   4.412901   2.639146     1.67   0.095  -.7749689    9.600772
     any_rej |  -8.506519   1.900663    -4.48   0.000 -12.24273   -4.770313
     ace_arb |   3.930222   2.030649     1.94   0.054  -.0615021    7.921946
       dd_ld |   5.344259   1.896223     2.82   0.005   1.61678    9.071738
       _cons |   88.21233   9.052014     9.75   0.000   70.41844    106.0062
------------------------------------------------------------------------------
```

APPENDIX FOUR: Model Building and Analysis of D/R BMI Ratio as an Independent Predictor of CrCl at 5 Years Post-transplant

i. Multiple linear regression model with all variables significant at p≤0.2:

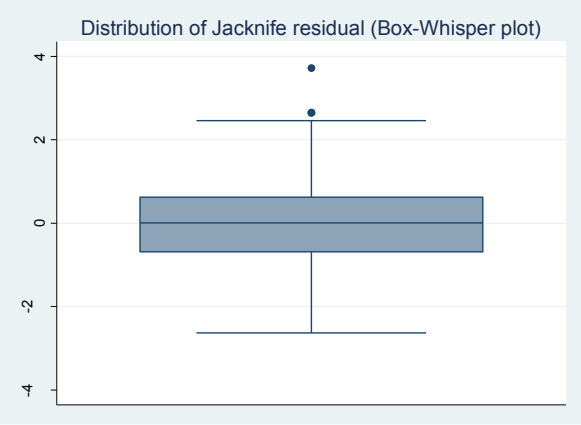
```
i: regress  crcl_y5_adj bmi_ratio i.r_BMIcat d_age i.d_race_cat r_age
i.r_race_cat i.g_match i.hla_ab_mm any_rej ace_arb dd_ld if index_k==1 &
ecd_10==0 & tx_num==1
i.r_BMIcat    _Ir_BMIcat_0-3  (naturally coded; _Ir_BMIcat_0 omitted)
i.d_race_cat  _Id_race_ca_0-3 (naturally coded; _Id_race_ca_0 omitted
i.r_race_cat  _Ir_race_ca_0-4 (naturally coded; _Ir_race_ca_0 omitted)
i.g_match     _Ig_match_0-3   (naturally coded; _Ig_match_0 omitted)
i.hla_ab_mm   _Ihla_ab_mm_0-4 (naturally coded; _Ihla_ab_mm_0 omitted)

      Source |       SS       df       MS      Number of obs =     302
-------------+------------------------------   F( 22,   279) =    4.68
       Model |  34981.1185    22  1590.05084   Prob > F      =  0.0000
    Residual |  94809.2949   279  339.818261   R-squared     =  0.2695
-------------+------------------------------   Adj R-squared =  0.2119
       Total |  129790.413   301  431.197387   Root MSE      =  18.434
------------------------------------------------------------------------------
 crcl_y5_adj |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
   bmi_ratio |  -5.310982   4.805692    -1.11   0.270  -14.771   4.149
_Ir_BMIcat_1 |   2.763986   11.27295     0.25   0.806  -19.426  24.954
_Ir_BMIcat_2 |   7.443378   2.639696     2.82   0.005    2.247  12.639
_Ir_BMIcat_3 |   10.47265   3.503857     2.99   0.003    3.575  17.370
       d_age |  -.4414028   .1096662    -4.02   0.000    -.657   -.225
_Id_race_c~1 |  -8.495431   5.350085    -1.59   0.113  -19.027   2.032
_Id_race_c~2 |  -4.835099   8.125116    -0.60   0.552  -20.829  11.159
_Id_race_c~3 |  (dropped)
       r_age |  -.3625033   .0943963    -3.84   0.000    -.548   -.176
_Ir_race_c~1 |   .0131517   5.280911     0.00   0.998  -10.382  10.408
_Ir_race_c~2 |   8.641603   5.959126     1.45   0.148   -3.088  20.372
_Ir_race_c~3 |  -.7044043    11.8955    -0.06   0.953  -24.120  22.711
_Ir_race_c~4 |  -2.114726    11.8772    -0.18   0.859  -25.495  21.265
 _Ig_match_1 |   -2.20567    3.25916    -0.68   0.499   -8.621   4.209
 _Ig_match_2 |   5.012198   3.788639     1.32   0.187   -2.445  12.470
 _Ig_match_3 |   5.044264   3.254198     1.55   0.122   -1.361  11.450
_Ihla_ab_m~1 |   .5678703   4.786863     0.12   0.906   -8.855   9.990
_Ihla_ab_m~2 |   2.716372   4.182062     0.65   0.517   -5.516  10.948
_Ihla_ab_m~3 |  -3.241069   4.496248    -0.72   0.472  -12.091   5.609
_Ihla_ab_m~4 |   2.561516   4.952692     0.52   0.605   -7.187  12.310
     any_rej |  -6.380559    2.32688    -2.74   0.006  -10.961  -1.800
     ace_arb |   6.412271   2.688206     2.39   0.018    1.120  11.704
       dd_ld |   4.970478   2.859119     1.74   0.083    -.657  10.598
       _cons |   100.9889   9.326069    10.83   0.000   82.630  119.347
------------------------------------------------------------------------------
```

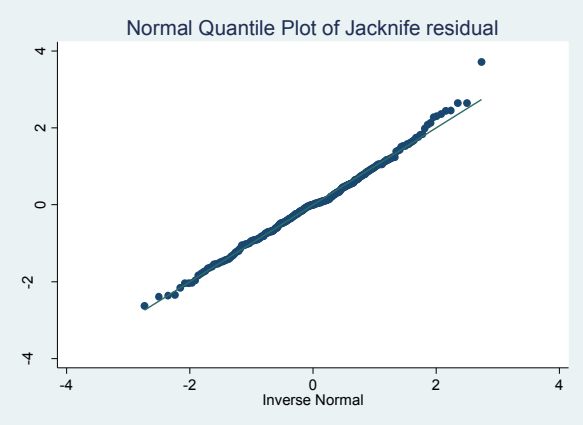
ii. Final multiple linear regression model:

```
xi: regress  crcl_y5_adj bmi_ratio i.r_BMIcat d_age  r_age i.g_match any_rej
ace_arb dd_ld if index_k==1 & ecd_10==0 & tx_num==1

i.r_BMIcat     _Ir_BMIcat_0-3  (naturally coded; _Ir_BMIcat_0 omitted)
i.g_match      _Ig_match_0-3   (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     312
-------------+------------------------------   F( 12,   299) =    8.13
       Model |  33989.4077    12  2832.45065   Prob > F      =  0.0000
    Residual |   104193.31   299   348.47261   R-squared     =  0.2460
-------------+------------------------------   Adj R-squared =  0.2157
       Total |  138182.718   311  444.317422   Root MSE      =  18.667
------------------------------------------------------------------------------
 crcl_y5_adj |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
   bmi_ratio |  -2.685605   4.603846    -0.58   0.560  -11.745   6.374
_Ir_BMIcat_1 |   7.008812   11.07099     0.63   0.527  -14.778  28.795
_Ir_BMIcat_2 |   8.769795   2.597955     3.38   0.001    3.657  13.882
_Ir_BMIcat_3 |   9.495292   3.402116     2.79   0.006    2.800  16.190
       d_age |  -.4582812   .1076771    -4.26   0.000    -.670   -.246
       r_age |   -.403078   .0914619    -4.41   0.000    -.583   -.223
 _Ig_match_1 |  -2.369071   3.138173    -0.75   0.451   -8.544   3.806
 _Ig_match_2 |   5.201708   3.703446     1.40   0.161   -2.086  12.489
 _Ig_match_3 |   3.984498   3.151552     1.26   0.207   -2.217  10.186
     any_rej |  -6.455801   2.217298    -2.91   0.004  -10.819  -2.092
     ace_arb |   5.585733   2.586418     2.16   0.032     .495  10.675
       dd_ld |   4.673725   2.301136     2.03   0.043     .145   9.202
       _cons |   94.72128   7.505603    12.62   0.000   79.950 109.491
------------------------------------------------------------------------------
```

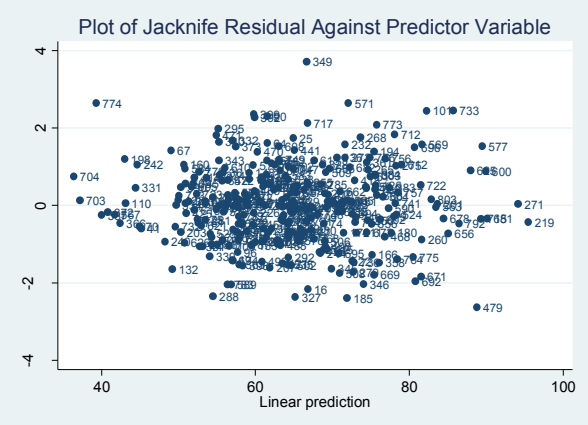
iii. Regression diagnostics for final model:

Verifying normality:

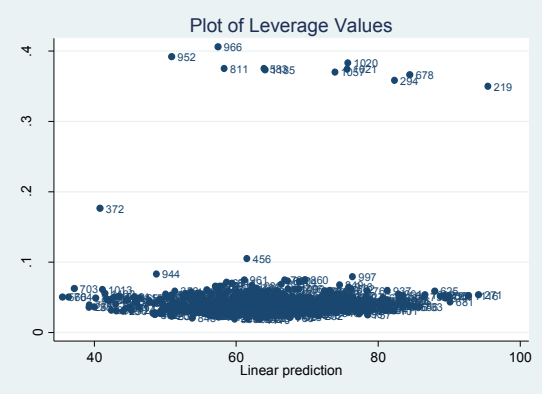




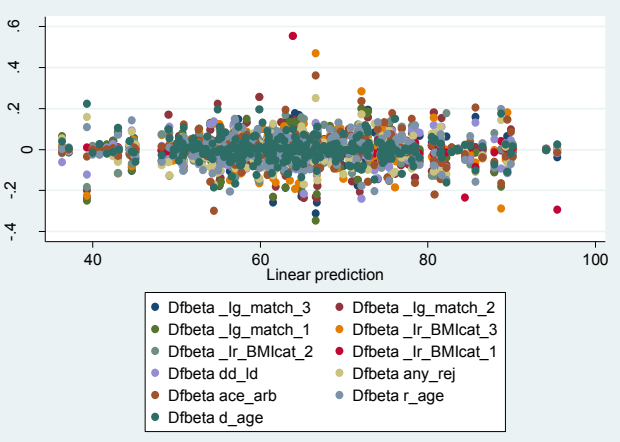
For checking equal variance assumption:

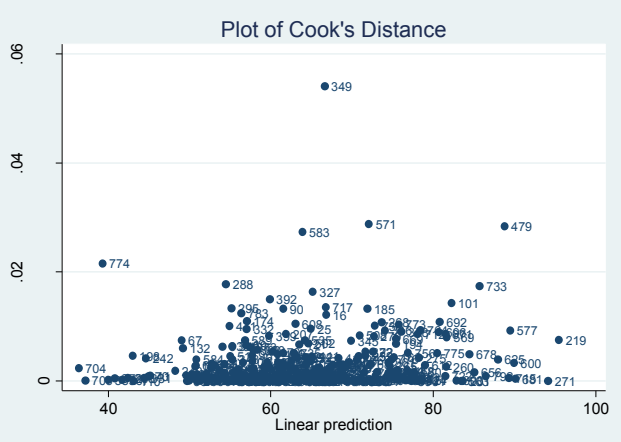


To detect outliers in independent variables:



To measure influence of individual observations on regression coefficients:





iv. Final regression model – influencial and high leverage excluded:

```
xi: regress  crcl_y5_adj bmi_ratio i.r_BMIcat d_age  r_age i.g_match any_rej
ace_arb dd_ld if index_k==1 & ecd_10==0 & tx_num==1 & h<0.08
> & cook<0.012
i.r_BMIcat      _Ir_BMIcat_0-3  (naturally coded; _Ir_BMIcat_0 omitted)
i.g_match       _Ig_match_0-3   (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     292
-------------+------------------------------   F( 11,   280) =   11.38
       Model |  32344.0693    11  2940.36993   Prob > F      =  0.0000
    Residual |  72332.4655   280  258.330234   R-squared     =  0.3090
-------------+------------------------------   Adj R-squared =  0.2818
       Total |  104676.535   291  359.713178   Root MSE      =  16.073
------------------------------------------------------------------------------
crcl_y5_adj |      Coef.   Std. Err.      t    P>|t|   [95% Conf. Int]
-------------+----------------------------------------------------------------
   bmi_ratio |  -.3585314   4.556577    -0.08   0.937   -9.328   8.610
_Ir_BMIcat_1 |  (dropped)
_Ir_BMIcat_2 |   8.447652    2.31593     3.65   0.000    3.888  13.006
_Ir_BMIcat_3 |     9.2806   3.110691     2.98   0.003    3.157  15.403
       d_age |  -.5005304   .0969172    -5.16   0.000    -.691   -.309
       r_age |  -.3397123   .0822534    -4.13   0.000    -.501   -.177
 _Ig_match_1 |   2.266239   2.804227     0.81   0.420   -3.253   7.786
 _Ig_match_2 |    11.7536   3.346903     3.51   0.001    5.165  18.341
 _Ig_match_3 |   8.366038   2.830541     2.96   0.003    2.794  13.937
     any_rej |  -6.216545   1.966503    -3.16   0.002  -10.087  -2.345
     ace_arb |   5.494269   2.299917     2.39   0.018     .966  10.021
       dd_ld |   6.268092   2.048857     3.06   0.002    2.234  10.301
       _cons |   86.01391   7.184515    11.97   0.000  71.871  100.156
```

* coefficient dropped as no underweight subjects in this data-set

v. Multiple linear regression- final model with recipient BMI category removed

```
. xi: regress  crcl_y5_adj bmi_ratio d_age  r_age i.g_match any_rej ace_arb
dd_ld if index_k==1 & ecd_10==0 & tx_num==1

i.g_match    _Ig_match_0-3     (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     312
-------------+------------------------------   F(  9,   302) =    8.99
       Model |  29199.0935     9  3244.34372   Prob > F      =  0.0000
    Residual |  108983.625   302  360.872929   R-squared     =  0.2113
-------------+------------------------------   Adj R-squared =  0.1878
       Total |  138182.718   311  444.317422   Root MSE      =  18.997
------------------------------------------------------------------------------
 crcl_y5_adj |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
   bmi_ratio |  -10.25425   4.016789    -2.55   0.011  -18.158  -2.349
       d_age |  -.4095158    .108147    -3.79   0.000    -.622   -.196
       r_age |  -.3500104   .0909461    -3.85   0.000    -.528   -.171
 _Ig_match_1 |  -1.900047   3.146678    -0.60   0.546   -8.092   4.292
 _Ig_match_2 |   5.477725   3.761237     1.46   0.146   -1.923  12.879
 _Ig_match_3 |   4.600124   3.193468     1.44   0.151   -1.684  10.884
     any_rej |  -6.098273   2.242325    -2.72   0.007  -10.510  -1.685
     ace_arb |   5.677101    2.61803     2.17   0.031     .525  10.828
       dd_ld |   5.238996   2.334898     2.24   0.026     .644   9.833
       _cons |   102.1564   7.333305    13.93   0.000   87.725 116.587
------------------------------------------------------------------------------
```

vi. Exploratory analysis:

Final model fit with eGFR at 1 yr as a predictor

```
xi: regress  crcl_y5_adj  crcl_y1_adj bmi_ratio i.r_BMIcat d_age  r_age
i.g_match any_rej ace_arb dd_ld if index_k==1 & ecd_10==0 & tx_n
> um==1
i.r_BMIcat    _Ir_BMIcat_0-3   (naturally coded; _Ir_BMIcat_0 omitted)
i.g_match     _Ig_match_0-3    (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     311
-------------+------------------------------   F( 13,   297) =   22.31
       Model |  68003.4205    13  5231.03234   Prob > F      =  0.0000
    Residual |  69629.7078   297  234.443461   R-squared     =  0.4941
-------------+------------------------------   Adj R-squared =  0.4719
       Total |  137633.128   310  443.977833   Root MSE      =  15.312
------------------------------------------------------------------------------
 crcl_y5_adj |      Coef.   Std. Err.      t    P>|t| [95% Conf. Int]
-------------+----------------------------------------------------------------
 crcl_y1_adj |   .6780436   .0566519    11.97   0.000    .566    .789
   bmi_ratio |  -1.431416    3.78198    -0.38   0.705  -8.874    6.011
_Ir_BMIcat_1 |   13.15492   9.096011     1.45   0.149  -4.745   31.055
_Ir_BMIcat_2 |   4.570644   2.171504     2.10   0.036    .297    8.844
_Ir_BMIcat_3 |   2.963858   2.855681     1.04   0.300  -2.656    8.583
       d_age |  -.1046326   .0930774    -1.12   0.262   -.287    .0785
       r_age |  -.0870446   .0801439    -1.09   0.278   -.244    .0706
 _Ig_match_1 |  -.5912474   2.585964    -0.23   0.819  -5.680    4.497
 _Ig_match_2 |  -.1813594   3.075363    -0.06   0.953  -6.233    5.870
 _Ig_match_3 |   3.193528     2.5885     1.23   0.218  -1.900    8.287
     any_rej |  -3.462808   1.835328    -1.89   0.060  -7.074     .149
     ace_arb |   3.903293   2.129216     1.83   0.068   -.286    8.093
       dd_ld |    2.61452   1.897052     1.38   0.169  -1.118    6.347
       _cons |   24.62688   8.456107     2.91   0.004   7.985   41.268
------------------------------------------------------------------------------
```

Final model fit with D/RBSAR as a predictor

```
xi: regress  crcl_y5_adj  BSA_ratio i.r_BMIcat d_age  r_age i.g_match
any_rej ace_arb dd_ld if index_k==1 & ecd_10==0 & tx_num==1
i.r_BMIcat      _Ir_BMIcat_0-3      (naturally coded; _Ir_BMIcat_0 omitted)
i.g_match       _Ig_match_0-3       (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS            Number of obs =     312
-------------+------------------------------         F( 12,   299) =    8.11
       Model |  33944.7802    12  2828.73168         Prob > F      =  0.0000
    Residual |  104237.938   299  348.621866         R-squared     =  0.2457
-------------+------------------------------         Adj R-squared =  0.2154
       Total |  138182.718   311  444.317422         Root MSE      =  18.671
------------------------------------------------------------------------------
 crcl_y5_adj |      Coef.   Std. Err.      t    P>|t|   [95% Conf. Interval]
-------------+----------------------------------------------------------------
   BSA_ratio |   3.842122   8.342042     0.46   0.645    -12.574    20.258
_Ir_BMIcat_1 |   6.243953    11.0936     0.56   0.574    -15.587    28.075
```

_Ir_BMIcat_2	9.692482	2.618477	3.70	0.000	4.539	14.845
_Ir_BMIcat_3	11.21257	3.360558	3.34	0.001	4.599	17.825
d_age	-.48142	.1056268	-4.56	0.000	-.689	-.273
r_age	-.4048273	.0914068	-4.43	0.000	-.584	-.224
_Ig_match_1	-1.757472	3.344395	-0.53	0.600	-8.339	4.824
_Ig_match_2	4.67872	3.864155	1.21	0.227	-2.925	12.283
_Ig_match_3	4.091752	3.163302	1.29	0.197	-2.133	10.316
any_rej	-6.214085	2.240406	-2.77	0.006	-10.623	-1.805
ace_arb	5.629622	2.586106	2.18	0.030	.540	10.718
dd_ld	4.496972	2.28007	1.97	0.049	.009	8.983
_cons	88.22807	10.92101	8.08	0.000	66.736	109.719

APPENDIX FIVE: Model Building and Analysis of D/R BMI Ratio as an Independent Predictor of Annualized Change in eGFR

i. Multiple linear regression model with all variables significant at p≤0.2:

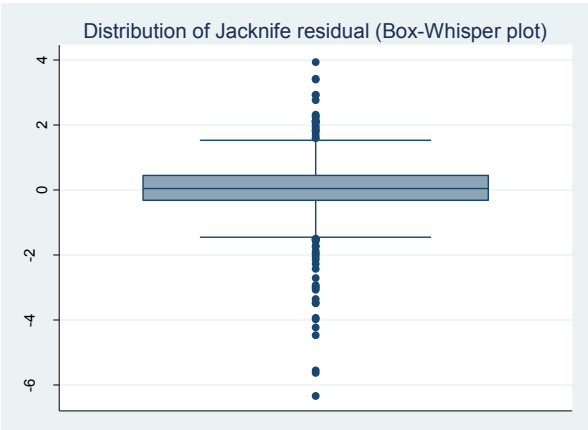
```
xi: regress  SLOPE_eGFR bmi_ratio i.r_BMIcat r_age i.g_match i.pra_cat
ace_arb  any_rej dd_ld if index_k==1 & ecd_10==0 & tx_num==1
i.r_BMIcat   _Ir_BMIcat_0-3    (naturally coded; _Ir_BMIcat_0 omitted)
i.g_match    _Ig_match_0-3     (naturally coded; _Ig_match_0 omitted)
i.pra_cat    _Ipra_cat_0-2     (naturally coded; _Ipra_cat_0 omitted)

      Source |       SS       df       MS      Number of obs =     543
-------------+------------------------------   F( 13,   529) =    6.13
       Model |  3762.87296    13  289.451766   Prob > F      =  0.0000
    Residual |  24990.0677   529  47.2402036   R-squared     =  0.1309
-------------+------------------------------   Adj R-squared =  0.1095
       Total |  28752.9407   542   53.049706   Root MSE      =  6.8732
------------------------------------------------------------------------------
  SLOPE_eGFR |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
   bmi_ratio |   1.500402   1.321021     1.14   0.257  -1.094    4.095
_Ir_BMIcat_1 |  -8.560556   2.381628    -3.59   0.000 -13.239   -3.881
_Ir_BMIcat_2 |   1.235705   .7475357     1.65   0.099   -.232    2.704
_Ir_BMIcat_3 |    2.64851   .9297573     2.85   0.005    .822    4.474
       r_age |  -.0123062   .0244706    -0.50   0.615   -.0603    .035
 _Ig_match_1 |   1.646951   .8946548     1.84   0.066   -.110    3.404
 _Ig_match_2 |   .7413019   1.021705     0.73   0.468  -1.265    2.748
 _Ig_match_3 |   2.080504   .9125728     2.28   0.023   .287    3.873
 _Ipra_cat_1 |  -.6731893   .7265785    -0.93   0.355   -2.100    .754
 _Ipra_cat_2 |  -.5231085    1.89897    -0.28   0.783   -4.253   3.207
     ace_arb |   .8941588   .6557423     1.36   0.173   -.394    2.182
     any_rej |  -3.478781   .6266578    -5.55   0.000  -4.709   -2.247
       dd_ld |   1.317918    .646284     2.04   0.042    .048    2.587
       _cons |  -3.489004   2.091538    -1.67   0.096  -7.597    .619
------------------------------------------------------------------------------
```

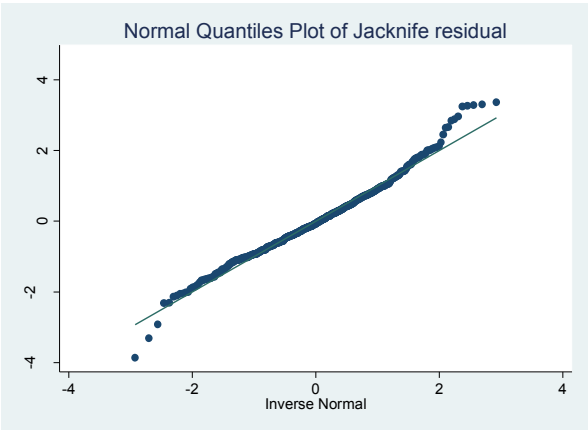
ii. Final multiple linear regression model:

```
. xi: regress  SLOPE_eGFR bmi_ratio i.r_BMIcat i.g_match  any_rej dd_ld  if
index_k==1 & ecd_10==0 & tx_num==1
i.r_BMIcat    _Ir_BMIcat_0-3   (naturally coded; _Ir_BMIcat_0 omitted)
i.g_matc      _Ig_match_0-3    (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     560
-------------+------------------------------   F(  9,   550) =    8.09
       Model |  3411.69455     9  379.077172   Prob > F      =  0.0000
    Residual |  25766.9327   550  46.8489686   R-squared     =  0.1169
-------------+------------------------------   Adj R-squared =  0.1025
       Total |  29178.6273   559  52.1979021   Root MSE      =  6.8446
------------------------------------------------------------------------------
  SLOPE_eGFR |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
   bmi_ratio |   1.634644   1.285086     1.27   0.204   -.889    4.159
_Ir_BMIcat_1 |  -8.001571   2.241523    -3.57   0.000 -12.404   -3.598
_Ir_BMIcat_2 |   1.282553   .7167296     1.79   0.074   -.125    2.690
_Ir_BMIcat_3 |    2.60645    .879739     2.96   0.003    .878    4.334
 _Ig_match_1 |   1.461543   .8649524     1.69   0.092   -.237    3.160
 _Ig_match_2 |   .4982062   .9978522     0.50   0.618  -1.461    2.458
 _Ig_match_3 |   2.049172   .8776025     2.33   0.020    .325    3.773
     any_rej |  -3.369454   .6033017    -5.59   0.000  -4.554   -2.184
       dd_ld |   1.508665   .6097785     2.47   0.014    .310    2.706
       _cons |  -4.142022   1.705636    -2.43   0.015  -7.492   -.7916
------------------------------------------------------------------------------
```

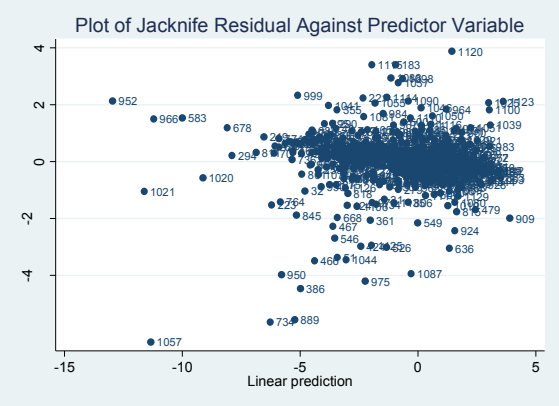
iii. Regression diagnostics for final model:

Verifying normality:

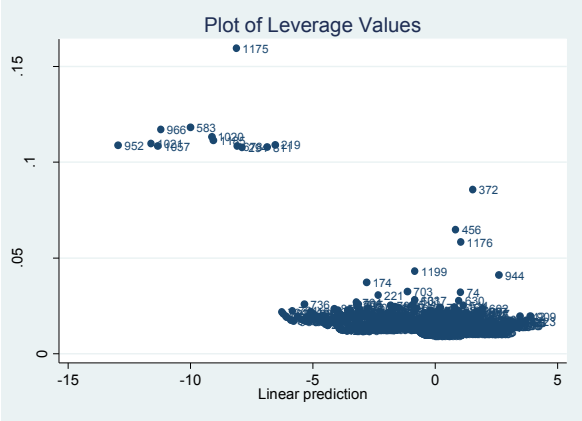




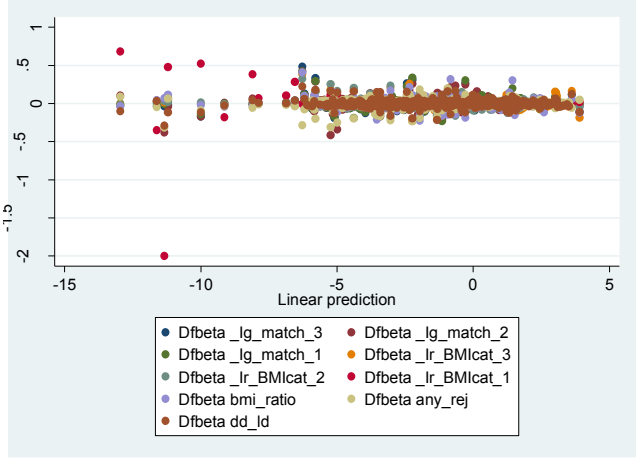
For checking equal variance assumption:

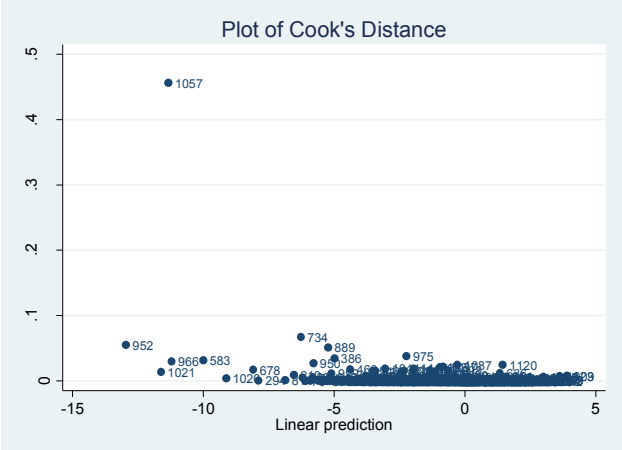


To detect outliers in independent variables:



To measure influence of individual observations on regression coefficients:





iv. Final regression model – influencial and high leverage excluded:

```
xi: regress  SLOPE_eGFR bmi_ratio i.r_BMIcat i.g_match  any_rej dd_ld  if
index_k==1 & ecd_10==0 & tx_num==1  & h<0.035 & cook<0.007
i.r_BMIcat    _Ir_BMIcat_0-3   (naturally coded; _Ir_BMIcat_0 omitted)
i.g_match     _Ig_match_0-3    (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     517
-------------+------------------------------   F(  8,   508) =    7.55
       Model |  1083.22738     8  135.403423   Prob > F      =  0.0000
    Residual |  9114.90694   508  17.9427302   R-squared     =  0.1062
-------------+------------------------------   Adj R-squared =  0.0921
       Total |  10198.1343   516  19.7638262   Root MSE      =  4.2359
------------------------------------------------------------------------------
  SLOPE_eGFR |      Coef.   Std. Err.      t    P>|t|   [95% Conf Int]
-------------+----------------------------------------------------------------
   bmi_ratio |   .9130172   .9283238     0.98   0.326   -.910    2.736
_Ir_BMIcat_1 |  (dropped)
_Ir_BMIcat_2 |   .2696088   .4592248     0.59   0.557   -.632    1.171
_Ir_BMIcat_3 |   1.207213   .5784059     2.09   0.037    .070    2.343
 _Ig_match_1 |   1.144771   .5611005     2.04   0.042    .042    2.247
 _Ig_match_2 |   -.394167   .6568314    -0.60   0.549  -1.684    .896
 _Ig_match_3 |   1.232824   .5681803     2.17   0.030    .116    2.349
     any_rej |  -1.885577   .3926171    -4.80   0.000  -2.656   -1.114
       dd_ld |   1.512859     .39693     3.81   0.000    .733    2.292
       _cons |  -2.447623   1.197741    -2.04   0.042  -4.800   -.0944
------------------------------------------------------------------------------
```

v. Multiple linear regression- final model with recipient BMI category removed

```
xi: regress  SLOPE_eGFR bmi_ratio  i.g_match  any_rej dd_ld  if index_k==1 &
ecd_10==0 & tx_num==1
i.g_match         _Ig_match_0-3       (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     561
-------------+------------------------------   F(  6,   554) =    8.21
       Model |  2468.01568     6  411.335946   Prob > F      =  0.0000
    Residual |  27754.0526   554  50.0975679   R-squared     =  0.0817
-------------+------------------------------   Adj R-squared =  0.0717
       Total |  30222.0683   560  53.9679791   Root MSE      =   7.078

------------------------------------------------------------------------------
  SLOPE_eGFR |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
   bmi_ratio |  -1.540651   1.118865    -1.38   0.169   -3.738    .657
 _Ig_match_1 |   1.722366   .8842089     1.95   0.052    -.014   3.459
 _Ig_match_2 |   .1054421   1.023861     0.10   0.918   -1.905   2.116
 _Ig_match_3 |   1.962463   .9038672     2.17   0.030     .187   3.737
     any_rej |  -3.520127   .6215931    -5.66   0.000   -4.741  -2.299
       dd_ld |   1.375903   .6290754     2.19   0.029     .140   2.611
```

```
       _cons |   .1318723   1.429965     0.09   0.927   -2.676   2.940
------------------------------------------------------------------------------
```

vi. Exploratory analysis:

Final model fit with eGFR at 1 yr as a predictor

```
xi: regress  SLOPE_eGFR  crcl_y1_adj bmi_ratio i.r_BMIcat i.g_match  any_rej
dd_ld  if index_k==1 & ecd_10==0 & tx_num==1
i.r_BMIcat        _Ir_BMIcat_0-3      (naturally coded; _Ir_BMIcat_0
omitted)
i.g_match         _Ig_match_0-3       (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS      Number of obs =     556
-------------+------------------------------   F( 10,   545) =    7.57
       Model |  3535.39577    10  353.539577   Prob > F      =  0.0000
    Residual |  25444.9157   545  46.6879187   R-squared     =  0.1220
-------------+------------------------------   Adj R-squared =  0.1059
       Total |  28980.3114   555  52.2167774   Root MSE      =  6.8329
------------------------------------------------------------------------------
  SLOPE_eGFR |      Coef.   Std. Err.      t    P>|t|  [95% Conf. Int]
-------------+----------------------------------------------------------------
 crcl_y1_adj |  -.0079542   .0161347    -0.49   0.622   -.039    .023
   bmi_ratio |   1.575674   1.296725     1.22   0.225   -.971    4.122
_Ir_BMIcat_1 |  -7.897682   2.244219    -3.52   0.000 -12.306   -3.489
_Ir_BMIcat_2 |   1.404049   .7220702     1.94   0.052   -.014    2.822
_Ir_BMIcat_3 |   2.681545   .8848957     3.03   0.003    .943    4.419
 _Ig_match_1 |   1.533468   .8685688     1.77   0.078   -.172    3.239
 _Ig_match_2 |   .5568722   1.003467     0.55   0.579  -1.414    2.528
 _Ig_match_3 |   2.071943   .8771514     2.36   0.019    .348    3.794
     any_rej |  -3.487498    .613407    -5.69   0.000  -4.692   -2.282
       dd_ld |   1.636525   .6244714     2.62   0.009    .409    2.863
       _cons |  -3.633926   2.026108    -1.79   0.073  -7.613    .346
------------------------------------------------------------------------------
```

Final model fit with D/RBSAR as a predictor

```
 xi: regress  SLOPE_eGFR  BSA_ratio i.r_BMIcat i.g_match  any_rej dd_ld  if
index_k==1 & ecd_10==0 & tx_num==1
i.r_BMIcat        _Ir_BMIcat_0-3      (naturally coded; _Ir_BMIcat_0 omitted)
i.g_match         _Ig_match_0-3       (naturally coded; _Ig_match_0 omitted)

      Source |       SS       df       MS            Number of obs =     560
-------------+------------------------------         F(  9,   550) =    7.91
       Model |  3345.36496     9  371.707217         Prob > F      =  0.0000
    Residual |  25833.2623   550  46.9695679         R-squared     =  0.1147
-------------+------------------------------         Adj R-squared =  0.1002
       Total |  29178.6273   559  52.1979021         Root MSE      =  6.8534
------------------------------------------------------------------------------
  SLOPE_eGFR |      Coef.   Std. Err.      t    P>|t|   [95% Conf. Interval]
-------------+----------------------------------------------------------------
```

```
   BSA_ratio |   .9855793    2.19464     0.45   0.654    -3.325    5.296
_Ir_BMIcat_1 |  -7.795827   2.256173    -3.46   0.001   -12.227   -3.364056
_Ir_BMIcat_2 |   1.081326   .7107341     1.52   0.129     -.314    2.477
_Ir_BMIcat_3 |   2.222513   .8580204     2.59   0.010      .537    3.907
 _Ig_match_1 |   1.564051   .9053088     1.73   0.085     -.214    3.342
 _Ig_match_2 |    .332923   1.029395     0.32   0.747    -1.689    2.354
 _Ig_match_3 |   2.038574   .8807782     2.31   0.021      .308    3.768
     any_rej |  -3.358642   .6058821    -5.54   0.000    -4.548   -2.168
       dd_ld |   1.600164   .6082716     2.63   0.009      .405    2.794
       _cons |  -3.382163   2.629264    -1.29   0.199    -8.546    1.782
------------------------------------------------------------------------------
```

ABBREVIATIONS
-
GLOSSARY OF TERMS

Abbreviation	Full
ACEI	angiotensin-converting enzyme inhibitor
ALERT	Assessment of Lescol in Renal Transplantation
ARB	angiotensin receptor blocker
ATG	anti-thymocyte globulin
BMI	body mass index
BSA	body surface area
CAN	chronic allograft nephropathy
C-G	Cockcroft-Gault
CIT	cold ischemia time
CKD	chronic kidney disease
CNI	calcineurin inhibitor
Cr	Creatinine
CrCl	creatinine clearance
D/RBMIR	donor to recipient body mass index ratio
D/RBSAR	donor to recipient body surface area ratio
D/RBWR	donor to recipient body weight ratio
D/RHR	donor to recipient height ratio
DD	deceased donor
DGF	delayed graft function
DM	diabetes mellitus
DTPA	diethylene triamine pentaacetic acid
eGFR	estimated glomerular filtration rate
ESRD	end stage renal disease
GFR	glomerular filtration rate
HLA	human leukocyte antigen
ICAM	intercellular adhesion molecule
ICAM-1	intercellular adhesion molecule-1
IL-1	interleukin-1
IL-6	interleukin-6
IQR	interquartile range
IS	immunosuppression
KV/RBSAR	kidney volume to recipient body surface area (volume/BSA) (ml/m2)
KV/RBWR	kidney volume to recipient body weight ratio
KW/RBMIR	kidney weight to recipient body mass index ratio
KW/RBSAR	kidney weight to recipient body surface area ratio
KW/RBWR	kidney weight to recipient body weight ratio
KW/RLBWR	kidney weight to recipient lean body weight ratio
LRD	living related donor
LUD	living unrelated donor
MCP-1	monocyte chemoattractant protein-1
MDRD	Modification of Diet in Renal Disease
MDRD1	Modification of Diet in Renal Disease 1
MDRD2	Modification of Diet in Renal Disease 2
MHC	major histocompatibility complex

Abbreviation	Full
MMF	mycophenolate mofetil
PRA	panel reactive antibody
RANTES	Regulated on Activation, Normal T-cell Expressed and Secreted
Rh	rhesus
RR	relative risk
SD	standard deviation
SEM	standard error of the mean
TNF-α	tumor necrosis factor-alpha
TXSA/RBWR	transplant cross-sectional area to recipient body weight ratio
UNOS	United Network for Organ Sharing
USRDS	United States Renal Data System

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