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Impact of immunosuppressive medications on the risk of renal allograft failure due to recurrent glomerulonephritis

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Impact of immunosuppressive medications on the risk of renal allograft failure due to recurrent glomerulonephritis

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Abstract

Background: Recurrent glomerulonephritis is third most common cause of kidney transplant failure.

Methods: We used the United States Renal Data System to determine the association of routine post-transplantation immunosuppressant use with time to renal allograft failure due to recurrent glomerulonephritis. Immunosuppressants were treated as time-varying covariates. The study-cohort included patients with kidney failure due to glomerulonephritis who received first kidney transplant between 1990 and 2003. Important confounders were identified through a systematic review of literature and missing values in the dataset were handled by multiple imputation.

Results: The study cohort included 41,272 patients with a median follow-up of 51 (22 – 90) months. Ten-year overall graft survival (including death as graft loss) and death-censored graft survival was 56.2% (55.5% - 56.9%) and 70.5% (69.8% - 71.1%) respectively. Ten-year incidence of graft loss due to recurrent glomerulonephritis was 2.6% (2.3 – 2.8%). Use of cyclosporine, tacrolimus, azathioprine or mycophenolate mofetil was not associated with risk of graft failure due to recurrent glomerulonephritis after adjusting for important covariates. There was no difference of recurrent glomerulonephritis causing graft failure between cyclosporine and tacrolimus or between azathioprine and mycophenolate mofetil. Change in any immunosuppressant during follow-up was independently associated with graft loss due to recurrence (HR 1.31, 95%CI 1.07–1.60, p=0.01).

Conclusion: Routinely used post-transplantation immunosuppressants have no impact on the risk of graft loss due to recurrent glomerulonephritis.

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1.0 Introduction

1.1 End Stage Renal Disease and Renal Replacement Therapy

End Stage Renal Disease (ESRD) is chronic irreversible renal failure that has reached a point where renal replacement therapy is necessary to sustain life. The incidence of ESRD is increasing in most parts of the world. In the United States (US), the number of patients receiving treatment for ESRD was 333 per million population in 2002. This represents nearly a 300% increase since 1980 [1]. The incidence continues to rise at a rate of 0.2-1.4% each year [1]. The prevalence of ESRD was 1,435 per million population in 2002 in the United States, which is 2.5% higher than the previous year and 56% higher than that in 1992 [1]. In Canada, 4 515 new patients entered an ESRD program in 2000, compared to only 1,228 in 1981[2]. Similarly, in 2000, 24,921 Canadians belonged to ESRD programs compared to 5,549 in 1981 [2].

Treatment options for end stage renal disease include dialysis and kidney transplantation. The annual per patient cost of dialysis in the United States Medicare population is approximately US$63,000 while that for a functioning transplant is US$15,700 [3]. The actual transplant itself costs US$100,000 [3]. With these figures, it is apparent that a functioning transplant graft that survives longer than two years is the most economical treatment for end stage renal disease.

Kidney transplantation is also the best option both in terms of quantity as well as quality of life for patients of end stage renal disease [4]. Laupacis *et. al.* followed 168 Canadian patients with end-stage renal failure for a mean of 19.5 months after kidney transplantation [5]. They found that health related quality of life at six months after

transplantation was significantly better compared to the pre-transplant values and remained so at least for two years following transplantation. Annual cost of dialysis was CAD $66,782 (in 1994) and was similar to the cost of care for the first year after transplantation (CAD $66,290). During the second year, however, the cost of care for transplanted patients was considerably less at CAD $27,875. Better quality of life and lower costs associated with renal transplantation were seen in all patient subgroups.

If a kidney transplants fails, patients can return to dialysis. Because of the increasing incidence of renal transplants and increasing prevalence of renal transplant patients, the overall number of patients returning to dialysis due to a failed kidney transplant has increased steadily. In the United States, more than 4,000 patients return to dialysis annually because of a failed transplant. This accounts for almost 5% of incident dialysis patients in the United States [6], despite the fact that short-term renal transplant survival (also called allograft or graft survival) has improved extensively during the last decade [7]. Loss of functioning renal allograft and return to dialysis is associated with a significantly higher risk of death compared to a functioning transplant [8]. In Canada, the adjusted risk of death was found to be greater than three-fold higher in renal-transplant patients who returned to dialysis due to graft failure compared to those with functioning transplant [9].

Graft survival continues to improve in renal transplant patients. One-year graft survival for deceased donor kidney transplants has improved from 70% in 1990 to approximately 90% in 2000 [7]. The projected half-life of renal allograft (defined as time at 50% of transplants functioning at one year fail) has improved as well from 7.6 years in 1988 to 11.6 years in 1995. As a result of this improved one-year graft survival, a current focus in renal transplantation has shifted to developing strategies for improving *long-term* graft survival.

A specific area of interest is the development of the primary renal disease that caused renal failure in the native kidneys in the transplanted kidney. Such "index disease recurrence" is the third most common cause of allograft failure (following chronic allograft nephropathy and death with functioning graft) after the first year [10]. Disease recurrence most commonly occurs in a condition known as glomerulonephritis, which is a generic term used for immunologically mediated kidney disease that primarily affects the kidney filter (see section 1.3).

Despite the prevalence of index disease recurrence, this topic has not been extensively studied [11]. Several factors may explain the minimal attention paid to recurrent glomerulonephritis. Heterogeneity of various types of glomerulonephritis, unpredictable risk of recurrence and clinical course, small number of patients with individual types of glomerulonephritis needing multicenter collaboration and poorly understood pathophysiology and treatment of glomerulonephritis in the native kidney are among some of these [11].

The present study is an effort to understand the risk factors associated with allograft loss due to recurrent glomerulonephritis in the transplanted kidney.

1.2 Trends in immunosuppressive medication use in kidney transplantation

Patients undergoing kidney transplantation receive medications that suppress the immune system. This is done to prevent graft loss due to rejection. Such medications are called "immunosuppressive medications" or "immunosuppressives" and are continued as long as the renal allograft remains functional.

Immunosuppressives have changed over time. In the 1960s and 1970s, **azathioprine** and **prednisone** were the predominantly used immunosuppressive medications. In the

1980s, a new class of potent immunosuppressive medications called calcineurin inhibitors (CNI) was introduced. '**Cyclosporine**' was the first widely-available calcineurin inhibitor to be introduced and led to a remarkable decrease in acute rejection rates and vastly improved one-year allograft survival [12;13]. In the 1990s, another calcineurin inhibitor called **tacrolimus** was introduced and was also shown to significantly reduce the acute rejection rates [14;15]. The 1990s also saw the introduction of **mycophenolate mofetil** (MMF), an immunosuppressant that belongs to a drug class called 'antimetabolites'. Three pivotal trials showed that mycophenolate mofetil use was associated with reduction in acute rejection rates in the first 6 months of transplantation [16-18]. Currently used immunosuppressive regimens frequently include a combination of these three drug classes, namely a calcineurin inhibitor (either cyclosporine or tacrolimus), an antimetabolite (either azathioprine or mycophenolate mofetil), and steroids.

Data from observational studies have shown large shifts in immunosuppressant use for renal transplant patients over the last decade. In the 1980s, a combination of cyclosporine, azathioprine, and steroids was the predominantly used anti-rejection regimen for kidney transplantation. In the 1990s, the use of tacrolimus and mycophenolate mofetil became more prominent. Data on 84,000 transplant recipients from the United Network for Organ Sharing (UNOS) renal transplant registry [19] show that the use of cyclosporine decreased from greater than 80% to just over 40% in unsensitized (i.e. those without pre-formed anti-HLA antibodies) transplant recipients between 1995 and 2001. In contrast, the use of tacrolimus increased from less than 20% to greater than 50% of kidney transplants during the same period. Similarly, the use of azathioprine in unsensitized recipients decreased from approximately 80% to less than 10% while the use of mycophenolate mofetil increased from less than 20% to nearly 90%.

During this time, four distinct combinations of immunosuppressive medications have emerged. These include cyclosporine and azathioprine, cyclosporine and mycophenolate mofetil, tacrolimus and azathioprine, and tacrolimus and mycophenolate mofetil. Takemoto [19] found that the 2-year graft survival of cyclosporine and azathioprine combination was 83% and was significantly lower than that for the other three combinations (85-87%). There was no difference between cyclosporine and mycophenolate mofetil, tacrolimus and azathioprine or tacrolimus and mycophenolate mofetil at two years. Partially as a result of these data, the use of azathioprine at the time of transplantation has reduced to less than 2% of transplants in 2003 [20].

The choice of regimen is often center-specific rather than patient-specific. Observational studies have shown that centers tend to choose particular combinations of the calcineurin inhibitors and the antimetabolites in a majority of their patients irrespective of patient characteristics [19]. Takemoto [19] classified the transplant centers according to preferred use of immunosuppressive medication at the time of transplantation. Centers using cyclosporine in greater than 80% of patients and tacrolimus in less than 20% of patients were classified as cyclosporine centers. Similarly, centers that used tacrolimus in greater than 80% patients and cyclosporine in less than 20% patients were classified as tacrolimus centers. When classified in this way, 60% of centers in 1995 were cyclosporine centers and none were tacrolimus centers. These statistics had changed dramatically by 2001, at which time the proportion of cyclosporine centers dropped to 34% while 39% were tacrolimus centers. When transplant centers were classified according to antimetabolite use as above, the proportion of azathioprine centers decreased from 44 - 62% (in patients previously unsensitized and sensitized to HLA antigen respectively) in 1995 to less than 10% in 2001. In contrast, the proportion of mycophenolate mofetil centers increased to 85% in 2001.

1.3 Glomerulonephritis and End-Stage Renal Failure Requiring Transplantation

Glomerulonephritis is a generic term used for immunologically mediated kidney disease that primarily affects the portion of the kidney that filters the blood of its impurities and toxins. These filters are called *glomeruli* and inflammation of glomeruli is termed *glomerulonephritis*. Glomerulonephritis can be a component of a systemic disease like systemic lupus erythematosus, which is termed 'secondary glomerulonephritis'. Glomerulonephritis can also occur as an isolated renal disease, which is termed 'primary glomerulonephritis'. Glomerulonephritis is classified into different categories based on histopathological features of the involved kidney. Broad histological classifications of glomerulonephritis include minimal change glomerulonephritis, focal segmental glomerulosclerosis, membranous glomerulonephritis, membranoproliferative glomerulonephritis, IgA nephritis, and crescentic glomerulonephritis. Many of these are further divided into sub-categories and have unique ICD-9 codes (Appendix 1).

Glomerulonephritis is the cause of renal failure in 20 to 40% of those who undergo renal transplantation [21]. In the United States, the absolute number of patients undergoing kidney transplantation for renal failure due to glomerulonephritis has increased from 2,975 in 1996 to 4,077 in 2004. Since the incidence of end stage renal disease due to diabetes and hypertension continues to increase rapidly, as is the acceptance of diabetic patients for kidney transplantation, the proportion of patients undergoing renal transplantation because of glomerulonephritis has decreased from 29.1% to 24.1% during the same period. [22]

1.4 Index Glomerulonephritis Recurrence in Transplanted Kidneys

Virtually all types of glomerulonephritis can recur in the transplanted graft. However, the frequency of recurrence and the proportion of recurrent disease that results in

graft loss vary with the type of the glomerulonephritis [21]. For example, graft loss due to recurrent disease is relatively common in cases of type II membranoproliferative glomerulonephritis, with up to 25% of such renal transplant recipients losing the graft due to recurrence in the transplanted kidney. In contrast, graft loss due to recurrent disease is uncommon in lupus nephritis [21].

The incidence of recurrent glomerulonephritis in renal transplants in the published literature varies from 6% to 19% in all transplants. Similarly, the incidence of graft loss due to recurrent glomerulonephritis varies from 1.1 to 4.4% in all transplants [21]. Neumayer [23] studied 697 patients who received kidney transplant between 1980 and 1990, 328 of which had glomerulonephritis as primary cause of kidney failure. Of these 328 patients, 157 (47.9%) had biopsy confirmed glomerulonephritis. During their follow up period, 49 patients (6% of the total transplants) were documented to have recurrent glomerulonephritis in a kidney biopsy. Of these 49 patients, a biopsy of the pre-transplant native kidney was available in only 22 patients (6 of whom had glomerulonephritis in the pre-transplant biopsy). This study illustrates the difficulty in ascertaining the diagnosis of recurrent glomerulonephritis. The diagnosis of glomerulonephritis is often, but not always, based on a kidney biopsy. Clinical features such as nephrotic-range proteinuria, hematuria, an active urine sediment, hypertension or appropriate clinical or laboratory features frequently permit the clinician to make the diagnosis of glomerulonephritis with a reasonable certainty without a kidney biopsy. Sometimes, the risk of doing a kidney biopsy outweighs the potential benefits. Using clinical data, only a broad diagnosis of glomerulonephritis can be made without a more specific type of glomerulonephritis.

A study from the Renal Allograft Disease Registry including 1,557 transplants between 1984 and 1994 found that 76 patients developed biopsy proven glomerulonephritis

after a mean follow up of 7.3 years [24]. A subsequent study from the same registry [25] reported that 158 patients of 4913 transplants between 1987 and 1996 developed recurrent or *de-novo* glomerulonephritis. The primary cause of renal failure was not restricted to glomerulonephritis in either of these studies and patients with diabetes were also included, thus the proportion of patients with recurrent glomerulonephritis is not clear from this data.

Briggs *et. al.* studied the European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA) database and reported on 29,594 patients whose primary cause of renal failure was glomerulonephritis and who received a renal transplant between 1980 and 1991. Overall, 6,081 (20.6%) transplants failed during this period. Recurrent disease was diagnosed in only 1% of total transplants and accounted for 4.8% of total grafts lost [26].

Briganti *et. al.* [27] used data from the Australia and New Zealand Dialysis and Transplant registry (ANZDATA) to study recurrent glomerulonephritis. Of 3998 patients who were transplanted between 1988 and 1997, they identified 1,505 patients whose primary disease was due to biopsy-proven glomerulonephritis. Fifty-two of these patients (3.4%) lost their graft due to recurrent glomerulonephritis. Using survival analysis, they found that the 10-year risk of graft loss due to recurrent glomerulonephritis was 8.4% (95% CI 5.9% - 12%).

Table 1 lists the studies that have reported the risk of recurrent disease for specific types of glomerulonephritis along with the subsequent risk of graft loss. IgA glomerulonephritis is the most common type of glomerulonephritis in the native kidney and is the most common form of glomerulonephritis leading to end stage renal disease [21]. Histological recurrence of mesangial IgA deposition has been reported to be as high as 50-60% [28] whereas clinically important recurrence is reported in between 15 and 35% of cases

[28] (Table 1). Graft loss due to recurrent IgA nephropathy is not trivial, since 1.3% to 16% of such grafts are lost due to recurrent disease (Table1). Focal segmental glomerulosclerosis constitutes another important cause of recurrent glomerulonephritis, which can recur in 20% to 57% of the transplants leading to graft loss in 2.3% to 42.9% of them. (Table1). Recurrence rate is even higher (80%) in second transplant if the first is lost due to recurrent focal segmental glomerulosclerosis [28]. Membranoproliferative glomerulonephritis, especially the type II variant, has probably the highest risk of recurrence in the renal allograft as well as a very high risk of graft loss due to recurrent glomerulonephritis. Lupus nephritis is a form of secondary glomerulonephritis that has a very low risk of recurrence in transplantation. Graft loss due to recurrent lupus nephritis is very rare. The low risk is in part due to the current practice to proceed with kidney transplantation only after the disease is in remission for at least six months [28]. Some authors have suggested that calcineurin inhibitor based immunosuppression protocols are effective in preventing recurrence of lupus nephritis [29].

Table 1: Risk of recurrent glomerulonephritis and graft loss due to recurrence after kidney transplantation

Type of GN*	Study	Year	N	Follow-up in months (SD)	Risk of recurrence	Risk of graft loss due to recurrence
IgA Nephropathy and Henoch Schonlein purpura	Odum [30]	1994	51	3-183	33.3%	9.8%
	Hartung [31]	1995	128	45.9(10)	36.7%	7.0%
	Kessler [32]	1996	84	68.1(37.2)	15.5%	4.8%
	Frohnert [33]	1997	53	78 (median)	26%	5.7%
	Ohmacht [34]	1997	61	54	23%	16%
	Bungardner [35]	1998	61	61	29.5%	9.8%
	Freese [36]	1999	104	67	12.5%	5.8%
	Kim YS [37]	2001	90	2-264	21.1%	2.2%
	Wang [38]	2001	48	52 (Median)	29%	8.3%
	Ponticelli [39]	2001	106	70.4(50.5)	35%	3.8%
	Andresdottir[40]	2001	79	67.2(54)	21.5%	1.3%
	Choy [41]	2003	75	100(5.8)	18.7%	4.0%
	Moriyama [42]	2005	49	67.8(19.9)	26.5%	9.8%
Focal and Segmental Glomerulosclerosis	Senggutuvan [43]	1990	59		22.0%	
	Tejani [44]	1992	132		20.5%	
	Artero [45]	1992	78	1-65	32.1%	18.0%
	Butani [46]	1999	27		29.6%	11.1%
	Dall'Amico [47]	1999	32		56.3%	31.3%
	Choi [48]	2001	28	70 (median)	46.4%	42.9%
	Kim SJ [49]	2001	22		40.9%	
	Abbott [50]	2001	3,861	35.5(29.2)		2.6%
	Jungraithmayr [51]	2005	8		25%	12.5%
	Hubsch [52]	2005	28	27(15)	57.1%	
	Pardon [53]	2006	35		34.3%	17.1%
Membranous Nephropathy	Marcen [54]	1996	6		50%	33.3%
	Cosyns [55]	1998	30	Up to 120	29%	15%
Membranoproliferative Glomerulonephritis	Andresdottir [56]	1997	32		37.5%	
	Andresdottir [57]	1999	13	14 (0.2-38)	84.6%	61.5%
	Braun [58]	2005	75		41.4%	14.7%
	Little [59]	2006	43		49%	
					(continued on next page)	

Table 1(Contd):

Type of GN*	Study	Year	N	Follow-up in months (SD)	Risk of recurrence	Risk of graft loss due to recurrence
Lupus Nephritis	Rivera [60]	1990	8		0	0
	Nossent [61]	1991	28		3.6%	
	Nyberg [62]	1992	16		43.8%	6.25%
	Stone [63]	1998	107	62.6	8.4%	3.7%
	Azevedo [64]	1998	48		10.4%	4.2%
	Goral [65]	2003	54		27.8%	1.9%
	Deegens [66]	2003	23		4.4%	
	Dong [29]	2005	14		0	0
	Verdejo [67]	2005	20	36(35)	0	0
	Moroni [68]	2005	35		8.6%	0
Crescentic GN and GN associated with small vessel vasculitis (Wagener's and microscopic polyangitis)	Nachman [69] (Pooled Analysis of 10 studies)	1999	127	4-89	17.3%	1.6%
	Deegens[70]	2003	43	62(57)	2.3%	0
	Elmedhem [71]	2003	9	62	22.2%	
Hemolytic Uremic Syndrome	Ducloux (Meta-analysis of ten studies) [72]	1998	159		27.8%	19%
	Lahlou [73]	2000	25		56%	
	Quan [74]	2001	68		8.8%	7.6%
	Artz [75]	2003	50		22%	

*GN: Glomerulonephritis

Association of recurrent glomerulonephritis with renal allograft survival

Recurrence of index glomerulonephritis is an important predictor of graft survival. Data from the Renal Allograft Disease Registry in the United States show that patients with recurrent glomerulonephritis were 1.9 times (95% CI 1.6 to 2.4) more likely to experience graft loss at 5 years compared to those without recurrence [25]. Recurrent glomerulonephritis was the third most common cause of graft loss (after chronic rejection

and death due to other causes) and accounted for 18.5% of total graft loss in the aforementioned Australian study [27].

1.5 Immunosuppressive Treatment of Glomerulonephritis

A variety of immunosuppressive medications have been used to treat primary and recurrent glomerulonephritis with varying success. A detailed list of published literature detailing the efficacy of immunosuppressives for treatment of glomerulonephritis in the native kidney is provided in Appendix 2. Cyclosporine (CyA) has been shown to be effective in both membranous nephropathy [76] and focal segmental glomerulosclerosis [77]. Mycophenolate mofetil has been used with some success in membranous nephropathy [78;79], resistant minimal change disease [79],[80] and focal segmental glomerulosclerosis [80]. Mycophenolate mofetil has also been used in different types of recurrent glomerulonephritis [81;82]. Azathioprine is often used as a maintenance therapy for lupus nephritis [83] and has been shown to be as effective as pulse cyclophosphamide with fewer side effects [84]. Newer maintenance therapies like mycophenolate mofetil have been compared with azathioprine-based maintenance regimens for lupus nephritis [85;86](Appendix 2). Recent reports from small case series suggest that treatment with tacrolimus is associated with complete or partial remission in severe focal segmental glomerulosclerosis [87;88] , resistant membranous nephropathy [89] and lupus nephritis [90].

1.6 Risk Factors for Renal Allograft Failure

Renal transplant can fail due to a variety of causes that can be broadly classified into early and late causes. Early graft failure occurs within the first year after transplantation while late graft failure occurs more than one year after transplantation. The most common causes of early graft loss include acute rejection, patient death from other causes, vascular

thrombosis, and primary non-functioning graft [91]. The most common causes of late graft loss include chronic allograft nephropathy, patient death from other causes, and recurrent disease leading to graft dysfunction [91;92].

Researchers have identified several factors that are associated with renal transplant failure. Factors that have been shown to be associated with graft and patient survival include:

i) **Donor source**: live donor transplants are associated with significantly better graft survival compared to deceased donor transplants [91;93;94].

ii) **Donor cause of death**: grafts from donors with traumatic death survive longer than those from donors with non-traumatic death [94-100]

iii) **Transplant center**: Studies from the United States have shown that volume of transplant procedures at participating transplant centers is associated with graft survival [94]. Gjertson [101] showed that transplant center accounted for 27.9% and 15.8% respectively of the total accountable variation in 1-year and 5-year graft survival. They also found that the role of transplant center has weakened in the recent years, the contributed accountable variability attributed to transplant centers dropping to 17% in 1996 compared to 30% in 1994 for 1-year graft survival [101].

iv) **Sensitization**: The presence of pre-existing anti HLA antibodies in high titres is associated with decreased graft survival [94]. Pre-existing HLA antibodies are assessed by a test called Panel Reactive Antibody (PRA) testing that involves testing a patient's serum against a panel of common HLA antigens encountered in the population. The "percent PRA" is the proportion of these HLA antigens to which the patient's serum reacts. A percent PRA of >50% is considered as 'high PRA' and indicates a highly sensitized recipient.[50].[102-108]

v) **Histocompatibility**: The extent of HLA matching between the donor and recipient influences the risk of rejection and subsequent graft loss. The greater the degree of HLA match, the better is the transplant survival [94;96;97;100;105;106;109-113].

vi) **Year of transplant**: Transplants that have been performed in recent years have better survival compared to those performed in past [50;94;97;100;114;115].

vii) **Cold ischemia time**: Most studies show that longer cold ischemia time – that is, the time from removal of the graft from the donor to the implantation in the recipient - is associated with worse graft survival [96;97;104;106;109;112;116-119]. However, Marcen [120] did not find an increased risk of graft failure with cold ischemia time >24 hours.

viii) **Donor age**: Most studies show that increased donor age is associated with worse graft survival [91;93;94;97;102-104;106;108-111;113;121-123]. Some studies have found a curvilinear relationship between donor age and graft survival with an increased risk of graft loss with both the very young and very old donor age [100;115;119]

ix) **Previous transplants**: Grafts in patients who are transplanted for a second time have shorter survival than those not previously transplanted [50;96;98;105;106;112;114;124].

x) **Race of the recipient**: Graft survival is shorter in black recipients compared to others [50;91;94;97;99;105;106;119;122;124-128].

xi) **Recipient's body size**: Increased body size of the recipient, measured either as the body mass index or body surface area, is associated with a shorter graft survival [112].

xii) **Recipient age**: Several studies have shown that the risk of graft loss increases with increased recipient age [96] [129] [121] [98;100;103;107;108;118]while others have shown a decreased risk with increasing age [93;114;115;117;126;130]. Others, still, show that the risk is non-linear and is higher at both extremes of age [97;119].

Few studies have tried to identify patient and transplant factors that are associated with allograft loss due to recurrent disease. Apart from the underlying type of glomerulonephritis, the duration of follow-up is important for the risk of recurrence. As the follow-up time increases, the overall risk of recurrence also increases [21]. One large study measured the effect of ten factors on the risk of graft loss due to recurrent disease in 1505 renal transplant recipients [27]. Of the ten factors examined (including recipient age, recipient sex, peak level of panel reactive antibody, duration of dialysis, type of glomerulonephritis, donor age, donor sex, source of allograft, cold-ischemia time and number of HLA mismatches), only three factors (type of glomerulonephritis, sex of recipient, and peak panel reactive antibodies) were independently associated with graft loss due to recurrent disease [27]. Freedman [131] studied 58 patients with glomerulonephritis as the primary disease who underwent kidney transplantation between 1977 and 1987. Patients were grouped as those receiving cyclosporine alone, azathioprine alone or initial cyclosporine for three months followed by azathioprine. They did not find any difference in the incidence of recurrent disease in the three groups though time to recurrence was significantly shorter (mean 2.3 vs. 21.8 months, $p<0.002$) in the group that received only cyclosporine.

Risk factors for the recurrence of specific types of glomerulonephritis have also been described. Abbott *et. al.* [50] used the United States Renal Data System database to identify

3861 patients with focal segmental glomerulosclerosis who had undergone renal transplantation. They found that recipient age, recipient race, previous rejection episode, and previous transplant were each associated with an increased risk of graft loss due to recurrent disease. Baum *et. al.* [132] studied 752 patients with focal segmental glomerulosclerosis who underwent transplantation in the North American Pediatric Renal Trials and Collaborative Studies database and found that transplants from live donors were more often lost due to recurrent disease ($p=0.06$) compared to cadaver donor transplants. Some studies have suggested that the risk of recurrent IgA glomerulonephritis increases with a decreased age at transplantation [21;39;133] while there is inconsistent data regarding the role of living versus cadaver donor. Bumgardner [35], Freese [36] and Andresdottir [40] have each found that live donor transplant was associated with increased risk of recurrent IgA nephropathy. Wang [38] found that recurrence was more likely in live related donor versus live unrelated donor, whereas Kim [37] did not find any difference between related and unrelated living donor. Despite this, graft survival from live related donors was not significantly different than cadaver or live unrelated donor [41]. An HLA-identical donor has been associated with an increased risk of recurrent disease in type 1 membrano-proliferative glomerulonephritis [21]. Data regarding risk of factors of recurrence of other types of glomerulonephritis are scarce.

Since glomerulonephritis is an immunological disease, immunosuppressive medications are the mainstay of treatment. Throughout the life of their graft, renal transplant recipients receive the same immunosuppressive medications that are often used to treat glomerulonephritis. Despite this, glomerulonephritis can recur in transplant and lead to transplant failure.

Newer anti-rejection medications, like mycophenolate mofetil and tacrolimus, are more potent immunosuppressive medications compared to azathioprine and tacrolimus, respectively. In kidney transplant recipients, mycophenolate mofetil has been shown to be a clearly superior immunosuppressive agent compared to azathioprine in large randomized trials as mycophenolate mofetil leads to a significantly decreased risk of acute rejection compared to azathioprine [16;17]. Similarly, use of tacrolimus in patients with kidney transplantation leads to a lower incidence of acute rejection compared to cyclosporine [14;15]. Systematic reviews have confirmed superior efficacy of tacrolimus compared to cyclosporine in preventing acute rejection [134;135] and prolonging 3-year graft survival [135]. Both tacrolimus [136;137] and mycophenolate mofetil [137;138] have been used with some success to reverse refractory acute rejection episodes that may occur despite being treated by cyclosporine and/or azathioprine. Though direct comparative studies of azathioprine versus mycophenolate mofetil and of cyclosporine versus tacrolimus are few, the available data suggests that tacrolimus [87] and mycophenolate mofetil [86] are superior to cyclosporine and azathioprine respectively in certain types of glomerulonephritis. Therefore, one might expect that mycophenolate mofetil and tacrolimus may be more effective in preventing recurrent disease after transplantation.

The role of immunosuppressive medications on the risk of recurrent disease in transplanted glomerulonephritis has not been well studied. The type of immunosuppressive medication used after transplantation is a potentially modifiable factor that treating nephrologists may consider when choosing immunosuppressive therapy for a new transplant recipient. Thus, if a particular immunosuppressive medication is associated with a decreased risk of recurrence, it could lead to individualization of post-transplant therapy.

1.7 Summary

The incidence and prevalence of end stage renal disease continues to increase in North America. Kidney transplantation is the preferred treatment option for end stage renal disease. Glomerulonephritis is an immunologically mediated disease that is responsible for kidney failure in approximately one out of four kidney transplant recipients. Kidney transplant recipients continue to receive lifelong immunosuppressive medications after transplantation to prevent transplant failure due to rejection. These very same medications are used to treat glomerulonephritis. Despite this, glomerulonephritis can recur in transplant kidney and lead to transplant failure. Newer immunosuppressive medications - namely mycophenolate mofetil and tacrolimus - are more potent and therefore have led to decreased graft loss due to rejection compared to azathioprine and cyclosporine respectively. Owing to better immunosuppressive action, they might also decrease the incidence of recurrent glomerulonephritis after transplantation. Since kidney transplants are now surviving longer, recurrent disease has become an important and pertinent issue in everyday practice and has become a major hurdle in improving long-term graft survival. Thus, studies are urgently needed to identify modifiable factors that can lead to improved graft and patient survival.

2.0 Methods

This study is a secondary analysis of a national registry of all patients with end stage renal disease, including those undergoing renal transplantation. Since the Canadian registry of organ transplantation does not contain information on immunosuppressive medications, we had to use registry data from the United States. This registry is called the United States Renal Data System (USRDS).

2.1 The United States Renal Data System

The United States Renal Data System (USRDS) is a national data reporting system that collects, analyzes, and distributes information about end-stage renal disease in the United States. The USRDS is funded directly by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in conjunction with the Centers for Medicare & Medicaid Services (CMS).

The USRDS captures information about all patients in the United States who have end stage renal disease and are receiving renal replacement therapy. Reporting to USRDS is mandatory for all centers that treat patients with end stage renal disease. Reporting to USRDS is required for payment of costs for treating each end stage renal disease patient from the centers for Medicare & Medicaid Services. Therefore, it is both legally and financially necessary for American health care institutions that treat patients with end stage renal disease to report data to USRDS. Such requirements likely make the USRDS more complete than registries that rely upon voluntary reporting.

Prior to 1995, CMS stored information about end stage renal disease patients in the Program Management and Medical Information System (PMMIS) database. Since 1995, this

information has been integrated into the Renal Beneficiary and Utilization System (REBUS), which is an online information transaction system, and eventually the Renal Management Information System (REMIS) in 2003.

The USRDS collects information regularly about all American patients with end stage renal disease until their death. The USRDS gets data from multiple sources including the Centers for Medicare and Medicaid Services, the United Network for Organ Sharing (UNOS), the Centers for Disease Control and Prevention (CDC) surveillance data, and special studies like Dialysis Morbidity and Mortality Study. The USRDS co-ordinating center has developed a centralized database by integrating these data on patients with end stage renal disease. They use this database to maintain and update data on patient demographics, clinical and biochemical measurements, renal replacement therapy, treatment history, and all medical service events reported in the medical claims database.

2.1.1 Registration of new ESRD patients into the USRDS

Each dialysis unit and transplant center in the US is required to complete the CMS Medical Evidence Form (CMS 2728) when a patient starts renal replacement therapy with either hemodialysis, renal transplant, or peritoneal dialysis [139](Appendix 4). Prior to 1995, this form was required for Medicare patients only. Since 1995, completion of this form is required for all new patients with end stage renal disease. Every time a patient changes treatment modality, such as switching from hemodialysis to renal transplantation, the CMS 2728 needs to be completed again. In addition, patients stopping dialysis for more than twelve months must have another CMS 2728 completed. This ensures that the reason for discontinuing dialysis for a patient is determined. If transplant kidney fails and the patient returns to dialysis, the form needs to be re-completed. Similarly, this form needs to

be completed for every transplant patient with functioning transplant for longer than three years to determine Medicare eligibility [139].

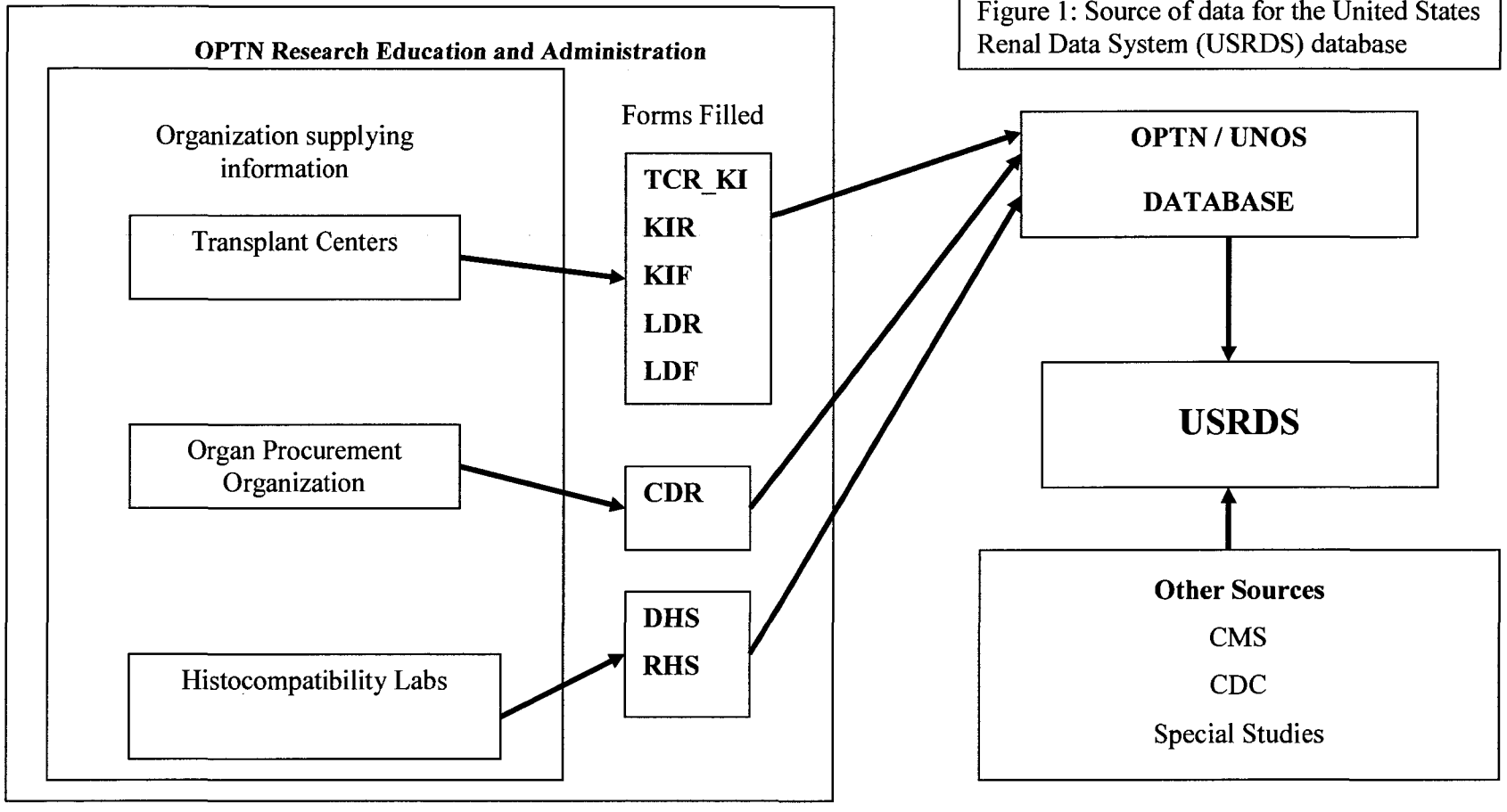
The CMS Medical Evidence Form summarizes important information about each patient. This includes patient age, gender, height, weight, residential address, renal replacement therapy, date of starting renal replacement therapy, co-morbidities, baseline biochemical tests, and if patient had received transplant, date of transplant and status of transplant (meaning whether the transplant is functioning or failed). The primary cause of renal failure is recorded using International Classification of Diseases (ICD)-9 codes.

2.1.2 Source of data on patients with kidney transplantation

The Centers for Medicare & Medicaid Services started collecting data on renal transplants in the early 1980s. The United States Congress established the Organ Procurement and Transplantation Network (OPTN) in 1984 under the National Organ Transplant Act to form a unified network with a combined public-private partnership. The United Network for Organ Sharing (UNOS) was awarded the OPTN contract in 1986 and has continued to administer the Organ Procurement and Transplantation Network since. The United Network for Organ Sharing started collecting data on kidney transplants in 1988. Since 1994, the United Network for Organ Sharing has been the sole location of data on patients with kidney transplantation. USRDS uses UNOS transplant files as the primary source of data regarding transplant events of the patients with end stage renal disease since 1988.

The following figure (Figure 1) illustrates the mechanism of data collection by OPTN/UNOS that is forwarded to the USRDS.

Figure 1: Source of data for the United States Renal Data System (USRDS) database



Key: TCR_KI: Transplant Candidate Registration form
KIR: Transplant Recipient Registration form
KIF: Transplant Recipient Follow-up form
LDR: Live donor Registration form
LDF: Live Donor Follow-up form
CDR: Cadaver Donor Registration form
DHS: Donor Histocompatibility form
RHS: Recipient Histocompatibility form
CMS: Centers for Medicare & Medicaid Services
CDC: Centers for Disease Control and Prevention
OPTN: Organ Procurement and Transplant Network
UNOS: United Network for Organ Sharing
(Adapted from Figure 2 in Dickinson et al, 2005 [140])

Thus, three types of organizations (transplant center, organ procurement organization and histocompatibility laboratories) collect primary data in the prescribed forms as shown in Figure 1. The United Network for Organ Sharing prepares data files using information from these forms. The USRDS uses these files as the primary source of transplant data. The USRDS collects information from other sources like the Center for Medicare & Medicaid Services, the Centers for Disease Control and Prevention (CDC) and special studies conducted by the USRDS regarding other aspects of end stage renal disease treatment like dialysis. The USRDS then integrates this information into its data files called Standard Analysis Files (SAFs).

Information contained in the following forms (Appendix 4) [141] is entered into the USRDS and supplement information in the CMS Medical Evidence Form. These forms are presented in Figure 1 and Table 2:

1. **Transplant Candidate Registration Form** – This is generated by transplant centers for patients who are on national waiting list for deceased donor transplantation. These forms are also generated for live donor transplants. They provide demographic information, including age, sex, race, education and employment, blood group, comorbidities (diabetes, hypertension, coronary artery disease among others) and primary diagnosis.
2. **Kidney Transplant Recipient Registration Form** – This is the primary source of a transplant event. In addition, as mentioned above, the Medical Evidence Form and CMS Paid Claims Records are used to identify additional transplant events. This form is provided by the transplant center and provides information regarding donor kidney biopsy, cold and warm ischemia time, immediate/delayed graft function, rejection episodes and initial immunosuppressive treatment.

3. **Kidney Transplant Recipient Follow-up Form** - Transplant centers are required to provide follow up information by filling this form six months after transplant and then annually at each anniversary of the date of transplant. This form records information regarding functioning of the transplant, immunosuppressive medications, and - if transplant had failed - the date and cause of graft loss.
4. **Donor Histocompatibility Form** – This records information about Histocompatibility of the donor and is provided by the laboratory that tests the donor.
5. **Recipient Histocompatibility Form** – This form contains information about the recipient's histocompatibility and is generated after a transplant event. The laboratory that tests the recipient, provides this form.
6. **Live Donor Registration Form** and **Deceased Donor Registration Form** are generated soon after transplantation and contain information about the donor variables.

Table 2: Information contained in various forms received by United Network for Organ Sharing (Complete information, on forms are provided in appendix 4)

Form	Source of form	Information contained in the form
Transplant Candidate Registration Form	Transplant Center	Demographic information, including age, sex, race, education and employment, blood group, comorbidities (diabetes, hypertension, coronary artery disease among others) and primary diagnosis.
Kidney Transplant Recipient Registration Form	Transplant Center	Donor kidney biopsy, cold and warm ischemia time, immediate/delayed graft function, rejection episodes and initial immunosuppressive treatment.
Kidney Transplant Recipient Follow-up Form	Transplant Center	Function of the transplant, immunosuppressive medications, and - if transplant had failed - the date and cause of graft loss.
Donor Histocompatibility Form	Histocompatibility Lab	HLA typing of Donor
Recipient Histocompatibility Form	Histocompatibility Lab	HLA typing of recipient, HLA cross-match
Live Donor Registration Form	Transplant Center	Demographics, viral serology, blood group, kidney function, blood pressure
Deceased Donor Registration Form	Organ Procurement Organization	Demographics, cause of death, blood group, kidney function, medical history

2.1.3 USRDS Data quality

USRDS data undergo multiple stages of data cleaning, conversion, validation, and consolidation [142]. The United Network for Organ Sharing performs electronic checks for inconsistencies in the data including the identification of improbable values and questions the

treating centre to resolve such problems. The Scientific Registry of Transplant Recipients (SRTR), which collaborates with the USRDS, reports monthly to the Organ Procurement and Transplant Network regarding data discrepancies and data quality issues in the USRDS. Data quality specialists at Organ Procurement and Transplant Network resolve these issues by directly contacting the transplant centers [141].

In 1999, UNet^{sm} system was introduced for data collection and verification process. UNet^{sm} incorporated the Transplant Information Electronic Data Interchange (Tiedi) system, which is electronic web-based system. Since then, data completeness has improved and the lag between an event and its recording in the USRDS has decreased. Prior to 1999, 11 months were required to validate 80% of the records. Since UNet was introduced, this time has decreased to 4 months [141].

Two studies, albeit old, have directly examined data quality in the USRDS. One compared data from USRDS to that in the Michigan Kidney Registry [143] for 7,600 patients who had undergone renal replacement therapy. This study found that more than 95% of Medicare-eligible patients from the Michigan Kidney Registry had a matching record in the USRDS database. It also found greater than 90% agreement for demographic variables between the two databases. A second study included four national samples totalling 1,692 incident patients in 1986-87 [144]. For these patients, the USRDS data entries were compared with on-site source data including medical records, discharge summaries, transplant summaries, and billing records. Overall agreement rate for more than fifty variables was 90.6%, with a range of 87% to 94.9%, which was lower than ideal. Variables with the highest agreement included dates of birth, death, and start of renal replacement therapy.

The USRDS data set has been previously used in a large number of published studies involving patients of chronic renal failure receiving dialysis and transplantation. The inclusion criteria variable in our present study (primary etiology of renal failure) [145] and outcome variable (aetiology of graft loss) [121;146] have previously been used in studies involving the USRDS database. Published studies using the USRDS database have also used variables that code immunosuppressive medication which is our primary exposure variable [147;148].

2.2 Data Layout in the United States Renal Data System

Data in the USRDS are organized in Standard Analysis Files (SAFs). The SAFs that were used in this study include:

1. **'PATIENTS'** – This data file contains one record for every patient enrolled in the USRDS. It contains basic demographic information including patient age, sex, and date of death. Basic information about each patient's end stage renal disease is also recorded and includes the primary cause of end stage renal disease, date of first renal replacement therapy, date of first transplant, total number of transplants and date and cause of death. This file is used to identify incident cohorts based on the date when treatment for end stage renal disease was started or first transplant occurred.
2. **'TX'** – This file summarizes information about some important demographic and treatment related variables of each transplant recipient including date of transplantation, date of transplant failure, and demographic information about both the donor and the recipient. The unit of observation in this file is the individual transplant.

3. **'TXUNOS'** – This file contains *all* information collected at the time of transplant for all transplants since 1987. It integrates variables from several sources mentioned above and thus contains the entire baseline covariates collected by these different sources. The unit of observation in this file is individual transplant.
4. **'TXFUUNOS'** – This file contains follow-up information on all transplants. The follow-up forms are completed by each treatment center six months after the transplant and then annually afterwards. This file contains the cause as well as the date of all transplant failures. The unit of observation in this file is the follow-up visit of each patient.
5. **'TXIRUNOS'** – This file contains information on baseline immunosuppressive drugs started at the time of transplantation. The unit of observation is the individual immunosuppressive medication started at the time of transplantation.
6. **'TXIFUNOS'** – This file identifies the immunosuppressive drugs that were being used at each follow-up visit. This information is obtained six month after transplant and then annually. The unit of observation in this file is the immunosuppressive medication at every follow-up visit.

2.3 Study Inclusion Criteria

Patients were included in this study if they had their first kidney transplantation between 1990 and 2003. This time interval was selected to capture changes in immunosuppressive medication use over the last decade. Patients prior to 1990 were not included in the study because clinical management of renal transplants was considerably different in the 1980s.

To be included in the study, the primary cause of renal failure had to be either primary or secondary glomerulonephritis. The 'PDIS' variable in the 'PATIENTS' file

records the primary cause of end stage renal disease with International Classification of Diseases (ICD)-9 codes from the Medical Evidence Form (2728) (Appendix 4). A list of ICD codes for causes of renal failure is attached to every form to assist the person completing the form to choose the appropriate ICD-9 code. A pathologically specific diagnosis of glomerulonephritis is usually based on histopathological examination of a kidney biopsy. For example, a diagnosis such as IgA Nephropathy or Berger's disease (ICD code 58381) is always based on histology from a biopsy and is therefore likely to be highly reliable. In contrast, a diagnosis of 'Glomerulonephritis, Histologically not examined' (ICD code 5829) is less specific and is usually not based on biopsy results. These patients are diagnosed as having glomerulonephritis on clinical grounds alone. Many clinical and laboratory features allow physicians to make clinical diagnosis of glomerulonephritis with reasonable certainty, although the exact histological type may not be possible to diagnose on clinical grounds alone. Physicians can also enter 'Etiology Unknown' (ICD code 7999) when they are uncertain about the cause of renal failure or if the information is unavailable. Therefore, the 'PDIS' variable and its codes are likely to be very specific but possibly less sensitive for glomerulonephritis cases. The ICD codes used to identify patients who had glomerulonephritis as cause of renal failure are presented in appendix 1.

Coding for primary disease causing end stage renal disease ('PDIS') was missing for 9.7% of all patients (11,819 out of 121,716 transplants) between 1991 and 2000. In a direct comparison study, the primary cause of renal failure recorded in the USRDS agreed with the clinical records in 79.4% of patients [144].

Patients with end stage renal disease due to glomerulonephritis were excluded if they underwent multi-organ transplantation. These patients were excluded because their immunosuppressive regimen differs from single organ kidney transplantation.

2.4 Primary Outcome

The primary outcome of the study was time to renal allograft loss due to recurrent glomerulonephritis. This was defined as loss of renal allograft function due to recurrent glomerulonephritis with return to dialysis or re-transplantation. The USRDS database records the date of graft loss for grafts that fail.

The USRDS determines transplant failure primarily from the Kidney Transplant Recipient Follow up Form (Appendix 4) that is recorded in the UNOS or REBUS database. In addition, other sources were used to ascertain whether a transplant has failed. A kidney transplant recipient can have one of three outcomes: return to dialysis due to failure of the transplant kidney; die with a functioning transplant; or continue to have a functioning transplant. A new Medical Evidence Form is required when renal transplant patients return to dialysis and therefore serves as an additional source of data on transplant failure. Deaths are notified using end stage renal disease Death Notification Form (2746). (Appendix 4). The USRDS assumes the date of graft failure written in Kidney Transplant Recipient Follow-up form to be the date of graft failure unless death or a new transplant identified by other sources of data occurs prior to this date. If the date of graft failure was missing in the Kidney Transplant Recipient Follow-up form, then the USRDS uses the first of the following dates as the date of graft failure [149]:

1. Date of death.
2. Date of subsequent transplant.
3. Date of return to dialysis for a period greater than 60 days, indicated by dialysis billing records.
4. Date of return to dialysis as indicated in the Medical Evidence Form

5. Date of graft nephrectomy as indicated in United Network for Organ Sharing follow up record or Medicare record.

In the previously referenced validation study conducted in 1986-87 [144], recorded transplant failure agreed with the clinical records in 88.4% of the examined cases. The date of graft failure was within 30, 60, and 90 days of that recorded in the medical files in 82.8%, 89.7% and 94.3% cases respectively. Date of death agreed exactly with medical records in 83.2% cases, whereas it was within 60-days in all 100% of the cases.

The cause of graft loss was determined from the Kidney Transplant Recipient Follow up Form. (Appendix 4). In this form, the options for the field 'Cause of graft failure' included: acute rejection; chronic rejection; primary failure; graft thrombosis; infection; urological complications; recurrent disease; and other. A diagnosis of recurrent glomerulonephritis is usually, but not always, based on histological data from a renal biopsy. The policy of doing a transplant kidney biopsy may vary between transplant centers for isolated urinary abnormalities with preserved kidney function. However, most physicians would proceed with a renal biopsy when the function of a transplanted kidney deteriorates progressively with no identifiable cause. Therefore, a diagnosis of recurrent glomerulonephritis is almost always based on a kidney biopsy revealing glomerulonephritis. In the event that a diagnosis of index glomerulonephritis was based on clinical grounds alone and a biopsy of the transplanted kidney showed glomerulonephritis, then it would be reasonably classified as 'recurrent glomerulonephritis'. Misclassification of the cause of graft loss can occur when neither the native nor transplanted kidney was biopsied. However, such misclassification would likely occur in both directions and would therefore be unbiased.

To be classified as graft loss due to recurrent glomerulonephritis, patients had to have a graft loss that was due to recurrent glomerulonephritis. This was determined by the 'Cause of graft failure' field from the Kidney Transplant Recipient Follow-up Form with a code of "8" for "recurrent disease". This variable from the USRDS database has been used in previous published studies [121;146].

2.5 Primary Exposure Variables

The covariates that were of primary interest in the analysis were immunosuppressive medications. Patients with kidney transplants need lifelong immunosuppressive medications to prevent rejection. Many patients continue the medications they started at the time of transplantation, even when the graft starts to fail. However, medications may be changed for reasons such as adverse effects of medications, rejection episodes, certain infections, malignancies, or chronic allograft nephropathy. Occasionally, recurrent disease in someone transplanted for glomerulonephritis might also prompt medications changes. Thus immunosuppressive medications used after transplantation may change over time, that is, they may be "time-dependent".

Information about the immunosuppressive medications started at the time of transplantation comes from the Kidney Transplant Recipient Registration Form. At each successive follow up (first at six months and then annually), the Kidney Transplant Recipient Follow up Form records all information about the utilization of ongoing immunosuppressive medications. In the USRDS dataset, variable 'RX_CD' codes for immunosuppressive medications used at the time of transplantation (in the file 'TXIRUNOS') or at each follow up after transplantation (in the file 'TXIFUNOS'). This variable has been used in previously published studies [147;148].

In the primary analysis, the immunosuppressive medications cyclosporine, tacrolimus, azathioprine and mycophenolate mofetil were entered as time-dependent covariates. To examine the validity of this approach, we did a number of sensitivity analyses. Details of these approaches are provided in section 2.11 (Analysis – Multivariate modeling).

The second covariate of primary interest was the year of transplantation. To determine if the risk of graft loss due to recurrent glomerulonephritis had changed over time, the association of transplantation year with the primary outcome was examined by creating dummy variables for the transplant periods 1995-1997, 1998-2000 and 2001-2003 with transplant years 1990-1994 as the reference period. This was chosen as the reference period because major changes in the use of immunosuppressive medications occurred primarily after 1994.

2.6 Potential Confounders

Different strategies can be used when constructing multivariate models. One of the most commonly used model-building strategies uses automated variable selection based on the significance level of each variable. Several authors have pointed out that variable selection based on P-values can lead to several problems [150-152] including:

- Overestimated regression estimates (i.e. biased away from null) [151;152]
- Standard errors of regression estimates that are biased low with resulting confidence intervals that are too narrow and 'p' values that are too small [151;152]
- The automated variable selection methods use tests like F-test to determine whether to include or exclude a variable in the model. These tests were intended to be used to test prespecified hypothesis, and therefore do not have the claimed distribution [152]

- The inclusion of variables in final model that are not clinically or biologically sensible [150;151].
- The inclusion of variables with overestimated regression coefficients since variable selection depends on estimated regression coefficients rather than their true values [152].

The USRDS dataset is very large, containing several hundred variables. The use of automated variable selection for constructing multivariate models from this dataset is likely to be associated with the above problems and lead to spurious results or an over-fitted model. It is therefore important to use previously collected information to identify the clinically important potential confounders that should be inserted in the final model and kept there regardless of their association with the outcome in the final model [151].

We therefore took the following steps to identify and control for important potential confounders associated with renal allograft failure to include in the final model. First, we conducted a systematic review of the literature to identify all studies published after 1995 that examined factors associated with all-cause renal allograft survival. We did not restrict the search strategy to graft loss due to recurrent glomerulonephritis for two reasons. First, only a limited number of studies have examined the factors that determine graft failure due to recurrent disease [27;30;42;49;50;59;69]. Except one of these studies [27], these studies included patients with only one specific type of glomerulonephritis. Second, we wanted to include factors associated with overall graft survival since it was important to control for confounders associated with other causes of graft failure that were treated as censored in our analysis [153]. In a Cox regression model for time to failure due to a specific cause, failure due to other causes is treated as censored. If independent predictors of the causes of graft failure that are censored are included in the regression model, the censoring can be viewed as non-informative conditional to included covariates [153]. That is, the patients who are

censored for causes of graft failure other than recurrent glomerulonephritis do not provide any information about recurrent glomerulonephritis beyond what is known from the covariates included in the model (non-informative censoring conditional to included covariates) [153]. This is a reasonable assumption since other causes of graft loss (including chronic rejection and death) are unlikely to be associated with recurrent glomerulonephritis. Including covariates associated with other causes of graft failure in the model will produce less biased estimates [153]. Since the standard of care has considerably changed in the field of transplantation in the last decade, we restricted the search to studies published after 1995 to identify the factors associated with graft survival in the study period.

The search strategy used for this review is presented in Appendix 3. All retrieved citations were reviewed to identify studies that used a multivariate model to identify independent predictors of renal allograft survival. All variables that the authors tested for inclusion in their final multivariate model were tabulated. As confounders in the regression models of the present study, we included all variables that were examined in at least five studies from our systematic review and were found to be independently associated with graft survival in greater than 20% of those studies.

In addition, we consulted experts in the field of kidney transplantation to identify factors believed by physicians in the area to be associated with graft survival. These factors were also included in the final model.

The search strategy yielded 178 citations (Figure 2). After reviewing the titles and abstracts, we identified 73 studies that were potentially eligible. Seventy-two of these references that were available in full were retrieved, and one paper written in Chinese could not be retrieved. The retrieved papers were examined in detail for inclusion in the review. Fifty three studies met inclusion criteria with 19 studies being excluded for the following

reasons: multivariate analysis not performed (11); review study only without primary data (1); randomized trial without secondary analysis (1); duplicate study (1); different study population (Re-transplants only-1, Non-heartbeating donors-2); and outcome other than graft survival examined (2).

Table 3 shows the important characteristics of the included studies. The majority of the studies (24/53) were from the United States with sample sizes ranging from 109 to 75,812. Eighteen studies used a multi-center registry database. A majority of them (15/18) used data from the same source as our study, namely, the United Network of Organ Sharing. The remaining reports were single center studies that used retrospective primary data collection. A majority of the studies used Cox regression modelling to identify independent predictors of the outcome and individual studies tested between four and twenty-two variables for inclusion in the multivariable model. Figure 3 shows potential determinants of graft failure that were examined in multivariate models in previous studies from literature.

Figure 2: Search results and study selection to identify published reports identifying independent predictors of renal allograft survival.

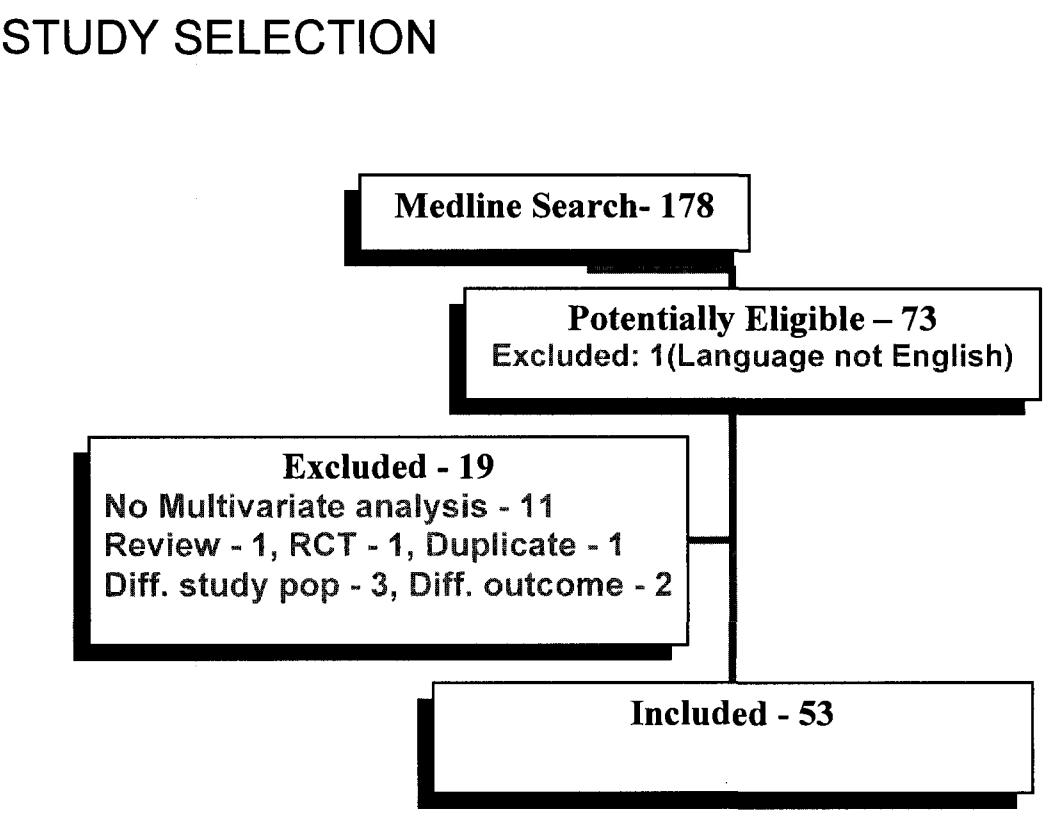


Table 3: Characteristics of studies included in the systematic review to identify independent risk factors of renal allograft survival.*

Sr. No.	Study	Year	Country	Single/Multicenter	Database	N	Model	Outcome
1	Su X.	2004	US	M	UNOS/USRDS	33443	Cox	G
2	Sagedal S	2004	Norway	S	-	471	Cox	G-cen
3	Weiss-Salz	2004	Israel	M		325	Logistic	G
4	Fitzgerald	2004	US	M	UNOS	29239	cox	G-cen
								G-un
								Pt
5	El-Groudy	2004	Egypt	S	-	650	cox	G-cen
6	Loven	2003	Sweden	S	-	534	cox	G
7	Wu Jianyong	2003	China	S		1,095	Cox	G
8	El-Groudy	2003	Egypt	S	-	1400	cox	Pt*
9	Pessione	2003	France	M	EFG	7209	cox	G
10	Ponticelli	2002	Italy	S		864	Cox	G
11	Meiere-Kriesche	2002	US	M	USRDS	40,289	Cox	G-CS(CAN)
12	Galante	2002	Brazil	S		1,544	Cox	G-Cen
13	Breitenfeldt	2002	Germany	S	-	927	cox	G-cen
								Pt
14	Roodnat	2001	Netherlands	S	-	722	cox	G-cen
								Pt
15	Bresnahan	2001	US	M	UNOS/SRTR	48280	logistic	1yr-G
16	Meier-Kriesche	2001	US	M	USRDS	73707	cox	G-cen
								Pt
17	Gjertson	2001	US	M	UNOS	8422		G
18	Abbot	2001	US	M	USRDS	3861	cox	G- CS
								G- Unc
19	Gjertson DW	2000	US	M	UNOS	75,812	Logistic	
20	Arrazola	2000	US	S	-	1188	?	G
21	Michelon	2000	Brazil	S		347	cox	G
22	Boom	2000	Netherlands	S		734	cox	G
23	Ojo	2000	US	M	USRDS	8070	cox	G
24	Prommool	2000	Canada	S		522	cox	G- Cen
25	Roodnat	2000	Netherlands	S		509	cox	G
26	Matas	2000	US	S		937	cox	G
27	Mange	2000	US	S		277	cox	G
28	Matas	2000	US	S		1199	cox	G- Cen
29	Morris	1999	UK	M		6363	cox	G
30	Agraz	1999	Spain	S		412	logistic	G- Cen
31	McLaren	1999	UK	S		681	cox/logistc	G
32	Hillebrand	1999	Germany	S		450	?	G
33	Cho	1999	US	M	UNOS	15262	cox	G
34	Pelletier	1998	US	S	-	1360	cox	G-Cen
35	Jang	1998	S. Korea	S		128	Wilcoxon/Fisher	G
36	Broekroelofs	1998	Netherlands	S		367	Cox	G-Cen
37	Giral-Classe	1998	France	S		843	cox	G

Table 3(Contd): Characteristics of studies included in the systematic review to identify independent risk factors of renal allograft survival

Sr.No.	Study	Year	Country	S9gle/Multicenter	Database	N	Model	Outcome
38	Marcen	1998	Spain	S		437	cox	G
								Pt
39	Cecka	1998	US					
40	Schnitzler	1997	US	M	USRDS	29900	cox	
41	Pfaff	1997	US	M	SEOPF	13478	?	G
42	Ojo	1997	US	M	USRDS	37216	cox	G
43	Lee	1997	US	M	UNOS	22837	cox	G - CS
44	Boratynska	1996	Poland	S		109	Cox	
45	Jin	1996	S.Korea	S		680	cox	G
46	Chertow	1996	US	M	UNOS	31251	cox	G
47	Cho YW	1996	US	M	UNOS	26682		
48	Park K	1996	South Korea	S		1275		
49	Bumgardner	1995	US	S		182	cox	G
50	Tesi	1995	US	S		236	?	G
51	Cole	1995	Canada	S		634	cox	G
52	Cosio	1995	US	S		547	cox	G-Cen
53	Kapsner	1995	Germany	S				G

Key:

US: United States; M: Multicenter; S: Single center

G: Graft survival, unspecified; G-Cen: Death censored graft survival

G-Unc: All cause graft survival; Pt: Patient survival; G-CS: Cause specific graft survival

USRDS: United States Renal Data System

UNOS: United Network for Organ Sharing

SRTR: Scientific Registry of Transplant Recipients

EFG: Establissement Francais des Greffes database

SEOPF: South Eastern Organ Procurement Foundation database

CAN: Chronic allograft nephropathy

Figure 3: Predictors of renal allograft survival tested in a multivariable model in the studies included in systematic review of the literature.

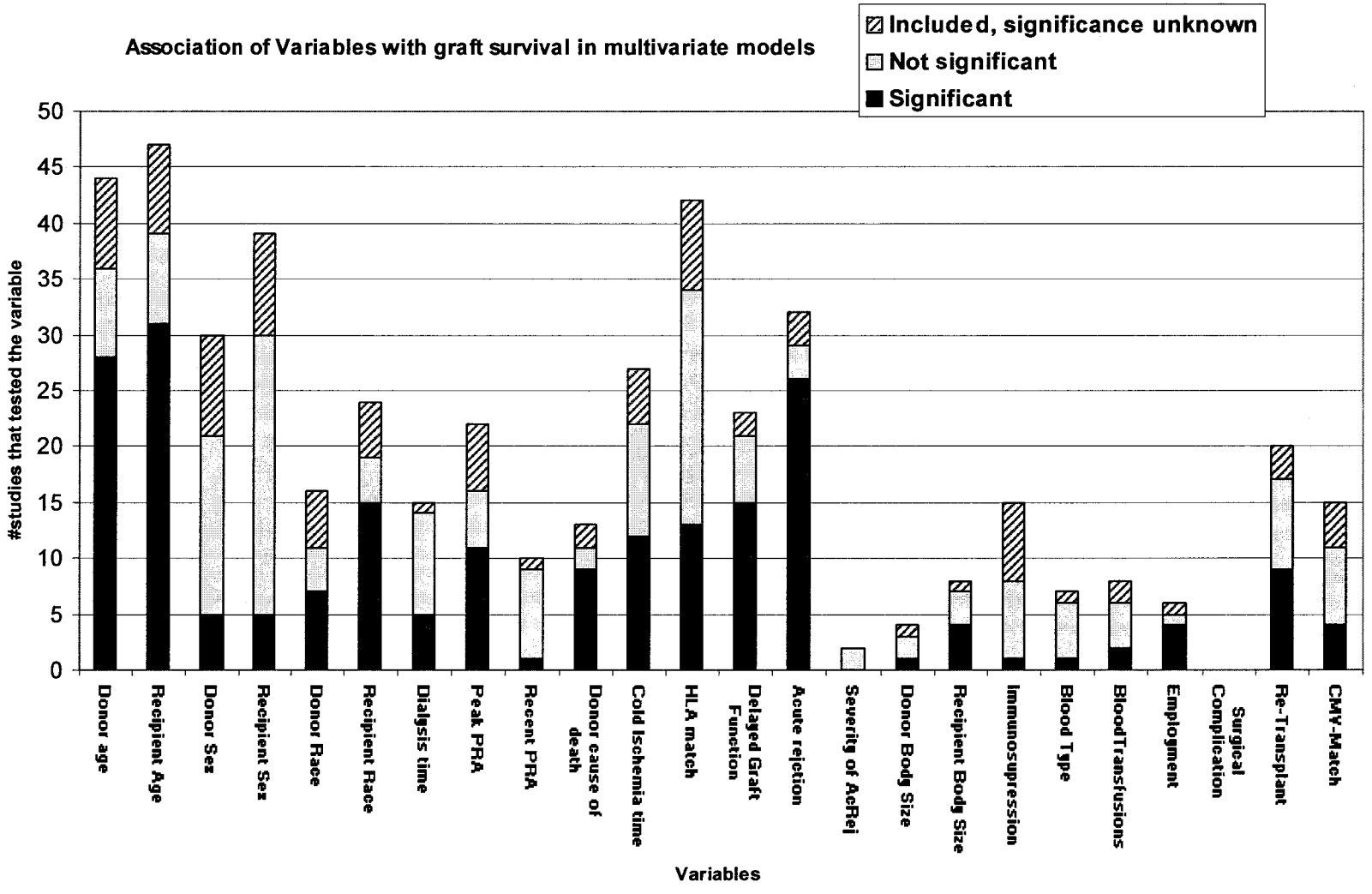


Table4: Independent predictors of graft survival in published literature since 1995.
(No of studies: 53)

Covariate	Total no of publications that studied the covariate	Studies that found significant independent association N	Proportion of studies that found significant independent association (%)
Recipient Age	47	31	66
Donor Age	44	28	64
HLA mismatch	42	13	31
Recipient sex	39	5	13
Acute Rejection	32	26	81
Donor Sex	30	5	17
Cold ischemia time	27	12	44
Delayed graft function	26	15	58
Recipient Race	24	15	63
Peak PRA	22	11	50
Previous transplant	21	9	43
Donor Race	16	7	44
Duration of dialysis	15	5	33
CMV-matching	15	4	27
Immunosuppression	14	1	7
Donor cause of death	13	9	69
Live / Cadaver donor	10	4	40
Primary cause of ESRD	10	7	70
Current PRA	10	1	10
Pre-transplant blood transfusion	8	2	25
Transplant year / era	8	6	75
Recipient history of diabetes	8	6	75
Recipient body size	8	4	50
Employment status	6	4	67
Blood type	6	0	0
Hepatitis B status	5	2	40
Donor hypertension	5	4	80
Donor creatinine	5	2	40
Warm ischemia time	5	0	0
Transplant Center	4	2	50
Dialysis modality	4	0	0
Donor body size	4	1	25
Local or shipped organ	3	2	67
Hepatitis C status	2	0	0
Recipient hypertension (preTx)	2	0	0
Primary Payer	2	1	50
ACE inhibitor use	1	0	0

Overall, 37 variables available at the time of transplantation were examined in these reports (Table 4). The shaded rows in table 4 indicate the variables that were tested in at least 5 studies and were found to be significant in greater than 20% of them. We did not consider any covariates that were measured after transplantation since the dataset used for our study had limited information regarding such follow-up variables. Twenty-nine variables were examined in five or more studies. Twenty-five of these variables were found to be independent predictors of graft outcome in more than 20% of the studies that tested them (Figure 3). However, we excluded all covariates that were missing in more than 15% of observations in the USRDS dataset since the relative efficiency of multiple imputation decreases as the fraction of missing information increases [154]. This excluded five variables including pre-transplant blood transfusion, donor hypertension, donor creatinine, CMV antibody matching and a history of diabetes in the recipient. Finally, we excluded "previous transplant" since our study cohort was restricted to patients with first transplant.

Therefore, the covariates included in our final model included: donor age; recipient age; donor sex; recipient sex; donor race; recipient race; duration of dialysis; peak panel reactive antibody; donor type and cause of death if cadaver donor; cold ischemia time; number of HLA antigens that match; delayed graft function; acute rejection; hepatitis B surface antigen status; employment status; recipient body mass index; and transplant period. In addition, the model was adjusted by stratification by transplant center. This was done because three studies from the United States have shown that transplant center is an important determinant of graft survival [91;101;155]. The average annual transplant volume at each center was entered in a univariate Cox model to examine its association with graft loss due to recurrent disease. Based on exploration in separate univariate models, we

classified transplant center into two groups, centers with <50 transplants/year or with >=50 transplants per year.

2.7 Analysis - Descriptive statistics of baseline covariates

Continuous variables were described using the mean and standard deviation while categorical variables were described using proportions. Cold ischemia time was categorised as <12 hr, 12-24 hours and >24 hours. Previous studies have shown that nearly half of the transplanted kidneys from a deceased donor are stored for longer than 20 hours [156]. Cold ischemia time longer than 24 hours has been shown to be associated with increased risk of delayed graft function [97]. In contrast, live donor transplants have a very short cold ischemia time, usually less than three to four hours. Since our dataset contained both live and cadaver donors, the cold ischemia time was not distributed normally. We therefore categorized this variable into clinically relevant intervals.

A highly sensitised recipient was defined as one with peak PRA (panel reactive antibody) titre test showing presence of preformed anti HLA antibodies against greater than or equal to 50% of the common HLA antigens in population, according to a standard definition [157;158].

Duration of dialysis was highly skewed to the right since a few patients had been on dialysis for a very long prior to transplantation. Concomitantly, patients who had a pre-emptive transplant had zero dialysis time. Median duration of dialysis prior to transplant has increased from approximately one year in 1995 to more than two years in 2003 [159]. Therefore this variable was categorized into no dialysis (pre-emptive transplant), <=12 months of dialysis, 12 to 36 months, and >36 months of dialysis. Delayed graft function was defined as the need for dialysis during first week after transplantation. Kaplan-Meier

methods were used to estimate unadjusted 10-year probability of graft loss due to recurrent disease.

2.8 Analysis - Handling of missing values in baseline covariates

The number and proportion of missing or nonsense values of each baseline covariate is given in Table 5. The missingness was non-monotonic, meaning that the variables were not ordered sequentially such that a missing value for variable x meant a missing value for variable x + 1. Missing values were assumed to be *missing at random,* meaning that probability of missing data in a given variable could be related to the value of other variables but not to its own actual value. The missing at random assumption is impossible to test [154]. However, we believe it is reasonable in this situation given the large size of the database and large number of centers involved.

Table 5: Missing and nonsense values of the covariates in the study cohort

Covariate	N	Missing values		Nonsense values	
		N (%)	Value Label	n (%)	Value label
Recipient Gender	41,272	2 (0)	Unknown	0	-
Recipient Race	41,272	0	-	0	-
Donor Gender	41,272	1351 (3.27)	Unknown	0	-
Donor Race	41,272	1448 (3.51)	Unknown	0	-
HLA* Mismatches	41,272	3838 (9.30)	Missing	0	-
Delayed graft function	41,272	632 (1.53) 246 (0.60)	Missing Unknown	0	-
Treated for acute rejection	41,272	660 (1.60)	Missing	0	-
Donor Type (Living / Cadaver)	41,272	0	-	0	-
Recipient Age (yr)	41,272	0	-	1 (0) <1%	101 year 0 years
Donor Age (yr)	41,272	3267 (7.92)	Missing	<1%	0 years
Peak PRA* (%)	41,272	3685 (8.93)	Missing	0	-
Most recent PRA*	41,272	3660 (8.87)	Missing	0	-
CIT* in all transplants (hr)	41,272	6492 (15.73)	Missing	0	-
CIT in cadaver donor Transplants	25,441	2089 (8.21)	Missing	0	-
Duration of dialysis (months)	41,272	0	-	0	-
Primary payer	41,272	16648 (40.14)	Missing	0	-
Highest education level	41,272	13597 (32.78) 5788 (13.96)	Missing Unknown	0	-
Employment status	41,272	619 (1.49) 4678 (11.28)	Missing Unknown	0	-
Donor cause of death	25,441	1125 (4.42)	Missing	0	-
Cadaver Donor history of hypertension	25,441	8642 (33.97) 189 (0.74)	Missing Unknown	0	-
Cadaver Donor history of diabetes	25,441	8649 (34.00) 98 (0.39)	Missing Unknown	0	-
Hepatitis B surface antigen	41,272	613 (1.49) 1347 (3.26) 1402 (3.40) 208 (0.5)	Missing Unknown Not done Can't disclose	0	-
Anti Hepatitis C Antibody	41,272	614 (1.49) 11517 (27.91) 1525 (3.69) 206 (0.5)	Missing Unknown Not done Can't disclose	0	-

HLA: Human leucocyte antigen, PRA: Panel reactive antibody, CIT: Cold ischemia time

To impute missing values, we used multiple imputation with a Markov Chain Monte Carlo (MCMC) method. Multiple imputation produces estimates that are consistent and asymptotically normal when the data are missing at random [154]. A Markov Chain is a sequence of random variables in which the distribution of each element depends only on the value of the previous one. The goal of a MCMC simulation is to construct a Markov chain that is long enough to stabilize the distribution of its elements to one that is stationary. We used the data augmentation type of MCMC multiple imputation because the missingness was non-monotonic. We assumed a multivariate normal model, which considers that all variables have a normal distribution and each variable can be expressed as a linear function of all other variables. Although these assumptions appear strong, the MCMC method works well even if some variables do not have normal distribution [154;160].

Multiple imputation using the MCMC method is an iterative process. It is accomplished by repeating two steps – an imputation step (I-step) and a posterior step (P-step). In the first step (the I-step), the MCMC method initially calculates the means and covariance matrices of all variables having complete observations (complete case analysis). A regression estimate of the variable containing a missing value is obtained by regressing it on all other variables (again using only complete cases).

For example, consider a dataset with only 2 variables ("X" and "Y") of which only "Y" has missing values. In the first step, we create a regression estimate of missing "Y" values using the following linear model:

$$\hat{\mathbf{y}}_i = a + b\mathbf{x}_i + s_{x.y}\mathbf{u}_i$$

where $\hat{\mathbf{y}}_i$ is the estimate of Y for patient i, a and b are regression parameter estimates, $\mathbf{x}_i$ is the value of variable X for patient i, $\mathbf{u}_i$ is a random draw from the distribution of the error term,

and $s_{x.y}$ is the estimate of standard deviation of the residuals. This model permits missing values of "Y" to be estimated using the value of "X" for that observation.

Using the resulting dataset (that now contains no missing values for Y), the means and covariance matrices for each variable are recalculated. In the next step (P-step), the newly calculated means and covariances are used to make random draws from the posterior distribution of means and covariances. To get the posterior distribution, Jeffrey's non-informative prior distribution, that contains little or no information about the parameters, was used. The newly drawn means and covariances are again used to generate new values of the missing data and the whole process is repeated. These two steps- the I-step and the P-step, are repeated in an iterative process until the iterates converge to a stationary distribution. The imputations that are produced during the final iteration are used to form a complete dataset.

This process was then repeated multiple times to create several imputed datasets. The regression modelling strategy was then applied to each of the datasets to generate parameter estimates and standard errors that are unique to each dataset. Parameter estimates from each regression model were then combined to give the final results.

We took following steps to implement multiple imputation for our dataset:

a) Important covariates that needed to be included in the model were determined (see section 2.6).
b) Donor age, recipient age and body mass index were continuous variables and were assumed to be normally distributed.
c) Duration of dialysis, peak panel reactive antibody status, cold ischemia time were categorized into variables that contained two or more levels (see section 2.7). Imputation of these variables was handled by initially creating indicator variables for each level,

except the reference category, with the indicator variables being coded as '0' or '1' [154]. The missing values of these indicator variables were imputed (along with missing values for all other variables) restricting their imputed value to between zero and one. The imputed indicator variable (including one for 'reference level' allocated value of (1-(sum of value of all indicator variables)) with the highest value was deemed the imputed value of the original multilevel categorical variable.

Consider a variable Y that has three levels. Two indicator variables 'Y1' and 'Y2' were created and coded as '0' or '1' depending on the original value of Y (i.e. Y1=1 when Y is the middle level value). We used PROC MI in SAS to impute missing values of Y1 and Y2 for all observations with a missing Y with values between 0 and 1. We then created a variable 'Y0' to contain the imputed value of Y. For an observation with imputed value for Y1 of 0.45 and an imputed value for Y2 of 0.2, we initially assigned Y0 a value of $(1 - 0.45 - 0.2) = 0.35$. Finally, since Y1 has the largest value of Y0, Y1, and Y2, the imputed value for Y is its middle level value.

For this analysis, multiple imputation was implemented using 'Proc MI' in SAS9.1. We generated five sets of data using the multiple imputation approach. We used 500 iterations to generate the first dataset to ensure that convergence was obtained prior to drawing the first imputed dataset. The other four were generated each after additional 200 iterations. These five datasets were then analyzed separately using the strategy delineated in sections 2.10-2.13 below. The regression estimates obtained were then combined using 'proc MIANALYZE' in SAS.

2.9 Analysis – Missing values follow-up visits

Because immunosuppressant utilization was the primary exposure variable in the study, we studied "missingness" of the follow-up visits and immunosuppressant information in detail.

Follow-up after transplantation is expected after 6 months and then annually at each anniversary of the date of transplantation. There can be a lag period between an event occurring and the time when the USRDS receives a report about the event. Prior to 1999, 11 months were required to validate 80% of the record. After 1999, this period had decreased to 4 months [141]. For the present analysis, observation time for each patient went from the transplant date to the earliest occurrence of graft failure from any cause, patient death, or 31 December 2002 to account for possible lag time in reporting events that occurred in 2003. Of all patients, 38,237 (92.86%) patients had all of their follow up dates recorded during the valid observation period between the date of transplantation and the end of observation. 5,462 (13.2%) patients did not have a 6-month follow-up visit. The majority of these patients had less than one-year of follow-up. Considering patients with more than one year of follow-up, only 603 (1.9%) patients did not have a 6-month follow-up visit.

2.9.1 Patterns of Missing follow-up visits

The following "patterns of missingness" were seen in patients followed for more than two years. Patients could miss one visit but then return for the next follow-up visit (Pattern A). Patients could also miss two consecutive visits before returning for a follow-up visit (Pattern B). Finally, patients could miss two or more visits in a row (Pattern C) without returning for follow up. Table 6 shows these frequencies for these patterns of missingness.

Table 6: Patterns of missing follow-up visits in patients with greater than two years of follow-up.

Pattern of follow-up*	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	35,757	86.64	35,757	84.51
A	358	0.87	36,115	86.52
B	45	0.11	36,160	86.60
C	5,112	12.39	41,272	100.00

Follow-up pattern:

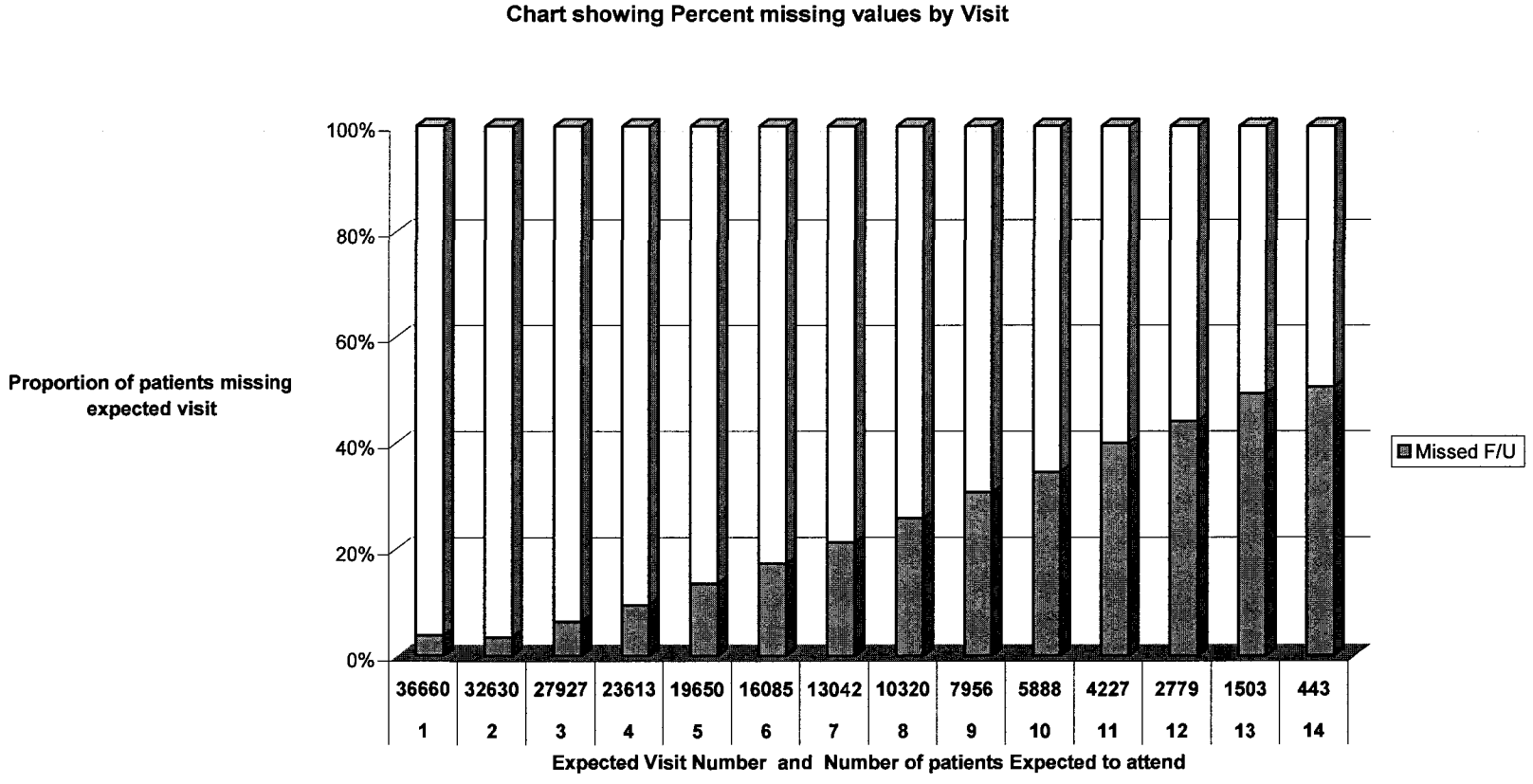
A-One missing visit followed by return
B-Two visits missing followed by return
C-Two or more consecutive visits missing
0-Other patients.

Patients who miss a follow-up are more likely to return to their physician if they get sick again or if their transplant function worsens. It is therefore possible that once a patient with previously missed follow-up visits returns, they are more likely to experience a change in immunosuppressive medication than those patients who miss follow-up but have good graft function. A majority of patients who missed follow-up visits missed two or more consecutive follow-up visits without returning for follow-up. Such patients are less likely to have experienced change in medications. The association of missingness with graft outcome is described below.

2.9.2 Relationship of missing follow-up visits with duration of observation

We found that the proportion of patients who missed a follow up visit increased as the duration of observation increased. Thus, the proportion of patients who missed first, second and third follow up respectively was 3.8%, 3.4% and 6.4% (Figure 4). However, 21.4% of patients missed their seventh expected follow-up visit, which was six years after transplantation. The proportion patients who did not have a follow-up form completed increased to nearly 50% after 12 years of transplantation (Figure 4).

Figure 4: Proportional bar diagram showing proportion of patients with missing visits by duration of observation.



2.9.3 Proportion of missing visits

Mean expected number of follow-up visits per patient was 4.82 (SD 3.48) while mean actual follow-up visits per patient were 4.15 (SD 3.31). Mean missing follow-up visits were 0.67 (SD 1.52) per patient while median number of missing follow-up visits per patient was 0 (inter-quartile range 0 – 1). 79.1% of the patients missed less than 5% of their expected number of follow up visits. A further 5.5% of patients missed 5-25% of the expected number of visits. 6.5% patients missed more than half of their expected number of follow up visits (Table 7). 8,432 (20.4%) of all patients missed their last expected follow-up visit and 5,036 (12.2%) patients missed the next to last follow-up visit. Of these, 4,878 (11.8%) patients had last two consecutive follow-up visits missing.

Table 7: Frequency of Missing follow up visits as proportion of Expected visits

Percent expected follow-up missing	No of Patients	Proportion of patients missing N = 41272
< 5	32655	79.12
5 – 15	1120	2.71
16 – 25	1138	2.76
26 – 35	1613	3.91
36 – 45	835	2.02
46 – 55	1050	2.54
56 – 65	634	1.54
66 – 75	472	1.14
76 – 85	426	1.03
86 – 95	187	0.45
> 95	1142	2.77

2.9.4 Relationship of missingness with graft outcome

We observed a significant relationship between the likelihood of missingness and graft outcome. Of the patients with a surviving graft at the end of observation, 25.1%

missed more than five percent of expected number of follow-ups. In contrast, 21.7% of patients who died and 5% of patients with graft failure missed more than 5% of follow-up visits ($p<0.001$) (Table 8A and 8B). Similarly, patients who lost graft due to recurrent glomerulonephritis tended to have more complete follow-up. Thus, 97.2% of the patients who lost a graft due to recurrent disease attended greater than 95% of expected number of follow-up visits. This proportion was significantly greater than the rest of the patients, of whom only 78.9% attended greater than 95% of expected follow up visits ($P<0.001$). These results suggest that patients with properly functioning transplants are more likely to miss follow up visits compared to patients with graft dysfunction.

Table 8A: Frequency of missing follow-up visits by graft status

Percent expected follow-up missing	Pt alive with functioning graft N (%)	Graft failure N (%)	Death N (%)
< 5%	21,742 (74.9)	7,550 (95.0)	3,363 (78.3)
6 – 25%	1,975 (6.8)	100 (1.3)	183 (4.3)
26 - 55%	3,018 (10.4)	135 (1.7)	245 (5.7)
>55%	2,299 (7.9)	215 (2.7)	501 (11.7)
Total	29,034 (100)	7,944 (100)	4,292 (100)

Table 8B: Frequency of missing follow-up visits by graft failure due to recurrence

Percent expected follow-up missing	Patients with Graft failure due to recurrence N (%)	Other Patients N (%)
< 5%	546 (97.2)	32,109 (78.9)
6 – 25%	3 (0.5)	2,255 (5.5)
26 - 55%	5 (0.9)	3,493 (8.6)
>55%	8 (1.4)	2,853 (7.0)
Total	562 (100)	40,710 (100)

Similarly, there was a clear association between a missing last follow-up visit and graft outcome. The proportion of patients who missed their last follow up visit was 24.2% in

patients with a surviving transplant, 21.5% in those who died with functioning transplant and only 6.1% in those who lost their graft without dying (P<0.0001) (Table 9). The proportion of patients who missed their last two follow ups was 14.3%, 13.6% and 1.8% respectively in patients who had functioning graft, who died with a functioning graft, and who had graft failure without dying, respectively.

Table 9: Association of missing last visits with outcome

Missing Visit	Graft Functioning			All Cause graft loss			Pt died			Recurrence		
	#Miss	N	%	# Miss	N	%	# Miss	N	%	# Miss	N	%
Last Visit	7027	29034	**24.2%**	483	7944	**6.1%**	922	4294	**21.5%**	62	562	**11.0%**
2nd last visit	4206	23157	**18.2%**	181	5244	**3.5%**	601	3273	**18.4%**	6	449	**1.3%**
3rd last visit	3470	20058	**17.3%**	103	4217	**2.4%**	431	2866	**15.0%**	5	356	**1.4%**
Last 2 visits	4148	29034	**14.3%**	146	7944	**1.8%**	584	4294	**13.6%**	6	562	**1.1%**

Thus, it is clear that most missing values occurred toward the end of follow-up period and in patients with good graft function. Such patients who do not return for follow-up and have good graft function would be significantly less likely to have had changes in their medication because their good outcomes. Therefore, we chose to fill missing values in follow-up visits by using the last-observation-carry-forward method. That is, when a visit was missing and patient returned for next follow-up, we assumed that the medications from the previous visit were continued at the time of the missing visit. When two consecutive visits were missing, we assumed that the medications at the time of the previous follow-up were continued till the end of follow-up or graft failure, whichever occurred first.

2.10 Analysis – Controlling for confounding by indication

It is possible that medications were changed because kidney transplant started to fail due to recurrent disease. In such a case, it would be clearly inappropriate to assign any subsequent graft loss to the new drug since its start was the result of, rather than cause of, recurrent glomerulonephritis. We took the following steps to control for such confounding by indication:

a) We first created a time-dependent variable indicating if and when any change in medications (compared to baseline) occurred during follow-up. This variable took the value of '1' after any change in any of the medications from baseline, and '0' previously. This time-dependent variable was entered into a Cox model along-with all fixed covariates (see section 2.6) including immunosuppressive medications at baseline. This model determined if any change in medications from baseline during follow-up period was independently associated with graft loss due to recurrence.

   We created a variable indicating the cumulative number of follow-up visits when any of the immunosuppressive medications were changed from the previous visit. If more than one medication was changed at the same follow-up visit, it was considered to be a single change. We then categorised the cumulative number of changes into four levels including no change, changes at one follow-up visit, changes at two follow-up visits, and changes at three or more follow-up visits. This time-dependent variable was expressed as an ordinal type (i.e. single variable with four ordinal categories) or a nominal type (i.e. using three indicator variables, one each for category '1', '2', '3', and category '0' as reference category) and entered into two separate Cox models. We compared these three models (one with a binomial variable indicating any change and

two models with 4 categories of change in medication as described above) using the likelihood ratio test for the difference in the degrees of freedom to determine the best form to model medication changes. This showed that the model with any change in medication did not differ significantly from the other models. Therefore, in the final model, we entered any change as a binomial time-varying variable to control for confounding by indication.

b) We built a model with a 6-month lag between the initiation of medication and its effect. A 6 month lag was used because studies showing a benefit of cyclosporine in membranous glomerulonephritis required 6 to 12 months of treatment with cyclosporine before an effect of the medication was seen [161;162]. Cyclosporine treatment for six months in patients with focal segmental glomerulosclerosis was shown to be more likely to induce remission of proteinuria and preserve renal function compared to placebo [163]. Studies using mycophenolate mofetil in various glomerulonephritis have used a 6 month [164] to 36 month [84] course of mycophenolate mofetil. Therefore, we used six-month lag between initiation of immunosuppressive therapy and its potential effect on outcomes. Thus, for instance, if a medication was started at time 4 months, it was assumed to be effective starting from time 10 months in the model.

c) We did a subgroup analysis examining patients who did not have any change in their medications during follow-up. In this model, we entered medications at baseline as fixed covariates along with other confounders.

2.11 Analysis – Multivariate modeling

We used extended Cox regression modelling to determine whether exposure to the four immunosuppressive medications were associated with time to graft loss due to recurrent

glomerulonephritis. The start of observation was the date of transplantation. The end of observation was the date of graft loss due to recurrence of glomerulonephritis, date of graft loss due to other causes, death, or date of last follow-up. Observation was censored for the latter three events. All variables that were deemed to be important covariates (see section 2.6 above) were included in the model as fixed covariates.

Exposure to the immunosuppressive medications was expressed as time-dependent covariates. Time-dependent covariates change value during the observation time. Immunosuppressive medication exposure is an example of a time-dependent covariate since patients can go on and off the medications during the observation period. Improper handling of time-dependent covariates, most notably treating them as fixed variables, can result in biased results [165]. Analyzing time-dependent variables using time-dependent covariate techniques potentially avoids these biased results [153].

We coded each immunosuppressive medication as 1 or 0 indicating whether the patient was exposed to them or not, respectively. Azathioprine and mycophenolate mofetil belong to the same class of immunosuppressants called 'antimetabolites', and it is highly unusual that a patient is on both medications simultaneously. We therefore considered such records as data errors. There were 1,000 patients (2.4%) who were on both medications simultaneously at some time during their observation. If patients were reportedly exposed to both anti-metabolites simultaneously, they were randomly assigned to either azathioprine or mycophenolate mofetil. Similarly, cyclosporine and tacrolimus belong to the same class of drugs called 'calcineurin inhibitors' and they also are never used simultaneously. Therefore, the 494 patients (1.2%) who were coded as receiving both drugs simultaneously at some time during their observation period were randomly allocated to either cyclosporine or tacrolimus.

We created the time-dependent covariates representing immunosuppressive medications using the following steps:

a) First, we determined the follow-up time from the date of transplantation to the date of graft loss due to recurrent disease, graft loss due to other causes, death, or end of follow-up time. Since the dataset is very large (more than 200,000 observations among the imputed five datasets) and longest follow up time was large (14years*365.25 = 5113.5 days), we expressed follow up time in months. The time of each event was rounded to the nearest value in months.

b) We then created 168 variables to equal the maximum possible follow up in months (14 years*12 months), in addition to a variable for baseline use of medication (baseline variable), to code for use of each immunosuppressive medication at each month of follow-up. We coded each time dependent covariate as '0' to indicate no current use and '1' to indicate current use of the medication at the corresponding month.

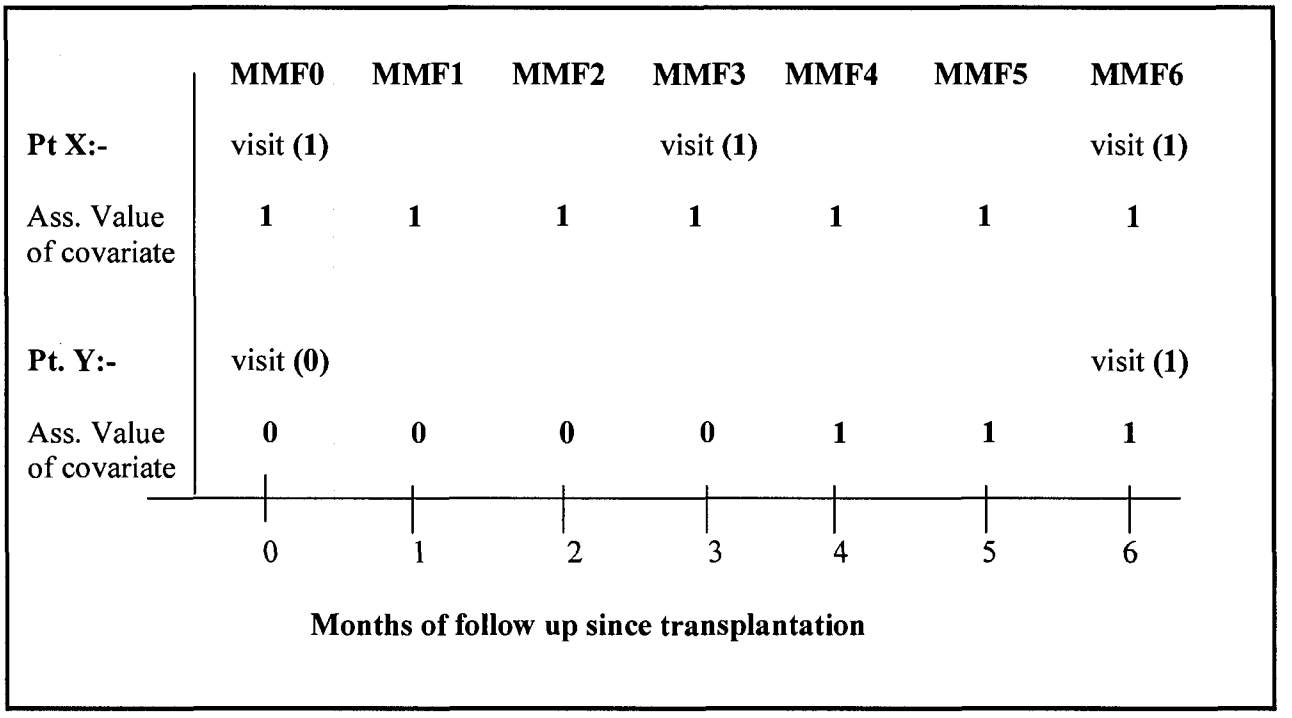
c) If there was no change in medication between two *actual* follow up visits, we assigned the same value as the two *actual* visits to all variables corresponding to the months of follow up in the interval between the *actual* visits. If there was a change in medications between follow up visits, we randomly picked a follow-up month between the two visits as the time of medication change. This was done using a computer-generated random number with a uniform distribution. The value of the time-dependent covariate at the previous visit was assigned to all months up to the randomly selected month and was switched to the other value for all subsequent months.

This process was repeated for the entire follow up period and allowed more than one change in the use of medication. This process is illustrated in the following examples.

Consider patient X who was started on mycophenolate mofetil at the time of transplantation (Figure 5). He has follow up records at 3 and 6 months. He was receiving mycophenolate mofetil at the time of transplantation as well as at both his follow up times. Variable 'MMF0' is a variable indicating the use of MMF at baseline and variables 'MMF1' to 'MMF6' indicate use of mycophenolate mofetil at months one to six, respectively. In this case, all of the variables from MMF0 to MMF6 are assigned the value '1' indicating that this patient was exposed to mycophenolate mofetil during the period of 0 months to 6 months.

Consider a second patient (Y) who was not started on mycophenolate mofetil at the time of transplantation (Figure 5). She has her first follow up visit at six months after transplantation. At this visit, her records indicate that she is on mycophenolate mofetil. Clearly, she was started on mycophenolate mofetil sometime between date of transplantation and her 6-month follow up date. Again time-dependent variables MMF0 to MMF6 are created to indicate use of mycophenolate mofetil at baseline and at each subsequent follow-up month respectively. We now use uniform random distribution to generate an integer between 0 and 6. Suppose the program generates number '4'. We then assign MMF0 to MMF3 the value '0' to indicate absence of mycophenolate mofetil use and assign the value '1' to MMF4 to MMF6 to indicate subsequent exposure to mycophenolate mofetil.

Figure 5: Coding of immunosuppressive medications as time-varying covariates



The final model included variables expressing use of the four immunosuppressive medications (azathioprine, mycophenolate mofetil, cyclosporine and tacrolimus) as time varying covariates along with important confounding covariates. In addition, we included a variable indicating any change in medications during follow-up as time varying variable (see section 2.10) that would take a value of '0' until any medication were changed and '1' after the change until graft loss or end of follow-up period. To control for confounding by indication, we built a lag time of six months between the initiation of medications and outcome.

In the immunosuppressive medications, we considered the following pre-specified comparisons. Firstly, among the antimetabolites, both azathioprine and mycophenolate mofetil were compared to no antimetabolites and with each other. Secondly, two calcineurin inhibitors, namely cyclosporine and tacrolimus, were compared with each other as well as

with patients who were not on any calcineurin inhibitors. We used the 'test' statement in 'Proc Mianalyze' in SAS to test the linear hypotheses that azathioprine and mycophenolate mofetil were not significantly different and that cyclosporine and tacrolimus were not significantly different. Bonferroni's adjustment for multiple comparisons was used to decide significant difference between these pairs of medications.

We used 'Proc Phreg' in SAS to estimate the Cox regression model for each of the five imputed datasets. We stratified the models based on number of transplants done at the transplant centers annually, into centers with greater than or less than 50 transplants per year. The results of these five estimates were combined using 'Proc Mianalyze'.

We determined the factors that predicted first change in immunosuppressive medications using a separate Cox regression model. For this model, the start of observation period was date of transplantation and end of observation period was date of first change in medications or end of follow-up (date of graft loss or 31/12/2003), whichever was earlier. Patients were censored if they did not have any medication change during follow-up. We considered all baseline fixed covariates (see section 2.6), as well as use of immunosuppressive medications at the time of transplantation for this model.

2.12: Analysis - Sensitivity Analyses

Sensitivity analyses were performed to determine the robustness of the model. First, we used separate models in which we varied lag time between three months or twenty-four months to measure the impact of varying lag time on parameter estimates. Next, we repeated the analysis after excluding patients who had two or more consecutive missing follow-up records after the first 18 months of transplantation to determine the effect of missing values on the estimates. Finally, a selected subgroup analysis was conducted in patients in whom

the medications were not changed during follow-up. For these people, we determined the association of baseline immunosuppressive medications with the risk of graft loss due to recurrent glomerulonephritis to examine the effect of medications when they are not changed throughout the follow-up period thus avoiding any confounding by indication.

2.13 Analysis – Sample size and power calculations

Sample size calculations based on time-dependent covariates are complicated [166]. Therefore, our sample size calculation was based on the number of potential confounders that we anticipated would be needed to adequately control for confounding. To ensure that parameter estimates of our proportional hazards model are within 2.5% of the true parameter measure, experts recommend a minimum of 10 events per variable (EPV) in model [167]. With less than 10 EPV in model, parameter estimates tend to be biased. The accuracy of the estimates increases as the EPV increases to 25. We had anticipated that we might need to control for up to 20 fixed covariates. With additional variables for immunosuppressive medications and year of transplantation, we had anticipated 25 variables in the initial model. Thus we would need a minimum of 25 x 10 = 250 events, and ideally 25 x 25 = 625 events, over the observation period of 14 years to adequately control for confounding.

The lower 95% confidence limit for 10-year graft loss due to recurrent glomerulonephritis in the aforementioned Australian study was 5.9% [27] giving a 10-year survival rate of 94.1% (censored for death and other causes of graft loss). Assuming a constant hazard rate over time, the cumulative hazard can be calculated from the equation $S(t) = \exp(- H*t)$ where S(t) is survival at time t, H is hazard rate, and t is time. For a survival of 0.941 at 10 years, the constant hazard rate is thus 0.006081 per year. Due to staggered recruitment over 14 years, the average follow-up will be approximately 8 years. If

the hazard remains constant for 8 years, the 8-year survival rate would be 0.9225 (i.e. exp (-0.006081*8)). Therefore, the lower 95% confidence limit of 8-year graft loss due to recurrent glomerulonephritis would be 5.3%. Thus we projected a required sample size of 4,245 recipients of transplantation who had glomerulonephritis as primary renal disease to have 225 events and 11,793 recipients to have 625 events. In post-hoc analysis, we had 22 variables in the model and 562 events of graft loss due to recurrent glomerulonephritis. This gave us 25.5 events per variable, which is considered adequate for obtaining unbiased estimates.

3.0 Results

3.1 The Study Cohort

The USRDS dataset contained records for 1 516 251 patients with end-stage renal disease. The cause of renal failure was unknown or nonsensical in 8.0% of these patients. 195,307 patients had renal failure due to glomerulonephritis. Of these patients, 41 936 patients underwent a first kidney transplantation between January 1, 1990 and December 31, 2003. After excluding patients who received multi-organ transplant, the study cohort contained 41 272 patients (Figure 6).

Figure 6: Study cohort creation

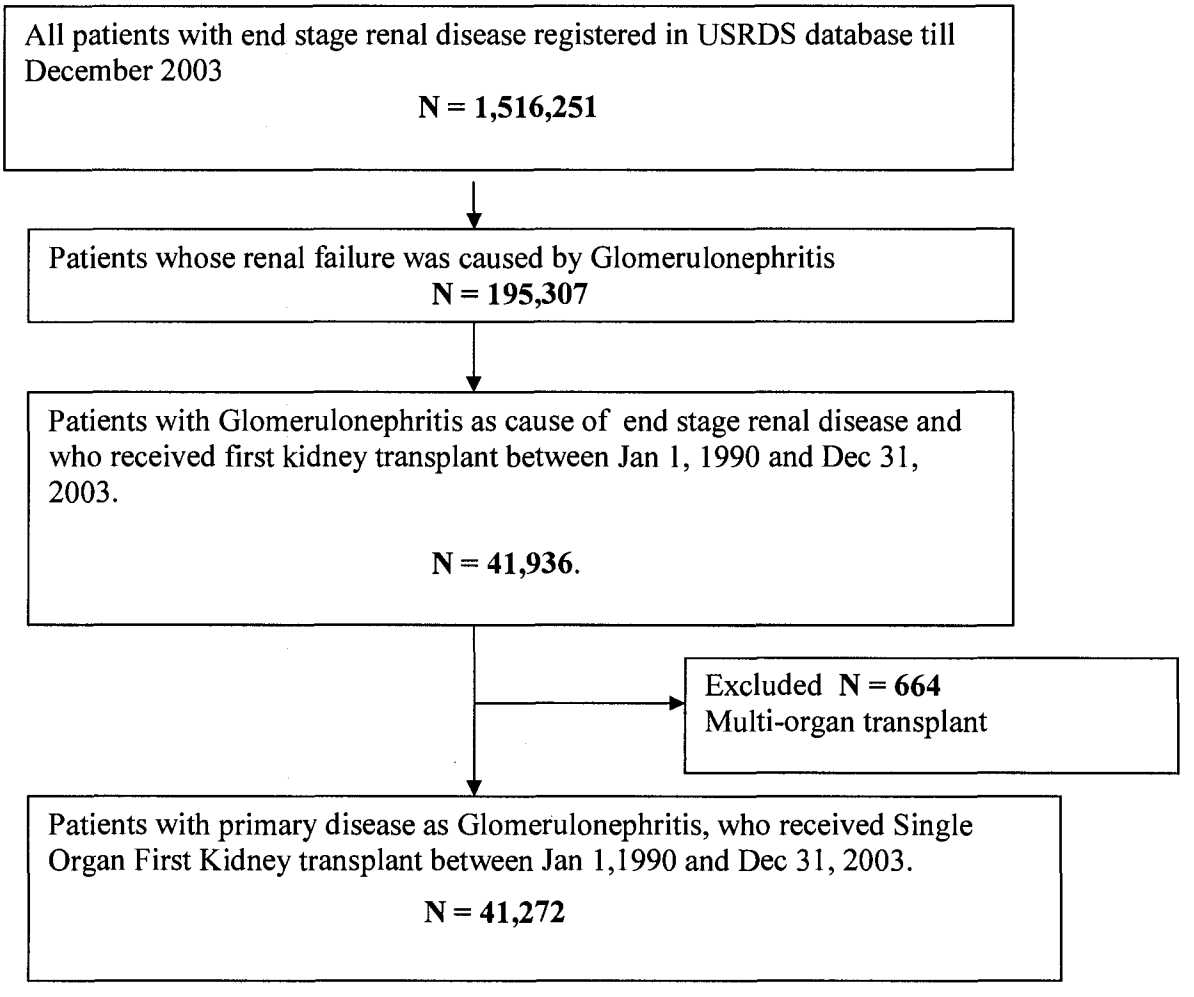


Table 10 shows the important characteristics of the study cohort. Transplant recipients were more likely to be male and ranged from 8 to 71 years of age. More than a third of the total transplants used a live donor. Focal segmental glomerulosclerosis was the most common specified histological cause of glomerulonephritis (20.6%) followed by IgA nephropathy (6.7%). However, the type of glomerulonephritis was unspecified in 42.2% of the patients. Only 3,582 (8.7%) of the patients underwent transplant without any prior dialysis. 15.8% of the patients needed dialysis during the first week following transplantation while 11.7% were treated for acute rejection.

Table 10: Baseline characteristics of 41,272 patients in the study cohort

Covariate		Mean (SD) or Proportion (%)
Recipient gender	Male	56.7
Recipient Race	White	70.9
	Black	21.9
	Asian	5.9
	Native	1.1
	Other	0.3
Donor gender	Male	52.1
Donor race	White	81.3
	Black	11.5
	Asian	2.7
	Native	0.4
	Other	0.6
Recipient Age (years)		40.19 (14.9)
Donor Age (years)		35.61 (15.1)
No of HLA* matches	0	10.1
	1	18.1
	2	19.6
	3	28.7
	4	10.0
	5	5.8
	6	6.7
Delayed graft function	Yes	15.8
	No	82.0
Treated for acute rejection	No	88.3
	Yes / No biopsy	5.9
	Yes / Biopsy positive	4.9
	Yes / biopsy negative	0.9
Donor type	Cadaver	61.6
	Live	38.4
Peak PRA* (%)		10.9 (22.6)
CIT* in all transplants (hours)		14.8 (12.2)
CIT* in cadaver donor Transplants (hours)		21.1 (9.4)
Duration of dialysis (months)		27.9 (32.8)
Primary payer	Medicare	32.1
	Private	15.5
	Other	12.1
	Unknown	40.3
Highest education level	Less than college	29.2
	College or more	24.0
	Unknown	46.8
Employment status	Unable to work	32.1
	Able to work	56.1
	Unknown	11.8

*HLA: Human Leucocyte Antigen, PRA: Panel Reactive Antibody, CIT: Cold ischemia time.

3.2 Descriptive statistics of baseline covariates before and after multiple imputation

Table 11 shows descriptive statistics of baseline covariates using complete case analysis (i.e. excluding missing observations) or the first dataset created using multiple imputation. The mean or proportions of all baseline covariates were essentially identical between the two datasets (Table 11).

Table 11: Descriptive statistics of baseline covariates from complete case data and from the first imputed dataset.

		Mean (SD) or n (%)			
Covariate (N' for complete case analysis)		**Complete Case**		**First imputed dataset (N = 41,272)**	
Recipient gender (N'=41270)	Male	23,411	(56.7)	23,412	(56.7)
Recipient Race (N'=41,272)	White	29,253	(70.8)	29,253	(70.8)
	Black	9,028	(21.9)	9,028	(21.9)
	Non-Black, Non-white	2,991	(7.3)	2,991	(7.3)
Donor gender (N'=39,921)	Male	21,504	(53.9)	22,214	(53.8)
Donor race (N'=39,824)	White	33,553	(84.2)	34,965	(84.7)
	Black	4,766	(12.0)	4,766	(11.6)
	Non-Black, Non-White	1,505	(3.8)	1,541	(3.7)
Recipient Age (years)(N'=41,272)		40.2	(14.9)	40.2	(14.9)
Donor Age (years) (N'=38,005)		35.6	(15.1)	35.6	(15.1)
Number of HLA* Match between donor and recipient (N'=37,434)	0	3,763	(10.0)	4,043	(9.8)
	1	6,798	(18.2)	7,428	(18.0)
	2	7,323	(19.6)	8,233	(20.0)
	3	10,739	(28.7)	11,670	(28.3)
	4	4,114	(11.0)	4,771	(11.5)
	5	2,181	(5.8)	2,508	(6.1)
	6	2,516	(6.7)	2,619	(6.3)
Delayed graft function(N'=40,392)	Yes	6,539	(16.2)	6,692	(16.2)
Treated for acute rejection (N'=40,612)	No	36,225	(89.2)	36,866	(89.3)
	Yes / No biopsy	2,402	(5.9)	2,402	(5.8)
	Yes / Biopsy positive	1,985	(4.9)	2,004	(4.9)
Donor type (N'=40,147)	Live	15,831	(39.4)	15,831	(38.3)
	Cadaver/Trauma	10,326	(25.7)	10,810	(26.2)
	Cadaver/Non-trauma	13,990	(34.9)	14,631	(35.5)
Peak PRA>50% (N'=35,587)		2977	(7.9)	3,205	(7.8)
Cold ischemia time (N'=39,183)	< 12 hours	18,818	(48.0)	20,295	(49.2)
	12 – 24 hours	12,725	(32.5)	12,725	(30.8)
	>24 hours	7,640	(19.5)	8,252	(20.0)
Duration of dialysis (N'=41,272)	0 – 12 months	11,470	(27.8)	11,470	(27.8)
	12 – 36 months	15,392	(37.3)	15,392	(37.3)
	>36 months	10,828	(26.2)	10,828	(26.2)
Employment status (N'=35,809)	Able to work	22,544	(63.0)	25,830	(62.6)
Hepatitis B surface Ag(N'=37,692)	Positive	554	(1.5)	554	(1.3)
Body Mass Index of recipient(N'=38,825)		25.4	(5.7)	25.4	(5.6)

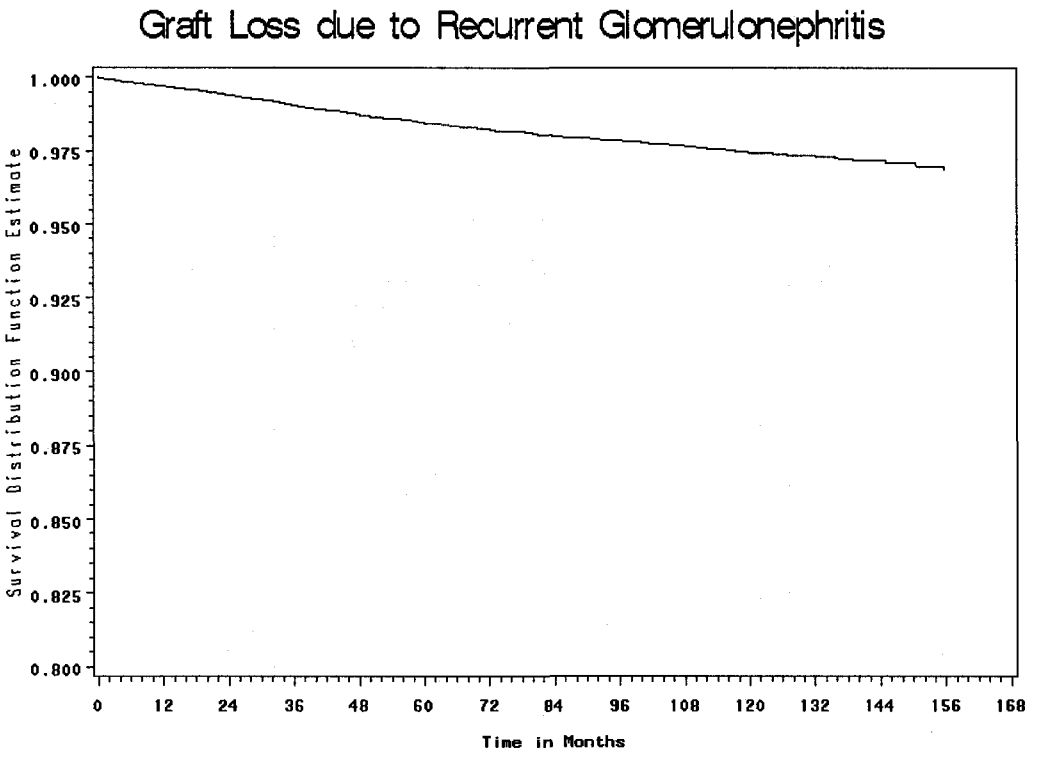
*HLA: Human Leucocyte Antigen, PRA: Panel Reactive Antibody, CIT: Cold ischemia time.

3.3 Graft survival

Of the 41 272 patients, a total of 12,238 (29.7%) grafts failed during the observation period. Of these, 7 811 (18.9%) patients lost their graft prior to death while 4 427 (10.7%) patients died with a functioning graft. The cause of the allograft loss was not recorded in 486 (1.2%) patients and the date of graft loss was unavailable in 41 (1.0%) patients. 562 patients (1.4% of study cohort) lost their graft due to recurrent glomerulonephritis. Thus, recurrent glomerulonephritis was responsible for 7.2% (95% CI 7.0 – 7.5%) of the total grafts lost while the patient was alive.

Median graft survival (including death as graft loss) was 12.3 years (95% confidence interval 12.0 to 12.7 years). Ten-year, all-cause graft survival (including death as graft loss) was 56.2% (95% confidence interval 55.5% - 56.9%) and death-censored graft failure was 70.5% (95% confidence interval 69.8% to 71.1%). The 10-year probability of graft loss due to recurrent disease in all patients was 2.6% (95% confidence interval 2.3% - 2.8%). The survival curve of graft loss due to recurrent glomerulonephritis is shown in Figure 7.

Figure 7: Graft loss due to recurrent glomerulonephritis



3.4 Determining the form of continuous variables in univariate Cox regression models

We determined the best form for the association of continuous covariates with time to graft loss due to recurrence by entering the continuous variable in a univariate Cox regression model with loss due to recurrence as the outcome. We then divided the continuous variable into quintiles and entered them into model either as an ordinal variable or as four categorical (or dummy) variables as described by Hosmer and Lemeshow [168]. To compare two models using the likelihood ratio test, the difference in the log likelihood (i.e. $\Delta G2$) of the two models was calculated. This difference follows a chi-square distribution with degrees of freedom (ΔDF) equal to the difference in the degrees of freedom between the two models being compared. If a model had significantly lower log likelihood, we decided that it had a significantly better fit than its comparator. For example, if the

model likelihood was significantly lower for the categorical model compared to continuous model by the likelihood ratio test, we considered this as indicative of significant non-linearity. In addition, we plotted regression estimates of the quintiles for visual inspection for evidence of non-linearity. If important non-linearity was demonstrated, we tried to model the variable using polynomials, log-transformations, or clinically meaningful categories based on results of the quintiles model.

3.4.1 Recipient Age

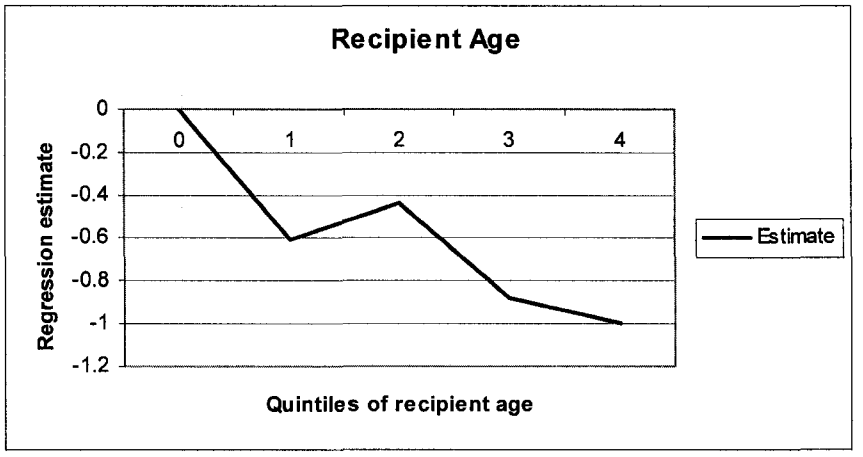
Recipient age had a significant negative association with the risk of graft loss due to recurrent disease. Table 12 shows the univariate models of recipient age for association with graft failure due to recurrent glomerulonephritis.

Table 12: Univariate models for recipient age

Model No.	Model	Model – 2logL	DF	Model 'p'	Δ G2	'p' for Δ G2
1	Continuous	10953.7	1	<0.0001		
2	Quintiles as ordinal variable	10974.4	1	<0.0001		
3	Quintiles as categorical (4 indicator variables)	10960.8	4	<0.0001	7.1 compared to #1	0.07

The log likelihood of the model in which recipient age was entered as a continuous variable (model #1, Table 12) is lower than that of the other two models, suggesting that the model with recipient age as a linear continuous variable had a better fit compared to that in which quintiles were entered as 4 dummy variables (model #3, Table 12). Figure 8 displays the regression estimates of quintiles of recipient age for each quintile and also demonstrates a negative trend with no important non-linearity. Therefore recipient age was entered in the model as a continuous variable in 10-year units.

Figure 8: Graph showing regression estimates of recipient age quintiles plotted against recipient age quintiles



3.4.2 Donor Age

Donor age contained important non-linearity. Only the third and fourth quintile (quintile # 2 and #3 in figure 9) were associated with a significantly higher risk of graft loss due to recurrence compared to the lowest quintile (HR for quintile#2 1.48, 95% CI 1.14-1.91, p=0.003; HR for quintile#3 1.38, 95% CI 1.06-1.80, p=0.02, both compared to the lowest quintile #0).

Figure 9: Graph showing regression estimates of donor age quintiles plotted against donor age quintiles

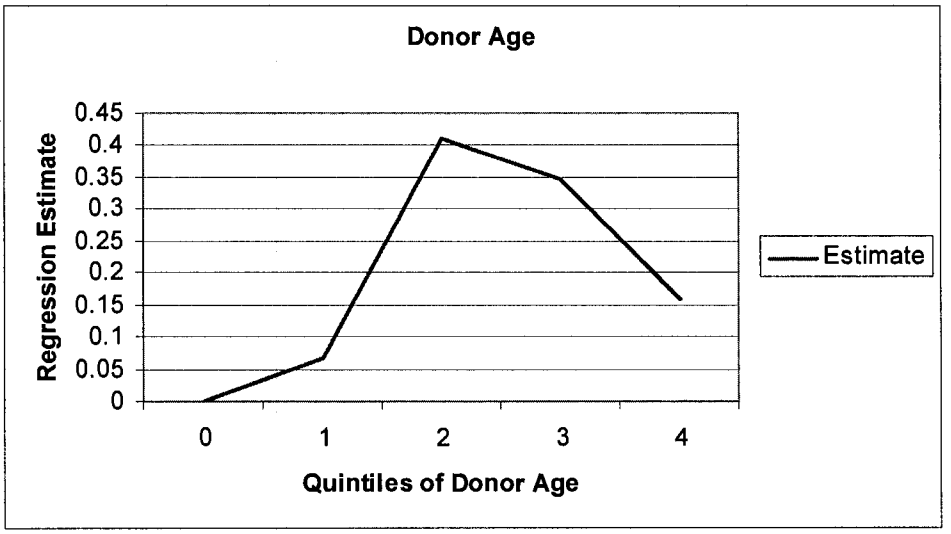


Figure 9 shows regression estimates of each donor age quintile. It clearly demonstrates a non-monotonic curvilinear trend. The risk of graft failure due to recurrence was greatest for quintiles 2 and 3. These two quintiles were associated with significantly greater risk than quintile #0 (p=0.003 and p=0.015 respectively). Quintiles #1 (HR 1.07, 85% CI 0.81-1.41, p=0.61) and quintile #4 (HR 1.11, 95% CI 0.83-1.47, p=0.49) were not significantly different than quintile #0. Non-linearity was also evident in the univariate models with the quintile model (model #3, Table 13) being superior to the model with donor age as a continuous variable (model #1, table 13)($\Delta G2 = 11.7$, $\Delta DF = 3$, p=0.01).

This non-linearity could not be modelled adequately with polynomials (table 13). The model with logarithm of donor age had the best fit to the data (model #6 in table 13), but eliciting meaningful clinical inferences from variables in logarithmic form is difficult. We therefore categorised donor age into clinically meaningful categories based on results from the quintiles model (Figure 9). This was done by combining quintiles #0 and #1, and

quintiles #2 and #3. The highest quintile (quintile #4) represented the last category of donor age >45 years. The model using these categories (model #7, Table 13) was superior to donor age as a continuous variable (model #1, Table 13) ($\Delta G2=12.8$, $\Delta DF=1$, $p=0.0003$ by likelihood ratio test). This model (model #7, Table 13) was not significantly different than the categorical quintile model (model #3 in Table 13 bellow) ($\Delta G2=1.4$, $\Delta DF=2$, $p=0.50$). Therefore we categorised donor age into three categories and entered two indicator variables (one each for donor age 30-45 years and donor age > 45 years) in the model, leaving donor age <30 years as the reference category.

Table 13: Univariate models of donor age.

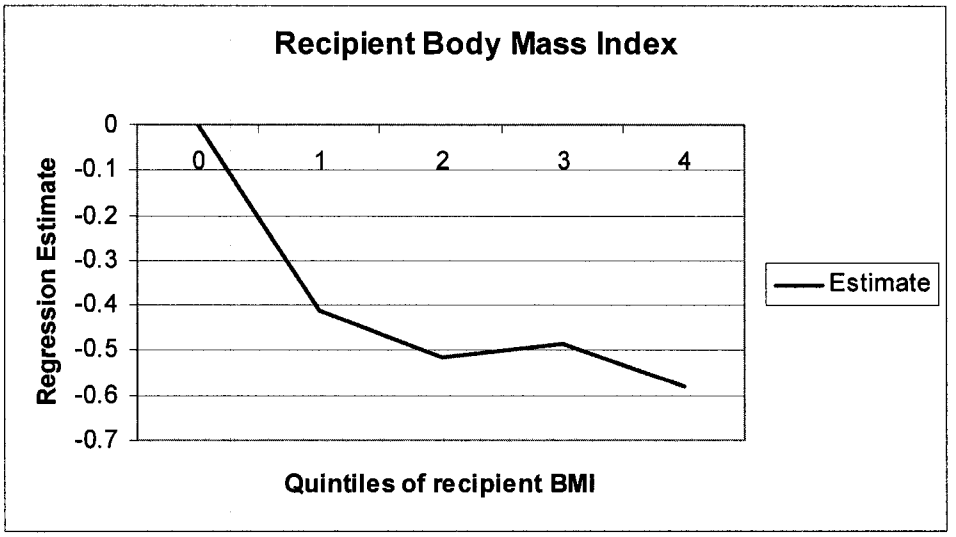
Model No.	Model	Model – 2logL	DF	Model 'p'	ΔG2	'p' for ΔG2
1	Continuous	11283.2	1	0.15		
2	Quintiles as Ordinal	11282.7	1	0.10		
3	Quintiles as categorical (4 indicator variables)	11271.8	4	0.009	11.4 Compared to #1	0.01
4	Donor age + donor age^2	11281.8	2	0.18	10.0 Compared to #3	0.007
5	Donor age + donor age^2 + donor age^3	11279.2	3	<0.0001	7.8 Compared to #3	0.003
6	Log of donor age	11260.7	1	0.2	11.1 Compared to#3	0.01
7	Donor age in 3 groups (<30, 30-45, >45years)	11270.4	2	0.0006	12.8 Compared to #1	0.0003
					1.4 Compared to #3	0.50

3.4.3 Body Mass Index (BMI)

BMI also showed important non-linearity in its significant association with the graft loss due to recurrence. Figure 10 shows regression estimates of quintiles of donor age

plotted against the quintiles. This graph demonstrates that as BMI increases, risk of graft loss due to recurrence decreases, but the protective effect plateaus quickly.

Figure 10: Graph showing regression estimates of quintiles of recipient BMI plotted against quintiles of recipient BMI



Compared to the lowest quintile (quintile #0), all other quintiles showed a significantly decreased risk of graft loss due to recurrence, with very similar regression estimates and hazard ratios (hazard ratios of quintiles #1, #2, #3 and #4 0: 66, 0.60, 0.62, and 0.56, respectively). The model of quintiles as categorical variable (model #3 in table 14) was significantly better than the BMI as continuous variable (model #1 in table 14) by likelihood ratio test ($p=0.02$) suggesting important non-linearity. We therefore explored different models with BMI in various other forms. Both the logarithm of BMI and clinically recognized categories (<25, 25-30, >30) did not adequately model the nonlinearity. The model in which BMI was entered as a squared term (Model #5, Table 14) was significantly better ($\Delta G2= 6.2$, $\Delta DF= 1$; $p=0.01$ by likelihood ratio test) than the model with BMI was entered as a linear term (model #1, Table 14). This polynomial model (model#5, Table 14)

was not significantly different than the categorical quintile model (model #3 in Table 14) ($\Delta G2=3.5$, $\Delta DF=2$; $p=0.17$) and used fewer degrees of freedom. We therefore entered BMI with BMI squared in the multivariate model.

Table 14: Univariate models for recipient body mass index

Model No.	Model	Model – 2logL	DF	Model 'p'	ΔG2	'p' for ΔG2
1	Continuous	11266.4	1	<0.0001		
2	Quintile as ordinal	11264.5	1	<0.0001		
3	Quintile as categorical (4 indicator variables)	11256.8	4	<0.0001	9.6 Compared to #1	0.022
4	Log of BMI	11263.0	1	<0.0001	6.2 Compared to #3	0.10
5	BMI + BMI^2	11260.2	2	<0.0001	6.2 Compared to #1	0.01
					3.5 Compared to #3	0.17
6	BMI in 3 groups (<25, 25-30, >30)	11274.0	2	0.005	17.2 Compared to #3	0.0001

BMI: Recipient body mass index

3.5 Change in immunosuppressive medications during follow-up

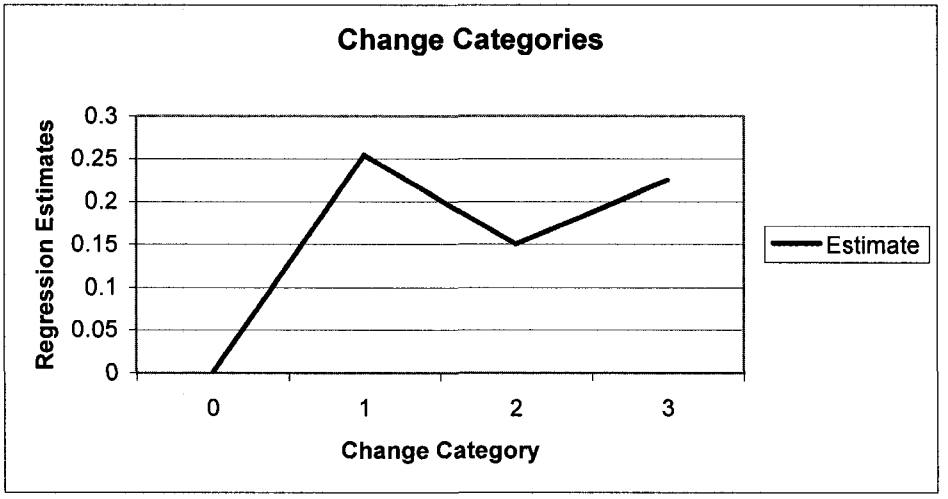
Table 15 shows the proportion of patients who had changes in medication during follow-up visits. More than half of the study group had no medication changes during their follow up while a quarter had only one medication change.

Table 15: Categories of change in medication based on number of follow-up visits in which at least one of the immunosuppressive medications was changed

Medication Change	Change Category	No. of Patients	Proportion
No changes	0	21,087	51.1 %
Change at one visit	1	9,488	23.0%
Changes at two visits	2	5,962	14.4%
Changes at 3+ visits	3	4,735	11.5%
		41,272	100.0%

Cox models were used to explore the association of any medication changes with the risk of graft loss due to recurrence by expressing the medication changes as a three-level categorical time-dependent covariate. We observed that patients with only 1 medication change had significantly greater risk of subsequent graft loss due to recurrent disease (HR 1.29, 95%CI 1.06-1.57; p=0.01) compared to those with no medication changes during follow-up. This risk was similar to patients with two changes (HR 1.16, 95% CI 0.89 – 0.51; p=0.27) and three or more changes (HR 1.25, 95% CI 0.90-1.74; p=0.18). Figure 11 presents these parameter estimates and illustrates why we combined these three categories combined into one level that indicated at least one change during follow-up. Thus, 20,185 (48.9%) of the patients experienced a change in at least one in their immunosuppressive medications during follow up. When classified in this manner, patients with at least one change in their medications during follow-up were significantly more likely to experience graft loss due to recurrent glomerulonephritis (HR 1.27, 95% CI 1.06-1.53; p=0.009) after controlling for all confounders including baseline immunosuppressive medications started at the time of transplantation.

Figure 11: Graph showing regression estimates of categories of change in medication plotted against categories of medication changes



3.6 Association of immunosuppressive medications with risk of graft failure due to recurrent disease

Table 16 shows the result of Cox regression analysis with medication use as time dependent covariates controlled for both all fixed baseline covariates as well as medication changes, also expressed as a time-dependent covariate (section 3.5). None of the four immunosuppressive medications were independently associated with a risk of graft failure due to recurrent disease. There was no significant difference between azathioprine and mycophenolate mofetil (p=0.21). Similarly, tacrolimus was not significantly different than cyclosporine (p=0.38). Patients who had at least one change in their immunosuppressive medications during follow-up were significantly more likely to experience graft failure due to recurrent disease (HR 1.21, 95% confidence interval 1.00-1.47, p=0.05). The transplant year was independently associated with graft loss due to recurrent glomerulonephritis.

Table 16: Effect of immunosuppressive medications as time varying covariates on risk of graft failure due to recurrence. No Lag time

Variable		Parameter Estimate	Std Error	HR	95% CI	P
Donor Age (years)	**< 30**	Ref		**Ref**		
	30 –45	0.29	0.10	**1.33**	(1.09, 1.64)	**0.01**
	> 45	0.11	0.12	**1.12**	(0.88, 1.42)	**0.37**
Recipient Age (years)	**Each 10 years**	-0.19	0.03	**0.83**	(0.78, 0.88)	**0.00**
Donor Sex	**Male**	-0.08	0.09	**0.93**	(0.78, 1.10)	**0.38**
Recipient Sex	**Male**	0.09	0.09	**1.09**	(0.92, 1.30)	**0.32**
Donor Race	**White**	Ref		**Ref**		
	Black	0.05	0.16	**1.05**	(0.77, 1.42)	**0.77**
	Other	-0.27	0.28	**0.76**	(0.44, 1.33)	**0.34**
Recipient Race	**White**	Ref		**Ref**		
	Black	-0.10	0.13	**0.90**	(0.70, 1.17)	**0.44**
	Other	-0.11	0.20	**0.89**	(0.60, 1.33)	**0.58**
Dialysis Duration (Months)	**0**	Ref		**Ref**		
	1 – 12	0.64	0.18	**1.89**	(1.33, 2.68)	**0.00**
	12 – 36	0.39	0.19	**1.48**	(1.03, 2.14)	**0.04**
	> 36	0.02	0.21	**1.02**	(0.67, 1.55)	**0.93**
Peak PRA*	**> 50%**	0.18	0.18	**1.20**	(0.84, 1.71)	**0.32**
Donor Type	**Living**	Ref		**Ref**		
	Cadaver – trauma	0.05	0.18	**1.05**	(0.74, 1.49)	**0.80**
	Cadaver – nontrauma	0.08	0.17	**1.09**	(0.78, 1.51)	**0.62**
Cold ischemia time	**< 12 hours**	Ref		**Ref**		
	12 – 24 hours	-0.33	0.16	**0.72**	(0.52, 0.98)	**0.04**
	> 24 hours	-0.44	0.18	**0.65**	(0.45, 0.92)	**0.02**
HLA* Matching	**Each additional match**	0.00	0.03	**1.00**	(0.94, 1.06)	**0.97**
Delayed graft function	**Yes**	0.65	0.12	**1.91**	(1.52, 2.40)	**0.00**
Acute Rejection	**None**	Ref		**Ref**		
	Treated without biopsy	-0.14	0.17	**0.87**	(0.62, 1.22)	**0.43**
	Biopsy Proven	0.39	0.16	**1.47**	(1.07, 2.02)	**0.02**
Transplant Year	**1990 – 1994**	Ref		**Ref**		
	1995 – 1997	-0.17	0.12	**0.85**	(0.66, 1.08)	**0.18**
	1998 – 2000	-0.29	0.16	**0.75**	(0.55, 1.02)	**0.07**
	2001 - 2003	-0.63	0.24	**0.53**	(0.33, 0.85)	**0.01**
Hepatitis B surface Ag	**Positive**	-0.52	0.50	**0.60**	(0.22, 1.60)	**0.31**
Able to work	**Yes**	-0.05	0.10	**0.95**	(0.78, 1.15)	**0.58**
Body Mass Index	**BMI**	-0.02	0.01	**0.98**	(0.96, 1.00)	**0.01**
	BMI Square	0.00	0.00	**1.00**	(1.00, 1.00)	**0.29**
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Table 16 (Contd): Effect of immunosuppressive medications as time varying covariates on risk of graft failure due to recurrence. No Lag time

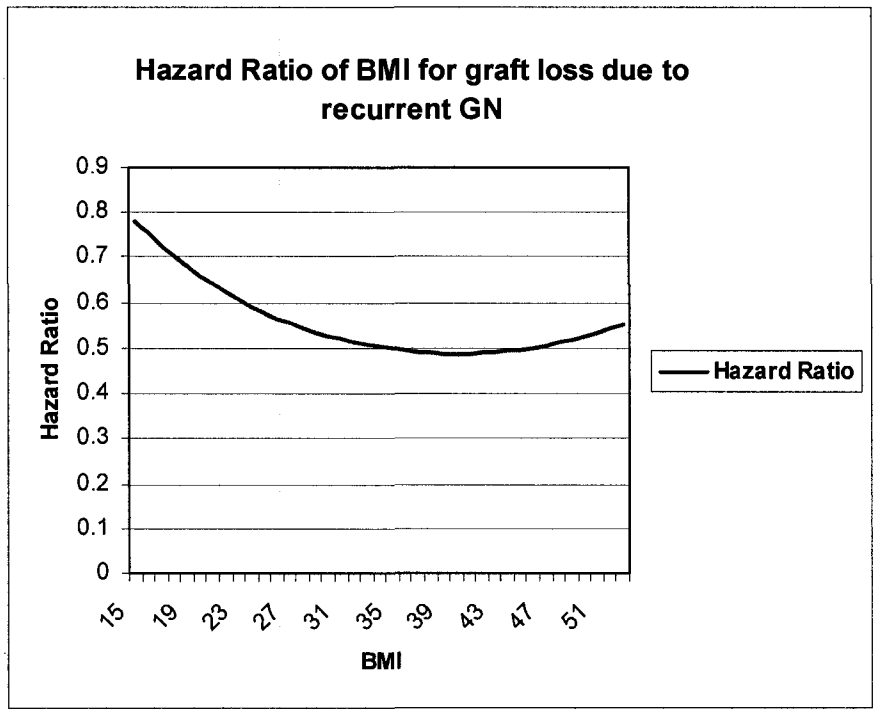
Variable		Estimate	StdErr	HR	95% CI	P
Antimetabolite use	**None**	Ref		**Ref**		
	Azathioprine	-0.09	0.12	**0.92**	(0.72, 1.17)	**0.49**
	Mycophenolate mofetil	0.08	0.12	**1.09**	(0.85, 1.38)	**0.50**
Calcineurin inhibitor	**None**	Ref		**Ref**		
	Cyclosporine	-0.08	0.17	**0.92**	(0.66, 1.29)	**0.64**
	Tacrolimus	0.03	0.19	**1.03**	(0.71, 1.49)	**0.87**
At least one Change in medication during follow-up	**Yes**	0.19	0.10	**1.21**	(1.00, 1.47)	**0.05**

PRA: Panel reactive antibody, HLA: Human leucocyte antigen

The variables that significantly increased the risk of graft loss due to recurrent disease included increased donor age, duration of dialysis, delayed graft function, and biopsy confirmed acute rejection. On the other hand, an increase of 10 years in recipient age decreased the risk of graft loss due to recurrence by 17.1% (95% confidence interval 11.5% to 22.4%, $p<0.001$). Body mass index was significantly associated with the risk of graft loss ($p=0.015$ for the linear hypothesis of $BMI + BMI^2 = 0$), with the adjusted association between BMI and graft loss due to recurrent glomerulonephritis shown graphically below in figure 12. Thus, it appears that the risk of recurrent disease associated with BMI decreases until the BMI is 40, above which the risk increases.

Compared to cold ischemia time of less than 12 hours, both cold ischemia time of 12 – 24 hours (HR 0.72, 95% confidence interval 0.52-0.98, p=0.04) and cold ischemia time >24 hours (HR 0.65, 95% confidence interval 0.45 to 0.92, p=0.02) protected against the risk of graft loss due to recurrence. This was surprising as higher cold ischemia time is associated with increased risk of death censored graft loss, as discussed in greater detail in Discussion (Section 4.3).

Figure 12: Estimated hazard ratios of recipient body mass index



3.6.1 Impact of introducing lag time between change in medication and outcome

Table 17 shows the effect of introducing a lag time of six months between the change in medication and outcome. As can be seen, there was no important change in the hazard ratios of any of the four immunosuppressive agents. Azathioprine was not significantly different than mycophenolate mofetil (p=0.10) and cyclosporine was not significantly different than tacrolimus (p=0.40). The risk associated with at least one change in medication during follow-up is somewhat greater with the lag between start of medications and outcome.

Table 17: Effect of immunosuppressive medications as time varying covariates on risk of graft failure due to recurrence. Lag time = 6 months

Variable		Parameter Estimate	Std Error	HR	95% CI	P
Donor Age (years)	**< 30**	Ref		**Ref**		
	30 –45	0.29	0.10	**1.33**	(1.08, 1.63)	**0.01**
	> 45	0.11	0.12	**1.11**	(0.87, 1.42)	**0.39**
Recipient Age (years)	**Each 10 years**	-0.19	0.03	**0.83**	(0.78, 0.88)	**0.00**
Donor Sex	**Male**	-0.08	0.09	**0.93**	(0.78, 1.10)	**0.38**
Recipient Sex	**Male**	0.09	0.09	**1.09**	(0.92, 1.30)	**0.31**
Donor Race	**White**	Ref		**Ref**		
	Black	0.04	0.16	**1.04**	(0.77, 1.42)	**0.78**
	Other	-0.28	0.28	**0.76**	(0.43, 1.33)	**0.33**
Recipient Race	**White**	Ref		**Ref**		
	Black	-0.10	0.13	**0.90**	(0.70, 1.17)	**0.44**
	Other	-0.11	0.20	**0.89**	(0.60, 1.33)	**0.58**
Dialysis Duration (Months)	**0**	Ref		**Ref**		
	1 – 12	0.63	0.18	**1.89**	(1.33, 2.68)	**0.00**
	12 – 36	0.39	0.19	**1.48**	(1.02, 2.14)	**0.04**
	> 36	0.02	0.21	**1.02**	(0.67, 1.54)	**0.94**
Peak PRA*	**> 50%**	0.18	0.18	**1.20**	(0.84, 1.71)	**0.32**
Donor Type	**Living**	Ref		**Ref**		
	Cadaver – trauma	0.04	0.18	**1.05**	(0.74, 1.49)	**0.80**
	Cadaver – nontrauma	0.08	0.17	**1.09**	(0.78, 1.51)	**0.62**
Cold ischemia time	**< 12 hours**	Ref		**Ref**		
	12 – 24 hours	-0.34	0.16	**0.72**	(0.52, 0.98)	**0.04**
	> 24 hours	-0.43	0.18	**0.65**	(0.45, 0.92)	**0.02**
HLA* Matching	**Each additional match**	0.00	0.03	**1.00**	(0.95, 1.06)	**0.95**
Delayed graft function	**Yes**	0.65	0.12	**1.91**	(1.51, 2.40)	**0.00**
Acute Rejection	**None**	Ref		**Ref**		
	Treated without biopsy	-0.14	0.17	**0.87**	(0.62, 1.23)	**0.43**
	Biopsy Proven	0.38	0.16	**1.47**	(1.07, 2.01)	**0.02**
Transplant Year	**1990 – 1994**	Ref		**Ref**		
	1995 – 1997	-0.20	0.13	**0.82**	(0.64, 1.04)	**0.11**
	1998 – 2000	-0.33	0.16	**0.72**	(0.53, 0.98)	**0.03**
	2001 - 2003	-0.68	0.24	**0.51**	(0.32, 0.81)	**0.00**
Hepatitis B surface Ag	**Positive**	-0.52	0.50	**0.60**	(0.22, 1.60)	**0.30**
Able to work	**Yes**	-0.05	0.10	**0.95**	(0.79, 1.15)	**0.59**
Body Mass Index	**BMI**	-0.02	0.01	**0.98**	(0.96, 1.00)	**0.01**
	BMI Square	0.00	0.00	**1.00**	(1.00, 1.00)	**0.29**
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Table 17 (Contd): Effect of immunosuppressive medications as time varying covariates on risk of graft failure due to recurrence. Lag time = 6 months

Variable		Estimate	Std Err	HR	95% CI	P
Antimetabolite use	**None**	Ref		**Ref**		
	Azathioprine	-0.13	0.13	**0.88**	(0.68, 1.13)	**0.30**
	Mycophenolate mofetil	0.09	0.13	**1.10**	(0.85, 1.40)	**0.47**
Calcineurin inhibitor	**None**	Ref		**Ref**		
	Cyclosporine	-0.07	0.20	**0.93**	(0.62, 1.41)	**0.74**
	Tacrolimus	0.03	0.22	**1.03**	(0.67, 1.60)	**0.88**
Change in medication during follow-up	**Yes**	0.27	0.10	**1.31**	(1.07, 1.60)	**0.01**

*HLA: Human Leucocyte Antigen, PRA: Panel Reactive Antibody

Table 18 shows effect of varying lag time to 3 months, 6 months or 24 months. There was no change in the hazard ratios of azathioprine, cyclosporine and mycophenolate mofetil. The hazard ratio of tacrolimus for a lag time of 24 months is lower than one, opposite to that in the other models. Risk associated with any change in medication progressively increases as the lag time between change in medications and their effect increases.

Table 18: Effect of varying lag time on the estimated risk of graft loss due to recurrence associated with medications.

		No lag time			3 month lag time			6 month lag time			24 month lag time		
		HR	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**p**
Antimetabolite use	**None**	**Ref**			**Ref**			**Ref**			**Ref**		
	Azathioprine	**0.92**	(0.72, 1.17)	**0.49**	**0.88**	(0.69, 1.13)	0.32	**0.88**	(0.68, 1.13)	**0.30**	**0.94**	(0.73, 1.21)	0.63
	Mycophenolate mofetil	**1.09**	(0.85, 1.38)	**0.50**	**1.09**	(0.85, 1.390	0.50	**1.10**	(0.85, 1.40)	**0.47**	**1.17**	(0.87, 1.56)	0.29
Calcineurin inhibitor	**None**	**Ref**			**Ref**			**Ref**			**Ref**		
	Cyclosporine	**0.92**	(0.66, 1.29)	**0.64**	**0.93**	(0.67, 1.31)	0.68	**0.93**	(0.62, 1.41)	**0.74**	**0.97**	(0.66, 1.44)	0.89
	Tacrolimus	**1.03**	(0.71, 1.49)	**0.87**	**1.07**	(0.73, 1.56)	0.73	**1.03**	(0.67, 1.60)	**0.88**	**0.84**	(0.53, 1.32)	0.44
Change in medication during follow-up	**Yes**	**1.21**	(1.00, 1.47)	**0.05**	**1.23**	(1.01, 1.49)	**0.04**	**1.31**	(1.07, 1.60)	**0.01**	**1.54**	(1.22, 1.93)	**<0.01**

3.6.2 Effect of excluding patients with two or more consecutive missing follow-up visits.

When we repeated the analysis after excluding patients with more than two consecutive missing follow-up visits, we found no changes in the parameter estimates of the calcineurin inhibitors, whereas those for the antimetabolites increased as shown in the Table 19 below. However, none of these new estimates were significantly different than zero. Once again, there was no significant difference between either azathioprine and mycophenolate mofetil (p=0.43) or cyclosporine and tacrolimus (p=0.31).

Table 19: Effect of immunosuppressive medications as time varying covariates on risk of graft failure due to recurrence after excluding patients with more than two consecutive missing visits. No Lag time

Variable		Parameter Estimate	Std Error	HR	95% CI	P
Antimetabolite use	**None**	Ref		**Ref**		
	Azathioprine	0.05	0.16	**1.06**	(0.77, 1.45)	**0.74**
	Mycophenolate mofetil	0.13	0.26	**1.21**	(0.88, 1.67)	**0.25**
Calcineurin inhibitor	**None**	Ref		**Ref**		
	Cyclosporine	-0.04	0.23	**0.96**	(0.61, 1.53)	**0.87**
	Tacrolimus	0.13	0.26	**1.14**	90.69, 1.89)	**0.62**
Change in medication during follow-up	**Yes**	0.24	0.13	**1.27**	(0.97, 1.65)	**0.08**

3.6.3 Subgroup analysis in patients who had no change in medications during follow-up

We studied the subgroup of patients in whom immunosuppressive medications were not changed during follow-up (Table 20).

Table 20: Association of baseline medication with risk of graft loss due to recurrence in patients who had No Change in medication during follow-up.

Variable		Estimate	StdErr	HR	95% CI	P
Donor Age (years)	**< 30**					
	30 –45	0.34	0.16	**1.40**	(1.04, 1.90)	**0.03**
	> 45	0.36	0.17	**1.44**	(1.03, 2.02)	**0.04**
Recipient Age (years)	**Each 10 years**	-0.27	0.05	**0.76**	(0.69, 0.84)	**0.00**
Donor Sex	**Male**	-0.12	0.13	**0.89**	(0.69, 1.14)	**0.34**
Recipient Sex	**Male**	0.15	0.13	**1.16**	(0.90, 1.50)	**0.25**
Donor Race	**White**	Ref		**Ref**		
	Black	-0.09	0.24	**0.91**	(0.57, 1.46)	**0.70**
	Other	-0.30	0.40	**0.74**	(0.34, 1.62)	**0.46**
Recipient Race	**White**	Ref		**Ref**		
	Black	-0.15	0.19	**0.86**	(0.59, 1.25)	**0.42**
	Other	-0.14	0.28	**0.87**	(0.50, 1.51)	**0.62**
Dialysis Duration (Months)	**0**	Ref		**Ref**		
	1 – 12	0.60	0.27	**1.83**	(1.08, 3.12)	**0.03**
	12 – 36	0.47	0.28	**1.60**	(0.93, 2.76)	**0.09**
	> 36	-0.01	0.32	**0.99**	(0.53, 1.84)	**0.98**
Peak PRA	**> 50%**	0.36	0.25	**1.43**	(0.88, 2.34)	**0.15**
Donor Type	**Living**	Ref				
	Cadaver – trauma	0.43	0.24	**1.53**	(0.95, 2.47)	**0.08**
	Cadaver – nontrauma	0.27	0.23	**1.31**	(0.84, 2.05)	**0.25**
Cold ischemia time	**< 12 hours**	Ref		**Ref**		
	12 – 24 hours	-0.57	0.22	**0.56**	(0.37, 0.86)	**0.01**
	> 24 hours	-0.72	0.25	**0.49**	(0.30, 0.80)	**0.00**
HLA Matching	**Each additional match**	0.01	0.05	**1.01**	(0.92, 1.10)	**0.87**
Delayed graft function	**Yes**	0.77	0.16	**2.16**	(1.57, 2.98)	**0.00**
Acute Rejection	**None**	Ref		**Ref**		
	Treated without biopsy	-0.18	0.26	**0.83**	(0.50, 1.38)	**0.47**
	Biopsy Proven	0.63	0.22	**1.87**	(1.22, 2.88)	**0.00**
Transplant Year	**1990 – 1994**	Ref		**Ref**		
	1995 – 1997	0.08	0.19	**1.09**	(0.75, 1.57)	**0.67**
	1998 – 2000	-0.27	0.25	**0.76**	(0.47, 1.23)	**0.27**
	2001 – 2003	-0.76	0.31	**0.47**	(0.25, 0.87)	**0.02**
Able to work	**Yes**	-0.16	0.14	**0.85**	(0.65, 1.12)	**0.26**
Body Mass Index	**BMI**	-0.03	0.01	**0.97**	(0.95, 0.99)	**0.02**
	BMI Square	0.00	0.00	**1.00**	(1.00, 1.00)	**0.56**
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Table 20 (Contd): Association of baseline medication with risk of graft loss due to recurrence in patients who had No Change in medication during follow-up.

Variable		Estimate	StdErr	HR	95% CI	P
Antimetabolite use	**None**	Ref		**Ref**		
	Azathioprine	-0.11	0.20	**0.90**	(0.60, 1.34)	**0.60**
	Mycophenolate mofetil	-0.36	0.22	**0.70**	(0.45, 1.07)	**0.10**
Calcineurin inhibitor	**None**	Ref		**Ref**		
	Cyclosporine	0.03	0.34	**1.03**	(0.53, 1.99)	**0.94**
	Tacrolimus	-0.02	0.37	**0.98**	(0.47, 2.04)	**0.95**

PRA: Panel reactive antibody, HLA: Human leucocyte antigen

None of the baseline medications were associated with risk of graft loss due to recurrent glomerulonephritis, though the hazard ratios associated with mycophenolate mofetil and tacrolimus are less than one. Donor age, duration of dialysis, delayed graft function and biopsy proven acute rejection were still associated with a significant increased risk while recipient age, cold ischemia time and most recent transplant era were again associated with a decreased risk. Body mass index was also significantly associated with a non-linear relationship. In addition, cadaver donor (traumatic death) tended to have increased risk compared to live donor.

3.7 Predictors of change in medications during follow-up

Since change in immunosuppressive medication was an important independent predictor of graft loss due to recurrent glomerulonephritis, we determined predictors of at least one change in medications using time to first change as outcome in a Cox regression model. Table 21 lists the result of this analysis. Transplant recipients of older and black donors, and those who were Hepatitis B surface antigen positive were more likely to have their medications changed during follow-up. Increasing recipient age, male donor, high panel reactive antibody titer and delayed graft function decreased the risk of any change in

immunosuppressive medications during follow-up. Compared to the patients who were transplanted between 1990-1994, transplants performed between 1995-1997 and 1998-2000 were significantly more likely to undergo medication change while transplant performed in the most recent period of 2001-2003 were significantly less likely to undergo change in immunosuppressive medications. Transplant centers with higher annual volume of transplants were less likely to change medications during follow-up.

Patients who were started on mycophenolate mofetil at the time of transplantation were significantly less likely to have any change in medication during follow-up compared to patients who were not started on any antimetabolites ($p<0.001$) as well as patients who were started on azathioprine ($p<0.001$) even after adjusting for multiple comparisons. Among the calcineurin inhibitors, both cyclosporine and tacrolimus started at the time of transplantation were protective from a subsequent change in medications compared to no calcineurin inhibitors at baseline ($p<0.001$ for both comparisons) even after adjusting for multiple comparisons, but there was no significant difference between the two types of calcineurin inhibitors ($p=0.69$).

Table 21: Predictors of at least one change in medications during follow-up period

Variable		Parameter Estimate	Std Error	HR	95% CI	P
Donor Age (years)	**< 30**					
	30 –45	0.06	0.02	**1.06**	(1.02, 1.10)	**0.00**
	> 45	0.09	0.02	**1.10**	(1.06, 1.14)	**0.00**
Recipient Age (years)	**Each 10 years**	-0.04	0.01	**0.96**	(0.95, 0.97)	**0.00**
Donor Sex	**Male**	0.01	0.01	**1.01**	(0.98, 1.04)	**0.62**
Recipient Sex	**Male**	-0.03	0.01	**0.97**	(0.95, 1.00)	**0.06**
Donor Race	**White**					
	Black	0.06	0.02	**1.07**	(1.02, 1.12)	**0.01**
	Other	0.04	0.04	**1.04**	(0.96, 1.13)	**0.37**
Recipient Race	**White**					
	Black	-0.02	0.02	**0.98**	(0.94, 1.02)	**0.30**
	Other	0.00	0.03	**1.00**	(0.94, 1.07)	**0.94**
Dialysis Duration (Months)	**0**					
	1 – 12	0.00	0.03	**1.00**	(0.95, 1.06)	**0.93**
	12 – 36	-0.04	0.03	**0.96**	(0.91, 1.02)	**0.17**
	> 36	-0.03	0.03	**0.98**	(0.92, 1.03)	**0.41**
Peak PRA	**> 50%**	-0.06	0.03	**0.95**	(0.89, 1.00)	**0.05**
Donor Type	**Living**					
	Cadaver – trauma	0.02	0.03	**1.02**	(0.97, 1.09)	**0.40**
	Cadaver – nontrauma	0.03	0.03	**1.03**	(0.98, 1.09)	**0.24**
Cold ischemia time	**< 12 hours**					
	12 – 24 hours	0.03	0.03	**1.03**	(0.98, 1.08)	**0.31**
	> 24 hours	0.04	0.03	**1.04**	(0.99, 1.10)	**0.15**
HLA Matching	**Each additional match**	-0.01	0.00	**0.99**	(0.98, 1.00)	**0.11**
Delayed graft function	**Yes**	-0.23	0.02	**0.79**	(0.76, 0.82)	**0.00**
Acute Rejection	**None**					
	Treated without biopsy	-0.02	0.03	**0.98**	(0.92, 1.04)	**0.51**
	Biopsy Proven	0.02	0.03	**1.02**	(0.95, 1.08)	**0.64**
Transplant Year	**1990 – 1994**					
	1995 – 1997	0.58	0.02	**1.78**	(1.71, 1.85)	**0.00**
	1998 – 2000	0.31	0.03	**1.37**	(1.30, 1.44)	**0.00**
	2001 – 2003	-0.70	0.03	**0.50**	(0.47, 0.53)	**0.00**
Hepatitis B Surface Ag	**Positive**	0.14	0.06	**1.15**	(1.02, 1.29)	**0.02**
Able to work	**Yes**	-0.02	0.02	**0.98**	(0.95, 1.02)	**0.30**
Body Mass Index	**BMI**	0.00	0.00	**1.00**	(1.00, 1.00)	**0.35**
	BMI Square	0.00	0.00	**1.00**	(1.00, 1.00)	**0.62**
Transplant Center	**Each 25 transplants per year**	-0.01	0.00	**0.99**	(0.99, 1.00)	**0.00**
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Table 21 (Contd): Predictors of at least one change during follow-up period

Variable		Estimate	StdErr	HR	95% CI	Probt
Antimetabolite use	**None**					
	Azathioprine	-0.02	0.02	**0.98**	(0.94, 1.03)	**0.38**
	Mycophenolate mofetil	-0.37	0.02	**0.69**	(0.66, 0.73)	**0.00**
Calcineurin inhibitor	**None**					
	Cyclosporine	-0.44	0.03	**0.64**	(0.61, 0.68)	**0.00**
	Tacrolimus	-0.45	0.03	**0.64**	(0.60, 0.68)	**0.00**

PRA: Panel reactive antibody, HLA: Human leucocyte antigen

4. Discussion

We used a secondary database analysis to study the association between the most commonly used immunosuppressants and the risk of renal allograft loss due to recurrent glomerulonephritis. We found that azathioprine, mycophenolate mofetil, cyclosporine and tacrolimus were not associated with the risk of graft loss due to recurrent glomerulonephritis. Furthermore, there was no difference between azathioprine and mycophenolate mofetil or between cyclosporine and tacrolimus with respect to this outcome. Changes in any of the immunosuppressive medications during follow-up were a significant predictor of graft loss due to recurrence. Renal transplants performed in recent years were less likely to be lost due to recurrent disease compared to previous years. Higher donor age, longer time on dialysis, delayed graft function, and biopsy confirmed acute rejection were independently and significantly associated with an increased risk of graft loss due to recurrent disease while greater recipient age and cold ischemia time were associated with a significantly decreased risk. Recipient body mass index was also significantly associated with graft loss due to recurrent glomerulonephritis in a non-linear fashion.

4.1 Incidence of graft loss due to recurrent glomerulonephritis.

The 10-year probability of graft loss due to recurrent glomerulonephritis observed in our study (2.6%) was lower than that observed by Briganti [27] in Australia, but higher than that reported by Briggs [26] from a European registry. The proportion of total graft failures that was accounted for by recurrent glomerulonephritis in this study was consistent with previous reports from the United States [11] and Europe [26]. Briganti *et. al.* [27] included patients only if the index glomerulonephritis causing end stage renal disease was

histologically confirmed. This criterion excluded 18.2% of patients with glomerulonephritis who did not have a renal biopsy performed. Our study and that by Briggs *et. al.* did not restrict inclusion to biopsy confirmed glomerulonephritis. In the European registry (ERA-EDTA), 53.9% of patients with glomerulonephritis as the cause of end stage renal disease did not have a kidney biopsy. In our study, 42.2% of the patients who were diagnosed as glomerulonephritis had an unspecified histological type of glomerulonephritis. A large number of patients who develop end stage renal disease due to glomerulonephritis do not undergo kidney biopsy and the diagnosis is made on clinical and biochemical grounds with reasonable certainty. Excluding such a large group of patients from an analysis will result in the loss of a large amount of information. It may also lead to biased results that are not generalizable for the entire population of patients with glomerulonephritis.

To avoid this problem, we chose to include the diagnosis of glomerulonephritis on clinical ground to reflect what happens in the clinical milieu. Our estimate of the incidence of graft loss due to recurrent glomerulonephritis thus represents a more generalizable estimate from available data. Our finding may still be an underestimate since experts believe that recurrent glomerulonephritis is underdiagnosed [11;21].

4.2 Immunosuppression and graft loss due to recurrent glomerulonephritis

The lack of association between immunosuppressive therapy and the risk of graft loss due to recurrent glomerulonephritis raises several possibilities. Though a previous study had also failed to find such an association [131], it involved a very small number of patients. Our study was large with sufficient power to detect a potential effect of the medications. Moreover, our study directly compared mycophenolate mofetil and tacrolimus with azathioprine and cyclosporine, respectively. This was not done in previous studies.

Differences in the underlying pathogenic mechanism of acute rejection and glomerulonephritis may explain lack of efficacy of the immunosuppressants against graft loss due to recurrent glomerulonephritis. Acute rejection involves cellular immunity in the majority of cases and rejection purely mediated by humoral immunity is uncommon [169;170]. Most immunosuppressive medications used in transplant patients are less effective in protecting against antibody-mediated rejection than cellular-mediated rejection. The risk of graft loss is also higher in antibody-mediated rejection [169]. Pathogenic mechanisms of glomerulonephritis are poorly understood, though humoral immunity plays an important role in many types of glomerulonephritis [171]. Recurrent focal segmental glomerulosclerosis is also thought to be caused by a circulating humoral factor [172]. It is possible that transplant immunosuppressants, being less effective against humoral immunity, are less effective in preventing the recurrence of glomerulonephritis compared to preventing acute cellular rejection.

The transplant recipients are on immunosuppressive therapy even prior to the onset of recurrent disease. Thus it is possible that the medications may be able to prevent the *initiation* of recurrent disease in some cases. Clinically diagnosed recurrent glomerulonephritis may represent the most severe forms of glomerulonephritis, which are not modifiable by the immunosuppressive therapy. Our study was not designed to study *onset* of recurrent glomerulonephritis since retrospectively collected data are unsuitable for this purpose. A prospective study with a clear and uniform definition of recurrent glomerulonephritis (including guidelines on biopsy) is needed to determine if any of the immunosuppressive medications might prevent the initiation of recurrent disease.

It is possible that immunosuppressant medications are more effective in certain types of glomerulonephritis. We could not do a subgroup analysis by the individual types of

glomerulonephritis due to the small number of events within the individual types of glomerulonephritis.

Immunosuppressive medications are changed or discontinued if patients experience adverse effects, infections, malignancies, or graft dysfunction. Reduction in dose or discontinuation of mycophenolate mofetil has previously been shown to be associated with increased risk of acute rejection [173;174], all-cause graft loss [175], and death censored graft loss [174]. We found that a change in any immunosuppressive medication was associated with an increased risk of graft loss due to recurrent glomerulonephritis. The medications themselves did not have any impact on the risk of graft loss due to recurrence. Therefore, change in immunosuppressive medication is more likely to be a marker of the poor outcome rather than a cause of recurrent disease. This is supported by the finding that the risk associated with change in medications increased as the estimated lag period between change in medications and their putative onset of action increased.

4.3 Independent predictors of graft loss due to recurrent glomerulonephritis

We found that transplants performed in the most recent years were at a lower risk of graft loss due to recurrent disease. This finding is consistent with the reported improvement in overall graft survival in transplants performed in recent years compared to previous years [94;97;100]. This reduced risk was not explained by the newer immunosuppressive medications. Observational studies [176] have shown that patients receiving kidney transplants in more recent years have better control of blood pressure compared to those transplanted in the past. Campistol *et. al.* [176] found that use of angiotensin converting enzyme (ACE) inhibitors was significantly more prevalent in patients transplanted in 1998 compared to those transplanted in 1990 (22.2% vs. 9.7%). Kasiske *et. al.* [177] also found

that use of ACE inhibitors increased significantly during 1993-2002 compared to transplants performed prior to 1993 (25% vs. <5%). A large body of evidence has documented protective effects of ACE inhibitors in preventing progression of renal disease and delay of renal failure in native kidney glomerulonephritis like focal segmental glomerulosclerosis [178] and IgA nephropathy [179]. Published guidelines also recommend the use of ACE inhibitors in recurrent glomerulonephritis [180]. Studies have shown that the use of lipid lowering medications called 'statins' progressively increased in transplant recipients in the last decade [181]. Use of statins in transplant recipients is also associated with improved blood pressure control independent of lipid levels [182]. Both experimental [183] and clinical [184-187] evidence suggests that treatment with statins is associated with reduced proteinuria. This finding was confirmed in a recent meta-analysis [188], which found that statins were associated with 1.22ml/min per year slower loss of glomerular function rate. It is likely that such measures like increased use of ACE inhibitors or angiotensin receptor blockers, better control of hypertension, and an increased use of statins have played a major role of preventing graft loss due to recurrent disease.

Both acute rejection and delayed graft function increased the risk of graft failure due to recurrent glomerulonephritis, similar to their effect on other causes of graft loss. Both of these events lead to a decreased nephron mass and impaired kidney function. It is conceivable that kidneys, which start with a lower renal function, are more likely to fail when recurrent glomerulonephritis sets in. It is less clear whether either delayed graft function or acute rejection can also increase the risk of *initiating* recurrent disease. Delayed graft function is associated with an activation of the immune system and an increased subsequent risk of acute rejection [189;190]. Halloran *et. al.* [191] found that renal injury and resulting inflammation led to increased expression of MHC class I and II products, β2

microglobulin and TGF-β. It is possible that experiencing these responses early after transplantation could prime the immune response and lead to subsequent immunologically mediated damage in susceptible individuals. Similar mechanisms may also predispose to recurrent glomerulonephritis, although direct evidence is lacking.

The protective effect of increased cold ischemia time (CIT) for the risk of graft loss due to recurrence was not seen in an earlier study [27] and contrasts to its association with increased risk of graft loss due to other causes seen in our patients as well as in literature [97;106;109]. Previous reports have included only cadaver donor transplants, since CIT is uniformly short in live donor transplants. Our study included both live and cadaver donor transplants, but was controlled for the type of donor. The protective effect of CIT persisted after removing delayed graft function from the model, which is a mediator of the adverse effects of increased cold ischemia time on other causes of graft loss like chronic allograft nephropathy. Thus the protective effect of increased cold ischemia time on the risk of graft loss due to recurrent glomerulonephritis represents a new finding. It is possible that it represents uncontrolled confounding and deserves further study.

Compared to no dialysis before transplantation, risk of graft loss due to recurrent disease was significantly greater in patients with duration of dialysis from 0 to 12 months. As dialysis time increased to greater than 36 months, the risk was not significantly different from that of a pre-emptive transplantation. Patients undergoing pre-emptive transplant may have less aggressive form of glomerulonephritis that allows time to plan for transplant before dialysis is required. Risk of recurrence in transplanted kidney is known to decrease with prolonged dialysis in certain glomerulonephritis such as lupus nephritis [28].

4.4 Internal validity of the study

Several strengths of our study make it internally valid. It is one of the largest studies evaluating graft loss due to recurrent glomerulonephritis and had an adequate number of events per variable to control for confounding effects of covariates. We selected variables for inclusion in the model based on a systematic review of the literature rather than on the 'p' value of each individual variable. This ensured that all important potential confounding factors were included in the model. We included variables known to be associated with causes of graft failure other than recurrent glomerulonephritis, thus minimising bias arising from competing risks [153].

We used multiple imputation techniques to handle the missing values in the covariates. Most statistical packages automatically delete an observation from analysis if any of the variables included in the model has a missing value for that observation. When there are a large number of variables in a regression model - with some of them having even a small proportion of missing values - such an approach can lead to a large reduction in the number of cases that are actually used in the analysis. This method, also called *complete case analysis* or *listwise deletion*, leads to considerable information loss and thereby diminished precision of the estimates. Listwise deletion produces unbiased estimates only when the data are *Missing Completely At Random* (MCAR) [192], though the effective power decreases for all variables as the proportion of missingness increases [192]. When the values of a variable are *Missing At Random* (MAR), listwise deletion produces biased regression estimates of not only the variable with missing values, but of the other variables in the model as well [192]. Another common approach to handle missing data in categorical variables is to use a separate indicator variable to denote observations with missing values for that variable. Studies have shown that entering such indicator variables into a regression

model leads to biased estimates of other categories of the variable [193] even if the data are *Missing Completely At Random.*

In most clinical situations, data are *Missing At Random* (MAR) rather than *Missing Completely At Random* or *Missing Not at Random* [193]. Multiple imputation techniques use non-missing information from other variables to estimate missing values assuming that the values are *Missing At Random.* Multiple imputation technique uses random draws from residuals and creates multiple datasets with different imputed values for the same missing elements to account for the uncertainty involved in estimating the missing values. Studies have shown that use of multiple imputation leads to unbiased estimates [154;193] when data are *Missing At Random.*

We found that changes in immunosuppressive medications were very common during follow-up. Often studies treat medications started at the time of transplantation as fixed or time-independent, to determine their association with the outcome. Even in a randomized trial, large numbers of crossovers between the treatment groups can threaten the validity of an intention-to-treat analysis. In an observational study like ours, patients are not allocated randomly to a particular medication. Assigning outcome to medications used at the start of observation period essentially treats them as 'fixed' or 'time-independent' and can lead to biased estimates [165]. We considered the time varying nature of the immunosuppressive medications while assigning outcomes to individual medication. A major problem associated with using time varying covariates is confounding by indication. We used a variable indicating any change in medication and a lag time of 6 months between change in medication and outcome to control for confounding by indication. Therefore our findings are less likely to be due to such confounding, although residual confounding cannot be ruled out.

Certain limitations of our study should be pointed out. The only available study [144] that reported validation of certain variables in the USRDS data was carried out in 1987-88 and agreement regarding the diagnosis of glomerulonephritis was confirmed in only 79.4% of cases, which is less than ideal. Similarly, the date of transplant failure and patient death was also not completely accurate, being within 60-days in 89.7% and 100% cases respectively. Moreover we did not restrict the diagnosis of glomerulonephritis to one confirmed by biopsy. This raises possibility of misclassification of recurrent glomerulonephritis, which is likely to be non-differential with respect to the use of medications. Such non-differential misclassification can result in estimates that are biased towards null (i.e. towards hazard ratio of 1.0).

4.5 External validity of the study

This study is the largest examination of the association between immunosuppressive medications and the risk of graft loss due to recurrent disease. We used the United States Renal Data System dataset that records more than 95% of transplants performed in the United States. We also did not restrict inclusion criteria to a biopsy confirmed disease to reflect the real world scenario where a diagnosis of glomerulonephritis is made in a large proportion of patients without kidney biopsy. Thus, our findings apply to the population of all patients in North America who are diagnosed as having kidney failure due to glomerulonephritis undergoing first kidney transplantation.

4.6 Importance and relevance of the study

Recurrent glomerulonephritis is the third most common cause of kidney transplantation and its incidence is increasing [11]. Our evidence suggests that individualising commonly

used anti-rejection immunosuppressive medications may not impact graft loss due to recurrent glomerulonephritis. Efforts should therefore be directed to other measures like optimum control of blood pressure and maximising the use of ACE inhibitors and statins. Efforts made to lower the risk of delayed graft function and acute rejection may decrease graft loss due to recurrent glomerulonephritis. Our study also highlights the need for uniform guidelines to define recurrent glomerulonephritis to minimize misclassification. Finally, since change in immunosuppressive medications is a strong predictor of poor outcome, close monitoring for circumstances leading to medication change (adverse effects, early signs and markers of worsening kidney function like microalbuminuria) may provide opportunity for early diagnosis of recurrence and a potential window for intervention.

4.7 Future directions

A prospective cohort study of patients with kidney failure due to glomerulonephritis will allow for more precise definition of the disease and determination of time of disease recurrence (defined as onset of urinary abnormalities or worsening of renal function) and time since onset of recurrence to graft loss. Such a study would be able to explore impact of measures like blood pressure control, and the use of ACE inhibitors and statins. Some transplant programs routinely request protocol biopsies of the transplant kidney at regular interval irrespective of functioning of the transplant kidney. This provides another potential approach as a study of protocol biopsies prior to onset of recurrent disease and comparing them with those who do not develop recurrent disease may shed light on some of the pathogenic processes that occur prior to onset of recurrent disease.

4.8 Conclusions

Common antimetabolites (azathioprine and mycophenolate mofetil) and calcineurin inhibitors (cyclosporine and tacrolimus) used in kidney transplantation have no impact on the risk of graft loss due to recurrent glomerulonephritis. Any change in the immunosuppressive medications is an independent predictor of graft loss due to recurrent glomerulonephritis.

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Appendix 1: Types and ICD-9 codes of glomerulonephritis eligible for the study

ICD-9	Suffix	Type of Glomerulonephritis
5829	A	Glomerulonephritis, Histologically not examined
5821	A	Focal glomerulosclerosis, focal sclerosing glomerulonephritis
5831	A	Membranous nephropathy
5832	A	Membranoproliferative glomerulonephritis type 1, difuse membranoproliferative glomerulonephritis
5832	C	Dense deposit disease, Membranoproliferative glomerulonephritis type 2
58381	B	IgA nephropathy, Berger's disease (Proven by immunofluorescence)
58381	C	IgM nephropathy (Proven by immunofluorescence)
5804	B	Rapidly progressive glomerulonephritis
5834	C	Goodpasture's syndrome
5800	C	Post infectious glomerulonephritis, SBE
5820	A	Other proliferative glomerulonephritis
7100	E	Lupus Erythematosus, (SLE nephritis)
2870	A	Henoch-Schonlein syndrome
7101	B	Scleroderma
2831	A	Hemolytic uremic syndrome
4460	C	Polyarteritis
4464	B	Wegener's granulomatosis
5839	C	Nephropathy due to heroin abuse and related drugs
4462	A	Vasculitis and its derivatives
5839	B	Secondary glomerulonephritis, other

Appendix 2: Evidence of efficacy immunosuppressive medications in glomerulonephritis

MMF in IgA Nephritis

Author / Year	Follow-up	N	Type of study	Outcome	Results	Comments
Maes BD / 2004 [194]	3 year	MMF-21, placebo-13	RCT	Proportion of patients with >25% decrease in proteinuria or >50% increase in s. creatinine	No difference in the two groups.	Small trial. 5 Pts discontinued therapy.
Chen X / 2002 [195]	18 months	MMF-31, prednisone-31	RCT, open label	Proteinuria	Proteinuria 0.6g/d in MMF Vs 1.4g/d in prednisone, $p<0.05$. Remission 44.4% in MMF Vs 19.1% inprednisone, $p<0.05$	Not sure if truly randomized allocation

MMF in lupus nephritis

Author / Year	Follow-up	N	Type of study	Outcome	Results	Comments
Chan / 2000,2001 [85;86;196]	12 months	MMF-21, Cyp x 6mth f/b Aza x 6mth -21	RCT	Complete remission defined as proteinuria<0.3g/d with normal urine sediment, albumin and <15% increase in s. creatinine. Partial remission defined as proteinuria bet 0.3-2.9 g/d and albumin > 30	MMF: 81% complete remission, 14% partial remission Cyp/Aza: complete remission 76%, partial remission 14%	MMF used for induction of remission. Active treatment control group

				g/d		
	63months			Composite of ESRD or death	Graft survival: No diference, Composite of ESRD or death tended to be better in MMF group (p=0.062)	Suggests MMF equally effective in long term compared to Aza
Hu W/ 2002 [164]	6 months	MMF-23, cyclophosphamide-23	Nonrandomized trial	50% reduction in proteinuria	MMF: 69.6% Cyp: 47.8%	
Contreras G /2004 [84]	72 months	MMF-20, AZA-19, cyclophosphamide-20	RCT	Event free survival from composite endpoint of death or chronic renal failure	MMF: 90% Aza: 80% Cyp: 40%	MMF used for maintaining remission.

MMF in nephrotic syndrome

Author / Year	Follow-up	N	Type of study	Outcome	Results	Comments
Zhao / 2003 [197]		19 patients minimal change disease or mesangial proliferation of refractory nephrotic syndrome	Case series,	Proteinuria	12/19 had complete remission	
Bayazit / 2004 [198]	24 month	10 children Mesangial prolfration-4, MPGN-3, sclerosing-2, other proliferative-1	Case series	Proteinuria	Reduction without remission in 6/10	.
Bagga / 2003 [199]	17 months	19, steroid dependent. (MCNS-10, FSGS-3)	Case series	Frequency of relapses, steroid sparing	Relapse rate decreased from 6.6 to 2 episodes/yr. Mean steroid dose decreased from 0.7 to	

					0.3 mg/kg/d	
Day / 2002 [80]	12 month	7 frequent relapsers, MCNC/FSGS	Case series	Remission	6/7 achieved remission, sustained at 12 month in 5/7	

MMF in other Glomerulonephritis

Author / Year	Follow-up	N	Type of study	Outcome	Results	Comments
Choi / 2002 [79]	>3mth	46 patients MCNS-6, FSGS-18, MN-17	Case series	Proteinuria, s.creatinine	Urine p/cr decreased from 4.7 to 1.1, p<0.001 No change in s. creatinine	Significant reduction in proteinuria in MCNS, FSGs and membranous nephropathy
Miller / 2000 [78]	8mth	16 Pt of NS and membranous nephropathy, 15/16 stroid resistant	Case series	Proteinuria	Mean proteinuria unchanged, but 6/16 had >50% reduction in proteinuria	.
Nowack / 1999 [200]	14 month	11 Pt of vasculitis (WG-9, MPA-2)	Case series	Maintenance of remission	10/11 maintained remission	

Cyclosporine in Focal Segmental Glomerulosclerosis

Author / Year	Follow-up	N	Type of study	Outcome	Results	Comments
Cattran / 1999 [163]	24 month	Placebo: 23 Cyclosporine: 26	RCT	Proteinuria 50% reduction in Ccr	Complete or partial remission in 70% in CyA Vs 4% in placebo gr. A wk 26(p<0.01) though 60% relapse by wk 78. >50% reduction in Ccr	Largest RCT of CyA in FSGS

					seen in 25% Cya Vs 52% controls ($p<0.05$)	
Liberman /1996 [201]	6 month	Placebo:13 Cyclosporine: 12	RCT	Proteinuria	12/12 pts in CyA arm experienced decreased proteinuria Vs 2/13 in placebo arm	Pediatric patients, double blind

Cyclosporine in membranous nephropathy

Author / Year	Follow-up	N	Type of study	Outcome	Results	Comments
Cattran / 2001 (19) [162]	18 month	Placebo: 23 Cyclosporin: 28	RCT	Proteinuria	75% of CyA Vs 22% of placebo had remission ($p<0.001$), 43% relapsed.	
Cattran / 1995 [161]	12 month	Placebo: 8 Cyclosporine: 9	RCT	Change in Ccr	Difference in Ccr slope 1.6(0.3-3.0, $p=0.02$) in favour of CyA	

Appendix3: Search strategy used to identify determine risk factor of graft failure in kidney transplantation.

Database: Ovid MEDLINE(R) <1966 to March Week 1 2005>
Search Strategy:

---

1 Kidney Transplantation/ (53291)
2 Graft Survival/ (25114)
3 Kidney Failure, Chronic/ (50094)
4 2 or 3 (74348)
5 1 and 4 (14324)
6 risk factors/ (253308)
7 *proportional hazards models/ (453)
8 6 or 7 (253687)
9 5 and 8 (945)
10 limit 9 to (humans and english language and yr=1995 - 2005) (615)
11 from 10 keep 1-615 (615)

Appendix 4: End stage renal disease data forms

- CMS Medical Evidence form, CMS-2728
- End Stage Renal Disease Death Notification, CMS-2746
- United Network for Organ Transplantation forms
    i. Transplant Candidate Registration Form
    ii. Kidney Transplant Recipient Registration Form
    iii. Cadaver Donor Registration Form
    iv. Living Donor Registration
    v. Recipient Histocompatibility Form
    vi. Donor Histocompatibility Form
    vii. Kidney Transplant Recipient Follow-up Form

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
CENTERS FOR MEDICARE & MEDICAID SERVICES

FORM APPROVED
OMB NO. 0938-0046

END STAGE RENAL DISEASE MEDICAL EVIDENCE REPORT MEDICARE ENTITLEMENT AND/OR PATIENT REGISTRATION

A. COMPLETE FOR ALL ESRD PATIENTS

1. Name *(Last, First, Middle Initial)*

2. Health Insurance Claim Number

3. Social Security Number

4. Full Address *(Include City, State, and Zip)*

5. Phone Number
( )

6. Date of Birth
____/____/____
MM DD YYYY

7. Sex
☐ Male ☐ Female

8. Ethnicity
☐ Hispanic: Mexican ☐ Hispanic: Other ☐ Non-Hispanic

9. Race *(Check **one** box only)*
☐ White
☐ Black
☐ American Indian/Alaskan Native
☐ Asian
☐ Pacific Islander
☐ Mid-East/Arabian
☐ Indian sub-Continent
☐ Other, specify _____
☐ Unknown

10. Medical Coverage *(Check **all** that apply)*
a. ☐ Medicaid
b. ☐ DVA
c. ☐ Medicare
d. ☐ Employer Group Health Insurance
e. ☐ Other Medical Insurance
f. ☐ None

11. Is Patient Applying for ESRD Medicare Coverage? *(if **YES**, enter address of Social Security office)*
☐ Yes ☐ No

CITY STATE ZIP

12. Primary Cause of Renal Failure *(Use code from back of form)*

13. Height
INCHES OR CENTIMETERS

14. Dry Weight
POUNDS OR KILOGRAMS

15. Employment Status *(6 mos. prior and current status)*

Prior	Current	
☐	☐	Unemployed
☐	☐	Employed Full Time
☐	☐	Employed Part Time
☐	☐	Homemaker
☐	☐	Retired due to Age/Preference
☐	☐	Retired (Disability)
☐	☐	Medical Leave of Absence
☐	☐	Student

16. Co-Morbid Conditions *(Check **ALL** that apply currently or during last 10 years)* *See instructions
a. ☐ Congestive heart failure
b. ☐ Ischemic heart disease, CAD*
c. ☐ Myocardial infarction
d. ☐ Cardiac arrest
e. ☐ Cardiac dysrhythmia
f. ☐ Pericarditis
g. ☐ Cerebrovascular disease, CVA, TIA*
h. ☐ Peripheral vascular disease*
i. ☐ History of hypertension
j. ☐ Diabetes (primary or contributing)
k. ☐ Diabetes, currently on insulin
l. ☐ Chronic obstructive pulmonary disease
m. ☐ Tobacco use (current smoker)
n. ☐ Malignant neoplasm, Cancer
o. ☐ Alcohol dependence
p. ☐ Drug dependence*
q. ☐ HIV positive status ☐ Can't Disclose
r. ☐ AIDS ☐ Can't Disclose
s. ☐ Inability to ambulate
t. ☐ Inability to transfer

17. Was pre-dialysis/transplant EPO administered?
☐ Yes ☐ No

18. Laboratory Values Prior to First Dialysis Treatment or Transplant *See Instructions.

LABORATORY TEST	VALUE	DATE	LABORATORY TEST	VALUE	DATE
a. Hematocrit (%)			e. Serum Creatinine (mg/dl)		
b. Hemoglobin (g/dl)*			f. Creatinine Clearance (ml/min)*		
c. Serum Albumin (g/dl)			g. BUN (mg/dl)*		
d. Serum Albumin Lower Limit (g/dl)			h. Urea Clearance (ml/min)*		

B. COMPLETE FOR ALL ESRD PATIENTS IN DIALYSIS TREATMENT

19. Name of Provider

20. Medicare Provider Number

21. Primary Dialysis Setting
☐ Hospital Inpatient ☐ Dialysis Facility/Center ☐ Home

22. Primary Type of Dialysis
☐ Hemodialysis ☐ IPD ☐ CAPD ☐ CCPD ☐ Other

23. Date Regular Dialysis Began
____/____/____
MM DD YY

24. Date Patient Started Chronic Dialysis at Current Facility
____/____/____
MM DD YY

25. Date Dialysis Stopped
____/____/____
MM DD YY

26. Date of Death
____/____/____
MM DD YY

C. COMPLETE FOR ALL KIDNEY TRANSPLANT PATIENTS

27. Date of Transplant	28. Name of Transplant Hospital	29. Medicare Provider Number for Item 28
____/____/____ MM DD YY		

Date patient was admitted as an inpatient to a hospital in preparation for, or anticipation of, a kidney transplant prior to the date of actual transplantation.

30. Enter Date	31. Name of Preparation Hospital	32. Medicare Provider Number for Item 31
____/____/____ MM DD YY		

33. Current Status of Transplant

☐ Functioning ☐ Non-Functioning

34. If Nonfunctioning, Date of Return To Regular Dialysis	35. Current Dialysis Treatment Site
____/____/____ MM DD YY	☐ Hospital Inpatient ☐ Dialysis Facility/Center ☐ Home

D. COMPLETE FOR ALL ESRD SELF-DIALYSIS TRAINING PATIENTS (MEDICARE APPLICANTS ONLY)

36. Name of Training Provider	37. Medicare Provider Number of Training Provider

38. Date Training Began	39. Type of Training
____/____/____ MM DD YY	☐ Hemodialysis ☐ IPD ☐ CAPD ☐ CCPD

40. This Patient is Expected to Complete *(or has completed)* Training and Will Self-dialyze on a Regular Basis.	41. Date When Patient Completed, or is Expected to Complete, Training
☐ Yes ☐ No	____/____/____ MM DD YY

I certify that the above self-dialysis training information is correct and is based on consideration of all pertinent medical, psychological, and sociological factors as reflected in records kept by this training facility.

42. Printed Name and Signature of Physician Personally Familiar with the Patient's Training	43. UPIN of Physician in Item 42

E. PHYSICIAN IDENTIFICATION

44. Attending Physician *(Print)*	45. Physician's Phone No.	46. UPIN of Physician in Item 44
	( )	

PHYSICIAN ATTESTATION

I certify, under penalty of perjury, that the information on this form is correct to the best of my knowledge and belief. Based on diagnostic tests and laboratory findings, I further certify that this patient has reached the stage of renal impairment that appears irreversible and permanent and requires a regular course of dialysis or kidney transplant to maintain life. I understand that this information is intended for use in establishing the patient's entitlement to Medicare benefits and that any falsification, misrepresentation, or concealment of essential information may subject me to fine, imprisonment, civil penalty, or other civil sanctions under applicable Federal laws.

47. Attending Physician's Signature of Attestation *(Same as Item 44)*	48. Date
	____/____/____ MM DD YY

49. Remarks

F. OBTAIN SIGNATURE FROM PATIENT

I hereby authorize any physician, hospital, agency, or other organization to disclose any medical records or other information about my medical condition to the Department of Health and Human Services for purposes of reviewing my application for Medicare entitlement under the Social Security Act and/or for scientific research.

50. Signature of Patient *(Signature by Mark Must Be Witnessed.)*	51. Date
	____/____/____ MM DD YY

G. PRIVACY ACT STATEMENT

The collection of this information is authorized by section 226A of the Social Security Act. The information provided will be used to determine if an individual is entitled to Medicare under the End Stage Renal Disease provisions of the law. The information will be maintained in system No. 09-70-0520, "End Stage Renal Disease Program Management and Medical Information System (ESRD PMMIS)", published in the Privacy Act Issuance, 1991 Compilation, Vol. 1, pages 436–437, December 31, 1991, or as updated and republished. Collection of your Social Security number is authorized by Executive Order 9397. Furnishing the information on this form is voluntary, but failure to do so may result in denial of Medicare benefits. Information from the ESRD PMMIS may be given to a congressional office in response to an inquiry from the congressional office made at the request of the individual; an individual or organization for a research, demonstration, evaluation, or epidemiologic project related to the prevention of disease or disability, or the restoration or maintenance of health. Additional disclosures may be found in the *Federal Register* notice cited above. You should be aware that P.L. 100-503, the Computer Matching and Privacy Protection Act of 1988, permits the government to verify information by way of computer matches.

H. FOR ESRD NETWORK USE ONLY IN CASES REFERRED TO ESRD MEDICAL REVIEW BOARD

52. Network Confirmed as ESRD	53. Authorized Signature	54. Date	55. Network Number
☐ Yes ☐ No		____/____/____ MM DD YY	

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR MEDICARE & MEDICAID SERVICES

FORM APPROVED
OMB NO. 0938-0448

ESRD DEATH NOTIFICATION

END STAGE RENAL DISEASE MEDICAL INFORMATION SYSTEM

1. PATIENT'S LAST NAME	FIRST	MI	2. HEALTH INSURANCE CLAIM NUMBER

3. PATIENT'S SEX	4. PATIENT'S STATE OF RESIDENCE	5. DATE OF BIRTH	6. DATE OF DEATH
a. ☐ Male b. ☐ Female		MONTH DAY YEAR	MONTH DAY YEAR

7. PROVIDER NAME AND ADDRESS (CITY AND STATE)

8. PROVIDER NUMBER	9. PLACE OF DEATH (Check one)	10. WAS AN AUTOPSY PERFORMED?
	a. ☐ Hospital b. ☐ Dialysis c. ☐ Home d. ☐ Other	a. ☐ Yes b. ☐ No

11. CAUSES OF DEATH (Enter code form List of Causes below.)

a. Primary Cause ☐

b. Were there Secondary Causes? ☐ No ☐ Yes, Specify (1) ☐ (2) ☐ (3) ☐ (4) ☐

LIST OF CAUSES

CARDIAC
23 Myocardial infarction, acute
24 Hyperkalemia
25 Pericarditis, incl. cardiac tamponade
26 Atherosclerotic heart disease
27 Cardiomyopathy
28 Cardiac arrhythmia
29 Cardiac arrest, cause unknown
30 Valvular heart disease
31 Pulmonary edema due to exogenous fluid

VASCULAR
35 Pulmonary embolus
36 Cerebrovascular accident including intracranial hemorrhage
37 Ischemic brain damage/Anoxic encephalopathy
38 Hemorrhage from transplant site
39 Hemorrhage from vascular access
40 Hemorrhage from dialysis circuit
41 Hemorrhage from ruptured vascular aneurysm
42 Hemorrhage from surgery (not 38, 39 or 41)
43 Other hemorrhage (not Codes 38-42, 72)
44 Mesenteric infarction/ischemic bowel

INFECTION
49 Septicemia, due to vascular access
50 Septicemia, due to peritonitis
51 Septicemia, due to peripheral vascular disease, gangrene
52 Septicemia, other
53 Pulmonary infection (bacterial)
54 Pulmonary infection (fungal)
55 Pulmonary infection (other)
56 Viral Infection, CMV
57 Viral Infection, Other (not 64 or 65)
58 Tuberculosis
59 A.I.D.S.
60 Infections, other

LIVER DISEASE
64 Hepatitis B
65 Other viral hepatitis
66 Liver-drug toxicity
67 Cirrhosis
68 Polycystic liver disease
69 Liver failure, cause unknown other

GASTRO-INTESTINAL (see also 50)
72 Gastro-intestinal hemorrhage
73 Pancreatitis
74 Fungal peritonitis
75 Perforation of peptic ulcer
76 Perforation of bowel (not 75)

OTHER
80 Bone marrow depression
81 Cachexia
82 Malignant disease, patient ever on immunosuppressive therapy
83 Malignant disease (not 82)
84 Dementia, incl. dialysis dementia, Alzheimer's
85 Seizures
86 Diabetic coma, hyperglycemia, hypoglycemia
87 Chronic obstructive lung disease (COPD)
88 Complications of surgery
89 Air embolism
90 Accident related to treatment
91 Accident unrelated to treatment
92 Suicide
93 Drug overdose (street drugs)
94 Drug overdose (not 92 or 93)
98 Other identified cause of death, please specify: _____
99 Unknown

12. FOR ALL DEATHS INDICATE YES/NO

Renal replacement therapy discontinued prior to death: ☐ Yes ☐ No

If Yes, check one of the following:

a. ☐ Following HD and/or PD access failure
b. ☐ Following transplant failure
c. ☐ Following chronic failure to thrive
d. ☐ Following acute medical complication
e. ☐ Other

13. IF DECEASED RECEIVED A TRANSPLANT

a. Date of most recent transplant ☐☐ ☐☐ ☐☐ MONTH DAY YEAR

b. Was kidney functioning (patient not on dialysis) at time of death? ☐ Yes ☐ No ☐ Unknown

c. Did transplant patient resume chronic maintenance dialysis prior to death? ☐ Yes ☐ No

14. REMARKS

15. NAME OF PHYSICIAN	16. SIGNATURE OF PERSON COMPLETING THIS FORM	DATE

This report is required by law (42, U.S.C. 426; 20 CFR 405, Section 2133). Individually identifable patient information will not be disclosed except as provided for in the Privacy Act of 1974 (5 U.S.C. 5520; 45 CFR Part 5a).

Transplant Candidate Registration Form

(Please print or type all information) FORM APPROVED: O.M.B. NO. 0915-0157 Expiration Date: 12/31/2002

Submitting this paper form does not add your patient to the waiting list.

Provider Information

Organ Registered: **Kidney**

Provider Number _____ UNOS Center Code _____ Center Name _____

Date placed on list: _____

Candidate Information

Name: _____ (Last / First / MI) Previous Surname: _____

DOB: _____ SSN: _____ HIC: _____ Gender: ○ Male ○ Female

State of Permanent Residence: _____ Permanent Zip Code: _____ Waiting Zip Code: _____

Ethnicity ○ Hispanic/Latino ○ Non-Hispanic/Non-Latino

Race

- ○ White
- ○ Black or African American
- ○ American Indian or Alaskan Native
- ○ Asian
- ○ Native Hawaiian or other Pacific Islander
- ○ Mid-East or Arabian
- ○ Indian Sub-Continent

Citizenship (Select one)

- ○ U.S. Citizen
- ○ Non-Resident Alien
- ○ Resident Alien

Home country: _____

Highest Education Level (Select one)

- ○ None
- ○ Grade School (0-8)
- ○ High School (9-12)
- ○ Attended College/Technical School
- ○ Associate/Bachelor Degree
- ○ Post-College Graduate Degree
- ○ Unknown

Medical Condition (Select one)

- ○ Patient in Intensive Care Unit
- ○ Hospitalized, but not in Intensive Care Unit
- ○ Not hospitalized

Patient on Life Support

(Please provide for all patients regardless of medical status)

○ Yes ○ No

(Check applicable)

- ☐ ECMO
- ☐ PGE
- ☐ Ventilator
- ☐ IABP
- ☐ IV Inotropes
- ☐ Other mechanism Specify: _____

VAD Brands

- ○ Cardio West
- ○ Abiomed
- ○ Novacor
- ○ Heartmate
- ○ Thoratec
- ○ Other VAD, specify: _____

Functional Status (Select one) (How does patient perform daily activities?)

- ○ No activity limitations. (NYHA Class I or Class II)
- ○ Performs activities of daily living with some assistance. (NYHA Class III)
- ○ Performs activities of daily living with total assistance. (NYHA Class IV)
- ○ N/A Patient hospitalized
- ○ Unknown

Employment Status (Select one) (Working = Employed, Home, School)

- ○ Working Full Time
- ○ Working Part Time By Choice
- ○ Working Part Time Due to Disease
- ○ Working Part Time, Reason Unknown
- ○ Not Working By Choice
- ○ Not Working Due to Disease
- ○ Not Working, Unable to Find Employment
- ○ Not Working, Reason Unknown
- ○ Retired
- ○ Employment Status Unknown
- ○ Patient Less Than Five Years Old

Previous Transplants

○ Yes ○ No

If Yes, give the number of previous transplants for each organ type and latest transplant date.

	Number	Date
Kidney		
Liver		
Pancreas (whole)		
Pancreas (islet cells)		
Heart		
Lung		
Intestine		
Bone Marrow		

Source of Payment

(Check Yes, No or Unknown for each secondary source of payment)

Primary (Largest %, Select one)	Secondary		
○ Medicare	○ Y	○ N	○ U
○ Medicaid	○ Y	○ N	○ U
○ US/State Government Agency	○ Y	○ N	○ U
○ Private Insurance	○ Y	○ N	○ U
○ HMO/PPO	○ Y	○ N	○ U
○ Self	○ Y	○ N	○ U
○ Donation	○ Y	○ N	○ U
○ Free Care	○ Y	○ N	○ U
○ Dept. of Veterans Affairs			
○ Pending			
○ Foreign Govt., Specify: _____			

Transplant Candidate Registration Form

FORM APPROVED: O.M.B. NO. 0915-0157 Expiration Date: 12/31/2002

Name: _____

Clinical Information

Height _____ ft. _____ in. OR _____ cm
Weight _____ lbs. OR _____ kg

ABO Blood
Group: _____
Rh: _____

Primary Diagnosis
(Use codes) _____
If other, specify: _____

General Medical Factors

Diabetes
- ○ No Diabetes
- ○ Insulin Dependent Diabetes
- ○ Non-Insulin Dependent Diabetes
- ○ Diabetes, Dependency Unknown
- ○ Unknown

Dialysis
- ○ No Dialysis
- ○ Hemodialysis
- ○ Peritoneal Dialysis

Peptic Ulcer Disease
- ○ No
- ○ Yes, Drug Treated
- ○ Yes, Not Drug Treated
- ○ Yes, Drug Treatment Unknown
- ○ Unknown

Angina/Coronary Artery Disease
- ○ No
- ○ Angina, Unstable
- ○ Angina, Stable
- ○ Angina, Stability Unknown
- ○ Unknown

Drug Treated Systemic Hypertension ○ Y ○ N ○ U
Symptomatic Cerebrovascular Disease ○ Y ○ N ○ U
Symptomatic Peripheral Vascular Disease ○ Y ○ N ○ U
Drug Treated COPD ○ Y ○ N ○ U
Pulmonary Embolism (within last 6 months) ○ Y ○ N ○ U
Any Previous Transfusions ○ Y ○ N ○ U
Any Previous Malignancy ○ Y ○ N ○ U
(Exclude non-melanoma skin cancer)
PRA > 10% (with DTT or DTE testing) ○ Y ○ N ○ U

Most recent absolute Creatinine _____ mg/dl
Total Serum Albumin _____ g/dl

Kidney Medical Factors

Exhausted vascular access ○ Y ○ N ○ U
Exhausted peritoneal access ○ Y ○ N ○ U
Age of diabetes onset _____ yrs
Creatinine clearance _____ ml/min
Creatinine clearance method:
○ Isotope ○ Calculated ○ Measured Standard

Person completing form: _____ Date completed: _____

Kidney Transplant Recipient Registration Form

(Please print or type all information) FORM APPROVED: O.M.B. NO. 0915-0157 Expiration Date: 12/31/2002

Provider Information

Provider Number | Center Code | Transplant Center Name | Surgeon Name | UPIN Number

Recipient Information

Name: Last First MI Transplant Date:

DOB: SSN: HIC: Gender: ○ Male ○ Female

Patient Status

Primary Diagnosis (Use code) Specify:

Patient Status

Date: of Report or Death

○ Living

○ Dead Cause of Death: (Use code)

Specify:

○ Retransplanted prior to hospital discharge

Transplant Hospitalization

Date of discharge from transplant center:

Date of admission to transplant center:

Was patient transferred from another hospital prior to transplant?

○ Yes ○ No

If Yes, date of admission to transferring hospital:

Medical Condition at Time of Transplant (Select one)

○ Patient in Intensive Care Unit

○ Hospitalized, but not in Intensive Care Unit

○ Not hospitalized

Patient on Life Support ○ Yes ○ No

(Please provide for all patients regardless of medical status)

Functional Status (How does the patient perform activities of daily living? Select one)

○ No activity limitations. (NYHA Class I or Class II)

○ Performs activities of daily living with some assistance. (NYHA Class III)

○ Performs activities of daily living with total assistance. (NYHA Class IV)

○ N/A Patient hospitalized

○ Unknown

Employment Status (Select one) (Working = Employed, Home, School)

○ Working Full Time

○ Working Part Time By Choice

○ Working Part Time Due to Disease

○ Working Part Time, Reason Unknown

○ Not Working By Choice

○ Not Working Due to Disease

○ Not Working, Unable to Find Employment

○ Not Working, Reason Unknown

○ Retired

○ Employment Status Unknown

○ Patient Less Than Five Years Old

Donor Information

Donor Type:

UNOS Donor ID Donor Name: Last First

Source of Payment (Check Yes, No or Unk for each secondary source)

Primary (Largest %, Select one)	Secondary		
○ Medicare	○ Y	○ N	○ U
○ Medicaid	○ Y	○ N	○ U
○ US/State Government Agency	○ Y	○ N	○ U
○ Private Insurance	○ Y	○ N	○ U
○ HMO/PPO	○ Y	○ N	○ U
○ Self	○ Y	○ N	○ U
○ Donation	○ Y	○ N	○ U
○ Free Care	○ Y	○ N	○ U
○ Dept. of Veterans Affairs			
○ Foreign Gov't. Specify:			

Pretransplant Clinical Information

Previous Kidney Transplants ○ Yes ○ No

If Yes, number of previous kidney transplants:

Previous Tx	Transplant Date	Graft Failure Date
Most recent		
2nd most recent		
3rd most recent		

Pretransplant Dialysis

○ None ○ Hemodialysis ○ Peritoneal dialysis

If Yes, date first dialyzed:

Average daily insulin: ____ units

Serum Creatinine at time of transplant: ____ mg/dl

Creatinine clearance: ____ ml/min

Creatinine clearance method:

○ Isotope ○ Calculated ○ Measured standard

Pretransplant Serology

HIV	Screening	P	N	U	ND	I	C
	Confirmation	P	N	U	ND	I	C
CMV	IgG	P	N	U	ND	I	C
	IgM	P	N	U	ND	I	C
	DNA	P	N	U	ND	I	C
Hepatitis B	Core Antibody	P	N	U	ND	I	C
	Surface Antigen	P	N	U	ND	I	C
	HBV DNA	P	N	U	ND	I	C
Hepatitis C	Antibody Screen	P	N	U	ND	I	C
	RIBA Test	P	N	U	ND	I	C
	HCV RNA	P	N	U	ND	I	C
Epstein Barr Virus	IgG	P	N	U	ND	I	C
	IgM	P	N	U	ND	I	C
	DNA	P	N	U	ND	I	C

Kidney Transplant Recipient Registration Form

FORM APPROVED: O.M.B. NO. 0915-0157 Expiration Date: 12/31/2002

Name: _____

Biopsy of Donor Kidney at Transplant Center

- ○ No biopsy done
- ○ Frozen Left Kidney
- ○ Permanent Left Kidney
- ○ Frozen Right Kidney
- ○ Permanent Right Kidney
- ○ Frozen En-bloc Kidney
- ○ Permanent En-bloc Kidney

Kidney Results:

Glomerulosclerosis %	Fibrosis	Arteriolosclerosis
○ 0-5	○ None	○ None
○ 6-10	○ Mild	○ Mild
○ 11-15	○ Moderate	○ Moderate
○ 16-20	○ Large	○ Large
○ >20		

Pretransplant Blood Transfusions:
○ 0 ○ 1-5 ○ 6-10 ○ >10 ○ Unk

Date of last transfusion: _____

Donor specific transfusions? ○ Yes ○ No ○ Unk

Number of previous pregnancies:
○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ >5 ○ Unk

Any known malignancies since listing: ○ Yes ○ No ○ Unk

Transplant Clinical Information

Multiple Organ Recipient: _____

Procedure Type: _____

Preservation Information

Total Cold Ischemic Time: _____ hrs
Anastomotic Time: _____ min
Warm Ischemic Time: _____ min
Total Pump Time: _____ hrs _____ min

Number of blood transfusions at time of transplant: _____

Post Transplant Clinical Information

Graft Status: ○ Functioning ○ Failed

Resumed maintenance dialysis: ○ Yes ○ No

If Yes, date resumed: _____
Dialysis center provider #: _____
Dialysis center name: _____
If failed, date of graft failure: _____

Cause of graft failure (Check Yes, No or Unknown for each contributory cause of graft failure)

Primary (Check one)	Contributory		
○ Hyperacute rejection			
○ Acute rejection	○ Y	○ N	○ U
○ Primary failure			
○ Graft thrombosis	○ Y	○ N	○ U
○ Infection	○ Y	○ N	○ U
○ Surgical complications	○ Y	○ N	○ U
○ Urological complications	○ Y	○ N	○ U
○ Recurrent disease	○ Y	○ N	○ U
○ Other: _____	Other: _____		

Most recent Serum Creatinine prior to discharge: _____ mg/dl

Did kidney produce > 40 ml of urine in the first 24 hours? ○ Y ○ N

Did patient need dialysis within first week? ○ Y ○ N

Did Creatinine decline by 25% or more in first 24 hours on 2 separate serum samples taken within the first 24 hours? ○ Y ○ N

Rejection Information

Patient treated for rejection? ○ Y ○ N
If Yes, biopsy done? ○ Y ○ N
If Yes, rejection confirmed? ○ Y ○ N

BANFF Level: ○ Y ○ N
Stages: ○ 1A ○ 1B ○ 2 ○ 3

Height _____ ft. _____ in. OR _____ cm
Weight _____ lbs. OR _____ kg

Treatment

Immunosuppressive Information

Are any medications given currently for maintenance or anti-rejection? ○ Y ○ N

Did the patient participate in any clinical research protocol for immunosuppressive medications: ○ Y ○ N
If Yes, specify: _____

Other Therapy

Photopheresis ○ Y ○ N
Plasmapheresis ○ Y ○ N
Total Lymphoid Irradiation (TLI) ○ Y ○ N

Biologicals/Vaccines

Cytogam (CMV) ○ Y ○ N
Gamimune N 10% ○ Y ○ N
Gammagard SD ○ Y ○ N
Acyclovir (Zovirax) ○ Y ○ N
Ganciclovir (Cytovene) ○ Y ○ N
HBIG (Hepatitis B Immune Globulin) ○ Y ○ N
Flu Vaccine (Influenza virus) ○ Y ○ N
Other: _____
Other: _____

Person completing form: _____ Date completed: _____

Cadaver Donor Registration Form

(Please print or type all information) FORM APPROVED: O.M.B. NO. 0915-0157 Expiration Date: 12/31/2002

Provider Information

OPO Provider Number | Center Code | OPO Center Name | Donor Hospital Provider Number | Donor Hospital Name

Date of Referral call: _____ **Recovered outside U.S:** ○ Y ○ N If Yes, country: _____

Donor Information

UNOS Donor ID: _____

Name: _____ (Last) _____ (First) DOB: _____ If Unknown, give age: _____

Gender: ○ Male ○ Female Home City: _____ State: _____ Home Zip Code: _____

Ethnicity ○ Hispanic/Latino ○ Non-Hispanic/Non-Latino

Race

- ○ White
- ○ Black or African American
- ○ American Indian or Alaska Native
- ○ Asian
- ○ Native Hawaiian or other Pacific Islander
- ○ Mid-East or Arabian
- ○ Indian Sub-Continent

Citizenship (Select one)

- ○ U.S. Citizen
- ○ Resident Alien
- ○ Non-Resident Alien, specify country
  Home country: _____

Cause of Death (Select one)

- ○ Anoxia/Cardiac Arrest
- ○ Cerebrovascular/Stroke
- ○ Head Trauma
- ○ CNS Tumor
- ○ Other, specify: _____

Mechanism of Death (Select one)

- ○ Drowning
- ○ Seizure
- ○ Drug Intoxication
- ○ Asphyxiation
- ○ Cardiovascular
- ○ Electrical
- ○ Gunshot Wound
- ○ None of the Above
- ○ Stab
- ○ Blunt Injury
- ○ Sudden Infant Death
- ○ Intracranial Hemorrhage /Stroke
- ○ Death from Natural Causes

Circumstances of Death (Select one)

- ○ Motor Vehicle Accident
- ○ Alleged Suicide
- ○ Alleged Homicide
- ○ Alleged Child Abuse
- ○ Non-Motor Vehicle Accident
- ○ Death from Natural Causes
- ○ None of the Above

Procurement and Consent

Was donor suitable for procurement of organs: ○ Y ○ N

If No, select one primary reason:

- ○ HIV +
- ○ HCV +
- ○ Hepatitis B +
- ○ Tuberculosis
- ○ Brain death criteria not met
- ○ Other, specify: _____
- ○ Medical History
- ○ Social History
- ○ Cancer
- ○ Age

Was Death reported to Medical Examiner/Coroner:

- ○ No
- ○ Medical examiner consented
- ○ Medical examiner refused consent
- ○ Unknown

Was the donor's wish to donate organs known to the family prior to donation request: ○ Y ○ N ○ U

Was a formal organ donation request made: (Select one)

- ○ No
- ○ Yes, family initiated
- ○ Approached by physican
- ○ Approached by nurse
- ○ Approached by clergy
- ○ Approached by OPO Coordinator
- ○ Approached by Social Worker
- ○ Other, Specify: _____

Written consent for organ donation obtained by: (Select one)

- ○ No consent obtained
- ○ OPO Coordinator
- ○ Social Worker
- ○ Other, specify:
- ○ Physician
- ○ Nurse
- ○ Clergy

Was the consent based solely on written documentation of the patient? ○ Y ○ N

If Yes, indicate mechanisms:

- ☐ Driver's license
- ☐ Donor card
- ☐ Donor registry
- ☐ Living will
- ☐ Attorney in fact

Other, specify: _____

Consent Information

Tissue Requested ○ Y ○ N

If no, reason code: _____

Other, Specify: _____

Tissue Consented ○ Y ○ N

If no, reason code: _____

Other, Specify: _____

Clinical Information

ABO Blood

Group: _____ Rh: _____

Height _____ **ft.** _____ **in.** **OR** _____ **cm**

Weight _____ **lbs.** **OR** _____ **kg**

Person completing form: _____ Date completed: _____

Cadaver Donor Registration Form

FORM APPROVED: O.M.B. NO. 0915-0157 Expiration Data: 12/31/2002

Name: _____

Terminal Lab Data (U=Unknown, ND=Not Done)

Serum Creatinine _____ mg/dl
BUN _____ mg/dl
Total Bilirubin _____ mg/dl
SGOT/AST _____ u/ml
SGPT/ALT _____ u/ml
Protein in urine ○ Y ○ N ○ U
Last Serum sodium prior to procurement > 170 mEq/l: ○ Y ○ N ○ U
Pancreas: (PA donors only)
Serum Lipase _____ u/L
Serum Amylase _____ u/L

Medications given to donor (24 hours prior to cross clamp)

Anticonvulsants	○ Y	○ N	○ U
Antihypertensives	○ Y	○ N	○ U
Vasodilators	○ Y	○ N	○ U
Dopamine	○ Y	○ N	○ U
Dobutamine	○ Y	○ N	○ U
DDAVP	○ Y	○ N	○ U

Other, specify: _____
Other, specify: _____
Other, specify: _____

Serology

Anti-HIV I	P	N	U	ND	I	C
Anti-HIV II	P	N	U	ND	I	C
Anti-HTVL I	P	N	U	ND	I	C
Anti-HTVL II	P	N	U	ND	I	C
RPR-VDRL	P	N	U	ND	I	C
Anti-CMV	P	N	U	ND	I	C
HBsAg	P	N	U	ND	I	C
Anti-HBC	P	N	U	ND	I	C
Anti-HCV	P	N	U	ND	I	C

Donor Management (Pretreatment medications given after brain death declared and 24 hours prior to procurement)

Did donor receive prerecovery medication: ○ Y ○ N ○ U
If Yes, check Yes, No or Unknown for each of the following:

Steriods	○ Y	○ N	○ U
Diuretics	○ Y	○ N	○ U
T3	○ Y	○ N	○ U
T4	○ Y	○ N	○ U

Other, specify: _____
Other, specify: _____
Other, specify: _____
Other, specify: _____

Transfusion units prior to surgery: (This hospitalization)
○ 0 ○ 1-5 ○ 6-10 ○ >10 ○ Unk
Transfusion units intraoperatively:
○ 0 ○ 1-5 ○ 6-10 ○ >10 ○ Unk
Three or more inotropic agents at time of incision: ○ Y ○ N
Cardiac arrest since neurological event that lead to declaration of brain death: ○ Y ○ N
If Yes, duration of resuscitation: _____ min

Clinical Infection: ○ Y ○ N ○ U

Source	Confirmed by Culture
☐ Blood	○ Y ○ N
☐ Lung	○ Y ○ N
☐ Urine	○ Y ○ N
☐ Other, specify: _____	○ Y ○ N

Heart Donor's Cardiac Function

History of previous MI: ○ Y ○ N
LV ejection fraction: _____ %
Method:
○ Echo
○ MUGA
○ Angiogram
If LV ejection fraction < 50%:
Segmental abnormalities ○ Y ○ N
Global abnormalities ○ Y ○ N
Coronary angiogram: ○ Y ○ N
If Yes, normal: ○ Y ○ N
If abnormal, number of vessels with > 50% stenosis: ○ 1 ○ 2 ○ 3
Inotropic support: ○ Y ○ N
If Yes, list the agents used at acceptance and at time of procurement:

At Acceptance:

Agent	Dosage (mg/kg/min)	Time Started (military time)
1		
2		
3		
4		

At Time of Procurement:

Agent	Dosage (mg/kg/min)	Time Started (military time)
1		
2		
3		
4		

Right heart catheterization: ○ Y ○ N
If Yes:
CVP _____ PCW Pressure _____
PA Systolic _____ CO _____
PA Diastolic _____
Biopsy Performed:
○ No Biopsy
○ Yes, Myocarditis
○ Yes, Negative Biopsy Result
○ Yes, Other Diagnosis, Specify
Specify: _____

Person completing form: _____ Date completed: _____

Cadaver Donor Registration Form

FORM APPROVED: O.M.B. NO. 0915-0157 Expiration Date: 12/31/2002

Name: _____

Donor History

Chemical Use:

Cigarette Use (> 20 pack years) -Ever	○ Y	○ N	○ U
AND continued in last six months	○ Y	○ N	○ U
Alcohol Dependency -Ever	○ Y	○ N	○ U
AND continued in last six months	○ Y	○ N	○ U
IV Drug Use -Ever	○ Y	○ N	○ U
AND continued in last six months	○ Y	○ N	○ U
Cocaine Use -Ever	○ Y	○ N	○ U
AND continued in last six months	○ Y	○ N	○ U
Other Drug Use -Ever	○ Y	○ N	○ U
AND continued in last six months	○ Y	○ N	○ U

History of Diabetes: ○ Y ○ N ○ U

If Yes, duration:
○ 0-5 Years ○ 6-10 Years ○ >10 Years ○ Unk

Insulin Dependent: ○ Y ○ N

If Yes, how long:
○ 0-5 Years ○ 6-10 Years ○ >10 Years ○ Unk

History of Hypertension: ○ Y ○ N ○ U

If Yes, duration:
○ 0-5 Years ○ 6-10 Years ○ >10 Years ○ Unk

If Yes, method of control:

Diet	○ Y	○ N	○ U
Diuretics	○ Y	○ N	○ U
Other Hypertensive Medication	○ Y	○ N	○ U

History of Cancer: ○ Y ○ N ○ U

If Yes, cancer free interval _____ years.

If Yes, Primary site: (Select one)

Skin
- ○ Squamous, basal cell
- ○ Melanoma

CNS Tumor
- ○ Astrocytoma
- ○ Glioblastoma multiforme
- ○ Medulloblastoma
- ○ Neuroblastoma
- ○ Angioblastoma
- ○ Meningioma
- ○ Intracranial surgery
- ○ Intracranial no surgery
- ○ CNS Other

Genitourinary
- ○ Bladder
- ○ Uterine Cervix
- ○ Uterine body Endometrial
- ○ Uterine body
- Choriocarcinoma
- ○ Vulva
- ○ Ovarian
- ○ Penis, Testicular
- ○ Prostate
- ○ Kidney
- ○ Unknown genitourinary

Gastrointestinal
- ○ Esophageal
- ○ Stomach
- ○ Small Intestine
- ○ Colo-rectal
- ○ Liver & biliary tract
- ○ Pancreas

- ○ Breast
- ○ Thyroid
- ○ Tongue/Throat
- ○ Larynx
- ○ Lung (include bronchial)
- ○ Leukemia/Lymphoma
- ○ Other, specify: _____

Cancer at procurement

Intracranial	○ Y	○ N	○ U
Extracranial	○ Y	○ N	○ U
Skin	○ Y	○ N	○ U

Lifestyle Factors:

History of prison	○ Y	○ N	○ U
Tattoos	○ Y	○ N	○ U
Sexual promiscuity	○ Y	○ N	○ U

Other: _____

Other: _____

Other: _____

Organ Recovery

Recovery Date (donor to OR): _____

Non-Heart beating donor:	○ Y	○ N	
If Yes, controlled:	○ Y	○ N	○ U
If Yes, core cooling used:	○ Y	○ N	○ U

If Yes, estimated warm ischemic time: _____ min

Clamp date: _____

Clamp time (Military time): _____ Time zone: _____

Left Kidney Biopsy: ○ Y ○ N	**Right Kidney Biopsy:** ○ Y ○ N
Glomerulosclerosis %	Glomerulosclerosis %
○ 0-5	○ 0-5
○ 6-10	○ 6-10
○ 11-15	○ 11-15
○ 16-20	○ 16-20
○ > 20	○ > 20
Pump: ○ Y ○ N	**Pump:** ○ Y ○ N
Flow rate: _____ cc's/min	Flow rate: _____ cc's/min
Perfusion pressure Systolic: _____ mm/Hg	Perfusion pressure Systolic: _____ mm/Hg
Perfusion pressure Diastolic: _____ mm/Hg	Perfusion pressure Diastolic: _____ mm/Hg

Liver biopsy:	○ Y	○ N	
% Fatty:			
○ 0-19	○ 20-35	○ > 35	
Portal infiltrates:	○ Y	○ N	
Fibrosis:	○ Y	○ N	
Pump	○ Y	○ N	

Flow rate: _____ cc's/min

Perfusion pressure Systolic: _____ mm/Hg

Perfusion pressure Diastolic: _____ mm/Hg

Lung:

pO_2 on 100%: _____

Left Lung:

Bronchoscopic abnormalities:	○ Y	○ N
If Yes, purulent drainage:	○ Y	○ N
Chest X-ray abnormalities:	○ Y	○ N
If Yes, Infiltrate:	○ Y	○ N

If Yes: ☐ Upper ☐ Mid ☐ Lower

Right Lung:

Bronchoscopic abnormalities:	○ Y	○ N
If Yes, purulent drainage:	○ Y	○ N
Chest X-ray abnormalities:	○ Y	○ N
If Yes, Infiltrate:	○ Y	○ N

If Yes: ☐ Upper ☐ Mid ☐ Lower

Person completing form: _____ Date completed: _____

Cadaver Donor Registration Form

FORM APPROVED: O.M.B. NO. 0915-0157 Expiration Date: 12/31/2002

Name: _____

Kidney Right -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Kidney Left -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Kidney Double/Enbloc -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Pancreas -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Pancreas Segment 1 -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Pancreas Segment 2 -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Liver -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Liver Segment 1 -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Liver Segment 2 -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Intestine -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Intestine Segment 1-
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Intestine Segment 2 -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Heart -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Lung Right -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Lung Left -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Lung Double/En-bloc -
Reason Code: _____ Other Specify: _____
Discard Code: _____ Other Specify: _____
Recov. Team # _____ Placed by: _____ Type Share: _____
Flush Solution: _____ Other Specify: _____
Storage Solution: _____ Other Specify: _____
Recipient Name SSN Provider # - Center Code - Tx Center Name

Person completing form: _____ Date completed: _____

Living Donor Registration

(Please print or type all information) FORM APPROVED: O.M.B. NO. 0915-0157 Expiration Date: 12/31/2002

Provider Information

Provider Number _____ Center Code _____ Recipient Transplant Center Name _____

Donor Information

Donor ID: _____

Name: _____ (Last) _____ (First) Transplant Date: _____

DOB: _____ SSN: _____ Gender: ○ Male ○ Female Blood Type: _____ Rh: _____

Home City: _____ Home State: _____ Home Zip Code: _____

Living Donor Type: (Indicate the relationship of the donor to the recipient by checking one.)

Living, Biologically Related
- ○ Parent
- ○ Child
- ○ Identical Twin
- ○ Full Sibling (Not Identical Twin)
- ○ Half Sibling
- ○ Other Relative, specify: _____

Living, Biologically Unrelated
- ○ Spouse
- ○ Other, specify: _____

Ethnicity ○ Hispanic/Latino ○ Non-Hispanic/Non-Latino

Race
- ○ White
- ○ Black or African American
- ○ American Indian or Alaska Native
- ○ Asian
- ○ Native Hawaiian or other Pacific Islander
- ○ Mid-East or Arabian
- ○ Indian Sub-Continent

Citizenship (Select one)
- ○ U.S. Citizen
- ○ Resident Alien
- ○ Non-Resident Alien, specify country
  Home country: _____

Highest Education Level (Select one)
- ○ None
- ○ Grade School (0-8)
- ○ High School (9-12)
- ○ Attended College/Technical School
- ○ Associate/Bachelor Degree
- ○ Post-College Graduate Degree
- ○ Unknown

Source of Payment

(Check Yes, No or Unknown for each secondary source of payment)

Primary (Largest %, Select one)	Secondary		
○ Medicare	○ Y	○ N	○ U
○ Medicaid	○ Y	○ N	○ U
○ US/State Government Agency	○ Y	○ N	○ U
○ Private Insurance	○ Y	○ N	○ U
○ HMO/PPO	○ Y	○ N	○ U
○ Self	○ Y	○ N	○ U
○ Donation	○ Y	○ N	○ U
○ Free Care	○ Y	○ N	○ U
○ Dept. of Veterans Affairs			
○ Pending			
○ Foreign Govt. Specify: _____			

Clinical Information

Height _____ ft. _____ in. OR _____ cm

Weight _____ lbs. OR _____ kg

Serology

HIV	Screening	P	N	U	ND	I	C
	Confirmation	P	N	U	ND	I	C
CMV	IgG	P	N	U	ND	I	C
	IgM	P	N	U	ND	I	C
	DNA	P	N	U	ND	I	C
Hepatitis B	Core Antibody	P	N	U	ND	I	C
	Surface Antigen	P	N	U	ND	I	C
	HBV DNA	P	N	U	ND	I	C
Hepatitis C	Antibody Screen	P	N	U	ND	I	C
	RIBA Test	P	N	U	ND	I	C
	HCV RNA	P	N	U	ND	I	C
Epstein Barr Virus	IgG	P	N	U	ND	I	C
	IgM	P	N	U	ND	I	C
	DNA	P	N	U	ND	I	C

Creatinine: (Kidney donors)
Preoperative: _____ mg/dl
At Discharge: _____ mg/dl

Kidney Procedure Type:
- ○ Transabdominal
- ○ Laparoscopic
- ○ Flank

Blood Pressure (mmHg)
Systolic Preoperative: _____ Systolic at Discharge: _____
Diastolic Preoperative: _____ Diastolic at Discharge: _____

Length of hospital stay: _____ days

Bleeding requiring transfusion:
○ 0 ○ 1-5 ○ 6-10 ○ >10 ○ Unk

Infections during hospitalization: ○ Y ○ N

Pulmonary Embolism during hospitalization: ○ Y ○ N

Return to OR after recovery of donor organ: ○ Y ○ N

Date of Death: _____
Cause of Death: ○ Donation Related ○ Other Cause

Organ Recovery

Organ Recovery Date: _____

Recovered outside the U.S: ○ Y ○ N
Specify Country: _____

Donor Recovery Facility _____

Donor Workup Facility _____

Organ(s) Recovered _____ Recipient Name: Last _____ First _____

Recipient SSN _____

UNOS/PHS/HCFA 3/22/01

Person completing form: _____ Date completed: _____

Recipient Histocompatibility Form

(Please print or type all information) FORM APPROVED: O.M.B. NO. 0915-0157 Expiration Date: 12/31/2002

Provider Information

Lab Provider Number | Center Code | Lab Center Name | Tx Provider Number | Center Code | Tx Center Name

Recipient Information

Name: Last First MI

Organ(s):

Transplant Date:

DOB: SSN: HIC: Gender: ○ Male ○ Female

Donor Information

Donor Type:

UNOS Donor ID Donor Name: Last First

Test Information

HLA typing done: ○ Y ○ N
If Yes, complete Section I.

PRA testing done: ○ Y ○ N
If Yes, complete Section II.

Crossmatch done: ○ Y ○ N
If Yes, complete Section III.

Donor retyped at your center: ○ Y ○ N
If Yes, complete Section IV.

Section I - Recipient HLA Typing

Date Typed:

Cell Source: (Use code)

Typing Method Class I:

○ Serology ○ Other, specify:

○ DNA

A:	Bw4:
A:	Bw6:
B:	Cw:
B:	Cw:

Typing Method Class II:

○ Serology ○ Other, specify:

○ DNA

DR:	DQ:
DR:	DQ:
DR51:	DPw:
DR52:	DPw:
DR53:	

Section II - Panel Reactive Antibody (%PRA)

Most Recent Serum Date:

Cell Type: Cell Source: Technique: PRA%:

Peak Serum Date:

Cell Type: Cell Source: Technique: PRA%:

Section III - Crossmatch

A. Most Recent

Serum Date: Cell Type: Target Source: Technique: Result:

Auto Crossmatch positive: ○ Y ○ N ○ Not done ○ U

B. Positive Crossmatch with any other sera by any other method: ○ Y ○ N

If Yes, give most recent positive Serum Date(s):

Serum Date: Cell Type: Target Source: Technique: Result:

Auto Crossmatch positive: ○ Y ○ N ○ Not done ○ U

Section IV - Donor Retyping

Date Typed:

Cell Source: (Use code)

Typing Method Class I:

○ Serology ○ Other, specify:

○ DNA

A:	Bw4:
A:	Bw6:
B:	Cw:
B:	Cw:

Typing Method Class II:

○ Serology ○ Other, specify:

○ DNA

DR:	DQ:
DR:	DQ:
DR51:	DPw:
DR52:	DPw:
DR53:	

Person completing form: Date completed:

Donor Histocompatibility Form

(Please print or type all information) FORM APPROVED: O.M.B. NO. 0915-0157 Expiration Date: 12/31/2002

Provider Information

OPO Provider Number _____ Center Code _____ OPO Center Name _____

Lab Provider Number _____ Center Code _____ Lab Name _____

Donor Information

UNOS Donor ID _____ Donor Name: Last _____ First _____ Donor Type: _____

Donor Center Histocompatibility Typing

Was HLA typing performed on this donor?

○ Y ○ N ○ U

Date Typed: _____

If donor HLA typed, complete the remainder of this section.

If donor was not HLA typed or typing status is Unknown, sign and return the form.

Target Source: (Select one)

- ○ Peripheral Blood Lymphocytes
- ○ Lymph Nodes
- ○ Spleen
- ○ Solid Matrix
- ○ Multiple
- ○ Thymocytes
- ○ Cell lines/Clonal Cells

Typing Method Class I:

○ Serology ○ Other, specify: _____

○ DNA

A:	Bw4:
A:	Bw6:
B:	Cw:
B:	Cw:

Typing Method Class II:

○ Serology ○ Other, specify: _____

○ DNA

DR:	DQ:
DR:	DQ:
DR51:	DPw:
DR52:	DPw:
DR53:	

Recipient of a Living Donor Information

Living Recipient Name: Last _____ First _____ SSN: _____ Organ: _____

Tx Provider Number: _____ Center Code: _____ Tx Center Name: _____

Haplotype Match Information: (Select one)

○ 0 ○ 0.5 ○ 1 ○ 1.5 ○ 2 ○ Unk ○ N/A Donor Not Typed

Person completing form: _____ Date completed: _____

Kidney Transplant Recipient Follow-Up Form

(Please print or type all information) FORM APPROVED: O.M.B. NO. 0915-0157 Expiration Date: 12/31/2002

Provider Information

Provider Number | Center Code | Transplant Center Name

Follow-Up Provider Number | Center Code | Follow-Up Center Name

Physician Name | Physician UPIN

Follow-Up care provided by:
- ○ Transplant Center
- ○ Non-Transplant Center Specialty Physician
- ○ Primary Care Physician (HMO/PPO)
- ○ Other, specify: _____

City | State | Zip

Recipient Information

Transplant Date: _____

Name: _____ (Last / First / MI) Discharge Date: _____

DOB: _____ SSN: _____ HIC: _____ Gender: ○ Male ○ Female

Donor Information

Donor Type: _____

UNOS Donor ID | Donor Name: Last | First

Patient Status at Time of Follow-Up (Select one)

Date: _____ Patient Report, Death or Retransplant

- ○ Living
- ○ Dead Cause of Death: _____ (Use code)
  Specify: _____
- ○ Lost to Follow-Up
- ○ Retransplanted since last Follow-Up

Patient transferred to new provider: ○ Y ○ N

If Yes, transferred to UNOS member ○ Y ○ N

Transfer Date: _____

New Provider Number | New Provider Name

Hospitalizations during follow-up period: ○ Y ○ N ○ U

Number of transplant related hospitalizations: _____

Was patient in ICU: ○ Y ○ N ○ U

Noncompliance

Patient noncompliant during follow-up period: ○ Y ○ N ○ U

If Yes, indicate areas of noncompliance
- ☐ Immunosuppression medication
- ☐ Patient unable to afford immunosuppression medications
- ☐ Other medication
  Other medication, specify: _____
- ☐ Other therapeutic regimen
  Other therapeutic regimen, specify: _____

Functional Status at Follow-Up (Select one) (How does the patient perform activities of daily living?)
- ○ No activity limitations. (NYHA Class I or Class II)
- ○ Performs activities of daily living with some assistance. (NYHA Class III)
- ○ Performs activities of daily living with total assistance. (NYHA Class IV)
- ○ N/A Patient hospitalized
- ○ Unknown

Employment Status (Select one) (Working = Employed, Home, School)
- ○ Working Full Time
- ○ Working Part Time By Choice
- ○ Working Part Time Due to Disease
- ○ Working Part Time, Reason Unknown
- ○ Not Working By Choice
- ○ Not Working Due to Disease
- ○ Not Working, Unable to Find Employment
- ○ Not Working, Reason Unknown
- ○ Retired
- ○ Employment Status Unknown
- ○ Patient Less Than Five Years Old

Clinical Information

Height _____ **ft.** _____ **in.** **OR** _____ **cm**

Weight _____ **lbs.** **OR** _____ **kg**

Graft Status ○ Functioning ○ Failed

Dialysis since last follow-up: ○ Y ○ N ○ U

Resumed maintenance dialysis ○ Y ○ N ○ U

If Yes, date resumed: _____

Dialysis center provider #: _____

Dialysis center name: _____

If functioning, most recent Serum Creatinine: _____ mg/dl

If failed, failure date: _____

Cause of graft failure (Check Yes, No or Unknown for each contributory cause of graft failure)

Primary (Check one)	Contributory
○ Acute rejection	○ Y ○ N ○ U
○ Chronic rejection	○ Y ○ N ○ U
○ Primary failure	
○ Graft thrombosis	○ Y ○ N ○ U
○ Infection	○ Y ○ N ○ U
○ Urological complications	○ Y ○ N ○ U
○ Recurrent disease	○ Y ○ N ○ U
○ Other: _____	Other: _____

Kidney Transplant Recipient Follow-Up Form

FORM APPROVED: O.M.B. NO. 0915-0157 Expiration Date: 12/31/2002

Name: _____

Patient treated for rejection: ○ Y ○ N ○ U

Number of rejection events: _____

Serology

HIV	Screening	P	N	U	ND	I	C
	Confirmation	P	N	U	ND	I	C
CMV	IgG	P	N	U	ND	I	C
	IgM	P	N	U	ND	I	C
	DNA	P	N	U	ND	I	C
Hepatitis B	Core Antibody	P	N	U	ND	I	C
	Surface Antigen	P	N	U	ND	I	C
	HBV DNA	P	N	U	ND	I	C
Hepatitis C	Antibody Screen	P	N	U	ND	I	C
	RIBA Test	P	N	U	ND	I	C
	HCV RNA	P	N	U	ND	I	C
Epstein Barr Virus	IgG	P	N	U	ND	I	C
	IgM	P	N	U	ND	I	C
	DNA	P	N	U	ND	I	C

Post transplant malignancies* ○ Y ○ N ○ U

Please report each type of Malignancy only once in the follow-up process.

Donor related	○ Y	○ N	○ U
Recurrence of pre-transplant tumor	○ Y	○ N	○ U
Post Tx De Novo solid tumor	○ Y	○ N	○ U
Post Tx Lymphoproliferative Disease and Lymphoma	○ Y	○ N	○ U

* **If Yes, complete Post Transplant Malignancy form.**

Treatment

Immunosuppressive Information

Were any medications given during the follow-up period for maintenance or anti-rejection:	○ Y	○ N
If no maintenance medications are currently given, did the physician discontinue all immunosuppressive medications:	○ Y	○ N
Did the patient participate in any clinical research protocol for immunosuppressive medications:	○ Y	○ N

If Yes, specify: _____

Other Therapy

Photopheresis	○ Y	○ N
Plasmapheresis	○ Y	○ N
Total Lymphoid Irradiation (TLI)	○ Y	○ N

Biologicals/Vaccines

Cytogam (CMV)	○ Y	○ N
Gamimune N 10%	○ Y	○ N
Gammagard SD	○ Y	○ N
Acyclovir (Zovirax)	○ Y	○ N
Ganciclovir (Cytovene)	○ Y	○ N
HBIG (Hepatitis B Immune Globulin)	○ Y	○ N
Flu Vaccine (Influenza virus)	○ Y	○ N

Other: _____

Other: _____

Person completing form: _____ Date completed: _____