CHAPTER 6: RENAL TRANSPLANTATION IN MALAYSIA

Influence of Non Immunological Factors on Long-term Survival

Summary

- There were a total of 1400 renal transplantation reported to National Renal Registry between 1993-2002
- The risk of graft failure in all transplants decreased by 25%, and the risk of patient death fell by 39% for patients transplanted in 1998 to 2002 compared to those transplanted in 1993 to 1997.
- A number of recipient and transplant characteristics were independently associated with graft failure. Recipients aged 55 years or older had a 63% higher risk of graft failure; diabetics – a 44% higher risk; polycystic kidney disease – a 2.4 fold increase in risk, cadaveric renal transplants – 2.3-fold and anti-HCV positivity a 2.1-fold increase in risk of graft failure.
- Recipient characteristics associated with poorer patient survival were recipients aged 40 to 54 years - relative risk of 2.03; 55 years or older -relative risk 3.90; received cadaver donor graft - relative risk 3.94; and with HBsAg seropositivity - relative risk 1.88.
- Very preliminary analysis suggests that there might be a slight graft survival advantage associated with the use of tacrolimus and mycophenolate mofetil.

Introduction

Organ transplantation is an established form of treatment for various end stage organ failures. The success of organ transplantation over the last 2 decades has been widely attributed to the introduction of cyclosporine A (CsA). Since the introduction of CsA into clinical practice by Calne and Starzl in the late 1970's and early 1980's [1-4], many transplant centres around the world have reported at least 80-85% one-year renal allograft survival [5]. These impressive results with CsA were also extended into the field of other organ transplantation [4,6,7]. However, despite the short-term success of renal allograft with CsA, the UCLA multicentre data demonstrated that the half-life of primary cadaver renal allograft was 7.7 years in pre-CsA as well as post-CsA era [8]. Eurotransplant data also revealed somewhat similar observations (half-life of 9.7 vs 11.6 years for pre-CsA and post-CsA era respectively) [9]. Thus, while CsA has clearly improved the survival of renal allograft in the short-term, the long-term outcome is less certain. Chronic allograft failure in kidney transplantation is always conveniently attributed to allograft rejection. However, there are increasing data to suggest that the non-immunologic factors may play a significant contribution to chronic renal allograft dysfunction.

The first successful renal transplantation was carried out in Hospital Kuala Lumpur (HKL) on the 15th of December 1975. The transplant programme in Malaysia was almost exclusively living related programme until 1987 when many patients sought commercial living unrelated transplantation in India. It was only in 1996 when such activities were proscribed that the number of commercial living unrelated transplants dropped. However, this was taken over by commercial cadaver transplant activity in China. (Table 6.1)

In the early years, the immunosuppressive protocol used was azathioprine and corticosteroids until 1992 when cyclosporine A (CsA) based triple therapy was introduced for all new transplant recipients. Despite the improvement in the short-term results of renal transplantation during the past decade, the rate of attrition of kidney grafts after the first year has remained constant. According to large registry data, the half-life of kidney grafts has not changed very much.

When analyzing our data, the overall unadjusted patient and graft survival rates appears to have improved for those transplanted in 1998-2002 compared to those done in 1993-1997 (Figure 6.2 and 6.3). The 5-year patient survival rates for the cohorts of 1998-2002 and 1993-1997 were 92% and 88%, respectively, while rates for 5-year graft survival were 82% and 76%, respectively (Table 6.2 and 6.3), despite the increasing proportions of older and diabetic transplant recipients. (Table 6.4)

Table 6.5 shows that rejection as the cause of graft failure in our kidney transplantation patients has remained stable particularly since CsA based triple therapy was introduced in 1992.

As we have made no major policy changes in our kidney transplantation protocol over the last decade, the evident lengthening of graft half-life prompted us to evaluate potential patient and transplant characteristics (non immunological factors) as predictors of long-term graft survival.

Table 6.1 Place of Renal Transplantation 1993-2002

Year	1993		1994		1995		1996		1997	
	No	%	No	%	No	%	No	%	No	%
HKL	36	26	33	16	36	35	33	22	29	23
UH	3	2	5	2	10	10	6	4	6	5
Other local	0	0	0	0	0	0	0	0	0	0
India	86	61	143	70	21	20	5	3	7	6
China	13	9	21	10	35	34	104	70	80	65
Other overseas	2	1	1	0	1	1	1	1	2	2
TOTAL	140	100	203	100	103	100	149	100	124	100

Year	1998		1999		2000		2001		2002	
	No	%	No	%	No	%	No	%	No	%
HKL	33	33	36	30	28	20	33	21	29	18
UH	7	7	16	13	19	13	22	14	14	9
Other local	0	0	1	1	1	1	2	1	0	0
India	6	6	5	4	9	6	8	5	11	7
China	50	51	60	50	80	56	78	50	97	60
Other overseas	3	3	2	2	0	0	6	4	2	1
TOTAL	99	100	120	100	143	100	156	100	163	100

Table 6.2 Unadjusted Transplant Patient Survival related to Year of transplant 1993-2002

Year	1993-1997		1998-2002	
Interval (months)	% survival	SE	% survival	SE
6	96	1	96	1
12	95	1	95	1
24	94	1	93	1
36	92	1	92	1
48	90	1	92	1
60	88	1	92	1

SE = standard error

Table 6.3 Unadjusted Graft Survival related to Year of transplant 1993-2002

Year	1993-1997		1998-2002	
Interval (months)	% survival	SE	% survival	SE
6	93	1	93	1
12	92	1	91	1
24	89	1	88	1
36	84	1	86	1
48	80	2	84	2
60	76	2	82	2

SE = standard error

Figure 6.2 Unadjusted Transplant Patient Survival related to Year of transplant 1993-2002

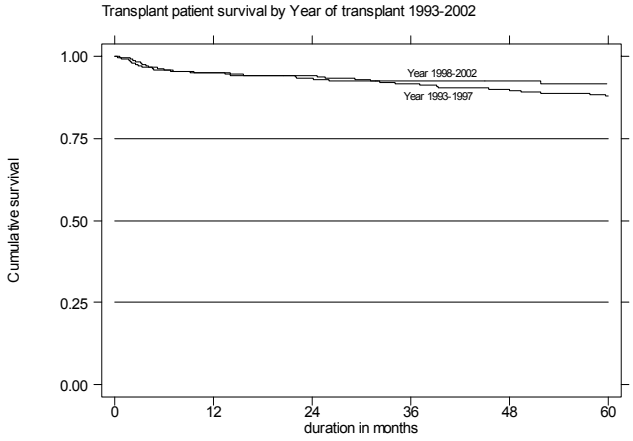


Figure 6.3 Unadjusted Graft Survival related to Year of transplant 1993-2002

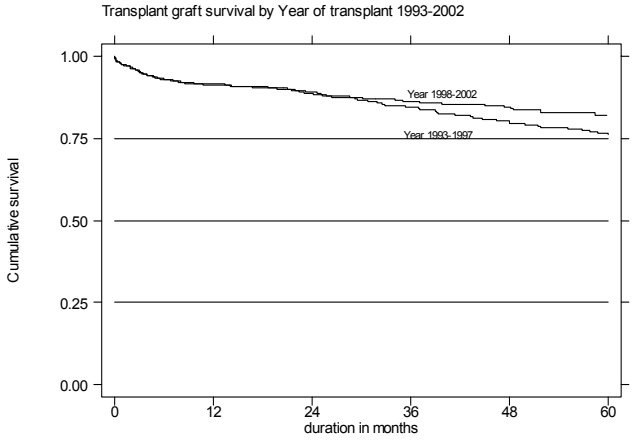


Table 6.4 Renal Transplant Recipients' Characteristics 1993-2002

Year	1993	1994	1995	1996	1997
New Transplant patients	140	203	103	149	124
Mean age ±sd	38±13	38±12	35±12	38±11	35±12
% Male	60	67	57	56	65
% Diabetic	10	10	12	9	11
% HBsAg	8	8	6	11	5
% Anti-HCV+	16	8	12	15	6

Year	1998	1999	2000	2001	2002
New Transplant patients	99	120	143	156	163
Mean age ±sd	37±11	37±13	39±13	40±13	40±13
% Male	60	62	64	62	56
% Diabetic	9	11	13	16	14
% HBsAg	5	4	4	4	6
% Anti-HCV+	15	8	6	13	7

Table 6.5 Causes of Graft Failure 1993-2002

Year	1993		1994		1995		1996		1997	
	No	%	No	%	No	%	No	%	No	%
Rejection	1	25	1	14	5	45	4	40	11	58
CsA or drug toxicity	1	25	0	0	0	0	0	0	0	0
Ureteric obstruction	0	0	1	14	1	9	0	0	0	0
Vascular causes; RAS/ thrombosis	1	25	1	14	1	9	1	10	4	21
Renal disease; recurrent/de novo	0	0	0	0	0	0	2	20	0	0
Technical complication	0	0	0	0	0	0	0	0	0	0
Others	0	0	0	0	1	9	0	0	1	5
Unknown	1	25	4	57	3	27	3	30	3	16
TOTAL	4	100	7	100	11	100	10	100	19	100

Year	1998		1999		2000		2001		2002	
	No	%	No	%	No	%	No	%	No	%
Rejection	18	60	12	60	13	57	7	41	12	48
CsA or drug toxicity	0	0	0	0	0	0	0	0	1	4
Ureteric obstruction	0	0	0	0	0	0	0	0	0	0
Vascular causes; RAS or thrombosis	1	3	0	0	3	13	1	6	0	0
Renal disease; recurrent or de novo	1	3	0	0	0	0	1	6	1	4
Technical complication	0	0	0	0	3	13	1	6	0	0
Others	2	7	0	0	2	9	1	6	1	4
Unknown	8	27	8	40	2	9	6	35	10	40
TOTAL	30	100	20	100	23	100	17	100	25	100

Methods

The data of all renal transplantation done in the years 1993 to 2002 that were reported to the National Renal Registry (NRR) were analysed and reviewed without exclusion. Until 31st December 2002 there were a total of 1400 of renal transplantations reported to NRR (Table 6.6). The data was stratified to reflect differences in 1) recipient demography: race, gender, age, body mass index (BMI); 2) medical factors: primary disease, co-morbid conditions (diabetes mellitus, cardiovascular diseases, hepatitis B and C status), duration of dialysis; 3) social factors: smoker or non smoker; and 4) transplant factors: type of transplant and the immunosuppressants used. Using Cox proportional hazard modeling, we studied the association of these variables with graft and patient survival. Covariates of interest were: year of transplant, age, gender, ethnic, primary diagnosis, smoking status, type of transplant, BMI, diabetes, whether they were ever Hepatitis B surface Antigen (HBsAg) or anti- Hepatitis C (HCV) antibody positive, HLA matching, cardiovascular disease and prior dialysis time.

Results and Discussion

The overall transplant patient survival rate from 1993 to 2002 was 95%, 92% and 89% at one year, three years and five years respectively, while the overall graft survival rate was 91%, 85% and 78% respectively (Table 6.7). These survival rates are comparable to the USRDS data [10].

I. Factors Affecting Outcome

Demography

Age

Patient survival rates decreased with increasing age. Recipients aged 55 years or older had the lowest patient survival rate at 5 years (74%), followed by recipients aged 40-54 (86%), aged 20-39 (93%), while recipients under age 20 had the highest patient survival rate (97%) (Table 6.8). The lowest 5-year graft survival rate (67%) was noted among older recipients over 55 years of age. There was no significant difference in 5-year graft survival rates among recipients in the other age groups (Table 6.9). This observation is consistent with other published data where older recipients despite lower rejection rate had poorer graft and patient survival rates [11-13]. This is attributed to a higher incidence of atherosclerotic diseases in the older age group. A higher proportion of older patients died with functioning graft.

Ethnicity

The recipients' ethnicity seemed to influence both 5-year graft and patient survival rates. Chinese recipients had the highest graft and patient survival rates at 80% and 90%, respectively. (Tables and Figures 6.10 & 6.11). However this observed advantage disappeared with adjustments for other covariates (age, gender, smoking status, BMI, type of transplant, diabetes, hepatitis status, HLA match, cardiovascular disease and prior dialysis time).

Table 6.6 Renal Transplant performed between 1993-2002

Year	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
New transplant patients	140	203	103	149	124	99	120	143	156	163
Died	3	12	5	14	20	11	14	20	23	19
Returned to dialysis	4	7	11	10	19	30	20	23	17	25
Lost to F/U	0	1	0	1	0	1	2	1	2	1
Functioning graft at 31st December	133	316	403	527	612	669	753	852	966	1084

Table 6.7 Unadjusted Transplant Patient and Graft Survival 1993-2002

	Patient Survival		Graft Survival	
Interval (months)	% survival	SE	% survival	SE
6	96	1	93	1
12	95	1	91	1
24	94	1	89	1
36	92	1	85	1
48	91	1	81	1
60	89	1	78	1

SE=standard error

Figure 6.7 Unadjusted Transplant Patient and Graft Survival 1993-2002

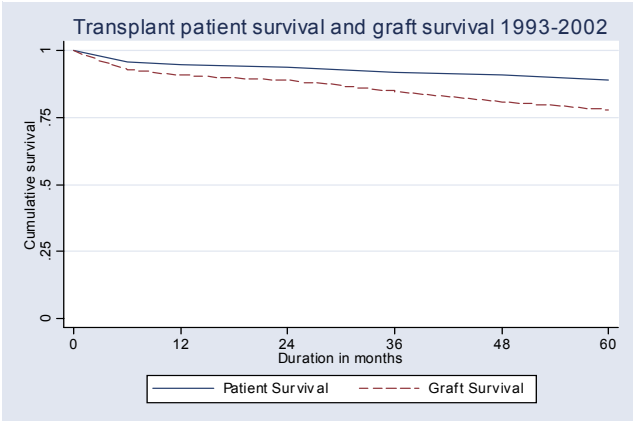


Table 6.8 Unadjusted Transplant Patient Survival related to Age 1993-2002

Age	<20		20-39		40-54		>=55	
Interval (months)	% survival	SE	% survival	SE	% survival	SE	% survival	SE
6	98	1	97	1	94	1	95	2
12	98	1	96	1	93	1	93	2
24	98	1	96	1	91	1	89	3
36	97	2	95	1	90	1	83	4
48	97	2	93	1	89	1	81	4
60	97	2	93	1	86	2	74	5

SE = standard error

Table 6.9 Unadjusted Graft Survival related to Age 1993-2002

Age	<20		20-39		40-54		>=55	
Interval (months)	% survival	SE	% survival	SE	% survival	SE	% survival	SE
6	90	3	93	1	93	1	95	2
12	89	3	91	1	92	1	93	2
24	88	3	89	1	89	1	88	3
36	83	4	86	1	85	2	81	4
48	77	5	82	2	82	2	78	4
60	77	5	79	2	78	2	67	5

SE = standard error

Figure 6.8 Unadjusted Transplant Patient Survival related to Age 1993-2002

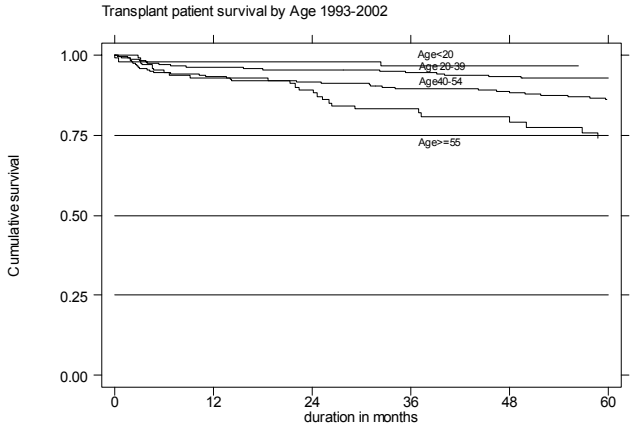


Figure 6.9 Unadjusted Graft Survival related to Age 1993-2002

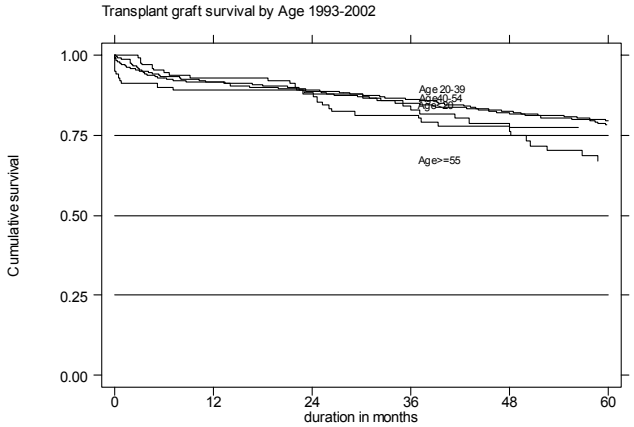


Table 6.10 Unadjusted Patient Survival related to Ethnicity 1993-2002

Ethnic	Malay		Chinese		Indian		Others	
Interval (months)	% Survival	SE	% Survival	SE	% Survival	SE	% Survival	SE
6	94	2	97	1	93	2	95	2
12	92	2	96	1	93	2	92	3
24	90	2	95	1	92	3	90	3
36	88	2	93	1	87	3	89	3
48	86	3	92	1	86	4	88	4
60	85	3	90	1	86	4	88	4

SE=standard error

Table 6.11 Unadjusted Graft Survival related to Ethnicity 1993-2002

Ethnic	Malay		Chinese		Indian		Others	
Interval (months)	% Survival	SE	% Survival	SE	% Survival	SE	% Survival	SE
6	88	2	94	1	93	2	90	3
12	85	2	93	1	91	3	87	4
24	80	3	91	1	86	3	86	4
36	76	3	88	1	75	4	82	4
48	74	3	84	1	70	5	80	4
60	72	3	80	1	66	5	79	5

SE=standard error

Figure 6.10 Unadjusted Transplant Patient Survival related to Ethnicity 1993-2002

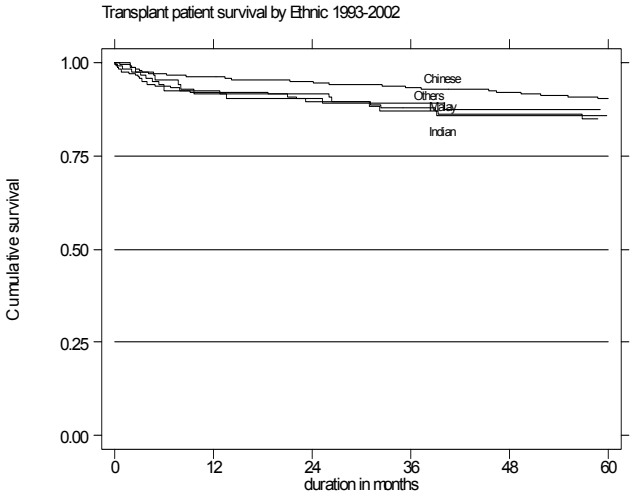
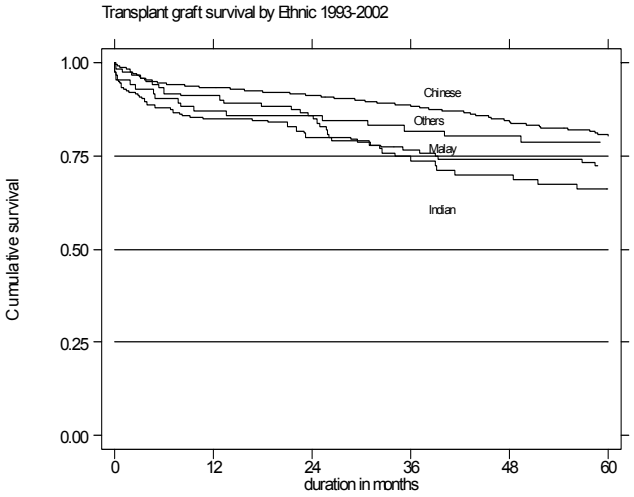


Figure 6.11 Unadjusted Graft Survival related to Ethnicity 1993-2002



Gender

Recipients' gender had no significant impact on both the graft and patient survival rates in our group of patients.

Body Mass Index

Graft survival rate improved with increasing BMI. Recipients with BMI less than 18.5 had the poorest 5 year graft survival rate (73%) compared with recipients with BMI 18.5-25 (77%) and BMI more than 25 (82%) (Table and Figure 6.12). In contrast, Paul Terasaki et al [14] and Chertow et al [16] reported that large size recipients were found to have poorer outcome. This discrepancy may be because BMI in our patients was probably more of a nutritional marker. [15].

Primary Renal Disease and Co-morbid Conditions

Diabetes mellitus

One-year patient survival was similar in diabetics and non-diabetics; however 5-year patient survival was 90% and 83% respectively for diabetics and non-diabetics. The graft survival rate between diabetics and non-diabetics were almost similar. (Tables and Figures 6.13 & 6.14). Kim et al [17] reported similar findings while Nampoory et al [18] observed lower patient and graft survival in diabetics. However, after adjustment for other risk factors, there was no significant difference in patient survival but graft survival in diabetic recipients was poorer compared to non-diabetics (Tables 6.24 & 6.24).

Hepatitis B

The data were stratified according to the presence or absence of HBsAg. HBsAg seronegative recipients had better graft and patient survival than HBsAg positive recipients. The 5-year patient survival rate for recipients positive and negative for HBsAg was 81% and 90%, respectively, while the 5 year graft survival rate was 69% and 79%, respectively (Tables and Figures 6.15 & 6.16). This observation is similar to reports from other workers.

The 5-year patient survival for transplant recipients with positive HBsAg was 78%, while that for haemodialysis patients with seropositive for HBsAg was 66%. However, this data has to be interpreted with caution as there might be selection bias where only healthy HBsAg positive patients were transplanted. Furthermore this direct comparison does not take into account other potential confounding factors.

Hepatitis C

The data were stratified according to the presence or absence of anti-HCV. Anti-HCV seronegative recipients had better graft outcome than anti-HCV positive recipients. The 5- year graft survival rate for recipients positive and negative for anti-HCV were 62% and 81%, respectively (Table and Figure 6.17). However, unlike graft survival, there was no significant difference in 5-year patient survival rate for those positive or negative for anti-HCV. Reports in literature were mixed. While Batty et al [19] observed poorer patient survival among recipients with positive anti-HCV, Hassan et al [20] reported similar patient and graft survival among anti-HCV positive and negative recipients.

Table 6.12 Unadjusted Graft Survival related to BMI 1993-2002

BMI	<18.5		18.5-25		>25	
Interval (months)	% Survival	SE	% Survival	SE	% Survival	SE
6	89	2	93	1	96	1
12	89	2	91	1	95	1
24	87	3	88	1	93	2
36	82	3	84	1	89	2
48	73	4	81	1	87	2
60	73	4	77	2	82	3

SE=standard error

Figure 6.12 Unadjusted Graft Survival related to BMI 1993-2002

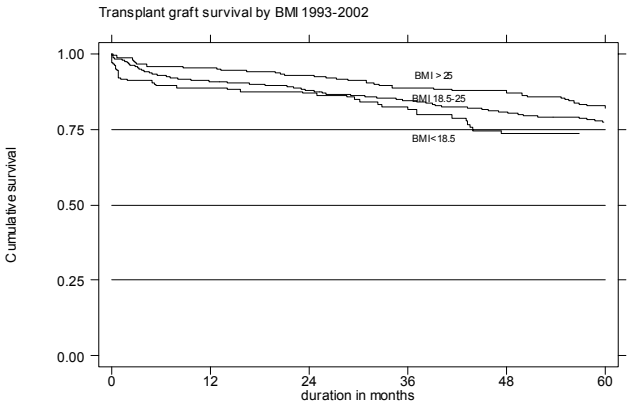


Table 6.14 Unadjusted Graft Survival related to Diabetes Mellitus 1993-2002

Diabetes Mellitus	Non-diabetic		Diabetic	
Interval (months)	% Survival	SE	% Survival	SE
6	92	1	96	1
12	91	1	93	2
24	88	1	91	2
36	85	1	87	3
48	81	1	83	3
60	78	1	76	4

SE=standard error

Table 6.13 Unadjusted Patient Survival related to Diabetes Mellitus 1993-2002

Diabetes Mellitus	Non-diabetic		Diabetic	
Interval (months)	% Survival	SE	% Survival	SE
6	96	1	96	1
12	95	1	93	2
24	94	1	92	2
36	92	1	89	3
48	91	1	88	3
60	90	1	83	4

SE=standard error

Figure 6.13 Unadjusted Patient Survival related to Diabetes Mellitus 1993-2002

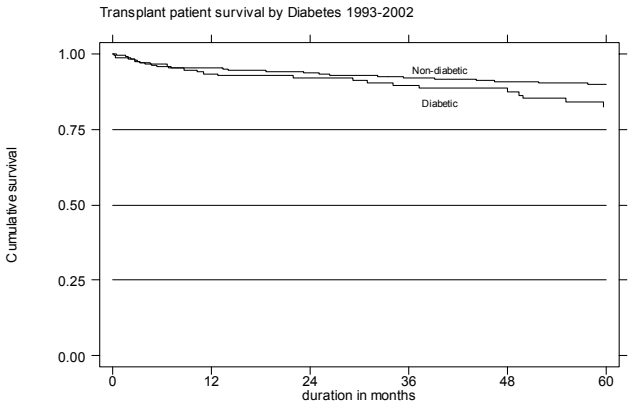


Figure 6.14 Unadjusted Graft Survival related to Diabetes Mellitus 1993-2002

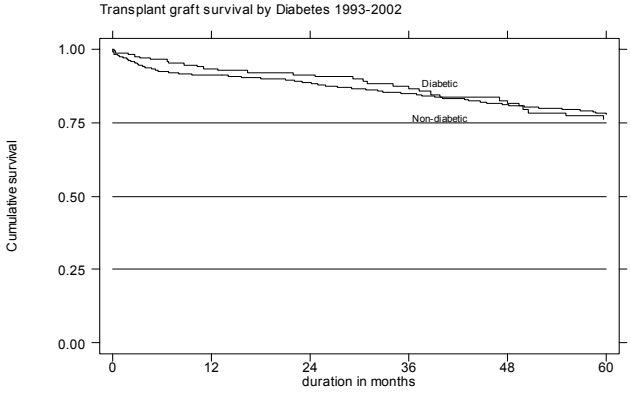


Table 6.15 Unadjusted Patient Survival related to HbsAg status 1993-2002

Ever HbsAg	Negative		Positive	
Interval (months)	% Survival	SE	% Survival	SE
6	96	1	93	2
12	95	1	90	3
24	94	1	89	3
36	92	1	85	4
48	91	1	84	4
60	90	1	81	4

SE=standard error

Figure 6.15 Unadjusted Patient Survival related to HbsAg status 1993-2002

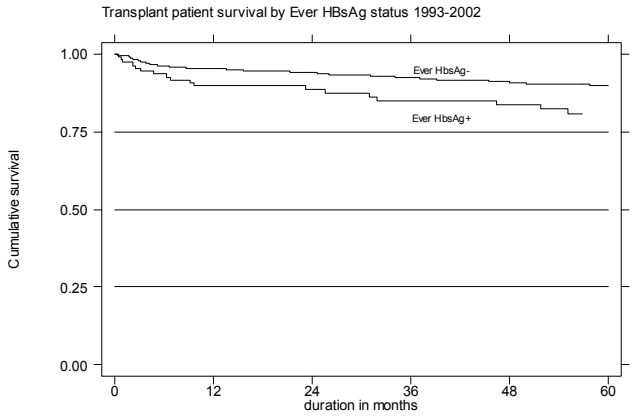


Table 6.16 Unadjusted Graft Survival related to HBsAg status 1993-2002

Ever HbsAg	Negative		Positive	
Interval (months)	% Survival	SE	% Survival	SE
6	93	1	88	3
12	92	1	84	3
24	89	1	82	4
36	86	1	76	4
48	82	1	73	4
60	79	1	69	5

SE=standard error

Figure 6.16 Unadjusted Graft Survival related to HBsAg status 1993-2002

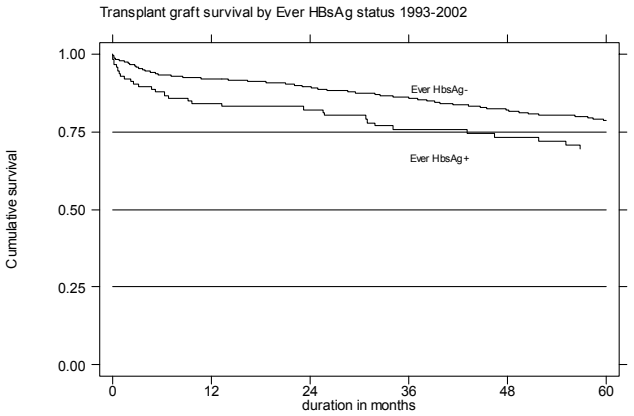
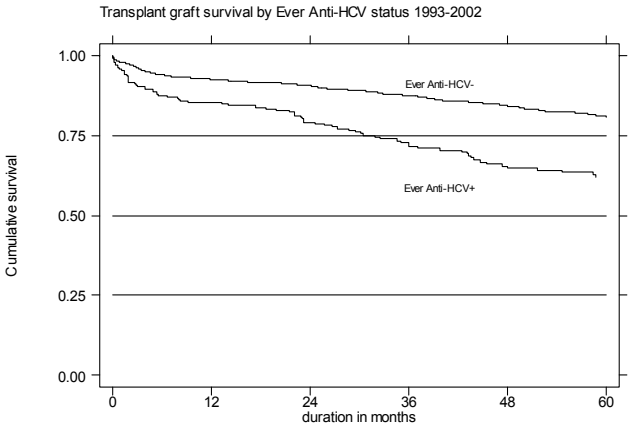


Table 6.17 Unadjusted Graft Survival related to Anti-HCV status 1993-2002

Ever Anti-HCV	Negative		Positive	
Interval (months)	% Survival	SE	% Survival	SE
6	94	1	88	2
12	93	1	85	2
24	91	1	79	3
36	87	1	72	3
48	84	1	65	3
60	81	1	62	4

SE=standard error

Figure 6.17 Unadjusted Graft Survival related to Anti-HCV status 1993-2002



Cardiovascular Disease

Cardiovascular disease (CVD) in this report is defined as anyone with any of one or more of the following disorders at initial notification to the Registry: cardiac failure, ischaemic heart disease, cerebrovascular accident, peripheral vascular disease and non accidental amputation. Patients with CVD had poorer outcome. The 5-year patient survival rates for recipients with CVD and without CVD were 77% and 90% respectively, while the 5 year graft survival rates were 65% and 79% for those with and without CVD (Tables and Figures 6.18 & 6.19). Woo et al [21] also reported similar observation. However, it would be interesting to compare the graft survival after deaths with functioning graft were censored.

Duration of Dialysis

The 3-year patient survival rates for recipients who underwent dialysis less than one year, one to three years and more than three years before transplantation were 94%, 91% and 88% respectively, while the graft survival rates were 88%, 84% and 80% for the same durations of dialysis prior to transplantation. (Tables and Figures 6.20 & 6.21). Casio et al [22] reported that increased time on dialysis before transplant was associated with decreased patient survival and they attributed this to higher prevalence of left ventricular hypertrophy and greater infection risk.. Mange and Caciarelli [23-24] had reported independently that increased duration of dialysis prior to transplant was associated with higher risk of acute rejection post transplant.

Table 6.18 Unadjusted Transplant Patient Survival related to Cardiovascular Disease 1993-2002

Anti-HCV	No		Yes	
Interval (months)	% Survival	SE	% Survival	SE
6	96	1	95	2
12	95	1	93	3
24	94	1	89	3
36	92	1	86	4
48	91	1	83	4
60	90	1	77	4

SE=standard error

Table 6.19 Unadjusted Graft Survival related to Cardiovascular Disease 1993-2002

Anti-HCV	No		Yes	
Interval (months)	% Survival	SE	% Survival	SE
6	93	1	93	3
12	92	1	91	3
24	89	1	87	3
36	85	1	79	4
48	82	1	72	5
60	79	1	65	5

SE=standard error

Figure 6.18 Unadjusted Transplant Patient Survival related to Cardiovascular Disease 1993-2002

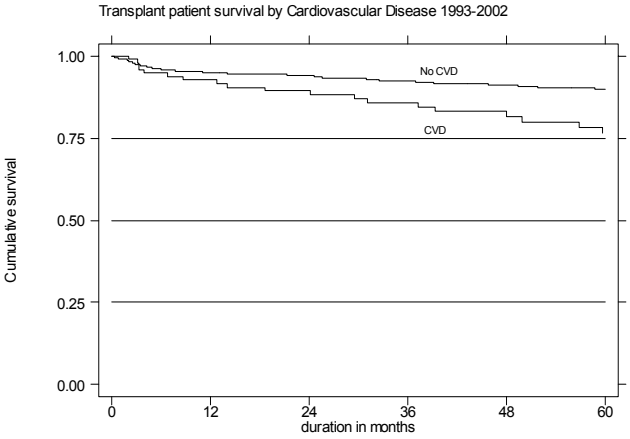


Figure 6.19 Unadjusted Graft Survival related to Cardiovascular Disease 1993-2002

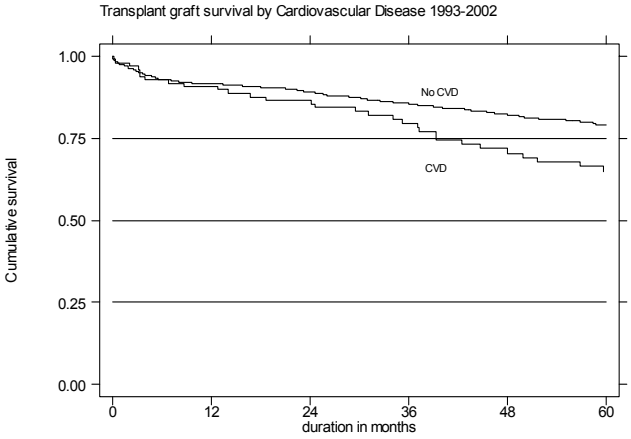


Table 6.20 Unadjusted Transplant Patient Survival related to Prior Dialysis Duration 1993-2002

Prior dialysis time	<1 years		1-<3 years		>=3 years	
Interval (months)	% Survival	SE	% Survival	SE	% Survival	SE
6	97	1	96	1	92	2
12	97	1	94	1	91	2
24	96	1	93	1	89	2
36	94	1	91	1	88	2
48	92	1	90	2	87	2
60	90	1	90	2	87	2

SE=standard error

Table 6.21 Unadjusted Graft Survival related to Prior Dialysis Duration 1993-2002

Prior dialysis time	<1 years		1-<3 years		>=3 years	
Interval (months)	% Survival	SE	% Survival	SE	% Survival	SE
6	95	1	93	1	88	2
12	94	1	91	1	86	2
24	92	1	88	2	83	2
36	88	1	84	2	80	3
48	84	1	79	2	79	3
60	80	2	76	2	77	3

SE=standard error

Figure 6.20 Unadjusted Transplant Patient Survival related to Prior Dialysis Duration 1993-2002

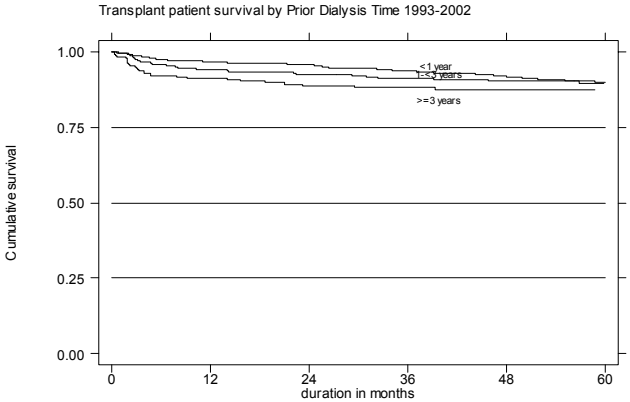
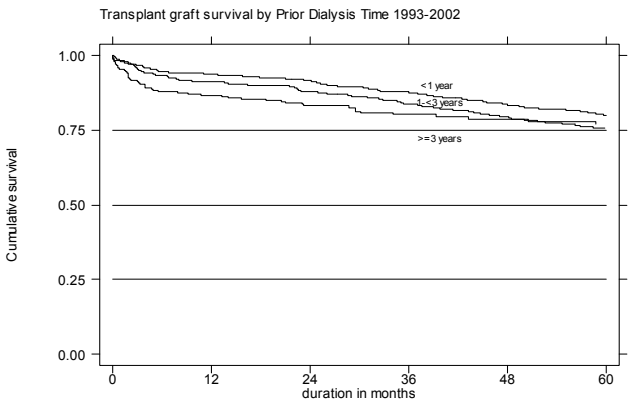


Figure 6.21 Unadjusted Graft Survival related to Prior Dialysis Duration 1993-2002



Transplant Factors

Type of Transplant

The outcome of transplantation for kidneys from four different donor sources are shown in Figures 6.22 & 6.23 and demonstrated substantial difference in patient and graft survival rates. Cadaver donor grafts had the poorest patient and graft survival rates. The 5-year graft survival for recipients of cadaver donor grafts was 72%, commercial living donor grafts was 74%, while commercial cadaver donor grafts and living donor grafts were 81%. The 5-year patient survival rates also differed in these 4 groups at 83% for cadaver transplantation, 87% for commercial living transplantation, 89% for commercial cadaver transplantation and 94% for live related transplantation.

The differences in graft survival rates among these 4 donor sources were significant even after adjustment for other risk factors such as age, gender, ethnic, year of transplant, smoking status, BMI, diabetes, hepatitis B and C, HLA match, cardiovascular disease and prior dialysis time (Table 6.25). Hence other immunological and non immunological factors such as acute rejection, panel reactive activity, cold ischaemic time, number of previous transplants, donor factors and the effect of immunosuppressive regime may contribute to these observed difference in outcome.

Table 6.22 Unadjusted Transplant Patient Survival related to Type of Transplant 1993-2002

Type of Transplant	Commercial Cadaver		Commercial Live Donor		Live Donor		Cadaver	
Interval (months)	% Survival	SE	% Survival	SE	% Survival	SE	% Survival	SE
6	97	1	96	1	98	1	88	3
12	96	1	95	1	97	1	86	3
24	94	1	94	1	97	1	84	3
36	92	1	91	2	96	1	83	3
48	91	1	90	2	95	1	83	3
60	89	1	87	2	94	1	83	3

SE=standard error

Table 6.23 Unadjusted Graft Survival related to Type of Transplant 1993-2002

Type of Transplant	Commercial Cadaver		Commercial Live Donor		Live Donor		Cadaver	
Interval (months)	% Survival	SE	% Survival	SE	% Survival	SE	% Survival	SE
6	95	1	94	1	93	1	82	3
12	94	1	93	1	92	2	79	3
24	91	1	90	2	90	2	74	4
36	89	1	84	2	86	2	72	4
48	85	2	78	3	83	2	72	4
60	81	2	74	3	81	2	72	4

SE=standard error

Figure 6.22 Unadjusted Transplant Patient Survival related to Type of Transplant 1993-2002

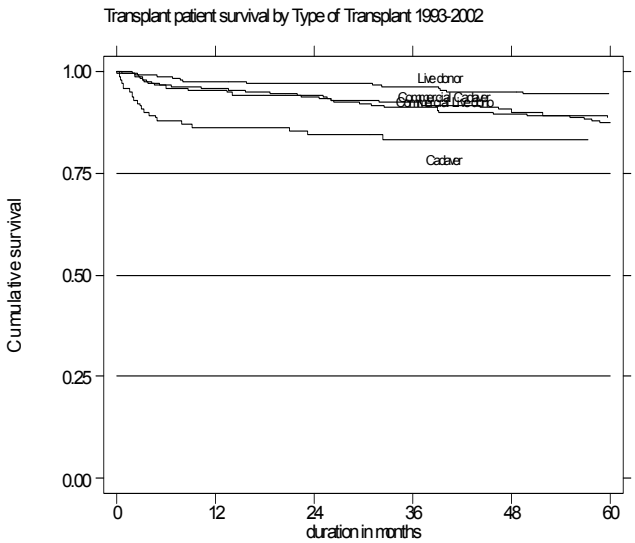


Figure 6.23 Unadjusted Graft Survival related to Type of Transplant 1993-2002

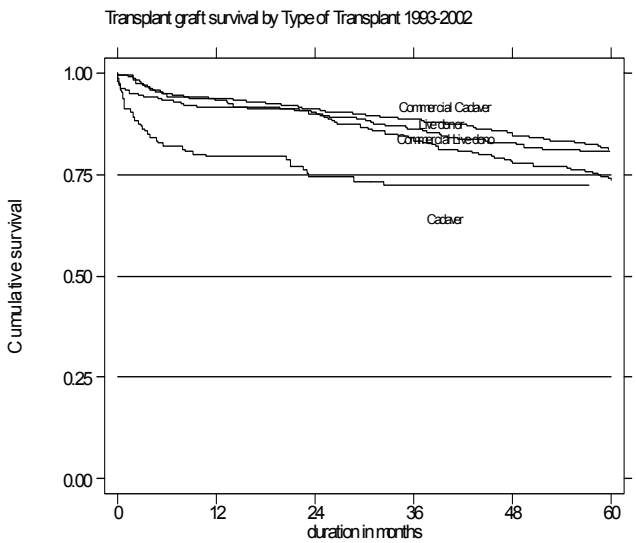


Table 6.24 Risk factors for Transplant Patient Survival 1993-2002

Factors	N	Hazard ratio	95% CI	P value
Year of transplant:				
1993-1997 (ref.*)	719	1.00		
1998-2002	681	0.61	(0.40,0.94)	0.024
Age at transplant:				
<20	100	0.44	(0.13,1.44)	0.175
20-39 (ref.*)	652	1.00		
40-54	524	2.03	(1.36,3.02)	0.001
>=55	124	3.90	(2.35,6.46)	0.000
Gender:				
Male (ref.*)	856	1.00		
Female	544	0.87	(0.62,1.22)	0.415
Primary diagnosis:				
Unknown (ref.*)	618	1.00		
Diabetes Mellitus	151	1.52	(0.95,2.43)	0.077
GN / SLE	433	0.77	(0.49,1.19)	0.238
Polycystic kidney	21	2.37	(0.94,5.60)	0.069
Obstructive nephropathy	57	1.86	(0.97,3.57)	0.061
Others	120	1.14	(0.63,2.06)	0.657
Type of Transplant:				
Commercial cadaver (ref.*)	603	1.00		
Commercial live donor	290	1.26	(0.84,1.89)	0.268
Living donor	341	1.05	(0.61,1.80)	0.872
Cadaver	145	3.94	(2.11,7.39)	0.000
HbsAg:				
Negative (ref.*)	1287	1.00		
Positive	113	1.88	(1.16,3.02)	0.009
Anti-HCV:				
Negative (ref.*)	1183	1.00		
Positive	217	0.90	(0.56,1.44)	0.664
Prior dialysis time:				
<1 years	717	1.00		
1-<3 years	417	1.41	(0.97,2.06)	0.074
>=3 years	266	1.13	(0.66,1.94)	0.646

* ref: Reference group

Figure 6.24 Adjusted Transplant Patient Survival related to Year of Transplant 1993-2002
(Adjusted for age, gender, primary diagnosis, type of transplant, HBsAg and Anti-HCV status)

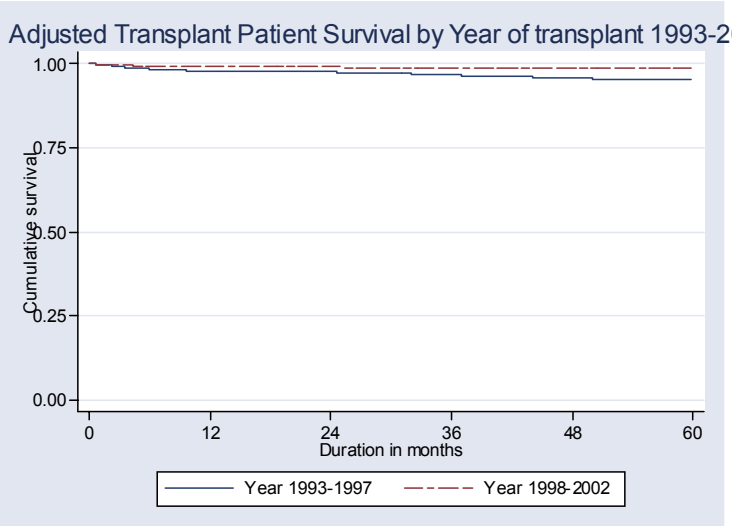
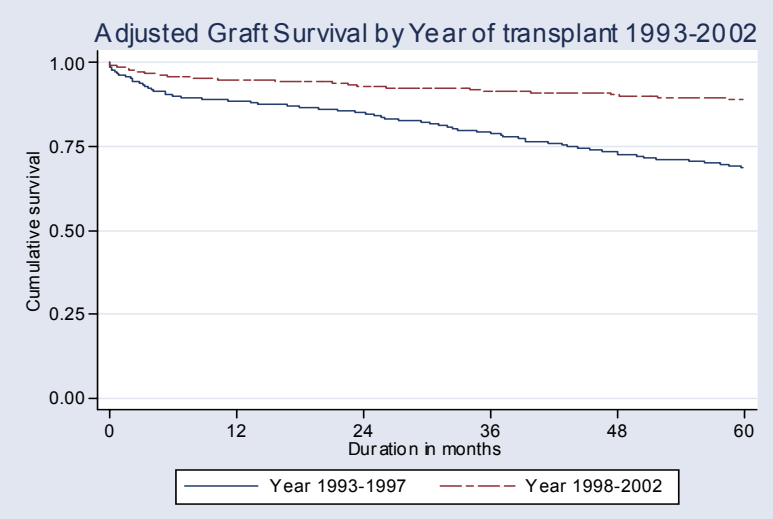


Table 6.25 Risk factors for Graft Survival 1993-2002

Factors	N	Hazard ratio	95% CI	P value
Year of transplant:				
1993-1997 (ref.*)	719	1.00		
1998-2002	681	0.75	(056,1.01)	0.060
Gender:				
Male (ref.*)	856	1.00		
Female	544	0.88	(0.70,1.10)	0.270
Age at transplant:				
<20	100	0.91	(0.57,1.46)	0.706
20-39 (ref.*)	652	1.00		
40-54	524	1.08	(0.84,1.39)	0.546
>=55	124	1.63	(1.11,2.38)	0.011
Primary diagnosis:				
Unknown (ref.*)	618	1.00		
Diabetes Mellitus	151	1.44	(1.00,2.08)	0.049
GN / SLE	433	1.02	(0.78,1.34)	0.864
Polycystic kidney	21	2.38	(1.15,4.90)	0.019
Obstructive nephropathy	57	1.33	(0.81,2.19)	0.259
Others	120	1.32	(0.88,1.98)	0.178
Type of Transplant:				
Commercial cadaver(ref.*)	603	1.00		
Commercial live donor	290	1.43	(1.08,1.90)	0.014
Living donor	341	1.15	(0.84,1.60)	0.384
Cadaver	145	2.26	(1.45,3.50)	0.000
HbsAg:				
Negative (ref.*)	1287	1.00		
Positive	113	1.60	(1.15,2.22)	0.005
Anti-HCV:				
Negative (ref.*)	1183	1.00		
Positive	217	2.10	(1.62,2.72)	0.000
BMI:				
<18.5 (ref.*)	178	1.00		
18.5-25	949	0.66	(0.47,0.92)	0.013
>25	273	0.49	(0.33,0.74)	0.000
Prior Dialysis Time				
<1 year	717	1.00		
1-<3 years	417	1.24	(0.96,1.60)	0.093
≥3 years	266	0.87	(0.60,1.25)	0.453

* ref: Reference group

Figure 6.25 Adjusted Graft Survival related to Year of Transplant 1993-2002
(Adjusted for age, gender, primary diagnosis, type of transplant, BMI, HBsAg and Anti-HCV status)



Risk Factors for Patient and Graft Survival 1993-2002

Results obtained from Cox proportional hazards model adjusted for multiple covariates are shown in Tables 6.24 and 6.25. Hazard ratios should be compared to the reference risk of 1.00, arbitrarily assigned to one group for each characteristic.

The risk of graft failure in all transplants had decreased by 25% while the risk of patient death decreased by 39% for those transplanted in 1998 to 2002 compared to those transplanted in 1993 to 1997 (Tables 6.24 & 6.24 and Figures 6.24 and 6.25). The risk of graft failure was also higher for recipients aged 55 years or older, diabetics, recipients with HBsAg seropositivity, and anti-HCV seropositivity, those with polycystic kidney disease as primary diagnosis, cadaver transplantation, and commercial live donor graft , while the risk of graft failure was reduced by 34% for recipients with normal BMI (Table 6.25).

The risk of patient mortality was increased for recipients aged 40 years and older, cadaver renal transplant recipients, and those with HBsAg seropositivity (Table 6.24).

It is interesting to note that in this cohort of patients, the risk of graft failure was increased by 44% for recipients with diabetes compared with non-diabetics. However, there was no significant difference in patient mortality. The 3- and 5-year unadjusted patient survival for diabetics compared to non diabetics were 89% & 83% versus 92% & 90%, respectively. The 3- and 5-year unadjusted HD patient survival rates for diabetics were 64% and 46%, respectively (Table 6.26 and 6.27). Hence, ESRD patients with diabetes mellitus who underwent renal transplantation appear to have better outcome compared to those continuing on haemodialysis. However, this data has to be interpreted with caution as there might be selection bias where only healthy diabetic patients were transplanted. Furthermore this direct comparison did not take into account other potential confounding factors. Nevertheless, it may be concluded that diabetic transplant recipients were at least not worse off compared to their counterparts on haemodialysis.

Effect of Newer Immunosuppressive Agents on Graft Survival

Results from the previous section showed that the risk of graft failure had decreased by 25% for the 1998-2002 cohort compared to the 1993-1997 cohort. One possible explanation for this result could be the increasing use of newer immunosuppression agents such as mycophenolate mofetil (MMF) and tacrolimus (FK506) in recent years. The table below shows the exposure of 1400 recipients between 1993 and 2002 to the various immunosuppressive agents:

Year of transplant	1993-1997	1998-2002
Ever on CsA, No. (%)	683 (95%)	53 (79%)
Ever on AZA, No. (%)	626 (87%)	254 (37%)
Ever on MMF, No. (%)	18 (3%)	332 (49%)
Ever on tacrolimus, No. (%)	2 (0%)	109 (16%)
TOTAL	719 (100%)	681 (100%)

We therefore determined the effect of exposure to the newer immunosuppressive agents on graft survival. We compared the effect of Azathioprine versus MMF, and that of CsA versus FK506.

Azathioprine versus MMF

Figure 6.28 shows the slight advantage in graft survival in patients on MMF versus azathioprine on crude analysis which became more obvious after adjustment for known confounding factors (Figure 6.29) On crude analysis there appeared to be slight advantage associated with the use of MMF as shown in Figure 6.28. However, there were more patients who were older and had diabetes among more recent transplants. Hence the adjusted graft survival as shown in Figure 6.29 which showed better graft survival with the use of MMF. This result is consistent with reports from large trials such as the Tri-continental trial [27].

Table 6.26 Unadjusted Transplant Patient Survival related to Diabetes Mellitus 1993-2002

Diabetes Mellitus	Non-diabetic		Diabetic	
Interval (months)	% Survival	SE	% Survival	SE
6	96	1	96	1
12	95	1	93	2
24	94	1	92	2
36	92	1	89	3
48	91	1	88	3
60	90	1	83	4

SE=standard error

Table 6.27 Unadjusted HD Patient Survival related to Diabetes Mellitus 1993-2002

Diabetes Mellitus	Non-diabetic		Diabetic	
Interval (months)	% Survival	SE	% Survival	SE
6	95	0.2	93	0.3
12	92	0.3	87	1
24	86	0.4	74	1
36	81	1	64	1
48	76	1	54	1
60	72	1	46	1

SE=standard error

Cyclosporine versus Tacrolimus

This analysis was confined only to subjects who were exclusively on either CsA or tacrolimus. Patients exposed to both CsA and tacrolimus were excluded from analysis as they might possibly be given tacrolimus as rescue therapy for steroid resistant rejection. There appears to be a slight advantage associated with the use of tacrolimus as shown in Figure 6.30 which again is more obvious once adjustments were made for age and diabetes mellitus status as shown in Figure 6.31.

Vincenti et al [28] in their US Multicenter Trial comparing tacrolimus and cyclosporine based immunosuppressive therapy reported that tacrolimus based therapy resulted in significant reduction in graft failure risk. It is also interesting to note that in our analysis, the better graft survival with the use of tacrolimus based therapy appears to be enhanced after adjusting for risk factors such as age and diabetes. This may be explained by preferential use of tacrolimus based therapy in higher risk patients as per Ministry of Health protocol.

Although the preliminary results suggest that the use of tacrolimus and MMF might be the explanation for the observed superior graft and patient survival rates for the 1998-2002 cohort compared with the 1993-1997 cohort, this analysis is limited by the small number of patients, missing data on details of drug utilization and treatment indication. Hence, a properly conducted study would be necessary to further clarify this observation.

Figure 6.28 Transplant graft survival: AZA vs MMF 1993-2002

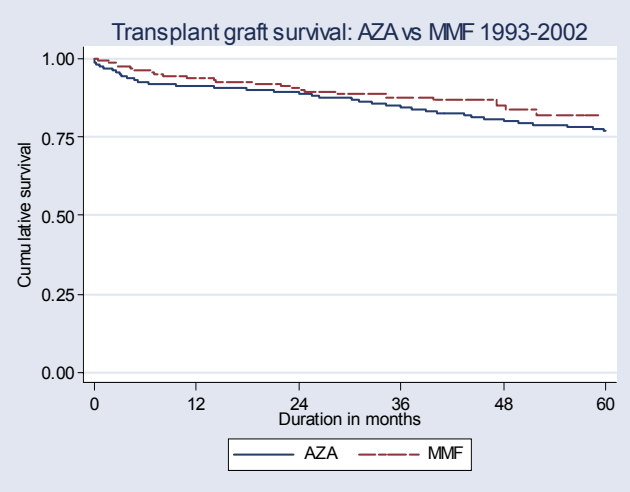


Figure 6.29 Adjusted transplant graft survival: AZA vs MMF 1993-2002

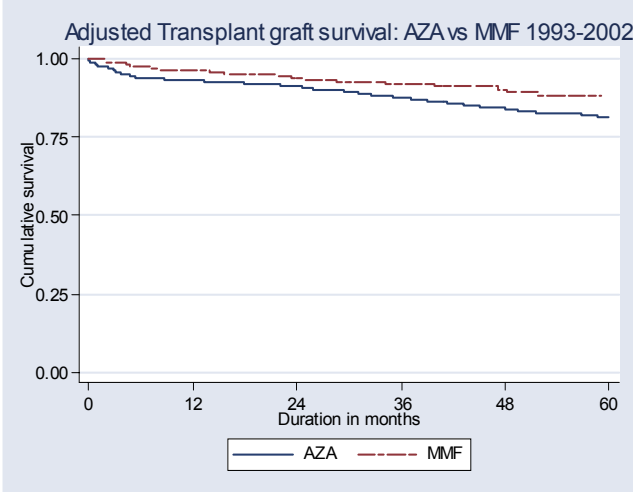


Figure 6.30 Transplant graft survival: CsA vs FK506 1993-2002

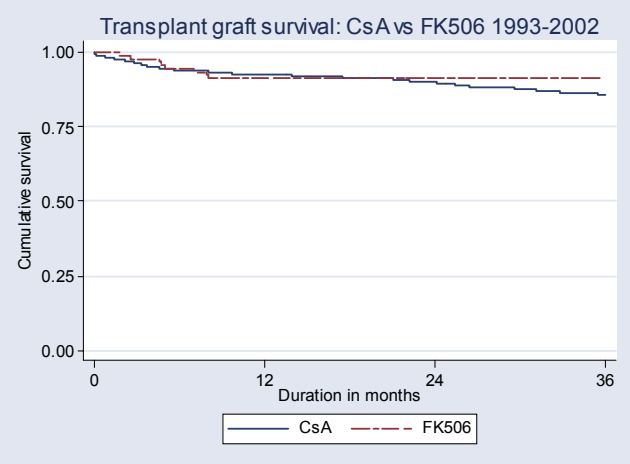
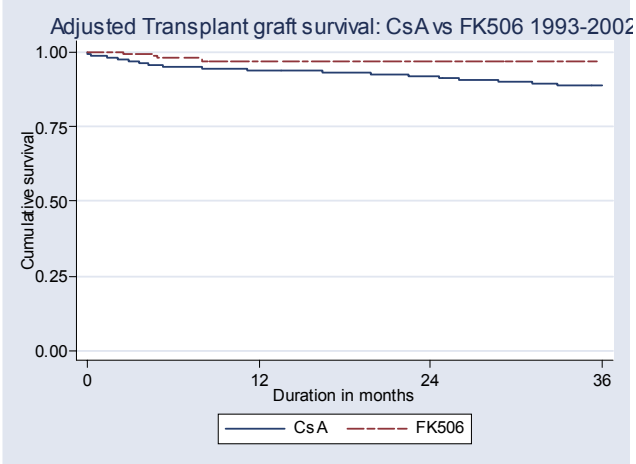


Figure 6.31 Adjusted transplant graft survival: CsA vs FK506 1993-2002



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