CHAPTER 2

Graft Survival Trends in Kidney Transplants:
An Analysis of the UNOS Database

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INTRODUCTION

Since the inception of the UNOS database in 1987, renal transplantation in the U.S. has seen significant changes including a dramatic increase in the number of waitlisted patients and marked improvement in graft survival over the past 20 years. That improvement has come—despite the inclusion of older recipients and donors in transplant programs—because of pharmacological and surgical advances. Pharmacological advances have been seen not only in the immunosuppression armamentarium, but also in the wide range of antibiotics, antiviral and antifungal drug treatments currently available. This has led to a significant decrease in acute rejection rates as well as improved patient survival. However the marked improvement has been in short-term renal graft survival (1). Long-term graft survival has not changed much.

Many immunological and non-immunological factors that exert profound influence on both short- and long-term graft survival have been identified. The immunological factors include HLA matching and pre-transplant PRA level, though the importance of HLA matching has been decreasing with the increasing efficacy of new immunosuppressants over the years (2). Non-immunological factors include donor and recipient characteristics as well as primary renal disease. Some racial groups carry more risk factors for graft failure as well as have variable access to health care. To ensure kidneys from older donors function for the lifespan of the potential recipient, donor-recipient age-matching has been performed.

Analyzing the latest UNOS data, we have revisited some of the points raised in previous issues of Clinical Transplants, putting extra emphasis on the demographic factors involved in graft survival.

METHODS

There were 289,321 renal transplants reported to the OPTN/UNOS Registry in the 21-year period from January 1988 to December 2008. After excluding recipients of multi-organ transplants and 79 foreign transplants, analyses were performed of 263,223 transplant recipients of which 92,636 received living donor (LD) kidneys, and 170,587 received deceased donor (DD) kidneys. Statistical analyses were performed using STATA/MP v.10.0 (StataCorp, College Station, TX). Unadjusted graft survival rates were estimated using Kaplan-Meier analysis, and statistical comparisons of survival curves were done by log-rank test. Categorical variables were compared by means of the chi-square test, with a two-tailed \( p \)-value of \(<0.05 \) considered significant. Graft survival was calculated from the date of transplant to the date of patient death or re-transplantation. Death with a functioning graft was considered graft failure.
RESULTS

The results are summarized in the following figures:

There has been a progressive increase in the total number of kidney transplants performed annually since the late 1980s. This was mainly due to the dramatic increase in the number of LD. The number of DD transplants has also been increasing, though at a much slower rate, reaching a plateau around 2006–2008. The greater number can be attributed to an increase in DD, age 40-65, during the years 2000 through 2005 (3).

The majority of living donors continue to come from the 18-50 age group, with a peak increase in the early to mid 2000s. A steady increase in donors age 51 years and older started to occur in the mid 1990s, and included those age 60 and above. The majority of LD kidney recipients came from the 18-50 age group. Since the early 2000s, the number of recipients age 51 years and above has been rising steadily.
Among LD kidney recipients, graft survival was superior in the 18-50 age group, and clearly inferior in recipients 60 and above. A similar trend was observed in DD kidney recipients. The significantly worse outcomes for older patients could be attributed to age-related co-morbidities such as increased rates of cardiovascular disease that result in shorter patient survival post-transplant, compared with younger patients. It is interesting that recipients in the youngest age group—18 and below—had graft survival rates similar to those of recipients in the 51-59 age group. One possible explanation is that younger patients have less reserve compared with adults and thus may not fare so well in the face of surgical complications.

As with living donors, the majority of deceased donors and their recipients were in the 18-50 age group. While the number of young DD (less than 18 years old) has been slowly falling since the late 1980s, older DD (51 and above) have been steadily increasing in number (4). As a result of age matching between donors and recipients, there is a corresponding increase in the number of older DD kidney recipients, especially those age 60 and above (3).

**Figure 3. Age distribution of DD & DD recipients.**

**Figure 4. Graft survival by age of (A) LD and (B) DD recipients.**
Among the various ethnic groups, Whites received the highest proportion of LD transplants and lowest proportion of DD transplants. The converse was true for Blacks, who received the highest proportion of DD kidney transplants and lowest proportion of LD transplants. Asians had the second lowest proportion of LD transplants and the second highest proportion of DD kidney transplants (after the Blacks).

Across all racial groups, siblings made up the majority of living donors followed by child-to-parent donation among Blacks and Hispanics. In Blacks, Hispanics, Asians and Other racial groups, child-to-parent kidney donation made up a slightly higher proportion, compared with parent-to-child donation. The converse was however true for Whites. Spousal donation was most common among Asians compared with other racial groups. Looking at the overall donor-recipient relationship (pie chart), sibling donors still made up the majority, with parent-to-child and child-to-parent donors of equal proportion. Surprisingly, there was a greater proportion of donations from unrelated donors than from spouses/partners.
For potential living donors, willingness to donate a kidney is likely influenced by their perception of the benefits and risks of kidney donation. It is unsurprising, then, that the majority of living donors had education at least up to college level since that suggests greater exposure to media and other avenues of public information about the benefits of living kidney donation and its minimal negative impact on a donor’s health.

![Figure 7. Racial differences in donors’ education level.](image)

![Figure 8. 10 year graft survival of patients according to race in (A) LD and (B) DD.](image)

It has previously been reported that the longest graft survivals were seen in Asians, while the shortest graft survivals were seen in Blacks (1, 3). In the latest UNOS data series this has again proven true for both LD and DD kidney recipients. In the next two figures, we look at two possible pre-transplant factors that affect graft survival, comparing them across different racial groups.
An elevated BMI has been reported to be significantly associated with worse graft survival independent of patient survival (5). The present analysis reinforces that earlier finding: the highest BMI is clearly associated with worst short- and long-term graft survival. This could be due to the many co-morbidities associated with obesity, such as diabetes mellitus, hypertension and cardiovascular complications, all of which could have a detrimental effect on renal allograft survival.

![Figure 9. Graft survival by recipient’s Body Mass Index (BMI).](image)

The majority of Asian LD and DD kidney recipients had a BMI (18.5-24.9) pre-transplant which was ideal by World Health Organization standards. Conversely, the majority of Black LD and DD kidney recipients were obese (pre-transplant BMI ≥ 30). With the many co-morbidities associated with obesity, this could be one of the factors causing Black recipients to have the worst graft survival.

![Figure 10. BMI distribution among (A) LD and (B) DD recipients.](image)
The presence of pre-transplant DM is associated with worse short- and long-term graft survival, with the survival difference increasing each year, post-transplant. This can be attributed to the many co-existing cardiovascular complications present in diabetic patients, some of which could have been compounded by the use of immunosuppressants—e.g., calcineurin inhibitors that can worsen blood pressure control, or mTOR-inhibitors that can exacerbate hyperlipidemia. Parekh et al. have also shown that DM is a risk factor for delayed graft function, another factor that worsens short- and long-term graft outcomes (6).

Figure 11. Graft survival by presence of diabetes mellitus (DM).

Figure 12. Presence of DM at registration among (A) LD and (B) DD recipients.

Although the majority of LD and DD kidney recipients did not have pre-transplant DM, it is noteworthy that Asian recipients—who have the best long-term graft survival rates—also had the smallest proportion of patients with pre-transplant DM. Whites, Blacks and Hispanics had similar proportions of LD kidney recipients with pre-transplant DM. Among DD kidney recipients, Hispanics and those categorized as “Other” (i.e., Non-White, non-Black, non-Asian) had the highest proportion of pre-transplant DM.
Exploring other factors that could affect graft survival, we saw that patients who have had at least a graduate education tended to do better than those with education that is minimal or only up to the college level. This could be due to better understanding of the process of kidney donation, which may lead to greater effort in self-care and better compliance in taking medications and making lifestyle modifications. In this analysis, 2,053 recipients who were less than 5 years old were excluded, as were 37,509 recipients whose education record was not available.

The majority of all recipients received an education somewhere up to the college level. However, the largest proportion with at least a graduate degree was among Asians, while Hispanics had the largest proportion with little or no education. Again, this could be one of the factors in why Asians have good long-term graft survival.

Delayed graft function—defined as a need for dialysis in the first week post-transplant, is associated with poorer long-term outcomes (7). In recipients with DGF, the rate of graft loss is highest in the first year, post-transplant, though from the second post-transplant year, on, it becomes similar to the rate experienced by those without DGF. This finding is similar to those of the USRDS (8) and the John Radcliffe Hospital in the United Kingdom (9). However, Boom et al. in the Netherlands reported that though DGF is one of several risk factors for acute rejection and sub-optimal function at one year, it is not independently associated with an increased rate of graft loss (10).
Patients who produced urine in the first 24 hours post-transplant probably did not have DGF, and had better short- and long-term graft survival. The highest rate of graft loss among those who did not produce urine in the first 24 hours came in the first year post-transplant, similar to the analysis for patients with DGF (Fig. 15). For this analysis, data was missing for 51,384 patients, and unavailable for 2,006 patients.

Similarly, patients whose serum creatinine declined by at least 25% in the first week post-transplant, a marker of improved solute clearance from the transplanted kidney, experienced significantly better long-term graft function up to 10 years. Because collection of data for this variable was only from October 25, 1999, data was not available for 144,652 patients.

Since June 30, 2004, data has been made available on acute rejection (AR) episodes between transplantation and hospital discharge. Six-year survival rates for patients with at least one early AR episode are clearly inferior to the rates for those who have not had an early AR episode, with this difference in survival seen as soon as one year post-transplant. This confirms previous observations that early AR episodes have an adverse effect on long-term graft outcome. Information about AR was available for only 76,952 recipients.

Figure 16. Long-term graft function in patients who did and did not produce urine in the first 24 hours post-transplant.

Figure 17. Long-term graft survival according to recipients’ decline in serum creatinine by at least 25% in the first week.

Figure 18. Six year graft survival of patients according to any acute rejection episodes between transplant & discharge.
Looking at recipients’ current panel reactive antibody (PRA) score, those with the lowest and highest scores (PRA <10 and PRA >50, respectively) had almost similar long-term graft survival. It is likely that recipients with higher PRA scores were given more potent immunosuppression as a result of their perceived higher immunological risk, and this led to improved graft survival. In contrast, recipients with perceived moderate immunological risk (i.e., PRA 10-50) were probably not given very potent immunosuppression from the start, which means they could have had more AR episodes—inferable from the fact that their rate of graft loss was indeed higher even at one year post-transplant.

Figure 19. 10 year graft survival of patients according to ABO blood group compatibility. Bar chart shows the proportion of donor-recipients with various blood group combinations.

The incidence of AR episodes was also highest in ABO-incompatible recipients (6.9% vs. 3.9% vs. 3.1% in ABO-incompatible, ABO-identical and ABO-compatible recipients, respectively, p<0.001). The slightly higher incidence of AR episodes in ABO-identical recipients—compared with ABO-compatible recipients—could be due to the higher number of DD kidney recipients in the former group.

Figure 20. 10 year graft survival of patients according to current PRA.
Among DD kidney recipients, those with zero HLA mismatch had the best long-term graft survival. As expected, patients with 5-6 HLA mismatches had the worst long-term graft survival. Graft survival rates of patients with 1-4 HLA mismatches fell in between.

Among LD kidney recipients, it is surprising that those with 5-6 matched HLA loci had the worst long-term graft survivals. Those who were matched at 3-4 HLA loci had the best graft survivals, while patients with zero matches fell in between.

Figure 21. 10 year graft survival of patients according to (A) HLA mismatch (MM) in DD and (B) HLA matching in LD.

Looking at the degree of HLA matching among LD kidney recipients, the majority received a kidney from donors who were matched for at least 3-4 HLA loci. Among the different races, Whites and Hispanics received the highest proportion of fully matched kidneys, while Asians and Blacks received the highest proportion of zero-matched kidneys.

Among DD kidney recipients, Asians received the highest proportion of 5-6 HLA loci mismatched kidneys and (along with Blacks) the lowest proportion of fully matched kidneys. Whites received the highest proportion of zero HLA mismatch kidneys & the lowest proportion of 5-6 HLA loci mismatched kidneys. This reflects the racial distribution in the DD population, the majority of whom are Whites, Blacks and Hispanics (pie chart).

Figure 22. Racial differences in HLA match (LD) & mismatch (DD). Pie chart shows the racial distribution of deceased donors.
Patients at an advanced stage of chronic kidney disease who were transplanted before they required dialysis had significantly better short- and long-term graft survival rates. Among those who had started on dialysis, pre-transplant, peritoneal dialysis patients had better long-term outcomes compared with hemodialysis patients.

Short- and long-term graft survivals were clearly better in first transplants compared with re-transplants. Patients who underwent re-transplants tended to have higher PRA, and a significantly higher percentage had an episode of AR between transplant and hospital discharge compared with patients who had first transplants (5.4% vs. 3.6%, respectively, p<0.001). As shown in Figure 18, patients who have had at least one early AR episode had significantly worse graft survival.

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**Figure 23. Graft survival in first transplants vs. re-transplants. Bar chart shows the current PRA distribution among first and re-transplant recipients.**

**Figure 24. Graft survival according to initiation of dialysis pre-transplant.**
DISCUSSION

The rise in number of transplants performed annually corresponds to the increase in number of patients on the wait list. While the number of pediatric donors (i.e., under 18 years of age) has remained fairly constant for both LD and DD, the number of older donors—especially those over 50—have been steadily increasing. Gill et al. previously demonstrated, using UNOS data, that living donation from a donor over 55 yielded better graft and patient survival rates than did DD transplantation with even a standard-criteria donor (11). However, the number of LD kidney transplants appears to have reached a plateau since 2007. The rise in number of DD over 50 years of age reflects the increasing use of expanded-criteria donors. As a result of this—along with the possibility that older recipients have more co-morbidities—only a third of DD grafts will survive beyond 10 years. As previously reported by Chavalitdhamrong et al., transplants from older extended criteria donor (ECD) kidneys (over 70) were associated with a higher risk of graft loss, especially when such kidneys were transplanted into recipients under 60 years old (12).

Better graft outcomes were reported among Asians as early as the 1990s, partly due to the low incidence of sensitization and low incidence of acute and chronic rejection, and the high prevalence of primary disease etiologies that have been associated with excellent long-term prognoses, especially IgA nephropathy and chronic glomerulonephritis (13,14). From figures 8-14, we can see that Asians possess several other factors associated with good long-term graft survival—BMI under 30, absence of pre-transplant DM, and higher education level. The observation that Blacks have had lower graft survival rates compared with Whites has been noted in some (3,15,16) but not all studies (17). Explanations offered for this poorer survival include a higher degree of sensitization and more pre-transplant co-morbidities (14).

Though the degree of pre-transplant sensitization, as measured by a recipient's PRA level, is an important determinant of graft survival, advances in our immunosuppression armamentarium has allowed us to overcome this by using more potent immunosuppressants. With the advent of newer, more sensitive solid phase assays, not only can a recipient's PRA level be ascertained with greater accuracy, but HLA antibodies in each recipient's serum can be identified with reasonable accuracy. This has allowed individualization of immunosuppression, which has led to significant improvements in short-term graft outcome (1).

It is not surprising that DD kidney recipients with zero HLA mismatches had the best short- and long-term survival rates (Fig. 21), showing that histocompatibility still plays an important role in graft survival despite pharmacological and surgical advances in recent years. It is of note that, with the majority of DD being Whites—reflecting the overall ethnic make-up of the U.S.—a higher proportion of Whites, compared with the other ethnic groups, received zero HLA mismatched kidneys, and a lower proportion received 5-6 HLA mismatched kidneys.

SUMMARY

We have summarized data on 92,636 living donor (LD) and 170,587 deceased donor (DD) kidney transplants reported to the OPTN/UNOS registry from January 1988 to December 2008. The increase in number of kidney transplants performed annually is mainly due to the increase in number of LD. The majority of LD, DD and their respective recipients, come from the 18-50 age group. Sibling donors made up the majority of LD, though there was a greater proportion of donations from unrelated donors than from spouses/partners.

Graft survival has been significantly better in the 18-50 age group, compared with younger and older recipients, likely due to their better physical condition and lower number of co-morbidities. Asians appear to have superior graft survival, compared with Whites, Hispanics and Blacks. Part of the reason could be due to a larger proportion of them having an ideal BMI at transplant, as well as a smaller proportion having pre-transplant diabetes mellitus with its associated medical complications, leading to a detrimental effect on graft survival. Furthermore,
a greater proportion of Asians had at least a college education compared with recipients of other ethnic groups, suggesting they could have a better understanding of the lifestyle modifications required after kidney transplantation, which would give rise to better compliance and hence better outcomes post-transplant.

Delayed graft function (DGF), the absence of urine production in the first 24 hours post-transplant, as well as a lack of decline in serum creatinine by at least 25% in the first week post-transplant were all associated with poor short- and long-term graft survival. An early acute rejection (AR) episode, which could be antedated by any of the above, also leads to poorer short- and long-term outcomes. It is of note that the majority of recipients who underwent re-transplants had a higher PRA compared with first transplants. With their higher immunological risk, it is unsurprising that a significantly higher number had early AR episodes, and hence poorer short- and long-term graft outcomes.

REFERENCES