He is immortal, not because he alone among creatures has an inexhaustible voice, but because he has a soul, a spirit capable of compassion and sacrifice and endurance.

*WILLIAM FAULKNER*, Nobel Prize acceptance speech
Chapter Eight

Introduction

The major issue in transplantation continues to be the shortage of donor organs. The number of cadaveric transplants has grown by only 16 percent over the past decade (Figure 8.1). To make up for the shortage of cadaveric kidneys, transplant centers have increasingly used kidneys from living donors. Indeed, the number of living-related transplants has grown by 68 percent over the past ten years, while the number of transplants from distantly related or unrelated donors has increased ten-fold. This growth has not, however, kept pace with the need for donor kidneys. As a result, the rate of transplantation (per 100 dialysis patient years) has declined, as the incidence of ESRD has increased (Figure 8.2).

Rates of cadaveric kidney donations have fallen slightly over the past several years (Figure 8.6). Rates of donations from living donors continue to be higher among women than men, and lowest among Asians.

Rates of cadaveric and living kidney donations vary geographically (Figure 8.7). While reasons for these variations are not readily apparent, additional efforts in regions with low rates could increase the overall rate of donation.

The inadequate supply of organs has led to increasing waiting times for kidney transplants, as well as widening gaps in the disparities in waiting times among different age and racial groups (Figure 8.5). Waiting times for blacks, for example, already longer than those of whites, are increasing at a greater rate. Over the past six years the median waiting time has increased 49 percent for whites, but 64 percent for blacks. Particularly distressing is the almost two-fold increase in waiting times for children, and the fact that increments in waiting times have been proportionally greater for younger recipients (Figure 8.5). Waiting times also vary by geographic region (Figure 8.4).

Correlations between regional differences in waiting times (Figure 8.4) and rates of cadaveric organ donation (Figure 8.7) are not easy to discern. This could be due, in part, to differences in the proportions of cadaveric kidneys that are transplanted locally, regionally, or nationally. We examined the proportions of cadaveric kidneys retrieved in each Organ Procurement Organization (OPO) that are transplanted as 1) mandated zero-antigen mismatches, 2) paybacks (local or regional), 3) local (not as paybacks), 4) regional (not as paybacks), or 5) unknown (Figure 8.8). Among the different OPOs, the number of cadaveric kidneys retrieved and allocated as mandated, zero-antigen mismatches varies from 0.2 percent in an OPO centered in Oakland, California, to 17.9 percent in an OPO in Minnesota and the Dakotas. The proportion of kidneys transplanted locally in these two OPOs is 91.5 percent and 68.5 percent, respectively. Local variances that allow OPOs to opt out of part or all of the UNOS allocation system, along with other factors, may explain some of these differences.

Outcomes after kidney transplantation continue to improve. After adjusting for multiple baseline patient and transplant characteristics, the rate of graft failure (defined as death with a functioning graft, the resumption of maintenance dialysis, or retransplantation) was 23 percent lower in 1998–2000 compared to 1994–1997 (Table 8.a). Similarly, the rate of death-censored graft failure (with the resumption of dialysis or re-transplantation) was 29 percent lower, while adjusted mortality declined by 12 percent (Figure 8.9). Although risk factors associated with poor outcomes do not necessarily cause those outcomes, they do suggest areas that might be studied in order
to better understand causes and thereby target areas that might improve outcomes.

Kidneys from living donors are 30–35 percent less likely to fail than are kidneys from cadaveric donors (Figure 8.12), an advantage that extends to both death-censored graft failure and mortality. Interestingly, there are few differences in outcomes between kidneys of living related donors compared to those of distantly related or living unrelated sources (Figure 8.12). The living kidney advantage is independent of tissue typing (Table 8.a), but it could be due to the lack of ischemia reperfusion injury or other factors not included in this analysis.

A number of characteristics of the transplant recipient are associated with graft failure. Compared to recipients 18–44 years old, for example, both younger and older recipients have lower graft survival (Figure 8.15). In the case of children and adolescents, this reduced graft survival appears to be due entirely to a higher risk of death-censored graft failure. The opposite is true for older recipients, who have a lower risk of death-censored graft failure, but an increased risk of death.

Compared to whites, blacks have a higher rate of graft failure (Figure 8.18). This appears to be entirely due to a higher rate of death-censored graft failure, because mortality is actually lower for blacks compared to whites (Table 8.a). Other racial groups have better graft survival than whites (Figure 8.18). Similarly, Hispanics have better graft survival and reduced mortality compared to non-Hispanics (Figure 8.21).

Patients whose ESRD is caused by diabetes have better death-censored graft survival than patients with a primary diagnosis of glomerulonephritis (Figure 8.24). The mortality of the diabetic patients is so much higher, however, that their overall graft survival is lower. Similar associations are evident for ESRD from hypertension. In contrast, patients with cystic kidney disease have better graft survival than patient with glomerulonephritis.

In terms of socioeconomic factors, recipients who are better educated have better graft survival (Figure 8.27), as do those with the ability to work (Figure 8.30), which may reflect both comorbidity and socioeconomic status. Similarly, having private insurance (compared to Medicare) as a primary payor likely reflects employment and/or socioeconomic status, and is also associated with better graft survival (Figure 8.33).

The time that a patient is on dialysis prior to transplantation is also an important risk factor for graft failure, and especially for mortality (Figure 8.36). Compared to patients on dialysis less than one year prior to transplant, patients who receive a pre-emptive transplant have a 35 percent lower rate of graft failure. Patients on dialysis one year or longer are more likely to have graft failure, principally from death with a functioning graft (Table 8.a).

The condition of the donor kidney has a major effect on graft survival. Older kidneys are much more likely to fail compared to younger kidneys (Figure 8.39), and are associated not only with a higher rate of death-censored graft failure, but also with a higher likelihood of death with function (Table 8.a). Kidneys from African American donors are associated with a higher rate of graft failure. Since kidneys from African Americans may have fewer nephrons than kidneys from whites, this observation could be consistent with the hypothesis of “inadequate” nephron-dosing. Similarly, kidneys from donors who are significantly smaller than the recipients have reduced graft survival.

Human leukocyte antigen (HLA) mismatches continue to be important risk factors for graft and patient survival. Indeed, there is an almost linear gradation in the increment of risk associated with each HLA mismatch (Figure 8.48). Individuals who have high panel reactive antibody status, i.e. have antibodies that react to more than 50 percent of a panel of cells from the general population, also have a much higher risk of graft failure and death (Figure 8.54). Finally, individuals with positive serology for cytomegalovirus, or who receive a kidney from a donor who is serologically positive for cytomegalovirus, are at increased risk for graft failure, death-censored graft failure, and mortality (Figure 8.57).
There was substantial geographic variation in the rates of transplantation in 2000, from 2.5 per 100 dialysis patient years in Mississippi to 13.1 in North Dakota (Figure 8.3). Rates are lowest in the Southeast, and highest in the north central and northwestern states. These rates may be affected by differences in patient populations or in the availability of organs, which are not included in the analysis.

The median waiting time (from being placed on the UNOS cadaveric transplantation waiting list to receiving a kidney) varies from 161 days in Kentucky to 821 days in Massachusetts, a five-fold difference (Figure 8.4). Waiting times vary by recipient age, being shortest for children and adolescents and longest for those age 18–44 (Figure 8.5). Waiting times are similar for men and women, but shorter for whites compared to individuals of other races (Figure 8.5, right panel). These times are not adjusted for differences in patient populations or in the availability of organs.

Cadaveric kidney donation rates vary substantially by recipient age, gender, and race (Figure 8.6). There is less variation in living donation rates, except for the understandably low rates among the very young and very old. There is also a large geographic variation in donation rates (Figure 8.7). The allocation of cadaveric kidneys, and the reasons for these allocations, differ across the country (Figure 8.8).

**Figure 8.3** per 100 dialysis patient years, 2000, unadjusted. **Figure 8.4** waiting time in days, cadaveric transplants only, 2000, by state, unadjusted; state defined as the state in which a patient is listed, not necessarily the state of residence. **Figure 8.5** cadaveric transplants only. **Figure 8.6** donors younger than 70, only those organs eventually transplanted. **Figure 8.7** rate per million population, donors younger than 70, 1999, by HSA (residence of recipient), only those organs eventually transplanted, unadjusted. **Figure 8.8** organs transplanted in 1995–2000; includes only kidneys transplanted in first-time, kidney-only recipients. Each pie diagram shows data from a separate Organ Procurement Organization (OPO). Kidneys are allocated preferentially 1) anywhere in the U.S. under the zero-antigen mismatch program, 2) if not 1, then anywhere in the U.S. as a payback, 3) if not 1 or 2, then locally, or 4) if not 1, 2 or 3, then within the region (indicated by different colors). Abbreviations for OPOs are those designated by the United Network for Organ Sharing, & can be found at www.unos.org.
Organ sharing, by UNOS region & organ procurement organization (OPO)

City in which OPO is located
To determine factors associated with outcomes after kidney transplantation, we examined graft failure (defined as death with a functioning graft, the resumption of maintenance dialysis, or re-transplantation), death-censored graft failure (defined as the resumption of maintenance dialysis or retransplantation), and death with a functioning graft. Table 8.a presents the 18 characteristics with the greatest effect on graft survival. Even after adjusting for all other 17 characteristics, there was a 23 percent improvement in graft survival between 1994–1997 and 1998–2000. Despite changes in immunosuppressive medications and patient care, a number of traditional recipient risk factors continue to be associated with graft survival, including age, race, ethnicity, and primary cause of ESRD. Also associated with graft survival are several recipient characteristics that may reflect socioeconomic status, such as the highest education level achieved, employment status (which may also reflect disease severity) and the source of primary payment. Information on these characteristics has been collected by UNOS since 1994.

Graft survival improved between 1994–1997 and 1998–2000. The Kaplan-Meier survival curves are similar before and after adjusting for the other recipient or donor characteristics listed in Table 8.a (Figure 8.9). This suggests that the improvement in graft survival is likely due to changes in other characteristics of the patients or their care, such as the particular immunosuppressive agents used.

There has been only a small improvement in one-year (unadjusted) graft survival, from 84.9 percent in 1994 to 90.3 percent in 1999 (Figure 8.10). On the other hand, the half-life (unadjusted) of grafts that survive at least one year improved from 11.1 months in 1999 (Figure 8.10). On the other hand, the half-life (unadjusted) of grafts that survive at least one year improved from 11.1 months in 1999 to 15.5 months in 2000 (Figure 8.11). Graft survival for living donor kidneys is similar whether or not the donor is related to the recipient, and much better than graft survival for cadaveric donor kidneys (Figure 8.12). These similarities and differences in one-year graft survival changed little between 1994 and 2000 (Figure 8.13). The half-life of living donor kidneys, however, increased more than the half-life of cadaveric kidneys over this time period (Figure 8.14).

Table 8.a Cox proportional hazards models modeling all-cause graft failure, death-censored graft failure (return to dialysis), & death, 1994–2000 combined. Patients with multiple organ transplants are excluded. In the first column are the 18 patient or transplant characteristics (covariates) that most closely correlate with graft failure, & the proportion of the population with each characteristic. The hazard ratios in columns 3, 6, & 9 indicate the relative risk of graft failure and death-censored graft failure, respectively.
risk associated with each characteristic for graft failure, death-censored graft failure, & death, respectively. Also shown are the 95 percent confidence intervals & P-values for each hazard ratio. Hazard ratios should be compared to the reference risk of 1.00, arbitrarily assigned to one category for each characteristic. Abbreviations: HLA, human leukocyte antigen; BSA, body surface area; R, recipient; D, donor; PRA, panel reactive antibody; CMV, cytomegalovirus. Figures 8.9 & 8.12 unadjusted (Kaplan-Meier) & adjusted (Cox proportional hazards) graft survival (months); adjusted probabilities adjusted for all covariates shown in Table 8.a. Figures 8.10 & 8.13 probabilities estimated using the Kaplan-Meier method. Figures 8.11 & 8.14 estimates conditional on one-year of graft survival & interpreted as the estimated time at which 50 percent of grafts would have failed given that each patient's graft survived the first year post-transplant.

*Note that some of the covariates include "unknown" levels. Because these levels are excluded from the table, the associated percentages may not sum to 100 percent.
Recipient age has a major effect on graft survival (Figure 8.15), although differences due to recipient age are less marked after taking other recipient and donor characteristics into account. Improvements in one-year graft survival (Figure 8.16), and half-lives (Figure 8.17) are similar for recipients of different ages.

Graft survival for blacks continues to be less than that of other races (Figure 8.18), although the effect of race is less marked when other variables are also taken into account. The difference in one-year graft survival between blacks and patients of other races did not change substantially between 1994 and 2000 (Figure 8.19). In contrast, graft half-lives increased more for whites and patients of other races than for blacks (Figure 8.20).

Hispanic recipients have better graft survival than non-Hispanics (Figure 8.21). Interestingly, the differences in one-year graft survival associated with ethnicity have diminished (Figure 8.22). For example, one-year graft survival in 1994 was 89.3 for Hispanics and 84.6 in non-Hispanics, compared to 91.5 and 90.2 in 1999. In contrast, differences in half-lives increased over the same time period (Figure 8.23). Half-lives for Hispanic and non-Hispanic recipients were 11.4 and 11.1 years in 1994, compared to 22.3 and 17.8 years in 1999.

Graft survival for patients with ESRD due to diabetes or hypertension is less compared to that of patients with other causes of ESRD (Figure 8.24). Differences in one-year graft survival (Figure 8.25) and in half-lives (Figure 8.26) attributable to the primary cause of ESRD may have increased in recent years.

**Figures 8.15, 8.18, 8.21, & 8.24** 1994–2000 combined, unadjusted (Kaplan-Meier) & adjusted (Cox proportional hazards) graft survival (months); adjusted probabilities adjusted for all covariates shown in Table 8.a. **Figures 8.16, 8.19, 8.22, & 8.25** probabilities estimated using the Kaplan-Meier method. **Figures 8.17, 8.20, 8.23, & 8.26** estimates conditional on one year of graft survival & interpreted as the estimated time at which 50 percent of grafts would have failed given that each patient’s graft survived the first year post-transplant.
Recipient ethnicity

8.21 - Kaplan-Meier graft survival

8.22 - first-year graft survival

8.23 - conditional half-lives

Recipient primary cause of disease

8.24 - Kaplan-Meier graft survival

8.25 - first-year graft survival

8.26 - conditional half-lives
Socioeconomic factors are associated with outcomes after kidney transplantation. Recipients with a college degree, for example, have better graft survival than recipients without one (Figure 8.27). Interestingly, education has a greater effect on the rate of late graft failure, manifested by differences in half-lives (Figure 8.29), than on one-year graft survival (Figure 8.28). It is possible that this late versus early effect of education is due to differences in adherence to immunosuppressive medications.

Patients who are able to work full or part-time have better graft survival than those unable to work (Figure 8.30). Differences in one-year graft survival (Figure 8.31) and in half-lives (Figure 8.32) attributable to employability have persisted over the past few years.

Insurance status may reflect overall socioeconomic status. Recipients with Medicare as the primary payor for the transplant have lower graft survival than recipients with private insurance or another primary payor (Figure 8.33). The effects on graft survival associated with the primary payor are less after adjustment for other patient and transplant characteristics. Differences in one-year graft survival associated with payor source were relatively constant between 1994 and 2000 (Figure 8.34), while differences in the effects on half-lives may have increased slightly (Figure 8.35).

Patients who receive a pre-emptive transplant have better graft survival than those on dialysis before transplantation (Figure 8.36). This difference persists even after adjustment for other characteristics. In contrast, differences due to the number of years on dialysis diminish significantly with adjustment for other risk factors. Differences in one-year graft survival associated with pre-transplant dialysis exposure were relatively constant over the 1994–2000 period (Figure 8.37), while the advantage of pre-emptive transplantation with respect to long-term graft survival (manifested by half-lives) may have increased in this same period (Figure 8.38).

Figures 8.27, 8.30, 8.33, & 8.36 1994–2000 combined, unadjusted (Kaplan-Meier) & adjusted (Cox proportional hazards) graft survival (months); adjusted probabilities adjusted for all covariates shown in Table 8.4. Figures 8.28, 8.31, 8.34, & 8.37 probabilities estimated using the Kaplan-Meier method. Figures 8.29, 8.32, 8.35, & 8.38 estimates conditional on one year of graft survival & interpreted as the estimated time at which 50 percent of grafts would have failed given that each patient's graft survived the first year post-transplant.
The age of the donor kidney is a strong correlate to graft survival. Donor age exhibits a “U-shaped curve,” with younger and older kidneys having reduced allograft survival compared to kidneys 18–44 years old (Figure 8.39). However, after adjusting for other variables, the relatively lower graft survival with younger donor kidneys is no longer evident. The effect of donor age on one-year graft survival has not changed over the past few years, being primarily related to kidneys from older donors (Figure 8.40). During this time, the half-lives of younger kidneys have improved more than the half-lives of kidneys from donors age 60 and older (Figure 8.41).

The gender of the donor continues to have a small effect on graft survival. Recipients of kidneys from males have better graft survival than those receiving kidneys from females (Figure 8.42). This difference persists even after adjustment for other characteristics. Differences in one-year graft survival (Figure 8.43) and half-lives (Figure 8.44) associated with donor gender were relatively constant between 1994 and 2000.

The race of the donor kidney also correlates with graft survival. Recipients of kidneys from blacks have lower graft survival (Figure 8.45). After adjusting for other variables, however, this difference is less marked. The effect of donor race on one-year graft survival appears to have decreased over the past few years (Figure 8.46), while the effect on the half-life has increased for whites and patients of other races (Figure 8.47).

The number of human leukocyte antigen (HLA) mismatches continues to be associated with graft survival. The lower the number of mismatches, the better the graft survival (Figure 8.48). These differences are, however, reduced after adjusting for other recipient and donor characteristics. The association between HLA mismatches and one-year graft survival (Figure 8.49), as well as half-lives (Figure 8.50), has been relatively constant over the last few years.

Figures 8.39, 8.42, 8.45, & 8.48 1994–2000 combined, unadjusted (Kaplan-Meier) & adjusted (Cox proportional hazards) graft survival (months); adjusted probabilities adjusted for all covariates shown in Table 8.a. Figures 8.40, 8.43, 8.46, & 8.49 probabilities estimated using the Kaplan-Meier method. Figures 8.41, 8.44, 8.47, & 8.50 estimates conditional on one year of graft survival & interpreted as the estimated time at which 50 percent of grafts would have failed given that each patient’s graft survived the first year post-transplant.
Donor race

8.45 - Kaplan-Meier graft survival

8.46 - first-year graft survival

8.47 - conditional half-lives

HLA mismatches

8.48 - Kaplan-Meier graft survival

8.49 - first-year graft survival

8.50 - conditional half-lives
Some donor kidneys may be too small for their recipients. Body surface area (BSA) has been shown to correlate with kidney size and functional capacity in normal individuals. Large (BSA >2.2 m²) or mid-sized (BSA 1.6–2.2 m²) recipients of kidneys from small (BSA <1.6 m²) donors have lower graft survival compared to that of recipients equivalent to or smaller in size than their donors (Figure 8.51). These differences are reduced, but not eliminated, after adjusting for other variables. The effect of recipient-to-donor size differences on one-year graft survival (Figure 8.52) and half-lives (Figure 8.53) has been relatively constant over time.

Patients with antibodies that react to a large proportion of cells from individuals randomly selected from the general population have reduced graft survival. Graft survival for recipients with panel reactive antibodies (PRA) >50 percent is significantly reduced (Figure 8.54), even after adjusting for other recipient and donor characteristics. The effect of PRA status on one-year graft survival (Figure 8.55) and half-lives (Figure 8.56) has been relatively constant over time.

The serological status of the recipient and donor influence the risk for cytomegalovirus (CMV) disease after kidney transplantation. The risk for CMV infection is probably lowest for transplants where both the donor and recipient are seronegative for CMV. Interestingly, individuals with low CMV risk have significantly better graft survival (Figure 8.57), although this difference is not so apparent after adjusting for other recipient and donor characteristics. The effect of CMV risk on one-year graft survival (Figure 8.58) and on half-lives (Figure 8.59) has been relatively constant over the last few years.

Increasing cold ischemia time (CIT) is associated with lower graft survival (Figure 8.60). However, the differences in graft survival are reduced after adjusting for other recipient and donor characteristics. The effect of CIT on one-year graft survival (Figure 8.61) and half-lives (Figure 8.62) has been relatively constant over the last few years.

**Figures 8.51, 8.54, 8.57, & 8.60** 1994–2000 combined, unadjusted (Kaplan-Meier) & adjusted (Cox proportional hazards) graft survival (months); adjusted probabilities adjusted for all covariates shown in Table 8.a. **Figures 8.52, 8.55, 8.58, & 8.61** probabilities estimated using the Kaplan-Meier method. **Figures 8.53, 8.56, 8.59, & 8.62** estimates conditional on one year of graft survival & interpreted as the estimated time at which 50 percent of grafts would have failed given that each patient’s graft survived the first year post-transplant. **Figures 8.60–62** cadaveric kidneys recipients only.
Patient populations & analytical methods

♦ Figure 8.1: transplant counts by donor source. These counts are obtained through a combination of UNOS and CMS data. For patients with a known living donor of unknown type, we assume a living related donor.

♦ Figure 8.5: median waiting times for patients transplanted between 1995 and 2000. Only first-time, kidney-only recipients of a cadaveric kidney are included; patients with pre-emptive transplants are excluded. Times are calculated from the date of listing to the date of transplantation. Median times are mapped by state in Figure 8.4.

♦ Figure 8.6: organ donation rates. The numerators include all donors younger than 70 whose kidneys were not discarded. Denominators are obtained from the U.S. census. Rates are calculated as the number of donated kidneys (excluding discarded organs) divided by the population, and multiplied by one million to yield donations per million population. Figure 8.7 presents maps of these rates.

♦ Figure 8.8: organ shipping and sharing practices by Organ Procurement Organization (OPO). Each OPO is represented by a pie chart that details the percentage of harvested organs transplanted locally or regionally, designated as payback organs, or transplanted as part of the zero-antigen mismatch program. All first-time, kidney-only, cadaveric transplants between 1995 and 2000 are included.

♦ Table 8.a: results from three separate Cox proportional hazards models. All first-time, kidney-only transplants between 1994 and 2000 with known recipient age and donor type are included in the models.

♦ Figures 8.9–62 present more detail on certain covariates listed in Table 8.a. Included are Kaplan-Meier graft survival curves, along with adjusted graft survival curves obtained from the all-cause graft failure Cox proportional hazards model used in Table 8.a. Adjusted survival curves are calculated as the expected survival of the average patient in the population, adjusting for all covariates detailed in the table. Following the survival curves are trends in estimated one-year survival probabilities, estimated using the Kaplan-Meier method, and trends in estimated conditional graft half-lives. These half-life estimates are conditional on one year of graft survival, and are calculated using an exponential approximation to the survival curve. These can be interpreted as the estimated time until 50 percent of kidneys transplanted in the given year would fail, given that a graft survives the first year post-transplant. Note that, since cold ischemia time applies only to recipients of cadaveric kidneys, this covariate is not included in Table 8.a. To produce Figures 8.60–62, the models are rerun using only recipients of cadaveric kidneys.

Conclusions

♦ In the past ten years, growth in the number of cadaveric (16 percent increase), living related (68 percent increase), and living unrelated (a ten-fold increase) donors has not been enough to meet the demand for kidney transplants.

♦ Because the incidence of ESRD has increased at a faster rate than the number of kidney donors, the rate of kidney transplants per 100 patient years on dialysis has declined over the past ten years.

♦ Waiting times for cadaveric kidney transplants have steadily increased.

♦ Graft survival and patient survival have improved in the past ten years.

♦ Over the last four years, one-year graft survival rates have been largely unchanged, while half-lives (reflecting the rate of graft loss after the first year), in most cases, have remained relatively constant over time.

♦ Both biological and socioeconomic factors are associated with graft survival.