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The mortality risk with graft function has decreased among children receiving a first kidney transplant in the United States

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Abstract

Mortality has decreased in children with end stage kidney disease. Decreases in mortality during dialysis and improved graft survival contributed to this improvement. However, it is unknown if rates of death with graft function have also improved. We measured this in first transplant recipients under 21 years old registered in the USRDS. Cox models were used with a time-dependent renal replacement therapy modality variable to estimate the hazard ratios for death with graft function associated with a 1-year increment in the calendar year of transplant. There were 157,201 person-years of observation among 17,468 recipients with 82.2% of study time during graft function and 17.8% during dialysis after graft failure. There were 2003 deaths (12.7 deaths/1000 person-years) overall of which 985 occurred with graft function (7.6 deaths/1000 person-years) and 1018 occurred during dialysis after graft failure (36.1 deaths/1000 person-years). Each 1-year increment in calendar year of first transplant was associated with a significantly lower risk of death, both over all observation (HR 0.97 [0.96, 0.98]) and focusing on time with graft function (HR 0.98 [0.97, 0.99]). Living donation was significantly associated with better survival while dialysis after graft failure was associated with a much higher mortality risk (HR 4.85 [4.40, 5.35]) compared with graft function. Thus, the risk of death with graft function has decreased in children receiving a first kidney transplant. Increasing living donation and minimizing dialysis may further improve outcomes.

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Keywords

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INTRODUCTION

Kidney transplantation is the treatment of choice for children and adolescents with end stage kidney disease (ESKD).[1] Dialysis therapy, either prior to transplant or after graft failure, is associated with worse survival and quality of life and greater costs compared to transplant.[2-6] Unlike adults, almost all children with ESKD are eligible for transplant in the United States (US).[7] Nevertheless, children receiving a kidney transplant have a life expectancy 20 years shorter than the general population.[8]

The first kidney transplant was performed in a child 50 years ago and there have since been significant improvements specific to the care of transplant recipients,[9] including improvements in immunosuppression protocols, and in infectious disease monitoring, prophylaxis, and treatment. In addition, advances in surgical techniques have allowed successful transplantation in smaller and younger children. These changes may have affected outcomes.[10-12]

Patient survival has improved over time for pediatric transplant recipients.[3, 13] Although there are many possible reasons, there are three major paths to better survival of transplant recipients: improvements in graft survival, decreases in mortality risk following graft failure, and decreases in the risk of death with graft function. Graft survival has improved over time for pediatric recipients.[13] Because mortality rates are lower for patients with graft function than for those being treated with dialysis,[2, 3] improvements in graft survival will result in improved patient survival. We recently showed that patient survival has also improved over time among children receiving dialysis.[7] Therefore, decreased mortality risk following return to dialysis after graft failure may also have contributed to decreases in overall mortality. It remains unknown if the risk of death with graft function has changed over time. Half of deaths following pediatric kidney transplant occur in patients with graft function.[3] We aimed to determine whether the risk of death with graft function has changed over calendar time among children and adolescents who received their first kidney transplant from 1990-2010 in the US. Based on prior work,[2, 3, 7, 13-15] we hypothesized that mortality rates improved over time.

RESULTS

Patient characteristics

We identified 17,468 children and adolescents who received their first kidney transplant at <21 years of age from January 1990 until December 2010. The cohort was followed for a median of 8.4 years (interquartile range (IQR) 4.2-13.6 years), with 157,201 person-years of observation, of which 129,146 person-years (82.2%) were during graft function, with the remainder during dialysis after graft failure.

Table 1 summarizes the characteristics of patients receiving their first kidney transplant during the observation period. The age at first transplant remained stable but the proportion of all first transplants in recipients 18-21 years of age decreased from 30.2% in 1990-1994 to 22.1% in 2005-2010. Consistent with data from the general US population,[16] the proportion of recipients classified as "Other" race (not White or Black) increased over the observation period. Primary kidney disease, socioeconomic status (SES), duration of dialysis before first transplant, proportion of pre-emptive transplants, and primary insurance coverage appeared stable from 1990-2010. The proportion of living donor first transplants was lower in the most recent, compared with earlier periods. The greatest amounts of missing data were in the earliest time period and involved the insurance coverage and co-morbidity variables. Few patients had ≥1 recorded co-morbidity; however, the proportion of subjects with at least one recorded co- morbidity was higher in 2005-2010 compared to earlier.

Table 2 summarizes the crude all-cause mortality rates and recorded causes of death for the cohort. There were 2003 deaths during observation (12.7 deaths per 1000 person-years); 5 deaths occurred during the transplant surgery. Of all deaths, 985 (49.2%) occurred during graft function (7.6 deaths per 1000 person-years) and the remaining 1018 (50.8%) deaths were during dialysis after graft failure (36.1 deaths per 1000 person-years).

Among those who died, the median time from first transplant to death was 6.6 years (IQR 2.5- 10.9 years) at any time after first transplant, 3.9 years (IQR 0.6-8.6 years) for those who died with graft function, and 8.8 years (IQR 5.3-11.9 years) for those who died after graft failure. The length of follow-up was not equal for all subjects.

The 5-year patient survival was 93.2% for those receiving a first transplant from 1990-1994, 95.3% for those receiving a first transplant from 1995-1999, and 95.1% for those receiving a first transplant from 2000-2004. Kaplan-Meier survival curves for the cohort are shown in Figure 1.

The most commonly recorded causes of death with a functioning allograft that were not missing (33.1%) or unknown (18.7%) were infection (16.0%), cardiovascular (14.3%), or malignancy (7.2%). The proportion of deaths during graft function attributed to cardiovascular disease or infection did not appear to change over time (Table 2). Cause of death during dialysis after a failed transplant was missing in 15.8% and the most commonly recorded causes were cardiovascular (42.9%) or infection (12.7%).

Changes in mortality over the observation period

Table 3 shows the hazard ratios (HR) for all-cause mortality per 1-year increment in calendar year of first transplant from 1990-2010. In the adjusted model, each 1-year increment in calendar year of first transplant was associated with a HR of 0.97 (95% confidence interval (CI) 0.96, 0.98) for death at any time after the first transplant. Focusing on time with graft function, each 1-year increment in calendar year of first transplant was associated with a lower mortality risk (adjusted HR of 0.98, 95% CI 0.97, 0.99). Removing insurance coverage and co-morbidity status from the models did not change the point estimates or confidence intervals for the HRs for death.

Insurance coverage and co-morbidity status were more frequently missing in the 1990-1994 time period. To examine the impact of missing covariate data, we conducted a sensitivity analysis, restricting the cohort to subjects who received their first transplant from 1995-2010. The all-cause mortality HRs for patients transplanted from 1995-2010 were similar in magnitude compared to the full cohort, with an adjusted HR of 0.98 (95% CI 0.96, 0.99) during all observation time after transplant and an adjusted HR of 0.99 (95% CI 0.97, 1.00) during periods of graft function.

There was a significant interaction between recipient age and year of transplant in univariate models examining survival at any time after first transplant (p=0.006); this interaction did not reach significance in univariate models focused on time with graft function (p=0.06). We also show results of analyses stratified by age in Table 4. There was a greater improvement in survival over calendar time for children <5 years of age at transplant than for those ≥5 years old during all observation time after first transplant and when focusing on observation with graft function.

The associations between other variables included in the multivariable models and mortality are shown in Figure 2. Higher mortality risk was independently associated with the presence of ≥1 recorded co-morbidity, public insurance (versus no coverage), lower estimated SES, “Other” primary disease, and female gender. Receiving a living donor transplant was associated with a substantially lower risk of death, even in models adjusted for renal replacement therapy modality (graft function versus dialysis after graft failure). Younger recipient age was associated with a higher risk of death during graft function. Black race was associated with a higher risk of death than white race at any time after the first transplant, but not when comparisons were limited to time with graft function. There were no significant associations between mortality and the degree of human leukocyte antigen (HLA) mismatch or donor age (data not shown). Treatment with dialysis after graft failure was associated with a 4.85 times higher risk of death (95% CI 4.40, 5.35) compared to periods of graft function. Each additional year of dialysis prior to first transplant was associated with a small but significantly higher risk of death with graft function (0.3% increased risk of death, p=0.01) and of death at any time after transplant (0.4% increased risk of death, p=0.001).

DISCUSSION

We examined changes in survival during graft function among over 17,000 US children and adolescents who received their first kidney transplant from 1990-2010. Although we found significant improvements in mortality risk over calendar time, these improvements amounted to a decrease in mortality of about 3% per year during all observation time after first transplant and about 2% per year during periods of graft function. Similar to what we previously observed in children with ESKD initially treated with dialysis,[7] survival improved for both the youngest and older children after transplantation, but appeared to be greater for children <5 years of age.

Others have examined changes in patient survival over calendar time in children undergoing kidney transplantation.[2, 3, 10, 15, 17] An analysis of the Scientific Registry of Transplant

Recipients (SRTR) included children <18 years of age receiving a kidney transplant in the US and reported that mortality decreased by about 5% per calendar year[13]–a substantially larger improvement than we observed. In contrast to our findings that younger children (<5 years of age) may have seen greater improvements than older children, that study found no difference in improvements in mortality risk by recipient age. The differences in the magnitude of the improvement over time and in the observed associations with age between studies may be due to several factors. For example, the analysis of SRTR data included repeat transplants, did not adjust for renal replacement therapy modality, and used the missing indicator method to deal with missing covariate data, potentially leading to bias.[18] We adjusted for renal replacement therapy modality in order to examine changes in the rates of death with graft function to consider the relative contribution of improvements specific to transplant or dialysis care.

Several factors may have contributed to the observed decreases in mortality in our study. Changes in immunosuppression protocols have occurred over the observation period, with fewer children receiving prednisone at transplant or 1 year follow-up.[11] The percentage of children receiving lymphocyte depleting induction therapy decreased from 50% in 1996 to 6% in 2000, increasing again to 22% in 2009.[10] Lymphocyte depleting therapy has been associated with a higher risk of post-transplant lymphoproliferative disorder, but not death.[19] Regarding infection, the first randomized, placebo-controlled trial of acyclovir prophylaxis against cytomegalovirus infection in kidney transplant recipients was published in 1989.[20] A recent meta-analysis found that cytomegalovirus prophylaxis was associated with a 37% reduction in all-cause mortality among solid organ transplant recipients.[21]

Relatively healthier transplant recipients in more recent years may have biased towards the improved survival over time that we observed. However, we noted that the proportion of recipients with at least one identified co-morbidity appeared to increase over time. Additionally, changes in the demographics of transplanted children may have influenced the results. Adolescents have a high risk of graft loss and late-onset rejection likely due to poor adherence with immunosuppressant medication.[22-24] However, over the study period, we observed a decrease in the proportion of patients who were 18-21 years of age—the age group at highest risk of graft failure.[23]

In 2005, towards the end of our observation period, the Share 35 policy was enacted to provide children <18 years of age with increased access to kidneys from deceased donors <35 years of age.[25] Accordingly and as noted above, between 2005 and 2010, there was a decrease in the proportion of transplant recipients who were 18-21 years of age. After 2005, we also observed a decrease in the proportion of patients receiving living donor transplants, but no change in the percentage of pre-emptive transplants, as recently reported by others.[13] It is possible that the Share 35 policy contributed to the recent decrease in the percentage of patients receiving living donor grafts. As access for children to deceased donor transplants improved due to shorter waiting times, the pressure to pursue living donation may have fallen. An increasing prevalence of medical conditions in the general population that may preclude donation (i.e. hypertension, diabetes), or other factors, may also have contributed to the lower proportion of living donors.[26] These trends are distinct from other countries, where rates of living kidney donation appear to be increasing over time.[27] Living donation,

when available, should remain the preferred type of transplant, not only because of its positive impact on graft survival,[10, 11] but because we observed that living donation was independently associated with a significantly lower risk of death after transplantation—even after adjustment for renal replacement therapy modality. This suggests that the survival advantage of living donor recipients is not exclusively mediated through superior graft survival, confirming unadjusted observations from other US registry data.[28]

We identified several factors associated with a higher risk of death with graft function. As shown in prior studies, lower SES was associated with higher mortality risk.[3] Similar to children with ESKD treated with dialysis, a higher risk of death after transplant was observed in females compared with males.[2, 3, 7] The biological basis for this finding is unknown and conflicts with data in the general pediatric population where males have a higher mortality risk than females.[29] While deserving further study, it is notable that in children with chronic kidney disease, female gender was an independent risk factor for left ventricular hypertrophy.[30] It is also possible that the higher risk of death in females with ESKD is due to a higher prevalence of systemic inflammatory diseases in females compared with males.[31] We stress that the associations between these covariates and mortality risk after first transplant must be interpreted with caution. Our study was not designed to identify risk factors for death and we did not test for multiple interactions.

We acknowledge several limitations to the present analysis. Residual confounding by variables not captured in the US Renal Data System (USRDS) may have contributed to the associations observed.[32] For example, most co-morbidity data in the USRDS is more relevant to adults than to children with ESKD and does not capture conditions such as developmental delay or pulmonary disease that have themselves been associated with decreased survival in children receiving maintenance dialysis.[33] Because USRDS data is extracted from administrative forms often completed by non-clinical staff, there is a potential for under reporting of co-morbidities and misclassification of underlying diagnoses. Additionally, we were unable to formally test changes in cause-specific mortality over time due to the large amount of missing cause of death data. Adjustment for SES was limited because median household income by zipcode provides an imperfect estimate of individual SES. Control for insurance coverage and co-morbidities was also limited due to a large amount of missing data before 1995. In addition, there have been changes in public insurance access for children over the observation period, and changes to the way co-morbidities are captured into the USRDS.[7, 34] We used multiple imputation to estimate missing covariates; although this method is preferred over analyses including only subjects with complete data and over the missing indicator method,[35, 36] it does have limitations. A sensitivity analysis including only patients transplanted after 1995, when missing data were far less common, returned results of similar direction and magnitude to the models including the entire cohort.

In conclusion, the present study showed a significant decrease in all-cause mortality rates from 1990-2010 among first kidney transplant recipients <21 years old. Improvements in the rate of death with graft function were smaller than the improvements in mortality rates observed without adjustment for renal replacement therapy modality. The magnitude of the improvement was smaller in the oldest patients. While cause of death was often missing, it is

noteworthy that infection and cardiovascular disease remain the most commonly recorded causes of death with graft function. The results of this study, combined with other studies, suggest that the observed improvements over time in patient survival after kidney transplant are likely due to a combination of the effects of improved graft survival,[13] improved dialysis care,[7] and improved transplant care. These results are encouraging, but further improvement is needed. Additional interventions to improve survival might include efforts to increase living donation, targeted approaches to minimizing cardiovascular disease and infection, and emphasis on strategies to improve graft survival.

METHODS

Data source and population

This was a retrospective cohort study of children and adolescents recorded in the USRDS database. As previously described, the USRDS includes virtually all children treated for ESKD in the US.[6, 7, 37] Patient data for the USRDS is extracted from administrative forms, including the 2728 form, which is mandatory for all patients with ESKD. These forms are signed by the treating physician but are often completed by non-clinical staff working with the patients.

We included patients receiving a first kidney transplant at <21 years of age, between January 1, 1990 and December 31, 2010, and followed until December 31, 2010. We included children up to 21 years of age as many pediatric centers continue to treat individuals >18 years old. We divided the observation interval into four approximately equal periods to highlight how patient characteristics and the amount of missing data have changed over time.[6, 7] The Institutional Review Board at the Montreal Children-s Hospital approved the study.

Primary exposure and outcome variables

The *primary exposure* was the calendar year of first kidney transplant. The *primary outcome* was all-cause mortality. Deaths are reported to the USRDS using the Death Notification Form and from the National Vital Statistics Database.[6, 37]

Association between year of initiation and mortality rate

We calculated all-cause mortality rates (deaths per 1000 person-years of observation) for each year of first transplant from 1990-2010 and examined plots of the data. Although there was year-to-year variability in mortality, overall, mortality rates decreased gradually and linearly with year of first transplant; there were no clear ‘step’ changes. Therefore, the calendar year of first transplant was analyzed as a continuous variable in 1-year increments.

We generated Kaplan-Meier curves showing survival over the observation period and also report 5-year survival for each time period where all recipients had at least 5 years of follow-up (1990-2004). We used Cox models to estimate the association between calendar year of first kidney transplant and the relative mortality risk during graft function (HR with 95% CI). The HRs were expressed in terms of 1-year calendar time increments. Time zero was the date of first kidney transplant. Patients were censored at death, end of observation,

or third transplant (to simplify modeling). Initial models did not distinguish observation time with graft function from observation time during dialysis following graft failure. To focus on changes in the risk of death with graft function over calendar time, we fit additional models including a time-dependent 'status' variable (functioning transplant versus dialysis after graft failure)[2]; status was updated at 3-month intervals. In these models, all patients started observation with graft function; status was changed to 'failed, on dialysis' at graft failure, and back to 'functioning graft' at re-transplant. The reference status was a functioning graft. Proportionality of hazards for the exposure of calendar time was confirmed by examining plots of the data.

We also report causes of death after transplantation during graft function and during dialysis after graft failure. Cause of death was determined from the USRDS Death Notification Form that was updated in 1990 to include 59 causes of death. The form was again modified in 2004 to include 70 causes of death divided into cardiac, vascular, infection, liver disease, gastrointestinal, metabolic, endocrine, "Unknown," and "Other" categories.[6, 7, 37]

Covariates

Models were adjusted for recipient gender, race, SES, age at first kidney transplant, primary kidney disease, insurance coverage, number of co-morbidities, and time on dialysis prior to transplant. SES was estimated using median household income by zipcode and classified by quartile within the US Census data (2000).[38] We also examined several donor characteristics: living versus deceased donor source, degree of HLA mismatch (categorized as the number of mismatches: 0-1, 2-3, or 4-6), and donor age. A quadratic recipient age at first transplant term was included to model the U-shaped relationship between age and mortality risk, where mortality increases with decreasing age in the youngest children, and increases with increasing age in older children. We considered possible interactions between year of first transplant and age at first transplant, categorized as <5 years versus ≥5 years of age, based on our prior study in children initiating ESKD treatment with dialysis and the age categories reported in the USRDS annual report.[6, 7] The age-stratified models did not include a quadratic age term.

In additional models, insurance coverage and the number of recorded co-morbidities were excluded due to limitations of these variables. Both of these variables had relatively larger amounts of missing data, especially in earlier time periods. In addition, insurance status pertains to coverage at the time of ESKD initiation and may not reflect insurance status for the duration of observation since Medicare is time-limited after transplant for those <65 years of age and eligibility for Medicaid and/or private insurance may change over time. Furthermore, the majority of co-morbidities captured by the USRDS 2728 ESKD initiation form are not specific for the pediatric population and include categories such as atherosclerotic heart disease, chronic obstructive pulmonary disease, and alcohol/drug dependence.[7, 37] Finally, reporting of both insurance coverage and co-morbidity has changed, with updates to the USRDS 2728 form in 1995 and 2005.[7, 37]

Imputation of missing data

We used multiple imputation methods[35] to estimate the values of missing covariates, as previously described.[7] In brief, the imputation method uses the distribution of values for patients with non-missing data, together with the distributions of all other variables in the model, to estimate the values of missing data. Because most of the missing data were in the earliest time period, we fit additional models including only patients who received their first transplant after 1995 to assess the impact of missing data on the results.

Data analyses were performed using SAS 9.2 (Cary, North Carolina) and S-plus 6.1. A 2-sided P value <0.05 was considered statistically significant.

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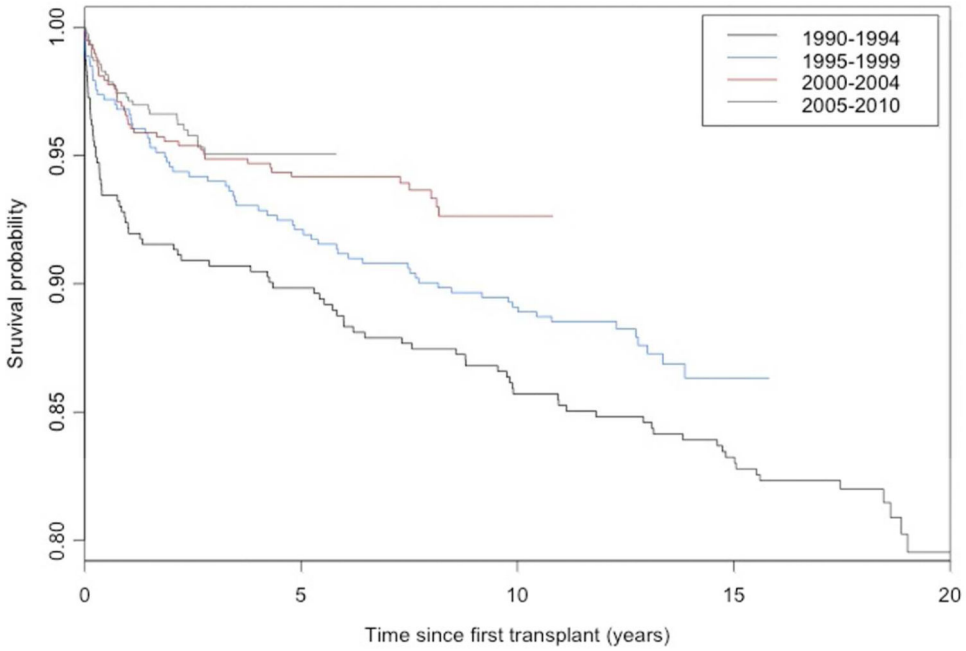

Figure 1. Kaplan-Meier estimate of survival for children receiving their first kidney transplant in the United States in successive time periods

The number of individuals still under observation at 1, 2, 5, 10, 15, and 20 years after first kidney transplant is indicated in the table below the curves. The log-rank p-value for comparisons between time periods was <0.0001.

Table for number at risk to accompany Figure 1

Time period	Years after first kidney transplant						
	0	1	2	5	10	15	20
1990-1994	3738	3603	3572	3459	3153	2783	284
1995-1999	4039	3974	3937	3834	3550	413	-
2000-2004	4300	4242	4207	4081	531	-	-
2005-2010	5386	4540	3480	742	-	-	-

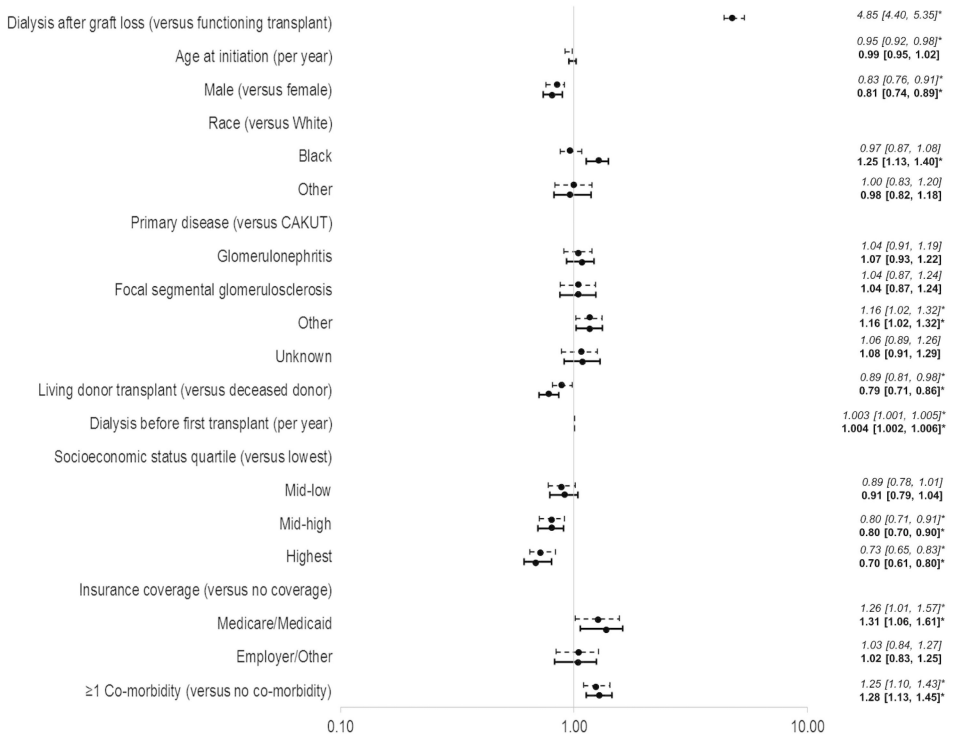

Figure 2. Adjusted covariate hazard ratios for all-cause mortality after kidney transplant

The hazard ratios (HR) for each covariate (circles) and their 95% confidence intervals (vertical bars) are plotted on a logarithmic scale. Models focusing on observation with graft function are shown by the dashed horizontal lines with the HR [95% confidence interval] displayed in italics at the right side of the figure. Models focusing on all observation time after first transplant are shown by the solid horizontal lines with the HR [95% confidence interval] displayed in bold at the right side of the figure. *Indicates a statistically significant HR.

Models were adjusted for recipient age, recipient age squared, donor (living versus deceased), gender, primary renal disease, socioeconomic status quartile, duration of dialysis before first transplant, race, insurance coverage, and number of co-morbidities. Model focusing on observation with graft function was also adjusted for renal replacement therapy modality (graft function versus dialysis after graft failure—a time-dependent variable).

Table 1

Patient characteristics

Year of first kidney transplant	**1990-1994**	**1995-1999**	**2000-2004**	**2005-2010**
Number of first transplants	3740	4041	4300	5387
Age at first transplant (years)	15.4 (9.4-18.6)	14.8 (9.3-18.0)	14.8 (9.3-18.0)	15.0 (9.3-17.7)
Recipient 18-21 years old at first transplant	1130 (30.2)	1017 (25.2)	1055 (24.5)	1190 (22.1)
Males	2186 (58.5)	2369 (58.6)	2496 (58.1)	3136 (58.2)
Race				
White	2780 (74.3)	2976 (73.7)	3107 (72.3)	3544 (65.8)
Black	756 (20.2)	840 (20.8)	852 (19.8)	924 (17.2)
Other	204 (5.5)	225 (5.6)	341 (7.9)	919 (17.1)
Primary kidney disease				
Congenital anomalies of the kidney and urinary tract	690 (18.5)	1057 (26.2)	1256 (29.2)	1662 (30.9)
Glomerulonephritis	996 (26.6)	1024 (25.3)	885 (20.6)	904 (16.8)
Focal segmental glomerulosclerosis	355 (9.5)	478 (11.8)	522 (12.1)	719 (13.4)
Other	835 (22.3)	915 (22.6)	1006 (23.4)	1205 (22.4)
Unknown	315 (8.4)	306 (7.6)	392 (9.1)	602 (11.2)
Missing	549 (14.7)	261 (6.5)	239 (5.6)	295 (5.5)
Socioeconomic quartile				
Lowest	716 (19.1)	745 (18.4)	795 (18.5)	962 (17.9)
Mid-Low	694 (18.6)	686 (17.0)	751 (17.5)	956 (17.8)
Mid-High	948 (25.4)	942 (23.3)	1032 (24.0)	1236 (22.9)
Highest	1187 (31.7)	1314 (32.5)	1500 (34.9)	1797 (33.4)
Missing	195 (5.2)	354 (8.8)	222 (5.2)	436 (8.1)
Years on dialysis before first transplant	0.6 (0.0-1.4)	0.7 (0.0-1.5)	0.8 (0.0-1.8)	0.8 (0.0-1.7)
Living donor first transplant	1944 (52.0)	2301 (56.9)	2533 (58.9)	2321 (43.1)
Pre-emptive first transplant	845 (22.7)	979 (24.2)	1066 (24.8)	1393 (25.9)
Primary Insurance Coverage				
Medicare/Medicaid	939 (25.1)	1008 (24.9)	1267 (29.5)	1910 (35.5)
Employer/Other	857 (22.9)	2010 (49.7)	2501 (58.2)	2943 (54.6)

Year of first kidney transplant	1990-1994	1995-1999	2000-2004	2005-2010
No coverage	123 (3.3)	256 (6.3)	247 (5.7)	234 (4.3)
Missing	1821 (48.7)	767 (19.0)	285 (6.6)	300 (5.6)
Co-morbidities				
None	1580 (42.3)	3106 (76.9)	3754 (87.3)	4425 (82.1)
≥ 1 Co-morbidity	361 (9.7)	352 (8.7)	278 (6.5)	665 (12.3)
Missing	1799 (48.1)	583 (14.4)	268 (6.2)	297 (5.5)

Data presented as median (interquartile range) or n (%).

Table 2

Crude all-cause mortality rates and cause of death

	Year of first kidney transplant				
	1990-1994	**1995-1999**	**2000-2004**	**2005-2010**	**Entire Interval**
Person-years of observation	57869	49397	33942	15993	157201
Total number of deaths	911	606	352	134	2003
Crude all-cause mortality rate (per 1000 person-years)	15.7	12.3	10.4	8.4	12.7
Deaths during graft function (% of all deaths)	387 (42.5)	305 (50.3)	196 (55.7)	97 (72.4)	985 (49.2)
Deaths during dialysis after graft failure (% of all deaths) *	524 (57.5)	301 (49.7)	156 (44.3)	37 (27.6)	1018 (50.8)
Recorded cause of death [a] **by post-transplant renal replacement therapy (% of deaths by modality)**					
Missing					
N (% of deaths with graft function)	141 (36.4)	94 (30.8)	56 (28.6)	35 (36.1)	326 (33.1)
N (% of deaths after graft failure)	74 (14.2)	43 (14.4)	34 (21.8)	9 (25.0)	160 (15.8)
Unknown					
N (% of deaths with graft function)	71 (18.3)	55 (18.0)	41 (20.9)	17 (17.5)	184 (18.7)
N (% of deaths after graft failure)	55 (10.5)	30 (10.0)	10 (6.4)	1 (2.8)	96 (9.5)
Infection					
N (% of deaths with graft function)	62 (16.0)	42 (13.8)	34 (17.3)	20 (20.6)	158 (16.0)
N (% of deaths after graft failure)	70 (13.4)	39 (13.0)	16 (10.3)	4 (11.1)	129 (12.7)
Cardiovascular					
N (% of deaths with graft function)	40 (10.3)	51 (16.7)	32 (16.3)	18 (18.6)	141 (14.3)
N (% of deaths after graft failure)	236 (45.2)	119 (39.8)	65 (41.7)	15 (41.7)	435 (42.9)
Malignancy					
N (% of deaths with graft function)	29 (7.5)	29 (9.5)	10 (5.1)	3 (3.1)	71 (7.2)
N (% of deaths after graft failure)	6 (1.1)	5 (1.7)	1 (0.6)	0 (0.0)	12 (1.2)
Other					
N (% of deaths with graft function)	22 (5.7)	15 (4.9)	12 (6.1)	1 (1.0)	50 (5.1)
N (% of deaths after graft failure)	46 (8.8)	36 (12.0)	11 (7.0)	7 (19.4)	100 (9.9)
Hemorrhage					

	Year of first kidney transplant				
	1990-1994	**1995-1999**	**2000-2004**	**2005-2010**	**Entire Interval**
N (% of deaths with graft function)	8 (2.1)	9 (2.9)	4 (2.0)	2 (2.1)	23 (2.3)
N (% of deaths after graft failure)	15 (2.9)	12 (4.0)	6 (3.8)	0 (0.0)	33 (3.3)
Trauma					
N (% of deaths with graft function)	12 (3.1)	8 (2.6)	3 (1.5)	1 (1.0)	24 (2.4)
N (% of deaths after graft failure)	7 (1.3)	7 (2.3)	6 (3.8)	0 (0.0)	20 (2.0)
Metabolic					
N (% of deaths with graft function)	2 (0.5)	2 (0.7)	4 (2.0)	0 (0.0)	8 (0.8)
N (% of deaths after graft failure)	13 (2.5)	8 (2.7)	7 (4.5)	0 (0.0)	28 (2.8)

[a] Infectious causes included: septicemia, peritoneal access, peritonitis, hepatitis, viral infection, tuberculosis, AIDS, or central nervous system, heart, lung, abdomen, or genitourinary infections. Cardiovascular causes included: acute myocardial infarction, pericarditis, cardiac tamponade, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest (cause unknown), valvular heart disease, congestive heart failure, pulmonary embolus, or cerebrovascular accident including intracranial hemorrhage.

[*] includes 5 deaths during the transplant surgery.

Table 3

All-cause hazard ratios for mortality after first kidney transplant (1990-2010)

	All observation after first transplant	Observation with graft function
Unadjusted (calendar year of first transplant)	0.97 [0.96, 0.98][a]	0.98 [0.97, 0.99][a]
Adjusted model[*]	0.97 [0.96, 0.98][a]	0.98 [0.97, 0.99][a]

Data are shown as hazard ratio [95% confidence intervals] for mortality per 1-year increment in calendar year of first transplant.

[a]Indicates statistically significant hazard ratio.

[*]Adjusted for recipient age, recipient age squared, donor (living versus deceased), gender, primary renal disease, socioeconomic status quartile duration of dialysis before first transplant, race, insurance coverage, and number of co-morbidities. Models focusing on observation with graft function (last column) were also adjusted for renal replacement therapy modality (graft function versus dialysis after graft failure—a time-dependent variable).

Table 4

Age-stratified mortality after first kidney transplant (1990-2010)

	All observation after first transplant		Observation with graft function	
	Age <5 years	**Age ≥5 years**	**Age <5 years**	**Age ≥5 years**
Number of first transplants	2359	15104	2359	15104
Person-years of observation	20378	136824	18896	110250
Total number of deaths	223	1775	178	807
Crude all-cause mortality rate (per 1000 person-years)	10.9	13.0	9.4	7.3
Hazard ratios for all-cause mortality per 1-year increment in calendar year of first kidney transplant				
Unadjusted (calendar year of first transplant)	0.94 [0.92, 0.97][a]	0.97 [0.96, 0.98][a]	0.95 [0.93, 0.98][a]	0.98 [0.97, 0.99][a]
Adjusted model[*]	0.95 [0.92, 0.98][a]	0.98 [0.97, 0.99][a]	0.96 [0.93, 0.98][a]	0.98 [0.97, 0.99][a]

Data are shown as hazard ratio [95% confidence intervals] for mortality, unless otherwise indicated.

[a] Indicates statistically significant hazard ratio.

[*] Adjusted for recipient age, donor (living versus deceased), gender, primary renal disease, socioeconomic status quartile, duration of dialysis before first transplant, race, insurance coverage, and number of co-morbidities. Models focusing on observation with graft function (last two columns) were also adjusted for renal replacement therapy modality (graft function versus dialysis after graft failure—a time-dependent variable).