CENTER CHARACTERISTICS AND KIDNEY TRANSPLANT CANDIDATE OUTCOMES

By

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To Amy and Caila

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There are approximately half of a million patients diagnosed with End-Stage Renal Disease (ESRD) currently in the United States. There are two general classes of treatment for ESRD, maintenance dialysis and kidney transplantation. Kidney transplantation is considered the preferred treatment for ESRD patients who are medically cleared for the surgical procedure as it is associated with an improved quality of life and longer life expectancy. A kidney transplant may derive from a living or a deceased donor. For patients to receive a deceased donation, they must be placed on a waiting list at a transplant center. There are currently approximately 240 kidney transplant centers in the United States. There are numerous characteristics that vary among transplant centers.

An important question is whether or not these center factors are associated with prospective transplant candidate survival. Moreover, whether these center factors are applicable to all transplant candidates or have differential effects on certain patients is also unclear. This study examined these questions using a national database containing patient-level information on outcomes for all adult solitary kidney transplant candidates from 1995–2000. Results of this study indicate that transplant center characteristics are significantly associated with patient survival after listing. Of the center characteristics, expected waiting time had the greatest impact

on candidate survival. Candidates listed at centers with the longest expected waiting time had a 32% increased hazard for death, translating to approximately two and a half years of reduced life expectancy, as compared to candidates listed at centers with a relatively short expected waiting time. The main findings were applicable to the general candidate population as well as high-risk candidate subgroups.

Results of this study may be utilized to inform patients and caregivers about the important impact of characteristics of transplant centers on prospective survival for candidates of kidney transplantation. Investigation into applications of these findings in healthcare policy, for different transplant populations, and in other medical contexts will be examined in follow-up studies deriving from this study.

CHAPTER 1
INTRODUCTION

Kidney transplantation is regarded as the most effective treatment modality for End-Stage Renal Disease (ESRD) patients who are medically cleared for the surgical procedure. As of October, 2006, there were over 65,000 patients listed to receive a solitary kidney transplant in the United States. The number of candidate listings has increased by 60% over the past decade and the number of candidates has increased across all age, ethnic, and gender groups. Over the corresponding era, the number of available kidneys deriving from deceased donors increased, but at a much more modest rate. As a result, the difference between the availability of and demand for kidney transplantation has markedly increased. One of the most important implications of this temporal shift has been a significant increase in expected waiting times and increased death rates for kidney transplant candidates awaiting the procedure. This trend is particularly troubling for transplant candidates and the healthcare sector for two primary reasons. First, kidney transplantation has been shown to double a patient's life expectancy as compared to the alternative treatment modality of maintenance dialysis, and, as such, delayed access to transplantation places patients at an increased risk of mortality. Second, increased duration of dialysis prior to transplantation has deleterious effects on recipients following transplantation, resulting in a cohort of patients with increased risk for morbidity and mortality after the procedure.

There are approximately 240 transplant centers currently operating in the United States. Among transplant centers, there is significant variability in expected waiting times for candidates to receive a transplant. In addition, performance evaluations suggest that outcomes for transplant recipients vary significantly related to the quality of care at individual transplant centers. Research also indicates that centers with the highest transplant volume are associated with improved patient and graft survival following the transplant procedure. Moreover, both short-term complication rates and long-term survival for transplant recipients are significantly variable based on the quality of the donor organ. The proportion of high- and low-quality donor organs also is variable throughout regions of the country and at individual centers. Cumulatively, there are multiple factors that may potentially influence a patient's prognosis relative to the selection of a particular center. The current evidence suggests that patients have incentives to receive a transplant as early as possible, at the best performing center, and receive the highest quality donation. However, despite these known effects, there has not been a comprehensive study to examine the joint impact of these factors on transplant candidate outcomes. This information is particularly salient given the expanded candidate waiting list and associated time to transplantation. In addition, the reliability of historical transplant center factors on prospective patient outcomes has not been thoroughly evaluated. Transplant candidate characteristics and prognoses are also widely variable based on age, ethnicity, primary cause of ESRD, and clinical presentation. Whether certain transplant center profiles are more applicable to patients with different prognoses and care needs has not been previously investigated. In particular, certain patient groups (including individuals over the age of 65, African-Americans, and the obese) have differential survival rates on dialysis and following transplantation relative to the general cohort of patients. In this regard, center characteristics may have a unique impact on these subgroups. The purpose of this dissertation is to analyze the association of transplant center factors with patient outcomes, which may ultimately be used to guide candidate and caregiver decision making to select specific centers for a kidney transplant. The specific aims of this study are to

I. Determine whether characteristics of transplant centers (volume, performance ratings, waiting time, and donor quality) are significantly associated with candidate mortality after listing for a solitary kidney transplant.

II. Determine the relative impact of center characteristics and estimate transplant candidate survival rates at incremental levels that may be utilized as a tool for selection of a center.

III. Determine the significance and relative impact of transplant center characteristics on candidate mortality after listing for a solitary kidney transplant in three high-risk patient groups (elderly, obese, and African-Americans patients).

This study will be carried out utilizing a national database containing the population of renal transplant candidates listed for transplantation in the United States. The database contains patient-level information and de-identified indicators of transplant centers. The results of this study will be applicable for assessing the importance of transplant center factors and potentially used to help guide patients and caregivers in their selection of a center. Although there are other factors which may influence the selection of a center, an objective measure of the impact of these transplant center factors may be crucial for informing potentially life-altering decisions. Secondary outcomes of this study will include descriptive analyses of transplant center characteristics across the United States and to assess the reliability of historical center factors on prospective levels.

Chapter 2 provides a brief historical background of kidney transplantation and treatment of ESRD patients, a summary of the relevant literature in this research area, and a conceptual framework for this study. Chapter 3 provides descriptive statistics of the candidate population and transplant centers as well as statistical methodology for conducting this study. Chapter 4 includes the results of the analyses and tables and figures depicting the outcomes of the models. Chapter 5 includes discussion of the findings, and Chapter 6 includes conclusions and potential follow-up studies deriving from this research.

CHAPTER 2
BACKGROUND

Kidney Transplantation for End-Stage Renal Disease Patients

In 2004 there were nearly half a million ESRD patients in the United States (1). This count has increased more than three-fold since 1988, partially explained by increased rates of hypertension, diabetes, improved clinical detection, and an aging population. The most common treatment modality for ESRD patients is maintenance dialysis. Dialysis is classified as either hemodialysis or peritoneal, and both modalities require the use of a machine for renal function replacement either at a designated facility or home-based. The alternative treatment for ESRD patients is kidney transplantation. The first kidney transplant was performed in 1954 by Dr. Joseph Murray between identical twins. Significant advances in surgery, immunology, pharmacy, and clinical care have contributed to widespread application of kidney transplantation and over 16,000 transplants were performed in the United States fifty years later in 2004. The procedure is generally classified in two broad forms: deceased donor and living donor transplantation. Deceased donors are the source of the majority of transplants, although living transplant rates have increased significantly over the past fifteen years.

Variation in Patient Outcomes by Providers of Healthcare

The notion that patient outcomes vary based on characteristics of the provider of care has been investigated in a variety of medical contexts. There is extensive evidence in the United States to suggest that there are differences in patient outcomes as a function of the individual caregiver, hospital, and region of the country. Schrag et al. investigated the association of hospital procedure volume and mortality following surgery for colon cancer (2). The study found significantly improved outcomes associated with hospitals with increased volume, although it was also noted that the variance in outcomes based on other factors was significantly higher. Utilizing a national Medicare claims database, a 2005 study concluded that providers with higher volume were associated with reduced morbidity rates after radical prostatectomy (3). Examining the treatment of patients with acute myocardial infarction, Krumwell et al. found significant geographic and physician specialty variation in the use of efficacious drug therapy in the United States (4). Diminished outcomes have also been demonstrated for individual surgeons with fewer procedure experiences relative to high and intermediate volume surgeons (5). A national study also found significantly reduced short- and long-term outcomes for cardiac transplant recipients at low-volume centers, which comprised more than half of all centers in the United States (6). Treatment modality and outcomes for patients with myocardial infarction have also been demonstrated to vary by region of the country (7). Additional research supports the concept that geography variations may be important based on particular patient groups (8).

There are numerous additional studies that support the notion that variation in treatment modality and quality of care exists within the United States. These variations suggest that patient selection of particular providers is important and supports the efforts of agencies charged with identifying quality of care between healthcare providers. The evidence also implies that there are potential mechanisms to overcome quality disparities, which include information concerning processes of care at higher performing providers. As the quality of care and rate of medical errors has been questioned and highlighted in recent years, the demand for transparency of information related to outcomes associated with individual institutions and caregivers has proliferated (9). However, there is also mixed evidence as to whether more transparent information regarding provider performance is associated with patient selection of providers or subsequent outcomes. In the context of cardiac bypass surgery, research suggested that report cards (i.e., performance evaluation of providers) had a positive impact on outcomes and processes of care (10,11). Furthermore, there was some evidence that positive report grades influence future utilization for hospitals (12). However, additional reports indicate a lack of awareness among patients concerning performance ratings and a general failure to incorporate ratings in provider selection (13–15). In general, there is a perception in the research and medical communities that variations exist between healthcare providers, but techniques for measuring performance in an equitable manner, interpreting provider evaluations properly, and disseminating information regarding provider quality of care in a manner that is useful to both providers and consumers are both challenging and inexact and will require significant improvement in the years to come.

Factors Associated with Kidney Transplant Center Performance

In the field of kidney transplantation there has also been significant research dedicated towards determining “center effects” associated with outcomes for transplant recipients. In the early days of transplantation these effects were suspected and causes for differences in outcomes for patients attributed to effects other than known medical risk factors were initially considered. In 1986, Burdick and Williams found differences in outcomes associated with patient residence in metropolitan versus those patients that were classified as “out-of-town” (16). This early report suggested that there may be specific care mechanisms for transplant patients that were associated with patient outcomes. An additional report determined that significant differences in patient outcomes were associated with transplant centers that were independent of utilization of specific immunosuppressive regimens and human leukocyte antigen (HLA)–matched recipients (17). This report also suggested that center differences were not confined to the immediate post-transplant period, as graft survival differences related to centers accrued for patients with function after three months post-transplant. This conclusion inferred that processes of care may also be implicated as a causal mechanism associated with center variations. Additional research suggested a “learning curve” associated with immunosuppressive regimens at transplant centers (18). In this case, centers that were able to incorporate the newest, most efficacious regimens were associated with superior outcomes. The report also concluded that variation between centers were minimal for low risk transplants, but derived mostly from treatment of higher risk patients. In this sense, higher risk patients were more sensitive to care practices, and care for these patients may be more complex; differences in centers are more observable for these subgroups. Ogura et al. described characteristics of centers related to different outcomes kidney transplant recipients (19). One important conclusion of this study was that while complication rates did not significantly vary between high- and low-performing centers, graft survival following complications was significantly different. The report found that low-performing centers did have a significantly higher proportion of at risk patients, but adjusted survival rates did not obviate differences. Moreover, the majority of differences between centers existed in the initial six months post-transplant rather than long-term divergences. This report found no significant differences based on the volume of transplants at centers; however, there is extensive literature suggesting improved outcomes at high volume centers in subsequent reports.

Performance evaluations have been produced and published for kidney transplant centers since 1991. The Scientific Registry of Transplant Recipients (SRTR) publishes these reports online and includes classification of centers as either significantly above, below or not significantly different than expected based on the national experience. The 2005 report indicated that among the 191 transplant centers with at least 50 kidney transplants between July 2002 and December 2004, approximately 15% were identified as having statistically higher or lower survival rates compared to the national experience (20). Along with this information being freely available to the patients and referring physicians, insurance carriers may utilize this information for negotiation of contracts with particular centers. A 2006 study, however, suggested that in aggregate these report cards had no significant influence on selection of centers for transplant recipients with the possible exception in younger and more highly educated patients (21). The manuscript found a positive correlation with center performance on a year-to-year basis but that this association reduced over time. Other questions remain whether performance ratings are true reflections of center practice and whether adjustment techniques are sufficient to control for patient variability and associated outcomes (22). As compared to other contexts in which performance evaluations have been conducted, kidney transplant patients have less acuity and longer follow-up periods, and the models have significantly less predictive ability. These factors suggest that performance evaluations in the field of kidney transplantation may be subject to influential factors that may not represent center quality care.

Kidney Transplant Center Volume and Patient Outcomes

There is significant variability in the size and scope of kidney transplant centers. Center volume may be a function of geographic location, presence of competitive centers, academic affiliation and service to underprivileged patients, inclusion of pediatric programs, use of multi-organ transplants, and the proportion of living versus deceased donor kidney transplantation. Early reports indicated that centers with high volume of procedure were associated with improved outcomes. A comparison of high-, mid-, and low-volume centers utilizing national data from 1987 to 1991 demonstrated a 19% increase in one-year graft survival in high-volume centers as compared to low-volume centers (19). This report indicated that there were lower rates of immediate graft function independent of demographic characteristics of recipients at lower-volume centers, but no significant differences in acute rejection episodes. A 1997 United Network of Organ Sharing (UNOS) report concluded that there was significant variation in outcomes at kidney transplant centers, these effects were most apparent in the first-year post-transplantation, and, furthermore, that inferior outcomes were most common among small transplant centers (23). An examination of ten-year survival rates in the United States examined the association of patient outcomes transplanted at centers with large volume (>1000 transplants over ten years) versus lower-volume centers (24). Conclusions of this study included that there was a mildly beneficial effect of large centers, but that these effects were reduced in lower-risk transplants. In addition, this research suggested that large centers were associated with improved outcomes, more notably with elderly recipients and spousal living donations, and, in contrast to previous reports, that differences were most apparent only after two to three years post-transplantation. In an analysis among living transplant recipients, Gjertson detected improved outcomes associated with large centers and that among small centers there were significantly more variable outcomes (25). The most recent evidence of the center volume effect derived from a 2004 manuscript examining outcomes from 1996 to 2000 for both liver and kidney transplant recipients. The primary conclusion of the study was that the highest quartile transplant centers (which transplanted a median number of 167 patients annually) were associated with improved patient outcomes, but there was no detectable difference among the remaining volume level centers in terms of the main outcome of overall graft loss (26). The research also suggested that center effects were most evident within 90 days post-transplantation, but without substantial clinically significant differences in recipient or donor factors associated with centers at different volume strata.

The Impact of Waiting Time on Outcomes for Kidney Transplant Candidates

The survival advantage of kidney transplantation as compared to the alternative treatment of maintenance dialysis was suspected for many years and formalized by Wolfe et al. (27). This analysis utilized a time-dependent model assessing the impact of a solitary kidney transplant in reference to a comparable cohort of medically cleared and wait-listed candidates. The results indicated that transplantation approximately doubled life expectancies for recipients. Wolfe and colleagues (27) further reported that the relative advantage was observable across age, gender, and ethnic strata. The analysis also indicated that there was a significant immediate mortality risk associated with the transplant procedure, but that this risk was obviated within a year of transplantation and the benefits observable thereafter. The survival advantage of kidney transplantation has subsequently been reported in other countries with variations in healthcare structure and patient socio-demographic characteristics (e.g., Australia, New Zealand, and Canada) (28–30). In addition, this advantage extends to higher risk recipients including transplantation of lower quality donor kidneys, candidates over seventy years of age, and obese patients (31–33).

The majority of patients that are listed as candidates for transplantation have already initiated dialysis therapy. As such, waiting time associated with the duration of dialysis is a significant mortality risk for renal transplant candidates prior to the procedure. In addition, there are a number of retrospective analyses that indicate that the duration of dialysis exposure is associated with deleterious outcomes following transplantation. In a single center study, Cosio et al. demonstrated that pre-transplant dialysis was a significant risk factor for post-transplant patient death and overall graft loss (34). Another single center study utilizing transplant data from 1980 to 1995 indicated that these effects were particularly noteworthy among living donor transplant recipients (35). A retrospective analysis deriving from a national database extended this concept by demonstrating that the time on dialysis had a dose-dependent risk on subsequent graft loss and patient death after both living and deceased donor transplantation (36). This analysis reported that even six to twelve months of pre-transplant dialyses was associated with a 37% increase in long-term graft loss as compared to patients without exposure to dialysis. In addition, this study suggested that there was a relatively similar effect in patients with ESRD secondary to diabetes, glomerulonephritis, and hypertension. A separate study confirmed this direct association between the duration of pre-transplant dialysis and the rate of allograft loss in living transplant recipients utilizing registry data in the United States (37). Still yet another study investigated the association between duration of pre-transplant dialysis and rate of allograft loss utilizing a paired-kidney design. This design, though, allowed only outcomes for kidneys deriving from the same donor transplanted to one individual with short dialysis exposure and another recipient with extended dialysis exposure. This design allowed for control of donor characteristics and the potential confounder that patients with extended dialysis had a greater proclivity to accept lower-quality donations. Results indicated that recipients with less than six months of pre-transplant dialysis had over two-fold improved ten-year graft survival as compared with patients with greater than twenty-four months pre-transplant dialysis.

The accumulated evidence highlights the significant benefit of transplantation relative to dialysis as a treatment modality and additionally emphasizes the importance of rapid acquisition of a transplant. The growing wait list for transplantation and the extended waiting times to transplantation from a deceased donor source continue to subject patients to dialysis for longer durations. A transplantation committee report indicated that at the given trajectories, waiting times may average ten years in the next decade (38). Moreover, the differences in waiting times have become increasingly variable across regions of the country. As such, a patient’s active selection of transplant centers may have increased importance in future years. For candidates that plan on being placed on waiting lists for a deceased donor transplant, the prospective waiting time may be one of the primary criteria for this decision.

Donor Quality and Transplant Recipient Outcomes

The association of characteristics of donor kidneys with outcomes after transplantation have been investigated from the early years of transplantation (39). Studies have identified the history of disease among donors, anatomical characteristics of kidneys, biopsy results of the donor kidney, donor and recipient cytomegalovirus status and HLA matching, and donor demographic characteristics as significant risk factors for transplant outcomes (40–48). In aggregate, the combination of risk factors of a donor kidney, most notably the age of the donor, is acknowledged to convey highly variable life expectancies and graft survival for the prospective transplant recipient. There have been several attempts to quantify this aggregated risk of donor characteristics and estimate survival rates based on these levels. The Organ Procurement and Transplantation Network (OPTN) instituted a formalized definition of marginal kidneys in 2002 with the advent of the Expanded Criteria Donor (ECD) (44,49). These deceased donor kidneys were demonstrated to convey a 70% or greater risk for graft loss for transplant recipients relative to an ideal class of donations and were characterized by a donor age over 60 or over 50 accompanied with two additional risk factors including a history of hypertension, elevated terminal donor creatinine, or cerebrovascular cause of death. Nyberg et al. developed a more granulated scoring system based on four transplant characteristics association with six-month renal function level and demonstrated significant variability in outcomes by donor risk groups utilizing a national cohort (43). An alternative risk index has been utilized to create donor risk groups and demonstrated the association with complication rates as well as long-term patient and graft survival (50). This alternative risk index derived from a retrospective analysis indicated that relative to an ideal class of deceased donations (constituting approximately 11% of donations), the highest risk class of donations had a three-fold risk for graft loss. In addition, the analysis demonstrated that the risk for graft failure was particularly notable in the first year post-transplantation, but also persisted for patients with graft retention after one year.

Research indicates that there is significant geographic variability in donor quality with certain transplant network regions having an over 50% likelihood of low-quality donations (51). A portion of this effect may be related to the issue that transplant centers in areas with extended waiting lists may also be more apt to utilize lower-quality kidneys in order to avoid patient deaths on the waiting list. However, there is clear relationship that transplant candidates who list for a kidney in certain regions are more likely to receive higher-risk donor kidneys. Beyond regional effects, there is also likely a transplant center relationship, as centers have variable acceptance practices of donor kidneys. One of the primary purposes of the ECD policy was to identify high-risk kidneys and allow patients to consent to receive these kidneys with the potential benefit of receiving a donation more rapidly. The decision to list for an ECD kidney is often strongly influenced by transplant physicians and other patient advocates. A 2006 study demonstrated that patients who listed for an ECD at centers with a high proportion of ECD candidates had no relative benefit in the amount of waiting time for transplantation (52). In contrast, candidates who listed for ECD kidneys at centers with a low proportion of ECD candidates in fact do receive their transplants much more rapidly. In addition, those patients that listed for a lower-quality organ at centers with a low proportion of ECD candidates were much more likely to actually receive a lower-quality donation.

There are not any explicit policies directing which renal transplant candidates should receive lower-quality kidneys. A national transplant committee report suggested that the candidates most likely to benefit from transplantation are those with decreased life expectancy on dialysis (38). A retrospective analysis indicated that elderly and diabetic patients often receive equivalent benefit from an ECD if it can be received with significantly reduced exposure time to dialysis as compared to a standard criteria donation (SCD) with longer dialysis exposure time (53). In contrast, younger, and presumably healthier, patients have reduced life expectancies when accepting lower-quality organs early after transplantation as opposed to waiting longer for a higher-quality donation. Research also suggests that quality-adjusted life years (QALYs) may be suboptimal for some patients who accept an ECD kidney early after ESRD onset (54). This study also reported that these results varied based on transplant candidate characteristics, inferring that this decision should be patient dependent.

In summary, there is significant evidence indicating that the quality of a donor organ has a marked impact on patient outcomes. Secondly, there is wide variability in the quality of donor organs at a regional level. Additionally, candidate listing practices for lower quality organs at a particular transplant center affect progression along waiting lists and the quality of transplanted organs. Moreover, the decision to accept lower-quality donations appears to be variable based on candidate prognosis and health status. In aggregate, the significant influence of donor quality on recipient outcomes is clear; however, the association of the proportion of high-risk transplants on a prospective candidates' mortality is unknown.

High-Risk Kidney Transplant Patients

Even though kidney transplantation is a lifesaving procedure across all candidate groups, outcomes for recipients significantly vary as a function of demographic and clinical characteristics. Individual differences in outcomes between patient groups have been described based on known medical prognoses analogous to the general population, but there are also unique characteristics particular to the transplant population which distinguish patient risk groups. For this study, three distinct classes of high-risk transplants which have variable representation at transplant centers in the United States and have known association with inferior transplant outcomes will be examined: African-Americans, obese, and elderly transplant candidates.

African-American Transplant Recipients

African-Americans comprised approximately 32% prevalent cases of the ESRD population in the United States in 2004 (55). Survival rates for African-Americans are improved on dialysis relative to Caucasians (56). However, among transplant recipients, African-Americans have significantly higher rates of acute rejection and graft loss (57). There have been multiple explanations purported regarding these relatively inferior outcomes among African-Americans including immunological differences, socioeconomic factors, and delayed access to transplantation (58–60). Alexander et al. distinguished unique steps in the transplant process including medical suitability, interest in transplant, completion of a transplant workup, and acceleration on the transplant waiting list. He found racial disparities at several steps in the process (61). Additional research indicated significant differences in attitudes toward seeking (or obtaining) a transplant between African-Americans and Caucasians, but that these differences alone did not explain disparities in access to transplantation (62).

Differences in rates of transplantation to African-Americans are also partially explained by lower donation rates among African-Americans. Between 1995 and 2004, African-American donations comprised between 13–15% of all living donations and 10–13% of all deceased donations (20). In addition, progression along the deceased donor candidate waiting list is partially predicated on HLA matching (63). HLA-antigens generally are more similar among race groups, and the reduced donation rates among African-Americans affects longer waiting times on dialysis and increased deaths on the waiting list for this group. In addition, African-Americans are more likely than Caucasians to have presensitization or histocompatability reactivity to particular donors which eliminates potential donor sources (64). A single center report in 2002 suggested that disparities in outcomes by race could be reduced by encouraging hepatitis B vaccination and utilizing hepatitis C donor kidneys, subsequently reducing waiting times for African-American candidates (65).

An alternative explanation for the documented reduced outcomes following transplantation in African-Americans is more poorly controlled hypertension (66). In addition, lower economic status may have a strong role in rates of return to dialysis following transplantation (67). As immunosuppressive medication is a necessary and expensive maintenance component to graft survival, noncompliance and lack of access to medication regimens is a significant risk for graft loss. Butkus et al. found higher rates of noncompliance by African-American recipients at their center, but concluded that racial differences were not fully attributable to immunosuppressive regimens and more likely due to poor HLA-matching and socioeconomic factors (68). African-Americans also experience higher rates of delayed graft function and higher rates of acute rejection (69). Elevated risk of complications often necessitates more potent levels of immunosuppressive medications and increases the risk of infection and other medication side effects.

Cumulatively, there appear to be a combination of medical, sociological, and economic etiologies for reduced outcomes in African-Americans. African-Americans represent a significant portion of the transplant candidate population and have unique care needs. The observation that African-American patients have improved survival prior to transplantation on dialysis yet significantly reduced outcomes following transplantation suggest that there may be special consideration for selection of a transplant center in this cohort. In this sense, estimated benefits of listing at centers with the presence of certain factors may be particularly important for these candidates and specific information regarding estimated survival in this stratum of patients important.

Obese Transplant Recipients

Rates of obesity in the United States have grown substantially, and obesity has been implicated as a significant cause of death in the general population (70). Obesity has also been implicated as an independent cause of ESRD and cardiovascular morbidity (70–74). Epidemiological evidence suggests that the effect of obesity for ESRD patients is a paradoxical area of medicine. Among patients that reach ESRD, high body mass index (BMI) is reported to be protective for dialysis patients (75–79). While the cause(s) for this association are not clearly known, there have been multiple hypotheses yielding multiple contributing factors (80). In contrast, among transplant recipients, studies indicate that recipients with both low and high BMI have diminished survival following transplantation (81,82). Moreover, obesity has also been associated with increased complication rates, costs, length of stay, and delayed graft function following the procedure (81,83–85).

Despite the findings that obese patients have relatively superior survival as compared to non-obese patients and inferior survival following transplantation, they still receive a significant survival benefit associated with transplantation (31,86). However, due to the relatively poor short- and long-term outcomes of obese patients following transplantation, certain transplant centers exclude patients based on BMI and others advocate aggressive weight loss prior to transplantation (87,88). Other centers report acceptable results for transplantation in obese and morbidly obese recipients (89,90). In addition, among ESRD patients, obese patients have lower rates of listing for transplant then overweight patients despite equivalent survival rates (75). Collectively, there is an established risk for deleterious outcomes among obese patients following transplantation and variable acceptance of this population as viable transplant candidates.

The differential survival rates of obese transplant candidates suggest that the impact of dialysis time may be different in this cohort. This may be reflected in the incentives to list at particular transplant centers among this group based on expected waiting times. In addition, the impact of other center factors including performance ratings, donor quality, and high volume centers has not been specifically investigated in this population. A limiting factor for these patients may be the willingness of centers to accept them as viable transplant candidates; however, among those centers that do list obese patients, listing decisions may be particularly critical in this population.

Elderly Transplant Recipients

Fifty percent of the incident ESRD cases in the United States in 2004 were patients 65 years of age or older (elderly) (91). Even though the rate of elderly transplant candidates have doubled in the past decade, only 14% of transplant candidates are over the age of 65 (20). Therefore, it appears that transplantation is a viable treatment modality in only a small subset of elderly ESRD patients. However, the entire explanation for the lack of access for older individuals is unclear. Many of elderly ESRD patients have contraindications to transplant or are generally not medically viable for the surgical procedure. The greatest projected increase in life span associated with transplantation is among younger recipients; however, even among patients 70 to 74 years old, transplantation is associated with a significant reduction in mortality (27). Elderly transplant candidates are more likely to receive kidneys from older donors and have significantly higher death rates on the transplant waiting list (51,53). Elderly recipients are at higher risk for infectious death following transplantation, rates that are accelerated with increased exposure to pre-transplant dialysis and varying levels of immunosuppressive regimens

(92). Rates of acute rejection are relatively lower in elderly recipients, but this may also be indicative of tailored immunosuppressive regimens and immune incompetence (93,94).

Elderly recipients have still been shown to benefit from transplantation; however, the absolute benefit, in terms of years of life gained, is substantially less than younger recipients. In fact, evidence suggests a significant loss of scarce resources in terms of donor kidney life-years and economic loss to payers of ESRD patients due to transplantation of younger donors to older recipients (95). Even though increased donor age is a risk factor for graft loss among the elderly, the evidence suggests that only younger transplant recipients survive long enough to receive the full benefits of a younger donation on average. The Eurotransplant program has been developed specifically to address this concern by directly allocating older donations to older recipients in combination with reduced cold ischemia and waiting time on dialysis (96). The distinction in this program is the older participants are mandated to receive organs from older donors but the tradeoff of receiving an organ more rapidly and with less ischemic effect may offset the risks associated with a lower quality donation. Although age is not a factor in OPTN allocation policy in the US, caregivers have substantial influence in directing the types of donations to particular transplant candidates. These decision-making processes may vary at the transplant center level based on experience, the proportion of older donations available in a particular service area, and length of candidate waiting lists. Also, research has demonstrated that due to the elevated mortality risk of elderly patients on dialysis, acceptance of lower-quality organs in exchange of receiving a transplant more rapidly may be a viable option for this cohort (53). In other words, the relationship of the competing risks of extended waiting time on dialysis and lower quality donations appears to be unique in the elderly subset of transplant candidates. However, these decisions depend largely on the amount of waiting time reduced and the availability of quality donations. These factors are widely variable at transplant centers and the estimated impact of center characteristics is likely to be unique for this high-risk subset of patients.

Conceptual Framework

The conceptual model for this study is based upon the work of Grossman and the model of the health production function (97). This model examines the role of individual decision making in the production of health and the investment of human capital to improve individual outcomes. Fundamental to this theory is that health is predicated on multiple factors of which health care represents one of many explanatory factors. Other determining factors include individual characteristics, environmental conditions, and behavioral components. In this framework, individuals demonstrate a demand for health care. This demand is not for health care per se, but for health and the subsequent utility which derives from health. In this sense, individuals are not solely subject to external constraints but are active participants in their own health status and future prognosis. Additionally, while individuals demand health, they do not value it over all other goods reflected by choices that have known deleterious impact. In addition to the utility associated with increased health, there is also an investment component of health. Health represents an investment as it allows for increased individual production as well as future utility. Implicit in this model is that individuals value health and always seek to maximize their level of health and associated utility.

The health production function is represented by a declining slope with potentially nonlinear deceleration over time. Individuals are endowed with a particular stock of health that depreciates over time subject to effects of aging as well as other potential health shocks such as disease onset or accidents. Grossman illustrated this depreciation based on individual investment in health utilizing Equation 2-1.

$$H_{i+i} – H_i = I_i - \delta_i H_i \qquad (2\text{-}1)$$

This equation characterizes the loss in health with δ_i representing the rate of depreciation in the ith period, H_i representing the stock of health, and I_i representing the investment of the individual in this period. From an economic perspective, the investment component of health is determined by the marginal benefit of receiving the desired level of health. In this framework, individuals' health value is also a function of their wage rate and utility as well as the cost of producing the level of health. In this formulation, the investment component can be more specifically characterized as a function of the amount of medical care sought in the period as well as the stock of human capital and time as illustrated in Equation 2-2.

$$I_i = I_i\,(M_i, TH_i, E_i) \qquad (2\text{-}2)$$

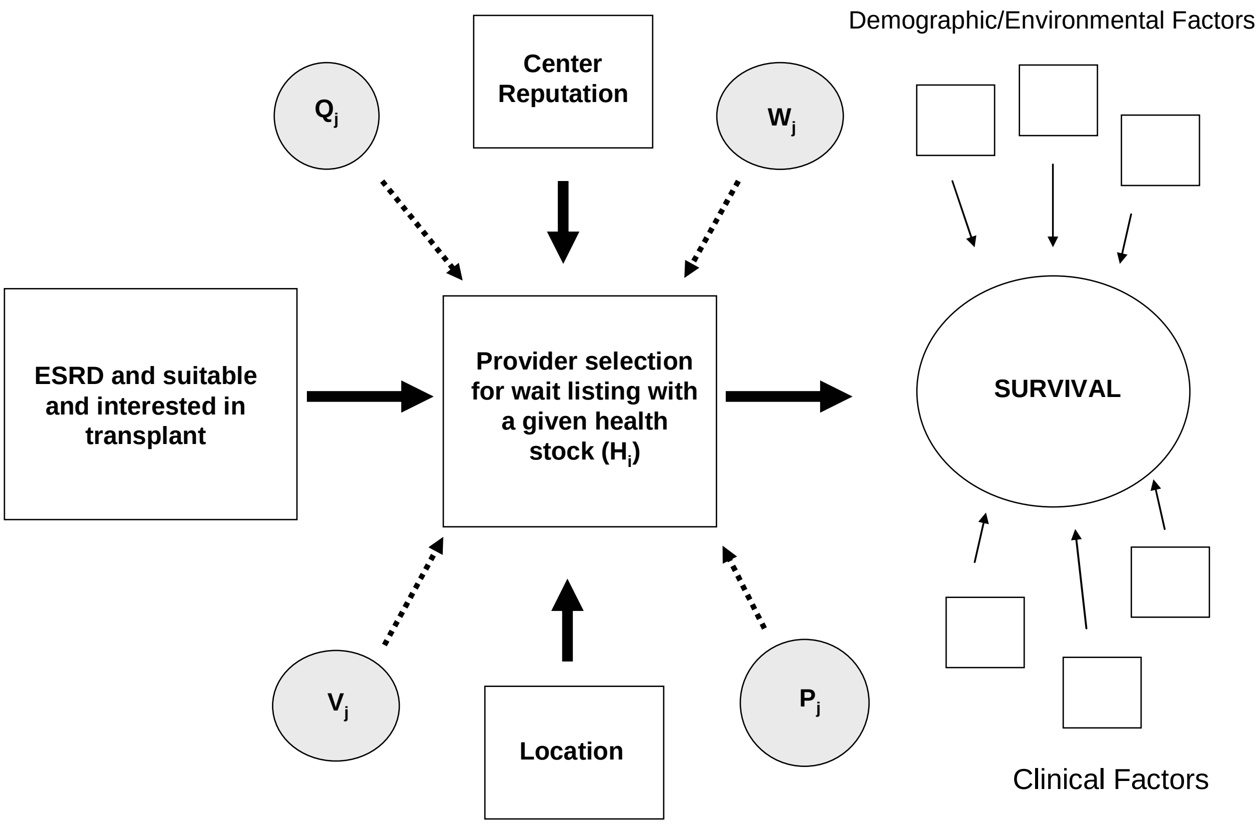
In this case, E_i represents the stock of human capital, TH_i represents the time component of investment in health, and M_i represents medical care for the individual. Utilizing this framework, this study will examine the effect of center characteristics on outcomes for renal transplant candidates. In this context, the medical care component of the Grossman model is not homogenous. The type of medical care, represented by characteristics of the listing center may have differential impact on patient survival. In this sense this study will investigate the level of future health that is independently determined by selection of center. Furthermore, under the Grossman framework in which the investment and utility deriving from investment may vary based on an individual's prior health status and individual characteristics, this study will investigate the impact of these decisions in certain high-risk patient groups. Utilizing this framework, the research question focuses on the effect of the selection of center on outcomes controlling for a patient's latent healthcare stock and timing of candidate listing. These characteristics include the age, race, gender, length of dialysis, insurance, body mass index, education, and clinical presentation of the individual. Individuals can be viewed as producers of their health and this production as a function of the type of medical care sought. Therefore, rather than a single indicator for medical care utilization, the selection of a center can be further discriminated as a function of center characteristics, in this case the proportion of high-risk kidneys, center volume, center performance and expected waiting time as depicted in Equation 2-3.

$$M_i = M_i(P_j, V_j, Q_j, W_j) \tag{2-3}$$

In this extension of the Grossman framework, medical care for individual i is a function of the proportion of high-risk kidneys (P), transplant volume (V), quality of center (Q), and expected waiting time(W) at a given center j. Selection of center j will in turn have an impact on future health status and the associated utility derived from this level of health. Figure 2-1 depicts this framework for ESRD patients that select a medical care through a specific center. More broadly, health status in future periods are a function of past health status, depreciation rates, and investment in health, including the type of medical care attained.

The evidence to date suggests that there is significant association of transplant center characteristics with outcomes for kidney transplant candidates. However, the joint estimation of these factors is unclear, but is crucial towards informing potential candidates and caregivers regarding choices for centers of care. While the individual effects of center performance and volume, waiting time, and organ quality have been evaluated for transplant recipients, the interaction of these factors and relative benefit has not been investigated and has not been examined for prospective transplant candidates. This study will examine the role of these center characteristics in order to estimate circumstances that offer the best prognoses for transplant candidates and maximize patient long-term outcomes.

Results of this study will be important at several levels. This study will examine whether there is an important association of transplant center factors with outcomes for candidates of transplantation. Failure to find any significant associations will suggest that candidates have an incentive to select centers based on convenience, logistics, or other determinates of their quality of life. However, significant factors that are found may be important to guide patients and other caregivers of where to list for a transplant that can affect their mortality risk. In particular, candidates that have a choice in their selection of centers or have the resources to travel outside a local area may have an incentive to discriminate between centers based on these characteristics. Furthermore, this study will highlight whether these factors are uniformly applicable to the candidate population or have differential impact in high-risk patient groups. A finding of a significant interaction in this regard would suggest that certain patient groups would be more advised to list at particular centers based on their mortality risk. Moreover, a significant interaction would imply that there may be cases in which the entire transplant process could become more efficient and provide benefit to the full complement of transplant candidates. If certain center factors are more important to certain patient groups and less important to others, then it follows that allocating patients to the respective locations may improve outcomes for the entire population. Identification of the importance of transplant factors that are associated with candidate mortality may also provide insights for future augmentation of the transplant and allocation processes. For those factors that are amenable, alteration of these characteristics and development of infrastructure to support a process that fosters these characteristics would be important. Finally, results of this study may be generalizable to other areas of medicine in which there is great variability in patient characteristics and risk level and a choice of potential centers. In recent years, there has been an increased emphasis on patient decision-making and transparent information for consumers of healthcare services. This study will elucidate the importance of an aspect of these guidelines over a broad timeline in a significant patient population. Most importantly, this study aims to provide important evidence to inform patients and caregivers about the impact of center characteristics on their long-term prognosis.



Accessing medical care through certain providers may be associated with a differential health deterioration rate:
M_i = M(Pj, Vj, Qj, Wj)

Figure 2-1. Conceptual Framework based on Grossman's Health Production Function

CHAPTER 3
MATERIALS AND METHODS

Overview

The primary purpose of this study is to examine the association of center characteristics with mortality for renal transplant candidates. The general approach will be to estimate levels of four center characteristics utilizing data prior to candidate listing and evaluate the association of these characteristics with candidate mortality in the years after listing. This study will be a retrospective analysis of observational data derived from a national registry database. The outcomes of this study will determine whether each of the tested center characteristics are significantly associated with candidate mortality and the relative effect of high and low levels of these factors among those that are significant. Furthermore, this study will estimate life expectancy for candidates at incremental levels of significant factors that may ultimately be utilized as a guide for center selection. Finally, this study will reevaluate the significance and life expectancies for candidates that are of particular high risk and may have unique needs with respect to center selection.

Data

This study will utilize a national transplant registry which is administered by the SRTR in order to conduct the analysis. The SRTR database contains information for all transplants performed in the United States. Information is collected at all centers on a mandatory basis utilizing data collection forms at several time points for transplant patients corresponding to their transplant status and has been utilized extensively for government-sponsored reports and peer-reviewed research publications. Data is collected electronically and files are distributed at cost for the purpose of research to groups following submission of a research and security plan. For this study, the data that will be utilized will include information deriving from the form at the time of transplant candidate listing, the form submitted at the time of transplantation, and follow-up forms after transplantation. In addition to data collected from transplant centers, files are enriched with data from Medicare and the Social Security Administration for data fields pertaining to patient death or re-initiation of dialysis following transplantation.

The database contains patient-level data including donor and recipient demographic information, primary clinical characteristics, and a numerical (de-identified) code for transplant centers. The unit of analysis for this study will be adult patients (at least 18 years of age at the time of listing) that are placed on the waiting list for a solitary kidney transplant as indicated in the database. Pediatric patients (candidates less than 18 years of age) and candidates listed for multi-organ transplants will be excluded from this study in order to examine a more homogenous population. Candidates and recipients at centers with very low volume (less than ten transplants per year) will also be excluded as estimates of center factors are less reliable. These candidates represent a significant minority of all national candidates. In addition, recipients of living donor transplants will be excluded from this study as they are less applicable for candidates placed on transplant waiting lists for a deceased donor transplant. The study population will consist of all remaining candidates that were listed for a solitary deceased donor transplant between 1995 and 2000. This period was selected to represent a relatively recent cohort, but with follow-up time sufficient to evaluate the impact of transplant center factors on long-term patient outcomes. Current files that will be utilized for the analysis have follow-up information through early 2006. In addition, data will be utilized from 1992 to 1999 to assess transplant characteristics based on three years of information accrual prior to candidate listing.

Dependent Variables

The primary outcome variable in the study will be transplant candidate mortality after listing. Candidates will be followed from the time of listing until the earliest of death or last follow-up time as indicated in the database. Patient death is indicated in the database with internal variables derived from center follow-up forms as well as populated from Social Security master files. The earliest of these dates in cases of discrepancies will be utilized as an endpoint for the study. Mortality will be compared between study groups utilizing survival models based on time to death following candidate listing. Models will be censored at the time of living transplantation to limit results to recipients from deceased donors. A secondary endpoint will be candidate death prior to the date of transplant. This model will be censored at the time of transplantation, limiting events to the pre-transplant period. An additional secondary endpoint will be overall graft loss following transplantation. These models will be initiated at the time of transplantation for the same study groups and patients will be followed until a last follow-up date or the date of overall graft loss. Overall graft loss is defined as the composite endpoint of either patient death or loss of the transplanted kidney indicated by a return to dialysis or re-transplantation. Additional descriptive information will include the correlation of historical center characteristics with prospective levels after candidate listing, the association between center characteristics and the distribution of these characteristics within transplant regions.

The purpose of the primary endpoint is to examine the overall survival rate for patients based on levels of center characteristics. While other factors are clearly important to patients and caregivers, measures of death and graft loss are objective "hard endpoints" that are clearly defined. In addition, this data is readily available and reliable, and mortality rates are generally interpretable for consumers of the research and comparable across study contexts. As the primary variables of interest have all been shown to have some association with outcomes following transplantation, the question remains whether the variables will prospectively impact candidate survival for listed patients and how important the factors are relative to each other.

The purpose of the secondary outcomes is to determine whether differences that exist by center characteristics are most directly related to pre- or post-transplant mortality.

Explanatory Variables of Interest

The primary explanatory variables of interest will be four transplant level characteristics: center volume, center performance rating, center proportion of ECDs and the proportion of patients reaching transplantation. Each of these will be assessed based on data for the three years prior to the year of listing for the transplant candidate. The variables will be categorized into quintiles based on their distribution over the study period and implemented as dummy variables in statistical models. Each of these characteristics will be estimated according to an individual candidate's year of listing based on retrospective center characteristics over the previous three years. Transplant volume will be estimated based on the average number of deceased donor transplants in the three years prior to candidate listing. Performance ratings (also known as standardized mortality ratios) will be constructed utilizing data for deceased donor transplants from the prior three years of candidate listings. Ratings will be determined utilizing the equivalent methodology as the SRTR, which publishes center performance ratings on public websites (98). These ratings are produced based on the ratio of the number of actual events (in this case, patient deaths) to the expected number of events based on characteristics of the center population. The value of this ratio will be utilized for the purpose of this study based on three-year outcomes. The proportion of high-risk deceased donor transplants will be based on the dichotomous ECD criteria and defined as the proportion of ECDs (among all deceased donor transplants) over the prior three years. Transplant center waiting time will be indicated by the proportion of patients that receive a deceased donor transplant within the three-year period prior to listing. This proportion will be calculated by Kaplan-Meier models and censored at the time of patient's delisting, transfer to other centers, or receipt of a living transplant.

The center characteristics are selected for three primary reasons. First of all, the factors have been shown to be associated with patient outcomes following transplantation based on retrospective analysis. As such, it is reasonable to surmise that prospective evaluation of these factors will have an impact on candidate outcomes following listing. Secondly, the information regarding these characteristics is all publicly available and as such could be incorporated into decision-making processes for candidates and their caregivers in order to assist with center selection. Lastly, these factors have wide regional variability as well as variable representation among centers within regions. This is important from a methodological perspective as it will more readily allow for the detection of effects of these factors on patient outcomes. In addition, the center variability highlights the potential decisions that candidates may make regarding their choice of center selection.

There are a total of 260 transplant centers with unique identification numbers in the database within the study period. A portion of these centers discontinued their programs within the study period and several programs were newly initiated within the time frame. In order to accurately estimate effects based on transplant center characteristics, centers with less than ten deceased donor transplants per year of operation will be excluded from the study. Among the centers, 184 (71%) had at least ten deceased donor transplants per year. These centers accounted for 97% of all deceased donor transplants over this period. The distribution of the average annual number of deceased donor transplants is displayed in Figure 3-1. The median (and 25th / 75th percentile) number of deceased donor transplants at these centers was 30 (19 / 48), ranging from 10 to 177. The median proportion of ECD transplants (of all deceased donor transplants) was 11%, ranging from 0% to 30%. The distribution of the proportion of ECD transplants is illustrated in Figure 3-2. The proportion of candidates receiving a deceased donor transplant within three years after listing also varied significantly over the study period. The range of this proportion was 11% to 91% with a median level of 57%. The distribution of this proportion of candidates receiving a deceased donor transplant is displayed in Figure 3-3. Standardized mortality ratios ranged from 0 (indicating no events over the time period) to close to 4.0 (indicating four times as many events as would be expected based on characteristics of the transplant population at the center). The distribution of the mortality ratios by center are displayed in Figure 3-4.

Additional Explanatory Variables

Multivariate models will incorporate a number of adjustment variables that are considered to be independently associated with the mortality or waiting time to transplant for candidates. Candidate age will be utilized as it is strongly associated with death rates as well as the likelihood to receive a transplant over time. Age will be categorized into groups as 18–44, 45–54, 55–64, and 65+. Candidate race will be used in the models categorized as Caucasian, African-American, Asian, Hispanic, and Other. Caucasians have significantly higher mortality rates on the waiting list relative to other race groups as well as greater likelihood to receive a transplant. Candidate gender will be used in the models; there is some indication that gender is associated with likelihood to progress more rapidly on the waiting list. Candidate primary cause of ESRD will be dichotomously represented in the models as diabetes or other. Diabetics with ESRD have significantly higher death rates and less likelihood to reach transplantation. Candidate BMI will be categorized into levels representing different health status (Missing, 13–19, 20–24, 25–29, 30–34, 35+). Obese candidates have been shown to have a slower progression to transplant and superior survival after dialysis initiation. Additional variables that will be utilized to control for potential selection bias in center choice will include candidate education and insurance status. Education will be dichotomously represented as a college degree or higher, or less than a college degree. Insurance status will be categorized as private, Medicare, or other. Obese candidates will be defined as those with a calculated BMI greater than 30 kg/m^2 and elderly patients will be classified as those that are 65 years of age or older at the time of listing.

A secondary outcome for the study will include post-transplant graft and patient survival. These models will include only those candidates that receive a deceased donor transplant and will be initiated at the time of transplantation with follow-up until death, graft loss, or the last follow-up period. Cox models will be adjusted for transplant characteristics that are associated with outcomes after transplantation including HLA mismatching level, donor age, cold ischemia time, donor race, and pre-transplant dialysis time, in addition to adjustment factors utilized in the primary outcome models.

Statistical Analysis

The primary analyses used in the dissertation to evaluate the study aims will be performed with survival models. Survival models (also known as time to event analyses) are appropriate in contexts with a known time origin, in this case the time of candidate listing, and with well-defined follow-up period and events. In addition, as in the case for this data, subjects have variable follow-up periods, and survival models are capable of incorporating these different follow-up periods in the analyses (as opposed to other types of regression models). Each subject (transplant candidate) has a known candidate listing date as well as a last follow-up date, which may be death or the last follow-up period. For these analyses death will be treated as the event of interest and patients that do not die over the study period will be censored at the last follow-up period. This form of censoring is commonly referred to as right-censoring. Models for secondary outcomes will be censored at the time of transplantation and additionally an alternative model will use the time of transplantation as the origin point.

Analyses for examining factors associated with patient outcomes will use a survivor function S(t), which gives the probability of survival until a given time, t. S(t) is a monotonically decreasing function which is initiated at a survival probability of one and decreases with subsequent events over time as indicated graphically on the horizontal axis. The rate of decline of the survival function is utilized as a measure of the risk at a particular event time and is generally regarded as the hazard function $\lambda(t)$. The hazard function can generally be written as shown in Equation 3-1.

$$\lambda(t) = d/dt\,(-\ln[S(t)]) \qquad (3\text{-}1)$$

The analyses will also utilize Kaplan-Meier methodology (also known as the product-limit method) to compare the survival function among sample strata. This methodology is nonparametric and is appropriate when exact dates are known for events (rather than aggregated across intervals), which is the case with the current data. Comparisons of the survival function between study groups will be made with the Log-Rank test which is generally the statistically most powerful test for making unadjusted comparisons between study groups. Censoring will be assumed to be noninformative as last follow-up information is generally a product of the most recent data available and there are few cases of patients that are lost to follow up in this cohort.

To compare outcomes between study groups adjusted for potential confounding factors, hazard functions will be compared utilizing Cox proportional hazard models. Cox models are semi-parametric and are not reliant on a specific distributional form of a survival function supporting the robust nature of the results. An assumption that is applicable for the Cox model is that the hazard ratio of covariates in the model is proportional over time (i.e., additive changes in covariates cause multiplicative changes in the hazard functions). For continuous covariates this will be tested explicitly by entering an interaction term of the covariate in question with time into the model. In the case of categorical covariates, assessment of proportionality will be made by visual inspection of the log-log survival function. The Cox model can be written in the form depicted in Equation 3-2.

$$h_i(t) = h_o(t) \exp(\beta_1 x_{i1} + \beta_2 x_{ik} + \ldots + \beta_k x_{ik}) \tag{3-2}$$

where i = individual, t = time, x = covariate of interest, and k = number of covariates

The Wald test will be utilized to test the two-sided hypothesis that a center characteristic is significantly associated with patient mortality (H_o: $\beta_1 = 0$ versus H_a: $\beta_1 \neq 0$) using the equation $z = \beta_1/(SE)_{\beta_1}$. In addition, results will be displayed as adjusted hazard ratios relative to a reference level of the center factors. Cox models will also be used to estimate adjusted survival rates following candidate listing for combinations of center-level variables. These results will be presented in tabular form with applicable standard error estimates.

Study Aim I

Kaplan-Meier and multivariate Cox models will be used to test the hypothesis that the individual center characteristics are associated with wait-list candidate survival. Kaplan-Meier models will be constructed for each individual center characteristic based on quintile levels of the variable utilized as strata in the model. Results will be displayed graphically and tested with Log-Rank tests. Cox models will be used incorporating all center characteristics simultaneously along with other potential confounding factors as described previously. Overall significance, hazard ratios, and confidence intervals for center characteristics will be displayed in tabular form.

Study Aim II

Cox models will be utilized to estimate survival rates for candidates at multiple permutations of center characteristic levels. Only center characteristics that were shown to be significantly associated with candidate mortality will be utilized for this study aim. The baseline hazard function of the model will be adjusted with incremental levels of the center factors that span the range of these variables, and all survival estimate combinations will be displayed in tabular form.

Study Aim III

In order to evaluate the effect of center characteristics in three high-risk candidate groups, the methodology described in study aims I and II will be utilized strictly in subsets of candidates. The same explanatory variables will be utilized in Cox models without the variable applicable to the designation of the high-risk subset. For models restricted to the elderly, age categories will be reclassified within the elderly cohort. With the subset of African-American patients, candidate race will be removed from the models. For the obese cohort, new categorization of BMI will be used for patients with BMI > 30 kg/m^2. Survival estimates, as described in study aim II, will be conducted for each subset of high-risk patient in a similar fashion.

Potential Selection Bias

The primary aim of the study is to evaluate the independent effect of center characteristics on transplant candidate mortality. However, one of the limitations of this retrospective analysis will be the possibility that mortality rates at centers are correlated with the patient's selection of these centers. In particular, patients that are well informed, have higher educational background, or have resources that allow them to travel to centers of their choice or make informed decisions about centers that are of higher quality, and these patients may also have a lower risk profile. There is data to support the notion that performance measures do not influence transplant center selection in aggregate; however, this may not fully incorporate more subtle patient characteristics (21). The effect of this bias may be to overestimate the influence of center characteristics, assuming that "better" patients select centers that also have better outcomes.

The primary strategy of the study to account for this potential bias will be to statistically control for patient characteristics that may influence center selection as well as mortality. These patient-level variables that will be adjusted for in the outcome models will include age, primary diagnosis, race, gender, primary insurance coverage, and education level. These factors will be assumed to provide adequate control for characteristics of patients associated with center selection related to overall health level, education, affluence level and interaction with the healthcare system. In addition, examination of the secondary outcome of candidate mortality prior to transplantation will provide insight on the degree of selection bias that exists. In particular, mortality rates prior to transplantation are significantly less associated with care provided by the transplant center, and significant differences in pre-transplant mortality are more likely attributable to patient characteristics. Evaluation and comparison of pre- and post-transplant mortality effects by center characteristics will therefore serve as a verification of any observed associations.

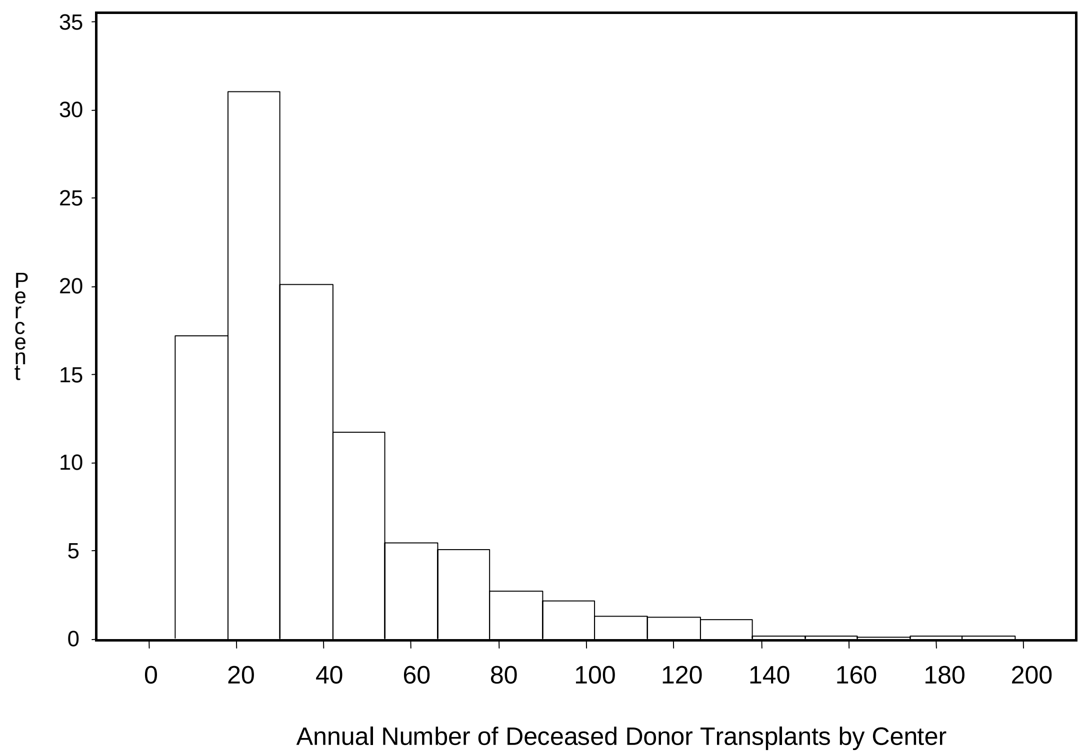


Figure 3-1. Distribution of the Annual Number of Deceased Donor Transplants by Center

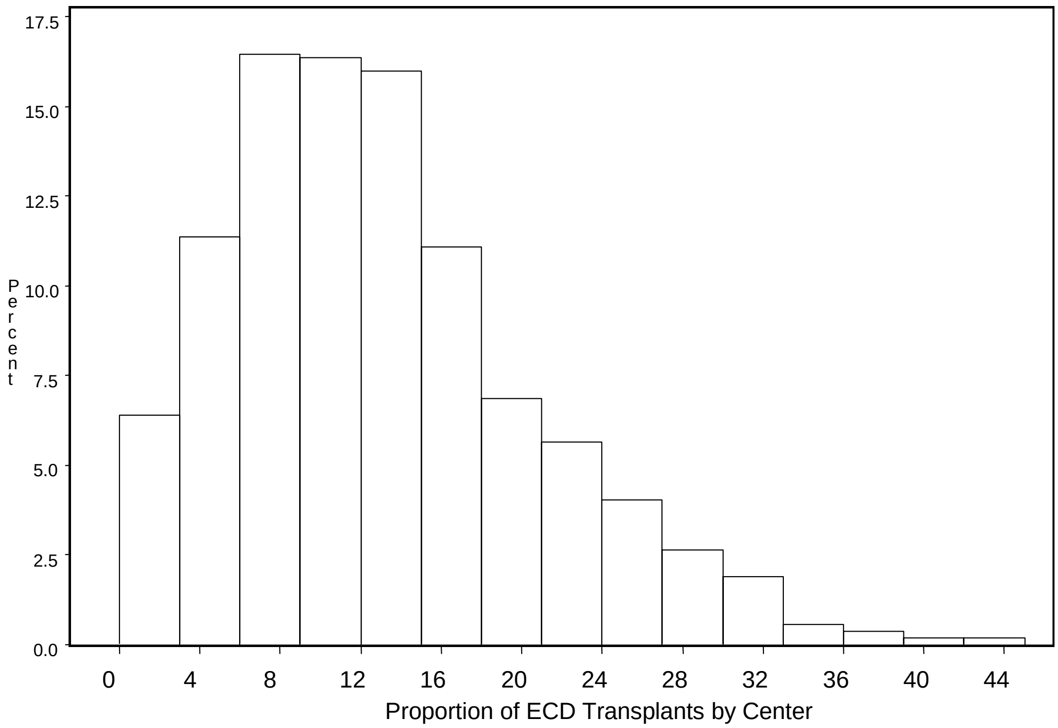


Figure 3-2. Distribution of the Proportion of ECD Transplants by Center

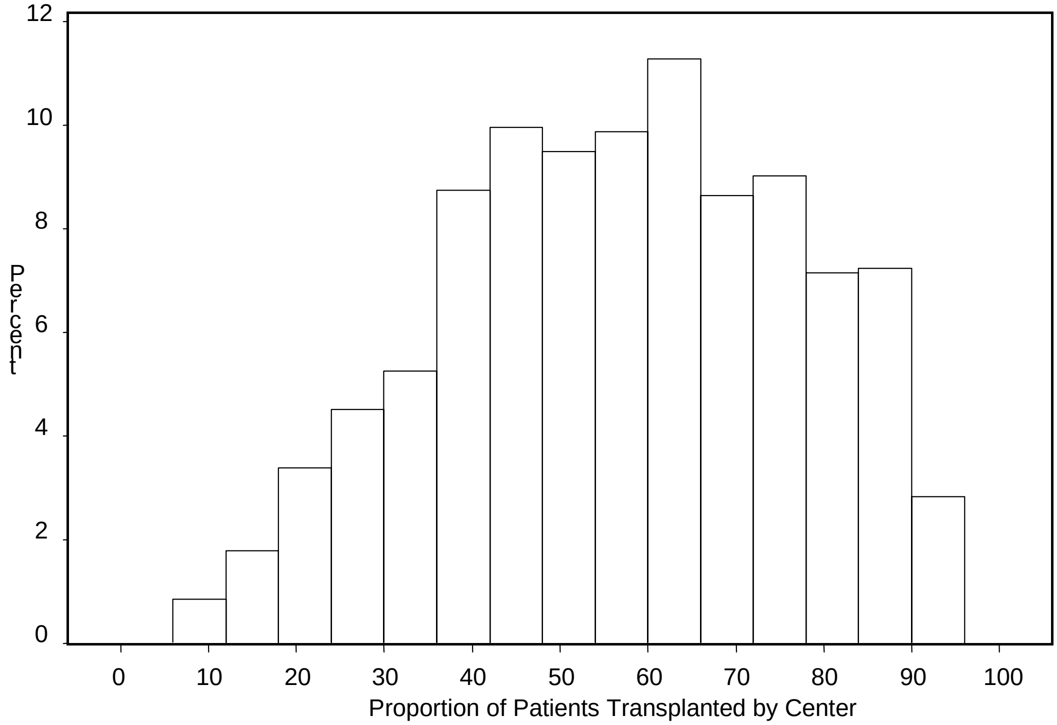


Figure 3-3. Distribution of the Proportion of Candidates Receiving a Deceased Donor Transplant within Three Years by Center

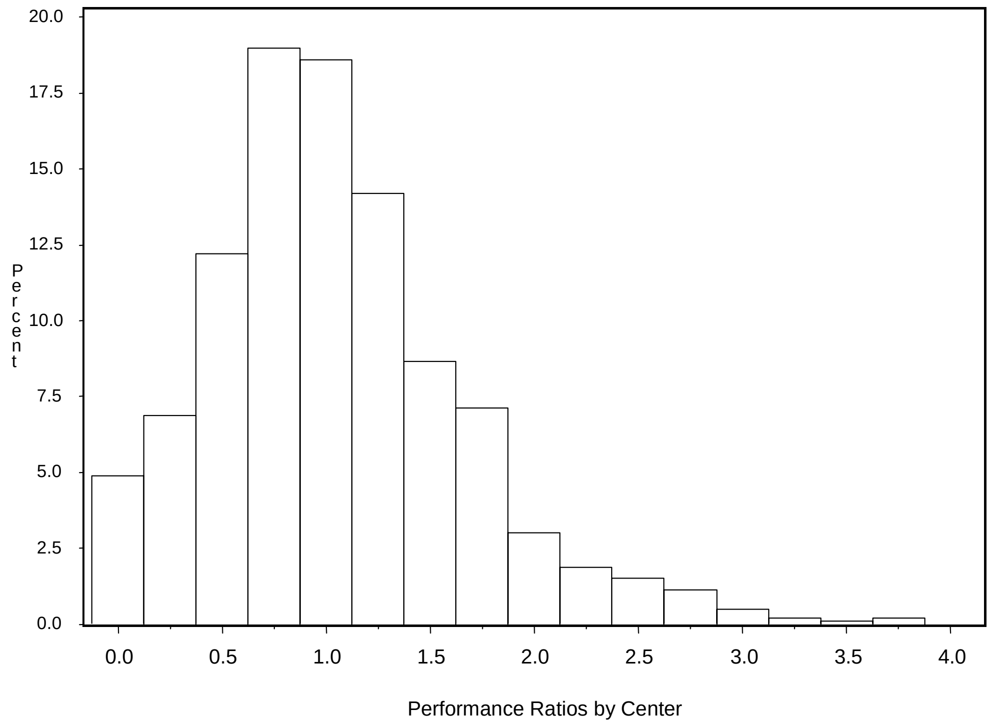


Figure 3-4. Distribution of Standardized Mortality Ratios by Center

CHAPTER 4
RESULTS

Study Population

There were 108,928 adult solitary kidney transplant candidates in the study population. Table 4-1 displays descriptive statistics about the candidate population from 1995–2000. Within the study period, 8% of candidates were 65 years or older, 59% of candidates were male, 28% were African-American, 28% had diabetes as a primary cause of ESRD, 15% of candidates had a college degree or more, 48% had type-O blood, and 55% of candidates had Medicare as their primary insurance payer. Among candidates with known BMI levels, 21% were obese and among candidates with known Panel Reactive Antibody (PRA) level at listing, 31% were sensitized (i.e., PRA > 0).

Rate of Transplantation by Center

Transplant centers for each listing year were categorized based on the proportion of candidates that received a deceased donor transplant within three years after being placed on the waiting list. Center categories for this proportion were assigned by quintiles as follows: Q1 = [7.0–38.5], Q2 = [38.6–51.6], Q3 = [51.7–63.1], Q4 = [63.2–76.7], and Q5 = [76.8–96.0]. Table 4-2 displays candidate characteristics by the center proportion of transplants categorized by quintile. The most notable differences by center category were among patients with private primary insurance coverage (Q1=45% vs. Q5=40%), African-American recipients (Q1=32% vs. Q5=21%), and sensitized patients (Q1=30% vs. Q5=39%). The number of candidates and the median proportion of patients reaching transplantation at three years for candidates in each group were as follows: Q1 (n=30478, median = 28.4), Q2 (n=24271, median = 45.4), Q3 (n=22768, median = 58.1), Q4 (n=18858, median = 67.3), and Q5 (n=12553, median = 83.0).

Transplant Center Volume

Transplant centers for each listing year were categorized based on the average number of deceased donor transplants three years prior to the year of candidate listing. Center categories for volume were assigned by quintiles as follows: Q1 = [10.0–18.8], Q2 = [18.9–26.3], Q3 = [26.4–36.6], Q4 = [36.7–53.7], and Q5 = [53.8–195.0]. Table 4-3 displays candidate characteristics by center volume quintile. The most notable differences by center category were among patients with a college degree (Q1=17% vs. Q5=22%), and patients with private primary insurance coverage (Q1=36% vs. Q5=45%). The number of candidates and median annual transplant volume for candidates in each group were as follows: Q1 (n=8462, median = 15.7), Q2 (n=12597, median = 23.0), Q3 (n=16433, median = 31.0), Q4 (n=24370, median = 44.0), Q5 (n=47066, median = 88.0).

Center Donor Quality

Transplant centers for each listing year were categorized based on the proportion of expanded criteria donor transplants three years prior to the year of candidate listing. Center categories for the ECD proportion were assigned by quintiles as follows: Q1 = [0–6.4], Q2 = [6.5–9.9], Q3 = [10.0–13.4], Q4 = [13.5–18.9], Q5 = [19.0–44.0]. Table 4-4 displays candidate characteristics by center ECD proportion quintile. The most notable differences by center ECD proportion category were among patients with private primary insurance coverage (Q1=39% vs. Q5=43%), elderly patients (Q1=7% vs. Q5=10%), African-American patients (Q1=25% vs. Q5=32%), sensitized patients (Q1=36% vs. Q5=27%), diabetic patients (Q1=30% vs. Q5=26%), and obese patients (Q1=19% vs. Q5=23%). The number of candidates and the median proportion of ECD transplants for candidates in each group were as follows: Q1 (n=17980, median = 4.4), Q2 (n=19229, median = 8.3), Q3 (n=22768, median = 11.8), Q4 (n=24139, median = 15.7), Q5 (n=24812, median = 24.0).

Center Performance Ratings

Transplant centers for each listing year were categorized based on the ratio of observed to expected deaths at one year utilizing data for recipients three years prior to the year of candidate listing. Center categories for volume were assigned by quintiles as follows: Q1 = [0–0.56], Q2 = [0.57–0.83], Q3 = [0.84–1.09], Q4 = [1.10–1.45], Q5 = [1.46–3.80]. Table 4-5 displays candidate characteristics by center performance quintile. The most notable differences by center performance category was among patients with private primary insurance coverage (Q1=43% vs. Q5=35%), African-American patients (Q1=25% vs. Q5=34%) and patients with a college degree (Q1=21% vs. Q5=18%). The number of candidates and the median ratio of observed to expected deaths for deceased donor transplants by candidates in each group were as follows: Q1 (n=17939, median = 0.37), Q2 (n=23865, median = 0.72), Q3 (n=27705, median = 0.96), Q4 (n=23972, median = 1.26), Q5 (n=15447, median = 1.70).

Association between Transplant Center Characteristics

The median center volume and performance ratings were relatively stable over the period (Table 4-6). In contrast, the proportion of patients transplanted at three years significantly declined throughout the study period, and the proportion of ECD transplants increased over time. Also indicated in the table, the total number of candidates increased steadily over the study period.

There was no significant correlation between the volume of deceased donor transplants with the other three center characteristics investigated in the study (Table 4-7). There was a significant negative association between the proportion of patients transplanted at three years with the proportion of ECD transplants; however, the proportion of patients transplanted at three years was not correlated with performance ratios. The ratio of observed to expected patient deaths at one year was positively correlated with the ECD proportion between centers. Centers with a higher proportion of ECD transplants had less patients transplanted at three years and worse (i.e., higher ratios) performance ratings.

Reliability of Historical Center Characteristics

The volume of transplants was positively associated with several characteristics of the centers at listing (Table 4-8). On average, listing for a transplant at a center with higher volume was positively associated with the volume of transplants at the center at the time of transplantation. Candidates who listed at centers with historically smaller number of patients transplanted also had longer durations between listing and receiving a transplant. In a similar fashion, patients who listed at centers with historically higher proportion of ECD transplants also were more likely to be transplanted at centers with a higher proportion of ECD transplants. In addition, recipients that listed at centers with better performance ratios also were transplanted at centers with better ratios during the year of transplantation. In general, characteristics of transplant centers at the time of listing were still evident at the time of transplantation.

Kaplan-Meier Candidate Survival by Center Characteristics

Figure 4-1 displays candidate survival by quintile level of the proportion of patients transplanted at three years prior to listing. There was a stepwise and significant association between a higher proportion of patients transplanted and higher candidate survival over the study period ($p < 0.001$). The proportion of candidates surviving at ten years following listing was 56% at centers with the highest proportion of patients reaching transplantation as compared to 50% at centers with the lowest proportion. Ten-year survival at centers with lowest proportion of ECD transplants was 54% as compared to 50% at high ECD centers (Figure 4-2). Time to death following listing by transplant volume was not statistically significant different (Figure 4-3). The proportion of candidates surviving at ten years based on center performance ratios, ranged from 51–54% in the lowest-performing and highest-performing centers respectively (Figure 4-4).

Multivariate Cox Model for Primary Outcome of Candidate Mortality

The primary outcome of the study was candidate mortality after listing for transplantation. Results of the Cox proportional hazard model for patient mortality including the center study characteristics categorized by quintile level are displayed in Table 4-9. Relative to Caucasian candidates, all other racial groups had significantly lower mortality after listing. Older age was significantly associated with increased mortality including a two-fold risk for candidates over the age of 65 years (adjusted hazard ratio [AHR] = 3.24, 95% confidence interval [C.I.] 3.13–3.35). Patients with a primary diagnosis of diabetes had an approximate 88% increase in the hazard ratio for death relative to patients without the diagnosis. Patients with type-A and type-AB blood had a reduced hazard ratio for death relative to type-O candidates. Patients that were listed as highly sensitized (PRA > 30) had a 34% increase hazard ratio for death after listing relative to non-sensitized candidates. Low BMI levels ($\leq$ 18 kg/m^2) and BMI levels above 35 had an increased hazard ratio for death relative to candidates with BMI between 19–25 kg/m^2. Patients with less than a college education had an increased likelihood of mortality (AHR=1.08, 95% C.I. 1.05–1.12). Candidates with Medicare as a primary insurance payer had significantly elevated mortality relative to candidates with private insurance. Candidates on dialysis at the time of listing had an elevated hazard for death relative to candidates that were listed prior to dialysis initiation.

Among center characteristics, the rate of transplantation had the strongest association with candidate mortality after listing. Candidates that listed at centers with the lowest percentage of patients reaching transplantation at three years had a 32% increased relative hazard for death (AHR = 1.32, 95% C.I. 1.27–1.38) relative to candidates listing at centers with the highest percentage of patients reaching transplantation. In addition, there was a stepwise association between levels of the center proportion of patients transplanted. Transplant volume was not significantly associated with mortality between any of the groups. The center proportion of ECD transplants was associated with candidate mortality between candidates listed at centers with the highest proportion of ECD transplants (AHR = 1.04, 95% C.I. 1.00–1.08) relative to candidates listed at centers with the lowest proportion of ECDs. Candidates listed at centers with the lowest performance measures had a 14% increase in hazard ratio for death (AHR = 1.14, 95% C.I. 1.10–1.19) relative to candidates listed at centers with the highest performance.

The Cox proportional hazard model results for the outcome of receiving a deceased donor transplant following listing is displayed in Table 4-10. There was a highly significant association of receipt of transplant by centers with historically different proportions of candidates receiving transplants. The hazard for patients receiving a transplant at centers with the lowest rate was over 5-fold decreased (AHR = 0.17, 95% C.I. 0.16–0.17) relative to centers with highest rates of transplantation. There was also a stepwise and significant increase in the hazard ratio by center level. Center volume was also associated with the hazard rate of transplant with the most notable difference between candidates at the smallest centers less likely to receive a transplant (AHR=0.94, 95% C.I. 0.90–0.98) relative to candidates at the highest volume centers. There was a varied association between center levels of ECDs, with candidates at centers with a high proportion of ECD transplants more likely to receive a transplant (AHR = 1.10, 95% C.I. 1.07–1.14). Candidates at different performance centers also had mildly different time to transplantation; however, there was no distinct pattern between levels.

The association of center characteristics with post-transplant mortality for candidates who acquired a deceased donor transplant within the study period is displayed in Table 4-11. There was no significant association between hazard ratios for post-transplant mortality with candidates listed at centers with different rates of transplantation or proportion of ECD transplants.

Candidates listed at centers with small volume (AHR=1.10, 95% C.I. 1.03–1.18) had an elevated hazard ratio for post-transplant mortality; however this association was not statistically significant among candidates listed at the smallest centers. Candidates listed at centers with the lowest performance levels had a 20% increased hazard for death (AHR= 1.20, 95% C.I. 1.11–1.29). The model for post-transplant graft loss resulted in similar findings. There was no significant association between graft loss and candidates listed at centers with different rates of transplant, there was mixed results for center volume, and candidates listed at centers with lower performance levels had elevated post-transplant graft loss (Table 4-12). One distinction in for the outcome of graft loss, as compared to patient mortality, was that candidates listed at centers with highest ECD transplants had a significantly elevated hazard for post-transplant graft loss (AHR=1.08, 95% C.I. 1.02–1.15) relative to candidates listed at centers with a lowest ECD proportion. In addition, the model excluding characteristics of the donor organ (e.g., donor age and ECD) indicated that centers with high ECD levels were more significantly associated with post-transplant mortality (AHR=1.14, 95% C.I. 1.07–1.23) and graft loss (AHR=1.18, 95% C.I. 1.12–1.25).

Center performance level had a significant and stepwise association with candidate mortality prior to transplantation (Table 4-13). Specifically, candidates that listed at centers with lower historical performance levels had higher mortality rates prior to transplantation. Candidates that listed at centers with the lowest performance levels had a 13% (AHR = 1.13, 95% C.I. 1.08–1.18) elevated hazard for death relative to candidates that listed at centers with the highest historical performance levels. Alternatively, candidates listed at centers with historically different rates of transplantation, center volume or ECD proportion had minimal association with pre-transplant mortality.

Outcomes among High-Risk Candidate Groups

Models were repeated for candidate mortality limited to subsets of high-risk patients. These models were generated for African-American, elderly, and obese candidates adjusted for the same covariates with the exception of the variable describing the high-risk characteristic. In addition, models including interaction terms for the center factors and high-risk characteristics were generated and hypotheses tested for whether high and low levels of center factors were more important for high-risk groups relative to their candidate counterparts.

Among African-American candidates, the rate of transplantation had a highly significant and stepwise association with mortality (Table 4-14). Candidates listed at centers with the lowest transplant rates had a 28% increased hazard for death (AHR=1.28, 95% C.I. 1.18–1.38) over the study period. African-American candidates listed at centers with varying volume levels had no significant difference in mortality. African-American candidates listed at centers with the highest proportion of ECD transplants had a significantly elevated hazard for death (AHR=1.09, 95% C.I. 1.02–1.16) relative to candidates listed at centers with a low proportion of ECD transplants. African-American candidates listed at centers with the lowest performance ratio also had an increased hazard for death (AHR = 1.14, 95% C.I. 1.06–1.22) relative to candidates listed at centers with the highest performance ratio.

The model including interaction terms between center characteristics and race groups (limited to African-American and Caucasians) indicated that the association of center effects with mortality was not different by race. The difference between centers with a high and low rate of transplantation ($p=0.42$), high and low volume centers ($p=0.83$), high and low ECD centers ($p=0.48$) and high and low performance ratio ($p=0.84$) was not different between the two candidate race groups.

The rate of transplantation had a highly significant and stepwise association with candidate mortality among elderly candidates (Table 4-15). Elderly candidates listed at centers with the lowest transplant rates had a 26% increased hazard for death (AHR=1.26, 95% C.I. 1.13–1.40) over the study period. There was not an association between center volume with mortality for elderly candidates. The proportion of ECD transplants was associated with mortality with those elderly candidates listed at centers with a mid-level of ECDs having a reduced hazard for death (AHR=0.90, 95% C.I. 0.82–0.99) relative to candidates listed at centers with a high proportion of ECDs. Elderly candidates listed at centers with the lowest performance ratio also had a significantly increased hazard for death (AHR = 1.23, 95% C.I. 1.11–1.36) relative to candidates listed at centers with the highest performance ratio.

The model including interaction terms between center characteristics and age groups (limited to 18–44 and 65+ age groups) indicated that the proportion of ECD transplants was significantly more important in younger age groups than in the elderly (AHR=1.07, 95% C.I. 1.01–1.13). Other center factors did not demonstrate a significantly different impact in younger versus older patients: rate of transplant (p=0.41), transplant volume (p=0.36), and performance ratio (p=0.61).

As displayed in Table 4-16, the rate of transplantation had a highly significant and stepwise association with candidate mortality for obese candidates. Obese candidates listed at centers with the lowest transplant rates had a 33% increased hazard for death (AHR=1.33, 95% C.I. 1.22–1.45) relative to candidates listed at centers with the highest transplant rates. There was no association between center volume and candidate mortality for obese candidates. The proportion of ECD transplants was also not significantly associated with mortality. Obese candidates listed at centers with the lowest performance ratio had a significantly increased hazard for death (AHR = 1.11, 95% C.I. 1.01–1.21) relative to candidates listed at centers with the highest performance ratio. There was no significant differences in the effect of center listing for volume (p=0.27), center performance level (p=0.63), transplant rate (p=0.87), or center proportion of ECD transplants (p=0.13) between obese and non-obese patients.

Expected Survival by Center Characteristics

Expected survival estimates displayed on Table 4-17 indicate the average expected survival based on the level of the center characteristic indicated holding all other center and candidate characteristics at their average level. Results indicate that a candidate's expected survival is markedly different by levels of center levels of the proportion of patients transplanted at three years. Average candidates listed at centers with 82% of patients transplanted at three years have almost 2.5 years increased expected survival relative to patients listed at centers with 10% of patients transplanted within three years. Differences in expected survival between extreme center volume levels were mildly different ranging from 10.4 to 10.9 years. Candidates listed at centers with few ECD transplants had an expected survival of 10.8 years as compared to candidates listed at centers with 32% of ECD transplants, who had an expected survival of 10.5 years on average. Candidates listed at centers with low performance ratings (i.e., high standard mortality ratios) had a 10.1 year expected survival as compared to candidates listed at centers with high performance, who had an expected survival of 11.2 years.

Table 4-18 displays expected survival rates for candidates at hypothetical combinations of center characteristics. The case examples demonstrate differences in expected survival across ranges of the center proportion transplanted and by extreme levels of the other three center characteristics. In particular, the estimates demonstrate the differences in life expectancy relative to the proportion transplanted with either the "worst" combination of other factors as compared to the "best" combination of the other three factors. Among centers with the lowest proportion of candidates reaching transplantation, the variation in average life expectancies ranged from 9.3 to 10.3 years. Centers with a mid level of proportion transplanted and the "worst" combination of additional factors had an average life expectancy of 10.2 years as compared to the best combination of additional factors at 11.6 years. Average life expectancy was notably higher within centers with high proportion of transplant candidates, ranging from 11.5 to 13.1 years.

The expected survival for African-American patients following listing ranged from 9.5 years to 11.5 years at centers with a historically low versus high proportion of candidates reaching transplant at three years respectively (Table 4-19). The variation in life expectancies varied little by center volume. The average life expectancy ranged from 9.6 to 10.3 years by centers with a high and low proportion of ECD transplants respectively. Similarly, average life expectancies for African-Americans ranged from 9.6 to 10.6 years based on the historical center performance level with higher performance centers associated with longer life expectancies.

The center characteristic with the largest range in life expectancies for elderly candidates was associated with the center transplant rate (Table 4-20). Specifically, elderly candidates listed at centers with the highest proportion of candidates transplanted at three years had an expected 6.5 years of life expectancy as compared to elderly candidates at centers with the lowest proportion of candidates reaching transplantation, the life expectancy was 5.6 years. There was mild fluctuation in life expectancy by center volume for elderly candidates, but no notable pattern among levels. In a similar fashion, life expectancy for elderly candidates was highest associated with listing at centers with mid-levels of ECD transplants; however, the life expectancy between low and high centers was similar. Average life expectancies by levels of center performance ratios ranged from 6.1 years in the highest performance centers to 5.3 years in the lowest performance centers.

Average expected life years for obese candidates at centers with a low transplant rates was 8.2 as compared to 10.2 years for candidates listed at centers with the highest proportion of candidates reaching transplantation (Table 4-21). Life expectancies varied minimally based on center volume with no detectable pattern for an association of longer life expectancy with higher of lower volume. Expected life years for obese candidates listed at centers with a low ECD proportion was 9.0 years as compared to candidates listed at centers with a high ECD proportion with 8.7 years. Average life expectancy after listing also varied at centers based on performance level; candidates at the highest performing centers had 9.1 expected life years as compared to 8.4 years at the lowest performing centers.

Table 4-1. Transplant candidate characteristics

Candidate characteristic	Level	%
Age at listing	18–44	43
	45–54	28
	55–64	21
	65+	8
Race	Caucasian	54
	African-American	28
	Asian	5
	Hispanic	11
	Other	2
Gender	Male	59
	Female	41
Primary cause of ESRD	Diabetes	28
	Other	72)
Candidate BMI	13–18	2
	19–30	59
	30+	16
	Missing	23
Candidate education level	Less than college degree	60
	College degree or more	15
	Missing	25
Blood type	O	48
	A, B or AB	52
Candidate primary insurance	Private	42
	Medicare	55
	Other/missing	3
Candidate peak PRA level	0	63
	1–30	19
	30+	10
	Missing	8
Sample Size		**108928**

Table 4-2. Candidate characteristics by center proportion of transplants within three years

Candidate characteristic	Level	Center rate of transplantation category *				
		Q1	Q2	Q3	Q4	Q5
Gender	Male (%)	59	59	60	59	59
Blood type	Type-O (%)	48	47	48	49	48
Education	College degree (%) ^	21	22	19	20	18
Primary insurance	Private (%)	45	42	38	40	40
Age	65+ (%)	8	9	8	8	8
Race	African-American (%)	32	30	29	24	21
PRA level	> 0 (%) ^	30	29	29	34	39
Primary diagnosis	Diabetes	28	28	27	28	27
BMI	30+ (%) ^	22	22	21	21	21

* Categories represent the quintiles of the proportion of patients receiving a transplant by three years: Q1 = [7.0–38.5], Q2 = [38.6–51.6], Q3 = [51.7–63.1], Q4 = [63.2–76.7], Q5 = [76.8–96.0]. ^ The proportions for these categories exclude missing levels.

Table 4-3. Candidate characteristics by center volume category

Candidate characteristic	Level	Center volume category *				
		Q1	Q2	Q3	Q4	Q5
Gender	Male (%)	59	59	59	59	59
Blood type	Type-O (%)	48	47	48	48	48
Education	College degree (%) ^	17	20	20	19	22
Primary insurance	Private (%)	36	36	39	41	45
Age	65+ (%)	9	8	8	8	8
Race	African-American (%)	23	29	29	33	26
PRA level	> 0 (%) ^	29	30	32	32	32
Primary diagnosis	Diabetes	27	27	27	28	28
BMI	30+ (%) ^	22	22	22	22	21

* The categories represent the quintile levels of deceased donor transplant volume: Q1 = [10.0–18.8], Q2 = [18.9–26.3], Q3 = [26.4–36.6], Q4 = [36.7–53.7], Q5 = [53.8–195.0]. ^ The proportions for these categories exclude missing levels.

Table 4-4. Candidate characteristics by center ECD proportion category

Candidate characteristic	Level	Center ECD proportion category *				
		Q1	Q2	Q3	Q4	Q5
Gender	Male (%)	58	59	59	59	60
Blood type	Type-O (%)	48	48	48	48	47
Education	College degree (%) ^	20	22	19	21	20
Primary insurance	Private (%)	39	41	40	43	43
Age	65+ (%)	7	7	8	8	10
Race	African-American (%)	25	27	27	29	32
PRA level	> 0 (%) ^	36	32	33	30	27
Primary diagnosis	Diabetes	30	28	28	27	26
BMI	30+ (%) ^	19	21	22	21	23

* The categories represent the quintile levels of the proportion of ECD transplants: Q1 = [0–6.4], Q2 = [6.5–9.9], Q3 = [10.0–13.4], Q4 = [13.5–18.9], Q5 = [19.0–44.0]. ^ The proportions for these categories exclude missing levels.

Table 4-5. Candidate characteristics by center performance category

Candidate characteristic	Level	Center performance category *				
		Q1	Q2	Q3	Q4	Q5
Gender	Male (%)	59	58	59	60	59
Blood type	Type-O (%)	48	48	48	48	48
Education	College degree (%) ^	21	22	22	19	18
Primary insurance	Private (%)	43	43	44	40	35
Age	65+ (%)	8	8	8	9	9
Race	African-American (%)	25	27	28	29	34
PRA level	> 0 (%) ^	30	30	34	32	30
Primary diagnosis	Diabetes	27	27	28	28	26
BMI	30+ (%) ^	21	20	21	22	23

* The categories assigned by quintile of standard mortality ratios (observed/expected deaths): Q1 = [0–0.56], Q2 = [0.57–0.83], Q3 = [0.84–1.09], Q4 = [1.10–1.45], Q5 = [1.46–3.80].
^ proportion excludes missing levels

Table 4-6. Median levels of center characteristics over time

	1995	1996	1997	1998	1999	2000
Volume	45.7	46.0	47.7	47.0	49.3	48.0
Proportion transplanted	61.5	56.6	54.3	49.1	47.7	45.5
ECD proportion	8.4	10.4	13.1	14.0	14.8	14.7
Performance ratio	0.98	0.98	0.91	0.94	0.96	0.92
Candidate listings	16412	16836	17490	18685	19270	20235

Table 4-7. Correlation coefficients between center characteristics

Linear correlation (p-value)	Volume	Proportion transplanted	ECD proportion	Performance ratio
Volume	—	0.01 (0.71)	0.04 (0.24)	-0.05 (0.09)
Proportion transplanted	0.01 (0.71)	—	-0.21 (<0.001)	—
ECD proportion	0.04 (0.24)	-0.21 (<0.001)	—	0.08 (0.01)
Performance ratio	-0.05 (0.09)	0.04 (0.19)	0.08 (0.01)	—

Table 4-8. Center characteristics at the time of transplantation

	Median center characteristics at the year of transplantation			
Level at the time of listing	Volume	Time to transplant (months)	ECD proportion	Performance ratio*
Q1	20	36	9	0.75
Q2	28	27	11	0.79
Q3	34	21	13	0.83
Q4	46	17	16	1.08
Q5	93	12	23	1.13

* based only on patients transplanted during the year candidate was transplanted

Table 4-9. Adjusted hazard ratios for patient mortality after listing for transplantation

Candidate characteristic (reference level)	Level	Adjusted hazard ratio	95% confidence interval	
Candidate race (Caucasian)	African-American	0.91	0.89	0.93
	Asian	0.59	0.56	0.63
	Hispanic	0.71	0.69	0.74
	Other	0.79	0.73	0.85
Candidate age (18–44)	45–54	1.73	1.69	1.78
	55–64	2.43	2.36	2.50
	65+	3.24	3.13	3.35
Primary diagnosis (Non-Diabetic)	Diabetes	1.88	1.84	1.92
Blood type (Type O)	A	0.93	0.91	0.95
	AB	0.86	0.82	0.91
	B	1.02	0.99	1.05
PRA level (Zero)	1–30	1.07	1.04	1.10
	30+	1.34	1.30	1.39
	Missing	1.43	1.38	1.48
BMI (19–25)	13–18	1.28	1.19	1.38
	26–30	0.96	0.93	0.98
	31–35	1.00	0.97	1.04
	36–40	1.17	1.11	1.23
	41+	1.22	1.13	1.33
	Missing	0.99	0.96	1.02
Education level (College)	Less than College	1.08	1.05	1.12
	Missing	1.14	1.10	1.18
Primary insurance (Private)	Medicare	1.34	1.31	1.37
	Other	0.35	0.20	0.63
	Missing	1.01	0.95	1.08
Dialysis status at listing (None)	Hemodialysis	1.36	1.31	1.40
	Peritoneal dialysis	1.39	1.34	1.45
	Unknown	1.43	1.31	1.56
Proportion transplanted (Highest – Q5)	Lowest – Q1	1.32	1.27	1.38
	Low – Q2	1.25	1.20	1.30
	Mid – Q3	1.17	1.12	1.21
	High – Q4	1.17	1.12	1.21
Center volume (Largest – Q5)	Smallest – Q1	1.00	0.96	1.04
	Small – Q2	1.04	1.00	1.07
	Mid – Q3	0.99	0.96	1.02
	Large – Q4	0.98	0.95	1.00
ECD proportion (Lowest – Q1)	Low – Q2	1.02	0.98	1.05
	Mid – Q3	1.00	0.96	1.03
	High – Q4	1.00	0.96	1.03
	Highest – Q5	1.04	1.00	1.08
Performance Ratio (Best – Q1)	Good – Q2	1.02	0.99	1.06
	Mid – Q3	1.07	1.04	1.11
	Bad – Q4	1.09	1.05	1.13
	Worst – Q5	1.14	1.10	1.19

Table 4-10. Adjusted hazard ratios for receipt of transplant following listing

Candidate characteristic (reference level)	Level	Adjusted hazard ratio	95% confidence interval	
Proportion transplanted (Highest – Q5)	Lowest	0.17	0.16	0.17
	Low	0.31	0.29	0.32
	Mid	0.46	0.45	0.48
	High	0.59	0.57	0.61
Center volume (Largest – Q5)	Smallest	0.94	0.90	0.98
	Small	0.97	0.94	1.00
	Mid	1.02	0.99	1.06
	Large	0.98	0.95	1.00
ECD proportion (Lowest – Q1)	Low	1.07	1.04	1.11
	Mid	1.09	1.05	1.12
	High	1.10	1.07	1.14
	Highest	1.02	0.99	1.06
Performance ratio (Best – Q1)	Good	0.95	0.92	0.98
	Mid	0.93	0.90	0.96
	Bad	0.95	0.92	0.98
	Worst	0.97	0.94	1.01

* Model additionally adjusted for candidate race, age, primary diagnosis, blood type, PRA level, BMI level, education level, primary insurance payer, and dialysis at the time of listing.

Table 4-11. Adjusted hazard ratios for post-transplant mortality

Candidate characteristic (reference level)	Level	Adjusted hazard ratio	95% confidence interval	
Proportion transplanted (Highest – Q5)	Lowest	0.97	0.90	1.04
	Low	1.01	0.94	1.08
	Mid	1.01	0.95	1.08
	High	1.03	0.97	1.10
Center volume (Largest – Q5)	Smallest	1.05	0.97	1.14
	Small	1.10	1.03	1.18
	Mid	0.98	0.92	1.05
	Large	1.06	1.00	1.11
ECD proportion (Lowest – Q1)	Low	1.05	0.98	1.12
	Mid	1.04	0.98	1.11
	High	1.05	0.99	1.13
	Highest	1.06	0.99	1.14
Performance ratio (Best – Q1)	Good	1.01	0.95	1.09
	Mid	1.08	1.01	1.15
	Bad	1.16	1.08	1.24
	Worst	1.20	1.11	1.29

* Model additionally adjusted for recipient race, age, primary diagnosis, PRA level, BMI level, education level, primary insurance payer, pre-transplant dialysis time, donor age, expanded criteria donation, HLA-mismatching, cold ischemia time, and recipient and donor gender.

Table 4-12. Adjusted hazard ratios for post-transplant overall graft loss

Candidate characteristic (reference level)	Level	Adjusted hazard ratio	95% confidence interval	
Proportion transplanted (Highest – Q5)	Lowest	0.94	0.88	1.00
	Low	0.97	0.92	1.02
	Mid	0.98	0.93	1.03
	High	1.02	0.97	1.07
Center volume (Largest – Q5)	Smallest	0.99	0.93	1.06
	Small	1.13	1.07	1.19
	Mid	1.05	1.00	1.11
	Large	1.10	1.06	1.15
ECD proportion (Lowest – Q1)	Low	1.05	1.00	1.11
	Mid	1.07	1.01	1.12
	High	1.08	1.02	1.14
	Highest	1.08	1.02	1.15
Performance ratio (Best – Q1)	Good	1.03	0.97	1.09
	Mid	1.09	1.03	1.15
	Bad	1.15	1.09	1.22
	Worst	1.17	1.10	1.24

* Model additionally adjusted for recipient race, age, primary diagnosis, PRA level, BMI level, education level, primary insurance payer, pre-transplant dialysis time, donor age, expanded criteria donation, HLA-mismatching, cold ischemia time, and recipient and donor gender.

Table 4-13. Adjusted hazard ratios for pre-transplant mortality

Candidate characteristic (reference level)	Level	Adjusted hazard ratio	95% confidence interval	
Proportion transplanted (Highest – Q5)	Lowest	0.99	0.94	1.04
	Low	1.01	0.96	1.07
	Mid	0.99	0.94	1.05
	High	1.05	0.99	1.11
Center volume (Largest – Q5)	Smallest	1.01	0.96	1.06
	Small	1.04	0.99	1.08
	Mid	1.01	0.97	1.04
	Large	0.96	0.93	0.99
ECD proportion (Lowest – Q1)	Low	1.01	0.97	1.05
	Mid	0.98	0.94	1.02
	High	0.97	0.93	1.01
	Highest	1.00	0.96	1.04
Performance ratio (Best – Q1)	Good	1.03	0.99	1.07
	Mid	1.07	1.02	1.11
	Bad	1.06	1.02	1.10
	Worst	1.13	1.08	1.18

*Model additionally adjusted for candidate race, age, primary diagnosis, blood type, PRA level, BMI level, education level, primary insurance payer, and dialysis at the time of listing.

Table 4-14. Adjusted hazard ratios for mortality for African-American candidates

Candidate characteristic (reference level)	Level	Adjusted hazard ratio	95% confidence interval	
Proportion transplanted (Highest – Q5)	Lowest	1.28	1.18	1.38
	Low	1.22	1.12	1.32
	Mid	1.14	1.05	1.24
	High	1.18	1.09	1.29
Center volume (Largest – Q5)	Smallest	1.02	0.94	1.11
	Small	1.04	0.97	1.11
	Mid	1.00	0.95	1.06
	Large	0.98	0.94	1.03
ECD proportion (Lowest – Q1)	Low	1.01	0.95	1.08
	Mid	1.01	0.95	1.08
	High	1.01	0.95	1.08
	Highest	1.09	1.02	1.16
Performance ratio (Best – Q1)	Good	1.05	0.98	1.13
	Mid	1.09	1.02	1.17
	Bad	1.10	1.03	1.17
	Worst	1.14	1.06	1.22

*Model additionally adjusted for candidate age, primary diagnosis, blood type, PRA level, BMI level, education level, primary insurance payer, and dialysis at the time of listing.

Table 4-15. Adjusted hazard ratios for mortality for elderly candidates

Candidate characteristic (reference level)	Level	Adjusted hazard ratio	95% confidence interval	
Proportion transplanted (Highest – Q5)	Lowest	1.26	1.13	1.40
	Low	1.23	1.10	1.36
	Mid	1.18	1.06	1.31
	High	1.14	1.02	1.26
Center volume (Largest – Q5)	Smallest	1.01	0.90	1.12
	Small	1.05	0.95	1.15
	Mid	0.94	0.87	1.03
	Large	0.94	0.87	1.01
ECD proportion (Lowest – Q1)	Low	0.95	0.86	1.05
	Mid	0.90	0.82	0.99
	High	0.97	0.88	1.07
	Highest	0.99	0.91	1.09
Performance ratio (Best – Q1)	Good	1.02	0.93	1.12
	Mid	1.06	0.96	1.16
	Bad	1.14	1.04	1.25
	Worst	1.23	1.11	1.36

*Model additionally adjusted for candidate race, primary diagnosis, blood type, PRA level, BMI level, education level, primary insurance payer, and dialysis at the time of listing.

Table 4-16. Adjusted hazard ratios for mortality for obese candidates

Candidate characteristic (reference level)	Level	Adjusted hazard ratio	95% confidence interval	
Proportion transplanted (Highest – Q5)	Lowest	1.33	1.22	1.45
	Low	1.23	1.12	1.34
	Mid	1.15	1.05	1.26
	High	1.14	1.04	1.25
Center volume (Largest – Q5)	Smallest	0.96	0.88	1.06
	Small	0.96	0.89	1.05
	Mid	1.02	0.94	1.09
	Large	0.95	0.89	1.01
ECD proportion (Lowest – Q1)	Low	1.02	0.94	1.10
	Mid	0.98	0.91	1.06
	High	1.01	0.93	1.10
	Highest	1.05	0.97	1.14
Performance ratio (Best – Q1)	Good	0.95	0.88	1.04
	Mid	1.02	0.94	1.11
	Bad	1.07	0.98	1.16
	Worst	1.11	1.01	1.21

* Model additionally adjusted for candidate age, race, primary diagnosis, blood type, PRA level, education level, primary insurance payer, and dialysis at the time of listing.

Table 4-17. Candidate life expectancy (in years) after listing by levels of center characteristics

Center characteristics*	Q1	Q2	Q3	Q4	Q5
Proportion transplanted at three years	10.0	10.4	11.0	11.0	12.4
Center volume	10.7	10.4	10.8	10.9	10.7
ECD proportion	10.8	10.7	10.8	10.8	10.5
Performance ratio	11.2	11.0	10.6	10.5	10.1

* categories assigned by quintile levels of center characteristics: performance ratio (observed/expected deaths): Q1 = [0–0.56], Q2 = [0.57–0.83], Q3 = [0.84–1.09], Q4 = [1.10–1.45], Q5 = [1.46–3.80]; the proportion of ECD transplants: Q1 = [0–6.4], Q2 = [6.5–9.9], Q3 = [10.0–13.4], Q4 = [13.5–18.9], Q5 = [19.0–44.0]; the proportion of patients receiving a transplant by three years: Q1 = [7.0–38.5], Q2 = [38.6–51.6], Q3 = [51.7–63.1], Q4= [63.2–76.7], Q5 = [76.8–96.0]; and deceased donor transplant volume: Q1 = [10.0–18.8], Q2 = [18.9–26.3], Q3 = [26.4–36.6], Q4 = [36.7–53.7], Q5 = [53.8–195.0].

Table 4-18. Life expectancy after listing at hypothetical center characteristic levels

	Proportion transplanted*	Volume**	ECD proportion^	Standardized mortality ratio^^	Expected survival
Case #1	Low	Low	High	High	9.3
Case #2	Low	Mid	Mid	Mid	10.1
Case #3	Low	High	Low	Low	10.3
Case #4	Mid	Low	High	High	10.2
Case #5	Mid	Mid	Mid	Mid	11.1
Case #6	Mid	High	Low	Low	11.6
Case #7	High	Low	High	High	11.5
Case #8	High	Mid	Mid	Mid	12.5
Case #9	High	High	Low	Low	13.1

*proportion of candidates receiving a deceased donor transplant at three years. **deceased donor transplant volume. ^proportion of ECD transplants of all deceased donor transplants. ^^ratio of observed to expected one year patient deaths.

Table 4-19. Life expectancy after listing for African-American candidates by center characteristic levels

Center characteristics*	Q1	Q2	Q3	Q4	Q5
Proportion transplanted at three years	9.5	9.9	10.4	10.1	11.5
Volume	10.0	9.8	10.1	10.2	10.1
ECD proportion	10.3	10.2	10.2	10.2	9.6
Performance ratio	10.6	10.2	10.0	9.9	9.6

* categories assigned by quintile levels of center characteristics: performance ratio (observed/expected deaths): Q1 = [0–0.56], Q2 = [0.57–0.83], Q3 = [0.84–1.09], Q4 = [1.10–1.45], Q5 = [1.46–3.80]; the proportion of ECD transplants: Q1 = [0–6.4], Q2 = [6.5–9.9], Q3 = [10.0–13.4], Q4 = [13.5–18.9], Q5 = [19.0–44.0]; the proportion of patients receiving a transplant by three years: Q1 = [7.0–38.5], Q2 = [38.6–51.6], Q3 = [51.7–63.1], Q4= [63.2–76.7], Q5 = [76.8–96.0]; and deceased donor transplant volume: Q1 = [10.0–18.8], Q2 = [18.9–26.3], Q3 = [26.4–36.6], Q4 = [36.7–53.7], Q5 = [53.8–195.0].

Table 4-20. Life expectancy after listing for elderly candidates by center characteristic levels

Center characteristics*	Q1	Q2	Q3	Q4	Q5
Proportion transplanted at three years	5.6	5.7	5.8	6.0	6.5
Volume	5.7	5.6	6.0	6.0	5.7
ECD proportion	5.7	5.9	6.1	5.8	5.7
Performance ratio	6.1	6.0	5.9	5.6	5.3

*Categories assigned by quintile levels of center characteristics: performance ratio (observed/expected deaths): Q1 = [0–0.56], Q2 = [0.57–0.83], Q3 = [0.84–1.09], Q4 = [1.10–1.45], Q5 = [1.46–3.80]; the proportion of ECD transplants: Q1 = [0–6.4], Q2 = [6.5–9.9], Q3 = [10.0–13.4], Q4 = [13.5–18.9], Q5 = [19.0–44.0]; the proportion of patients receiving a transplant by three years: Q1 = [7.0–38.5], Q2 = [38.6–51.6], Q3 = [51.7–63.1], Q4= [63.2–76.7], Q5 = [76.8–96.0]; and deceased donor transplant volume: Q1 = [10.0–18.8], Q2 = [18.9–26.3], Q3 = [26.4–36.6], Q4 = [36.7–53.7], Q5 = [53.8–195.0].

Table 4-21. Life expectancy after listing for obese candidates by center characteristic levels

Center characteristics*	Q1	Q2	Q3	Q4	Q5
Proportion transplanted at three years	8.2	8.7	9.2	9.2	10.2
Volume	9.1	9.1	8.7	9.1	8.8
ECD proportion	9.0	8.9	9.1	8.9	8.7
Performance ratio	9.1	9.4	8.9	8.7	8.4

*Categories assigned by quintile levels of center characteristics: performance ratio (observed/expected deaths): Q1 = [0–0.56], Q2 = [0.57–0.83], Q3 = [0.84–1.09], Q4 = [1.10–1.45], Q5 = [1.46–3.80]; the proportion of ECD transplants: Q1 = [0–6.4], Q2 = [6.5–9.9], Q3 = [10.0–13.4], Q4 = [13.5–18.9], Q5 = [19.0–44.0]; the proportion of patients receiving a transplant by three years: Q1 = [7.0–38.6], Q2 = [38.5–51.6], Q3 = [51.7–63.1], Q4= [63.2–76.7], Q5 = [76.8–96.0]; and deceased donor transplant volume: Q1 = [10.0–18.8], Q2 = [18.9–26.3], Q3 = [26.4–36.6], Q4 = [36.7–53.7], Q5 = [53.8–195.0].

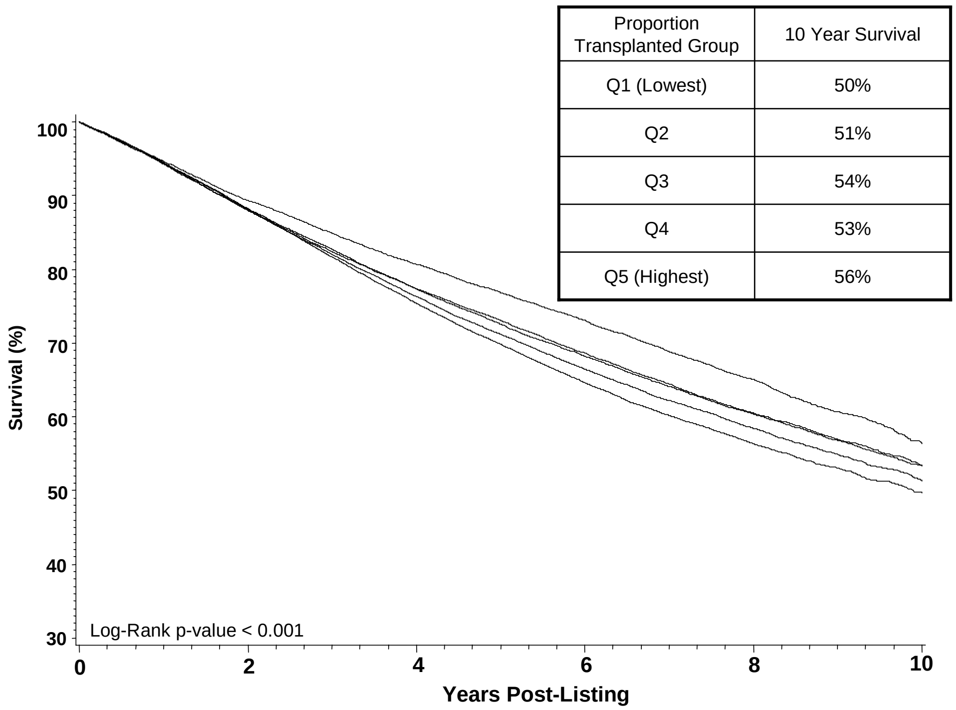


Figure 4-1. Kaplan-Meier plot of candidate survival by center rate of transplant

ECD Proportion Group	10 Year Survival
Q1 (Lowest)	54%
Q2	53%
Q3	52%
Q4	53%
Q5 (Highest)	50%

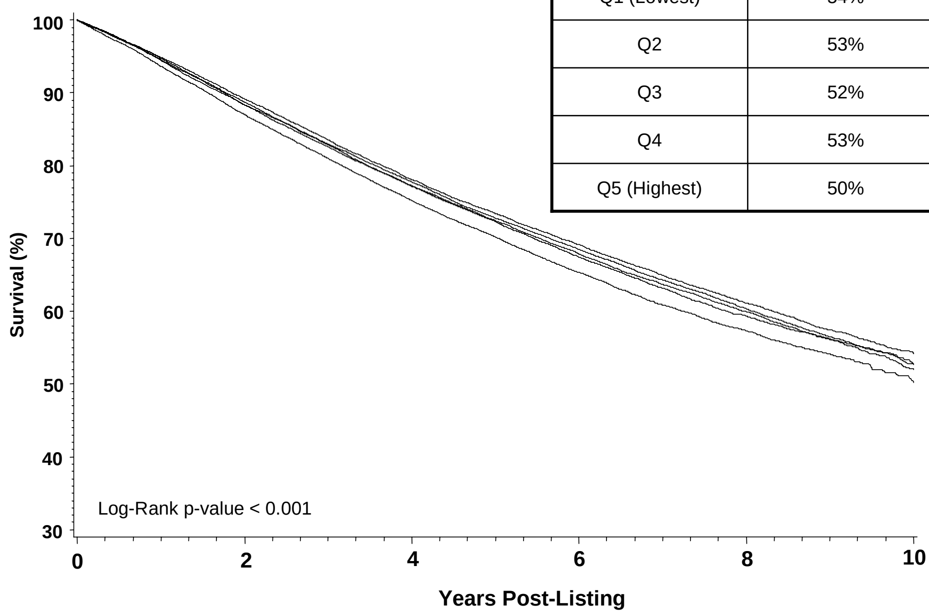


Figure 4-2. Kaplan-Meier plot of candidate survival by center proportion of ECD transplants

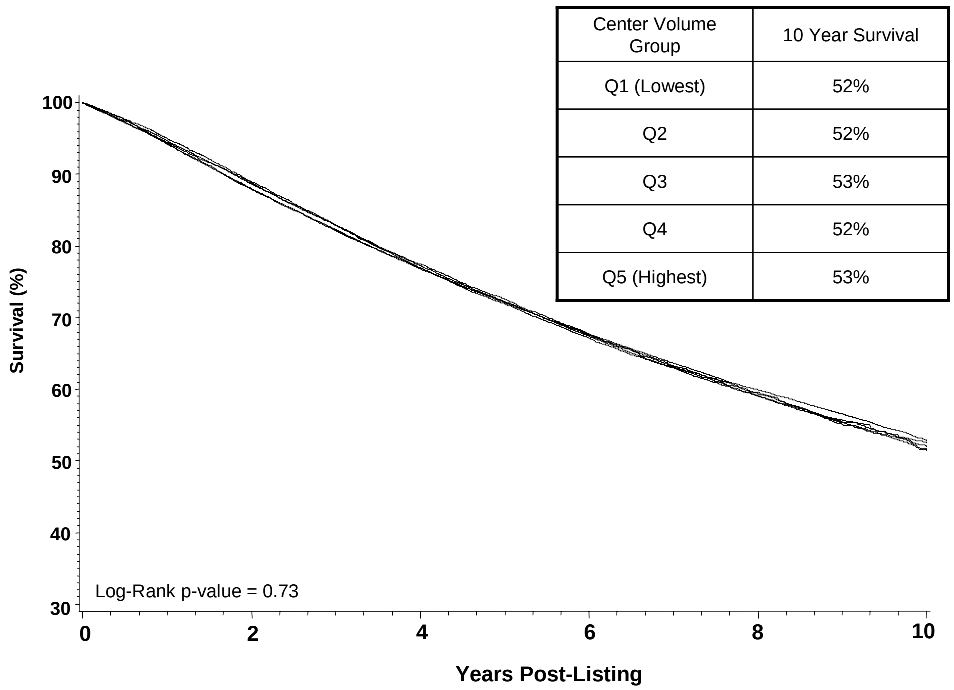


Figure 4-3. Kaplan-Meier plot of candidate survival by center volume

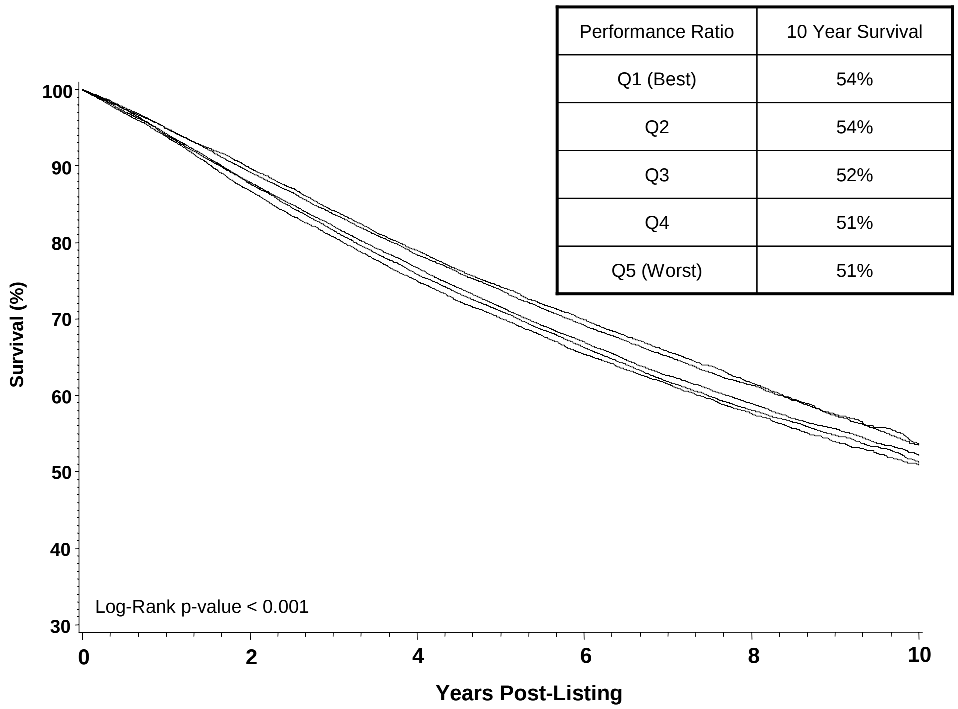


Figure 4-4. Kaplan-Meier plot of candidate survival by center performance ratio

CHAPTER 5
DISCUSSION

ESRD is a pervasive and growing public health concern in the United States. Both the cumulative number of ESRD patients and proportion of individuals with risk factors for future ESRD development have increased significantly over the recent era. The past two decades have also witnessed the growth and acceptance of kidney transplantation as the most effective treatment modality for patients suffering from ESRD. Correspondingly, the number of patients selecting transplantation for treatment of ESRD has also significantly increased. The rapid rise in the number of candidates has increased waiting times to acquire a transplant and increased mortality among patients on the waiting list for transplantation. In response, there have been significant efforts on the part of the transplant community to identify efficiencies in the transplant process, to increase donation rates, and to develop strategies to prolong the lifespan of donations while simultaneously maintaining equitable access to patients.

The explanatory variables of primary interest in this study, the four center characteristics (waiting time, performance level, patient volume, and donor risk level), have generally been shown to be associated with outcomes for transplant recipients. However, the significance and magnitude of these effects for a prospective transplant candidate has not been specifically evaluated. Furthermore, the integration of these factors to assess the relative effects provides a basis by which patients and caregivers can compare potential centers of listing relative to the impact on candidate prognoses. In fact, the selection of a transplant center is a common situation, but in many cases, these decisions may be made by default. Patients that are in this circumstance may often simply follow the advice of primary physicians who, for geographic purposes or personal preferences, refer patients indiscriminately to a particular transplant center. Thus, in the predominant number of cases, there is little active decision making on the part of the transplant candidate or referring physician as to which center is most appropriate for the patient's needs or if alternative centers may in fact provide a different prognosis for that patient. This dissertation attempted to provide data to elucidate the impact of center selection that could potentially inform these decisions. That is, the questions remain, is there a marked difference for candidate outcomes (e.g., mortality or graft survival) based on the choice of center that they list for a transplant? Secondly, if there is a difference, what characteristics of the centers are most important to candidate prognoses? Finally, are these characteristics generalizable to the entire candidate population or are they relatively more important to select groups that have various prognoses by treatment modality (i.e., dialysis or transplant)?

The main findings of this study indicate that center characteristics are indeed significantly associated with patient outcomes. Furthermore, the study demonstrates that these center characteristics vary in their relative effect and that these effects somewhat differ in high-risk subsets of the candidate population. The most direct implication of the study is that candidates and referring physicians have an incentive to incorporate characteristics of transplant centers into decisions to select centers of care. Further research related to these findings and healthcare implications of the study results will be discussed in the proceeding section.

For the purpose of simulating the circumstance that new onset transplant candidates must face in selecting a center, the study was specifically designed to utilize past levels of center characteristics rather than levels that were associated with the center at the time of transplantation. Clearly, candidates will not be aware of the characteristics of centers at the time that a donor organ is offered and must base decisions on levels prior to the time of listing. This study utilized the aggregated center levels from three years prior to the time of candidate listing as a representation of these characteristics. In fact, the analysis demonstrated a significant association of historical levels of center characteristics with levels of these same characteristics at the time of transplantation. This is important information for prospective candidates to assess the reliability of center characteristics to assist with their selection of a center. The results indicate center factors in this study are relatively stable and can be utilized on a prospective basis for comparing centers. An important caveat to this finding, however, is that, as demonstrated in the study, waiting times for candidates to reach transplantation are continuing to expand. Thus, this greater time period is associated with a greater opportunity for center characteristics to alter. Based on this study period, center volume has been relatively stable over time, waiting times have increased, and the utilization of ECD donations have increased. It is also worthy of note that center performance ratios are fairly consistent over time. That is, performance ratios at a center at the time of listing are similar to the performance ratios at the time of transplant on average. The performance ratio is presented as a measure of quality of care, and it might be expected that, due to random events or changes in practice, this value might significantly vary over time. Results of the analysis suggest that listing at a center with high performance is generally accompanied by a high performance level at the time of transplantation.

The associations between center characteristics and candidate outcomes found in this study were relatively consistent with the literature investigating the impact on transplant recipients. In particular, longer waiting times, better performance ratings, and a lower proportion of ECD transplants all translated to superior outcomes for transplant candidates from the time of listing. However, the degree of these associations and the relative importance of these characteristics are of particular importance in this study. The historical proportion of candidates that reach transplantation at three years demonstrated a highly significant and dose-response relationship with outcomes for candidates. Candidates listed at centers with the slowest rate of transplantation had a 32% elevated hazard for death over the study period relative to candidates listed at centers with the most rapid rate of transplantation. This finding is perhaps not surprising, as there are two clear explanations for this association. One is that transplantation has been demonstrated to convey a significant survival benefit over the alternative treatment modality of maintenance dialysis which is typically initiated prior to candidate listing. Therefore, a portion of this effect is likely attributable to the fact that candidates at centers with longer waiting times accumulate relatively higher cases of mortality prior to reaching transplantation. In addition, the cumulative effects of dialysis have a significant impact on post-transplantation mortality. Therefore, those candidates that reach transplantation with longer waiting times and exposure to dialysis also have poorer outcomes. Cumulatively, findings from this dissertation demonstrate that for an average candidate, there is a significant survival benefit that can be attributed to listing at a center with reduced expected time to transplantation.

The relative hazard associated with increased waiting time adjusted for potential confounding factors is important in demonstrating the independent effect of this characteristic on candidate mortality. However, the interpretation of this relative risk is not always straightforward to clinicians or patients. In order to relate the findings of this study in terms that could be useful to a broader audience, the study also estimated the median survival of candidates from the time of listing. Results of the analysis demonstrate that the average candidate has approximately two and a half years longer expected survival (12.4 years versus 10.0 years) by listing at a center with a rapid versus delayed rate of transplantation. Furthermore, as the center groupings represent quintiles, there are approximately 20% of centers that have the reduced waiting times, suggesting that they are not uncommon situations. However, there is also likely a regional component to waiting times, and within certain regions, centers with reduced waiting times may be scarcer; therefore, future studies may be useful to elucidate the regional availability of centers with rapid rates of transplant.

Research suggests that centers with the highest transplant volume have superior patient outcomes. This has been interpreted as related to quality of care associated with greater experience with the surgical procedure, greater infrastructure and coordination of services to transplant patients, and availability of ancillary services. In contrast to these research accounts, center volume was not significantly associated with candidate survival in this study. This difference may partially reflect the relative unimportance of center volume as compared to other factors examined in the study as well as the reduced impact of volume for transplant candidates as compared to recipients. Many candidates for transplantation do not survive to the time at which a transplant may be offered and others may become unviable for transplant due to health deterioration. As such, the impact of center volume, which has shown some association between the largest centers and recipient outcomes, may be diluted. It is also possible that smaller centers have a greater opportunity to follow patients prior to transplantation and, despite the lack of facilities, the long-term advantages of larger centers are balanced by increased follow-up care. Past reports suggest that the effect of volume on recipient outcomes in not linear, but is generally found to be superior in the top volume centers only. However, this study excluded candidates listed at very small centers (<10 deceased donor transplants per year) in order to obtain stable estimates of pre-listing characteristics; in this regard, the impact of volume may also only be highlighted at extreme levels and less evident among centers with slightly larger volume in this study.

The quality of deceased donations are highly variable, translating to almost three-fold hazard ratio for graft loss for a recipient with the lowest quality donors relative to an ideal class of donations (49,50). As such, there is a clear incentive for transplant candidates to acquire the highest quality donation available, holding all other factors equal. There are also significant regional variations in the proportion of high-risk donations. The expanded criteria policy was initiated in 2002, mandating that candidates prospectively consent as to whether they would be willing to receive an ECD transplant. Therefore, candidates have some control over whether they will receive a lower-quality kidney. The potential benefit of listing for an ECD kidney is that candidates may receive their transplant more rapidly than having to wait for a SCD. In fact, research indicates that this may be an advisable strategy for some candidates, at least at centers that selectively list patients (53,99). However, regardless of the listing strategies, candidates that list at a center with a lower proportion of ECD kidneys should theoretically have an advantage over candidates that are listed at centers with a high proportion of ECDs. For candidates that are unwilling to accept an ECD, a lower proportion of ECDs should expedite their acceleration on the waiting list. In contrast, candidates that are willing to accept ECDs should still have a greater opportunity to receive a SCD at a center with a lower proportion of ECDs. Moreover, centers with higher rates of ECD transplants may also have a higher-risk donor pool of organs within risk classes, though this has not been demonstrated explicitly. This study indicated that candidates have a significantly elevated mortality risk (AHR = 1.04, $p<0.05$) by listing at centers with the highest proportion of ECDs as compared to listing at centers with the lowest proportion of ECDs. This increased hazard translated to approximately four months of reduced expected survival among candidates listing at centers with the highest proportion of ECD transplants as compared to centers with the lowest proportion of ECDs. However, the study also demonstrated that this effect was significantly higher for post-transplant survival and, in particular, when eliminating characteristics of donors from the model. Therefore, the study suggests that candidates that list at centers with lower quality donations are more likely to receive a lower quality organ for those who survive to the time of the procedure. Furthermore, outcomes for recipients are significantly reduced at centers with a greater utilization of higher-risk organs. The study also suggests that there is a correlation between centers that use a greater proportion of higher-risk organs for centers that have longer waiting times. In other words, centers that have longer waiting times may be more likely to accept lower-quality organs in order to ameliorate the candidate volume. From the candidate perspective, waiting time remains the most critical center factor associated with survival; however, for centers with similar waiting times, the quality of donor organs may remain a modifier of center selection. In addition, this study did not specifically examine this effect in patients that actually list for or receive lower-quality organs. Follow-up studies addressing center selection specifically for candidates willing to accept lower-quality organs (or for those not willing to accept lower-quality organs) may also elucidate important center factors that are pertinent to the candidate population.

Performance evaluations are conducted and published by the SRTR and readily accessible to the public through written reports and the internet. Evaluations are constructed based on standard mortality ratios which calculate the observed number of events (graft losses or deaths) at a transplant center relative to what would be expected given the characteristics of the recipient population over a fixed interval of time. Theoretically, this ratio is indicative of quality of care and center performance for their recipient population. In fact, the study indicated that candidates listed at centers with the best historical performance have significantly better outcomes as compared to candidates listed at centers with the worst performance ratings ($AHR=1.14$, $p< 0.01$). This elevated risk translated to an approximate one year of increased survival for the average transplant candidate between centers with the best and worst ratings.

However, an important consideration associated with this finding is that a portion of this effect was observed prior to transplantation. This may imply that centers with higher ratings have better pre-transplant care, but also may be suggestive of increased patient selection criteria. This notion will be explored in more detail later in the discussion.

One of the main goals of this study, beyond evaluating the significance of individual center characteristics, was to ascertain the relative importance of these factors. The general conclusion that is evident from our study is that the waiting time at a transplant center is the most important modifier of decisions to select a center among the characteristics examined. The hazard ratios and estimated survival years from the time of listing for candidates suggest that while other factors may incrementally impact candidate outcomes, waiting time clearly has the strongest effect on patient mortality. Even in the presence of a combination of ideal characteristics of other factors, differences in expected waiting time remain the predominant determinant of candidate outcomes. In this regard, the average candidate and their caregivers may have a strong incentive to assess the expected waiting times at centers in the decision-making process for the selection of a transplant center. The additional knowledge of objective information about the center and characteristics which may influence their outcomes should be available and disseminated to patients in order to help them make informed decisions. In many instances, patients simply may rely on the advice of a referring physician and have no significant participatory role in this decision which may have life-altering implications. Results of this study and subsequent research deriving from this paradigm may be used to inform patients and their caregivers about the ramifications of these important decisions and the impact on their survival. In addition, strategies to disseminate this information to patients and caregivers in an interpretable fashion are clearly needed in future efforts deriving from this study.

There are certainly additional factors that may affect an individual candidate's selection of a center that were not incorporated in this analysis, including the geographic location of the center, the prestige or personal familiarity with the center and personnel, and the comfort level with the caregivers at the center itself. These factors may be very important to candidates, but should be considered relative to the impact of other characteristics evaluated in this study. Moreover, centers clearly cannot be defined only by the characteristics outlined in this study. The specific factors investigated in this study were based on past research and the degree to which information was readily available characterizing centers. However, each center is unique in its physical structure and design, environmental conditions, and medical personnel expertise and experience. Centers also vary in their academic affiliation, the degree to which they provide services as part of a safety net program, the coordination and relationship of surgical and medical departments, physical capacity, the availability of dialysis services, and connection with other dialysis centers as well as innumerable medical protocols. The degree to which these other factors may impact candidate outcomes is unknown and this uncertainty must be taken into consideration. Specifically, this study demonstrates the impact of factors in a typical situation for an average candidate; however, a broad host of factors may certainly modify these estimates or be particular pertinent to an individual candidate. Therefore the results of the study must be interpreted and utilized with these caveats in mind and not be viewed as an omnipotent guide to center selection that cannot be superseded by other conditions.

Another important aspect of this study was to assess the degree to which center characteristics were significant and relatively important to all candidates or whether these characteristics had a particular impact in certain subsets of the candidate population. To this end, the study examined the association of center characteristics specifically in three "high-risk" subsets of patients: African-Americans, the elderly, and obese candidates. In general, results indicated that center characteristics remain important to these high-risk subsets of the population, particularly the center rate of transplantation. One of the potential implications of this portion of the analysis was to identify factors that may have differential effect in certain subgroups that may suggest efficiencies in the transplant process. That is, in the case that specific factors could be shown to be important to certain groups, but not others, it would be possible that candidates could simultaneously benefit based on listing at centers with the presence of factors that are suited to their needs. In contrast, if center factors were relatively equally important to all subgroups, the analysis may suggest the preferred center characteristics for candidates, but candidates could obviously not all seek to list at these centers simultaneously. Broadly, the latter case is suggested by the analysis. That is, while there are factors that appear to have a somewhat differential impact in the subgroups examined in the study, the main findings are applicable to all groups. This may imply that results of the study can still be applicable to candidate populations that have the ability to seek out centers with the preferred characteristics, but cannot be generalized to the entire candidate population. As the primary characteristic influencing candidate survival is the rate of transplantation associated with the transplant center, primarily an increase in donation rates would be needed to significantly reduce waiting times across centers.

The categorization of African-Americans as a "high-risk" subset of the population is generally a reflection of an increased rate of graft loss for these patients following transplantation. This elevated risk has been attributed to immunological factors as well as socioeconomic characteristics of this population (58). However, in contrast, African-Americans have superior survival on dialysis relative to Caucasians and equivalent patient survival following transplantation (53,100). Therefore, given these potentially differential effects of transplant-related factors on African-Americans, the hypothesis that selection of centers may also be unique to this portion of the candidate population was justified. Results of the analysis indicate that, as for the general candidate population, listing at a center with the most rapid rate of transplantation is the most important factor among the variables in the study for African-American candidates. The 28% elevated increased hazard for candidates that list at centers with the longest expected waiting times as compared to candidates that list at centers with the shortest waiting times was the most substantial center characteristic in the analysis. On average, African-Americans have longer waiting times than their Caucasian counterparts due to the distribution of HLA antigens in the donor population, which has been a significant component of the organ allocation algorithm. African-Americans have a smaller likelihood of receiving additional points that are ascribed to HLA-matching with a potential donor kidney as part of the allocation of deceased donor organs (101,102).

Even though average waiting times are longer for African-Americans, as this analysis demonstrates, it is still highly beneficial for African-American candidates to list at centers with reduced expected waiting times. In fact, the study indicates that expected survival is two years longer for candidates that list at centers with the shortest time to transplant (11.5 years) as compared to candidates that list at centers with the longest expected waiting times (9.5 years). Another interesting result of the analysis is that African-Americans have a significantly increased survival associated with centers with a low proportion of ECD transplants. The 9% increased hazard for mortality after listing associated with African-American candidates that list at centers with the highest ECD proportion was significantly higher than the general population. This is consistent with the literature that African-Americans may derive a greater benefit by receiving a higher quality donation even at the expense of additional dialysis exposure as compared to

Caucasian candidates, despite the fact that historically African-Americans are more likely to receive an ECD transplant (51,53). Candidates that listed at centers with the lowest proportion of ECD transplants had 10.3 years of average life expectancy after listing as compared to 9.6 years among African-Americans that listed at centers with highest proportion of ECD transplants. The effect of center volume was not statistically significant in this portion of the candidate population. Center performance ratios also had a similar estimated impact for African-American candidates as compared to the general population.

Elderly patients comprise a significant and growing portion of the dialysis population. Elderly patients comprised 8% of the candidate population over the study period, but have a three-fold risk for mortality following listing relative to the youngest candidate age group. Elderly candidates are at significantly higher risk for death while on dialysis as well as after transplantation. However, elderly candidates still receive a significant benefit from transplantation with an almost doubling of life expectancy relative to remaining on dialysis therapy (27). In addition, there is evidence that elderly candidates have heightened incentive to receive transplants more rapidly, even at the expense of receiving a lower quality donation (53).

The analysis indicates that, as with the general population, the most important center characteristic for elderly candidates is the rate of transplantation. Elderly candidates listed at centers with the lowest proportion of candidates reaching transplantation had a 26% increased hazard for mortality as compared to the candidates listed at centers with the longest expected waiting times. This translated to a difference of approximately one year in expected survival for the average elderly candidate. The magnitude of the hazard associated with longer waiting times was reduced as compared to the general population and may reflect that the impact of transplant centers is less important to elderly candidates due to higher death rates on dialysis due to other clinical factors. That is, as a significantly higher proportion of elderly candidates die prior to reaching transplantation, the accrued benefit from transplantation is observed in a smaller portion of the population.

As opposed to the general population, for elderly candidates, there was no significant association between the volume and the ECD proportion at the listing center. As with the reduced effect of the center rate of transplantation, this may reflect the reduced importance of center characteristics as compared to the competing risks of other clinically based factors that are particularly relevant for elderly ESRD patients. However, the non-significant finding associated with ECD proportions may also demonstrate that elderly candidates that list at these centers may receive some additional benefit by receiving these organs more rapidly. One notable difference in the elderly population was the increased association of center performance ratings with candidate outcomes. The analysis indicates that elderly candidates have a significant difference in mortality when listing at centers with the highest performance ratios, a 23% increased hazard for death as compared to listing at centers with the lowest performance ratios. This effect translated to an estimated one additional year of life expectancy between centers of extreme performance ratings (6.1 years versus 5.3 years). It is possible that, due to the unique care needs and relative fragility of elderly candidates, the quality of care between centers is most evident in these patients. In fact, past reports investigating the nature of “center effects” suggest that differences between centers are primarily reflective of outcomes in higher-risk populations. As such, as opposed to younger candidates in whom lower quality of care may result in greater complication rates or reduced quality of life, the impact on mortality in relatively healthier subsets may still be marginal. However, another explanation for these findings may relate to potential selection bias among elderly candidates. The effect of selection bias is a greater risk in elderly patients for whom many underlying health conditions and co-morbidities that are not represented in the database can influence outcomes.

As outlined in the methodology portion of the study, there is some potential for selection bias as a contributing factor to the results. While there are universal contraindications for criteria for transplant candidacy, some centers may invoke additional screening processes which contribute to differences in mortality (103,104). In the context of this study, this may result in bias in results in the case that centers that list a more selective cohort of patients also were more highly represented by certain center characteristics in the analysis. For instance, in this case if centers which traditionally had higher center performance ratios also were more selective in candidate screening, this association may bias certain results of the study. Specifically, the disproportionate representation of non-codified factors may contribute to differences in outcomes and inappropriately elevate the effect of performance criteria. As described in the methodology, there were two fundamental strategies to obviate this potential confounding effect. One strategy was to adjust for factors that may account for patients that are selectively listed. These include age, race, patient primary insurance, and education level. In fact, these factors were adjusted for in the analysis and had statistically significant associations with candidate mortality. The additional strategy was to partition the follow-up period to pre- and post-transplant survival. The purpose of this partitioned analysis is that transplant centers typically have significantly less interaction with candidates prior to transplantation and would be less likely to have an impact on survival prior to transplantation related to quality of care. In contrast, centers may have a much stronger association with candidates during the transplant procedure and post-transplant care. Therefore, differences that occur prior to transplantation are more likely related to factors other than center quality of care and may reflect a certain degree of patient selection.

The results of the model for pre-transplant mortality indicate a significant association of standard mortality ratios with death prior to transplantation, while none of the other center factors examined had a significant association. Candidates listed at centers with the lowest performance ratios had a 13% elevated mortality prior to transplantation as compared to candidates listed at centers with the best mortality ratios. In addition, this association was particularly notable in elderly candidates. This finding must be interpreted carefully and, in particular, may be indicative of selection bias of "better patients" to centers with higher performance ratings. In practice, transplant centers are not the primary caregivers of patients prior to transplantation. In contrast, centers are responsible for listing candidates and determining whether they meet certain medical criteria, but are not typically responsible for patient care in the interim between candidacy and the transplant procedure. One of the main purposes for this sub-analysis was to determine the potential influence of certain selection biases that may occur and influence the main outcome of patient survival after candidacy. This portion of the model most likely indicates that centers with better performance ratings either list healthier candidates, leading to lower pre-transplant mortality, or are located in areas with lower morbidity among the dialysis population, or there are other environmental factors which are significantly variable. The fact that this association was stronger among elderly patients, in which selective listing of patients may be significantly stronger, further suggests the influence of patient selection. Although center performance was not the most significant factor for candidates in the primary outcome model, the degree to which an association did exist may in part reflect this patient selection rather than improved quality of care by the transplant center.

The other important implication of this finding is that models evaluating center performance may not fully account for underlying health conditions and exogenous factors that significantly influence mortality but are not associated with quality of care. That is, as candidate survival rates are positively correlated with transplant outcomes even after adjustment for other risk factors, this may imply that other non-codified factors are associated with outcomes that are not accounted for with risk adjustment. Future investigation into the degree to which center performance is impacted by candidate mortality rates independent of other transplant-related factors is important to distinguish these effects. The interpretation of center standard mortality ratios is generally that they are indicative of quality of care. In fact, insurance companies and government oversight committees may further use these criteria for business purposes and to investigate centers for inappropriate care practices (22). In contrast, if performance ratios are merely indicative of selective listing practices, than these additional interpretations relating quality of care to performance are unwarranted. Furthermore, if this association is not justified then there are potential dangers that centers will limit access to patients in an effort to improve performance ratings, but at the same time certain patients may not acquire the benefit of transplantation as a result. Given the results in this study, performance ratios only had a mild association with candidate mortality, but even this limited effect should be interpreted with caution given these potential caveats.

Obese patients represent a unique subset of the transplant candidate pool for several reasons. The population of obese candidates and transplant recipients is significantly growing consistent with the growth rates among the general ESRD population (100). Moreover, obese patients have a unique "paradoxical" survival advantage on maintenance dialysis. However, obese patients also have significantly elevated risk for post-transplant graft loss and mortality (105). This study indicates that despite this relatively reduced mortality on dialysis prior to transplantation and increased mortality following transplantation, the most important center characteristic of obese candidates remains the rate of transplantation. Obese candidates significantly benefit from transplantation and as compared to other center characteristics have the most significantly increased survival expectancy associated with listing at centers with reduced waiting times as compared to other factors of center volume, performance, or ECD proportion. Center volume was not associated with differential outcomes for obese patients. Obese candidates that listed at centers with the highest proportion of ECD transplants had an elevated risk for death at a similar level to the overall candidate population. Candidates that listed at centers with the lowest performance ratio also had an elevated risk for mortality. Similar to elderly patients, the issue of whether this effect is due to transplant center quality of care versus patient selection is unknown; however, among high-risk patients the opportunity for this selection bias is likely stronger. On the other hand, centers treating obese candidates and recipients may require greater quality of care due to the increased potential for surgical complications and morbidity associated with obese transplant recipients. The most important results is that expected candidate survival for the average obese candidate ranges from 8.2 years to10.2 years for listing at centers with the longest and shortest waiting times respectively. Consistent with the general candidate population, results of the study indicates that obese candidates have a significant survival advantage by listing at centers with a rapid rate of transplantation.

In general, results of the study for higher-risk patients were consistent as for the general candidate population. As discussed previously, this indicates that broad efficiencies in the transplantation process are not readily indicated by the study in which certain portions of the population may be best served by particular centers. In contrast, the study suggests that all patients have an incentive to list at centers with reduced waiting times above all other center characteristics. Given this information, the question remains as to which patients will utilize this information. Intuitively, the answer will likely be those patients who are best informed or educated or have the means to travel to centers with an ideal set of characteristics. Alternatively, if the information were well known among the entire candidate population, the net effect would be that waiting times would eventually be relatively equivalent. That is, the effect of candidates seeking centers with reduced waiting times would eventually balance these differences. Whether or not this is realistic is not clear; however, in terms of equity and eliminating geographic disparities in access to transplantation, these objectives may be ideal. Particularly given the fact that more vulnerable candidate groups are less likely to benefit from the results of the study, future efforts to educate these portions of the population and provide access to centers with ideal characteristics are warranted.

In the framework of Grossman's health production function, the study suggests that patient and caregiver behavior, specifically the selection of a center, has a significant impact with the subsequent deterioration rate of transplant candidate health. As described in Grossman's model, patients arrive at a given period (in this case, at the time of candidacy) with a given stock of health. From that point, decisions to seek health care and the "investment" in future stock of health are related to their prognosis and subsequent utility. Beyond simply seeking medical care as outlined as an important factor in Grossman's paradigm, this study suggests that the specific center at which care is sought is a significant modifier of patient outcomes. In addition, consistent with the health production function, certain individual characteristics alter the effects of future health. Whether patients' decision-making processes are related to their own demand for utility or current stock of health is not fully addressed in this study. However, the study does suggest that patients that are more informed, motivated, or able to seek care outside of their immediate region have an improved prognosis through selection of a medical center. An individual's investment in health through the selection of a center has a profound effect on transplant candidate survival consistent with the health production function paradigm.

There have been significant efforts from private and public agencies, individual patients, and patient advocates to provide transparent healthcare information to the population. One of the significant challenges in these efforts is to disseminate information in a coherent and useful manner to patients. Certainly, in recent years patients are more likely to interact with healthcare professionals with a greater arsenal of information obtained through research, personal communications, or web-based services. The degree to which this information increases the likelihood to seek appropriate care or facilitates the healthcare interaction is not fully known and is likely context dependent. However, as the trend towards more informed patients is not likely to decline in future years, a major focus of researchers and caregivers is to disseminate the most meaningful and interpretable data to consumers of this information. An additional challenge related to this trend is to dispel increased levels of misinformation that may also be obtained from the same sources.

Transplantation is somewhat unique to other fields of medicine due to the volume and granularity of information that exists related to mandatory data collection. In this sense, this field has a particular opportunity to provide evidence-based recommendations to patients and their caregivers. However, transplantation is not unique to other medical contexts in that there is a significantly competitive market, and advertisement of a center may entail numerous unsubstantiated or at least subjective components. Future work detailing strategies by which to disseminate information to patients will be a necessary corollary to this study. Furthermore, given that transplantation is a complex science, relaying the most pertinent information to concerned parties is a significant obstacle.

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CHAPTER 6
CONCLUSIONS AND FUTURE WORK

The primary findings of this research suggest that transplant centers are associated with significantly variable survival for candidates of renal transplantation. This information is important for prospective candidates and caregivers to facilitate decisions in their selection of a center of care. There are multiple factors which may ultimately determine the specific center at which a candidate receives care; however, objective information which may have life-altering ramifications is critical to disseminate to affected individuals. Results of the study indicate that multiple factors are important, the magnitude of the effects vary significantly, and the most critical factor for a candidate among the center characteristics examined is the expected duration of the waiting list. Candidates have a significantly longer expected life span by listing at a center with a reduced waiting time independent of other center factors. In addition, this finding is valid across the three high-risk subgroups examined with slight variations in the magnitude of the effect. For centers with similar expected waiting times, other factors examined in the study also modify expected survival for prospective candidates.

The results of this study can be summarized to inform transplant candidates that it is useful to “shop around” for transplant centers, and a key characteristic in these comparisons should be the expected waiting time to transplant. However, one of the realities in this population is that not all patients are capable of listing at centers across the country either for logistical, financial, or insurance constraints. Therefore, those patients that are more affluent, educated, or generally have fewer barriers to mobilizing are the candidates that can benefit from this information. Alternatively, patients from lower socioeconomic status or with more complicated health conditions may not be able to identify centers in a more narrow region with significantly reduced waiting times. The degree to which centers are available with more desirable characteristics at a national and regional basis across the country will be an important investigation for future work. In this regard, one of the potential follow-up projects of this study is to construct an application that incorporates these results and allows candidates to identify centers. This could be generated with the capability to incorporate given constraints (e.g., in a certain region) and allow transparent information regarding the availability of centers and the associated impact on candidates' prognoses. This could be a critical step in the dissemination of results to a broad audience rather than through traditional scientific publications by which information may reach only selected patients and caregivers.

Another interesting and important result of this study is the identification of potential selection bias associated with center performance ratings. These ratings have important implications to transplant centers related to government oversight, contracting with insurance agencies, and advertising to potential candidates and referring physicians as a marker of good quality of care. However, if these ratings are related to pre-transplant candidate selection (as suggested by this study) then further investigation of the utility of performance evaluations in the field of transplantation is warranted. Additional study investigating the association of other center factors, such as patient proximity to the center, center experience with specific patient groups, and in relation to the quality of care of dialysis centers associated with a transplant center may complement the findings of this study. In addition, replication of the analysis in several other high-risk groups, such as diabetic patients, patients with a history of cardiovascular disease, or pediatric populations, may also generate important information for subgroups of the growing ESRD population. Moreover, results may be applicable to other forms of organ transplantation and more broadly to other forms of health care in which provider selection could have an important impact on patient prognosis.

The immediate follow-up work for this study will entail disseminating results through peer-reviewed manuscripts and discussion of these topics in scientific meetings. Beyond extending the results to other populations and medical contexts, strategic efforts to communicate findings directly with patients are an important endeavor. This is particularly salient in this context in which centers may or may not have a vested interest to transmit this information to patients. Ultimately, the results of the study will be most useful when there is shared information among patients and caregivers, and it is utilized jointly to make potentially life-altering decisions in selection of a transplant center

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BIOGRAPHICAL SKETCH

Jesse D. Schold, Ph.D., M.Stat., M.Ed., completed his doctorate program in 2007 in the department of Health Services Research, Management and Policy at the University of Florida in the College of Public Health and Health Professions. Dr. Schold received his undergraduate training at Emory University. After receiving a B.A., he worked in the healthcare setting for several years and then enrolled in graduate studies at North Carolina State University. Dr. Schold received both a Master of Statistics and a Master of Education in the year 2000. After two years working in industry as a statistician, Dr. Schold began work as a research coordinator in the Department of Medicine at the University of Florida. During his experience, he also enrolled as a doctoral student in the Health Services Research program. Dr. Schold is currently an Associate Instructor in the Department of Medicine and has had peer-reviewed scientific articles published in journals including *Transplantation, the Journal of the American Society of Nephrology, Diabetes Care, the Clinical Journal of the American Society of Nephrology, Seminars in Dialysis, Blood, Clinical Transplant, Biology of Blood and Marrow Transplantation, and the American Journal of Transplantation*. Dr. Schold plans to continue work in an academic setting in the fields of transplantation and health services research.