Predicting One-year Kidney Graft Failure and Death with

Cardiovascular and Immunological Factors

By

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DISSERTATION

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LIST OF ABBREVIATIONS

AUC	Area under curve
BMI	Body mass index
CMS	Center of Medicare and Medicaid
eGFR	estimated glomerular filtration rate
ESRD	End stage renal disease
KT	Kidney transplantation
NKF	National Kidney Foundation
PSR	Program Specific Reports
OPTN	Organ Procurement Transplant Network
SRTR	Scientific Registry of Transplant Recipients
UNOS	United Network Organ Sharing

SUMMARY

Comorbid medical issues significantly increase the risk of graft failure and mortality among kidney transplantation recipients. In particular, cardiovascular and immunological factors increase the levels of uncertainty and risk associated with transplantation. However, few predictor models are available to help to inform healthcare providers which candidates with those factors are at the greatest risk for graft failure and patient death. The purpose of this study was to determine the impact of cardiovascular and immunological factors on kidney graft failure and patient death at the one-year post-kidney transplant mark. This study developed four predictive models according to donor types (deceased or living) and outcomes (graft failure or mortality) using national transplantation registry data ($n = 218,657$), from the Scientific Registry of Transplantation Recipients, by a 7:3 split-sample methodology for internal validation.

Cardiovascular factors included obesity, physical limitation, peripheral- and cerebrovascular diseases, and diabetes. Immunological factors were panel reactive antibodies, human leukocyte antigen DR mismatching, history of kidney transplantation, ABO incompatibility, and donor-recipient relationship. The four models developed by the derivation datasets satisfied Goodness of Fit and showed accuracy measured by the area under curves (AUC) in receiver operating characteristic curves (AUC = 0.642-0.727). The calibration calculated by the validation datasets indicated a coefficient value near 1.0, meaning an agreement between observed- and predictive- probabilities. And lastly, the survival rates of high-risk candidates receiving transplants predominated over the rates of high-risk candidates on the waiting list (*Median* = 22.7 vs. 19.1 years).

Kidney transplant outcomes, defined as graft success and patient survival in one year after kidney transplantation, are the objective criteria for the transplant community to evaluate the quality of an organ transplant process. Patients are categorized into the high-risk group when cardiovascular diseases or immunological barriers exist, and the access of this group to kidney transplants is limited. However, the benefits of transplantation for the high-risk group were unknown. These four models will help to quantify and predict the risks of transplant outcomes in high-risk candidates and eventually, the models will screen the most appropriate candidates. Lastly, these models will enable the transplant community to utilize most efficiently one of the most limited and scarce resources, donated kidneys.

I. INTRODUCTION

Six million patients in the United States suffer from end stage renal diseases (ESRD), and the number of ESRD patients grows by 20,000 every year [United States Renal Data System (USRDS), 2016]. Among those with ESRD, about 70% have received renal replacement therapies and 29% have functioning kidneys due to kidney transplantation. Though the cost of the first year after kidney transplant surgery is about $151,190 for each recipient, that cost goes down to $32,914 per person-year in the second year after the transplant. In contrast, hemodialysis costs $87,561 per person-year, and peritoneal dialysis costs $66,751 per person-year (Tanriover et al., 2013). Moreover, previous studies indicate significant survival benefits associated with kidney transplants compared to other renal replacement treatments (Cassuto et al., 2010; Gill et al., 2013). Therefore, kidney transplants are characterized as the efficient option for patients with ESRD.

The kidney transplant waiting list in the United States increases by approximately 100 new candidates every day [National Kidney Foundation (NKF), 2015]. About one hundred thousand patients with end stage renal diseases are currently waiting for kidney transplantation. Specifically, 16,896 patients received new kidneys in 2013, yet every day 12 patients waiting for a kidney transplant die (NKF, 2015). In terms of supply and demand, available donated kidneys are exiguous. Thus, finding the most suitable and equitable method of allocating donated kidneys, and enhancing the outcomes of their use are now the top priorities of the transplant community. To achieve these goals, the Center of Medicare and Medicaid Services (CMS) has become a regulatory body and has implemented objective criteria to assess the quality of U.S. organ transplant programs (Dickinson et al., 2008). The clinical outcomes of transplants, measured by graft success and patient survival rates one year after kidney transplantation, have improved since the CMS has begun its oversight of transplant centers in 2007 (Hamilton, 2013).

Despite the strict oversight exercised by the CMS, studies suggest a possible disparity in the allocation of kidneys (Orandi et al., 2014; Pelletier, Phillips, Rajab, Pesavento, & Henry, 2014; Van Wagner & Skaro, 2013). Transplant candidates who have pre-transplant existing conditions such as cardiovascular diseases, obesity, diabetes, or immunological incompatibility, are classified as high-risk patients. They are more likely to have poor post transplant outcomes such as a high ratio of graft failure or mortality (High Risk Renal Transplant Group, 2009; Weimert & Alloway, 2007). Also, high risk candidates are more likely to receive poor quality kidneys, resulting in a higher risk of failure to function compared to high risk candidates receiving good quality kidneys (Metzger et al., 2003). The combination of patients possessing high risk conditions and the use of high risk donated kidneys negatively affects graft success and patient survival after transplant surgery (Wu et al., 2005).

Evidence shows that transplant programs are becoming more reluctant to risk performing transplant surgery on high risk candidates or to use high risk kidneys in transplantation (Abecassis et al., 2009). This trend of transplant centers to avoid risk can result in a lower number of transplant surgeries being performed on high risk patients even though those patients are the ones who could gain the most survival benefit from transplant surgery (outweighing the survival benefit gained from long term dialysis therapy). In addition, the transplant programs' tendency to select less risky candidates may result in unequal kidney transplant opportunities among candidates. In addition, the high risk transplant recipients who have poor transplant outcomes experience a significant "psychosocial transition" meaning life disruption and suffering (Ouellette, Achille, & Paquet, 2009, p. 1137). The family members also experience "disenfranchised grief" and their quality of life is threatened (Gill & Lowes, 2014, p. 1272). And according to the review of Muduma, Odeyemi, Smit-Palmer, and Pollock (2016), the costs of kidney transplant graft rejection are from $21,000 to $135,172 depending on the degree and types of rejections.

Co-morbid medical issues, particularly cardiovascular and immunological factors, increase the level of uncertainty and risk associated with kidney transplants. Accurate identification of transplant candidates with co-morbidities is critical in order to prevent the misuse and loss of valuable donated kidneys, as well as avoiding disparities in access to kidney transplants, and curtailing the psychosocial stress of patients and family members.

However, few predictive models are available that help identify which candidates with those factors are at greatest risk for graft failure and patient mortality. One-year kidney transplant outcomes are the indicators of long term graft success and patients' survival, as well as the objective criteria for the CMS to assess the quality of organ transplant programs. Disparities in access to kidney transplants may exist for high risk patients because many high risk patients who might negatively affect a program's overall transplant outcomes have been precluded from kidney transplant surgeries. Little is known about the one-year transplant outcomes of deceased and living donor KT and survival benefit of high risk candidates especially for those who underwent deceased donor KT known for its larger number of transplantation and worse outcomes. And no model exists to estimate the one-year transplant outcomes of high-risk candidates, especially those with cardiovascular diseases or contributory immunological factors. The expected outcome of this study is to develop an accurate and comprehensive evaluation strategy for assessing kidney transplant candidates. If successful, this research will identify the most appropriate candidates for kidney transplants, and eventually achieve the equitable allocation of donated kidneys among candidates.

The purpose of this study was to determine the impact of cardiovascular disease and immunological factors on graft success and patient survival at one-year post transplantation. The specific objectives of this study and the hypotheses tested were:

(1) To develop a predictive model that estimates kidney transplantation graft success and patient survival rates at one-year post transplantation, with a special focus on cardiovascular and immunologic factors. The study hypothesized that transplant candidates with immunological and cardiovascular factors will have higher graft failure and mortality compared with candidates without those factors.

(2) To determine the reliability and validity of the predictive model for the kidney transplant recipients. The study hypothesized that the model created for this study (based on national kidney transplant registry data) will predict transplant outcomes consistently and accurately.

(3) To determine the survival differences between patients with cardiovascular and immunologic factors who underwent deceased kidney transplants versus those patients with the same factors who remained on the waiting list. The study hypothesized that survival differences exist among transplant candidates and that they can be utilized to screen optimal candidates.

II. REVIEW OF LITERATURE

A.   **<u>Introduction</u>**

In March 2015, the number of patients with ESRD who had waited for kidney transplant surgery for more than 3 years reached about 35,000 patients, or more than 30% of the waiting list candidates [Organ Procurement and Transplant Network (OPTN), 2015a]. This fact indicates that the number of available donated kidneys has been very limited since the time when kidney transplant surgery became successful in 1954 (Morris, 2004). The situation requires accurate matching and placement of scarce donated kidneys (Leppke et al., 2013), as well as strict monitoring of the quality of transplant processing (i.e., pre, peri, and post transplant care). One way to determine the quality of a kidney transplant is by evaluating the post-transplant outcomes: the success of grafts and patient survival after transplant surgery. Numerous factors occurring through the transplant process impact those outcomes. However, the pre-transplant condition of candidates has been used to identify the most suitable candidates and to preclude candidates whose prognosis is expected to be poor.

Evidence from White et al. (2015) clearly shows that many high risk candidates are precluded from receiving transplant surgery, especially after a strict evaluation by the regulating body, CMS. Previous studies identified multiple factors determining 'high risk', including the comorbidities of recipients and donor-recipient immunology (High Risk Renal Transplant Consensus Group, 2009). However, little is known about the survival benefits of kidney transplants in these high risk patients. An accurate and valid predictive model focusing on the one year outcome of high risk transplants does not exist in spite of two existing databases, the Scientific Registry of Transplant Recipients (SRTR) and the United Network Organ Sharing (UNOS), which contain multivariate donor and recipient factors, such as the pre-existing characteristics of donors and recipients; compatibility information; immunosuppressive agents used; and other pre- and post- transplant information (Leppke et al., 2013) sourced by the Organ Procurement and Transplant Network (OPTN) which collects data from transplant programs.

An overview of the Program Specific Reports, which are the key to transplant outcome assessment, will be described herein. Also, previous studies which identified the primary factors of determining high risk recipients will be discussed. And existing predictive models and their limitations will be addressed to introduce the need of a model which estimates graft success and patient survival rates for recipients with high risk factors.

B.   **Kidney transplantation outcomes: Definition**

1.   **Transplant outcomes in Program Specific Reports**

In 1984, the National Organ Transplant Act established the Organ Procurement and Transplantation Network (OPTN) to create "a national registry for organ matching" under the Health Resources and Services Administration (HRSA) of the US Department of Health and Human Services (Leppke et al., 2013, p. 50). The HRSA contracts with the Scientific Registry of Transplant Recipients (SRTR) to analyze the organ procurement systems and the performance of transplant programs (Leppke et al., 2013). The SRTR collects data from 1) OPTN (regarding transplant programs, organ procurement systems, and histo-compatibilty laboratories), 2) CMS, and 3) the Social Security Administration's master file of deaths. Then it processes the data by cleaning and reorganizing it; and every 6 months it provides reports that are specific to individual transplant programs and organ procurement systems (Leppke et al., 2013). Thus, these program-specific reports (PSR) indicate the statistical results of each transplant program's performance. The CMS utilizes the PSRs to assess program eligibility for Medicare reimbursement, which ultimately determines the continuing operation of each transplant program (White et al., 2015).

The PSRs are designed to help government bodies, regulators, payers, and the public evaluate the performance of transplant centers and to identify which programs may need further inspection (Dickinson et al., 2008). The reports examine three primary factors for evaluating transplant programs. Those are 1) the procurement of donor organs; 2) the care for patients awaiting organs; and 3) the post-transplant outcomes. To determine the quality of the performance of transplant programs, CMS pays the most attention to post-transplant results. It analyzes the success of grafts and patient survival rates one year after transplant surgery, which correlates with the level of risk involved during transplant surgery and follow-up care. In the PSRs, poor performances are defined as a combination of high ratios of excess graft failures or death (50% more actual graft

failure or deaths than expected), with a high degree of graft failure or death (the absolute number of deaths observed is three or more than were expected), and being statistically significant (less than 5% of a one-sided p value) (Dickinson et al., 2008).

2. **Risk adjustment analysis of graft failure and patient death**

In the United States, fifty eight organ procurement organizations manage donor registration and coordinate the donor allocation process for approximately 1,000 transplant programs (Organdonor.gov, 2015). The characteristics of donors and recipients, as well as the transplant teams, vary in each transplant program, and evaluation without considering these differences can result in a wide variation of recorded transplant outcomes (Dickenson et al., 2008). Thus, one standardized evaluation method is not appropriate to measure the performance of every transplant program. The PSR employs a risk adjustment method to consider various factors which can affect the performance of transplant programs. The method works by calculating an expected risk value for each transplant program's outcomes. For example, one transplant program may perform transplant surgeries for patients who are generally older than those of other transplant programs. Considering the lower graft success and patient survival rates for the elderly, the PSR analysis divided the recipients into two groups, 18-64 years old and 65 years old and greater, to calculate each group's survival rates. The recipients in each group were expected to follow the national survival rates. Thus, for each group, the actual survival numbers in each transplant program are multiplied by the national survival rates of the corresponding age groups, and the sum indicates the expected survival rates of that particular transplant program.

3. **The positive effects of Program Specific Reports**

With the PSR, the CMS regulator monitors the performance of different transplant programs, and the PSR identifies (or flags) the problems of individual transplant programs. The CMS further investigates those problems and determines the individual programs' qualifications for Medicare reimbursement eligibility (Van Wagner & Skaro, 2013). Hamilton (2013) argued that since the PSR reports and the rules of CMS became effective, transplant outcomes have improved. That is, the standardized mortality ratio of transplant recipients decreased to 1.17 from 2.05 during the first year post-transplant period. Hamilton (2013) noticed that transplant programs flagged by CMS tended to lower their transplant volume. In other words, patients on the wait list were

less likely to receive transplant surgery. However, the author believed this trend might be a trade off for improved outcomes and eventually, transplant recipients would benefit from the improved performance of the flagged transplant programs. The impact of the PSR on the transplant community are strong enough to change the community's view toward transplant outcomes and to take them more seriously.

4.   **The limitation and ethical issues of Program Specific Reports**

However, the limitations of the PSR still remain. Patients with ESRD may be placed at a disadvantage by the unintended consequences of a negative PSR concerning the patient's associated transplant program. Van Wagner and Skaro (2013) outlined the three primary limitations of the PSR. First, the quality of the data cannot be warranted. From the entry of data to its processing, errors such as missing data or incorrect data entry can occur. These mistakes in data capture may result in discrepancies between the actual data and the data examined in the PSR. The second limitation is that, due to the size and amount of the data collection, the PSR may have difficulty identifying the relevant data. For example, the PSR lacks the relevant data for risk adjustment regarding diseases such as the diseases of donated kidneys (e.g., interstitial fibrosis) or for the pre-transplant comorbidities of the recipients. And lastly, the third primary limitation of the PSR involves an aspect of the report methodology. According to Van Wagner and Skaro (2013), the observed-to-expected ratios of PSRs show "random variation across patient outcomes" (p. 213) but they do not capture the variation across the different transplant programs. Zenios, Atias, McCulloch, and Petrou (2011) criticized PSRs, saying that the Generalized Mixed-Effect method is superior in terms of providing a more accurate and realistic evaluation of transplant outcome differences among centers.

Van Wagner and Skaro (2013) emphasized that PSRs can discourage transplant programs from providing transplant surgery to high-risk patients, thus harming the equitable allocation of donated kidneys. For example, recipients who have suffered from coronary artery disease prior to their transplant surgery could be negatively affected in terms of short term and long term patient survival. And in order for transplant programs to avoid negative outcomes, evidence has shown that patients with these coronary artery diseases are less likely to receive transplantations (Van Wagner & Skaro, 2013). Although it should be noted that transplant recipients with cardiovascular disease showed higher five year survival rates (82.8%) than those of the population with ESRD

who remained on dialysis (34% USRDS) (Jeloka et al., 2007). Van Wagner and Skaro (2013) warned that transplant programs might pay more attention to CMS approval rather than the benefit and care of their patients. In addition, the authors indicated that the strict oversight of CMS discouraged the transplant programs from developing and practicing innovative treatment protocols, including immunologically incompatible kidney transplants.

C.   **High risk in kidney transplantation**

Kidney transplant surgery for patients with ESRD involves peri-operative stresses and post-operative immunosuppressive therapy (Simmons, 1971), which is strongly associated with comorbidities such as cardiovascular diseases (Glicklich & Vohra, 2014). Thus, the patients who could not tolerate peri- and post-transplant therapy and consequently might have poor transplant outcomes,were initially defined as high risk recipients (Simmons, 1971). However, the definitions of 'high risk' currently have become more delicate and will be introduced herein.

Simmons (1971) categorized high risk recipients as patients who were older than 45 years or as patients who had received kidneys from deceased donors. That was because more than 40% of the recipients' kidneys that the author studied, failed to function within one year after transplant surgery. It should be noted that graft failure is currently defined in the transplant community as one of these events: returning to hemodialysis or peritoneal dialysis; re-transplantation; or death. Graft failure in patients who stay alive is attributed predominantly to acute rejection (SRTR, 2013; The University of Michigan Kidney Epidemiology and Cost Center, 2011). However, since 1970, new immunosuppressive medications as well as innovative surgery techniques have emerged, and the ratio of acute rejection has decreased from 33.9% in 1996 to 6% in 2000 (Meier-Kriesche, Schold, Srinivas, & Kaplan, 2004). Accordingly, the concept of high risk needed to be redefined, and thus the High Risk Renal Transplant Consensus Group (2009) re-defined 'high risk' in transplant recipients as having three primary components: comorbid medical risk; immunological risk; and psycho-social risk.

1.   **Comorbid medical risks**

In the United States, in 2014, ESRD was caused primarily by diabetes (40%) and hypertension (30%) and affected about 110,000 patients (USRDS, 2014a). These patients with ESRD

were characterized by having multiple comorbidities which resulted in their shorter life expectancy compared to those without ESRD (Prichard, 2000). Liu et al. (2010) identified congestive heart failure (44.3%), atherosclerotic heart disease (41.2%), and peripheral vascular diseases (38%) as the most common comorbidities other than diabetes (53.4%) in 2000. Wu et al. (2005) examined the effects of comorbidities on kidney transplant outcomes. The authors agreed that diabetes (30.3%) and heart failure (11.9%) were the most common comorbidities among kidney recipients ($n = 715$) at one transplant center. The authors quantified multiple comorbidities and calculated the Charlson Co-morbidity Index (CCI) scores. They found that greater CCI scores were associated with higher patient mortality. Among the various comorbidities, the High Risk Renal Transplant Consensus Group (2009) agreed that cardio and peripheral vascular diseases, obesity, and diabetes mellitus were the highest medical risk factors of high risk patients.

a. **Cardiovascular disorders**

Among all instances of graft failure, death with a functioning kidney was the main cause of graft loss. Thirty-one percent of the deaths with functioning kidneys were associated with cardiovascular diseases (USRDS, 2014b). Although the incidents of cardiovascular disease are lower in kidney transplant recipients, possibly because of their elimination of hemodynamic and uremic burdens related to dialysis, when compared to those who remain on the waiting list (and who continue dialysis), kidney recipients still have a 3 - 5 times higher number of cardiovascular disease than the general population does (Sarnak et al., 2003).

Cardiovascular morbidity and mortality are attributed predominantly to coronary vascular diseases in patients with ESRD (Marroquin & Weisbord, 2011). Thus, Jeloka et al. (2007) questioned the transplant outcomes of high risk patients who had previous or existing coronary artery diseases. This retrospective study examined 459 transplant recipients. Of those, 61 patients were classified as high risk patients who had cardiovascular diseases such as a history of angina, or myocardial infarction (MI), or the results of coronary angiograms ($\geq 50\%$ narrowing in left main and/or $\geq 70\%$ in any other coronary vessels). The authors found 1) a significantly lower 5 year patient survival for the high-risk group ($n = 61$ or 82.8%) vs. the low-risk group ($n = 368$ or 93.1%, $p = 0.004$); 2) a non-significant 5 year graft survival difference between high risk (84.1%) and low risk group (74.8%, $p = 0.08$); 3) a non-significant 5 year death-censored graft failure difference between the high

risk (90%) and the low risk group (87.3%, $p = 0.25$). The authors concluded that the survival rates of the high risk group were allowable and better than that of the dialysis population (34%), thus suggesting that high-risk patients with coronary diseases should not be precluded from kidney transplant surgery. However, it should be noted that this study focused on long-term outcomes after transplant surgery, for which the significance might have been attenuated through time periods.

Israni et al. (2012) hypothesized that the metabolic syndrome after a kidney transplant was associated with cardiovascular diseases and new onset diabetes, leading to kidney graft failure. The authors analyzed subset data ($n = 2253$) of the Patient Outcomes in the Renal Transplantation Study. They found that the metabolic syndrome of kidney recipients predicted graft failure within 5 years post transplant, HR = 1.64 (95% CI = 1.26-2.14, $p = 0.0003$), and coronary heart diseases were also significantly associated with graft failure 5 years post transplant, HR = 5.48 (95% CI = 3.27-9.20, $p < 0.0001$).

Pelletier et al. (2014) suggested that the cardiovascular diseases of kidney recipients existing prior to transplant surgery were significant risk factors for graft failure. The authors retrospectively collected cardiovascular information and classified it into 3 categories: heart diseases (left ventricular ejection fraction, history of MI, coronary artery revascularization), vascular diseases (lower extremity amputation, lower extremity bypass, carotid diseases), and diabetes (type 1). For both living ($n = 706$) donor and deceased ($n = 586$) donor recipients, coronary artery occlusion was the most common disease among them (living donor recipients: n = 108 or 15.3%; deceased donor recipients: $n = 84$ or 14.3%). Among those comorbidities, a history of MI strongly predicted one year graft failure (likelihood ratio test $p = 0.026$) for deceased donor recipients compared with the model associated with recipients without cardiovascular diseases. For living donor recipients, type 1 diabetes significantly increased the one-year graft failure prediction by a likelihood ratio p value of 0.031. The authors concluded that cardiovascular diseases are the obvious predictors of poor transplant outcomes. Additionally, the authors identified changes in the predicted number of graft failures occurring with cardiovascular comorbidities and effectively argued that cardiovascular comorbidities should be incorporated into the PSR to evaluate transplant center performance further. However, the Pelletier study had limitations, including 1) a relatively lower number of graft loss events, 2) a single transplant center, 3) a higher ratio of Caucasian

donors and recipients, 4) shorter times using dialysis, 5) a lower panel reactive antibody, 6) more ABO

compatible, 7) cross match-negative kidney transplants, and 8) private insurance.

González Monte et al. (2015) were interested in the effects of left ventricular systolic

dysfunction (LVSD) or ejection fraction (EF) on kidney graft outcomes. In one center, the authors divided kidney

recipients into two groups: case (EF < 50%) and control groups (EF ≥ 50%) and examined their graft functions

and survival. The authors found that left ventricular systolic dysfunction was associated with significantly lower

graft survival (79% vs. 100%, p = 0.04) but was not a significant predictor for patient survival (84.3% vs. 94.8%).

And interestingly, left ventricular systolic dysfunction was significantly associated with a delayed graft function

than the control group (19.8 vs. 12 days, p = 0.01). The authors speculated that the lower systolic function of the

heart was associated with low cardiac output and intravascular volume, which aggravated ischemia-reperfusion of

the kidney and caused delayed recovery of kidney function. Atherosclerosis in large arteries such as the carotid or

peripheral artery is strongly associated with cardiovascular events and may affect transplant outcomes indirectly.

Claes et al. (2013) hypothesized that the prevalence of arterial stiffness and calcifications are high for patients

with ESRD, and kidney transplant recipients ultimately have an increased risk of cardiovascular diseases related

to aortic stiffness and calcification. The authors conducted a prospective study (n = 253) in one transplant center

and found that aortic calcification at the time of transplant was related to subsequent cardiovascular events,

including major adverse cardiac events, cerebro-vascular accidents, peripheral vascular diseases, and sudden

cardiac death, HR = 1.09 (95% CI = 1.02-1.17). The authors measured aortic pulse wave velocity on the carotid-

femoral area and found it was also a significant predictor of CV events, HR=1.45 per 1 m/s (95% CI = 1.2-1.8).

Brar et al. (2013) examined the kidney recipients (n = 80,880) of the U.S. Renal data

system to identify the relationship between peripheral vascular diseases and outcomes of kidney transplantation

defined by graft failure and death. The duration of graft survival differed between patients with peripheral

vascular diseases ($M \pm SD$ = 55.3 ± 0.4 months) and those without peripheral vascular diseases ($M \pm SD$ = 60.8 ±

0.06 months). And peripheral vascular disease was an independent factor of patient death after kidney

transplantation.

b.   **Obesity**

In 2012, the prevalence of obesity [a body mass index (BMI) ≥ 30 for adults] reached 34.9% in the United States and became epidemic (Ogden, Carroll, Kit, & Flegal, 2014). The Centers for Disease Control and Prevention (CDC) acknowledged the complications related to obesity for the general population (CDC, 2015). However, in spite of the survival benefits from a high BMI for patients with ESRD, or the obesity paradox (Park, 2014), a few studies suggested that obesity was related to poor transplant outcomes. Gore et al. (2006) examined 27,377 transplant recipients' data which were collected by the UNOS between 1997 and 1999. More than 50% (n = 14,276) of the recipients had a BMI greater than or equal to 25, which indicated overweight recipients. Among them, 14% (n = 3891) of the recipients were obese (BMI 30-34.9) and 5% (n = 1590) were morbidly obese (BMI > 40). The authors found that obesity was related to delayed graft function (a need for dialysis therapy during the first week post transplant periods, p < 0.001) and graft failure (p = 0.001). The authors speculated that obesity could cause sympathetic and renin-angiotension system activation, which resulted in hypertension and damage to the transplanted kidney. Adipose tissue itself secretes leptin, which stimulates the inflammation process of cytokine (i.e., TGF- β) and results in glomeruloscrelosis, which is a common glomerular disease related to ESRD (D'Agati, Kaskel, & Falk, 2011). Obesity also may indirectly affect transplant outcomes by causing cardiovascular diseases. Lentine et al. (2012) examined 1,102 kidney recipients in one transplant center where 25% of the recipients were obese (BMI ≥ 30). They found that a 19% increase in the relative risk of cardiac events (heart failure, atrial fibrillation, and MI) was associated with a 5 point increase in a recipient's BMI.

c.   **Diabetes mellitus**

Diabetes was the primary common cause of ESRD (prevalence rates of 37.7% among 636,905 patients with ESRD) in 2012. Further, about 34% of the patients who waited for a kidney transplant (n = 81,981) had diabetes. The survival rates of patients with ESRD are improved by kidney transplantations (Schnuelle, Lorenz, Tred, & Van Der Woude, 1998). However, the complications of diabetes mellitus and the risk of diabetic nephropathy still remain after transplantation, and they result in graft failure and the death of the patients. González-Posada, Hernandez, Genis, Perez, and Sanchez (2004) examined the effects of pre-transplant

diabetes on transplant outcomes in 3,365 recipients. Among the recipients, 4.6% (n = 156) had pre-existing diabetes, and the effects of diabetes on this group's graft failure rate was significant (RR 1.68; p = 0.0089).

2. **Immunologic risks**

    a. **ABO incompatible kidney transplantation**

The historical finding of different blood types in 1900 (A, B, and O) and 1902 (AB) (Hosoi, 2008) elucidated diverse blood groups in humans. The surface of red blood cells have A and B antigens ABO blood types are determined their anti-A or anti-B antibodies in the blood. Tissues from blood type A do not elicit hyper acute or acute antibody-mediated rejection (Nguyen, Kiss, Goldman, & Carcillo, 2012) when the tissues are transplanted to the blood type A or AB. In other words, they are compatible.

The stagnant number of deceased donors compared to the sharp increase in the number of patients with ESRD emphasizes the importance of living donor transplantation. However, the probability of ABO incompatibility among the entire population in the United States is 35%, which mirrors a similar possibility of ABO incompatibility between living donors and candidates (Warren et al., 2004). To overcome this barrier, Alexandre and her team (1987) performed ABO incompatibility transplantations by employing desensitizing processes, including plasmapheresis and splenectomies. Desensitization is a pre-conditioning treatment which causes decreasing antibodies (Lefaucheur & Glotz, 2014). Currently, there are three main strategies for desensitization: B-cell depletion; elimination of iso-haemagglutinins; and intensified immunosuppression (Zschiedrich et al., 2015).

Between 1995 and 2009, 738 ABO incompatible transplants were performed in the United States (Montgomery et al., 2012). The authors compared the outcomes of the 738 ABO incompatible transplants with those of ABO compatible kidney transplants which were matched by confounding variables (i.e., diabetes, crossmatching, age, year of transplant, insurance type, peak % panel reactive antibody, and dialysis periods). Patient survival rates were not significantly different between the ABO incompatible transplants (96.8%, 93.7%, 88.3%, and 74.5% at 1, 3, 5, and 10 years) and the ABO compatible transplants (97.8%, 94.9%, 90.7%, and 75.1%; HR 1.19, p = 0.2). However, graft losses were more frequent for the ABO incompatible cases (5.9%, 10.4%, 17.4%, and 27.1% at 1, 3, 5, and 10 years) compared with those for ABO compatible cases (2.9%,

6.4%, 11.0%, and 23.9%; p = 0.001), which was attributed to significantly higher graft loss during the immediate post transplant periods (within 14 days). ABO incompatible kidney transplant recipients require desensitization or preconditioning treatments to be successful. However, complications related to these were reported by Lentine and her colleagues (2014). Post-operative complications including wound infection, pneumonia, urinary tract infections, and hemorrhage were more frequent for ABO incompatible kidney transplant cases.

b.   **Human leukocyte antigen mismatching**

Unlike B-cell receptors, T-cell receptors recognize antigens which are positioned on the surface proteins of other cells. These proteins, Major Histocompatibility Complex (MHC) molecules, determine the acceptance or rejection of transplanted organs, or, their compatibility (Owen, Punt, & Stranford, 2013). Specifically, the human MHC molecules are called Human Leukocyte Antigens (HLA). They are located on chromosome 6 and divided into class I, class II, and class III (Klein & Sato, 2000). Class I and class II play a role in the body's immune reaction as well as organ transplants and have 3 and 5 loci, respectively (HLA class I: -A, -B, and - Cw; HLA class II: -DR, DQ, -DP, -DM, and -DO) (Mahdi, 2013). When a kidney is transplanted, the recipient's immune system recognizes the HLA molecules of the donated kidney, and it activates T-cells, which produce cytokines and chemokines resulting in the activation of innate immunity (Mahdi, 2013). HLA matching in kidney transplantation means that both the donor and the recipient have identical pairs of HLA-A, -B, and -DR antigens (two antigens at each locus) or that the recipient has antigens which are absent in the donor kidney (Takemoto et al., 2000). For HLA-matched (*n* = 7,614) and -mismatched transplants (*n* = 81,364) occurring between 1987 and 1999, the 10 year graft survival rates were greater for HLA-matched transplantations (52%) compared with those of HLA-mismatched transplantations (37%) (Takemoto et al., 2000). The authors also identified that HLA-mismatched transplant surgery had poor outcomes, including patient survival rates, rejections, and graft failures. The effects of HLA on graft failure differs by its locus. For example, HLA-DR, -A, and -B affects graft loss in the first 6 months, 2 years, and long-term periods after transplant surgery, respectively (Mahdi, 2013).

c.   **Panel reactive antibody**

Generally, humans do not develop antibodies against HLA. In other words, they are not sensitized to HLA antigens (OPTN, 2015b). However, medical events can cause kidney transplant candidates to develop HLA antibodies, potentially causing the risk of acute rejection, delayed graft functioning, or long term complications (Cecka, 2010). For example, after three or more pregnancies, about 30-50% of females develop HLA antibodies which although temporary can last a long time. Multiple blood transfusions can increase the probability of developing HLA antibodies. And most importantly, a failed graft from previous transplant surgery can cause HLA antibodies to develop.

In order to quantify the presence of HLA antibodies or the level of sensitization to HLA in transplant candidates, their blood is tested for its reaction to lymphocytes and then compared to the reaction of a panel of 100 blood donors representative of local potential HLA reactors. This test measures the relative cyto-toxicity of the blood, or the candidate's amount of panel reactive antibody (PRA). The PRA score of 80% for a transplant candidate indicates that the candidate's serum reacts in 80 out of 100 panel blood samples, and indicates that the candidate would develop acute rejection in 8 out of 10 times. The conclusion would be that the candidate is highly sensitized.

Equipment to measure anti-HLA antibodies has improved, and now a new way of calculating HLA sensitivity has emerged and replaced the PRA test. Unacceptable levels of HLA antigens (from the transplant candidates' point of view) are incorporated into the calculation of the PRA score to indicate an unacceptable level of risk for the transplant candidate (Cecka, 2010). This calculated PRA, or cPRA, employs both class I HLA and class II HLA for the calculation, and reflects a more accurate measurement of sensitization. For example, if the candidate has antibodies to HLA -A1,-B35,-DR11,-DQ7 and -C7, these are unacceptable antibodies and used to analyze cPRA considering ethnicity. The cPRA value of 83% for these unacceptable antibodies indicates that 83 out of 100 donors would have the same antigens resulting in kidney rejection or a positive cross match (OPTN, 2015c). The historic study of Patel and Terasaki (1969) first reported the significant graft failure rate (80%) of 30 positively cross matched kidney transplants ($n = 30$) in contrast to the failure rate (3%) of negatively cross matched kidney transplants ($n = 195$). Lee and his team (2002) also identified that HLA

antibodies were associated with allograft rejection. Subsequently, the presence of anti-HLA antibodies was correlated to hyper acute and antibody mediated rejections, and showed the candidate contraindicated for a kidney transplant. However, desensitization or preconditioning by plasmapheresis, and the intravenous provision of immune globulin, both enabled transplant candidates to overcome the barrier of anti-HLA antibodies or HLA-incompatibility. Montgomery et al. (2011) remarked that HLA incompatible kidney transplants, made possible by desensitization protocol, showed superior survival rates when compared to dialysis treatment survival rates. This result shows that highly sensitized candidates who would die on the waiting list can be helped by HLA-incompatible kidney transplant surgery with desensitization treatments. However, it should be noted that HLA-incompatibility kidney transplantation still involves poor outcomes: higher graft loss and mortality. Orandi et al. (2014) found that positive cross match transplantation was associated with increased graft loss and mortality in the first year after transplant.

d.   **T-cell and B-cell flow cytometry and crossmatching**

Patel and Terasaki (1969) conducted a historical study about the detrimental effects of the presence of antibodies in recipients, and their impact on transplant outcomes. The authors studied the graft failures of positive cross matching transplants (the reaction between the donor's lymphocytes and the serum of transplant candidate) and found that 24 out of 30 recipients with positive cross matching had graft failures. However, when it came to negative cross matching, only 8 out of 195 kidney recipients had graft failure, leading the authors to emphasize the critical and ethical need for performing crossmatching tests prior to the transplantations. The complement-dependent lympho cyto-toxicity (CDC) test has been utilized to detect and identify the HLA antibodies of kidney transplant candidates (Bray, Tarsitani, Gebel, & Lee, 2011). However, this method has numerous shortcomings: 1) not quantifying antibody strength; 2) not indicating the specific antibody; and 3) not being able to predict the possibility of candidates having a positive crossmatch with any given donor. The method of crossmatching to detect antibodies has evolved to Flow Cytometry, which is a sensitive process that can examine T and B lymphocytes simultaneously (Bray, Tarsitani, Geble, & Lee, 2011). Graff et al. (2009) examined 66,594 kidney recipients from the OPTN registry data. They found that T-cell positive crossmatching by flow cytometry was associated with graft failure within 1 year with an HR of 1.71 ($p < 0.0001$) for both living

donor and deceased donor transplants, when positive crossmatching was compared with T-cell and B-cell negative crossmatching.

    3.   **Psychosocial risks**

        Immuno-suppressive medications are critical for maintaining the functions of donated organs for long-term time periods. Nevins, Kruse, Skeans, and Thomas (2001) studied the relationship between non-adherence with one of the immune-suppressive medications such as azathioprine and transplant outcomes using a medication bottle with an electronic monitor sealed in the cap for five years. The authors found that non-adherence during 90 days after kidney transplant is associated with a 14-fold increased risk of acute rejection and a 4 fold increased risk of loss of transplanted kidneys. Based on the study results, the authors speculated that adherence to medications requiring a complicated regimen (e.g., tacrolimus or cyclosporine) would be far poorer than adherence to azathioprine which has a relatively simple regimen of a once a day dose.

        Tanriover, Stone, Mohan, Cohen, and Gaston (2013) indicated that non-adherence to immune-suppressive medications is associated with multiple factors, including the complicated medication regimen (multiple drugs and their different schedules), a lack of instructions, adverse effects, and difficulty accessing medications due to financial issues. The authors stated that about 50% of non-adherence to medications could be related to the lack of access to medications due to financial issues. According to the authors, a 70kg adult transplant recipient would pay from $10,000 to $25,000 for immune-suppressive medications depending on the medication regimens. The patients with ESRD are eligible for Medicare coverage regardless of their age. Medicare has become the primary payer for over 70% of kidney transplantation surgery (Woodward et al., 2001). Medicare Part B currently covers the immune-suppressive medications up to 3 years after kidney transplant surgery, which has significantly improved kidney graft success and survival rates for patients with low family income (< $36,033). However, transplant recipients must pay for immune-suppressive medications after the first 3 years unless they meet the eligibility criteria of Medicaid and Medicare ($\geq$ 65 years old, people with disabilities, or low income). Relatively young transplant recipients without insurance coverage are at risk for losing their transplanted kidney due to the financial cost of immune-suppressive medications. In order to extend the period of Medicare coverage, the Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act

of 2011 was proposed in the 112th Congress. However, the bill was not sent to a vote (Tanriover et al., 2013).

Other than financial issues, Lin, Fetzer, Lee, and Chen (2011) found that the recipient's age, the time period after a kidney transplant, and support by health care providers all affected adherence to health care recommendations in a cross sectional study in Taiwan. Conversely, Lalić, Veličković-Radovanović, Mitić, Paunović and Cvetković (2014) could not find significant effects on adherence to medications due to age, gender, or time after the transplant surgery. However, the authors found that forgetfulness was a significant factor (88.2%, $n = 15$) for adherence to medications.

One in 4 patients with kidney disease experiences depression. Kidney recipients often suffer depression in spite of the optimal clinic outcomes of kidney transplants (Chilcot, Spencer, Maple, & Mamode, 2014). Dobbels et al. (2008) studied UNOS data ($n = 47,899$) and found that 3,360 transplant recipients experienced depression within 3 years of transplant surgery. Depression was strongly associated with poor transplant outcomes (graft failure: HR = 2.10, $p < 0.001$; return to dialysis: HR = 1.97, $p < 0.001$; and death with a functioning graft: HR = 2.24, $p < 0.001$). The authors did not find that suicide from depression caused poor transplant outcomes. However they speculated that poor outcomes were due to multiple mechanisms such as 1) cardiovascular diseases associated with the inflammation caused by depression or antidepressant medications, and 2) non- adherence to treatment regimens, particularly medications.

D.   **Current predictive models and their limitations**

The organ transplant area is mainly characterized by the scarcity of organs and the severity of the conditions of transplant recipients. The number of candidates awaiting organ transplant outnumbers the supply of donated organs. Thus, providing donated organs to candidates who most likely will benefit from a transplant is critical to achieving the best transplant outcomes. However, high risk candidates may wait for a transplant longer than those with lower risks. And high risk patients are apt to be precluded from transplant surgeries in order for the institution to achieve better transplant outcomes, as defined by the CMS. This, however, may result in a disparity between the numbers of high and low risk candidates receiving transplant surgeries.

Wasson, Sox, Neff, and Goldman (1985) discussed that "clinical prediction rules" which emerged from "systematic clinical observations" could lower the uncertainty which is involved in clinical practice (p. 793). Models estimating prognosis or predicting survival have been introduced in the heart failure and heart transplant field. For example, Aaronson et al. (1997) developed multivariable proportional hazard survival models using 268 patients with heart failure and their 80 clinical characteristics. And Levy et al. (2006) developed the Seattle Heart Failure Model which estimates the survival rates of patients with heart failure calculated by clinical information (e.g., laboratory values, medications, and medical devices). Ketchum and Levy (2011) argued that these models are critical for "facilitating patient and provider understanding of likely outcomes, prediction of which can be suboptimal when based on holistic clinician assessment alone" (p. 205).

However, in the transplant community, few accurate and consistent predictive models are available to help to inform which candidates with comorbidities are at greatest risk for undesirable outcomes: graft failure and patient death. In order to identify an optimal living donor for a kidney transplant, Tiong et al. (2009) built a model which predicted the degree of kidney graft function and the survival rate in living donor kidney transplantations using UNOS data. The model was derived from 20,085 cases of living donor kidney transplants recorded in UNOS data from 2000 and 2003. The kidney graft function in this model was measured by estimated glomerular filtration rates (eGFR), which were calculated by using the Modification of Diet in Renal Disease equation. The pre-transplant donor variables were age, gender, race, donor and recipient relationship, type of procurement procedure (open or laparoscopic nephrectomy), BMI, serum creatinine, and HLA mismatch. And the pre-transplant recipient variables were age, gender, BMI, race, etiologies of renal failure, induction therapy, and types of immune-suppressive medications (e.g., mycophenolate mofetile, sirolimus, or calcineurin inhibitors). Using Cox or linear multivariable regression models, the authors developed nomograms which became the graphical calculating tools. The authors assessed their internal validity by correlating predictive and observed eGFR values (1 year after transplant surgery) with the r-square value of 0.13. And for 5-year graft survival, the internal validity was measured by concordance indexes which estimate the probability of concordance between the predicted and the actual survival rates, scaled from 0.5 to 1 (0.71 with pre-transplant variables). The authors integrated these results into the nomograms and developed web-based software to calculate the outcomes.

Even though the r-square value of 0.13 for the correlation between observed and predicted eGFR values indicated the modest ability of the model to predict the graft function, the authors anticipated that these calculating tools would be beneficial not only for selecting optimal donors but also for assessing transplant candidates. However, the authors warned that the nomograms, developed as they were from a national database, might not be applicable for unique transplant centers. Another limitation of this model is that it was restricted only to the living donor kidney transplantations, the number of which ($n = 5,535$) was equal to less than 50% of deceased kidney transplant cases ($n = 11,570$) in 2014 (NKF, 2015). Importantly, this model did not include the comorbidities of recipients and donors, which might affect the transplant outcomes or results.

Kasiske et al. (2010) also developed a predictive model. This model was derived from deceased donor kidney transplant cases in US renal data system data from 2000 to 2006. The ultimate outcome of the study was graft failure in 5 years, defined as either: a return to dialysis therapy, re-transplantation, or death with a functioning graft. The authors identified 11 variables: donor age, recipient race, history of transplant, recipient age, primary etiology of ESRD, hepatitis C, donor history of hypertension, recipient insurance, donor cause of death, and HLA antigen mismatches. The authors assessed the internal validity of their model by using US renal data sorted by its impact on "the ability of the model to correctly discriminate patients who experienced graft loss within time t, from those who did not" (Kasiske et al., 2010, p. 949). The result was modestly calculated as the C statistics of 0.649, the values of which are preferred to be greater than 0.70 (Kasiske et al., 2010).

The authors presented several limitations of this model. First, this model did not compare the mortality of those on the waiting list with those selected for transplant, which might enable clinicians and patients to determine the survival benefit of a kidney transplant. Second, this model did not include living donor transplant cases. Lastly, the authors questioned whether comorbidity data from the CMS Medical Evidence Report were valid. The Health Care Financing Administration Medical Evidence Report for ESRD has documented baseline data including the comorbidities of patients who developed ESRD, as recorded on Form 2728 (CMS.gov, 2015). This Form 2728 is designed to be completed by the attending nephrologist, especially addressing the 20 comorbidities including heart failure, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, hypertension, and diabetes. Longenecker et al. (2000) examined the sensitivity and specificity of Form 2728 using

the previously studied prospective cohort research (Choice for Healthy Outcomes in Caring for ESRD) for

dialysis patients who also had comorbidities. Among the 20 comorbidities collected by Form 2728, diabetes and

hypertension had relatively high sensitivity (0.75 and 0.77, respectively). However, the sensitivity of many other

comorbidities was intermediate: peripheral vascular disease (0.40), myocardial infarction (0.43), coronary artery

disease (0.48), heart failure (0.52), cerebral vascular disease (0.47), and cardiac arrest (0.5). Longenecker et al.

(2000) noted that the low sensitivity of Form 2728 was associated with under-reported comorbidities of the ESRD

patients, which might result in a bias of further studies which examined their effects. Thus, Kasiske et al. (2010)

emphasized the need for reliable and valid comorbidity data for developing predictive tools. In spite of these

limitations, Kasiske et al. (2010) argued this predictive calculating model would provide practical information to

clinicians and patients about the risks involved before and after transplant surgery. However, the web-based

calculator to examine the risk is not available at this time (http://www.txscores.org).

Shabir et al. (2014) criticized the limitations of previous models and developed the predictive model of 5

year transplant outcomes associated with the recipients' condition during the first 12 months post transplantation.

The authors argued that this model might be more applicable in clinical practice. The authors especially focused

on 5 year transplant outcomes because the medium-term outcomes of kidney transplantation continue to be poor,

in spite of significant improvement in the graft and patient survival rates one year after transplant surgery ever

since calcineurin inhibitors were introduced (Lamb, Lodi, & Meier-Kriesche, 2011). The authors retrospectively

collected data from multiple hospital settings in Europe (n = 651) from 1999 and 2006. In addition to recipient

and donors' demographics and clinical traits, the authors collected post operative events (e.g., delayed graft

function, acute rejection etc.), recipient variables (e.g., BMI, blood pressure, imuno-suppressive medications etc.),

and laboratory test results (serum creatinine, urea etc.). Among numerous variables, the race/age of recipients, the

history of acute rejection, urine albumin-creatinine ratios, serum albumin, and eGFR were the variables most

associated with death-censored and overall transplant failure at 5 years. A web-based calculator is available for

this model (http://www.renalmed.co.uk/risk-calculator).

Shabir et al. (2014)'s retrospective study incorporated numerous clinical laboratory values. However, it has several limitations. First, the pre-transplant comorbidities of recipients were not included in the model despite its being meaningful for predicting 5 year transplant outcomes using 1 year transplant variables. Second, this model is not appropriate to identify an optimal transplant candidate who benefits from transplant surgery. Finally, this model is not optimal to predict and address one year post transplant outcomes, which is currently a critical criterion of eligibility for Medicare reimbursement.

Interestingly, Pieloch et al. (2015) developed the kidney transplant morbidity index (KTMI), a scoring system to determine the impact of pre-transplant comorbidities on 3 year transplant outcomes (e.g., graft and patient survival). From UNOS registry worksheets, the scoring system captured pre-transplant conditions such as age, the periods of dialysis, diabetes, coronary artery disease, cerebral vascular disease, peripheral vascular diseases, BMI, history of transplant, and functional status. The authors utilized UNOS data ($n = 100{,}261$) and calculated graft success and patient survival 3 years after transplant surgery by using the Cox proportional hazards regression models. It should be noted that the authors calculated these outcomes controlling for donor characteristics (e.g., age, type), cold ischemic time, and importantly, HLA matching. The KTMI scores were the sum of comorbidities with assigned numbers from zero to 11. The authors found a strong but negative relationship between the KTMI scores and 3 year transplant outcomes, and thus the negative relationship was incorporated into the model in order to determine high risk transplant candidates. This KTMI scoring system emphasizes the important impact of pre-transplant conditions on transplant outcomes. However, this model oversimplified the impact of these comorbidities on transplant outcomes by weighting the comorbidities from zero to 2 without statistical estimation.

E.   **Demand of one-year graft failure and one-year death prediction models with**

          cardiovascular and immunological factors

The transplant community has strived to develop more accurate and clinically applicable predictive models. In spite of developing these predictive tools, little is known and little has been done to develop the model which estimates one year transplant outcomes of high risk candidates, especially those with cardiovascular diseases or immunological risk factors. After the CMS rules overseeing the outcomes of transplant programs became effective, the transplant centers became reluctant to conduct kidney transplant surgery on high risk transplant candidates. And so the gap between the demand for kidneys versus their supply has become larger and worse (Shabir et al., 2014). More than 2,500 donated kidneys, or greater than 17% of the procured kidneys from deceased donors, are discarded every year without being transplanted (Reese et al., 2015). While transplant outcomes are promising, disparities in access to kidney transplants still exists for high risk patients because many high risk patients have been precluded from kidney transplant surgeries due to their potential negative effect on transplant outcomes. Although the difference in the rates of survival for high risk patients receiving kidney transplantation versus the rates of survival for high risk patients remaining on the high risk waiting list may exist, its magnitude has not been quantified. An accurate and valid predictive kidney graft and patient survival model is required to determine the impact of high risk factors, particularly regarding cardiovascular and immunological risk factors, and thus to predict transplant outcomes.

III. THEORETICAL FRAMEWORK

A.   **<u>Introduction</u>**

Kidney transplant surgery is one of the treatment options available to patients with ESRD; however, the surgery's rate of successful outcome, defined by graft success and patients' survival, needs improvement. National registry data indicate that rejection is the leading cause of graft failure, and cardiovascular diseases cause many kidney recipients to die in spite of their having a functioning kidney graft (SRTR, 2013). The theoretical principle to explain these phenomena is the individual and combined impact of immunological and cardiovascular factors prior to transplant surgery.

B.   **<u>Immunological barriers in kidney transplantation</u>**

Immediately after receiving an organ from a genetically non-identical donor, a recipient's body undergoes an immune response from the body's innate or adaptive immune system. This response indicates rejection, and it will destroy the transplanted organ if otherwise untreated (Nankivell & Alexander, 2010). Rejection is predominantly caused by antibody-mediated and T-cell-mediated mechanisms, and it may occur within minutes or years after transplantation.

Antibodies developed by B-cells eliminate antigens of bacteria and viruses in order to defend human bodies. In kidney transplants, antibody mediated reactions occur when antibodies combine 1) antigens of red blood cells of ABO blood groups, 2) the human leukocyte antigens, and 3) endothelial cell antigens. Human blood groups A, B, and O were defined by the 1900 landmark observation of forming agglutination or clumping between different blood samples (Zschiedrich et al., 2015). Each blood type except type AB exhibits antibodies against other blood types. For example, kidney recipients' antibodies against group A1 and group B are considered incompatible (Zschiedrich et al., 2015). These inborn antibodies respond to ABO antigens, which are expressed in the vascular endothelial cells in the kidney graft. These reactions involve the activation of complement cascades, endothelial cell damage, and micro-hemorrhages and thrombi, thus resulting in kidney graft failure (Schiffer & Kielstein, 2011).

The human leukocyte antigens (HLA) process antigens and present to T-cells, an occurrence characterized as the adaptive immune response. Among various HLA coded by chromosome 6, those involved with immunity are categorized into class I and class II (Klein & Sato, 2000). These HLA are expressed on the endothelium of the donor peritubular and glomerular capillaries (Nankivell & Alexander, 2010). Prior to kidney transplant surgery, the majority of recipients do not develop antibodies against HLA antigens. However, pregnancy, blood transfusions, or previous transfusions cause antibodies against HLA. These antibodies attack HLA on the endothelium, and they damage endothelial cells and cause inflammation, which results in endothelial necrosis, apoptosis, and the detachment of endothelial cells from the basement membrane as well as micro-thombi, hemorrhage, and arterial-wall necrosis/infarction (Nankivell & Alexander, 2010).

This acute antibody-mediated rejection is characterized by antibody-vascular endothelium interaction, whereas chronic antibody-mediated rejection involves transplanted glomerulopathy, multi lamination of the basement membranes of the peritubular capillaries, and transplant arteriopathy (Muduma, Odeyemi, Smith-Palmer, & Pollock, 2016). This chronic antibody rejection is commonly associated with non-adherence to immunosuppressive medications (Halloran et al., 2010).

T-cell mediated rejection is the most common type of acute kidney rejection. It is caused by the activation of recipient T-cells (CD4 T-cell) by donor antigens in the kidney graft (Nankivell & Alexander, 2010). Activated T-cells are differentiated as type 1 and 2 helper T-cells and type 17 helper T-cells, which enter the kidney graft and destroy it. During the acute rejection periods, T lymphocytes invade the renal tubular and cause tubulitis, interstitial fibrosis, and tubular atrophy. The presence of cytokines such as interleukin 2 is a key signal of T-cell activation. Therefore, immunosuppressive medications such as calcineurin inhibitors predominately target interleukin-2 pathways to interrupt T-cell activation and the rejection process (Higgins, Daga, & Mitchell, 2014). In past decades, the immunobiology underpinning kidney transplants has expanded, and the acute rejection rate within one year after kidney transplant surgery now has become less than 15% however, the rate of long-term kidney survival has not changed (Nankivell & Alexander, 2010).

C.   **Cardiovascular diseases in kidney transplantation**

Approximately 80-95% of kidneys donated from living donors function normally, whereas 50-95% of kidneys from deceased donors resume normal function immediately after kidney transplantation (Malyszko, Lukaszyk, Glowinska, & Durlik, 2015). However, in spite of the normal functioning of kidneys after transplantation, the rate of mortality sharply increases in the short term after transplantation (Wolfe et al., 1999). This can be explained by the affect of the remaining cardiovascular risks from previous chronic kidney diseases (Palepu & G V Ramesh, 2015). The patients who underwent kidney transplant surgery were on the waiting list for a median period of 13.5 years according to their blood types and immunological sensitization (Organ Procurement and Transplant Network, 2016). During the waiting period, the impact of chronic and end-stage kidney diseases on the patient's cardiovascular condition resulted in cardiomyopathy and atherosclerosis, which are characterized as cardiorenal syndrome type 4 or the "condition of primary chronic kidney disease leading to a reduction in cardiac function and/or increased risk of cardiovascular events" (Clementi et al., 2013, p. 64). The relationship between kidney diseases and cardiovascular disease is bidirectional and multi-factorial.

Among the causes of ESRD, diabetic (*n* = 247, 257 or 34.5%) and hypertensive nephropathy (n = 165,634 or 25.1%) are the most common causes of ESRD in the United States (NKF, 2016). Uncontrolled blood glucose provokes oxidative stress and inflammation, which results in a change in the structure of the kidneys described as "alterations in glomerular permeability, glomerular hyperfiltation, glomerular basement membrane thickening, mesangial matrix synthesis and, ultimately, the development of glomerulosclerosis and interstitial fibrosis" (Gallagher & Suckling, 2016, p. 2). Constant hypertension can cause ischemia and hyper filtration of the kidney and result in glomerulosclerosis (Tylicki & Rutkowski, 2003).

Uremic toxins and inflammation uremia refers to the condition, which the kidney does not efficiently eliminate the predominant components of urine: urea or the organic compound produced by protein metabolism (Depner, 2001). The accumulated urea in the blood is considered a toxin, and the velocity of urea elimination is a marker of dialysis efficiency (Depner, 2001). Dialysis therapies have rescued patients with ESRD from uremic syndrome, which potentially causes death. However, regular or intermittent dialysis therapies are not yet enough to maintain optimal blood urea levels, thus leading to the high

mortality of patients with ESRD. Depner (2011) called this phenomenon the "residual syndrome". It is associated with cardiovascular disease in patients with ESRD in terms of the inflammation process (Tonelli, Karumanchi, & Thadhani, 2016).

One uremic toxin, indoxyl sulfate, stimulates pro-inflammatory cytokines, including the tumor necrosis factor, interleukin-1, and interleukin-6 (Lekawanvijit et al., 2010). These cytokines stimulate the cardiac cell signaling, such as migoten-activated protein kinase and nuclear factor-kappa B, which cause left ventricular remodeling by myocyte hypertrophy, fibrosis, degradation of matrix, necrosis, and apoptosis (Lekawanvijit et al., 2010; Mann, 2011). Indoxyl sulfate stimulates monocyte activation (Ito et al., 2013), which causes (1) endothelial adhesion, (2) migration and/proliferation of vascular smooth muscle cells, and (3) hyper coagulability by increasing the von Willebrand factors (Brunet et al., 2011). This eventually results in vascular dysfunction and atherosclerosis (Ross, 1999).

Kremezin or AST-120 promotes the fecal elimination of indoxyl sulfate and this eventually decreases the amount of indoxyl sulfate, which is expected to prevent cardiovascular disease and stunt the progress of chronic kidney diseases (Armstrong, Granick, & Simon, 2013). Kremezin is widely used in Japan, Korea, and the Philippines for patients with chronic kidney diseases (Wu et al., 2014). However, it has not yet been approved by the U.S. Food and Drug Administration. Kremezin demonstrates delayed artherosclerosis in mice with chronic kidney diseases (Six et al., 2015), and it has been claimed that it delays the progress of chronic kidney diseases (Wu et al., 2014). However, a randomized controlled study in multiple settings did not show the benefit of kremezin for delaying chronic kidney disease (Schulman et al., 2015).

Neurohormonal hyper-activation is common in kidney diseases. The primary reason for activation of the sympathetic nervous system in chronic and end-stage renal disease is renal ischemia. Oxygen demand by kidney ischemia contributes to an increase in adenosine, which activates renal afferent linked to the part of the brain controlling blood pressure and "sympathetic outflow" (Park, 2012, p.3). Increased blood pressure and sympathetic outflow result in the activation of the sympathetic nervous system (Koomans, Blankestijn, & Joles, 2004). In addition, renal ischemia can also activate the renin-angiotensin system and produce the bioactive peptide angiotensin II, which binds to the AT1 receptors and results in vascular constriction, an increase in heart

contractions, vascular/cardiac hypertrophy, inflammation, and oxidative stress (Timmermans et al., 1993). This hyperactivity of the sympathetic nervous system can cause hypertension, arrhythmia, left ventricular hypertrophy, constriction of the coronary artery, and atherosclerosis (Park, 2012).

Oxidative stress is predominant among patients with chronic and end-stage renal disease due to multiple factors including uremic toxins (D'Apolito et al., 2010; Yamada et al., 2012) and impaired nitric oxide supply (Vaziri, 2001). Under the uremic condition, the reactive oxidative stress is increased and impairs nitric oxide supply (D'Apolito et al., 2010). Nitric oxide is a lipophilic gas that is produced by endothelial nitric oxide synthase and mediates endothelial functions (Qian & Fulton, 2013). The reactive oxygen species, including superoxide anion, hydroxyl radical, hydrogen peroxide, and hypochlorous acid, inactivates nitric oxide by converting it to peroxynitrie thus impairing the functions of endothelial cells. This eventually causes vascular contraction, cardiac cell hypertrophy, and fibrosis. The kidney itself plays a role in producing antioxidant enzymes, such as glutathione peroxidase; thus oxidative stress is predominant in chronic and end-stage kidney disease (Tonelli, Karumanchi, & Thadhani, 2016).

Erythropoietin is produced by the kidneys. It promotes the development of red blood cells; however, in chronic and end-stage renal disease, its synthesis is impaired, and patients develop anemia (Tsuruya, Eriguchi, Yamada, Hirakata, & Kitazono, 2015). This erythropoietin deficiency anemia is associated with a concentric change of the heart, or left ventricular hypertrophy, which is associated with cardiac arrhythmia and sudden death (Gansevoort et al., 2013).

Goodman et al. (2000) found that calcification of the coronary artery was common in young adults with ESRD, and he speculated that impaired mineral metabolism was the key factor. When the filtration function of the kidney is impaired, phosphate accumulates and stimulates the following sequential responses: (1) hyperparthyrodism, and (2) a decrease in calcitriol, which is associated with vascular calcification (Mary et al., 2015). Phosphorus itself can provoke oxidative stress and impair the nitric oxide pathway (Tsuruya et al., 2015).

And lastly, metabolic syndrome, defined by hyperglycemia and hyperlipidemia, is more common in patients who underwent peritoneal dialysis compared with hemodialysis therapy (Harmankaya et al., 2015). The dialysis solution used for peritoneal dialysis contains glucose, which exhibits not only peritoneal but also systemic

body effects (Harmankava et al., 2015), which can increase the risk of atherosclerosis and coronary artery disease. Dialysis therapy involves direct contact between the blood and dialysis membrane, which can cause systemic inflammation and sequential reactions to cardiovascular diseases (Tsuruya et al., 2015).

D.   **Conclusion**

Kidney graft rejection is the primary reason for graft failure, and the mechanisms of rejection include but are not limited to antibody (pre-determined and newly developed) mediated and T-cell mediated rejection. The ESRD involves various cardiovascular disease factors that are not resolved immediately after kidney transplantation. And kidney transplantation itself involves peri-operative stress, including acute hemodynamic change by intravenous fluid challenge and bleeding. These immunological and cardiovascular factors are the primary risks associated with kidney transplants. Therefore, this knowledge will support the study, which will determine the impact of immunological and cardiovascular factors on kidney transplant outcomes (shown in Figure 1).

Figure 1.   The impacts of immunological barriers and cardiovascular comorbidities on graft failure and patient death in kidney transplantation
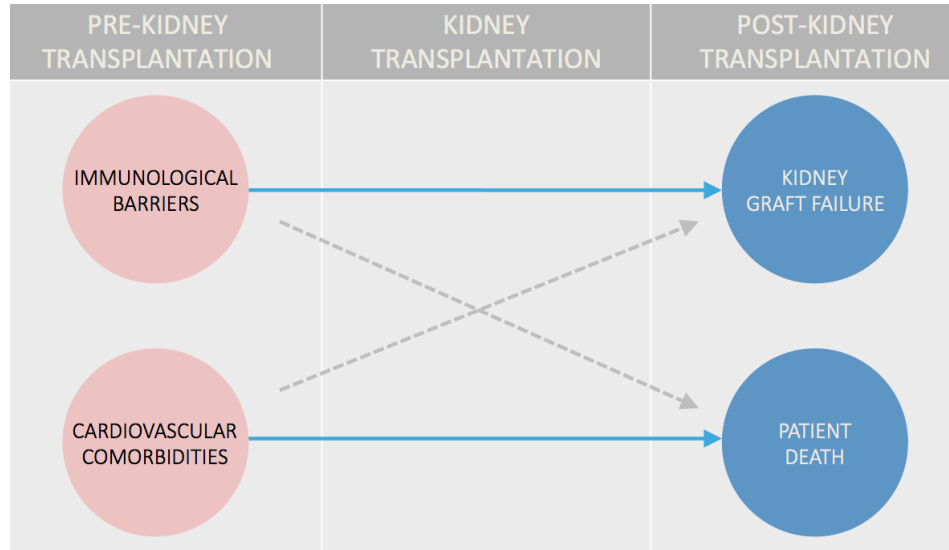
IV. RESEARCH METHODS

A.   **Design**

The research design for this study was a retrospective study using national registry data to assess kidney graft failure rates and patient mortality over different time periods after transplant surgeries, such as at the one-year anniversary mark, or over a significantly longer period of time.

B.   **Data source**

The data source was the national transplant registry data compiled by the Scientific Registry of Transplant Recipients (SRTR). Since 1987, the SRTR has collected data from the 1) Organ Procurement Transplant Network, 2) the Center of Medicare and Medicaid Services, and 3) the Social Security Administration's master file of deaths. The SRTR analyzes the organ procurement systems and the performance of transplant programs by examining outcomes. The database of the SRTR comprises demographic and clinical information on all wait-listed candidates, donors, and transplant recipients in the United States. This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system include data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The health Resources and Services Administration (HRSA), U, S. Department of Health and Human Services Provides oversight to the activities of the OPTN and SRTR Contractors.

C.   **Sample**

     1.   **Selection criteria**

The patients ($n = 218{,}657$) of this study were adult (≥ 18 years old) patients who had kidney transplant surgeries between January 1, 2000, and September 2, 2014, in the United States. Patients who had kidney transplant surgeries prior to January 1, 2000 were excluded from the study to control the effects of covariates such as new immunosuppressive medications (calcineurin inhibitor: tacrolimus), which became available in 1994. As noted by Morris (2004), transplant outcomes between the era prior to 2000 and after 2000 differed significantly. Also, any subjects who received kidney transplants after September 2, 2014, were excluded because their one-year transplant outcomes were not available in the database. The patients received either deceased donor or living donor kidneys for their transplantation. However, transplantation recipients who received

multiple organs, such as patients who received a kidney as well as a liver, heart, lung, or pancreas, were excluded from the study. The data used in this study were available through a data use agreement with the SRTR, which was subject to the approval of the Institutional Review Board of the University of Illinois at Chicago.

2.   **Sample Size**

In order to estimate the sample size, prognostic prediction models generally employ the events per variable ratio, which is required to be greater than or equal to 10 to avoid over fitting issues (Pavlou et al., 2015). The events on which this study was focused were kidney graft failures and patient deaths. This study applied a maximum of 31 predictors. The number of kidney graft failure and death in each deceased donor and living donor KT exceeded 400 events which were greater than 310 events (31 predictors X 10 events). Therefore, this study satisfied the required sample size to develop the prediction model.

D.   **Measurement and covariates**

The independent variables of this study included the demographic and clinical traits of donors and candidates for transplantation. The variables related to the candidates' cardiovascular diseases were 1) coronary artery diseases, 2) peripheral vascular diseases, 3) cerebrovascular diseases, 4) physical limitations, 5) the body mass indexes, 6) types of diabetes, and 7) their history of hypertension. Immunological risk factors were collected by 1) ABO types, 2) ABO incompatibility, 3) panel reactive antibodies, 4) human leukocyte antigen mismatches, 4) the relationship between donor and recipient, and 4) the previous history of organ transplants. Other demographic and clinical traits of candidates were 1) age, 2) gender, 3) race/ethnicity, 4) causes of end-stage renal diseases (ESRD), 5) type/duration of dialysis, and 6) types of kidney transplant procedures. In order to control the effect of quality of donated kidneys, the donor variables included 1) age, 2) BMI, 3) race, 4) kidney function calculated by the glomerular filtration rate, and 6) their history of comorbidities, including hypertension, diabetes, and hepatitis C infection. The circumstances of the deceased donors such as cause of death and donation time after cardiac death were also included.

The estimated glomerular filtration rates (eGFR) of donors (age ≥ 18 years) were calculated by the Modification of Diet in Renal Disease (MDRD) study equation using serum creatinine (mg/dl), age, race/ethnicity, and gender (National Institute of Diabetes and Digestive and Kidney Disease, 2016; Puzantian & Townsend, 2013).

$$eGFR \ (ml/min/1.73m^2) = 175 \ X \ (Scr)^{-1.154} \ X \ (Age)^{-0.203} \ X \ (0.742 \ if \ female) \ X \ (1.212 \ if \ Black)$$

And the eGFR of deceased donors who were < 18 years old was calculated by the Bedside Schwartz equation using serum creatinine (mg/dl) and height (cm) (Schwartz & Work, 2009).

$$eGFR \ (ml/min/1.73m^2) = (0.41 \ X \ Height \ in \ cm)/serum \ creatinine \ (mg/dL)$$

It should be noted that for living donors, the transplant community did not agree upon the threshold of eGFR for selecting a potential living donor (Kher & Mandelbrot, 2012). Davis and Delmonico (2005) suggested that the eGFR of living donors should be greater than or equal to 80 ml/min per $1.73m^2$ body surface area. However, this value does not reflect a change in eGFR based on aging (Rule et al., 2004). According to Rule et al. (2004), the eGFR of males decreased by 4.6 mL/min every 10 years, and that of females declined by 7.1 mL/min/decade. Likewise Kher & Mandelbrot (2012) criticized the controversy over eGFR levels. In the study which is the subject of this dissertation, 36.2% (n = 29,726) of the living donors had an eGFR < 80 prior to kidney transplantation. Currently, the Untied Network for Organ Sharing (UNOS) does not indicate any contraindication criteria for the eGFR of living donors. However, Kher & Mandelbrot (2012) suggested that the relative contraindication of clearance as 2 standard deviations below mean for ages which indicated 32,688 (39.8%) donors out of the total 82,145 living donors in this study, which would harm the power of this study if these observations were treated as missing.

Using secondary data, Grams et al. (2015) developed the calculator which estimated 15-year risk of ESRD of living donor candidates. Grams et al. (2015) considered eGFR < 45 ml/min per $1.73m^2$ of BSA as the absolute contraindication for kidney donation and excluded the group of eGFR < 45ml/min per $1.73m^2$ from their study. Therefore, this study set the acceptable minimum value of eGFR as the minimum creatinine clearance of 45ml/min per $1.73m^2$. And the study treated eGFR values < 45 ml/min per $1.73m^2$ as missing (n = 574 or 7.0%).

For deceased donors, acute kidney injury can occur depending on the circumstances of the donor's death, but generally it is reversible (Klein et al., 2013). Therefore, UNOS determines the quality of donated kidneys using two categories: kidneys from the donors whose serum creatinine was < 1.5 mg/dl and those whose serum creatinine level was ≥ 1.5mg/dl.

One year after kidney transplantation, there was no difference on the graft failure and patient death rates for acutely injured kidneys compared to kidneys without acute injury (Klein et al., 2013). The dataset of this study had serum creatinine ranging from 0.1 to 25 mg/dl, although the high creatinine levels were likely data entry errors. Klein et al (2013) studied the kidneys from deceased donors (n = 1,235) and their creatinine levels ranged from 0.3 to 4.9 mg/dl. Considering the reversible nature of acute injuries to kidneys from deceased donors, and in light of the previously noted Klein study (Klein et al., 2013), for the deceased donors, this study treated serum creatinine levels greater than 5.0 as incorrect data entry and missing values (n = 846 or 0.6%). After treating missing values, the eGFR was calculated based on the MDRD (> 18 years) and Bedside Schwartz equations (≤ 18 years).

The BMI of the original data ranged from 0.3 to 277,154, which was likely associated with incorrect data entry. Previous studies (Lentine et al., 2009; Lentine et al., 2012) that analyzed BMI using SRTR data did not specify these extreme outliers except in the recent study of Massie et al. (2016). Massie and his colleagues excluded the values of BMI of less than 17 or greater than 45. These values of BMI between 17 and 45 captured approximately between the 5th and 95th percentile of the United States population (Flegal, Carroll, Kit, & Ogden, 2012). Thus, this study accepted BMIs that ranged from 17 and 45 for both donors and recipients. Cases demonstrating BMI values beyond the range of 17 to 45 were treated as missing information.

The duration of dialysis was calculated by the number of days between the initiation of dialysis and either the transplantation dates for recipients or the date of death for candidates. The maximum value of dialysis duration reached about 70 years for both candidates and recipients. The Social Security Amendments of 1972 were passed in October 1972, and the Medicare coverage for outpatient dialysis became effective from July 1, 1973 (Centers for Medicare & Medicaid Services, 2012). It is very likely that predominant patients with ESRD started dialysis therapy in outpatient settings under this coverage, and the dialysis start dates prior to July 1, 1973 likely represented incorrect data entry. Therefore, this study treated dialysis dates prior to July 1, 1973 as missing

observations.

The primary dependent variables were 1) graft failure within the one-year post transplant period [defined as returning to hemodialysis or peritoneal dialysis, re-transplantation, or patient death with functioning (Kasiske et al., 2010)] and 2) patient death within one year after transplant surgery. Another dependent variable of interest was the amount of time between the two events; that is, between the transplant surgery and the graft failure or death. It was shown that these transplant outcomes have improved, especially for the programs that were flagged by CMS from relative ratio of 2.05 to 1.17 (Hamilton, 2013). This indicates that the oversight of CMS influenced the outcomes of transplantation. Therefore, this study also separately calculated the relationship between covariates and transplant outcomes after June 28, 2007

E.   Management of Missing Data

Missing information was common in the secondary dataset; for example, approximately half of the recipients did not indicate whether or not they had coronary artery diseases (deceased donor KT: $n = 65,730$ or 48.2%; living donor KT: $n = 34,343$ or 41.8%). Massie, Kuricka, and Segev (2014) specified that erroneous data entry by different transplant programs caused data to be missing from the dataset. However, data which did not include patients who had missing data, showed results similar to that of data with patients whose missing covariates were imputed (Cassuto et al., 2010). And importantly the pattern of missing data was inconsistent (Sweet, 2012). Therefore, it can be presumed that data is randomly missing dependent on which transplant programs supply the data (Allison, 2001).

Based on the assumption of randomly missing data, this study employed a listwise deletion method. In spite of discarding all missing observations, this study had a sufficient sample size, and it did not lose its ability to identify the relationships between independent and dependent variables. According to the suggestion of Clarke and Cossette (2000) for handling missing data, the coronary artery disease variable, for which the missing observations ≥ 15 % of the patients, was excluded in the development of the predictive models. However, this variable was one of the primary variables for examining one of the study's hypothesis: the impact of coronary artery diseases on patient survival rates. Therefore, this study separately developed the patient survival models using coronary artery diseases variables and examined its validity and reliability in spite of a limited total number of patients.

F.   <u>**Data Analysis**</u>

    1.   <u>**Specific Aim 1: Development of the Predictive Models**</u>

Continuous variables were categorized into clinically relevant strata by generating another variable to organize and summarize the clinical characteristics of the study cohort. Demographic and clinical traits were described as counts and proportions with cross-tabulation. Inferential statistics for this study utilized the chi-square test for cross-tabulation and the t-test for continuous variables. Uni- and bi-variate Cox proportional hazard regression analysis was utilized for calculating the degree of impact of individual predictors on survivals. The Kaplan-Meier method and the Log-Rank test were used to examine, according to risk factors, the statistical significance of the differences in the recipients' absolute survival from the time of transplant until the graft loss and patient death. A Multivariate Cox proportional hazard regression was utilized to estimate the proportional hazards of graft loss and patient death associated with the donor-recipient characteristics and the cardiovascular and immunological risk factors. This study hypothesized that cardiovascular and immunological factors would impact graft failure and patient deaths; therefore, the predictors or covariates were selected by purposefully using the p value of 0.05. And this study developed four predictive models according to donor types (deceased- and living-) and transplant outcomes (graft failure- and patient death) as like SRTR risk adjustment models (SRTR, 2016).

To develop and validate the model, this study employed the split-sample methodology (Wasson, Sox, Neff, & Goldman, 1985). Previous research had utilized a 7:3 ratio for model development and validation based on the SRTR database (Kasiske et al., 2010). Therefore, this study also randomly divided the deceased donor and living donor kidney recipients into two different sets for deriving the model (Deceased donor KT: $n = 95,558$ or 70%; Living donor KT: $n = 57,502$ or 70%) and for validating the model (Deceased donor KT: $n = 40,954$ or 30%; Living donor KT: $n = 24,643$ or 30%) (shown in Figure 2).

Figure 2.   Split-sample method of data

10/1/1987   1/1/2000   9/2/2014   9/2/2015

Excluded $n = 218,657$ Excluded

Deceased Donor KT   Living Donor KT
$n = 136,512$ $n = 82,145$

70%   30%   70%   30%
Model   Model   Model   Model
Derivation   Validation   Derivation   Validation
$n = 95,558$ $n = 40,954$ $n = 57,502$ $n = 24,643$
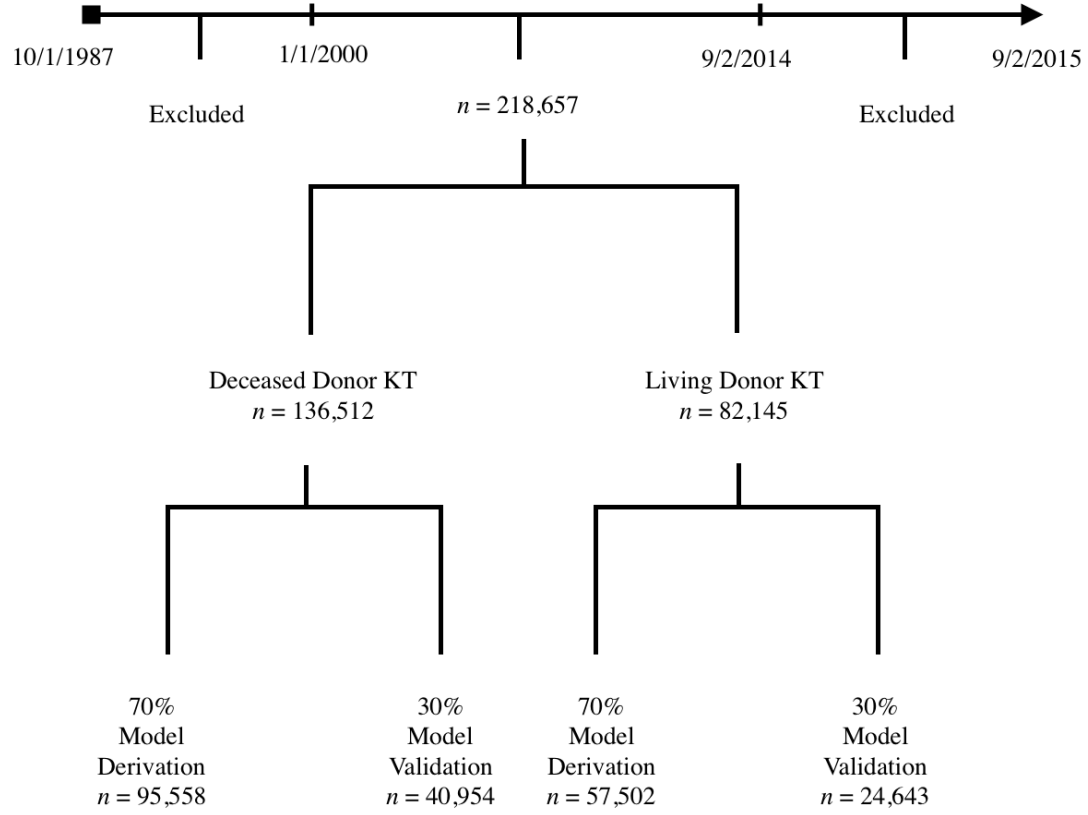
2.   **Specific Aim 2: Determining the Validity and Reliability of the Predictive Models**

Model evaluation was determined using the model's satisfying Goodness of Fit test. Goodness of Fit tests were performed by calculating Cox-Snell residuals, which indicate the difference between the observation of the outcome variables of this study and predictions through each of the four multivariate models (Hosmer, Lemeshow, & May, 2008). Model fitness can be examined by plotting the cumulative hazard of the Cox-Snell residuals, which should show a 45-degree line if the model fits the data.

To determine validity, this study performed a calibration of each model using validation datasets. The prognostic index is "the product of Cox proportional hazard models" and is calculated by a weighted sum of the coefficients of the model (Royston & Altman, 2013, p 3). The prognostic index was calculated for each patient, and this prognostic index was regressed against (1) graft failure and (2) patient death. The outcomes or coefficients of this logistic regression (near 1.0) indicates the agreement between observed probabilities and predicted probabilities (Kasiske et al., 2010).

In addition to the calibration method, this study also calculated the area under the curves (AUC) of the receiver operating curves to determine if the prediction models can discriminate between (1) kidney transplant recipients who failed kidney grafts or died, and (2) those who had functioning kidney and survived at one-year after kidney transplantation. As a general rule, Fishcer, Bachmann, and Jaeschke (2003) indicated that an AUC of 0.7 – 0.9 explained "moderate accuracy" whereas, an AUC of 0.5–0.7 indicated "low accuracy" (p. 1047).

The reliability of the predictive models was determined if the models could reveal the consistent values of the AUC in the derivation and validation datasets. In addition, Harrell's C of all models was calculated for both derivation and validation data and compared to evaluate if the general predictive power of the models was consistent.

3.   **Specific Aim 3: Determine the Survival Difference**

Utilizing common cardiovascular and immunological factors, the survival differences between patients with cardiovascular and immunologic factors who underwent deceased kidney transplants (versus those with the same factors who remained on the waiting list) were calculated by the Cox regression method. Stata 14.0 was utilized for all analyses of the study (StataCorp, 2015).

V. RESEARCH RESULTS

A.   **Kidney transplant outcomes**

1.   **One-year kidney graft failure**

The absolute number and rates of kidney graft failure have continuously decreased over the period between 2000 and 2014, even as the total number of transplantations increased for both deceased and living donor KT (shown in Figure 3 and Table 1).

Figure 3.   One-year kidney graft failure rates by donor types from 1988 through 2014
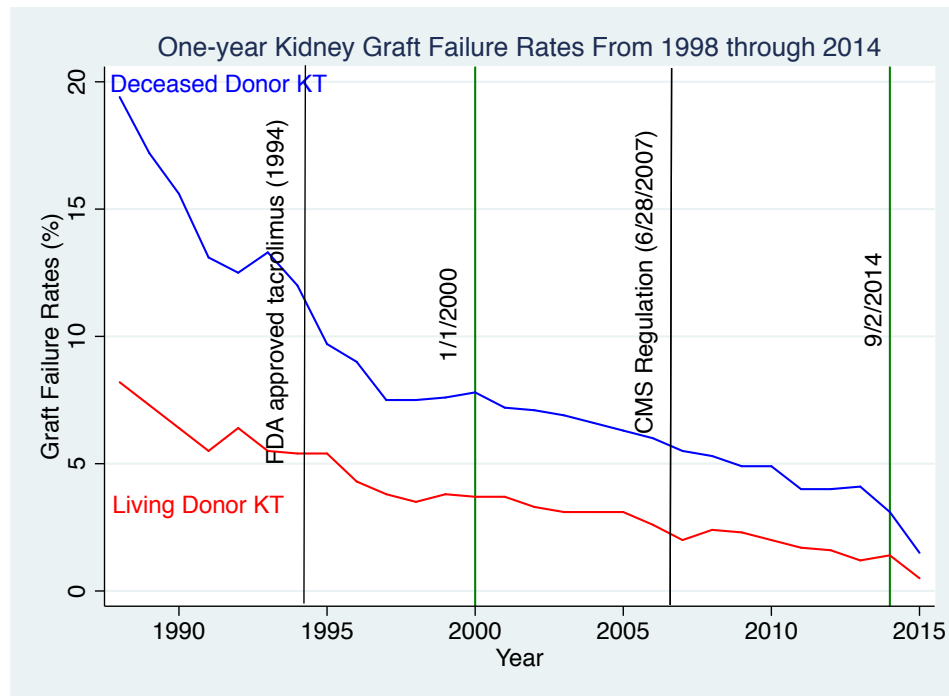
TABLE I

ONE-YEAR GRAFT FAILURE TRENDS

Year	Deceased Donor KT			Living Donor KT		
	Graft Failure	Total Transplantation	%	Graft Failure	Total transplantation	%
2000	599	7677	7.8	186	5040	3.7
2001	561	7761	7.2	203	5471	3.7
2002	573	8040	7.1	188	5636	3.3
2003	559	8101	6.9	184	5851	3.1
2004	573	8746	6.6	188	6077	3.1
2005	577	9162	6.3	185	5968	3.1
2006	586	9766	6.0	154	5962	2.6
2007	535	9816	5.5	113	5577	2.0
2008	515	9778	5.3	134	5532	2.4
2009	474	9656	4.9	136	5896	2.3
2010	489	9895	4.9	115	5851	2.0
2011	414	10312	4.0	91	5323	1.7
2012	406	10114	4.0	82	5185	1.6
2013	423	10423	4.1	62	5324	1.2
2014	335	10835	3.1	74	5160	1.4

However, the number of kidney graft failures in one-year kidney transplantation significantly differs between deceased donor and living donor kidney transplantation. Among recipients ($n = 136,512$) who underwent deceased donor KT surgeries between January 1, 2000 and September 2, 2014, a total 7,564 kidney grafts failed. Comparatively, during the same time period, a total 2,095 living donor recipients who underwent transplantation lost their kidney grafts within one year. The primary cause of graft failures was graft thrombosis in both living donor ($n = 458$ or 48.9%) and deceased donor ($n = 987$ or 34.8%) KT. The second leading reason for kidney graft failures in deceased donor KT was primary failure ($n = 534$ or 18.8%), while being rejection in living donor KT ($n = 149$ or 15.9%). Rejection was another common reason for graft failure in deceased KT ($n = 388$ or 13.7%). It should be noted, however, that greater than 50% of information was missing for causes of graft failure for both deceased donor KT ($n = 4,724$ or 62.5%) and living donor KT ($n = 1,158$ or 55.3%) (shown in Table 2).

TABLE II

ONE-YEAR KIDNEY GRAFT FAILURE IN KIDNEY TRANSPLANTATION

Primary causes of one-year graft failure	Kidney Transplantation				x^2 (df)	p
	Deceased Donor KT (n = 136,512)		Living Donor KT (n = 82,145)			
Rejection	388	(13.7)	149	(15.9)	189.6	< 0.001
Primary failure	534	(18.8)	72	(7.7)		
Graft thrombosis	987	(34.8)	458	(48.9)		
Infection	153	(5.4)	22	(2.3)		
Surgical complication	181	(6.4)	85	(9.1)		
Urological complication	41	(1.4)	12	(1.3)		
Recurrent diseases	20	(0.7)	17	(1.8)		
Other	536	(18.9)	122	(13.0)		
Missing data[a]	4,724	(62.5)	1,158	(55.3)		
Total	7,564		2,095			

[a] Missing data was not included to calculate the proportion of the causes of graft failure.

2.   **One-year patient death**

Unlike the sharp decrease in kidney graft failures after the availability of new calcineurin inhibitors on the market, the rates of patient death were steady in both living donor and deceased donor KT. Interestingly, the mortalities were largely decreased after the Center of Medicare and Medicaid started to oversee transplant programs for their one-year kidney graft failure and patient death after kidney transplantation rates in June 28, 2007 (shown in Figure 4).

Figure 4.   One-year kidney patient death rates by donor types from 1988 through 2014
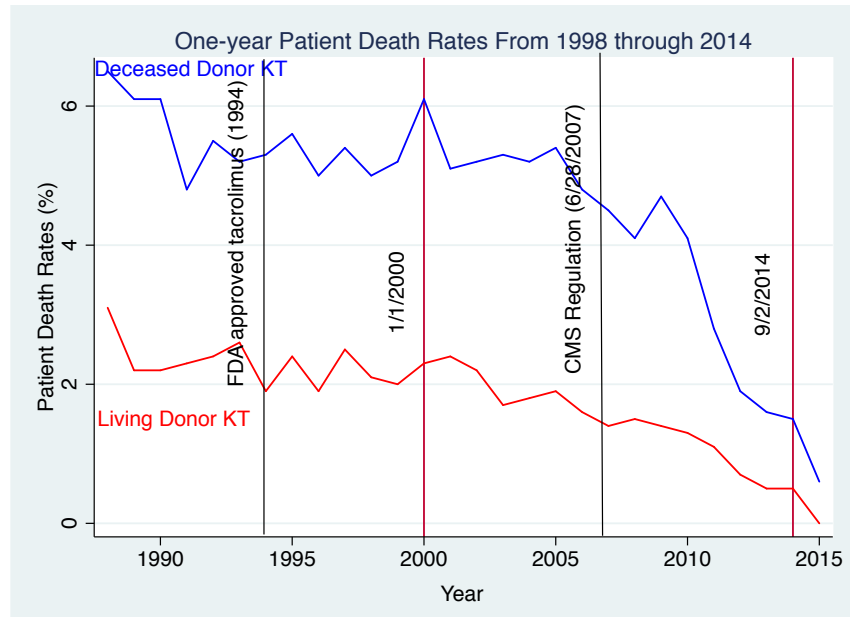
For transplant surgeries that occurred between January 1, 2000, and September 2, 2014, the number of patient deaths in the first year after kidney transplant surgeries was higher for deceased donor kidney recipients ($n = 5,646$) as compared to living donor kidney recipients ($n = 1,266$) (shown in Table 3).

TABLE III

ONE-YEAR DEATH TRENDS

Year	Deceased Donor KT			Living Donor KT		
	Death	Total Transplantation	%	Death	Total transplantation	%
2000	466	7677	6.1	115	5040	2.3
2001	398	7761	5.1	129	5471	2.4
2002	419	8040	5.2	125	5636	2.2
2003	428	8101	5.3	98	5851	1.7
2004	452	8746	5.2	107	6077	1.8
2005	499	9162	5.4	115	5968	1.9
2006	469	9766	4.8	97	5962	1.6
2007	444	9816	4.5	77	5577	1.4
2008	403	9778	4.1	82	5532	1.5
2009	452	9656	4.7	80	5896	1.4
2010	406	9895	4.1	76	5851	1.3
2011	287	10312	2.8	59	5323	1.1
2012	188	10114	1.9	38	5185	0.7
2013	171	10423	1.6	29	5324	0.5
2014	166	10835	1.5	24	5160	0.5

The majority of information for cause of death were missing in both deceased donor- (74.7%) and living donor- (81.3%) KT. However, the primary cause of death in first-year post kidney transplantation was cardiovascular diseases for both living ($n = 101$ or 42.6%) and deceased ($n = 508$ or 35.6%) donor kidney transplantation. Among cardiovascular diseases, death caused by myocardial infarction was the most common reason (deceased donor KT: $n = 228$ or 16% vs. Living donor KT: $n = 53$ or 22.4%). Infection was the second leading and known cause of death for both transplantation [living donor kidney transplant ($n = 39$ or 16.5%) vs. deceased donor kidney transplantation $n = 290$ or 20.3%].

TABLE IV

ONE-YEAR PATIENT DEATH IN KIDNEY TRANSPLANTATION

Primary causes of one-year patient death	Kidney Transplantation				t or x^2 (df)	p
	Deceased Donor KT (n = 136,512)		Living Donor KT (n = 82,145)			
Myocardial infarction	228	(16)	53	(22.4)	35.12 (12)	< 0.001
Arterial embolism	9	(0.6)	3	(1.3)		
Pulmonary embolism	32	(2.2)	8	(3.4)		
Other cardiovascular diseases	184	(12.9)	26	(11)		
Infection	290	(20.3)	39	(16.5)		
Graft failure	14	(1)	2	(0.8)		
Cerebrovascular diseases	55	(3.9)	11	(4.6)		
Malignancy	2	(0.1)	0	(0)		
Hemorrhage	76	(5.3)	13	(5.5)		
Graft failure	14	(1)	2	(0.8)		
Multiorgan failure	55	(3.9)	9	(3.8)		
Other	310	(21.7)	37	(15.6)		
Unknown	97	(6.8)	21	(8.9)		
Missing data[a]	4,220	(74.7)	1,029	(81.3)		
Total	5,646		1,266			

[a] Missing data was not included to calculate the proportion of the causes of graft failure.

Overall, kidney transplant outcomes determined by kidney graft failure and patient death were significantly different between deceased and living donor kidney transplantation. The outcomes for living donor kidneys were superior to those of deceased donor kidneys. Therefore, this study identified uni-/bi-variate and multivariate predictors for kidney graft failures and patient deaths according to donor type: deceased donors and living donors.

B.   **Descriptive Statistics**

1.   **Age and gender of candidates at kidney transplantation**

The mean age of recipients at the time of deceased donor KT was 51.8 years old ($SD = 13.1$) and candidates who received living donor KT were younger ($M \pm SD = 47 \pm 13.9$) (shown in Figure 5, Table 5). Males predominated in both deceased donor ($n = 82,704$ or 60.6%) and living donor ($n = 53,808$ or 60.4%) KT (shown in Figure 6, Table 6).

Figure 5.   Age of candidates at kidney transplantation
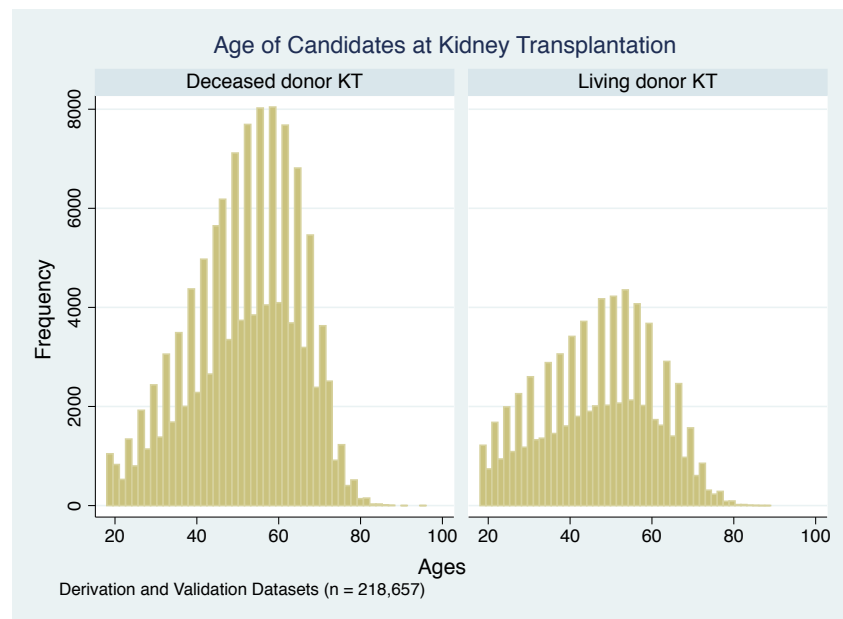
Figure 6.   Gender of candidates

Gender of Candidates
Deceased donor | Living donor
39.4% / 60.6% | 39.6% / 60.4%
Male Female
Derivation and Validation Datasets (n = 218,657)
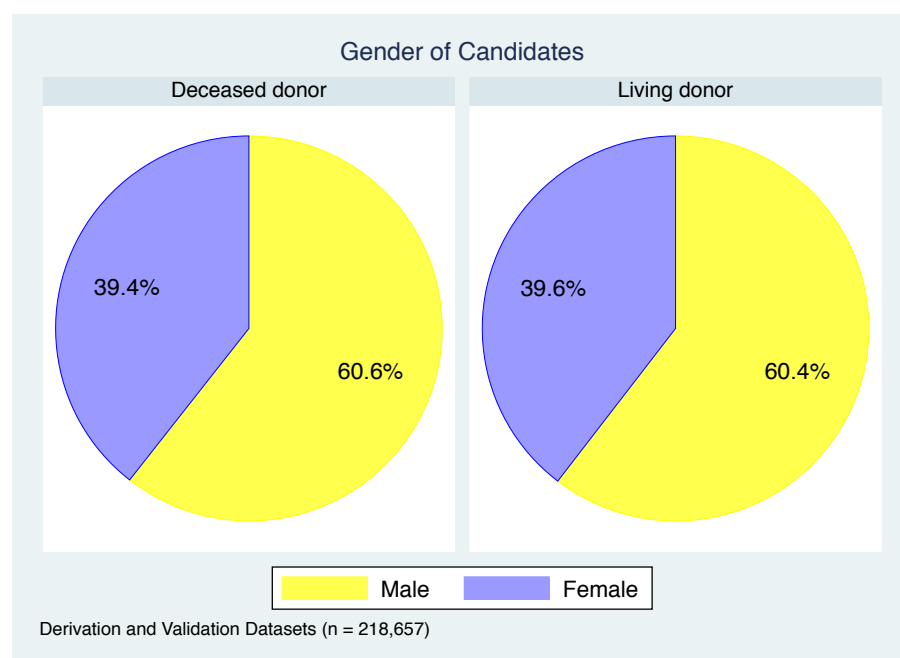
TABLE V

DESCRIPTIVE STATISTICS OF CANDIDATES CHARACTERISTICS

Demographic and clinical information of candidates	Kidney Transplantation				t or x^2	p
	Deceased Donor KT ($n = 136,512$)		Living Donor KT ($n = 82,145$)			
Age at transplant [mean ± SD (range)]	51.8 ± 13.1 (18-96)		47.0 ± 13.9 (18-89)		81.0	< 0.001
Candidates gender						
Male	82,704	(60.6)	49,640	(60.4)	38.7	< 0.001
Female	53,808	(39.4)	32,505	(39.6)		
Candidates race/ethnicity						
Caucasian	63,632	(46.6)	54,746	(66.7)	10,013	< 0.001
Asian	7,922	(5.8)	3,344	(4.1)		
Black	42,779	(31.3)	11,904	(14.5)		
Hispanic/Latino	19,756	(14.5)	11,028	(13.4)		
Others	2,422	(1.8)	1,120	(1.4)		
Missing data	1	(< 0.1)	3	(<0.1)		
Clinical Traits						
ABO types						
A type	49,754	(36.5)	31,119	(37.9)	277.8	< 0.001
A2 type	310	(0.2)	180	(0.2)		
AB type	7,280	(5.3)	3,140	(3.8)		
B type	17,617	(12.9)	10,832	(13.2)		
O type	61,551	(45.1)	36,874	(44.9)		
Candidates BMI (kg/m^2) (mean ± SD, range)	27.7 ± 5.3 (17 - 45)		27.4 ± 5.3 (17 - 45)		12.4	< 0.001
BMI < 18.5	2,222	(1.7)	1,501	(1.9)	164.0	< 0.001
18.5 ≤ BMI < 25	43,176	(32.5)	27,640	(34.9)		
25 ≤ BMI < 30	45,632	(34.4)	26,818	(33.8)		
30 ≤ BMI < 35	28,588	(21.5)	16,064	(20.3)		
BMI ≥ 35	13,134	(9.9)	7,275	(9.2)		
Missing data	3,760	(2.7)	2,847	(3.5)		
Primary causes of renal failure					3,771	< 0.001
Glomerular disease	32,078	(23.7)	25,644	(31.5)		
Diabetes	35,425	(26.2)	18,166	(22.3)		
Polycystic kidney disease	11,944	(8.8)	9,253	(11.4)		
Hypertensive nephrosclerosis	32,460	(24.5)	12,963	(15.9)		
Congenital, familial, metabolic	2,249	(1.7)	2,002	(2.5)		
Renovascular diseases	4,750	(3.5)	2,205	(2.7)		
Tubular/ Interstitial diseases	5,701	(4.2)	4,240	(5.2)		
Neoplasms	470	(0.3)	340	(0.4)		
Others	10,354	(7.6)	6,503	(8.0)		
Missing data	1,081	(0.8)	820	(1.0)		

TABLE V (continued)

DESCRIPTIVE STATISTICS OF CANDIDATES CHARACTERISTICS

Demographic and clinical information of candidates	Kidney Transplantation				t or x^2	p
	Deceased Donor KT (n = 136,512)		Living Donor KT (n = 82,145)			
Dialysis types					17,541	< 0.001
No dialysis	11,621	(8.5)	24,424	(29.7)		
Hemodialysis	26,328	(19.3)	14,300	(17.4)		
Peritoneal dialysis	5,262	(3.9)	3,124	(3.8)		
Unknown types of dialysis	92,238	(67.6)	39,283	(47.8)		
Dialysis, unknown	1,061	(0.8)	1,010	(1.2)		
Missing data	12	(0.01)	4 (< 0.1)			
Dialysis duration prior to transplant (yearsa) (mean ± SD, range)	3.6 ± 3.2 (0 – 36)		1.3 ± 2.1 (0 – 36.8)		188.2	< 0.001
0 < Duration < 1	27,899	(20.5)	49,648	(60.5)	47,563.7	< 0.001
1 ≤ Duration < 2	18,361	(13.5)	15,326	(18.7)		
2 ≤ Duration < 3	20,264	(14.9)	7,346	(9.0)		
3 ≤ Duration < 4	18,685	(13.7)	3,903	(4.8)		
4 ≤ Duration < 5	15,212	(11.2)	2,080	(2.5)		
5 ≤ Duration <10	30,317	(22.3)	3,028	(3.7)		
Duration ≥ 10	5,515	(4.0)	717	(0.9)		
Missing data	259	(1.9)	97	(0.1)		
Cardiovascular Diseases						
Functional status					1444.2	< 0.001
No limitation	32,029	(26.6)	23,064	(32.1)		
Some limitation	76,142	(63.3)	42,514	(59.3)		
Total limitation	4,926	(4.1)	1,239	(1.7)		
Unknown	7,136	(5.9)	4,930	(6.9)		
Missing data	16,279	(11.9)	10,398	(12.7)		
Diabetes history						
Non-diabetes	90,112	(66.2)	58,535	(71.3)	1764.9	< 0.001
Type 1 diabetes	3,891	(2.9)	3,757	(4.6)		
Type 2 diabetes	24,114	(17.7)	10,613	(12.9)		
Type other	386	(0.3)	217	(0.3)		
Type unknown	16,101	(11.8)	7,669	(9.3)		
Diabetes unknown	1,482	(1.1)	1,324	(1.6)		
Missing data	426	(0.3)	30	(<0.1)		
Peripheral vascular disease (PVD)					313.9	< 0.001
Non- history of PVD	124,620	(91.6)	75,558	(92)		
History of PVD	5,427	(4)	2,602	(3.2)		
Unknown	5,978	(4.4)	3,944	(4.8)		
Missing data	487	(0.4)	41	(0.1)		
Coronary artery diseases (CAD)					114.6	< 0.001
No CAD	62,175	(87.8)	42,880	(89.7)		
History of CAD	5,817	(8.2)	3,154	(6.6)		
Unknown	2,790	(3.9)	1,768	(3.7)		
Missing data	65,730	(48.2)	34,343	(41.8)		
Hypertension						
No history of HTN	18,319	(14.5)	10,904	(14.4)	34.099	< 0.001
History of HTN	103,913	(82.5)	62,294	(82.1)		
Unknown	3,794	(3.0)	2,639	(3.5)		
Missing data	10,486	(7.7)	6,308	(7.7)		

TABLE V (continued)

DESCRIPTIVE STATISTICS OF CANDIDATES CHARACTERISTICS

Demographic and clinical information of candidates	Kidney Transplantation				t or x^2	p
	Deceased Donor KT ($n = 136,512$)		Living Donor KT ($n = 82,145$)			
Cerebrovascular diseases (CVD)					403.1	< 0.001
Non-history of CVD	117,375	(93.2)	71,187	(93.8)		
History of CVD	3,490	(2.8)	1,675	(2.2)		
Unknown	5,131	(4.1)	3,036	(4.0)		
Missing data	10,516	(7.7)	6,247	(7.6)		
Immunological status						
PRA (mean ± SD, range)	22.0 ± 32.9 (0 -100)		11.9 ± 24.3 (0-100)		75.3	< 0.001
PRA < 80%	116,200	(87.1)	75,288	(95.2)	3669.9	< 0.001
80 ≤ PRA ≤ 100%	17,272	(12.9)	3,809	(4.8)		
Missing data	3,040	(2.2)	3,048	(3.7)		
Human leukocyte antigen mismatching						
0 A antigen mismatching	24,135	(17.8)	18,774	(23.1)	10096.0	< 0.001
1 A antigen mismatching	49,339	(36.3)	42,790	(52.6)		
2 A antigen mismatching	62,300	(45.9)	19,852	(24.4)		
Missing data	738	(0.5)	729	(0.9)		
0 B antigen mismatching	19,973	(14.7)	12,861	(15.8)	14556.3	< 0.001
1 B antigen mismatching	34,800	(25.6)	40,182	(49.4)		
2 B antigen mismatching	80,998	(59.7)	28,373	(34.9)		
Missing data	741	(0.5)				
0 DR antigen mismatching	28,855	(21.3)	17,010	(20.9)	2188.0	< 0.001
1 DR antigen mismatching	58,630	(43.2)	42,694	(52.5)		
2 DR antigen mismatching	48,253	(35.5)	21,694	(26.6)		
Missing data	774	(0.6)	747	(0.9)		
ABO incompatibility						
ABO compatible	136,200	(99.8)	81,197	(98.9)	1097.4	< 0.001
ABO incompatible	56	(0.04)	770	(0.9)		
A2 incompatible	256	(0.2)	178	(0.2)		
Missing data	0	(0)	0	(0)		
Relationship of donor- candidate						
Living related			48,655	(59.2)		
Living unrelated			33,480	(40.8)		
Unknown			1	(< 0.01)		
Kidney transplantation history						
No history of KT	119,627	(87.6)	73,975	(90.1)	297.8	< 0.001
History of kidney transplantation	16,885	(12.4)	8,170	(10.0)		
Missing data	0	(0)	0	(0)		
Transplant procedure				0 (0)		
Left kidney	63,185	(46.3)	71,428	(87.0)		
Right kidney	69,301	(50.8)	10,717	(13.0)		
En-block	2,319	(1.7)	0			
Sequential kidney	1,707	(1.3)	0			
Missing data	0	(0)	0 (0)			

TABLE VI

DESCRIPTIVE STATISTICS OF DONOR CHARACTERISTICS

Demographic and clinical information of donors	Kidney Transplantation				t or x^2	p
	Deceased Donor KT (n = 136,512)		Living Donor KT (n = 82,145)			
Donor age at transplant [mean ± SD (range)]	38.2 ± 16.6 (0-88)		41.0 ± 11.4 (15-84)		- 43.2	< 0.001
Donor gender					8045.6	< 0.001
Male	81,543	(59.7)	32,817	(40.0)		
Female	54,969	(40.3)	49,328	(60.0)		
Donor race/ethnicity					338.5	< 0.001
Caucasian	95,574	(70.0)	56,890	(69.3)		
Asian	3,052	(2.2)	2,819	(3.4)		
Black	17,714	(13.0)	10,505	(12.8)		
Hispanic/Latino	18,929	(13.0)	10,929	(13.3)		
Others	1,243	(0.9)	1,002	(1.2)		
Donor BMI (kg/m^2) (mean ± SD, range)	26.9 ± 5.5 (17 - 45)		26.9 ± 4.3 (17-45)		-1.3	0.183
BMI < 18.5	3,936	(3.0)	630	(0.8)	6300.4	< 0.001
18.5 ≤ BMI < 25	50,530	(39.0)	26,569	(33.6)		
25 ≤ BMI < 30	47,274	(36.5)	31,021	(39.2)		
30 ≤ BMI < 35	20,566	(15.9)	14,356	(18.1)		
35 ≤ BMI	7,166	(5.5)	6,522	(8.2)		
Estimated GFR					8015.6	< 0.001
Stage 1 (GFR ≥ 90)	51,237	(38.1)	33,492	(42.3)		
Stage 2 (GFR 60 - 89)	46,754	(34.8)	42,035	(53.1)		
Stage 3a (GFR 45 - 59)	20,090	(15.0)	3,633	(4.6)		
Stage 3b (GFR 30-44)	10,816	(8.0)	0			
Stage 4 (GFR 15 - 29)	5,002	(3.7)	0			
Stage 5 (GFR < 15)	479	(0.4)	0			
Missing data	2,134	(1.6)	1,985	(3.6)		
Hepatitis C						
Negative for HCV	133,319	(97.7)				
Positive for HCV	3,193	(2.3)				
Missing data	0	(0)				
Hypertension					15,326	< 0.001
Non-history of hypertension	99,383	(72.8)	55,751	(96.1)		
0-5 Years	17,760	(13.0)	862	(1.5)		
6-10 Years	5,984	(4.4)	119	(0.2)		
> 10 years	6,504	(4.8)	71	(0.1)		
HTN, duration unknown	5,950	(4.4)	363	(0.6)		
Unknown	925	(0.7)	873	(1.5)		
Missing data	6	(< 0.1)	24,106	(29.4)		
Diabetes						
No diabetes	127,158	(93.2)				
0-5 Years	4,481	(3.3)				
6-10 Years	1,601	(1.2)				
> 10 years	1,647	(1.2)				
Diabetes, duration unknown	1,025	(0.8)				
Unknown	593	(0.4)				
Missing data	7	(<0.1)				

TABLE VI (continued)

DESCRIPTIVE STATISTICS OF DONOR CHARACTERISTICS

Demographic and clinical information of donors	Kidney Transplantation			
	Deceased Donor KT (n = 136,512)	Living Donor KT (n = 82,145)	t or x^2	p
Causes of death				
Anoxia	27,623 (20.2)			
Cerebrovascular/ Stroke	51,306 (37.6)			
Head trauma	53,575 (39.2)			
CNS tumor	820 (0.6)			
Others	3,183 (2.3)			
Missing data	5 (0.1)			
Donation after circulatory death (DCD)				
Non-DCD donors	122,029 (89.40			
DCD donors	14,460 (10.6)			
Missing data	23 (<0.1)			

2.   **Race/ethnicity of candidates**

The majority of recipients were Caucasian (deceased donor KT: n = 63,632 or 46.6%; living

donor KT: n = 54,746 or 66.7%), which was followed by Black (deceased donor KT: n = 42,779 or 31.3%; living

donor KT: n = 11,904 or 14.5%). The larger number (n = 19,756 or 14.5%) of a Hispanic/Latino population

received deceased donor KT when compared with those for living donor KT (n = 11,028 or 13.4%) (as shown in

Figure 7).

Figure 7.   Race/ethnicity of candidates

Race/ethnicity of Candidates
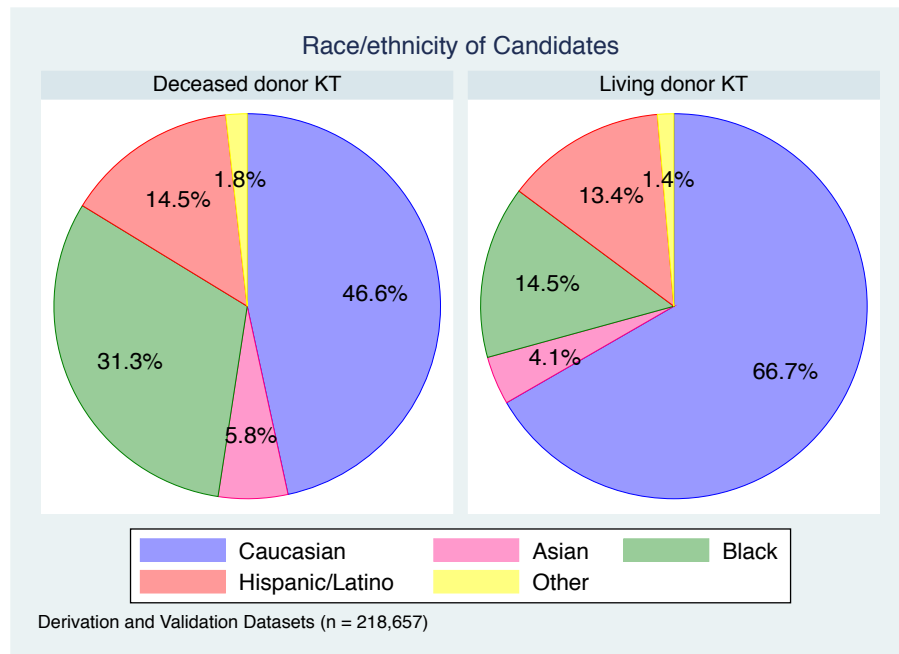
3.   **End-stage renal disease causes of candidates**

        In deceased donor KT, the three leading causes of ESRD were diabetic nephropathy (*n* = 35,425 or 26.2%), hypertensive nephrosclerosis (*n* = 32,460 or 24.1%), and glomerular diseases (*n* = 32,708 or 23.7%). However, in living donor KT, glomerular diseases was a leading cause of end-stage renal diseases (*n* = 25,644 or 31.5%), which was followed by diabetic nephropathy (*n* = 18,166 or 22.3%) and hypertensive nephrosclerosis (*n* = 12,963 or 15.9%) (shown in Figure 8).

Figure 8.   End-stage renal disease causes of candidates
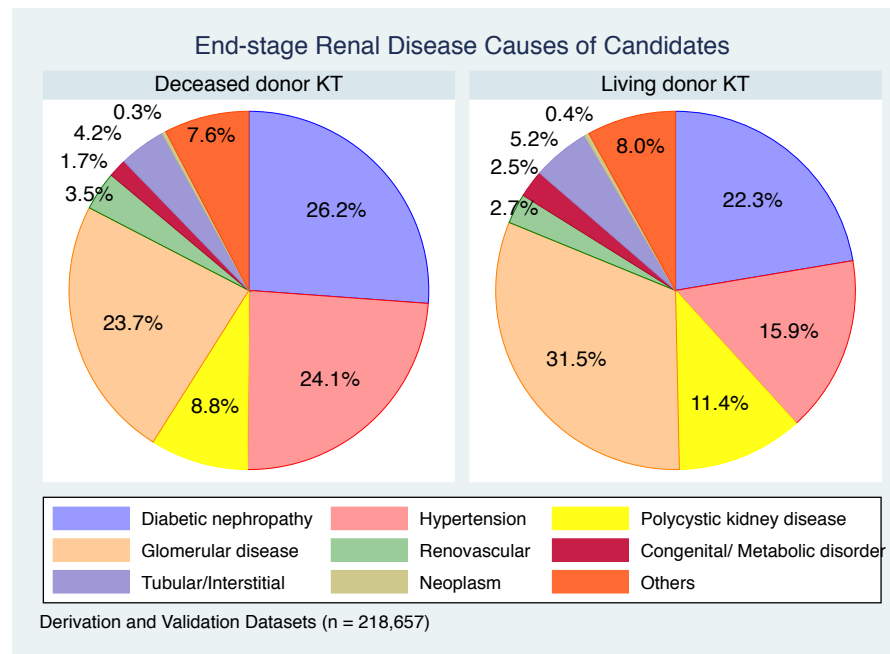
4.   **Dialysis therapies of candidates**

The majority of recipients had dialysis therapy prior to kidney transplantation. However, 29.7% (n = 24,424) of living donor KT recipients did not have dialysis therapies prior to surgery, whereas 8.5% (n = 11,621) did not have such in deceased donor KT (shown in Figure 9).

Figure 9.   Dialysis therapies of candidates
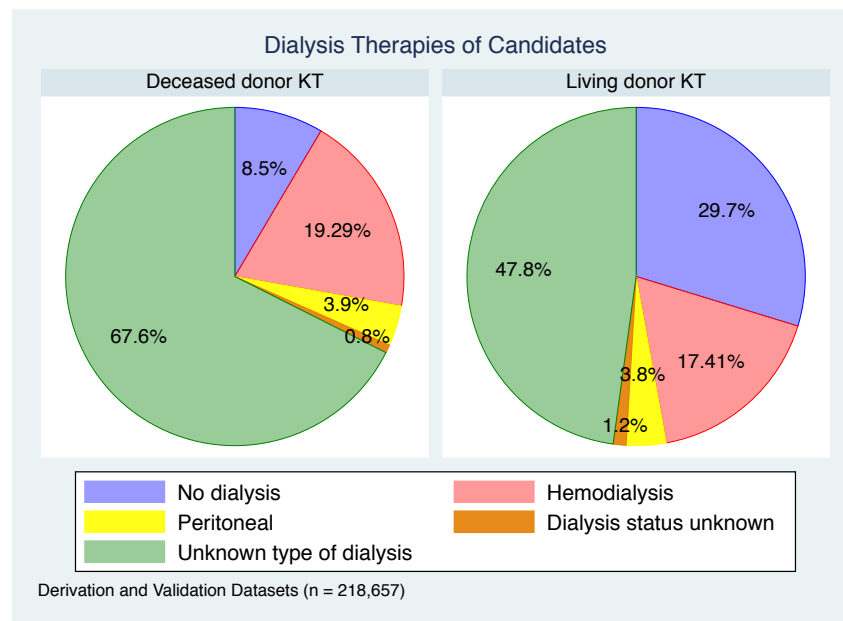
Regardless of dialysis types, the durations of dialysis therapy were longer in the candidates who underwent deceased donor KT ($M \pm SD = 3.7 \pm 3.2$ years) compared with those received living donor KT ($M \pm SD = 1.3 \pm 2.1$ years), $t(188.2)$, $p < 0.001$ (shown in Figure 10).

Figure 10.　　Dialysis therapy duration of candidates
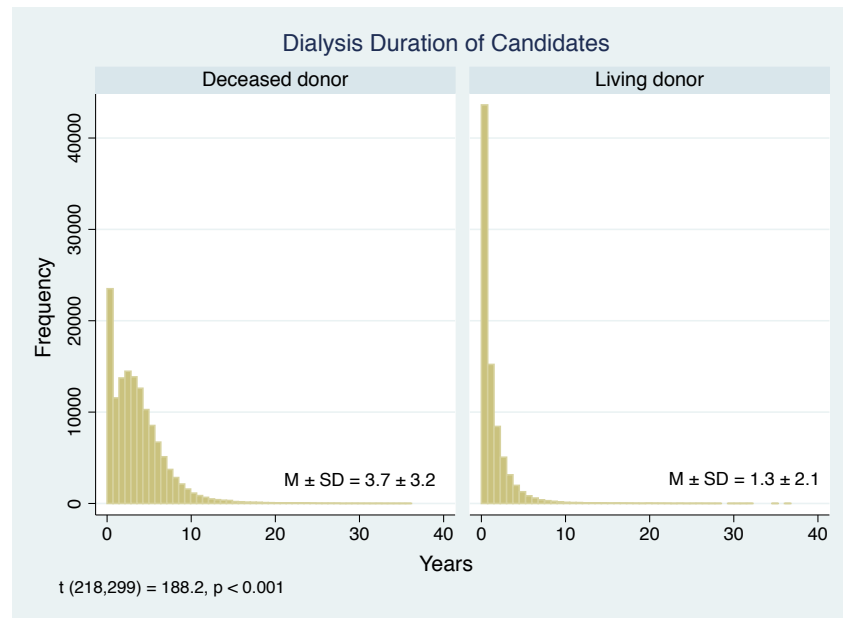
5.   **Transplant surgery procedures of candidates**

In deceased donor KT, a majority of candidates received either left side (n = 63,185 or 46.3%) or right side (n = 69,30l or 50.8%) donor kidneys. En-bloc kidney transplant surgery was performed in 2,319 (1.7%) cases of deceased donor KT. In living donor KT, left-side kidney transplantation predominated (n = 71,428 or 87.0%) (shown in Figure 11).

Figure 11.   Transplant surgery procedures of candidates
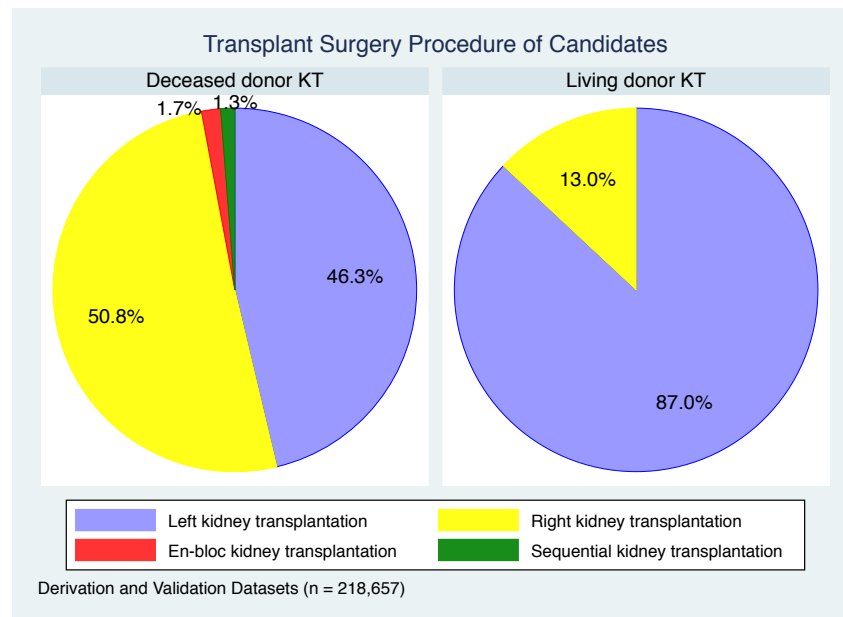
6. **<u>Age of donors</u>**

For donor characteristics, the mean age of donors in deceased KT was 38.2 years old ($SD = 16.6$) whereas the mean ages of living donors were 41.0 years old ($SD = 11.4$) (shown in Figure 12). For living donor, the ages ranged from 15 to 84 years old whereas, those of deceased donors were between 0 to 88 years old. Among the deceased donors < 12 month ($n = 703$), 84% of them ($n = 591$) was associated with en-block kidney transplantation.

Figure 12.   Age of donors at kidney transplantation

Age of Donors at Kidney Transplantation
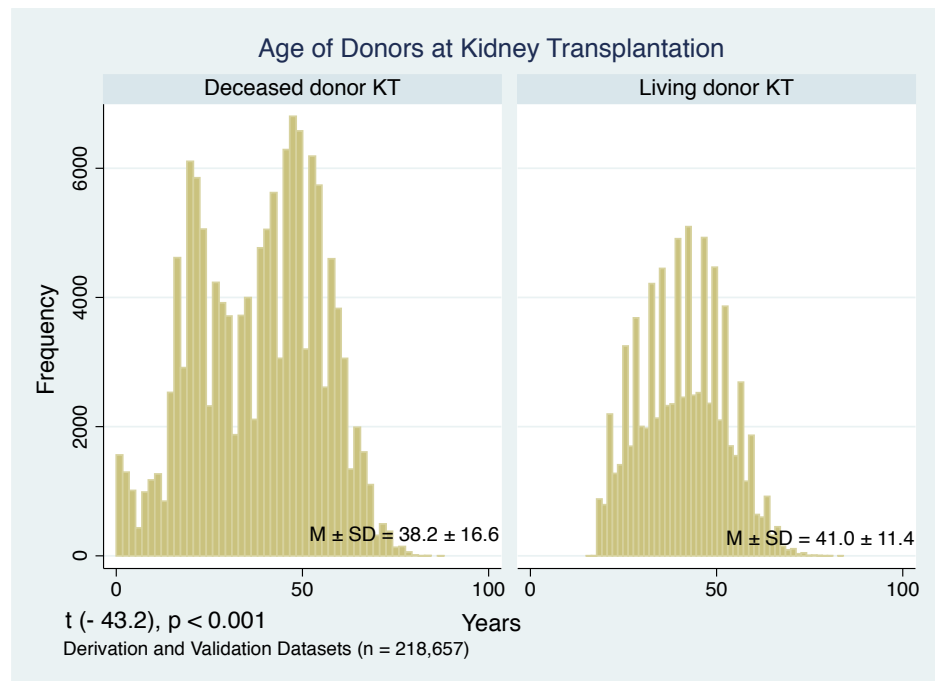
7. **Gender and race/ethnicity of donors**

Majority of donors in deceased donor KT were male (n = 81, 543 or 59.7%) however, female donors predominated in the living donor KT (n = 49,328 or 60.0%) (shown in Figure 13).

Figure 13.   Gender of donors

Derivative and Validative Datasets (n = 218,657)
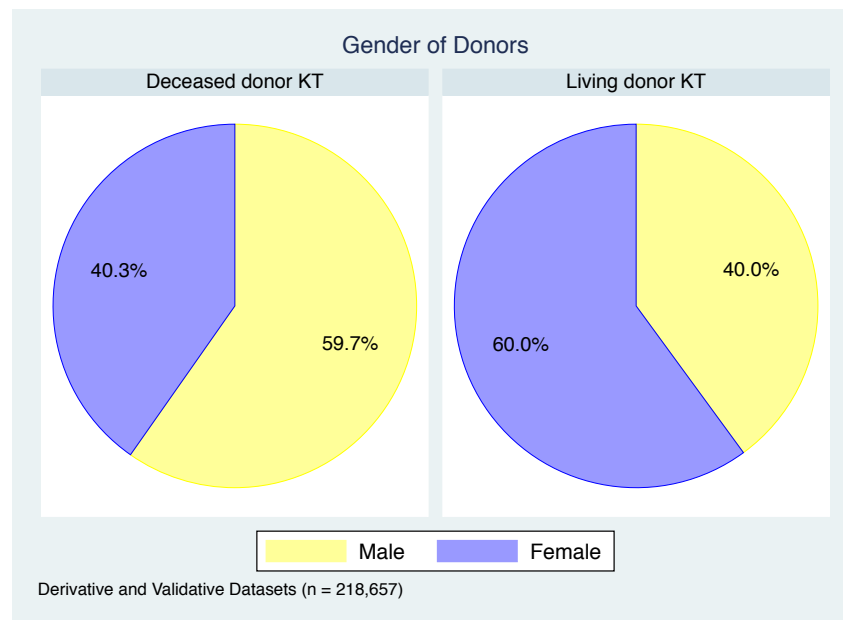
Among all race/ethnicity of donors, the predominant donors were Caucasian in both deceased donor KT (n = 95,574 or 70.0%) and living donor KT (n = 56,890 or 69.3%), which was followed by Hispanic/Latino group (Deceased donor KT: n = 18,929 or 13.9%; Living donor KT: n = 10,929 or 13.3%). Approximately 13% of each donor groups were Black donors (Deceased donor KT: n = 17,714; Living donor KT: n = 10,505) (shown in Figure 14).

Figure 14.   Race/ethnicity of donors
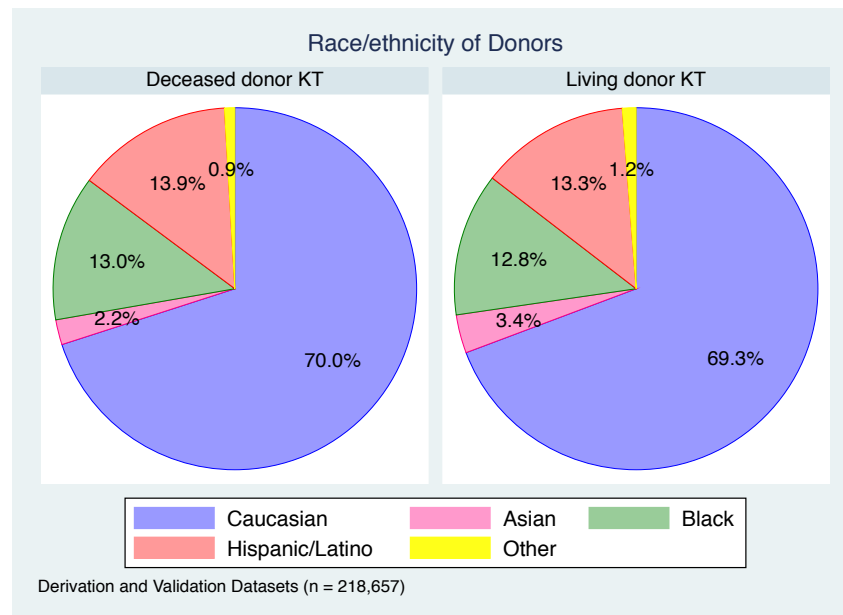
8.   **Serum creatinine and estimated glomerular filtration rate of donor kidneys**

The mean serum creatinine of deceased donors were 1.1 ($SD = 0.6$), whereas that of living donors were 0.8 ($SD = 0.2$) (shown in Figure 15). For donor characteristics, the function of donated kidneys varied based on estimated glomeruli filtration rates (eGFR) per the Modification of Diet in Renal Disease Study equation. The mean eGFR of deceased donors were 86.3 ($SD = 44.8$) and that of living donors were 89.1 ($SD = 23.7$) (shown in Figure 16). A majority of the deceased donors had normal (GFR $\geq$ 90 ml/min/1.73m^2) ($n = 51,237$ or 38.1%) or mildly decreased (GFR 60 - 89 ml/min/1.73m^2) ($n = 46,754$ or 34.8%) glomerular filtration rate. For living donor KT more than 95% of donors had normal or mildly decreased kidney function before transplant surgery ($n = 75,527$ or 95.4%). Among living donors, however, a small number at 3,633 or 4.6% had mild to moderately decreased kidney function (GFR 45 - 59 ml/min/1.73m^2) (shown in Figure 17).

Figure 15.   Serum creatinine of donors
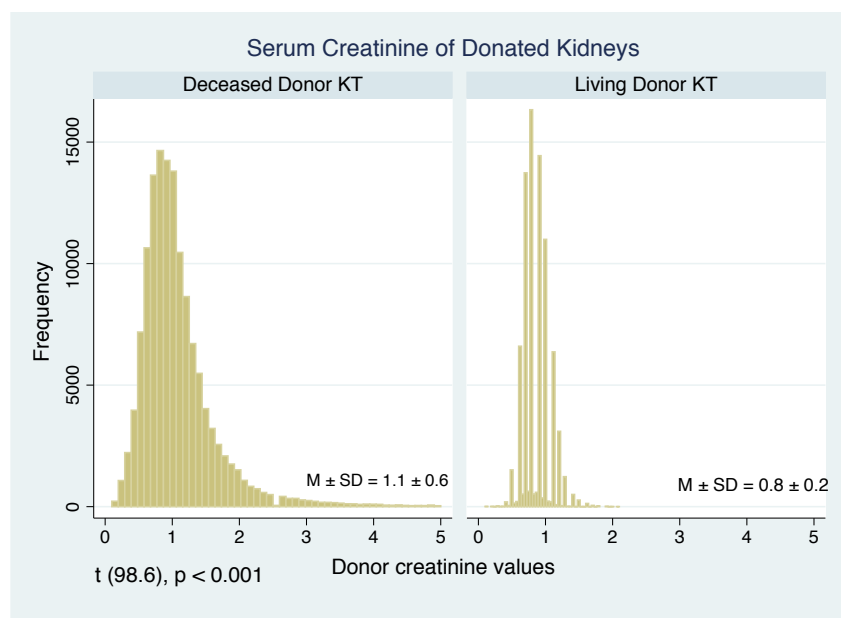
Figure 16.   Estimated glomerular filtration rates of donors (histogram)
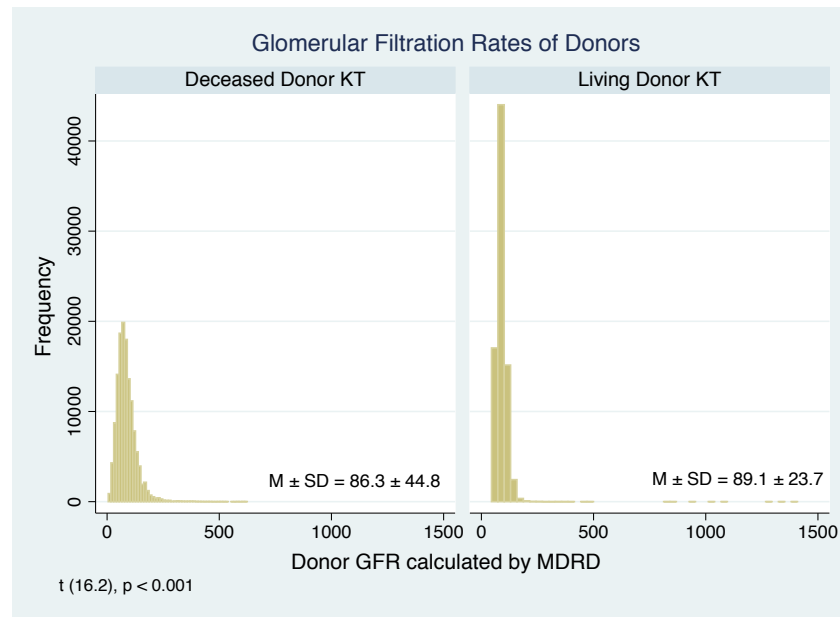
Figure 17.   Estimated glomerular filtration rates of donor kidneys
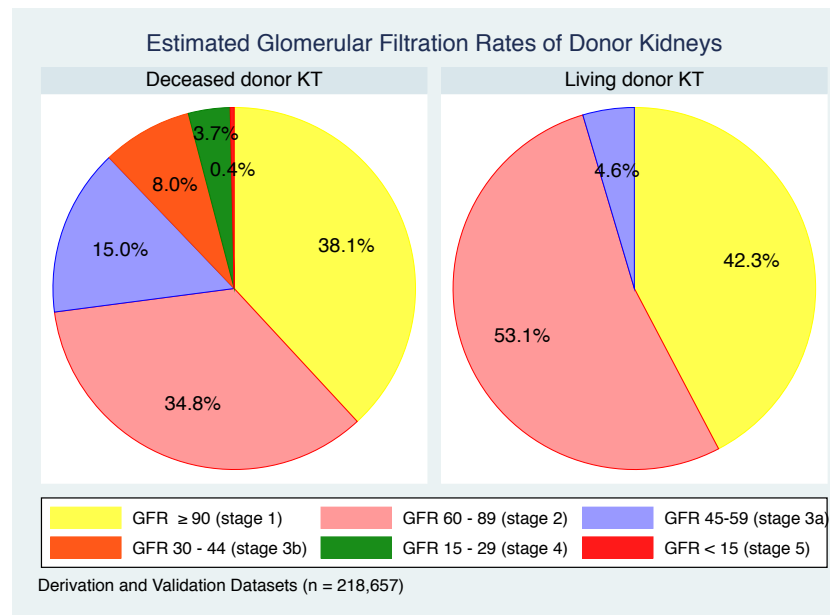
9.   **Hypertension history of donors**

Approximately, 27% (*n* = 36,198) of deceased donors had a history of hypertension and 4.8% of this group (*n* = 6,504) had hypertension greater than 10 years. However, a majority (*n* = 55,751 or 96.1%) of living donors did not have hypertension and only 71 or 0.1% had hypertension greater than 10 years (shown in Figure 18).

Figure 18.   Hypertension history of donors

Hypertension (HTN) History of Donors
Deceased donor KT
Living donor KT

Legend:
- Non-hypertension
- 0-5 years of HTN
- 6-10 years of HTN
- > 10 years of HTN
- HTN, but unknown duration
- Unknown about HTN history

Derivation and Validation Datasets (n = 218,657)
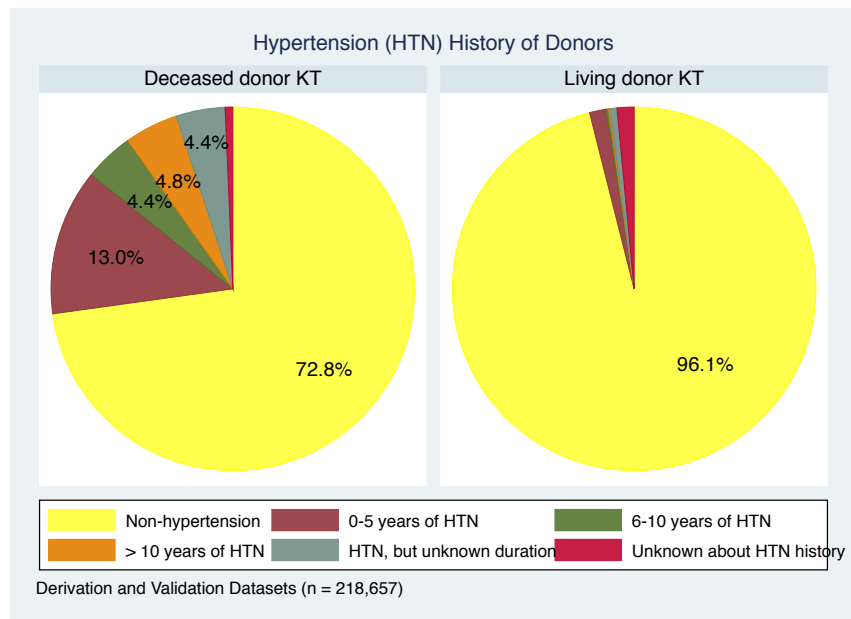
10.   **Diabetes history of donors**

   While none of the living donors had diabetes, 6.5% (*n* = 8,754) of deceased donors had a history

of either type 1 or type 2 diabetes (shown in Figure 19).

Figure 19.   Diabetes history of donors

Derivativion and Validation Datasets (n = 136,512)
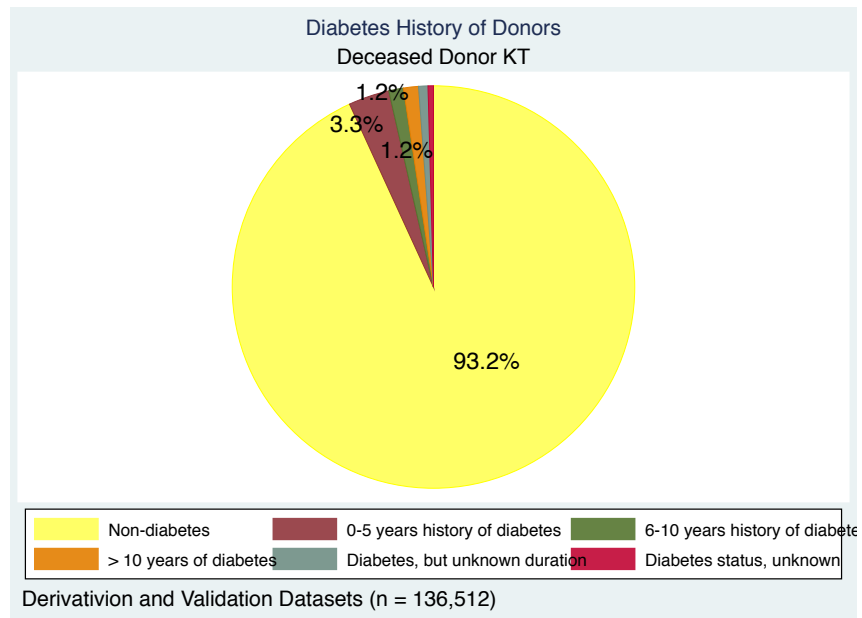
11.   **The body mass index of donors**

The body mass indexes (m/kg^2) of donors did not differ according to donor type: decease donor ($M \pm SD = 26.9 \pm 5.5$) and living donors ($M \pm SD = 26.9 \pm 4.3$), $t(-1.3)$, $p = 0.183$ (shown in Figure 20).

Figure 20.   The body mass index of donors

Body Mass Index of Donors

Deceased Donor KT (n = 129,346)   _Living Donor KT (n = 75,623)_

Mean ± SD = 26.9 ± 5.5   Mean ± SD = 26.9 ± 4.3

t (-1.3), p = 0.183
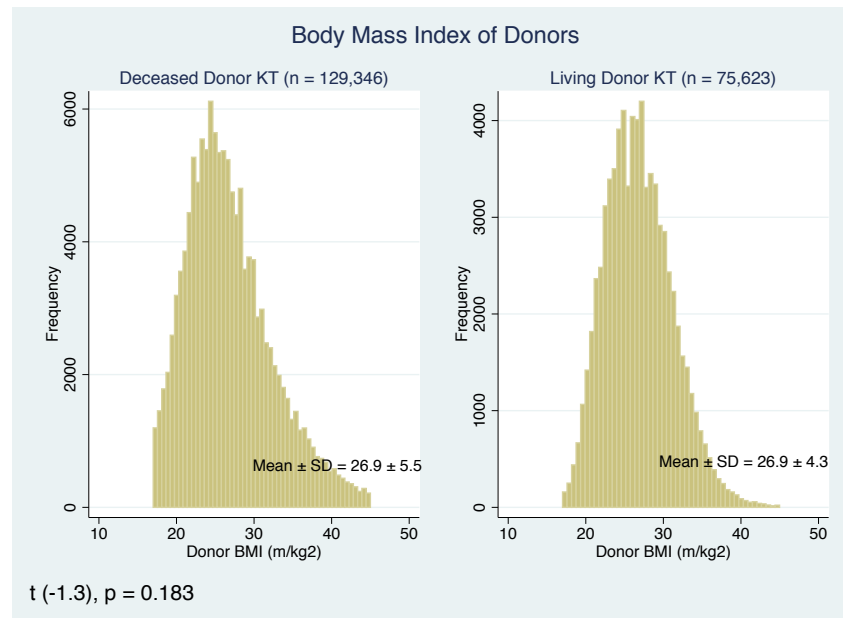
12.   **<ins>Hepatitis C virus infection of donors</ins>**

And it should be noted that 2.3% (*n* = 3,193) of deceased donors were hepatitis C virus carriers (shown in Figure 21).

Figure 21.   Hepatitis C virus infection of donors

Hepatitis C virus Infection of Donors
Deceased Donor KT

2.3%

97.7

Negative-HCV   Positive-HCV

Derviation and Validation Data of Deceased Donors (n = 136,512)
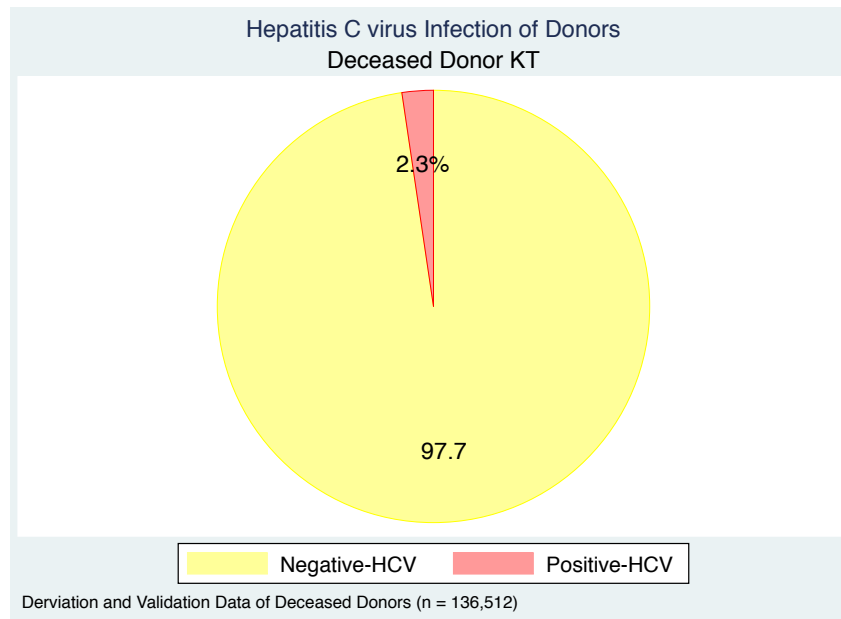
13.   **Causes of death and donation after cardiac death of the deceased donors**

For deceased donor KT, information about donor death circumstances was available. Head trauma (n = 53,575 or 39.3%) and cerebrovascular/stroke (n = 51,306 or 37.6%) were the primary causes of death. Anoxia was the third leading cause (n = 27,623 or 20.2%). Further, donation of kidneys after cardiac death was common (n = 122,029 or 89.4%) (shown in Figure 22).

Figure 22.   Causes of death and donation after cardiac death of the deceased donors
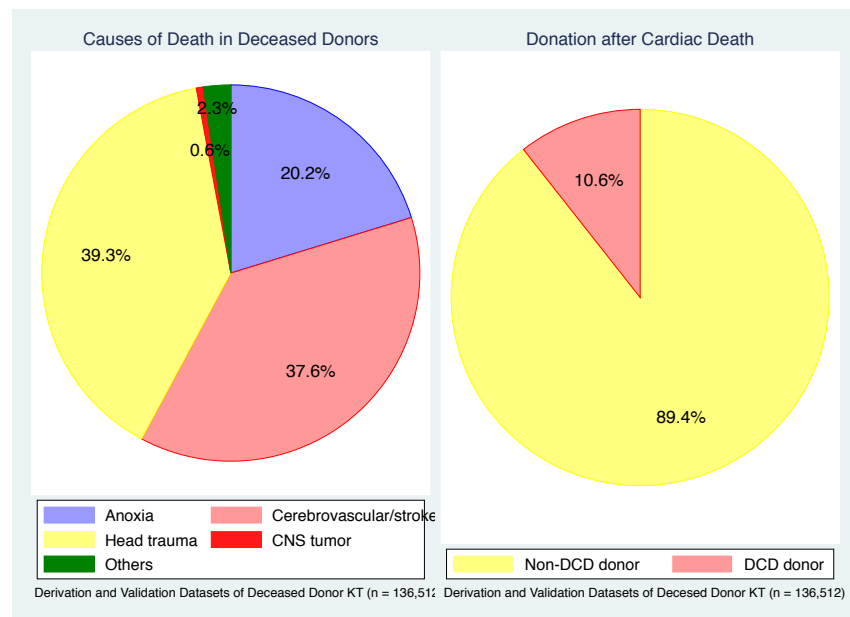
14.   <u>**Cardiovascular comorbidities of candidates**</u>

a.   **Coronary artery disease**

Among KT recipients with information about coronary artery diseases, 8.2% (n = 5,817) of candidates for deceased donor KT had coronary artery disease and 6.6% (n = 3,154) of living donor KT candidates had coronary artery disease (shown in Figure 23).

Figure 23.   Coronary artery diseases of candidates

Coronary Artery Diseases of Candidates

Deceased donor KT	Living donor KT
3.9%	3.7%
8.2%	6.6%
87.8%	89.7%

Non-coronary artery disease (CAD)   History of CAD
CAD, Unknown

Derivation and Validation Datasets (n = 218,657)
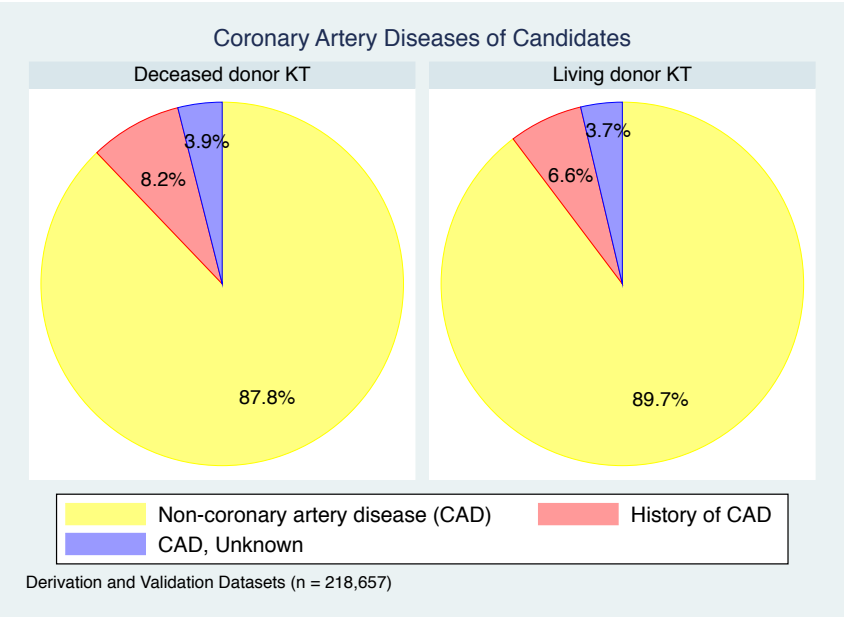
b.   **Peripheral vascular diseases of candidates**

Peripheral vascular diseases were found in 4% (*n* = 5,427) of deceased donor KT

recipients. 3.2% or 2,602 living donor KT recipients had peripheral vascular diseases (shown in Figure 24).

Unlike coronary artery disease, missing information for peripheral vascular disease was low (deceased donor KT:

n = 487 or 0.4%; living donor KT: *n* = 41 or 0.1%).

Figure 24.   Peripheral vascular diseases of candidates
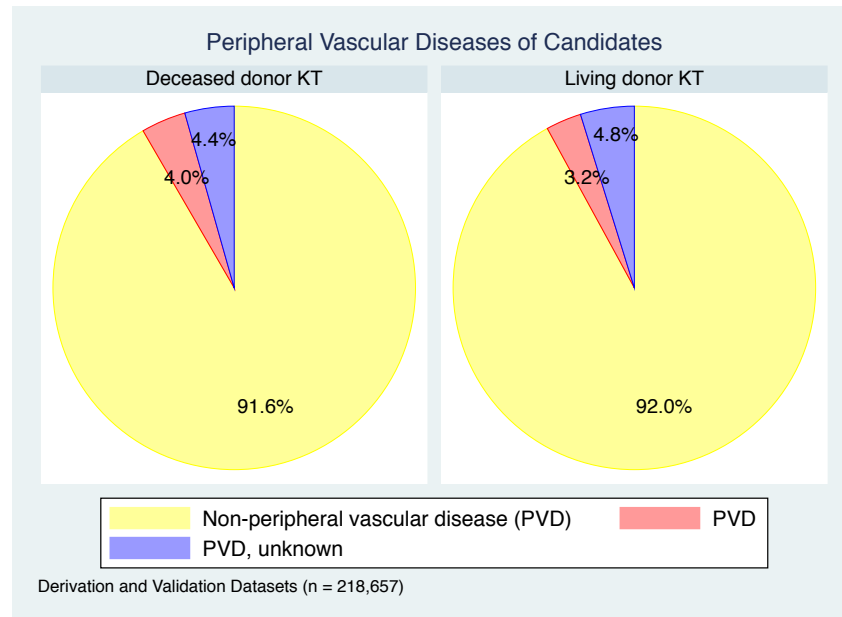
c.   **Cerebrovascular diseases of candidates**

Cerebrovascular diseases of recipients were found in both deceased donor KT (2.8% or *n* = 3,490) and living donor KT (2.2% or *n* = 1,675) (shown in Figure 25). Approximately 8% of candidates did not have information regarding cerebrovascular diseases in both types of KT.

Figure 25.   Cerebrovascular diseases of candidates
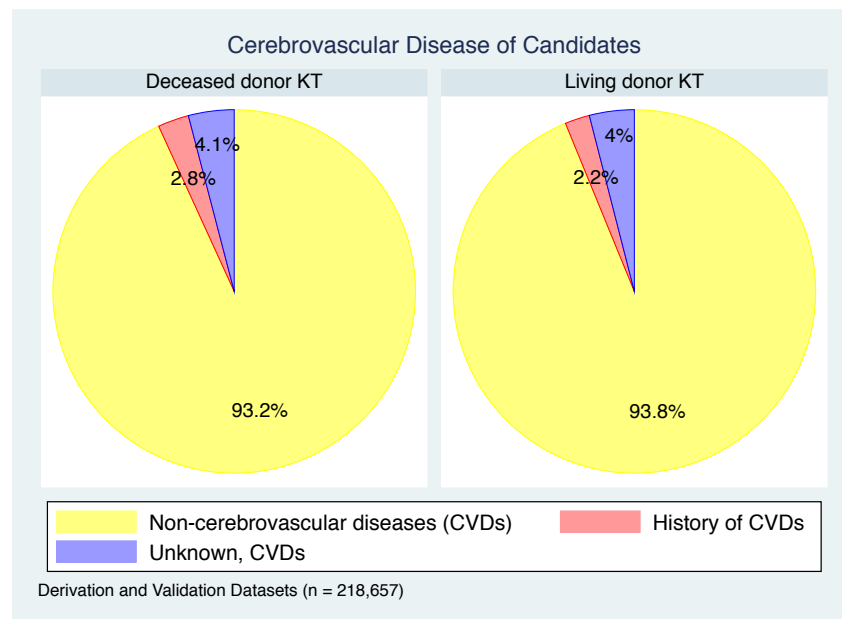
d.   **Physical limitation of candidates**

Physical limitation were categorized into three degrees of limitation: total, some, and non-limitation. Recipients greater than 50% had some degree of physical limitation (deceased donor KT: $n = 76,142$ or 63.3%; living donor KT: $n = 42,514$ or 59.3%). The number of recipients with total physical limitation was larger in recipients who received deceased donor KT ($n = 4,926$ or 4.1%) compared with those in candidates who received living donor KT ($n = 1,239$ or 1.7%) (shown in Figure 26). In both types of KT, about 12% did not have information regarding physical limitation.

Figure 26.   Physical limitation of candidates
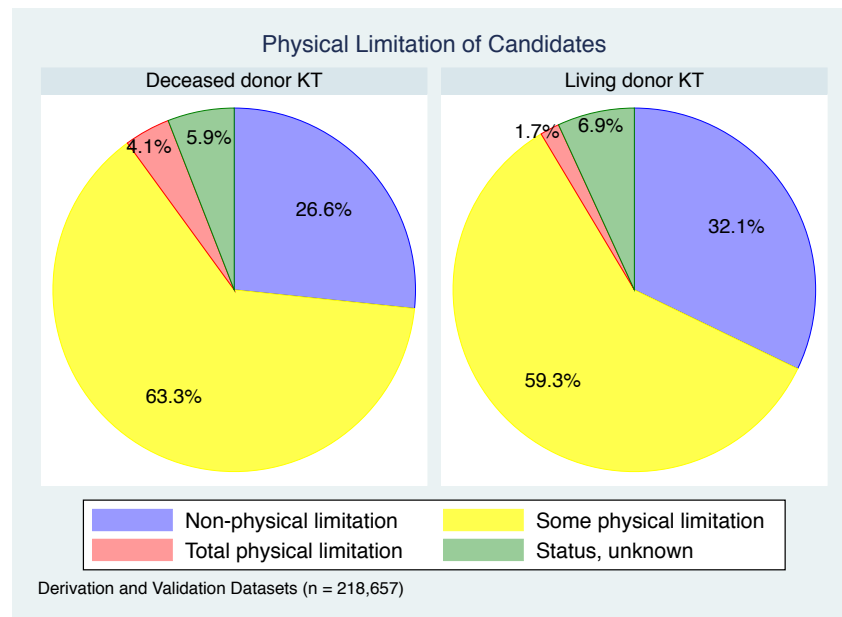
e.   **The body mass index (BMI) (kg/m^2) of candidates**

Average BMI differed between the candidates who underwent deceased donor ($M \pm SD =$ 27.7 ± 5.3*)* and living donor transplantation *(M ± SD =* 27.4 ± 5.3)*, t* (12.4), p < 0.001 (shown in Figure 27). Obesity calculated by BMI indicated that about 30% (*n* = 43,176) of candidates who received deceased donor KT were obese or had a BMI ≥ 30. For recipients who received living donor KT, 26% or 23,339 were obese. Underweight (BMI < 18.5) candidates were 1.7% (*n* = 2,222) and 1.9% (*n* = 1,501) for deceased donor- and living donor- KT surgeries (shown in Figure 28).

Figure 27.   The body mass index of candidates
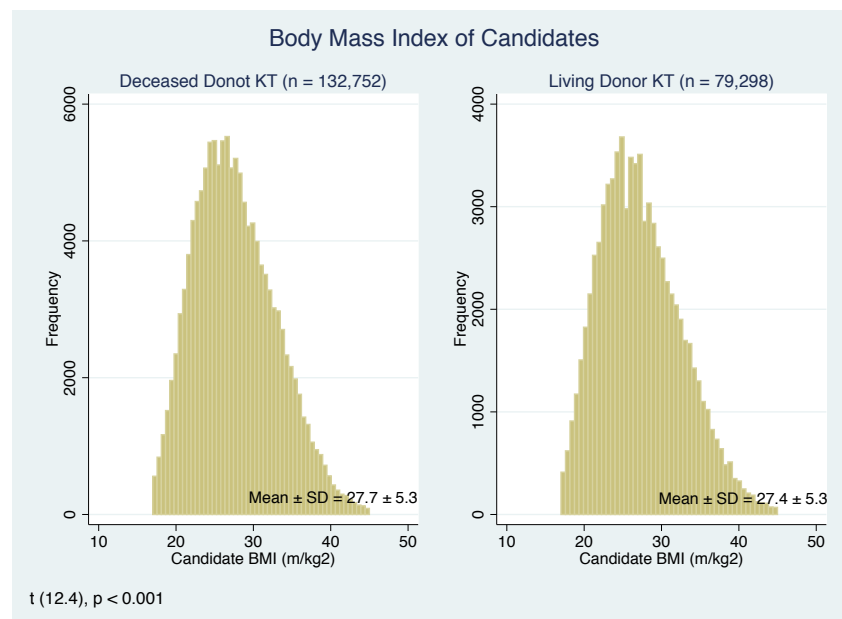
Figure 28.   The BMI classification of candidates
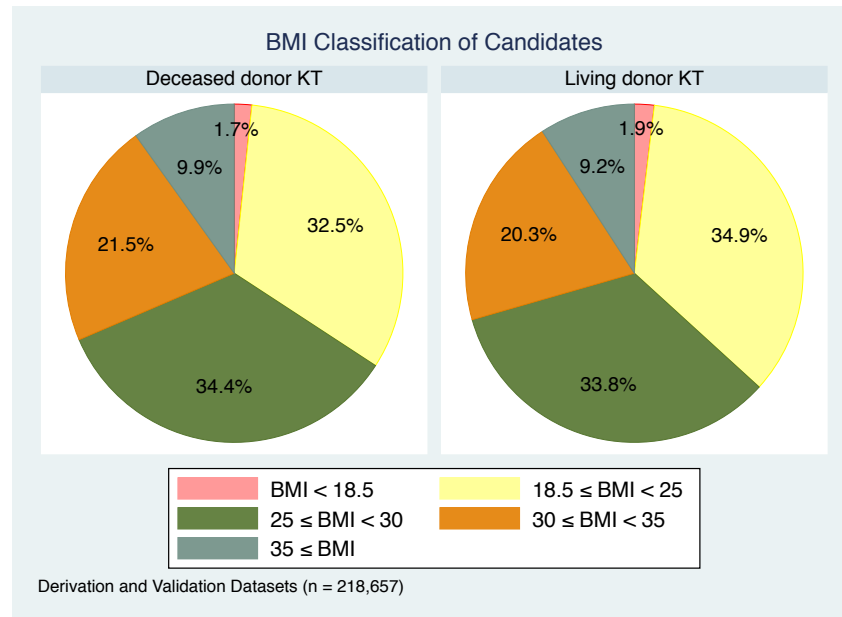
f. **Diabetes and hypertension histories of candidates**

Non-diabetic candidates were greater than 50% in both deceased and living donor KT.

Type 2 diabetes in deceased donor KT and living donor KT were 24,114 (17.7%) and 10,613 (12.9%),

respectively. The number of type 1 diabetes was larger in candidates (n = 3,757 or 4.6%) whose kidneys were

donated by living donors compared with those from deceased donors (n = 3,891 or 2.9%) (shown in Figure 29).

Hypertension was common in candidates. Approximately, 80% of candidates had taken anti-hypertension

medications (deceased donor KT: n = 103,913 or 82.5%; living donor KT: n = 62,294 or 82.1%) (shown in Figure

30)

Figure 29.   Diabetes types of candidates
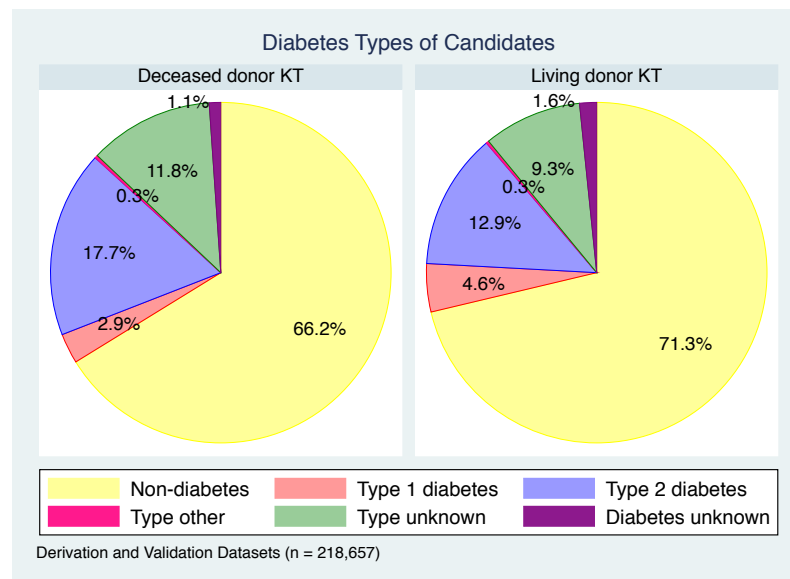
Figure 30.   Hypertension history of candidates
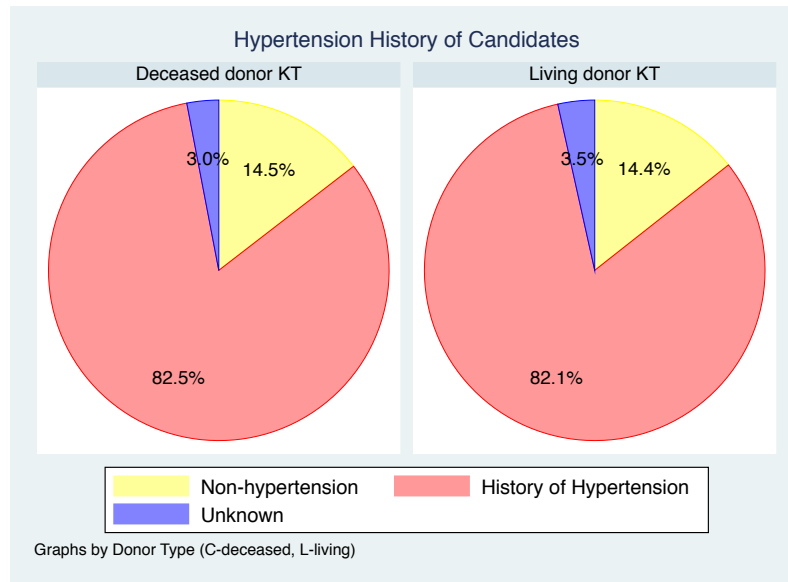
15. **Immunological Factors of Candidates**

 a.   **Blood types and ABO mismatching**

  Recipients with blood group type O received the most transplant surgeries (deceased donor KT: n = 61,551 or 45.1%; living donor KT: n = 36,874 or 44.9%) whereas those with type AB blood received the least transplant surgeries (deceased donor KT: n = 7,280 or 5.3%; living donor KT: n = 3,140 or 3.8%), except for patients with type A2 blood (shown in Figure 31).

Figure 31.   ABO types of candidates
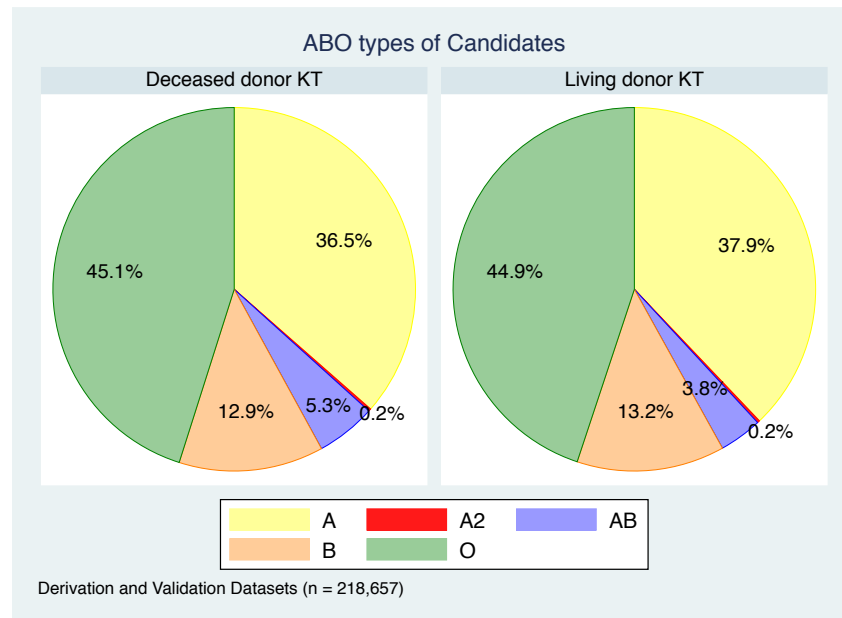
ABO incompatibility KT between candidates and recipients were 0.9% in living donor KT ($n =$ 770). In contrast, only 0.04% KT cases ($n = 56$) were ABO incompatible in deceased donor KT. A2 incompatible KT was found in 0.2% of KT cases in both types of KT (deceased donor KT: $n = 178$; living donor KT: $n = 256$) (shown in Figure 32).

Figure 32.   ABO compatibility and incompatibility kidney transplantation
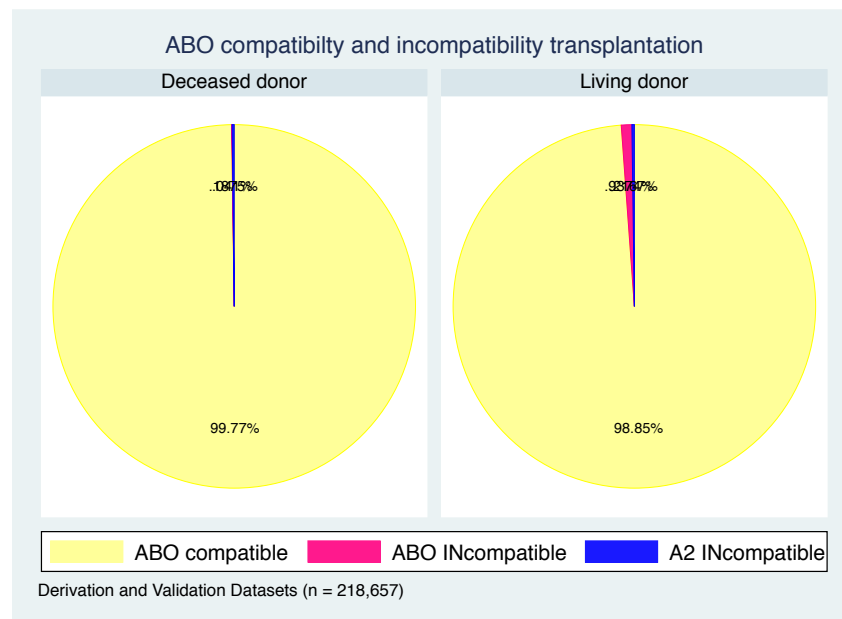
b. **Panel reactive antibody of candidates**

The degree of panel reactive antibody (PRA) were higher in deceased donor KT

($M \pm SD = 22.0 \pm 32.9$ %) than living donor KT ($M \pm SD = 11.9 \pm 24.3$ %) (shown in Figure 33).

Figure 33. Panel reactive antibody of candidates
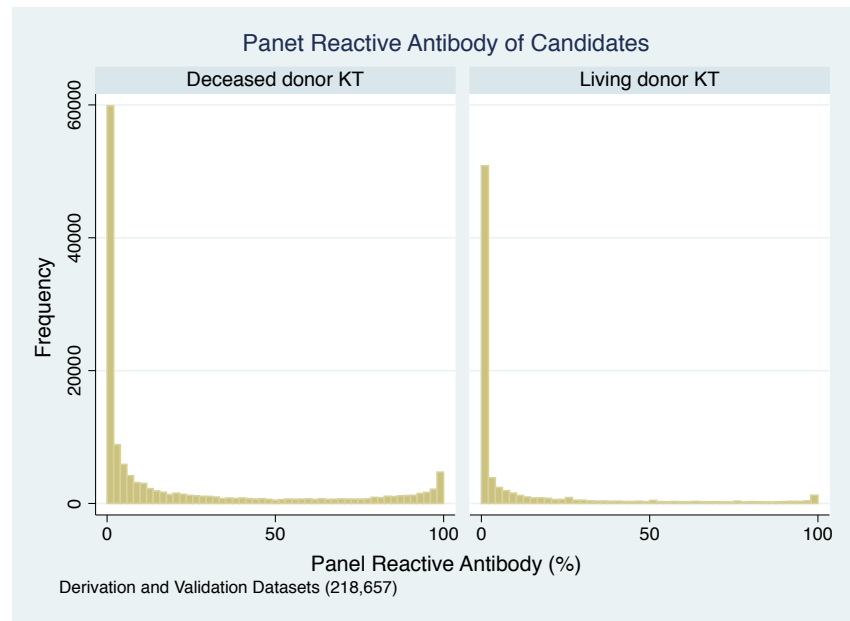
A larger number of patients were highly sensitized (PRA ≥ 80%) in deceased donor KT

(n = 17,272 or 12.9%) compared with those in living donor KT (n = 3,809 or 4.8%) (shown in Figure 34).

Figure 34.   Panel reactive antibody and sensitized candidates

Panel Reactive Antibody and Sensitized Candidates

Deceased donor KT	Living donor KT
12.94%	4.816%
87.06%	95.18%

PRA < 80%   80 ≤ PRA ≤ 100%

Derivation and Validation Datasets (n = 218,657)
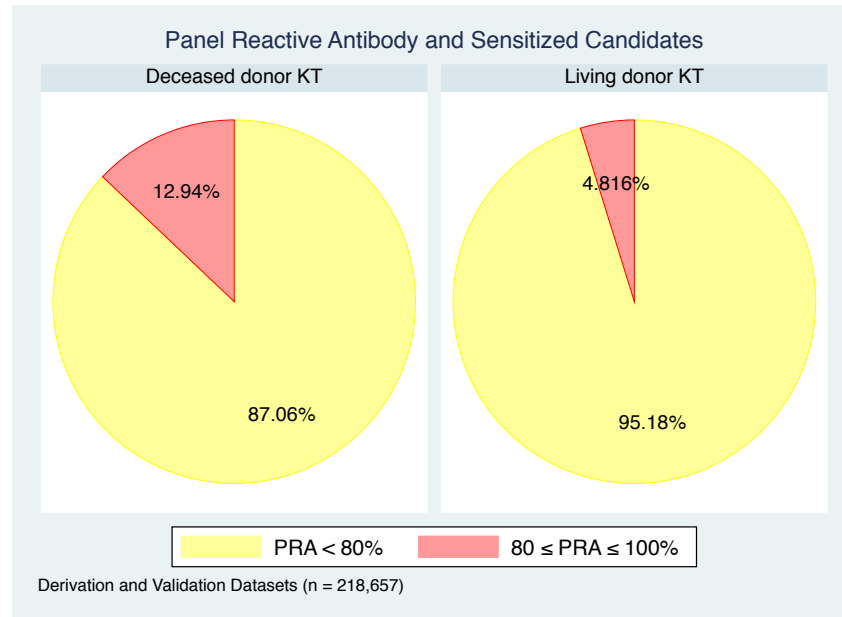
c. **Human leukocyte antigen mismatching**

The human leukocyte antigen has three types: A, B, and DR and the degree of

mismatching ranges from zero to two. Two A antigen mismatch was common in deceased donor KT ($n = 62,300$

or 45.9%), whereas 52.6% ($n = 42,790$) of living donor KT had one A antigen mismatch. For B antigen mismatch,

59.7% ($n = 80,998$) of deceased donor KT had 2 antigen mismatch and 34.9% ($n = 28,373$) of living donor KT

had 2 antigen mismatch. One DR mismatch was common in both deceased ($n = 58,630$ or 43.2%) and living

donor KT ($n = 42,694$ or 52.5%) (shown in Figure 35).

Figure 35.   Human leukocyte antigen mismatching
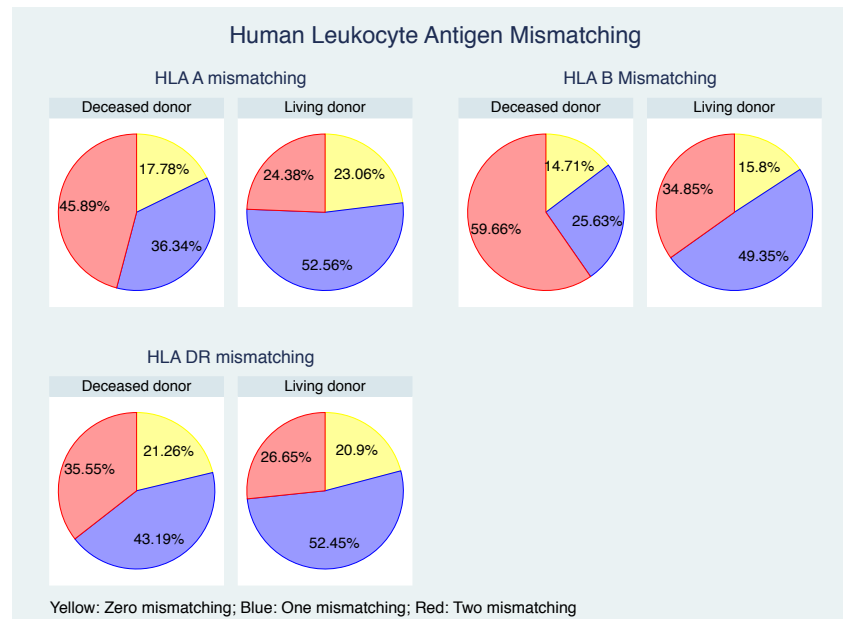
d. **History of kidney transplantation**

A majority of candidates never had kidney transplantation previously, but approximately 10% of patients had kidney transplantation surgery (deceased donor KT: n = 16,885 or 12.4%; living donor KT: n = 8,170 or 10.0%) (shown in Figure 36).

Figure 36. Kidney transplantation history of candidates
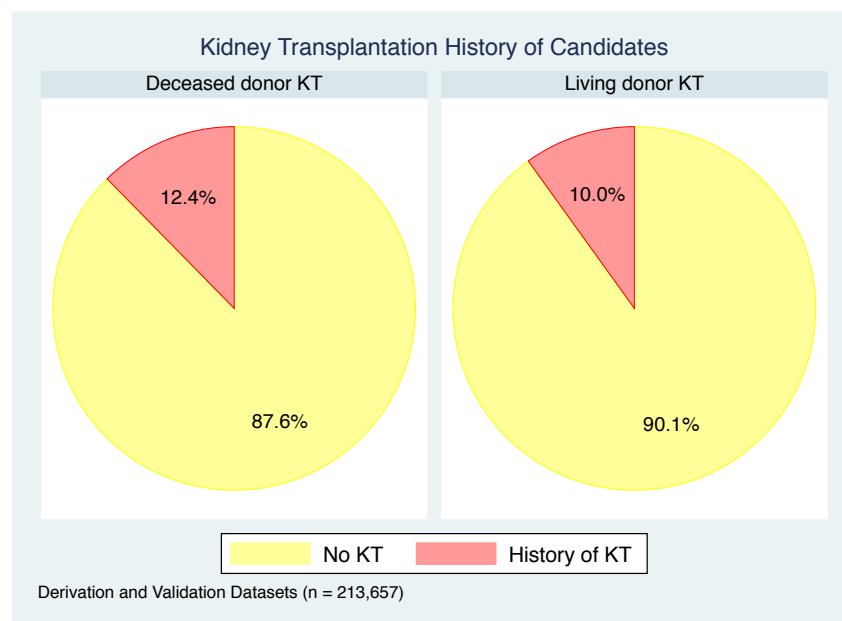
e.   **Donor-recipient relationship**

Among recipients who underwent living donor KT, 59.2% ($n = 48,655$) of donors were living related donors (shown in Figure 37).

Figure 37.   Relationship between donor and candidate
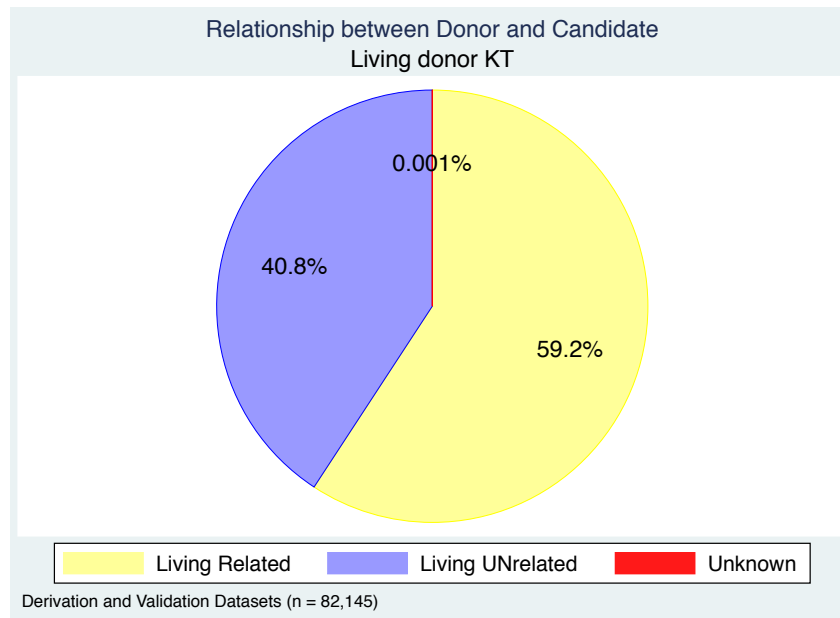
C.   **Specific Aim 1: The predictive models**

   1.   **Univariate and multivariate analyses**

      a.   **Coronary artery disease**

               Coronary artery disease is a significant predictor of one-year graft failure for deceased

KT (HR = 1.177, 95% CI = 1.024-1.353, $p = 0.022$). However, in living donor KT, the hazard ratio for kidney

graft failure was HR = 1.103 (95% CI = 0.833-1.459, $p = 0.494$) of patients with coronary artery disease was not

significant n and log-rank test indicated a non-significant difference in kidney graft failure between patients with

and without coronary artery disease ($p = 0.767$) (shown in Figure 38).

Figure 38.   One-year graft failure of candidates by coronary artery disease
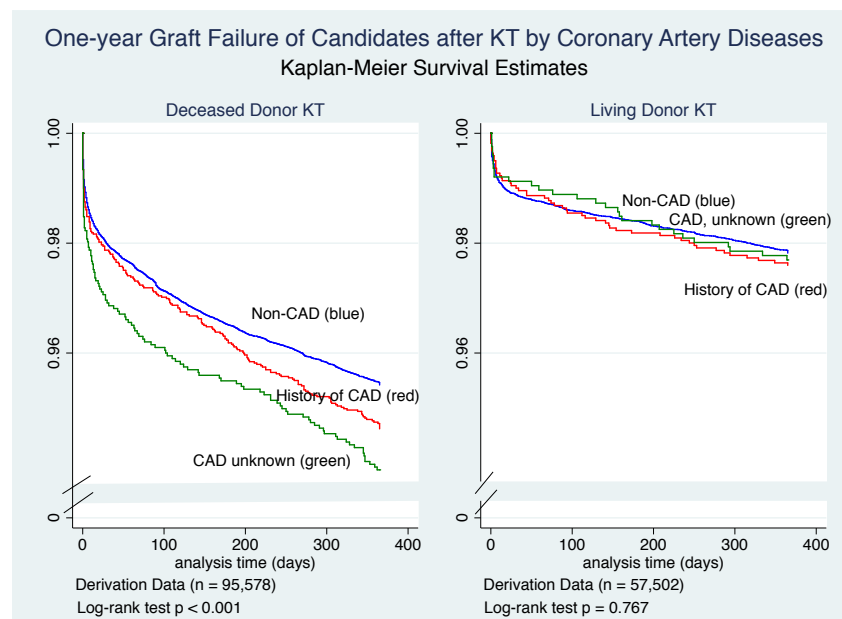
However, for one-year patient death after KT, coronary artery disease was a significant predictor for both deceased donor KT and living donor KT. Patients with coronary artery disease had a hazard of death about 200% greater than those without coronary artery diseases after deceased or living donor KT: Deceased donor KT, HR = 2.217 (95% CI = 1.950-2.520, $p < 0.001$); Living donor KT, HR = 2.740 (95% CI = 2.124-3.534, $p < 0.001$) (shown in Figure 39).

Figure 39.   One-year death of candidates after KT by coronary artery disease
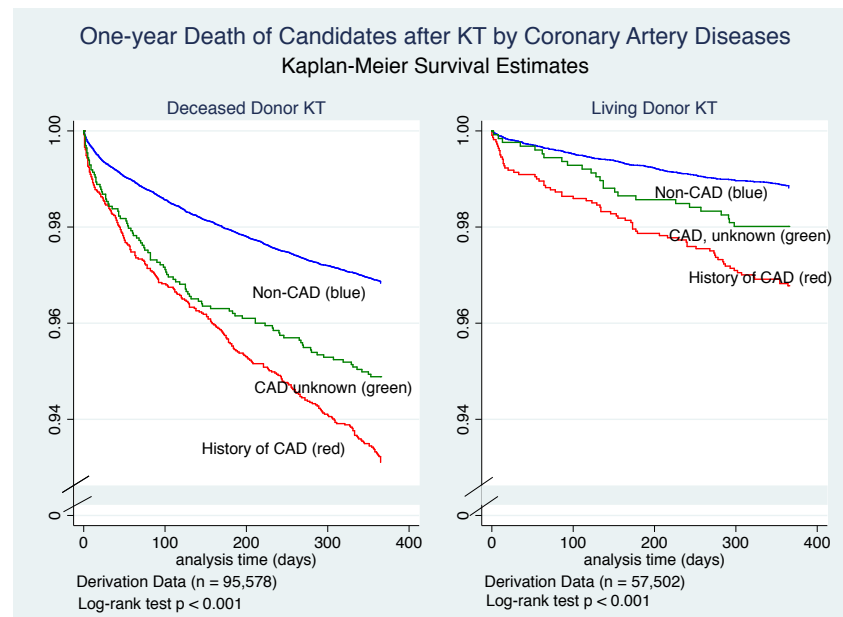
b.   **<u>Peripheral vascular diseases</u>**

Peripheral vascular disease did not predict one-year graft failure in deceased KT significantly, however, it was a significant predictor in living donor KT. The hazard ratio for one-year graft failure in living donor KT by peripheral vascular disease was 1.323, (95% CI = 1.024-1.711, p = 0.032) when it comes to comparing the patients without peripheral vascular diseases (shown in Figure 40).

Figure 40.   One-year graft failure of candidates after KT by peripheral vascular disease (PVD)
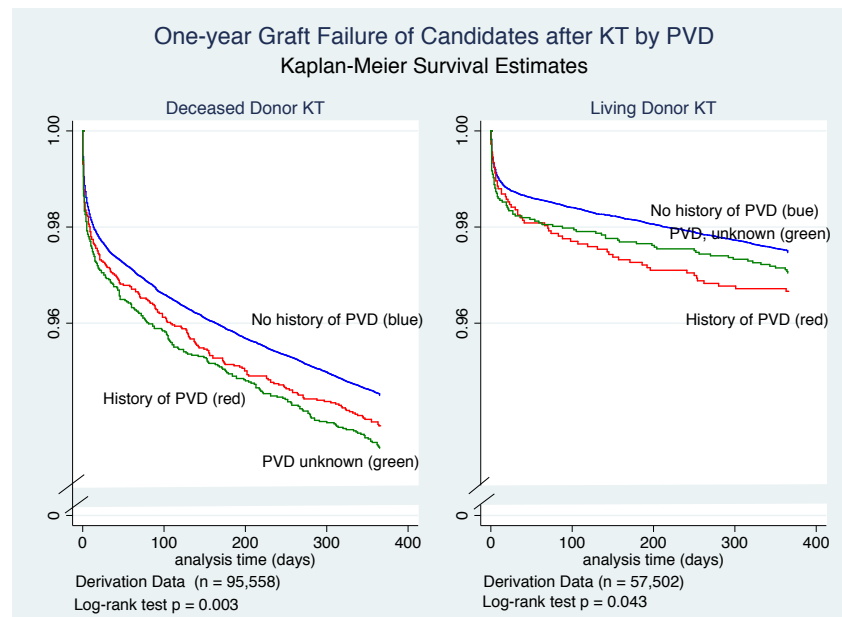
The impact of peripheral vascular disease on one-year patient death was significant. In deceased donor KT, the hazard ratio of patient death for patients with peripheral vascular diseases was 1.951 (95% CI = 1,729-2.203, $p < 0.001$). Whereas patients who had peripheral vascular diseases and received living donor KT had hazard ratio of death as 2.739 (95% CI = 2.151-3.487, $p < 0.001$) of one year death first compared to the patients without peripheral vascular diseases (shown in Figure 41).

Figure 41.　　One-year death of candidates after KT by peripheral vascular disease (PVD)
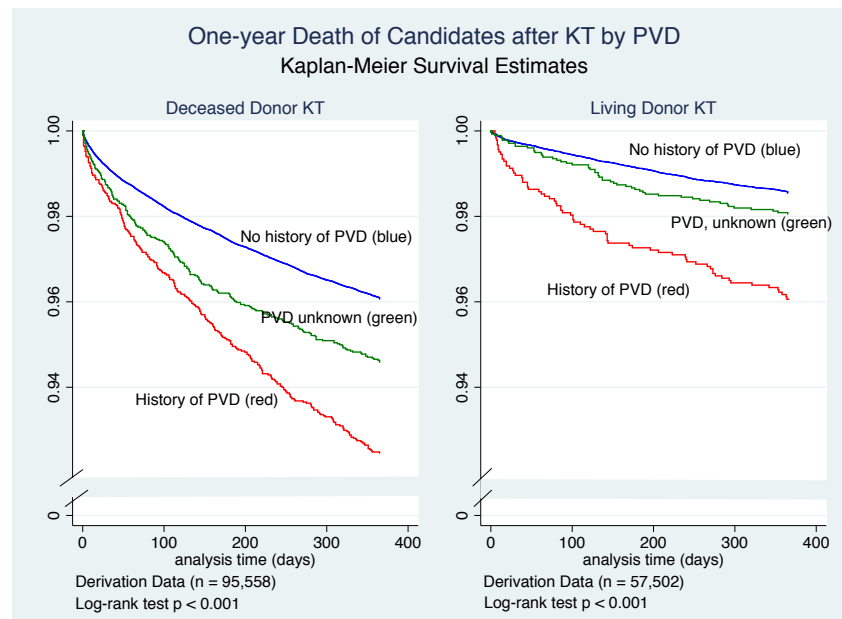
c.   **Cerebrovascular diseases**

Cerebrovascular disease was not a significant predictor of one-year graft failure in both deceased and living donor KT: Deceased donor KT, HR = 0.946 (95% CI =0.795-1.125, *p* = 0.530); Living donor KT, HR = 1.104 (95% CI = 0.781-1.559, *p* = 0.576) (shown in Figure 42).

Figure 42.   One-year graft failure of candidates after KT by cerebrovascular disease (CVD)
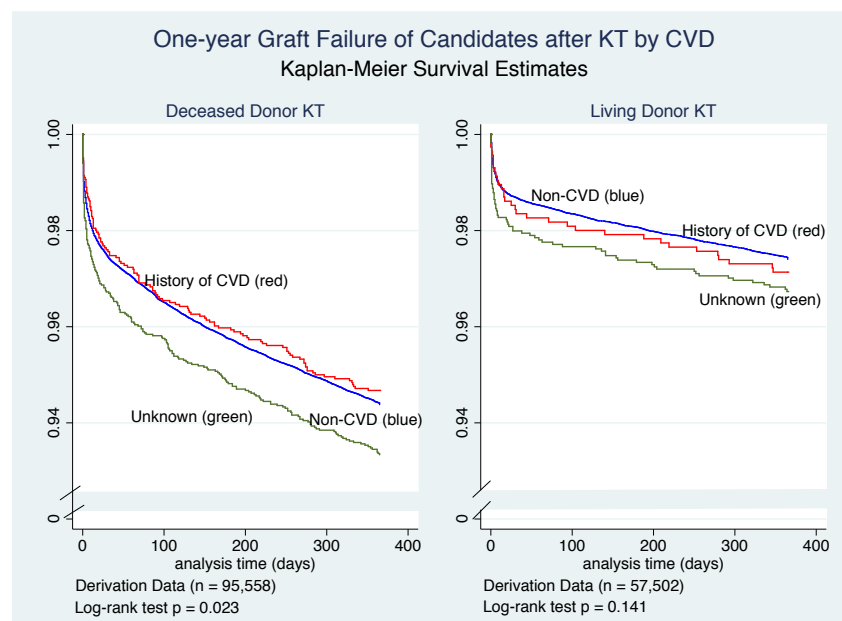
However, among patients with cerebrovascular diseases (n = 2,460) who received deceased donor KT, 152 patients died in one-year after kidney transplantation and the hazard ratio was 1.513 (95% CI = 1.286-1.780, p < 0.001). In contrast, the hazard ratio of patient death for living donor KT with cerebrovascular disease was 2.471 (95% CI 1.817-3.359, p < 0.001) (shown in Figure 43).

Figure 43.   One-year death of candidates after KT by cerebrovascular disease (CVD)
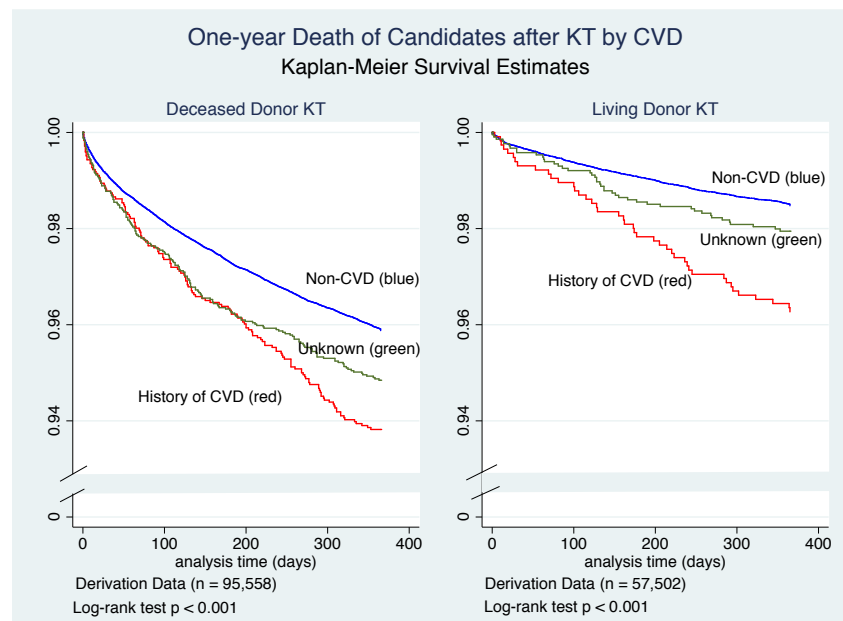
d. **Physical limitation**

The degree of physical limitation was a significant predictor in one-year patient death. Patients with total limitation had hazard rates of one-year patient death 229% greater than those without limitations, Deceased donor KT, HR = 2.294, 95% CI = 2.032-2.59, p < 0.001); Living donor KT, HR = 2.579 (95% CI = 1.838-3.617, p < 0.001) (shown in Figure 44).

Figure 44.   One-year death of candidates after KT by physical limitation
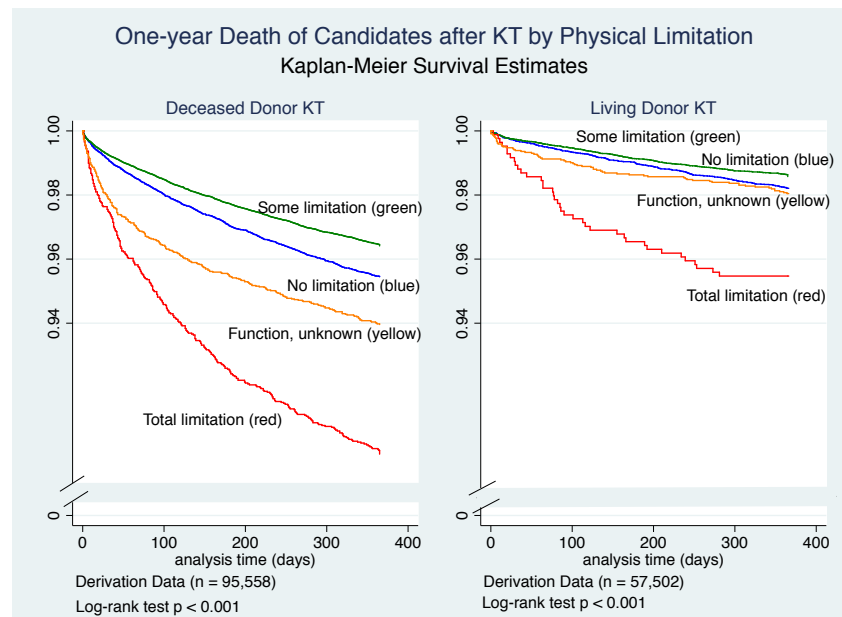
However, the risk of graft failure of the homebound or totally limited candidates was not significantly as high as that of candidates without physical limitation in both deceased KT, HR = 1.103 (95% CI = 0.967-1.258, p = 0.145) and living donor KT, HR = 0.883 (95% CI = 0.586-1.329, p = 0.550) (shown in Figure 45).

Figure 45.　　One-year graft failure of candidates after KT by physical limitation
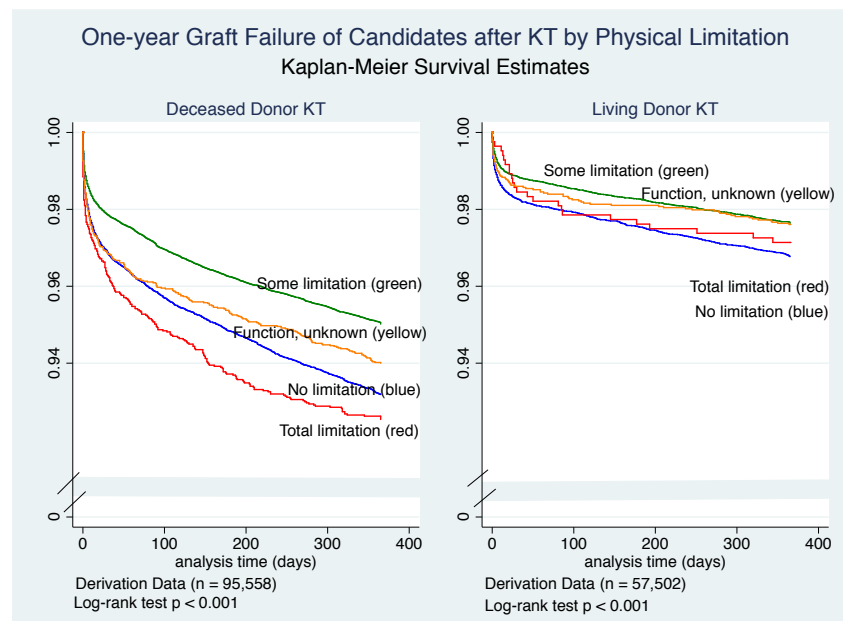
e.   **Diabetes**

Any type of diabetes was a significant predictor of one-year patient death. For example, patients with type 1 and type 2 diabetes encountered a one-year death 55% greater than patients without diabetes if they receive deceased donor KT: Type 1 diabetes: HR = 1.552 (95% CI = 1.307-1.844, $p < 0.001$); Type 2 diabetes: HR = 1.525 (95% CI = 1.407-1.653, $p < 0.001$). Especially for living donor KT, patients with type 2 diabetes had a hazard ratio of 2.103 (95% CI = 1.772-2.497, $p < 0.001$) with regard to one year death compared to those without diabetes (shown in Figure 46).

Figure 46.   One-year death of candidates after KT by diabetes types
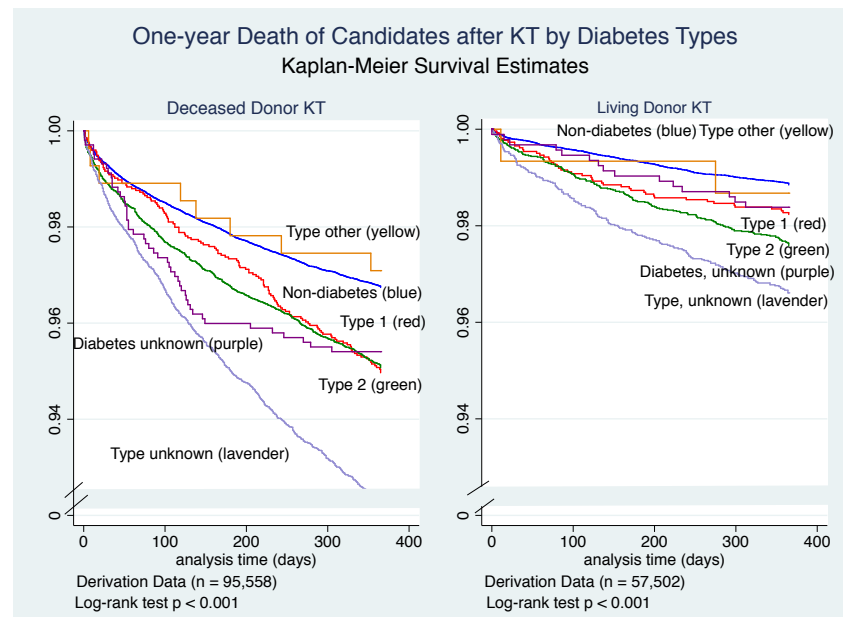
In contrast, patients with type 2 diabetes had a hazard of graft failure 15% and 30% less than patients without diabetes when they received deceased donor and living donor KT, respectively: Deceased donor KT: HR = 0.848 (95% CI = 0.785-0.915, $p < 0.001$); Living donor KT: HR = 0.694 (95% CI = 0.583-0.827, $p < 0.001$) (shown in Figure 47).

Figure 47.　　One-year graft failure of candidates after KT by diabetes types

One-year Graft Failure of Candidates after KT by Diabete Types
Kaplan-Meier Survival Estimates
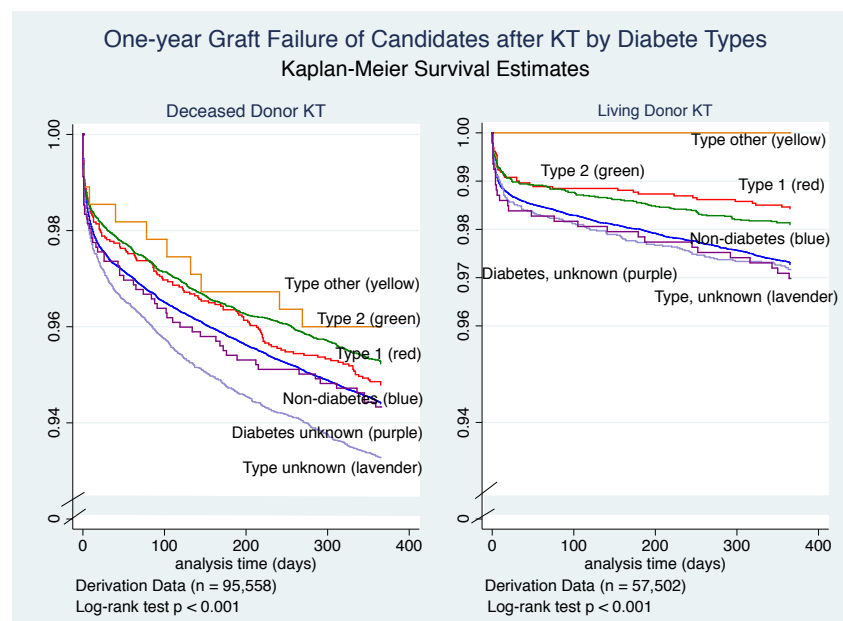
f.   **The body mass index of candidates**

Underweight patients who received kidneys from deceased donors did not have a significant hazard of kidney graft failure compared with normal body weight patients whose hazard ratio indicated 0.870 (95% CI = 0.736-1.028, *p* = 0.102). However, the negative impact of being underweight was found in living donor KT. Except the morbid obese group (BMI ≥ 30), all groups had the hazard ratios of which values were less than 1 and significant (shown in Figure 48).

Figure 48.   One-year graft failure of candidates after KT by BMI
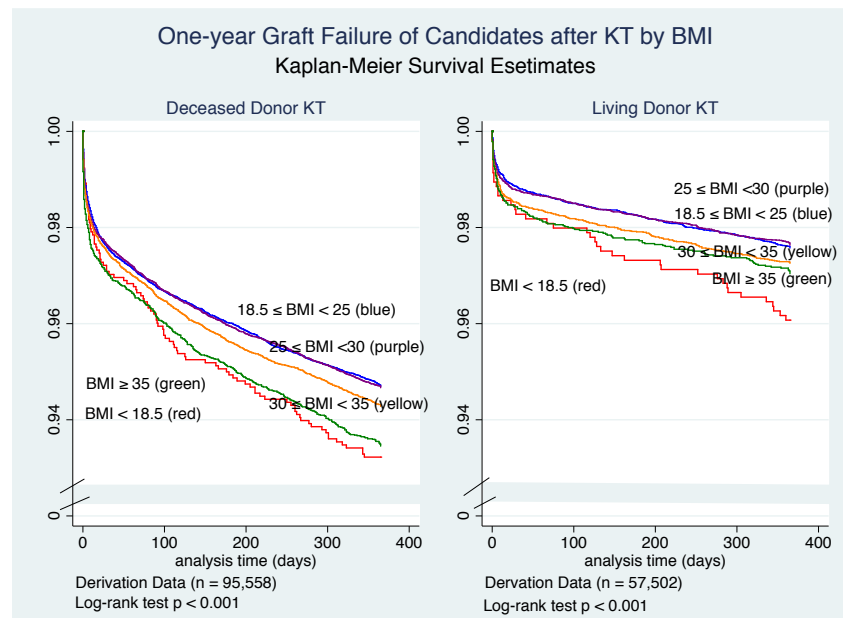
BMI was not a significant predictor of patient death in deceased donor KT. However, in living donor KT one unit increase in BMI increases the hazard of patient death by 3% with HR = 1.032 (95% CI = 1.019-1.045, $p < 0.001$). And morbid obesity had a hazard ratio for patient death as 1.909 (95% CI = 1.052-3.463), $p = 0.033$ compared with that of being underweight (shown in Figure 49).

Figure 49.   One-year death of candidates after KT by BMI
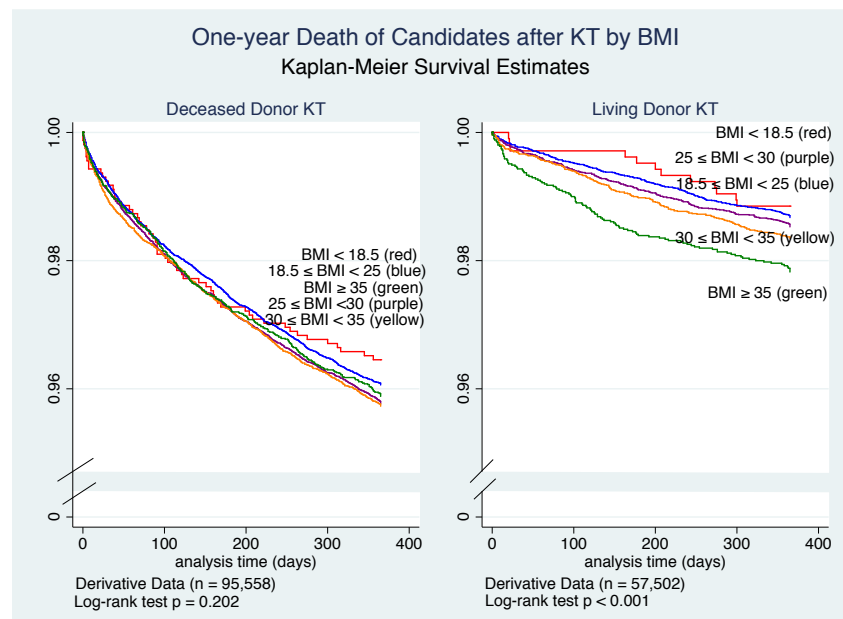
g.   **Hypertension**

The patients with hypertension showed better graft survival with deceased donor KT, HR = 0.819 (95% CI 0.761-0.882, *p* < 0.001) however, living donor KT Hypertension history was not significant predictor of graft failure and patient death in both deceased and living donor KT (shown in Figure 50 and Figure 51).

Figure 50.   One-year graft failure of candidates after KT by hypertension (HTN)
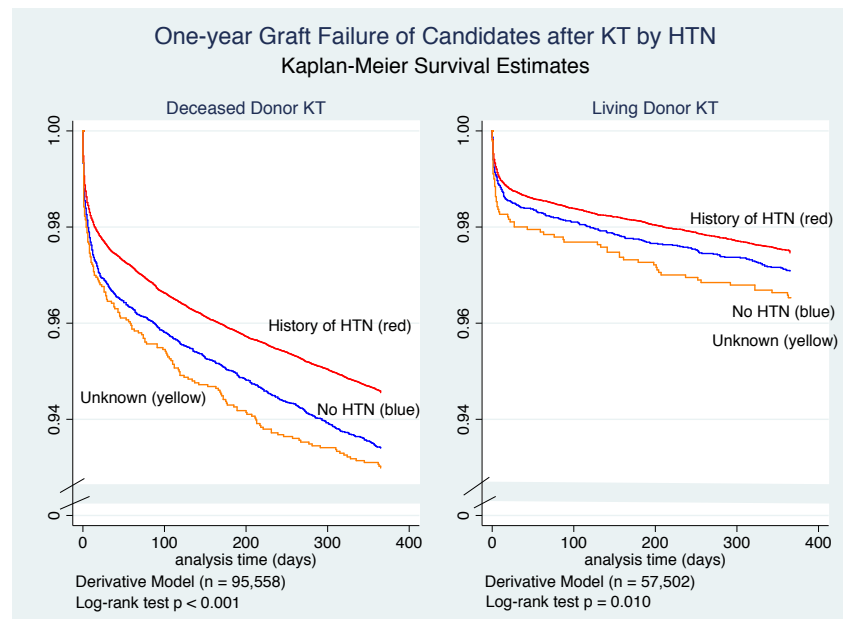
Figure 51.   One-year death of candidates after KT by hypertension (HTN)

One-year Death of Candidates after KT by HTN
Kaplan-Meier Survival Estimates
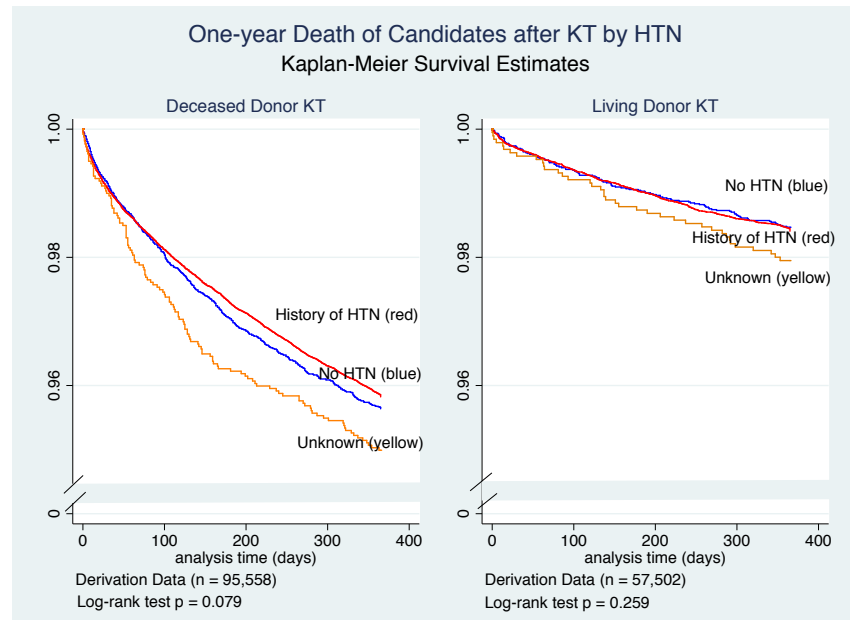
h.   **Immunological Factors**

1)   **ABO blood types**

For the reference group of A, the candidates with AB bloody type had 20% less risk of one-year graft failure in deceased donor KT, HR = 0.804 (95% CI = 0.701-0.921, p = 0.002), whereas, B type had a hazard ratio of 1.170 (95% CI = 1.003-1.365, p = 0.046) in living donor KT when compared to A type (shown in Figure 52). However, it should be noted that none of the ABO types were a significant predictor of one-year patient death in both deceased- and living- donor KT (shown in Figure 53).

Figure 52.   One-year graft failure of candidates after KT by ABO blood types
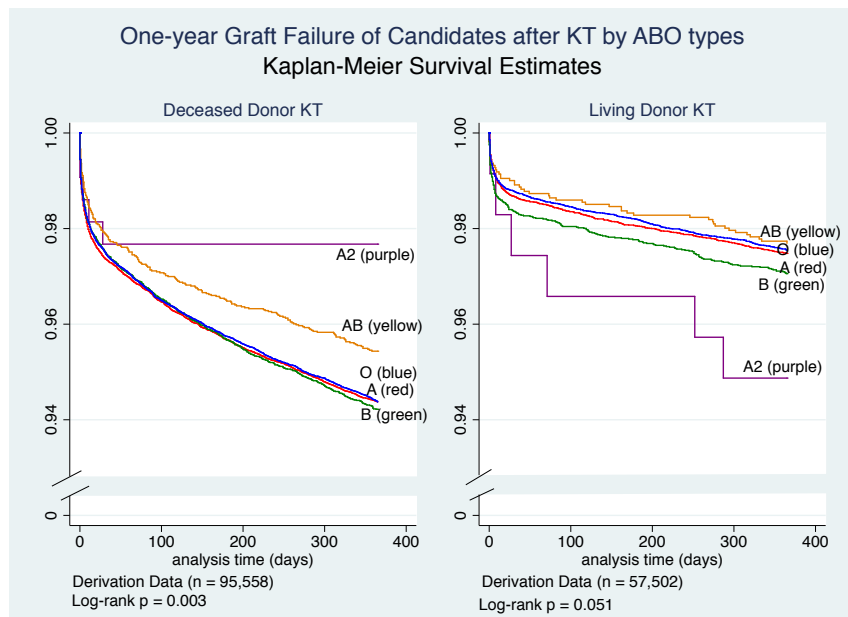
Figure 53.   One-year death of candidates after KT by ABO blood types
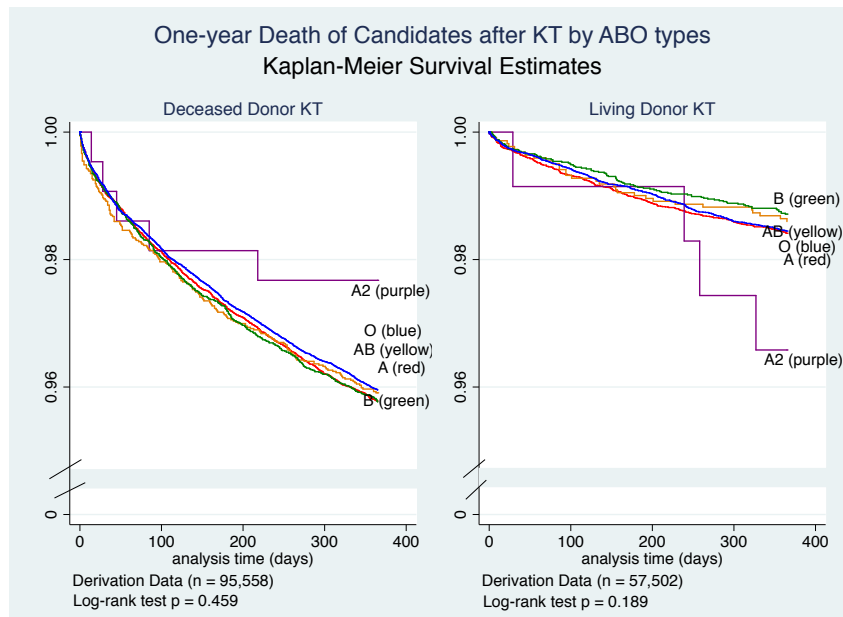
2) **ABO incompatibility in living donor kidney transplantation**

When it comes to ABO incompatibility, patients who underwent kidney transplantation with an ABO incompatible donor had a hazard ratio of 2.502 or 71% that they would encounter graft failure in a shorter duration than patients who received kidneys from ABO compatible donors (95% CI = 1.772 - 3.532, $p < 0.001$) (shown in Figure 54). The hazard ratio for one year death of ABO incompatibility in living donor KT for the reference group of ABO compatible KT was also significant (HR = 1.838, 95% CI = 1.104-3.062, $p = 0.019$) (shown in Figure 55).

Figure 54.　One-year graft failure after KT by ABO blood types compatibility
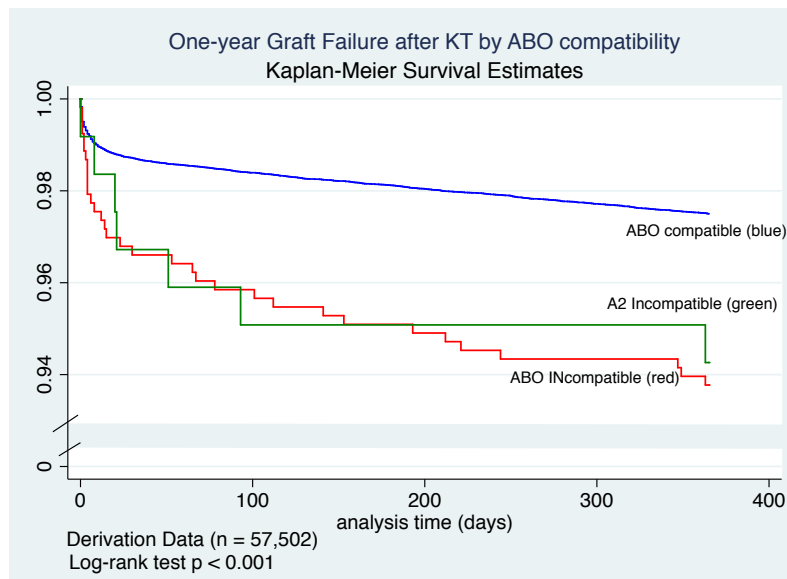
Figure 55.   One-year death after KT by ABO blood types compatibility
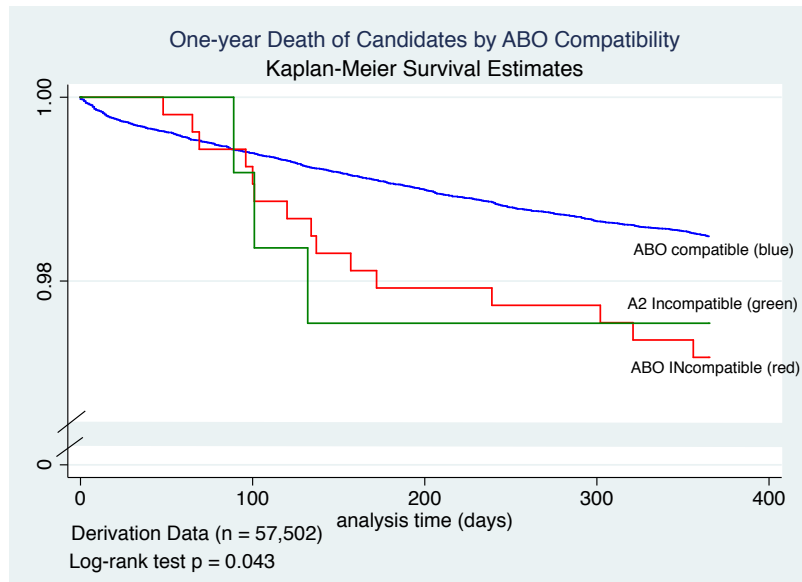
3)   **Panel reactive antibody**

For deceased donor KT recipients, a 1% increase in PRA increases the hazard of a graft failure by 0.2%, HR = 1.002 (95% CI = 1.002-1.003, $p < 0.001$). However, highly sensitized patients (PRA ≥ 80%) encountered a hazard 22% greater than patients with low PRA (< 80%), HR = 1.217 (95% CI = 1.129-1.312, $p < 0.001$). In terms of living donor KT, PRA increased the hazard by 0.6% by every one percentage of PRA, HR = 1.006 (95% CI = 1.004-1.008, $p < 0.001$) and high sensitized patients (PRA ≥ 80%) had a hazard of graft failure 80% greater than patients with low PRA (< 80%), HR = 1.812 (95% CI = 1.505-2.183, $p < 0.001$) (shown in Figure 56).

Figure 56.   One-year graft failure of candidates after KT by panel reactive antibody (PRA)
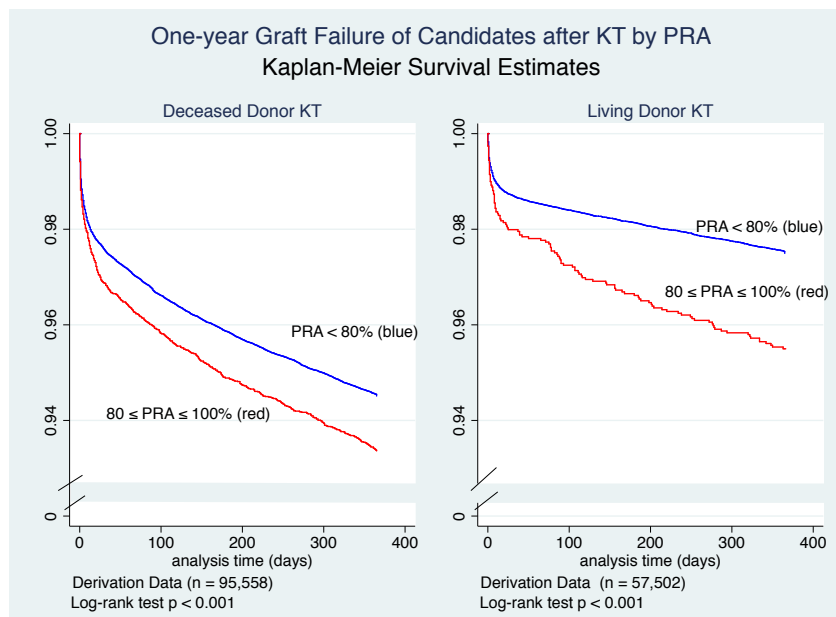
The degree (%) of PRA did not impact one-year patient death significantly, HR = 1.000 (95% CI = 0.999-1.001, p = 0.451). In contrast, highly sensitized living donor KT recipients encountered one-year patient death with a hazard ratio of 1.733 (95% CI = 1.357-2.212, p < 0.001) (shown in Figure 57).

Figure 57.　One-year death of candidates after KT by panel reactive antibody (PRA)
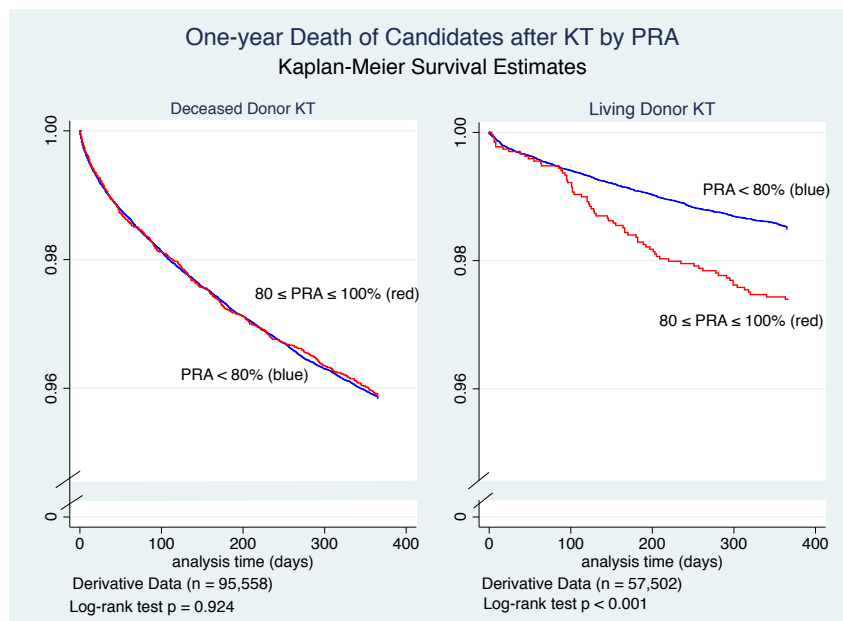
4)   **Human leukocyte antigen mismatching**

The higher degrees of human leukocyte antigen mismatching (HLA) had greater hazard ratios of one year graft failure and patient death with regard to zero antigen mismatching. For example, when it comes to one-year graft failure, the hazard ratio of two A antigen mismatching was 27% greater than that of zero A antigen mismatching, HR = 1.273 (95% CI = 1.175-1.379, $p < 0.001$). And the hazard ratio of two B and DR antigen mismatching was 1.406 (95% CI = 1.289-1.535, $p < 0.001$) and 1.500 (95% CI = 1.388-1.622, $p < 0.001$), respectively (shown in Figure 58, Figure 59, and Figure 60).

Figure 58.   One-year graft failure of candidates after KT by HLA-A mismatching
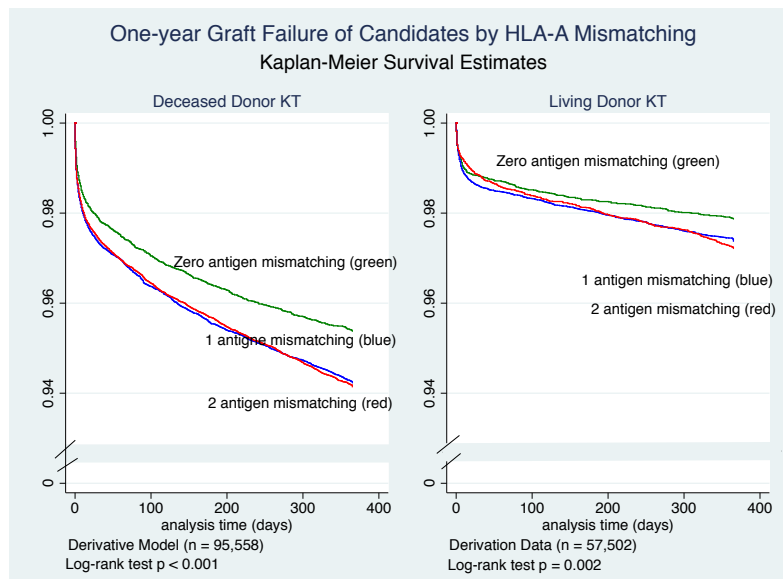
Figure 59.   One-year graft failure of candidates after KT by HLA-B mismatching
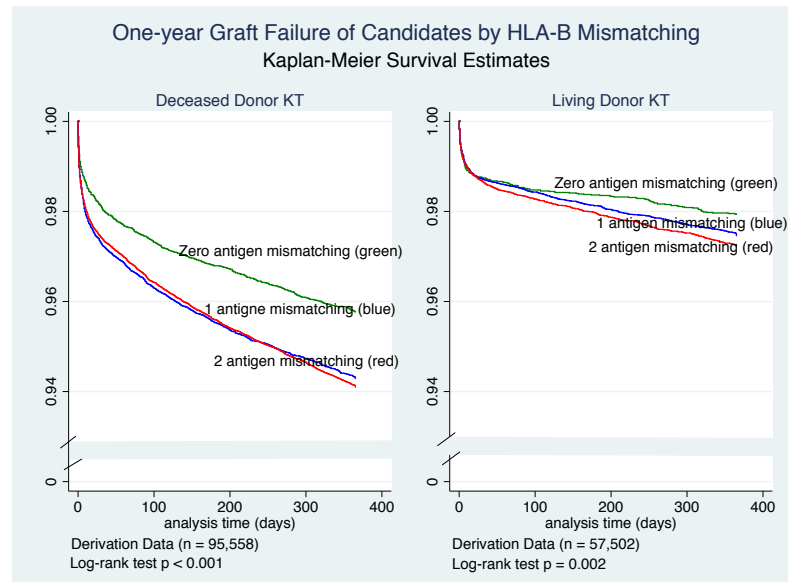
Figure 60.   One-year graft failure of candidates after KT by HLA-DR mismatching
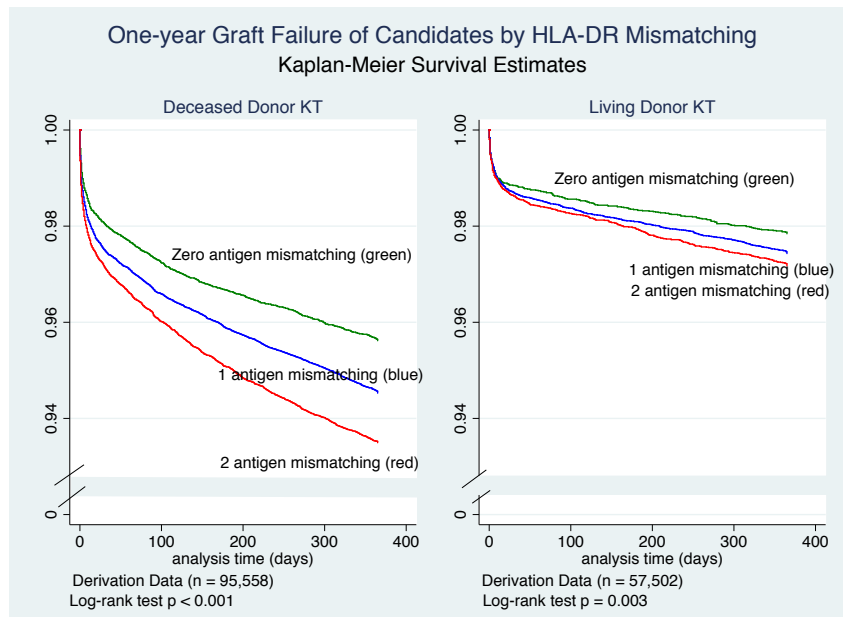
The negative impacts of human leukocyte antigen mismatching were also found in patient death for both living and deceased donor KT (shown in Figure 61 and Figure 62). And especially for HLA-DR mismatching, a larger degree of mismatch had a greater hazard rate for patient deaths (shown in Figure 63).

Figure 61.   One-year death of candidates after KT by HLA-A mismatching
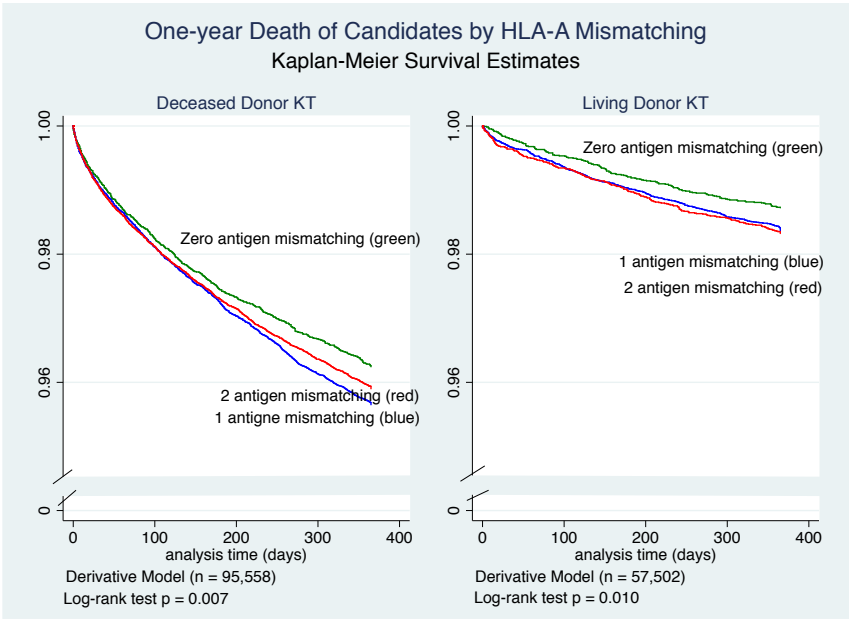
Figure 62.   One-year death of candidates after KT by HLA-B mismatching
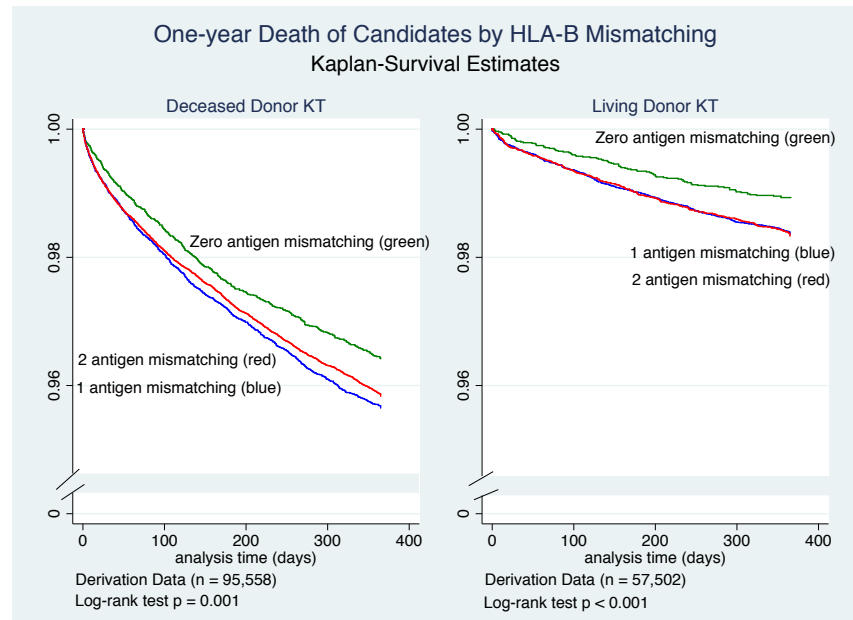
Figure 63.   One-year death of candidates after KT by HLA-DR mismatching
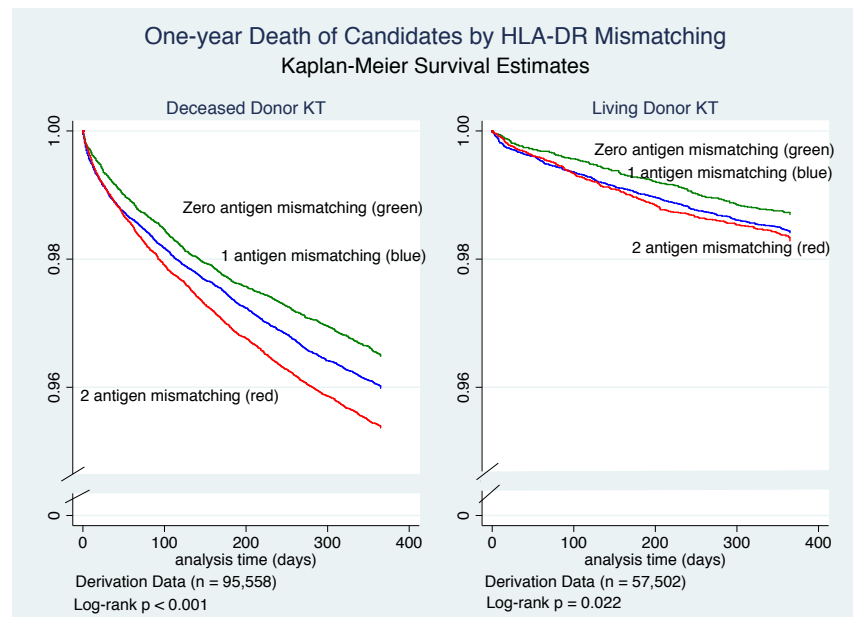
5)   **Donor-recipient relationship**

The relationship between donors and recipients affected one-year graft failure significantly. The hazard of one-year graft failure in living unrelated KT was approximately 1.15 times greater than that in living related KT, HR = 1.147 (95% CI = 1.035-1.271, p = 0.009) (shown in Figure 64). However, it is noteworthy that the relationship did not impact on one-year patient death in living donor KT (shown in Figure 65).

Figure 64.   One-year graft failure of candidates by donor-candidate relationship
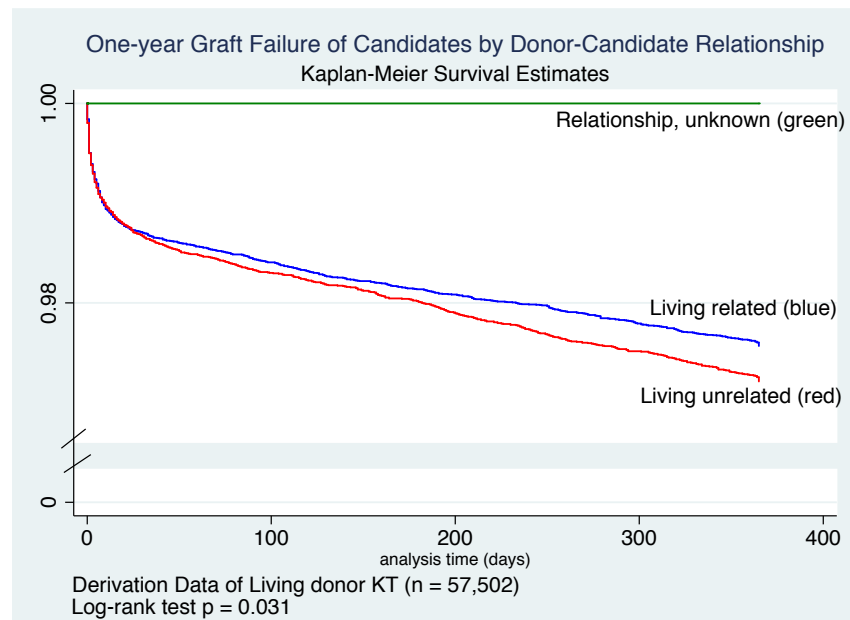
Figure 65.   One-year death of candidates by donor-candidate relationship
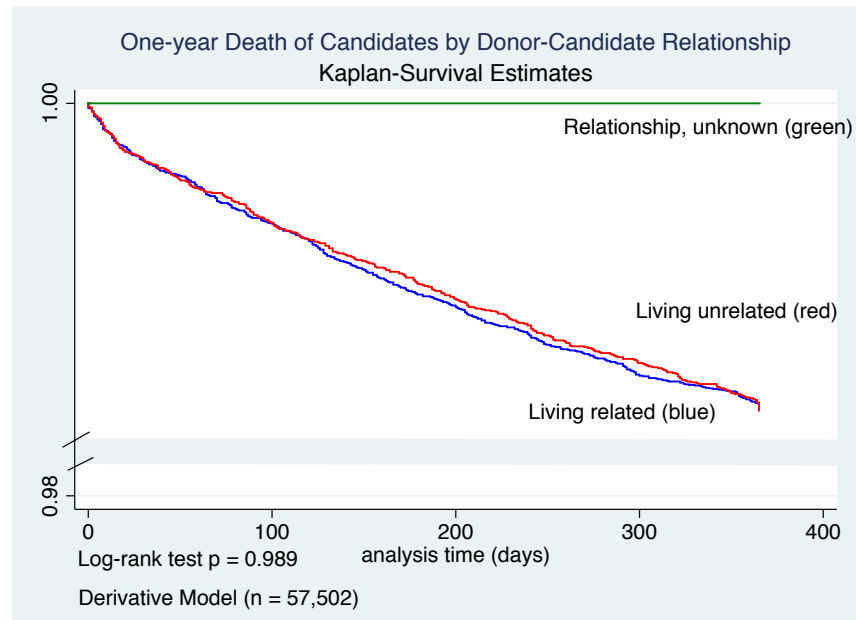
6)   **History of kidney transplantation**

For the deceased donor KT, the risk of graft failure of candidates with previous KT history is 1.4 times as high as that of candidates without KT history, HR = 1.388 (95% CI = 1.290 - 1.493, $p < 0.001$). And the risk of graft failure in the living donor KT was 1.2 times higher for the candidates who had KT previously compared with those without KT history, HR = 1.215, (95% CI 1.037-1.422, $p = 0.016$) (shown in Figure 66). However, KT history was not a significant predictor of patient death in 1 year after both deceased and living donor KT (shown in Figure 67).

Figure 66.   One-year graft failure of candidates after KT by KT history
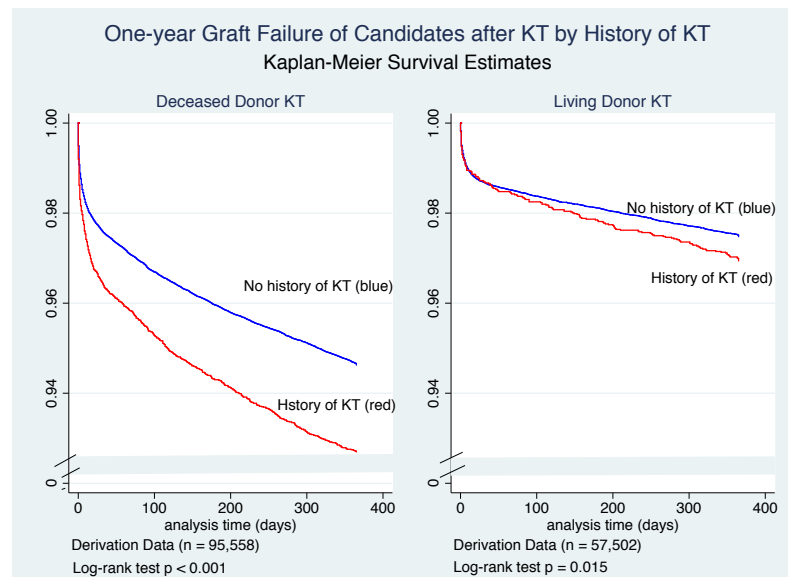
Figure 67.   One-year death of candidates after KT by KT history
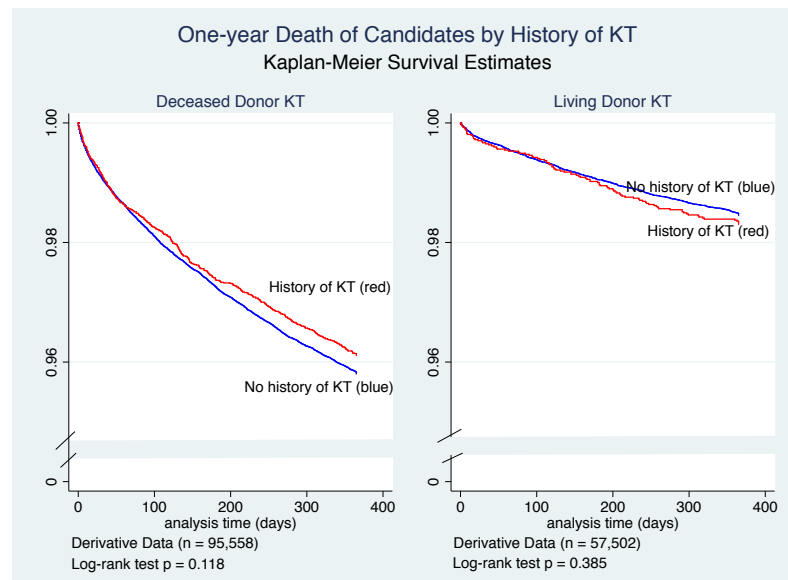
i.   **Age of candidates**

The ages of recipients at kidney transplantation were significant predictors of patient

death in both living and deceased donor KT. A one-year increase in age increased the hazard of patient death by

approximately 4% in deceased donor KT, HR = 1.039 (95% CI = 1.036-1.042, $p < 0.001$) and living donor KT,

HR = 1.043 (95% CI = 1.037-1.048, $p < 0.001$). For graft failure, a one-year increase in age was related to a 0.9%

decrease in the hazard in living donor KT, HR = 0.991 (95% CI = 0.986-0.995, $p < 0.001$), but age was not

associated with graft failure in deceased donor KT.

j. **Gender of candidates**

    Being female was associated with a 44% increase in the hazard of failure in kidney grafts

from living donors, HR = 1.453 (95% CI = 1.313-1.610, $p < 0.001$). However, gender did not impact graft failure

in deceased donor KT (shown in Figure 68).

Figure 68. One-year graft failure of candidates by gender
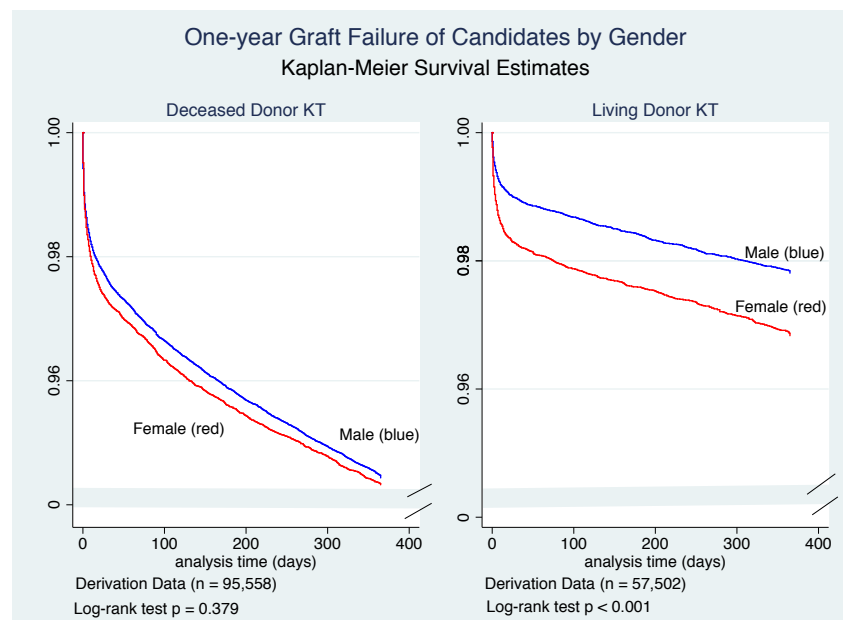
In deceased donor KT, for the reference group of male, the hazard rate of death for female was 15% less, HR = 0.840 (95% CI = 0.788-0.897, $p < 0.001$). And in living donor KT, the female group had 17% decrease in hazard of death, HR = 0.827 (95% CI = 0.722-0.949, $p = 0.007$) compared with that of male (shown in Figure 69).

Figure 69.   One-year death of candidates by gender
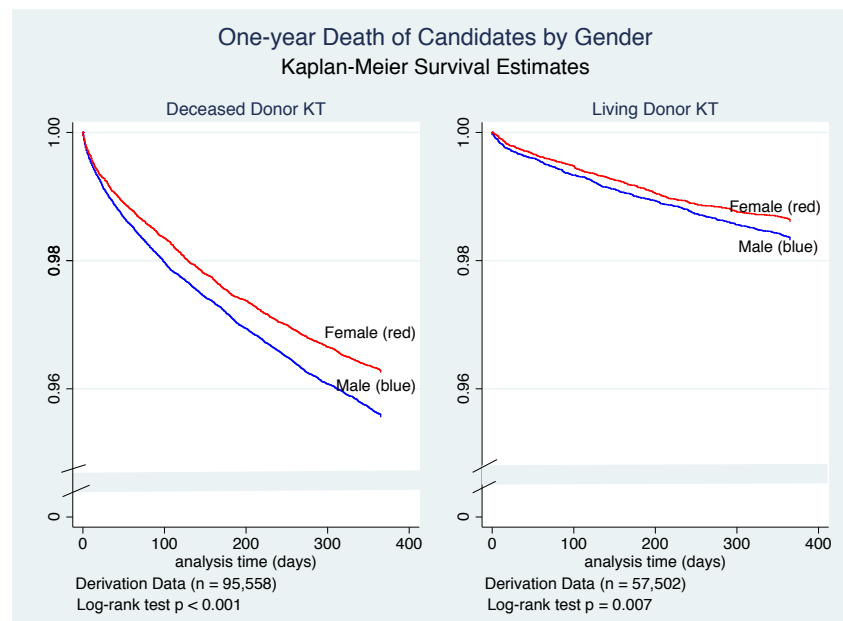
k.   **Race/ethnicity of candidates**

Race/ethnicity was a relevant factor for one-year kidney graft failure in both deceased and living donor KT. When it compared with a Caucasian population, a Black population had a relative increase of 27% ($p < 0.001$) and 32% ($p < 0.001$) in the hazard of graft failure if they received kidneys from deceased and living donors, respectively. In deceased donor KT, the risk of graft failure was 17% less among the Hispanic/Latino population when compared with a Caucasian population. However, the risk of living donor kidney graft failure was not different between a Caucasian and Hispanic/Latino population (shown in Figure 70).

Figure 70.   One-year graft failure of candidates by race/ethnicity
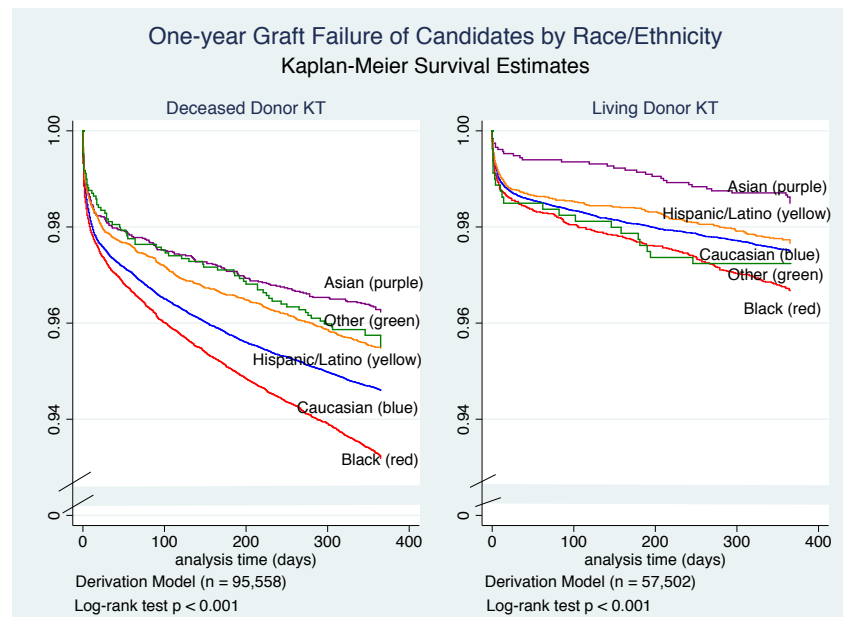
However, when it comes to one-year death, the Black population did not show a relatively high risk. Black population had a relatively 11% less hazard of patient death compared with that of a Caucasian population when undergoing deceased donor KT. In living donor KT, Black race/ethnicity did not impact on patient death significantly, HR = 1.084 (95% CI = 0.906-1.298, p = 0.378). For one-year death, the Hispanic/Latino group had an approximately relatively 27% less hazard of patient death compared with a Caucasian population in both living and deceased donor KT: Deceased donor KT: HR = 0.731 (95% CI = 0.612-0.809, p < 0.001); Living donor KT: HR = 0.707 (95% CI = 0.567-0.881, p = 0.002). It should be noted that Caucasian patients showed the increase in hazard of death compared with other race/ethnicity group (shown in Figure 71).

Figure 71.   One-year death of candidates by race/ethnicity
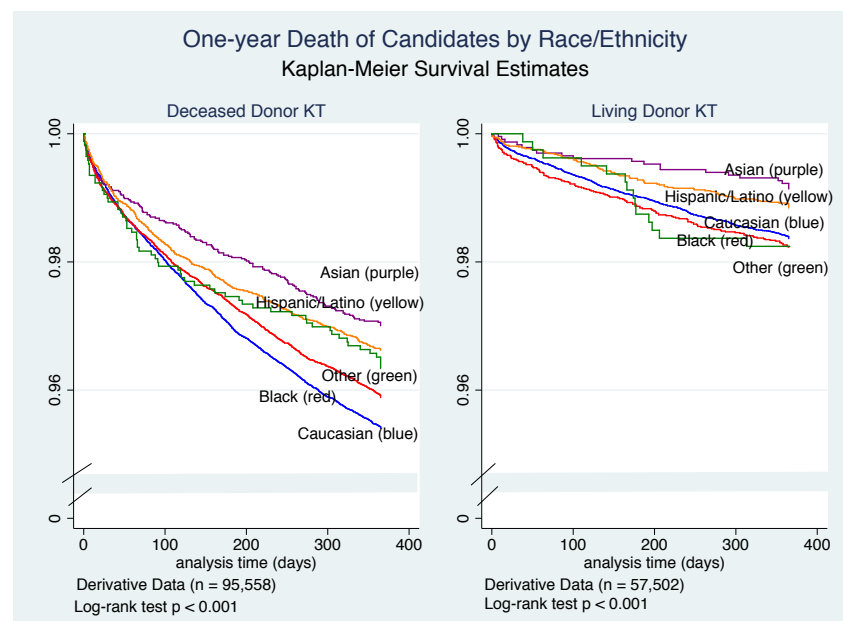
l.   **Causes of end stage renal diseases**

While the causes of end-stage renal disease impacted kidney graft failure and patient death, the degrees of impact varied according to donor type and diseases. In deceased donor KT, polycystic kidney disease was associated with a relatively 25% less hazard of graft failure with regard to diabetic nephropathy, HR = 0.754 (95% CI = 0.669-0.849, p < 0.001). In contrast, tubular and interstitial disease was related to about a 21% greater hazard of graft failure when compared with diabetic nephropathy (95% CI = 1.062-1.386, p = 0.004). In living donor KT, compared with diabetic nephropathy, glomerular disease and tubular/interstitial disease were associated with relatively greater 37- 60% risk of graft failure (shown in Figure 72).

Figure 72.   One-year graft failure of candidates by causes of ESRD
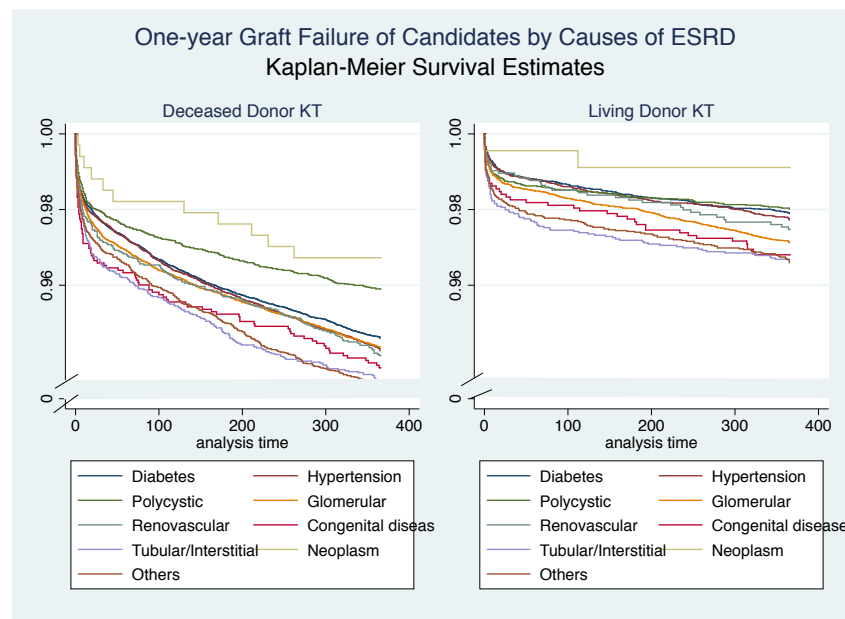
In contrast to graft failure, ESRD caused by hypertension nephropathy/nephroscleroiss, polycystic kidney disease, glomerular disease, and renovascular disease had a less hazard for one-year death in both deceased and living donor KT compared with that caused by diabetic nephropathy (shown in Figure 73). For example, glomerular disease was associated with a less than 50% hazard of patient death in both deceased and living donor KT: Deceased donor KT: HR = 0.467 (95% CI = 0.425-0.512, $p < 0.001$); Living donor KT: HR = 0.378 (95% CI = 0.315-0.453, $p < 0.001$).

Figure 73.   One-year death of candidates by causes of ESRD
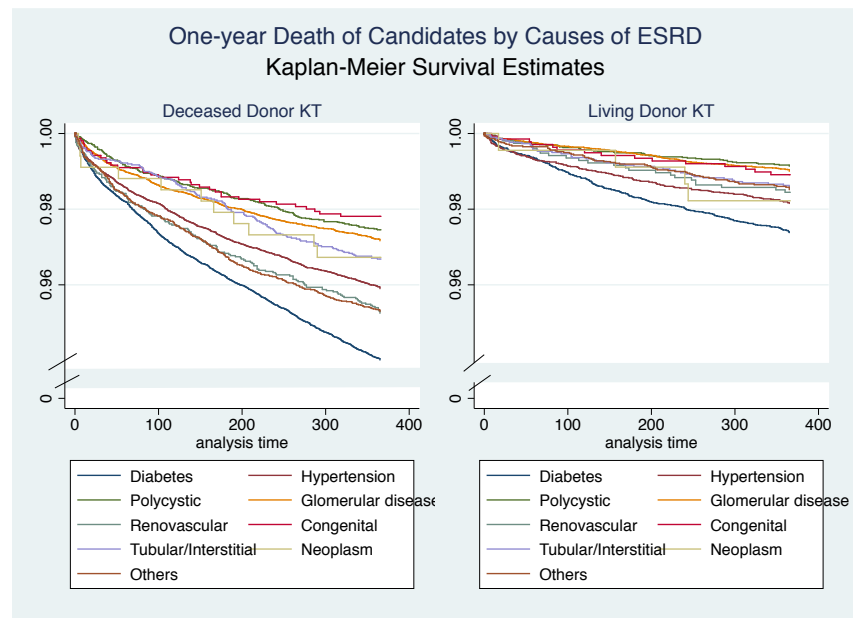
m. **Dialysis types and duration of candidates**

Regardless of type, dialysis therapies prior to KT such as hemodialysis or peritoneal dialysis were significant predictors of graft failure and patient death. In deceased donor KT, patients who had hemodialysis and peritoneal dialysis had about 2.07 times higher one-year graft failure first compared with patients without dialysis therapy prior to KT, Hemodialysis (HR = 2.069, 95% CI = 1.847-2.316, $p < 0.001$); Peritoneal dialysis (HR = 1.943, 95% CI = 1.661-2.274, $p < 0.001$) (shown in Figure 74). In living donor KT, these renal replacement therapies were also associated with graft failure by about 60 and 80% hazard rates, Hemodialysis (HR = 1.614, 95% CI = 1.396-1.866, $p < 0.001$); Peritoneal dialysis (HR = 1.819, 95% CI = 1.437-2.304, $p < 0.001$).

Figure 74. One-year graft failure of candidates by dialysis types
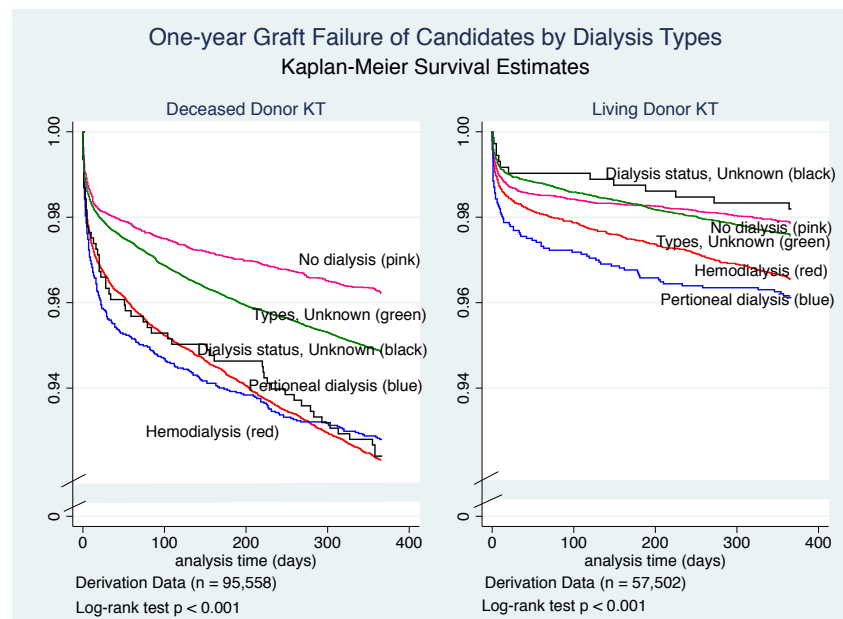
In deceased donor KT, the risk of patient death was 85% and 55% higher among patients who underwent hemodialysis and peritoneal dialysis therapy, respectively: Hemodialysis: HR = 1.856 (95% CI = 1.636-2.107, $p < 0.001$); Peritoneal dialysis therapy: HR = 1.558 (95% CI = 1.294-1.875, $p < 0.001$) (shown in Figure 75). However, in living donor KT, the hazard ratio of death was about 2.5 times higher in patients with dialysis therapies compared those who did not have dialysis therapies: Hemodialysis: HR = 2.500 (95% CI = 2.059-3.036, $p < 0.001$), Peritoneal dialysis: HR = 2.374 (95% CI = 1.734-3.250, $p < 0.001$).

Figure 75.   One-year death of candidates by dialysis types
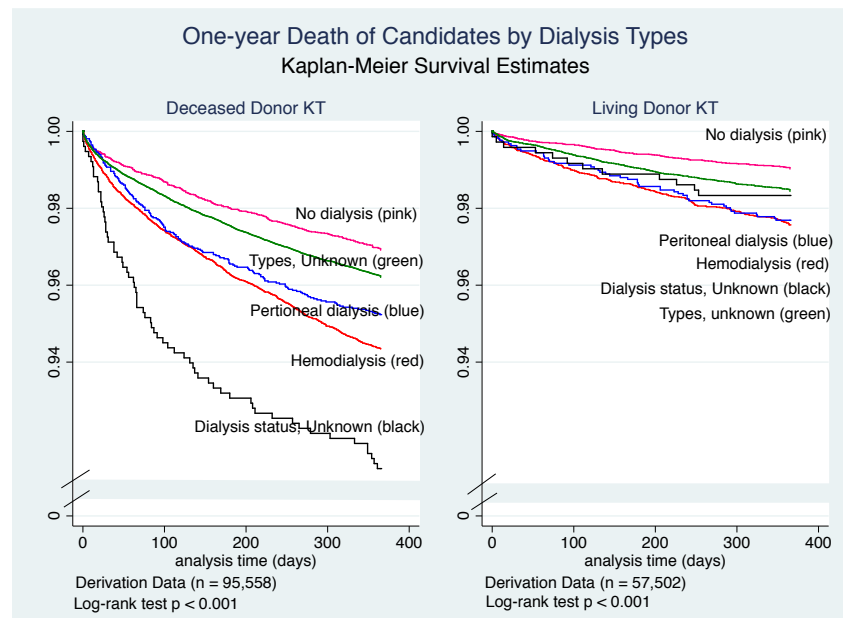
A one-year increase in dialysis duration increased the hazard of graft failure by approximately 4% in both deceased and living donor KT, Hemodialysis: HR = 1.043 (95% CI = 1.037-1.050, $p < 0.001$); Peritoneal dialysis: HR = 1.048 (95% CI = 1.031-1.066, $p < 0.001$). Especially for patients who had dialysis therapies greater than 10 years, they had more than two times the hazard in graft failure compared to

those with dialysis therapies of less than one year, Deceased donor KT; HR = 2.194 (95% CI = 1.945-2.474, $p <$ 0.001); Living donor KT: HR = 2.492 (95% CI = 1.710-3.633, $p < 0.001$).

n.   **Kidney transplant procedures**

Compared to left sided kidney transplantation, right sided kidney transplantation had a relative increase of 7% and 40% in graft failure of deceased donor KT and living donor KT, respectively, Deceased donor KT: HR = 1.077 (95% CI = 1.020-1.138, $p = 0.008$); Living donor KT: HR = 1.395 (95% CI = 1.220-1.597, $p < 0.001$) (shown in Figure 76). The risk of graft failure was 64% higher among patients who received en-black kidney transplantation surgery than among those who received left sided kidney, however, the risk of patient death was 46.1% lower among those who received en-black kidney transplantation surgery, HR = 0.539 (95% CI = 0.391-0.743, $p < 0.001$) (shown in Figure 77).

Figure 76.   One-year graft failure of candidates by transplant procedure
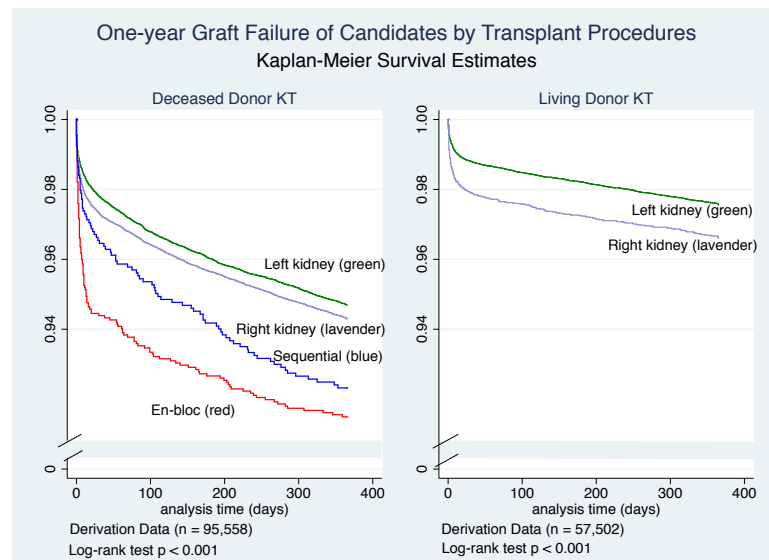
Figure 77.   One-year death of candidates by transplant procedure
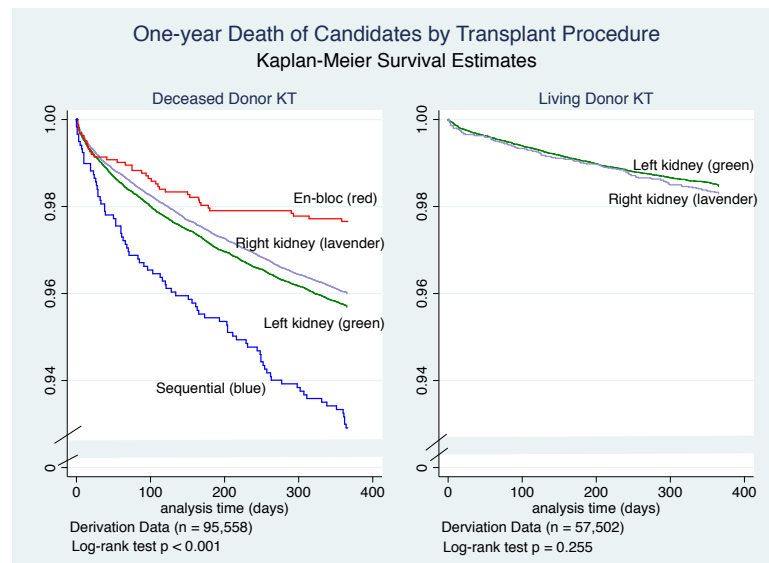
o.   **Donor age, gender, and race/ethnicity**

A one-year increase in donor's age increased the hazard of one-year graft failure and

patient death by approximately 1% in both deceased and living donor KT. The kidneys from female donors were

associated with an increase in the hazard of one-year graft failure and patient death in both deceased and living

donor KT. Compared with the kidneys from Caucasian donor, the kidneys from the Black population had the risk

of one-year graft failure 126% higher in deceased donor KT ($p < 0.001$) and 140% higher in living donor kidney

transplantation ($p < 0.001$) (shown in Figure 78). However, risk of one-year death approximately equal in both the

Caucasian and Black group (shown in Figure 79).

Figure 78.   One-year graft failure of candidates by donor's race/ethnicity
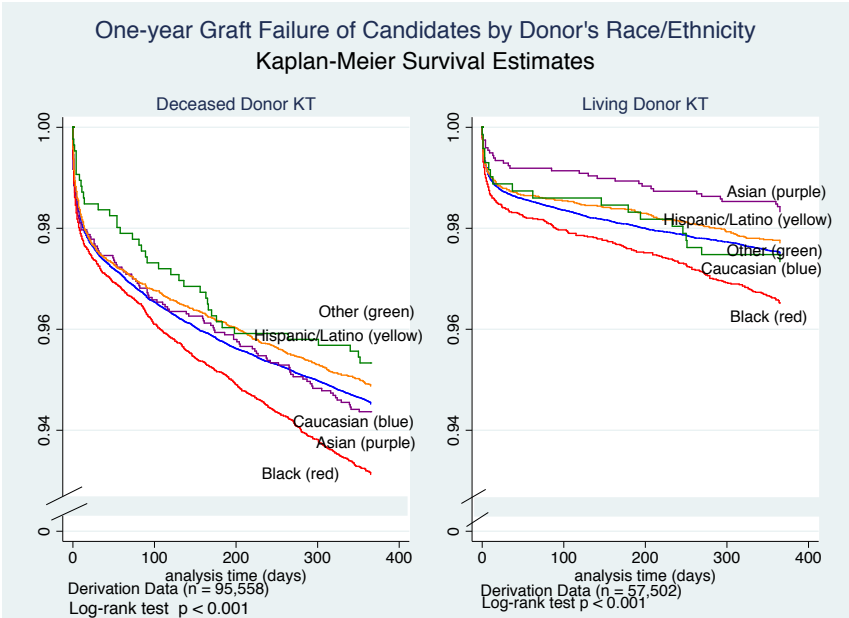
Figure 79.   One-year death of candidates by donor's race/ethnicity
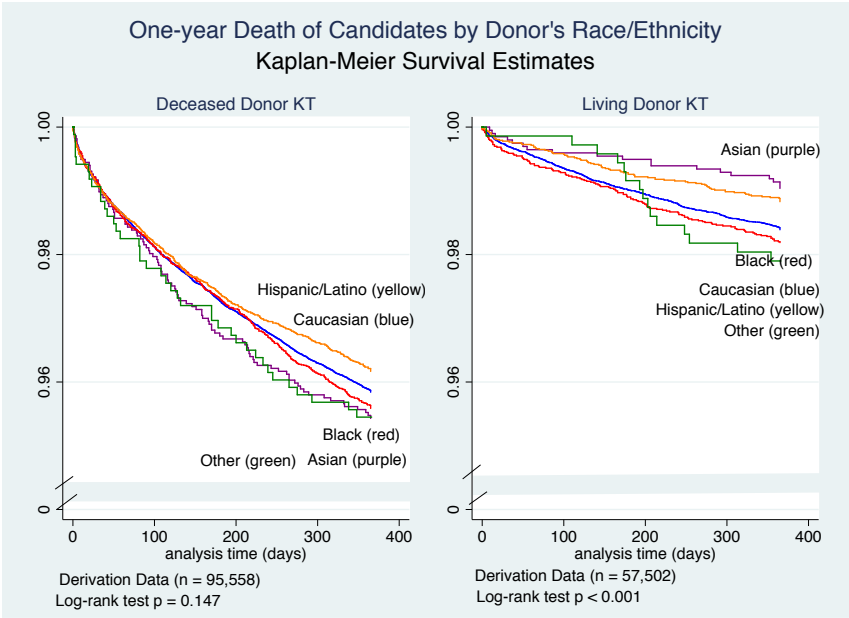
p.   **Estimated glomerular filtration rate**

Kidney functions defined by estimated glomerular filtration rates were relevant factors of graft failure and patient death. For deceased donor KT, kidneys from the donors with GFR 30-44 or moderate to severely decrease kidney function had a relative increase of 48% in graft failure compared with kidneys from donors with normal kidney functions, HR = 1.482 (95% CI = 1.231-1.612, $p < 0.001$). And the risk of graft failure was 36% higher among patients who received a kidney from living donors with GFR 45-59 or mild to moderately decreased kidney functions, HR = 1.357 (95% CI = 1.073-1.715, $p < 0.011$) (shown in Figure 80).

Figure 80.   One-year graft failure of candidates by donor's eGFR

One-year Graft Failure of Candidates by Donor's eGFR
Kaplan-Meier Survival Estimates
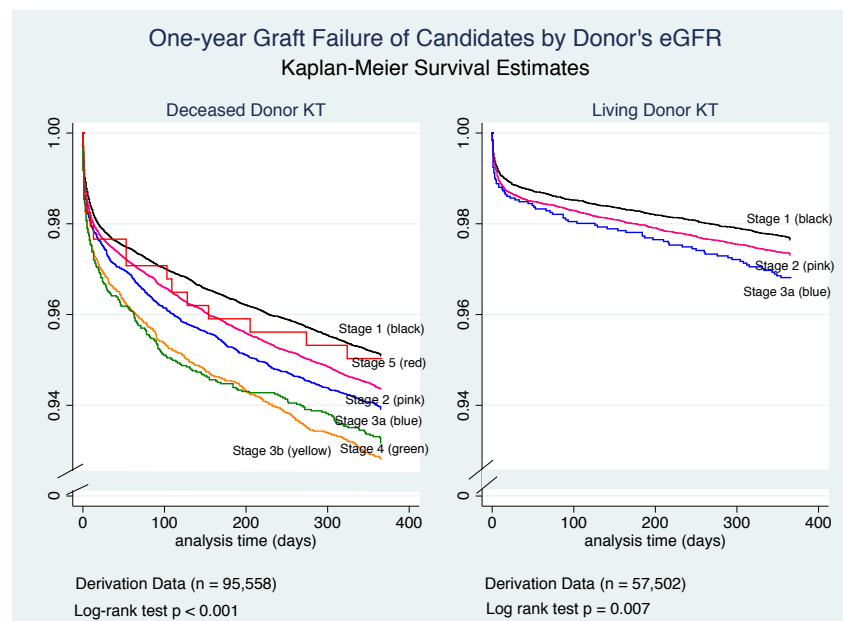
Compared with normal function of donated kidneys, patients who received kidneys from deceased donors with GFR 30-44 or moderate to severely decreased kidney function had a 33% probability to encounter death first, HR = 1.331 (95% CI = 1.185-1.496, $p < 0.001$). And a kidney from living donors with GFR 45-59 or mild to moderately decreased kidney function had a 70% probability of facing death first, HR = 1.701 (95% CI = 1.276-2.267, $p < 0.001$) (shown in Figure 81).

Figure 81.   One-year death of candidates by donor's eGFR

One-year Death of Candidates by Donor's eGFR
Kaplan-Meier Survival Estimates
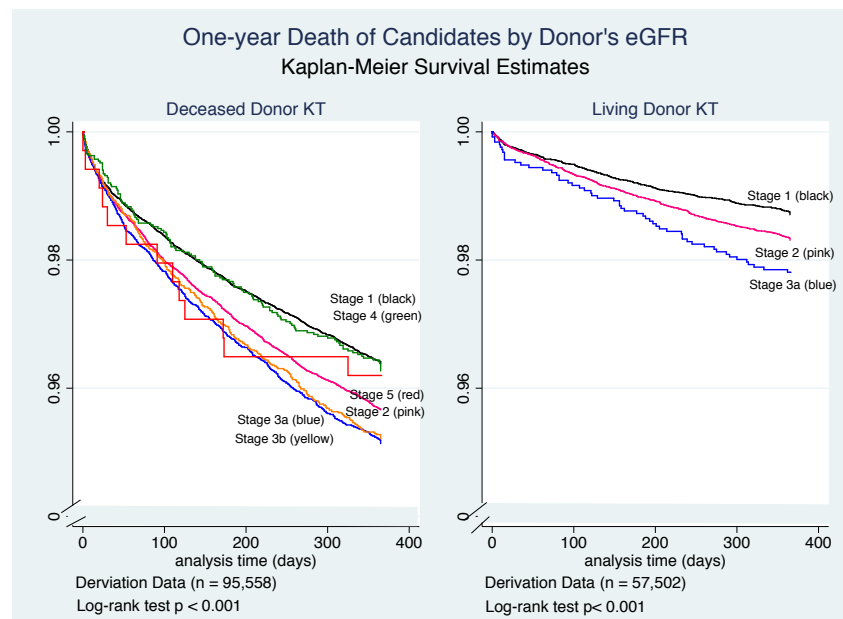
q.   **Hypertension and diabetes of donors**

Unlike living donor KT, a history of donor hypertension was associated with KT outcomes in deceased donor KT. For example, in kidneys from deceased donors with hypertension greater than 10 years, the risk of graft failure was 205.5% higher than for kidneys from donors without hypertension, $HR = 2.055$ (95% CI = 1.858-2.272, $p < 0.001$) (shown in Figure 82).

Figure 82.   One-year graft failure of candidates by donor's HTN
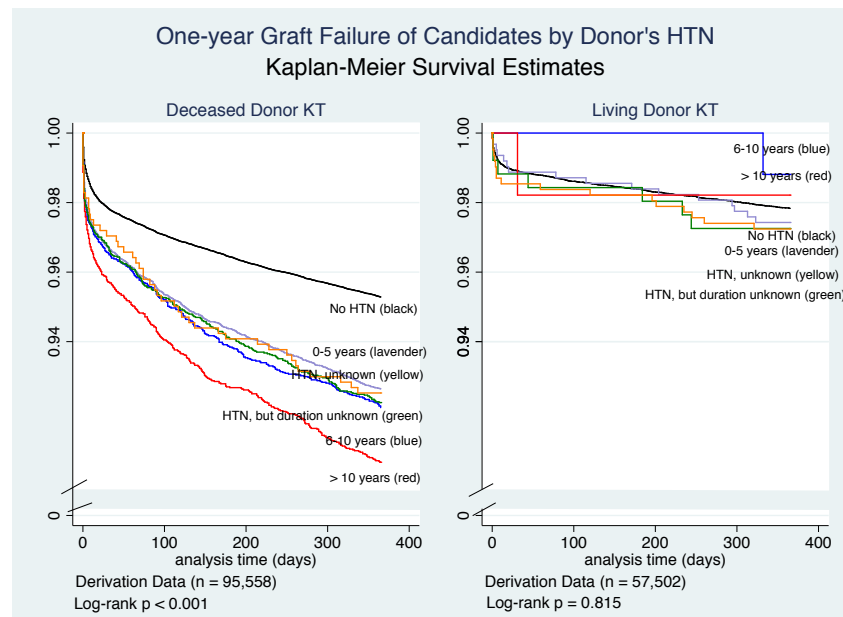
Whereas, the risk of death was 55% higher among the same donors compared with among deceased donors without hypertension, 1.555 (95% CI = 1.369-1.767, *p* < 0.001) (shown in Figure 83).

Figure 83.   One-year death of candidates by donor's HTN
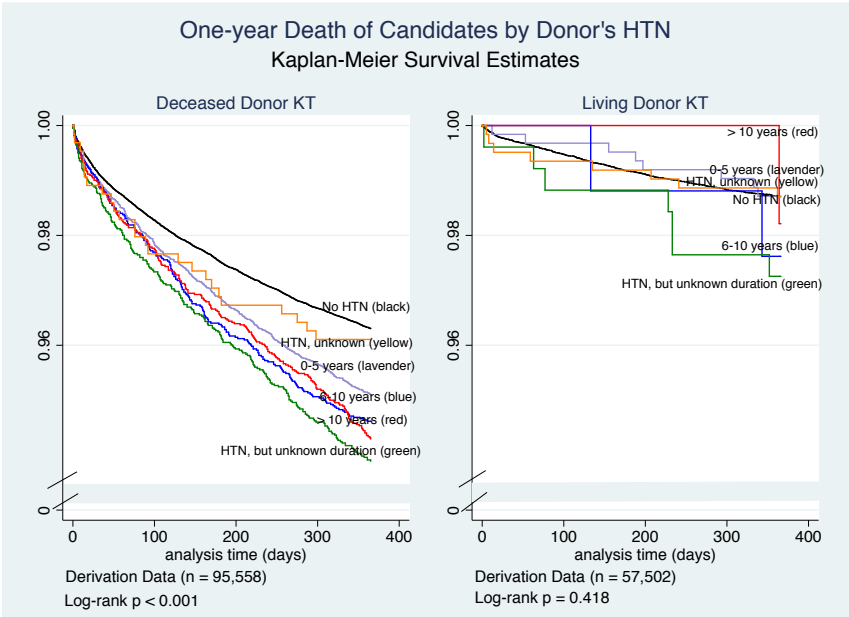
Likewise hypertension, a long-term history of diabetes was significantly associated with poor outcomes in deceased donor KT (shown in Figure 84 and Figure 85).

Figure 84.   One-year graft failure of candidates by deceased donor's diabetes
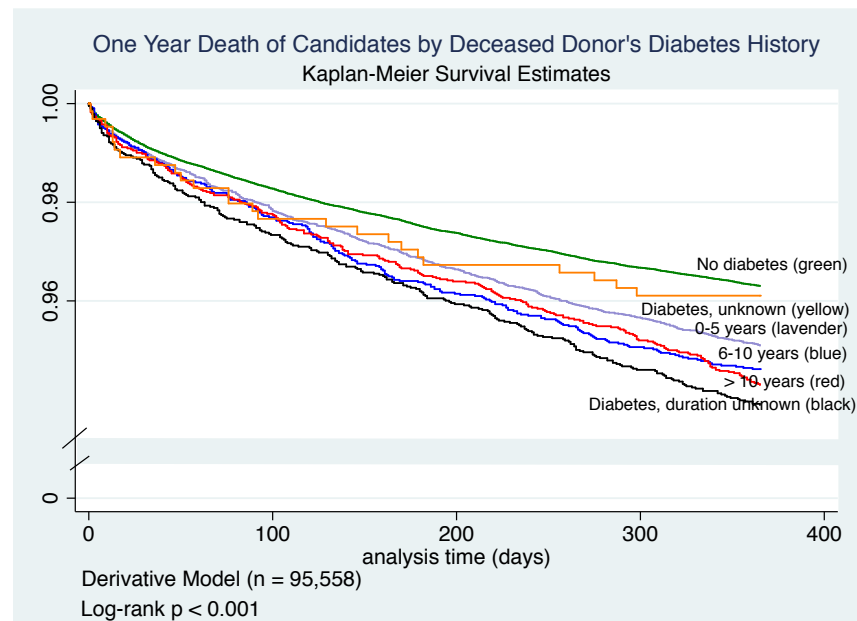
Figure 85.   One-year death of candidates by deceased donor's diabetes
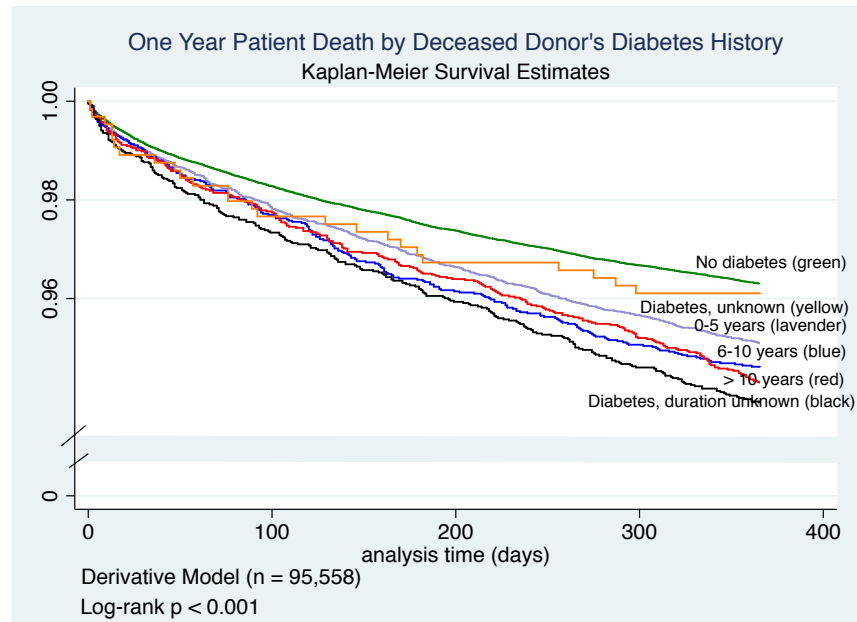
r. **Hepatitis C virus infection (HCV)**

Donor's hepatitis C infection was not associated with risk of one-year graft failure significantly (shown in Figure 86). However, the risk of one year death in the candidates who received kidneys from the deceased donors with HCV was 1.7 times higher than those donated by non-HCV deceased donors, HR = 1.704 (95% = 1.451-2,001, $p < 0.001$) (shown in Figure 87).

Figure 86.   One-year graft failure of candidates by donor's hepatitis C virus infection
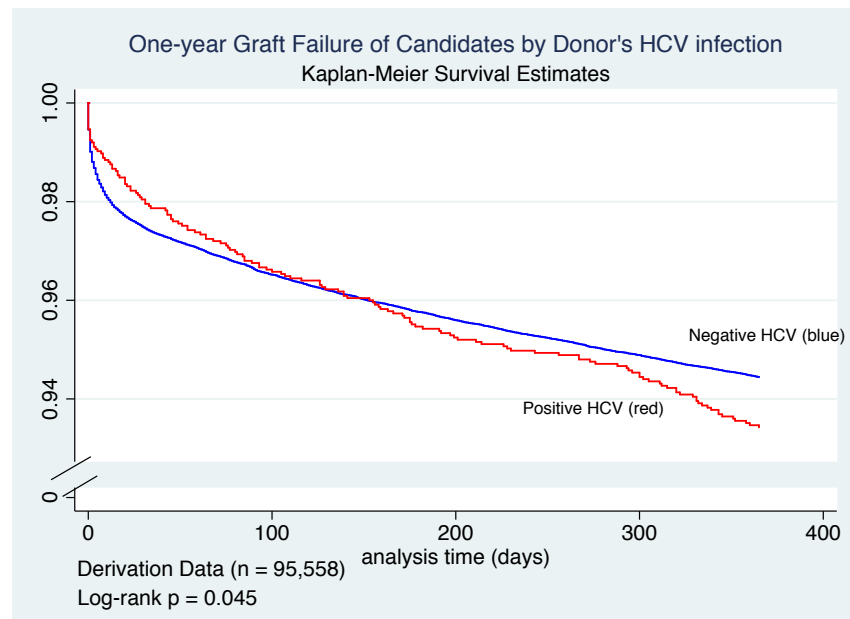
Figure 87.   One-year death of candidates by donor's hepatitis C virus infection

One-year Death of Candidates by Donor's Hepatitis C virus infection
Kaplan-Meier Survival Estimates

Negative HCV (blue)

Positive HCV (red)

analysis time (days)

Derivation Model (n = 95,558)
Log-rank p < 0.001
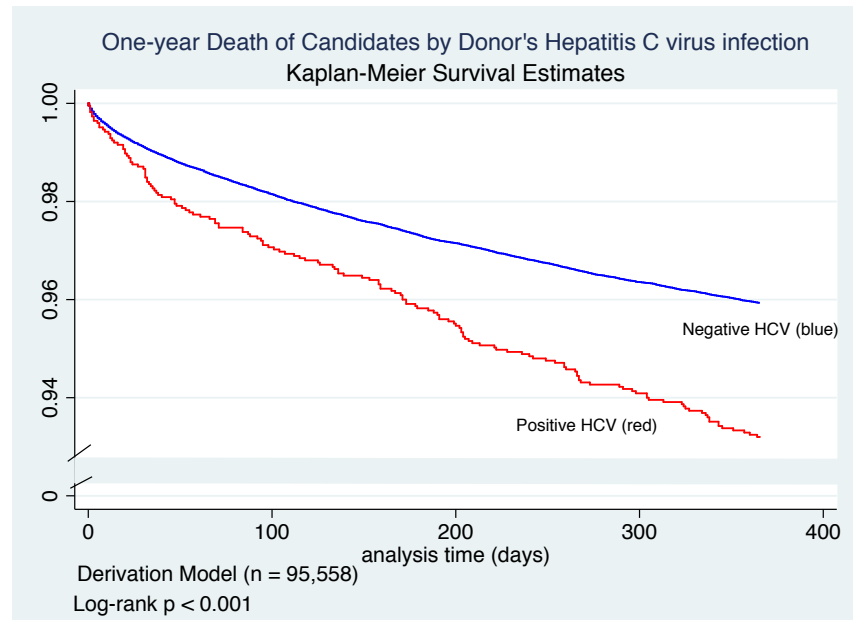
s.   **Death circumstances**

When it comes to the deceased donor KT, the circumstances of donor death impacted

outcomes significantly. For example, compared with anoxia, donors who died from stroke or cerebrovascular

disease were associated with greater hazard of graft failure, HR = 1.607 (95% CI = 1.490-1.733, $p < 0.001$) and

patient death, HR = 1.652 (95% CI = 1.510-1.807, $p < 0.001$) (shown in Figure 88 and Figure 89).

Figure 88.   One-year graft failure of candidates by deceased donor's causes of death

One-year Graft Failure of Candidates by Deceased Donor's Causes of Death
Kaplan-Meier Survival Estimates
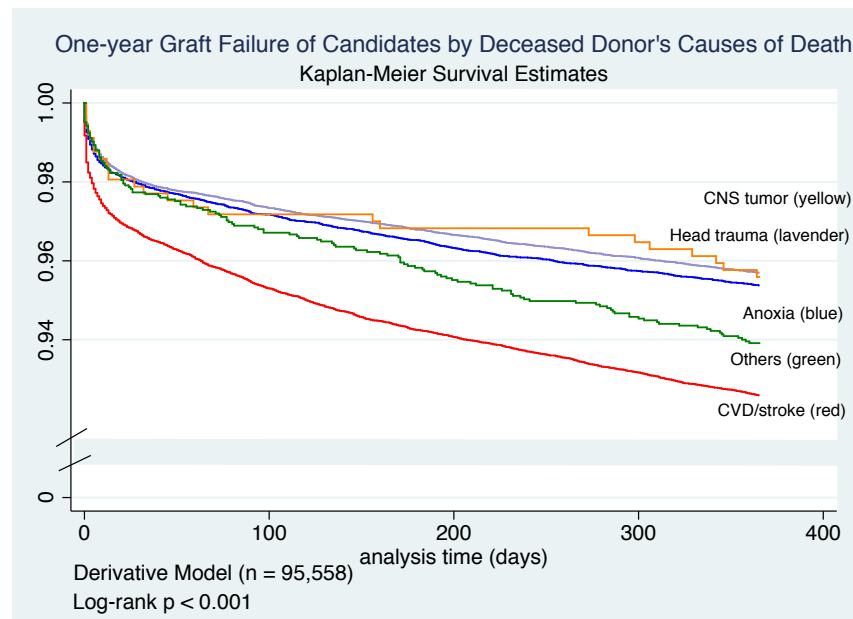
Figure 89.   One-year death of candidates by deceased donor's cause of death
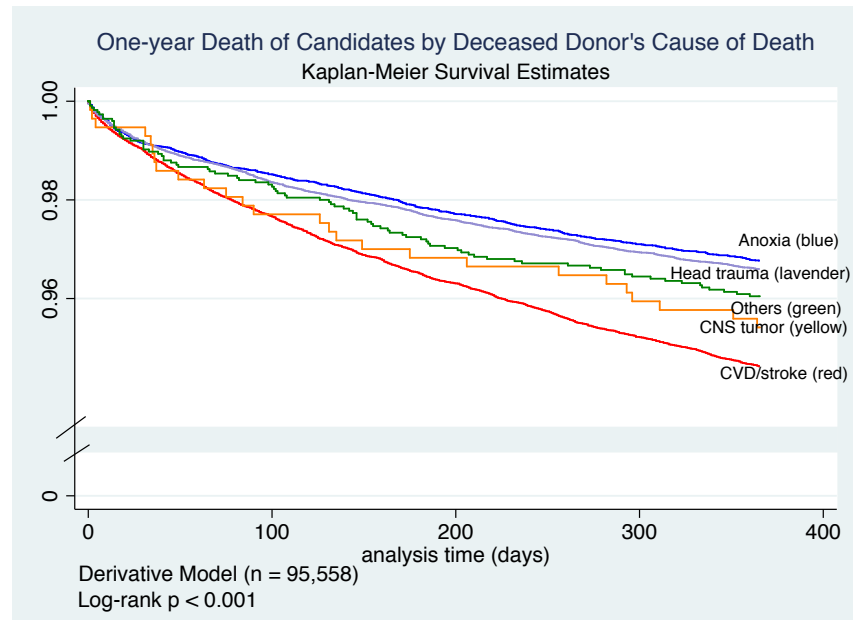
And kidneys from donors who donated kidneys after cardiac death had a 10% increase in hazard of graft failure compared with those prior to cardiac death, HR = 1.098 (95% CI = 1.009-1.195, *p* = 0.028) (shown in Figure 90). However, either donated kidneys prior or after cardiac death was not significantly associated with patient death (shown in Figure 91).

Figure 90.   One-year graft failure of candidates by donated kidneys after cardiac death
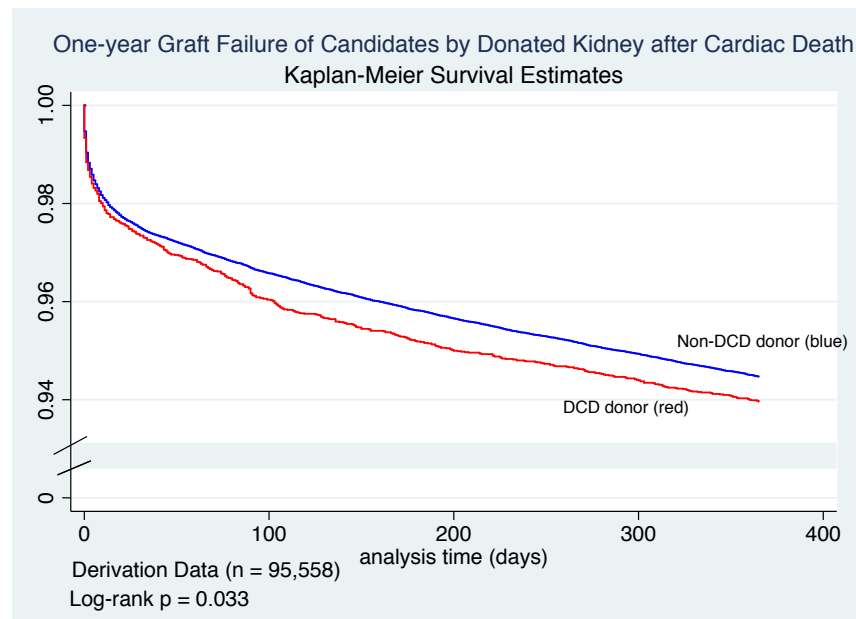
Figure 91.　　One-year patient death of candidates by donated kidneys after cardiac death

One-year Death of Candidates by Donated Kidneys after Cardiac Death
Kaplan-Meier Survival Estimates

DCD donor (red)

Non-DCD donor (blue)

Derivative Data (n = 95,558)　analysis time (days)
Log-rank p = 0.063
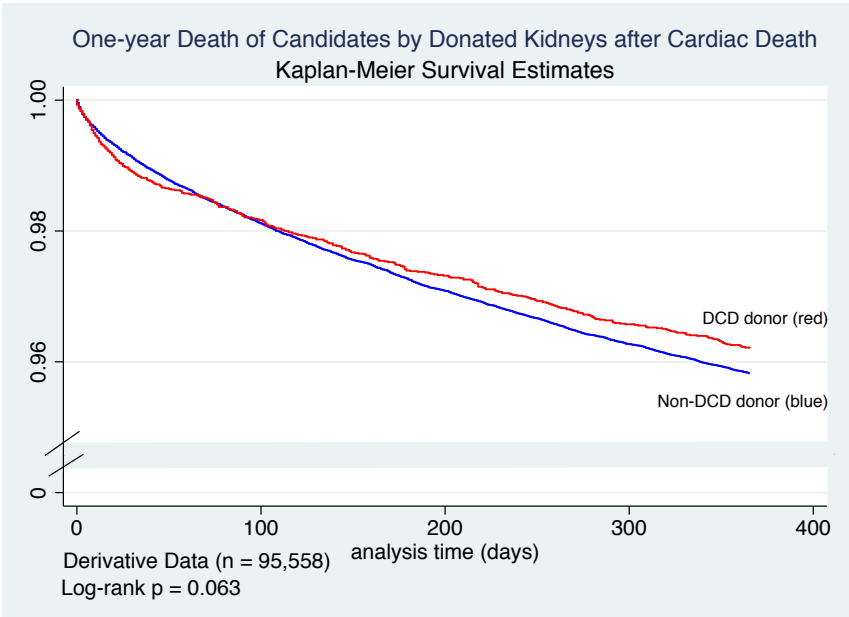
2.   **<u>Multivariate analyses</u>**

To develop the predictive and multivariate models, each variable which was significant at the 5 percent level ($p < 0.05$) by uni- and bi-variate analyses were entered to develop the four models: One-year graft failure model for deceased donor KT; One-year graft failure model for living donor KT; One-year patient death model for deceased donor KT; One-year patient death model for living donor KT (shown in Table 7, Table 8). Immunological and cardiovascular predictors were selected and added if the individual coefficient of predictors in the preliminary models indicated significant effects using p values of 0.05. When each factor was deleted, the p-value of the partial likelihood ratio was examined to assure that the deleted predictor was not a significant covariate.

TABLE VII

UNI-/BI-VARIATE AND MULTIVARIATE ANALYSIS FOR ONE-YEAR GRAFT FAILURE OF DERIVATION DATASETS

| | Deceased Donor Kidney Transplantation (Derivative Model) | | | | | | | Living Donor Kidney Transplantation (Derivative Model) | | | | | | |
| | Univariate | | | | Multivariate | | | Univariate | | | | Multivariate | | |
Variable	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p
Demographic														
Candidate age at transplant	- 0.002	0.998 (0.996-1.000)	0.106					- 0.011	0.989 (0.986-0.993)	< 0.001		- 0.011	0.989 (0.985-0.993)	< 0.001
Candidate gender														
Male		Reference		0.379					Referece		< 0.001			
Female	0.022	1.022 (0.968-1.079)	0.435					0.374	1.453 (1.313-1.610)	< 0.001		0.364	1.439 (1.287-1.609)	< 0.001
Candidate race/ethnicity														
Caucasian		Reference		< 0.001		Reference			Reference		< 0.001		Reference	
Asian	- 0.367	0.693 (0.601-0.798)	< 0.001		-0.404	0.667 (0.568-0.784)	< 0.001	- 0.522	0.593 (0.423-0.831)	0.002		-0.572	0.564 (0.344-0.924)	0.023
Black	0.237	1.268 (1.195-1.345)	< 0.001		0.120	1.128 (1.049-1.212)	0.001	0.279	1.322 (1.156-1.511)	< 0.001		-0.085	0.919 (0.691-1.223)	0.562
Hispanic/Latino	- 0.183	0.833 (0.763-0.910)	< 0.001		-0.214	0.807 (0.728-0.895)	< 0.001	- 0.075	0.928 (0.792-1.087)	0.353		0.025	1.025 (0.779-1.349)	0.861
Others	- 0.192	0.825 (0.657-1.037)	0.053		-0.254	0.776 (0.604-0.997)	0.047	0.092	1.097 (0.719-1.674)	0.668		-0.085	0.919 (0.532-1.588)	0.762
Clinical Traits														
ABO types														
A type		Reference		0.004					Reference		0.051			
A2 type	- 0.898	0.407 (0.169-0.980)	0.045					0.707	2.027 (0.907-4.532)	0.085				
AB type	- 0.218	0.804 (0.701-0.921)	0.002					-0.084	0.920 (0.692-1.222)	0.564				
B type	0.030	1.030 (0.947-1.123)	0.484					0.157	1.170 (1.003-1.365)	0.046				
O type	0.002	1.002 (0.944-1.064)	0.942					-0.029	0.972 (0.867-1.089)	0.620				
Candidates BMI (kg/m^2)	0.005	1.005 (0.999-1.011)	0.082		0.016	1.016 (1.010-1.022)	< 0.001	1.009	0.999-1.019	0.073		0.021	1.021 (1.010-1.031)	< 0.001
BMI < 18.5		Reference		< 0.001					Reference		< 0.001			
18.5 ≤ BMI < 25	- 0.144	0.866 (0.732-1.024)	0.093					- 0.476	0.622 (0.476-0.812)	< 0.001				
25 ≤ BMI < 30	- 0.140	0.870 (0.736-1.028)	0.102					- 0.501	0.606 (0.464-0.792)	< 0.001				
30 ≤ BMI < 35	- 0.062	0.940 (0.793-1.115)	0.479					- 0.353	0.703 (0.534-0.925)	0.012				
35 ≤ BMI	0.108	1.114 (0.933-1.332)	0.233					- 0.271	0.763 (0.568-1.025)	0.072				
Primary causes of renal failure														
Diabetic nephropathy		Reference		< 0.001		Reference			Reference		< 0.001		Reference	
HTN nephrosclerosis	0.060	1.061 (0.983-1.145)	0.126		-0.011	0.989 (0.907-1.078)	0.800	0.079	1.082 (0.903-1.298)	0.393		0.066	1.069 (0.877-1.302)	0.510
Polycystic kidney	-0.283	0.754 (0.669-0.849)	< 0.001		-0.229	0.795 (0.695-0.909)	0.001	-0.056	0.946 (0.767-1.167)	0.602		0.022	1.022 (0.815-1.281)	0.850
Glomerular disease	0.048	1.049 (0.972-1.133)	0.220		0.069	1.072 (0.982-1.170)	0.121	0.317	1.373 (1.185-1.591)	< 0.001		0.278	1.321 (1.117-1.563)	0.001
Renovascular	0.082	1.086 (0.943-1.261)	0.283		-0.087	0.916 (0.774-1.085)	0.310	0.182	1.199 (0.857-1.678)	0.289		0.178	1.195 (0.846-1.689)	0.313
Congenital	0.140	1.151 (0.935-1.415)	0.184		0.185	1.203 (0.952-1.520)	0.122	0.422	1.524 (1.108-2.097)	0.010		0.339	1.404 (0.983-2.005)	0.062
Tubular and interstitial	0.193	1.213 (1.062-1.386)	0.004		0.233	1.262 (1.088-1.465)	0.002	0.471	1.601 (1.273-2.015)	< 0.001		0.389	1.475 (1.142-1.905)	0.003
Neoplasms	-0.514	0.598 (0.330-1.082)	0.089		-0.759	0.468 (0.222-0.984)	0.045	-0.869	0.420 (0.104-1.686)	0.221		-0.735	0.480 (0.119-1.931)	0.301
Others	0.210	1.233 (1.111-1.369)	< 0.001		0.211	1.235 (1.092-1.396)	0.001	0.487	1.628 (1.336-1.983)	< 0.001		0.434	1.543 (1.236-1.927)	< 0.001

TABLE VII (continued)

UNI-/BI-VARIATE AND MULTIVARIATE ANALYSIS FOR ONE-YEAR GRAFT FAILURE OF DERIVATION DATASETS

| Variable | Deceased Donor Kidney Transplantation (Derivative Model) | | | | | | | Living Donor Kidney Transplantation (Derivative Model) | | | | | | |
| | Univariate | | | | Multivariate | | | Univariate | | | | Multivariate | | |
	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p
Dialysis types														
No dialysis		Reference		< 0.001		Reference			Reference		< 0.001		Reference	
Hemodialysis	0.727	2.069 (1.847-2.316)	< 0.001		0.617	1.853 (1.567-2.191)	< 0.001	0.478	1.614 (1.396-1.866)	< 0.001		0.352	1.421 (1.201-1.683)	< 0.001
Peritoneal dialysis	0.665	1.943 (1.661-2.274)	< 0.001		0.694	2.003 (1.637-2.452)	< 0.001	0.598	1.819 (1.437-2.304)	< 0.001		0.419	1.521 (1.168-1.979)	0.002
Types, unknown	0.713	2.041 (1.548-2.690)	< 0.001		0.733	2.082 (1.499-2.893)	< 0.001	- 0.181	0.835 (0.480-1.451)	0.522		-0.311	0.733 (0.362-1.483)	0.387
Dialysis, unknown	0.318	1.374 (1.236-1.528)	< 0.001		0.210	1.234 (1.064-1.432)	0.006	0.125	1.133 (0.999-1.285)	0.052		-0.010	0.990 (0.854-1.147)	0.890
Dialysis duration (years)	0.043	1.043 (1.037-1.050)	< 0.001		0.043	1.044 (1.035-1.053)	< 0.001	0.047	1.048 (1.031-1.066)	< 0.001		0.058	1.060 (1.038-1.083)	< 0.001
0 < Duration < 1		Reference		< 0.001					Reference		< 0.001			
1 ≤ Duration < 2	0.128	1.136 (1.028-1.256)	0.013					0.254	1.289 (1.130-1.469)	< 0.001				
2 ≤ Duration < 3	0.168	1.183 (1.074-1.303)	0.001					0.175	1.192 (0.994-1.428)	0.057				
3 ≤ Duration < 4	0.139	1.149 (1.039-1.269)	0.007					0.401	1.494 (1.204-1.854)	< 0.001				
4 ≤ Duration < 5	0.241	1.273 (1.149-1.410)	< 0.001					0.256	1.292 (0.950-1.756)	0.102				
5 ≤ Duration < 10	0.335	1.397 (1.284-1.521)	< 0.001					0.462	1.587 (1.254-2.009)	< 0.001				
Duration ≥ 10	0.786	2.194 (1.945-2.474)	< 0.001					0.913	2.492 (1.710-3.633)	< 0.001				
Cardiovascular Diseases														
Functional status														
No limitation		Reference		< 0.001		Reference			Reference		< 0.001			
Some limitation	- 0.327	0.724 (0.680-0.771)	< 0.001		-0.116	0.890 (0.799-0.992)	0.036	- 0.305	0.737 (0.659-0.826)	< 0.001				
Total limitation	0.098	1.103 (0.967-1.258)	0.145		0.383	1.467 (1.242-1.733)	< 0.001	- 0.125	0.883 (0.586-1.329)	0.550				
Unknown	-0.129	0.879 (0.777-0.995)	0.041		-0.010	0.990 (0.860-1.141)	0.894	- 0.304	0.738 (0.585-0.931)	0.011				
Diabetes history														
Non-diabetes		Reference		< 0.001					Reference		< 0.001			
Type 1 diabetes	- 0.076	0.927 (0.785-1.096)	0.376					- 0.556	0.574 (0.420-0.783)	< 0.001				
Type 2 diabetes	- 0.165	0.848 (0.785-0.915)	< 0.001					-0.365	0.694 (0.583-0.827)	< 0.001				
Type other	- 0.345	0.708 (0.392-1.280)	0.253					- 46.07		1				
Type unknown	0.189	1.208 (1.117-1.306)	< 0.001					0.037	1.038 (0.876-1.230)	0.667				
Diabetes unknown	0.013	1.013 (0.782-1.313)	0.921					0.101	1.107 (0.761-1.610)	0.597				
Peripheral vascular disease (PVD)				0.003							0.043			
Non- history of PVD		Reference											Reference	
History of PVD	0.113	1.119 (0.981-1.277)	0.094					0.280	1.323 (1.024-1.711)	0.032		0.389	1.476 (1.108-1.965)	0.008
Unknown	0.189	1.208 (1.069-1.364)	0.002					0.159	1.173 (0.938-1.465)	0.161		0.122	1.129 (0.868-1.469)	0.365
Coronary artery diseases (CAD)														
No CAD		Reference		< 0.001							0.767			
History of CAD	0.163	1.177 (1.024-1.353)	0.022					0.098	1.103 (0.833-1.459)	0.494				
Unknown	0.299	1.349 (1.123-1.620)	0.001					0.055	1.056 (0.728-1.532)	0.774				
Hypertension				< 0.001							0.010			
No history of HTN		Reference							Reference					
History of HTN	- 0.199	0.819 (0.761-0.882)	< 0.001					- 0.141	0.869 (0.752-1.003)	0.055				
Unknown	0.065	1.067 (0.909-1.252)	0.428					0.177	1.194 (0.907-1.571)	0.206				
Cerebrovascular diseases (CVD)				0.020							0.141			
Non-history of CVD		Reference							Reference					
History of CVD	- 0.056	0.946 (0.795-1.125)	0.530					0.099	1.104 (0.781-1.559)	0.576				
Unknown	0.177	1.194 (1.047-1.362)	0.008					0.234	1.264 (0.994-1.608)	0.056				

TABLE VII (continued)

UNI-/BI-VARIATE AND MULTIVARIATE ANALYSIS FOR ONE-YEAR GRAFT FAILURE OF DERIVATION DATASETS

| | Deceased Donor Kidney Transplantation (Derivative Model) | | | | | | | Living Donor Kidney Transplantation (Derivative Model) | | | | | | |
| | Univariate | | | | Multivariate | | | Univariate | | | | Multivariate | | |
Variable	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p
Immunological status														
PRA (%)	0.002	1.002 (1.002-1.003)	< 0.001					0.006	1.006 (1.004-1.008)	< 0.001				
PRA < 80%		Reference		< 0.001		Reference			Reference		< 0.001		Reference	
80 ≤ PRA ≤ 100%	0.196	1.217 (1.129-1.312)	< 0.001		0.136	1.146 (1.043-1.259)	0.004	0.595	1.812 (1.505-2.183)	< 0.001		0.443	1.558 (1.272-1.908)	< 0.001
Human leukocyte antigen mis matching														
0 A antigen mismatching		Reference		< 0.001					Reference		0.002			
1 A antigen mismatching	0.227	1.255 (1.154-1.363)	< 0.001					0.210	1.234 (1.076-1.414)	0.003				
2 A antigen mismatching	0.242	1.273 (1.175-1.379)	< 0.001					0.268	1.308 (1.121-1.526)	0.001				
0 B antigen mismatching		Reference		< 0.001		Reference			Reference		0.002			
1 B antigen mismatching	0.308	1.361 (1.263-1.498)	< 0.001		0.145	1.156 (1.028-1.300)	0.016	0.206	1.229 (1.045-1.444)	0.012				
2 B antigen mismatching	0.341	1.406 (1.289-1.535)	< 0.001		0.159	1.173 (1.046-1.314)	0.006	0.301	1.352 (1.145-1.596)	< 0.001				
0 DR antigen mismatching		Reference		< 0.001		Reference			Reference		0.003		Reference	
1 DR antigen mismatching	0.228	1.256 (1.162-1.357)	< 0.001		0.081	1.085 (0.985-1.194)	0.097	0.176	1.193 (1.036-1.373)	0.014		0.159	1.172 (1.008-1.364)	0.040
2 DR antigen mismatching	0.406	1.500 (1.388-1.622)	< 0.001		0.220	1.247 (1.128-1.377)	< 0.001	0.272	1.313 (1.125-1.532)	0.001		0.205	1.227 (1.024-1.471)	0.027
ABO incompatibility														
ABO compatible		Reference		0.770					Reference		< 0.001			
ABO incompatible	0.312	1.364 (0.440-4.231)	0.591					0.917	2.502 (1.772-3.532)	< 0.001		0.826	2.284 (1.556-3.352)	< 0.001
A2 incompatible	- 0.161	0.855 (0.443-1.637)	0.629					0.832	2.299 (1.094-4.831)	0.028		0.460	1.584 (0.593-4.228)	0.359
Relationship between donor and recipient														
Living related				`					Reference		0.031		Reference	
Living unrelated								0.137	1.147 (1.035-1.271)	0.009		0.173	1.188 (1.045-1.351)	0.008
Kidney transplantation history														
No history of KT		Reference		< 0.001		Reference			Reference		0.015			
History of KT	0.328	1.388 (1.290-1.493)	< 0.001		0.337	1.401 (1.274-1.541)	< 0.001	0.195	1.215 (1.037-1.422)	0.016				
Transplant procedure				< 0.001							< 0.001			
Left kidney		Reference				Reference			Reference				Reference	
Right kidney	0.075	1.077 (1.020-1.138)	0.008		0.111	1.117 (1.051-1.187)	0.001	0.333	1.395 (1.220-1.597)	< 0.001		0.306	1.357 (1.173-1.570)	< 0.001
En-block	0.495	1.640 (1.381-1.947)	< 0.001		1.071	2.918 (2.363-3.602)	< 0.001							
Sequential kidney	0.379	1.460 (1.185-1.801)	< 0.001		-0.099	0.906 (0.710-1.156)	0.427							

TABLE VII (continued)

UNI-/BI-VARIATE AND MULTIVARIATE ANALYSIS FOR ONE-YEAR GRAFT FAILURE OF DERIVATION DATASETS

Variable	Deceased Donor Kidney Transplantation (Derivative Model)							Living Donor Kidney Transplantation (Derivative Model)						
	Univariate				Multivariate			Univariate				Multivariate		
	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p
Donor age at transplant	0.016	1.016 (1.015-1.018)	< 0.001		0.011	1.422 (1.288-1.569)	< 0.001	0.008	1.008 (1.003-1.012)	< 0.001		0.011	1.011 (1.006-1.017)	< 0.001
Donor gender				< 0.001							0.156			
Male		Reference				Reference			Reference					
Female	0.247	1.280 (1.213-1.351)	< 0.001		0.140	1.150 (1.080-1.224)	< 0.001	0.076	1.079 (0.971-1.198)	0.157				
Donor race/ethnicity														
Caucasian		Reference		< 0.001		Reference			Reference		< 0.001		Reference	
Asian	0.027	1.027 (0.858-1.230)	0.769		-0.049	0.952 (0.773-1.173)	0.647	- 0.411	0.663 (0.468-0.937)	0.020		0.090	1.094 (0.663-1.806)	0.725
Black	0.231	1.260 (1.170-1.357)	< 0.001		0.190	1.210 (1.110-1.319)	< 0.001	0.333	1.395 (1.215-1.601)	< 0.001		0.439	1.551 (1.154-2.084)	0.004
Hispanic/Latino	- 0.069	0.933 (0.860-1.013)	0.098		0.043	1.044 (0.949-1.148)	0.376	- 0.093	0.911 (0.776-1.070)	0.256		-0.042	0.959 (0.724-1.270)	0.770
Others	- 0.167	0.846 (0.619-1.155)	0.292		-0.095	0.909 (0.637-1.296)	0.598	0.058	1.059 (0.673-1.668)	0.803		0.149	1.161 (0.650-2.071)	0.614
Donor BMI (kg/m^2)														
BMI < 18.5		Reference		< 0.001							0.002			
18.5 ≤ BMI < 25	- 0.251	0.778 (0.640-0.946)	0.012						0.614 (0.446-0.846)	0.003				
25 ≤ BMI < 30	- 0.245	0.782 (0.644-0.951)	0.014						0.600 (0.436-0.826)	0.002				
30 ≤ BMI < 35	- 0.173	0.841 (0.690-1.025)	0.087						0.697 (0.503-0.965)	0.030				
35 ≤ BMI	- 0.034	0.976 (0.787-1.188)	0.748					1.2	0.753 (0.533-1.063)	0.107				
Kidney function according to GFR														
Stage 1 (GFR ≥ 90)		Reference		< 0.001		Reference					0.007		Reference	
Stage 2 (GFR 60 - 89)	0.142	1.153 (1.080-1.230)	< 0.001		0.090	1.095 (1.018-1.177)	0.015		1.146 (1.028-1.277)	0.014		0.158	1.171 (1.035-1.324)	0.012
Stage 3a (GFR 45 - 59)	0.221	1.247 (1.150-1.354)	< 0.001		0.102	1.107 (1.009-1.214)	0.031		1.357 (1.073-1.715)	0.011		0.310	1.364 (1.056-1.761)	0.017
Stage 3b (GFR 30 - 44)	0.393	1.482 (1.346-1.631)	< 0.001		0.306	1.357 (1.219-1.512)	< 0.001							
Stage 4 (GFR 15 - 29)	0.343	1.409 (1.231-1.612)	< 0.001		0.408	1.503 (1.289-1.753)	< 0.001							
Stage 5 (GFR < 15)	0.014	1.014 (0.629-1.635)	0.954		-0.287	0.750 (0.374-1.505)	0.419							
Hepatitis C														
Negative for HCV		Reference		0.033										
Positive for HCV	0.176	1.193 (1.014-1.403)	0.033											

TABLE VII (continued)

UNI-/BI-VARIATE AND MULTIVARIATE ANALYSIS FOR ONE-YEAR GRAFT FAILURE OF DERIVATION DATASET

| | Deceased Donor Kidney Transplantation (Derivative Model) | | | | | | | Living Donor Kidney Transplantation (Derivative Model) | | | | | | |
| | Univariate | | | | Multivariate | | | Univariate | | | | Multivariate | | |
Variable	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p
Donor Hypertension														
Non-history of hypertension		Reference		< 0.001		Reference			Reference		0.802			
0-5 Years	0.455	1.576 (1.465-1.695)	< 0.001		0.212	1.237 (1.132-1350)	< 0.001	0.210	1.234 (0.763-1.944)	0.391				
6-10 Years	0.529	1.697 (1.517-1.898)	< 0.001		0.258	1.295 (1.136-1.476)	< 0.001	- 0.631	0.532 (0.075-3.782)	0.528				
> 10 years	0.720	2.055 (1.858-2.272)	< 0.001		0.374	1.454 (1.288-1.641)	< 0.001	-0.217	0.805 (0.113-5.721)	0.828				
Duration, unknown	0.506	1.659 (1.480-1.859)	< 0.001		0.184	1.202 (1.052-1.374)	0.007	0.217	1.242 (0.591-2.615)	0.567				
HTN, unknown	0.469	1.598 (1.202-2.124)	0.001		0.066	1.069 (0.756-1.511)	0.707	0.223	1.250 (0.774-2.021)	0.362				
Donor Diabetes														
No diabetes		Reference		< 0.001		Reference								
0-5 Years	0.367	1.443 (1.268-1.642)	< 0.001		0.141	1.151 (0.994-1.334)	0.060							
6-10 Years	0.531	1.701 (1.401-2.066)	< 0.001		0.321	1.378 (1.106-1.718)	0.004							
> 10 years	0.562	1.754 (1.445-2.131)	< 0.001		0.400	1.491 (1.204-1.848)	< 0.001							
Duration, unknown	0.368	1.444 (1.110-1.879)	0.006		0.068	1.070 (0.794-1.442)	0.657							
Diabetes, unknown	0.471	1.601 (1.148-2.233)	0.006		0.382	1.466 (0.982-2.188)	0.061							
Donor Causes of death														
Anoxia		Reference		< 0.001		Reference								
CVD/Stroke	0.474	1.607 (1.490-1.733)	< 0.001		0.272	1.311 (1.195-1.439)	< 0.001							
Head trauma	-0.081	0.922 (0.850-1.000)	0.051		0.013	1.013 (0.921-1.114)	0.792							
CNS tumor	-0.063	0.939 (0.630-1.396)	0.754		-0.312	0.732 (0.452-1.186)	0.205							
Others	0.272	1.313 (1.097-1.570)	0.003		0245	1.277 (1.048-1.557)	0.015							
Donation after circulatory death (DCD)														
Non-DCD donors		Reference		0.033		Reference								
DCD donors	0.093	1.098 (1.009-1.195)	0.028		0.352	1.422 (1.288-1.569)	< 0.001							

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TABLE VIII

UNI-/BI-VARIATE AND MULTIVARIATE ANALYSIS FOR ONE-YEAR DEATH OF DERIVATION DATASETS

| | Deceased Donor Kidney Transplantation (Derivative Model) | | | | | | | Living Donor Kidney Transplantation (Derivative Model) | | | | | | |
| | Univariate | | | | Multivariate | | | Univariate | | | | Multivariate | | |
Variable	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p
Demographic														
Candidate age at transplant	0.038	1.039 (1.036-1.042)	< 0.001		0.036	1.037 (1.033-1.040)	< 0.001	0.042	1.043 (1.037-1.048)	< 0.001		0.042	1.043 (1.036-1.050)	< 0.001
Candidate gender														
Male		Reference		< 0.001		Reference			Referece		0.007			
Female	- 0.174	0.840 (0.788-0.897)	< 0.001		-0.125	0.882 (0.820-0.949)	0.001	- 0.189	0.827 (0.722-0.949)	0.007				
Candidate race/ethnicity														
Caucasian		Reference		< 0.001		Reference			Reference		< 0.001		Reference	
Asian	- 0.435	0.647 (0.552-0.758)	< 0.001		-0.443	0.642 (0.541-0.761)	< 0.001	-0.646	0.524 (0.336-0.818)	0.004		-0.385	0.681 (0.424-1.094)	0.112
Black	- 0.112	0.894 (0.833-0.960)	0.002		-0.181	0.835 (0.766-0.909)	< 0.001	0.081	1.084 (0.906-1.298)	0.378		0.028	1.029 (0.834-1.269)	0.793
Hispanic/Latino	- 0.313	0.731 (0.612-0.809)	< 0.001		-0.352	0.703 (0.626-0.790)	< 0.001	- 0.347	0.707 (0.567-0.881)	0.002		-0.365	0.694 (0.536-0.899)	0.006
Others	- 0.230	0.795 (0.617-1.023)	0.075		-0.342	0.710 (0.541-0.931)	0.013	0.071	1.074 (0.632-1.823)	0.792		-0.275	0.759 (0.392-1.471)	0.415
Clinical Traits														
ABO types														
A type		Reference		0.459								0.189			
A2 type	- 0.608	0.545 (0.226-1.310)	0.175					0.748	2.113 (0.789-5.660)	0.137				
AB type	- 0.031	0.969 (0.838-1.121)	0.675					-0.115	0.891 (0.621-1.280)	0.533				
B type	0.008	1.008 (0.913-1.113)	0.872					-0.204	0.815 (0.654-1.017)	0.070				
O type	-0.042	0.959 (0.895-1.028)	0.240					-0.028	0.972 (0.834-1.121)	0.698				
Recipients BMI (kg/m^2)	0.005	1.005 (0.999-1.011)	0.082					0.032	1.032 (1.019-1.045)	< 0.001		0.017	1.017 (1.003-1.032)	0.022
BMI < 18.5		Reference		0.202								0.002			
18.5 ≤ BMI < 25	0.105	1.111 (0.850-1.452)	0.442					0.146	1.157 (0.649-2.065)	0.621				
25 ≤ BMI < 30	0.178	1.195 (0.915-1.562)	0.191					0.251	1.285 (0.721-2.291)	0.395				
30 ≤ BMI < 35	0.188	1.207 (0.921-1.582)	0.172					0.369	1.446 (0.807-2.593)	0.215				
35 ≤ BMI	0.151	1.162 (0.878-1.539)	0.293					0.646	1.909 (1.052-3.463)	0.033				
Primary causes of renal failure														
Diabetic nephropathy		Reference		< 0.001		Reference			Reference		< 0.001		Reference	
HTN nephrosclerosis	- 0.387	0.679 (0.626-0.737)	< 0.001		-0.044	0.957 (0.844-1.085)	0.489	- 0.352	0.704 (0.584-0.847)	< 0.001		-0.155	0.856 (0.692-1.059)	0.152
Polycystic kidney	- 0.873	0.418 (0.362-0.482)	< 0.001		-0.447	0.640 (0.531-0.770)	< 0.001	-1.117	0.327 (0.247-0.434)	< 0.001		-0.671	0.511 (0.374-0.698)	< 0.001
Glomerular disease	- 0.762	0.467 (0.425-0.512)	< 0.001		-0.174	0.841 (0.729-0.970)	0.017	-0.973	0.378 (0.315-0.453)	< 0.001		-0.504	0.604 (0.485-0.753)	< 0.001
Renovascular	- 0.236	0.790 (0.670-0.930)	0.005		0.048	1.049 (0.858-1.282)	0.641	-0.528	0.590 (0.390-0.893)	0.013		-0.617	0.540 (0.329-0.885)	0.015
Congenital	-1.023	0.359 (0.256-0.505)	< 0.001		-0.163	0.850 (0.588-1.228)	0.386	-0.886	0.412 (0.246-0.692)	< 0.001		-0.471	0.624 (0.306-1.274)	0.196
Tubular and interstitial	-0.605	0.546 (0.457-0.653)	0.042		-0.133	0.876 (0.707-1.085)	0.224	-0.629	0.533 (0.387-0.735)	< 0.001		-0.400	0.670 (0.453-0.991)	0.045
Neoplasms	-0.616	0.540 (0.298-0.977)	0.042		-0.779	0.459 (0.217-0.970)	0.042	-0.393	0.675 (0.252-1.081)	0.434		-0.230	0.795 (0.295-2.140)	0.649
Others	-0.246	0.782 (0.695-0.880)	< 0.001		0.131	1.140 (0.969-1.340)	0.113	-0.574	0.563 (0.434-0.731)	< 0.001		- 0.248	0.780 (0.573-1.063)	0.116

TABLE VIII (continued)

UNI-/BI-VARIATE AND MULTIVARIATE ANALYSIS FOR ONE-YEAR DEATH OF DERIVATION DATASETS

| | Deceased Donor Kidney Transplantation (Derivative Model) | | | | | | | Living Donor Kidney Transplantation (Derivative Model) | | | | | | |
| | Univariate | | | | Multivariate | | | Univariate | | | | Multivariate | | |
Variable	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p
Dialysis types														
No dialysis		Reference		< 0.001		Reference			Reference			< 0.001			
Hemodialysis	0.619	1.856 (1.636-2.107)	< 0.001		0.718	2.051 (1.699-2.476)	< 0.001	0.916	2.500 (2.059-3.036)	< 0.001		0.603	1.828 (1.404-2.381)	< 0.001
Peritoneal dialysis	0.443	1.558 (1.294-1.875)	< 0.001		0.714	2.042 (1.612-2.586)	< 0.001	0.864	2.374 (1.734-3.250)	< 0.001		0.521	1.684 (1.144-2.480)	0.008
Types, unknown	1.080	2.945 (2.262-3.834)	< 0.001		1.059	2.883 (2.104-3.950)	< 0.001	0.536	1.709 (0.952-3.068)	0.072		0.382	1.466 (0.706-3.044)	0.305
Dialysis, unknown	0.210	1.233 (1.096-1.388)	0.001		0.254	1.290 (1.093-1.522)	0.003	0.469	1.599 (1.340-1.907)	< 0.001		0.132	1.141 (0.913-1.427)	0.246
Dialysis duration prior to transplant	0.024	1.025 (1.016-1.034)	< 0.001		0.053	1.054 (1.043-1.066)	< 0.001	0.065	1.068 (1.051-1.084)	< 0.001		0.100	1.105 (1.080-1.131)	< 0.001
0 < Duration < 1		Reference		< 0.001					Reference			< 0.001			
1 ≤ Duration < 2	0.049	1.050 (0.937-1.177)	0.404					0.587	1.799 (1.520-2.129)	< 0.001				
2 ≤ Duration < 3	0.077	1.080 (0.967-1.205)	0.171					0.640	1.896 (1.529-2.351)	< 0.001				
3 ≤ Duration < 4	0.074	1.076 (0.962-1.205)	0.200					0.924	2.519 (1.966-3.226)	< 0.001				
4 ≤ Duration < 5	0.173	1.189 (1.058-1.334)	0.004					1.101	3.008 (2.228-4.061)	< 0.001				
5 ≤ Duration < 10	0.222	1.249 (1.134-1.374)	< 0.001					0.787	2.196 (1.640-2.941)	< 0.001				
Duration ≥ 10	0.370	1.447 (1.240-1.689)	< 0.001					1.439	4.215 (2.767-6.420)	< 0.001				
Cardiovascular Diseases														
Functional status														
No limitation		Reference		0.001		Reference			Reference			< 0.001		Reference	
Some limitation	- 0.243	0.785 (0.727-0.846)	< 0.001		0.061	1.063 (0.940-1.203)	0.332	- 0.230	0.795 (0.684-0.923)	0.003		-0.087	0.917 (1.127-1.978)	0.005
Total limitation	0.830	2.294 (2.032-2.591)	< 0.001		1.119	3.061 (2.603-3.599)	< 0.001	0.947	2.579 (1.838-3.617)	< 0.001		0.902	2.465 (1.637-3.714)	< 0.001
Unknown	0.297	1.346 (1.184-1.530)	< 0.001		0.454	1.574 (1.358-1.823)	< 0.001	0.091	1.095 (0.839-1.429)	0.503		0.282	1.325 (0.981-1.790)	0.066
Diabetes history														
Non-diabetes		Reference		< 0.001		Reference			Reference			< 0.001			
Type 1 diabetes	0.439	1.552 (1.307-1.844)	< 0.001		0.333	1.395 (1.124-1.731)	0.003	0.430	1.537 (1.135-2.080)	0.005				
Type 2 diabetes	0.422	1.525 (1.407-1.653)	< 0.001		0.140	1.150 (1.010-1.311)	0.035	0.744	2.103 (1.772-2.497)	< 0.001				
Type other	-0.115	0.892 (0.445-1.785)	0.746		-0.257	0.773 (0.366-1.633)	0.500	0.139	1.149 (0.287-4.608)	0.844				
Type unknown	0.881	2.414 (2.230-2.614)	< 0.001		0.469	1.599 (1.407-1.817)	< 0.001	1.089	2.972 (2.506-3.527)	< 0.001				
Diabetes unknown	0.355	1.426 (1.068-1.904)	0.016		0.081	1.084 (0.763-1.542)	0.652	0.339	1.403 (0.839-2.347)	0.196				
Peripheral vascular disease (PVD)				< 0.001							< 0.001			
Non- history of PVD		Reference				Reference			Reference					Reference	
History of PVD	0.669	1.951 (1.729-2.203)	< 0.001		0.298	1.348 (1.181-1.538)	< 0.001	1.007	2.739 (2.151-3.487)	< 0.001		0.401	1.493 (1.127-1.978)	0.005
Unknown	0.329	1.389 (1.214-1.590)	< 0.001		0.090	1.095 (0.934-1.283)	0.264	0.292	1.339 (1.015-1.764)	0.038		-0.068	0.935 (0.487-1.794)	0.839
Coronary artery diseases (CAD)														
No CAD		Reference		< 0.001					Reference			< 0.001			
History of CAD	0.796	2.217 (1.950-2.520)	< 0.001					1.008	2.740 (2.124-3.534)	< 0.001				
Unknown	0.491	1.635 (1.336-2.001)	< 0.001					0.518	1.679 (1.119-2.518)	0.012				
Hypertension				0.079							0.259			
No history of HTN		Reference							Reference						
History of HTN	-0.045	0.956 (0.874-1.046)	0.331					0.040	1.041 (0.856-1.266)	0.690				
Unknown	0.143	1.154 (0.954-1.397)	0.136					0.295	1.343 (0.935-1.929)	0.111				
Cerebrovascular diseases (CVD)				< 0.001							< 0.001			
Non-history of CVD		Reference							Reference					Reference	
History of CVD	0.414	1.513 (1.286-1.780)	< 0.001					0.905	2.471 (1.817-3.359)	< 0.001		0.453	1.573 (1.116-2.217)	0.010
Unknown	0.231	1.260 (1.085-1.463)	0.002					0.301	1.351 (0.997-1.831)	0.052		0.257	1.293 (0.656-2.547)	0.458

TABLE VIII (continued)

UNI-/BI-VARIATE AND MULTIVARIATE ANALYSIS FOR ONE-YEAR DEATH OF DERIVATION DATASETS

Variable	Deceased Donor Kidney Transplantation (Derivative Model)							Living Donor Kidney Transplantation (Derivative Model)						
	Univariate				Multivariate			Univariate				Multivariate		
	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p
Immunological status														
PRA (%)	- 0.001	1.000 (0.999-1.001)	0.451					0.003	1.003 (1.001-1.006)	0.015				
PRA < 80%		Reference		0.924		Reference			Reference		< 0.001		Reference	
80 ≤ PRA ≤ 100%	- 0.005	0.995 (0.906-1.093)	0.924		0.191	1.210 (1.079-1.357)	0.001	0.550	1.733 (1.357-2.212)	< 0.001		0.017	1.624 (1.193-2.212)	0.002
Human leukocyte antigen mismatching														
0 A antigen mismatching		Reference		0.007					Reference		0.004			
1 A antigen mismatching	0.148	1.160 (1.057-1.273)	0.002					0.250	1.284 (1.077-1.531)	0.005				
2 A antigen mismatching	0.089	1.093 (0.998-1.197)	0.054					0.275	1.317 (1.079-1.606)	0.007				
0 B antigen mismatching		Reference		0.001					Reference		< 0.001			
1 B antigen mismatching	0.198	1.219 (1.097-1.356)	< 0.001					0.438	1.549 (1.243-1.930)	< 0.001				
2 B antigen mismatching	0.154	1.167 (1.060-1.284)	0.002					0.450	1.568 (1.250-1.968)	< 0.001				
0 DR antigen mismatching		Reference		< 0.001		Reference			Reference		0.024		Reference	
1 DR antigen mismatching	0.135	1.145 (1.049-1.250)	0.003		0.055	1.057 (0.960-1.163)	0.259	0.200	1.221 (1.019-1.463)	0.030		0.161	1.175 (0.955-1.445)	0.127
2 DR antigen mismatching	0.282	1.325 (1.213-1.448)	< 0.001		0.118	1.125 (1.019-1.241)	0.019	0.276	1.318 (1.081-1.607)	0.006		0.261	1.298 (1.031-1.634)	0.026
ABO incompatibility														
ABO compatible		Reference		0.871					Reference		0.043		Reference	
ABO incompatible	-0.512	0.599 (0.084-4.256)	0.609					0.609	1.838 (1.104-3.062)	0.019		0.782	2.186 (1.201-3.979)	0.011
A2 incompatible	0.037	1.031 (0.515-2.063)	0.931					0.470	1.599 (0.515-4.968)	0.417		0.828	2.289 (0.735-7.126)	0.153
Relationship between donor and recipient														
Living related				`					Reference		0.989			
Living unrelated								0.005	1.005 (0.880-1.148)	0.938				
Kidney transplantation history				0.118							0.069			
No history of KT		Reference				Reference								
History of KT	- 0.078	0.925 (0.839-1.020)	0.118		0.199	1.220 (1.078-1.380)	0.002	0.093	1.098 (0.889-1.355)	0.391				
Transplant procedure				< 0.001							0.255			
Left kidney		Reference							Reference					
Right kidney	- 0.076	0.927 (0.870-0.987)	0.018					0.108	1.114 (0.924-1.343)	0.256				
En-block	- 0.619	0.539 (0.391-0.743)	< 0.001											
Sequential kidney	0.511	1.667 (1.340-2.074)	< 0.001											

TABLE VIII (continued)

UNI-/BI-VARIATE AND MULTIVARIATE ANALYSIS FOR ONE-YEAR DEATH OF DERIVATION DATASETS

| Variable | Deceased Donor Kidney Transplantation (Derivative Model) | | | | | | | Living Donor Kidney Transplantation (Derivative Model) | | | | | | |
| | Univariate | | | | Multivariate | | | Univariate | | | | Multivariate | | |
	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p
Donor age at transplant	0.018	1.019 (1.017-1.021)	< 0.001		0.009	1.009 (1.007-1.012)	< 0.001	0.011	1.011 (1.005-1.017)	< 0.001				
Donor gender				< 0.001							0.036			
Male		Reference							Reference					
Female	0.109	1.115 (1.047-1.188)	0.001					0.145	1.156 (1.009-1.324)	0.037				
Donor race/ethnicity														
Caucasian		Reference		0.147		Reference			Reference		< 0.001			
Asian	0.097	1.102 (0.901-1.346)	0.345		0.147	1.159 (0.930-1.444)	0.190	- 0.519	0.595 (0.377-0.939)	0.026				
Black	0.060	1.061 (0.969-1.163)	0.201		0.133	1.143 (1.031-1.266)	0.011	0.119	1.126 (0.934-1.358)	0.214				
Hispanic/Latino	-0.083	0.921 (0.838-1.012)	0.086		0.068	1.071 (0.962-1.191)	0.211	-0.322	0.2725 (0.581-0.904)	0.004				
Others	0.093	1.098 (0.800-1.505)	0.564		0.380	1.463 (1.056-2.027)	0.022	0.265	1.303 (0.781-2.175)	0.310				
Donor BMI (kg/m²)														
BMI < 18.5		Reference		0.017							0.101			
18.5 ≤ BMI < 25	0.054	1.056 (0.918-1.214)	0.445					- 0.028	0.972 (0.501-1.889)	0.934				
25 ≤ BMI < 30	0.153	1.165 (1.013-1.341)	0.033					- 0.018	0.982 (0.506-1.905)	0.957				
30 ≤ BMI < 35	0.151	1.162 (0.999-1.352)	0.051					0.160	1.174 (0.601-2.294)	0.639				
35 ≤ BMI	0.171	1.186 (1.011-1.391)	0.036					0.291	1.337 (0.655-2.732)	0.425				
Glomerular filtration rate (GFR) calculated by MDRD														
Kidney function according to GFR														
Stage 1 (GFR ≥ 90)		Reference		< 0.001		Reference					< 0.001			
Stage 2 (GFR 60 - 89)	0.186	1.204 (1.117-1.298)	< 0.001		0.085	1.089 (1.003-1.182)	0.043	0.270	1.310 (1.136-1.511)	< 0.001				
Stage 3a (GFR 45 - 59)	0.303	1.354 (1.234-1.485)	< 0.001		0.176	1.193 (1.078-1.320)	0.001	0.531	1.701 (1.276-2.267)	< 0.001				
Stage 3b (GFR 30-44)	0.286	1.331 (1.185-1.496)	< 0.001		0.163	1.177 (1.036-1.336)	0.012							
Stage 4 (GFR 15 - 29)	0.031	1.031 (0.862-1.234)	0.736		0.120	1.127 (0.931-1.365)	0.219							
Stage 5 (GFR < 15)	0.055	1.057 (0.612-1.825)	0.843		0.255	1.291 (0.712-2.341)	0.400							
Hepatitis C														
Negative for HCV		Reference		< 0.001		Reference								
Positive for HCV	0.533	1.704 (1.451-2.001)	< 0.001		0.499	1.647 (1.380-1.967)	< 0.001							

TABLE VIII (continued)

UNI-/BI-VARIATE AND MULTIVARIATE ANALYSIS FOR ONE-YEAR DEATH OF DERIVATION DATASETS

Variable	Deceased Donor Kidney Transplantation (Derivative Model)							Living Donor Kidney Transplantation (Derivative Model)						
	Univariate				Multivariate			Univariate				Multivariate		
	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p	β	HR (95% CI)	p	Log rank p	β	HR (95% CI)	p
Hypertension														
Non-history of hypertension		Reference		< 0.001					Reference		0.475			
0-5 Years	0.284	1.329 (1.217-1.451)	< 0.001					0.074	1.077 (0.557-2.081)	0.826				
6-10 Years	0.380	1.462 (1.278-1.674)	< 0.001					0.574	1.775 (0.443-7.118)	0.418				
> 10 years	0.442	1.555 (1.369-1.767)	< 0.001					0.280	1.323 (0.186-9.410)	0.780				
Duration, unknown	0.506	1.658 (1.459-1.885)	< 0.001					0.722	2.059 (0.977-4.340)	0.058				
HTN, unknown,	0.048	1.049 (0.707-1.555)	0.785					-0.032	0.969 (0.482-1.948)	0.929				
Diabetes														
No diabetes		Reference		< 0.001		Reference								
0-5 Years	0.112	1.118 (0.946-1.322)	0.189		- 0.071	0.931 (0.776-1.118)	0.443							
6-10 Years	0.458	1.582 (1.254-1.994)	< 0.001		0.239	1.270 (0.980-1.656)	0.070							
> 10 years	0.661	1.936 (1.564-2.398)	< 0.001		0.504	1.655 (1.316-2.082)	< 0.001							
Duration, unknown	0.142	1.153 (0.822-1.616)	0.410		-0.055	0.946 (0.660-1.357)	0.764							
Diabetes, unknown	- 0.107	0.898 (0.541-1.491)	0.678		-0.355	0.701 (0.406-1.211)	0.203							
Causes of death														
Anoxia		Reference		< 0.001		Reference								
CVD/Stroke	0.502	1.652 (1.510-1.807)	< 0.001		0.156	1.168 (1.052-1.297)	0.004							
Head trauma	0.040	1.041 (0.947-1.145)	0.406		0.060	1.062 (0.956-1.180)	0.262							
CNS tumor	0.337	1.401 (0.946-2.074)	0.092		0.236	1.266 (0.840-1.909)	0.260							
Others	0.197	1.218 (0.977-1.519)	0.080		0.131	1.140 (0.892-1.457)	0.294							
Donation after circulatory death (DCD)														
Non-DCD donors		Reference		0.067										
DCD donors	-0.098	0.906 (0.816-1.007)	0.067											

a. **One-year graft failure model for deceased donor KT**

Physical limitation and BMI of recipients were significant factors of one-year graft failure among cardiovascular factors. And high PRA, high degree of HLA B and DR mismatch, and previous KT history were relevant factors among immunological factors. For recipient demographic and clinical characteristics, race/ethnicity, the causes of ESRD, dialysis types/duration, and transplant procedures were important factors. Among donor factors, age, gender, race/ethnicity, eGFR, history of hypertension and diabetes, death by stroke/cerebrovascular diseases, and donation after cardiac death were predictors. The model employed 4 immunological factors, 2 cardiovascular factors, 4 recipient factors, and 8 donor factors. The proportional hazards regression model indicated its significance with a likelihood ratio of 1386.8 (56), $p < 0.001$.

b. **One-year graft failure model for living donor KT**

In addition to PRA and HLA DR mismatch, this model included ABO incompatibility and relationship between donors and recipients (4 immunological factors). BMI and peripheral vascular disease were included as cardiovascular factors (2 cardiovascular factors). Age at kidney transplantation and gender were included in addition to race/ethnicity, the causes of ESRD, and dialysis types/duration (6 recipient factors). For donor characteristics, ages, race/ethnicity, eGFR were included (3 donor factor). The proportional hazard regression model was significant by a likelihood ratio of 330.2 (37), $p < 0.001$.

c. **One-year patient death model for deceased donor KT**

For immunological factors, PRA, HLA DR mismatch, and previous KT history were included (3 immunological factors). Physical limitation, peripheral vascular diseases, and diabetes history were significant cardiovascular factors (3 cardiovascular factors). Race/ethnicity, causes of ESRD, dialysis types/duration, ages at transplantation, and gender were indicated as recipient factors (5 recipient factors). In addition to age and race/ethnicity of donors, donors' eGFR, hepatitis C history, and diabetes were included. And cause of death was a significant factor (5 donor factors). The model was statistically significant with a likelihood ratio of 1845.8 (53), $p < 0.001$.

d.   **One-year patient death model for living donor KT**

Donor characteristics were not included. However, PRA, HLA DR mismatch, and ABO

compatibility were significant predictors (3 immunological factors). Physical limitation, peripheral vascular

disease, cerebrovascular disease, and BMI were included as cardiovascular factors (4 cardiovascular factors). And

among recipient factors, race/ethnicity, causes of ESRD, dialysis types/duration, and age at kidney transplantation

were contained (4 recipient factors). The likelihood ratio was 479.12 (31) with p values of < 0.001, which

indicates the significance of the model.

D.   **Specific aim 2: Validity and reliability of the predictive models**

1.   **Validity**

a.   **Goodness of Fit test**

Goodness of fit tests were performed by calculating Cox-Snell residuals which indicates

the difference between the observation of the outcome variables of this study and that predicted by each of four

multivariate models (Hosmer, Lemeshow, & May, 2008). Model fit can be examined by plotting the Nelson-

Aalen cumulative hazard estimator for the Cox-Snell residual, which should show a 45-degree line if the model

fits data correctly.

It should be noted that Cleves, Gutierrez, Gould, and Marchenko (2010) indicated that

prior failures and censoring of data in survival analyses could cause a reduced effective sample which was

associated with the outliers of Cox-Snell residuals. The authors argued that this small size of outliers could cause

the variability about the 45-degree reference line but did not indicate a failure of Goodness of fit test.

Cox-Snell residuals for four models were calculated and extreme values or outliers of

residuals were identified. Likewise Cleves, Gutierrez, Gould and Marchenko (2010) indicated the small portion of

outliers were found in the right-hand tail of each distribution of Cox-Snell residuals and were excluded to plot

Cox-Snell residuals (e.g., deceased donor KT graft failure: n = 150 or 0.19%; living donor KT graft failure n = 59

or 0.11%; deceased donor KT patient death: n = 83 or 0.10%; and living donor KT patient death: 38 or 0.09%.

Each plot of the four models aligned with a 45-degree reference line, which indicates that the four models well fit

each of the four datasets.

Figure 92.   Goodness of Fit test of deceased donor KT one-year graft failure prediction model
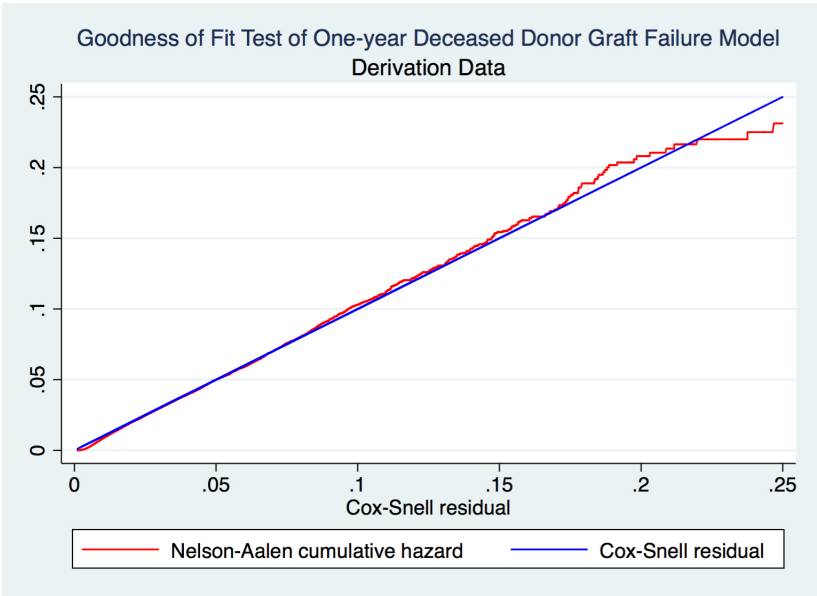

Figure 93.   Goodness of Fit test of living donor KT one-year graft failure prediction model
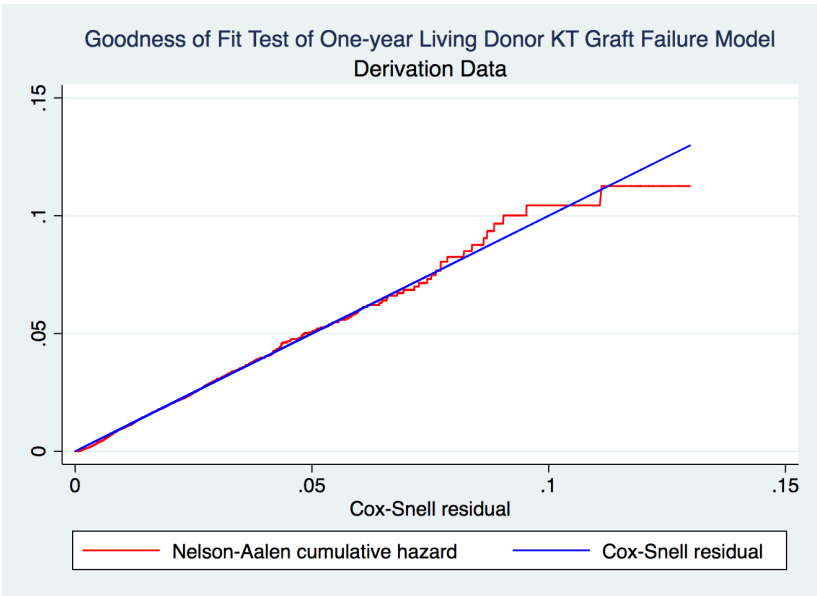
Figure 94.   Goodness of Fit test of deceased donor KT one-year death prediction model
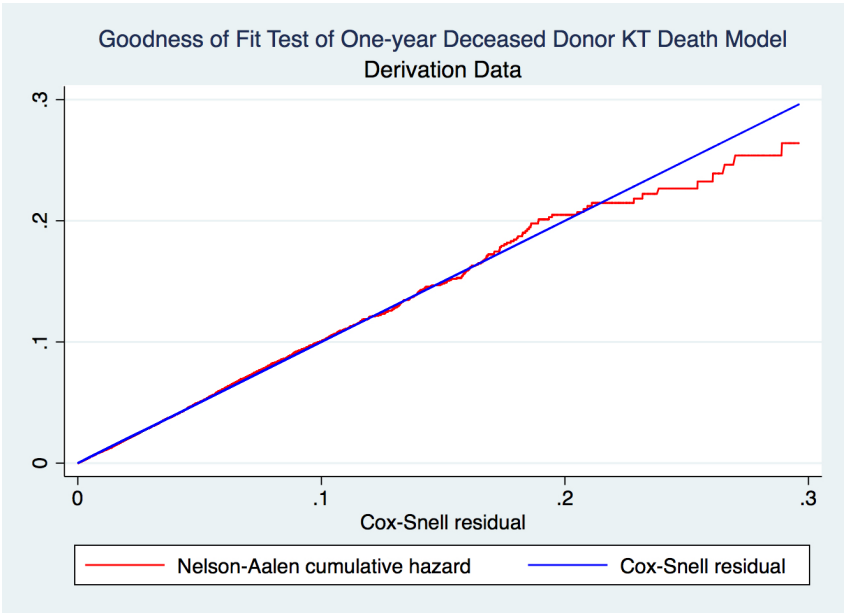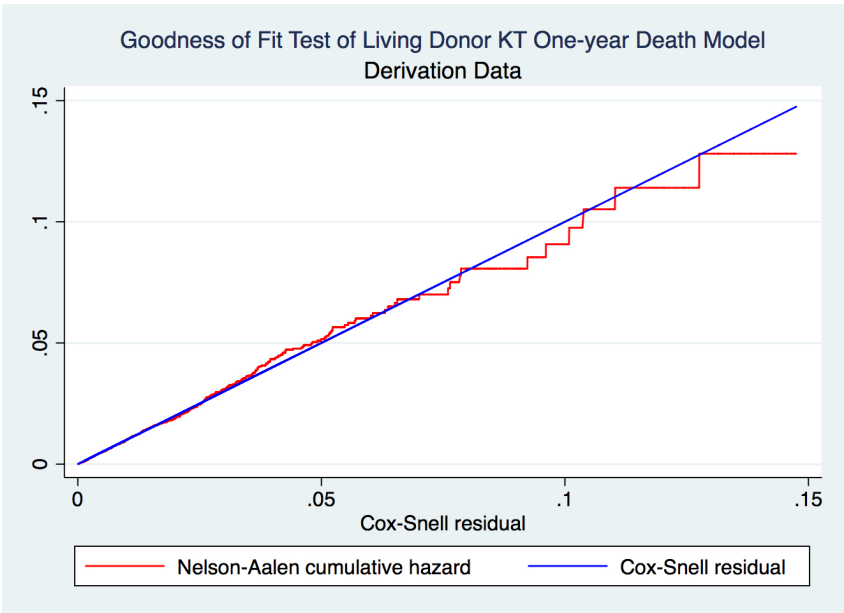

Figure 95.   Goodness of Fit test of living donor KT one-year death prediction model

b.   **Calibration**

Calibration statistics were calculated by examining the regression coefficient on a

prognostic index in the validation data. The prognostic index is "the product of Cox proportional hazard models"

and calculated by a weighted sum of coefficients of the model (Altman & Roymand, 2013, p. 3). A regression

coefficient near to one indicates optimal calibration or how well the predicted risks compare to the observed

outcomes. All four models had a coefficient near to one which was within 95% CI. For example, the deceased

donor KT graft failure model (validation data) had a $\beta = 1.043$ (95% CI $= 0.959$-1.127) (shown in Figure 96). The

living donor KT graft failure model (validation data) indicated a $\beta = 1.022$ (95% CI $= 0.914$-1.130) (shown in

Figure 97). And the deceased donor KT patient death model (validation data) had a $\beta = 1.039$ (95% CI $= 0.966$-

1.112) (shown in Figure 98). Whereas, the living donor KT patient death model (validation data) indicated a $\beta =$

1.018 (95% CI $= 0.882$-1.154) (shown in Figure 99).

Figure 96.   Calibration statistics of deceased donor KT one-year graft failure prediction model

Figure 97. Calibration statistics of living donor KT one-year graft failure prediction model
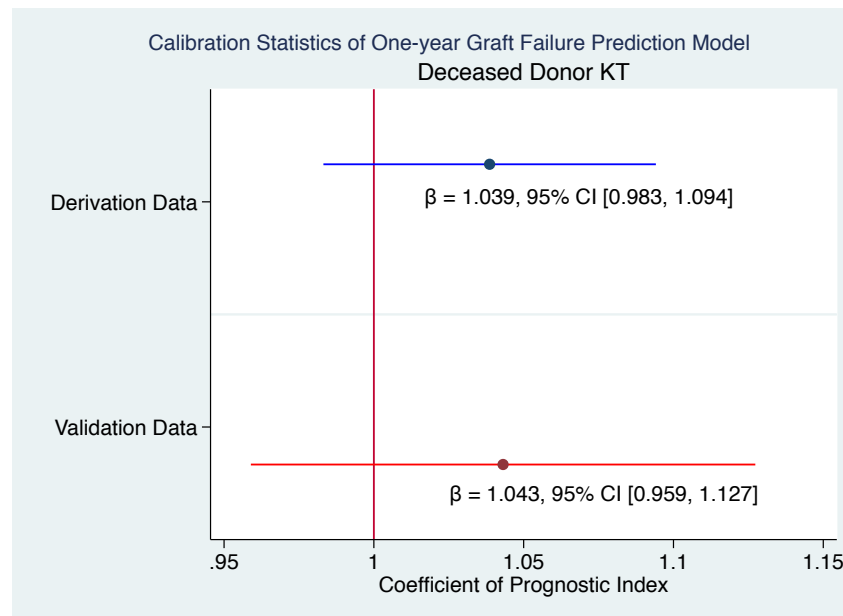

Figure 97. Calibration statistics of living donor KT one-year graft failure prediction model

Figure 98. Calibration statistics of deceased donor KT one-year death prediction model
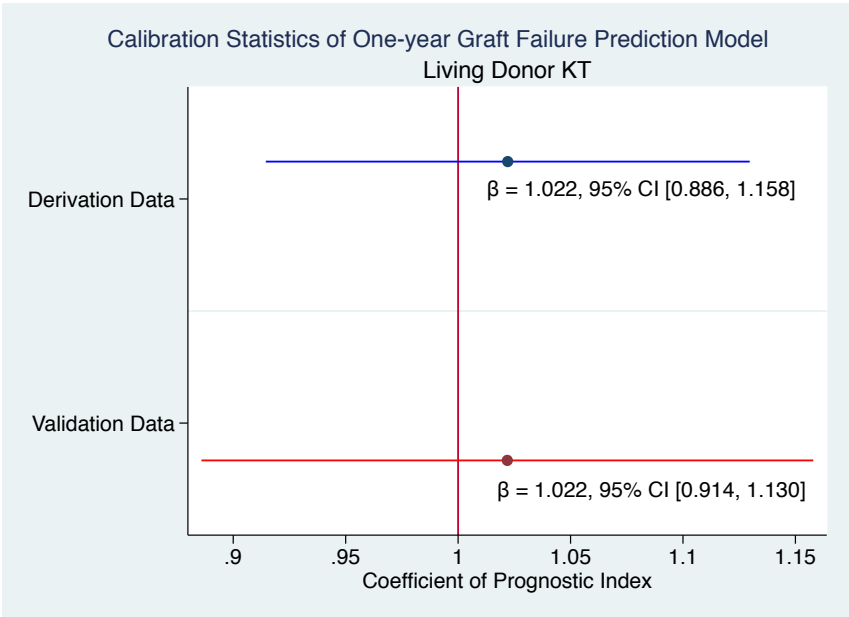

Figure 98. Calibration statistics of deceased donor KT one-year death prediction model
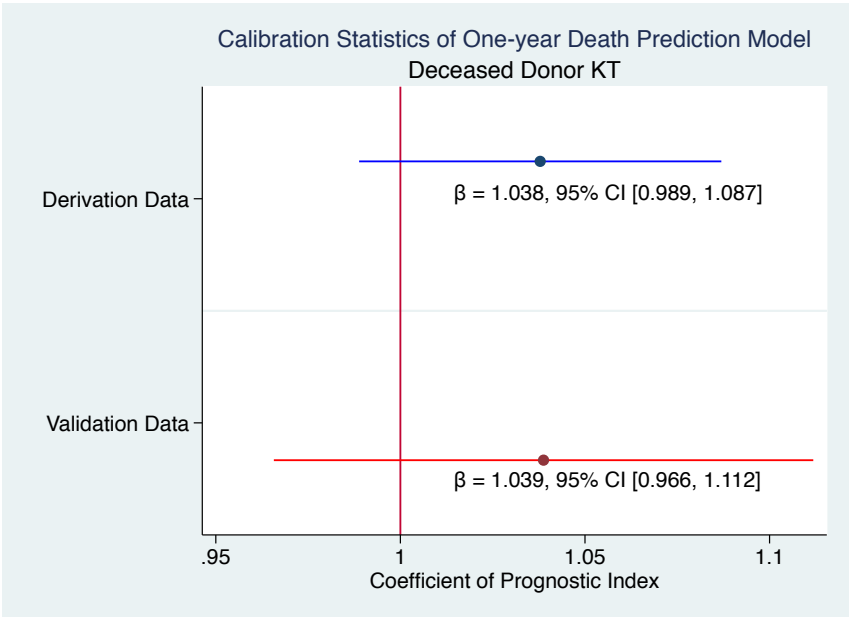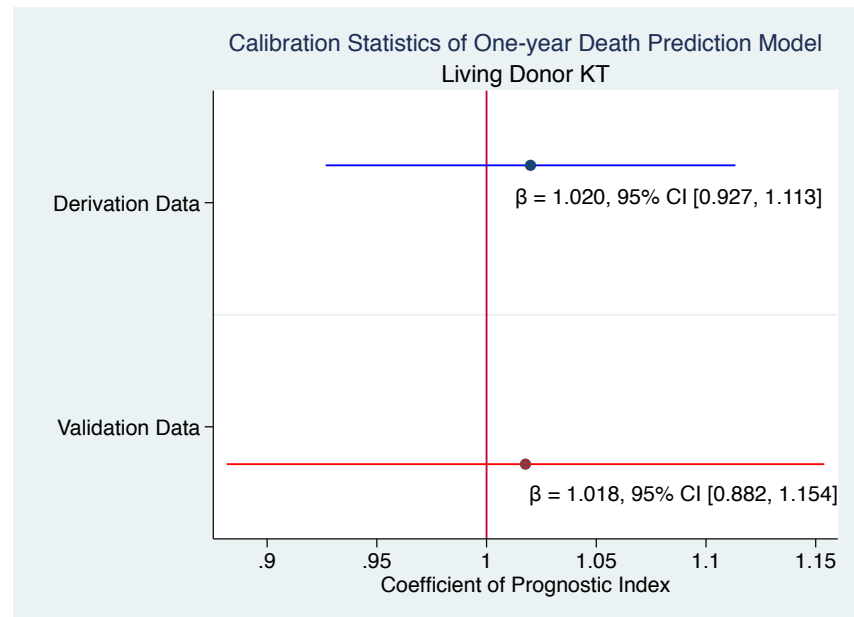
Figure 99.   Calibration statistics of living donor KT one-year death prediction model

c.   **Model discrimination test**

A model discrimination test was performed with receiver operating curves. The graft failure models for both deceased and living donors indicated the area under curves as 0.660 and 0.642, respectively (shown in Figure 100 and Figure 101). And the patient death model for deceased donors showed the area under curves as 0.708 (shown in Figure 102). And the one-year death model of living donor KT indicated AUC of 0.727 (shown in Figure 103).

Figure 100.   Discrimination test by receiver operating curve: Deceased donor KT graft failure model

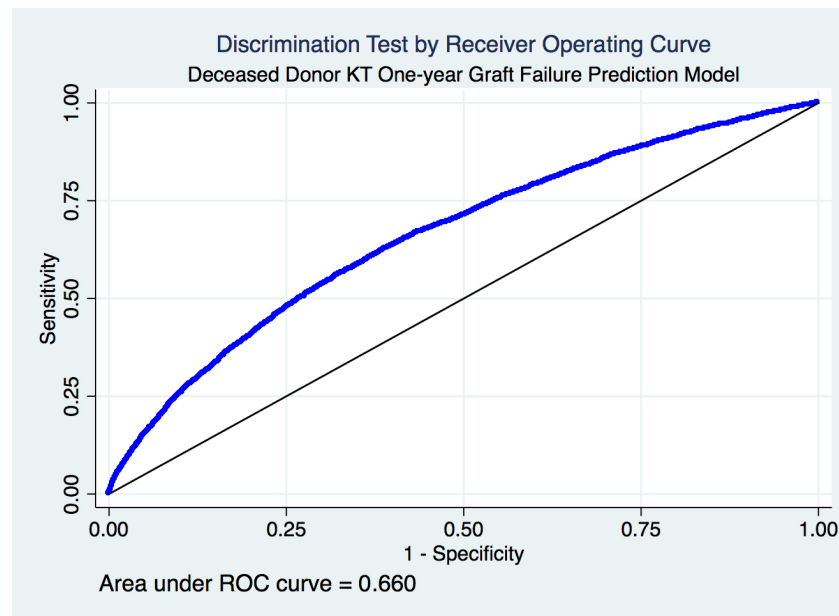Figure 101.   Discrimination test by receiver operating curve: Living donor KT graft failure model

Figure 102.   Discrimination test by receiver operating curve: Deceased donor KT death model

Figure 103.   Discrimination test by receiver operating curve: Living donor KT death model

Discrimination Test by Receiver Operating Curve
Living Donor KT One-year Death Prediction Model

Area under ROC curve = 0.727

2.   **Reliability**

All four predictive models showed the consistent values of AUC in the derivation and validation datasets. In addition, Harrell's C of all models was calculated for both derivation and validation data and compared to evaluate if the general predictive power of the models was consistent.

Figure 104.   Test of consistency by receiver operating curves: Deceased donor KT graft failure models

Figure 105.   Test of consistency by receiver operating curves: Living donor KT graft failure models
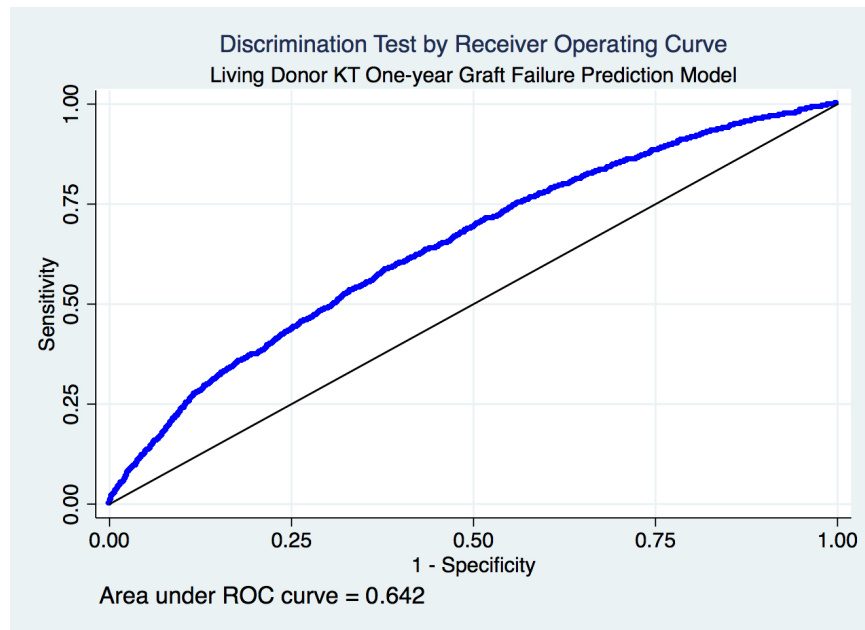

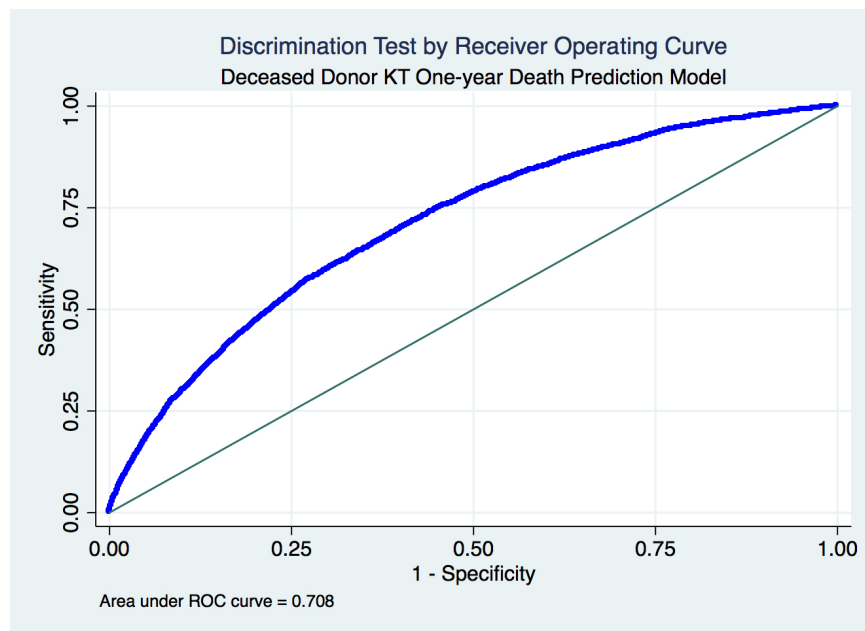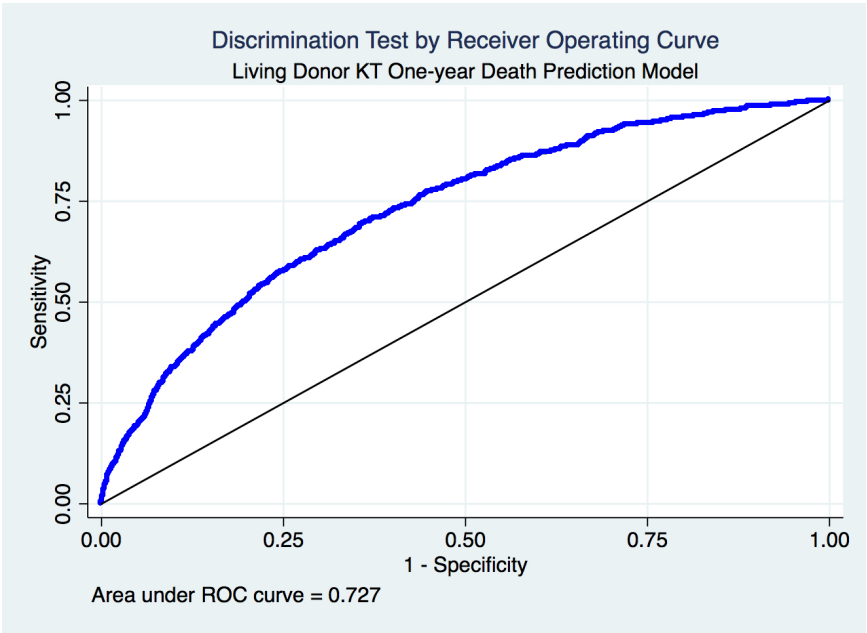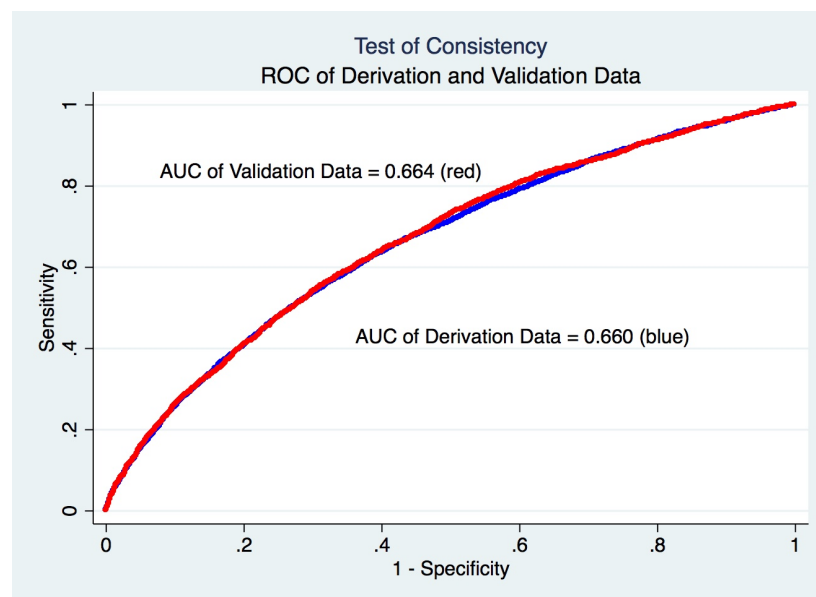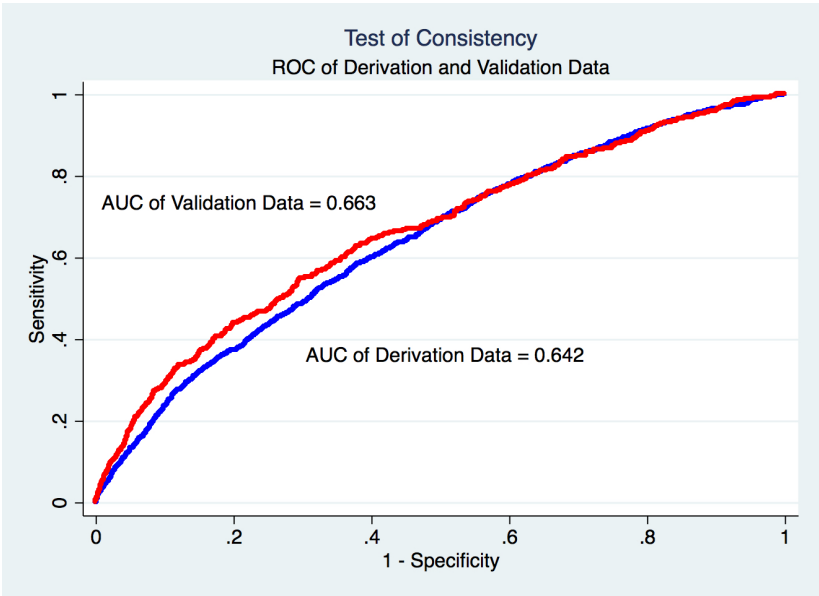Figure 106.   Test of consistency by receiver operating curves: Deceased donor KT death models
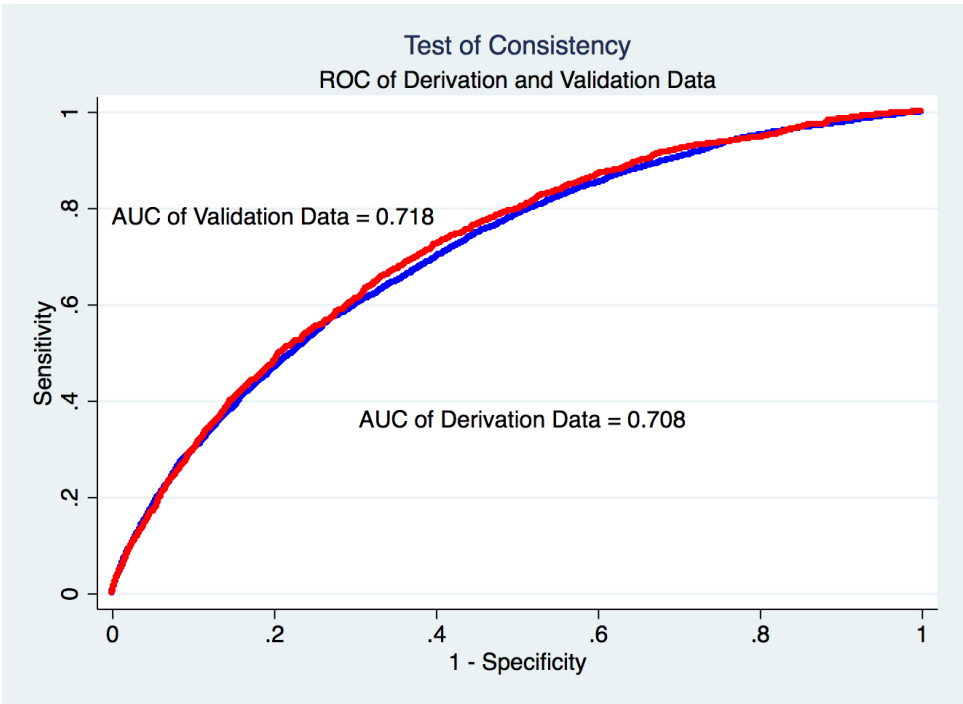
Figure 107.   Test of consistency by receiver operating curves: Living donor KT death models
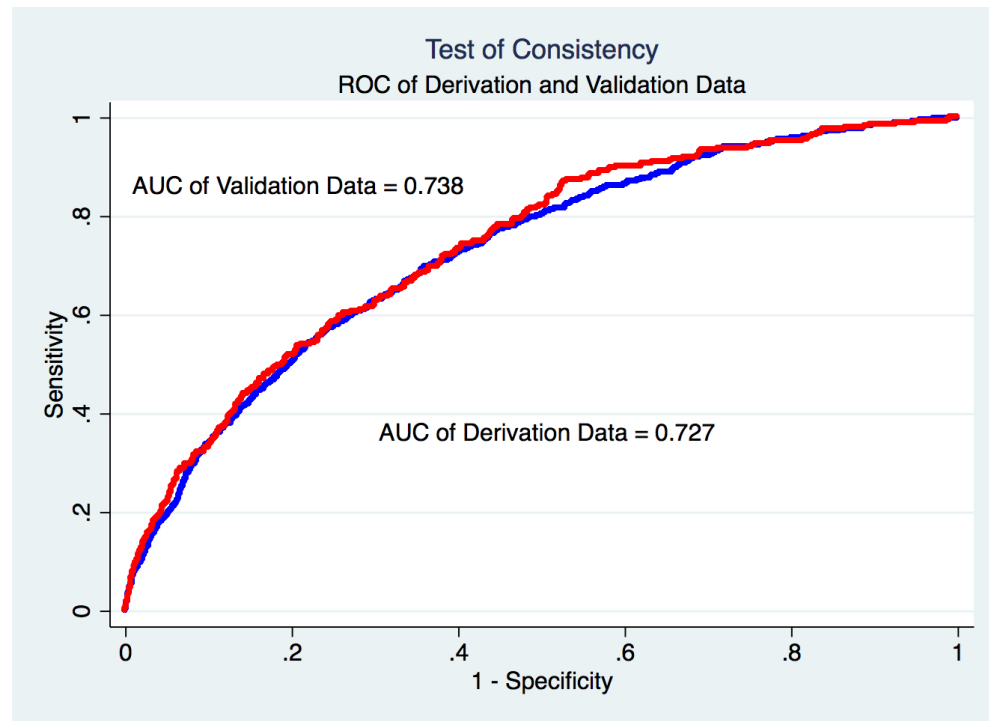
TABLE IX

PREDICTIVE MODLES HARREL C'S STATISTICS

Models		Harrell's C statistics (95% CI)					
		Derivation Data according to CMS regulation		Derivation Data	Validation Data	Derivation Data including CAD[a]	SRTR risk-adjustment model[b]
		Before 6/28/2007	After 6/28/2007				
One-year Graft Failure Model	Deceased Donor KT	0.659 (0.648-0.670)	0.651 (0.638-0.663)	0.657 (0.659-0.665)	0.660 (0.648-0.673)	0.644 (0.634-0.657)	0.658
	Living Donor KT	0.644 (0.625-0.662)	0.653 (0.626-0.676)	0.643 (0.628-0.659)	0.662 (0.638-0.686)	0.650 (0.630-0.671)	0.661
One-year Death Model	Deceased Donor KT	0.710 (0.699-0.722)	0.703 (0.690-0.716)	0.705 (0.696-0.713)	0.715 (0.703-0.728)	0.715 (0.702-0.728)	0.715
	Living Donor KT	0.734 (0.713-0.755)	0.733 (0.697-0.769)	0.731 (0.712-0.749)	0.739 (0.711-0.766)	0.733 (0.708-0.759)	0.755

[a]CAD = coronary artery disease

[b]Scientific Registry of Transplant Recipient (2015) did not provide confidential interval of statistics results.

E.   **Specific aim 3: Survival difference between candidates on the waiting list and transplantation**

       recipients

Among active candidates on the waiting list who died prior to KT, the medial survival duration from

listing were 4.2 years (*SD* = 6.5 years). However, medial survival duration from listing was longer in both

deceased donor KT (*Median* = 8.5, *SD* = 4.4) and living donor KT recipients (*Median* = 7.6, *SD* = 4.1). Cox

proportional hazard regression was calculated in three groups: active candidates; deceased donor KT recipients,

and living donor KT recipients (listed on the waiting list) controlling covariates: physical limitation; peripheral

vascular disease; BMI; PRA; ages at listing; race/ethnicity; causes of ESRD; and dialysis types/duration. The

median survival duration of active candidates on the waiting list were 11.7 years (*SE* = 0.1). Whereas, deceased

donor KT recipients survived longer with a median 23.7 years (*SE* = 0.6) (shown in Figure 108).

Figure 108.   Survival difference between candidates on the waiting list and transplant recipients
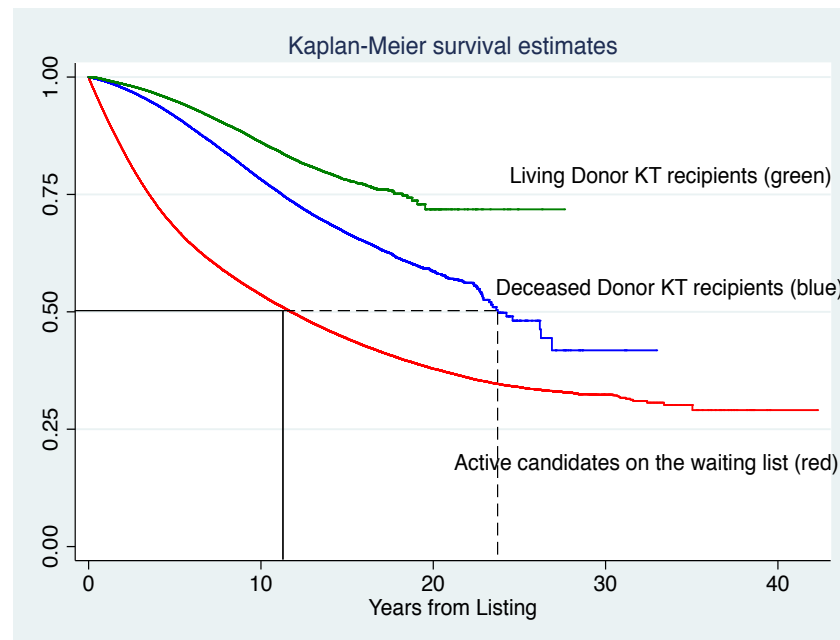
VI. DISCUSSION

Across kidney transplantation process from the evaluation to surgery, not only the patients and their family members but also the health care providers experience uncertainty. The patients are concerned about the availability of donated kidneys during their waiting time, the compatibility of the donors, and unpredictable health conditions after their kidney transplantation (Martin, Stone, Scott, & Brashers, 2010). And the health care providers are also uncertain if the candidates, especially those with complex comorbidities and immunological barriers, will benefit from kidney transplantation. And importantly, the transplant programs are not free from a concern either: they wonder whether they can satisfy the expected rates of graft success and patient survival at one-year after kidney transplantation which determine Medicare coverage of kidney transplantation costs, and which can affect the continuation of those programs. These program results indicate the quality of individual programs' transplant processing, including their transplant surgeries and their immediate care after transplantation (Dickinson et al., 2008). To dispel this uncertainty in the transplant community, the predictive models focusing on one-year kidney transplant outcomes by candidates' cardiovascular comorbidities and immunological barriers were developed. Therefore, the findings, usefulness, and limitations of the predictive models of one-year graft failure and patient death derived from this study are discussed herein.

A.   **Results**

     1.   **Specific aim 1: Development of predictive models**

          a.   **One-year deceased donor KT graft failure model**

The cardiovascular factors in this model included BMI and physical limitation. Currently, kidney transplantation of obese patients, defined by BMI $\geq$ 40, is contraindicated in one center, while these patients commonly undergo kidney transplantation in another center (Oberholzer et al., 2013). Wu, Dawson, and Levings (2016) recently reviewed previous studies about the relationship between obesity and cardiovascular diseases of obese patients prior to KT, complications related to obesity such as infection, and prolonged ischemia times for donated organs. The authors speculated that pro-inflammatory conditions induced by adipose tissues in obese patients were associated with organ rejections and graft failure in kidney transplantation. However, it should be noted that the BMI is not a valid diagnostic indicator for obesity (Romero-Corral et al., 2008).

For example, similar BMI levels could indicate different amounts of visceral adipose tissues depending on the patient's race (Lim et al., 2011). Wu et al. (2016) argued that future research should measure obesity more accurately by fat composition, visceral adipose tissues, muscle mass, and bone density in order to determine the impact of obesity on transplant outcomes.

Interestingly, in a bivariate analysis of BMI, BMI < 18.5 groups had poor one-year kidney graft success rates compared with other groups whose BMI were greater than or equal to 18.5. While current studies focus on the adverse effects of obesity on kidney transplant outcomes, this bivariate analysis highlighted the importance of the patient's nutritional status in one-year graft success after KT. Molnar et al. (2011) indicated that malnutrition, measured by serum albumin levels, was associated with kidney graft failure and patient death, even up to 6 years after transplantation. The authors speculated that the malnourished patients were at "malnutrition-inflammation complex" status (p. 1007) and were prone to have cytomegalovirus infection and multiple comorbidities.

The degree of immobility of candidates is an important predictor of one-year graft failure in deceased donor KT. Dusseux et al. (2015) included the degree of immobility of elderly patients as an evaluation criterion for kidney transplantation. However, previous literature did not specify the relationship between patient immobility and poor transplantation outcomes. It can be speculated that the poor outcomes resulting from physical limitation are associated with unmet oxygen demand due to cardiovascular diseases and inaccessibility to post-transplant or primary care.

High sensitization, indicated by PRA $\geq$ 80%, is a significant predictor of one-year graft failure. Having a high PRA indicates longer waiting times for KT and a lower possibility of identifying compatible donors. Currently "HLA compatibility at the allele level" is considered the most accurate way to determine compatibility with donors (Kumar, 2015, p. 571). It is represented as A-, B-, and DR- mismatching (Kumar, 2015). Among A-, B-, and DR-, this study found that HLA - B and -DR mismatching is a significant predictor of one year-graft failure in decease donor KT. In particular, the model of this study showed the impact of HLA-DR mismatching on one-year kidney transplantation outcomes. Antibody mediated rejection by a donor-specific antibody is known for being an obstacle to maintaining kidney graft function long-term (Sun & Yang, 2013). Antibody mediated rejection is mainly associated with HLA antigens, especially for HLA class II (-DR, -

DM, -DO, -DP, -DQ). Among HLA class II, HLA-DR matching between donors and candidates is linked with antibody mediated rejection caused by (1) activation of the endothelial cells of the donated kidney capillaries, and (2) provoking pro-inflammatory conditions (e.g., inducing T17 helper cells and suppressing regulatory T cells) (Lion et al., 2016).

Previous kidney transplantation history is one of the most significant immunological factors. It is explained by the adaptive immune mechanism. Tinckam, Rose, Hariharan, and Gill (2016) indicated that previous kidney transplantation could cause long-term B memory cell formations in the candidates, which provokes "allo-immune memory" and eventually results in kidney graft rejection (p. 1). The authors found that candidates who had a high PRA and repeated HLA mismatching against the new kidneys, had a higher ratio of graft failure compared with patients without repeated HLA mismatching.

The poor outcome in En-block and donor right kidney transplant surgery is an interesting finding of this model. En-block kidney transplantation is known as pediatric en-bloc kidney surgery. It was introduced to utilize the kidneys from deceased children for adult candidate transplantation, and to overcome their limited nephron mass (Mwipatayi, Leong, Subramanian, & Picardo, 2013). The surgery involves linking two single pediatric kidneys by vascular anastomoses which are associated with the risk of vascular thrombosis and graft failure per Mwipatayi et al. (2013)'s review.

The implantation of a left donated kidney in the right iliac fossa is a common KT procedure and using a donor's left kidney is preferred because it has a longer renal vein, which allows the venous anastomosis to be less challenging and which prevents injury to the "delicate right kidney renal vein" (Tso & Pearson, 2014, p.120). In contrast, the donor's right kidney has been associated with a shorter renal vein and renal vein thrombosis (Dols, Fok, & Ijzermans, 2010). In addition, the significant predictors related to donated kidneys were kidneys from non-heart-beating donors and patients who died by strokes. For example, kidneys from donors whose hearts were not beating have acute injuries caused by suboptimal blood and oxygen supply due to cardiac arrest warm and pulseless ischemia time (5 minutes) (Morrisey & Monaco, 2014). Donors who died from a stroke or cerebral-vascular disease are associated with an increase in sympathetic activity and hypo perfusion toward the kidneys as well as inflammatory conditions provoked by cytokines (Pratschke et al., 2001). This explains their poor rate of one year

graft success. Although donated kidneys procured after cardiac or brain death could relieve the organ shortage, their worse outcomes are the "trade-offs" (Niederhaus & D'Alessandro, 2014, p. 605).

b.   **One-year living donor KT graft failure model**

Cardiovascular factors including BMI and peripheral vascular disease are important predictors of one-year graft failure in the living donor KT model. The significance of peripheral vascular disease can be explained by the role of iliac circulation: supplying blood and nutrition to the implanted kidney (Kirt et al., 2014; Laging et al., 2015). Immunological factors which were considered were PRA levels, HLA-DR mismatching, ABO incompatibility, and the relationship between the donor and the recipient. In spite of advanced desensitization therapies (e.g., plasmapheresis, and thymoglobulin), ABO incompatible kidney transplants resulted in worse outcomes compared with ABO compatible KT.

For living donor kidney transplantations, using a kidney donated by an unrelated person was a significant factor of graft failure. Currently, the national transplant registry collects mismatching information of HLA-A, HLA-B, and HLA-DR loci. However, the importance of HLA class II antigens has been addressed and HLA-DQ antibodies received attention due to their significant negative impact on transplant outcomes (Attas et al., 2015). Fujimoto et al (2015) reported that antibody mediated rejection caused by HLA-DQ antibodies were not responsive, unfortunately, to traditional desensitization therapy such as plasmapheresis, immunoglobulin, and monoclonal antibody therapy. Because HLA-DQ mismatching is more likely linked with unrelated living donors because HLA are inherited from the parents.

c.   **One-year deceased donor KT death model**

Interestingly, this model shared the common cardiovascular and immunological factors such as physical limitation, peripheral vascular disease, PRA, HLA -DR mismatching and history of KT. In addition to physical limitation and peripheral vascular disease, having diabetes was a significant predictor. Diabetes itself involves cardiovascular comorbidities, and its link to death can be understood. However, this model speculates that simultaneous kidney-pancreas transplants could be an option for the patients with diabetes. Currently, the UNOS allows certain type 1 diabetics and certain type 2 diabetics to undergo simultaneous kidney-pancreas transplantation. Those certain patients are those with ESRD who receive insulin therapy and have c-peptide levels of less than or equal to 2ng/ml, or those with ESRD who have c-peptide levels greater than 2 ng/ml

with BMI less than 28 kg/m^2 (OPTN, n.d.). The Perez-Saez and Pascual (2015) studies revealed that the survival

benefits of diabetics receiving simultaneous kidney-pancreas transplants were superior to the benefits for the

diabetic patients who underwent deceased donor KT, without a simultaneous pancreas transplant.

It should be noted that in bivariate analyses for impact of diabetes on deceased donor KT

patient death, type 1 and type 2 diabetes were associated with less risk of patient death when it compared with

non-diabetes. The harmful effects of diabetes on patient death in multivariabe analyses can be explained by the

possible interaction between diabetes and other cardiovascular diseases such as peripheral vascular disease,

physical limitation, or dialysis types. Interestingly, the model indicated that black patients have 36% less risk of

one-year death after KT compared with that of Caucasian patients, HR = 0.642 (95% CI = 0.541-0.761, $p < 0.001$).

d.   **One-year living donor KT death model**

This model also had common cardiovascular and immunological factors but the new

variable, candidates' cerebrovascular diseases were recognized. Interestingly, Lentine et al. (2008) argued that

smoking was a significant predictor of new onset cerebrovascular disease after KT. Therefore, the findings from

this study could support the importance of smoking cessation in kidney candidates and recipients to prevent

cerebrovascular disease and related deaths. And not surprisingly, dialysis therapy and its duration were important

predictors in all of four models. This information can be found elsewhere using different cohorts (Remport et al.,

2011). In contrast to one-year deceased donor KT death model, one-year living donor KT death model indicated

that black patients does not have significant risk of one-year death after KT compared with that of Caucasian

patients (HR = 1.029, 95% CI = 0.834-1.269, $p = 0.793$).

2.   **Specific aim 2: Validity and reliability of the predictive models**

Overall, all four predictive models satisfied the goodness of fit test. The fitting of the model

indicates that the model must have provided "an adequate summary of the data upon which it is based" and the

model explains "the middle of data" (Hosmer, Lemeshow, & May, 2008, p. 169). Calibration tests of the four

models in validation datasets were obtained by logistic regression of the weighted sum of coefficient values of

individuals against the graft failure and patient death. The outcome of regression statistics was that the coefficient values were near 1.0, which indicated an agreement between observed and predicted risks (Kasiske et al., 2010).

Both one-year graft failure predictive models had AUC of ROC as 0.660 and 0.642, respectively, which indicates that the models have modest abilities to discriminate risk for each candidate. However, the two one-year death predictive models showed AUC of ROC as 0.708 and 0.727, respectively, which explains that these models have moderate accuracy (Akobeng, 2006). The Harrell's C statistics of all four models were compared with (1) the SRTR risk adjustment models, (2) derivation data which included coronary artery disease data, and (3) the models if before and after 6/28/2007, at the point CMS regulation began (shown in Table VIII). Interestingly, Harrell's C statistics or the general predictive power of Cox regression models showed similar results. The results of living donor KT were superior to those of deceased donor KT in both graft failure and death models. It can be assumed that the impact of high-risk criteria on transplant outcomes has not changed, regardless of CMS's regulation. And most importantly, the accuracy of the models did not sharply increase after including coronary artery disease information even though it is an important predictor on patient death.

Prediction models primarily are assessed for their performance by calibration/ discrimination and are evaluated by several methods including bootstrap, cross-validation, or separate external validation (Moons et al., 2014). Therefore, the previous studies that developed prediction models did not necessarily employ the concept of reliability. However, the study which is the subject of this dissertation examined the reliability and consistency of the four models in two different datasets (derivation data and validation data) by ROC, and it obtained comparable AUC results for reliability or consistency.

3.   **Specific aim 3: Determining the survival differences**

The survival benefits of deceased donor kidney transplantation in high risk patients were superior to those of patients who remained on the waiting list (covariates: physical limitation, peripheral vascular disease, BMI, PRA; ages at listing; race/ethnicity; causes of ESRD; and dialysis types/duration). And this finding is supported by Laging et al (2015) who argued that the KT recipients with a high degree of pre-transplant cardiovascular comorbidities should not excluded from kidney transplant surgery. In terms of immunological barriers, it is still controversial whether the patients on dialysis are benefited from having ABO incompatible kidney transplantation. For example, Axelrod et al. (2015) argued the benefits of ABO incompatible KT in terms

of its costs. They held that ABO incompatible kidney transplantation is expensive. However, its costs were well justified by comparison with the costs related to dialysis and comorbidities. However, Held and McCormick (2015) objected to the argument supporting the efficiency of ABO incompatible KT because its risks of poor transplant outcomes remained high, and this could eventually decrease life expectancy and deteriorate the quality of life.

B.   **Implications**

1.   **Implications for clinical practice**

The evaluation of candidates for kidney transplantation involves medical, psychosocial, and financial assessment (Pham, Pham, Pham, Parikh, Danovitch, 2010). Through the medical evaluation process, it is determined if the candidates have cardiovascular comorbidities and immunological barriers opposing their potential deceased or living donors. The implications of this study in clinical settings are as follows.

The predictive models derived from this study can provide quantified relative risks for candidates with cardiovascular and immunological factors who undergo either deceased donor KT or living donor KT. Therefore, health care providers, patients, and their family members would expect one-year transplant outcomes when they start the evaluation process. Especially for health care providers, they can use the models to emphasize the importance of modifiable cormobidities: physical limitation, peripheral vascular disease, and BMI. The health care providers and candidates may intervene and modify those comorbidities during the transplant evaluation process. And for immunological factors, the health care providers and candidates can be encouraged to identify more compatible donors in terms of living related, ABO compatible, and HLA-B, - DR matching.

2.   **Implications for policy**

Currently, transplant community relies on the one-year graft failure and patient death prediction model developed by the SRTR called the risk adjustment models. The models' roles are very critical for CMS to determine the quality of the transplant process in transplant programs across the United States. However, the limitations of these models should be addressed. First, the selection of variables in the SRTR risk adjustment models were not theory-driven. The models utilized the statistical method called Least Absolute Shrinkage and Selection Operator to derive "the most predictive set of variables from a larger set of possible predictors" (Snyder et al., 2015, p.292). Therefore, these models missed relevant variables. For example, HLA-DR mismatching was

missed in one-year graft and patient death models. And, ABO incompatibility and donor-recipient relationships are not included. Also, candidates' physical limitations, history of cerebrovascular disease, and types of dialysis therapies are missing, which were significant in the models which were the subject of this dissertation. Members of the transplant community have been concerned about these missing variables, and they raised the question that the expected transplant outcomes predicted by the SRTR risk adjustment models could be biased (Pelletier et al., 2014). For example, the candidates with total physical limitation, cerebrovascular disease history, HLA-DR mismatching, or long-term hemodialysis therapy could have lower expected transplant outcomes according to this study's models. In contrast, the models from SRTR treat these candidates as non-risk patients because of not having these variables in the models. These biased results could falsely flag transplant programs which provide KT to patients with cardiovascular and immunological risks and cause them to avoid doing kidney transplantation for these high risk patients. The predictive models developed by this author were driven by a theoretical framework: the relationship between cardiovascular and immunological factors, and transplant outcomes can correctly quantify the risk factors of high risk candidates and can more correctly justify their expected outcomes.

C.   **Limitations**

This study has several limitations. First of all, the quality of the SRTR dataset should be warranted for its reliability and validity. The transplant community has an advantage of having nationwide information concerning all donors, candidates, and recipients collected by pre-determined forms and entered by the staff of transplant teams. However, the information obtained on these forms is optional and inconsistent. Therefore, for example, an enormous amount of information in the dataset regarding coronary artery disease is missing.

In addition to missing data, some continuous variables are not reliable and valid. For example, the BMI scores ranged from 0.1 to about 200,000 in the original dataset. Such a range is most likely associated with data entry error. Also, the comorbidity information captured by the SRTR is only dichotomous (e.g., yes, no, and unknown) information about diseases. Therefore the degree of the diseases' severity is not indicated. In addition, this study does not include psychosocial information which could affect adherence to medication and treatments, which in turn is related to inferior transplantation outcomes.

Another limitation of this study is that the study could not capture the impact of interaction of immunological and cardiovascular disease on kidney transplantation outcomes. For example, tacrolimus is a

calcineurin inhibitor which has been widely used in solid organ transplantation. However, a calcineurin inhibitor itself, it constricts renal blood vessels and causes thrombotic microangiopathy in kidneys, resulting in kidney graft failure. And tacrolimus is associated with a metabolic syndrome such as new onset of diabetes and hyperlipidemia in kidney transplant recipients (Malvezzi & Roosting, 2015). The patients with greater immunological risks will take higher dosages of these immunosuppressing medications, which will provoke or aggravate cardiovascular diseases.

This study could not explain if the quality of life of patients with cardiovascular and immunological factors would be improved after kidney transplantation. Immunological barriers require multiple desensitization therapies. This requires frequent visits to the hospital prior to and after kidney transplantation. Furthermore, immunological medications involve various adverse effects which could impact the recipient's quality of life. The psychological stress from patients being uncertain about kidney transplant outcomes and from financial burdens for treatments can overwhelm the patients. Cardiovascular comorbidities can be aggravated by kidney transplant surgery itself and increase the length of stay in the hospital. This question should be further explored and addressed in another study: Can kidney transplantation improve not only survival rates, but can it benefit the high risk patient's quality of life? And lastly, certain variables were time-dependent however, this study used covariate data collected at baseline only. Thus, it is recommended that future studies consider employing time-dependent Cox regression when it comes to analyzing SRTR data.

D.   **<u>Conclusion</u>**

In summary, the models predicting one year graft failure and patient death rates for patients with cardiovascular and immunological factors satisfied internal validation tests, and showed from modest to fair accuracy. Survival benefits were shown in patients with cardiovascular and immunological risk factors when they underwent kidney transplantation compared to when they remained on dialysis. These models may be utilized as a strategy for (1) an accurate and comprehensive evaluation of kidney transplant candidates, (2) intervening modifiable cardiovascular factors and identifying the most compatible donors prior to kidney transplantation, and (3) claiming that the risk prediction models should employ variables presented in this study for justifying high risk candidates receiving KT, which eventually could lead to the most efficient use of scarce resources, donated kidneys.

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AT CHICAGO

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Approval Notice
Initial Review (Response To Modifications)

September 4, 2015

Jongwon Yoo, BSN
Department of Biobehavioral Health Science
845 South Damen Avenue
M/C 802
Chicago, IL 60612
Phone: (312) 550-4822 / Fax: (312) 996-7934

RE: Protocol # 2015-0889
        "The Incorporation of Cardiovascular and Immunogical Burdens into a Kidney Transplant Model to Predict 1 year Graft Success and Patient Survival."

Dear Dr. Yoo:

Your Initial Review (Response To Modifications) was reviewed and approved by the Expedited review process on September 3, 2015. You may now begin your research

Please note the following information about your approved research protocol:

Protocol Approval Period: **September 3, 2015 - September 2, 2016**
Approved Subject Enrollment #:   **100000**
Additional Determinations for Research Involving Minors: **These determinations have not been made for this study since it has not been approved for enrollment of minors.**
Performance Sites: **UIC**
Sponsor: **None**

Research Protocol(s):

    a)   **The Incorporation of Cardiovascular and Immunologic Risk Factors into a Kidney Transplant Graft and Patient Survival Model to Predict Graft Success and Patient Survival, Version 1, 8-18-15**

Informed Consent(s):

    a)   **Waiver of Informed Consent granted under [45 CFR 46.116(d)]**

Your research meets the criteria for expedited review as defined in 45 CFR 46.110(b)(1) under the following specific category:

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
08/24/2015	Initial Review	Expedited	08/25/2015	Modifications Required
08/28/2015	Response To Modifications	Expedited	09/03/2015	Approved

Please remember to:

→ Use your **research protocol number** (2015-0889) on any documents or correspondence with the IRB concerning your research protocol.

→ **Review and comply with all requirements on the enclosure,**
   "UIC Investigator Responsibilities, Protection of Human Research Subjects"
      (*http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf*)

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 996-0548. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Brandi L. Drumgole, B.S.
Assistant Director
Office for the Protection of Research Subjects

cc: Mariann R. Piano, Department of Biobehavioral Health Science, M/C 802
       Catherine J. Ryan, Faculty Sponsor, M/C 802

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VITA

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Education

6/2013-Present	Ph.D. in Nursing, University of Illinois at Chicago
	Dissertation title: *Predicting One-year Kidney Graft Failure and Death with Cardiovascular and Immunologic Factors*
8/2010-5/2013	Master of Science in Nursing, Adult & Gerontology Primary Care Nurse Practitioner Program, University of Illinois at Chicago
3/2000-2/2004	Bachelor of Science in Nursing, Seoul National University, South Korea

Certifications

- Certified Clinical Transplant Coordinator, The American Board for Transplant Certification.
- Certified Heart Failure Nurse (CHFN®), American Association of Heart Failure Nurses.
- Certified Continence Care Nurse (CCCN™), Wound, Ostomy and Continence Nursing Certification Board.
- Certified Wound Care Nurse (CWCN™), Wound, Ostomy and Continence Nursing Certification Board.
- State of Illinois, Certified Nurse Practitioner.
- State of Illinois, Registered Nurse.
- South Korea Registered Professional Nurse

Professional Activities

5/2014-Present	Advanced Nurse Practitioner, Post Pancreas/Kidney Transplant University of Illinois Hospital & Health Science, Division of Transplant Surgery.
7/2012-7/2015	Lecturer, Physiology of Seminar for Excellence in Nursing Science, University of Illinois at Chicago, College of Nursing.
1/2011-5/2014	Graduate Teaching Assistant, University of Illinois at Chicago, College of Nursing.
3/2006-7/2010	Charge Nurse, Samsung Medical Center, South Korea, Coronary Care Unit.

Publications

Park, K. H., Park, J. H., & **Yoo, J. W**. (2008). *The guidelines for management of pressure ulcers*. Seoul, South Korea: Korean Wound Management Society.

Presentation

Yoo, J. W., Ryan, C., & Piano, M. (2013). *Acute Heart Failure after Kidney Transplantation*. Poster Presentation. 2013 Midwest Nursing Research Society Conference

Extracurricular Activities

2013/8-5/2014	Vice President, Sigma Theta Tau Alpha Lambda Chapter
8/2012-5/2013	President, Graduate Student Nurses Organization, College of Nursing, University of Illinois at Chicago
8/2011-5/2012	Vice President, Graduate Student Nurses Organization, College of Nursing, University of Illinois at Chicago

Military Experience

1/2004-1/2006   Performed mandatory military service in 520th Maintenance Company, 194th Maintenance Battalion, 23rd Area Support Group, 8th United States Army of Camp Humphreys.

8/2005   Noncommissioned Officer Academy (Primary Leadership Development Course) Camp Jackson, Uijongbu, Korea

2006   Dedication Medal from American Red Cross

2006   Army Commendation Medal, Awarded by Colonel Gregory L. Johansen

2005   Army Achievement Medal, Awarded by Colonel Carleton M. Smith

2004   Certificate of Achievement, Awarded by Lieutenant Colonel S. Elkins

Awards and Honors

2016   Seth and Denise Rosen Memorial Research Award, College of Nursing, University of Illinois at Chicago

2016   Certification of recognition for Outstanding performance and dedication, Transplant Surgery Division, Department of Surgery. University of Illinois Hospital.

2014   W. E. Van Doren scholarship, College of Nursing, University of Illinois at Chicago

2014   Chieko Onoda Endowed Scholarship, College of Nursing, University of Illinois at Chicago

2013   Seoul National University Alumni Association of ChicagoScholarship

2013   W. E. Van Doren scholarship, College of Nursing, University of Illinois at Chicago

2013   Elizabeth M. Roche scholarship, College of Nursing, University of Illinois at Chicago

2013   Chancellor's Student Service & Leadership Award, University of Illinois at Chicago

2013   Virginia M. Ohlson Scholarship Award, College of Nursing, University of Illinois at Chicago

2012   Seoul National University Alumni Association of ChicagoScholarship

2012   Scholarship of the Academy of International Leadership Development College of Nursing, University of Illinois at Chicago

2012   Laurette Kirstein Scholarship for the 2012-2013 Academic Year, University of Illinois at Chicago

2011   Seoul National University Alumni Association of ChicagoScholarship

2011   Honor Society of Nursing, Sigma Theta Tau International

2011   Scholarship of the Elizabeth M. Joyce Estate Scholarship, College of Nursing, University of Illinois at Chicago

2011   Scholarship from the Academy of International Leadership Development, College of Nursing, University of Illinois at Chicago

2011   Scholarship of Korean-American Association of Chicago

2010   Scholarship of Korean Nurses Association of Chicago

Professional Organization Membership

2014   International Transplant Nurses Society

2012   Heart Failure Society of America

2011   Sigma Theta Tau Nursing Honor Society, Alpha Lambda Member

DISCLAIMER

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