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Association of Baseline Viral Serology and Sirolimus Regimens with Kidney Transplant Outcomes:
A Fourteen Year Registry-Based Cohort Study in the US

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Analysis and interpretation of data: Santos, Wen, Casey, Womer

Drafting of the manuscript: Santos

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Statistical analysis: Wen
Abstract

Background:

The risks for transplant outcomes associated with baseline viral serostatus in kidney transplant recipients (KTR) on sirolimus have not been widely studied.

Methods:

We performed a cohort-study of 61 590 adult KTR in 2000-2013. We used Cox regression models to determine the adjusted hazard ratio (aHR) of patient death, death-censored graft loss and posttransplant malignancy associated with the baseline serostatus [+ or -: Hepatitis B core (HBc), Hepatitis C (HCV), Epstein Barr (EBV) or Cytomegalovirus (CMV)] in KTR on sirolimus+mycophenolate (SRL+MPA) or sirolimus+tacrolimus (SRL+Tac), relative to the control-regimen: tacrolimus+mycophenolate (Tac+MPA)

Results:

Compared with Tac+MPA, SRL+MPA and SRL+Tac were associated with higher risks of 5-year mortality [(aHR=1.41 95%CI= 1.23-1.60) and (aHR= 1.59, 95% CI= 1.38-1.83), respectively] and death-censored graft loss, [(aHR= 1.41, 95% CI= 1.24-1.60) and (aHR= 1.38, 95% CI= 1.21-1.57), respectively]. In KTR with negative pretransplant EBV, CMV, HBc or HCV serostatus, SRL+MPA not SRL+Tac was associated with a lower risk of posttransplant malignancy compared with control [(aHR=0.27, 95%CI=0.10-0.72 ), (aHR=0.61, 95%CI=0.43-0.88), (aHR=0.79, 95%CI=0.64-0.97) and (aHR=0.80, 95%CI=0.65-0.98); respectively for SRL+MPA] and [(aHR=0.98, 95%CI=0.52-1.80), (aHR=0.69, 95%CI=0.46-1.06), (aHR=0.83, 95%CI=0.66-1.06) and (aHR=0.85, 95%CI=0.67-1.07); respectively for SRL+Tac]. In KTR with positive serostatus to any of the above viruses, SRL+MPA or SRL+Tac was not associated with a different malignancy risk compared with control.
Conclusion:

Compared with Tac+MPA, SRL-regimens were associated with higher risks for patient death and graft loss; although, SRL+MPA was associated with a lower risk for posttransplant malignancy in kidney allograft recipients with negative pre-transplant HBc, HCV, EBV or CMV serology.
Introduction

A primary or reactivation viral infection after kidney transplantation can have serious impact on patient and graft outcomes. Direct effects of viral infections can range from nonspecific systemic syndromes to tissue invasive diseases involving the allograft or other organs [1,2]. By further impairment of host immune defenses, some viruses can promote other opportunistic infections [2,3]. Indirect effects of viral infections include alteration of surface human leukocyte antigen expression and release of growth factors and chemokines that can lead to acute and chronic rejection [2, 4, 5, 6]. Viral infections can directly promote posttransplant malignancies by causing dysregulation in cellular proliferation-antiproliferation pathways [2, 6].

Potent immunosuppression which has reduced graft rejection rates and improved graft survival rates after kidney transplantation can promote viral infections which by various mechanisms can contribute to allograft failure and recipient morbidity and mortality [1]. The impairment of immune control of viral oncogenes by immunosuppression can also lead to posttransplant malignancies [2, 6, 7-18]. Interestingly, some animal and human studies have shown that a class of immunosuppressant drugs, the mammalian target of rapamycin (mTor) inhibitors, also possess anti-viral and anti-neoplastic properties [18,35,20,21,22].

Laboratory studies have shown an important role for mTOR signaling in the pathogenesis of fungal, parasitic and viral infections [23, 24] and in oncogenesis [ 25-28]. Accumulating evidence from clinical studies suggest that in transplant recipients, mTOR-inhibitors participate in the inhibition of replication and clearance of Polyoma BK virus [29], reduce the incidence of Cytomegalovirus (CMV) infections and its complications [30,31] and suppress Hepatitis C virus
(HCV) recurrence [31]. Similarly, clinical studies have shown the anti-cancer properties of mTOR-inhibitors. Kahan et al. reported that compared with other immunosuppressants, mTOR-inhibitors were associated with lower incidence rates for all malignancies, post-transplant lymphoproliferative diseases (PTLD), renal cell carcinomas, and skin cancers [22]. An observational study by Kauffman and colleagues showed that mTOR-inhibitor use was associated with a 56% reduction in the risk for de novo solid cancer after kidney transplantation [32]. A US database study showed that with 1 exception, the incidence of cancer was decreased by 26% with the use of sirolimus compared with nonsirolimus immunosuppression [33]. The data from the clinical trial, CONVERT study showed that (calcineurin inhibitor) CNI conversion to sirolimus compared to CNI continuation was associated with a significant reduction in the incidence of skin cancers and total malignancies in kidney transplant recipient [34,35]. Hence, an immunosuppressant that inhibits both viral activation and oncogenesis would provide additional unique benefits to organ transplant recipients. Unfortunately, association between transplant outcomes and the effects of pretransplant viral serology and posttransplant mTor inhibitor regimens have not been widely explored. Therefore, using SRTR data on 61 590 kidney transplants in the US from 2003 through 2013, we conducted this observational cohort study in order to investigate the risks for post-transplant patient death, graft loss and post-transplant malignancy associated with sirolimus regimens and pre-transplant viral serostatus of KTR. Our findings presented in this manuscript could provide the basis for utilizing baseline serology as an important factor to consider in drug selection and outcomes prognostication related to sirolimus regimens.
Patients and Methods

This study which used data from the Scientific Registry of Transplant Recipients (SRTR) and was approved by the University of Florida Institutional review board. The SRTR system includes 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), and has been described elsewhere. The Health Resources and Services Administration provides oversight to the activities of the OPTN and SRTR contractors.

A retrospective cohort design was used to investigate outcomes associated with 2 common sirolimus regimens in relation to the pretransplant viral serostatus of adult kidney-only transplant recipient (KTR) in the United States from January 1, 2000 through December 31, 2013. KTR who survived the first transplant year free of cancer or graft loss, and met the inclusion criteria were included in the study. Follow-up started after the 12th month of kidney transplant, until the earliest of the following: 1. End of fifth transplant year, 2. Re-transplantation, 3. Death, or 4. end of SRTR follow-up. Endpoints for this study included patient death, death-censored graft loss, and post-transplant malignancy (consisting of de novo tumors and posttransplant lymphoproliferative disorders censored for death or graft loss), (21). Analyses focused on the association of outcomes to the interactions between HBc, HCV, EBV or CMV pretransplant antibody serostatus and sirolimus and mycophenolate with/without steroid (SRL+MPA) or sirolimus and tacrolimus with/without steroid (SRL+Tac) regimen.
Based on SRTR files, the following pretransplant viral antibody serostatus classified as positive (+) or negative (-), were included for analysis in this study: Hepatitis B core (HBc), Hepatitis C virus (HCV), Cytomegalovirus (CMV), and Epstein Barr Virus (EBV).

KTR cohorts were formed based on the immunosuppression regimen continuously used for a minimum duration of 6 months immediately before and including the twelfth-month posttransplant follow-up. Based on the SRTR immunosuppression follow-up files, KTR were on the same regimen at discharge, 6\textsuperscript{th} month and 12\textsuperscript{th} month follow-up, or only at the 6\textsuperscript{th} month and 12\textsuperscript{th} month follow-up, with a different regimen at discharge. The study-cohorts consisted of KTR on sirolimus and mycophenolate mofetil or sodium with/without steroids (SRL+MPA) and sirolimus and tacrolimus with/without steroids (SRL+Tac) regimens. The reference or control cohort consisted of KTR on tacrolimus and mycophenolate with/without steroids (Tac+MPA). Use of steroids was disregarded in cohort stratification, but was corrected for in the multivariable models. Due to their distinctly different management requirements, recipients with positive human immunodeficiency virus (HIV) serology were excluded from this study. Also excluded from this study were KTR who had a malignancy, died or lost their allograft within the first 12 months of transplant; recipients of nonrenal organ transplant; and, those with missing data on baseline serology or maintenance immunosuppression at pertinent follow-up periods.

From among the KTR who would have met the study inclusion criteria except for the duration of sirolimus regimen use specified above, the following cohorts were formed for additional analyses of outcomes: 1. KTR who were on a sirolimus regimen at discharge and the 6\textsuperscript{th} month follow-up only, with different regimens at 12\textsuperscript{th} month follow-up; and, 2. KTR who were on a
sirolimus regimen either at discharge or the 6th month follow-up only with different regimen/s at other relevant follow-up times, or at discharge and the 12th month follow-up, but not at the 6th month follow-up.

Statistical Analysis
Baseline cohort characteristics were presented using means with standard deviations for continuous variables and proportions (percentages) for categorical variables. Differences in means and proportions were compared with the Student’s t test and Chi-square test, respectively. The viral serology statuses, and sirolimus regimens, and literature-based outcomes-specific risk factors (36), were used as independent co-variates in the main and sirolimus regimen x viral serostatus interaction Cox multivariable regression models (subsequently termed Cox models) for patient death, death-censored graft loss and malignancy occurrence censored for death or graft loss (21, 37-40) in the 4 years following the posttransplant month-12 follow-up, i.e. 5 years posttransplant. A co-variates for year of transplant after 2009 was included to adjust for any confounding influence on the study outcomes of the clinicians’ prescribing behavior as result of a Federal Drug Administration alert to all US physicians on June 2009 regarding the increased mortality associated with conversion of calcinuerin inhibitor-based immunosuppression to sirolimus [41]. Additional Cox regression analyses with the same outcomes and covariates as in the main study cohorts were performed on KTR who were on SRL+MPA or SRL+Tac within the first transplant year but did not meet the required duration of treatment specified for inclusion in the study. The unadjusted odds ratio for death in 5 years, after 1-year conditional survival, for each specific cause (infections, cardio-vascular diseases, malignancies or any organ failure) were compared between the sirolimus regimens and the standard Tac+MPA regimen. In all Cox
multivariable analyses, co-variates other than drug regimens or viral serostatuses were selected based on previously published studies [36]. Conformity of the Cox models with the proportionality of hazards assumption were verified by visually inspecting the complementary log-log survival plots for the primary explanatory variables and examining the Schoenfeld residual plots. The risk factors predictive of the continuous use of either SRL+MPA or SRL+Tac regimens vs. Tac+MPA in the study treatment period were assessed by multivariable logistic regression analysis. Results of the Cox or logistic regression models were reported as hazard ratio (HR) or odds ratio (OR), respectively with the 95% confidence interval (CI) for each covariate. All analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was based on a p-value < .05 and all confidence intervals used a 95% threshold.

Results

Study population and demographics

We studied 61 590 adult kidney transplant cases from Jan 1, 2000 through December 31, 2013 with conditional malignancy-free, patient and graft survival at 1 year. 2659 (4.3%) were on SRL+MPA, 2167 (3.5%) on SRL+Tac and 56 764 (92.2%) on Tac+MPA. The baseline characteristics of the study cohorts are shown in Table 1. The Hepatitis B core and CMV antibody seropositivity rates differed statistically among the groups but there were no significant differences in the antibody seropositivity to HCV and EBV among the cohorts, (Table 1). Utilization of T cell-depleting antibodies for induction was highest in the Tac+MPA cohort, while use of maintenance corticosteroids was lowest in the SRL+Tac cohort (Table 1).
**Predictors of being maintained on sirolimus for at least 6 months immediately before and including the first transplant year**

The likelihood of being maintained on SRL+MPA or SRL+Tac instead of Tac+MPA was increased with African American recipient race and decreased with the following factors: CMV+ serostatus, older age, PRA>20%, transplantation year after 2009 and alemtuzumab induction (Table 2). Predictors of being maintained on SRL+MPA versus the other regimens were ECD kidney, coronary artery disease and male sex of transplant recipient. Obesity is associated with a lower likelihood of being maintained on SRL+Tac than the other regimens. Between the 2 sirolimus regimens, the likelihood of being maintained on SRL+MPA instead of SRL+Tac was increased with the following factors: obesity, transplant after year 2009, alemtuzumab induction or first as opposed to repeat transplant (Table 2).

**Sirolimus regimen and viral serology as independent risk factors for outcomes**

The 5-year mortality, graft loss and posttransplant malignancy risks associated with the SRL+MPA and SRL+Tac regimens were analyzed with the Cox model using the Tac+MPA regimen as reference (Fig. 1,2,3). The mortality risks were higher in the SRL+Tac and SRL+MPA cohorts compared with the reference group

\[(HR=1.41, \ 95\% \ CI=1.23-1.60; \ p<.001) \text{ and } (HR=1.59, \ 95\% \ CI=1.38-1.83; \ p<.001),\]

respectively. Compared with a negative serostatus, a positive HCV serostatus was associated with a higher mortality risk (HR=1.53, 95% CI=1.35-1.74; p<.001), while a positive EBV or CMV serostatus was associated with a lower mortality risk (HR=0.85, 95% CI=0.77-0.94; p<.001) and (HR=0.89, 95% CI=0.83-0.96; p=.005); respectively), and a positive HBc serostatus
was not associated with a significantly different mortality risk (HR=0.93, 95% CI=0.83-1.05; p=.23). The 5-year cause-specific death rates in the immunosuppression cohorts are depicted in Figure 4. Cardiovascular disease was the most common cause of death; and the unadjusted risks of death associated with the sirolimus regimens were not different from the reference regimen in any of the specific causes analyzed (organ failure, cardio-vascular disease, infection and malignancy), (Figure 4).

Figure 2 shows that the SRL regimens were associated with higher 5-year death-censored graft loss (DCGL) risk than the Tac+MPA regimen [(SRL+MPA: HR=1.41, 95% CI=1.24-1.60; p<.001) and (Tac+SRL: HR=1.38, 95% CI=1.21-1.57; p<.001)]. Compared with a negative serostatus, a positive HCV serostatus was associated with a higher risk of graft loss (HR=1.50, 95% CI=1.33-1.70; p<.001). The relative risks for DCGL associated with other viral serostatuses were not significant as shown in Fig. 2.

Relative to the Tac+MPA regimen, the risk of death or graft loss-censored posttransplant malignancy (PTM) was 20 % lower with the SRL+MPA regimen and was not significantly different with the SRL+Tac regimen [(HR=0.80, 95% CI=0.65-0.98; p=.03) and (HR=0.82, 95%CI=0.65-1.03; p=.09); respectively] Compared with a negative serostatus, a positive HCV serostatus was associated with a higher risk of PTM (HR=1.24, 95% CI=1.02-1.52; P=.02), while a positive HBc or CMV serostatus was associated with a lower risk of PTM [(HR=0.80 95% CI=0.68-0.95; p<.01) and (HR=0.82 , 95% CI=0.76-0.90; p<.001), respectively], (Figure 3). As depicted in Figure 3, ATG or alemtuzumab induction was associated with a higher PTM risk than basiliximab induction (HR=1.27, 95% CI=1.15-1.40; p<.001) and [(HR=1.30, 95%
CI=1.10-1.54; p=.002), respectively]. A steroid-containing maintenance regimen was associated with a higher risk of PTM than a steroid-free regimen (HR=1.14, 95% CI=1.04-1.25; p=.003).

**Sirolimus regimen and viral serology interaction as risk factor for outcomes**

After determining the adjusted risks independently associated with each of the sirolimus regimens and viral serology statuses, multiple Cox models were constructed to analyze the risks for outcomes associated with the interaction between baseline viral serostatus and sirolimus regimen (Figures 5, 6, 7). The Tac+MPA regimen was used as the reference or control in all of the analyses.

**Mortality Risk**

Figure 5 depicts that compared with control, most sirolimus regimen-viral serostatus interactions were associated with statistically higher risks for patent death in 5 years, except in: SRL regimen in HCV+ KTR [(SRL+MPA: HR=1.50, 95% CI=0.93-2.26), (SRL+Tac: HR=1.41, 95% CI=0.84-2.27)]; SRL+MPA in HBc+ KTR (HR=1.38, 95%CI=0.84-2.25) and SRL+Tac in EBV-KTR (HR=1.41, 95%CI=0.96-2.06).

**Death-censored graft loss risk**

Regardless of concomitant pretransplant viral serostatus, most sirolimus regimens were associated with higher risk for DCGL than control except with SRL+Tac in HBc+, HCV+, and CMV-transplant recipients (Figure 5).
Post-transplant malignancy risk, censored for death or graft-loss

Relative to the reference regimen (Tac+MPA), the 5-year risk of posttransplant malignancy (PTM) was lower with SRL+MPA, not SRL+Tac in KTR with HBc-, HCV-, EBV- or CMV-serostatus pre-transplant; (Fig. 7). The highest de novo PTM risk reduction point estimate of 73% was seen in EBV- recipients on SRL+MPA (HR=0.27, 95% CI=0.10-0.72), followed by 39% in CMV- recipients on SRL+MPA (HR=0.61, 95% CI=0.43-0.88). No risk reduction for PTM was seen in KTR with positive viral serostatus pretransplant and placed on either SRL+MPA or SRL+Tac (Figure 7).

Outcomes in KTR with sirolimus use at other periods in first transplant year

In KTR who received SRL+MPA or SRL+Tac within the first transplant year, albeit outside of the study periods above; the adjusted relative risk for death was 3 times higher in KTR on SRL+MPA at discharge and 6th month follow-up only compared with KTR on SRL+MPA or SRL+Tac in the study periods, [HR=4.29, 95% CI=2.31-7.97 vs. HR=1.41, 95% CI=1.23-1.60 or HR=1.53, 95% CI=1.35-1.74, respectively], [Figure 8]. Due to database and sample size limitations, we were unable to analyze the factors related to the switch or discontinuation of sirolimus regimens.

Discussion

Our study of 62 315 adult recipients of kidney transplants over a 14-year period based on the United States SRTR focused on the association between 5-year transplant outcomes and baseline Hepatitis B core, Hepatitis C, CMV and EBV serostatus of kidney allograft recipients with 1-year conditional cancer and graft-loss free survival exposed to 2 sirolimus regimens in the 6 or
more months immediately before and including the first transplant year anniversary. We also examined factors predictive of the sustained use of sirolimus within the period mentioned. The primary results of our study demonstrated that the interaction between pre-transplant viral serostatus and posttransplant sirolimus regimen [(SRL+MPA or SRL+Tac) maintained for at least 6 months into the first transplant year], were associated with varying posttransplant malignancy risks. Negative HBc, HCV, EBV or CMV serostatus was associated with a risk reduction for de novo cancer in KTR maintained on SRL+MPA, not SRL+Tac. A positive (HBc, HCV, EBV or CMV) serostatus was not associated with a significant difference in de novo cancer risk with either SRL regimens, SRL+MPA or SRL+Tac (versus the reference regimen). With few exceptions, regardless of their baseline viral serostatus, mortality and graft loss risks were higher in KTR maintained on sirolimus regimens compared to those maintained on Tac+MPA Our findings could enable the use of pretransplant viral antibody serostatus in the decision-making process regarding the use of SRL+MPA, or SRL+Tac, or Tac+MPA as maintenance regimen in kidney transplant rejection prophylaxis. For patients already on sirolimus regimens, knowledge of the interaction between the specific regimen and baseline viral serostatus may help in the prognostication of for transplant outcomes.

The overall Cox model for including all 62 315 recipients showed that sirolimus-containing regimens were associated with higher risks of patient death. This is consistent with the findings in a meta-analysis that included 21 randomized controlled trials with 5963 patients [35]. In that report, any sirolimus regimen was associated with a 43% increased risk of death; whereas, in our current retrospective study involving 4826 patients, stratified analysis of sirolimus regimens showed that the risk of death relative to the reference regimen was higher by 54% with
SRL+Tac, and by 37% with SRL+MPA. Due to database limitation, we were unable to test whether the prodiabetic, prodyslipidemic, and nephrotoxic complications of the combined SRL+Tac regimen could have contributed to the higher mortality in KTR treated with the regimen especially in the HCV-positive KTR [31, 42-55]. Our findings in kidney transplants are consistent with the finding of Wagner et al. in liver transplants wherein SRL+MPA was associated with a more favorable outcome than SRL+Tac in HCV+ patients [Figure 5], [53]. In another study, Luan, et al showed that in HCV seropositive KTR, mycophenolate lowered, while tacrolimus seemed to have increased the risk for patient mortality [16]. The reduced risk of mortality associated with a positive CMV or EBV serostatus in the main Cox model was likely driven by the large size of the Tac+MPA cohort which comprised 92% of the sample [Table 1]. This is supported by the stratified Cox analyses results that showed lower mortality risk with Tac+MPA than with any of the sirolimus regimens regardless of the concomitant CMV or EBV serostatus of the KTR [Fig. 1].

The main Cox models showed that the 2 sirolimus regimens were associated with a higher risks of death-censored graft loss than Tac+MPA. The Cox models with interactions showed that regardless of the viral serostatus of KTR, SRL-containing regimens were as sociated with higher risk of graft loss than Tac+MPA; except with SRL+Tac in HBc+ or HCV+ KTR. With the recent introduction of more efficacious regimens for HCV treatment, the implications of our findings may become limited to KTR with contraindications or unsuccessful response to HCV treatment [56].
According to our analysis of the CONVERT trial adverse reaction data [57], sirolimus regimens were associated with a lower risk of malignancy versus non-sirolimus regimens at the 2-year follow-up [crude risk ratio 0.35, (95% CI=0.20-0.59)]. A retrospective database analysis by Kauffman, et.al. showed that sirolimus was associated with a de novo cancer risk reduction of 0.39 (95% CI=0.24-0.64), [32]. In our study, the risk reduction for cancer was significant at 20% for SRL+MPA but not for SRL+Tac [(SRL+MPA: HR=0.80, 95% CI=0.65-0.98) and (SRL+TAC:HR=0.82, 95%CI=0.65-1.03)]. Our study differed from the 2 preceding studies in its larger sample size, its stratification of SRL regimens into SRL+MPA and SRL+Tac, and its analysis of interactions between SRL and viral serology. Compared to the study of Kaufman et al., we analyzed outcomes based on longitudinal immunosuppression data at 3 points after transplant and not on discharge information alone and we studied SRL+MPA, not SRL+calcineurin inhibitor only [17].

We have found a significantly higher risk of death in KTR who were on sirolimus at discharge and 6th month (but the regimen was not successfully continued to the 12th month of transplant) compared with KTR whose SRL regimens were successfully continued to the 12th month of transplant after initial use at or before discharge or 6th month follow-up [Figure 8]. As the factors that affected the decision to discontinue the sirolimus regimens were not reported in SRTR, we can only hypothesize that discontinuation of sirolimus regimens may have indicated complications and/or poor patient conditions that increased the risk of death.

Our study provides a unique perspective in the consideration of sirolimus regimens in kidney retransplants by highlighting the important relationships between transplant outcomes and the
interactions between the baseline viral serostatus and posttransplant SRL regimens of KTR. Our study limitations include those inherent in an observational analysis [58], and lack of information on the following: tacrolimus and sirolimus blood levels, incidence of posttransplant viral infections and treatment given. Due to the underreporting of specific malignancy types to SRTR (59), we used the standard analysis files’ aggregated data on de novo malignancy and PTLD. Therefore, our report cannot provide sufficiently powered analyses on the relationships between specific malignancy types, sirolimus regimens and transplant outcomes. Despite its shortcomings, we used the SRTR as our data source relying on the established acceptance of this database in well-regarded transplantation publications (10, 21, 32, 39, 60).

In conclusion, our retrospective study demonstrated that compared with standard Tac+MPA immunosuppression, the lower risk of malignancy associated with sirolimus regimen is seen with SRL+MPA, not with SRL+Tac in KTR with negative pretransplant antibody serology to Hbc, HCV, EBV or CMV; neither sirolimus regimen was associated with a different malignancy risk in KTR with positive pretransplant antibody serology to any of the foregoing viruses. With a few exceptions, a sirolimus-containing regimens were associated with higher risks of patient death and death-censored graft loss than the Tac+MPA regimen regardless of the recipient’s baseline viral serostatus. Our findings may be informative in planning posttransplant immunosuppression with sirolimus-containing regimens and in prognosticating 5-year outcomes in KTR already receiving SRL regimens.
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FIGURE LEGEND

Figure 1. 5-Year Patient Mortality, Main Cox Model

Figure 2. 5-Year Death-Censored Graft Loss, Main Cox Model

Figure 3. 5-Year Malignancy Risk Factors, Main Cox Model

Figure 4. 5-Year Cause Specific Crude Death Rates in Cohorts with 1 Year Conditional Survival

Figure 5. 5-Year Risk for Patient Death, Viral Serostatus-Sirolimus Interaction Cox Models

Figure 6. 5-Year Risk for Death-Censored Graft Loss, Viral Serostatus-Sirolimus Interaction Cox Models

Figure 7. 5-Year Risk for Malignancy, Viral Serostatus-Sirolimus Interaction Cox Models

Figure 8. 5-Year Outcomes Associated with Different Durations of Sirolimus Regimen Use in the First Transplant Year
Figure 1  5 Year Patient Mortality, Main Cox Model

| Risk Factors                  | HR   | 95% CI  | Risk Factors                  | HR   | 95% CI  |
|-------------------------------|------|---------|-------------------------------|------|---------|
| SRL+MPA                       | 1.41 | 1.23-1.60| Cardiovasc. Dis.              | 1.43 | 1.32-1.55|
| SRL+Tac                       | 1.59 | 1.38-1.83| Steroid                       | 1.24 | 1.15-1.34|
| Hepatitis B core Ab+          | 0.93 | 0.83-1.05| Transplant post-2009          | 0.31 | 0.28-0.34|
| Hepatitis C Ab+               | 1.53 | 1.35-1.74| Diabetes Mellitus             | 2.39 | 2.06-2.77|
| Epstein Barr Ab+              | 0.85 | 0.77-0.94| Glomerulonephritis            | 1.26 | 1.07-1.48|
| Cytomegalovirus Ab+           | 0.89 | 0.83-0.96| Hypertension                  | 1.65 | 1.42-1.93|
| ATG Induction                 | 0.91 | 0.84-0.99| Other CKD                     | 1.61 | 1.37-1.90|
| Alemtuzumab Induction         | 1.02 | 0.88-1.18| Age of Recipient in Yr.       | 1.047| 1.04-1.05|
| Other Induction               | 1.03 | 0.94-1.13| Dialysis History +           | 1.59 | 1.42-1.78|
| ECD Kidney                    | 1.73 | 1.55-1.93| Prior kidney transplant       | 1.40 | 1.24-1.58|
| Standard Kidney               | 1.33 | 1.22-1.45| HLA mm> 3                     | 1.02 | 0.95-1.10|
| PRA >/= 20%                   | 0.98 | 0.90-1.07|                              |      |         |

Models adjusted for other covariates, not shown: Recipient African American Race HR=1.00, 95% CI=0.92-1.08, Recipient Gender HR=1.94, 95% CI=0.83-1.02.

Legend: SRL+MPA, sirolimus and mycophenolate; SRL+Tac, sirolimus and tacrolimus.
### Figure 2 5 Year Death-Censored Graft Loss, Main Cox Model

| Risk Factors                 | HR   | 95% CI  | Risk Factors               | HR   | 95% CI  |
|-----------------------------|------|---------|----------------------------|------|---------|
| SRL+MPA                     | 1.41 | 1.24 - 1.60 | Steroid                   | 1.14 | 1.05 - 1.24 |
| SRL+Tac                     | 1.38 | 1.21 - 1.57 | Transplant post-2009      | 0.28 | 0.25 - 0.31 |
| Hepatitis B core+           | 1.01 | 0.90 - 1.13 | Diabetes Mellitus         | 1.59 |         |
| Hepatitis C Ab+             | 1.50 | 1.33 - 1.70 | Glomerulonephritis        | 1.43 | 1.35 - 1.87 |
| Epstein Barr Ab +           | 0.92 | 0.84 - 1.01 | Hypertension              | 1.62 | 1.38 - 1.91 |
| Cytomegalovirus Ab+         | 1.03 | 0.96 - 1.11 | Other CKD                 | 1.52 | 1.29 - 1.79 |
| ATG                         | 0.96 | 0.88 - 1.05 | Age of Recipient in Yr.   | 0.97 | 0.96 - 0.974 |
| Alemtuzumab                 | 1.17 | 1.00 - 1.35 | Dialysis History +       | 1.45 | 1.30 - 1.62 |
| Other Induction             | 1.08 | 0.99 - 1.19 | Recipient, AA Race       | 1.62 | 1.50 - 1.75 |
| ECD Kidney                  | 2.15 | 1.92 - 2.42 | Prior kidney transplant   | 1.09 | 0.98 - 1.21 |
| Standard Kidney             | 1.25 | 1.15 - 1.35 | Recipient Female          | 0.97 | 0.91 - 1.04 |
| PRA >/= 20%                 | 1.11 | 1.02 - 1.20 | Donor, AA Race            | 1.30 | 1.19 - 1.42 |
| HLA mm >/= 3                | 1.09 | 1.02 - 1.18 |                          |      |         |

Legend: SRL+MPA, sirolimus and mycophenolate; SRL+Tac, sirolimus and tacrolimus;
Figure 3  5 Year Malignancy Risk Factors, Main Cox Model

| Risk Factors                  | HR   | 95% CI   | Risk Factors                  | HR   | 95% CI   |
|-------------------------------|------|----------|-------------------------------|------|----------|
| SRL+MPA                       | 0.80 | 0.65 - 0.98 | Transplant post-2009          | 0.31 | 0.28 - 0.34 |
| SRL+Tac                       | 0.82 | 0.65 - 1.03 | Diabetes Mellitus             | 0.70 | 0.60 - 0.79 |
| Hepatitis B core+             | 0.80 | 0.68 - 0.95 | Glomerulonephritis            | 1.05 | 0.92 - 1.20 |
| Hepatitis C Ab+               | 1.24 | 1.02 - 1.52 | Hypertension                  | 0.80 | 0.70 - 0.92 |
| Epstein Barr Ab +             | 0.98 | 0.86 - 1.10 | Other CKD                     | 1.03 | 0.89 - 1.19 |
| Cytomegalovirus A +           | 0.82 | 0.76 - 0.90 | Age of Recipient in Yrs.      | 1.058| 1.055 - 1.062|
| ATG                           | 1.27 | 1.15 - 1.40 | Dialysis History +           | 0.77 | 0.70 - 0.84 |
| Alectuzumab                   | 1.30 | 1.10 - 1.54 | Recipient, AA Race            | 0.60 | 0.53 - 0.67 |
| Other Induction               | 0.88 | 0.77 - 0.99 | Recipient Female              | 0.75 | 0.69 - 0.82 |
| Steroid-Maintained            | 1.14 | 1.04 - 1.25 | Recipient BMI (kg/m²)         | 1.03 | 0.95 - 1.13 |

Legend: SRL+MPA, sirolimus and mycophenolate; SRL+Tac, sirolimus and tacrolimus.
Figure 4  5 Year Cause-Specific Death Rates in Cohorts with Conditional 1 Year Survival

Cumulative Death Rate (Percent in 5 years)

| Cause of Death     | Tac+MPA  | SRL+Tac | SRL+MPA |
|--------------------|---------|---------|---------|
| Other organ failure| 7.2%    | 8.3%    |         |
| Trauma/Suicide     | 2.3%    | 2.1%    |         |
| Malignancy          | 12.3%   | 11.6%   |         |
| Hemorrhage          | 0.5%    | 1.7%    |         |
| Pulmonary embolism  | 0.5%    | 0.8%    |         |
| Cardiovascular      | 12.4%   | 21.5%   | 24.9%   |
| Infection           | 13.7%   |         |         |

Crude Odds Ratio for Death Associated with Sirolimus Regimens under Specific Causes

| Regimen               | Other organ failure | Cardiovascular DIs | Malignancy | Infections |
|-----------------------|---------------------|--------------------|------------|------------|
|                       | OR 95% CI           | OR 95% CI          | OR 95% CI  | OR 95% CI  |
| SRL+MPA (vs. Tac+MPA) | 1.22 0.74-2.00      | 1.14 0.82-1.58     | 0.76 0.47-1.23 | 1.09 0.72-1.64 |
| SRL+Tac (vs. Tac+MPA) | 1.00 0.56-1.78      | 0.95 0.65-1.38     | 0.93 0.56-1.50 | 1.08 0.69-1.67 |
Figure 5  5 Year Risk for Patient Death, Viral Serostatus-Sirolimus Interaction Cox Models

| Risk Factors | HR  | 95% CI      | Risk Factors | HR  | 95% CI      |
|--------------|-----|-------------|--------------|-----|-------------|
| HBC+ Referent* | 1.00 | 1.00 -1.00 | EBV+ Referent* | 1.00 | 1.00 - 1.00 |
| SRL+MPA       | 1.50 | 0.93 -2.26  | SRL+MPA      | 1.37 | 1.19 - 1.58 |
| SRL+Tac       | 1.41 | 0.84 -2.27  | SRL+Tac      | 1.62 | 1.40 - 1.89 |
| HBC- Referent* | 1.00 | 1.00 -1.00 | EBV- Referent* | 1.00 | 1.00 - 1.00 |
| SRL+MPA       | 1.40 | 1.22 -1.61  | SRL+MPA      | 1.66 | 1.19 - 2.31 |
| SRL+Tac       | 1.61 | 1.39 -1.86  | SRL+Tac      | 1.41 | 0.96 - 2.06 |
| HCV+ Referent* | 1.00 | 1.00 -1.00 | CMV+ Referent* | 1.00 | 1.00 - 1.00 |
| SRL+MPA       | 1.38 | 0.84 -2.25  | SRL+MPA      | 1.38 | 1.18 - 1.62 |
| SRL+Tac       | 2.02 | 1.24 -3.31  | SRL+Tac      | 1.52 | 1.28 - 1.80 |
| HCV- Referent* | 1.00 | 1.00 -1.00 | CMV- Referent* | 1.00 | 1.00 - 1.00 |
| SRL+MPA       | 1.41 | 1.23 -1.61  | SRL+MPA      | 1.46 | 1.17 - 1.83 |
| SRL+Tac       | 1.56 | 1.35 -1.81  | SRL+Tac      | 1.76 | 1.38 - 2.24 |

| ATG | Alport | Age | AA Race | Sex Freq. | CVOD | DMI 1st CED | ON 1st CED | hTR 1st CED | Dialysis Preop. | Transpl >3000 | PRA >50% | HLA mismt | Diabetic | Status | ECD | SCD |
|-----|--------|-----|---------|-----------|-----|-------------|-------------|-------------|----------------|-------------|----------|-----------|----------|--------|-----|-----|
| H.R. | 91.04 | .81 | <.001  | 1.96 | 1.43 | 2.40 | 1.286 | 1.65 | <.001 | 1.59 | <.001 | 0.31 | .66 | 1.02 | 1.40 | 1.34 | 1.73 | 1.33 | <.001 |

Legend: Sirolimus, SRL; Mycophenolate, MPA; Tacrolimus, Tac; *Referent, Tac+MPA; **Each model adjusted for viral serostatus-SRL interactions, the other 3 viral serostatuses and the covariates in the table.
Figure 6  5 Year Risk Factors for Death-Censored Graft Loss, Viral Serostatus-Sirolimus Interaction Cox Models

| Serostatus x SRL Regimen | HR    | 95% CI    |
|--------------------------|-------|-----------|
| HBC+ Referent*           | 1.00  | 1.00-1.00 |
| SRL+MPA                  | 2.02  | 1.40-2.91 |
| SRL+Tac                  | 1.16  | 0.73-1.83 |
| HBC- Referent*           | 1.00  | 1.00-1.00 |
| SRL+MPA                  | 1.36  | 1.15-1.55 |
| SRL+Tac                  | 1.40  | 1.22-1.61 |
| HCV+ Referent*           | 1.00  | 1.00-1.00 |
| SRL+MPA                  | 1.56  | 1.02-2.37 |
| SRL+Tac                  | 1.17  | 0.68-2.00 |
| HCV- Referent*           | 1.00  | 1.00-1.00 |
| SRL+MPA                  | 1.40  | 1.23-1.60 |
| SRL+Tac                  | 1.40  | 1.22-1.60 |

| Serostatus x SRL Regimen | HR    | 95% CI    |
|--------------------------|-------|-----------|
| EBV+ Referent*           | 1.00  | 1.00-1.00 |
| SRL+MPA                  | 1.38  | 1.20-1.58 |
| SRL+Tac                  | 1.34  | 1.16-1.55 |
| EBV- Referent*           | 1.00  | 1.00-1.00 |
| SRL+MPA                  | 1.65  | 1.19-2.30 |
| SRL+Tac                  | 1.60  | 1.16-2.19 |
| CMV+ Referent*           | 1.00  | 1.00-1.00 |
| SRL+MPA                  | 1.39  | 1.18-1.63 |
| SRL+Tac                  | 1.47  | 1.26-1.72 |
| CMV- Referent*           | 1.00  | 1.00-1.00 |
| SRL+MPA                  | 1.46  | 1.18-1.80 |
| SRL+Tac                  | 1.22  | 0.96-1.53 |

Legend: SRL: Mycophenolate, MPA: Tacrolimus, Tac: Referent, Tac+MPA: *Each model adjusted for viral serostatus-SRL interactions, the other 3 viral serostatus and the covariates in the table.
Figure 7  5 Year Risk for Malignancy, Viral Serostatus-Sirolimus Interaction Cox Models

| Risk Factors | HR   | 95% CI   | Risk Factors | HR   | 95% CI   |
|--------------|------|----------|--------------|------|----------|
| HBC+; Referent* | 1.00 | 1.00 - 1.00 | EBV+; Referent* | 1.00 | 1.00 - 1.00 |
| SRL+MPA       | 0.82 | 0.34 - 2.01  | SRL+MPA       | 0.87 | 0.71 - 1.08  |
| SRL+Tac       | 0.36 | 0.10 - 1.43  | SRL+Tac       | 0.79 | 0.62 - 1.02  |
| HBC-; Referent* | 1.00 | 1.00 - 1.00  | EBV-; Referent* | 1.00 | 1.00 - 1.00  |
| SRL+MPA       | 0.80 | 0.65 - 0.98  | SRL+MPA       | 0.27 | 0.10 - 0.71  |
| SRL+Tac       | 0.85 | 0.67 - 1.07  | SRL+Tac       | 0.98 | 0.52 - 1.80  |
| HCV+; Referent* | 1.00 | 1.00 - 1.00  | CMV+; Referent* | 1.00 | 1.00 - 1.00  |
| SRL+MPA       | 1.10 | 0.45 - 2.71  | SRL+MPA       | 0.93 | 0.73 - 1.19  |
| SRL+Tac       | 0.45 | 0.11 - 1.83  | SRL+Tac       | 0.89 | 0.67 - 1.18  |
| HCV-; Referent* | 1.00 | 1.00 - 1.00  | CMV-; Referent* | 1.00 | 1.00 - 1.00  |
| SRL+MPA       | 0.79 | 0.64 - 0.97  | SRL+MPA       | 0.61 | 0.43 - 0.88  |
| SRL+Tac       | 0.83 | 0.66 - 1.06  | SRL+Tac       | 0.69 | 0.46 - 1.04  |

Legend: Sirolimus, SRL: Mycophenolate, MPA: Tacrolimus, Tac* Referent: Tac+MPA; **Each model adjusted for viral serostatus-SRL interactions, the other 3 viral serostatuses and the covariates in the table.
Figure 8  5 Year Outcomes Associated with Sirolimus Regimens at Different Periods in the First Transplant Year

|                  | HR | 95% CI       |                  | HR | 95% CI       |                  | HR | 95% CI       |
|------------------|----|--------------|------------------|----|--------------|------------------|----|--------------|
| **Patient Death:** |    |              | **Patient Death:** |    |              | **Patient Death:** |    |              |
| SRL+MPA          | 4.29 | 2.31 - 7.97  | SRL+MPA          | 1.27 | 0.56 - 2.45  | SRL+MPA          | 1.41 | 1.23 - 1.60 |
| SRL+Tac          | 1.18 | 0.47 - 2.97  | SRL+Tac          | 1.11 | 0.52 - 2.38  | SRL+Tac          | 1.53 | 1.35 - 1.74 |
| **Graft Loss, DC:** |    |              | **Graft Loss, DC:** |    |              | **Graft Loss, DC:** |    |              |
| SRL+MPA          | 1.19 | 0.43 - 3.28  | SRL+MPA          | 0.61 | 0.27 - 1.41  | SRL+MPA          | 1.42 | 1.24 - 1.60 |
| SRL+Tac          | 1.16 | 0.57 - 2.38  | SRL+Tac          | 1.71 | 0.99 - 2.93  | SRL+Tac          | 1.36 | 1.20 - 1.53 |
| **Malignancy:**  |    |              | **Malignancy:**  |    |              | **Malignancy:**  |    |              |
| SRL+MPA          | 1.01 | 0.13 - 7.97  | SRL+MPA          | 1.04 | 0.33 - 3.30  | SRL+MPA          | 0.80 | 0.65 - 0.98 |
| SRL+Tac          |    |              | SRL+Tac          |    |              | SRL+Tac          |    |              |

SRL Regimen at discharge + month-6, not at month-12

SRL Regimen at discharge only, month 6 only, or discharge + month-12 only

SRL Regimen at month-6 + month-12, with/without SRL at discharge

Referent: Tac+MPA at month-12 AND at month-6 +/- at discharge.
Legend: SRL+MPA, sirolimus and mycophenolate; SRL+Tac, sirolimus and tacrolimus; DC, death-censored; ISA, insufficient sample for analysis.
| Variables | sirolimus and mycophenolate<sup>a</sup> N=2659 | sirolimus and tacrolimus<sup>a</sup> N=2167 | tacrolimus and mycophenolate<sup>a</sup> N=56 764 | P Value |
|-----------|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------|
| Pretransplant Viral Serology: | | | | |
| Hepatitis B antibody + | 180 (6.8) | 168 (7.8) | 4426 (7.8) | .02 |
| Hepatitis C antibody + | 122 (4.6) | 98 (4.5) | 2517 (4.4) | .92 |
| Epstein Barr Virus + | 2339 (88.0) | 1881 (86.8) | 49663 (87.5) | .48 |
| Cytomegalovirus + | 1616 (60.8) | 1381 (63.7) | 37092 (65.3) | <.001 |
| Donor Type: | | | | <.001 |
| Expanded Criteria Deceased | 363 (13.6) | 195 (9.0) | 4963 (8.7) | |
| Standard Criteria Deceased | 1159 (43.6) | 1054 (48.6) | 29140 (51.3) | |
| Living | 1137 (42.8) | 918 (42.4) | 22661 (39.9) | |
| Donor Age, years: Mean (SD) | 41.8 (14.6) | 38.1 (14.8) | 38.7 (14.7) | <.001 |
| Recipient Age, years: Mean (SD) | 48.7 (13.4) | 46.2 (13.6) | 49.3 (13.7) | <.001 |
| Recipient Race: | | | | .11 |
| Black | 697 (26.2) | 599 (27.6) | 14585 (25.7) | |
| Other | 1962 (73.8) | 1568 (75.4) | 42179 (74.3) | |
| Recipient Gender: | | | | <.001 |
| Male | 1741 (65.5) | 1264 (58.3) | 33881 (59.7) | |
| Female | 918 (34.5) | 903 (41.7) | 22883 (40.3) | |
| Previous Kidney Transplant: | | | | <.001 |
| Yes | 242 (9.1) | 304 (14.0) | 6483 (11.4) | |
| No | 2417 (90.9) | 1863 (86.0) | 50281 (88.6) | |
| Recipient BMI: > = 30 kg/m<sup>2</sup> | 807 (31.9) | 522 (25.6) | 17797 (32.7) | <.001 |
| CAD or CAD-equivalent<sup>b</sup> | 414 (15.6) | 245 (11.3) | 6728 (11.8) | <.001 |
| Pretransplant PRA: PRA >/= 20% | 565 (21.2) | 520 (24.0) | 15269 (26.9) | <.001 |
| HLA mismatch > 3 | 1501 (63.6) | 1193 (60.9) | 33756 (59.9) | <.001 |
| Primary Kidney Disease: | | | | <.001 |
| Diabetes Mellitus | 614 (23.1) | 424 (19.6) | 13314 (23.5) | |
| Glomerulonephritis | 609 (22.9) | 560 (25.8) | 13563 (23.9) | |
| Hypertension | 714 (26.9) | 525 (24.2) | 13647 (24.0) | |
| Polycystic Kidney Disease | 259 (9.7) | 225 (10.4) | 5818 (10.2) | |
| Other | 463 (17.4) | 433 (20.0) | 10422 (18.4) | |
| Pretransplant Dialysis History: | | | | .25 |
| No (Preemptive transplant) | 500 (18.8) | 374 (17.3) | 10600 (18.7) | |
| Yes | 2159 (81.2) | 1793 (82.7) | 46164 (81.3) | |
| Transplant Year: | | | | <.001 |
| 2000- 2009 | 2230 (83.9) | 2053 (94.7) | 33324 (58.7) | |
| 2010-2013 | 429 (16.1) | 114 (5.3) | 23440 (41.3) | |
| Steroids in Regimen: | | | | .02 |
| Induction Antibody Agent: | | | | <.001 |
| antithymocyte globulin | 1161 (43.7) | 1300 (44.9) | 25573 (45.1) | |
| alemtuzumab | 112 (4.2) | 35 (1.2) | 5637 (9.9) | |
| basiliximab | 764 (28.7) | 855 (29.6) | 13358 (23.5) | |
| Other | 622 (23.4) | 702 (24.3) | 12196 (21.5) | |
a Based on Scientific Registry of Transplant Recipients Immunosuppression Records Collected at discharge, month-6 and month-12 follow-up, recipients were on same regimen with or without steroids at discharge, 6th month and 12th month or at 6th month and 12th month.

b CAD=Coronary Artery Disease including angina or coronary artery disease. CAD-equivalent included Diabetes Mellitus, Peripheral Vascular Disease and Cerebro-vascular disea
TABLE 2. Adjusted Odds Ratio for Continuous Sirolimus Regimen Use for a Minimum of 6 Months Immediately Before and Including the Twelfth Transplant Month in Adult Kidney Allograft Recipients

| Predictor Variable (Reference) | SRL + MPA vs. Tac+ MPA | SRL + Tac vs. Tac + MPA | SRL + MPA vs. SRL + Tac |
|-------------------------------|------------------------|------------------------|------------------------|
|                               | HR 95% CI              | HR 95% CI              | HR 95% CI              |
| Pretransplant Viral Serology: |                        |                        |                        |
| Hepatitis Bc antibody + (-)   | 0.83 [0.70 0.99]       | 0.98 [0.82 1.17]       | 0.87 [0.68 1.12]       |
| Hepatitis C antibody + (-)    | 1.02 [0.83 1.25]       | 0.84 [0.66 1.07]       | 1.23 [0.90 1.70]       |
| Epstein Barr Virus + (-)      | 1.12 [0.98 1.28]       | 1.10 [0.95 1.27]       | 1.00 [0.82 1.22]       |
| Cytomegalovirus + (-)         | 0.82 [0.75 0.90]       | 0.95 [0.85 1.05]       | 0.88 [0.77 1.02]       |
| Donor Type:                   |                        |                        |                        |
| ECD\(^a\) (Living)           | 1.63 [1.40 1.89]       | 1.18 [0.98 1.42]       | 1.35 [1.07 1.71]       |
| SCD\(^b\) (Living)           | 0.90 [0.81 0.99]       | 0.99 [0.88 1.10]       | 0.88 [0.76 1.03]       |
| Recipient Age                 | 0.99 [0.99 0.998]      | 0.987 [0.98 0.99]      | 1.01 [1.00 1.014]      |
| Recipient Race: Black (Other) | 1.13 [1.02 1.26]       | 1.12 [1.00 1.25]       | 0.98 [0.84 1.14]       |
| Recipient Sex: Female (Male)  | 0.85 [0.77 0.93]       | 1.07 [0.97 1.18]       | 0.80 [0.70 0.92]       |
| Previous Kidney Transplant: + (-) | 0.90 [0.76 1.06] | 1.25 [1.07 1.46] | 0.74 [0.60 0.93] |
| Recipient BMI: >30(<30) kg/m² | 0.99 [0.90 1.09]       | 0.83 [0.75 0.93]       | 1.18 [1.02 1.36]       |
| >1 CAD or CAD-equivalent \(^c\) | 1.26 [1.11 1.43]       | 0.91 [0.78 1.07]       | 1.32 [1.08 1.61]       |
| PRA: PRA >20% (<20%)          | 0.87 [0.78 0.98]       | 0.88 [0.78 1.00]       | 0.97 [0.82 1.15]       |
| HLA mismatch > 3 (<3)         | 0.95 [0.86 1.04]       | 0.88 [0.79 0.97]       | 1.08 [0.93 1.24]       |
| Primary Disease               |                        |                        |                        |
| Diabetes Mellitus (PCKD)      | 1.01 [0.85 1.19]       | 0.90 [0.75 1.08]       | 1.17 [0.91 1.50]       |
| Glomerulonephritis (PCKD)     | 0.96 [0.81 1.14]       | 0.87 [0.73 1.04]       | 1.13 [0.89 1.45]       |
| Hypertension (PCKD)           | 1.13 [0.96 1.33]       | 0.91 [0.76 1.09]       | 1.26 [0.98 1.61]       |
| On dialysis (pre-emptive transp.) | 0.98 [0.86 1.10] | 1.10 [0.96 1.26] | 0.92 [0.77 1.11] |
| Transplant after 2009 (before 2009) | 0.30 [0.26 0.33] | 0.09 [0.07 0.11] | 3.21 [2.53 4.08] |
| Induction Drug:               |                        |                        |                        |
| ATG (basiliximab)             | 0.92 [0.83 1.02]       | 0.90 [0.80 1.01]       | 0.96 [0.82 1.12]       |
| alemtuzumab (basiliximab)     | 0.43 [0.35 0.54]       | 0.15 [0.10 0.23]       | 2.31 [1.41 3.76]       |

SRL+MPA, sirolimus and mycophenolate; SRL+Tac, sirolimus and tacrolimus; Tac+MPA, tacrolimus and mycophenolate;

\(^a\)ECD, Expanded Criteria Deceased

\(^b\)SCD, Standard Criteria Deceased
CAD=Coronary Artery Disease including angina or coronary artery disease. CAD-equivalent included Diabetes Mellitus, Peripheral Vascular Disease and Cerebro-vascular disease