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Brief Communication: Delayed Graft Function and Acute Rejection Following HLA-Incompatible Living Donor Kidney Transplantation

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Abstract

Incompatible living donor kidney transplant recipients (ILDKTr) have pre-existing donor-specific antibody (DSA) that, despite desensitization, may persist or reappear with resulting consequences, including delayed graft function (DGF) and acute rejection (AR). To quantify the risk of DGF and AR in ILDKT and downstream effects, we compared 1,406 ILDKT to 17,542 compatible LDKT recipients (CLDKTr) using a 25-center cohort with novel SRTR linkage. We characterized DSA strength as positive-Luminex, negative-flow crossmatch (PLNF); positive-flow, negative-cytotoxic crossmatch (PFNC); or positive-cytotoxic crossmatch (PCC). DGF occurred in 3.1% of CLDKT, 3.5% of PLNF, 5.7% of PFNC, and 7.6% of PCC recipients, which translated to higher DGF for PCC recipients (aOR=$_{1.03}1.68_{2.72}$). However, the impact of DGF on mortality and DCGF risk was no higher for ILDKT than CLDKT (p interaction>0.1). AR developed in 8.4% of CLDKT, 18.2%

of PLNF, 21.3% of PFNC, and 21.7% of PCC recipients, which translated to higher AR (aOR PLNF=$_{1.45}2.09_{3.02}$;PFNC=$_{1.67}2.40_{3.46}$;PCC=$_{1.48}2.24_{3.37}$). Although the impact of AR on mortality was no higher for ILDKT than CLDKT (p interaction=0.1), its impact on DCGF risk was less consequential for ILDKT (aHR=$_{1.34}1.62_{1.95}$) than CLDKT (aHR=$_{1.96}2.29_{2.67}$) (p interaction=0.004). Providers should consider these risks during pre-operative counselling, and strategies to mitigate them should be considered.

Keywords

HLA-incompatible; live donor; kidney transplantation; delayed graft function; acute rejection; highly sensitized; donor-specific antibody; clinical research/practice

INTRODUCTION

HLA-incompatible living donor kidney transplantation (ILDKT) allows for transplantation across donor-specific antibody (DSA) through the use of various desensitization protocols (1, 2). However, outcomes after ILDKT have been reported to be inferior compared to compatible LDKT (CLDKT), such as a 1.64-fold and 5.01-fold increased risk of graft loss at 1-year for recipients with a positive flow cytometric crossmatch and positive cytotoxic crossmatch, respectively (3). This may be a consequence of increased post-operative complications, including delayed graft function (DGF) and acute rejection (AR) (4–7), given the potential risk of post-desensitization resurgence of DSA. Thus, successful monitoring and management of HLA antibody remain a continued challenge for ILDKT recipients (ILDKTr).

DGF affects 4–10% of LDKT recipients and is a manifestation of ischemia-reperfusion injury (8–10). The extent of injury is dependent partly on innate and adaptive immune responses, which may be exacerbated by DSA at time of transplant (4, 8). Taken together with its associations of higher mortality and graft loss risk in LDKT recipients (11, 12), it is likely that DGF has a greater impact in ILDKTr. Likewise, AR affects 7.3–8.8% of LDKT recipients within 1 year and is believed to stem from T-cell and/or B-cell dependent pathways (13, 14). In light of its known association with DSA (15–17), AR is of significant concern in ILDKTr (18). Moreover, its deleterious effect on graft life further subjects ILDKTr to adverse long-term outcomes (6). However, as DGF and AR generally precede mortality and graft loss, anticipating these events may lead to more effective management and response to therapy (8, 15, 18, 19). Therefore, characterizing the risk of these outcomes in ILDKTr is important, and would better inform patient counselling.

We used a 25-center cohort linked to national registry data to quantify the risk of DGF and AR for ILDKTr, stratified by DSA strength, compared to CLDKT recipients (CLDKTr). We then sought to determine whether the impact of DGF and AR on subsequent mortality and graft loss was similar in ILDKTr and CLDKTr.

METHODS

Data Linkage

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data 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 (20). 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.

Study population

We included adults (≥18 years) who received a kidney-only transplant from HLA-incompatible living donors at 25 transplant centers across the United States from 9/24/1997 through 12/15/2016. We defined ILDKTr as those undergoing perioperative desensitization therapy for DSA prior to transplantation, as previously described (3). Briefly, all participating transplantation centers classified their ILDKTr by low, moderate, or high levels of DSA, which corresponded to positive Luminex, negative flow crossmatch (PLNF), positive flow, negative cytotoxic crossmatch (PFNC), or positive cytotoxic crossmatch (PCC), respectively (3). Some centers performed actual cell-based crossmatches, whereas others performed virtual crossmatches based on semi-quantitative DSA strength on solid-phase assays (3). Despite the variation in results of these assays and between each laboratory, each center's established mean fluorescence intensity benchmarks equated to the three categories evaluated in the present study (3). In view of the minimal risk associated with ABO-incompatible transplantation, patients who required both HLA and ABO barriers to be crossed (6.1% of ILDKTr) were categorized on the basis of their DSA strength (2, 3).

To understand how the risks of our outcomes varied in relation to CLDKT, we identified all recipients who received kidney-only transplants from compatible living donors at the same centers and time period (i.e. when each center was performing ILDKT) as their ILDKT counterparts. This study was approved by the Johns Hopkins University Institutional Review Board.

Outcomes

We studied DGF, AR, mortality, and death-censored graft loss (date of graft loss, retransplant, or return to maintenance dialysis). We defined DGF as the need for post-operative dialysis within 7 days following surgery, as reported to the OPTN (Transplant Recipient Registration Form). Likewise, the OPTN collects information (Transplant Recipient Follow-Up Form) on AR provided by centers at specific periods post-transplant (0–6 months and 7–12 months, annually thereafter), although exact dates are not reported (20). We defined AR as an AR event that occurred within the first year of transplant (i.e. during the first 2 reporting periods) according to center reports, based on previously published methods using SRTR data (21, 22). As a sensitivity analysis, we limited our definition of AR to only biopsy-proven AR events for recipients transplanted between 1997–2015; the OPTN removed biopsy-proven AR from the Transplant Recipient Follow-Up

Form in 2016. Results of this were consistent with our main analysis (Supplementary Table 1).

Risk of DGF and acute rejection

We used adjusted logistic regression to model the associations between: (i) DSA strength (CLDKT, PLNF, PFNC, PCC) and DGF, and (ii) DSA strength and AR. For both analyses, we adjusted for recipient (age, sex, race, body mass index [BMI], cause of end stage renal disease [ESRD], peripheral vascular disease, calculated PRA [cPRA)/PRA], years on dialysis, number of previous transplants, and year of transplant), donor (living donor kidney donor profile index [LKDPI]), and transplant characteristics (HLA mismatch, cold ischemia time). We excluded recipients who died <7 days from transplant (n=23, 0.01%), or who were missing data on DGF (n=1, 0.005%) or AR (n=205, 1.1%).

Risk of graft loss and mortality

To understand whether the impact of DGF and AR on subsequent mortality and graft loss was similar in ILDKTr and CLDKTr, we used adjusted Cox regression to quantify the association between: (i) DGF and mortality, (ii) DGF and death-censored graft failure (DCGF), (iii) AR and mortality, and (iv) AR and DCGF. We included an interaction term to determine whether the risk of mortality or DCGF differed for ILDKT compared to CLDKT recipients. Recipients were followed from date of transplant until the outcome of interest (i.e. death or DCGF) or administrative censorship on 9/1/2019. For all analyses, we adjusted for the same recipient, donor, and transplant characteristics as in the DGF and acute rejection analyses. As a sensitivity analysis, we removed recipients from analysis (ii) who had graft failure (n=226, 1.2%), or died (n=84, 0.4%) within 90 days from transplant since we were unable to discern primary non-function from DGF within 7 days from transplant, as currently reported to the OPTN.

Long-term trajectories of eGFR

We compared the five-year estimated glomerular filtration rate (eGFR; CKD-EPI equation) trajectories between ILDKTr and CLDKTr using adjusted mixed-effects linear regression, with a random effect for each individual. Recipients had a median of 3 (interquartile range [IQR]: 2–5) eGFR measurements. We included an interaction term to determine whether the eGFR slope differed over time between ILDKTr and CLDKTr. We used complete-case analysis to adjust for the same recipient, donor, and transplant characteristics as in previous analyses.

Statistical analysis

To compare characteristics of ILDKTr and CLDKTr, we used Pearson’s chi-squared tests for categorical variables, ANOVA for normally-distributed continuous variables, and the Kruskal-Wallis test for non-normally-distributed continuous variables. Recipients who received both depleting and non-depleting induction (n=312, 1.9%) were categorized as having depleting induction in Table 1. Unless otherwise specified, multiple imputation by chained equations with 10 imputations over 100 iterations was used to handle missing data (23). The extent of missing data ranged from 0.7%−25.5%. To account for within center

clustering of outcomes, we used a robust sandwich estimator. Confidence intervals are reported as per the method of Louis and Zeger. All analyses were performed using Stata 16.0/MP for Linux (College Station, Texas).

RESULTS

Study population

We identified 1,406 ILDKTr and 17,542 CLDKTr. Among ILDKTr, 376 (26.7%) were PLNF, 687 (48.9%) were PFNC, and 343 (24.4%) PCC transplants (Table 1). Compared to CLDKTr, ILDKTr were more likely to be younger (CLDKT: 48.5 years, PLNF: 46.9 years, PFNC: 45.5 years, PCC: 43.7 years) and female (CLDKT: 38.4%, PLNF: 55.6%, PFNC: 68.0%, PCC: 65.6%) ($p<0.001$ for all comparisons). ILDKTr were less likely to be pre-emptively transplanted (CLDKT: 35.6%, PLNF: 29.0%, PFNC: 22.1%, PCC: 16.0%), more likely to undergo dialysis for >6 years (CLDKT: 3.0%, PLNF: 6.6%, PFNC: 13.1%, PCC: 23.9%), to have undergone a prior transplant (CLDKT: 9.1%, PLNF: 23.9%, PFNC: 32.5%, PCC: 40.5%), and have c/PRA 100% (CLDKT: 0.7%, PLNF: 3.5%, PFNC: 9.8%, PCC: 17.5%) compared to their CLDKT counterparts ($p<0.001$ for all comparisons). ILDKTr were also more likely to receive kidneys from younger donors (CLDKT: 42.5 years, PLNF: 41.7 years, PFNC: 40.6 years, PCC: 40.7 years, $p<0.001$) and less likely to receive a kidney from a female donor (CLDKT: 60.6%, PLNF: 56. 6%, PFNC: 57.5%, PCC: 53.9%, $p=0.01$).

Delayed graft function

DGF occurred in 5.6% of ILDKTr and 3.1% of CLDKTr. Among ILDKTr, DGF occurred in 3.5% of PLNF, 5.7% of PFNC, and 7.6% of PCC recipients ($p<0.001$) (Figure 1). Compared to CLDKTr, there was no evidence of higher DGF risk in PLNF after adjusting for donor and recipient characteristics (adjusted odds ratio [aOR]=$_{0.62}0.97_{1.52}$; $p=0.9$) and PFNC (aOR=$_{0.73}1.43_{2.78}$; $p=0.3$), but PCC recipients had a 1.68-fold (aOR=$_{1.03}1.68_{2.72}$; $p=0.04$) higher risk of DGF.

Acute rejection

AR occurred in 20.6% of ILDKTr and 8.4% of CLDKTr. Among ILDKTr, AR occurred in 18.2% of PLNF, 21.3% of PFNC, and 21.7% of PCC recipients ($p<0.001$) (Figure 2). Overall, compared to CLDKTr, PLNF had a 2.09-fold (aOR=$_{1.45}2.09_{3.02}$; $p<0.001$), PFNC had a 2.40-fold (aOR=$_{1.67}2.40_{3.46}$; $p<0.001$), and PCC recipients had a 2.24-fold (aOR=$_{1.48}2.24_{3.37}$; $p<0.001$) higher risk of AR.

Impact of DGF on mortality and graft loss

Mortality—One-, five-, and ten-year cumulative mortality for ILDKTr with DGF (vs. without) was 6.4% (vs. 3.7%), 24.6% (vs. 11.9%), and 46.9% (vs. 27.0%) ($p<0.001$) (Figure 3A). One-, five-, and ten-year cumulative mortality for CLDKTr with DGF (vs. without) was 5.0% (vs. 1.4%), 16.5% (vs. 7.9%), and 34.4% (vs. 21.5%) ($p<0.001$) (Figure 3A). After adjustment, DGF was associated with significantly higher mortality risk in both ILDKTr (aHR=$_{1.17}1.73_{2.56}$; $p=0.006$) and CLDKTr (aHR=$_{1.18}1.41_{1.68}$; $p<0.001$); however, there was no statistically significant interaction between DGF and ILDKT status ($p=0.3$), indicating that the impact of DGF on risk of mortality was no higher for ILDKTr than for CLDKTr.

Graft loss—The thirty-day, one-, five-, and ten-year cumulative DCGF risk for ILDKTr with DGF (vs. without) was 24.5% (vs. 1.0%), 29.8% (vs. 3.4%), 43.4% (vs. 16.7%), and 56.9% (vs. 30.4%) (p<0.001) (Figure 3B). The causes of DCGF within 30 days for ILDKTr with DGF were AR (21.0%), primary failure (15.8%), hyperacute rejection (10.5%), infection (5.3%), surgical complications (5.3%), and other/unknown (42.1%). The thirty-day, one-, five-, and ten-year cumulative DCGF risk for CLDKTr with DGF (vs. without) was 13.4% (vs. 0.4%), 18.8% (vs. 1.3%), 29.1% (vs. 7.2%), and 41.6% (vs. 15.8%) (p<0.001) (Figure 3B). The causes of DCGF within 30 days for CLDKTr with DGF were graft thrombosis (57.5%), AR (9.6%), hyperacute rejection (4.1%), surgical complications (4.1%), infection (2.7%), primary non-function (1.4%), primary failure (1.4%), and other/unknown (19.2%). After adjustment, DGF was associated with significantly higher risk of DCGF in ILDKTr (aHR=$_{1.81}2.49_{3.42}$; p<0.001) and CLDKTr (aHR=$_{2.43}3.06_{3.85}$; p<0.001); however, there was no statistically significant interaction between DGF and ILDKT status (p=0.2), indicating that the impact of DGF on risk of DCGF was no higher for ILDKTr than for CLDKTr.

As a sensitivity analysis, we removed recipients who had graft failure or who died within 90 days from transplant. After adjustment, DGF was not associated with significantly higher risk in ILDKTr (aHR=$_{0.76}1.33_{2.33}$; p=0.3), but was associated with significantly higher risk for CLDKTr (aHR=$_{1.47}1.82_{2.25}$; p<0.001). There was no statistically significant interaction between DGF and ILDKT status (p=0.3).

Impact of acute rejection on mortality and graft loss

Mortality—One-, five-, and ten-year cumulative mortality for ILDKTr with AR (vs. without) was 3.9% (vs. 2.9%), 14.0% (vs. 11.1%), and 29.0% (vs. 26.7%) (p=0.3) (Figure 4A). One-, five-, and ten-year cumulative mortality for CLDKTr with AR (vs. without) was 2.0% (vs. 1.2%), 10.8% (vs. 7.7%), and 25.7% (vs. 21.4%) (p<0.001) (Figure 4A). After adjustment, AR was associated with significantly higher mortality risk in ILDKTr (aHR=$_{1.06}1.29_{1.58}$; p=0.01) and CLDKTr (aHR=$_{1.39}1.54_{1.71}$; p<0.001); however, there was no statistically significant interaction between AR and ILDKT status (p=0.1), indicating that the impact of AR on risk of mortality was no higher for ILDKTr than for CLDKTr.

Graft loss—The thirty-day, one-, five-, and ten-year cumulative DCGF risk for ILDKTr with AR (vs. without) was 1.1% (vs. 1.0%), 4.0% (vs. 3.3%), 28.8% (vs. 13.9%), and 41.1% (vs. 28.2%) (p<0.001) (Figure 4B). The thirty-day, one-, five-, and ten-year cumulative DCGF risk for CLDKTr with AR (vs. without) was 0.5% (vs. 0.3%), 3.5% (vs. 1.1%), 18.4% (vs. 6.4%), and 32.7% (vs. 14.6%) (p<0.001) (Figure 4B). After adjustment, AR was associated with significantly higher risk of DCGF in ILDKTr (aHR=$_{1.34}1.62_{1.95}$; p<0.001) and CLDKTr (aHR=$_{1.96}2.29_{2.67}$; p<0.001); however, there was a statistically significant interaction between AR and ILDKT status (p=0.004), indicating that the impact of AR on risk of DCGF was less consequential for ILDKTr as compared to their CLDKT counterparts.

Long-term trajectories of eGFR

After adjustment, ILDKTr and CLDKTr had comparable average eGFR immediately post-transplant (difference=$_{-0.68}0.69_{2.07}$ mL/min/1.73m^2, p=0.3). However, ILDKTr had faster

decline in eGFR per year compared to CLDKTr (difference in slope=$_{-1.23}$-1.00$_{-0.78}$ mL/min/1.73m^2 per year, p<0.001; decline over 5 years for ILDKT=$_{-9.75}$-8.67$_{-7.59}$ mL/min/1.73m^2 vs. CLDKT=$_{-3.98}$-3.66$_{-3.37}$ mL/min/1.73m^2).

DISCUSSION

In this multicenter study, we found that ILDKTr across all levels of DSA strength are at higher risk of AR, whereas only PCC ILDKTr are at increased risk of DGF, compared to CLDKTr. DGF developed in 3.5% of PLNF, 5.7% of PFNC, and 7.6% of PCC recipients, which translated in a 1.68-fold increase in the odds of developing DGF for PCC ILDKTr. Despite this, the impact of DGF on mortality or DCGF risk was no higher for ILDKTr compared to CLDKTr. Additionally, AR developed in 18.2% of PLNF, 21.3% of PFNC, and 21.7% of PCC recipients, which translated into a 2.09-fold, 2.40-fold, and 2.24-fold increase in the odds of developing AR for PLNF, PFNC, and PCC ILDKTr, respectively. Although the impact of AR on mortality risk was no higher for ILDKTr than for CLDKTr, its impact on DCGF risk was lower for ILDKTr (1.62-fold higher risk) than for CLDKTr (2.29-fold higher risk).

Several, mostly single-center reports of ILDKTr have found DGF risk to range from 2.4% −10.0%, and AR risk to range from 22.8%−43.0% (16, 24–28), although the overall incidence we report is 5.6% for DGF and 20.9% for AR. This might be due in part to our 25-center cohort, where we have the ability to account for between-center differences, as well as in improvements to clinical practice throughout the study period (1997–2016). Moreover, our findings of higher risk of AR for ILDKTr (25), but equivalent risk of DGF for PFNC recipients are consistent with prior single-center studies (28). However, we have expanded upon the existing literature linking our cohort with national data to provide broadly generalizable findings that are likely to be applicable to most ILDKT centers in the US.

Our findings regarding mortality and DCGF for ILDKTr and CLDKTr with DGF are somewhat consistent with a single center study conducted in Switzerland (4). The discordance may be explained by the differences in their study population (i.e. deceased donor transplant recipients) and lack of desensitization for some DSA+ recipients. Moreover, we found a higher risk of DCGF for ILDKTr and CLDKTr with AR. This finding is comparable to studies that found higher risk of graft loss for incompatible recipients with AR (6, 25, 29). Nevertheless, we have extended the literature through our study design, and additionally determined whether DGF and AR differentially impacts ILDKTr' and CLDKTr' risk of mortality and DCGF.

Our finding that AR on risk of DCGF is less consequential for ILDKTr compared to CLDKTr is interesting. This might result from the mechanistic differences in DSA formation between ILDKTr and CLDKTr who develop AR (18), where the impact of *de novo* DSA on DCGF risk may be greater than preformed/memory DSA. In fact, Aubert, Loupy et al. observed a 1.82-fold increase in DCGF risk for AMR recipients with *de novo DSA* compared to recipients with pre-existing DSA (30). Moreover, given the well-known relationship between AR and graft loss, particularly in the presence of DSA, it is possible that this may have led to more aggressive surveillance and management for ILDKTr. Taken

together with the possibility of earlier presentation of AR in patients with pre-existing DSA, it is also likely that ILDKTr are more responsive to treatment compared to CLDKTr (30).

Several limitations of our study are worth considering. Although we leveraged SRTR for accurate outcome ascertainment, the OPTN does not capture exact dates for AR events, its severity, or rejection types (cellular vs. antibody-mediated), including its causes (i.e. preformed DSA vs. *de novo* DSA), and treatment. Additionally, desensitization protocols, diagnosis and treatment as well as the reporting of AR may vary across centers, although our study was not designed to assess these discrepancies. Nevertheless, there is no obvious reason that the manner in which rejection is reported to the OPTN would differ between ILDKTr and CLDKTr, and thus should not bias our results. Although there is likely differential ascertainment of AR for ILDKTr (vs. CLDKTr) given their immunologic profile, our sensitivity analysis limiting our definition to include only biopsy-proven AR showed similar results to our main analysis. Moreover, we did not have data on the occurrence and causes of transplant nephrectomy. Despite these limitations, the major strength of our study is our robust study design: a large multicenter cohort linked to national registry data with >20 years of follow-up data and appropriate selection of controls.

In conclusion, PCC ILDKTr were significantly more likely to develop DGF and AR. There was no evidence of increased risk of DGF among PLNF and PFNC recipients, although both were at higher risk of developing AR. Moreover, the impact of DGF on mortality and DCGF risk was the same for ILDKTr and CLDKTr. Although the impact of AR on mortality risk was the same for ILDKTr and CLDKTr, its impact on DCGF risk was less consequential for ILDKTr than for CLDKTr. These findings underscore the importance of pre-operative counseling and post-operative surveillance of patients about the risks of these outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government. The analyses described here are the responsibility of the authors alone and do not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products or organizations imply endorsement by the U.S. Government.

ABBREVIATIONS

ACR	acute cellular rejection

AMR	antibody mediated rejection
aOR	adjusted odds ratio
AR	acute rejection
BMI	body mass index
cPRA	calculated panel reactive antibody
CLDKT	compatible living donor kidney transplantation
CLDKTr	compatible living donor kidney transplant recipients
DCGF	death-censored graft failure
DGF	delayed graft function
DSA	donor-specific antibody
HLA	human leukocyte antigen
HRSA	Health Resources and Services Administration
ILDKT	incompatible living donor kidney transplantation
ILDKTr	incompatible living donor kidney transplant recipients
IQR	interquartile range
LKDPI	living kidney donor profile index
PCC	positive cytotoxic crossmatch
PFNC	positive flow, negative cytotoxic crossmatch
PLNF	positive Luminex, negative flow crossmatch
PRA	panel reactive antibody
SD	standard deviation
SRTR	Scientific Registry of Transplant Recipients

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Antibody strength	DGF (%)[a]	Adjusted odds ratio	p-value[b]
CLDKT	**3.1**		Ref
PLNF	**3.5**	0.62 0.97 1.52	0.9
PFNC	**5.7**	0.73 1.43 2.78	0.3
PCC	**7.6**	1.03 1.68 2.72	**0.04**

0.5 1.0 1.5 2.0 2.5 3.0

Bold indicates p<0.05

[a]Proportion of recipients with DGF

[b]p-value of adjusted odds ratio

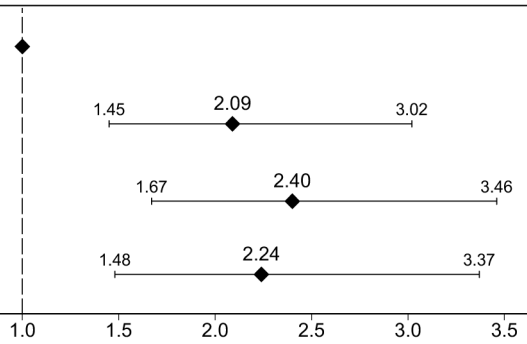
CLDKT, compatible live donor kidney transplant recipients; DGF; delayed graft function; PCC, positive cytotoxic crossmatch; PFNC, positive flow, negative cytotoxic crossmatch; PLNF, positive Luminex, negative flow crossmatch.

Figure 1.

Incidence of DGF according to DSA strength.

Although ILDKT recipients had significantly higher incidence of DGF compared to CLDKT recipients, only PCC ILDKT recipients had a statistically significant 1.68-fold higher risk of DGF.

Antibody strength	Acute rejection (%)[a]	Adjusted odds ratio	p-value[b]
CLDKT	**8.5**		Ref
PLNF	**18.2**	2.09 (1.45–3.02)	**<0.001**
PFNC	**21.3**	2.40 (1.67–3.46)	**<0.001**
PCC	**21.7**	2.24 (1.48–3.37)	**<0.001**



Bold indicates p<0.05

[a]Proportion of recipients with acute rejection

[b]p-value of adjusted odds ratio

CLDKT, compatible live donor kidney transplant recipients; PCC, positive cytotoxic crossmatch; PFNC, positive flow, negative cytotoxic crossmatch; PLNF, positive Luminex, negative flow crossmatch.

Figure 2.

Incidence of acute rejection according to DSA strength.

ILDKT recipients had a higher incidence of acute rejection compared to CLDKT recipients, and this translated to increased risk of acute rejection for ILDKT recipients regardless of DSA strength. For example, acute rejection occurred in 21.7% of PCC ILDKT recipients, which translated in a 2.24-fold higher risk of acute rejection compared to CLDKT recipients.

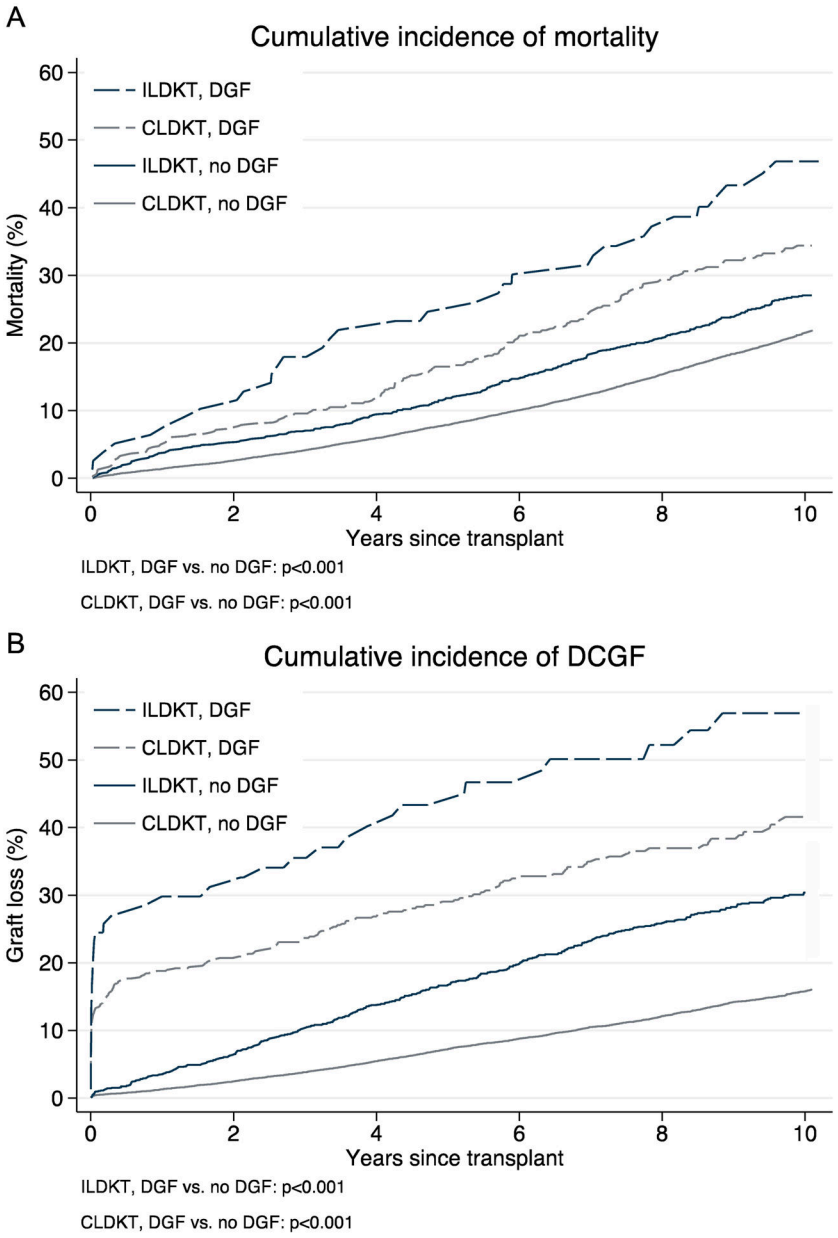


Figure 3.

Cumulative incidence of mortality and DCGF for ILDKT and CLDKT recipients with and without delayed graft function.

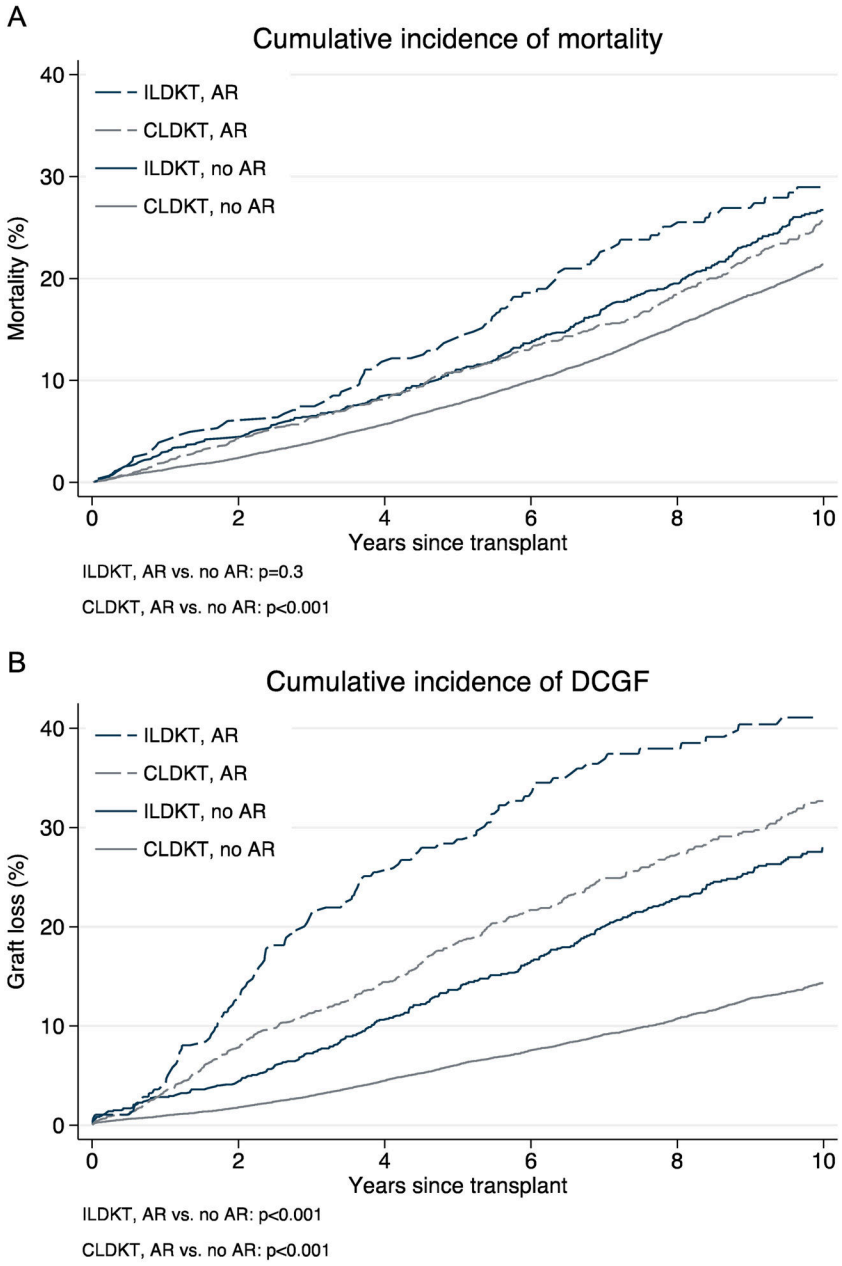


Figure 4.

Cumulative incidence of mortality and DCGF for ILDKT and CLDKT recipients with and without acute rejection.

Table 1.

Recipient characteristics, according to DSA strength.

Characteristics	CLDKT (n=17,542)	PLNF (n=376)	PFNC (n=687)	PCC (n=343)	p-value
Recipient					
Age (years), mean (SD)	48.5 (14.0)	46.9 (13.9)	45.5 (13.1)	43.7 (13.4)	<0.001
Female sex, %	38.4	55.6	68.0	65.6	<0.001
Race/ethnicity, %					<0.001
White	67.4	71.0	65.4	73.2	
Black	14.8	15.4	20.2	12.5	
Other	17.8	13.6	14.4	14.3	
BMI (kg/m^2), median (IQR)	26.9 (23.3, 31.2)	26.4 (22.8, 31.0)	26.0 (22.4, 30.8)	24.6 (21.5, 29.3)	<0.001
Cause of ESRD, %					<0.001
Glomerular diseases	30.2	31.4	39.6	39.0	
Diabetes	22.4	19.2	13.5	10.5	
Hypertension	16.8	10.1	14.3	14.3	
Polycystic kidney disease	11.1	13.8	9.2	7.9	
Other	19.5	25.5	23.4	28.3	
Years on dialysis, %					<0.001
Preemptive	35.6	29.0	22.1	16.0	
<2 years	44.9	41.8	37.4	28.6	
2–6 years	16.5	22.6	27.4	31.5	
>6 years	3.0	6.6	13.1	23.9	
c/PRA (%), %					<0.001
0	67.8	17.0	18.6	8.2	
1–20	14.9	12.8	13.1	7.3	
21–79	12.5	44.9	31.1	29.7	
80–97	3.4	18.6	20.8	29.2	
98	0.3	0.5	3.1	5.8	
99	0.4	2.7	3.5	2.3	
100	0.7	3.5	9.8	17.5	
Number of previous transplants, %					<0.001
0	89.6	71.6	61.3	51.3	
1	9.1	23.9	32.5	40.5	
≥2	1.3	4.5	6.2	8.2	
≥3 HLA mismatches, %	72.2	81.6	77.5	80.9	<0.001
Donor					
Age (years), mean (SD)	42.5 (11.9)	41.7 (12.0)	40.6 (12.0)	40.7 (11.8)	<0.001
Female sex, %	60.6	56.6	57.5	53.9	0.01
Race/ethnicity, %					<0.001
White	70.4	74.2	66.1	76.7	
Black	12.9	12.5	19.5	9.0	
Other	16.7	13.3	14.4	14.3	

Characteristics	CLDKT (n=17,542)	PLNF (n=376)	PFNC (n=687)	PCC (n=343)	p-value
Related donor, %	46.2	56.4	47.7	44.6	0.001
Transplant					
Cold ischemia time <8 h, %	96.2	93.6	96.3	97.6	0.09
Induction, %					<0.001
None	6.8	0.9	6.3	12.0	
Non-depleting	23.3	6.1	7.8	13.0	
Depleting	69.9	93.0	85.9	75.0	
Early steroid withdrawal, %	41.6	49.7	8.8	14.5	<0.001

BMI, body mass index; CLDKT, compatible live donor kidney transplant recipients; c/PRA, calculated/panel reactive antibody; ESRD, end stage renal disease; HLA, human leukocyte antigen; IQR, interquartile range; PCC, positive cytotoxic crossmatch; PFNC, positive flow, negative cytotoxic crossmatch; PLNF, positive Luminex, negative flow crossmatch; SD, standard deviation.