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Quantifying the Risk of Incompatible Kidney Transplantation: A Multicenter Study

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Incompatible live donor kidney transplantation (ILDKT) offers a survival advantage over dialysis to patients with anti-HLA donor-specific antibody (DSA). Program-specific reports (PSRs) fail to account for ILDKT, placing this practice at regulatory risk. We collected DSA data, categorized as positive Luminex, negative flow crossmatch (PLNF) (n = 185), positive flow, negative cytotoxic crossmatch (PFNC) (n = 536) or positive cytotoxic crossmatch (PCC) (n = 304), from 22 centers. We tested associations between DSA, graft loss and mortality after adjusting for PSR model factors, using 9669 compatible patients as a comparison. PLNF patients had similar graft loss; however, PFNC (adjusted hazard ratio [aHR] = 1.64, 95% confidence interval [CI]: 1.15–2.23, p = 0.007) and PCC (aHR = 5.01, 95% CI: 3.71–6.77, p < 0.001) were associated with increased graft loss in the first year. PLNF patients had similar mortality; however, PFNC (aHR = 2.04; 95% CI: 1.28–3.26; p = 0.003) and PCC (aHR = 4.59; 95% CI: 2.98–7.07; p < 0.001) were associated with increased mortality. We simulated Centers for Medicare & Medicaid Services flagging to examine ILDKT's effect on the risk of being flagged. Compared to equal-quality centers performing no ILDKT, centers performing 5%, 10% or 20% PFNC had a 1.19-, 1.33- and 1.73-fold higher odds of being flagged. Centers performing 5%, 10% or 20% PCC had a 2.22-, 4.09- and 10.72-fold higher odds. Failure to account for ILDKT's increased risk places centers providing this life-saving treatment in jeopardy of regulatory intervention.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CMS, Centers for Medicare & Medicaid Services; CPRA, calculated panel reactive antibody; DSA, donor-specific antibody; ILDKT, incompatible live donor kidney transplantation; IQR, interquartile range; MFI, mean fluorescence intensity; OPTN, Organ and

Procurement Transplantation Network; PCC, positive cytotoxic crossmatch; PFNC, positive flow, negative cytotoxic crossmatch; PLNF, positive Luminex, negative flow crossmatch; PRA, panel reactive antibody; PSR, program-specific report; SRTR, Scientific Registry of Transplant Recipients

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Introduction

Patients with anti-HLA donor-specific antibody (DSA) undergoing desensitization and subsequent live donor kidney transplantation (referred to as ILDKT, or incompatible live donor kidney transplantation, for the purposes of this article) enjoy a twofold survival benefit compared to similar patients who remain on dialysis while waiting for a compatible donor (1). For most highly sensitized patients the choice is not between ILDKT and a compatible (no DSA) transplant. Rather, long waits on dialysis and high mortality rates are the only alternatives to desensitization. Currently, algorithms for calculating center-specific expected outcomes do not consider the survival benefit derived from ILDKT. Furthermore, risk adjustments do not distinguish ILDKT from compatible transplants. Based on a recent survey of US transplant centers, ILDKT have become mainstream procedures, performed at approximately 50–70% of transplant centers nationwide (2).

Single-center reports suggest that ILDKT outcomes are not as good as compatible kidney transplants (3–5). However, differences in outcomes have not been well characterized outside of large-volume, more experienced centers. Regulatory organizations currently hold the outcomes of ILDKT patients to the same standard as compatible recipients, thereby potentially penalizing centers that perform these transplants. Better outcome data from ILDKT will inform future decisions about changing risk adjustments to encourage transplant centers to help their patients more fully realize the survival benefits associated with desensitization and ILDKT.

In the development of the program-specific reports (PSRs), centers are given ''credit'' for transplanting other high-risk groups. For example, a 70-year-old recipient faces a 30% higher risk of graft loss at 1 year than a 30-year-old recipient. However, the PSRs account for this, enabling a center to offer transplantation to the 70-year-old without fear of adverse regulatory actions provided that its outcomes are on par with other centers transplanting 70-year-olds (6). However, this is not the case for ILDKT: if risk does indeed exist with this practice, that risk is not currently captured in the PSRs, potentially increasing a center's risk of flagging and investigation by the Centers for Medicare & Medicaid Services (CMS).

We hypothesized that ILDKT is associated with an increased risk of graft loss and death compared to compatible live donor kidney transplantation. To quantify this risk in the context of the PSRs, we created a multicenter collaboration linking DSA strength of ILDKT recipients to other data already reported to the Scientific Registry of Transplant Recipients (SRTR). Then, to examine the effect of ILDKT on the risk of CMS flagging, we conducted stochastic simulations of CMS center evaluations based on the risk associated with ILDKT.

Methods

Study population and incompatible live donor kidney transplantation definition

We studied adult (>18 years of age), live donor, kidney-only recipients from 22 US transplant centers through December 2011. The population included all ILDKT performed at a given center as well as all compatible live donor kidney transplants performed at that center since the time they began doing ILDKT (in other words, from the date of each center's first ILDKT; the earliest ILDKT was performed in September 1997). Participating transplant centers provided the antibody strength prior to desensitization for ILDKT recipients, categorized as pretransplant positive Luminex, negative flow crossmatch (PLNF), positive flow, negative cytotoxic crossmatch (PFNC) or positive cytotoxic crossmatch (PCC). In some cases, these were actual cell-based crossmatches; in others, they were virtual crossmatches based on semi-quantitative DSA strength on solid-phase assays. Patients who had anti-HLA DSA and were also ABO-incompatible (n = 60, 5.8% of HLA-incompatible cohort) were considered part of the ILDKT population and were categorized based on the strength of the anti-HLA DSA as described above; a sensitivity analysis excluding these patients did not change any of our inferences.

At Johns Hopkins, reactions with test beads yielding mean fluorescence intensity (MFI) of >1000 have been considered Luminex positive. The range of MFI values reported to result in a positive flow crossmatch is quite broad (2000–20 000), and may be dependent on antibody class and specificity. PCC results have been associated with >10 000 MFI on phenotype panels. Significant variation in the results of solid-phase assays within and especially between laboratories has been well characterized (7,8). Each laboratory established its own MFI benchmarks that equate to the three crossmatch categories reported in this study.

Data linkage

Data provided by transplant centers were linked to the SRTR for (1) ascertainment of risk factors (other than DSA strength) in a manner consistent with the PSRs, and (2) reliable ascertainment of outcomes (graft loss and death). The SRTR supplements death ascertainment through linkage to the Social Security Death Master File and death and graft loss ascertainment through linkage to data from the CMS. The SRTR includes information on all donors, waitlisted transplant candidates and transplant recipients in the United States provided by members of the Organ Procurement and Transplantation Network (OPTN), and has been well-described elsewhere (9). The Health Resources and Services Administration, U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

Outcome definitions

All-cause graft loss was defined by the time between date of transplantation and either date of graft failure (marked by retransplantation, relisting, a return to dialysis or death) or last date of follow-up with a functioning graft, with

administrative censoring at the end of study. Death was defined by the time interval between date of transplantation and date of death or administrative end of the study.

Missing data

Because of changes from panel reactive antibody (PRA) to calculated PRA (CPRA) in 2009, we combined all information available about PRA and/or CPRA, and those missing data (6.7%) were assumed to have the mean PRA/CPRA for ILDKT patients at their level of antibody strength. ILDKT patients missing BMI or with BMI outside a realistic range of 14–50 kg/m^2 (8.0%) were assumed to have a BMI that was the average for their gender and antibody strength. All other variables were missing in <1% of ILDKT patients. Missingness in compatible recipients, the comparison population, was treated using casewise deletion.

Statistical analysis

Between-group characteristics were compared using chi-square test for categorical variables, analysis of variance for normally-distributed continuous variables, and the Kruskal-Wallis test for non-normally-distributed continuous variables. Mortality and graft loss were estimated using the Kaplan–Meier method and compared between groups using log-rank testing. Cox models were constructed to mirror (in terms of variable selection and functional form) the SRTR live donor kidney transplant PSR models for graft loss and mortality (6), with inclusion of DSA strength as an additional variable. Hazard ratios were obtained from the models for the time period up to 1-year posttransplant and after 1-year posttransplant, the former for its regulatory implications and the latter for its biologic and clinical relevance. A two-tailed p-value of <0.05 was considered statistically significant. Statistical analysis was performed using Stata 12.0 (StataCorp, College Station, TX).

Regulatory flagging simulation

To quantify the risk of CMS flagging that centers assume when they perform ILDKT, we conducted stochastic simulations of CMS center evaluations as previously described (10) for live donor kidney transplantation, using differing distributions of ILDKT use and risk. In other words, we simulated the likelihood of transplant centers being flagged by CMS for regulatory review, with an assumption (based on our previous survey (2)) that 30% of transplant centers performed no ILDKT, 40% of centers performed ILDKT for 5% of all of their live donor kidney transplants, 15% of centers performed ILDKT for 10% of all of their live donor kidney transplants and the remaining 15% of centers performed ILDKT for 20% of all of their live donor kidney transplants. We conducted separate simulations using the all-cause graft loss risk estimates for PFNC and PCC based on the data censored at 1 year. Each simulation was run for 1000 iterations. Probability of flagging was calculated based on centers' proportion of ILDKT as a function of their overall live donor kidney transplant volume and centers' ''risk quotient'' (a number assigned to each center representing center quality, such that a center with average performance had a risk quotient of 1.0 and a center with 50% higher risk had a risk quotient of 1.5). The risk quotient was randomly assigned and then centers were randomly assigned an ILDKT volume as a percent of overall live donor kidney transplant volume (0%, 5%, 10% or 20%). The effect of ILDKT on flagging risk was evaluated using logistic regression.

Results

Study population

Across the 22 participating centers, 10 694 live donor kidney transplants were performed. Of these transplants, 1025 (9.6%) were ILDKT, including 185 PLNF, 536 PFNC and 304 PCC transplants. ILDKT patients were more likely to be female (39.1% of compatible, 67.6% of PLNF, 68.1% of PFNC and 64.8% of PCC patients; $p < 0.001$), more likely to be covered by public insurance (38.6% of compatible, 42.7% of PLNF, 52.4% of PFNC and 59.5% of PCC patients; $p < 0.001$), and were less frequently dialysis-free at the time of transplantation (31.8% of compatible, 16.2% of PLNF, 13.4% of PFNC and 8.2% of PCC patients; $p < 0.001$) (Table 1). ILDKT patients were more likely to have previously received a transplant (14.7% of compatible, 36.8% of PLNF, 43.7% of PFNC and 56.6% of PCC patients; $p < 0.001$) and less likely to have undergone zero-HLA-mismatch transplantation (9.1% of compatible, 2.2% of PLNF, 1.7% of PFNC and 1.3% of PCC patients; $p < 0.001$). ILDKT patients also had substantially higher median peak PRA/CPRA values (0 [interquartile range [IQR]: 0–7] for compatible, 51 [IQR: 18–82] for PLNF, 57.5 [IQR: 14–93] for PFNC and 85 [IQR: 50–98] for PCC patients).

Graft loss

One-year unadjusted all-cause graft loss was 3.9%, 3.8%, 6.9% and 19.4% for compatible, PLNF, PFNC and PCC patients, respectively ($p < 0.001$). Five-year unadjusted all-cause graft loss was 16.6%, 20.2%, 28.8% and 39.9% for compatible, PLNF, PFNC and PCC patients, respectively (Figure 1). Compared to compatible patients, PLNF patients had a similar adjusted risk of all-cause graft loss in the first year posttransplant (adjusted hazard ratio [aHR] = 0.91; 95% confidence interval [CI]: 0.43–1.94; $p = 0.81$); however, PFNC (aHR = 1.64; 95% CI: 1.15–2.33; $p = 0.007$) and PCC (aHR = 5.01; 95% CI: 3.71–6.77; $p < 0.001$) patients had a significantly higher risk of all-cause graft loss in the first year posttransplant (Table 2). After the first year posttransplant, PLNF patients continued to have a similar adjusted risk of all-cause graft loss compared to compatible patients (aHR = 1.20; 95% CI: 0.83–1.75; $p = 0.33$); however, PFNC (aHR = 1.65; 95% CI: 1.36–1.99; $p < 0.001$) and PCC (aHR = 1.80; 95% CI: 1.42–2.29; $p < 0.001$) patients continued to have a significantly higher risk of all-cause graft loss.

Mortality

One-year unadjusted mortality was 2.0%, 1.6%, 3.9% and 8.9% for compatible, PLNF, PFNC and PCC patients, respectively ($p < 0.001$). Five-year unadjusted mortality was 9.3%, 9.6%, 12.9% and 19.1% for compatible, PLNF, PFNC and PCC patients, respectively (Figure 2). Compared to compatible patients, PLNF patients had a similar risk of death in the first year posttransplant (aHR = 0.83; 95% CI: 0.26–2.62; $p = 0.75$); however, PFNC (aHR = 2.04; 95% CI: 1.28–3.26; $p = 0.003$) and PCC (aHR = 4.59; 95% CI: 2.98–7.07; $p < 0.001$) patients had a significantly higher risk of death (Table 2). After the first year posttransplant, PLNF patients continued to have a similar adjusted risk of death compared to compatible patients (aHR = 0.84; 95% CI: 0.48–1.48; $p = 0.55$); however, PFNC (aHR = 1.32; 95% CI: 1.02–1.70; $p = 0.037$) and PCC (aHR = 1.51; 95% CI: 1.13–2.03;

Table 1: Characteristics of transplant recipients, by anti-HLA antibody strength

	Compatible (n = 9669)	Positive Luminex, negative flow crossmatch (n = 185)	Positive flow, negative cytotoxic crossmatch (n = 536)	Positive cytotoxic crossmatch (n = 304)	p-Value
Mean age at transplant (SD)	47.8 (13.8)	45.4 (12.7)	45.5 (12.6)	43.8 (13.2)	<0.001
Female sex	39.1%	67.6%	68.1%	64.8%	<0.001
Recipient race					0.034
White	68.3%	64.9%	67.7%	73.4%	
Black	15.2%	17.3%	18.7%	11.8%	
Hispanic/Latino	10.9%	9.2%	9.1%	11.8%	
Asian	4.7%	7.6%	3.0%	2.6%	
Public insurance	38.6%	42.7%	52.4%	59.5%	<0.001
Prior transplant	14.7%	36.8%	43.7%	56.6%	<0.001
Zero HLA mismatch	9.1%	2.2%	1.7%	1.3%	<0.001
Median peak PRA/CPRA (IQR)	0 (0–7)	51 (18–82)	57.5 (14–93)	85 (50–98)	<0.001
Mean recipient BMI (SD)	27.5 (5.8)	26.2 (5.4)	26.6 (6.2)	25.6 (5.5)	<0.001
ESRD diagnosis					<0.001
Glomerular disease	27.5%	36.2%	36.7%	35.2%	
Diabetes	23.8%	22.2%	14.7%	10.2%	
Hypertension	19.1%	7.6%	12.5%	15.8%	
Polycystic kidney disease	10.4%	10.3%	9.5%	8.2%	
Vascular disease	1.6%	1.1%	1.9%	2.0%	
Other	17.6%	22.7%	24.8%	28.6%	
Time on dialysis prior to recent transplant					<0.001
Preemptive	31.8%	16.2%	13.4%	8.2%	
<2 years	41.9%	28.6%	28.5%	16.8%	
2–6 years	14.4%	22.2%	18.1%	19.1%	
>6 years	11.9%	33.0%	40.1%	55.9%	
Recipient HCV	3.7%	8.1%	6.7%	5.3%	<0.001
Mean donor age (SD)	42.0 (11.7)	41.6 (11.3)	40.5 (11.7)	40.5 (11.8)	0.005
Living-related donor	42.8%	55.1%	45.9%	43.4%	0.005
Donor race					0.005
White	70.9%	69.2%	68.3%	76.3%	
Black	13.5%	14.0%	17.5%	8.5%	
Hispanic/Latino	10.6%	8.1%	9.7%	11.2%	
Asian	4.0%	8.1%	2.8%	3.3%	

CPRA, calculated panel reactive antibody; ESRD, end-stage renal disease; HCV, hepatitis C virus; IQR, interquartile range; PRA, panel reactive antibody; SD, standard deviation.

$p < 0.001$) patients continued to have a significantly higher risk of death.

Regulatory flagging simulation

In the stochastic simulation, increased ILDKT volume and increased antibody strength were associated with significantly increased odds of flagging for further regulatory scrutiny. Compared to centers of equal quality that performed no ILDKT, centers that performed 5%, 10% or 20% PFNC ILDKT had a 1.19-fold (95% CI: 1.15–1.23), 1.33-fold (95% CI: 1.28–1.39) and 1.73-fold (95% CI: 1.66–1.80) higher odds of CMS flagging, and centers that performed 5%, 10% or 20% PCC ILDKT had a 2.22-fold (95% CI: 2.14–2.32), 4.09-fold (95% CI: 3.91–4.28) and 10.72-fold (10.27–11.18) higher odds of CMS flagging than their equal quality counterparts (Table 3). Different centers in the simulation have different ''risk quotients''—a measure of center quality such that centers with a higher risk quotient have higher risk of graft loss within 1 year. A center with average performance (risk quotient = 1) had a 0.5% chance of getting flagged if it performed no ILDKT, but an 8.5% chance of getting flagged if it performed 20% PCC ILDKT. A center with 50% higher risk of adverse outcomes (risk quotient = 1.5) had a 4.7% chance of getting flagged if it performed no ILDKT, but a 29.0% chance of getting flagged if it performed 20% PCC ILDKT (Figure 3).

Discussion

In this 22-center US study of ILDKT, increased anti-HLA DSA strength was associated with worse graft outcomes and higher mortality following live donor kidney transplantation. Within the context of the SRTR models used by CMS, PLNF patients were similar to compatible patients in terms of all-cause graft loss and death. PFNC and PCC were associated with higher graft loss (aHR = 1.64; 95% CI: 1.15–2.33; p = 0.007 and aHR = 5.01; 95% CI: 3.71–6.77;

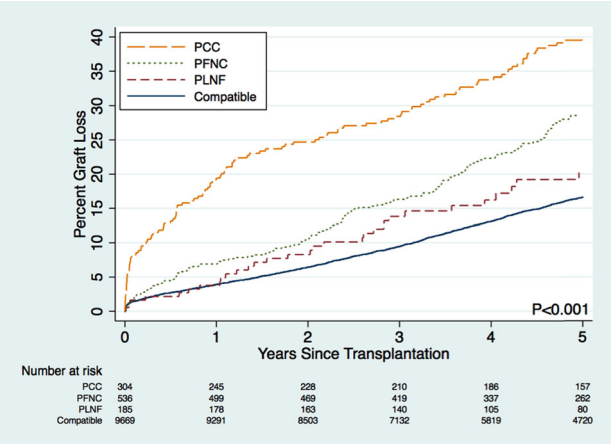

Figure 1: All-cause graft loss, by antibody strength. PCC, positive cytotoxic crossmatch; PFNC, positive flow, negative cytotoxic crossmatch; PLNF, positive Luminex, negative flow crossmatch.

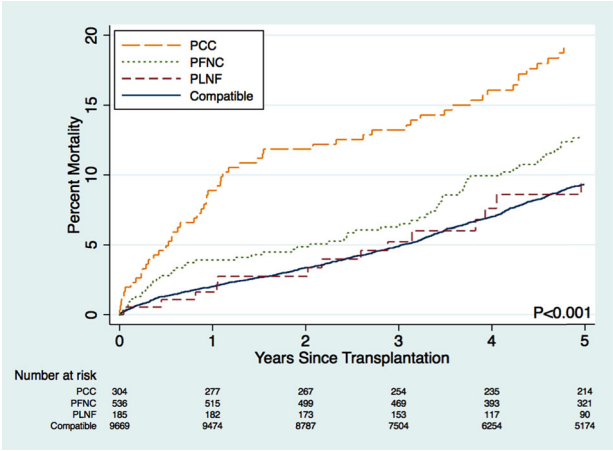

Figure 2: Posttransplant mortality, by antibody strength. PCC, positive cytotoxic crossmatch; PFNC, positive flow, negative cytotoxic crossmatch; PLNF, positive Luminex, negative flow crossmatch.

$p < 0.001$) and death (aHR 1.32; 95% CI: 1.02–1.70; $p = 0.037$) and aHR 1.51; 95% CI: 1.13–2.03; $p < 0.001$). Our simulation of CMS regulatory flagging suggested that an increasing proportion of a center's ILDKT volume led to significant increases in the odds of being flagged, even in the absence of poor performance. Centers that performed PFNC ILDKT as 20% of their volume were expected to have a 1.73-fold (95% CI: 1.66–1.80) higher odds of being flagged, and those that performed PCC ILDKT as 20% of their volume were expected to have a 10.72-fold (95% CI: 10.27–11.18) higher odds of being flagged.

The ILDKT literature has thus far been based on single-center data with insufficient sample sizes to quantify risk in a precise, generalizable manner (1,3–5,11–28). In addition, most of these single-center studies have been descriptive, with absent or limited control groups. Our findings of increased risk of graft loss and death with increasing level of antibody strength are consistent with previous single-center studies (29,30). Other studies have compared the outcomes of ILDKT to compatible live donor kidney transplantation, albeit with much less power to adjust for multiple confounding factors (3–5,31). Haririan et al (5) found that 41 patients with a positive flow crossmatch had a 2.6-fold higher risk of graft loss compared to patients matched on gender, race, age, prior kidney transplant and year of transplantation. The Mayo Clinic group reported a 5-year death-censored graft survival rate of 70.7% in 102 ILDKT patients, compared to 96.7% in compatible recipients matched for age and sex. They also found that PCC patients had a higher incidence of graft loss than PFNC patients at 1 year, although that difference was not statistically significant by 5 years.

Our study found no difference in patient or graft survival outcomes for PLNF patients compared to compatible patients. In a retrospective study of deceased and live donor kidney transplants, Gibney et al (32) reported that

Table 2: Adjusted risk of all-cause graft loss and mortality in the first year posttransplant and after the first year by antibody strength

	All-cause graft loss				Mortality			
Antibody strength	aHR <1 year	p-Value	aHR >1 year	p-Value	aHR <1 year	p-Value	aHR >1 year	p-Value
Compatible	Reference	—	Reference	—	Reference	—	Reference	—
Positive Luminex, negative flow crossmatch	0.91 (0.43–1.94)	0.81	1.20 (0.83–1.75)	0.33	0.83 (0.26–2.62)	0.75	0.84 (0.48–1.48)	0.55
Positive flow, negative cytotoxic crossmatch	1.64 (1.15–2.33)	0.007	1.65 (1.36–1.99)	<0.001	2.04 (1.28–3.26)	0.003	1.32 (1.02–1.70)	0.037
Positive cytotoxic crossmatch	5.01 (3.71–6.77)	<0.001	180[1] (1.42–2.29)	<0.001	4.59 (2.98–7.07)	<0.001	1.51[1] (1.13–2.03)	<0.001

aHR, adjusted hazard ratio.
Risk was adjusted based on the variables in the Scientific Registry of Transplant Recipients 1-year adjustment models for graft loss and mortality.
[1]Interaction term between antibody strength and time >1 year with p-value <0.01.

Table 3: Effect of incompatible live donor kidney transplantation (ILDKT) on risk of flagging by Centers for Medicare & Medicaid Services (CMS) in a simulation

	Odds ratio of regulatory flagging	
Center volume of ILDKT	Positive flow, negative cytotoxic crossmatch	Positive cytotoxic crossmatch
No ILDKT	Reference	Reference
5% ILDKT	1.19 (1.15–1.23)	2.22 (2.14–2.32)
10% ILDKT	1.33 (1.28–1.39)	4.09 (3.91–4.28)
20% ILDKT	1.73 (1.66–1.80)	10.72 (10.27–11.18)

PCC, positive cytotoxic crossmatch; PFNC, positive flow, negative cytotoxic crossmatch.
This simulation, run 1000 times, estimates the likelihood of transplant centers being flagged by CMS for regulatory review, with an assumption that 30% of transplant centers performed no ILDKT, 40% of centers performed ILDKT for 5% of all of their live donor kidney transplants, 15% of centers performed ILDKT for 10% of all of their live donor kidney transplants and the remaining 15% of centers performed ILDKT for 20% of all of their live donor kidney transplants. We conducted separate simulations using the all-cause graft loss risk estimates for PFNC and PCC. Probability of flagging was calculated based on centers' proportion of ILDKT as a function of their overall live donor kidney transplant volume and centers' ''risk quotient'' (a number assigned to each center representing center quality, such that a center with average performance had a risk quotient of 1.0 and a center with 50% higher risk had a risk quotient of 1.5). The risk quotient was randomly assigned and then centers were randomly assigned an ILDKT volume as a percent of overall live donor kidney transplant volume (0%, 5%, 10% or 15%). The effect of ILDKT on flagging risk was evaluated using logistic regression.
Compared to centers that performed no ILDKT, centers of equal quality that performed 5%, 10% or 20% PFNC ILDKT had 1.19-, 1.33- and 1.73-fold higher odds of CMS flagging, respectively, in a logistic regression model. Centers that performed 5%, 10% or 20% PCC ILDKT had 2.22-, 4.09- and 10.72-fold higher odds of CMS flagging, respectively. All p-Values are <0.001.

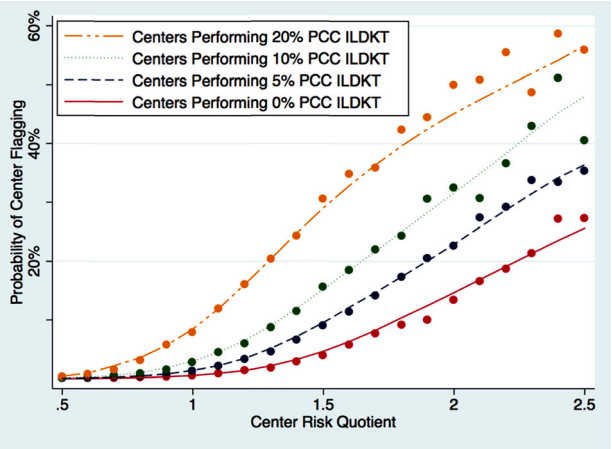

Figure 3: The effect of incompatible live donor kidney transplantation (ILDKT) on risk of flagging by Centers for Medicare & Medicaid Services in a simulation. Different centers in the simulation have different ''risk quotients''—a measure of center quality such that centers with a higher risk quotient have higher risk of graft loss within 1 year. A center with average performance (risk quotient = 1) had a 0.5% chance of getting flagged if it performed no ILDKT, but an 8.5% chance of getting flagged if it performed 20% PCC ILDKT. A center with 50% higher risk of adverse outcomes (risk quotient = 1.5) had a 4.7% chance of getting flagged if it performed no ILDKT, but a 29.0% chance of getting flagged if it performed 20% PCC ILDKT. PCC, positive cytotoxic crossmatch.

patients with DSA detected by Luminex but negative by cytotoxic crossmatch had worse graft survival but similar patient survival compared to compatible kidney transplant recipients. However, the authors did not report flow cytometric crossmatch results on these patients, so it remains unclear if the difference in graft survival in their study was because some of the patients were actually PFNC. Consistent with our findings, Loupy et al (33) showed equivalent graft and patient outcomes among recipients of deceased donor kidneys with pretransplant DSA detected by solid phase assay compared to those without DSA. However, the wide confidence intervals for PLNF estimates suggest that the risk associated with this strength of anti-HLA antibody remains incompletely characterized.

The strengths of this study include its multicenter design (22 centers), large sample size (n = 10 694) and control group (compatible kidney transplant recipients at the same center, adjusted for SRTR variables, with the statistical power to accommodate all of these variables in a regression model). Participating centers represent more than one-fifth of the 2011 US live donor kidney transplant volume, permitting quantification of the risk associated with increasing antibody strength without the limitations associated with existing single-center reports.

Limitations include heterogeneity across the 22 centers with respect to HLA antibody testing and interpretations of these assays, especially when comparing DSA strength (34). Significant variation exists in the management of interfering agents such as auto-antibody and therapeutic agents in solid-phase immunoassays and their subsequent interpretation (35). Even under tightly controlled circumstances, there is still significant variability in the assessment of antibody strength (36). Centers have their own thresholds of MFI and mean channel shifts that constitute a positive crossmatch. For cell-based assays, there is significant center-level variation in the conduct and materials of the crossmatch, and also in the threshold for positivity (37). However, our study design accounted for this in two ways. First, we asked each center to classify each patient as PLNF, PFNC and PCC in order to find a common classification system and allow for the development of the largest cohort of ILDKT patients to date. Second, we only included patients who underwent desensitization, so as to only study those that the centers

felt had sufficiently strong DSA to warrant the risks and costs of desensitization. Desensitization strategies, treatment of antibody-mediated rejection and management of persistent postoperative DSA vary across centers. This study was not designed to assess these differences, nor to determine the best management of these clinical challenges; however, it does provide a real-world snapshot of the aggregate outcomes that results from these various practices.

This multicenter study of ILDKT quantifies the risk for both patients and transplant centers associated with desensitizing and transplanting patients with preexisting DSA. Even after adjusting for all of the variables in the PSRs, there is a 1.64- and 5.01-fold increase in the risk of graft loss and a 2.04- and 4.59-fold increase in the risk of death for PFNC and PCC patients, respectively, in the first year posttransplant. PFNC and PCC patients continued to have elevated risk of graft loss and death after the first year posttransplant compared to compatible patients. For centers that perform 20% PFNC and 20% PCC as percentages of their overall live donor kidney transplant volume, there is a 1.73- and 10.72-fold increase in the odds of flagging by CMS compared to centers of equal quality that do not perform ILDKT. These findings warn of significant regulatory risk associated with ILDKT. Confirmation of our previous single-center demonstration of ILDKT survival benefit (1) on a multicenter level is necessary to better inform whether the increased regulatory scrutiny is justified or biased against beneficial treatment based on best evidence. The outcomes also serve as a benchmark for the assessment of the efficacy of new innovations and best practices for the relatively young field of HLA-incompatible 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*.

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