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Patient and Graft Survival After A1/A2-incompatible Living Donor Kidney Transplantation

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Background. ABO type B and O kidney transplant candidates have increased difficulty identifying a compatible donor for living donor kidney transplantation (LDKT) and are harder to match in kidney paired donation registries. A2-incompatible (A2i) LDKT increases access to LDKT for these patients. To better inform living donor selection, we evaluated the association between A2i LDKT and patient and graft survival. **Methods.** We used weighted Cox regression to compare mortality, death-censored graft failure, and all-cause graft loss in A2i versus ABO-compatible (ABOc) recipients. **Results.** Using Scientific Registry of Transplant Recipients data 2000–2019, we identified 345 A2i LDKT recipients. Mortality was comparable among A2i and ABOc recipients; weighted 1-/5-/10-y mortality was 0.9%/6.5%/24.2%, respectively, among A2i LDKT recipients versus 1.4%/7.7%/22.2%, respectively, among ABOc LDKT recipients (weighted hazard ratio [wHR], ${}_{0.81}1.04_{1.33}$; $P = 0.8$). However, A2i recipients faced higher risk of death-censored graft failure; weighted 1-/5-/10-y graft failure was 5.7%/11.6%/22.4% for A2i versus 1.7%/7.5%/17.2% for ABOc recipients (wHR in year 1 = ${}_{2.24}3.56_{5.66}$; through year 5 = ${}_{1.25}1.78_{2.53}$; through year 10 = ${}_{1.15}1.55_{2.07}$). By comparison, 1-/5-/10-y wHRs for A1-incompatible recipients were ${}_{0.63}1.96_{6.08}/{}_{0.39}0.94_{2.27}/{}_{0.39}0.83_{1.74}$. **Conclusions.** A2i LDKT is generally safe, but A2i donor/recipient pairs should be counseled about the increased risk of graft failure and be monitored as closely as their A1-incompatible counterparts posttransplant.

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ABO type B and O kidney transplant (KT) candidates experience greater barriers to transplantation than type A and AB candidates, due to decreased chances of ABO compatibility.[1-7] Type B and O candidates combined represented 70.1% of the kidney waitlist in July 2022 and 63.5% of waitlist additions between January 1995 and June 2022. Type B and O donors, however, represented just 59.4% of deceased donors in 2021.[8] ABO type B and O candidates also outnumber type B and O potential living donors (PLDs) in kidney paired donation (KPD) registries, leading to longer waitlist times.[9-12] In fact, 1 y after KPD registration, 42.6% of type O candidates remain on the waitlist, compared with just 21.2%

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and 24.0% of type A and AB candidates, respectively.[9] As a result, KT candidates with blood types B and O spend twice as long on the waitlist than candidates with type A and AB blood (1935 and 1851 versus 1207 and 853 d, respectively, in 2015).[2] Moreover, most waitlist candidates with blood type B are Black, Hispanic, or Asian[2,3,7]; these ethnicities comprised 62.2% of the waitlist as of July 2022.[8] This contributes to disparities in wait times for candidates of these ethnic groups since the nation's deceased donor population is mostly White, a group in which blood type B only has an incidence of 9%.[13]

KT across the A2 barrier (A2 → O, A2 → B, A2B → B) is believed to be safer than that across the A1 barrier (A1 → O, A1 → B, A1B → B) because A2 kidneys express fewer A antigens on their renal endothelial surfaces.[4,5,14] The Organ Procurement and Transplantation Network (OPTN) introduced a voluntary variance in 2002, allowing A2 and A2B kidneys to be allocated to type B recipients.[2] In 2014, A2-incompatible (A2i) became part of the standard allocation system under the Kidney Allocation System (KAS), provided a certain center-specific anti-A_2 titer threshold was met.[2,3,15] With the potential to improve access to living donor kidney transplantation (LDKT) for blood group B and O recipients,[16-18] A2i donor/recipient matching is a promising modality for LDKT.

The majority of research on ABO-incompatible (ABOi) LDKT has been performed in Japan, where ABOi KT comprises 30% of their LDKTs.[19] Results varied between single-center studies,[20-22] but registry analyses and meta-analyses generally reported similar outcomes between ABOi and ABO-compatible (ABOc) KT recipients in terms of patient and graft survival.[19] Unfortunately, these results are country specific because of differences in recipient and donor risk pools, waitlist criteria, etc. Within the United States, single-center studies have reported good outcomes for A2i LDKT compared with ABOc LDKT but were weakly powered to compare graft or patient survival.[6,16,23-25] Additionally, 3 registry studies, the most recent with data through 2013, found no evidence of increased risk of death or graft failure from A2i KT compared with ABOc KT. However, 52.3%, 60.3%, and 52.1% of the populations of these studies consisted of deceased donor kidney transplantation (DDKT) recipients, and no stratified analysis of LDKT recipients was performed.[1,2,7] There is an established benefit in patient and graft survival for LDKT compared with DDKT in the overall population[26]; however, the differential risk of A2i LDKT, if any, remains unknown. Furthermore, although A2i is considered to be safer than A1-incompatible (A1i) KT, a prior registry analysis found that among ABOi LDKT recipients, there was no difference between A1 and A2 donors in terms of patient or overall graft survival,[14] which brings into question the field's current assumptions regarding A2i. Understanding the risks of A2i LDKT is critical for informing donor counseling, immunosuppression regimens, and KPD matching algorithms.

To address this knowledge gap, we conducted a national cohort study to characterize trends in the use of A2i LDKT over time and to compare patient and graft survival between A2i and A1i LDKT and ABOc LDKT.

MATERIALS AND METHODS

Data Source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the OPTN. The Health Resources and Services Administration, US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. This dataset has previously been described elsewhere.[27]

Study Population

The study population consisted of adult, first-time KT recipients with blood type B or O in the United States between January 1, 2000, and December 31, 2019, located using SRTR data. This study received an exemption from the Johns Hopkins Institutional Review Board. In total, 58 018 participants at 245 centers were identified, of whom 345 received an A2i LDKT and 57 674 received an ABOc LDKT.

Temporal Trends in A2i LDKT

The number of LDKTs were counted for each year between January 1, 2000, and December 31, 2019. A histogram was constructed to depict the distribution of A2i LDKTs over this time period.

Outcomes

Posttransplant mortality, death-censored graft failure, and all-cause graft loss were studied. Death-censored graft failure was defined as the date of graft loss, retransplant, or return to maintenance dialysis with censoring for patient death. All-cause graft loss was defined as the earliest date at which a patient experienced graft loss, retransplant, a return to maintenance dialysis, or death.

Risk of Mortality and Graft Failure

Odds-weighted[28] Cox proportional hazards models were used to compare posttransplant outcomes (mortality, death-censored graft failure, and all-cause graft loss) between A2i versus comparable ABOc LDKT recipients. Weights were constructed in 2 steps. First, we constructed a logistic regression model with A2i status as the outcome, conditional on transplant year, recipient body mass index (BMI), recipient and donor age, recipient and donor sex, recipient and donor race-ethnicity, recipient peak calculated panel reactive antibody (cPRA), duration of pretransplant dialysis, and transplant center. Using this model, we calculated predicted odds of being an A2i recipient; this value was used as the weight for ABOc recipients, whereas A2i recipients were assigned a weight of 1.[28] LDKT recipients with missing donor age (n = 2) were excluded from all survival analyses. Missing indicator variables were constructed for recipient BMI and peak cPRA to allow for the inclusion in survival analyses of recipients with missing BMI (n = 3495) or peak cPRA values (n = 9198). Postweighting cohort balance was assessed by comparing standardized mean differences on all variables included in the models.

Patient Mortality and Graft Failure in A1i LDKT Recipients

In a separate analysis, the methods described above were repeated to compare mortality, death-censored graft failure, and all-cause graft loss between A1i versus comparable ABOc LDKT recipients. This analysis considered a total of 57 770 participants, of whom 96 received an A1i LDKT and 57 674 received an ABOc LDKT. A1i transplants were performed at 27 of 275 transplant centers.

Risk of Acute Rejection

Weighted odds ratios (wORs) were estimated by logistic regression to compare episodes of acute rejection (AR) within 6 and 12 mo following LDKT between A2i and ABOc recipients. Weights were constructed by the same method used for the weighted survival analyses described above.

Statistical Analysis

Confidence intervals and *P* values are 2-sided with an alpha of 0.05. Confidence intervals are reported according to the methods of Louis and Zeger.[29] All analyses were performed using Stata 16.0/MP for Linux (College Station, TX).

RESULTS

Study Population

Compared with the 57 674 ABOc LDKT recipients examined in this study, the 345 A2i LDKT recipients were older at the time of transplant (median [interquartile range (IQR)] age of 53 y [40–62 y] versus 49 y [37–59 y]; $P < 0.001$), spent more time on the waitlist (median [IQR] years of 0.81 [0.38–1.82] versus 0.63 [0.29–1.35]; $P < 0.001$), and were less likely to have comorbid hypertension (58.3% versus 68.2%; $P < 0.001$; Table 1). ABOc and A2i LDKT recipients were comparable in terms of sex (39.1% versus 35.4% female; $P = 0.2$), racial composition (76.0% versus 78.6% White, 5.3% versus 5.8% Asian, 17.2% versus 15.4% Black, and 1.6% versus 0.3% other; $P = 0.2$), peak cPRA values (24.9% versus 27.8% with cPRA >20; $P = 0.3$), preemptive transplant (31.8% versus 30.4%; $P = 0.6$), years on dialysis (median [IQR] years of 0.70 [0–1.83] versus 0.77 [0–2.12]), and living kidney donor profile index (median [IQR] 9.47 [–3.57 to 23.45] versus 9.88 [–2.41 to 26.43]; $P = 0.26$). A2i LDKTs were more likely to have been performed after the implementation of KAS ($P < 0.001$) and more likely to be part of KPD ($P < 0.001$). Proportions of transplants conducted at centers performing an average of >50 LDKTs per year were similar between ABOc and A2i LDKTs (45.1% versus 42.0%; $P = 0.3$).

Compared with ABOc recipients, A2i recipients more often used thymoglobulin (54.5% versus 40.6%; $P < 0.001$) and/or steroids (76.5% versus 70.0%; $P < 0.01$) for induction immunosuppression, and less often used basiliximab (13.3% versus 27.1%; $P < 0.001$) (Table 2). For maintenance immunosuppression, A2i recipients more often received tacrolimus (92.9% versus 82.8%; $P < 0.001$) and/or mycophenolate mofetil (97.0% versus 90.4%; $P < 0.001$) but were less likely to receive cyclosporine (4.2% versus 12.9%; $P < 0.001$) and/

TABLE 1.

Characteristics of adult patients receiving an A2i (A2 to O/B; or A2B to B) vs ABOc (O to O/B; or B to B) living donor kidney transplant

Characteristics	A2i LDKT recipients, n = 345	Compatible LDKT, recipients, n = 57 674	*P*
Age at transplant, median (IQR)	53 (40–62)	49 (37–59)	<0.001
Female	122 (35.4%)	22 527 (39.1%)	0.2
Race			
White	271 (78.6%)	43 812 (76.0%)	0.2
Asian	20 (5.8%)	3071 (5.3%)	
Black	53 (15.4%)	9896 (17.2%)	
Other	1 (0.3%)	895 (1.6%)	
BMI, median (IQR)	26.59 (23.79–31.27), (n = 330)	27.07 (23.55–31.15), (n = 54 194)	0.8
Cause of end-stage renal disease			
Hypertension	56 (16.2%)	11 017 (19.1%)	0.7
Diabetes	81 (23.5%)	13 664 (23.7%)	
Polycystic kidney disease	43 (12.5%)	7024 (12.2%)	
Glomerular sclerosis	34 (9.9%)	4981 (8.6%)	
Glomerulonephritis	47 (13.6%)	8600 (14.9%)	
Tumor	1 (0.3%)	236 (0.4%)	
Other	83 (24.1%)	12 117 (21.0%)	
Diabetes	101 (29.3%)	16 482 (28.6%)	0.8
Hypertension	201 (58.3%)	39 334 (68.2%)	<0.001
Peak calculated PRA			
0–20	249 (72.2%)	43 321 (75.1%)	0.3
21–80	32 (9.3%)	4186 (7.3%)	
81–100	6 (1.7%)	1027 (1.8%)	
No data	58 (16.8%)	9140 (15.8%)	
Preemptive transplant	105 (30.4%)	18 366 (31.8%)	0.6
Years on dialysis, median (IQR)	0.77 (0–2.12), (n = 344)	0.70 (0–1.82), (n = 57 650)	0.3
Years on waitlist, median (IQR)	0.81 (0.38–1.82), (n = 288)	0.63 (0.29–1.35), (n = 48 619)	<0.001
Performed after KAS	157 (45.5%)	14 676 (25.4%)	<0.001
Performed at high-volume center[a]	145 (42.0%)	26 016 (45.1%)	0.3
Kidney paired donation	74 (21.4%)	3287 (5.7%)	<0.001
LKDPI	9.88 (–2.41 to 26.43), (n = 261)	9.47 (–3.56 to 23.45), (n = 37 991)	0.3

[a]High-volume centers were those that performed an average of at least 50 LDKTs per year, 2000–2019.

A2i, A2-incompatible; ABOc, ABO-compatible; BMI, body mass index; IQR, interquartile range; KAS, Kidney Allocation System; LDKT, living donor kidney transplantation; LKDPI, living kidney donor profile index; PRA, panel reactive antibody.

TABLE 2.

Medications used for induction and maintenance immunosuppression among A2i and ABOc LDKT recipients

Medication	A2i (N = 345)	ABOc (N = 57 674)	*P*
Induction			
muromonab-CD3/ orthoclone	1 (0.3%)	120 (0.2%)	0.5
Thymoglobulin	180 (54.5%)	20 575 (40.6%)	<0.001
non-rabbit anti-thymocyte globulin	2 (0.6%)	549 (1.1%)	0.6
Daclizumab	27 (8.2%)	3848 (7.6%)	0.7
Basiliximab	44 (13.3%)	13 739 (27.1%)	<0.001
Rituximab	4 (1.2%)	302 (0.6%)	0.1
Alemtuzumab	56 (17.0%)	7609 (15.0%)	0.3
Steroid	260 (76.5%)	39 852 (70.0%)	0.01
Maintenance			
Cyclosporine	14 (4.2%)	7301 (12.9%)	<0.001
Tacrolimus	313 (92.9%)	46 927 (82.8%)	<0.001
MMF	327 (97.0%)	51 221 (90.4%)	<0.001
mTOR	6 (1.8%)	3726 (6.6%)	<0.001
Azathioprine	1 (0.3%)	599 (1.1%)	0.3
Steroid	227 (66.8%)	38 371 (67.4%)	0.8

A2i, A2-incompatible; ABOc, ABO-compatible; LDKT, living donor kidney transplantation; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin.

TABLE 3.

Characteristics of adult living kidney donors in A2i (A2 to O/B; or A2B to B) vs ABOc (O to O/B; or B to B) living donor kidney transplants

Characteristics	A2 incompatible LDKT donors, n = 345	Compatible LDKT donors, n = 57 674	*P*
Age at referral, median (IQR)	44 (36–53) (n = 345)	41 (32–50) (n = 57 672)	<0.001
Female	217 (62.9%)	35 020 (60.7%)	0.4
Race			
White	299 (86.7%)	45 744 (79.3%)	<0.01
Asian	9 (2.6%)	2543 (4.4%)	
Black	36 (10.4%)	8515 (14.8%)	
Others	1 (0.3%)	872 (1.5%)	
HLA mismatch >0	12 (3.5%)	4341 (7.6%)	<0.01

A2i, A2-incompatible; ABOc, ABO-compatible; IQR, interquartile range; LDKT, living donor kidney transplantation.

or mammalian target of rapamycin inhibitor (1.8% versus 6.6%; $P < 0.001$).

A2i donors were older than ABOc donors (median [IQR] age of 44 y [36–53 y] versus 41 y [32–50 y]; $P < 0.001$), and they showed no sex differences (62.9% versus 60.7% female; $P = 0.4$; Table 3). Although A2i and ABOc LDKT recipients showed no racial differences ($P = 0.2$), A2i donors were more likely to be White (86.7% versus 79.3%), less likely to be Asian (2.6% versus 4.4%), and less likely to be Black (10.4% versus 14.8%; $P < 0.01$).

Temporal Trends in A2i LDKT

The number of A2i LDKT has increased over time (Figure 1). Only 12 A2i LDKTs were reported in the United States in the year 2000, the start of our study period. This increased to 50 A2i LDKTs reported in 2019, the final year of our study period.

TABLE 4.

Weighted failure estimates and hazard ratios for mortality and graft failure in the comparison between A2i and ABOc living donor kidney transplant recipient outcomes

Outcome	A2i	ABOc	wHR	*P*
Mortality				
1 y	0.9%	1.4%	$_{0.22}0.67_{2.11}$	0.5
5 y	6.5%	7.7%	$_{0.52}0.86_{1.41}$	0.5
10 y	24.2%	22.2%	$_{0.75}1.02_{1.39}$	0.9
15 y	39.7%	38.6%	$_{0.76}0.99_{1.29}$	0.9
Overall	–	–	$_{0.81}1.04_{1.33}$	0.8
Death-censored graft failure				
1 y	5.7%	1.7%	$_{2.24}3.56_{5.66}$	<0.001
5 y	11.6%	7.5%	$_{1.25}1.78_{2.53}$	<0.01
10 y	22.4%	17.2%	$_{1.15}1.55_{2.07}$	<0.01
15 y	37.0%	26.3%	$_{1.19}1.56_{2.04}$	<0.01
Overall	–	–	$_{1.18}1.54_{2.02}$	<0.01
All-cause graft failure				
1 y	6.3%	2.8%	$_{1.50}2.32_{3.59}$	<0.001
5 y	16.6%	13.4%	$_{1.03}1.39_{1.87}$	0.03
10 y	38.1%	32.4%	$_{1.03}1.29_{1.62}$	0.03
15 y	60.7%	50.9%	$_{1.06}1.30_{1.60}$	0.01
Overall	–	–	$_{1.05}1.29_{1.58}$	0.02

A2i, A2-incompatible; ABOc, ABO-compatible; wHR, weighted hazard ratio.

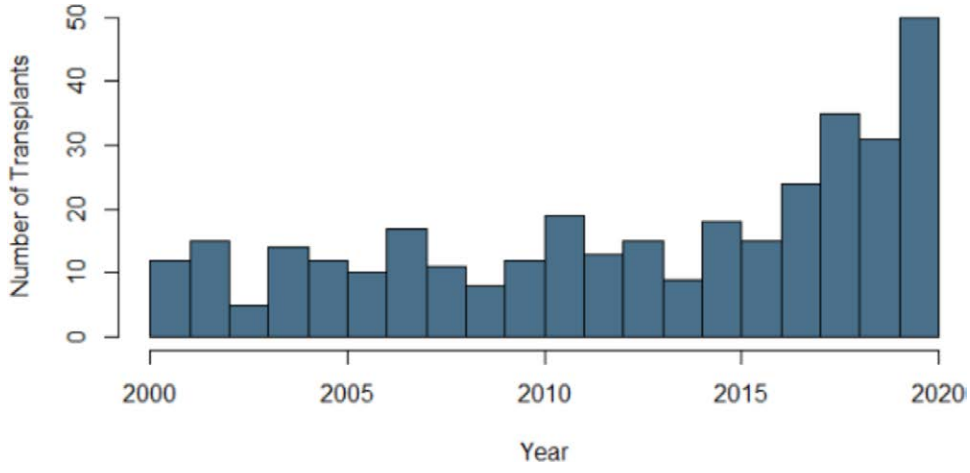

FIGURE 1. Number of recorded A2i LDKT per year, 2000–2019. A2i, A2-incompatible; LDKT, living donor kidney transplantation.

Cohort Balance

Postweighting, confounding variables were adequately balanced between A2i and ABOc recipients (**Table S1, SDC**, http://links.lww.com/TXD/A459).

Mortality

One-y, 5-y, and 10-y mortality rates were 0.9%, 6.5%, and 24.2%, respectively, among A2i LDKT recipients, and 1.4%, 7.7%, and 22.2%, respectively, among ABOc LDKT recipients ($P = 0.5$; $P = 0.5$; $P = 0.9$; Table 4). There was no difference in weighted posttransplant mortality when comparing A2i with ABOc recipients (weighted hazard ratio [wHR] = $_{0.81}1.04_{1.33}$; $P = 0.8$; Figure 2A).

Death-censored Graft Failure

One-y, 5-y, and 10-y death-censored graft failure was 5.7%, 11.6%, and 22.4%, respectively, among A2i LDKT recipients, and 1.7%, 7.5%, and 17.2%, respectively, among ABOc LDKT recipients ($P < 0.001$; $P < 0.01$; $P < 0.01$). Overall, A2i LDKT recipients faced a 54% higher risk of death-censored graft failure than comparable ABOc recipients (wHR = $_{1.18}1.54_{2.02}$; $P < 0.01$; Figure 2B).

All-cause Graft Loss

One-y all-cause graft loss was 6.3% among A2i versus 3.0% among ABOc LDKT recipients ($P < 0.001$; wHR = $_{1.50}2.32_{3.59}$). Five-y all-cause graft loss was 16.6% among A2i versus 13.4% among ABOc LDKT recipients ($P = 0.03$; wHR = $_{1.03}1.39_{1.87}$). Ten-y (38.1% versus 32.4%; $P = 0.03$; wHR = $_{1.03}1.29_{1.62}$) graft loss was also higher among A2i LDKT recipients as compared with ABOc recipients. Overall, A2i recipients faced a 29% higher risk of all-cause graft loss (wHR = $_{1.05}1.29_{1.58}$; $P = 0.02$; Figure 2C).

Mortality and Graft Failure Among A1i Recipients

Our study included 96 A1i LDKT recipients. One-y mortality rates were 1.1% among A1i versus 1.6% among ABOc LDKT recipients (Table 5). Five-y mortality rates were 5.4% among A1i versus 7.9% among ABOc LDKT recipients ($P = 0.4$; wHR = $_{0.25}0.67_{1.78}$). Ten-y (17.2% versus 22.3%; $P = 0.5$; wHR = $_{0.40}0.78_{1.51}$) and 15-y (46.8% versus 38.3%; $P > 0.9$; wHR = $_{0.60}1.00_{1.67}$) mortality were also comparable among the 2 groups. Overall, mortality was comparable between the 2 groups (wHR = $_{0.70}1.16_{1.90}$; Figure 3A).

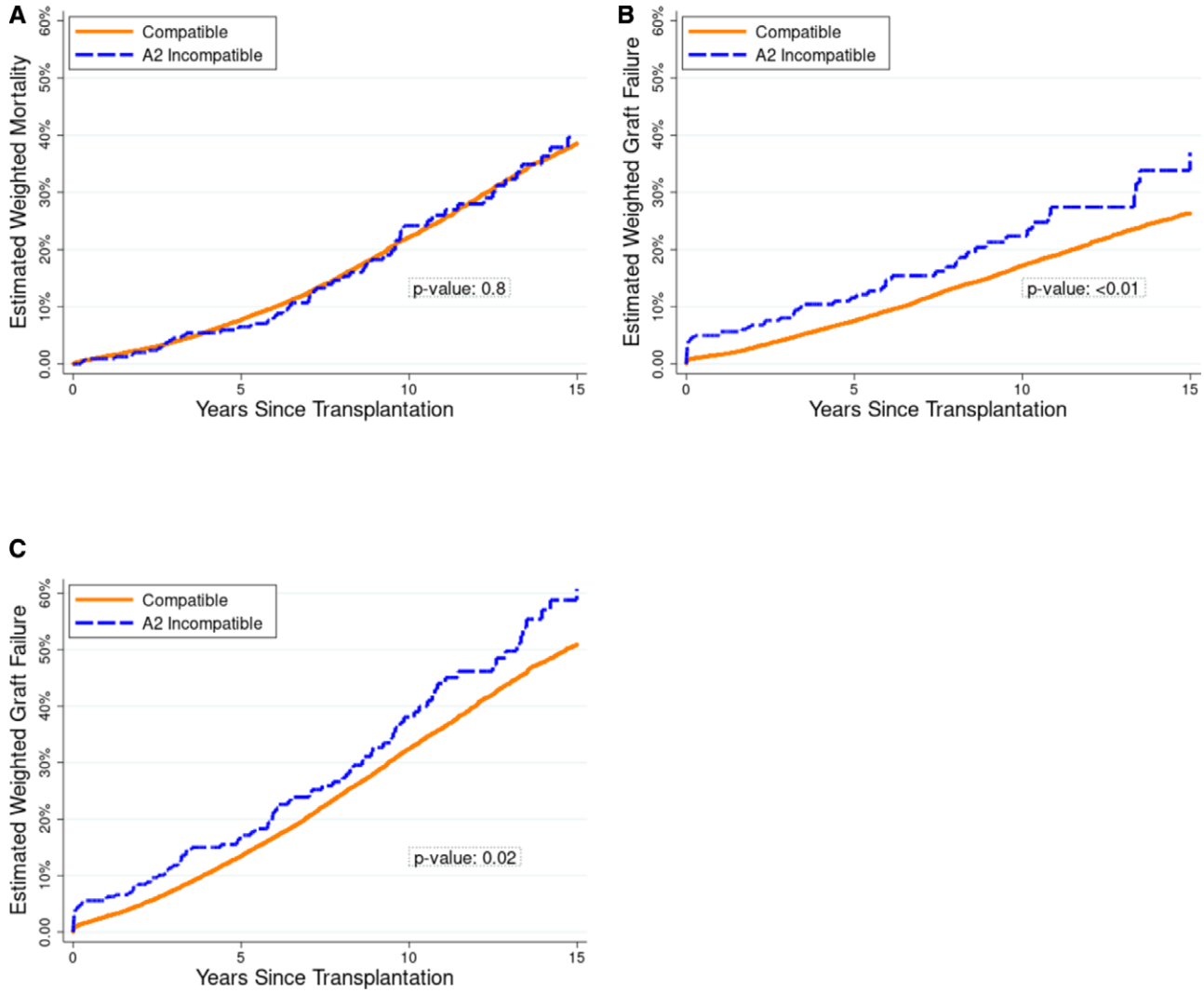

FIGURE 2. Posttransplant outcomes among A2i vs comparable ABOc LDKT recipients. Estimated weighted cumulative incidence of (A) mortality, (B) death-censored graft failure, and (C) all-cause graft loss after kidney transplant among patients who received an A2i or ABOc LDKT. A2i, A2-incompatible; ABOc, ABO-compatible; LDKT, living donor kidney transplantation.

TABLE 5.

Weighted failure estimates and hazard ratios for mortality and graft failure in the comparison between A1-incompatible and ABO-compatible living donor kidney transplant recipient outcomes

Outcome	A1i	ABOc	wHR	*P*
Mortality				
1 y	1.1%	1.6%	$_{0.09}0.68_{4.85}$	0.7
5 y	5.4%	7.9%	$_{0.25}0.67_{1.78}$	0.4
10 y	17.2%	22.3%	$_{0.40}0.78_{1.51}$	0.5
15 y	46.8%	38.3%	$_{0.60}1.00_{1.67}$	>0.9
Overall	–	–	$_{0.62}1.02_{1.67}$	0.9
Death-censored graft failure				
1 y	3.1%	1.7%	$_{0.63}1.96_{6.08}$	0.2
5 y	6.2%	7.3%	$_{0.39}0.94_{2.27}$	0.9
10 y	12.3%	16.4%	$_{0.39}0.83_{1.74}$	0.6
15 y	17.2%	25.8%	$_{0.42}0.83_{1.66}$	0.6
Overall	–	–	$_{0.41}0.81_{1.64}$	0.6
All-cause graft failure				
1 y	4.2%	3.0%	$_{0.54}1.45_{3.89}$	0.5
5 y	9.7%	13.5%	$_{0.39}0.79_{1.60}$	0.5
10 y	22.7%	32.3%	$_{0.43}0.75_{1.30}$	0.3
15 y	56.1%	50.9%	$_{0.57}0.90_{1.41}$	0.6
Overall	–	–	$_{0.55}0.87_{1.37}$	0.5

A1i, A1-incompatible; ABOc, ABO-compatible; wHR, weighted hazard ratio.

One-y death-censored graft failure was 3.1% among A1i versus 1.7% among ABOc LDKT recipients ($P = 0.2$; wHR = $_{0.63}1.96_{6.08}$). Five-y (6.2% versus 7.3%; $P = 0.9$; wHR = $_{0.39}0.94_{2.27}$) and 10-y (12.3% versus 16.4%; $P = 0.6$; wHR = $_{0.39}0.83_{1.74}$) death-censored graft failure, however, were comparable among the 2 groups. Overall, the 2 groups faced comparable death-censored graft failure (wHR = $_{0.41}0.81_{1.64}$; $P = 0.6$; Figure 3B).

Overall, A1i and ABOc LDKT recipients faced comparable all-cause graft loss (wHR = $_{0.55}0.87_{1.37}$; $P = 0.5$; Figure 3C). One-y, 5-y, and 10-y all-cause graft loss was comparable as well, at 4.2%, 9.7%, and 22.7%, respectively, among A1i, and 3.0%, 13.5%, and 32.3%, respectively, among ABOc LDKT recipients ($P = 0.2$; $P = 0.9$; $P = 0.6$).

Acute Rejection Among A2i Recipients

Weighted odds of AR at 6 and 12 mo post-LDKT were similar between A2i and ABOc recipients. Incidence of AR was 4.4% among A2i recipients and 3.5% of ABOc recipients by 6 mo (wOR = $_{0.83}1.40_{2.37}$; $P = 0.2$). By 12 mo, 10.0% of A2i recipients and 7.4% of ABOc recipients had experienced AR (wOR = $_{0.98}1.40_{2.01}$; $P = 0.07$).

DISCUSSION

In this retrospective registry analysis, we found that reported A2i LDKT has increased over time. We identified equivalent posttransplant mortality between A2i and similar ABOc LDKT recipients. There was, however, a higher risk of all-cause and death-censored graft loss for A2i LDKT recipients, especially in the earlier years posttransplant, most notably, a 3.56-fold higher risk of death-censored graft failure in the first year when compared with ABOc LDKT recipients; in contrast, there was only a 1.96-fold higher risk of death-censored graft failure experienced by A1i versus ABOc LDKT recipients in the first year posttransplant. Therefore, our findings suggest that A2i does confer some increased risk when compared with ABOc LDKT.

Our study demonstrates a continued increase in A2i LDKT, in accordance with trends identified in limited earlier studies.[1,7] However, since A1/A2 subtyping was not as frequent in the past,[30] the observed rise in A2i might also be attributable to this rise in subtyping. Furthermore, some A2is might have been excluded from appropriate classification in our analysis and recorded as ABOi instead if the corresponding subtype was not available for a type A donor who donated to a type O recipient. This misclassification would result in an underestimation of the frequency of A2i and A1i and possibly an inaccurate estimation of the true risk of patient and graft survival following A2i and A1i LDKT.

Several studies from Japan have previously compared outcomes between ABOi and ABOc LDKT recipients. Two single-center studies reported equivalent graft[21,22] and patient[22] survival, whereas a third reported decreased graft survival in ABOi recipients compared with ABOc recipients.[20] A registry analysis from Japan reported similar patient and graft survival between ABOi and ABOc recipients.[19] In contrast to most of these studies, our study found a slightly increased risk of graft loss for A2i recipients. Potential explanations for this difference include differences in patient population, immunosuppression, or other treatment protocols for LDKT recipients in the United States versus Japan. Within the United States, prior studies comparing A2i and ABOc KT recipients identified no difference in graft[1,2,7] or patient[2,7] survival. Of note, Redfield et al[1] reported that the adjusted relative risk of death-censored graft loss at 1- and 5-y posttransplant was similar between O, B, and AB recipients when compared with A recipients of an A2 graft, whereas we report on increased risk of death-censored graft failure in A2i LDKT recipients at these same time points. However, these past analyses did not stratify between DDKT and LDKT when calculating graft and/or patient survival, which may account for the discrepancies between their findings and ours. Moreover, we found that the difference in graft survival between A2i versus ABOc recipients was greatest in the first several years posttransplant. Duration of follow-up time may affect inference.

Our findings provide numerical support for the many single-center, small cohort studies that reported good graft[6,16,24] and patient[24] survival for A2i LDKT recipients. Specifically, Sorensen et al[6] reported on good long-term graft survival among 15 A2i LDKTs that took place in the 1990s, apart from 1 circulatory death at 9 mo posttransplant and 1 patient who exhibited considerable toxicity to calcineurin inhibitors. Bryan et al[16] reported good long-term graft survival as well by highlighting that 7 of the 9 A2i LDKTs at their center between 1986 and 2006 maintained functioning grafts through the end of their study period, albeit with 1 of the 7 being lost to follow-up at 9.2 y with a functioning kidney. Nelson et al[24] also reported success in 4 A2i LDKT recipients, as all 4 grafts remained functioning, with a mean follow-up of 71 mo posttransplant.

The higher risk of graft loss in A2i LDKT, especially during the first 5 y posttransplant, may be explained by differential PLD and candidate evaluation by the transplant center. LDKT is free of the time constraints associated with DDKT, which limits the ability to perform plasmapheresis and could lead to the acceptance of higher antibody titers for LDKT candidates compared with DDKT. However, such preoperative

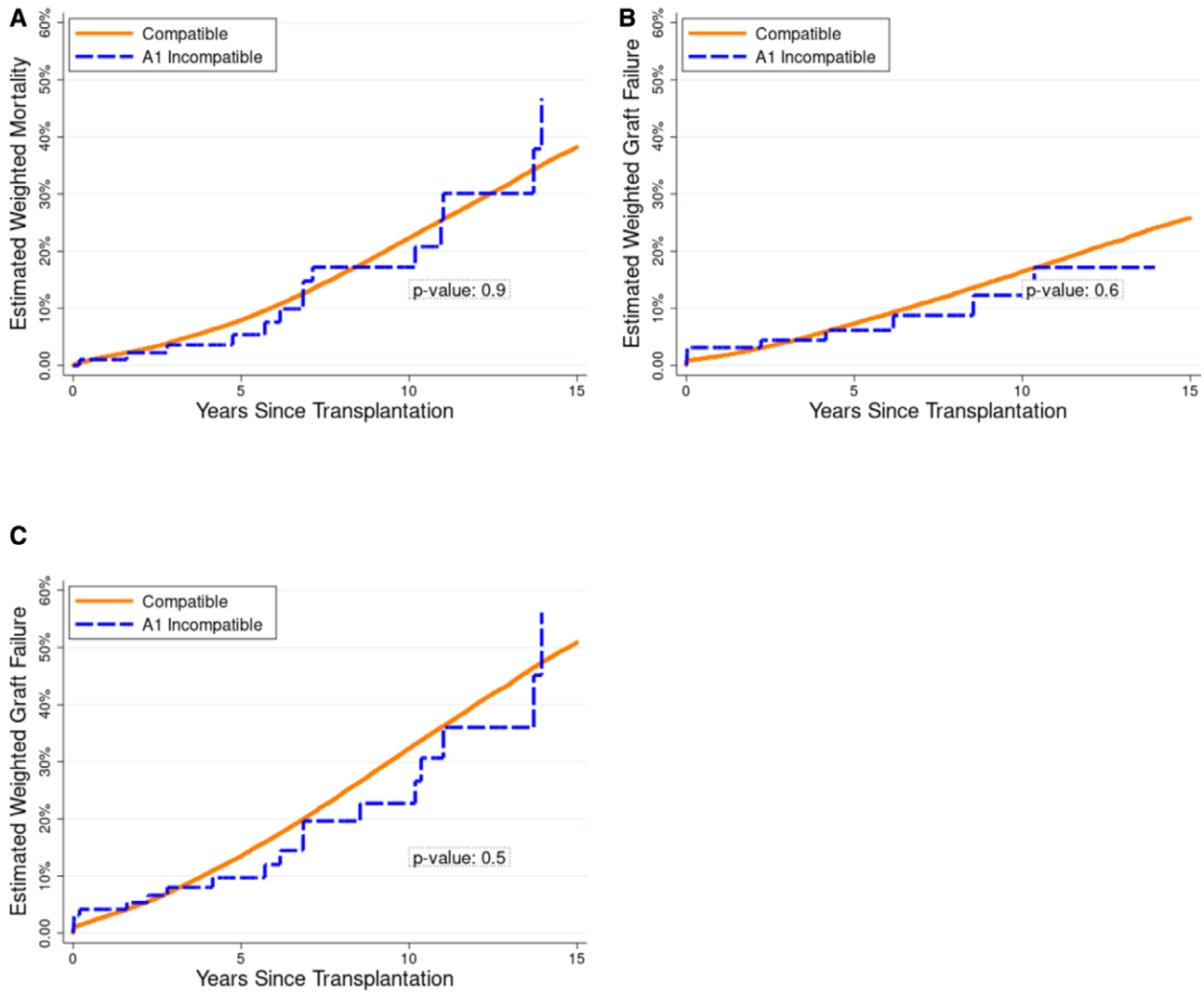

FIGURE 3. Posttransplant outcomes among A1i vs comparable ABOc LDKT recipients. Estimated weighted cumulative incidence of (A) mortality, (B) death-censored graft failure, and (C) all-cause graft loss after kidney transplant among patients who received an A1i or ABOc LDKT. A1i, A1-incompatible; ABOc, ABO-compatible; LDKT, living donor kidney transplantation.

precautions must be taken seriously as a prior single-center study reported on 1 patient with high anti-A antibody titers (anti-A_1 1:64, anti-A_2 1:32) losing their allograft because of hyperacute rejection after not receiving plasmapheresis.[23] Furthermore, PLD desire to donate to their intended candidate, rather than participate in KPD, may influence selection. One study reports more HLA mismatches in ABOi compared with ABOc LDKT,[31] which may also contribute to the increased risk of graft loss. Finally, the desire to pursue LDKT rather than wait for ABOc DDKT, as well as PLD desire to donate to their intended candidate, may influence patients and providers to accept an A2i living donor when they would not have accepted a comparable deceased donor.

Alternatively, the higher risk of early graft loss in A2i LDKT may be due to center-level variation in experience with ABOi and A2i KT, which may induce center-specific pretransplant desensitization and posttransplant monitoring procedures that are inadequate for A2i recipients. The significance of small fluctuations in the postoperative period is learned with experience,[32] so individual centers are differentially prepared to recognize and rescue deteriorating patients. Moreover, there is a current impression that non-A recipients of A2 kidneys do not need preconditioning or desensitization before transplantation (ie, they do not need therapeutic plasma exchange and can be treated as ABOc recipients) because A2 donors are functionally similar to type O donors.[33,34] However, these assumptions may be wrong for a subset of patients, especially in light of our findings of increased risk of death-censored graft failure among A2i versus ABOc LDKT recipients, which was not true for A1i versus ABOc LDKT recipients at any time point examined posttransplant. Perhaps these A2i patients require more careful monitoring and more aggressive treatment with therapeutic plasma exchange pretransplant and posttransplant than currently assumed to identify and alleviate these instances of early graft failure.

Despite the higher risk of adverse events (pneumonia, urinary tract infections, pyelonephritis, and wound infections) following ABOi LDKT in the early posttransplant period,[35] prior registry-based studies have demonstrated comparable long-term patient survival for ABOi LDKT,[14,36-39] and we similarly observed no difference in mortality in A2i versus ABOc recipients. Our research group has previously demonstrated the survival benefit for ABOi LDKT compared with remaining on the waitlist for an eventual ABOc DDKT or LDKT; a

similar survival benefit was seen when considering only A2i recipients.[38] Furthermore, delaying transplant and spending more time on dialysis, regardless of the length of dialysis, has been associated with increased graft failure following KT.[40] The cost of an ABOi or A2i KT itself may be higher than an ABOc KT because of desensitization and antibody reduction therapies,[12,34] but in addition to the aforementioned clinical benefits, ABOi and A2i KT confer long-term cost savings compared with remaining on dialysis and facing its associated morbidity and cost.[12,41] Additionally, the 2020 SRTR Annual Data Report lists overall waitlist mortality at 5.7 deaths per 100 person-years in 2020,[42] which corresponds to a 5-y survival of 74.6% and a 10-y survival of 55.6%. Survival post-A2i LDKT is substantially higher than these patients with an A2i potential donor would likely face on dialysis. Hence, given that the risk of graft loss in A2i LDKT will be equal to or less than that of ABOi LDKT and that patient survival post-A2i LDKT is higher than that on the waitlist or dialysis, our results should not be interpreted as contraindicating A2i LDKT when there is no other donor available. However, the added risk of graft loss that we report should be taken into consideration when comparing multiple donor candidates, evaluating KPD pairings, or counseling A2i donor/recipient pairs.

Our study must also be understood in the context of its limitations. Data from the SRTR contain no information on initial isohemagglutinin titers or pretransplant desensitization treatments. Hence, we are unable to discuss the role that these factors may play in our results. Nevertheless, since prior studies have found success following ABOi KT despite anti-A/-B titers,[43,44] whereas others have reported no correlation between these titers and the rate of graft survival[45] or the development of late antibody-mediated rejection,[46] the exclusion of titers from our analysis is not a major drawback. There may also be residual confounding present within our analysis from characteristics that are not measured in the SRTR database. Nonetheless, ABOc LDKT recipients and A2i LDKT recipients were comparable in most characteristics measured in our study, and it is unlikely that unmeasured confounders differ sufficiently between A2i versus ABOc recipients to affect our inference.

This registry analysis uniquely considered the differential risk of A2i LDKT in the United States and demonstrated comparable mortality to ABOc LDKT recipients, albeit with an increased risk of graft failure for A2i LDKT recipients. Despite this increased risk of graft failure, particularly in the earlier years posttransplant, A2i LDKT should not be contraindicated in KPD algorithms if there is no other donor available because it still provides better outcomes than staying on the waitlist or starting and remaining on dialysis. A2i LDKT remains an excellent treatment option, providing access to LDKT for many patients that would otherwise remain on the waitlist. Our findings further the field's understanding of the risks and benefits of A2i LDKT and should inform patient counseling, KPD matching algorithms, and postoperative monitoring procedures in the future.

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