ORIGINAL ARTICLE

Outcomes of ABO-incompatible kidney transplantation in older patients: a national cohort study

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ABSTRACT

Background
Outcomes of ABO-incompatible living donor kidney transplantation (ABOi LDKT) in older individuals have not been established.

Methods
This multicentric observational study, using data from the Korean Organ Transplantation Registry database, included 634 older patients (≥60 years) undergoing kidney transplantation. We compared clinical outcomes of ABOi LDKT (n = 80) with those of ABO-compatible LDKT (ABOc LDKT, n = 222) and deceased donor kidney transplantation (DDKT, n = 332) in older patients.

Results
Death-censored graft survival was similar between the three groups (P = 0.141). Patient survival after ABOi LDKT was similar to that after ABOc LDKT (P = 0.489) but higher than that after DDKT (P = 0.038). In multivariable analysis, ABOi LDKT was not risk factor (hazard ratio [HR] 1.73, 95% confidence interval [CI] 0.29-10.38, P = 0.548), while DDKT was significant risk factor (HR 3.49, 95% CI 1.01–12.23, P = 0.049) for patient survival. Although ABOi LDKT showed higher biopsy-proven acute rejection than ABOc LDKT, the difference was not significant after adjustment with covariates. However, ABOi LDKT was significant risk factor for infection (HR 1.66, 95% CI 1.12–2.45, P = 0.012).

Conclusions
In older patients, ABOi LDKT was not inferior to ABOc LDKT and was superior to DDKT for patient survival. ABOi LDKT can be recommended for older patients, rather than waiting for DDKT.

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Key words
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Introduction

Worldwide, the number of older patients with end-stage renal disease (ESRD) has been increasing [1]. As with younger patients, kidney transplantation (KT) reduces mortality in this older population, when compared with remaining on dialysis [2]. This survival benefit has been documented for patients over 70 years of age, including those who received a kidney based on expanded donor criteria [3]. However, the sustained shortage of deceased donors has led to growing interest in expanding the living donor pool, especially for older patients whose waiting list mortality is higher than that of younger patients.

ABO-incompatible living donor KT (ABOi LDKT) is a strategy to overcome the shortage of donor kidneys, although there have been conflicting reports regarding outcomes after this type of transplantation [4-9]. In Korea, the number of ABOi LDKTs has been rapidly increasing since 2007 [10,11]. A recent meta-analysis revealed that ABOi LDKT was associated with higher mortality and graft loss within the first 3 years, when compared with ABO-compatible LDKT (ABOc LDKT) [12]. These findings were attributed to ABOi LDKT being associated with a higher risk of rejection because of anti-blood group antibodies [13] and a higher risk of infectious complications resulting from the need for more potent immunosuppressive treatment [14]. On the other hand, Massie et al. recently reported long-term survival gain of ABOi LDKT compared to remaining waiting list [15]. However, outcomes of ABOi LDKT have not been well investigated in older transplant recipients. As older patients may have a less prominent immune response because of "immunosenescence" [16], this age group patients may be expected to have fewer rejection and more infectious complications than younger individuals after organ transplantation [17,18]. In this study, we compared clinical outcomes of ABOi LDKT to those of ABOc LDKT and deceased donor KT (DDKT) in older patients.

Materials and methods

Study population

We analyzed prospectively collected data from the Korean Organ Transplantation Registry (KOTRY), which contained 50.4% of total KTs performed in South Korea between May 2014 and December 2017 [19]. Among 3766 KTs, we defined older age as > 60 years because of increased post-transplant mortality at 60 years old confirmed with Cox model with penalized splines in entire KOTRY population (Figure S1). A total of 663 older patients underwent KT during this time period. Patients who underwent positive crossmatch KT (n = 24), dual KT (n = 2), or en-bloc KT (n = 1) and those without ABO compatibility data (n = 2) were excluded from this study. We did not exclude negative crossmatch with donor-specific antibody (XM-DSA+) KT based on the recent report on noninferior outcome [20]. Eligible patients were divided into three groups: ABOi LDKT (n = 80), ABOc LDKT (n = 222), and DDKT (n = 332). All DDKTs were ABO-compatible and crossmatch negative (Fig. 1).

Data collection

Patient demographics before transplantation were recorded. ABO types of both the donor and recipient were recorded, along with the presence or absence of ABO incompatibility. For the ABOi LDKT group, information regarding isoagglutinin titer for anti-A or -B antibody before and after desensitization and the use and dose of rituximab or intravenous immunoglobulin (IVIG) were recorded. Immunosuppressant and postoperative outcome information were recorded at discharge, at 6 and 12 months after KT, and then annually. Estimated glomerular filtration rate (eGFR) was recorded at the same times, as were other standard laboratory data. eGFR was regarded as zero if the graft was lost.

Graft failure and rejection

Graft failure was defined as return to dialysis or retransplantation, and patient death was censored during the analysis of graft failure. Only biopsy-proven acute rejection (BPAR) was regarded for analyzing rejection. Type of rejection (antibody-mediated or T cell–mediated rejection) was not analyzed because data missing in about half of study population. Information regarding the types of BPAR treatment was collected, with responses to treatment categorized as "complete resolution" (normalization of serum creatinine to the prerejection level), "incomplete resolution" (stabilization of serum creatinine at a level above the prerejection value), and "graft loss" (graft failure within 1 month after rejection). The worst of the three categories within 1 year after KT was counted for each patient.

Surgical complications and infectious complications

Complications related to transplant surgery and occurring within 6 months of the procedure were categorized as follows: hemorrhage at the surgical site, vascular thrombosis, wound infection, urine leakage, or urinary

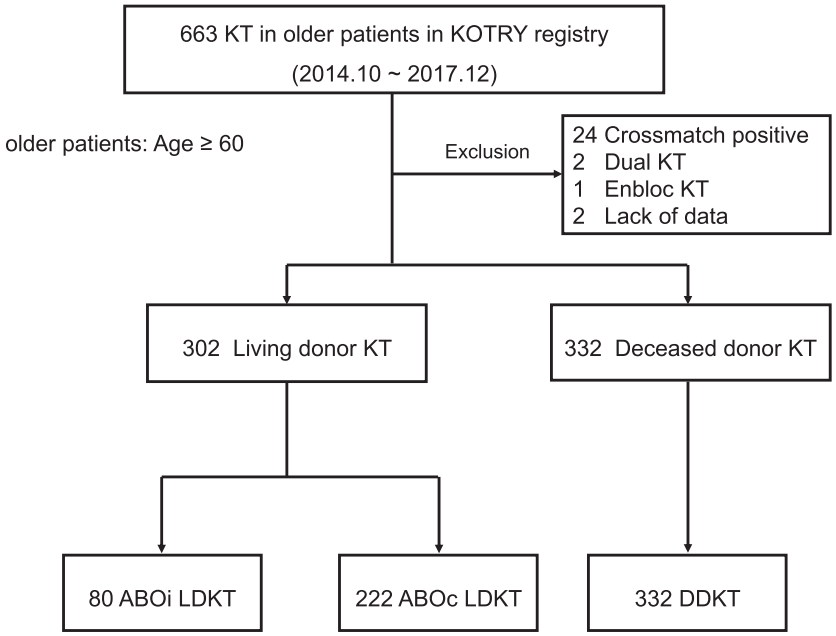

Fig. 1 Study population. CDC, complement dependent cytotoxicity; DSA, donor–specific antibody; FC, flow cytometry; HLA, human leukocyte antigen; LDKT, living donor kidney transplantation

stricture. Infectious complications for which hospital admission was required were categorized by pathogen and site of infection. Because the specific pathogen and type of quantitative measurement (eg, quantitative polymerase chain reaction for cytomegalovirus) were not recorded in KOTRY until January 2017, we categorized infections as simply bacterial, viral, or fungal infections or *Pneumocystis jiroveci* pneumonia (PJP). Bacterial infections were subclassified as urinary tract infection, pneumonia, or bacteremia. Positivity for each pathogen was determined according to each center's standards.

Statistical analysis

Because the superiority of ABOc LDKT over DDKT is well established, the main purpose of this study was to compare the outcomes of ABOi LDKT to those of the other two types of KT in older patients. Thus, comparative analyses (except for demographic data) were performed for ABOi LDKT vs ABOc LDKT and ABOi LDKT vs DDKT. Chi-square test or Fisher's exact test was performed for comparing categorical variables. For continuous variables, one-way analysis of variance or the Kruskal–Wallis test was used to compare demographics of the three groups, depending on whether the variable was normally distributed. Student's t-test was used to compare eGFR values. Survival analysis was performed using the Kaplan-Meier method, with the log-rank test. Univariable and multivariable Cox regression analyses were performed for survival outcomes, and adjusted models were determined with covariates of which P value was < 0.10 in univariable Cox and which were clinically important. Also, for death-censored graft survival, BPAR-free survival and infection-free survival, Cox regression was performed by Fine and Gray's model treating death as a competing risk. All analyses were performed using standard software (SPSS v23.0; IBM, Armonk, NY, USA and R freeware v3.6.3, R Foundation for Statistical Computing, Vienna, Austria). $P < 0.05$ was considered statistically significant.

Ethics approval and consent to participate

This study was conducted in accordance with the tenets of the Declaration of Helsinki and Declaration of Istanbul. The protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (no: 4-2020-0295), which provided an exemption for informed consent because of the retrospective feature of this study.

Results

Baseline characteristics

As shown in Table 1, the mean (± standard deviation) age of recipients was similar between the three groups (63.7 ± 3.2 [maximum, 71] years vs 63.9 ± 3.5

Table 1. Baseline characteristics

Variables	ABOi LDKT (n = 80)	ABOc LDKT (n = 222)	DDKT (n = 332)	P
Age, years	63.7 ± 3.2	63.9 ± 3.5	64.2 ± 3.6	0.430
Sex, males	56 (70.0%)	143 (64.4%)	212 (63.9%)	0.579
BMI, kg/m^2	24.9 ± 9.1	23.4 ± 3.1	23.6 ± 5.1	0.090
Cause of ESRD				0.101
Diabetes	33 (41.3%)	82 (36.9%)	110 (33.1%)	
Hypertension	9 (11.3%)	38 (17.1%)	72 (21.7%)	
Glomerular disease	17 (21.3%)	43 (19.4%)	64 (19.3%)	
Polycystic kidney disease	4 (5.0%)	6 (2.7%)	25 (7.5%)	
Other disease	2 (2.5%)	5 (2.3%)	12 (3.6%)	
Unknown	15 (18.8%)	48 (21.6%)	49 (14.8%)	
Dialysis duration, months	2 (1–17)	3 (1–13)	71 (39–102)	<0.001
Retransplantation	3 (3.8%)	17 (7.7%)	15 (4.5%)	0.216
DM	41 (51.2%)	110 (49.5%)	142 (42.8%)	0.183
CVD	15 (18.8%)	48 (21.6%)	79 (23.8%)	0.588
Donor age, years	52.5 ± 11.8	46.3 ± 12.0	53.9 ± 14.5	<0.001
Donor sex, males	33 (41.3%)	101 (45.5%)	231 (69.6%)	<0.001
XM–DSA+	6 (7.5%)	14 (6.3%)	2 (0.6%)	0.121
Induction agent				<0.001
IL–2 receptor antibody	67 (83.8%)	191 (86.0%)	226 (68.1%)	
Anti–thymocyte globulin	13 (16.2%)	31 (14.0%)	106 (31.9%)	

BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; ESRD, end–stage renal disease.

Table 2. Details for ABOi LDKT in the elderly

Variables	ABOi LDKT (n = 70)
Recipient blood type O	22 (31.4%)
ABO titer, baseline	
IgM	16 (8–32)
IgG	32 (16–128)
High titer (≥ 256)	9 (12.8%)
ABO titer, at transplantation	
IgM	1 (1–2)
IgG	4 (2–8)
Rituximab dose	
≤200 mg	50 (71.4%)
>200 mg	18 (25.7%)
No rituximab	2 (2.9%)
Number of plasmapheresis	4 (2–5)
Intravenous immunoglobulin use	33 (47.1%)

[maximum, 79] years vs 64.2 ± 3.6 [maximum, 77] years in the ABOi LDKT, ABOc LDKT, and DDKT groups, respectively, P = 0.430). Sex, body mass index, cause of ESRD, rate of retransplantation, and rate of pretransplant diabetes mellitus and cardiovascular disease (CVD) were similar between the three groups. Not surprisingly, dialysis duration of the ABOi LDKT group was significantly shorter than that of the DDKT group but similar to that of the ABOc LDKT group (2 [1–17] months vs 3 [1–13] months vs 71 [39–102] months in the ABOi LDKT, ABOc LDKT, and DDKT groups, respectively, P < 0.001). Donors were younger in the ABOc LDKT group than in the other two groups (P < 0.001). In addition, donor sex revealed a male predominance in the DDKT group, while the donor sex of the other two groups exhibited a female predominance (P < 0.001). Frequency of XM-DSA + was 7.5% in the ABOi LDKT, 6.3% in the ABOc LDKT, and 0.6% in the DDKT group, respectively (P = 0.121). All kidneys in the DDKT group were procured from brain-dead donors, with a mean cold ischemic time of 294 ± 143 minutes.

Pretransplant desensitization for ABOi LDKT

Data were available for 70 patients who underwent pretransplant desensitization, the details of which are shown in Table 2. All desensitization processes were performed according to the local policy. The blood group was type O in 22 (31.4%) patients. Median (interquartile range [IQR]) baseline ABO isoagglutinin titers were 1:16 (1:8–1:32) for IgM antibody and 1:32 (1:16–1:128) for IgG antibody. Nine (12.8%) patients had a high titer (defined as ≥ 1:256), and the highest baseline titer was 1:1024, which was present in one patient. After desensitization, the median (IQR) ABO isoagglutinin titer was reduced to 1:1 (1:1–1:2) for IgM antibody and 1:4 (1:2–1:8) for IgG antibody. No patient

Table 3. Surgical complications within 6 months after kidney transplantation

Variables	ABOi LDKT (n = 80)	ABOc LDKT (n = 222)	P vs *ABOi LDKT*	DDKT (n = 332)	P vs *ABOi LDKT*
Overall surgical complication	5 (6.2%)	7 (3.1%)	0.313	18 (5.4%)	0.787
Hemorrhage at operation site	3 (3.8%)	3 (1.4%)	0.192	4 (1.2%)	0.136
Vascular thrombosis	1 (1.3%)	0	0.265	0	0.194
Wound infection	0	1 (0.5%)	0.989	5 (1.5%)	0.588
Urine leakage	0	0	–	5 (1.5%)	0.588
Urinary stricture	1 (1.3%)	3 (1.4%)	0.713	6 (1.8%)	0.592

underwent KT with an ABO titer above 1:32 on the day of surgery.

No ABOi LDKT patient underwent splenectomy. Fifty (71.4%) patients received ≤ 200 mg rituximab, 18 (25.7%) received > 200 mg rituximab, and 2 (2.9%) received no rituximab before transplantation (Table 2). The median (IQR) number of plasmaphereses was 4 (2–5). The maximum number of plasmaphereses was 14, which were performed in the patient with the highest baseline ABO titer. IVIG was administered after plasmapheresis in 33 (47.1%) patients, at a dose of 100 mg/kg or 200 mg/kg.

Surgical complications

Within 6 months after transplantation, 30 (4.7%) patients experienced surgical complications. When compared with the ABOc LDKT and DDKT groups, the ABOi LDKT group exhibited no significant differences in surgical complications, including hemorrhage at the surgical site, vascular thrombosis, wound infection, urine leakage, or urinary stricture (Table 3). Hemorrhage occurred in only three patients in the ABOi LDKT group. These patients had initial ABO titers of 1:4, 1:8, and 1:64 and received plasmapheresis 2, 3, and 9 times, respectively.

Graft survival

During a mean follow-up period of 28.1 ± 12.8 months, death-censored graft failure occurred in 14 (2.2%) patients. The most common cause of graft loss was rejection (n = 6, 0.9%). Incidence rates (per 1000 patient year) of death-censored graft failure were 2.5 for ABOi LDKT, 1.8 for ABOc LDKT, and 6.6 for DDKT. On Kaplan-Meier analysis (Fig. 2a), death-censored graft survival was similar between all groups (P = 0.141). In univariate and multivariate Cox analysis, hazards for graft survival were not significantly different between three groups (Table 4).

Patient survival

Twenty-nine (4.6%) patients died during the study period. The most common cause of death was infection (n = 16, 2.5%), followed by CVD (n = 6, 0.9%). The causes of death in each group were as follows: ABOi LDKT group, infection (n = 2); ABOc LDKT group, infection (n = 1) and CVD (n = 2); and DDKT group, infection (n = 13), CVD (n = 4), cancer (n = 1), and unknown (n = 6). Infection-related death rates were 2.5% in the ABOi LDKT group, 0.9% in the ABOc LDKT group (P = 0.172, vs ABOi LDKT), and 3.9% in the DDKT group (P = 0.540, vs ABOi LDKT). CVD death rates were 0% in the ABOi LDKT group, 0.9% in the ABOc LDKT group (P = 0.540, vs ABOi LDKT), and 1.0% in the DDKT group (P = 0.420, vs ABOi LDKT). Incidence rates (per 1000 patient year) of patient death were 5.0 for ABOi LDKT, 2.7 for ABOc LDKT, and 14.5 for DDKT. On Kaplan-Meier analysis (Fig. 2b), patient survival in the ABOi LDKT group was similar to that in the ABOc LDKT group (P = 0.489) but significantly higher than that in the DDKT group (P = 0.038). In univariable and multivariable Cox analyses, ABOi LDKT was not significant risk factor for patient survival (hazard ratio [HR] 1.73, 95% confidence interval [CI] 0.29–10.38, P = 0.548), while DDKT had an hazard for patient death (HR 3.49, 95% CI 1.01–12.23, P = 0.049, Table 4).

Biopsy-proven acute rejection

Incidence rates (per 1000 patient year) of BPAR were 50.0 for ABOi LDKT, 30.0 for ABOc LDKT, and 47.2 for DDKT. On Kaplan-Meier analysis (Fig. 3c), BPAR-free survival in the ABOi LDKT group was significantly lower than that in the ABOc LDKT group (P = 0.050) but similar to that in the DDKT group (P = 0.908). In univariable Cox analysis, ABOi LDKT and DDKT were significant risk factor for BPAR (HR 1.72, 95% CI 1.00–2.96, P = 0.050 for ABOi LDKT and HR 1.60, 95% CI 1.08–2.38, P = 0.020 for

DDKT). However, after adjustment for confounders and competing risk analysis, hazards for BPAR were not significant in those two groups (HR 1.51, 95% CI 0.85–2.68, $P = 0.164$ for ABOi LDKT and HR 1.35, 95% CI 0.89–2.04, $P = 0.165$ for DDKT, Table 4).

In Table 5, treatment for BPAR occurred within 1 post-transplant year and corresponding response to anti-rejection treatment were demonstrated. The BPAR rate of the ABOi LDKT group (21.3%) was significantly higher than that of the ABOc LDKT group (11.7%, $P = 0.036$) but similar to that of the DDKT group (19.9%, $P = 0.784$). However, the rate of BPAR requiring anti-thymocyte globulin (ATG) or plasmapheresis plus IVIG in the ABOi LDKT group was similar to that in both the ABOc LDKT and DDKT groups.

Response to anti-rejection treatment in the ABOi LDKT group was similar to that in the ABOc LDKT group ($P = 0.558$) and DDKT group ($P = 0.614$). Approximately 65% of BPAR completely resolved with anti-rejection treatment, and this percentage was similar

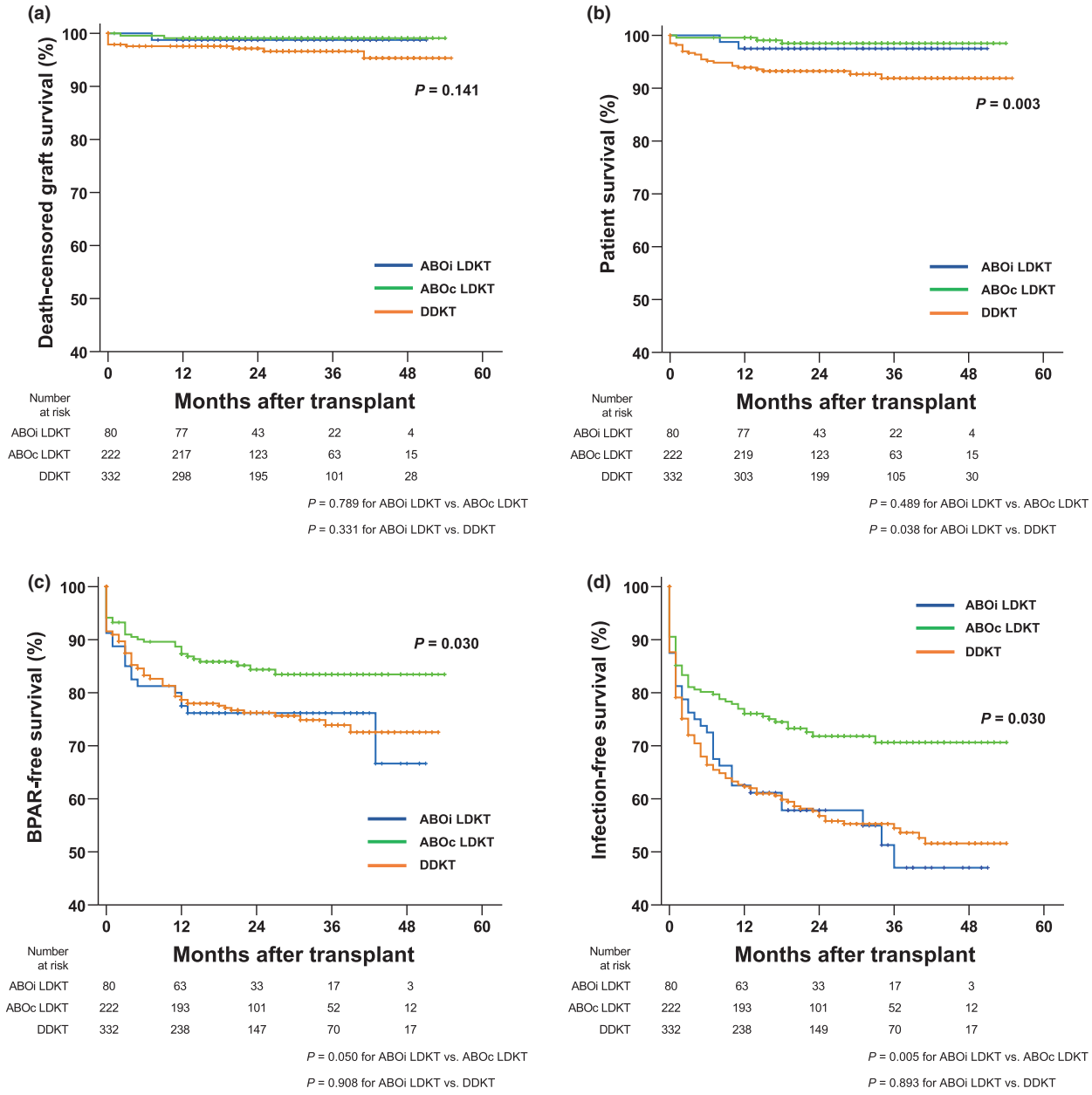

Fig. 2 Comparison of survival outcomes. (a) death–censored graft survival, (b) patient survival, (c) BPAR–Free survival, and (d) infection–free survival. ABOc, ABO–compatible; ABOi, ABO–incompatible; BPAR, biopsy–proven acute rejection; DDKT, deceased donor kidney transplantation; LDKT, living donor kidney transplantation

Table 4. Univariable and multivariable Cox analyses

	Univariable Cox		Multivariable Cox[¶]	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
For death–censored graft survival*				
ABOc LDKT	Reference		Reference	
ABOi LDKT	1.38 (0.13–15.25)	0.791	1.27(0.12–13.92)	0.847
DDKT	3.69 (0.72–16.64)	0.090	4.73(0.97–23.04)	0.054
For patient survival[†]				
ABOc LDKT	Reference		Reference	
ABOi LDKT	1.85 (0.31–11.09)	0.499	1.73 (0.29–10.38)	0.548
DDKT	5.52 (1.66–18.33)	0.005	3.49 (1.01–12.23)	0.049
For BPAR–free survival[‡]				
ABOc LDKT	Reference		Reference	
ABOi LDKT	1.72 (1.00–2.96)	0.050	1.51 (0.85–2.68)	0.164
DDKT	1.60 (1.08–2.38)	0.020	1.35 (0.89–2.04)	0.165
For infection–free survival[§]				
ABOc LDKT	Reference		Reference	
ABOi LDKT	1.78 (1.2–2.64)	0.004	1.66 (1.12–2.45)	0.012
DDKT	1.72 (1.28–2.31)	<0.001	1.18 (0.83–1.66)	0.353

Models for each outcome were determined with covairates of which P value was < 0.10 in univariable Cox and which were clinically important. Full results of Cox analysis were provided as supplement table.

*Multivariable Cox model for death–censored graft survival included donor age, donor sex, retransplantation, CVD.

[†]Multivariable Cox model for patient survival included donor age, BMI, dialysis duration, DM, CVD.

[‡]Multivariable Cox model for BPAR–free survival included sex, donor age, DSA.

[§]Multivariable Cox model for infection–free survival included donor age, sex, anti–thymocyte globulin, DM.

[¶]For death–censored graft survival, BPAR–free survival and infection–free survival, Cox regression was performed by Fine and Gray's model treating death as a competing risk.

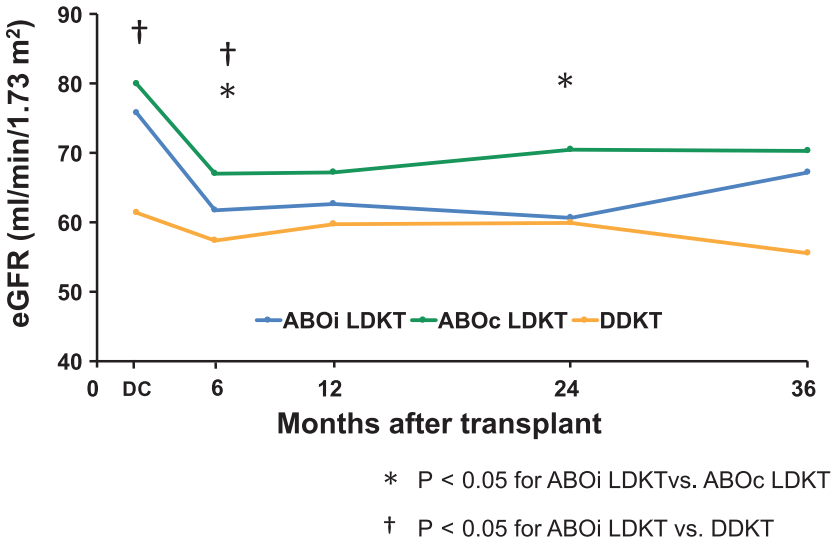

Fig. 3 Comparison of graft functions. ABOc, ABO–compatible; ABOi, ABO–incompatible; DC, discharge; DDKT, deceased donor kidney transplantation; LDKT, living donor kidney transplantation

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Table 5. Comparison of biopsy–proven acute rejection and treatment within 1 year after transplantation

Variables	ABOi LDKT (n = 80)	ABOc LDKT (n = 222)	P vs *ABOi LDKT*	DDKT (n = 332)	P vs *ABOi LDKT*
BPAR	17 (21.3%)	26 (11.7%)	0.036	66 (19.9%)	0.784
BPAR requiring each treatment					
Intravenous steroid pulse	11 (13.8%)	18 (8.1%)	0.142	53 (16.0%)	0.624
Anti–thymocyte globulin	1 (1.3%)	2 (0.9%)	0.787	6 (1.8%)	0.729
Plasmapheresis plus intravenous immunoglobulin	1 (1.3%)	4 (18%)	0.740	5 (1.5%)	0.864
Response to anti–rejection treatment			0.558		0.614
Complete resolution	9/17 (52.9%)	18/26 (69.3%)		43/66 (65.2%)	
Incomplete resolution	7/17 (41.2%)	7/26 (26.9%)		21/66 (31.8%)	
Graft loss	1/17 (5.9%)	1/26 (3.8%)		2/66 (3.0%)	

between the three groups (52.9%, 69.2%, and 65.2% in the ABOi LDKT, ABOc LDKT, and DDKT groups, respectively). In only four patients, graft loss occurred within 1 month after acute rejection, and the percentage of this outcome was also similar between the three groups (5.9%, 3.8%, and 3.0% in the ABOi LDKT, ABOc LDKT, and DDKT groups, respectively).

Infection

Incidence rates (per 1000 patient year) of infection which was needed for admission were 90.0 for ABOi LDKT, 55.2 for ABOc LDKT, and 86.7 for DDKT. On Kaplan-Meier analysis (Fig. 3d), infection-free survival in the ABOi LDKT group was significantly lower than that in the ABOc LDKT group (P = 0.005) but similar to that in the DDKT group (P = 0.893). In univariable Cox analysis, ABOi LDKT and DDKT were significant risk factor for infection (HR 1.78, 95% CI 1.2–2.64, P = 0.004 for ABOi LDKT and HR 1.72, 95% CI 1.28–2.31, P < 0.001 for DDKT). However, after adjustment for confounders and competing risk analysis, hazards for infection were not significant in the DDKT group (HR 1.18, 95% CI 0.83–1.66, P = 0.353), while ABOi LDKT was still significant risk factor for infection (HR 1.66, 95% CI 1.12–2.45, P = 0.012, Table 4).

In Table 6, details of infectious complications within 1 post-transplant year were demonstrated. The total infection rate was higher in the ABOi LDKT group than in the ABOc LDKT group (35.6% vs 21.2%, P = 0.042). When considering types of infections, the ABOi LDKT group had a higher rate of total bacterial infections than the ABOc LDKT (22.5% vs 12.6%, P = 0.035) and, especially, a higher rate of bacterial pneumonia (10.0% vs 2.3%, P = 0.007). Frequencies of viral and fungal infections were similar between the two groups. PJP occurred in 2 (2.5%) patients in the ABOi LDKT and no patient in the ABOc LDKT group, although this difference was not statistically significant. Rates of infectious complications were not significantly different between the ABOi LDKT and DDKT groups, although the frequency of viral infections was higher in the DDKT group (10.0% vs 18.1%, P = 0.081).

Graft function

Figure 3 shows changes in eGFR during the study period. At the time of discharge, mean eGFR of patients in

Table 6. Infectious complications within 1 year after transplantation

Variables	ABOi LDKT (n = 80)	ABOc LDKT (n = 222)	P vs *ABOi LDKT*	DDKT (n = 332)	P vs *ABOi LDKT*
Total infections	26 (35.6%)	47 (21.2%)	0.042	107 (32.2%)	0.963
Total bacterial infections	18 (22.5%)	28 (12.6%)	0.035	55 (16.6%)	0.212
Urinary tract infection	11 (13.8%)	21 (9.5%)	0.285	37 (11.1%)	0.514
Bacterial pneumonia	8 (10.0%)	5 (2.3%)	0.007	16 (4.8%)	0.106
Bacteremia	0	1 (0.5%)	0.735	4 (1.2%)	0.420
Viral infection	8 (10.0%)	22 (9.9%)	0.566	60 (18.1%)	0.081
Fungal infection	0	2 (0.9%)	0.540	5 (1.5%)	0.588
Pneumocystis jiroveci pneumonia	2 (2.5%)	0	0.070	2 (0.6%)	0.171

the ABOi LDKT group was 75.7 mL/min/1.73 m^2, which was similar to that in the ABOc LDKT group (80.0 mL/min/1.73 m^2, $P = 0.526$) but higher than that in the DDKT group (61.3 mL/min/1.73 m^2, $P < 0.001$). At 6 months after transplantation, mean eGFR of the ABOi LDKT group decreased somewhat but remained above 60 mL/min/1.73 m^2 and higher than that in the DDKT group throughout the study period. However, eGFR was significantly lower in the ABOi LDKT group than in the ABOc LDKT group at 6 months and 24 months after surgery.

Discussion

This is the first national cohort study examining the use of ABOi LDKT in older patients. We found that ABOi LDKT was comparable to ABOc LDKT and showed higher patient survival than DDKT although it was significant risk factor for infection. BPAR occurred more frequently in ABOi LDKT than ABOc LDKT, and it was not significant after adjustment for covariates in this older population.

KT has obvious benefits of survival gain and improved quality of life for older patients with ESRD. However, especially in countries with severe organ shortages like Korea [21], several years of waiting for an available deceased donor kidney contributes to waiting list mortality in older adults [22,23]. Accordingly, a number of researchers have suggested that LDKT be considered not only for younger patients but also for older ESRD patients because of its ability to improve survival [2,22,24,25]. ABOi LDKT is a good option for expanding the living donor pool, which shows excellent long-term outcomes [6,10,11]. Exchange donor programs are another strategy, but they are not available in several countries. In Korea, paired exchange program was nearly abandoned since start of ABOi KT at 2007. The reasons were as follows: (1) cost for desensitization treatment such as plasma pheresis and rituximab were covered by national medical insurance in nearly all Korean patients, (2) excellent outcome of ABOi LDKT [11], and (3) difficulties overcoming the ABO blood barrier, especially in blood type O patients [26]. So, comparison between paired exchange LDKT and ABOi LDKT was not included in this KOTRY study.

Little is known about the safety and outcomes in older patients of ABOi LDKT, which requires aggressive immunosuppressive treatment. Only two small studies have been conducted in this age group (in Japan), which showed similar graft and patient survival rates, when compared with ABOc LDKT [27,28]. Several large cohort studies in the United States involving patients of all ages reported that clinicians should be cautious about the short-term risks of graft loss and patient death in ABOi LDKT [4,14]. Ko et al [29] previously reported higher mortality of the KT patients underwent pretransplant desensitization in South Korea. However, they did not show significant mortality risk of ABOi LDKT in multivariable analysis. Also, they used retrospective data from Retro-KOTRY including KT performed between 2009 and 2012 [19,30].

The present study, using prospectively collected KOTRY data, demonstrated that graft survival of ABOi LDKT in older patients was not inferior to that of ABOc LDKT, despite a higher rate of BPAR within 1 post-transplant year. One possible explanation for this result is that, when present, the rejections in the ABOi LDKT group were not severe because of age-related attenuation of the immune response [17]. This hypothesis is supported by our observation that over 50% of BPAR in patients who underwent ABOi LDKT resolved completely with anti-rejection treatment. Infection was also more frequent with ABOi LDKT than with ABOc LDKT, but patient survival was similar between the two types of KT. This means that most infections in ABOi LDKT group did not lead to death and were successfully treated by antibiotics in our study population. Nevertheless, bacterial pneumonia and PJP were more frequent in the ABOi LDKT group (albeit not significantly for PJP), which are consistent with the results of a prior study [31]. Thus, one should remain vigilant about the possibility of these potentially life-threatening infections in patients who undergo ABOi LDKT.

This study showed patient survival of ABOi LDKT was not inferior to that of ABOc LDKT, which did not reflect the results of recent meta-analysis [12]. We hypothesized that higher comorbidity of older patients countervailed small increase of mortality risk in ABOi LDKT. In fact, pretransplant DM was about 50% and CVD was about 20% in our study population, which was much higher than results from other studies [4]. Furthermore, compared with DDKT, we found that patient survival was higher after ABOi LDKT. Although recent study reported ABOi LDKT was superior to waiting DDKT in terms of long-term survival [15] , no large cohort study has been previously conducted in older patients with ESRD. Considering that waiting list mortality increases in proportion to age [32], the survival gain of ABOi LDKT would be larger in older adults than in younger individuals. In this study, four CVD-related deaths were observed during the study period in

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patients who underwent DDKT, but none occurred in those who underwent ABOi LDKT. Furthermore, additional CVD deaths may have been present in the six patients in the DDKT group with an unknown cause of death. These differences in mortality between types of KT may be related to the longer duration of pretransplant dialysis in DDKT and are consistent with the results of prior studies [33,34]. As older patients usually have more risk factors for CVD than younger individuals, CVD-related deaths may be reduced by proceeding with ABOi LDKT rather than requiring these individuals to remain on the list waiting for a deceased donor kidney.

In the current study, rates of all infections within 1 post-transplant year were similar between ABOi LDKT and DDKT. There were more infection-related deaths after DDKT than after ABOi LDKT, although the difference was not statistically significant. This may be attributed to a greater percentage of patients receiving ATG induction in the DDKT group [35]. ATG is recommended for KT in older patients with a high risk of rejection or those receiving a kidney from a high-risk donor [36]. In general, kidneys from living donors are considered to have a much lower risk of rejection than kidneys from deceased donors. Although examining the effects of ATG induction in ABOi LDKT was not the purpose of this study, previous authors have recommended against using ATG in older patients undergoing KT to reduce the risk of severe infection [37]. For the same reason, low-dose (instead of higher-dose) rituximab could be recommended for older patients undergoing ABOi LDKT [38]. Over 70% of patients in the current study received $\leq$ 200 mg rituximab.

Concerns have been raised about increased bleeding tendency secondary to pretransplant plasmapheresis for ABOi LDKT. Krista et al. [4] reported higher hemorrhagic complications in ABOi LDKT than in ABOc LDKT. However, in the current study, we observed no significant differences in hemorrhage at the surgical site, as well as other surgical complications, between patients who underwent ABOi LDKT and those who underwent the other two types of KT. The lack of increased risk of hemorrhage may have been related to the absence of splenectomy in our patients who underwent ABOi LDKT. In fact, Krista et al. reported a much higher rate of hemorrhagic complications in their splenectomy group. Although plasmapheresis may increase the risk of bleeding complications, two of the three ABOi LDKT patients who experienced postoperative hemorrhage in our study underwent plasmapheresis less than the median number of times. Thus, our results suggest that ABOi LDKT may not lead to more surgical complications in older patients if rituximab-based desensitization is used.

This study has some limitations. Comparison with patients on the waiting list is not possible with data from KOTRY registry so there would be immortal time bias. Another limitation was that it examined only short- to intermediate-term outcomes. Also, we could not compare patients undergoing ABOi LDKT to matched controls undergoing the other types of KT because of the relatively small size of the study population. Lastly, because of the nature of registry data, heterogeneity of pretransplant desensitization protocol, missing data in details of ABOi LDKT, and lack of information about detailed type of BPAR were limitations of this study.

Conclusion

We demonstrated that ABOi LDKT was not inferior to ABOc LDKT and was even superior to DDKT in terms of patient survival. Therefore, ABOi LDKT can be recommended for older ESRD patients with eligible ABO-incompatible living donors rather than waiting for DDKT. Nevertheless, careful monitoring for infectious complications is required when performing ABOi LDKT in older adults.

Conflict of interest

The authors declare no conflicts of interest.

Author contribution

DGK had full access to all aspects of the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.DGK, JL, and KHH participated in the research design. DGK and MSK participated in the data acquisition. DGK and JL participated in the statistical analysis. MSK, OJK, CWJ, KWL, JY, and CA participated in the performance of the research. KHH supervised the study process.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Mortality hazard ratio as a function of age.

Table S1. Cox regression analysis for death-censored graft survival.

Table S2. Cox regression analysis for patient survival.

Table S3. Cox regression analysis for BPAR-free survival.

Table S4. Cox regression analysis for infection-free survival.

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