ORIGINAL ARTICLE

Clinical outcomes of ABO- and HLA-incompatible kidney transplantation: a nationwide cohort study

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SUMMARY

This was a nationwide cohort study to investigate the impact of anti-A/B and donor-specific anti-HLA (HLA-DSA) antibodies on the clinical outcomes in kidney transplant recipients (KTRs). We classified a total of 1964 KTRs into four groups: transplants from ABO-incompatible donors (ABOi, $n = 248$); transplants in recipients with HLA-DSA (HLAi, $n = 144$); transplants from combined ABOi and HLAi donors (ABOi + HLAi, $n = 31$); and a control group for whom neither ABOi nor HLAi was applicable (CONT, $n = 1541$). We compared the incidence of biopsy-proven acute rejection (BPAR), allograft and patient survival rates. The incidence of BPAR was higher in the HLAi and ABOi + HLAi groups relative to the CONT group; in contrast, it was not higher in the ABOi group. Death-censored graft survival rates did not differ across the four groups. However, relative to the CONT group, patient survival rate was reduced in the ABOi and ABOi + HLAi groups, and with infection being the most common cause of death. Further, multivariable analysis revealed that desensitization therapy because of ABOi or HLAi was independent risk factors for patient mortality. HLAi was a more important risk factor for BPAR compared with ABOi. However, pretransplant desensitization therapy for either ABOi or HLAi significantly increased the risk of infection-related mortality.

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ABO incompatibility, kidney transplantation, sensitization

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Introduction

Advances in immune suppression therapies and desensitization techniques enable kidney transplantation (KT) regardless of ABO or HLA incompatibility (ABOi and HLAi, respectively), the latter condition characterized by the presence of anti-HLA donor-specific antibodies (HLA-DSA) [1,2]. Indeed, the introduction of ABOi KT significantly increased potential opportunities for patient with end-stage renal disease (ESRD) around the world to receive KT [2–4]. KT attempts following HLA-DSA desensitization therapy also showed better survival outcomes compared with transplants in patients who were on dialysis or waiting lists, which justified transplantation in these patients [5].

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Both anti-A/B and HLA-DSA sensitization share multiple similarities while also demonstrating important different features. For example, desensitization is similar for both antibodies, essentially consisting of either rituximab (RTX) for B cell depletion coupled with plasmapheresis (PP) or intravenous immunoglobulin (IVIg) to remove pre-existing antibodies in the peripheral circulation [1,2]. However, the clinical outcomes have shown differing results; specifically, KT in pre-existing HLA-DSA still showed inferior clinical outcomes in terms of acute rejection and allograft survival rates compared with KT without HLA-DSA. In contrast, ABOi KT showed comparable clinical outcomes relative to ABO-compatible KT [1,6–11].

Previously, we reported that HLAi was a more significant factor for acute antibody-mediated rejection relative to ABOi. Further, ABOi may not provide an additive impact in combined ABOi and HLAi KT compared with single HLAi KT. However, similar to several prior reports, ours previous investigation was a single-centre study, with limited numbers of patients analysed [12–15]. In an effect to circumvent these issues, the current investigation utilized an established nationwide data repository from the Korea Organ Transplantation Registry (KOTRY) to investigate the comparative impacts of ABOi and HLAi on post-transplant clinical outcomes.

Subjects and methods

Study population

To compare the clinical outcomes of ABOi and HLAi KT, we analysed KOTRY data from the Korean Society for Transplantation [16]. Compiling data from 46 kidney transplantation centres, the KOTRY database contained a total of 4987 cases from conducted between 2009 and 2012, accounting for 92.1% of all KTs performed in Korea during this period. Of the 4987 cases, only 3043 were from living donors (61%). We excluded 1079 KT recipients for whom data regarding panel reactive antibodies (PRA) or cross-match tests were not available. Ultimately we included 1964 KTRs in the present investigation. We classified the patients as ABO-incompatible donors (ABOi, $n = 248$), HLA-incompatible donors (HLAi, $n = 144$), both ABOi- and HLA-incompatible donors (ABOi + HLAi, $n = 31$), and the control group, which had no ABOi or HLAi incompatibility (CONT, $n = 1541$; see Fig. 1). We defined HLAi as positive for both PRA (by solid-phase HLA antibody screening) and one of the following: positive cross-match test results or positive for anti-HLA donor-specific antibody by Luminex Single Antigen Assay. HLA-DSA data were available in 1941 recipients (98.8%). Therefore, HLAi was defined according to detection of HLA-DSA in those patients. In another 23 KTRs for whom HLA-DSA data were not available, we defined HLAi based on the positive result of PRA and cross-match test.

The study was approved by the local institutional review board (KC12RCMI0203).

Desensitization protocols for ABO- and HLA-incompatible kidney transplantation

The desensitization protocols for both ABO and HLA-DSA were described previously [1,2]. Briefly, both protocols consisted of RTX and PP with or without IVIg. Most centres used a single dose of RTX from 2 weeks to 1 month before the transplant, with dosage ranged from 100 to 375 mg/m^2. Total plasma exchange with 5% albumin or fresh-frozen plasma was conducted in most centres, but double-filtration plasmapheresis was utilized in some patients. The degree of PP was determined according to the baseline anti-A/B antibody titre or HLA-DSA level. Further, most centres administered prophylaxis for Pneumocystis jirovecii or cytomegalovirus infection.

Comparison of clinical outcomes

The clinical outcomes we investigated in this study included incidence of biopsy-proven acute rejection (early: ≤1 year from KT or late: >1 year from KT), BPAR-free survival rate, allograft and patient survival rates, causes of death and changes in allograft function measured as estimated glomerular filtration rate (eGFR). BPAR was diagnosed according to the Banff 2007 classification [17]. BPAR-free survival was defined as the time elapsed from transplantation to the first episode of BPAR. Serum creatinine levels were collected at 6 months intervals post-transplantation, and the eGFR for each concordant time was assessed using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [18]. Allograft survival rate was defined as the time from transplantation to the commencement of an alternative renal replacement therapy. Death was censored in the analysis of graft survival, and patient survival was defined as the time from transplantation until death regardless of any cause. All clinical parameters were compared across the four patient groups.

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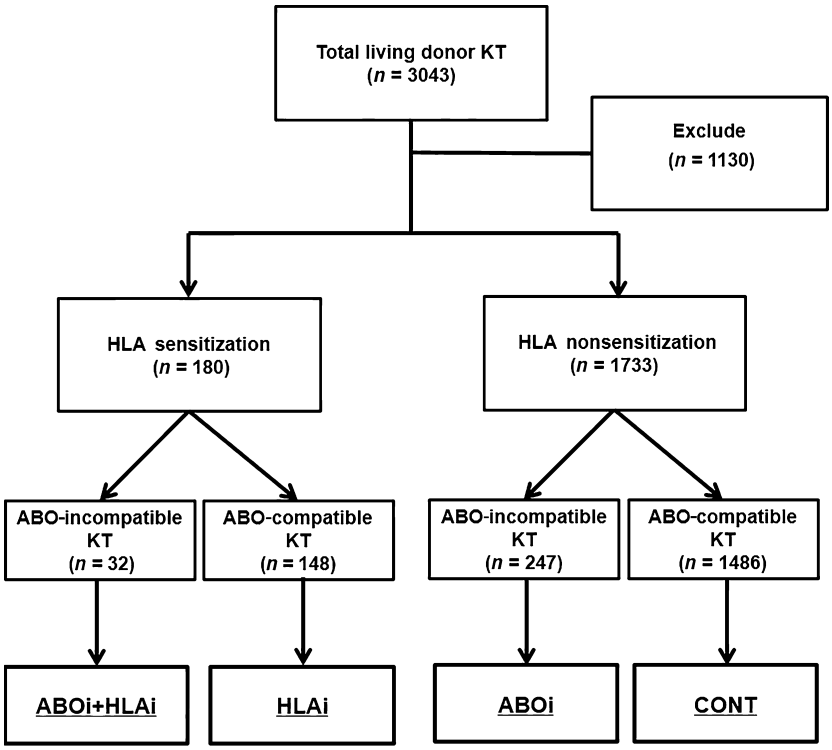

Figure 1 Distribution of the patient population according to ABO or HLA incompatibility. Of the 1922 KTR patients included in this study, 279 were ABO-incompatible KT, and another 1685 cases were ABO-compatible. Among the ABO-incompatible patients, those who were positive for PRA and cross-matched or positive for HLA-DSA were placed in the ABOi + HLAi group (n = 31), with the remainder categorized a ABOi (n = 248). Similarly, among the 1685 ABO-compatible patients, those who were positive for PRA and cross-matched or positive for HLA-DSA were placed in HLAi (n = 144), with the remaining patients placed in CONT (n = 1541). ABOi, ABO-incompatible; HLA, human leucocyte antibody; HLAi, positive for PRA and cross-matched or positive for HLA-DSA; HLA-DSA, donor-specific anti-HLA antibody; CONT, control group; KT, kidney transplantation; PRA, panel reactive antibody.

Statistical method

We present continuous data as mean ± standard deviation (or standard error) or median with interquartile range according to distribution. Data from each group were analysed using ANOVA with post hoc analysis (for the four-group comparisons), Student's t tests (for the two-group comparisons) or the Mann–Whitney test according to the data type. Categorical data were compared using Chi-squared tests or Fisher's exact tests, and we utilized Kaplan–Meier curves and log-rank tests to describe and compare the BPAR-free survival, graft survival and patient survival rates. Graft failure or patient death events per 100 patient-years with 95% confidence intervals (CIs) were calculated using the Poisson confidence interval. To define the risk factors that affected the allograft outcomes in the overall patient population, we used binary logistic or Cox proportional hazard regression analysis, with a P value less than 0.05 was considered to have statistical significance. As confounding variables for multivariable analysis, we selected significant factors for BPAR, allograft survival and patient survival in the previous studies. We selected donor type [19], re-transplant [20], and HLA mismatches [20] for BPAR; donor type [19], donor age [21] and DM [22] for allograft survival; and DM [22], recipient age [22] and dialysis duration[23] for patient survival. In the four-group comparisons, we obtained P values following Bonferroni's post hoc analysis. All statistical analyses were performed using SPSS v 21 (IBM Corp 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, USGLIBM Corp) and the statistical package MEDCALC version 15.5 (MedCalc, Mariakerke, Belgium).

Results

Baseline clinical and immunological patient characteristics

Table 1 describes baseline characteristics of the patients with our four groups. Recipient and donor age and gender did not differ across the four groups, but more male recipients were present in the ABOi and CONT groups

Table 1. Baseline demographic and immunologic characteristics of study population.

	ABOi + HLAi (n = 31)	HLAi (n = 144)	ABOi (n = 248)	CONT (n = 1541)
Recipient age, year	47.1 ± 9.0	45.8 ± 10.9	44.2 ± 12.4	42.6 ± 13.0
Donor age, year	39.4 ± 12.8	40.1 ± 11.8	42.7 ± 11.3	41.5 ± 11.3
Recipient gender [male, n (%)]	8 (25.8)‡,§	43 (29.9)‡,§	161 (64.9)	958 (62.2)
Donor gender [male, n (%)]	18 (58.1)	73 (50.7)	108 (43.5)	717 (46.5)
Duration of dialysis, months	22.0 ± 30.7	24.0 ± 35.9	19.6 ± 36.2	18.6 ± 34.1
Primary renal disease, n (%)				
Chronic glomerulonephritis	4 (12.9)	43 (29.9)	79 (31.9)	469 (30.4)
Diabetes mellitus	8 (25.8)	29 (20.1)	47 (19.0)	293 (19.0)
Hypertension	2 (6.5)	16 (11.1)	29 (11.7)	146 (9.5)
Polycystic kidney disease	0 (0)	3 (2.1)	13 (5.2)	70 (4.5)
Other	2 (6.5)	13 (9.0)	15 (6.0)	146 (9.5)
Unknown	15 (48.4)	40 (27.8)	65 (26.2)	417 (27.1)
Number of mismatched HLA	3.7 ± 1.5§	3.5 ± 1.5§	3.5 ± 1.7§	2.8 ± 1.7
Living related donor, n (%)	21 (67.7)	100 (69.4)‡	143 (57.7)§	1100 (71.4)
Re-transplant, n (%)	6 (19.4)‡,§	19 (13.2)‡,§	16 (6.5)	65 (4.2)
Panel reactive antibody >50%, n (%)	19 (61.3)‡,§	93 (64.6)‡,§	12 (4.8)	66 (4.3)
HLA-DSA, n (%)	27 (87.1)‡,§	128 (89.5)‡,§	0 (0)	0 (0)
Positive cross-match, n (%)	18 (58.1)‡,§	55 (38.2)‡,§	19 (7.7)	28 (1.8)
Desensitization**	31 (100)†,§	96 (67.1)‡,§	248 (100)§	3 (0.2)
Induction immunosuppression				
IL-2 Receptor antibody, n (%)	27 (90.0)	117 (87.3)‡,§	221 (94.4)	1308 (96.2)
Anti-thymocyte globulin, n (%)	3 (10.0)	17 (12.7)‡,§	13 (5.6)	48 (3.5)
Others, n (%)	0	0‡,§	0	3 (0.2)
No induction immunosuppression, n (%)	1 (3.2)	10 (6.9)‡,§	14 (5.6)	182 (11.8)
Maintenance immunosuppressive regimen				
TAC + MMF/MYF + steroid, n (%)	28 (90.3)§	122 (84.7)	224 (90.3)	1005 (65.2)
TAC + Other metabolite + steroid, n (%)	1 (3.2)§	7 (4.9)	7 (2.8)	145 (9.4)
CsA + MMF/MYF + steroid, n (%)	2 (6.5)§	13 (9.0)	17 (6.9)	337 (21.9)
CsA + Other metabolite + steroid, n (%)	0 (0)§	2 (1.4)	0 (0)	54 (3.4)

ABOi, ABO-incompatible; CONT, control group; CsA, cyclosporine HLA, human leucocyte antibody; HLAi, positive for PRA and cross-match, or positive for HLA-DSA; HLA-DSA, donor-specific anti-HLA antibody; IL-2, interleukin-2; n, number; MMF, mycophenolate mofetil; MYF, myfortic; TAC, tacrolimus.

*P < 0.05 versus ABOi + HLAi, †P < 0.05 versus HLAi, ‡P < 0.05 versus ABOi, §P < 0.05 versus CONT.

**Rituximab and plasmapheresis/intravenous immunoglobulin.

compared with the ABOi + HLAi or HLAi groups. Fewest living related donors and the CONT group exhibited the fewest mismatched HLAs. There were significantly more re-transplants, high PRAs (>50%) and positive cross-matches in both the ABOi + HLAi and HLAi groups relative to either the ABOi or CONT. All patients in ABOi + HLAi and ABOi and 67.1% in HLAi received pretransplant desensitization therapy. Across all four groups, the majority of patients received anti-IL-2 receptor antibody as the induction agent, but more patients received anti-thymocyte globulin in the ABOi+HLAi and HLAi groups than in the other two groups ($P = 0.05$, ABOi + HLAi versus CONT; $P = 0.12$, ABOi + HLAi versus ABOi; $P = 0.04$, HLAi versus ABOi; $P = 0.001$, HLAi versus CONT). The majority of patients received triple-drug maintenance immunosuppressive regimens with tacrolimus, mycophenolate mofetil and steroids. However, a significant number of patients in CONT group received cyclosporine A triple-drug regimens relative to the remaining patient groups. ($P = 0.001$, versus ABOi + HLAi; $P < 0.001$, versus HLAi; $P < 0.001$, versus ABOi).

Comparison of biopsy-proven acute rejection

The incidence of BPAR was the greatest in the ABOi + HLAi group (22.8%, 7/31), followed by HLAi (18.1%, 26/144), both significantly higher compared with the CONT group (10.4%, 161/1541; $P = 0.04$, ABOi + HLAi versus CONT; $P = 0.008$, HLAi versus CONT). No significant differences were observed in BPAR incidence between ABOi (12.1%, 30/248) and CONT groups (Fig. 2a). Late acute rejection occurred more often in HLAi (11/26, 42.3%) and ABOi + HLAi (3/7, 43%) relative to either ABOi (3/30, 10.0%; $P = 0.03$ versus HLAi, $P = 0.09$ versus ABOi + HLAi) or CONT (40/121, 24.8%; $P = 0.05$ versus HLAi, $P = 0.10$ versus ABOi + HLAi) (Fig. 2b). Further, rejection-free survival rates were significantly lower in ABOi + HLAi and HLAi groups compared with CONT group ($P = 0.01$, versus ABOi + HLAi; $P = 0.003$, versus HLAi; Fig. 2c). Multivariable logistic regression risk factor analysis showed that HLAi was an independent risk factor for BPAR after e adjusting for significant confounders such as donor type [19], re-transplant [20] and HLA mismatches [20] [odds ratio (OR) = 1.99, 95% confidence interval (CI): 1.20–3.29, $P = 0.007$; see Table 2]; in contrast, ABOi was not a significant risk factor for BPAR.

Comparison of allograft function and death-censored graft survival rates

Both the ABOi + HLAi and HLAi groups demonstrated superior allograft function 6 months post-transplant compared with ABOi and CONT groups; the observed differences appeared to dissipate 30 months following KT (Fig. 3). During follow-up, there were a total of 21 cases of death-censored allograft failure in this study cohort: 3 in ABOi and 18 in CONT; no allograft failures were observed in either HLAi or ABOi + HLAi groups; and no significant differences in death-censored allograft survival rates were observed across the four groups ($P = 0.333$). Overall graft failure rate per 100 patient-years was 0.49 (95% CI 0.30–0.75) in the total patient population. Graft failure rates per 100 patient-years were 0 (0–6.15), 0 (0–1.24), 0.64 (0.13–1.87) and 0.52 (0.30–0.82) for the ABOi + HLAi, HLAi, ABOi and CONT groups, respectively. In our multivariable analysis for allograft failure, neither HLAi nor ABOi was significant in univariate analysis and also after adjustment by significant confounders such as donor type [19], donor age [21] and DM [22] (Table 3).

Comparison of patient survival rates

At total of 20 KTRs suffered mortality during the study period: 1 in ABOi + HLAi, 2 in HLAi, 6 in ABOi and 11 in CONT groups. Overall, we observed 0.47 (95% CI 0.28–0.72) mortality events per 100 patient-years. Segregated by groups, the event rates per 100 patient-years were 1.67 (0.04–9.28), 0.68 (0.08–2.44), 1.28 (0.47–2.79) and 0.32 (0.16–0.57) in the ABOi + HLAi, HLAi, ABOi and CONT groups, respectively. The survival rate significantly reduced in the ABOi and ABOi + HLAi groups compared with CONT groups ($P = 0.004$ versus ABOi, $P = 0.005$ versus ABOi + HLAi); no significant difference was observed between ABOi and ABOi + HLAi groups ($P = 0.32$; Fig. 4). Infection was the most common cause of death in the ABOi + HLAi (1/1, 100%), HLAi (2/2, 100%) and ABOi groups (5/6, 82.3%). In contrast, the death rate because of infection was only 27.3% (3/11) in CONT group (Table 4). In the multivariable analysis of risk factors for death, pretransplant desensitization therapy (HR 3.40, 95% CI: 1.41–8.25, $P = 0.003$) was significant following adjustment for DM [22], recipient age [22] and dialysis duration [23]. However, neither HLAi nor ABOi was significant (Table 5).

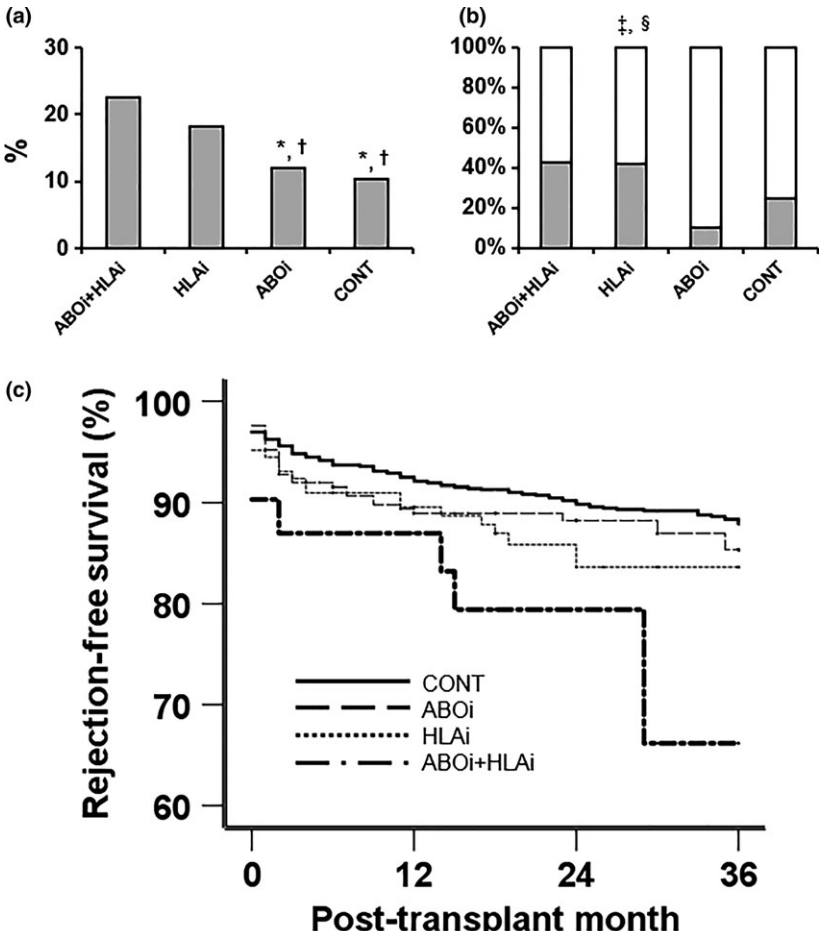

Figure 2 Comparison of the incidence of biopsy-proven acute rejection across the four groups. (a) Incidence of BPAR was increased in both ABOi + HLAi and HLAi as compared with either ABOi or CONT; (b) increased incidence of late rejections in ABOi + HLAi and HLAi groups relative to ABOi or CONT; (c) the overall BPAR-free survival rate was significantly lower in HLAi ($P = 0.045$) and ABOi + HLAi ($P = 0.018$) compared with CONT group. ABOi, ABO-incompatible; HLA, human leucocyte antibody; HLAi, positive for PRA and cross-matched or positive for HLA-DSA; HLA-DSA, donor-specific anti-HLA antibody; CONT, control group. $^{*}P < 0.05$ versus ABOi + HLAi, $^{\dagger}P < 0.05$ versus HLAi, $^{\ddagger}P < 0.05$ versus ABOi, $^{\S}P < 0.05$ versus CONT.

Table 2. Univariate and multivariable binary logistic analysis for biopsy-proven acute rejection.

	Crude models			Adjusted model		
	OR	95% CI	*P*	OR	95% CI	*P*
ABOi	0.82	0.56–1.20	0.29	0.85	0.52–1.39	0.52
HLAi	1.94	1.29–2.92	0.002	1.99	1.20–3.29	0.007

ABOi, ABO-incompatible; HLA, human leucocyte antibody; HLAi, positive for PRA and cross-match, or positive for HLA-DSA; MN, mismatch number.

Adjusted model: multivariable model including living unrelated donor (versus living related donor) [19], HLA MN [20], re-transplant [20].

Discussion

In this study, we utilized nationwide repositories of patient data to conduct comparative analysis of ABOi and HLAi in terms of clinical outcomes after KT. In contrast to ABOi, we report that HLAi was a significant risk factor for the development of BPAR suggesting that HLAi is more significant for rejection. However, both ABOi and HLAi were significantly associated with early patient mortality, mainly because of infections associated with pretransplant desensitization therapy.

In comparison with baseline characteristics, the proportion of male recipients was lower in both HLA-sensitized groups (ABOi + HLAi and HLAi) than in the two HLA nonsensitized groups (ABOi and CONT), consistent with the findings of our previous single-centre report [13]. The reason for this phenomenon is unclear. However, as history of pregnancy can be associated with the development of anti-HLA antibodies, female ESRD patients may be predisposed to sensitization [24,25]. Among the remaining variables, we observed increases in HLA mismatches, living unrelated donors (LURDs) and re-transplants in ABOi + HLAi and HLAi groups relative to CONT group. Interestingly, there were also increased numbers of HLA mismatches and LURDs in ABOi compared with CONT group, and the presence of more spousal donors in ABOi than in CONT group may provide an explanation for this finding.

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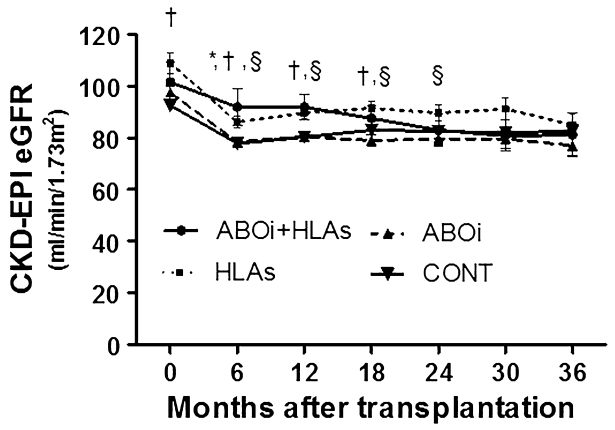

Figure 3 Comparison of the changes in renal allograft function. During the 18 months post-transplant, both the HLAi and ABOi + HLAi groups demonstrated higher graft function compared with CONT. However, note that these differences dissipated at 30 months following KT. ABOi, ABO-incompatible; HLA, human leucocyte antibody; HLAi, positive for PRA and cross-matched or positive for HLA-DSA; CONT, control group; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration disease. *$P < 0.05$ versus ABOi + HLAi, †$P < 0.05$ versus HLAi, ‡$P < 0.05$ versus ABOi, §$P < 0.05$ versus CONT.

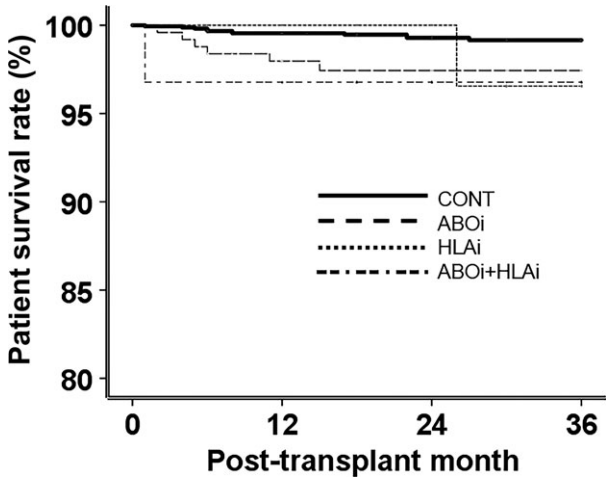

Figure 4 Comparison of the patient survival rates across the four groups. Note that mortality rates were reduced in ABOi ($P = 0.004$) and ABOi + HLAi ($P = 0.005$) relative to CONT. ABOi, ABO-incompatible; HLA, human leucocyte antibody; HLAi, positive for PRA and cross-matched or positive for HLA-DSA; HLA-DSA, donor-specific anti-HLA antibody.

Next, we compared incidences of BPAR across groups. In previous reports, including our own, transplantation across the HLA barrier resulted in higher rates of acute rejection compared with transplantation in nonsensitized patients [9–11,26]. In contrast, several reports using large registry patient data indicate that the acute rejection rate in ABOi KT is similar to that in ABO-compatible KT [27–30]. As expected, both HLA-sensitized groups (HLAi and ABOi + HLAi) showed a higher incidence of BPAR compared with CONT group. However, incidence of BPAR was no statistically different between ABOi + HLAi and HLAi or between ABOi and CONT groups. In addition, multivariable risk factor analysis revealed that HLAi irrespective of ABOi was a significant risk factor for BPAR, while ABOi was not. These findings suggest that sensitization to HLA itself can increase the risk of rejection, while ABO incompatibility between donor and recipient likely plays only a minor role. As previously suggested, these results may be explained by the lower immunogenic quality of ABO Ag compared with HLA [14,31].

Both the incidence and the timing of BPAR differed with respect to group. There were more late rejections in the ABOi + HLAi and HLAi groups relative to ABOi or CONT groups, consistent with previous reports suggesting a role for HLA-DSA in late rejection including chronic antibody-mediated rejection [32]. Surprisingly, significant, unexpected differences in allograft function were observed between groups. As shown in Fig. 3, ABOi + HLAi and HLAi groups demonstrated superior allograft function at 6 months post-transplant relative to both ABOi and CONT groups. Although the reason is unclear, it is possible that differences in gender distribution in the donors or recipients in each group

Table 3. Univariate and multivariable Cox proportional hazards analysis for graft failure.

	Crude models			Adjusted model		
	HR	95% CI	*P*	HR	95% CI	*P*
ABOi	0.84	0.25–2.87	0.78	0.87	0.25–2.96	0.82
HLAi	0.04	0–39.42	0.37	0.01	0–25.72	0.93

ABOi, ABO-incompatible; DM, diabetes mellitus; HLA, human leucocyte antibody; HLAi, positive for PRA and cross-match, or positive for HLA-DSA.

Adjusted model: multivariable model including living unrelated donor (versus living related donor) [19], donor age [21], DM [22].

Table 4. Comparison of causes of death.

	ABOi + HLAi (*n* = 1)	HLAi (*n* = 2)	ABOi (*n* = 6)	CONT (*n* = 11)
Infection, *n* (%)	1 (100)	2 (100)	5 (82.3)	3 (27.3)
Cardiovascular disease, *n* (%)	0 (0)	0 (0)	0 (0)	2 (18.2)
Malignancy, *n* (%)	0 (0)	0 (0)	0 (0)	1 (9.1)
Suicide, *n* (%)	0 (0)	0 (0)	0 (0)	1 (9.1)
Other, *n* (%)	0 (0)	0 (0)	1 (16.7)	4 (36.4)

ABOi, ABO-incompatible; CONT, control group; HLA, human leucocyte antibody; HLAi, positive for PRA and cross-match, or positive for HLA-DSA; *n*, number.

Table 5. Univariate and multivariable Cox proportional hazards analysis for patient death.

	Crude models			Adjusted model		
	HR	95% CI	*P*	HR	95% CI	*P*
ABOi	3.65	1.45–9.19	0.006	1.36	0.28–6.60	0.70
HLAi	1.89	0.55–6.44	0.31	0.96	0.15–6.22	0.96
DSZ	3.79	1.57–9.18	0.001	3.40	1.41–8.25	0.002

ABOi, ABO-incompatible; DM, diabetes mellitus; DSZ; desensitization using plasmapheresis and rituximab; HLA, human leucocyte antibody; HLAi, positive for PRA and cross-match, or positive for HLA-DSA.

Adjusted model: multivariable model including DM [22], recipient age [22], duration of dialysis [23].

contributed to the results [33]. Indeed, the proportion of male-to-female transplantation was higher in ABOi + HLAi and HLAi groups compared with ABOi and HLAi groups.

Despite the higher incidence of BPAR in the ABOi + HLAi and HLAi groups, allograft survival rate did not differ across the four groups, possibly because of short-term follow-up duration. In a previous study, the most important cause of allograft failure in highly sensitized KTRs was chronic antibody-mediated rejection (cAMR) which requires a considerable period for development [34]. However, the mean follow-up duration in this study was only 26.2 ± 9.7 months, which may not be sufficient for the progression of cAMR. Indeed, our previous single-centre experience also showed no difference in allograft survival rate between highly sensitized and nonsensitized groups in spite of significantly higher rates of acute antibody-mediated rejection in the former [9].

In contrast, patient survival rate was significantly lower in ABOi and ABOi + HLAi groups compared with the CONT group. Interestingly, the most common cause of death was infection in ABOi, HLAs and ABOi + HLAi groups, with infection-related mortality accounting for only 27.3% of death in the CONT group. We observed fewer cases of infection-related death in HLAi relative to ABOi, likely attributable to only 67% of the HLAi group receiving pre-transplant desensitization therapy compared with 100% of the patients in ABOi group. Ultimately, multivariable risk factor analysis revealed that desensitization attempts rather than ABOi or HLAi were more significant risk factors for patient mortality. Previous studies also indicated that infection-related mortality was increased in ABOi KT requiring desensitization, whereas tailored desensitization may decrease post-transplant infection [35,36]. These results suggest that the strength of desensitization itself, not the ABOi or HLAi, is the more important risk factor for infection-related death.

This study has some limitations. First, this nationwide registry analysis reflects the same limitations found in similar large registry analyses. While patient numbers are enhanced, important details for the endpoints are missing, thereby reducing the clinical utility of the findings. For example, the HLA-DSA and anti-A/B antibody titres were not available for analysis. Previous studies showed that the strength of DSA and anti-A/B antibody titres at both baseline and transplant was important risk factors for allograft rejection and failures [8,9,37–39]. If these data had been available, the impact of HLAi may have been more significant. Second, the follow-up duration of this registry is limited as mentioned previously; therefore, traditional risk factors for allograft failure in highly sensitized patients such as dialysis duration did not significantly affect on allograft outcome [5]. Third, we could not determine the specified desensitization protocols at each centre from the KOTRY database. Rituximab dose and number of plasma exchanges are important risk factors for infection and bleeding, but unfortunately could not be considered in this analysis [40–42].

In conclusion, HLAi was a more important risk factor for the development of BPAR than was ABOi in this nationwide patient analysis. However, desensitization efforts in patients with pretransplant ABOi or HLAi can increase infection-related mortality during the early post-transplant period. The results of this investigation suggest that in patients who are at high immunological risk, such as HLAi or ABOi patients, it is necessary to both prevent acute rejection and attempt to decrease infection-related complications.

Authorship

EJK: participated in designing this study and writing paper. JHY: participated in collecting and analysing data. CWY: participated in performing study. BHC: participated in designing study.

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Conflicts of interest

The authors declare no conflicts of interest.

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