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Original Research

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Impacts of Pre-transplant Panel-Reactive Antibody on Post-transplantation Outcomes: A Study of Nationwide Heart Transplant Registry Data

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AUTHOR'S SUMMARY

The prevalence of sensitized patients waiting for heart transplantation (HTx) is increasing. We assessed the prevalence and clinical impact of panel-reactive antibody (PRA) in patients undergoing HTx using real-world, nationwide, multi-center data. Among patients who underwent HTx during 2014–2021, 19.8% (n=161) had calculated PRA (cPRA) ≥50%. A total of 61 patients underwent desensitization treatment before HTx. More patients with cPRA ≥50% had significantly higher positive flow cytometry crossmatch at HTx and preformed donor-specific antibody than those with cPRA <50%. During follow-up, patients with cPRA ≥50% had significantly lower freedom from antibody-mediated rejection, but the overall survival rate was comparable to those with cPRA <50%.

ABSTRACT

Background and Objectives: The number of sensitized heart failure patients on waiting lists for heart transplantation (HTx) is increasing. Using the Korean Organ Transplantation Registry (KOTRY), a nationwide multicenter database, we investigated the prevalence and clinical impact of calculated panel-reactive antibody (cPRA) in patients undergoing HTx.
Methods: We retrospectively reviewed 813 patients who underwent HTx between 2014 and 2021. Patients were grouped according to peak PRA level as group A: patients with cPRA

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Conflict of Interest

The authors have no financial conflicts of interest.

Data Sharing Statement

The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization: Choi JO; Formal analysis: Kim D; Investigation: Kim D; Methodology: Kim D; Resources: Cho YH, Oh J, Cho HJ, Jung SH, Lee HY, Choi DJ, Kang SM, Kim MS, Kim JJ; Software: Kang SM; Supervision: Lee HY, Park JJ, Choi DJ, Kim JJ; Writing - original draft: Kim D; Writing - review & editing: Kim D, Cho YH, Sung K, Oh J, Cho HJ, Jung SH, Lee HY, Park JJ, Choi DJ, Kang SM, Kim JJ.

≤10% (n= 492); group B: patients with cPRA >10%, <50% (n=160); group C patients with cPRA ≥50% (n=161). Post-HTx outcomes were freedom from antibody-mediated rejection (AMR), acute cellular rejection, coronary allograft vasculopathy, and all-cause mortality.

Results: The median follow-up duration was 44 (19–72) months. Female sex, re-transplantation, and pre-HTx renal replacement therapy were independently associated with an increased risk of sensitization (cPRA ≥50%). Group C patients were more likely to have longer hospital stays and to use anti-thymocyte globulin as an induction agent compared to groups A and B. Significantly more patients in group C had positive flow cytometric crossmatch and had a higher incidence of preformed donor-specific antibody (DSA) compared to groups A and B. During follow-up, group C had a significantly higher rate of AMR, but the overall survival rate was comparable to that of groups A and B. In a subgroup analysis of group C, post-transplant survival was comparable despite higher preformed DSA in a desensitized group compared to the non-desensitized group.

Conclusions: Patients with cPRA ≥50% had significantly higher incidence of preformed DSA and lower freedom from AMR, but post-HTx survival rates were similar to those with cPRA <50%. Our findings suggest that sensitized patients can attain comparable post-transplant survival to non-sensitized patients when treated with optimal desensitization treatment and therapeutic intervention.

Keywords: Heart transplantation; Prognosis; Antibodies; Human leukocyte antigen

INTRODUCTION

Sensitization remains a major challenge in heart transplantation (HTx). Typically, sensitization occurs after transfusion, pregnancy, or prior transplantation due to an immune memory response.[1)2)] The number of sensitized heart failure (HF) patients awaiting HTx is increasing because the numbers of patients who were bridged with left ventricular assist devices (LVAD), pediatric patients with previous surgery using homografts, and patients awaiting re-transplantation are increasing.[3)] According to recent data from the registry of the International Society for Heart and Lung Transplantation (ISHLT), 19% of transplanted patients had panel-reactive antibodies (PRA) ≥20%, and 3.6% were highly sensitized (PRA ≥80%).[4)]

Sensitization increases wait time and limits access to available donors. Sensitization is associated with poor post-HTx outcomes, including rejection, coronary allograft vasculopathy (CAV), and mortality.[5)] Desensitization increases the chances of transplantation by increasing the number of available donors, decreasing wait-list time, and improving post-HTx survival. However, desensitization therapies are not standardized, and many transplantation centers have limited access to emerging agents. In this study, we analyze the clinical impacts of PRA in patients undergoing heart transplantation using real-world, multi-center data.

METHODS

Ethical statement

This study was approved by the Institutional Review Board of Samsung Medical Center (2014-06-009).

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Study population

Multi-center HTx data submitted to the Korean Heart Transplant Registry (KOTRY), the nationwide organ transplantation registry in Korea, were used in the present study.[6] From 2014 to 2021, a total of 813 patients underwent HTx. All patients were of East Asian ancestry. The KOTRY registry includes baseline and follow-up data of transplanted patients. After HTx, follow-up visits were recorded at 1, 6, and 12 months and annually after that. Post-transplantation outcomes included primary graft dysfunction, CAV, overall survival, acute cellular rejection (ACR), and antibody-mediated rejection (AMR). In cases of multiple rejections, only the first event was included.

PRA was measured by flow cytometry using human leukocyte antigen (HLA) Class I- and II-coated beads. Antibody specificities were determined by single-antigen Class I- and II-coated beads using Luminex technology.[7] Patients were grouped according to peak calculated PRA (cPRA) level as group A: patients with cPRA ≤10% (n=492); group B: patients with cPRA >10% and <50% (n=160); group C: patients with cPRA ≥50% (n=161).

Immunosuppression

Calcineurin inhibitor (CNI) based triple immunosuppressive therapy (tacrolimus, mycophenolate mofetil, and prednisone) was initially administered as maintenance therapy to most patients. Cyclosporine was administered if patients developed severe side effects from tacrolimus, such as seizures or encephalopathy. A regimen using a mammalian target of rapamycin (mTOR) inhibitor, either sirolimus or everolimus, in place of a CNI-free regimen, was prescribed to eligible patients, including those with renal insufficiency or malignancy. An mTOR inhibitor was administered in conjunction with a CNI in patients who developed rejection with graft dysfunction, cytomegalovirus infection, or CAV. A conventional CNI-based regimen was maintained for patients with intolerance to mTOR inhibitors. All HTx recipients underwent protocol-based regular evaluations at their transplantation clinics.[8,9] Rejection was diagnosed by endomyocardial biopsy and was defined according to the revised ISHLT classifications.[10]

Statistical analysis

Continuous variables are recorded as mean ± standard deviation, and categorical variables are reported as frequency and percentage. Baseline recipient/donor characteristics and clinical outcomes of HTx were compared among the three groups using one-way analysis of variance (ANOVA). Categorical variables were compared using the χ^2 or Fisher's exact test. Univariable testing was performed, including all database variables potentially associated with sensitization. Logistic regression analysis was performed to identify factors related to cPRA ≥50%. Variables for inclusion in the multivariable analysis were selected based on clinical relevance, evidence of association in previous research, and statistical significance ($p<0.1$) in univariable testing.[11] Variables significantly related to mortality in univariable testing ($p<0.10$) were further examined in multivariable analysis. The cumulative survival rates and incidence of events were assessed using the Kaplan-Meier method, and the statistical significance of curves was calculated using the log-rank test. All data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

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RESULTS

Clinical characteristics of study subjects

In our cohort, 19.8% (n=161) of patients had cPRA ≥50% (group C). Patients in group C were more likely to be female, listed as status 0, more likely to be treated with dialysis before transplant and have a previous history of HTx compared to groups A and B (**Table 1**). The proportions of congenital heart disease as a reason for transplant were comparable among the three groups. Significantly more patients in groups B and C were bridged with left ventricular assisting devices before HTx compared to group A. Significantly higher proportions of patients in group C received induction therapy with anti-thymocyte globulin (ATG). The median hospital stay after HTx was significantly longer in group C compared to groups A and B.

Regression analysis showed female sex (odd ratio [OR], 6.13; 95% confidence interval [CI], 4.08–9.20; p<0.001), re-transplantation (OR, 4.93; 95% CI, 2.25–10.8; p<0.001), pre-HTx renal replacement therapy (OR, 2.67; 95% CI, 1.26–3.24; p=0.004), and congenital heart disease (OR, 2.08; 95% CI, 1.01–7.17; p=0.048) to be associated with increased risk of sensitization (cPRA ≥50%) (**Table 2**).

Table 1. Comparisons of baseline characteristics among three groups according to pre-HTx cPRA values

Characteristics	Group A (n=492)	Group B (n=160)	Group C (n=161)	p value
Recipient age (years)	52.1±13.4	54.1±12.0	53.6±12.2	0.619
Recipient female sex	97 (19.7)	44 (27.5)	100 (62.5)	<0.001
Pre-transplant peak cPRA (%)	0	24.5 (16.3–32.8)	78 (62–93)	<0.001
Reasons for transplant				
Idiopathic DCMP	260 (52.7)	74 (46.3)	70 (43.8)	0.089
Ischemic	114 (23.1)	40 (25.0)	29 (18.1)	0.304
Congenital	16 (3.2)	2 (1.3)	8 (5.0)	0.164
Status at listing				
0	142 (28.8)	56 (35.0)	66 (41.3)	0.010
1	307 (62.3)	89 (55.6)	85 (53.1)	0.074
2	26 (5.3)	7 (4.4)	5 (3.1)	0.524
Body mass index (kg/m^2)	22.8±3.5	23.8±15.1	21.8±4.0	0.195
Re-transplant	13 (2.6)	7 (2.8)	17 (10.6)	<0.001
Hypertension	167 (33.9)	57 (35.6)	46 (28.7)	0.353
Diabetes mellitus	163 (33.1)	47 (29.4)	40 (25.0)	0.105
Pre-HTx mechanical ventilator	100 (20.3)	39 (24.4)	47 (29.4)	0.052
Pre-HTx dialysis	74 (15.0)	33 (20.6)	42 (26.3)	0.004
ECMO-bridged	88 (17.8)	32 (20.0)	30 (18.8)	0.847
LVAD-bridged	3 (0.6)	5 (3.1)	6 (3.7)	0.043
Desensitization	0 (0.0)	3 (1.9)	58 (36.0)	<0.001
Number of days on the waiting list	81 (24–210)	54 (20–236)	61 (21–202)	0.479
Donor age, years	40.5±11.6	40.5±12.3	40.1±11.8	0.141
Donor female sex	142 (28.8)	41 (25.6)	49 (30.6)	0.599
Induction with ATG	18 (3.7)	9 (5.7)	21 (13.0)	<0.001
Induction with basiliximab	329 (82.0)	137 (86.2)	121 (75.1)	0.145
Total ischemic time, minutes	176.6±57.8	165.1±62.5	170.9±63.6	0.098
Total CPB time, minutes	157.2±53.0	158.7±57.1	167.7±84.0	0.176
Length of hospital stay after HTx (days)	27 (24–39)	28 (26–34)	32 (29–63)	0.007

Values are presented as mean ± standard deviation, number (%), or median (range).
ATG = anti-thymocyte globulin; CPB = cardiopulmonary bypass; cPRA = calculated panel-reactive antibody; DCMP = dilated cardiomyopathy; ECMO = extracorporeal membrane oxygenation; HTx = heart transplant; LVAD = left ventricular assist device.

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Table 2. Factors associated with high sensitization (cPRA ≥50%)

Clinical factors	OR (95% CI)	p value
Age	1.013 (0.99–1.03)	0.111
Recipient sex (female)	6.13 (4.08–9.20)	<0.001
Re-transplantation	4.93 (2.25–10.8)	<0.001
Pre-HTx renal replacement therapy	2.67 (1.26–3.24)	0.004
Pre-HTx mechanical ventilator care	1.27 (0.78–2.06)	0.338
LVAD bridged heart transplantation	1.59 (0.29–8.77)	0.595
Congenital heart disease	2.08 (1.01–7.17)	0.048

CI = confidence interval; cPRA = calculated panel-reactive antibody; HTx = heart transplantation; LVAD = left ventricular assist device; OR = odd ratio.

Table 3. Desensitization therapies

Desensitization protocols	Values (n=61)
IVIG alone	5 (8.2)
Rituximab alone	6 (9.8)
Plasmapheresis alone	16 (26.2)
IVIG + plasmapheresis	2 (3.3)
Rituximab + plasmapheresis	25 (41.0)
IVIG + rituximab + plasmapheresis	6 (9.8)
Bortezomib-based therapy	1 (1.6)

Values are presented as numbers (%).
IVIG = intravenous immunoglobulin.

Desensitization therapy

Among sensitized patients, 61 underwent desensitization treatment. A total of 58 patients from group C (36.0%) and 3 from group B (1.9%) received desensitization based on physician decision. The initiation of desensitization and desensitization protocols were decided according to each center's protocol (**Table 3**). Patients who underwent desensitization treatment were more likely to be listed as status 0 and on mechanical ventilation than those who did not receive desensitization therapy. Patients who underwent desensitization treatment were more likely to receive anti-thymocyte globulin as induction therapy and had significantly longer hospital stays after HTx than those who did not receive desensitization treatment (**Supplementary Table 1**). The most commonly used desensitization protocol was rituximab + plasmapheresis (n=25, 41%), followed by plasmapheresis alone (n=15, 26.2%).

Post-transplant donor-specific antibodies and clinical outcomes

The median follow-up duration was 44 (19–72) months. During follow-up, group C had significantly lower freedom from AMR (**Table 4**). However, the three groups' overall survival rates were similar (**Figure 1**, **Table 4**). Primary graft dysfunction and CAV incidence were similar among the three groups.

We performed a subgroup analysis of group C according to induction agents and desensitization status (**Tables 5** and **6**). In the subgroup analysis of group C, the ATG induction group had significantly lower all-cause mortality than the basiliximab induction

Table 4. Comparisons of post-transplantation outcomes among three groups

Endpoints	Group A (n=492)	Group B (n=160)	Group C (n=161)	p value
Primary graft dysfunction	59 (12.0)	19 (12.0)	23 (14.4)	0.713
All-cause mortality	71 (14.4)	29 (18.1)	28 (17.4)	0.422
Freedom from AMR	389 (95.8)	237 (96.0)	142 (88.2)	<0.001
Freedom from ACR ≥2R	475 (96.5)	150 (93.8)	150 (93.2)	0.239
Freedom from CAV	24 (4.9)	6 (3.8)	5 (3.1)	0.595

Data are presented as number (percentage) or survival rate (standard error).
ACR = acute cellular rejection; AMR = antibody-mediated rejection; CAV = cardiac allograft vasculopathy.

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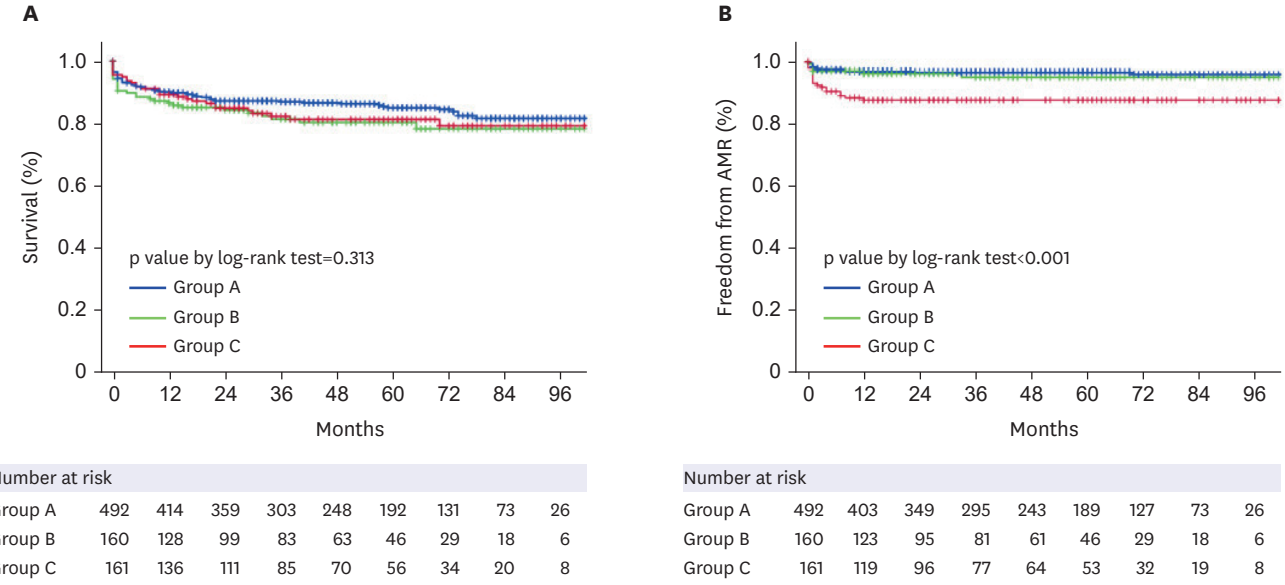

Number at risk									
Group A	492	414	359	303	248	192	131	73	26
Group B	160	128	99	83	63	46	29	18	6
Group C	161	136	111	85	70	56	34	20	8

Number at risk									
Group A	492	403	349	295	243	189	127	73	26
Group B	160	123	95	81	61	46	29	18	6
Group C	161	119	96	77	64	53	32	19	8

Figure 1. Post-HTx survival rates (A) and freedom from AMR (B) according to the pre-transplant PRA category.
AMR = antibody-mediated rejection; HTx = heart transplantation; PRA = panel-reactive antibodies.

Table 5. Subgroup analysis of group C according to induction therapy and desensitization treatment: stratified by induction therapy

	ATG induction (n=21)	Basiliximab induction (n=121)	p value
AMR	1 (4.8%)	18 (14.9%)	0.125
ACR ≥2R	3 (14.3%)	8 (6.6%)	0.228
All-cause mortality	1 (4.8%)	20 (16.5%)	0.007

Among 161 patients, data were missing in 19 patients.
ACR = acute cellular rejection; AMR = antibody-mediated rejection.

Table 6. Subgroup analysis of group C according to induction therapy and desensitization treatment: stratified by desensitization therapy

	Rituximab/bortezomib based desensitization (n=36)	Other desensitization (n=22)	No desensitization (n=103)	p value
Positive FXM	8 (22.2%)	6 (27.3%)	0 (0%)*†	<0.001
Preformed DSA	28 (77.8%)	14 (63.6%)	36 (35.0%)*†	<0.001
AMR	9 (25.0%)	4 (18.2%)	6 (5.8%)*†	0.005
ACR ≥2R	5 (13.9%)	2 (9.1%)	4 (3.9%)	0.111
All-cause mortality	4 (11.1%)	5 (22.7%)	19 (18.4%)	0.471

ACR = acute cellular rejection; AMR = antibody-mediated rejection; DSA = donor-specific antibody; FXM = flow cytometry crossmatch.
*p value <0.05 when compared to rituximab/bortezomib based desensitization group; †p value <0.05 when compared to other desensitization group.

group, while rejection rates were comparable. When group C was stratified by desensitization therapy, patients who underwent desensitization therapy had significantly higher preformed donor-specific antibody (DSA) and positive flow cytometric crossmatch (FXM) when compared to those who did not go desensitization therapy. Although the desensitization group had a significantly higher incidence of AMR than the non-desensitized group, all-cause mortality was comparable.

A significantly higher proportion of patients in group C had positive FXM at HTx than those in groups A and B (group A: 0.2% vs. group B: 1.3% vs. group C: 8.1%, p<0.001; **Supplementary Table 2**). Preformed DSA was present in 103 (12.6%) patients in our cohort. The proportion of patients with preformed DSA was significantly higher in group C

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compared to groups A and B (group A: 1.0% vs. group B: 13.1% vs. group C 48.1%, p<0.001). Among patients who had serial DSA follow-up after HTx, group C had significantly more frequent DSA at 1 month, 6 months, and 1 year after HTx. Post-HTx survival rates were similar between those with and without pre-formed DSA, but AMR was significantly higher in those with preformed DSA than those without preformed DSA (**Supplementary Figure 1**).

DISCUSSION

In this study, we assessed PRA's prevalence and clinical impact in patients undergoing HTx using real-world, nationwide, multi-center data. 1) Among patients who underwent HTx during 2014–2021, 19.8% (n=161) had cPRA ≥50%. 2) A total of 61 patients underwent desensitization treatment before HTx. 3) Significantly more patients with cPRA ≥ 50% had significantly higher positive flowcytometric crossmatch at HTx and preformed DSA compared to those with cPRA <50%. 4) During follow-up, patients with cPRA ≥ 50% had significantly lower freedom from AMR, but the overall survival rate was similar to those with cPRA <50%. Our findings suggest that sensitized patients can attain comparable post-transplant survival to non-sensitized patients when treated with optimal desensitization treatment and therapeutic intervention.

The prevalence of sensitized patients waiting for HTx is increasing. An ISHLT report showed a significant temporal increase of sensitized patients with PRA ≥80% during the past decades (0.9% during 1992–2000 vs. 2.3% during 2001–2009 vs. 3.6% during 2010–2018). In our cohort, 19.8% (n=161) of patients had cPRA ≥50%. Among those, 19 patients (2.3%) had PRA ≥80%. Female sex, re-transplantation, congenital heart disease, and pre-HTx renal replacement therapy were independent clinical factors in association with cPRA ≥50%. Patients bridged with LVAD were not independently associated with cPRA ≥50% or ≥80% (p=0.937 and p=0.772, respectively). This may be due to the small number of LVAD-bridged patients (n=14). This registry includes patients who underwent HTx between 2014 and 2021, and the Korean national insurance system has covered LVAD since September 2018. The impact of LVAD on sensitization in Korea needs to be defined in future studies among larger numbers of patients bridged with LVAD before HTx.

In our cohort, 61 (7.5%) patients underwent desensitization treatment before HTx. Recent studies used PRA >10% to define allosensitization, although many centers used cPRA >50% as a threshold for desensitization. Only 36% (n=58) of patients with cPRA ≥50% underwent desensitization in our cohort. This finding reflects the limited therapeutic options and access to desensitization therapy in Korea, where not all therapeutic options are reimbursed by the government, even though effective therapeutic approaches have been published for sensitized transplanted patients. This remains a significant challenge for sensitized patients waiting for HTx and their physicians.

Most current desensitization therapies originate from renal transplantation data. Plasmapheresis removes circulating antibodies. Intravenous immunoglobulin blocks Fcγ receptors with inhibition of the complement system, neutralizes autoantibodies and cytokines, and downregulates the B-cell receptor. Rituximab induces B cell apoptosis by binding to CD 20.[12] Kobashigawa et al. reported that sensitized HTx candidates treated with plasmapheresis, intravenous immunoglobulin, and rituximab showed a notable reduction in PRA and similar 5-year post-transplant outcomes (71.5% vs. 75.7%) compared to a non-

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sensitized control group. However, the treated sensitized group experienced a significantly higher rate of AMR.[13] In our cohort, the most commonly used desensitization protocol was a combination of rituximab and plasmapheresis (41%), followed by plasmapheresis alone (26.2%), suggesting limited access to evidence-based treatment. The current consensus by the American Heart Association does not support plasmapheresis as monotherapy because it does not suppress continued antibody production and ultimately results in the reemergence of alloantibodies.[14] This reflects the complex challenges inherent in transplantation medicine in Korea. Because reimbursement for other therapies is not approved, the optimal desensitization protocol is not available to sensitized patients waiting for transplants despite mounting research findings, mainly due to high costs.

Although proven effective in sensitized patients waiting for transplantation, the agents most used for desensitization therapy, including rituximab, intravenous immunoglobulin, and plasmapheresis, have limited and transient impacts on HLA antibody levels. In addition, these agents are associated with significant AMR rates because they do not exert direct effects on mature plasma cells, which are the source of HLA antibodies.[15-18] Patel et al.[19] reported that a regimen of bortezomib and plasmapheresis was effective for a more rapid reduction in antibody levels compared to rituximab-based desensitization. With increasing evidence for proteasome inhibitors, compensatory B cell proliferation in response to the depletion of antibody-producing cells and rebound of antibodies has been observed, which resulted in variable efficacy.[20] Promising results of combination therapy of proteasome inhibitor with costimulation blockade in highly sensitized HTx candidates were previously reported.[21][22] Patel et al.[23] demonstrated the efficacy and safety of complement inhibition using eculizumab. In this open-label, non-randomized design, highly sensitized patients (PRA ≥70%) with preformed DSA were treated with eculizumab during the first two months post-HTx. The risk of biopsy-proven AMR was significantly reduced (hazard ratio, 0.36; 95% CI, 0.14–0.95; p=0.032) compared to matched plasmapheresis/intravenous immunoglobulin patients, and survival at one-year post-transplant was 90%.[23]

Due to emerging novel desensitization regimens, the likelihood of successful transplantation is increased for sensitized patients on waiting lists. However, toxicity and cost may limit the benefits of desensitization. Some countries incorporate allosensitization into organ allocation protocols to improve waiting list mortality outcomes for highly sensitized patients.[24] Parajuli et al.[25] reported that allocation systems prioritizing highly sensitized patients improved waiting list mortality and increased transplantation rates in highly sensitized patients. However, implementing allosensitization into allocation strategies has some challenges, including heterogeneity among allosensitization data due to differences in thresholds and standards among HLA laboratories.[26] To improve waiting list mortality and post-transplantation outcomes in sensitized patients, further consensus is necessary regarding the use of allosensitization in allocation policies among transplantation societies, including HLA specialists.

Regarding post-HTx clinical outcomes, patients in group C, highly sensitized patients, had comparable post-HTx survival outcomes, but the incidence of AMR was significantly higher compared to that in groups A and B. Pre-formed DSA was significantly higher in group C, which increased the risk of AMR. Early studies showed reduced post-HTx survival in patients with PRA >10%.[18][27-29] Previously, Nwakanma et al.[5] described worse 5-year survival after transplantation in patients with PRA >25% compared to those with PRA 0 (65% vs. 74%, p<0.001). They reported that PRA was a significant predictor of mortality

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after transplantation in a retrospective analysis of 8,160 HTx patients using United Network of Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) data.[5] Recent multi-center studies reported significantly increased incidence of the composite endpoint, including death, graft loss/re-transplantation, biopsy-proven acute rejection, and CAV in patients with preformed HLA antibodies (29% vs. 14%, p<0.04). In our study, the prevalence of CAV was similar among the groups, potentially due to the median follow-up time of 44 months, which may not be long enough to detect CAV accurately. This relatively shorter follow-up period may have also influenced similar all-cause mortality rates among the groups, as CAV significantly impacts long-term survival in HTx patients.

There are several potential limitations in this study. First, there was missing data regarding DSA during follow-up after HTx. Data regarding C1q assay and non-HLA antibodies were also limited. Second, desensitization protocols, including regimens and when to start desensitization, were not standardized among transplant centers. In our cohort, highly sensitized patients who underwent desensitization treatment had significantly higher rates of positive FXM and preformed DSA than those who did not undergo desensitization. Therefore, the comparison of clinical outcomes between the desensitized and non-desensitized groups in highly sensitized patients was not adequate. Further prospective study is needed to assess the efficacy of desensitization in highly sensitized HF patients in Korea. Third, our cohort included only sensitized patients who underwent HTx. We were not able to analyze the clinical outcomes of sensitized patients who were on waiting lists. A previous study reported that broadly allosensitized patients were more likely to experience longer waiting times, decreased likelihood of transplant, and increased risk of death among lung transplant candidates.[30] Future studies should investigate the clinical outcomes of sensitized patients on waiting lists for HTx. Fourth, data with a longer follow-up are needed to determine the long-term clinical impact of pre-HTx sensitization, especially for the development of CAV, which is associated with long-term graft survival and post-transplant mortality. Fifth, our analysis did not include other possible risk factors related to sensitizations, such as previous viral infection, influenza vaccines, prior surgery, or transfusions before HTx. Lastly, the 2018 revision of the HTx waiting list criteria in Korea limits our study. This revision may have altered patient status classification and potentially affected baseline characteristics.

Among patients who underwent HTx during 2014–2021 enrolled in the KOTRY registry, 19.8% had cPRA ≥50%, and 2.3% had PRA ≥80%. Among patients with cPRA ≥50%, 36% underwent desensitization treatment before HTx. Significantly more patients with cPRA ≥50% had significantly higher rates of positive FXM and preformed DSA than those with cPRA <50%. During follow-up, patients with cPRA ≥50% had significantly lower freedom from AMR, but post-HTx survival rates were similar to those with cPRA <50%. Sensitized patients may attain comparable post-transplant survival to non-sensitized patients when treated with optimal desensitization treatment and therapeutic intervention. Further research should analyze clinical outcomes among sensitized patients on waiting lists and focus on how to improve transplantation outcomes in sensitized patients.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Clinical characteristics of patients with or without desensitization therapy

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Supplementary Table 2

Presence of DSA among three groups

Supplementary Figure 1

Post-HTx survival rates (A) and freedom from AMR (B) according to the presence of preformed DSA.

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