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Impact of IgG monitoring and machine learning based prediction on outcomes of ABO incompatible kidney transplantation in blood type O recipients

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ABO-incompatible kidney transplantation (ABO-i KT) facilitates transplantation across blood types; however, antibody-mediated rejection (ABMR) remains a major concern, particularly in blood type O recipients. This retrospective study evaluated the effect of immunoglobulin G (IgG) monitoring and machine learning (ML)-based IgG prediction on post-transplant outcomes in 408 ABO-i KT recipients treated between 2014 and 2020. In blood type O recipients, the introduction of IgG monitoring (Era 2) was associated with a significantly lower incidence of ABMR ($P = 0.041$) and acute rejection ($P = 0.037$) compared with Immunoglobulin M (IgM)-only monitoring (Era 1). A higher initial IgM titer was identified as a risk factor for ABMR. To address the absence of IgG data in the IgM-only cohort, an ML model was developed using 610 cases to predict pre-transplant IgG titers based on IgM levels, number of plasmapheresis sessions, and ABO blood type. The model demonstrated good predictive performance (mean absolute error [MAE] = 0.593, $R^2 = 0.721$) and indicated that 12.2% of type O recipients in the IgM-only era were estimated to have high IgG titers (≥1:64). These findings support the clinical utility of IgG monitoring and ML-based estimation to enhance immunologic risk stratification and optimize preconditioning strategies in ABO-i KT.

Kidney transplantation (KT) is the most effective treatment for improving both quality of life and long-term survival in patients with end-stage renal disease (ESRD)[1] The prevalence of ESRD is steadily increasing; however, the number of available donors remains insufficient, resulting in a persistent shortage[2] To overcome immunological incompatibilities between recipient and donor, living donor KT across immunological barriers has become more common, supported by advances in desensitization protocols and immunosuppressive therapies[3,4] In particular, ABO-incompatible (ABO-i) KT has gained traction. Modifications in desensitization strategies and reductions in postoperative complications associated with pre-transplant treatment have resulted in clinical outcomes comparable to those of ABO-compatible (ABO-c) KT[4–6]. Furthermore, recent studies have demonstrated that ABO-i KT yields superior patient survival compared to remaining on the deceased donor KT (DDKT) waiting list or receiving ABO-c DDKT after a prolonged waiting period[7,8].

The presence of anti-A/B antibodies, which develop from early childhood through approximately 10 to 12 years of age, directed against glycolipids and glycoproteins expressed on vascular endothelial cells and other tissues such as epithelial and mesangial cells, represents the primary immunological barrier to ABO-i KT[9,10]. These antibodies can induce antibody-mediated rejection (ABMR) through activation of the complement system, resulting in graft injury if not appropriately controlled[10–14]. Although recent evidence suggests that ABO antibody titers can rise after 2 weeks and contribute to late-onset ABMR, the first 2 weeks remain widely recognized as the critical period for establishing immunologic accommodation[15]. However, consensus is lacking regarding the optimal antibody titer threshold at transplantation, with reported acceptable values ranging

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from 1:4 to 1:32. Furthermore, the clinical significance of IgM versus IgG antibodies in ABO-i KT remains unclear[10,13,16–18].

IgM antibodies are potent activators of the classical complement pathway and are well-established as key mediators of hyperacute rejection[19]. While IgG antibodies are less effective at complement activation, they may still contribute to ABMR through mechanisms such as antibody-dependent cellular cytotoxicity[11]. In a previous institutional study, successful ABO-i KT was achieved in patients with high IgG titers (up to 1:256) when the IgM titer was reduced to ≤ 4 without any incidence of hyperacute rejection[20]. However, subsequent episodes of early ABMR—including one case of hyperacute rejection—in blood type O recipients with low IgM raised concern regarding the necessity of IgG monitoring in this subgroup[14]. Based on these observations, we hypothesized that discordantly elevated IgG titers may independently increase the risk of rejection, prompting a revision of our protocol to incorporate simultaneous monitoring of both IgG and IgM, specifically in blood type O recipients. This study aimed to compare the clinical outcomes of ABO-i KT when only IgM was examined with those observed during the combined IgG and IgM assessment.

Materials and methods

Patients

This retrospective observational study included adult patients (aged > 19 years) who underwent ABO-i KT between January 2014 and December 2020 at Asan Medical Center. Exclusion criteria were positive complement-dependent cytotoxicity-based (CDC) crossmatch (XM) ($n = 12$) or flow cytometry-based crossmatch (FCXM) ($n = 38$), prior transplantation ($n = 79$), and the presence of pre-transplant donor-specific antibodies (DSA) ($n = 79$). IgM was monitored exclusively in recipients with blood types A, B, and AB during the study period. For type O recipients, only IgM was monitored before June 2018 (Era 1), whereas both IgM and IgG were monitored simultaneously after June 2018 (Era 2). To develop a machine learning (ML) model for predicting pre-transplant IgG titers, 120 cases from 2012 to 2014 at Asan Medical Center— where both IgG and IgM were measured—and 74 type O recipients from Era 2 were included. Additional external data were incorporated from 416 adult ABO-i KT recipients at Severance Hospital, Seoul, Korea, between 2010 and 2023 to enhance model performance and generalizability. In total, 610 cases were used to train the prediction model. The study protocol was approved by the Institutional Review Board of Asan Medical Center, Republic of Korea, which waived the need for informed patient consent due to the retrospective design. This study was conducted in accordance with the ethical guidelines of the World Medical Association's Declaration of Helsinki.

Desensitization

The desensitization protocol at our center includes a single dose of a CD20 monoclonal antibody (rituximab), followed by plasmapheresis and intravenous immunoglobulin administration. During an outpatient clinic visit, patients received a single dose of rituximab (100 or 200 mg) approximately 1 week before the first plasmapheresis session. Plasmapheresis was initiated 1 to 3 weeks before KT, utilizing a centrifugal apheresis system (COBE Spectra; Terumo BCT, Lakewood, CO, USA). The plasmapheresis schedule was based on the initial antibody titer, with the assumption that one session reduces the antibody level by one titer for both IgM and IgG. For patients with a high IgG titer (≥ 1:1024), the number of plasmapheresis sessions was increased by two based on institutional experience. In Era 1, only IgM titers were monitored and reduced to 1:4 or lower for type O recipients. In Era 2, both IgM (≤ 1:4) and IgG (≤ 1:32) titers were monitored and managed pre-transplantation. Only IgM titers were monitored and reduced to 1:4 or lower before transplantation for non-type O recipients. Post-transplant, additional plasmapheresis sessions were performed if there was a rebound in IgG titers or clinical signs of rejection, such as increased serum creatinine levels or decreased urine output. Isoagglutinin titers were measured using standardized hemagglutination techniques: IgM titers by the immediate-spin (IS) tube method at room temperature and IgG titers by the anti-human globulin (AHG) phase after incubation at 37 °C. For each, serial twofold dilutions of patient serum were tested against 3% A1 or B cell suspensions, and the titer was defined as the highest dilution showing trace reactivity. HLA-A, -B, and DRB1 typing was performed by sequence-based typing, and DSA detection employed single antigen bead assays on a Luminex platform, with results reported as mean fluorescence intensity. In cases where ABO antibody titers rebounded during the first 2 weeks after transplantation, additional postoperative PP was selectively performed to reduce the titers below the predefined target threshold for each era[21].

Immunosuppression

Induction therapy consisted of basiliximab (Simulect) administered preoperatively and on postoperative day 4. Patients were initiated on a triple immunosuppressive regimen comprising tacrolimus, mycophenolate mofetil, and methylprednisolone. In selected patients aged ≥ 65 years, cyclosporine was used instead of tacrolimus due to an increased infection risk. Target trough levels during the initial postoperative period were set at 7–10 ng/mL for tacrolimus and 100–150 ng/mL for cyclosporine. After the first postoperative year, target concentrations were adjusted to 5–7 ng/mL for tacrolimus and 50–100 ng/mL for cyclosporine. Mycophenolate mofetil was initiated at 1.5 g/day and reduced to 1 g/day on postoperative day 5. Intraoperatively, 500 mg of methylprednisolone was administered, followed by a gradual taper to 5 mg twice daily over the first postoperative year.

Definition

All episodes of rejection were confirmed through kidney graft biopsy. Rejection was suspected when there was a 20% variation in baseline serum creatinine, de novo DSA, or clinical indication by the attending physician, prompting a kidney graft biopsy. Biopsy specimens were evaluated by pathologists according to the 2019 Banff classification criteria[22]. ABMR was defined by the presence of microvascular inflammation (glomerulitis and/or peritubular capillaritis with g + ptc ≥ 2), evidence of current or recent antibody interaction with the endothelium

(e.g., C4d positivity), and serologic confirmation of DSAs. T cell-mediated rejection (TCMR) was classified based on the presence of interstitial inflammation (i) and tubulitis (t), with grade IA defined as $i \geq 1$ and $t \geq 2$. Protocol biopsies were not performed; therefore, only biopsy-proven acute rejection (AR) was defined as rejection in this study. Rejection-free graft survival (RFGS) was defined as the duration from KT to the first instance of pathologically confirmed rejection. Graft survival (GS) was defined as the period from KT to either return to renal replacement therapy or graft failure. Infectious complications following ABO-i KT were defined as any infectious event requiring antibiotic therapy, including pneumonia, urinary tract infections, or surgical site infections. Initial IgM and IgG titers were defined as the first antibody measurements measured during the ABO-i KT evaluation. Pre-transplant IgM and IgG titers were the final measurements obtained immediately before KT, following the completion of preconditioning.

Data and statistical analysis

Continuous variables are presented as means with standard deviations (SDs) and were compared using Student's t-test or one-way analysis of variance (ANOVA), as appropriate. The Mann–Whitney U test or Kruskal–Wallis test was employed for non-normally distributed variables. Categorical variables are expressed as frequencies (percentages) and were compared using the chi-square or Fisher's exact tests when expected cell counts were small. Kaplan–Meier survival analysis compared graft and rejection-free survival between groups. Univariate analysis was conducted to assess associations between patient factors, including age, sex, panel reactive antibody (PRA) levels, presence of de novo DSA, number of pre-transplant plasmapheresis sessions, initial IgM titer, antibody monitoring strategy (IgM alone versus both IgM and IgG), and incidence of post-transplant ABMR. Multivariate analysis was performed to determine the adjusted impact of patient factors on post-transplant ABMR occurrence. A supervised ML model was developed to predict pre-transplant IgG titers on a continuous log2 scale. Model development employed the XGBoost Regressor (XGBoost version 2.1.4, Python 3.11.13) with four input features: ABO blood group, initial IgM titer, pre-transplant IgM titer, and the number of plasmapheresis sessions before KT[23,24]. Given the greater discrepancy between IgM and IgG titers observed in recipients with blood group O, a sample weighting strategy was applied, testing weights from 1.0 to 5.0. The final model selected was the XGBoost Regressor with a sample weight of 4.0 for blood group O, based on optimal training performance metrics, including mean absolute error (MAE) and the coefficient of determination (R^2). To further enhance model stability and address potential overfitting, we conducted grid search–based hyperparameter tuning across 162 combinations of the following hyperparameters—learning rate, max depth, reg alpha, and reg lambda—using fivefold cross-validation. All statistical analyses were conducted using SPSS Statistics version 26 (IBM, New York, NY, USA). A P value < 0.05 was considered statistically significant.

Results

Patient demographics and characteristics

A total of 408 patients were enrolled in this study and divided into three groups based on blood types and the period of IgM and IgG testing. Among them, 232 recipients with blood types A, B, or AB had only IgM titer monitored. For type O recipients, 102 patients were monitored only before June 2018 (IgM group, Era 1), and 74 patients were monitored for both IgM and IgG titers after June 2018 (IgG group, Era 2). The initial PRA class II (%) was significantly higher among type O recipients in Era 2 (13.67, SD = 23.26) compared to both non-O recipients (7.90, SD = 17.59) and type O recipients in Era 1 (6.95, SD = 15.62) ($P = 0.034$). Regarding isoagglutinin levels, the initial IgM anti-ABO titers were significantly higher in type O recipients (combined) than in non-O recipients; however, no significant difference was observed between the two O subgroups (5.0 ± 5.9, 5.9 ± 1.5, 6.3 ± 1.7; $P < 0.001$). In contrast, pre-transplant IgM titers measured after desensitization were lower in the IgG monitoring group (2.7 ± 2.0 vs. 2.6 ± 1.4 vs. 1.7 ± 1.9; $P = 0.030$). Other clinical variables, including hypertension, mean age, male sex distribution, body mass index (BMI), dialysis duration before transplantation, PRA class I (%), and HLA mismatches (ABDR, DR, and DQ), did not differ statistically among the three groups (Table 1).

Preconditioning strategies across the three groups before transplantation are summarized in Table 2. The IgM-O group received the highest average rituximab dose (195.26 mg), followed by the A, B, and AB groups (171.01 mg) and the IgG-O group (140.27 mg) ($P < 0.001$). Preconditioning CD19 and CD20 levels did not differ significantly across the groups. However, the A, B, and AB groups had the highest post-conditioning CD19 count (3.30) compared to the IgM-O group (2.32) and the IgG-O group (1.62) ($P = 0.002$). The number of plasmapheresis sessions before transplantation was significantly higher in the IgG-O group (5.04) than in the A, B, and AB groups (2.52) and the IgM-O groups (2.91) ($P < 0.001$).

Clinical outcomes

No statistically significant differences in GS, AR-free survival, and ABMR-free survival were observed between type O and non-type O recipients during the IgM-only period (Fig. 1).

As shown in Fig. 2, GS, AR-free survival, and ABMR-free survival were compared between type O and non-type O (A, B, AB) recipients during the IgG period. Although no statistically significant differences were observed, Fig. 2B shows a trend toward improved AR-free survival in type O recipients compared to non-type O recipients (P = 0.061).

As shown in Fig. 3, a comparison between the IgM-only period and the IgG period of type O recipients revealed no significant difference in GS; however, both AR and ABMR were significantly lower during the IgG period ($P = 0.037$ and $P = 0.041$, respectively).

These findings suggest that combined monitoring of IgG and IgM may be more effective in preventing post-transplant rejection in type O recipients. Hyperacute rejection occurred in one patient in the IgM-O group but was not observed in the other groups ($P = 0.22$). The incidence of rejection within 1 month post-transplant was significantly higher in the IgM-O group (0.098%, $n = 1$) than in the other groups ($P = 0.049$).

Variables	A, B, AB recipients ($n=232$)	O recipients ($n=176$)		p-value
		Era 1 (IgM) ($n=102$)	Era 2 (IgG) ($n=74$)	
Mean age, years	48.7 ± 11.7	47.3 ± 11.9	47.7 ± 12.7	0.55
Male sex, n (%)	156 (67.2)	68 (66.7)	43 (58.1)	0.34
BMI, kg/m^2	23.2 ± 3.5	23.1 ± 3.5	22.6 ± 3.5)	0.39
Diabetes mellitus, n (%)	89 (38.4)	29 (28.4)	17 (23.0)	0.026
Hypertension, n (%)	202 (87.1)	91 (89.2)	64 (86.5)	0.82
Dialysis before KT, months[a]	17.4 (31.4)	20.8 (38.1)	20.6 (42.1)	0.64
Initial IgM anti ABO titer, 2^n	5.0 ± 5.9	5.9 ± 1.5	6.3 ± 1.7	< 0.001*
Pre-transplant IgM anti ABO titer, 2^n	2.7 ± 2.0	2.6 ± 1.4	1.7 ± 1.9	0.030
PRA class I[a]	7.7 (9.0)	7.8 (2.0)	7.8 (4.3)	0.99
PRA class II[a]	7.9 (4.5)	7.0 (3.8)	13.7 (24.0)	0.034
HLA mismatch				
ABDR mismatch	3.4 ± 1.7	3.2 ± 1.6	3.4 ± 1.70	0.59
DR mismatch	1.2 ± 0.7	1.1 ± 0.6	1.1 ± 0.7	0.83
DQ mismatch	1.0 ± 0.7	0.9 ± 0.7	0.9 ± 0.7	0.26

Table 1. Demographics and clinical characteristics. Continuous variables are presented as means ± standard deviations, whereas categorical data are presented as numbers (%). [a]Dialysis before transplantation (months) and PRA class I and II data are presented as median (interquartile range [IQR]). IgM, Immunoglobulin M; PRA, panel reactive antibody; HLA, Human Leukocyte Antigen. *Statistical significance was observed between A, B, AB recipients and O recipients (combined), but not between the IgM and IgG subgroups within the O recipient group.

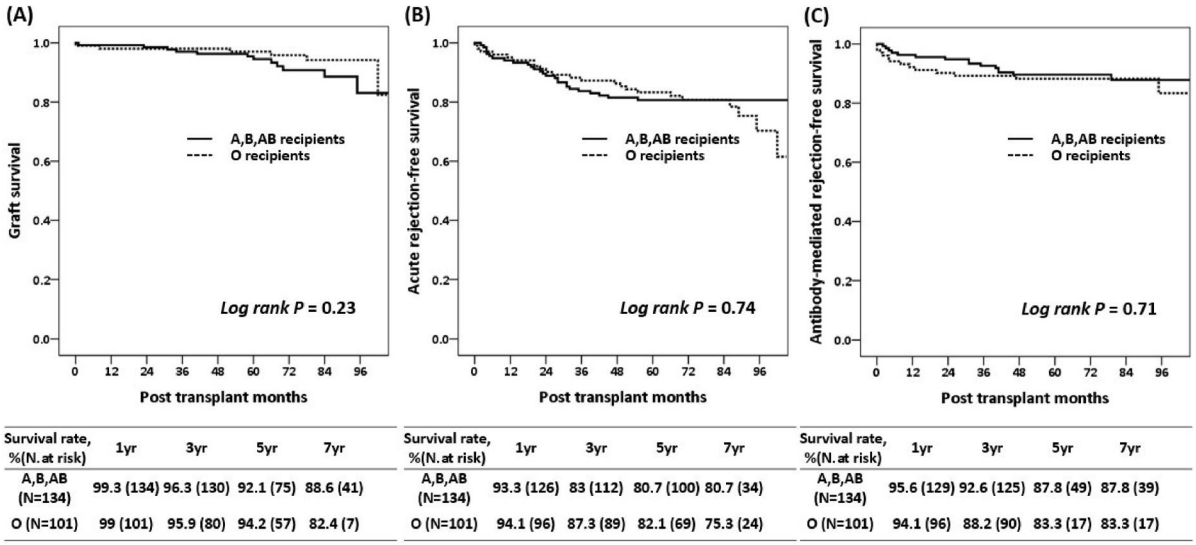
Variables	A, B, AB recipients ($n=232$)	O recipients ($n=176$)		p-value
		Era 1 (IgM) ($n=102$)	Era 2 (IgG) ($n=74$)	
Tacrolimus, n (%)	187 (80.6)	73 (71.6)	69 (93.2)	0.002
Cyclosporin, n (%)	45 (19.4)	29 (18.4)	5 (6.7)	0.009
Rituximab dose, mg	171.0 (65.7)	195.3 (46.5)	140.3 (49.4)	< 0.001
CD19 count, cells/μL	137.7 ± 99.6	150.6 ± 99.6	150.4 ± 87.0	0.34
CD20 count, cells/μL	134.7 ± 89.5	147.7 ± 98.6	148.6 ± 87.4	0.26
Post-conditioning CD19 count, cells/μL	3.3 ± 6.5	2.3 ± 2.6	1.6 ± 3.2	0.002
Post-conditioning CD20 count, cells/μL	0.1 ± 1.2	0.1 ± 0.7	0.1 ± 0.2	0.30
Pre-transplant plasmapheresis, n	2.5 ± 1.4	2.9 ± 1.6	5.0 ± 2.3	< 0.001

Table 2. Preconditioning before kidney transplantation.

However, no significant differences in rejection rates were observed at 6 months ($P=0.88$) and 1 year ($P=0.60$) post-transplantation among the groups. The mean number of post-transplant plasmapheresis sessions was significantly higher in the IgG-O group (3.36 ± 2.90) than in the A, B, AB group (0.45 ± 1.52) and the IgM-O group (0.16 ± 0.72) ($P<0.001$). Infectious complications requiring antibiotic treatment, including pneumonia, urinary tract infections, and surgical site infections, occurred in 16.4% of patients in the A, B, and AB groups, 18.6% of patients in the IgM-O group, and 16.2% in the IgG-O group, with no significant difference observed between groups ($P=0.87$) (Table 3).

Risk factors of ABMR in blood type O recipients

We employed the Cox proportional hazards model to examine factors associated with the occurrence of ABMR after ABO-i KT in type O recipients (Table 4). In univariate analysis, age and sex were identified as significant risk factors for ABMR occurrence post-transplantation ($P=0.050$ and $P=0.042$, respectively). The proportion of tacrolimus use and rituximab dose did not demonstrate statistical significance in relation to 1-year rejection. In multivariate analysis, female sex (OR = 2.61, 95% CI: 1.06–6.40, $P=0.036$) and higher pre-initial-transplant IgM titer (OR = 1.25, 95% CI: 1.01–1.55, $P=0.034$) were statistically associated with increased risk factors of post-transplant ABMR. Additionally, simultaneous monitoring of IgG and IgM before transplantation was associated with a reduced risk of ABMR (OR = 0.35, 95% CI: 0.14–0.87, $P=0.024$). These findings suggest that specific recipient characteristics and pre-transplant antibody monitoring may significantly affect ABMR risk in type O recipients.

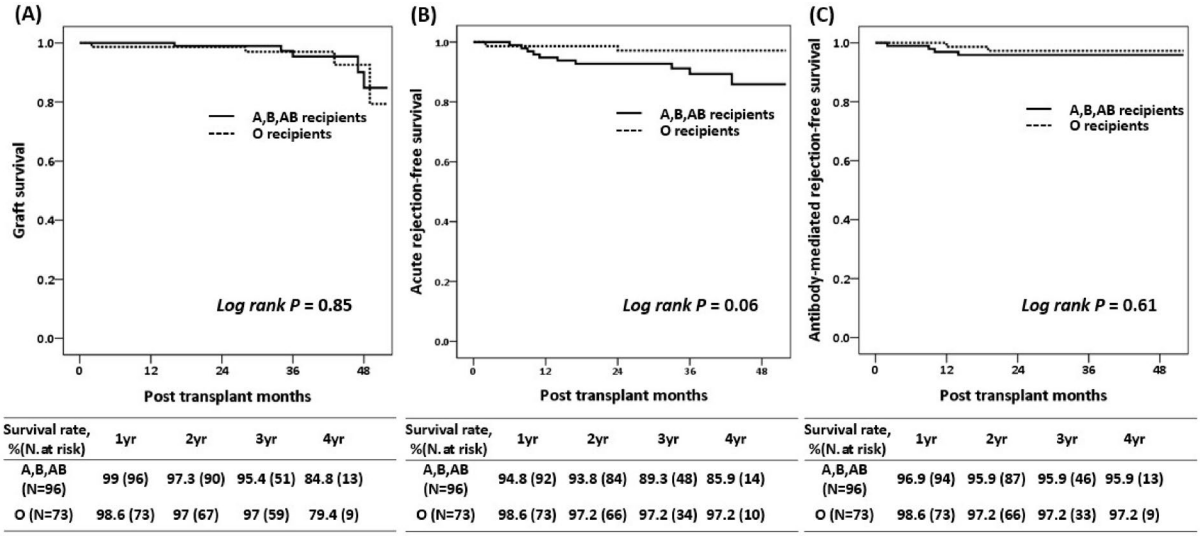


Survival rate, %(N. at risk)	1yr	3yr	5yr	7yr
A,B,AB (N=134)	99.3 (134)	96.3 (130)	92.1 (75)	88.6 (41)
O (N=101)	99 (101)	95.9 (80)	94.2 (57)	82.4 (7)

Survival rate, %(N. at risk)	1yr	3yr	5yr	7yr
A,B,AB (N=134)	93.3 (126)	83 (112)	80.7 (100)	80.7 (34)
O (N=101)	94.1 (96)	87.3 (89)	82.1 (69)	75.3 (24)

Survival rate, %(N. at risk)	1yr	3yr	5yr	7yr
A,B,AB (N=134)	95.6 (129)	92.6 (125)	87.8 (49)	87.8 (39)
O (N=101)	94.1 (96)	88.2 (90)	83.3 (17)	83.3 (17)

Fig. 1. Overall survival analysis between type O and A, B, and AB recipients during the IgM-only period. Kaplan–Meier curves show (**A**) graft survival, (**B**) acute rejection-free survival, and (**C**) ABMR-free survival.



Survival rate, %(N. at risk)	1yr	2yr	3yr	4yr
A,B,AB (N=96)	99 (96)	97.3 (90)	95.4 (51)	84.8 (13)
O (N=73)	98.6 (73)	97 (67)	97 (59)	79.4 (9)

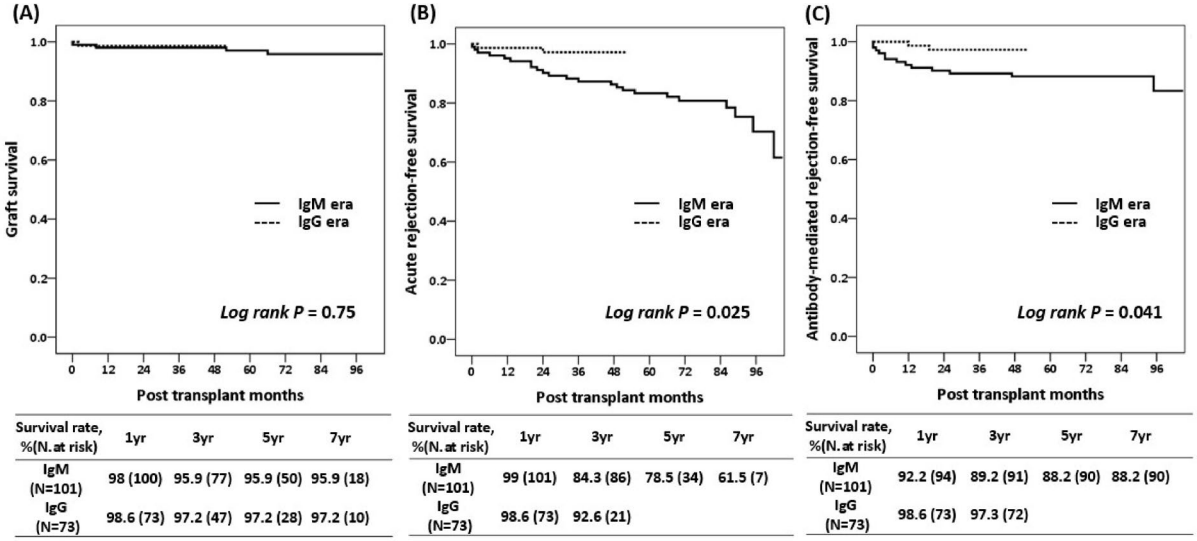
Survival rate, %(N. at risk)	1yr	2yr	3yr	4yr
A,B,AB (N=96)	94.8 (92)	93.8 (84)	89.3 (48)	85.9 (14)
O (N=73)	98.6 (73)	97.2 (66)	97.2 (34)	97.2 (10)

Survival rate, %(N. at risk)	1yr	2yr	3yr	4yr
A,B,AB (N=96)	96.9 (94)	95.9 (87)	95.9 (46)	95.9 (13)
O (N=73)	98.6 (73)	97.2 (66)	97.2 (33)	97.2 (9)

Fig. 2. Overall survival analysis between type O and A, B, and AB recipients during the IgG monitoring period. Kaplan–Meier curves show (**A**) overall graft survival, (**B**) acute rejection, and (**C**) ABMR.

Machine learning: prediction of pre-transplant IgG titer

To estimate pre-transplant IgG titers in patients monitored only for IgM, a supervised ML model using data from 610 ABO-i KT cases across two centers was employed. Among the three algorithms tested—Linear Regression, Random Forest Regressor, and XGBoost Regressor—the XGBoost Regressor had superior predictive performance, with an MAE of 0.593 and R^2 score of 0.721, outperforming both Linear Regression (MAE = 0.928, $R^2 = 0.440$) and Random Forest Regressor (MAE = 0.662, $R^2 = 0.698$). Therefore, the XGBoost model was selected for the final application. Table 5 presents the distribution of predicted IgG titers (converted from $\log_2$ to 1:x format). Most patients exhibited titers between 1:2 and 1:64, with 19 patients predicted to have ≥ 1:64 titers. Notably, all cases with predicted IgG titers ≥ 1:64 were blood group O recipients. Applying this model to the IgM-only cohort identified 29 patients (12.2%) who would have been classified as having high IgG titers (≥ 1:64) under IgG-monitoring criteria. These findings suggest that some patients may have been under-classified immunologically due to the absence of IgG titer monitoring. Figure 4 visualizes the predicted IgG stratified by ABO blood group, showing higher titers clustering in blood group O recipients despite comparable pre-transplant IgM levels. This observation suggests a distinct immunologic profile in O-type recipients, supporting the need for enhanced antibody monitoring in this subgroup.



Survival rate, %(N. at risk)	1yr	3yr	5yr	7yr
IgM (N=101)	98 (100)	95.9 (77)	95.9 (50)	95.9 (18)
IgG (N=73)	98.6 (73)	97.2 (47)	97.2 (28)	97.2 (10)

Survival rate, %(N. at risk)	1yr	3yr	5yr	7yr
IgM (N=101)	99 (101)	84.3 (86)	78.5 (34)	61.5 (7)
IgG (N=73)	98.6 (73)	92.6 (21)		

Survival rate, %(N. at risk)	1yr	3yr	5yr	7yr
IgM (N=101)	92.2 (94)	89.2 (91)	88.2 (90)	88.2 (90)
IgG (N=73)	98.6 (73)	97.3 (72)		

Fig. 3. Survival outcomes of type O recipients: comparison between the IgM-only and IgG monitoring periods. Graft survival (**A**) was similar between the two periods, while AR-free (**B**) and ABMR-free (**C**) survival were significantly improved during the IgG monitoring period ($P = 0.037$ and $P = 0.041$, respectively).

Variables	A, B, AB recipients ($n = 232$)	O recipients ($n = 176$)		p-value
		Era 1 (IgM) ($n = 102$)	Era 2 (IgG) ($n = 74$)	
Post-transplant plasmapheresis, n	0.4 ± 1.5	0.16 ± 0.7	3.4 ± 2.9	< 0.001
Hyperacute rejection, n (%)	0 (0)	1 (0.9)	0 (0)	0.22
1 month rejection, n (%)	0 (0)	2 (1.9)	0 (0)	0.049
6 months rejection, n (%)	7 (3.0)	4 (2.9)	2 (2.7)	0.88
1-year rejection, n (%)	13 (5.6)	5 (3.9)	2 (2.7)	0.60
Infectious complications[a], n (%)	38 (16.4)	19 (18.6)	12 (16.2)	0.86

Table 3. Post-transplant complications. Continuous data are presented as means ± standard deviations, whereas categorical data are presented as numbers (%). [a]Infectious complications are defined as any infectious event requiring antibiotic treatment.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, years	1.04 (1.00–1.10)	0.05	N/A	N/A
Female vs. Male	3.77 (0.85–16.75)	0.042	2.61 (1.06–6.40)	0.036
HLA-A, -B, -DR mismatch	1.09 (0.79–1.49)	0.59	N/A	N/A
PRA class I	0.90 (0.75–1.08)	0.28	N/A	N/A
PRA class II	0.97 (0.92–1.02)	0.26	N/A	N/A
Tacrolimus vs. cyclosporin	0.71 (0.32–9.23)	0.53	N/A	N/A
Rituximab dose, mg	1.00 (0.99 – 1.02)	0.51	N/A	N/A
IgG vs. IgM monitoring	0.23 (0.05–1.06)	0.06	0.35 (0.14–0.87)	0.024
Initial IgM anti-ABO titer ($/2^n$)	1.20 (0.98–1.48)	0.077	1.25 (1.01–1.55)	0.034
Preoperative plasmapheresis number	1.07 (0.85–1.34)	0.56	N/A	N/A

Table 4. Factors associated with the development of antibody-mediated rejection within 1 year after kidney transplantation in blood type O recipients. HLA, Human Leukocyte Antigen; PRA, panel reactive antibody; IgM, Immunoglobulin M; IgG, Immunoglobulin G.

Predicted IgG Titer	O-type Recipients	A/B-type Recipients	Total
1:1	2	3	5
1:2	1	55	56
1:4	1	55	56
1:8	17	20	37
1:16	18	2	20
1:32	34	0	34
1:64	19	0	19
1:128	9	0	9
1:256	1	0	1

Table 5. Distribution of Predicted Pre-Transplant IgG Titers by ABO Blood Group. Numbers in each cell represent the number of patients per group.

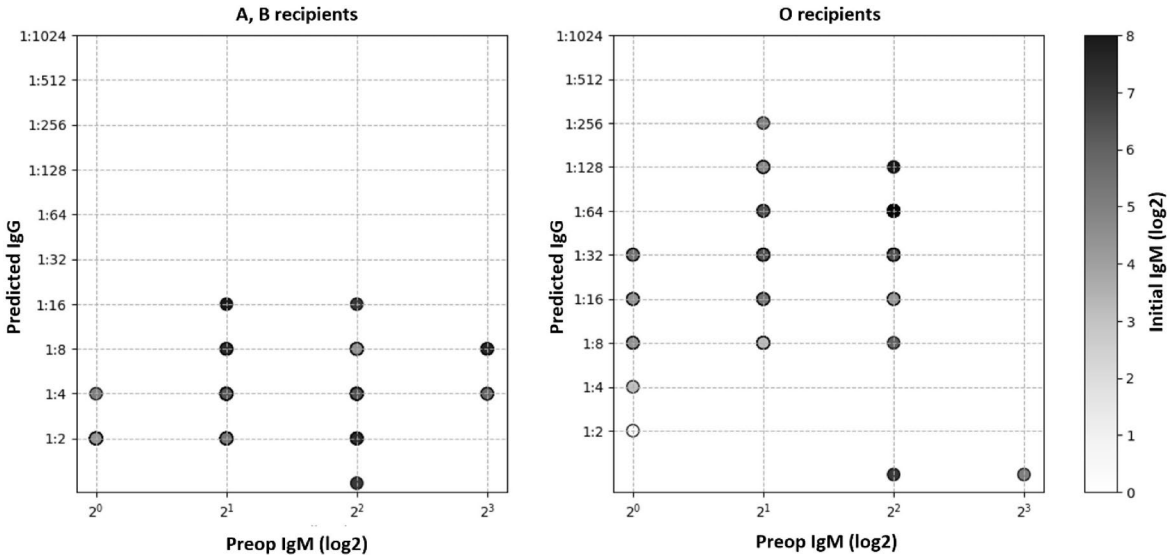


Fig. 4. Predicted pre-transplant IgG titers by ABO blood group, stratified by pre-transplant IgM levels (x-axis) and shaded by initial IgM titers (grayscale). The left panel shows A/B-type recipients; the right panel shows O-type recipients. Each dot represents a patient, plotted according to preoperative IgM titer (x-axis) and predicted IgG titer (y-axis). Grayscale intensity reflects initial IgM level (log_2 scale).

The left panel represents recipients with blood types A or B-, while the right panel shows recipients with blood type O.

Each dot corresponds to an individual patient, plotted according to their pre-transplant IgM titer (x-axis) and the predicted IgG titer (y-axis). Grayscale intensity indicates the magnitude of the initial IgM titer, expressed in log_2 values.

Discussion

This study demonstrated that type O recipients monitored for IgG titers exhibited a significantly lower incidence of AR (specifically ABMR) than those monitored solely for IgM titers. These results highlight the clinical importance of IgG in early rejection in blood group O recipients, suggesting it complements IgM in reducing early post-transplant rejection. Recipients in the IgG monitoring group underwent significantly more plasmapheresis sessions to achieve target titers and reached lower pre-transplant IgM titers after preconditioning, reflecting a more intensive desensitization strategy targeting IgG. Although the retrospective design limits causal inference, these findings suggest that incorporating IgG monitoring may improve rejection outcomes in type O recipients. Moreover, combining IgM (≤ 1:4) and IgG (≤ 1:16) titer monitoring as part of pre-transplant conditioning could facilitate successful ABO-i KT in type O recipients, mitigating their increased rejection risk. Our multivariate analysis indicated a trend associating higher pre-transplant IgM titers with post-transplant ABMR risk; however, further studies are warranted to confirm this relationship. These findings align with previous reports indicating elevated ABMR risk in type O recipients with higher isoagglutinin titers[13,25,26]. Type O recipients are predisposed to higher post-transplant ABMR and early graft loss in both ABO-i KT and liver transplantation[27].

IgG and IgM have distinct immunological roles in ABO-i KT. IgM antibodies play a crucial role in initiating immune responses by activating the complement system, which leads to the rapid elimination of foreign antigens.

Notably, in vivo findings suggest that IgM may have a greater capacity for complement activation, consistent with prior observations[19]. In contrast, IgG mediates long-term immunity through antibody-dependent cellular cytotoxicity, pathogen neutralization, and immunological memory, roles critical in ABO-i KT[11]. Our findings suggest that in type O patients, IgG may have clinical significance comparable to IgM in precipitating early ABMR, including hyperacute rejection. Additionally, we demonstrated that elevated antibody titers were associated with increased ABMR risk. Recent studies have identified elevated initial IgG titers, particularly high initial titers (≥ 1:256), low titer-reduction rates, and blood group O as significant risk factors for postoperative isoagglutinin rebound. Notably, high rebound titers (≥ 1:64) have been associated with an increased risk of ABMR. Given that blood type O recipients are more susceptible to pre-transplant resistance to desensitization and postoperative rebound, stricter preconditioning protocols may be warranted to mitigate the risk of ABMR in this subgroup[26,28]. In our study, following the implementation of a stricter IgG cut-off (≤ 1:16) in Era 2, the number of postoperative PP sessions significantly increased compared to Era 1, especially in blood group O recipients. This suggests that the reduction in ABMR observed in Era 2 may be attributable not only to improved preconditioning but also to the proactive management of post-transplant IgG rebound through additional PP treatments during the critical early post-transplant period.

The clinical significance of IgG has been further demonstrated by other studies, particularly in blood type O patients, where IgG levels play a critical role in influencing outcomes. Yang et al. emphasized that preventing ABMR requires careful management of IgG titers, considering their persistent elevation and propensity for rebound[14]. The role of IgG may extend beyond the immediate post-transplant period, potentially contributing to long-term ABMR risk, particularly when exacerbated by bacterial infection-induced IgG expansion[15]. Okada et al. demonstrated that IgG-targeted immunosuppressive strategies effectively reduced ABMR rates while minimizing the overall immunosuppressive burden, highlighting the potential of tailored IgG management to improve patient outcomes[25]. Furthermore, evidence suggests that specific IgG subclasses, such as IgG1, may be closely associated with complement activation and early rejection episodes[14]. These findings underscore the importance of monitoring and managing IgG levels to reduce the risk of early rejection and highlight the need for personalized immunosuppressive strategies in type O recipients.

A previous study at our institution found that monitoring IgM titers alone before and after transplantation was sufficient to achieve successful outcomes in ABO-i KT[17]. However, subsequent clinical experience revealed a significant discrepancy between IgM and IgG titers in blood type O recipients compared to other blood groups. Notably, a single case of hyperacute rejection occurred in a type O recipient shortly after reperfusion, leading to graft loss[14]. Following this incident, our institution revised its policy for type O recipients by lowering the target IgG titer to ≤ 16. Since the implementation of this revised protocol, type O recipients have achieved outcomes comparable to those of non-O recipients In contrast, for ABO-i KT in recipients with blood type A or B, ABO antibodies are predominantly of the IgM class. Consequently, lowering IgM levels is generally sufficient to reduce IgG below the target threshold without the need for separate IgG monitoring[29]. Our study focused on blood type O recipients, as they demonstrated the highest immunologic burden and clinical need for additional IgG monitoring. Through machine learning–based modeling, we demonstrated that 12.2% of patients with acceptable IgM titers still exhibited elevated IgG levels, placing them at potential immunologic risk. These findings support the need for routine IgG monitoring in type O recipients and offer a predictive tool to assist in individualized risk stratification.

Plasmapheresis-based desensitization can elicit different response patterns in IgM and IgG antibodies. IgM, which is predominantly intravascular, is efficiently removed by plasmapheresis. In contrast, IgG is less effectively cleared due to its higher extravascular distribution[30]. At our institution, when patients present with high IgG titers (≥ 1:1024), we schedule two additional plasmapheresis sessions beyond the initially planned regimen and, if necessary, continue these sessions until the day before or even the day of surgery to further reduce the risk of rebound. This approach has enabled successful ABO-i KT in patients with exceptionally high titer (up to 1:16,384) and may serve as a valuable strategy for other centers managing similar high-titer patients.

In the absence of IgG measurements during the IgM-only monitoring era, we developed an ML model to retrospectively estimate pre-transplant IgG titers. The model demonstrated good predictive performance (MAE = 0.593, $R^2 = 0.721$), and its accuracy improved when a sample weight of 4.0 was applied to recipients with blood group O. This finding suggests that type O recipients may have relatively higher IgG titers than non-O recipients at comparable IgM levels. Our study utilized XGBoost as the final predictive model due to its superior performance compared to linear regression and random forest models. Recent advances in machine learning have shown that XGBoost offers a favorable balance between accuracy, robustness, and computational efficiency, especially in complex medical datasets with nonlinear relationships[23,24]. It has increasingly been adopted in clinical research for risk prediction, biomarker modeling, and outcome forecasting. In our study, the accuracy of the XGBoost model further improved when additional sample weights were applied to blood type O recipients, suggesting its flexibility and adaptability to subgroup-specific patterns.

This study has some limitations. First, as a retrospective observational study, it is inherently subject to biases, including selection bias and confounding factors, which may affect the interpretation of the findings. Second, in Era 1, IgG titers were not routinely measured in type O recipients, making it challenging to precisely assess the role of IgG in patients who experienced ABMR. Third, the sample size, particularly in Era 2, may limit the generalizability of the results, as the cohort of type O recipients with comprehensive IgG monitoring was relatively small. Additionally, the study did not include protocol biopsies, relying instead on clinically indicated biopsies to confirm rejection. Given the limited number of rejection events, multivariate logistic regression analysis was restricted to a limited number of variables to avoid overfitting, which remains a potential limitation. Fourth, the IgG group included more patients receiving tacrolimus than cyclosporine. Although univariate analysis of 1-year rejection showed no significant association with tacrolimus use, this difference may have influenced study outcomes and limited comparability between groups. Finally, although our center employed standardized

preconditioning and immunosuppressive protocols, differences in institutional settings, ethnic groups, and titer measurement may affect the reproducibility and external applicability of these findings.

Conclusion

Our study suggests that achieving an IgG titer of ≤ 16 in type O recipients may enable safer and more effective ABO-i KT, even in high-titer cases. Incorporating IgG monitoring into pre-transplant protocols alongside IgM monitoring may reduce the risk of early ABMR, including hyperacute rejection. These findings highlight the importance of individualized preconditioning strategies tailored to the blood type and antibody profile. Future research should focus on prospective studies with larger cohorts to validate these findings and refine titer management strategies. Additionally, investigation into the mechanisms underlying IgG-mediated rejection, particularly in type O patients, and evaluating the role of specific IgG subclasses could provide valuable insights for optimizing immunosuppressive therapies.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Author contributions
Youngmin Ko, Dae-Hyun Ko, and Hyunwook Kwon contributed to the conception and design of the study and drafted the manuscript text. Jin-Myung Kim, Hye Eun Kwon, Sung Shin, Joo Hee Jung, Juhan Lee, and Young Hoon Kim were involved in the data acquisition, analysis, and interpretation. All authors reviewed the manuscript critically for important intellectual content and approved the final version submitted for publication.

Declarations

Competing interests
The authors declare no conflicts of interest related to this manuscript.

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