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Combined Impact of Pre-sensitization and Delayed Graft Function on Allograft Rejection in Deceased Donor Kidney Transplantation: Nationwide Cohort Study

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Abstract

The aim of this study is to investigate whether or not delayed graft function (DGF) and pre-transplant sensitization has a synergistic adverse effect on allograft outcome after deceased donor kidney transplantation (DDKT) using the Korean Organ Transplantation Registry (KOTRY) database, the nationwide prospective cohort. The study included 1,370 cases between May 2014 and June 2019. The cases were divided into 4 subgroups according to pre-sensitization and the development of DGF post-transplant (non-pre-sensitized-DGF(-)(n=1100), non-pre-sensitized-DGF(+)(n=133), pre-sensitized-DGF(-)(n=116), and pre-sensitized-DGF(+)(n=21)). We compared the incidence of biopsy-proven allograft rejection (BPAR), time-related change in allograft function, allograft or patient survival, and post-transplant complications across 4 subgroups. The incidence of overall BPAR and acute antibody-mediated rejection (ABMR) was significantly higher in the pre-sensitized-DGF(+) subgroup than in other 3 subgroups. In addition, multivariable cox regression analysis demonstrated that pre-sensitization combined with DGF is an independent risk factor for both overall BPAR (hazard ratio 3.253, $p = 0.005$) and acute ABMR (hazard ratio 7.589, $p < 0.001$). Moreover, DGF and pre-sensitization showed significant interaction. Pre-sensitization combined with DGF did not show significant impact on allograft function, and allograft or patient survival. In conclusion, pre-sensitization and DGF had a synergistic adverse impact on allograft rejection after DDKT.

Introduction

Delayed graft function (DGF) is a manifestation of acute kidney injury (AKI), which is more prevalent in deceased donor kidney transplantation (DDKT). The definition of DGF varies according to the study; however, it is mostly based on the use of dialysis within 1 week from transplant [1-3]. The mechanism underlying the development of DGF still needs to be unveiled, but it is suggested that post-ischemic acute tubular necrosis resulting from ischemia and reperfusion injury (IRI) developing during deceased donor management or recovery of organs, and calcineurin inhibitor (CNI) toxicity may be the major contributors [4]. The activation of adaptive immune system induced by DGF also increases the risk of allograft rejection.

Meanwhile, it is well known that the presence of preexisting donor-specific anti-human leukocyte antigen antibody (HLA-DSA), so-called "pre-sensitized state" is an important obstacle preventing successful kidney transplantation (KT) [5-9]. In such patients, HLA-DSA can increase the risk of acute or chronic antibody-mediated rejection (ABMR) resulting in worse allograft outcomes [10,11]. In the setting of DDKT, DGF combined with subclinical rejection resulted in far worse allograft outcomes. In addition, the detrimental impact of DGF on allograft was enhanced by the presence of pre-transplant HLA-DSA in DDKT [12].

Based on the above background, it is possible that DGF in patients with pre-sensitization has a synergistic adverse impact on the allograft outcomes. However, it has yet to be fully investigated and only a single center study is available [12]. In this regard, the aim of this study is to investigate the combined impact of DGF and pre-sensitization on the development of

allograft rejection using the well-established nationwide prospective cohort, Korean Organ Transplantation Registry (KOTRY).

Results

Baseline clinical and immunological patient characteristics

DGF developed in 11.2% (154/1370) out of the total DDKT recipients. Between pre-sensitized and non-pre-sensitized subgroups, no difference was detected in the frequency of DGF (10.8% vs. 15.3%, p=0.110). Table 1 describes baseline characteristics of the donor and recipients of four subgroups. Baseline estimated glomerular filtration rate (eGFR) was significantly lower in donors of DGF (+) subgroups irrespective of pre-sensitization. Cold ischemic time showed a longer tendency in DGF (+) subgroups irrespective of pre-sensitization without statistical significance. However, donor age, gender, body mass index (BMI), underlying disease including DM or hypertension (HTN) and the proportion of donors after cardiac death (DCD) or donors after brain death (DBD) did not differ significantly across 4 subgroups. Among recipient factors, there was a significantly longer dialysis vintage and also additional number of female patients in both pre-sensitized subgroups than in non-pre-sensitized subgroups. In addition, a previous KT history and the proportion of anti-thymocyte globulin (ATG) use as induction therapy were higher in the pre-sensitized subgroups than in the non-pre-sensitized subgroups. The proportion of DM as the primary renal disease was lower in the pre-sensitized subgroups than in the non-pre-sensitized subgroups. A significantly higher proportion of patients undergoing hemodialysis as the dialysis modality prior to KT were selected from the non-pre-sensitized-DGF(+) subgroup, when compared with the non-pre-sensitized-DGF(-) subgroup. Although the majority of

patients received tacrolimus as the main immunosuppressant, more patients in DGF(+) subgroups received sirolimus compared with DGF(-) subgroups.

Comparison of overall biopsy-proven allograft rejection (BPAR) and acute ABMR

The incidence of overall BPAR was the highest in the pre-sensitized-DGF(+) subgroup (33.3%, 7/21). The incidence rate of acute ABMR was higher in the pre-sensitized-DGF(+) subgroup (23.8%, 5/21) than in other 3 subgroups. The incidence of chronic ABMR was higher in pre-sensitized subgroups compared to non-pre-sensitized subgroups. In contrast, acute and chronic T-cell mediated rejection (TCMR) rate showed no statistically significant difference across four subgroups (Table 2).

The Kaplan-Meier curve showed that cumulative overall BPAR rate was highest in the pre-sensitized-DGF(+) subgroup (log rank; p=0.001 vs. non-pre-sensitized-DGF(-), p=0.014 vs. non-pre-sensitized-DGF(+), p=0.009 vs. pre-sensitized-DGF(-)) (Figure 2a). Similarly, cumulative acute ABMR rate was highest in the pre-sensitized-DGF(+) subgroup (log rank; p<0.001 vs. non-pre-sensitized-DGF(-), p=0.001 vs. non-pre-sensitized-DGF(+), p=0.009 vs. pre-sensitized-DGF(-)) (Figure 2b).

Risk factors of overall BPAR and acute ABMR

In the adjusted multivariable regression model, the hazard ratio (HR) of overall BPAR was the highest in pre-sensitized-DGF (+) subgroup compared to the reference of non-pre-sensitized-DGF(-) subgroup (HR 3.253, 95% CI: 1.423-7.434, p=0.005). A significant interaction was found between DGF and pre-sensitization (p=0.006) (Table 3a). Combination of pre-sensitization and DGF was also an independent risk factor for acute ABMR (HR 7.589

vs. non-pre-sensitized-DGF(-) subgroup, 95% CI: 2.644-21.777, p<0.001). Moreover, DGF and pre-sensitization showed statistically significant interaction (p<0.001) (Table 3b).

Comparison of the change in allograft function and death-censored allograft survival

At the end of the 3-year follow-up, allograft function measured by eGFR using chronic kidney disease-epidemiology collaboration (CKD-EPI) equation was the lowest in non-pre-sensitized-DGF(+) subgroup. The change in time-related allograft function of non-pre-sensitized-DGF(+) subgroup was significantly different from that of other subgroups in linear mixed model (Figure 3) (p<0.001 vs. non-pre-sensitized-DGF(-), p<0.001 vs. pre-sensitized-DGF(-), p=0.034 vs. pre-sensitized-DGF(+)).

Totally, 52 cases of allograft failure developed during the follow-up period. The main factor contributing to allograft loss was rejection (17/52, 32.7%), followed by primary graft failure (11/52, 21.2%). In non-pre-sensitized-DGF(-) subgroup, rejection was the main cause of allograft loss (13/33, 39.4%), followed by glomerulonephritis (4/33, 12.1%), primary graft failure (3/33, 9.1%). In non-pre-sensitized-DGF(+) subgroup, the main cause of allograft loss was primary graft failure (6/14, 42.9%), followed by rejection (3/14, 21.4%). In pre-sensitized-DGF(-) subgroup, both rejection and postoperative complications accounted for 33.3%, respectively. In pre-sensitized-DGF(+) subgroup, primary graft failure was the only reason for allograft loss. The Kaplan-Meier curve showed lowest death-censored allograft survival in the non-pre-sensitized-DGF(+) subgroup (log rank; p<0.001 vs. non-pre-sensitized-DGF(-), p=0.013 vs. pre-sensitized-DGF(-)); however, there was no significant difference compared with pre-sensitized-DGF(+) subgroup (log rank p=0.958) (Figure 4).

Comparison of patient survival and post-transplant complications

A total of 57 (4.1%) patients died in our cohort due to cardiovascular disease in 9 cases, infection in 27, malignancy in 4, others (liver disease, cerebral infarction, acute CNI toxicity, gastrointestinal bleeding, and acute rejection etc.) in 12, and unknown etiology in 5 cases. In each subgroup, 37 (3.4%) died in the non-pre-sensitized-DGF(-) subgroup, 16 (12.0%) in the pre-sensitized-DGF(+) subgroup, 4 (3.4%) in the pre-sensitized-DGF(-) subgroup, and none (0.0%) in the pre-sensitized-DGF(+) subgroup. The total death rate was the highest in the non-pre-sensitized-DGF(+) subgroup (p=0.001) (Table 4a).

There was no significant difference in development of BK virus-associated nephropathy (BKVAN), cerebrovascular disease, infectious complications and malignancy across the four subgroups (Table 4b). In regard to cardiovascular disease, the pre-sensitized-DGF(+) subgroup showed a lower incidence compared to non-pre-sensitized-DGF(+) subgroup (p=0.026). Although the overall infection rate did not differ across 4 subgroups (p=0.316), the incidence of *Pneumocystis jirovecii* pneumonia (PJP) infection was the highest in the pre-sensitized-DGF(+) subgroup (1/21, 7.1%, p=0.046).

Discussion

Pre-sensitization to HLA is a well-known pre-transplant factor, which can increase the risk for allograft rejection and allograft failure. Meanwhile, DGF is a well-known post-transplant factor, which also induces adverse allograft outcomes. This study demonstrated that the combination of post-transplant factor (DGF) and pre-transplant risk factor (pre-sensitization) had a synergistic adverse effect on allograft outcomes, especially higher incidence of allograft rejection.

First, we compared baseline characteristics of donors and recipients across 4 clinical subgroups. In terms of donor factors, baseline renal function was significantly lower in patients who showed DGF, which was consistent with previous studies, which reported that low baseline kidney function is a risk factor for DGF [13]. In contrast, there was no significant difference in the frequency of DGF between pre-sensitized and non-pre-sensitized subgroups, which suggests that pre-sensitization may not have a significant effect on the development of DGF. Among recipient factors, the dialysis was significantly prolonged in pre-sensitized subgroups, which suggested that sensitized subjects need longer wait time for DDKT allocation [14-16]. As expected, the proportion of female recipients was higher in both pre-sensitized subgroups [15] and the proportion of recipients with previous KT history was higher and tended to be high in both pre-sensitized subgroups than in non-pre-sensitized subgroups. In addition, although a majority of patients received primary maintenance immunosuppression with tacrolimus, a significantly higher number of patients received sirolimus in the non-pre-sensitized-DGF(+) subgroup. This finding suggested that physicians decided a switch from CNI to mammalian target of rapamycin (mTOR) inhibitor, given that CNI may contribute to delayed recovery of allograft function [17].

Second, we compared the incidence of overall BPAR according to pre-sensitization or the development of DGF. As a result, the incidence of overall BPAR was the highest in the pre-sensitized-DGF(+) subgroup and was mainly attributed to the increase in acute ABMR rather than acute and chronic TCMR as expected. Interestingly, pre-sensitization and DGF showed significant interaction with each other, which suggests their synergistic impact on the

development of acute ABMR. This finding can be explained by two factors. First, DGF per se can increase the immunogenicity of allograft, and thereby increase the vulnerability to immune reaction of pre-formed HLA-DSA. Indeed, IRI in DGF can up-regulate the major histocompatibility complex (MHC) class I and II antigens, and enhance the expression of adhesion and costimulatory molecules of allograft tissue [18-21]. Moreover, the IRI induces ligands of toll-like receptors (TLRs) and activate cells of the innate immune system, inducing activation and maturation of dendritic cells, followed by adaptive immune response [21]. Indeed, the previous studies demonstrated that DGF is associated with an increased risk of allograft loss and acute rejection [22,23]. Second, the conversion of CNI to mTOR inhibitor was more frequently detected in patients who suffered from DGF in this study, perhaps because CNI might be considered as a contributor to DGF. Lower suppressive potency of mTOR inhibitor for humoral immunity in comparison with tacrolimus is another possible cause of higher rate of acute ABMR in pre-sensitized-DGF(+) subgroup [24].

Surprisingly, pre-sensitization or DGF per se had no significant effect on the development of overall BPAR. The reason is unclear, but it may be attributed to the limited definition of both pre-sensitization and DGF in the study using a nationwide cohort. In case of pre-sensitization, since data of DSA were collected from 2017, the results of HLA-DSA were not available in some recipients. Therefore, in such recipients, we defined sensitization to HLA by the presence of panel reactive antibodies (PRA), together with positive crossmatch test results. Even though this definition is used for “pre-sensitization”, we cannot assess the degree of sensitization clearly. In case of DGF, the definition of DGF is varies among previous studies [25]. Indeed, the definition of DGF merely depends on the performance of

dialysis after KT, and the decision whether or not to perform dialysis can differ according to the transplant centers. In addition, due to the absence of detail data, individualized immunosuppression regimen according to immunologic risk stratification and the serum level of immunosuppressant in each recipient did not be considered in our analysis. Therefore, the aforementioned factors can induce bias that can affect the result of this study.

Interestingly, non-pre-sensitized-DGF(+) group showed worst allograft function at 36 months post-transplant follow-up and worst allograft survival. One of the possible reasons is the baseline status of the corresponding donor kidney (Suppl. Table 1). The donor of this group showed the least renal function at baseline and a relatively higher kidney donor profile index (KDPI) score. In addition, in 5 out of 14 patients with allograft loss in this group, primary non-function was the reason for allograft failure. All of the foregoing findings suggest that the baseline status of donor kidney was the worst in this group, which may result in a higher rate of allograft loss and also sustained low allograft function. In regard to allograft survival, the impact of the baseline kidney function can be more significant than allograft rejection during the limited follow-up duration. Hence, the allograft survival was not the lowest in the pre-sensitized-DGF(+) subgroup in spite of the highest rate of BPAR.

Lastly, we compared the post-transplant complications among the 4 subgroups. Non-pre-sensitized-DGF(+) subgroup showed the higher patient death rate. However, only 57 cases out of 1,370 kidney transplantation recipients (KTRs) were found and there was no patient death in the pre-sensitized-DGF(+) subgroup. Therefore, longer observations may be required to arrive at any conclusion. Compared with the post-transplant infection, no difference was

detected across 4 subgroups in most infection types, except that the rate of PJP infection was the highest in the pre-sensitized-DGF(+) subgroup. However, there was only 1 case of PJP infection, hence further investigation may be required to clarify this issue as well [26].

This study has some limitations. First, this nationwide registry analysis reflects similar limitations found in similar large registry analyses as shown in our previous studies [27]. 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 was not available for analysis in some patients, and we cannot use the class and the strength of DSA in the analysis, which has been reported as an important risk factor for allograft rejection and failure [6,10,28-30]. Second, the follow-up duration of this registry is limited as mentioned previously. Therefore, traditional risk factors for allograft failure such as DGF and pre-sensitization did not significantly affect allograft outcome. Third, we could not determine the specified protocols at each center in DDKT for highly sensitized recipients. Despite pre-transplant desensitization was performed in 37 recipients, including those whom with positive B-cell crossmatch, no data were available on the protocol. Some centers used rituximab to treat such patients, and others did not, but unfortunately, it was not considered in this analysis. Nevertheless, our study is the first prospective, multi-centered cohort study to investigate the association of DGF and pre-sensitization in allograft outcomes.

In conclusion, we have shown that combination of DGF and pre-sensitization to HLA had a detrimental impact on allograft outcome in terms of rejection. Therefore, we suggest that more careful monitoring or surveillance of allograft rejection is required. Further, we need to

use more intensified immunosuppression protocol to prevent allograft rejection when DGF occurred in DDKT with pre-sensitization.

Methods

Study population

We analysed KOTRY data from the Korean Society for Transplantation [31], compiling data from 30 kidney transplantation centers in Korea [32]. The KOTRY data includes 1,945 DDKT cases between May 2014 and June 2019, from which we excluded 575 DDKT recipients with unavailable data regarding PRA, HLA-DSA, crossmatch tests or DGF development. Therefore, we included 1,370 DDKT recipients in the present investigation and classified the patients into four subgroups according to the pre-sensitization and the development of DGF post-transplant: non-pre-sensitized-DGF(-) (n=1100), non-pre-sensitized-DGF(+) (n=133), pre-sensitized-DGF(-) (n=116), pre-sensitized-DGF(+) (n=21) (Figure 1). The median follow-up period of this study was 38.0 (interquartile range: 25.0-50.8) months.

We defined pre-sensitization to HLA by the presence of (i) HLA-DSA (by Luminex single antigen assay) or (ii) PRA (by solid-phase HLA antibody screening), combined with positive crossmatch test results. HLA-DSA data were available in 1,060 recipients (77.3%). Therefore, the sensitization to HLA was defined by the detection of HLA-DSA in those patients. In another 310 DDKT recipients for whom HLA-DSA data were not available, we defined sensitization to HLA based on the positive results of PRA and crossmatch test. Among 310 DDKT recipients, 5 recipients were sensitization to HLA with the presence of PRA and positive B-cell crossmatch. DGF was defined as the need for dialysis within 1 week of

transplantation. The medical records were reviwed after receiving informed consent[32]. This study was performed in accordance with the Declaration of Helsinki and the Declaration of Istanbul. The study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (KC14ONMI0460).

Definition of clinical outcomes

The clinical outcomes investigated in this study included the incidence of overall BPAR, acute ABMR, time-related changes in allograft function measured as eGFR, death-censored allograft survival rates, and post-transplant complications such as BKVAN, cardiovascular disease, cerebrovascular disease, infection and malignancy. BPAR was diagnosed according to the Banff 2013 classification [33]. Rejection-free allograft survival was defined as the time elapsed from transplantation to the first episode of BPAR. Serum creatinine levels were collected at six months and later at one-year intervals post-transplant. The eGFR for each concordant time was assessed using the CKD-EPI equation [34]. Allograft survival was defined as the time from transplantation to initiation with alternative renal replacement therapy. Cardiovascular disease is defined as cardiovascular death, myocardial infarction, ischemic heart disease with relevant clinical evidence (accompanied by therapeutic intervention or objective findings), new-onset congestive heart failure requiring hospitalization, and arrhythmia. Cerebrovascular disease included non-traumatic hemorrhagic or ischemic brain disease confirmed by computed tomography or magnetic resonance imaging [32]. BKVAN was diagnosed by allograft biopsy. All clinical parameters were compared across the four patient subgroups.

Statistical method

All continuous variables were expressed as mean ± standard deviation. If the variables followed the normal distribution, an analysis of variance (ANOVA) was performed. If the variables showed non-normal distribution, a Kruskal-Wallis test was performed. Tukey's method or Mann-Whitney test was performed as a post-hoc analysis. All categorical variables were compared using the chi-square test or Fisher's exact test and expressed as proportions. Withdrawal-censored allograft rejection rate and death-censored allograft survival rate were evaluated by using the Kaplan-Meier survival analysis and were compared using the log-rank test. The effects of DGF and pre-sensitization, and the interaction between DGF and pre-sensitization on overall BPAR or acute ABMR were analyzed via Cox proportional-hazards regression analysis. Baseline clinical and laboratory parameters showing significant differences (p value <0.1) in univariable analysis or known to affect allograft rejection were fitted into the multivariable model. We selected donor factors (age, cold ischemic time, KDPI) and recipient factors (BMI, mismatch number, prior KT history, PRA>50%) as confounders. Time-related allograft function between subgroups were compared using a linear mixed model. All missing data were censored from the last follow-up date. P values < 0.05 were statistically significant. All statistical analyses were performed using the SPSS® software, version 24 (IBM Corporation, Armonk, NY, USA) and Microsoft Excel 2016.

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Authors contributions

HL: participated in designing study, analyzing and interpreting the data, and writing the paper. YP: participated in analyzing the data, and writing the paper. THB: participated in collecting data. SHS: participated in collecting data. SHS: participated in collecting data. JY: participated in collecting data. CA: participated in collecting data. CWY: participated in collecting data. BHC: participated in designing study, analyzing and interpreting the data, and revising the paper. KOTRY study group: participated in collecting data.

Additional Information

Data availability

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

Competing interests

The authors declare no competing interests.

Consortia

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Figure legends

Figure 1

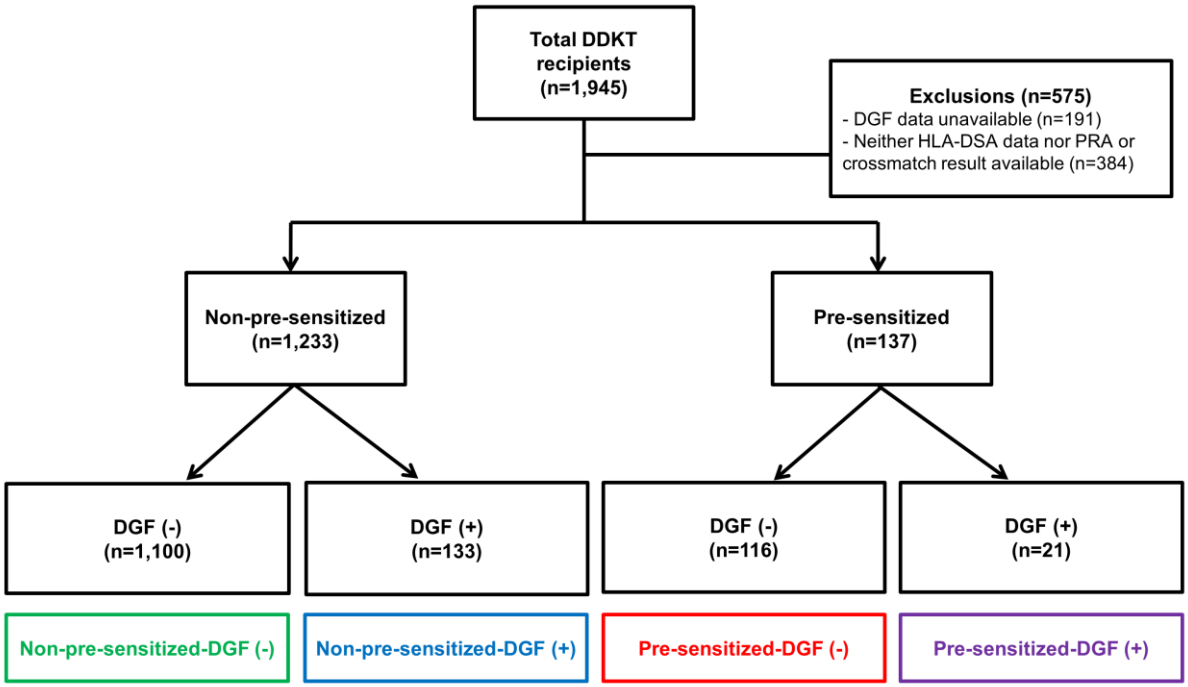


Figure 1. Distribution of the patient population according to DGF or pre-sensitization to HLA. DGF, delayed graft function; HLA, human leukocyte antigen; DDKT, deceased donor kidney transplantation; DSA, donor-specific antibody.

Figure 2

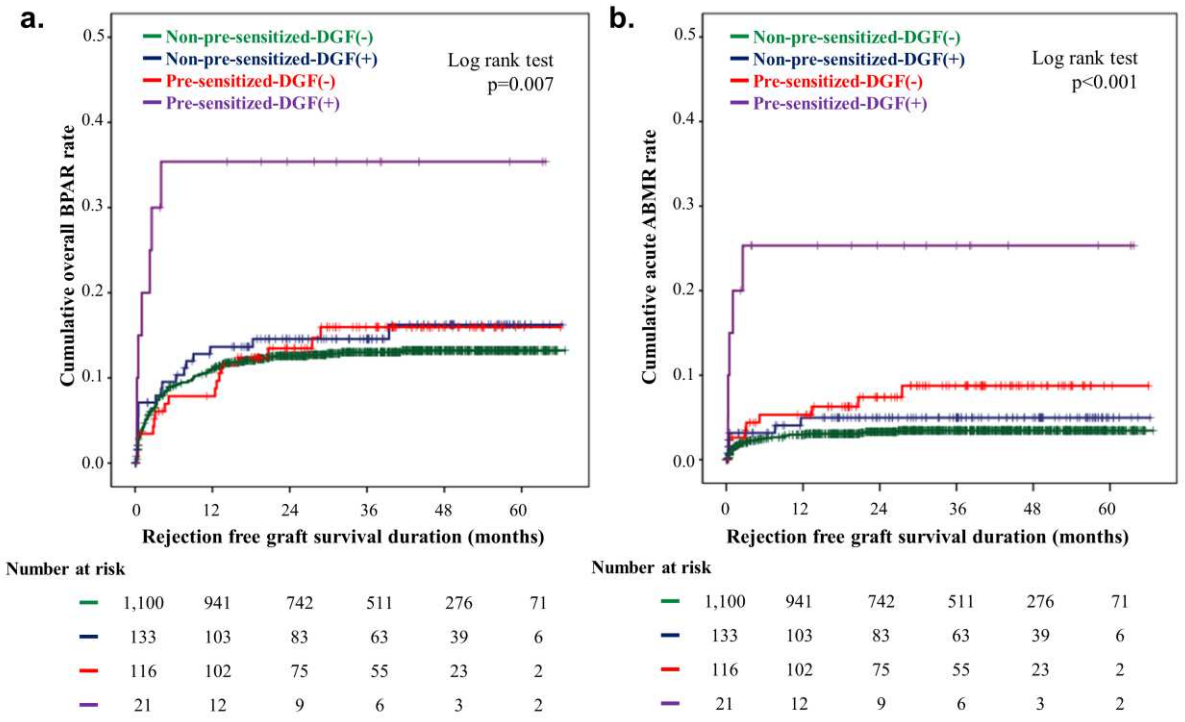


Figure 2. Kaplan-Meier estimates of withdrawal-censored cumulative (a) overall BPAR rate and (b) acute ABMR rate according to DGF and pre-sensitization status. The numbers below the figures denote the number of KTRs at risk in each subgroup. Note that both overall BPAR and acute ABMR rate increased in pre-sensitized-DGF(+) subgroup. DGF, delayed graft function; KTR, kidney transplantation recipient, BPAR, biopsy-proven allograft rejection, ABMR antibody-mediated rejection.

Figure 3

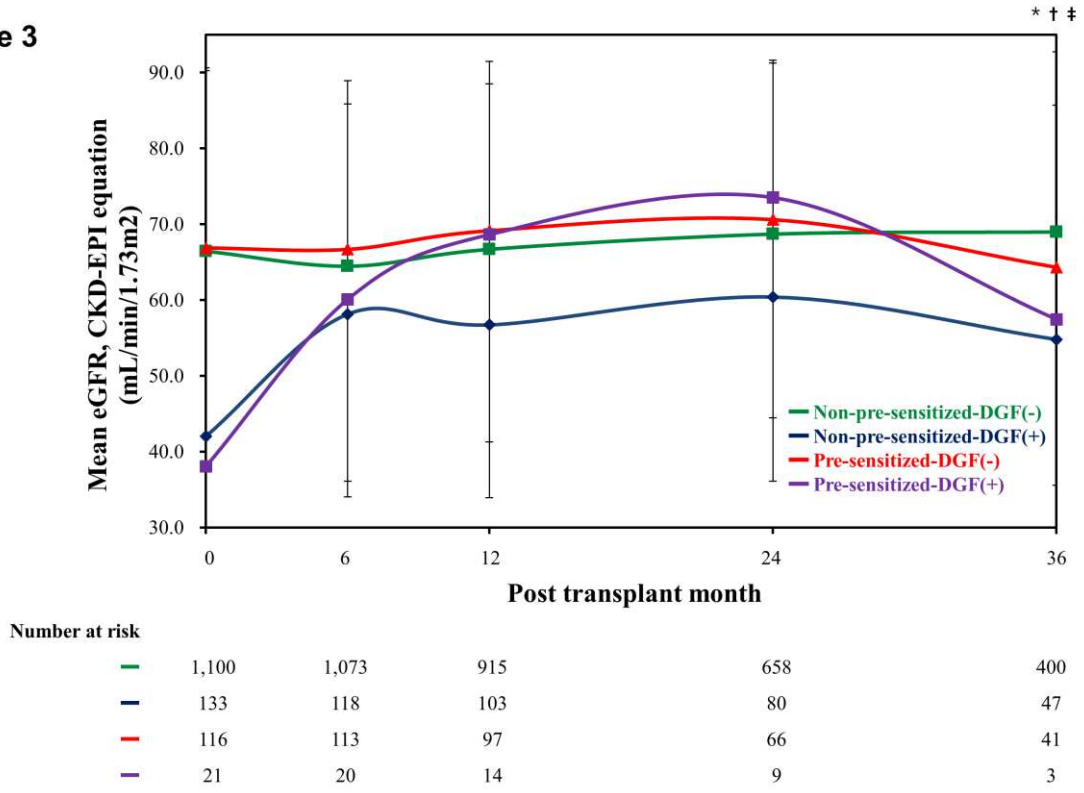


Figure 3. Comparison of the time-related changes in allograft function based on eGFR using CKD-EPI equation (mL/min/1.73m^2) according to DGF and pre-sensitization status. During 36 months, the non-pre-sensitized-DGF(+) subgroup showed the lowest allograft function compared with other subgroups. eGFR, estimated glomerular filtration rate; CKD-EPI, chronic kidney disease-epidemiology collaboration; DGF, delayed graft function.

* p<0.001 non-pre-sensitized-DGF(-) vs. non-pre-sensitized-DGF(+), † p<0.001 non-pre-sensitized-DGF(+) vs. pre-sensitized-DGF(-), ‡ p=0.034 non-pre-sensitized-DGF(-) vs. pre-sensitized-DGF(+).

Figure 4

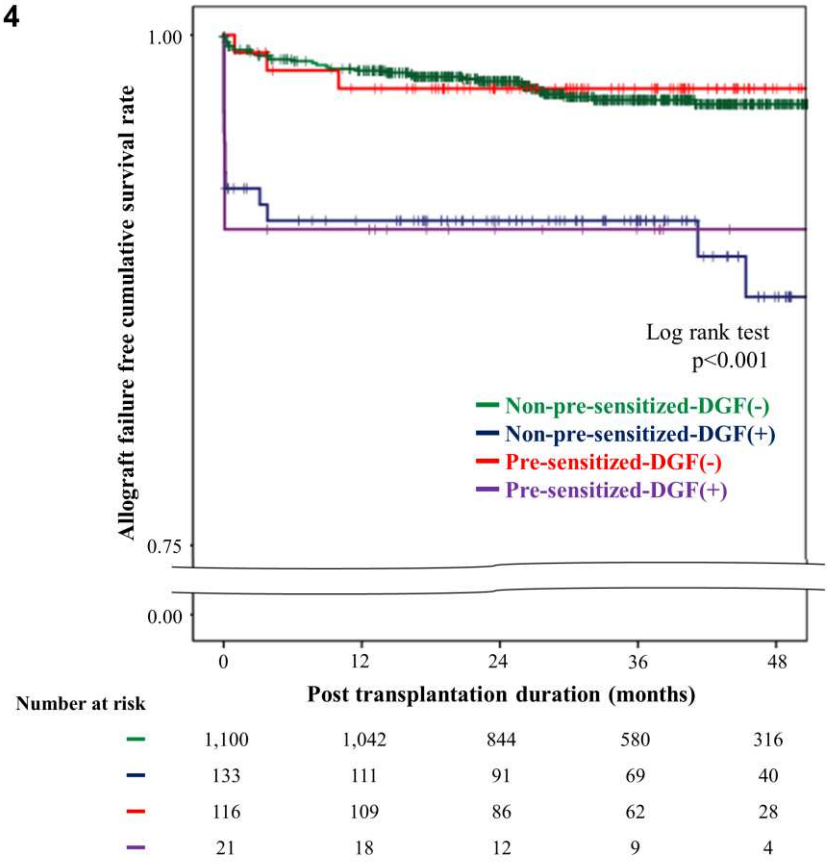


Figure 4. Kaplan-Meier estimates of death-censored allograft survival according to DGF and pre-sensitization status. The numbers below the figures denote the number of KTRs at risk in each subgroup. Note that the mortality rates were reduced in non-pre-sensitized-DGF(+) subgroup. DGF, delayed graft function; KTR, kidney transplantation recipient.

Table 1. Comparison of clinical and laboratory parameters among the 4 subgroups according to DGF and pre-sensitization status.

	Non-pre-sensitized (n = 1,233)		Pre-sensitized (n = 137)		*p*-value
	DGF (-) (n = 1,100)	DGF (+) (n = 133)	DGF (-) (n = 116)	DGF (+) (n = 21)	
Donors					
Age (years)	47.6 ± 14.9	48.3 ± 14.9	49.2 ± 13.6	47.0 ± 12.9	0.672
Male (n, %)	773 (70.3%)	95 (71.4%)	83 (71.6%)	12 (57.1%)	0.591
BMI (kg/m^2)	23.2 ± 3.7	23.5 ± 3.9	22.9 ± 3.6	23.0 ± 4.8	0.650
HTN (n, %)	261 (23.7%)	37 (27.8%)	21 (18.1%)	3 (14.3%)	0.194
DM (n, %)	120 (11.5%)	13 (9.9%)	12 (10.8%)	1 (5.0%)	0.772
DBD (n, %)	1059 (96.3%)	129 (97.0%)	112 (96.6%)	20 (95.2%)	0.967
DCD (n, %)	41 (3.7%)	4 (3.0%)	4 3.4%)	1 (4.8%)	0.967
eGFR (CKD-EPI) ($ml/min/1.73m^2$)	77.4 (43.2-107.1)	34.6 (21.2-64.5)[*]	72.2 (45.9-103.8) [†]	47.8 (27.2-98.8)	<0.001
Cold ischemic time (min)	290.1 ± 137.9	323.4 ± 136.5	284.4 ± 124.7	322.9 ± 142.2	0.083
KDPI (%)	66.0 (44.0-84.0)	71.0 (49.5-88.0)	64.0 (51.0-81.0)	67.0 (49.5-82.5)	0.262
Recipients					
Age (years)	51.3 ± 10.6	52.8 ± 11.1	51.1 ± 9.8	48.9 ± 12.3	0.283
Male (n, %)	680 (61.8%)	81 (60.9%)	38 (32.8%)[*, †]	9 (42.9%)	<0.001

BMI (kg/m^2)	23.0 ± 3.3	22.9 ± 3.3	22.0 ± 2.9*	22.8 ± 3.0	0.022
HTN (n, %)	989 (90.1%)	121 (91.0%)	97 (84.3%)	21 (100.0%)	0.093
DM (n, %)	314 (28.5%)	39 (29.3%)	17 (14.7%)*, †	4 (19.0%)	0.011
Dialysis modality (n, %)					
Hemodialysis	859 (78.1%)	117 (88.0%)*	97 (83.6%)	20 (95.2%)	0.009
Peritoneal dialysis	241 (21.9%)	16 (12.0%)*	19 (16.4%)	1 (4.8%)	0.009
Dialysis duration (months)	84.5 (53.6-113.4)	90.4 (50.3-113.9)	103.7 (68.5-136.0)* †	130.5 (108.9-161.2)*, †	<0.001
Previous KT history (n, %)	93 (8.5%)	15 (11.3%)	31 (36.7%)*†	4 (19.0%)	<0.001
Mismatch number (n)	3.4 ± 1.8	3.6 ± 1.6	3.8 ± 1.3*	3.6 ± 1.6	0.022
Induction therapy (n, %)					
ATG	311 (28.3%)	59 (44.4%)*	69 (59.5%)*, †	13 (61.9%)*	<0.001
Basiliximab	804 (73.2%)	88 (66.2%)	59 (50.9%)*, †	15 (71.4%)	<0.001
Main immunosuppressant (n, %)					
Tacrolimus	1077 (97.9%)	130 (97.7%)	115 (99.1%)	19 (90.5%)	0.091
Cyclosporin	17 (1.5%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	0.127
Sirolimus	8 (0.7%)	4 (3.0%)*	1 (0.9%)	1 (4.8%)	0.029
PRA > 50%	327 (29.7%)	40 (30.1%)	95 (81.9%)*, †	16 (76.2%)*, †	<0.001

Continuous variables are shown as mean ± standard deviation or median with interquartile range. Categorical variables are shown as number (proportions). DGF, delayed graft function; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; DBD, donor after brain death; DCD, donor after cardiac death; eGFR, estimated glomerular filtration; CKD-EPI, chronic kidney disease-epidemiology collaboration; KDPI, kidney donor profile index; KT, kidney transplantation; ATG, anti-thymocyte globulin; PRA, panel reactive antibody; DSA, donor-specific antibody.

* $p<0.05$ compared with non-pre-sensitized-DGF(-) subgroup, † $p<0.05$ compared with non-pre-sensitized- DGF(+) subgroup

Table 2. Comparison of rejection-related outcomes among the 4 subgroups according to DGF and pre-sensitization status.

	Non-pre-sensitized (n = 1,233)		Pre-sensitized (n = 137)		*p*-value
	DGF (-) (n = 1,100)	DGF (+) (n = 133)	DGF (-) (n = 116)	DGF (+) (n = 21)	
Overall BPAR (n, %)	139 (12.6%)	19 (14.3%)	17 (14.7%)	7 (33.3%)*	0.045
Acute ABMR (n, %)	35 (3.2%)	6 (4.5%)	9 (7.8%)*	5 (23.8%)*, †, ‡	<0.001
Acute TCMR (n, %)	107 (9.7%)	11 (8.3%)	9 (7.8%)	4 (19.0%)	0.405
Chronic active ABMR (n, %)	3 (0.3%)	2 (1.5%)	4 (4.3%)*	1 (4.8%)	<0.001
Chronic active TCMR (n, %)	10 (0.9%)	3 (2.3%)	1 (0.9%)	1 (4.8%)	0.198
Repeated acute rejection within 1 year (n, %)	41 (3.7%)	5 (3.8%)	5 (4.3%)	3 (14.3%)	0.106

Categorical variables are shown as number (proportions). DGF, delayed graft function; BPAR, biopsy-proven allograft rejection; ABMR, antibody-mediated rejection, TCMR, T-cell mediated rejection.

* $p<0.05$ compared with non-pre-sensitized-DGF(-) subgroup, † $p<0.05$ compared with non-pre-sensitized-DGF(+) subgroup, ‡ $p<0.05$ compared with pre-sensitized-DGF(-) subgroup.

Table 3. Multivariable Cox regression for independent predictors of (a) overall BPAR and (b) acute ABMR.

(a)	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	*p*-value for interaction
Donor age	1.014 (1.003-1.024)	0.012			
Cold ischemic time	0.998 (0.997-1.000)	0.016	0.998 (0.997-1.000)	0.035	
KDPI	1.006 (1.000-1.012)	0.049			
Recipient BMI	1.055 (1.012-1.099)	0.011			
Prior KT history	1.197 (0.766-1.869)	0.429			
Mismatch number	1.131 (1.036-1.235)	0.006	1.094 (0.984-1.217)	0.097	
PRA>50%	1.074 (0.793-1.455)	0.644			
Pre-sensitization & DGF					0.006
Non-pre-sensitized/DGF (-)	Reference		Reference		
Non-pre-sensitized/DGF (+)	1.210 (0.749-1.954)	0.437	1.309 (0.747-2.294)	0.347	
Pre-sensitized/DGF (-)	1.150 (0.695-1.902)	0.587	1.057 (0.604-1.848)	0.847	
Pre-sensitized/DGF (+)	3.489 (1.633-7.456)	0.001	3.253 (1.423-7.434)	0.005	

(b)	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	*p*-value for interaction
Donor age	0.998 (0.980-1.016)	0.835			
Cold ischemic time	0.999 (0.997-1.002)	0.601			
KDPI	0.997 (0.987-1.008)	0.588			
Recipient BMI	1.002 (0.924-1.087)	0.959			
Prior KT history	2.176 (1.124-4.213)	0.021	2.493 (1.201-5.177)	0.014	
Mismatch number	1.020 (0.875-1.188)	0.803			
PRA>50%	1.862 (1.097-3.159)	0.021			
Pre-sensitization & DGF					<0.001
Non-pre-sensitized/DGF (-)	Reference		Reference		

Non-pre-sensitized/DGF (+)	1.518 (0.638-3.608)	0.345	1.712 (0.657-4.459)	0.271
Pre-sensitized/DGF (-)	2.423 (1.165-5.041)	0.018	1.974 (0.872-4.470)	0.103
Pre-sensitized/DGF (+)	9.525 (3.730-24.326)	<0.001	7.589 (2.644-21.777)	<0.001

1,027 recipients were included in multivariable Cox regression model. Multivariable regression model was adjusted with parameters showing significant differences in baseline characteristics or known to affect allograft rejection. Parameters were as follows: donor factors (age, cold ischemic time, KDPI), Recipient factors (BMI, prior KT history, mismatch number, PRA>50%).

HR, hazard ratio; BPAR, biopsy-proven allograft rejection; ABMR, antibody-mediated rejection; DGF, delayed graft function; CI, confidence interval; BMI, body mass index; KDPI, kidney donor profile index; KT, kidney transplantation; PRA, panel reactive antibody.

Table 4. (a) Causes of death and (b) clinical outcomes among the 4 subgroups according to DGF and pre-sensitization status.

(a)	Non-pre-sensitized (n = 1,233)		Pre-sensitized (n = 137)		*p*-value
	DGF (-) (n = 1,100)	DGF (+) (n = 133)	DGF (-) (n = 116)	DGF (+) (n = 21)	
Total (n, %)	37 (3.4%)	16 (12.0%)	4 (3.4%)	0 (0.0%)	0.001
Cardiovascular disease (n, %)	7 (18.9%)	1 (6.4%)	1 (25.0%)	0 (0.0%)	
Infection (n, %)	20 (54.1%)	5 (31.3%)	2 (50.0%)	0 (0.0%)	
Malignancy (n, %)	1 (2.7%)	2 (12.5%)	1 (25.0%)	0 (0.0%)	
Others (n, %)	8 (21.6%)	4 (25.0%)	0 (0.0%)	0 (0.0%)	
Unknown (n, %)	1 (2.7%)	4 (25.0%)	0 (0.0%)	0 (0.0%)	

(b)	Non-pre-sensitized (n = 1,233)		Pre-sensitized (n = 137)		*p*-value
	DGF (-) (n = 1,100)	DGF (+) (n = 133)	DGF (-) (n = 116)	DGF (+) (n = 21)	
BKVAN (n, %)	32 (2.9%)	4 (3.0%)	5 (4.3%)	0 (0.0%)	0.713
Cardiovascular disease (n, %)	142 (12.9%)	25 (18.8%)	14 (12.1%)	0 (0.0%)†	0.071
Cerebrovascular disease (n, %)	10 (0.9%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0.737
Infection					
Overall (n, %)	277 (33.1%)	37 (37.4%)	37 (42.0%)	4 (28.6%)	0.316
CMV infection (n, %)	51 (6.1%)	4 (4.0%)	1 (1.1%)	0 (0.0%)	0.167
PJP infection (n, %)	5 (0.6%)	1 (1.0%)	1 (1.1%)	1 (7.1%)*	0.046
Malignancy (n, %)	77 (7.0%)	11 (8.3%)	9 (7.8%)	2 (9.5%)	0.916

Continuous variables are shown as mean ± standard deviation or median with interquartile range. Categorical variables are shown as number (proportions). DGF, delayed graft function; CNI, calcineurin inhibitor; BKVAN, BK virus associated nephropathy; CMV, cytomegalovirus; PJP, *Pneumocystis jirovecii* pneumonia.

Others: liver disease, cerebral infarction, acute CNI toxicity, gastrointestinal bleeding, intestinal obstruction, acute rejection etc.

* $p<0.05$ compared with non-pre-sensitized-DGF(-) subgroup, † $p<0.05$ compared with non-pre-sensitized-DGF(+) subgroup.

Figures

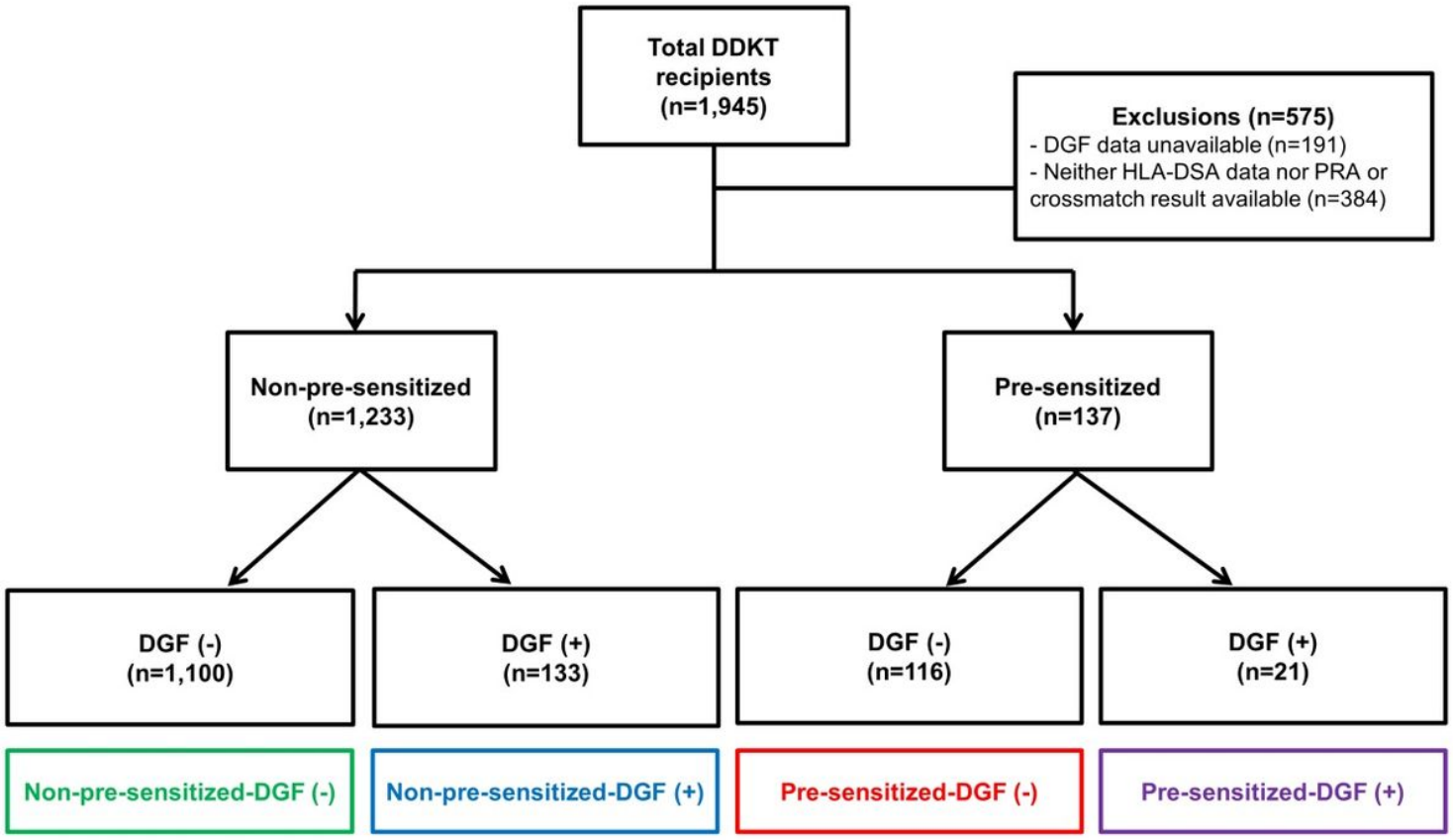


Figure 1

Distribution of the patient population according to DGF or pre sensitization to HLA. DGF, delayed graft function; HLA, human leukocyte antigen; DDKT, deceased donor kidney transplantation; DSA, donor specific antibody.

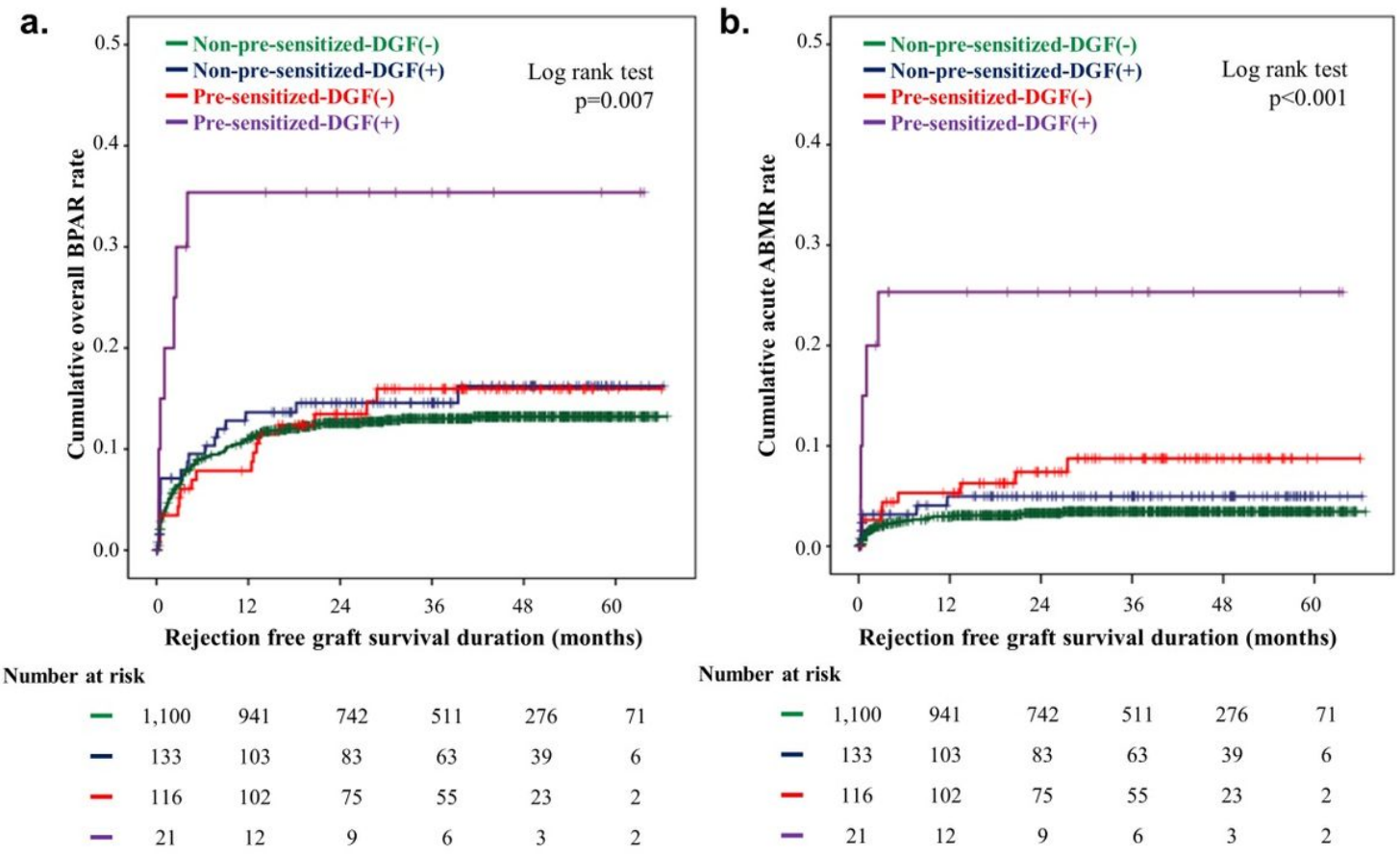
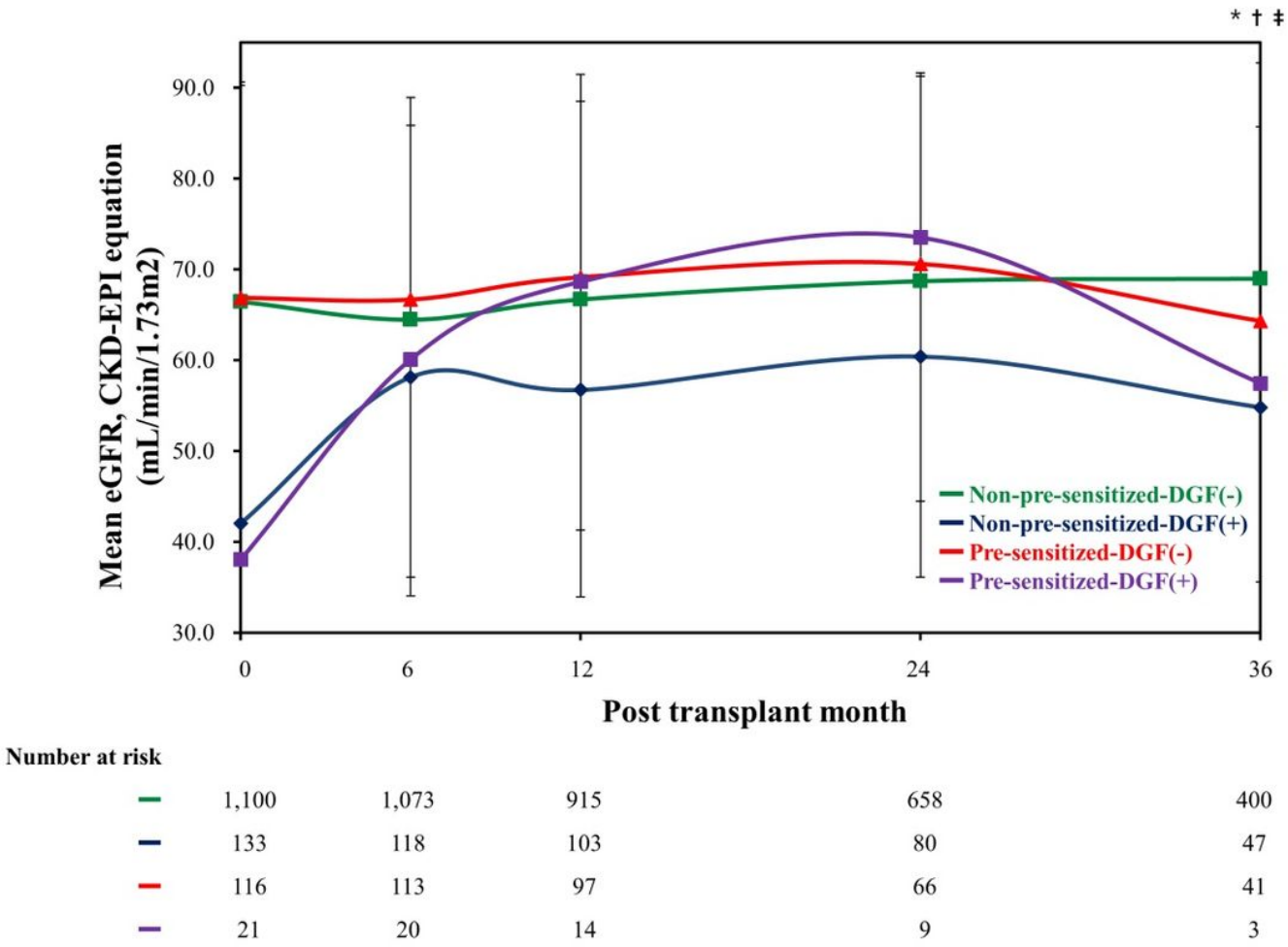


Figure 2

Kaplan Meier estimates of withdrawal censored cumulative (a) overall BPAR rate and (b) acute ABMR rate according to DGF and pre sensitization status. The numbers below the figures denote the number of KTRs at risk in each subgroup. Note that both overall BPA R and acute ABMR rate increased in pre sensitized DGF(+) subgroup. DGF, delayed graft function; KTR, kidney transplantation recipient, BPAR, biopsy proven allograft rejection, ABMR antibody mediated rejection.



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Comparison of the time-related changes in allograft function based on eGFR using CKD-EPI equation (mL/min/1.73m2) according to DGF and pre-sensitization status. During 36 months, the non-pre-sensitized-DGF(+) subgroup showed the lowest allograft function compared with other subgroups. eGFR, estimated glomerular filtration rate; CKD-EPI, chronic kidney disease-epidemiology collaboration; DGF, delayed graft function. * $p<0.001$ non-pre-sensitized-DGF(-) vs. non-pre-sensitized-DGF(+), † $p<0.001$ non-pre-sensitized-DGF(+) vs. pre-sensitized-DGF(-), ‡ $p=0.034$ non-pre-sensitized-DGF(-) vs. pre-sensitized-DGF(+).

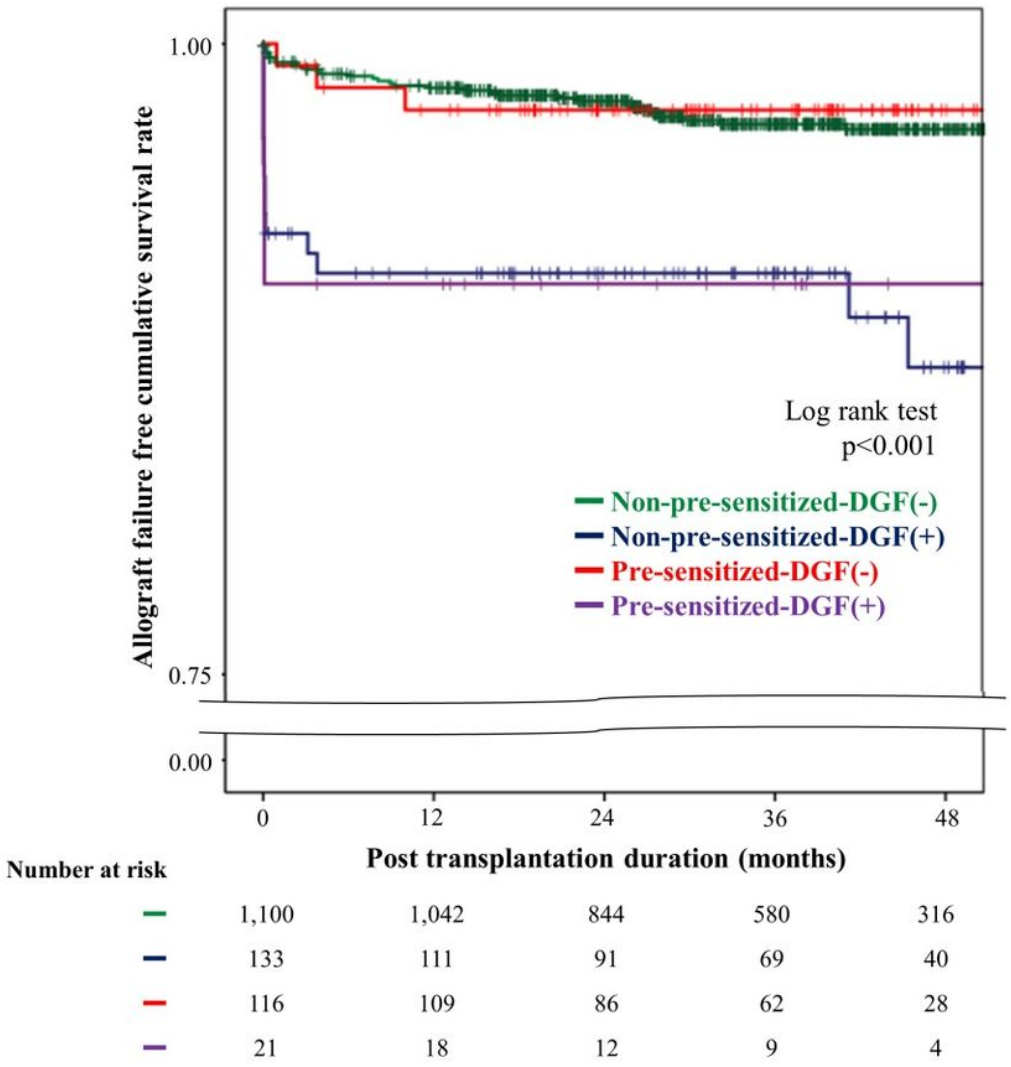

Figure 4

Kaplan Meier estimates of death censored allograft survival according to DGF and pre sensitization status. The numbers below the figures denote the number of KTRs at risk in ea ch subgroup. Note that the mortality rates were reduced in non pre sensitized DGF(+) subgroup . DGF, delayed graft function; KTR, kidney transplantation

Supplementary Files

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- LeeetalDGFandpresensitizationKOTRYSciRsuppl.doc