Pretransplant Calculated Panel Reactive Antibody in the Absence of Donor-Specific Antibody and Kidney Allograft Survival

James H. Lan,1,2,3 Matthew Kadatz,1,3 Doris T. Chang,4 Jagbir Gill,3,4,5,6 Howard M. Gebel,7 and John S. Gill3,4,8

Abstract

Background and objectives Panel reactive antibody informs the likelihood of finding an HLA-compatible donor for transplant candidates, but has historically been associated with acute rejection and allograft survival because testing methods could not exclude the presence of concomitant donor-specific antibodies. Despite new methods to exclude donor-specific antibodies, panel reactive antibody continues to be used to determine the choice of induction and maintenance immunosuppression. The study objective was to determine the clinical relevance of panel reactive antibody in the absence of donor-specific antibodies.

Design, setting, participants, & measurements Retrospective observational study of kidney allograft survival among 4058 zero HLA-A, B, DR, and DQB1-mismatched transplant recipients without antibodies to donor kidney antigens encoded by these HLA gene loci.

Results Among 4058 first and repeat transplant recipients, patients with calculated panel reactive antibody (cPRA) 1%–97% were not at higher risk of transplant failure, compared with patients with cPRA of 0% (death censored graft loss: hazard ratio, 1.07; 95% confidence interval, 0.82 to 1.41). Patients with cPRA ≥98% had a higher risk of graft loss from any cause including death (hazard ratio, 1.39; 95% confidence interval, 1.08 to 1.79) and death censored allograft failure (hazard ratio, 1.78; 95% confidence interval, 1.27 to 2.49). In stratified analyses, the higher risk of graft loss among patients with cPRA ≥98% was only observed among repeat, but not first, transplant recipients. In subgroup analysis, there was no association between cPRA and graft loss among living related transplant recipients.

Conclusions Calculated panel reactive antibody is poorly associated with post-transplant immune reactivity to the allograft in the absence of donor-specific antibody.

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Introduction

Immune risk stratification is essential to guide the choice of induction and maintenance of immunosuppression in kidney transplant recipients (1). Younger recipient age, previous transplant history, Black recipient ancestry, and the degree of HLA matching between donor and recipient are typical clinical indicators of immune risk. Additionally, panel reactive antibody (PRA) assessment is often used when considering immune risk stratification. In their landmark study, Patel and Terasaki (2) reported a high likelihood of hyperacute rejection when pretransplant crossmatches between recipient sera and donor lymphocytes were positive. Over time, this simple surrogate test was modified and used to estimate the likelihood of finding a compatible donor for a given transplant candidate by performing crossmatches using the patient’s serum against a panel of lymphocytes from blood donors that are representative of the local donor pool. The PRA was calculated as the percentage of donors to which a patient had reactive antibodies. The likelihood of compatibility with a random donor was simply (100 minus the percent of PRA). Eventually, the same PRA test was co-opted to guide decision making for induction and maintenance immunosuppression. Studies showing that higher levels of PRA correlated with rejection and the long-term risk of graft loss supported the notion that high PRA levels were a general indicator of immune risk (3–7). Accordingly, immunosuppressive protocols on the basis of pretransplant PRA were widely implemented in clinical trials and practice (8–10).

Despite the simplicity of the PRA test, it was recognized that this cell-based test was nonspecific and relatively insensitive (11). Positive crossmatches were not always due to clinically relevant anti-HLA antibodies, and negative crossmatches did not necessarily associate with long-term transplant survival. With the introduction of single-antigen bead testing in the early 2000s, laboratories acquired the ability to detect and characterize anti-HLA antibodies with...
exquisite sensitivity and specificity. In turn, single-antigen bead testing enabled transplant centers to define the precise HLA antibodies their patients possessed (12). This fundamental shift of antibody testing led to the replacement of PRA with a calculated value (calculated PRA, cPRA) by the United Network for Organ Sharing in October 2009 (13). Unlike PRA, which measures the breadth of recipient sensitization without considering donor specificity, entering cPRA values into the allocation system requires accurate determination and listing of antigens deemed as unacceptable, meaning a transplant candidate will not be allocated organs from donors who possess any of those antigens.

In 2006, Bray et al. (14) reported that PRA levels were not associated with allograft survival as long as donor-specific antibodies (DSAs) were not present. These observations were extended in a study showing that cPRA values were not associated with development of antibody-mediated rejection or graft loss in the absence of DSA (15). Interestingly, PRA determined by single-antigen bead testing was not associated with antibody-mediated rejection, although there was a trend toward higher cellular rejection in patients with PRA > 0 (16). Furthermore, a retrospective single-center study from Europe reported an association between PRA determined by solid phase assay and allograft survival in the absence of pretransplant DSA (17). Therefore, whether cPRA can be used as a surrogate for immune risk remains uncertain.

Despite this uncertainty, cPRA continues to be a key factor when deciding the choice of immunosuppression. For example, the use of nondepleting antibody induction and less intensive maintenance immunosuppressant drug regimens (i.e., steroid-sparing regimens) are typically reserved for patients with low to moderate PRA/cPRA levels, whereas patients with higher levels of sensitization receive depleting antibody induction and more intense maintenance immunosuppression (15,17–19). Studies to improve the understanding of the relevance of cPRA in the absence of DSA are therefore needed (20). The purpose of this analysis was to determine the association of cPRA with transplant outcomes among patients who were matched with their donors at the HLA-A, B, DR, and DQB1 gene loci and therefore cannot have antibodies specific to these donor antigens.

Materials and Methods

This study was approved by the local research ethics board and adheres to the principles of the Declaration of Helsinki. The clinical and research activities reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Data Sources

The standard analysis files of the United States Renal Data System were utilized for this analysis (21). These transplant files are on the basis of data from the Organ Procurement and Transplant Network.

Study Population

The study included adult patients ≥18 years of age who underwent a living or deceased donor kidney—only transplant between January 1, 2010 and October 1, 2014 with follow-up through October 1, 2017. The transplant dates were restricted to ensure all patients and donors had recorded typing for human leukocyte antigens at the A, B, DR, and DQB1 loci; a cPRA value (implemented in October 2009); and at least 3 years of post-transplant follow-up. The study cohort was limited to patients with recorded pretransplant cPRA and complete donor and recipient typing at the HLA-A, B, DRB1, and DQB1 gene loci. Only donor and recipient pairs who were HLA-A, B, DR, and DQB1 zero-antigen mismatched were included (n=4058); 3163 pairs were excluded when the HLA-DQB1 typing of the donor and/or recipient was broad (i.e., DQ1 instead of DQ5 or DQ6; DQ3 instead of DQ7, 8, or 9) and matching could not be ascertained.

Study Outcomes

The study outcome measures included graft loss from any cause including death, graft loss censored for patient death, and death with a functioning graft. In addition, we determined acute rejection rates during the first post-transplant year. Because acute rejection events are not validated, rejection events were not included after the first post-transplant year.

Analytical Methods

Patients were grouped by their peak pretransplant cPRA into the categories: 0%, 1%–29%, 30%–79%, 80%–97%, and 98%–100%. Characteristics of study patients were described using the median and quartiles for continuous variables, or frequencies and proportions for categorical variables. Group differences were compared using the chi-squared test or ANOVA as appropriate.

Association of cPRA with Study Outcomes

The time to graft failure from any cause including death, graft failure censored for patient death, and death with a functioning graft were determined by cPRA group using the Kaplan-Meier method, and group differences were compared with the log-rank test. Because the US cPRA calculator did not capture antibodies to HLA-DP, DQA, and Cw antigens for transplant recipients during the study timeframe, and these antibodies may be more frequent in repeat transplant recipients, we determined allograft survival separately in first and repeat transplant recipients. Similarly, because information regarding allele-specific HLA antibodies is not reported nationally, and because the likelihood of transplantation across allele-specific antibodies is less likely in zero-mismatched living related recipients, we determined allograft survival in the subset of living related transplant recipients. An additional subgroup analysis examined allograft survival in patients treated with depleting antibody, nondepleting antibody, and no antibody induction.

The relative hazard of allograft failure from any cause including death was determined using Cox proportional hazards multivariable regression analyses that included adjustment for group differences in established determinants.
of transplant outcome, including patient age, sex, race, diabetes as the cause of kidney failure, insurance type, dialysis vintage, donor source, deceased donor kidney donor profile index—a numeric measure that combines ten donor factors, including clinical parameters and demographics, to summarize into a single number the quality of deceased donor kidneys relative to other recovered kidneys (referenced to 2018) (22)—and type of induction immunosuppression. Similar models were constructed for the outcomes of allograft failure censored for death, and death with a functioning allograft. Cox model assumptions were tested, with plots of the log of the negative log of the estimated survival density function versus the log of survival time, and no violations were identified. The frequency of missing data was low (cause of kidney failure 1.7%, insurance 0.02%, induction 0.5%) and data were not differentially missing between cPRA groups. In all models, variables with missing data were assigned a category of “missing” to allow inclusion of all patients in the models. All analyses were conducted using Stata Statistical Software: Release 16 (College Station, TX: StataCorp LLC) (23).

Results

Figure 1 shows the assembly of the study cohort of 4058 zero HLA-A-, B-, DR-, and DQB1-mismatched kidney transplant recipients. Table 1 shows the study patient characteristics overall and by cPRA group. Patients with higher cPRA were more likely to be female, had longer pretransplant dialysis exposure, and more frequently received induction immunosuppression with a depleting antibody.

Figure 2, A–C shows the time to allograft failure from any cause, allograft failure censored for death, and death with a functioning allograft in patients grouped by cPRA during the mean follow up of 5 ± 2 years. The time to graft loss from any cause including death was shorter in patients with higher cPRA (Figure 2A), and this was due to a higher incidence of graft loss censored for death (i.e., return to dialysis or pre-emptive repeat transplantation; Figure 2B) among patients with cPRA 98%. The time to death with a functioning graft did not differ between cPRA groups (Figure 2C).

In stratified analyses among 2996 first and 1062 repeat transplant recipients, the higher risk of death-censored graft loss among patients with cPRA 98% was only observed among repeat transplant recipients (Figure 3). In a subgroup analysis among 1250 living related transplant recipients, cPRA was not associated with allograft survival (Figure 4A). In patient subgroups treated with depleting antibody induction and without antibody induction, patients with cPRA ≥98% had a shorter time to death-censored graft loss (Figure 4, B and D).

![Flowchart](image)
Multivariable Analyses

Table 2 shows the association of cPRA with the outcomes of graft loss from any cause including death, death-censored graft loss, and death with a functioning transplant after adjustment for clinically relevant confounders. Among first and repeat transplant recipients, patients with cPRA 1%–97% were not at higher risk of transplant failure compared with patients with cPRA of 0%. In contrast, patients with cPRA 98%–100% had a higher risk for graft loss from any cause (hazard ratio [HR]; 1.39, 95% confidence interval [95% CI], 1.08 to 1.79) and a higher risk for graft loss censored for death (HR, 1.78; 95% CI, 1.22 to 2.59).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients, n=4058</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>0%, n=1584</td>
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<tr>
<td>Median age, yr (Q1, Q3)</td>
<td>51 (40–60)</td>
<td>51 (39–60)</td>
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<tr>
<td>Male sex (%)</td>
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<td>Black</td>
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<td>10</td>
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<tr>
<td>Other</td>
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<td>6</td>
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<tr>
<td>Diabetes-related kidney failure (%)</td>
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<td>Other</td>
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<td>Duration of pretransplant dialysis yr (Q1, Q3)</td>
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</table>

cPRA, calculated panel reactive antibody; KDPI, Kidney Donor Profile Index.

*Living related donors were defined as sibling, children, or parent donors.

bSuppressed as per United States Renal Data System guidelines given limited no. of observations.

Figure 2. | Unadjusted Kaplan-Meier curves of time to graft loss from any cause including death, death-censored graft loss, and death with a functioning graft, by calculated panel reactive antibody group. Time to graft loss from any cause including (A) death, (B) death-censored graft loss, and (C) death with a functioning graft, by calculated panel reactive antibody (cPRA) group. The number of patients at risk for individual outcomes is provided in Supplemental Table 1.
CI, 1.27 to 2.49), but were not at higher risk for death with a functioning graft (HR, 0.92; 95% CI, 0.62 to 1.37) compared with patients with cPRA 0%.

**Acute Rejection**

The incidence of acute rejection in the first post-transplant year was 5% (95% CI, 4 to 6) (Table 3). The

**Figure 3.** Unadjusted Kaplan-Meier curves of time to death-censored graft loss among first transplant recipients and repeat transplant recipients. Time to death-censored graft loss among (A) n = 2996 first transplant recipients; (B) n = 1062 repeat transplant recipients. The number of patients at risk for individual outcomes is provided in Supplemental Table 2. cPRA, calculated panel reactive antibody.

**Figure 4.** Unadjusted Kaplan-Meier curves of subgroup analyses show time to death-censored graft loss among recipients of a living related transplant grouped by cPRA, patients treated with depleting antibody induction, patients treated with nondepleting antibody induction, and patients treated without antibody induction. Subgroup analyses show time to death-censored graft loss among (A) 1250 recipients of a living related transplant grouped by cPRA; (B) 2598 patients treated with depleting antibody induction; (C) 922 patients treated with nondepleting antibody induction; (D) 517 patients treated without antibody induction. The number of patients at risk for individual outcomes is provided in Supplemental Table 3.
incidence of acute rejection was significantly higher among patients with cPRA 98%–100% (10%, 95% CI 8 to 12). Among the subset of first transplant recipients, the incidence of acute rejection was 5% (95% CI 4 to 5), and the incidence of acute rejection did not differ between cPRA groups.

Discussion
Despite prevailing single-center studies that question the validity of using pretransplant cPRA level as an immune prognosticator of post-transplant outcomes independent of DSA status (14,15), cPRA continues to have a major influence on immunosuppression decisions and clinical trial designs (8–10,17–19). Recognizing the limitations of using a registry dataset to accurately classify pretransplant DSA status, we restricted the study cohort to recipients matched to their kidney donors at the HLA-A, B, DR, and DQB1 loci, thereby enabling determination of the association of cPRA with the risk of allograft failure independent of DSA to these HLA antigens. Under these study conditions, we observed that cPRA up to 97% was not associated with a higher risk of transplant failure. The higher risk of allograft failure associated with cPRA ≥98% was limited to repeat transplant recipients and was not observed among living related transplant recipients, suggesting the potential relevance of anti-DP, DQA, Cw, and allele-specific antibodies, which could not be directly assessed in this registry-based analysis. The study findings question the clinical importance of cPRA in the absence of DSA and challenge whether cPRA values should be considered when determining the course of post-transplant patient management. It is important to note the lack of an association between non-DSAs and outcomes as measured by a cPRA ≥98% in this cohort cannot be generalized to a population of nonzero HLA-mismatched recipients. Additionally, several key antibody characteristics (mean fluorescence intensity values above which antigens are considered unacceptable, historic versus current, repeat...
mismatch, complement activation, cytotoxic positive versus flow cytometric positive) that are used clinically to define unacceptable antigens vary widely between centers in the United States. As this information is not recorded in the Organ Procurement and Transplant Network database, the association of cPRA values with allograft survival in the absence of DSA cannot be accurately determined for patients who are HLA-A-, B-, DR-, or DQ-mismatched with their donors. Although future single-center studies may be helpful, such analyses may not have an adequate number of highly sensitized patients to inform the clinical relevance of cPRA in mismatched patients. The inclusion of information on how centers define unacceptable antigens for each kidney recipient and the use of pretransplant therapies such as plasmapheresis in the database should be considered to enable future analyses to determine the association of cPRA with outcomes independent of DSA in HLA mismatched recipients.

In contrast to patients with a cPRA between 0% and 97%, those with cPRA ≥98% had a higher risk of death-censored allograft failure and a higher incidence of rejection in the first post-transplant year, suggesting these patients were at a higher immunologic risk compared with those with lower cPRA values. We undertook specific subgroup analyses to better understand the lower graft survival in patients with cPRA ≥98%, including stratified analyses in first and repeat transplant recipients and an analysis of living related transplant recipients. These subgroup analyses suggest the most likely explanation for the higher risk of graft loss in patients with cPRA ≥98% is the presence of unrecognized preformed DSA, despite our study design of matching donor-recipient pairs at HLA-A, B, DR, and DQ/B; the fact that cPRA was not associated with graft survival in first transplant recipients suggests the potential importance of antibodies to HLA-DP, DQA, and Cw antigens, which were not included in the US cPRA calculator during the study timeframe but can have a deleterious effect in kidney transplantation (24–26). These antibodies may be more frequent in repeat transplant recipients (27–29). Importantly, our analysis is based predominantly on HLA data with low resolution. This is relevant because patients who are HLA matched with their donors on the basis of antigen-level typing may still develop allele-specific antibodies against their donors, which can lead to immune injury and graft loss. The possibility that the higher risk of graft loss in patients with cPRA ≥98% may be related to pretransplant or de novo allele-specific antibodies is suggested by the finding that cPRA was not associated with allograft outcomes among living related donor transplant recipients. Given the typical “en-bloc” inheritance of HLA haplotypes in living related transplants, the likelihood of transplantation across mismatched antigens or allele-specific DSA is likely to be lower in this group compared with recipients of an unrelated donor kidney transplant.

Another potential explanation for the higher rate of graft loss in patients with cPRA ≥98% is the presence of non-HLA antibodies, which have been shown to be pathogenic in kidney transplantation. Although data limitations preclude us from examining this possibility directly, previous studies have reported a poor association between PRA/cPRA values and the presence of antiendothelial cell antibodies (30,31), MICA antibodies (32), and angiotensin II type I receptor antibodies (33–35). For example, 82% of MICA-positive patients had a PRA of 0% (32), and 71% of kidney recipients with evidence of antiendothelial antibodies were classified as nonsensitized (PRA<10%) (30). Another study found that 28% of patients with angiotensin II type I receptor antibodies had no detectable anti-HLA antibodies (34). It also remains possible that high cPRA is a marker for a higher risk of T cell–mediated rejection (16). However, in studies utilizing the Elispot test to determine pretransplant cellular immune reactivity, PRA was not associated with a positive Elispot test (36).

Readers of this study should consider the inherent limitations of observational studies on the basis of registry data. Although we adjusted for variables that may confound the association between cPRA and graft survival, there may be residual confounders that are unaccounted for in our analysis. In unadjusted analyses, patients with cPRA ≥98% treated with depleting antibody induction and without any antibody induction had a shorter time to death-censored graft loss. Given the observational nature of the data, no conclusions about the use of different induction agents in patients within different cPRA groups can be made from this study. Of note, in multivariable analysis, there was no association between the type of induction

<table>
<thead>
<tr>
<th>Table 3. Acute rejection in the first post-transplant yr by calculated panel reactive antibody group</th>
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<tr>
<td>Group</td>
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<tr>
<td></td>
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<tr>
<td>cPRA (%)</td>
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<tr>
<td>0</td>
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<tr>
<td>1–29</td>
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<td>30–79</td>
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<tr>
<td>80–97</td>
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cPRA, calculated panel reactive antibody.
immunosuppression and allograft loss. Because longitudinal information about maintenance immunosuppression is not reliably recorded after transplantation, and there is no information on drug dosing or drug levels, our analyses do not account for potential differences in maintenance immunosuppression. Additionally, the data do not allow us to precisely determine the timing of acute rejection or the type of rejection. The extrapolation of the study findings to nonzero HLA-A-, B-, DR-, and DQBI-mismatched recipients is uncertain particularly without careful analyses to exclude the presence of DSA.

In summary, this study found no association between pretransplant cPRA <98% and the risk of kidney allograft failure among patients who were matched to their donors at HLA-A, B, DR, and DQBI antigens, and challenges the broad use of cPRA to guide immunosuppressive management. The higher risk of allograft failure in patients with cPRA ≥98% was limited to repeat transplant recipients and absent in living related recipients, suggesting the potential importance of DSAs to HLA-DP, DQA, Cw, and allelespecific antibodies. Further studies are needed to determine why study patients with cPRA ≥98% had a higher risk of graft loss.

Disclosures
H. Gebel reports consultancy agreements with Immucor and One Lambda, a division of Thermo Fisher; and serving as a scientific advisor or member of Scientific Registry of Transplant Recipients. J.S. Gill reports employment with St. Paul’s Hospital/University of British Columbia; receiving research funding and honoraria from Astellas Canada; and serving as a scientific advisor or member of Canadian Blood Services, the Canadian Organ Replacement Register, the Canadian Society of Transplantation, the American Society of Transplantation, and Declaration of Istanbul Custodial Group. J.S. Gill is also supported by a Canadian Institutes of Health Research (CIHR) foundation grant. J.H. Lan and M. Kadatz are supported by a Vancouver Coastal Health Research Institute (VCHRI) Mentored Clinician Scientist award. J.H. Lan reports receiving honorarium from Paladin Labs Inc. for consultant work and participation on advisory board. All remaining authors have nothing to disclose.

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Supplemental Material
This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.13640820/-/DCSupplemental.

Supplemental Table 1. Number of patients at risk for individual study outcomes after transplantation in the study cohort.

Supplemental Table 2. Number of patients at risk for individual study outcomes after transplantation among first and repeat transplant recipients.

Supplemental Table 3. Number of patients at risk for individual study outcomes after transplantation among living related transplant recipients and study patients stratified by induction.

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