Risk of kidney graft failure (GF) associated with HLA class II amino acid mismatches (AAMM) is highest during the first year after transplant for sensitized patients

Keith McCullough[1]; Loren Gragert[2]; Nick Brown[3], Ryan J. Urbanowicz[4], Alyssa N. Paynter[2], Malek Kamoun[3]
[1]Arbor Research Collaborative for Health; [2]Department of Medicine, Tulane; [3]Department of Pathology and Laboratory Medicine, University of Pennsylvania, [4]Department of Computational Biomedicine, Cedars-Sinai Medical Center

Introduction

Prior research has shown that HLA class II AAMM are predictive of GF and this impact is highest during the first 6 months post-transplant. The interaction between recipient sensitization, as measured by cPRA, and AAMM has not been explored as extensively. After exploring this association, we discovered that there may be different effects during different time periods, possibly due to changes in kidney allocation policy and procedures.

Aim and Abstract

Aim: We hypothesized that broader sensitization as measured by cPRA could serve as a useful biomarker for having a broader alloreactive T-cell repertoire that would increase risk of early graft failure (GF), so we analyzed whether the association between HLA class II amino acid mismatches (AAMM) and early GF is similar among sensitized patients compared to unsensitized patients.
Data: 2010-23 kidney transplants
Method: Cox survival models on graft failure (GF)
Results: Association between AAMM and GF during the first year may be higher among sensitized patients, but this effect may be less strong in more recent transplants
Conclusion: The effects of AAMM may differ for sensitized patients, but this difference may be affected by changes in kidney allocation and transplant procedures.

Methods and Materials

We analyzed data on 166,918 adult deceased-donor Scientific Registry of Transplant Recipients (SRTR) between 2010 and 2023 with varying calculated panel reactive antibody (cPRA) levels: <10%, 10-79% and 80%-100%. We imputed (x10) high resolution HLA-DRB1 and -DQB1 alleles from serologic antigen specificities using haplotype frequencies, then assigned AAMM.
We used Cox proportional hazards models controlling for donor and recipient factors (e.g. demographics, comorbidities), year of transplant (to control for secular trends in improved transplant recipient survival), antigen mismatches in the A, B, C, DRB1, and DQB1 loci (see factors listed in Table 1). We constructed separate models for first-year GF and for GF after the first year, conditional on surviving the first year.

Table 1: Descriptives: % of transplants or median (IQR)

	PRA < 10	PRA 10-79	PRA 80+
N	97489	37614	31815
Recipient factors			
Age at transplant	57 (46-65)	55 (44-64)	51 (41-60)
Diabetes (any indication)	40%	37%	29%
Diagnosis: hypertension	22%	21%	18%
Primary diagnosis: polycystic disease	7%	7%	7%
Primary diagnosis: glomerular disease	9%	10%	14%
Had prior transplant	3%	10%	45%
Body mass index (BMI)	28 (25-32)	28 (25-32)	27 (24-32)
Race/ethnicity: Asian	8%	8%	7%
Race/ethnicity: Black	33%	37%	36%
Race/ethnicity: Hispanic	19%	17%	18%
Race/ethnicity: White	39%	36%	37%
Donor factors			
Age	42 (29-53)	41 (29-51)	38 (26-48)
Weight	82 (69-97)	82 (69-97)	80 (68-95)
Expanded criteria donor (ECD)	18%	14%	7%
Donation after circulatory death	26%	24%	21%
Shared between OPOs	30%	32%	50%
Cause of death: anoxia	42%	41%	39%
Cause of death: CVA	27%	26%	23%
Cause of death: CNST	0%	0%	0%
Cause of death: Head trauma	28%	30%	35%
Cause of death: Other	3%	3%	3%
CMV negative	38%	38%	39%
History of hypertension	32%	30%	23%
Antigen mismatches			
Zero HLA A mismatches	8%	16%	24%
Zero HLA B mismatches	4%	12%	18%
Zero HLA DRB1 mismatches	13%	20%	31%
Zero HLA A, B, and DRB1 mismatches	3%	10%	11%

Figure 1: STROBE inclusion and exclusion

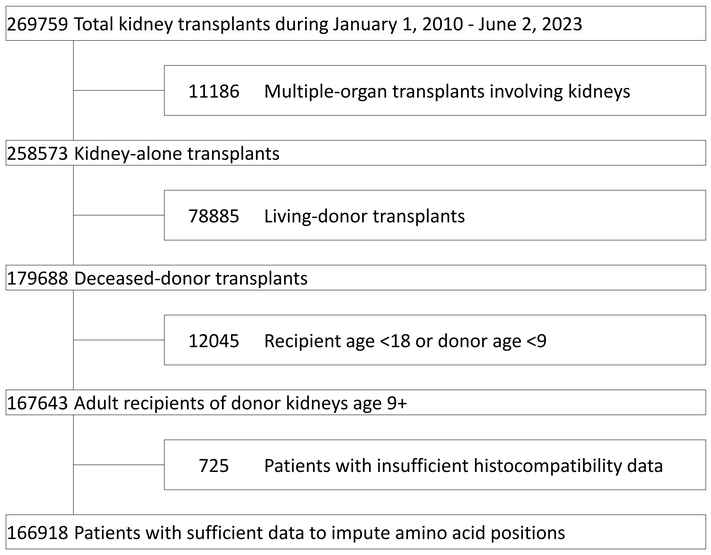


Figure 2. Adjusted hazard ratios (and 95% confidence intervals) of first-year graft failure associated with cPRA by 2010-14 v. 2015-23 transplant year

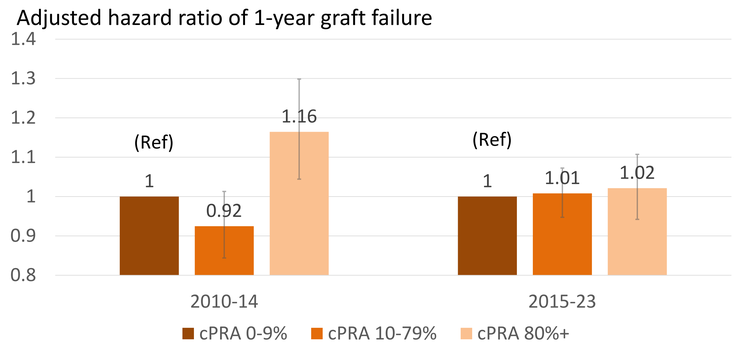


Figure 3. Adjusted hazard ratios (and 95% confidence intervals) associated with amino acid mismatch (AAMM) in specified loci, by recipient cPRA category and timeframe after kidney transplant

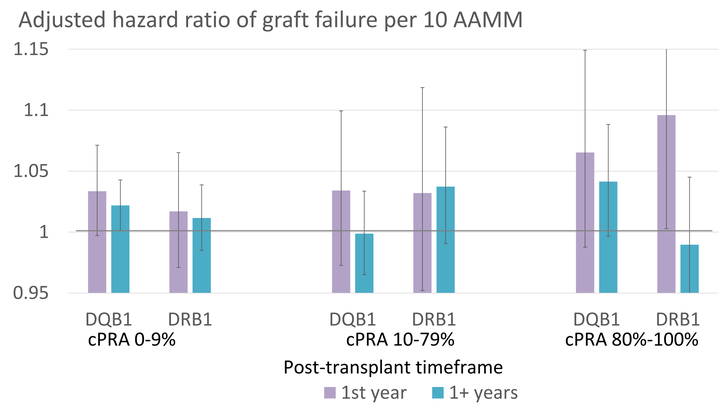
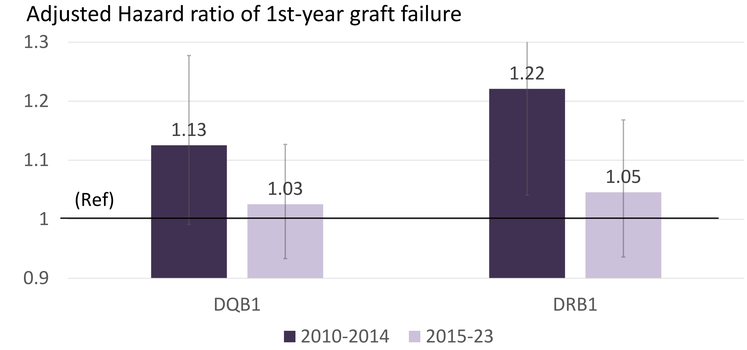


Figure 4. Among recipients with cPRA 80%+, adjusted hazard ratios (and 95% confidence intervals) per 10 AAMM in specified loci, by transplant year



Results

Table 1 shows information about the factors used to adjust the Cox regression models in these analyses.

Figure 1 shows the effects of the inclusion/exclusion criteria, per STROBE guidelines.

Figure 2 shows the association between cPRA and GF within one year of transplant, adjusted for the other factors described in table 1. Among transplants in 2010-2014, cPRA levels above 80% had elevated risk of 1st-year GF, with a hazard ratio of 1.16 (95% confidence interval 1.04-1.30, p = 0.006). After 2015, cPRA levels above 80% had a reduced association with 1st-year GF with a hazard ratio of 1.02 (p = 0.61).

Figure 3 shows that in the DRB1 locus, the adjusted hazard ratios (HRs) per 10 AAMM for first-year GF were higher for more broadly sensitized (cPRA 80%+) patients than for less broadly sensitized (cPRA <10%) patients. Among sensitized patients, in the DRB1 locus, the HR per 10 AAMM was 1.10 (95% CI 1.00-1.20, p=0.04) for first-year GF and 0.99 (0.94-1.05, p=0.71) after the first year. Among less broadly sensitized patients, in the DRB1 locus, the HR per 10 AAMM was 1.02 (95% CI 0.97-1.07, p=0.48) for first-year GF and 1.01 (0.99-1.04, p=0.39). The HR difference was smaller for DQB1.

Figure 4 shows that the risk associated with DRB1 AAMM among cPRA 80%+ recipients was lower after 2014. Among 2010-14 transplants, the adjusted hazard ratio per 10 AAMM in the DQB1 locus was 1.13 (p = 0.07) and in the DRB1 locus was 1.22 (p = 0.01). In 2015-23, these associations for DQB1 and DRB1 had adjusted hazard ratio of 1.03 (p = 0.60) and 1.05 (p=0.43) respectively. If we did not adjust for HLA antigen mismatch, these associations during the 2015-23 period for DQB1 had an adjusted hazard ratio of 1.05 (p = 0.11) and for DRB1 an adjusted hazard ratio of 1.08 (p = 0.05) among patients with cPRA 80%+, and 1.01 (p = 0.48) for DQB1 and 1.06 (p = 0.01) for DRB1 for patients with cPRA 0-9% (results not shown).

Discussion, conclusions

Discussion:
2014 change in kidney allocation rules:
The transplant allocation system was modified in December of 2014, mandating that in order to receive the bonus points associated with higher cPRA levels, unacceptable antigens justifying these higher cPRA levels had to be specified for each waitlist candidate. Prior to this change, it may have been that transplant centers were accepting higher risk offers due to these patients' reduced access to kidneys. While transplant centers may have different criteria for listing unacceptable antigens, depending on the level of reactivity, and also different approaches to immunosuppressive treatment, this change may have helped reduce the association between higher cPRA levels and graft failure, as illustrated by figure 2.
Possible effects of change in kidney allocation rules:

- Figure 2 shows that cPRA levels above 80% were associated with increased risk of graft failure within the first year after transplants occurring in 2010-2014, but this effect was substantially lower during 2015-23.
- The change may have had some impact on the association between AAMM and graft failure among patients with higher cPRA levels.
  - As illustrated by table 1, cPRA and zero DR antigen mismatches (AgMM) were correlated, with 13% of the cPRA <10% transplants being 0 DR AgMM while 31% of the cPRA 80%+ transplants were 0 DR AgMM. which makes sense because sensitized patients are more likely to require better-matching kidneys.
  - There was a slight tendency towards a stronger association in the post-2015 era, but this was not strong enough to explain the change in effect we saw.

Effects of DRB1 AAMM on GF within one year:

- *Overall*: DRB1 AAMM was associated with higher risk of early GF among more broadly sensitized patients (cPRA 80%+) (figure 3), adjusted for patient and donor characteristics and AgMM
- *2015-23 transplants*: this association was weaker (figure 4).
- If we did not adjust for antigen mismatch, the associations between DQB1 and DRB1 AAMM and 1st-year graft failure were still stronger for patients with cPRA 80%+ than for patients with cPRA 0-9%, although the difference in the strength of the association between these two groups did not achieve statistical significance.

Conclusion: While the associations are not strong enough to support policy or practice decisions, these results are consistent with AAMM possibly presenting more of a risk for broadly sensitized patients in terms of GF. Further investigation should be conducted to determine ways to further mitigate transplant risk among these patients.

Contact
Keith McCullough
Arbor Research Collaborative for Health
Email: keith.mccullough@arborresearch.org
Website:
Phone:

Project title: HLA Immunogenetics and Kidney Allograft Outcomes
NIH Grant number: R01AI173095
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