Eplet Mismatches and De Novo Donor-Specific Antibody Development in Pediatric Kidney Transplant Recipients

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Abstract

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Background: The presence of HLA de novo donor-specific antibodies (dnDSA) is associated, probably causally, with failure of kidney transplants. In a pediatric kidney transplant population, we sought to determine the extent to which eplet mismatches (MM) are associated with the development of dnDSA.

Methods: We performed a retrospective cohort analysis of pediatric kidney transplant recipients from 2008 to 2014 who underwent surveillance dnDSA testing and who had at least 3 years of follow up from the time of transplant. We used the National Marrow Donor Program's Haplostats platform to impute high-resolution HLA alleles from recipient and donor low resolution HLA alleles selecting the most commonly matched high-resolution typing. We then generated eplet

mismatches using HLA matchmaker version 2.0. Eplet mismatch exposure was modeled both on the continuous scale and with identified thresholds. We utilized Cox proportional hazards regression models to predict risk of dnDSA based on eplet MM, adjusting all models for age, donor type, and sex.

Results: A total of 133 subjects (median age 13 years, 64% male) met inclusion criteria. Of these, 44% developed persistent dnDSA (at least 2 positive tests) at a median of 19 months post-transplant. The presence of Class II eplet MM was associated with a 3% increase in risk for dnDSA per each additional eplet MM (HR 1.03, 95% CI 1.02-1.05); children with >5 MM had approximately a 3.5 fold increased risk for dnDSA development (HR=3.61, 95% CI = 1.70-7.67) relative to the risk among children with four or fewer MM. The presence of Class I MM was not associated with risk of development of dnDSA to any appreciable degree. Each DR and DQ MM was associated with a 6-7% increased risk of dnDSA (DR: HR 1.06, 95% CI: 1.03-1.10; DQ: HR 1.07, 95% CI 1.03-1.10); those with DR >2 MM and DQ >3 MM were each associated with increased risk of dnDSA development (DR: HR 2.02, 95% CI: 1.12-3.63; DQ: HR 1.92, 95% CI: 1.08-3.41).

Conclusion: The presence of Class II MM, but not Class I eplet MM, is predictive of increased risk of dnDSA development in pediatric transplant recipients.

ACKNOWLEDGEMENTS

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INTRODUCTION

Kidney transplant is the treatment of choice for children with end stage renal disease (ESRD). While modern immunosuppression has greatly improved kidney transplant recipient survival immediately post-operatively, little progress has been made in long-term graft survival over the last thirty years.[1,2] The need to prolong allograft life is arguably most important in children with end stage kidney disease (ESRD), many of whom need repeated transplants. Shortened allograft survival increases morbidity and mortality,[3,4] largely because of the burden of increased time on dialysis – dialysis has been shown to have a profound negative impact on childhood and adolescent development. Increased morbidity and mortality is further related to the increased degree of immunosuppression required for each subsequent kidney transplant and the associated sensitization.[5–7]

Alloimmunity is the greatest contributor to graft loss.[8–10] Both in children and in adults, the development of HLA de novo donor-specific antibodies (dnDSA) is a risk factor and part of the natural history for antibody-mediated rejection and other chronic alloimmune mediated processes, all of which lead to shortened allograft survival.[11–16] DnDSA development in the pediatric kidney transplant population is in the range of 23%-35%.[11,14,16,17]

In adults, class II eplet mismatches (MM) appear to be an independent risk factor for development of dnDSA, and are associated with decreased allograft survival[18] and transplant glomerulopathy in adults.[19–22] Eplet mismatches (MM) are MM between small sequences of polymorphic amino acid residues between donor and recipient HLA complexes which are critical for antibody binding. There is but limited literature on the possible association of class II eplet MM on development of dnDSA in children and adolescents. Due to factors such as the developing immune system of young children, immune activation with viral infections, and

decreased levels of adherence in the adolescent population, some postulate the role of eplet MM via dnDSA development in graft longevity may be greater in children who have received a kidney transplant than in their adult counterparts.

The ability to identify eplet mismatch thresholds that can predict poor graft survival would enable their physicians to tailor surveillance programs for monitoring of dnDSA.[5,23] Similarly, establishing eplet MM thresholds may allow tailoring of immunosuppression for patients identified at higher risk and allow minimization of immunosuppression for those at low risk.[6] Optimizing immunosuppression and managing risk of eplet mismatch would allow a decrease in alloimmune factors driving graft loss.[22]

The objective of this study is to evaluate the association of eplet MM with dnDSA development in the pediatric kidney transplant population and determine clinically meaningful thresholds of eplet MM.

METHODS

Study Design

We conducted a retrospective cohort study of all pediatric patients at Seattle Children's receiving a kidney transplant between January of 2008 and June of 2014. All individuals who received a kidney alone transplant during this time had surveillance donor-specific antigen (DSA) testing performed every three months for at least the first two years post-transplant. For the present analysis, we included just children age 19 years or less at time of transplant who had undergone kidney-alone transplant. Exclusion criteria included anyone with positive cross-match, the presence of DSA prior to transplant, or less than 3 years of follow-up. Clinical and demographic data were obtained through the Seattle Children's electronic health record.

HLA typing

High resolution haplotypes (A, B, C, DR, and DQ) were imputed from recipient and donor low resolution types using the National Marrow Donor Program's Haplostats platform. The HLA alleles with the highest frequency were selected with DQα derived from most commonly linked DRβ1 and DQβ. We then generated eplet mismatches using HLAMatchmaker version 2.0.[24–26] HLAMatchmaker is a structural algorithm that utilizes the known crystallized structure of antigen-antibody complexes to predict functional epitopes.

DSA testing and classification

The human leukocyte antigen (HLA) lab within Bloodworks Northwest (Seattle, WA) performed all the DSA testing. Bloodworks Northwest is a United Network for Organ Sharing-accredited laboratory specializing in testing for organ transplantation. Luminex technology (either the Luminex 200 or FLEXMAP 3D platform) was utilized for DSA screening using single-antigen beads (OneLambda, CA). Persistent DSA was defined as more than one positive DSA test for an individual patient with no MFI cut-off. Patients who only had one positive DSA test were considered negative for dnDSA. Determination of type of testing, either for-cause or surveillance-detected, was determined for each patient with a positive DSA test. This was done by looking at the indication for the test and by comparing the creatinine at the time of DSA test with the baseline in a window of 3-6 months prior as described by Engen, et al.[17] The for-cause group included those whose creatinine was at least 0.2 mg/dL above the determined baseline, often with documentation of testing due to concern of graft dysfunction.

Transplant Procedures

Induction immunosuppression included thymoglobulin or an IL-2 receptor antagonist (basiliximab or daclizumab) with methylprednisone. Our typical maintenance immunosuppression was tacrolimus, mycophenolate mofetil, and steroids for our high-risk population. Post-transplant tacrolimus goals were 10-12 ng/dl day 1-59 post-transplant, 7-10 ng/ml day 60-84 post-transplant, 5-7 ng/ml day 85-365 post-transplant, and 3-5 ng/ml for greater than 365 days post-transplant. Maintenance steroids only given to patients who required steroids for other underlying processes or who were on a sirolimus protocol. Mycophenolate mofetil dosing started in the operating room at 600 mg/m^2/dose (maximum 1000 mg/dose) IV every 12 hours. Mycophenolate mofetil dosing reduced to 450 mg/m^2/dose (maximum 750 mg/dose) every 12 hours once tacrolimus trough level was therapeutic. At day 14 post-transplant, mycophenolate mofetil dosing was decreased to 300 mg/m^2/dose (maximum 500 mg/dose) every 12 hours.

Along with surveillance DSA testing, patients received surveillance biopsies at 3-6 months, 12 months, and at approximately 24 months posttransplant. In the setting of elevated creatinine, for cause DSA testing was performed. A biopsy was performed prior to treatment for antibody-mediated rejection.

Statistical Analysis

The primary outcome was the development of any persistent dnDSA. For descriptive purposes, we further categorized dnDSA at the recipient level as Class I, Class II, and DR and DQ subclasses within Class II. We calculated the proportion of recipients with Class I dnDSA only, Class II dnDSA only, or both, as well as the proportion with any DR dnDSA and any DQ

dnDSA (DR and DQ being highly collinear). Eplet mismatch exposure was modeled both on the continuous scale, as total Class I and Class II mismatch counts, and as dichotomized counts. The threshold cut-points were identified after preliminary investigation that prioritized sensitivity using receiver operating characteristic (ROC) curves as >5 for Class I and Class II eplet MM counts, >3 DQ (α and β) subclass eplet MM counts, and >2 DR subclass eplet MM counts. Descriptive summaries of eplet mismatch counts included median and interquartile range for continuous counts and Kaplan-Meier plots for dnDSA development by dichotomized counts and by age at transplant (<4 years, 4-10 years, ≥11 years).

To estimate associations between dnDSA development and each mismatch count predictor, we utilized Cox proportional hazards regression models with Class I, Class II, DR subclass, and DQ subclass eplet MM as continuous predictors. Next, Cox proportional hazards regression model again used to demonstrate the risk of dnDSA at the chosen thresholds (>5 for Class I and Class II, >2 for DR, and >3 for DQ). All models included a priori selected covariates gender, age at transplant and donor type.

Due to concerns that recipients with dnDSA detected on routine DSA testing (surveillance) were inherently different from those with dnDSA detected in for-cause testing, and that the for-cause group would have more opportunity for a positive test, we generated Kaplan-Meier failure curves to describe the development of dnDSA by testing reason as well as eplet mismatch count. All testing was two-sided and conducted at the 0.05 level of significance without correction for multiple comparisons. Statistical analyses were performed using Stata version 15 (StataCorp., College Station, TX).

All research procedures were approved by the Seattle Children's institutional review board study 00000881.

RESULTS

Study Population

Of the 176 patients who were transplanted in the study period with DSA testing results, 133 remained eligible after excluding those with inadequate follow-up, multi-organ transplant, or pre-sensitization to allograft (figure 1). Fifty-eight patients, 44%, met the definition for persistent dnDSA with a median time to development of 19 months (Table 1). There was a higher percentage of males with dnDSA as opposed to those without dnDSA (71% vs. 59%). The dnDSA group also had longer median cold ischemia time (600 minutes vs. 282 minutes), less with living related transplant (24% vs. 41%), similar median class I eplet MM counts (9 vs. 8), but increased median class II eplet MM counts (14 vs. 7).

Relationship of class I and class II eplet MM and dnDSA

We found no evidence that class I MM count was related to the development of dnDSA (table 2). The relation between the number of Class II eplet MM and dnDSA is shown in Figure 2. For each additional class II eplet MM there was a 3% increase in dnDSA appearance (Hazard Ratio (HR)= 1.03, 95% Confidence Interval (CI) 1.02-1.05). Patients with 5 or more class II eplet MM were at a 3.6 fold increased risk (HR=3.61, 95% CI = 1.70-7.67) relative to patients with no more than 4 MM. Using 5 or more class II MM as a cut point, the sensitivity for the development of dnDSA was almost 95% and the specificity almost 50% (Figure 3).

Relationship of class II DQ and DR eplet MM and dnDSA

Both DQ and DR subclass eplet MM were associated with increased risk of developing dnDSA, DQ with a 7% increase in risk per each additional mismatch (HR 1.07, 95% CI 1.03-1.10) and DQ with 6% increase in risk per each additional mismatch (HR 1.06 95% CI 1.03-1.10) (Table 2). The presence of 2 or more DR eplet MM and 3 or more DQ eplet MM both demonstrated an approximate doubling of risk for dnDSA development (DR: HR=2.40, 95% CI 1.38-4.18; DQ: HR=1.86, 95% CI 1.05-3.30, respectively). At these cut-points, the sensitivity for predicting dnDSA development was >75%, with almost 50% specificity (Figure 4).

Description of dnDSA and of type of DSA testing

Among recipients who developed dnDSA, half developed Class II DSA only (52%), 36% developed both Class I and Class II, and just 12% developed only Class I (Table 3). The development of dnDSA differed little according to the age of the child at transplant (Figure 5). Of those who developed dnDSA, those that were detected with for-cause DSA testing developed dnDSA earlier and had less clear of a relationship with eplet MM. (Figure 6).

DISCUSSION

Summary and significance

The results of this study suggest that in children and adolescents who have undergone a kidney transplant, class II eplet MM are a risk factor for development of dnDSA. Class II subclasses of DR and DQ eplet MM both appear to be strong predictors of dnDSA, yet the individual contribution is difficult to ascertain given the high degree of collinearity between DQ and DR. Children with Class II eplet MM of >5 had a 3.6 fold increase in risk of dnDSA development. The threshold of >2 eplet MM for DR and >3 eplet MM for DQ both were

associated with a doubling of risk for dnDSA. In general, the findings of this study align well with the results of prior studies of adult and mixed (but predominantly adult) kidney transplant recipients.[21,22,27]

Our identified thresholds for clinically important eplet MM are lower than that of >11 eplet MM suggested by Wiebe.[22] We believe that in order to maximally identify those who may benefit from increased surveillance for DSA and/or for different targets of immunosuppression, priority should be given to a test threshold that yields a high sensitivity. Therefore, for children, at least, we recommend that a lower cut point be used, in the neighborhood of 5 or more Class II MM.

Limitations

There are several limitations to this current study. Because there have been changes in immunosuppression protocols over time - for example, since 2011 IL-2 receptor antagonists (basiliximab or daclizumab) are no longer used as routine induction therapy, in favor of thymoglobulin – the results may not be generalizable to current practice. (IL-2 receptor antagonists were shown to be a risk factor for dnDSA development by Engen, et al.[17]) Further, the high-resolution HLA typing upon which the eplet MM was determined is imputed. This does introduce unknown and unmeasured error; however, it is unlikely to lead to differential misclassification. Another limitation is the lack of consensus on definition of a positive DSA test, with disagreement regarding whether there should be an MFI cut-off. Instead of using an MFI cut-off, we required at least two positive DSA test to help avoid including no more than transient dnDSA appearance. Our study also was not powered to detect differences in association between eplet MM and type of DSA testing, surveillance testing vs. for-cause testing. Engen, et

al[17] demonstrated that the degree to which the allograft is affected appears to differ according to the reason for DSA testing, possibly reflecting different pathophysiologic processes. Finally, while we utilized distribution and ROC cure data to guide our choice in thresholds for Class II, DQ and DR eplet MM thresholds, the cut-points within this single center study remain somewhat arbitrary and are not generalizable to a larger pediatric kidney transplant population.

Future directions

Wiebe, et al[22] observed that those with high-risk eplet MM load are more likely to develop dnDSA with low tacrolimus trough levels, and that those with low risk eplet MM load are more tolerant of low tacrolimus trough levels. We suggest that this be examined in the pediatric population, and also the modulating ability of other forms of immunosuppression, such as the use of IL-2 antagonists for induction immunosuppression. Similarly, it is important to evaluate the modulating ability of viral infections on the association between class II eplet MM and dnDSA development.

Further research is required to delineate which specific class II eplet MM are high-risk for stimulating development of dnDSA, as certain eplet MM are likely to be more immunogenic and have a greater degree of expression within multiple HLA antigens. Such research will allow more sophisticated assignment of risk to the recipient than relying solely on MM count. Additional studies are also needed to determine clinically meaningful thresholds that are generalizable to other pediatric populations.

Beyond altering immunosuppression and surveillance programs, organ allocation is the other clinical application of eplet MM which would aim to decrease the baseline alloimmune risk of the recipient and thus improve long-term outcomes. Change in allocation based on eplet MM

has had considerable discussion in the literature,[18,28] especially in pediatrics given the frequent need for multiple transplantations.[29,30] The Transplantation Society of Australia and New Zealand has applied such an allocation to a segment of its pediatric recipients with the goal of decreasing sensitization for future re-transplantation.[31] The results of an initial small cohort study from this initiative with one-year follow-up revealed less class II dnDSA (2/8 recipients matched with exclusions for donors with high class II eplet MM compared to 7/11 matched without exclusions) and acceptable mean wait time to organ obtainment of 6.55 months for those recipients matched with exclusions to donors with high eplet MM.

Conclusion

The results of this study suggest that the presence of class II eplet MM, in particular DQ eplet MM, predicts an increased risk for dnDSA in the pediatric population. This has particular importance given the frequent need for multiple transplantations, procedures which themselves can lead to increase in sensitization related to class II eplet MM.[32]

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Tables and Figures

Table 1. Sample characteristics

N=133	0 or 1 +DSA test, N=75 (55%)	>1 +DSA test, N=58 (44%)
Age in years at transplant, median (range)	11 (1-19)	12 (2-19)
Male, n (%)	44 (59)	41 (69)
Transplant type, n (%)		
Deceased	39 (52)	36 (59)
Living Related	31 (41)	15 (25)
Living Unrelated Donor	5 (7)	10 (16)
Eplet mismatch count		
Class I (A, B, C) median (range)	8 (0-19)	9 (2-18)
Class II (DR, DQ) median (range)	7 (0-34)	14 (0-89)
DR median (range)	3 (0-17)	7 (0-45)
DQ median (range)	5 (0-17)	8 (0-44)

*All eplet mismatches are antibody verified

Table 2: Adjusted* hazard ratios for association between antibody verified eplet mismatch counts and development of persistent de novo donor-specific antibodies

	HR (95% CI)	P
Class I (A,B,C) eplet mismatches (per each additional mismatch)	1.01 (0.96-1.08)	0.62
Class I (A,B,C) eplet mismatch count > 5	1.86 (0.85-4.07)	0.12
Class II (DR,DQ) eplet mismatches (per each additional mismatch)	1.03 (1.02-1.05)	<0.01
Class II (DR,DQ) eplet mismatch count > 5	3.61 (1.70-7.67)	<0.01
DR eplet mismatches (per each additional mismatch)	1.06 (1.03-1.10)	<0.01
DR eplet mismatch count > 2	2.02 (1.12-3.63)	0.02
DQ eplet mismatches (per each additional mismatch)	1.07 (1.03-1.10)	<0.01
DQ eplet mismatch count > 3	1.92 (1.08-3.41)	0.03

*Adjusted for age, donor type, sex of recipient

Table 3. De novo donor-specific antibody characteristics

Class I DSA only	7 (12%)
Class II DSA only	30 (52%)
Both Class I and II	21 (36%)
Any DR	33 (57%)
Any DQ	43 (74%)
Median onset post-transplant (IQR)	19 months (12,28)

FIGURE 1

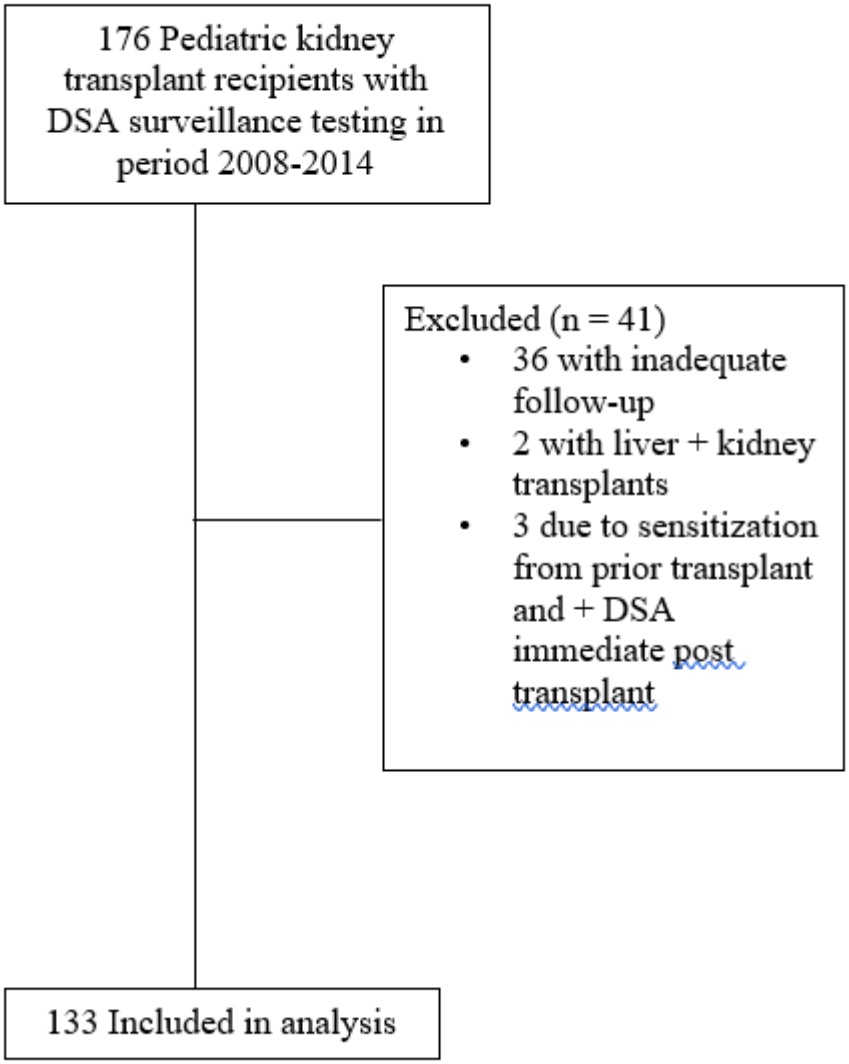
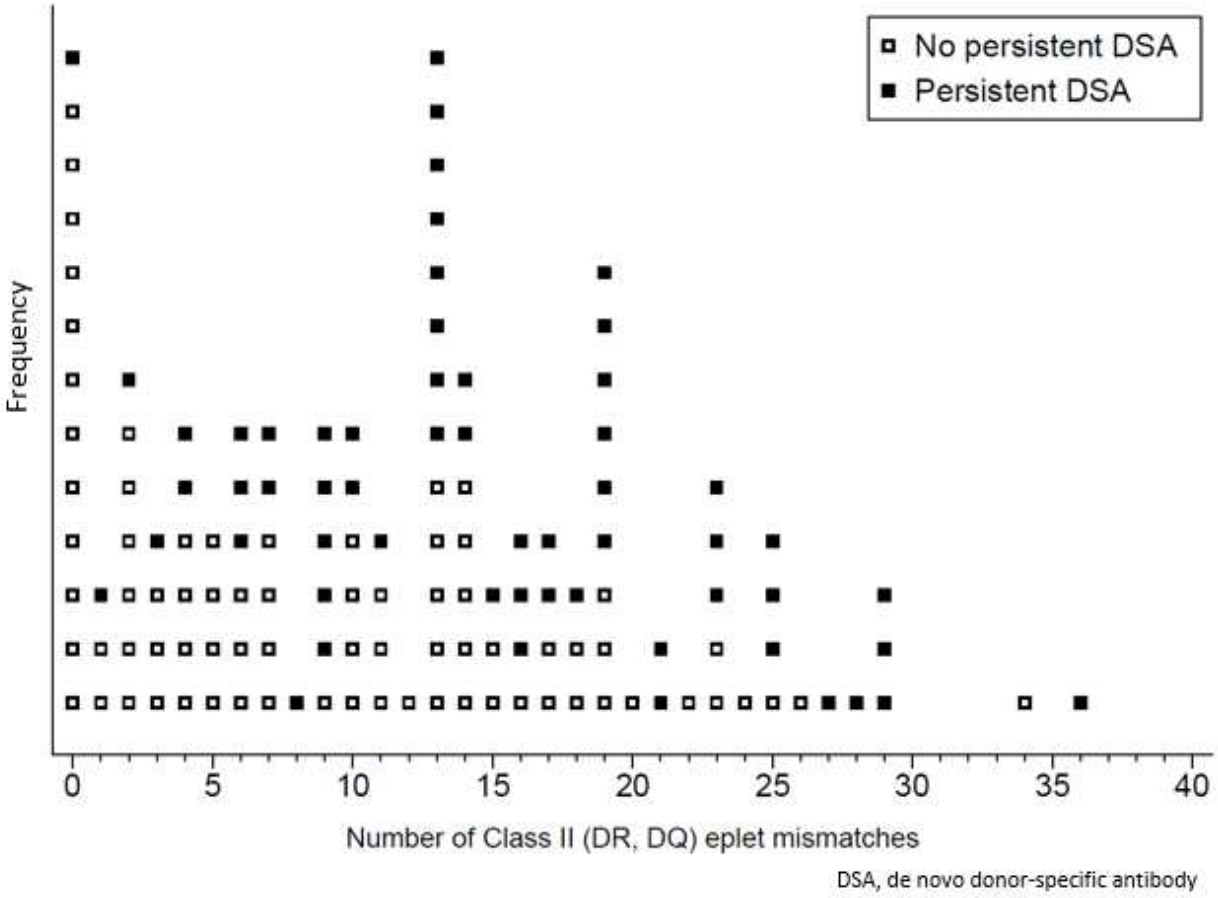

176 Pediatric kidney transplant recipients with DSA surveillance testing in period 2008-2014
Excluded (n = 41)
• 36 with inadequate follow-up
• 2 with liver + kidney transplants
• 3 due to sensitization from prior transplant and + DSA immediate post transplant
133 Included in analysis

Figure 2: Distribution of de novo donor-specific antibody development by class II eplet mismatch count



DSA, de novo donor-specific antibody

Figure 3. ROC curve for development of persistent de novo donor-specific antibodies by number of Class II antibody-verified eplet mismatches

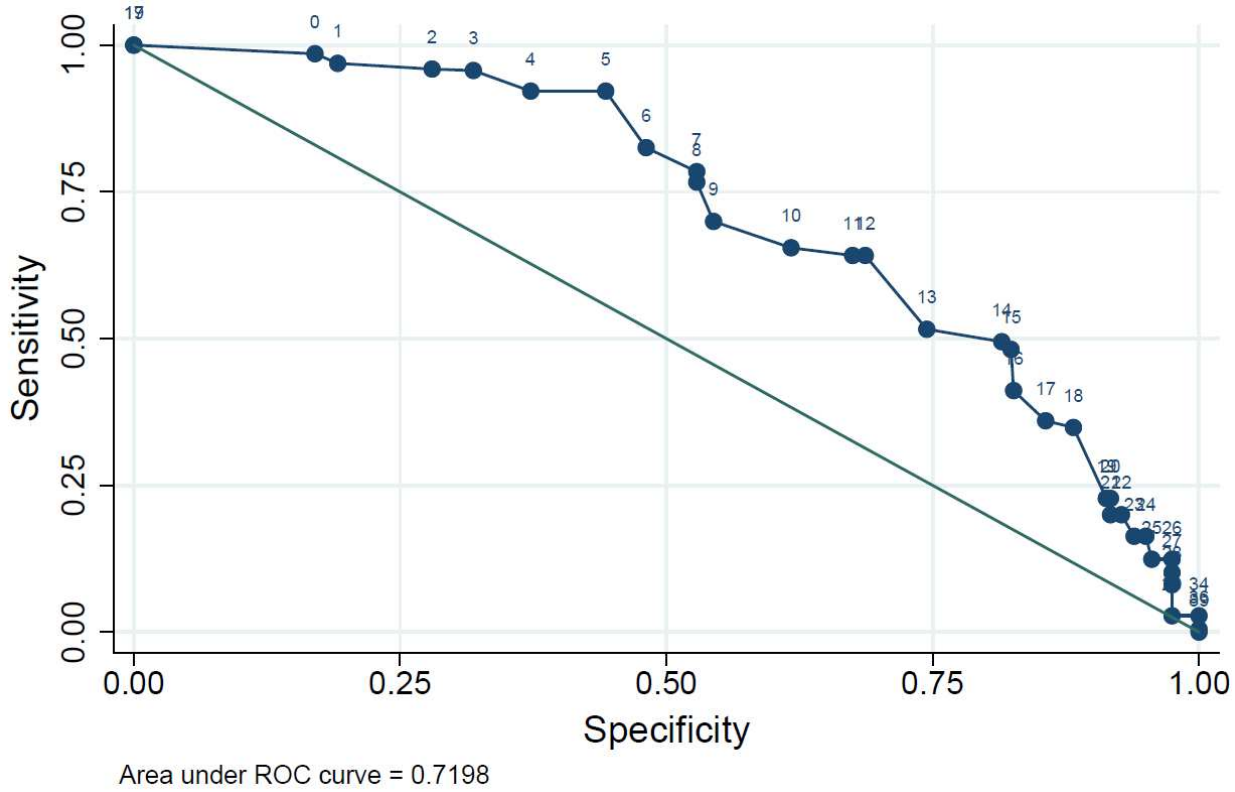


Figure 4: ROC curve for development of de novo donor-specific antibodies by number of DR and DQ antibody verified eplet mismatches

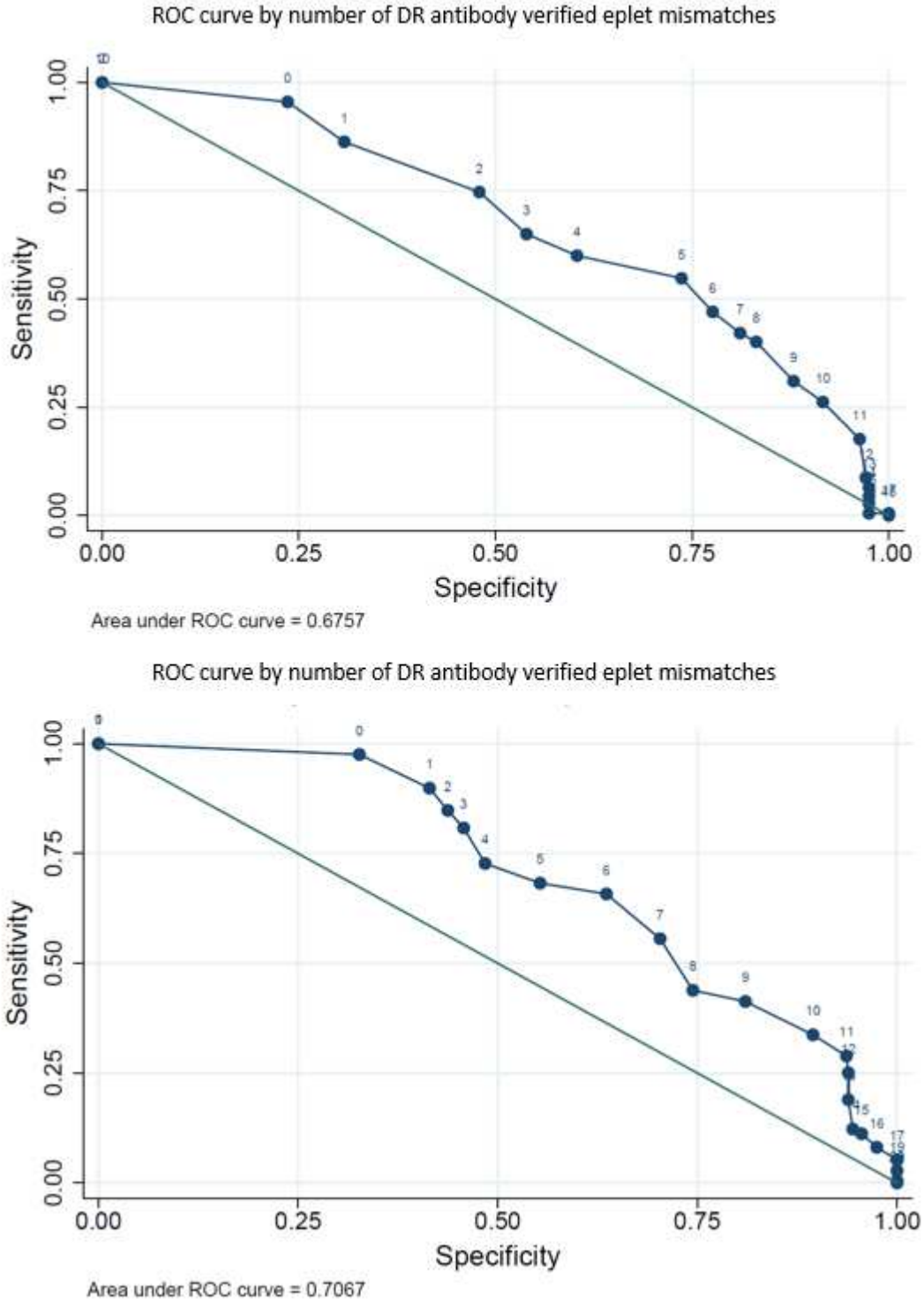


Figure 5: Kaplan-Meier failure curves to development of de novo donor-specific antibody for different age groups

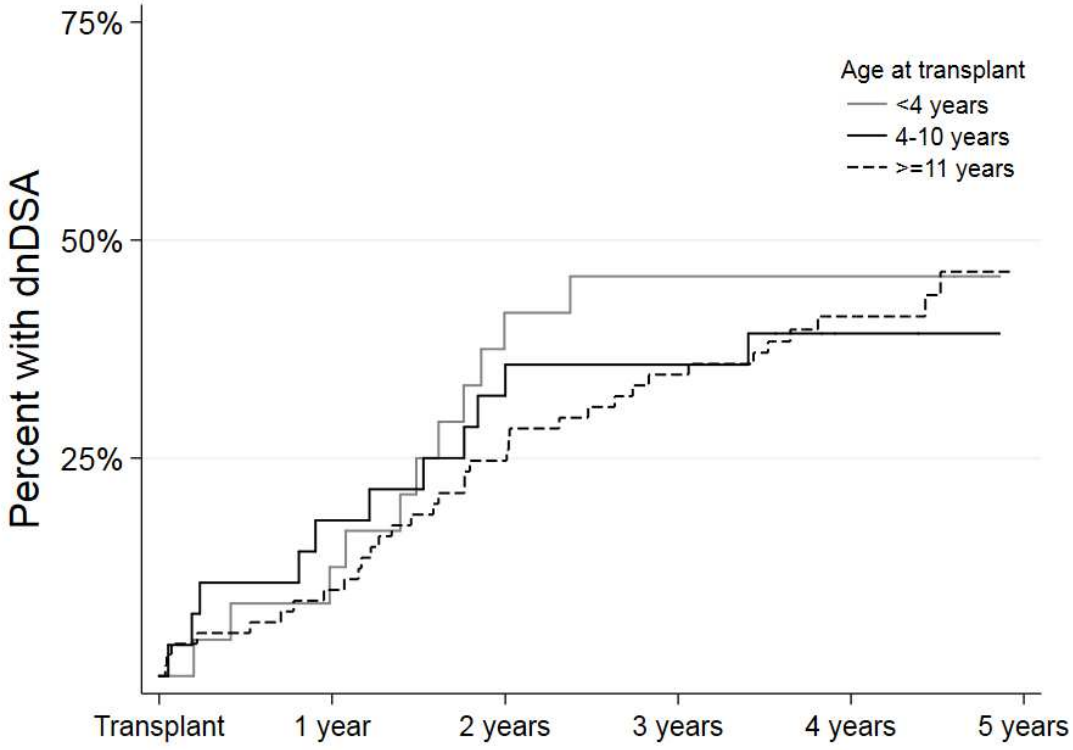


Figure 6: Kaplan-Meier failure curves for de novo donor-specific antibody development by eplet mismatch count and reason for DSA testing