Comparison of alloimmune risk stratification methods for pediatric kidney transplants: correlation with outcomes from a single-center transplant program

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Introduction

Even with the advancement of modern immunosuppression, alloimmune-mediate rejection following exposure to non-self HLA antigens remains the most common cause of graft failure following kidney transplant. Numerous risk stratification approaches, ranging from traditional antigen level matching to newer molecular eplet-based and indirectly recognizable HLA epitope-based algorithms, have been devised to assess the alloimmune risk of donor-recipient pairings. Although several methods have been extensively evaluated individually, few studies have directly compared these approaches against one another using the same cohort. Here we evaluated alloimmune risk stratification by HLA-DR/DQ molecular eplet mismatch, indirect T-cell recognition of mismatched peptides (PIRCHE), and traditional antigen level matching, and compare their correlation with de novo donor-specific antibody (dnDSA) development and graft failure in a cohort of pediatric kidney transplant patients.

Materials and Methods

We performed a retrospective single-center study of pediatric kidney transplants consisting of 234 consecutive patient-donor pairs from 2003-2024. Most cases involved white non-Hispanic/Latino recipients, followed by black or African American recipients, Hispanic/Latino recipients, and then other groups. Patients who were lost to follow-up or moved on to adult transplant programs were censored at the last follow-up. The duration of follow-up ranged from 1 to 217 months, with a median of 35 months.

Two-field donor and recipient HLA typing were obtained through clinical NGS typing (Holotype, Omixon). Anti-HLA antibodies were monitored using LABScreen Single Antigen beads (One Lambda).

Transplant cases were stratified into immunologic risk categories according to:

1. **HLA-DR/DQ molecular eplet mismatch (HLAMatchmaker)[1]**
   Low: DR<7 and DQ <9; Med: DR ≥7 and DQ ≤14 or DR 0-6 and DQ 9-14; High: DQ ≥15
2. **Prediction of indirect T-cell recognition of mismatched peptides:**
   PIRCHE v4.2.85, netMHCIIpan-3.0_IMGT-3.47, 5 locus (A,B,C,DRB1, DQB1)[2]
3. **Prediction of indirect T-cell recognition of mismatched peptides:**
   PIRCHE v4.2.85, Frost-1.1_IMGT-3.54, 5 locus (A,B,C,DRB1, DQB1)[2]
4. **Antigen mismatches at HLA-A, -B, -DRB1**
5. **Antigen Mismatches at HLA-DRB1 only**

Per PIRCHE, Frost is a newly developed predictor for peptide binding by HLA-DRB1 that uses Artificial Neural Networks (ANN) trained on binding data from the IEDB database.

Correlations between the risk stratification categories, dnDSA development (MFI >1000 x 2, MFI > 5000), and clinical outcomes were analyzed.

Of the 234 transplants, 28 experienced graft failure during the follow-up period. 7 cases of graft failure were determined to be nonimmune mediated and excluded. Time to alloimmune rejection-mediated graft failure was determined from the resumption of dialysis date.

Rising serum creatinine (Cr) is indicative of decreasing kidney filtration, and often results from immune-mediated rejection of the allograft, including acute cellular (T-cell mediated) rejection and antibody-mediated rejection. However, other non-alloimmune causes of Cr spikes can also be seen in the post-transplant setting, including dehydration, ureterovesical obstruction, CMV and BK viremia, etc. Consequently, we censored cases of rising Cr when chart review revealed definitive non-alloimune causes.

Event-free survival Kaplan-Meier curves were generated and hazard ratios and P-values (log-rank test for significance) between the groups were calculated.

Results

Lower HLA-DR/DQ molecular eplet mismatch has been shown to confer lower risk of dnDSA development[1]. Similarly, among the alloimmune risk stratification methods, we saw the strongest correlation to DSA development with HLA-DR/DQ molecular eplet mismatch. Although eplet mismatches, PIRCHE scores, and antigen level mismatches all were significantly associated with DSA-free survival, only HLA-DR/DQ molecular eplet mismatch stratification was significantly associated with the development of strong DSAs > 5000 MFI.

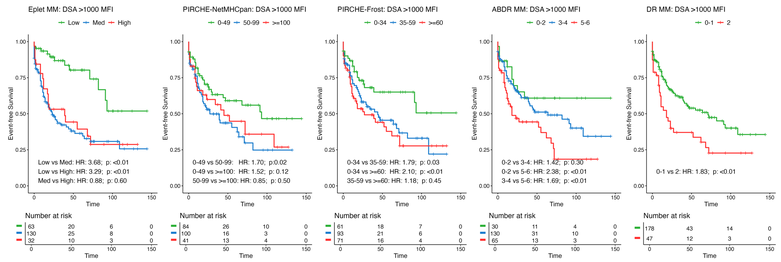

Figure 1 Correlation between immunologic risk stratifications and the development of any DSA > MFI 1000 detected from at least 2 separated sample dates. Event time indicates the date when the DSA first crossed MFI of 1000.

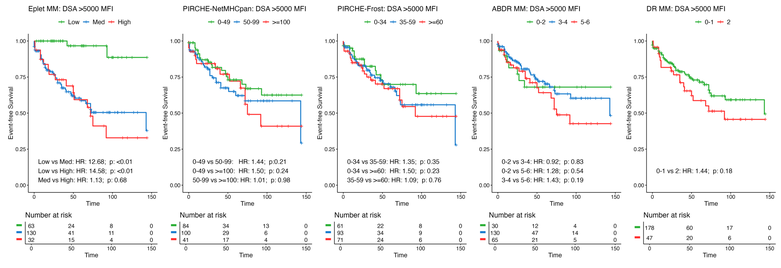

Figure 2 Correlation between immunologic risk stratifications and the development of strong DSAs > MFI 5000.

Examining the risk of graft damage from alloimmune rejection, low HLA-DR/DQ molecular eplet mismatch and low PIRCHE-II Frost scores were both significantly associated with reduced risk of serum Cr spikes > 3.0mg/dL compared to those with higher HLA-DR/DQ molecular eplet mismatch and PIRCHE-II Frost scores.

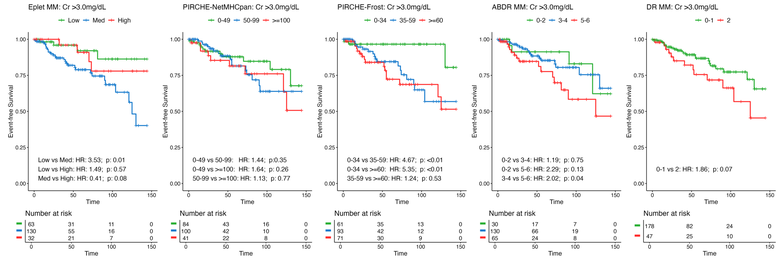

Figure 3 Correlation between immunologic risk stratifications and serum creatinine >3.0mg/dL (post establishment of the graft Cr baseline, typically measured at 1 month post-transplant).

Finally, HLA-DR/DQ molecular eplet mismatch, PIRCHE-II Frost, and antigen mismatch stratifications were all significantly associated with the risk of alloimmune mediated graft failure. Interestingly, while the original PIRCHE-II NetMHCpan scores failed to show a statistically significant association with alloimmune mediated graft failure, the newly developed PIRCHE-II Frost scores showed the strongest association with alloimmune mediated graft failure.

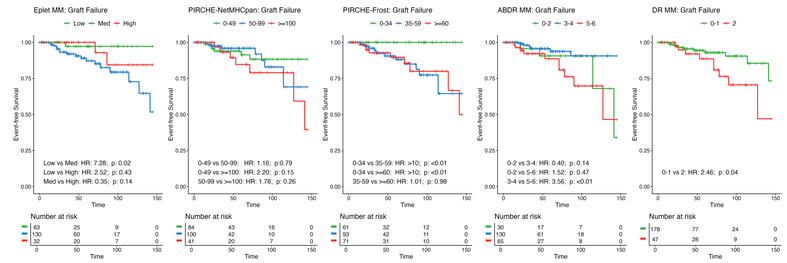

Figure 4 Correlation between immunologic risk stratifications and risk of alloimmune mediated graft failure

Consistent with published data from other studies, unfortunately, black and African American pediatric kidney transplant recipients from our program also suffered significantly higher rates of DSA development and worse clinical outcomes compared to white non-Hispanic/Latino recipients.

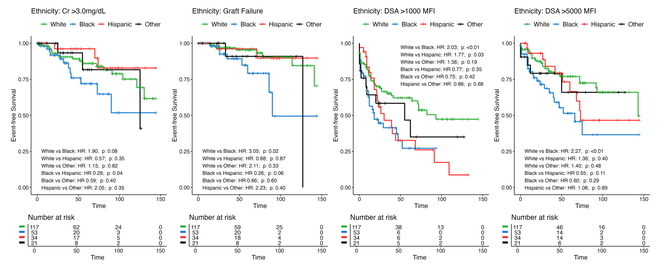

Figure 5 Ethnicity and race disparities among pediatric kidney transplant outcomes

Conclusions

- **Low HLA-DR/DQ molecular eplet mismatch confers lower risk of dnDSA development for pediatric kidney transplants**
- **PIRCHE-II Frost scores best correlate with the risk of significant alloimmune mediated graft damage and subsequent graft failure**

References

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2. www.pirche.com PMID: 28613392 DOI: 10.1111/ajt.14393
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