HLA-DR Molecular Mismatch Stratifies the Risk for Early Acute Cellular Rejection in Lung Transplant Recipients

Qingyong Xu[1], Mitchell Ellison II[1], Carlo Iasella[2], Matthias Niemann[3,4], Michael Sciullo[5], John McDyer[5], Chadi A. Hage[5], Norihisa Shigemura[6], Adiana Zeevi[1]

[1]Department of Pathology; [2]School of Pharmacy; [5]Department of Medicine; [6]Department of Cardiothoracic Surgery, University of Pittsburgh | [3]PIRCHE AG | [4]Charité Universitätsmedizin Berlin

INTRODUCTION

- HLA molecular mismatch (mMM) predicts post-transplant donor-specific antibody (DSA) development in kidney and heart transplant recipients
- Previously, we reported using a combination of 2 mMM algorithms in pediatric heart transplant cohorts to determine the risk of developing DSA and antibody-mediated rejection (ref #1)
- Emerging evidence suggests that mMM may also contribute to cellular alloimmune responses.
- Whether mMM predicts acute cellular rejection (ACR) in lung transplantation remains unknown.
- We evaluated DSA-derived mMM risk groups and early ACR in 713 lung transplant recipients.

METHODS

- Single-center cohort; transplant (January 2014–July 2025)
- High-resolution HLA typing by NGS, SSO/SSP, or imputation.
- mMM assessed by epMM (HLA Matchmaker v4.0) and PIRCHE-T2 (Predicted Indirectly Recognizable HLA Epitopes) v4
- DSA-derived locus-specific cutoffs assigned low-, intermediate-, and high-risk groups.
- Kaplan–Meier's and Cox regression analyses evaluated ACR ≥2 and ACR ≥3 within 12 months.

HLA-DR RISK CLASSIFICATION

INTERMEDIATE RISK epMM ≥ 16 and PIRCHE-T2 < 33	HIGH RISK epMM ≥ 16 and PIRCHE-T2 ≥ 33
LOW RISK epMM < 16 and PIRCHE-T2 < 33	INTERMEDIATE RISK epMM < 16 and PIRCHE-T2 ≥ 33

Risk cutoffs were derived from post-transplant DR-DSA (MFI>2000 in ≥ 2 samples) in the same cohort, using ROC analysis and Youden's Index for each mMM method (refs. #1 & 2)

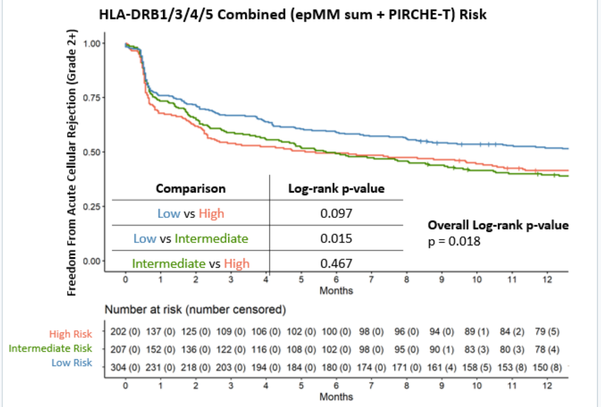
713 Lung transplant Recipients

449 (63.0%) ACR ≥2

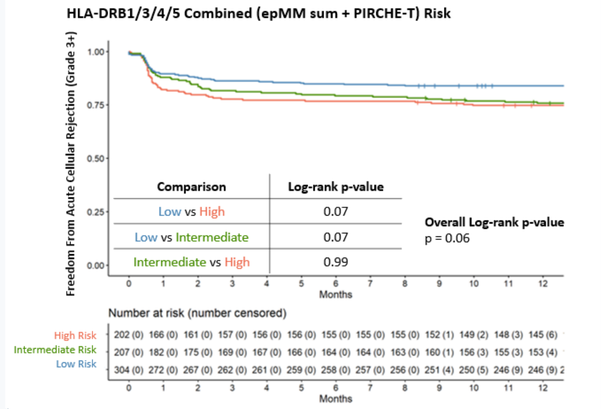
170 (23.8%) ACR ≥3

12 months Observation

ACR GRADE ≥2 FREE SURVIVAL



ACR GRADE ≥3 FREE SURVIVAL



ACR GRADE ≥2 FREE SURVIVAL

Univariate Cox Results

Risk Level	ACR Neg N (%)	ACR Pos N (%)	HR (CI)	P-value
High	73 (27.7)	129 (28.7)	1	1
Intermediate	62 (23.5)	145 (32.3)	1.09 (0.86-1.38)	0.4710
Low	129 (48.9)	175 (39.0)	0.80 (0.64-1.01)	0.0599

ACR GRADE ≥3 FREE SURVIVAL

Univariate Cox Results

Risk Level	ACR Neg N (%)	ACR Pos N (%)	HR (CI)	P-value
High	148 (27.7)	54 (31.8)	1	1
Intermediate	150 (28.1)	57 (33.5)	1 (0.69-1.46)	0.9869
Low	245 (45.9)	59 (34.7)	0.69 (0.47-0.99)	0.0446

LOCUS-SPECIFIC ASSOCIATION with ACR

HLA locus	ACR ≥2	ACR ≥3
HLA-A/B/C mMM	Not significant	Not significant
HLA-DQA1/DQB1 mMM	Not significant	Not significant

CONCLUSIONS

- DSA-derived HLA-DR mMM risk groups predict early ACR after lung transplantation.
- Only HLA-DR, but not HLA-A/B/C or HLA-DQ mMM, was associated with ACR risk.
- Findings support a potential link between humoral and cellular alloimmune responses and the utility of mMM for immunologic risk stratification.

Abbreviations: ACR, acute cellular rejection; DSA, donor-specific antibody; epMM, eplet mismatch; HR, hazard ratio; mMM, molecular mismatch.

REFERENCES

1. Ellison MA II, Xu Q, Zeevi A. Combined Molecular Mismatch Scores for Immunologic Risk Stratification in Pediatric Heart Transplantation. Curr Opin Organ Transplant. 2025;30:418–424.
2. Xu Q, Ellison MA II, Niemann M, et al. HLA Molecular Mismatch Refines Post-Transplant DSA Risk in Lung Transplant Recipients. J Heart Lung Transplant. 2026;45(5 Suppl):151.

Poster #1004, ASHI 2026, Qingyong Xu (xuq5@upmc.edu))