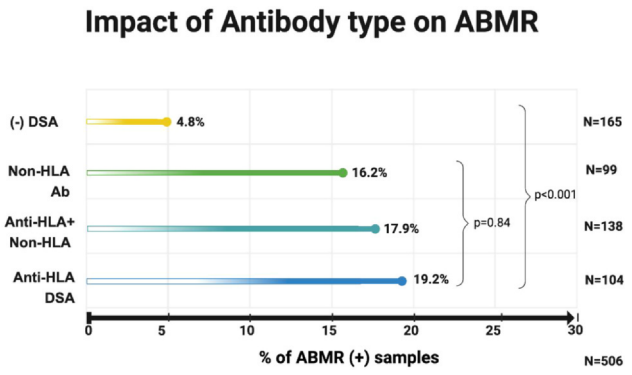
Conclusion: Non-HLA Abs were associated with a risk of ABMR similar to that of samples with anti-HLA Abs when assessed by MMDx. However, the coexistence of both Ab types did not result in a cumulative effect on the rates of ABMR



(420)

Pre-Transplant Proteomic Profiling to Define Molecular Signatures of Rejection Risk in Heart Transplant Recipients

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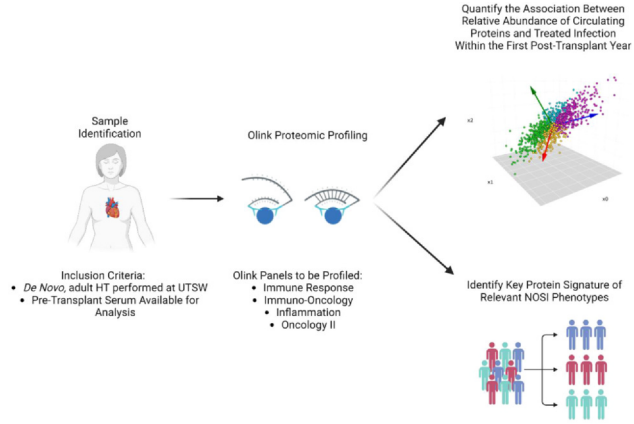
Purpose: Assessing the net state of immunosuppression (NOSI) at the time of heart transplantation (HT) remains a clinical challenge. As such, most HT programs protocolize baseline immunosuppressive (IS) therapies agnostic to recipient immunobiology. Proteomic profiling has emerged as a powerful tool for biomarker discovery that can highlight key biological pathways of interest. We hypothesized that pre-HT proteomic profiling could identify key biomarkers of rejection risk within the first post-transplant year.

Methods: 338 HT recipients who underwent HT between 1/2015 and 6/2024 had available pre-transplant serum for analysis. Mean recipient age was 52.5 years, and 28.1% of recipients were female. Our HT population was diverse, with 51.2% White, 30.8% Black, and 14.1% Hispanic recipients. We identified four key patient phenotypes after 1 year of follow-up: (1) patients with no histopathologic evidence of rejection and no infection, (2) patients with no histopathologic evidence of rejection and a serious infection, (3) patients with histopathologic rejection and a serious infection, and (4) patients with histopathologic rejection and no infection.

Proteomic profiling is being performed using the Olink platform, which uses proximity extension assay technology to identify and rapidly quantify proteins with high sensitivity and specificity. We are utilizing 4 Olink panels (92 proteins each) focusing on proteins reporting on inflammation and the immune response. In addition to identifying protein biomarkers associated with rejection within the first post-transplant year, we also plan to leverage novel unsupervised modeling approaches (LASSO, e.g.) to classify NOSI phenotypes.

Endpoints: We hypothesize that pre-transplant proteomic profiling will identify biomarkers of early rejection risk in HT candidates and will discriminate key NOSI phenotypes.



(421)

Heart Transplant Rejection Following Donation After Circulatory Death with Thoracoabdominal Normothermic Regional Perfusion

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Purpose: Donation after circulatory death (DCD) has expanded the donor pool and decreased time on heart transplant waitlist, but the impact of thoracoabdominal normothermic regional perfusion (TA-NRP) recovery on rejection rates has not been well established. We aimed to evaluate rejection rates associated with DCD TA-NRP recovery compared to donation after brain death (DBD).

Methods: All adult heart transplantations performed at our institution during 10/2022-8/2024 were included. All patients received maintenance immunosuppression with tacrolimus, mycophenolate mofetil, and steroids and underwent serial endomyocardial biopsies starting 1 week after transplant. Antithymocyte globulin was used for induction therapy. Descriptive statistics were described as number (%) and analysis was performed with 2-way ANOVA.

Results: There were 44 DCD TA-NRP and 82 DBD heart transplants during the study period, of which 15 received induction therapy (6 TA-NRP, 9 DBD). Baseline characteristics were similar between cohorts. One TA-NRP recipient died before their first biopsy with ACR 1R/1A on post-mortem pathology, and one DBD recipient also died before their first biopsy with no post-mortem pathology. Of the remaining patients, there were 23 (53.5%) TA-NRP and 51 (63.0%) DBD recipients with at least 1 treated rejection episode within the first year after transplant, of which 6 (3 TA-NRP, 3 DBD) received induction. Severity of rejection episodes are depicted in the table with no significant difference in ACR or AMR rates between cohorts. One-year survival (93.3% TA-NRP vs 94.0% DBD, p=0.86) was comparable between TA-NRP and DBD heart recipients.

Conclusion: DCD TA-NRP recovery is not associated with worse ACR, AMR, or 1-year survival rates in comparison to DBD recovery for heart transplantation. Future studies should evaluate long-term graft function and survival associated with TA-NRP recovery.

Number of patients with treated rejection episodes within 1 year of transplant.	TA-NRP (n=43)	DBD (n=81)	P-value
Acute cellular rejection (-ACR) (n, %)			0.93
ACR 1R	23 (53.5-%)	50 (61.7-%)	
ACR 2R	9 (20.9%)	16 (19.8-%)	
ACR 3R	3 (7.0%)	1 (1.2%)	
Antibody-mediated rejection (AMR) (n, %)			0.28
AMR 1	1 (2.3%)	1 (1.2%)	
AMR 2	2 (4.7%)	1 (1.2%)	
AMR 3	0	0	

(422)

Molecular Diagnostic Classification for Heart Allograft Rejection: A Validated and Automated System

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Purpose: Endomyocardial biopsies (EMB) gene expression profiling is a promising companion tool for rejection diagnosis. However, novel molecular diagnostic systems need to be validated and designed accessible for routine application in clinical practice to support diagnosis post heart transplantation.

Methods: We performed a multicenter, retrospective study (NCT06436027), collecting 591 FFPE-EMBs between 2011 and 2021 representative of the landscape of rejection (antibody-mediated rejection-AMR, n=188; acute cellular rejection-ACR, n=289; non-rejection, n=114). Tissue gene expression was analyzed using the Banff Human Organ Transplant gene panel. Molecular classifiers for AMR and ACR were built using supervised models, assessing thoroughly the performance. An automated molecular report was developed to provide a comprehensive visualization for clinical use.

Results: In the validation cohort (n=116), the molecular classifiers demonstrated strong diagnostic performance: AMR detection achieved an accuracy of 81.89% (ROC-AUC=0.831, Brier score=0.143), while ACR detection achieved 77.58% accuracy (ROC-AUC=0.812, Brier score=0.176). The molecular report provided real-time assessment of molecular-based rejection scores, while allowing to contextualize a novel biopsy within the reference set rejection landscape. In addition to delivering quantitative scores for AMR and ACR, clinical and biological information are recapitulated in each report, correlating the molecular findings with the pathophysiological insights from primary molecular pathways involved. This tool captured subtle molecular signals in cases of early or sub-clinical rejection, offering insights into potential risks even when histology was inconclusive. The automated nature of the report considerably reduces turnaround time, seamlessly integrating into clinical workflows.

Conclusion: The molecular diagnostic system, validated, and supported by an automated report, demonstrated reproducibility and reliability in identifying cardiac rejection. This system can complement standard pathology, reduce diagnostic uncertainty, and serve as a practical companion tool in the clinical management of heart transplant patients, ensuring timely and accurate diagnosis.

(423)

Clinical Implications of Early Post-Transplant Restrictive Hemodynamics in Absence of Primary Graft Dysfunction or Cardiac Allograft Rejection

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Purpose: Clinical implications of early post- transplant restrictive hemodynamics in absence of primary allograft dysfunction or cardiac allograft rejection are poorly understood. We sought to investigate the impact of restrictive cardiac allograft hemodynamic profile on cardiac graft survival.

Methods: We queried for first-time adult (age ≥18) single-organ heart transplant patients with available post-transplant hemodynamic data in the UNOS registry between 2023 and 2024. Patients with right atrial pressure ≥ 12, pulmonary artery diastolic pressure > 15, and cardiac index ≥ 2.2 L/min/m2 at 72 hours post-transplant in the absence of graft dysfunction and without evidence of acute rejection during index stay met criteria for a RH profile.

Results: 337 patients (34.3%) out of 984 patients had restrictive hemodynamic profile at 72 hours post-transplantation. Patients with RH were younger (53.3 ± 12.5 vs. 55.6 ± 12.0), had higher BMI (28.2 ± 5.3 vs. 27.5 ± 4.7), elevated pre-transplant PA systolic pressure (42.3 ± 14.1 vs. 40.3 ± 13.9 mmHg), DCD donor use (22.6% vs. 13.6), and prolonged donor ischemic time (4.04 ± 1.5 vs. 3.84 ± 1.5 (all $p < 0.05$). Patients with early restrictive hemodynamics had significantly higher incidence of acute kidney injury requiring dialysis post-transplant (20.8% vs. 14.7%, p=0.025), despite similar pre-transplant eGFR (87.4 ± 26.2 vs. 87.4 ± 28.2, p=0.987). Post-transplant cardiac allograft survival at 6-months was comparable in patients with early restrictive hemodynamics vs. those without (95.4% vs. 96.6%, log-rank p=0.700). (**Figure**)

Conclusion: Early restrictive hemodynamic profile is prevalent in heart transplant recipients in the recent era of DCD donor use. Both recipient and donor risk factors contribute to the development of early restrictive hemodynamics. Restrictive hemodynamics is associated with increased risk of renal failure requiring dialysis.