ISHLT December 2024 | Pediatrics
JOURNAL WATCH

Ryan Handoko, MD [1] & Anna Joong, MD[2]
[1] Children's Hospital Los Angeles, CA, USA
[2]Ann & Robert H Lurie Children's Hospital of Chicago, Chicago IL

Shahnawaz Amdani, MD
GUEST EDITOR
ISHLT.ORG

Prevalence and impact of recurrent rejection on pediatric heart transplant recipients

Amdani et al. *Journal of the American College of Cardiology 2024.* | https://doi.org/10.1016/j.jacc.2024.08.010

Study Highlights

Objective: In pediatric heart transplant (HT) recipients, long-term outcomes of recurrent rejection (RR) is incompletely understood in the modern era.

Methods:

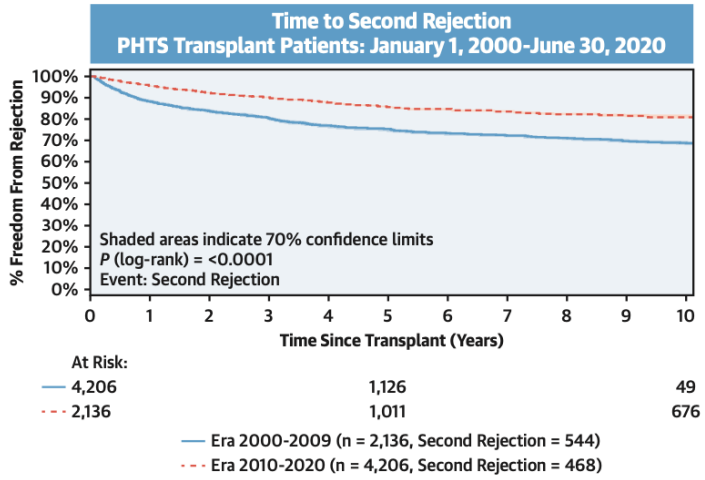
- Multicenter retrospective study of pediatric HT recipients (age <18 years) enrolled in Pediatric Heart Transplant Society (PHTS) database, from 2000-2020
- Stratified into early era (2000-2009) and current era (2010-2020)
- Primary outcome: evaluate freedom from RR in early vs current era
- Secondary outcomes: evaluate impact of RR on coronary artery vasculopathy (CAV) and graft loss, identify risk factors for RR, evaluate racial disparities associated with RR

Results:

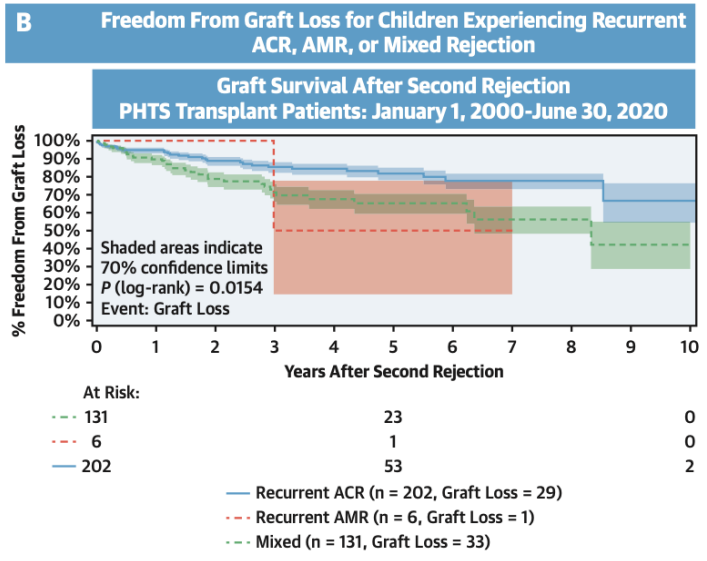
- Of **6,342 HT recipients**, 62% experienced 0, 21% experienced 1, and **17% experienced ≥2 rejection episodes** over 3.9 (IQR 1.3-7.5) years
- HT recipients in **current era** less likely to experience RR (**11%**) compared to early era (25%, p<0.0001, Figure A)
- **Lower graft survival** in RR compared to 0 or 1 rejection episode (p<0.0001)
- Among RR, lower graft survival in **recurrent mixed rejection** (65.3%) or **AMR** (50%), compared to ACR (81.8%, p=0.015, Figure B)
- Among RR, higher rates of CAV and graft loss in **Black children**
- Risk factors at HT for RR include: older age (HR 1.1), female (HR 1.1), Black race (1.3), early era (HR 2), and positive crossmatch (HR 1.3).

Conclusions: RR remains prevalent, albeit less frequent, in the current era. Children with RR are at higher risk of graft loss, especially those with recurrent mixed rejection or AMR. Racial disparities persist among children with RR.

A Freedom From Recurrent Rejection for Children Transplanted in the Earlier Era to Those Transplanted in the Current Era



B Freedom From Graft Loss for Children Experiencing Recurrent ACR, AMR, or Mixed Rejection



Reviewer's Comments

- This large registry analysis provides a contemporary update on RR in pediatric HT recipients.
- Improvements in clinical management and immunosuppressive strategies likely play a role.
- Identification of AMR or mixed rejection at the first or subsequent rejection episodes may warrant closer clinical scrutiny, given higher risk of graft loss.
- Further attention is warranted toward what underlies racial disparities, e.g. implicit bias, socioeconomic factors.

Limitations

- Heterogeneous multicenter population: biopsy-graded rejection, reports on CAV, and clinical diagnosis of rejection are center-specific.
- Limited details available on induction and baseline immmunosuppression used between groups
- Small number of recurrent AMR (n=6) compared to recurrent ACR (n=202) or mixed (n=131)
- No sub-analysis on rejection episodes diagnosed by clinical findings or echocardiogram and whether these associate with risk of CAV or graft loss

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Anusha Konduri[1], MBBS & Joseph Spinner[2], MD
[1]C.S . Mott Children's Hospital, University of Michigan, Ann Arbor, MI
[2]Baylor College of Medicine, Houston, TX

Shahnawaz Amdani, MD
GUEST EDITOR
ISHLT.ORG

Clinical Outcomes After a Biopsy Diagnosis of Antibody-Mediated Rejection in Pediatric Heart Transplant Recipients

Everitt M, et al. *J Heart Lung Transplant Sept* 2024 | https://doi.org/10.1016/j.healun.2024.08.017

Study Highlights

Objective: To understand the prevalence of antibody-mediated rejection **(**AMR) and impact of AMR on graft survival and patient outcomes in pediatric heart transplant recipients.
Methods: Retrospective review of all children in the Pediatric Heart Transplant Society (PHTS) Registry who underwent heart transplant (HT) between January 2015 - June 2022 and experienced ≥1 treated rejection episode. Survival outcomes were compared between AMR and acute cellular rejection (ACR). Secondary outcomes including infection, malignancy, and cardiac allograft vasculopathy (CAV) were also evaluated. Rejection episodes were excluded if there was no or incomplete biopsy assessment performed during AMR episode.
Results: 697 patients with rejection were included. AMR was identified in 261 (37%) patients while 436 (63%) had ACR only. 40% of patients with treated AMR had pAMR1i or 1h and 35% of treated ACR was 1R. The median time from HT to treated rejection was significantly shorter for AMR vs ACR (0.11 vs to 0.29 years; $p < 0.01$). Survival after AMR in the 1st year was lower than survival after ACR-only ($p<0.01$; see Fig). Factors predicting graft loss after AMR included younger age at HT, presence of congenital heart disease (CHD), and rejection associated with hemodynamic compromise. No significant differences between the 2 groups were observed in the time to CAV, infection, or malignancy.
Conclusions: AMR was associated with a higher rate of graft loss compared to ACR only when it occurred within the first year post-HT. Younger age at HT, history of CHD, and cardiac dysfunction during rejection were independent predictors of graft loss following AMR.

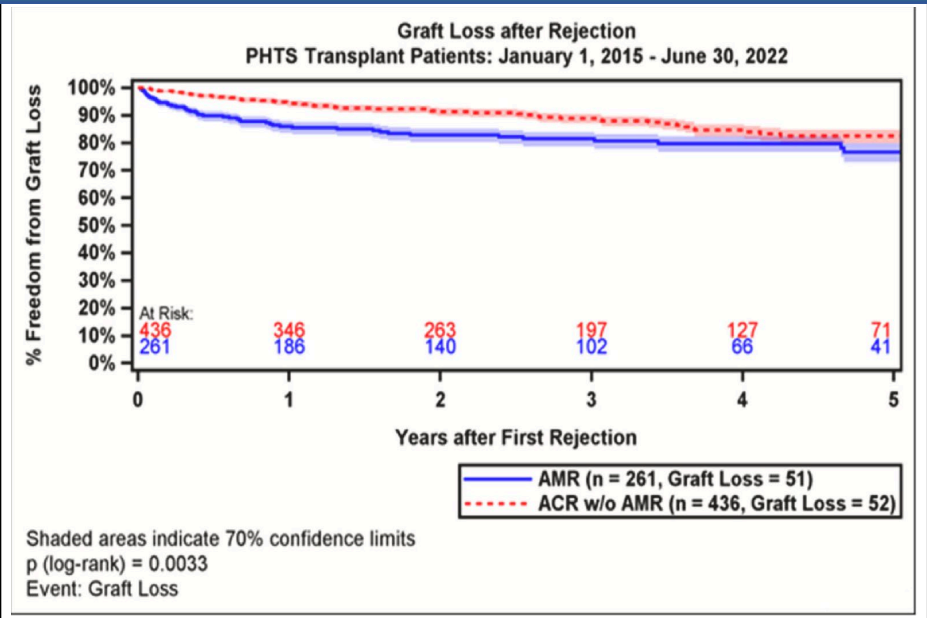

Table 2 Cox Hazard Regression Analysis of Predictors of Graft Loss After an Initial Episode of Rejection With AMR

Reviewer's Comments

- This analysis is the largest study to date of AMR in pediatric HT recipients treated for rejection and emphasizes the importance of early AMR on graft outcomes.
- The incidence of treated rejection and how it is treated does not appear to have significantly changed since previous reports describing pediatric AMR.
- There is considerable variability in treatment of AMR at pediatric HT centers, and the effectiveness of AMR therapies were not evaluated in this study.
- The high prevalence of "low-grade" rejection (1R, pAMR1h/i) of the overall treated rejection cohort suggests these patients had other clinical factors indicating therapy could be beneficial and that "low grade" rejection may have clinical significance.
- The incorporation of donor-derived cell-free DNA and molecular microscope may help elucidate the clinical relevance of these "low-grade" rejection episodes and play a role in evaluating response to rejection therapy.
- Younger age, CHD, and cardiac dysfunction were identified as independent predictors of graft loss after AMR; these patients may benefit from increased monitoring, more aggressive rejection treatment, or increased maintenance immunosuppression.

Limitations

- 1/4 rejection episodes excluded due to incomplete biopsy data.
- Analysis of CAV and other secondary outcomes likely limited by the overall study duration

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Brendan Floyd, MD, PhD[1] & Anna Joong, MD[2]
[1] Stanford Medicine Children's Health, Palo Alto, CA
[2] Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL

Shahnawaz Amdani, MD
GUEST EDITOR
ISHLT.ORG

Risk Factors of Post-Traumatic Stress in Pediatric Solid Organ Transplant Recipients

Hind T. et al. *Pediatric Transplantation 2024.* | https://doi.org/10.1111/petr.14854

Study Highlights

Objective: Individuals with end-stage organ failure are known to experience recurrent episodes of medical trauma, and many pediatric recipients of solid organ transplants develop post-traumatic stress symptoms (PTSS). Despite the association between PTSS and decreased quality of life, PTSS remain underappreciated as a major comorbidity. This study evaluated pre- and post-transplant factors associated with the development of PTSS in this population.

Methods:

- Retrospective, cross-sectional study of 86 pediatric solid organ transplant recipients (17 heart, 44 kidney, and 25 liver)
- Trauma symptoms were measured by the Child Trauma Screening Questionnaire (CTSQ)
- Demographic and clinical factors were tested for independent association with CTSQ scores

Results:

- The median post-transplant CTSQ score was 2 out of 10 (IQR 1-4)
- 22% were identified as high risk (score ≥5) for PTSD
- Higher CTSQ scores were associated with ICU days in the prior year, greater number of medications, and involvement with foster care
- Higher family functioning (measured by the Family Impact Module) was associated with lower CTSQ scores
- The median pre-transplant CTSQ score was 2 (IQR 1-6, N = 34), suggesting that PTSS develop before transplant and persist afterward

Conclusions:

- PTSS are prevalent in children and adolescents before and after solid organ transplant.
- Risk factors include recent adverse medical experiences and complexity, whereas family stability may be protective

Variable	Correlation	Fold difference	p-value
Baseline			
Age at diagnosis	0.27		0.013
Lifetime history of psychiatric condition		2.2	<0.001
Foster care		2.0	0.035
Contemporaneous			
Number of medications	0.30		0.006
Hospitalization days within 12 months	0.37		<0.001
ICU days within 12 months	0.38		<0.001
Family Impact Module	-0.44		<0.001

Model	Beta	Standard error	p-value	Adjusted R-squared
Primary				
ICU days within 12 months	0.21	0.075	**0.006**	0.26 (p<0.001)
Number of medications	0.13	0.066	**0.045**	
Foster care	2.58	1.13	**0.025**	
Lifetime history of psychiatric condition	1.39	0.78	0.079	
Primary plus Family Impact Module				
ICU days within 12 months	0.17	0.082	**0.043**	0.33 (p<0.01)
Number of medications	0.16	0.10	0.12	
Foster care	2.12	1.49	0.16	
Lifetime history of psychiatric condition	1.13	1.14	0.33	
Family Impact Module	-0.038	0.018	**0.040**	

Univariate screening (top) **and multivariable analysis** (bottom) **identify factors associated with post-transplant PTSS:** Medical complexity (ICU days and medications) and foster care involvement are associated with higher PTSS, while family stability may be protective.

Reviewer's Comments

- Routine screening with the aid of a validated instrument (CTSQ) highlights the substantial prevalence of post-traumatic stress symptoms in pediatric solid organ transplant recipients.
- As the primary associated factors (medical complexity, family stability) are not easily modifiable, subsequent work is needed to investigate interventions which may support children and their families.
- The evaluation of pre-transplant PTSS was exploratory and deserves further investigation, as this may be the opportune time to intervene.
- For heart transplant recipients, it may be helpful to distinguish between individuals with congenital heart defects compared with cardiomyopathies.

Limitations

- The single-center retrospective study design limits the generalizability of the results and the investigation of associated factors.
- Diversity of organs transplanted means that the number of individuals in each group is small and may obscure organ-specific factors.
- Developmental status (delays, neurodiversity) was not quantified, and divergence may impact or under-represent the prevalence of these symptoms.

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Joseph Stidham, MD[1] & Anna Joong, MD[2]
[1] Boston Children's Hospital, Boston, MA, USA
[2] Ann & Robert H Lurie Children's Hospital of Chicago, Chicago IL

Shahnawaz Amdani, MD
GUEST EDITOR
ISHLT.ORG

Mechanical circulatory support early after pediatric heart transplantation—an analysis from the Pediatric Heart Transplant Society

Simmonds et al. *Journal of Heart and Lung Transplantation 2024.* | https://doi.org/10.1016/j.healun.2024.09.003

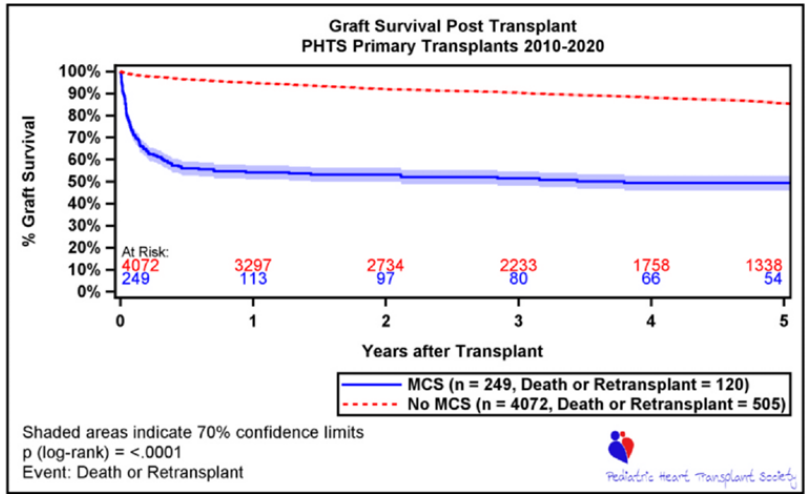
Study Highlights

Objective: Despite improvements in recent years post-transplant mortality remains highest in the first 30 days following transplant largely due to primary graft failure. This study investigates the predisposing factors, morbidity and mortality associated with mechanical circulatory support (MCS) for the treatment of primary graft failure.

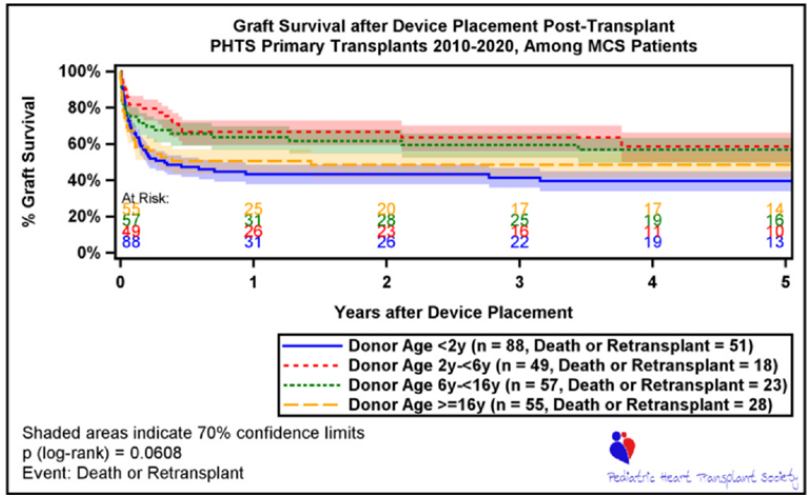
Methods: The PHTS database was used to analyse all primary heart transplants 2010-2020. The cohort was divided based on need for MCS within 30 days of transplant. Donor and recipient demographic factors, graft function and operative parameters (e.g., ischemic time, crossmatch, etc) were recorded. Characteristics of patients who did and did not require MCS were compared.

Results: 4,321 primary transplants were included. 249 (5.8%) required MCS. Of these 230 required ECMO, 19 required VAD. Using a Cox proportional hazard model CHD (p=0.0002), older donor age (p<0.0001), and longer ischemic time (p=0.018) were associated with increased MCS. Larger recipient BSA (p<0.0001) and higher donor LVEF (p=0.016) were associated with decreased need for MCS. Overall, 1-year survival in those requiring MCS was 54.2% compared with 94.8% in those who did not require MCS (p<0.0001). Patients who survived to 1 year had similar rates of late survival in both groups.

Conclusions: In total 5.8% of patients required MCS in the first month following transplantation. Mortality is high in pediatric patients supported with MCS for primary graft failure following heart transplantation. Despite this, those who survive to 1-year post-transplantation have comparable long-term survival to patients who did not require MCS.



Post-transplant survival. MCS, mechanical circulatory support



Graft survival following MCS by donor age.

Reviewer's Comments

- This large pediatric database study provides contemporary outcomes of early MCS use following heart transplantation with high mortality rates, with similar outcomes between early and recent eras.
- A trend was noted of improved survival for those supported first with VAD vs ECMO (68.4% vs 53.9%) though statistical significance was not reported.
- VAD was associated with a longer duration of MCS compared to ECMO (32 vs 6 days, p=0.0004). This may be reflective of different indications as 13/19 (68.4%) of VADs were used in an RVAD only configuration.
- Further investigation is warranted to determine the additive risk of independent donor and recipient factors. This may allow for better outcome prediction and matching of high-risk recipients to optimal organs to minimize post-transplant mortality.

Limitations

- As a retrospective registry study, the authors are limited to the dataset and important clinical characteristics such as pulmonary vascular resistance were not available.
- Heterogeneity of institutional practice may introduce bias in the threshold, timing, and type of MCS initiation.

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Dyan Z. Zhang[1], MBBS, MRCPCH and Joseph Spinner[2], MD
[1]The Hospital for Sick Children, Toronto, Canada
[2]Baylor College of Medicine, Houston, TX

Shahnawaz Amdani, MD
GUEST EDITOR
ISHLT.ORG

Association Between HsTnI and NTproBNP with Rejection and Graft Loss in Pediatric Heart Transplant Recipients

Magnetta et al. *Pediatric Transplantation November* 2024. | https://doi.org/10.1111/petr.14858

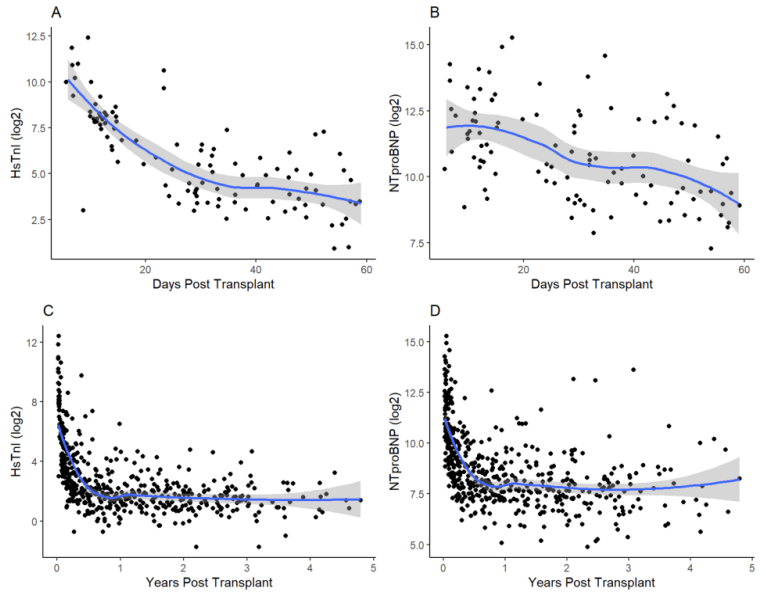
Study Highlights

Objectives: To describe the typical changes in high sensitivity Troponin I (hsTnI) and NTproBNP values early after pediatric heart transplant (HTx) and evaluate the association of hsTnI and NTproBNP with acute rejection (AR) and graft loss in pediatric HTx.

Methods: Single center retrospective analysis of banked serum sample levels of hsTnI and NTproBNP collected over 2 enrollment periods at the time of surveillance and for cause endomyocardial biopsy (EMB). Patients with samples drawn within 365 days post-HTx were included and followed for up to 5 years. For all analyses, hsTnI and NTproBNP were logarithm base 2-transformed. NTproBNP and hsTnI were plotted to demonstrate trends at varying timepoints post-HTx. NTproBNP and hsTnI values among samples with and without AR were compared with both univariable and multivariable analyses. Survival analysis with cox regression models were used to evaluate the relationships between NTproBNP and hsTnI values and other covariates with graft loss.

Results: A total of 580 samples from 53 HT recipients were included
- Precipitous decline in hsTnI and NTproBNP in first 60 days post-HTx
- Levels then remain relatively stable over next 5 years in absence of AR
- Median hsTnI is significantly higher in patients with AR (6.2ng/L vs 3.5ng/L, p<0.01) in both univariate and multivariate analysis
- Median NTproBNP did not differ between those with and without AR
- Those with graft loss had a significantly higher maximal NTproBNP (median 1996 vs 528pg/L, p=0.001) in the first 5 years post-HTx
- NTproBNP (HR 8.96; p=0.01) independently associated with graft loss

Conclusions: Elevation in hsTnI was associated with acute rejection and elevation of NTproBNP was associated with graft loss after pediatric HTx.



Characteristic	OR	95% CI	p
HsTnI (log_2)	1.33	1.09, 1.62	**0.004**
NTproBNP (log_2)	1.05	0.81, 1.35	0.72
Age at transplant (years)	1.07	1.01, 1.14	**0.028**
Female sex	1.57	0.71, 3.46	0.26
Ischemic time (min)	1.02	0.32, 3.24	0.97
Congenital heart disease listing diagnosis	1.82	0.82, 4.05	0.14
Positive crossmatch	1.76	0.62, 4.94	0.29

Characteristic	OR	95% CI	p
HsTnI (log_2)	1.35	1.09, 1.67	**0.006**
NTproBNP (log_2)	1.01	0.76, 1.33	0.96
Female sex	1.57	0.77, 3.20	0.22
Age at transplant (years)	1.08	1.01, 1.14	**0.018**

Legend (Left): Univariate analysis for AR
Legend (Top): Multivariate analysis for AR

	Univariable models			Multivariable model		
Characteristic	HR	95% CI	p	HR	95% CI	p
HsTnI (log_2)	2.14	1.04, 4.42	**0.039**	1.05	0.31, 3.51	0.94
NTproBNP (log_2)	3.91	1.59, 9.63	**0.003**	8.96	1.56, 51.5	**0.014**
Female sex	2.89	0.56, 15.0	0.21	30.0	1.25, 719.7	**0.036**
Age at transplant (Years)	0.94	0.82, 1.08	0.41	0.93	0.77, 1.13	0.45

Legend: Cox regression model for graft failure

Reviewer's Comments

- This is the first study which describes the expected trend of NTproBNP and hsTnI after pediatric HTx
- Unlike BNP, NTproBNP is not associated with AR, but it still has prognostic implications with high levels within 5-years post-HTx being independently associated with future graft loss
- Elevated hsTnI in the 1st yr post-HTx was associated with AR
- These more readily "available" biomarkers may add to the growing armamentarium of non-invasive surveillance tools which improve risk assessment for AR and may help reduce unnecessary EMB in pediatric HTx
- Future larger scale and prospective studies should evaluate the use of NTproBNP and hsTnI in conjunction with other non-invasive biomarkers, such as donor derived cell free DNA (dd-cfDNA), to improve risk assessment aimed to help improve outcomes after pediatric heart transplant

Limitations

- This was a single center retrospective analysis spread out over 2 different enrolment periods with a heterogenous cohort
- Graft function was not known and could not be correlated
- dd-cfDNA was not obtained so could not be compared with these biomarkers or added to predictive models
- There was a lack of consistent follow-up sera after treatment of AR which limited further assessment of association between hsTnI and AR
- Follow-up periods were highly variable and did not allow for assessment of longer-term outcomes