UCLA UCLA Previously Published Works

Title

Pediatric risk to orthotopic heart transplant (PRO) score: Insights from United Network for Organ Sharing (UNOS) waitlist mortality findings

Permalink

<https://escholarship.org/uc/item/48t860th>

Journal Pediatric Transplantation, 27(6)

ISSN

1397-3142

Authors

Raymundo, Stephanie Wilhalme, Holly Chaudhary, Anila [et al.](https://escholarship.org/uc/item/48t860th#author)

Publication Date

2023-09-01

DOI

10.1111/petr.14525

Peer reviewed

HHS Public Access

Pediatr Transplant. Author manuscript; available in PMC 2024 September 01.

Published in final edited form as:

Author manuscript

Pediatr Transplant. 2023 September ; 27(6): e14525. doi:10.1111/petr.14525.

Pediatric Risk to Orthotopic Heart Transplant (PRO) score: Insights from United Network for Organ Sharing (UNOS) waitlist mortality findings

Stephanie Raymundo, MD1, **Holly Wilhalme, MS**2, **Anila Chaudhary, MD**3, **Krystal Karunungan**4, **Juan Alejos, MD**5, **Neeraj Srivastava, MD, FAAP, MHA**⁵

1.Helen Devos Children's Hospital Pediatric Cardiology

2.University of California Los Angeles Department of Medicine Statistics Core

- 3.Children's Hospital of Philadelphia
- 4.University of California Los Angeles

5.University of California Los Angeles Mattel Children's Hospital

Abstract

Background: Pediatric heart transplant candidates on the waitlist have the highest mortality rate amongst all solid organ transplants. A risk score incorporating a candidate's individual risk factors may better predict mortality on the waitlist and optimize organ allocation to the sickest of those awaiting transplant.

Methods: Using the United Network for Organ Sharing (UNOS) database, we evaluated a total of 5542 patients aged 0–18 years old on the waitlist for a single, first time, heart transplant from January 2010-June 2019. We performed a univariate analysis on two-thirds (N=3705) of these patients to derive the factors most associated with waitlist mortality or delisting secondary to deterioration within 1 year. Those with a p-value<0.2 underwent a multivariate analysis and the resulting factors were used to build a prediction model using the Fine-Grey model analysis. This predictive scoring model was then validated on the remaining one-third of the patients $(N=1852)$.

Results: The Pediatric Risk to OHT (PRO) scoring model utilizes the following unique patient variables: blood type, diagnosis of congenital heart disease, weight, presence of ventilator support, presence of inotropic support, extracorporeal membrane oxygenation (ecmo) status, creatinine level, and region. A higher score indicates an increased risk of mortality. The PRO score had a predictive strength of 0.762 as measured by Area Under the ROC curve at 1 year.

Conclusion: The PRO score is an improved predictive model with the potential to better assess mortality for patients awaiting heart transplant.

Relevant social media pages: None

Reprint and corresponding author byline: Stephanie Raymundo, MD, Helen DeVos Children's Hospital Congenital Heart Center, 25 Michigan St NE #4200, Grand Rapids, MI 49503, stephanie.raymundo@helendevoschildrens.org.

Author Contributions: Dr. Stephanie Raymundo, Dr. Juan Alejos, and Dr. Neeraj Srivastava conceptualized the study. Dr. Stephanie Raymundo and Holly Wilhalme designed the study. Dr. Stephanie Raymundo, Dr. Anila Chaudhary and Krystal Karunungan drafted the initial manuscript. All authors critically reviewed the manuscript for important intellectual context and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Keywords

pediatric heart transplant; pediatric transplantation; risk factors; solid organ transplantation

INTRODUCTION

Waitlist mortality remains highest for pediatric orthotopic heart transplant (OHT) among all solid-organ transplants in the United States. Once patients are listed for OHT, they are sub-classified based on medical urgency (Status 1A, Status 1B, Status 2), with Status 1A denoting the greatest acuity. The criteria for Status 1A listing has been modified several times in attempt to assure that available organs are allocated to the most critical patients. However, there remains significant heterogeneity in the ability of listing status to accurately predict waitlist mortality, particularly among children^{1,2}. Mortality has also been found to vary considerably within Status 1A with up to a tenfold difference between patients within the group³. Collectively, these findings suggest that improvements in risk assessment of pediatric OHT candidates may assist in improving wait list mortality and optimizing organ allocation.

Clinical variations in mortality risk have been observed with various factors associated with greater waitlist mortality: younger age at listing⁴, ventilator support¹, presence of congenital heart disease^{1,3,4}, extracorporeal membrane oxygenation (ecmo) support^{1,3,5}, and racial and ethnic disparities^{1,3}. There are currently scoring systems to help predict post-transplant mortality in high risk patients, with risk of death increasing when a patient has more than one high risk criteria prior to transplantation⁶. No studies to date, however, have investigated the development of a pre-transplant risk calculator to predict mortality in children while awaiting heart transplant.

METHODS

This was a retrospective study of the Organ Procurement and Transplantation Network (OPTN) database which is a registry of organ transplants performed in the United States of America. The OPTN database was queried for demographic and clinical variables in 0–18 year old patients on the waitlist for a single organ heart transplant from January 2010 to June 2019. Patients who were repeat transplants or who were undergoing multiple organ transplants were excluded. A total of 5542 patients were included in the analysis.

The patients were randomly divided into a "derivation cohort" and a "validation cohort." The "derivation cohort" was used to develop the prediction model and the "validation cohort" was used to validate the model. The "derivation cohort" comprised two-thirds of the total number of patients $(N=3695)$. A Fine and Grey survival analysis of time to death or delisting secondary to deterioration within one year of listing was used to conduct a univariate analysis of the patient factors. Fine and Grey was chosen in order to account for competing risks⁷. Patients who were transplanted were considered a competing event and censored. Factors with a p-value of <0.2 were considered for inclusion in a multivariate predictive model and a combination of backwards selection and clinical expertise were used to build a prediction model using the Fine-Grey model survival model. We excluded patients

with a creatinine greater than 5 (n=14) as these were outliers. Only patients with complete case data for all variables chosen for the model were used. Missing data not considered for bivariate analysis. Status category at listing was used. The rms packing in R was used to construct a nomogram with the weight to each factor derived from the coefficient in the model. This predictive scoring model was validated on the "validation cohort" ($N=1852$) by comparing descriptive statistics of the clinical risk score with the "derivation cohort" as well as calculating the area under the ROC curve within the "derivation cohort". All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and Stata IC 16 (StataCorp LP, College Station, TX). This study was submitted to the institutional review board at the University of California-Los Angeles and determined that review was not required.

RESULTS

Of the 5,557 patients included in the study analysis, the majority were male (56.2%), white (53.3), and publicly insured (53.9%) (Table 1). Among age and weight categories, the greatest proportion of patients were \langle 1 year old (35.2%) and \langle 10 kg (40.8%), respectively. Patients were most commonly listed as Status 1A (65.2%) and with a diagnosis of congenital heart disease (50.8%) or dilated cardiomyopathy (32.6%). At the time of listing for transplant, some patients required significant cardio-respiratory support: 45.7% on vasopressors and inotropes, 20.1% on a mechanical ventilator, 11.6% with a ventricular assist device (VAD), 7.1% were on ecmo (extracorporeal membrane oxygenation), and 3.1% on renal replacement therapy.

Of the demographic and clinical factors evaluated, after a univariate analysis the following were found to have a significant (p-value <0.2) association with death or delisting: age, gender, insurance, race, blood type, diagnosis, weight, VAD use, inotrope use, ventilator use, defibrillator use, ecmo use, dialysis use, comorbid cancer, creatinine, and UNOS region (Table 2). These factors then underwent application of the multivariate predictive model (significance p-value <0.2), backwards selection, and clinical prioritization, the resulting factors together most associated with death or delisting were blood type, diagnosis (congenital heart disease vs other), weight, ventilator status, inotrope use, ecmo use, creatinine, and UNOS region (Table 3) and thus used to create the Pediatric Risk to OHT (PRO) scoring model (Figure 1). Each clinical factor within the scoring model is a scaled version of the proportion of that factor's contribution to the outcome (death or delisting while on the waitlist). The total points are mapped to the one-year mortality probability while on the waitlist with a higher score indicating an increased risk of mortality.

The PRO score had a predictive strength of 0.762 as measured by Area Under the ROC curve at 1 year (Figure 2). Applying the prediction model from the test data to the validation cohort resulted in an area under the ROC curve of 78.8 (95% CI 75.9, 81.8) and Brier score of 9.9 (95% CI 7.3–12.6) which resulted in an Index of Prediction of 12.5% indicating a moderate discrimination and an improvement relative to the null model ⁸. The derivation group had a PRO score mean of 0.65 (standard deviation 0.91) and median of 0.62, while the validation group had a PRO score mean of 0.65 (standard deviation of 0.92) and median of

0.61 (Figure 3). The PRO score was applied to patients within each listing criteria and made the previously homogenous patients in each category heterogenous (Figure 4).

DISCUSSION

Though each listing status for pediatric heart transplant has criteria, the population remains heterogeneous, especially within those listed as 1A. As a result, there is still a wide range of clinical acuity without a method by which to differentiate them. When the PRO score is applied to each listing status, the previously homogenous listing status becomes differentiated with a wide range of resulting scores (Figure 4). This study is unique as it utilizes a combination of clinical factors to provide the best estimate of the risk of mortality among patients awaiting heart transplant and provides a clinical tool for providers to utilize in risk assessment of their patients, such as when applying for exemptions when listing. For example, a 15 kg patient with congenital heart disease listed for heart transplant in Region 5 with AB blood type on ventilator support but no ecmo support and a most recent creatinine of 1.77 would result in a PRO score of 125 which corresponds to a waitlist mortality of approximately 0.25 (Figure 1). Prior studies have shown that weight, specifically less than 3 kg, ecmo and ventilation support, and inotropic support, are independently associated with increased risk of death in patients listed for heart transplant^{1,3,9,10}. Nonwhite race/minority ethnicity has been shown to be a risk factor for mortality in prior studies $1,3$; however, the current analysis did not find a statistically significant association of nonwhite race/minority ethnicity, inotropic support, and VAD support with mortality and thus was not included in the final calculation. This could be secondary to a change in the capture of patients within the cohort or a confounded association with other factors that we have now parsed out.

Multiple regions exist across the United States and are overseen by UNOS and there exist differences in mortality between regions which require further evaluation. There was a notable difference in mortality for patients awaiting heart transplant in patients located in region 10 and 11 compared to other regions. The cause for this difference was not apparent, but potential contributing factors may be multifactorial, including access, offer acceptance ratios, and center volume. It has been previously shown that there are differences in rates of heart transplantation at low volume centers, defined as less than 3 transplants a year, compared to high volume centers, defined as 10 transplants a year (36% vs 89% between 2002 to 2014)¹¹. Children at low volume centers had $>400\%$ risk of death while awaiting heart transplant when compared to those at high volume centers, though the exact cause for this is unknown and likely multifactorial¹¹. Thus, further elucidation of the factors within regions associated with patient mortality while awaiting heart transplant is needed.

There were limitations to the current study which are inherent to database studies such as errors in the database itself and lack of patient level clinical data (i.e. specific congenital heart disease diagnosis, bilirubin level, estimated GFR) which may affect the mortality risk awaiting transplant. Missing data (0.6%) was not considered for bivariate analysis as only patients with complete case data for all variables chosen for the model were used for the training set. The same patient population was used for both the derivation and validation of the scoring model, though the cohorts had similar characteristics (Table 4). Patients listed as ABO incompatible candidates are a unique situation as those listed may have a

risk profile more similar to an AB candidate. This is not inherently accounted for in our model. Finally, pediatric heart transplant listing criteria was changed in 2016 with the goal to more appropriately stratify patients and likely impact mortality while on the waitlist. As our cohort encompasses this change, it may have impacted the criteria we found associated with waitlist mortality.

The application of a standardized scoring system with individualized variables may allow for transplant of those most ill sooner, improving waitlist mortality as children who are sicker have the highest benefit from heart transplantation¹². Studies in adults have looked at using a more personalized approach to predict pre- and post-transplant death using algorithms and machine learning to address the heterogeneity in clinical status that is present amongst adults awaiting heart transplant¹³. This novel idea, if applied to pediatric patients, can potentially address the heterogeneity of pediatric patients and their varying risk of mortality while awaiting transplantation. In addition to guidance during listing, regularly scoring patients on the waitlist could assist with guidance regarding listing exemptions or considering offers, particularly in light of new program metrics such as pre-transplant mortality and offer acceptance rates. Future directions include completing prospective analysis to determine the effectiveness of a risk calculator in predicting mortality, external validation, scoring trend and impact on waitlist time, and impact on post-transplant outcomes.

CONCLUSION

In conclusion, the PRO score has the potential to predict mortality among pediatric patients awaiting heart transplant. These findings demonstrate that a higher score indicates an increased risk of mortality. With prospective application, this study aims to improve allocation of a limited resource and improve the mortality rate in pediatric patients awaiting heart transplant.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to Dr. Matthew Russell and Dr. Nancy Halnon for their guidance during this initiative. This research was supported by NIH National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR001881.

Data Availability Statement:

Raw data were generated at the Organ Procurement and Transplant Network (OPTN) database. Derived data that support the findings of this study are available from the corresponding author upon reasonable request.

ABBREVIATIONS

VAD ventricular assist device

REFERENCES

- 1. Mah D, Singh TP, Thiagarajan RR, et al. Incidence and risk factors for mortality in infants awaiting heart transplantation in the USA. J Heart Lung Transplant 2009;28(12):1292–1298. [PubMed: 19782580]
- 2. Goldstein BA, Thomas L, Zaroff JG, Nguyen J, Menza R, Khush KK. Assessment of Heart Transplant Waitlist Time and Pre- and Post-transplant Failure: A Mixed Methods Approach. Epidemiology 2016;27(4):469–476. [PubMed: 26928705]
- 3. Almond CSD, Thiagarajan RR, Piercey GE, et al. Waiting list mortality among children listed for heart transplantation in the United States. Circulation 2009;119(5):717–727. [PubMed: 19171850]
- 4. Jeewa A, Manlhiot C, Kantor PF, Mital S, McCrindle BW, Dipchand AI. Risk factors for mortality or delisting of patients from the pediatric heart transplant waiting list. J Thorac Cardiovasc Surg 2014;147(1):462–468. [PubMed: 24183905]
- 5. Denfield SW, Azeka E, Das B, et al. Pediatric cardiac waitlist mortality-Still too high. Pediatr Transplant Published online March 21, 2020:e13671. [PubMed: 32198830]
- 6. Davies RR, Russo MJ, Mital S, et al. Predicting survival among high-risk pediatric cardiac transplant recipients: an analysis of the United Network for Organ Sharing database. J Thorac Cardiovasc Surg 2008;135(1):147–155, 155.e1-e2. [PubMed: 18179931]
- 7. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation 2016;133(6):601–609. [PubMed: 26858290]
- 8. Kattan MW, Gerds TA. The index of prediction accuracy: an intuitive measure useful for evaluating risk prediction models. Diagn Progn Res 2018;2:7. [PubMed: 31093557]
- 9. Zakaria D, Frazier E, Imamura M, et al. Improved Survival While Waiting and Risk Factors for Death in Pediatric Patients Listed for Cardiac Transplantation. Pediatr Cardiol 2017;38(1):77–85. [PubMed: 27803956]
- 10. Zafar F, Castleberry C, Khan MS, et al. Pediatric heart transplant waiting list mortality in the era of ventricular assist devices. J Heart Lung Transplant 2015;34(1):82–88. [PubMed: 25447574]
- 11. Rana A, Fraser CD, Scully BB, et al. Inferior Outcomes on the Waiting List in Low-Volume Pediatric Heart Transplant Centers. Am J Transplant 2017;17(6):1515–1524. [PubMed: 28251816]
- 12. Singh TP, Almond CS, Piercey G, Gauvreau K. Risk stratification and transplant benefit in children listed for heart transplant in the United States. Circ Heart Fail 2013;6(4):800–808. [PubMed: 23704137]
- 13. Yoon J, Zame WR, Banerjee A, Cadeiras M, Alaa AM, van der Schaar M. Personalized survival predictions via Trees of Predictors: An application to cardiac transplantation. PLoS One 2018;13(3):e0194985. [PubMed: 29590219]

Figure 1:

Nomogram incorporating the variables of the final PRO score- a higher score indicates an increased 1 year waitlist mortality probability (Diagnosis: C= congenital, O= other, H= hypertrophic cardiomyopathy, R= restrictive cardiomyopathy, M= myocarditis, D= dilated cardiomyopathy). The ruler length for each clinical factor is a scaled version of the proportion of that factor's contribution (range of possible values times coefficient) divided by the maximum predictor contribution. The total points are mapped to the one-year mortality probably while on the waitlist. For example, a 15 kg patient with congenital heart disease listed for heart transplant in Region 5 with AB blood type on ventilator support but no ecmo support and a most recent creatinine of 1.77 would result in a PRO score of 125 which corresponds to a waitlist mortality of approximately 0.25

Area under the curve for derivation (training) cohort and validation cohort showing the PRO score with a predictive strength of 0.762.

PRO score distribution of the derivation (training) group and the validation group demonstrating a similar bell curve characteristic.

Figure 4:

PRO Score distribution within each listing status: 1A, 1B, and 2. Variation of scores within each status conveys the heterogeneity of the patients within that group. As expected, there is a greater distribution of higher scores within Status 1A compared to Status 1B and Status 2.

Table 1

Demographics of pediatric patients listed for heart transplant from January 2010 to June 2019.

Dialysis 170 (3.1) Creatinine, mean (SD) 0.54 (0.74) Albumin, mean (SD) 3.53 (0.79)

N (%)

3618 (65.2) 885 (16.0) 944 (17.0) $101 (1.8)$

 $19(0.3)$ 2822 (50 8) 1810 (32.6) $175 (3.1)$ $286 (5.1)$ $202 (3.6)$ $9(0.2)$ 234 (4.2) $78(1.4)$

511 (9.2) $136 (2.4)$ 4910 (88.4) 2539 (45.7) $1115 (20.1)$ 475 (8.5) 396 (7.1)

Table 2

Variables after a univariate analysis of predictors of 1 year waitlist mortality or delisting for worsening medical condition. Those with a p-value of <0.2 were then considered for inclusion in a multivariate predictive model, then a combination of backwards selection and clinical expertise were used to build a prediction model using the Fine-Grey model survival model.

Table 3

Fine and Grey Survival model with the final factors- Blood type, diagnosis, weight, ventilator, ecmo, creatinine, region- predicting 1 year waitlist mortality (delisting for worsening medical condition as a competing event).

Table 4:

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Pediatr Transplant. Author manuscript; available in PMC 2024 September 01.

Raymundo et al. Page 18

 $\boxed{\underline{\circ}}$

 \sim $\tilde{\epsilon}$ \overline{a} $\overline{5}$

 \overline{a}

Variable

 \circ

 \overline{r}

Author Manuscript

Author Manuscript

Raymundo et al. Page 19

123 (6.7%)

221 (6.0%)

344 (6.2%)

8 **8 526 (9.5%)** 356 (9.6%) 356 (9.6%) 356 (9.7%) 9 344 (6.7%) 221 (6.7%) 123 (6.7%)

 ∞ \circ