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Prolonged hospital length of stay after pediatric heart transplantation: A machine learning and logistic regression predictive model from the Pediatric Heart Transplant Society

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KEYWORDS:
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BACKGROUND: Heart transplantation (HT) is the gold standard for managing end-stage heart failure. Multiple quality metrics, including length of stay (LOS), have been used in solid organ transplantation. However, limited data are available regarding trends and factors influencing LOS after pediatric HT. We hypothesized that various donor, peri-transplant and recipient factors affect LOS after pediatric HT.

METHODS: We analyzed patients <18years at time of HT from January 2005 to December 2018 in the Pediatric Heart Transplant Society database, and examined LOS trends, defined prolonged LOS (PLOS = LOS>30days after HT), identified factors associated with PLOS and assessed outcomes.

RESULTS: Of 4827 patients undergoing HT, 4414 patients were discharged and included for analysis. Overall median LOS was 19days[13,34]. Median LOS was longer in patients with congenital heart disease(CHD = 25days[15,43] than with cardiomyopathy(CM = 17days[12,27] across all ages. Median LOS in age <1year was 26-days[16,45.5] and in age >10year was 16days[11,26]. PLOS was seen in 1313 patients(30%). Patients with PLOS were younger, smaller and had longer CPB times. There was no difference in utilization of VAD at HT between groups, however, ECMO use at listing(8.45% vs 2.93%,$p < 0.05$) and HT was higher in the PLOS group(9.22% vs 1.58%,$p < 0.05$). PLOS was more common in patients with previous surgery, CHD, single ventricle physiology, recipient history of

Abbreviations: LOS, length of stay; PLOS, prolonged length of stay; HT, heart transplantation; PHTS, pediatric heart transplant society; CHD, congenital heart disease; CM, cardiomyopathy; VAD, ventricular assist device; SLR, stepwise logistic regression; GB, gradient boosting; RF, random forests; UNOS, united network for organ sharing; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate

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cardiac arrest or CPR, end organ dysfunction, lower GFR, use of mechanical ventilation at HT and Status 1A at HT.

CONCLUSION: We present novel findings of LOS distribution and define PLOS after pediatric HT, providing a quality metric for individual programs to utilize and study in their practice.

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Heart transplantation (HT) is the gold standard for management of end-stage heart failure. Health care quality is defined as ''the degree to which healthcare services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.'' There is increasing emphasis on quality of care and payors use various quality metrics for making reimbursement decisions and for determinations of transplant centers of excellence. Assessment of quality of care in pediatric transplantation is challenging with administrative databases serving to define quality metrics comprised of structure, process or outcome metrics, however these may not incorporate clinically useful parameters.[1] Regulatory agencies such as United Network for Organ Sharing (UNOS) use posttransplant patient and/or graft outcome metrics to measure transplant center performance. Posttransplant length of stay (LOS) has been used, as a quality metric in liver and kidney transplantation. However, limited data are available regarding risk-adjusted LOS after pediatric HT. The development of these metrics is mostly driven by adult data. Therefore, few reliable, valid, and standardized metrics are available that are applicable to pediatrics. Furthermore, significant heterogeneity in pediatric patients limits universal application of the same metrics across different populations and programs.

LOS affects the cost of hospitalization and is a major modifiable component accounting for 25%-50% of the total expenditures.[2,3] Therefore, LOS after cardiac surgery is used as a quality metric by institutions, payors and health policy experts. A recent analysis using UNOS adult HT data, defined prolonged LOS (PLOS) as hospital stay >30days after HT.[4]

Due to the unique nature of pediatric patients, adult guidelines serve as poor correlates. Nevertheless, LOS as a quality metric and a surrogate for resource utilization will likely translate to pediatric HT, impacting assessment of transplant center performance and reimbursements. Furthermore, the absence of a consensus definition of PLOS, and lack of understanding of factors associated with PLOS, limits our ability to appropriately utilize LOS as a standardized quality metric. The development of a risk-adjusted measure of LOS can guide necessary interventions to reduce LOS and decrease healthcare costs.

We hypothesized that multiple donor, peritransplant and recipient factors influence LOS after HT. We analyzed the Pediatric Heart Transplant Society (PHTS) database to describe LOS trends across ages and diagnoses, defined PLOS, and subsequently identify factors associated with PLOS. Additionally, we aimed to develop a risk prediction model using machine-learning methods and compare it with traditional statistical methods.

Materials and methods

PHTS maintains a multicenter, prospective, event−driven database for pediatric patients (<18 years) listed for HT. Collection of date of discharge began in 2005, therefore data query spanned January 2005-December 2018, and included patients from multiple institutions (*Table S1*). Institutional Review Board approval was obtained at each institution. Information was collected on demographics and other patient data at listing, patient and procedural data at HT, and event data surrounding listing, transplantation, follow up and death.

Study population

All patients <18years of age at the time of HT with a recorded discharge date were included for analysis. Patients meeting the PHTS endpoint (death or transfer to another institution) prior to discharge, no reported discharge date, or with extremely short LOS (<3 days), were excluded from analysis.

Definition of length of stay

As no previous data was available to define PLOS for pediatric patients after HT, a dichotomous variable was created consistent with the goal of exploring a possible metric of performance. After preliminary examination of the cohort LOS data using the 70th percentile to define PLOS (see Results), a LOS >30 days from the time of HT was chosen. Additionally, 30days was chosen due to ease of use, its correlation with other quality indicators such as 30-day mortality and PLOS in adult HT.

Statistical analysis and prediction modeling

Categorical variables were expressed as numbers and percentages, and continuous variables as mean ± SD or median[IQR], as appropriate. Comparisons of categorical variables were made using chi-square and continuous variables using the Wilcoxon rank sum test or t-test. The count and percent of missing values for each candidate predictor variable was tabulated in the overall population and stratified by LOS >30 days, and the proportion of missing values in these groups was compared using a chi-square test.

Modeling algorithms(Figure 1): We compared three modeling algorithms: stepwise logistic regression (SLR), gradient boosting (GB), and random forests (RF). In SLR variables are included or excluded one at a time until a stopping criteria is met and stepwise models that undergo rigorous internal validation are valid for statistical prediction.[5] They are known to have inflated type 1 error rates for statistical inference.[6] Therefore, we interpret regression confidence intervals from this procedure as exploratory rather than confirmatory. GB develops an ensemble of weak prediction models.[7] Each individual prediction model in the ensemble attempts to correct previous model's errors, and the ensemble's aggregated

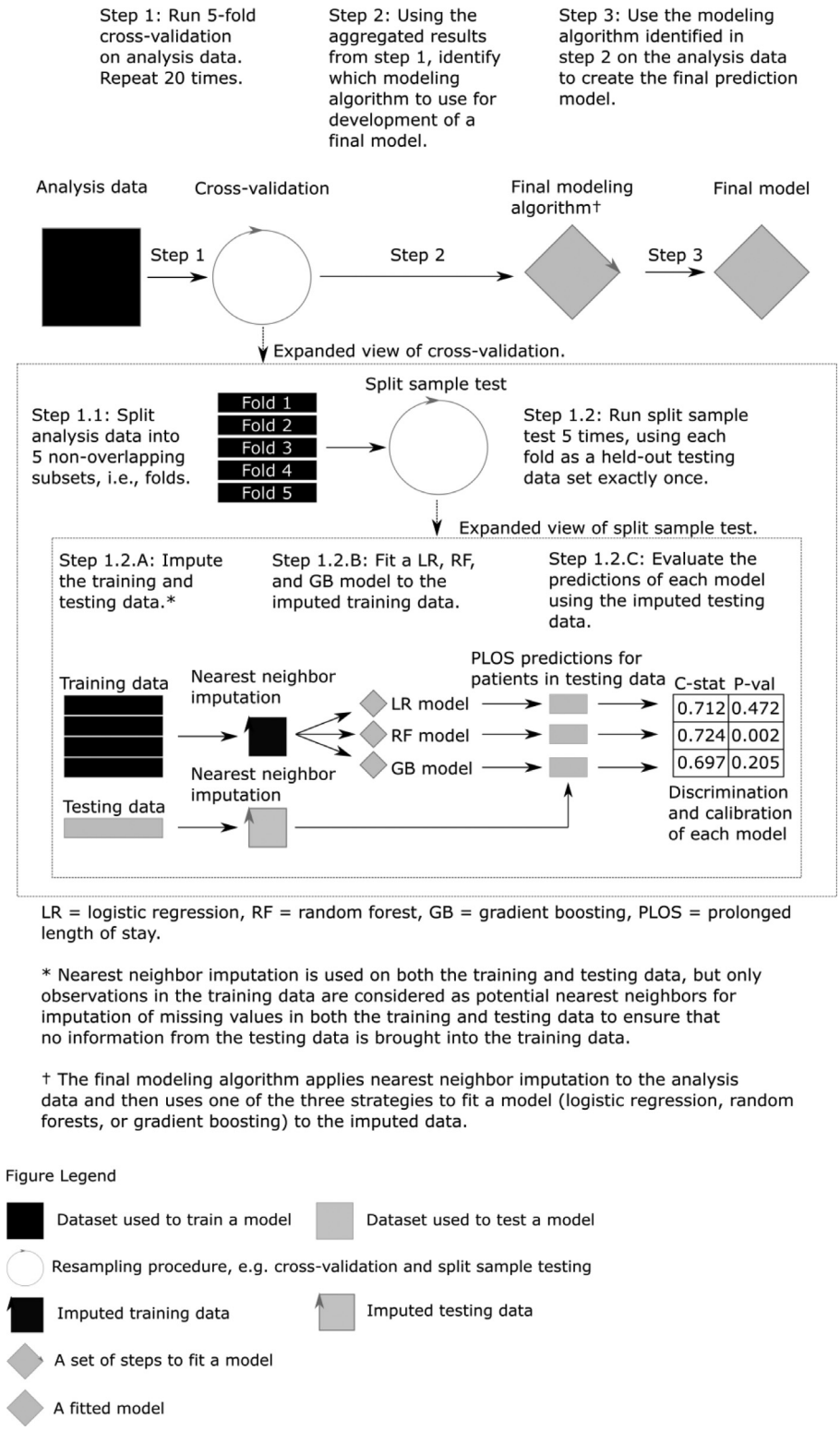

Figure 1 This flowchart depicts the overall approach of statistical analysis with various modelling algorithms.

prediction is more accurate than any of its individual models. We developed boosting models using decision trees as individual learners,[8] a technique recognized in numerous settings to be state of the art for statistical prediction.[9] Similar to boosting, RF constructs an ensemble of decision trees and aggregate predictions from the ensemble.[10] However, unlike boosting, RF de-correlates decision trees in the ensemble to reduce variance.[11]

Internal validation: We applied internal validation to identify the most effective algorithm for developing a final prediction model and to estimate the performance of the model when it is applied to new data.[12] We conducted 5-fold cross validation. Cross-validation is an extension of split-sample testing, which develops a model on a single training set and validates the model in a single testing set. *k*-fold cross-validation splits the available

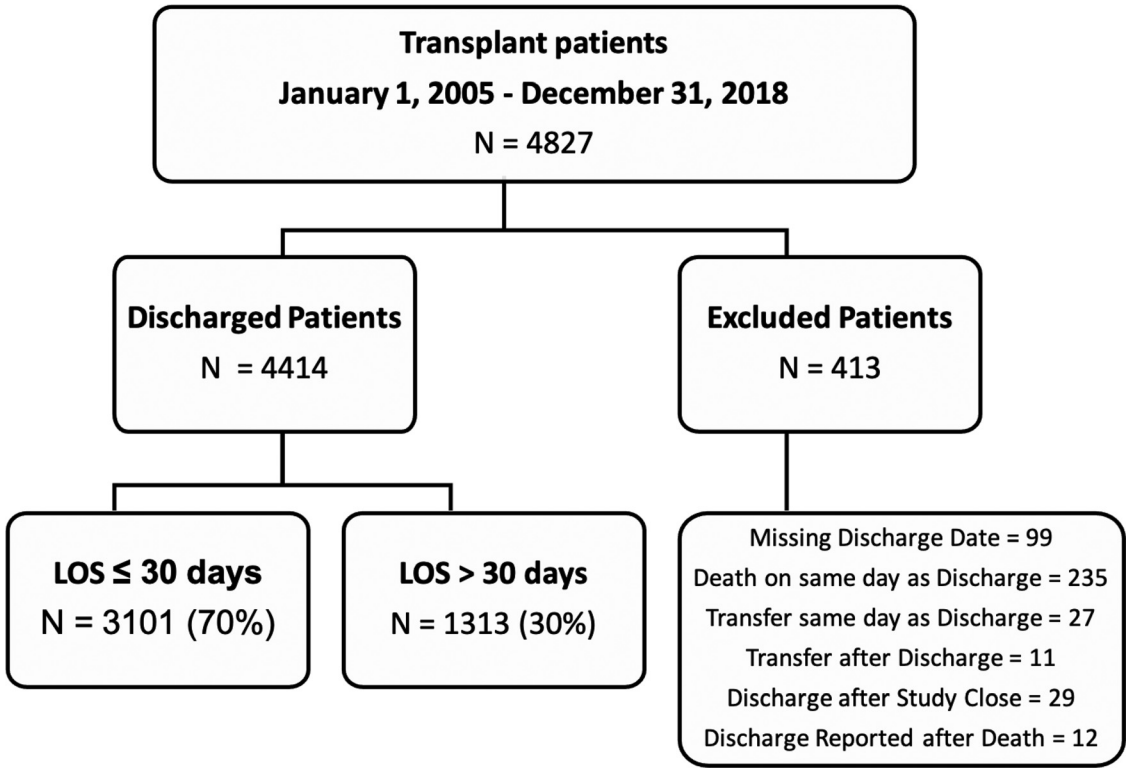

Figure 2 Overall patient cohort.

data into k non-overlapping subsets (i.e., folds), and then conducts split-sample testing k times, using each subset as a testing set one time. We set k equal to 5 so that the testing set would contain 20% of the analysis data (approximately 883 observations). We repeated 5-fold cross-validation 20 times to further reduce variation in our results attribuTable to sampling variability.

Measures of model performance: Model performance was evaluated according to discrimination and calibration, as per published guidelines.[13,14] Discrimination and calibration were measured using Harrell's concordance (C-) statistic and unreliability test, respectively.[15-17] Point estimates and 95% confidence intervals(CIs) for these metrics were computed empirically using results from internal validation. Point estimates were the median value of a performance metric, while the 2.5th and 97.5th percentiles defined lower and upper bounds for 95% CIs, respectively. We did not find previously published prediction models for LOS >30 days after HT among patients receiving mechanical circulatory support, so we did not analyze net reclassification improvement as it requires a baseline prediction model.

*Missing data: M*issing values were imputed after splitting data into training and testing sets during each replicate of cross-validation. All information from the testing data was withheld during this process. Specifically, missing values were imputed in both training and testing data using an imputation model that only leveraged the training data. Outcome values were not used to impute missing values, as this would imply knowing the outcome value before predicting it. A single imputed dataset was formed by applying a nearest neighbor imputation model to each predictor variable with missing values, separately. For each patient with a missing value for the current predictor variable, nearest neighbor imputation identifies k patients in the training data who are most similar to the current patient and have an observed value for the current predictor variable. An imputed value is created by aggregating the observed values for these k most similar patients. In the current study, 10 nearest neighbors were identified using Gower's distance and imputations were formed using the median for continuous and mode for categorical variables.[18]

Discrimination and Calibration: We visually assessed the discrimination and calibration of potential algorithms to develop a final prediction model as a function of the number of predictors included in the model. Using visual summaries, we selected a modeling algorithm to develop a final prediction model based on discrimination, calibration, and ease of interpretation. We estimated the discrimination and calibration of the selected modeling algorithm in the overall population and in subgroups defined by age, diagnosis, and sex. Last, we tabulated a summary of the final prediction model and provided step-by-step instructions to compute predictions for individuals using the final prediction model.

All analyses were conducted using SAS version 9.4, R version 4.0.3, and a number of open-source R packages.[19-23] All R code for the current analysis is publicly available at https://github.com/bcjaeger/length-of-stay.

Results

A total of 4827 patients received a HT during the study period. Of these, 413 were excluded as described in Figure 2 leaving 4414 patients for analysis.

Length of stay

Median LOS was 19[13,34] days and was longer in patients with CHD than with CM (25 [15,43] days vs 17[12,27] days; $p< 0.001$). Median LOS for "other" diagnoses was 19

Table 1 Distribution of LOS for Overall Cohort and Distribution of Patients With PLOS Based on Age at Transplant

Age (year) at transplant	Patients (n)	Mean LOS (days)	Median LOS [25-75] (days)	LOS ≤30 days n (%)	LOS >30 days n (%)
<1	1268	39.3	26 [16-45.5]	718 (56.6)	550 (43.4)
1-5	940	29.7	21 [14-36]	643 (68.4)	297 (31.6)
5-10	611	28.2	18 [12-31]	456 (74.7)	155 (25.3)
>10	1595	24.1	16 [11-26]	1284 (80.5)	311 (19.5)

[13,32] days. The median LOS in the <1year age group was longer than those >10years old (Table 1). Based on the described definition of PLOS, the overall cohort was divided into 70% patients with a LOS ≤30days (n = 3101) and 30% with a LOS >30days (n = 1313). The detailed demographic and clinical characteristics of the overall cohort are depicted in Table 2**.**

Demographics and clinical characteristics

Demographics and clinical characteristics associated with PLOS are described in Table 2. PLOS was associated with younger age, smaller BSA, longer CPB times, recipient history of cardiac arrest or CPR, and 1A listing status at transplant ($p < 0.001$). PLOS was also associated with CHD, single ventricle physiology and previous cardiac surgery ($p < 0.001$). There was no association between PLOS and VAD use at listing or HT. However, ECMO use at listing (8.45% vs 2.93%) or HT (9.22% vs 1.58%) was higher in the PLOS group ($p < 0.001$). Similarly, use of mechanical ventilation at HT was associated with PLOS ($p < 0.001$). Patients with PLOS were more likely to have end organ dysfunction as indicated by higher mean bilirubin ($p < 0.001$) and lower GFR (< 0.001). PLOS was also associated with lower graft survival (freedom from death or retransplant) by Kaplan Meier (p logrank = 0.0011, Figure 3).

LOS distribution from 2005 to 2018

We evaluated for era effect on LOS distribution. The number of HT increased annually from 151 in 2005 to 347 in 2018. However, distribution of patients with PLOS was similar.

Development of prediction model and internal validation

Stepwise logistic regression produced an internally validated C-statistic ranging from 0.62 using one predictor to 0.76 using 15 predictors(*Figure S1*). The C-statistic and the p -value for unreliable calibration increased rapidly until the model included 5 predictors and plateaued thereafter. The GB model exhibited a similar pattern as more predictors were included in the model(*Figure S2*). The missing values for candidate predictor variables in the overall population and stratified by LOS status are shown in *Table S2*. The discrimination and calibration of GB model was also lower for patients with CHD(*Table S3*). RF obtained similar discrimination and calibration compared to SLR and GB when 13 predictors were used but had poor discrimination and calibration with 5 predictors(**Figure S3**). As performance of the GB model was similar to that of SLR, we elected to develop the final prediction model using SLR method that provided the most interpreTable prediction model. Rankings of variable importance using SLR, RF, and GB are demonstrated in *Figure S4*.

Model summary for predictors of PLOS

Continuous mechanical ventilation at transplant, the first predictor selected by final stepwise prediction model, had an adjusted odds ratio of 3.38 for PLOS(Table 3). The second and third variables selected were CPB time and recipient age at HT. Use of ECMO at HT had an adjusted odds ratio of 3.5 for PLOS. The internally validated C-statistic, calibration intercept, and calibration slope for this modeling algorithm in the overall population are presented in (Table 4). Discrimination and calibration were adequate in subgroups based on age, diagnoses, and sex, with the lowest performance in patients with CHD (C-statistic: 0.69; p-value for unreliable calibration: 0.31). Further, adjusting for institution did not lead to a change in the interpretation of our final model(Figure S5).

We compared the prediction model for a low- and a high-risk patient demonstrating the difference in probability of PLOS(Table 5). Low-risk patient:(5-years-old with no previous surgeries, not on ECMO or VAD, not mechanically ventilated and with a CPB time of 2-hours) had a 14% probability of PLOS. However, if the same patient was on a VAD and was mechanically ventilated, the probability of PLOS increased to 46%.

Discussion

Our study is the first to provide insight into LOS trends after pediatric HT. The use of LOS as a quality metric is clearly important as it encompasses various domains of quality.[1,24,25] Furthermore, an improved understanding of factors affecting LOS can allow transplant centers to estimate their expected LOS, identify patients at risk for PLOS and counsel families accurately. Due to a paucity of LOS data in pediatric HT, heterogeneity of diagnoses and unique characteristics of pediatric patients unlike adults; extrapolation of adult data to estimate pediatric LOS trends is inherently flawed. Herein, we provide a rational basis for selecting 30 days as a “cut-off” for defining PLOS, evaluate

Table 2 Patient Characteristics by Prolonged Length of Stay After Heart Transplantation (PHTS 2005-2018)

Variable	Overall	Length of stay >30 days		*p*-value
		No	Yes	
Recipient Age, Years[a]	5.0 (0.76,13.04)	6.83 (1.17,13.80)	1.83 (0.45,9.51)	< 0.001
Status at Transplant: United States				< 0.001
1A	84.3%	81.6%	91.1%	
1B	10.7%	12.5%	6.01%	
2	5.07%	5.93%	2.87%	
Cardiopulmonary Bypass Time, minutes	154 (118,202)	146 (112,188)	177 (136,231)	< 0.001
Donor ischemic time (minutes)	216 (179,255)	214 (177,251)	223 (183,263)	< 0.001
Donor Age (years)	6.0 (1.17,15.00)	8.0 (1.75,16.00)	2.0 (0.67,12.00)	< 0.001
BSA (kg/m^2) at Transplant	0.68 (0.38,1.33)	0.81 (0.45,1.43)	0.49 (0.31,0.95)	< 0.001
Donor BSA (kg/m2)	0.86 (0.48,1.60)	1.03 (0.53,1.66)	0.61 (0.40,1.29)	< 0.001
Mechanical Support at Listing				< 0.001
Neither VAD nor ECMO	86.8%	88.1%	83.7%	
VAD	8.63%	8.96%	7.84%	
ECMO	4.58%	2.93%	8.45%	
Mechanical Support at Transplant				< 0.001
Neither VAD nor ECMO	73.5%	76.1%	67.4%	
VAD	22.6%	22.3%	23.4%	
ECMO	3.85%	1.58%	9.22%	
Time on List (months)	1.87 (0.69,4.21)	1.87 (0.69,4.24)	1.84 (0.72,4.07)	0.88
Bilirubin at Transplant (mg/dL)	0.70 (0.40,1.23)	0.60 (0.40,1.20)	0.70 (0.40,1.58)	< 0.001
Donor to Recipient Weight Ratio	1.30 (1.05,1.66)	1.28 (1.05,1.62)	1.35 (1.07,1.75)	< 0.001
Difference in Donor to Recipient Age (years)	1.51 (0.42,4.01)	1.68 (0.50,4.24)	1.09 (0.28,3.30)	< 0.001
Diagnosis Group				< 0.001
Cardiomyopathy	52.4%	59.0%	36.8%	
Congenital HD	44.6%	37.9%	60.5%	
Other	2.95%	3.03%	2.74%	
Donor Cause of Death				< 0.001
Anoxia	37.6%	36.9%	39.2%	
Cerebrovascular	7.86%	7.45%	8.83%	
Head Trauma	48.2%	50.3%	43.2%	
Other	6.34%	5.32%	8.76%	
Estimated Glomerular Filtration Rate, mL/min/1.73m^2				< 0.001
>90	54.1%	56.2%	49.0%	
60 to 90	32.1%	32.6%	30.9%	
<60	13.8%	11.1%	20.1%	
CHD: Single Ventricle	27.8%	22.7%	39.9%	< 0.001
Donor Ischemic Time >4-hour	33.7%	31.8%	38.3%	< 0.001
Donor to Recipient Weight Ratio > 1.5	33.9%	32.3%	37.9%	< 0.001
Donor Sex Female	41.9%	40.7%	44.8%	0.01
History at Listing: Cardiac Arrest/CPR	9.57%	7.96%	13.4%	< 0.001
History at Listing: GI/Nutrition	45.3%	44.0%	47.9%	0.09
Surgeries Prior to Listing	44.2%	38.2%	58.4%	< 0.001
ABO Incompatible at Transplant	7.49%	5.86%	11.4%	< 0.001
Continuous Invasive Mechanical Ventilation at Transplant	19.2%	11.5%	36.5%	< 0.001

[a]Table values are median (*p*25,*p*75) and percent for continuous and categorical variables, respectively.

the factors affecting LOS and develop a model to predict the probability of PLOS in pediatric HT patients.

Rising healthcare costs have led to the inclusion of quality metrics by payors for reimbursement decisions, leading to an increased emphasis on adapting cost-effective approaches with best clinical outcomes. Overall, HT is a resource intense field with a reported 3.7-fold variation (range:$329,477-$1,226,507) independent of center volume in HT hospitalization costs across the USA.[26] With inpatient hospitalization accounting for 25%-50% of total costs, LOS becomes a critical modifiable factor in reducing the cost of hospitalization. Our study improves the understanding of factors affecting LOS, allowing development of targeted approaches to minimize the factors leading to PLOS and thereby reducing costs.

We identified factors which impact LOS directly and/or indirectly, including patient age, BSA, and diagnosis (CHD and single ventricle physiology). These nonmodifiable factors may relate to increased peri-transplant clinical complexity in younger patients with CHD predisposing to longer recovery times. Not surprisingly, patients with PLOS were a sicker cohort, with higher priority listing statuses, end-organ

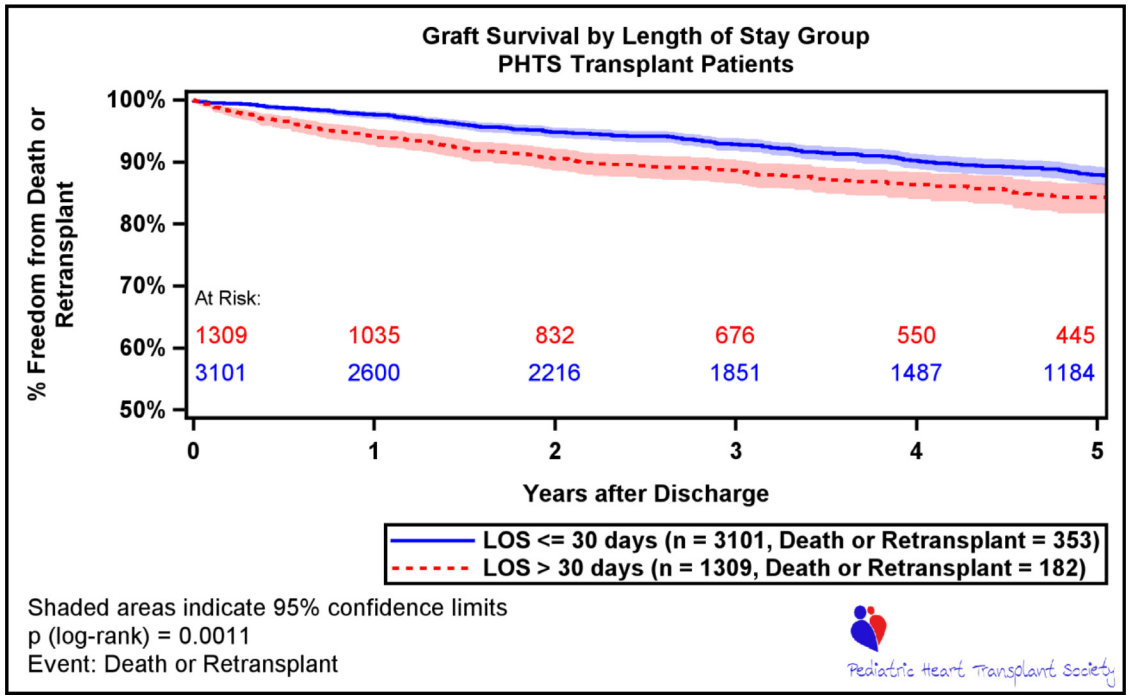

Figure 3 Kaplan Meier curve demonstrating graft survival (freedom from death or retransplant) by LOS group over time (time 0 is date of discharge; patients are censored at transfer to another institution or end of follow-up).

Table 3 Multivariable Adjusted Odds Ratios (95% Confidence Interval) for Prolonged Length of Stay Using the 5 Predictors Selected for Inclusion in the Final Prediction Model

Variable[a]	Mean (SD) or percent	Adjusted Odds ratio (95% CI)[c]
Recipient Age, per 6.22 years[b]	6.88 (6.22)	0.67 (0.62, 0.72)
Cardiopulmonary Bypass Time, per 73.1 min[b]	168 (74.7)	1.50 (1.39, 1.63)
Surgeries Prior to Listing		
No	55.8%	1 (reference)
Yes	44.2%	1.99 (1.70, 2.33)
Mechanical Support at Transplant		
Neither VAD nor ECMO	73.5%	1 (reference)
VAD	22.6%	1.51 (1.27, 1.80)
ECMO	3.85%	3.50 (2.42, 5.12)
Continuous Invasive Mechanical Ventilation at Transplant		
No	80.8%	1 (reference)
Yes	19.2%	3.38 (2.83, 4.05)

[a]Predictor variables included in the Table were selected using stepwise logistic regression. The number of predictor variables in the final model was optimized using internal validation of discrimination and calibration. Final model included: Recipient Age, Cardiopulmonary Bypass Time, Surgeries Prior to Listing, Mechanical Support at Transplant, Continuous Invasive Mechanical Ventilation at Transplant

[b]Odds ratios for continuous variables correspond to a one standard deviation change in the variable.

[c]Adjusted odds ratios account for all variables listed in the Table , simultaneously.

dysfunction, greater reliance on mechanical ventilation, and greater ECMO utilization. Though we did not identify any significant differences in the distribution of LOS seen in VAD supported patients over the span of the study, it is possible that the risks of increased HT surgical complexity in this VAD population were offset by the rehabilitation and clinical stability that device support offered. A higher incidence of PLOS was seen with use of ECMO at the time of listing or HT. Together, this suggests that early use of VAD over ECMO may help reduce LOS. Overall, the interconnectedness of these factors, a low- and high-risk group being clinically unique, may even suggest that the risk stratification for different programs may need to be individualized to account for the complexity of patients they care for.

In adult analyses, prior sternotomy and renal dysfunction are independently associated with LOS >14 days and discharge either <7days or >14 days after HT was associated with sub-optimal outcomes.[27,28] Crawford et.al. derived a Prolonged Hospitalization After HT Score in adults wherein older recipient, females, poor Karnofsky score, presence of diabetes, renal dysfunction, dialysis, mechanical ventilation, ECMO, previous cardiac surgery, VAD, pulmonary hypertension, longer waitlist times, older donor, recipient-donor sex mismatch and ischemic time >4hours were used to predict a longer LOS.[4]

We identified many overlapping as well as unique factors impacting LOS in pediatric patients. One such factor identified in our model is age at HT, with younger patients being more likely to have PLOS. This finding may relate to increased clinical complexity of lower weight and/or smaller BSA patients. Similarly, patients with CHD, for which a propensity exists as a HT indication in this younger

Table 4 Internally Validated Discrimination and Calibration of the Final Prediction model* in the Overall Population and in Subgroups Defined by Age, Diagnosis, and Sex

		Calibration		
Group	C-statistic (95% CI)	Intercept (95% CI)	lope (95% CI)	*p*-value
Overall	0.75 (0.72, 0.78)	-0.01 (-0.29, 0.26)	0.98 (0.82, 1.24)	0.39
Age group, years				
0 to < 1	0.73 (0.67, 0.78)	0.10 (-0.19, 0.41)	0.95 (0.64, 1.32)	0.31
1 to < 10	0.71 (0.66, 0.77)	-0.14 (-0.51, 0.18)	0.95 (0.68, 1.28)	0.33
≥ 10	0.72 (0.66, 0.79)	0.05 (-0.61, 0.66)	1.03 (0.70, 1.47)	0.49
Diagnosis				
Cardiomyopathy	0.73 (0.69, 0.79)	-0.06 (-0.48, 0.51)	1.02 (0.74, 1.34)	0.40
Congenital HD	0.69 (0.65, 0.74)	0.01 (-0.22, 0.29)	0.89 (0.71, 1.31)	0.31
Sex				
Female	0.73 (0.69, 0.77)	0.08 (-0.20, 0.41)	0.97 (0.73, 1.28)	0.43
Male	0.76 (0.72, 0.80)	-0.07 (-0.40, 0.27)	0.99 (0.79, 1.30)	0.37

Each point estimate (lower bound, upper bound) is the median (2.5th percentile, 97.5th percentile) value of model performance aggregated across all 100 replicates of repeated cross validation using 5 folds a total of 20 times. Discrimination and calibration were assessed using the concordance (C-) statistic and unreliability test. A *p*-value for miscalibration < 0.05 indicates evidence of miscalibration. A *p*-value > = 0.05 indicates that there is no evidence of miscalibration.

*Final model included: Recipient Age, Cardiopulmonary Bypass Time, Surgeries Prior to Listing, Mechanical Support at Transplant, Continuous Invasive Mechanical Ventilation at Transplant

population, are more likely to have previous sternotomies which further increases the risk of PLOS. Single ventricle physiology was associated with PLOS, but it was not an independent factor in predictive modeling due to overlap of various factors in younger children. Conversely, patients with CM are generally older with no previous surgeries, and thus post-operative recovery is shorter contributing to a shorter LOS compared to CHD. Similar to adults, organ dysfunction as depicted by elevated bilirubin and renal dysfunction lengthens the recovery period leading to PLOS.

Table 5 Solutions of the Multivariable Model to Predict Probability of PLOS for a Low Risk and High-risk Patient

		Low risk patient[b]		High risk patient[c]	
Variable	Regression coefficient	Patient data	Prediction term[d]	Patient data	Prediction term[d]
(Intercept)	-2.14414384[a]	1	-2.14414384	1	-2.14414384
Continuous Invasive Mechanical Ventilation at Transplant	1.21858721	0	0	1	1.21858721
Cardiopulmonary Bypass Time, minutes	0.00556084	120	0.66730132	120	0.66730132
Recipient Age, Years	-0.06467700	5	-0.32338500	5	-0.32338500
Surgeries Prior to Listing	0.68825571	0	0	0	0
Mechanical Support at Transplant					
Neither VAD nor ECMO	0	1	0	0	0
VAD	0.41449542	0	0	1	0.41449542
ECMO	1.25235257	0	0	0	0
Prediction[e]					
Log-odds	—		-1.80022751		-0.16714488
Probability	—		**0.14**		**0.46**

[a]Regression coefficients are rounded in the Table to 8 decimals to avoid rounding error.

[b]Patient aged 5 years, without continuous invasive mechanical ventilation at transplant, without any surgery prior to listing, with neither VAD nor ECMO at transplant, and who had a cardiopulmonary bypass time of 2 hours: **Probability of PLOS is about 14%.**

[c]Patient aged 5 years, with continuous invasive mechanical ventilation at transplant, without any surgery prior to listing, with VAD at transplant, and who had a cardiopulmonary bypass time of 2 hours. **Probability of PLOS is about 46%.**

[d]The prediction term is equal to the regression coefficient multiplied by the patient's data for the upper section of the Table . In the lower section, the log-odds prediction term is equal to the sum of the prediction terms above, and the probability prediction term is equal to the inverse logit of the the log-odds prediction term.

[e]To predict a patient's probability for length of stay > 30 days, first compute the log-odds, x, using the formula x = -2.14414384 + (Continuous Invasive Mechanical Ventilation at Transplant = Yes) * 1.21858721 + Cardiopulmonary Bypass Time, per 73.1 minutes * 0.00556084 + Recipient Age, per 6.22 years * -0.06467700 + (Surgeries Prior to Listing = Yes) * 0.68825571 + (Mechanical Support at Transplant = VAD) * 0.41449542 + (Mechanical Support at Transplant = ECMO) * 1.25235257. Next, convert x to a predicted probability using the inverse logit function: probability = exp(x) / (1 + exp(x))

However, in contrast to the adult literature, waitlist duration was not associated with PLOS in our population.

For development of a risk prediction model, we used traditional (SLR) as well as novel machine learning (GB and RF) methods. In our study, the following factors were finally included in the prediction model: recipient age, CPB time, mechanical ventilation at HT, surgeries prior to listing and use of VAD and/or ECMO at time of HT. Though use of machine learning techniques such as GB are often considered superior to the traditional SLR methods for predictive modeling, our analysis showed no such benefit. This risk prediction model, a first for pediatric patients, allows a quick estimation of the probability of PLOS for individual patient use.

Limitations

Limitations of our study include use of 30 days as the cutoff for PLOS. This was chosen after a careful analysis of the LOS distribution of the overall cohort. Knowing these limitations, we chose this cutoff as it also aligns well with other clinically important parameters including 30-day survival and readmission data. This study is additionally subject to limitations inherent to analyses of registry data, as they are bound by preexisting variables. However, PHTS provides a comprehensive, granular database using an event driven approach to minimize this risk. Additional confounders like social risk factors and medical conditions not delineated in the dataset may also have an impact on LOS. Furthermore, the impact of physician behavior, clinical management and other institutional practices on LOS cannot be assessed due to the nature of this database. Though exclusion of patients who died during the HT hospitalization may have impacted the results of this study, the risk of inappropriately truncating LOS data in such a complex group superseded their inclusion.

Conclusion

In summary, we present novel findings of LOS distribution and define PLOS after pediatric HT. This study is the first to inform about factors influencing LOS and develop a prediction model for PLOS. Furthermore, this provides a quality metric for individual programs to utilize and further study trends in their own practice. This tool will allow better risk stratification and counseling about expected LOS. Future studies are needed to assess the accuracy of this prediction model and guide clinical interventions to minimize the factors associated with PLOS.

Author contributions

All authors contributed to study design and data analysis. DG drafted the manuscript and all authors assisted with writing and critical revision of the manuscript.

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Disclosure statement

None

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2022.05.016.

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