Determining Factors of Heart Quality and Donor Acceptance in Pediatric Heart Transplants

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by

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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***Abstract*— There is substantial need to increase donor heart utilization in pediatric heart transplantation. Almost half of pediatric heart donors are discarded, despite nearly 20% waitlist mortality. Physicians have limited time to view heart condition data and decide to accept the donor heart once the heart becomes available. Due to the large amount of data associated with each donor heart and the lack of data-driven guidelines, physicians often do not have adequate metrics to determine acceptable heart quality. This research characterizes the differences in the clinical course between accepted and rejected pediatric donor hearts. A longitudinal study assessing the effect of static and dynamic measurements on the donor heart's function from the time of declaration of brain death to either disposal or heart procurement is developed by analyzing donor data via DonorNet, the system used by the United Network for Organ Sharing (UNOS) to match donors to a ranked order of recipients based on blood type, heart size, urgency status of the recipient, and other factors. Cardiovascular milieu (i.e. blood pressure, heart rate, medical management) and surrogate markers of organ perfusion, such as kidney and liver function, also inform our analyses and determine whether there are direct or indirect associations between these myriad markers and heart function. It also analyzes the proportion of measurements in stable and acceptable ranges over time, as well as typical minimum, maximum, and final measurements for different functions. All analyses are compared between accepted and rejected hearts using logistic regression and statistical analysis. Using the most recent measurements for each donor at 24 hours after brain death, the analysis identified significant factors in predicting donor heart acceptance: Left Ventricular Valve Dysfunction, Age, Shortening Fraction, and 4 Chamber Ejection Fraction. Additionally, visual tools were created as deliverables to aid physicians to decrease decision time and increase confidence in donor heart acceptance or rejection.**

Keywords — data science for healthcare, pediatric cardiology, donor characteristics, heart transplantation, medical decision making, United Network for Organ Sharing (UNOS)

I. INTRODUCTION

Despite advancements in the medical field, the utilization rate for organ donations for pediatric heart transplants remains low. The number of available pediatric donor hearts discarded reaches as high as 45% in the United States [1]. Due to numerous factors such as the high rejection rate, limited supply and the lack of universally accepted guidelines etc., children in need of a heart transplant generally spend up to 6 months on the waitlist, and an estimated 17% of children die while on the waitlist [2]. As part of a broader effort to increase the survival rate for patients on the waitlist, we investigated the factors contributing to donor heart utilization and provided deliverables for physicians to optimize the selection of donor hearts. The United Network for Organ Sharing (UNOS) created UNet and DonorNet to place candidates on waiting lists, match donors to recipients, and upload and view relevant data on donors [3]. Algorithms match donors and recipients in a tiered fashion based on recipient urgency and other factors that determine donor-recipient suitability [4]. Physicians are notified when their waitlisted patient is matched to a potential donor and have approximately one hour to decide to accept or reject the offer [5]. Factors including medical history, vitals, laboratory testing, radiological results, and distance from the hospital are viewed to inform this decision [6]. This process continues down the list of potential recipients until a heart is accepted or the donor is no longer viable [3]. The large amount of data given to physicians under the harsh time constraint can decrease the confidence in heart selection [7]. Accepting an inadequate heart increases risk of recipient morbidity and mortality which can result in possible program termination [1]. Conversely, rejecting a usable heart may lead to the candidate dying on the waitlist. This research compares the accepted and rejected hearts by analyzing the DonorNet data. The most important heart characteristics relating to acceptance and rejection are determined using logistic regression, thus providing an evidence-based approach for physicians to make this decision.

II. LITERATURE REVIEW

A majority of the available scientific literature regarding donor heart acceptance practices focuses on the larger adult experience and is generally not applicable to the pediatric population. The results of a recent international survey assessing pediatric donor heart acceptance practices

demonstrated wide practice variation between physicians, suggesting the need for data driven guidelines [7]. These results helped prompt a thorough review of the pediatric and adult literature to produce a consensus statement for the International Society of Heart and Lung Transplantation which suggested none of the 'static' donor characteristics (e.g. cause of death, history of CPR, cardiac enzyme levels, or inotrope exposure) were relevant for recipient outcomes. Seemingly, only donor ischemic time (the period of time a donor heart is outside a body) and ultrasound evidence of heart function (as demonstrated by an echocardiogram) influenced recipient survival after heart transplantation, although these assertions were extrapolated from small pediatric and larger adult studies and always used only the final, pre-transplant echocardiogram for assessment [8].

No study has attempted to assess the potential donor heart's response to impending brain death and the period afterwards, which are characterized by a supraphysiologic insult followed by a complete cessation of neurohormonal support by the body, respectively. Considering the pediatric heart's intrinsic ability to recover from significant stressors, it would be expected that given adequate time and medical support, most pediatric donor hearts should be salvageable for donation. The only way to determine this potential, however, is to assess the entirety of available donor data, and provide a complete representation of the donor heart's external stressors and its subsequent response and compare against physician's donor acceptance practices and ultimate recipient outcomes.

III. DATA DESCRIPTION

The data used in the analysis consists of three sets describing 7100 donors that were either accepted or rejected for a pediatric heart transplant from 2009 to 2020.

The first set was created to describe the test results of cardiovascular milieu (heart measurements), surrogate markers of organ perfusion (kidney and liver measurements) and inotropic agent levels (medication given to a patient to change the force of heart contractions).

- Heart Measurements: *blood pressure, heart rate, pulse, central venous pressure (CVP), troponin,* and *creatine kinase-MB (CKMB)*
- Kidney Measurements: *Creatinine, Sodium 170, Potassium, PAO2, Positive End-Expiratory Pressure (PEEP), Hemoglobin (HGB), Hematocrit* (*HCT*), and *Schwartz* score.
- Liver Measurements: *Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), Bilirubin* (direct and indirect), *Prothrombin, International Normalized Ratio (INR),* and *Model for End-stage Liver Disease (MELD)*
- Inotropic Measurements: *Dopamine, Dobutamine, Epinephrine, Milrinone, Vasopressin, and Norepinephrine,* and *Vasoactive Inotropic Score (VIS)*

The *Schwartz* score is a quantifiable calculation to assess the level of renal failure [9, 10]. The *MELD* score provides a singular measurement describing liver functioning [11]. *VIS*, a singular measurement calculated from the inotropic values, indicates the level of medication required for the heart to remain viable [12]. All variables contained time-stamped measurements, and all tests that were conducted on the potential donors starting from 24 hours before brain death until they were ultimately accepted for transplantation were included.

The second set of variables is a static set of identifying characteristics from each donor: *Donor ID,* Date and Time of *Brain death,* donor *Acceptance/Rejection, Date of Birth, Age, Height,* and *Weight*. These identifiers provide insight into demographic characteristics when analyzing other variables.

The final set is a summary of the echocardiogram (echo) measurements at various times in a donor's clinical life course. Each observation in the data includes the Donor ID, the time that the measurement was taken, and quantitative and qualitative measurements of heart function. These measurements include *Global Left Ventricular Dysfunction, Global Right Ventricular Dysfunction, Focal Left Ventricular Free Wall Dysfunction, Focal Interventricular Septal Dysfunction,* and *Focal Right Ventricular Free Wall Dysfunction.* Ordinal scores representing *Qualitative Status* and *Quantitative Status* of heart function were developed from these echo measurements to describe heart functioning as moderate to severe, mild, or normal at the time the tests were conducted.

The three subsets were combined to create a superset for evaluation. Variables were organized by Donor ID into a format with columns of the test name and corresponding value, the time of the test, and the identifying characteristics. For each Donor ID, there may be multiple measurements associated with different parts of the body at different times (*DT*). *Duration,* defined by the time difference between *BrainDeath* and *DT*, was calculated to determine the time after brain death these measurements were taken. Ranges of normal values for each test were included for each observation.

IV. DATA ANALYSIS

Data analysis was conducted on both an aggregate and individual level. Logistic regression analysis was performed on relevant variables to determine which ones were significant in predicting whether a heart was ultimately accepted or rejected.

A. Aggregate Level Analysis

In order to better understand how heart metrics changed over time and differed between accepted and rejected donors, a graphical data exploration was conducted on an aggregate level. Boxplots produced for each variable show every datapoint against time since brain death (in hours) to visualize measurement variability across the clinical course of the donors. Additional boxplots show the range of minimum, maximum, and final values, and whether they were in a normal

range [13]. These were all differentiated by age group and whether they were accepted or rejected. The analysis also included tables and plots showing the numbers and proportions of values that are too low, in range, and too high from 24 hours before brain death to 48+ hours after, differentiated by accepted/rejected. As an example, the Creatinine proportion plot can be seen in Fig. 1. All plots were combined into an html file organized by the associated organ or functioning. These four types of graphics enable physicians to visualize to what extent the measurements are similar for accepted and rejected donors and to quickly see information about the normal range of the variable.

B. Individual Level Analysis

Individual level analysis was also conducted in order to help physicians make more effective and confident decisions on whether to accept a donor heart by plotting each of the indicative scores (VIS for inotropic medications, Schwartz for kidneys, and MELD for liver) from brain death (for one individual donor) to acceptance or rejection. These are precise data points calculated using generally accepted formulas [9, 10, 11, 12]. These also show whether measurements were in the normal range. As seen by the light blue background in Fig. 2, this particular donor had all abnormal measurements for

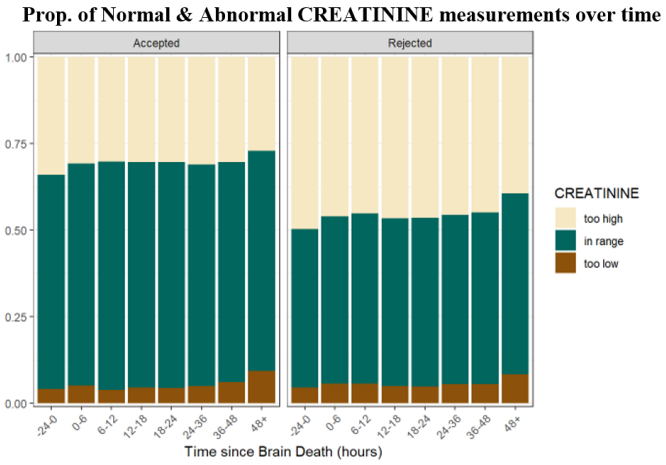

Fig. 1. The proportions of Creatinine over time for all accepted and rejected donors. Proportions of values that are too low are shown in brown, in range are shown in dark green, and too high are shown in tan.

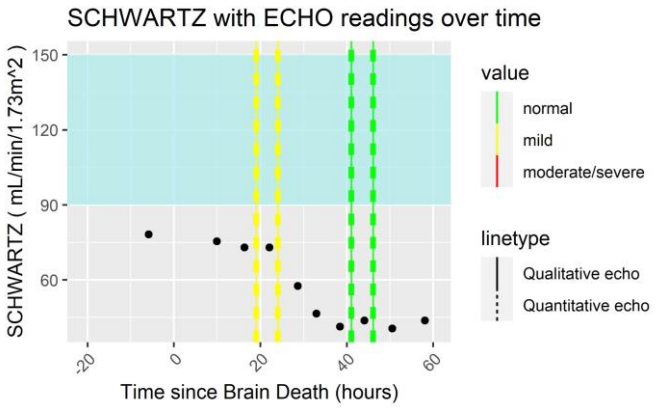

Fig. 2. The measurements of the Schwartz score and echo results over time for an individual donor.

their Schwartz score, indicating renal failure. Overlaying this plot are the ECHO results for that donor, both quantitative and qualitative, with red, yellow, and green vertical lines signaling an ECHO test at that time point that indicated moderate to severe heart dysfunction, mild heart dysfunction, and normal functioning, respectively. Quantitative and qualitative ECHO tests are often conducted at the same time, and may have different results, so they are distinguished by the type of line, either straight or dashed for qualitative and quantitative readings, respectively. As ECHO data provide the most objective measurement of heart functioning, physicians can visually determine how normal or abnormal a given donor is with respect to the given variables and general heart functioning.

C. Logistic Regression Analysis

Modeling techniques were used to determine the most important heart factors that contribute to a donor's acceptance. Due to the high percentage of missing data caused by different measurement time intervals for each variable, data imputation was required. The most recent measurement was used if a donor was missing data. Variables still with more than 80% of the data missing were excluded from the imputation, and only 25 variables met the criteria. The remaining missing data was imputed using predictive mean matching [14].

Logistic regression was performed on an 80% training set. The response variable (*Accepted*) was a binary variable indicating an accepted donor heart or not accepted. Static donor characteristics (*Age*, *Weight*, and *Height*), echo measurements (*Left Ventricular Dysfunction*, *Shortening Fraction*, and *4 Chamber Ejection Fraction, Qualitative Status, Quantitative Status)*, heart measurements (*Blood Pressure*, *Pulse*, and *CVP)*, *Body Temperature*, and *VIS* were the predictors at *t* hours after brain death. The model only considered a 24-hour period after brain death in order to create a scenario that simulates the reality as much as possible.

The predictor variables were selected by remaining variables with sufficient data and previous literature. *Age*,

Weight, *Height* were the only static donor identifiers that could influence donor heart acceptance at a fixed 24-hour duration. *Qualitative Status*, *Quantitative Status*, *Left Ventricular Dysfunction*, *Shortening Fraction*, and *4 Chamber Ejection Fraction* were the ECHO measurements used as predictors. Previous research indicated that ECHO measurements, especially ejection fractions, were significant in heart acceptance, so *Qualitative Status* and *Quantitative Status* were as summaries of ECHO measures, as well as the ejection fraction measures [8]. *Blood Pressure*, *Pulse*, and *CVP* were the only heart measurements with sufficient data and therefore included in the model. No liver or kidney variables contained sufficient data, so liver and kidney measurements were not included in the analysis. Previous research suggested no inotropes were relevant in heart acceptance, so *VIS* was the only inotropic included in the analysis as a representative of all inotropes to further investigate the claim [8]. *Body Temperature* was used as a predictor because it had sufficient data and was not part of any of the donor data groups, so it was decided it was relevant.

The regression model was analyzed by ANOVA to identify significant factors correlated to heart acceptance. A prediction model was developed on the 20% testing set [14]. The prediction model examined the results of the logistic regression model using sensitivity analysis and correlation matrix.

V. RESULTS

The aggregate level analysis identified many general trends for both accepted and rejected donor hearts. For accepted hearts, troponin, CKMB, and pulse all had values higher than the specified normal range, but decreased by about 73%, 59%, and 6% respectively in accepted donors. PEEP was in the specified normal range and decreased by about 19%. SGOT and SGPT had a 42% and 40% decrease in values, respectively, and became in their normal range by the 36-48 hour bins. In rejected hearts, PEEP, CVP, temperature, sodium, potassium, prothrombin, CKMB, troponin, and HGB were in their specified normal ranges for the majority of the time, while Bilirubin, INR, and PAO2 were not.

In both accepted and rejected hearts post brain death, blood pressure, bilirubin, CVP, and Schwartz increased by at least 5%. The values of PAO2 were higher than the normal range (i.e., greater than 100 mmHg), and notably increased by 15% for accepted hearts, and 26% for rejected hearts from 0 to 48+ hours. Variables that decreased at least 5% for both accepted and rejected hearts over this same time period include pulse, CKMB, HCT, HGB, VIS, Potassium, PEEP, Prothrombin, SGOT, and SGPT. Additionally, the aggregate analysis of SGOT and pH showed visually similar trends between accepted and rejected hearts, as seen in Fig. 3 and 4. Two variables, Troponin and Creatinine, had opposite trends for accepted and rejected donors. While troponin decreased by 73% for accepted hearts, it increased by 51% for rejected hearts (Fig. 5). Creatinine increased by 11% for accepted hearts and had more normal measurements as compared to rejected hearts, which decreased by 4% over time (Fig. 6).

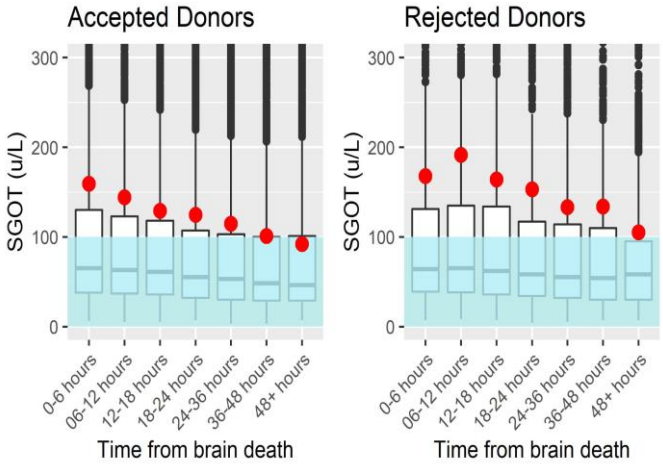

Fig. 3. SGOT measurements over time for accepted and rejected donors. The blue rectangle indicates the range of values considered to be normal SGOT levels, and the mean at each time bin is represented by the red dot

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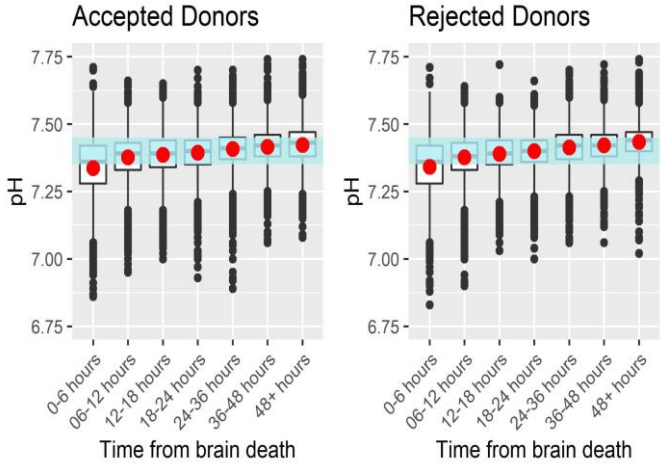

Fig. 4. pH measurements over time for accepted and rejected donors. The blue rectangle indicates the range of values considered to be normal pH levels, and the mean at each time bin is represented by the red dot.

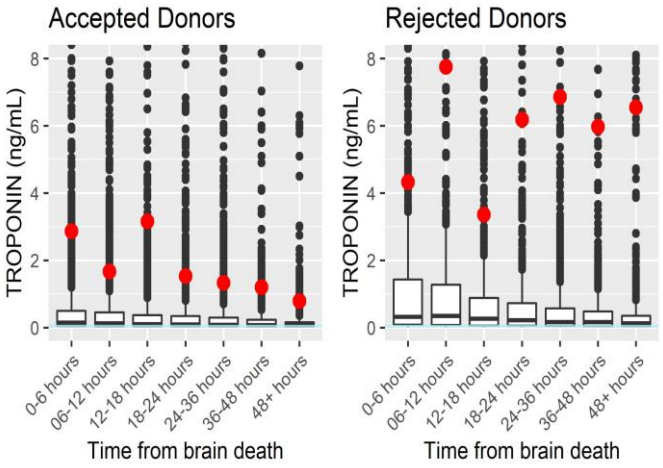

Fig. 5. Troponin measurements over time for accepted and rejected donors.The blue rectangle indicates the range of values considered to be normal troponin levels, and the mean at each time bin is represented by the red dot.

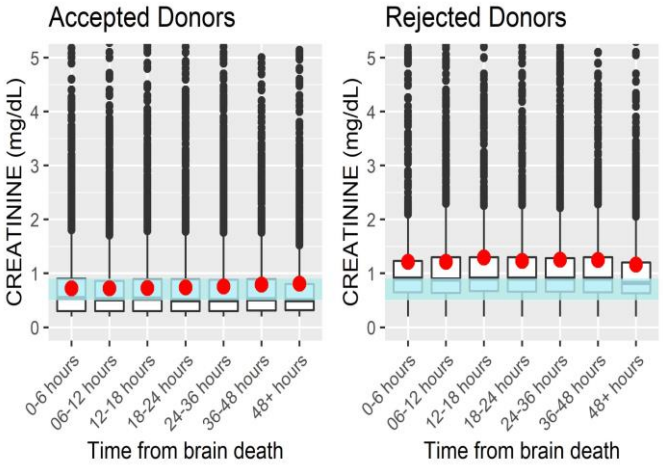

Fig. 6. Creatinine measurements over time for accepted and rejected donors. The blue rectangle indicates the range of values considered to be normal creatinine levels, and the mean at each time bin is represented by the red dot.

In comparing normal and abnormal measurements over time, the levels of HCT, pH, HGB, temperature, sodium, SGOT, potassium, CKMB, CVP, PEEP, prothrombin, and INR were all visually similar between accepted and rejected hearts. HCT values became more abnormal over time, while pH, HGB, Temperature, Sodium, SGOT, Potassium, and CKMB became more normal over time. CVP, PEEP, Prothrombin, and INR remained relatively constant over time. However, a Chi-square test was conducted on the number of normal and abnormal measurements for each time bin of the variables, and concluded that only the measurements for prothrombin and HGB were not significantly different. The remaining variables (other than PEEP and CKMB) had disproportionately more rejected hearts having abnormal measurements than expected and accepted hearts having less in the last duration bin of 48+ hours. Differences in variables between accepted and rejected donor hearts were evident in pulse, bilirubin, troponin, SGPT, and PAO2, as all of these variables had higher proportions of abnormal measurements in rejected hearts. On the contrary, Creatinine, diastolic blood pressure, and systolic blood pressure had higher proportions of abnormal measurements in accepted hearts. When looking at pulse and creatinine by age group for both accepted and rejected hearts, pulse values seem to fall within the normal measurement range until age 3, while for creatinine values for donors under 10 years old, there were more extreme outliers for accepted hearts compared to rejected hearts, as seen in Fig. 6.

When comparing measurements at the last duration value, the majority of the percentages of abnormal and normal measurements were similar between accepted and rejected hearts. pH, PEEP, HGB, HCT, temperature, dopamine, milrinone, SGOT, SGPT, prothrombin, CKMB, systolic blood pressure for ages 0-6 months and 6-12 years, diastolic blood pressure for ages 6-12 months, 1-3 years, 6-12 years, and 12+ years, pulse for ages 6-12 years, and creatinine for ages 10 and over all had less than a 2% difference between accepted and rejected hearts. Large differences between accepted and rejected heart values were found in bilirubin direct, troponin, systolic blood pressure for ages 6-12 months, diastolic blood pressure ages 0-6 months, and pulse ages 6-12 months.

Logistic regression was modeled on donor data 24 hours after brain death, and significant measurements correlated to heart acceptance were determined [14]. It identified two highly significant factors (p-value < 0.001) correlated to heart acceptance: *Age* and *Left Ventricular Dysfunction*. A correlation matrix of factors is visualized by the heatmap shown in Fig. 7.

A confusion matrix from the test set found the prediction model to have an 0.890 accuracy rate, with a 95% confidence interval: [0.7954, 0.952]. The sensitivity of the prediction model is shown in the ROC curve in Fig. 8. The area under the ROC curve is 0.79.

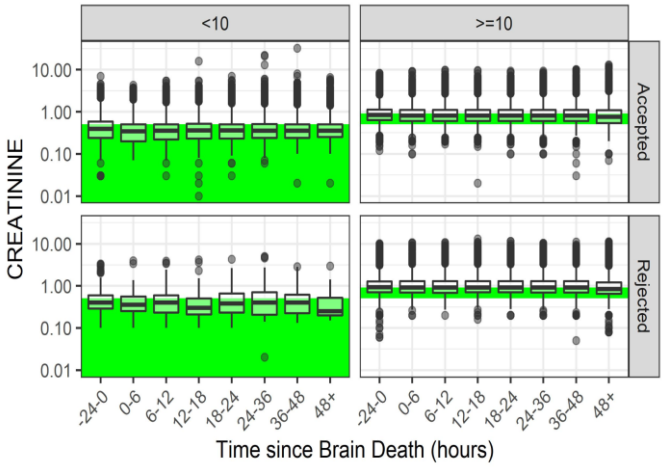

Fig. 6. Creatinine measurements over time by age group (less than 10 years old, and greater than or equal to 10 years old) for accepted and rejected donors.

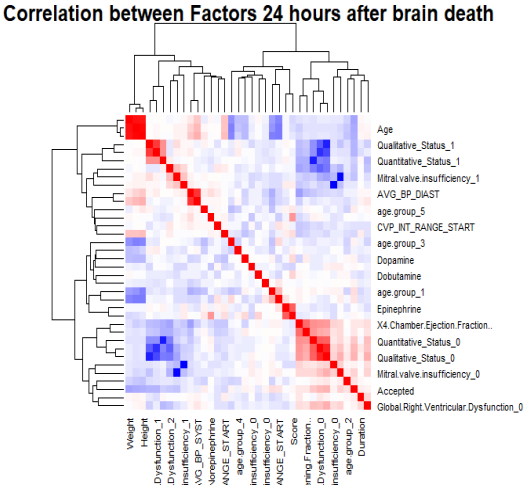

Fig. 7. Heatmap of correlation matrix of predicted values. A blue square represents a negative correlation. A red square represents a positive correlation.

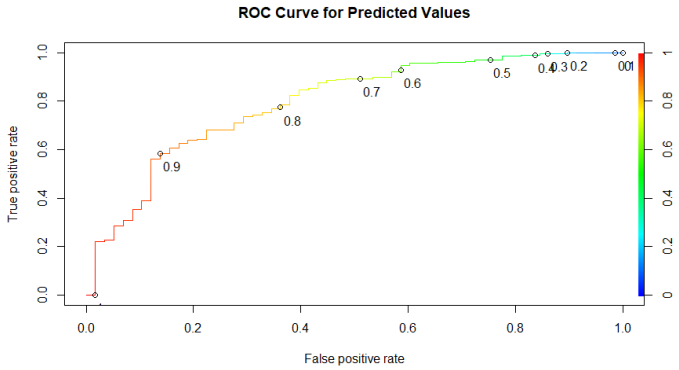

Fig. 8: Plot of ROC curve. Describes the true and false positivity rate for predicted values on the testing set.

VI. CONCLUSIONS

The plots of individual donor data provide a deliverable for physicians to view trends over time for the donor they are considering for their recipient. They can visually analyze trends over time and evaluate the functioning of the kidney and the liver through the Schwartz and MELD scores, as well as inotropic medications, and see how it is related to the functioning of the heart in relation to the given quantitative and qualitative ECHO readings.

The aggregate level analysis and the identification of trends among accepted and rejected heart donors provide information to physicians about the timeline of pediatric hearts following brain death and enables the comparison of accepted and rejected donor hearts. Future work in this area includes assessing the effect of modeling at different times after brain death. This will allow for a better understanding of heart function, and could identify optimal time ranges for heart extraction. Furthermore, data analysis on waiting lists and recipient data could improve understanding on donor-recipient compatibility, as well as identifying heart factors that contribute to both heart acceptance and successful transplants.

Ultimately, this research and future work will make the decision process for doctors faster and easier, and give them greater confidence in an optimal outcome for the recipient. By doing so, it is expected that fewer donor hearts will be rejected, and waitlist mortality for pediatric heart transplant recipients will decrease.

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