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Alternative methods for virtual heart transplant—Size matching for pediatric heart transplantation with and without donor medical images available

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Abstract

Background: Listed pediatric heart transplant patients have the highest solid-organ waitlist mortality rate. The donor-recipient body weight (DRBW) ratio is the clinical standard for allograft size matching but may unnecessarily limit a patient's donor pool. To overcome DRBW ratio limitations, two methods of performing virtual heart transplant fit assessments were developed that account for patient-specific nuances. Method 1 uses an allograft total cardiac volume (TCV) prediction model informed by patient data wherein a matched allograft 3-D reconstruction is selected from a virtual library for assessment. Method 2 uses donor images for a direct virtual transplant assessment.

Methods: Assessments were performed in medical image reconstruction software. The allograft model was developed using allometric/isometric scaling assumptions and cross-validation.

Results: The final predictive model included gender, height, and weight. The 25th-, 50th-, and 75th-percentiles for TCV percentage errors were −13% (over-prediction), −1%, and 8% (under-prediction), respectively. Two examples illustrating the potential of virtual assessments are presented.

Conclusion: Transplant centers can apply these methods to perform their virtual assessments using existing technology. These techniques have potential to improve organ allocation. With additional experience and refinement, virtual transplants may become standard of care for determining suitability of donor organ size for an identified recipient.

KEYWORDS
heart transplant, pediatric transplant, virtual fit assessment, virtual transplant

Abbreviations: AICc, corrected Akaike information criterion; BMI, Body mass index; BSA, body surface area; CHD, congenital heart disease; CT, computed tomography; DRBW, donor-recipient body weight; ECHO, echocardiography; HTx, heart transplantation; LOOCV, leave-one-out cross-validation; MAE, mean absolute error; MAPE, mean absolute percent error; MedAPE, median absolute percent error; ME, mean error; MR, magnetic resonance; mTCV, measured total cardiac volume; pTCV, predicted total cardiac volume; RMSE, root mean square error; TCV, total cardiac volume; USA, United States of America.

1 | INTRODUCTION

Allograft size matching for HTx is considered a clinically-relevant factor in patient outcomes.[1,2] Undersized allografts are at risk for cardiac output insufficiency, while oversized allografts are at risk for compression effects producing physiologic complications. The current clinical standard is to use the DRBW ratio as a standalone metric in allograft size matching.[1] A HTx center will list their patient with an institutionally determined DRBW ratio range that is often modified based on a patient's pathology or anatomy. Allograft shortages for the young pediatric population have pushed clinicians to aggressively expand donor pools (including the widening of DRBW ratio ranges) to increase probability of organ procurement.[3,4] Pediatric waitlist mortality in the USA for body weights ≤5 kg and ≤20 kg are 24% and 20% with the largest pediatric patients having an 11% mortality rate (similar to the current adult population).[3,5] This corresponds to approximately 70 pediatric patients dying on the waitlist annually while approximately 800 well-functioning donor hearts (18% of all allografts) are wasted annually.[3,6] Literature inconsistencies in defining an appropriate DRBW ratio range to predict fit-related outcomes (particularly in the pediatric patient), can potentially be explained by fundamental limitations with how this metric is clinically applied because the method does not directly consider pathological and developmental anatomical growth patterns.[2,7-18]

We leveraged allometric scaling concepts to derive the proposed statistical model. Allometry uses the power law functions from mathematics, for example, Equation 1, and starts with the fundamental understanding that human growth proceeds such that different features (anatomical structures) grow at different rates.

$$y = a * x^{b} \quad (1)$$

A scaling relationship is said to be isometric when the empirical ($\hat{b}$) and theoretical (b) scaling exponents are equivalent; otherwise, the relationship is allometric.

The first potential limitation of the current DRBW ratio metric methodology is how the listing range for a donor allograft is determined. Transplant centers will define a generalized upper and lower DRBW ratio range they are willing to accept for their listed patient. This center-specific range may be based on adult outcomes, which may explain why recent pediatric studies suggest that DRBW ratio ranges can be expanded.[1,10,14,16,19-22] Applying adult fit assessment techniques based on adult-defined DRBW ratio ranges could potentially be limiting pediatric fits due to lack of consideration for growth differences.

The second limitation of the current DRBW ratio metric methodology is that body weight, particularly in patients with heart failure, may be dissociated from cardiac anatomy.[23-27] Specifically, fluid retention, cachexia, and/or obesity can develop with acute or chronic illness having a much greater effect on weight than cardiac size. Progression of a pathologic state (eg, cardiomyopathy) further dissociates cardiac anatomy from body weight.

Clinicians have several methods to expand allograft acceptance range based on size. Select pediatric centers will set a patient's listed DRBW ratio range based on a categorical grouping of their age, that is, infant vs noninfant. However, the clinical reasoning for this practice is more related to the limited likelihood that an infant will be offered a more appropriate allograft in time, than related to general developmental patterns.[2,10,19,28] The X-ray cardiothoracic ratio may be used to expand the DRBW ratio ranges, but this practice primarily affects cardiomyopathy patients and a subset of CHD patients. The cardiothoracic ratio falls short on providing the full range of volumetric, geometric, and anatomical characteristics of a given patient's pathology.

Contemporary literature suggests potential applications of ECHO to predict allograft fit.[1,29,30] While ECHO-based methods are less likely to be influenced by obesity or fluid overload, both the DRBW ratio metric and ECHO methods may not account for patient and donor anatomical deviations. CHD patients represent a significant subset of listed pediatric patients; the unique anatomical structures are relevant factors in accepting a donor offer.

Recent virtual device implant fit assessments demonstrate the utility of a virtual assessment to accommodate patient-specific morphology.[31,32] The virtual implant strategically fuses a computational rendition of a medical device into a patient's CT or MR image to assess for potential compression effects.[31,33] The methods gleaned from virtual device implantation can be leveraged for allograft fit. For virtual HTx fit assessments to be feasible in the standard of care, the method must be expeditious and adaptable for the wide range of possible allografts.

This manuscript presents two methods of virtual HTx assessments to aid clinicians in predicting potential compression effects from donor offers. The first assessment (Method 1) relies on a linear regression model and library of allograft geometries while the second method takes advantage of donor CT/MR images. The use of donor CT/MR images for assessment (Method 2) is of course ideal; however, the approach will be rarely feasible because (a) the requisite images simply may not exist or (b) acquiring the images and assessing fit within the allotted time for donor acceptance/decline may be technically impractical. Typically, transplant centers have 1 hour to provisionally accept a donor offer and several hours thereafter to confirm an acceptance. To facilitate virtual HTx assessments when donor images are not available, a linear regression model combined with a library of normal heart reconstructions offers a suitable alternative.

2 | METHODS

2.1 | IRB approvals

The Phoenix Children's Hospital (Phoenix, AZ, USA) IRB approved this research; informed consent was not required.

2.2 | Normal heart patients

Subjects with normal cardiac anatomy (N = 97) with retrospective CT/MR images were identified by chart review. Subjects with no greater than mild dilation or obstruction of the great vessels deemed

to have a normal size heart by both the radiologist and the cardiologist were included. Subjects with pathologies (eg, anemia) or who received treatments (eg, some chemotherapy drugs) known to potentially affect the heart were excluded. Subject TCV reconstruction (ie, segmented geometry of the actual 3D cardiac image), modality type (CT/MR) of reconstruction, and 6 parameters at the time of scan were recorded. The 6 subject parameters that were considered as potential predictors (and their interactions) in the final allograft prediction model were gender, age, height, weight, BSA, and BMI. The reconstructed TCV geometries—derived from CT or MR imaging—were measured and are referred herein as the mTCVs. The TCV reconstructions and mTCV were preserved to build a virtual allograft library for performing virtual HTx fit assessments and to estimate regression coefficients, respectively.

2.3 | Reconstructions

Normal cardiac subject and HTx patient anatomical regions of interest were reconstructed from CT or MR volumetric images. The reconstructions were produced in the following sequential order: (a) images were segmented in Mimics Innovation Suite software (Materialise, Leuven, Belgium), (b) initial reconstructions were postprocessed in Geomagic Studio software (3D Systems, Rock Hill, SC, USA), and (c) the completed reconstructions were re-imported into the patient's images for quality evaluation using Mimics. The myocardium and anatomical structures deep to the myocardium exterior surface (including blood volumes) were defined as part of the TCV. The described TCV boundary is demonstrated in Figure 3 with a recipient's native heart (red) pretransplantation.

2.4 | Allograft prediction model development

Normal cardiac subject parameters and mTCV were used to develop and validate a linear regression model that predicts a healthy allograft TCV (pTCV). Nonparametric, Mann-Whitney *U*, and Kolmogorov-Smirnov hypothesis tests were performed ($\alpha = 0.05$, $H_0 = 0$) to ensure there were no statistically significant differences between the CT and MR populations based on either mTCV or other continuous parameters. Modality was also re-introduced to the final regression models to ensure that the variable was not adding any predictive power. Concern for potential variation in mTCV population values arises from CT and MR enhancing blood and myocardium tissue contrast differently. These tests were performed to support the justification of pooling the data without needing to account for modality.

The model was developed and validated by incorporating the mTCV and patient predictor values. Coefficients were estimated using a method that is robust to heteroscedasticity and outliers, namely iteratively reweighted least squares based on Huber weight function.[34] A 5-step process was implemented in R software (R Core Team, Vienna, Austria) to develop and evaluate an allograft prediction model.[35,36] First, multicollinearity was addressed by using a variance inflation factor cutoff threshold (≥20); specifically, collinear predictors were removed using a backward stepwise procedure. Second, a model search procedure based on the AICc with a difference cutoff threshold (≤3) was implemented to identify top potential predictive model structures.[37,38] Third, LOOCV was implemented to evaluate the top specifications. RMSE, ME, MAE, MedAPE and MAPE were used to evaluate the top models. Fourth, estimated coefficients and their bootstrap-derived confidence intervals were investigated. Finally, to ensure satisfactory levels of accuracy, the predictive performance of the proposed specifications was evaluated against alternative modeling approaches: quantile regression, random forests, and regression trees.

The modeling process was repeated on the following 3 data formats: untransformed, log-log transformed (allometric scaling assumption), and power transformed (forced isometric scaling assumption, for example, height was taken to the power of 3 to match the characteristic dimensional unit of volume). A forced isometric modeling process was considered because historical cardiac empirical study results, along with the assumptions that soft tissue density and gravity are constants, imply an isometric scaling between adult TCV and body weight.[39-41] Gender was not transformed and age was log transformed but not power transformed because it has a nonspatial characteristic unit.

2.5 | Virtual heart transplantation

Preoperative patient HTx images were reconstructed from either CT or MR scans. Donor allograft geometries for assessment were acquired by either (a) pulling a TCV geometry from the preconstructed virtual library or (b) reconstructed from donor CT or MR images. The donor pTCVs from gross parameters and the developed regression model were used to pull cardiac geometries with matching mTCV for transplant assessment. Using Mimics, the clinical team virtually transplanted the allograft by strategically fusing the geometry into the patient's CT or MR image by clinically considering how the allograft would need to be placed given the localized anatomy. The team did assess the fit by reviewing the allograft overlay in the recipient's cross-sectional images. Risk for fit-related complications was noted by clinicians when contours overlaid considerably onto critical structures (eg, aorta, airway, and diaphragm) and/or rigid structures (eg, ribs, sternum, and vertebral column). The surgeon performing the retrospective, virtual transplantation assessment was blinded to the actual transplant cases.

2.6 | Practical application

Model development and strategic workflow for how this could be applied in real time represent the primary aim for this effort. The intent of this stage was for an assessment of feasibility. To further test the practical application of this model, we share three actual cases of conventionally oversized donors. In one of these cases, actual donor images were available and a virtual HTx assessment was applied prospectively using a donor reconstruction. A prospective series employing donor images is planned.

TABLE 1 Normal cardiac subject demographics used to train and test the predictive models

Demographics of regression model training dataset (N = 97)	
Demographic characteristics	**Results**
Heart volume (mL)	535 ± 259 (36-1340)
Male	62
Female	35
CT	50
MR	47
Age (mo)	155 ± 70 (3-358)
Height (cm)	147 ± 31 (42-186)
Weight (kg)	53 ± 29 (2.8-139)
BSA (m^2)	1.46 ± 0.54 (0.18-2.59)
BMI (kg/m^2)	22.8 ± 7.2 (13.5-46.5)

Data are reported as mean ± standard deviation (range) or n (%).

3 | RESULTS

3.1 | Healthy heart demographics and CT/MR measurement comparison

The demographics of the normal cardiac population used in the statistical study (N = 97) are listed in Table 1 with 95% being of adolescent age or younger.[42] Young adults were available and therefore included to help ensure interpolated TCV predictions were made for the pediatric population. Two-sample Mann-Whitney *U* (*P*-value results ranging from 0.5467 to 0.0526) and Kolmogorov-Smirnov (*P*-value results ranging from 0.9414 to 0.1654) test results, comparing the CT (N = 50) and MR (N = 47) populations for mTCV, age, height, weight, BMI, and BSA, suggested no evidence against the null hypothesis that the distributions between the modalities were equivalent. The modality populations are illustrated with box-and-whisker plots in Figure 1A. Figure 1B further illustrates the CT and MR Age population

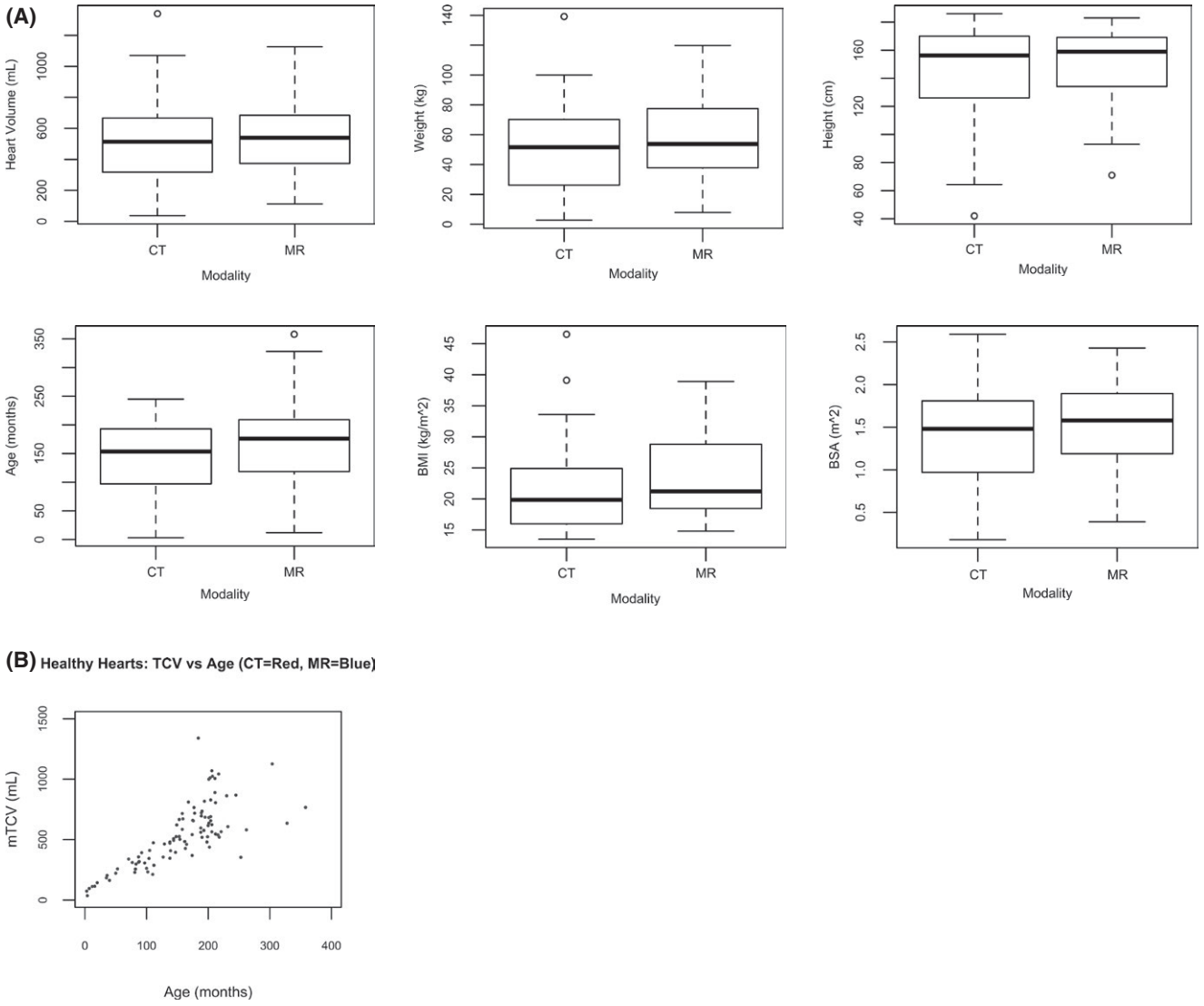

FIGURE 1 mTCVs for different modalities. The horizontal lines indicate the lower whisker, 25th-quartile, 50th-quartile, 75th-quartile, and upper whisker for CT (314, 513, and 674 mL) and for MR (356, 539, and 685 mL) in plot (A). Plot (B), in general, illustrates subject age is similar between the CT (red) and MR (blue) populations

distributions were similar. Furthermore, modality was found to not be a significant predictor, for example, was not adding predictive power, when added to both the Model-A and Model-B frameworks. The accumulated findings suggested (a) the CT and MR population distributions are similar and (b) and the mTCVs were consistent between modalities.

3.2 | Model development and validation

Two final models were developed with age considered (Model-A) and age excluded (Model-B) in the modeling process with results described in Table 2. Additionally, Table 2 depicts a 0.75 quantile regression variant of Model-B, that is, Model-B*, wherein underestimation is penalized three times more than overestimation.

The residual standard error and AICc values in Table 3 suggest that Model-A and Model-B are practically equivalent in terms of predictive performance, that is, Model-B performs negligibly better. This finding is verified by LOOCV, see Table 3 and Figure 2. The significant positive interaction of ln(Age) with ln(BSA) suggests that the positive effect of a unit change in BSA on pTCV becomes stronger as patients get older. The negative ln(BMI) coefficient in Model-A suggests that BMI is correcting for overweight that is "hidden" within the height-weight interaction represented by the BSA variable; that is, overweight and growth affected TCV differently. In particular, BMI needing to correct for body type hidden in BSA suggests that thoracic cavity space differences, which are more directly related to height than weight as discussed later, control TCV. Historical HTx observations further support that thoracic space dictates heart size because oversized allografts have been documented to shrink to the available cavity space in the small, pediatric recipient before the organ grows with the patient.[28,43] Model-B, relative to the negative effect of BMI and interaction of ln(Age) with ln(BSA) in Model-A, is a more intuitive model with directly measurable variables. Based on these factors, our group prefers Model-B in virtual HTx fit assessment.

The testing set's TCV prediction percentage errors for Model-B are −21%, −13%, 8%, and 16% for corresponding quartiles of 0.125, 0.250, .750, and .875, respectively. The TCV percentage errors are derived by using (mTCV−pTCV)/(mTCV). A negative error corresponds to an over-prediction. 75% of the testing set's TCV percentage errors ranged between −21% and 16%. The largest over-prediction error in the testing dataset was −56%.

Given that Model-B is intended to help clinicians expand donor pools in virtual HTx fit assessments, an under-prediction of TCV could be particularly clinically problematic. Based on test data, as shown in Figure 2, Model-B under-predicts allograft TCVs in approximately 50% of the cases. This result is expected based on the estimation method, which focuses on minimization of mean square error. Therefore, a corresponding 0.75 quantile regression model (Model-B*) was developed as a more conservative alternative. Model-B* reduces the risk of under-predicting TCV at the cost of increasing the likelihood of over-predicting TCV (see Table 3). The decreased ME and the increased MAPE and MedAPE (as well as corresponding standard deviations) in Table 3, were a forced consequence of the 0.75 quantile offsetting predictions to favor over-prediction (the positive shift trend from the circle to the triangular markers in Figure 2 on the left illustrate that Model-B* favors over-prediction).

While isometric scaling was forced in the modeling process, the log-log transformed fits performed superiorly and confirmed

TABLE 2 The final two allograft prediction models with their estimated coefficient values (bolded); bootstrap standard errors are shown in parentheses

Model-A

$$pTCV_{Model-A} = \exp\left(\alpha_1 + \left(\alpha_2 + \alpha_3 * \left[\frac{\ln(Age)-4.840}{0.849}\right]\right) * \left[\frac{\ln(BSA)-0.284}{0.481}\right] + \alpha_4 * \left[\frac{\ln(BMI)-3.079}{0.295}\right] + \alpha_5 * Gender + \frac{\alpha_6^2}{2}\right)$$

Parameter	1	2	3	4	5	6
α	**6.060** (0.027)	**0.664** (0.048)	**0.006** (0.018)	**−0.074** (0.037)	**0.104** (0.032)	**0.136** (0.012)

Model-B

$$pTCV_{Model-B} = \exp\left(\beta_1 + \beta_2 * \left[\frac{\ln(Ht)-4.963}{0.260}\right] + \left(\beta_3 + \beta_4 * \left[\frac{\ln(Ht)-4.963}{0.260}\right]\right) * \left[\frac{\ln(Wt)-3.795}{0.714}\right] + \beta_5 * Gender + \frac{\beta_6^2}{2}\right)$$

Parameter	1	2	3	4	5	6
β	**6.053** (0.027)	**0.340** (0.069)	**0.302** (0.057)	**0.016** (0.020)	**0.099** (0.032)	**0.132** (0.012)
β^*	**6.137** (0.041)	**0.282** (0.107)	**0.338** (0.084)	**0.015** (0.028)	**0.125** (0.028)	**0.000**

Developed standardization equations for mTCV and parameters

mTCV	Gender	Age	Height	Weight	BMI	BSA
$\frac{\ln(mTCV)-6.132}{0.621}$	Gender	$\frac{\ln(Age)-4.840}{0.849}$	$\frac{\ln(Ht)-4.963}{0.260}$	$\frac{\ln(Wt)-3.795}{0.714}$	$\frac{\ln(BMI)-3.079}{0.295}$	$\frac{\ln(BSA)-0.284}{0.481}$

Estimated coefficients correspond to standardized predictors (Gender (Male = 1, Female = 0), Age (mo), Height (cm), and Weight (kg)). For clarification, the exact formulations of standardized predictors are presented. Parameters α_6 and β_6 correspond to the residual standard error of each model and are used as bias correction factors which improve predictive performance. The 0.75 quantile regression model uses the same equation structure as Model-B but replaces β for β^*.

TABLE 3 Model performance on the training (top) and testing data (bottom). Predictive performance metrics were calculated using LOOCV

Model and prediction summaries			
	Model-A	Model-B	Model-B*
Model summary			
Residual standard error	0.136	0.132	-
AICc	11	10	-
Predictive summary			
RMSE (mL)	94	93	103
ME (mL)	1.6	1.2	−46
MAE (mL)	65	64	74
Median absolute error (mL)	49	46	53
MAPE	12.5%	12.7%	16.1%
MedAPE	9.5%	10.0%	11.4%

allometric scaling relationships. In fact, the relationship between TCV and body weight in the pediatric and young adult population is allometric ($\hat{b}=0.838$, bootstrap standard error = 0.032). The 95% bootstrap (percentile) confidence interval is ⟨0.77-0.90⟩ and provides evidence against the isometric hypothesis $b = 1$. The value of $\hat{b}$ mathematically suggests that adult-derived DRBW ratio boundary limits would unnecessarily limit pediatric donor pools: younger children have a relatively larger heart to body size when compared to older children/adults, which is already established in healthy individuals.[44-47]

3.3 | Virtual heart transplantation case examples

A retrospective case using Model-B (case 1) and a prospective case study in which donor medical images were available (case 3), are presented to illustrate the clinical value of virtual HTx fit assessments. Table 4 summarizes these virtual HTx fit assessments examples. Retrospectively Model-B was applied to the second case.

The first assessment is based on a patient (female, 7 months, 69 cm, 8.65 kg, heterotaxy with unbalanced atrioventricular canal and anomalous pulmonary venous return) in which the team accepted an allograft offer (female, 4 years, 109 cm, 19 kg). This transplant preceded the adoption of the process for regression model based virtual fit assessment described herein. Virtual assessment was retrospectively performed on available preoperative CT/MR images. DRBW and TCV ratios were 2.2 and 1.0, respectively. The TCV ratio between the recipient's measured volume and the recipient's predicted volume, if the recipient heart had been healthy, was 2.3, which is consistent with the degree of cardiac dysfunction and chamber dilation. The surgeon evaluated the virtual transplant of the offered allograft using the appropriate sized heart from the healthy heart library. Based on the virtual transplant imaging, the surgeon graded the donor as "slightly large" and expressed concern about potential compressive effects specifically the possibility of either pulmonary atelectasis and/or pulmonary venous compression. Clinically, fit-related complications were not observed.

The second example also preceded the use of the healthy heart library to prospectively evaluate donor offers. In this case, we also did not have advanced recipient imaging and therefore could not do a virtual HTx fit assessment. The patient was a 4-month-old female with familial dilated cardiomyopathy. She previously underwent a

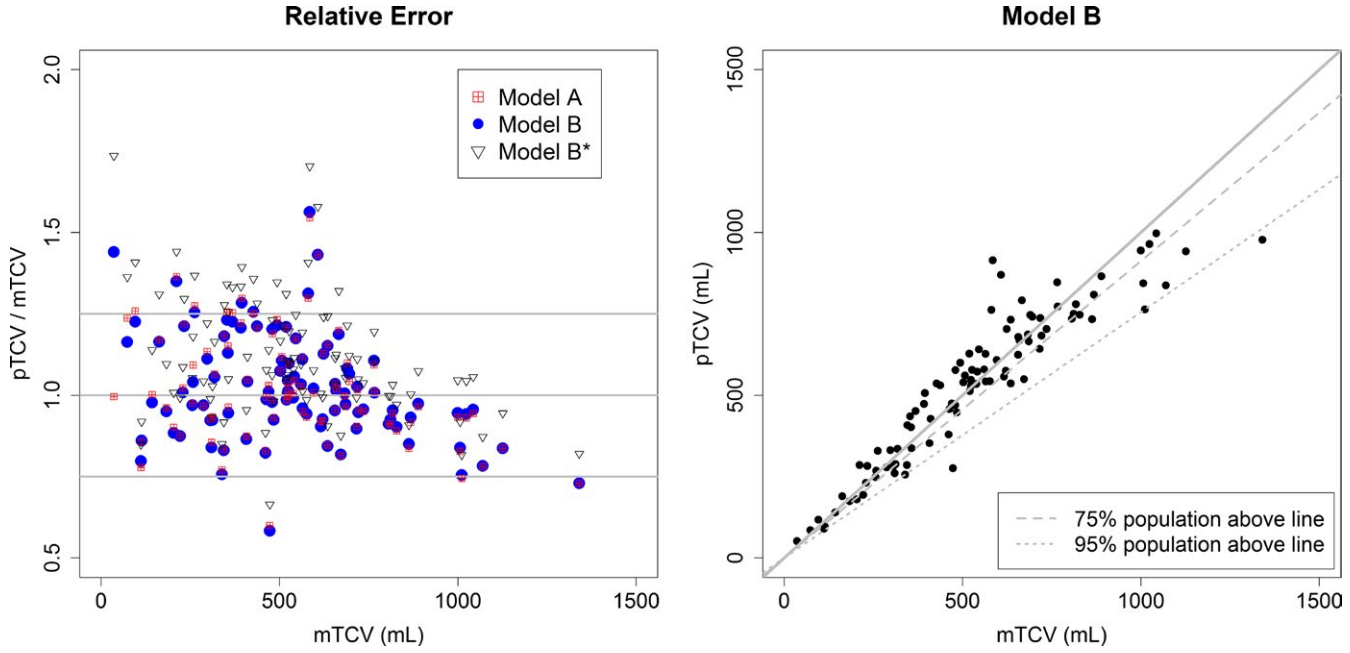

FIGURE 2 The predictive capability of models A, B and B* in terms of LOOCV relative error (left) and in terms of LOOCV pTCV vs mTCV (right) for Model-B

TABLE 4 Virtual HTx fit assessment demographics

Virtual heart transplant assessments		
	Assessment 1	**Assessment 3**
Assessment background		
Assessment type	Retrospective	Prospective
Method for allograft TCV determination	Model-B	Donor images
Perceived fit-related complications	Yes	No
Anatomical characteristics		
Recipient weight	8.7	28.2
Donor weight	19.0	60.0
DRBW	**2.2**	**2.1**
Recipient TCV	214	682
Donor TCV	214	398
TCV ratio	**1.0**	**0.6**
Postoperative outcomes		
Days to sternum closure	4	0
Days of mechanical support	3	1
Days in hospital	33	15
Fit-related complications	No	No
Fit complication mortality	No	No

Bold indicates ratio between donor and recipient.
Assessment 2 did not have the appropriate medical images needed to perform a virtual heart transplant fit assessment and therefore were not included in the current table.

pulmonary artery banding procedure in an attempt to encourage favorable reverse remodeling, and this approach did not seem to produce clinical benefit. At the time of transplant, the patient was 61 cm with a weight of 5 kg. The selected upper limit of the listed weight range in DonorNet was 17 kg. We received a heart offer from a 2.5-year-old male donor—96 cm, weight 16.4 kg. We used echo to determine donor and recipient volumes as described by Camarda et al[1] The recipient TCV was 190 mL and the donor with a reported LVedV of 24 mL had a predicted TCV of 170. The transplanted proceeded smoothly with chest closure in the operating room and discharge home from the hospital 13 days post transplant. We retrospectively applied the healthy heart library to the donor morphometrics and Model-B calculated a donor pTCV of 191 mL. In this case, both volumetric determinations suggested an acceptable fit with the echo TCV ratio of 0.9 and the retrospectively applied healthy heart model at 1.0 supporting the decision to proceed despite a DRBW of 3.3 which may be beyond the upper limit that many centers would even have had the opportunity to consider based on their max weight range entered into DonorNet at the time of listing.

The third assessment (previously reported by our group as a case study[48]), a listed patient (female, 10.3 years, 140 cm, 32 kg, hypoplastic left heart syndrome) was offered a donor allograft (female, 16.4 years, 163 cm, 60 kg) allograft. The DRBW offer was 1.9 with a significant height difference as well for a patient with a complex CHD, and therefore, the clinical team's initial inclination was to decline the offer. However, upon learning that the patient and donor had available CT medical images, a provisional yes on accepting the donor offer was made so the donor images could be electronically transmitted and a virtual HTx assessment performed. The patient and donor images were reconstructed, TCVs measured, and the donor allograft was virtually transplanted. As shown in Figure 3, the clinical team perceived no fit-related complications and found that the allograft was undersized relative to the recipient heart size (quantitatively the TCV ratio between donor and recipient was

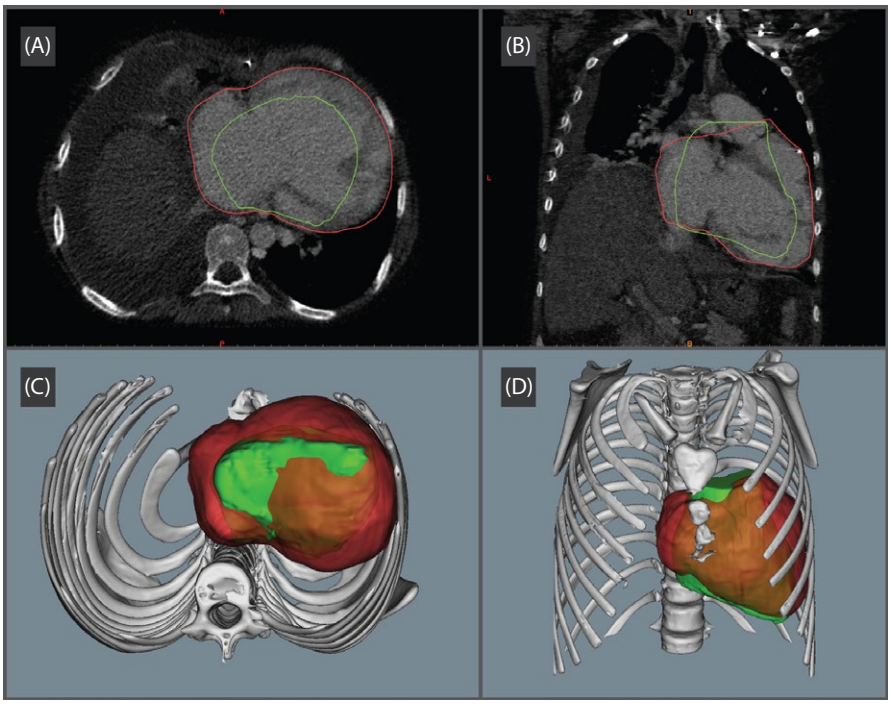

FIGURE 3 Illustration of a virtual HTx fit assessment with the third case. Native heart (red) and skeletal system (white) demonstrated with donor allograft (green). The clinical team can translate and rotate allograft into place or scroll through the three orthogonal image planes to assess the allograft fit, that is, review overlaps of allograft geometry (green contour line) onto key patient cardiothoracic structures. Sub-Images (A) and (B) show axial and coronal plane views and (C) and (D) show reconstruction views available during virtual assessment. The native heart demonstrates the TCV boundary used in the healthy heart library

0.6—see Table 4). The clinical team moved forward with transplant. No fit-related postoperative complications were observed. The chest closed in the operating room, and the patient was extubated within 24 hours and is thriving over 2 years later.

Model-B was retrospectively implemented for the third case. CT and ECHO measurements (Camarda et al[1]) both suggested the TCV was approximately 400 mL while Model-B computed the pTCV to be 580 mL (ie, a −45% prediction error). This is not unexpected given over-predictions as extreme as −56% were present in the testing dataset. There were 5 individuals (this third case's donor makes 6) with large over-predictions (≤−30%). Interestingly, despite the overestimate of donor TCV, the predicted donor-recipient TCV ratio was 0.85 which would have likely been deemed permissive for transplantation.

4 | DISCUSSION

The DRBW ratio is the current metric for allograft size matching. The main limitation of the DRBW method is that weight is not linearly related to cardiac size or anatomy. Furthermore, the DRBW ratio metric accounts for neither cardiomyopathy nor complex CHD, nor does applying adult-derived DRBW ratio ranges recognize allometric scaling. Aggressively expanding donor pool acceptance ranges out of perceived clinical necessity without an objective tool to predict acceptability, may expose patients to additional risk or lead physicians to decline otherwise acceptable organs due to uncertainty. We submit that virtual HTx fit assessments are a feasible method to account for patient aberrations with present-day technology which may help to reduce ambiguity in clinical decision-making. We have been using these techniques to inform our acceptable parameters for potential donors at the time of listing and have them ready when donors are under consideration that are at or near the conventional upper limits of size. With time, we expect to accumulate a larger volume of prospectively applied virtual transplant cases that demonstrate informed decision-making in the face of donor-recipient weight mismatches of uncertain significance.

To successfully perform an assessment, the recipient center needs applicable recipient volumetric CT or MR images and either (a) have donor parameters and an in-house virtual allograft library available, or (b) have donor CT or MR images electronically transferred. There also exists tremendous opportunity for data sharing as it relates to the healthy heart library. Centers should confirm the error results between pTCV and mTCV for their libraries due to unforeseen nuisance factors between center measurement methods (eg, imaging protocol, technician, etc.) or develop their own models using statistical methods similar to the ones presented here. The three case examples serve to demonstrate the potential utility of virtual fit assessments.

The first virtual assessment presented was a retrospective case in which the simulated decision process was based on patient parameters and Model-B. The retrospective case assessment by the surgeon using a model derived from the library suggested the potential for fit-related complications and a slightly oversized graft. The TCV ratio was calculated to be 1.0 and the transplant proceeded without identifiable fit-related complications. This suggests that although volumetric size matching and virtual transplantation may be able to provide confidence when the donor graft is smaller than the recipient heart (TCV ratio ≤1), more experience will be required to understand the acceptable limits of oversizing and whether visual concerns about compressive effects suggested by a virtual transplant necessarily translate to actual problems if the donor-recipient pair under consideration proceed to transplant.

The second case included the consideration of a potential donor with a DRBW of 3.3, which would be outside the range of consideration for even those centers with "expanded" weight ranges by conventional standards. In their 2012 paper from the United Kingdom, Kanani et al concluded "Our current policy involves accepting a maximum donor-recipient weight ratio of 3. These encouraging findings cautiously justify this policy, in an era when marginal donors are increasingly sought."[20] The practical problem is that there is no standardized weight-based guideline that can be broadly applied given the highly variable heart size to body weight relationship in children with various forms of end stage cardiac failure. We submit that volume-based donor-recipient size matching allows for donor pool expansion, that is, individualized to the abnormal size and anatomy of the failing pediatric recipient heart than any weight-based metric.

The third assessment was originally a unique case study with donor images used in supplemental patient care. The donor image virtual assessment augmented the team's clinical information to allow them to accept what was considered an oversized allograft based on the current clinical standard. One finding from the second case is that pTCV has limitations; these limitations in decision-making can be overcome when donor images are available, facilitating a virtual implantation. The testing set demonstrates that Model-B predicts pTCV well in the bulk of cases, but the model may bias over-prediction in a minority of cases, which is clinically preferable to a bias of under-prediction. In fact, Model-B* forces an over-prediction bias to help reduce the potential for under-predictions. The 75% weighting for Model-B* was chosen so only 1 in 4 cases would be under-predicted.

The 6 large over-predictions were investigated. The smallest TCV had a −44% error; this large error is most likely a consequence of this specific prediction being outside the TCV training set range. This first error demonstrates the importance of not extrapolating actual donor predictions. The remaining 5 errors were interpolation errors isolated to the preadolescent and adolescent age groups. These errors might be capturing a period immediately after a growth spurt and suggest TCV may not keep instant pace with body growth during puberty. A larger healthy heart population would be needed to (a) investigate whether there is a larger variance in the adolescent range due to growth pattern variations and (b) investigate whether multiple models (or a segmented regression model) for different age groups within pediatrics are needed, due to variations in growth mechanisms.

To facilitate our ability to expeditiously perform a virtual HTx assessment as a donor offer is received, our group has adopted a

practice of preprocessing pre-existing medical images for listed patients. Preprocessing includes importing medical images into Mimics, reconstructing the TCV, and performing a series of virtual assessments to identify the largest allograft TCV the clinical team is willing to generally consider. This information is then used to set listing parameters in UNOS. With donor images or donor parameters in hand, our group can perform a virtual assessment remotely within approximately 30 or 10 minutes, respectively.

The developed allograft prediction model predicts donor TCV relatively well, but there are limitations worth mentioning. First, users should be cautious when allograft parameters are outside the bounded ranges listed in Table 1. Second, the model has a 5:3 male bias in distribution due to the specific population of individuals having had healthy hearts imaged via CT or MR at our institution. Third, while extreme care was taken to include only subjects with normal cardiac anatomies/physiologies in the training dataset, all individuals were medically imaged for a clinical purpose; therefore, unknown nuisance factors may exist. Fourth, the sample size to train and test the final models (N = 97) is moderate. Fifth, the predictors used are still removed from cardiac anatomy; although this was our criticism of the DRBW ratio as a standalone metric, our justification is that the model is for predicting expected normal, healthy relationships (in donors) while pathologic recipients are actually measured. Sixth, imaging for fit assessment was targeted to coincide with end-diastole as gated to the electrocardiogram; however, given standard of care at our institute end-diastole imaging for CT was not always available. This may have been the most important source of error. Finally, imaged reconstructions may be performed around the time of listing but wait times will vary and children may continue to grow while waiting; thus, care must be taken when assessments of a donor are made with potentially outdated recipient reconstructions or measurements.

It should also be mentioned that while our primary goal to identify the maximum donor size in order to expand the donor pool, it is only with experience that we can begin to identify an "ideal" donor size and/or the practical limits of "oversizing" as this term takes on a wholly new meaning in the current context. Lastly, while sizable allograft over- and under-predictions can be large, most predictions were within a 21% TCV percentage error (MedAPE = 10%, standard deviation = 11%). Our group is working under the assumption that approximately *a* ± 20% TCV prediction error for the bulk of cases is acceptable. Of course, it is imperative that this and other models for volume based size matching minimize error. As previously described, the consequences of underestimating can be size related complications; similarly, oversize errors could also have consequences, that is, a center could decline a donor that might truly have been suitable based on erroneous size concerns.

Future work, currently underway at our center, will be needed to validate the use of (a) donor images and (b) the current predictive model and/or other models in virtual HTx assessments; assessing this tool for clinical use may be well suited to further retrospective as well as multicenter prospective studies. Next-generation predictive models should be developed and validated with the consideration of using readily available donor cardiac measurements (eg, ECHO, cardiothoracic ratio, etc.) and increasing training and testing population sizes. If virtual HTx assessments become commonplace, it may be preferable to move away from the use of a predictive TCV model (which we currently propose for virtual assessments) to a clinical standard where donor centers routinely obtain and provide targeted CT images at the time of donor offer.

5 | CONCLUSION

Virtual HTx is a valuable tool with the potential to expand the donor pool for a given recipient specifically by informing the transplant center as to the upper "safe" limits of potential donors. This manuscript elucidates two methods for "virtual transplantation," both of which require timely advanced imaging of the recipient. Method 1 uses a complex algorithm and a healthy heart library to derive a suitable "donor" to match the organ offer and the second method utilizes actual donor images to create a real-time 3D visual assessment of fit. However, we also share a case wherein we prospectively applied a previously reported ECHO technique; the key concept underlying these three different techniques is the idea that we believe that an opportunity exists to transition from weight-based size to volume-based size matching in cardiac transplantation. Virtual assessments, as presented in this manuscript, do not account for consequences of undersized allografts. While donor CT/MR images reduce ambiguity in allograft TCV, a TCV prediction model that considers at a minimum growth, is required for virtual assessments to be readily accessible. A larger dataset, perhaps through a multicenter study, is needed to fully optimize the allograft prediction model to (a) include adults and (b) account for atypical developmental growth patterns. Half of all consented cardiac donors in the United States are left unrecovered in which only 64% of the unrecovered cases were unused due to donor-related anatomical, physiologic, or infection reasons.[6] Virtual fit assessments and/or simple volumetric donor-recipient size matching can be applied within the normal time constraints of donor evaluation thereby improving organ allocation for individual recipients, and if broadly applied, for the system as a whole.

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AUTHORS' CONTRIBUTIONS

Jonathan D. Plasencia: Concept/design, data analysis/interpretation, drafting article, critical revision of article, approval of

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