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A Novel Method of Donor-Recipient Size Matching in Pediatric Heart Transplantation: A Total Cardiac Volume Predictive Model

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Abstract

Introduction—The pediatric heart transplant community uses weight-based donor to recipient size matching almost exclusively, despite no evidence to validate weight as a reliable surrogate of cardiac size. Donor size mismatch is the second most common reason for refusal of donor hearts in current practice (~30% of all refusals). While case-by-case segmentation of total cardiac volume (TCV) by computed tomography (CT) for direct virtual transplantation is an attractive option, it remains limited by the unavailability of donor chest CT. We sought to establish a predictive model for donor TCV based on anthropomorphic and chest x-ray cardiac measures.

Methods—Banked imaging studies from 141 subjects with normal CT chest angiograms were obtained and segmented using 3D modeling to derive TCV. CXR data was available for 62 of those subjects. Three predictive models of TCV were fit via multiple linear regression using the variables: (A) weight only; (B) weight, height, sex and age; (C) weight, height, sex, age, and 1-view AP CXR maximal horizontal cardiac width.

Results—Model C provided the most accurate prediction of TCV (optimism corrected R^2=0.99, testing set R^2 = 0.98, mean absolute percent error MAPE= 8.6%) and outperformed Model A (optimism corrected R^2=0.94, testing set R^2=0.94, MAPE = 16.1%) and Model B (optimism corrected R^2=0.97, testing set R^2=0.97, MAPE = 11.1%).

Conclusions—TCV can be predicted accurately using readily available anthropometrics and a 1-view CXR from donor candidates. This simple and scalable method of TCV estimation may provide a reliable and consistent method to improve donor size matching.

Introduction

Children listed for heart transplantation face the highest waiting list mortality in all transplant medicine with an annual mortality rate of approximately 17%[1]. Overall, 58% of

pediatric donor hearts were refused for pediatric transplantation from 2005 to 2014 and over 30% of potential donor organs are refused due to a perceived size mismatch by the candidate's care team[2]. Thirty four percent of all donor hearts are discarded and 20% of donor hearts without marginal criteria are discarded[3]. Though efforts to increase organ donation continue, attention has shifted to optimizing the organ allocation process and ensuring use of all viable organs[4,5].

Currently, donor-recipient body weight (DRBW) ratio is the primary measure used for donor-recipient size-matching in pediatric heart transplantation. Although body weight has been used as a surrogate measure for cardiac size, the precise relationship between body size and heart size has not been clearly defined in the pediatric population. Therefore, its use as the sole anatomic-based measurement to match donors to recipients for pediatric heart transplant may result in both unsuitable matches and missed transplant opportunities[5–7]. Unnecessarily refusing and passing organs on to the next recipient counteracts the intentions of priority-based organ allocation. Furthermore, DRBW-based size matching has not consistently been shown to correlate with outcomes, which provides incentive to look for additional size matching paradigms[8,9]. Previous studies have demonstrated the feasibility of expanding the donor upper limit of size match by direct visual confirmation of donor-to-recipient organ size match using cross-sectional imaging, often referred to as "virtual transplantation" [8–10]. While a direct virtual transplant is a more sophisticated approach to donor-recipient organ matching than DRBW, this is logistically challenging due to the limited availability of cross-sectional imaging for most donors and the time required for segmentation and planning.

We propose an alternative method where the recipient TCV is directly measured from a recent cross-sectional imaging study, and then compared to the predicted TCV of the donor to assess for donor:recipient mismatch due to oversizing. The predicted TCV would be derived from available clinical data using a predefined mathematical model. Using readily available anthropometric data, we sought to develop a predictive model for donor TCV. We produced several models for the prediction of TCV based on weight, height, sex, age, and CXR maximal horizontal cardiac width. We hypothesized that the inclusion of height, sex, age, and 1-view CXR maximal horizontal cardiac width would enhance the accuracy of predictive models when compared to a weight-based model.

Methods

Data Source

This study was approved by Cincinnati Children's Hospital Institutional Review Board prior to study initiation. A retrospective review of Cincinnati Children's Hospital Picture Archiving and Communication Systems (PACS) database was performed to identify pediatric and young adult patients (age 0–30 years) with normal cardiac anatomy on clinically indicated chest computed tomography angiography (CTA). Subjects with incomplete capture of cardiac structures or any clinically identified cardiac abnormality, including nonspecific chamber dilation, were excluded. Additional exclusions included subjects with pulmonary embolism, chronic anemia, large airway malformations, parenchymal lung disease, large intrathoracic mass, genetic syndrome, and body mass index

> 55. Demographic data was collected via chart review including date of birth, sex, ethnicity, race, weight, and height. Body surface and body mass index were derived from patient height and weight[11].

CT Segmentation for Total Cardiac Volume

CT data was imported into Mimics 3D medical modeling software (Materialise Inc., Belgium) and semi-automatic segmentation of the chest structures was performed, as previously described[8,10]. The TCV segmentation was defined as the myocardial mass and internal heart chamber volume bounded at the approximate levels of surgical anastomosis for a bicaval orthotopic heart transplantation. Each TCV measurement included the border of the myocardial mass up to the junction of the superior vena cava (SVC) and inferior vena cava (IVC) to the right atrium junction of the pulmonary veins to the left atrium, and the great arteries to the level of the aortic and pulmonary roots (Figure 1). The primary variable of interest was TCV as this is the expected major determinant for heart-size matching success in bicaval orthotopic heart transplantation. When available, the most recent CXR (anteroposterior projection, 1-view) was reviewed and cardiac width was measured as the distance between the left and right heart borders as described previously[12,13] (Figure 1–D). A 1-view anteroposterior projection CXR was used because this type of projection is routinely performed and available in critically ill transplant donor patients.

Model Construction

Variables with a strong correlation with TCV were selected for model inclusion. These predictors included weight (kg), height (cm), age (years), and maximal horizontal cardiac width (cm). Sex was included in prediction models as a binary variable. Data on maximal horizontal cardiac width was available for 62 subjects. The statistical programming language R was used for all modeling and statistical analysis. Multiple imputation as implemented by the Hmisc package function aregImpute (version 4.2.0)[14] was used to impute maximal horizontal cardiac width for those with unobserved values. All model predictors and TCV were included in the imputation model. A total of n=50 imputed datasets were generated using flexible parametric additive regression with three knots provided for each continuous variable. Ordinary least squares regression as implemented by the rms package function ols (version 5.1.3.1)[14] was used to predict TCV after transformation to the natural log scale. Log transformation was performed to account for allometric growth patterns through the pediatric age range[15,16].

Three primary models were developed. Model A used weight as the sole predictor and served as the base model to assess the performance of the current size matching process. Model B incorporated weight, height, sex, and age to assess the performance of additional anthropometric measures and sex on model predictions. Model C was similar to Model B, but with the addition of CXR 1-view maximal horizontal cardiac width and included imputed values whereas, no imputed values were used to develop Models A or B. An additive model with restricted cubic spline terms with knots placed at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles to capture potential non-linear associations was first fit to gauge feature importance based on degree of freedom adjusted chi-square tests for each term. Age provided the smallest contribution to model fit and was therefore modeled as a linear term to

reduce the model degrees of freedom. Four knots were retained for all other continuous predictors.

Analysis of Model Accuracy

Split-sample validation and internal resampling were used to assess model performance. A random selection of n=100 subjects were chosen to serve in the development set and the remaining n=41 subjects were held out to serve as the test set for split-sample validation. Internal resampling was conducted using 1000 bootstrap samples to obtain optimism corrected measures of model performance for the training set and full set of n=141 participants. The optimism corrected R^2, and mean absolute percent error (MAPE) are reported for the development set and for models containing all 141 subjects. The model R^2 and MAPE are reported for the full test set. Validation after multiple imputation was performed by averaging the values obtained for each multiply imputed dataset. Optimism correct estimates of model performance were obtained using the rms package function validate.

Inter-observer Variability

The primary observer (NAS) and an experienced imaging cardiologist (RAM) performed blinded intraobserver and interobserver repeat measurements of TCV on 10% of the subjects. Reliability of observations was assessed using intraclass correlation coefficient (ICC).

Results

Subject characteristics are summarized in Table 1. A 1-view CXR was available for 62 patients. There were no statistically significant differences in age, height, and weight between patients with or without a CXR. Male subjects (55%; median [IQR] = 9.8 [14.8] years) tended to be younger than female (15.0 [8.3] years) subjects on average (Wilcoxon rank-sum p-value = 0.02). The most common indications for CTA were evaluation for pulmonary embolus, trauma, and evaluation of anatomic abnormality such as a vascular ring or airway abnormality.

The univariate relationships between TCV and weight, height, age, and CXR heart width are shown in Figure 2. TCV is positively correlated with weight in a nonlinear manner with marked dispersion at higher weights. TCV is positively correlated with age but with high variability. TCV has an exponential relationship with height.

Model Performance

The parameters for model performance on a logarithmic scale for Models A, B, and C using split-and re-sampling technique are summarized in Table 2. There is incremental improvement in model performance with the inclusion of additional variables. Model C provides an accurate prediction of TCV (optimism corrected $R^2 = 0.98$, validation set $R^2 = 0.99$, mean absolute percent error MAPE = 1.11%) and performed better than Model A (optimism corrected $R^2 = 0.95$, validation set $R^2 = 0.94$, MAPE = 3.17%) and Model B (optimism corrected $R^2 = 0.97$, validation set $R^2 = 0.97$, MAPE = 2.19%) [See

Supplemental Table 1]. Model A is shown to have greater error at lower and upper weight range as shown in the calibration plots when compared to Models B and C (Figure 3).

The MAPE calculated after transforming the observed and predicted values back to the original TCV scale were 16.1% for Model A and 11.1% for Model B. The MAPE on the original scale is lowest for Model C at 8.6%. Model C has the lowest error across all age ranges (Figure 4A) and weight ranges (Figure 4B). Model C is more accurate at higher age and weight ranges. In general, there is higher error in TCV prediction for all models at lower age and weight ranges.

Reliability

For a randomly selected 10% of study subjects, reliability analysis was performed. The intraobserver ICC was 0.99 and the interobserver ICC was 0.99.

Discussion

The allometric relationship between body growth and heart growth is the basis for the weight-based criteria commonly used in pediatric cardiac transplantation, but this approach is confounded by uncertainty[17–19]. We now have robust imaging datasets that can directly define the relationships of body size to heart size. Consequently, the size match evaluation for heart transplant can and should be refocused on an evidence-based approach using such data. This study establishes an accurate method for estimating donor TCV using available clinical data and a multiple linear regression model. Though there is a complex relationship between indices of body size and TCV across the pediatric age range, we have shown that heart size can be accurately predicted by utilizing readily available patient specific measures. More importantly, this study describes the non-linear relationship of weight to allograft size and estimation methods using just weight which is key if a program, like ours, is still using weight for listing.

Most heart donors do not have cross-sectional imaging available for direct comparison of TCV, so we have devised a novel method for estimation of TCV to enable a size matching process for the clinical scenario where the recipient TCV is known. The TCV predictive models can be used by heart transplant centers to first determine the maximum weight limit for listing in UNOS and then to perform a rapid size match when a donor becomes available. At our institution, we recently started to select the maximum weight threshold by measuring the recipient TCV and comparing to the normative data for TCV. When a potential donor heart becomes available, a rapid size match assessment can be performed by comparing the directly measured recipient TCV to the predicted donor TCV provided using a predictive model.

Oversizing of donor hearts may lead to several immediate post-operative complications including pulmonary venous compression, bronchial compression, and post-operative open chest[18]. The uncertainty associated with weight-based size matching may cause donor centers to avoid borderline hearts; however, research focused on this hypothesis is needed. As shown in the case example below, a targeted approach to defining the upper limit of size

matching can mitigate this uncertainty and increase the available donor pool for specific patients.

Case Example

Patient A is a 16 year old male (weight 64kg, height 177cm, BSA 1.79m^2) with dilated cardiomyopathy with severe LV dysfunction status post Heartmate III VAD placement. He was listed for heart transplantation with an initial donor weight range of 60–80kg, corresponding to an upper limit of DRWR of 130%, consistent with the actual matched DRWR across the United States[2]. Using the process described above, the total cardiac volume from a CT scan was calculated to be 1164 cm^3. After comparing this TCV to the normal patient donor pool, the upper limit of the weight range was increased to 100kg. After 5 days at an increased listing weight, the patient was offered a suitable donor heart from a male donor (22 years old, weight 91.5 kg, height 182 cm, BSA 2.13m^2). The donor's predicted total cardiac volume using Model B was 978 cm^3 (~84% of recipient TCV). There were no intraoperative complications related to oversizing. He was extubated on post-operative day 1, transferred from the intensive care unit on post-operative day 8, and discharged on post-operative day 12.

We include heart width from 1-view CXR into this analysis because the majority of CXRs in the ICU are acquired as a single anteroposterior view, and heart width can be easily and repeatably measured[12,13]. The inclusion of CXR into the model provides an incremental improvement to model accuracy. To confirm that data imputation did not cause any bias toward model accuracy, the model analysis was repeated using only the 62 patients with CXR available. Bootstrap resampling was used rather than split sample validation for this method given the small sample size. The results are similar in that Model C (optimism corrected R^2 = 0.98, MAPE = 1.41%) outperforming Model B (optimism corrected R^2 = 0.97, MAPE = 2.17%) and Model A (optimism corrected R^2 =0.95, MAPE=3.01) as summarized in Table 3.

Model C has the lowest error of all models across nearly all weight and age ranges, as shown in Figure 4. The consistently low error suggests that this model performs well across all potential donor sizes. Model C differs from Model B only in the addition of CXR as a predictor variable and shows decreased error for older patients and those with higher weight. This suggests that the variability seen in TCV at higher weight is mitigated by the use of CXR as an additional predictor variable.

There was a relative increase in error for all models at lower age and weight. This is likely due to the difficulty in creating a universal model for a wide spectrum of subjects from infant to young adult. In smaller subjects, even small degrees of variance in TCV prediction resulted in a larger percent error. In future studies, this error may be improved by creating a separate TCV prediction model for infants.

We anticipate that predictive modeling for the estimation of TCV will have significant value for the heart transplantation community related to size matching and maximizing donor usage. DRWR-based size matching is not consistently associated with outcomes, so there is potential with volume-based size matching to improve short and long-term outcomes of

heart transplantation[4]. Gong et al. examined the effects of “undersizing” donor hearts in adult heart transplantation by using a validated anthropomorphic-based model for predicted heart mass (PHM) and found that the PHM was a better predictor of primary graft dysfunction when compared to size match based on total body weight[17]. Similarly, Kransdorf et al. demonstrated increased 1-year mortality for patients with undersized heart transplants based on PHM; undersizing based on weight, height, BSA, or BMI ratio had no effect on survival. Though PHM is shown to predict outcomes related to undersizing, it is not shown to predict outcomes related to oversizing of heart transplants[20].

This tool for predicted TCV can primarily be used to examine both short-term morbidity related to allograft oversizing (delayed chest closure, bronchial compression, prolonged length of stay, etc.) as well as mortality. TCV carries potential advantage over PHM in assessing for oversizing by encompassing the entirety of the graft volume rather than just the ventricular mass. Similarly, TCV-based size matching may have advantages over DRWR-based matching, as was noted in a recent retrospective review of pediatric heart transplantations in UNOS from 1989 to 2019 where TCV-based size matching ratio predicted survival and DRWR-based matching did not[21].

Though the focus of this manuscript is size mismatch, we recognize that donor:recipient matching for heart transplantation is a multifaceted system including donor organ quality, travel time, recipient stability, and immunological compatibilities. We believe that TCV provides a new additional measure to strengthen size match and will help mitigate the uncertainty of size matching though incorporation of multiple variables of donor size into a single measure.

This preliminary study of TCV for size matching must be validated in actual donor-recipient size matches before gaining widespread acceptance and use. Future studies will assess the reliability of TCV-based size matching in predicting adverse events related to oversizing in a retrospectively attained cohort of heart transplant recipients.

Limitations

This study is limited by being a single center retrospective study and potential bias from a convenience sample of patients. For widespread adoption of a cardiac volume-based size matching process, the model proposed in this study would need to be reproduced in a larger patient cohort. Additionally, control of operator error will be necessary to have comparable TCV values across institutions.

Measurement of TCV was found to be highly reliable within and between observers, which is likely attributable to the semi-automated nature of the 3D reconstruction protocol. Manual segmentation was required only for identifying the area of surgical anastomosis and several tissue interfaces. Despite this, there are minor differences between observers. Image segmentation is predominantly based on difference in contrast resolution between adjacent structures. Myocardium, liver, thymus, diaphragm and skeletal muscle have similar Hounsfield units, so segmentation of adjacent areas of these anatomic structures can lead to minor discrepancies amongst observers. Additionally, there is minor variation in the identification of surgical anastomosis cutoff location between observers.

Conclusion

TCV can be accurately predicted from readily available anthropometrics and CXR heart width. This simple method of TCV estimation can provide a reliable and consistent method to assess donor TCV. In future studies, TCV-based size matching can be used to set more accurate donor size criteria and assess the correlation of TCV with patient outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CT	Computed tomography
DICOM	Digital Imaging and Communications in Medicine
TCV	Total cardiac volume
UNOS	United Network for Organ Sharing

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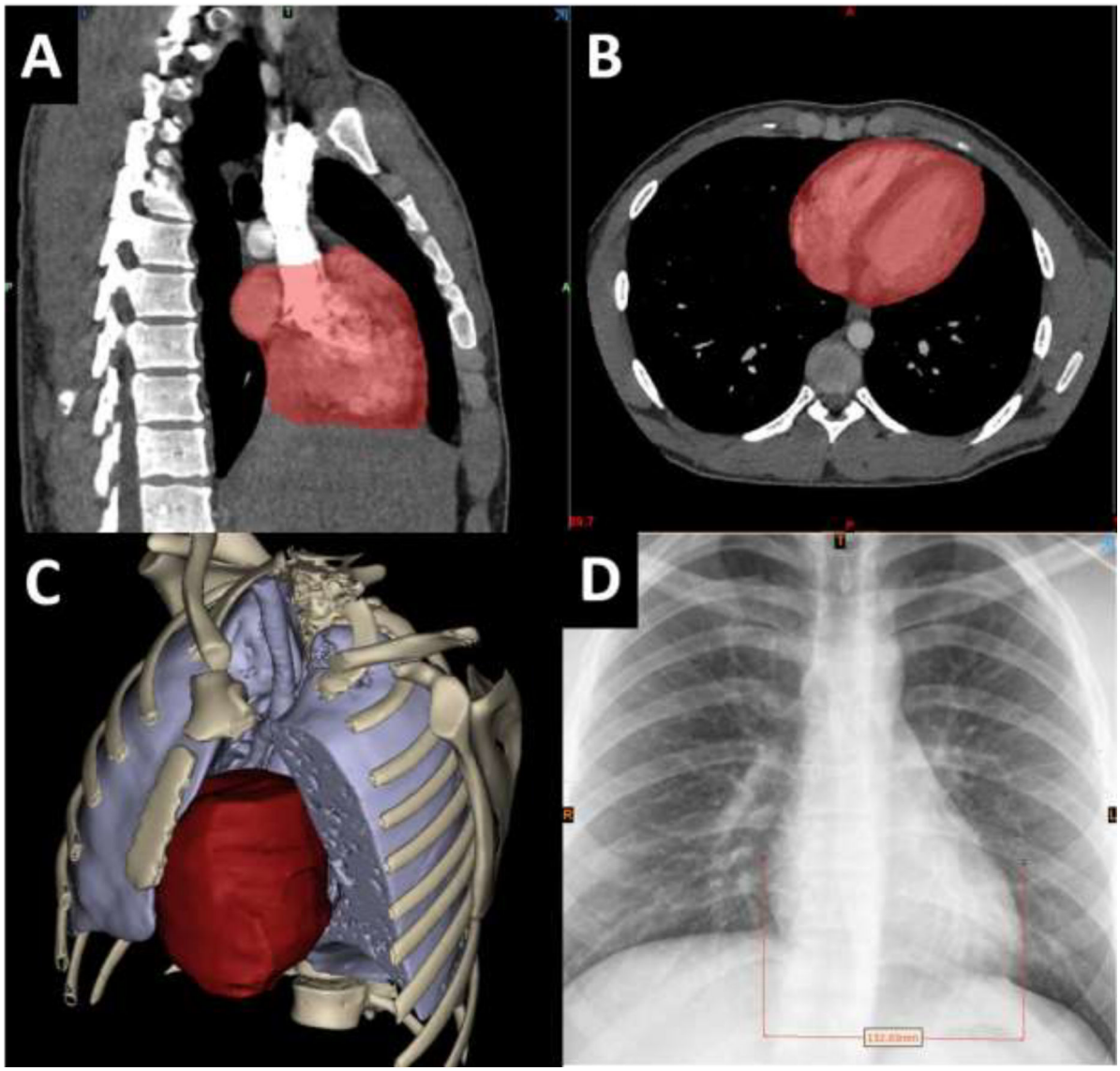

Figure 1.

An example 3D reconstruction showing A) sagittal view of segmentation mask showing SVC and IVC cutoff B) axial View of segmentation mask C) example 3d Reconstruction of heart, lungs, bones and D) example CXR heart diameter measurement.

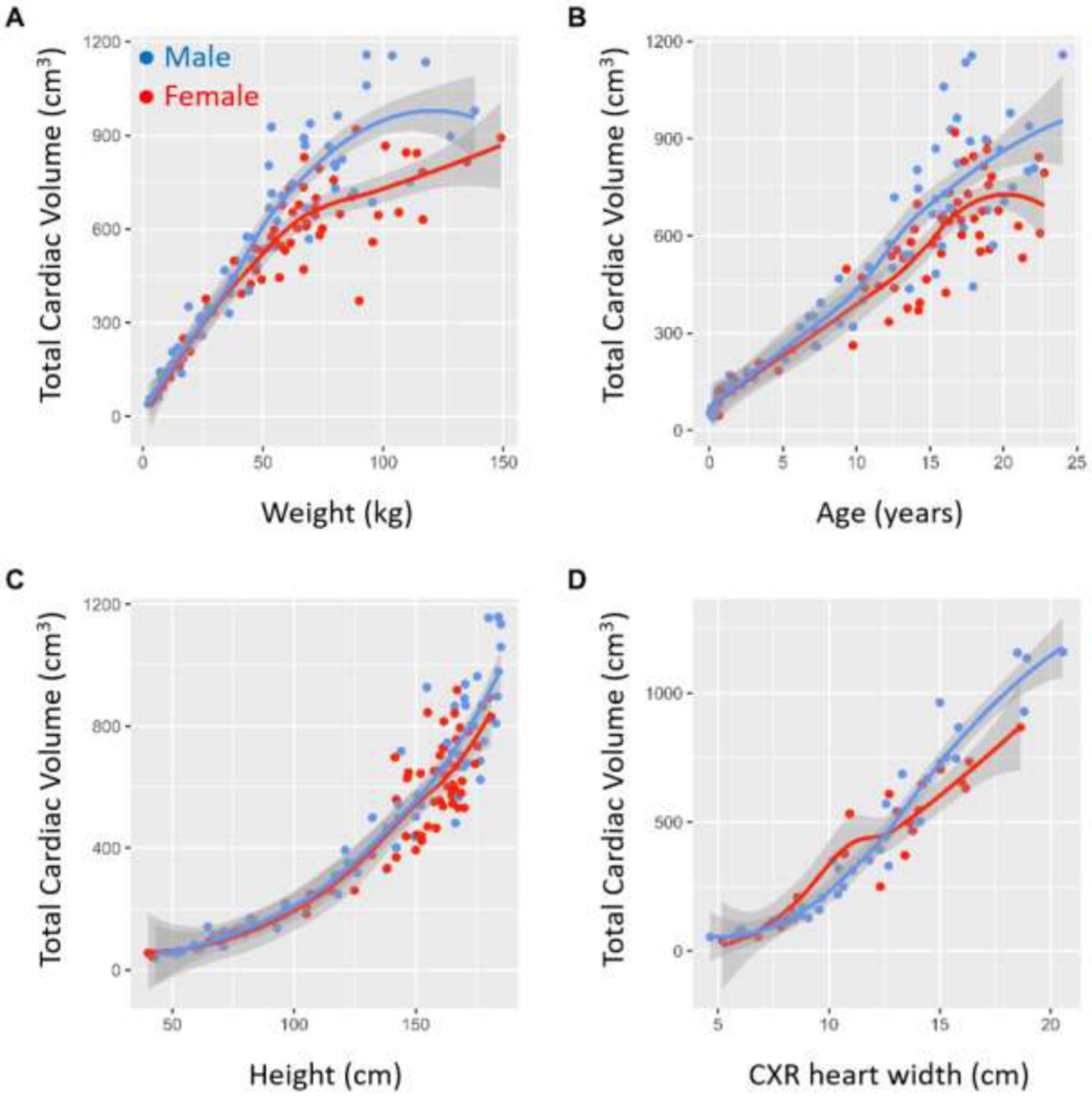

Figure 2.

Univariate relationship between predictor variables and TCV. Blue dots represent male patients and red dots represent female patients.

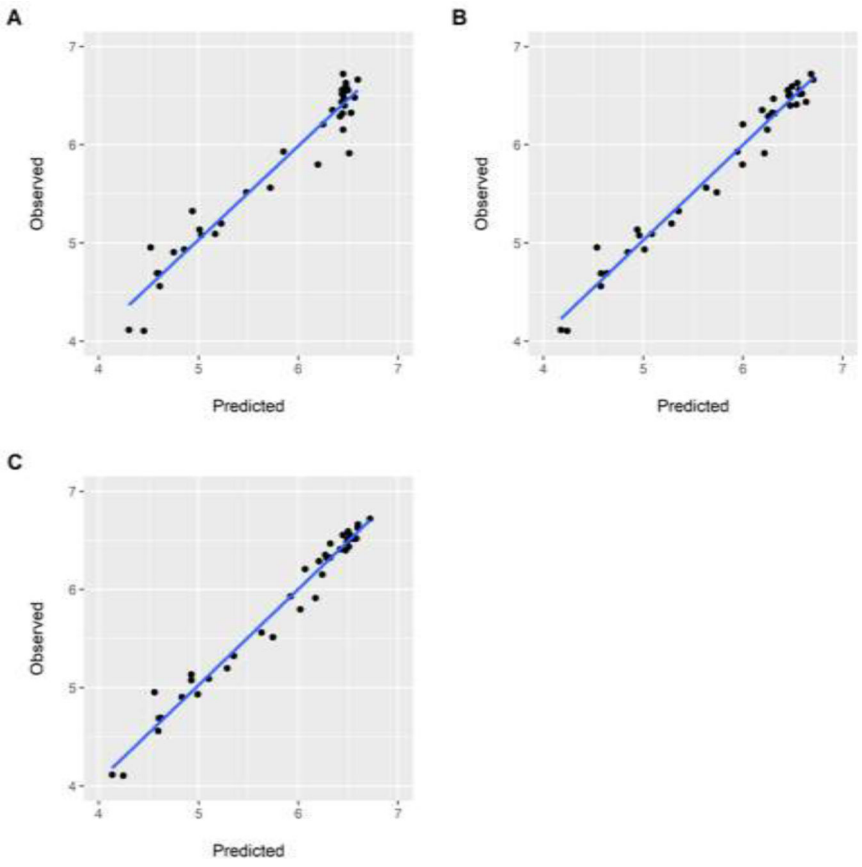

Figure 3.

Testing Set calibration plots of models A, B, and C show improvement in model performance and the least amount of scatter in Model C.

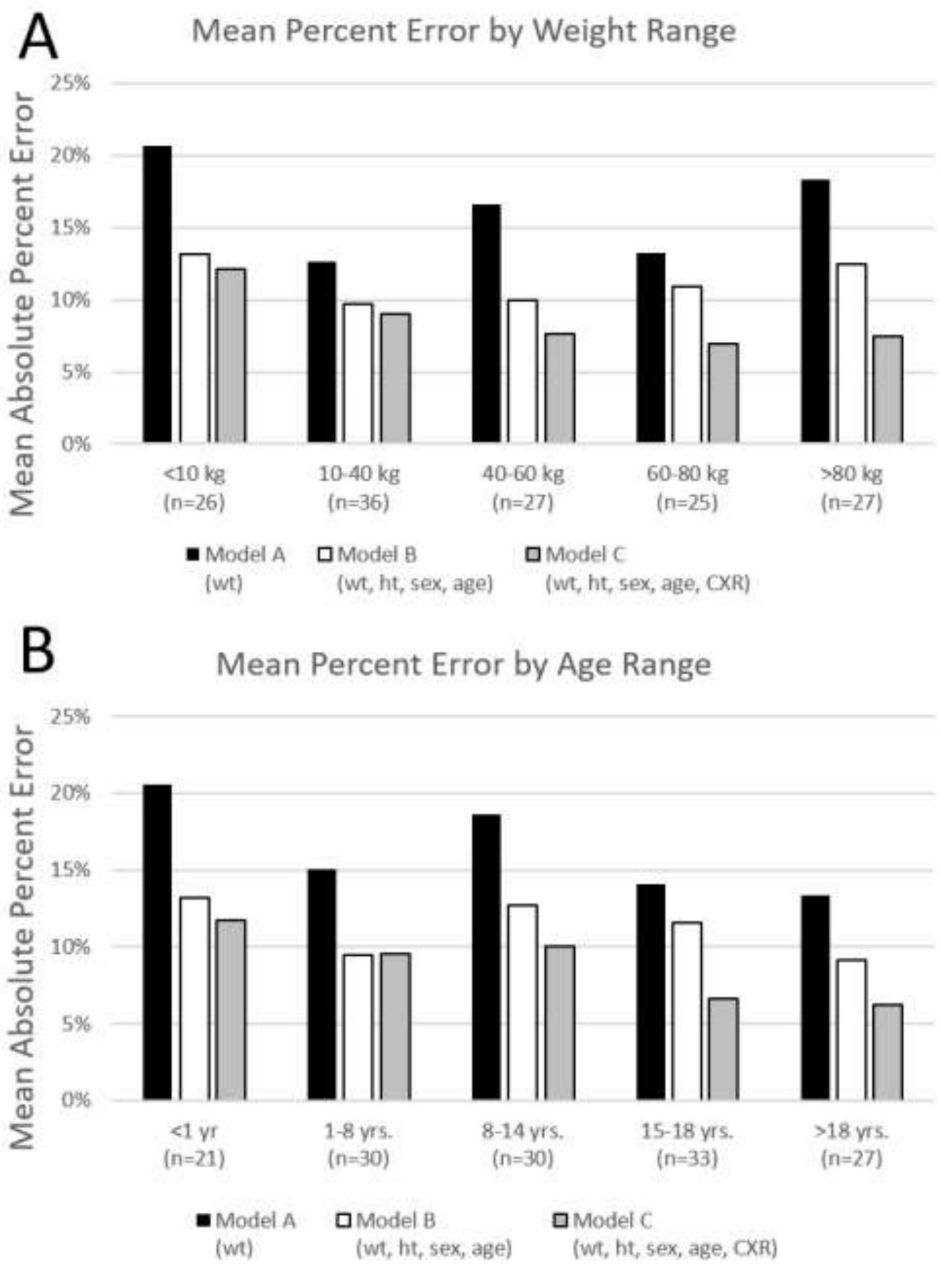

Figure 4.
Model Mean Absolute Percent Error subcategorized by A) weight range and B) age range.

Table 1:

Patient characteristics of 141 subjects.

	Median	IQR	Range
Weight (kg)	47.5	14.6 – 71.7	2.2 – 149
Height (cm)	150	95 – 167	40 – 185
Age (years)	13.5	3.1 – 17.2	0.1 – 24.8
BSA (m^2)	1.47	0.6 – 1.8	0.15 – 2.60

Table 2:

Model characteristics and performance (logarithmic scale) using split sampling

	Model A	Model B	Model C
Model terms	Weight	Weight, Height, Age, Sex	Weight, Height, Age, Sex, CXR Heart Diameter
Training set			
Sample size (n)	100	100	100
Optimism corrected R^2	0.95	0.97	0.98
MAPE	2.76	1.91	1.49
Testing set			
Sample size (n)	41	41	41
R^2	0.94	0.97	0.99
MAPE	3.17	2.19	1.11

Table 3.

Model characteristics and performance (log scale) for subject with CXR available

	Model A	Model B	Model C
Model terms	Weight	Weight, Height, Age, Sex	Weight, Height, Age, Sex, CXR Heart Diameter
Sample size (n)	62	62	62
Optimism corrected R^2	0.95	0.97	0.98
MAPE	3.01	2.17	1.41