ARTICLE TITLE:

PREDICTIVE MODELS FOR PULMONARY ARTERY SIZE IN FONTAN PATIENTS

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SUPPLEMENTARY MATERIALS:

Methods:

Due to the diversity of measurement metrics employed in previous literature, the relevant literature was classified into three categories (Table 1) based on their utility in validating the regression models of the pulmonary artery (PA) diameter as a function of BSA or age in Fontan patients. The studies that fall into the first category reported mean LPA and RPA diameters directly. The studies that comprise the second category reported findings in normalized metrics from which the mean PA diameter data needed to be derived, therefore we constructed a procedure as outlined in Figure S1 and explained below to extract the necessary data. The third is comprised of those studies that reported median data and could not be used for the validation process.

The Pulmonary Artery Index (PAI) is a normalized metric originally proposed by Nakata et al.[1] to serve as a prognostic indicator in the optimal selection of single ventricle patients for the Fontan palliation and is defined as:

$$PAI = \frac{PAA_r + PAA_l}{BSA} \tag{1}$$

Where PAA_r is the right PA area and PAA_l is the left PA area. Equation (1) may be re-written as:

$$PAI = \frac{2\,\overline{PA\ Area}}{BSA} \tag{2}$$

Where the $\overline{PA\ Area}$ is the average of the left and right PA area. The mean PA diameter is then determined from $\overline{PA\ Area}$ assuming the cross-section of the PA to be circular, provided the BSA is known. Tatum and colleagues[2] report mean BSA and mean age for their cohort at the initial and follow-up measurement and hence the information from this study was used to validate both Model-BSA and Model-Age.

Buheitel et al.[3] presented their measurements as systolic z-scores which are normalized against the mean PA size expected in healthy children. The CDC growth charts[4] were utilized to calculate the mean normal BSA at any age and this data was then applied to the normal PA growth curves reported by Rammos et al.[5] to obtain the mean normal PA size at any age. The mean normal PA size was used to de-normalize the z-scores and obtain the mean measured PA diameter at systole. Since Buheitel and colleagues only reported the mean age of their cohort, the data reported by this study was used to validate Model-Age only.

Some investigators such as Buheitel et al.[3] have measured and reported systolic PA diameters rather than the mean diameter (average of the systolic and diastolic diameter). The definition of distensibility (as defined by Bossers et al. [6]) was employed to determine the diastolic diameter (Equation 3), which we then used to find the mean (with regard to systole and

diastole) diameter. Of the investigations that have examined PA distensibility in Fontan patients (Table S2), the study conducted by Bossers et al.[6] reports the highest patient sample size. Based on their findings, we used a value of 0.15 for distensibility in our calculations according to their report.

$$Distensibility = \frac{A_{max} - A_{min}}{A_{max}} \quad (3)$$

Where A_{max} is the systolic diameter and A_{min} is the diastolic diameter.

Results and Discussion:

The break point analysis with BSA as the response variable and age as the independent variable yielded a value of 17.5 years with a standard error of 1.1 years for the entire cohort. Partitioning the data at 17.5 years, we found a statistically significant, strong positive correlation ($p<0.05$, $r=0.96$, $n=13$) between the BSA and age below the age of 17.5 (Figure S2). Beyond the age of 17.5 years, the slope the regression line was not significant ($p=0.265$).

Below the age of 17 years, BSA and age show a strong correlation indicating that age may serve well as a surrogate for the BSA. However, the dataset for the BSA-age correlation below the age of 17 years contains only ECC patients, since the age range for the non-ECC group was between 17.7 and 40.2. The presence of a breakpoint at approximately 17 years of age for the BSA-Age relation is consistent with the observation of a breakpoint at approximately 17 years for Model 2.

In the case of the non-ECC group, since dataset included only adults (age range 17.7 to 40.2), we performed comparisons between the adults of the ECC group and the non-ECC group. For the linear regression models obtained from the non-ECC group and the adults of the ECC group, where mean PA diameter was the response variable and BSA the explanatory variable, we observed a strong positive linear correlation for the ECC group and no correlation for the non-ECC group (Table S3). The disparity in the correlations between mean PA diameter and BSA for the adult ECC patients and adult non-ECC patients is substantial and warrants further investigation. Owing to the prevalent adoption of the ECC variation of the Fontan procedure however, it may be difficult to acquire the pertinent data to investigate this observation.

A representative measurement of the PA on which the size predicted by Model-BSA and the 95% confidence interval for the prediction have been overlaid, is shown in Figure S3.

References:

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Supplementary Tables

Table S1: Detailed Patient History

Study #	History	Fenestration
f001	Tricuspid atresia, bilateral SVCs	No
f002	Unbalanced complete AVSD. Left AV valve regurgitation, single SVC	Yes
f003	ccTGA, mitral atresia with DORV and PVS	NA
f004	DORV, mitral atresia	ND
f005	DILV	ND
f006	DORV, TGA, single SVC	NA
f007a	Dextrocardia with DORV and PS, bilateral SVCs	No
f007b	Dextrocardia with DORV and PS, bilateral SVCs	No
f008	Left atrial isomerism, dextrocardia, unbalanced AVSD with interrupted IVC	No
f009	DILV, DORV	Yes
f010c	Dextrocardia, left atrial isomerism, common AV valve	NA
f011a	Dextrocardia, right atrial isomerism, unbalanced AV septal defect	ND
f012a	TGA, interrupted aortic arch	ND
f012b	TGA, interrupted aortic arch	ND
f012c	TGA, interrupted aortic arch	ND
f013	occlusion device at LPA, tricuspid atresia, single SVC	NA
f014	DORV, DIRV, VSD, single SVC	ND
f015	ccTGA, mitral atresia, PVS, single SVC	NA
f016a	HLHS	ND
f017	DILV, TGA, subaortic stenosis	NA
f018a	DORV, Pulmonary atresia, bilateral SVCs	NA
f018b	DORV, Pulmonary atresia, bilateral SVCs	NA
f019	DILV, DORV, PVS, single SVC	No
f020	DILV, Hypoplastic RV	NA
f021	Left atrial isomerism, unbalanced AV septal defect, hypoplastic LV, bilateral SVCs	No
f022	Aortic atresia, VSD, single SVC	Yes
f023	DILV, hypoplastic RV, pulmonary atresia	NA
f024	Pulmonary atresia, AV discordance, absent left atrioventricular connection	NA
f025	DILV	ND
f026b	HLHS	No
f026c	HLHS	No
f027	Tricuspid atresia, VSD	ND
f028a	ccTGA, Subaortic stenosis, interrupted arch	ND
f028b	ccTGA, Subaortic stenosis, interrupted arch	ND
f029a	TGA, VSD, coarctation	ND

f029b	TGA, VSD, coarctation	ND
f030	HLHS, coarctation, right hemi-anomalous pulmonary venous return	Yes
f031	PAIVS with coronary fistulae	Yes
f033a	HLHS	Yes
f034a	HLHS	Yes
f035	Unspecified single left ventricle	NA
f037	Mitral atresia	NA
f038	HLHS	Yes
f040	DILV	NA
f042a	DILV, VA discordance, VSD, Coarctation	NA
f042b	DILV, VA discordance, VSD, Coarctation	NA
f043	DILV	No
f044	ccTGA, Truncus with atresia	No
f045	DILV, Hypoplastic left AV valve	No
f046	DILV	No
f047a	HLHS	Yes
f048a	Tricuspid atresia	NA
f048b	Tricuspid atresia	NA
f049a	Tricuspid atresia	NA

ND, No data available; SVC, Superior Vena Cava; AVSD, Atrioventricular Septal Defect; AV Atrioventricular; TGA, Transposition of the Great Arteries; ccTGA, Congenitally corrected Transposition of the Great Arteries; DORV, Double Outlet Right Ventricle; PVS, Pulmonary Valve Stenosis; VSD, Ventricular Septal Defect; RV, Right Ventricle; DILV, Double Inlet Left Ventricle; HLHS, Hypoplastic Left Heart Syndrome; PAIVS, Pulmonary Atresia with intact ventricular septum;

Table S2: A summary of publications reporting mean distensibility data for pulmonary arteries in Fontan patients

Ref No.	Authors	Sample Size	Distensibility	LPA Distensibility	RPA Distensibility
[7]*	Morgan et al.(RA Group) (1998)	6	-	0.41	0.45
[7]*	Morgan et al.(BC Group)(1998)	5	-	0.37	0.33
[8]	Robbers-Visser et al. (2008)	14	0.22	-	-
[6]	Bossers et al. (2016)	23	0.15	-	-

LPA, Left Pulmonary Artery; RPA, Right Pulmonary Artery;
* Morgan et al. classified their patient sample into two groups and reported their findings separately for each group.

Table S3:

A comparison of linear regression models fitted to the adult non-ECC group and adult ECC patients. In both cases, the explanatory variable is BSA and the response variable is the PA diameter. The p-value provided is for the individual F-test of the corresponding parameter estimate.

Group	Sample size	Parameter	Estimate	Std. Error	95% Confidence Interval		p-value	Correlation coefficient
Adult ECC	11	Slope	16.34	2.94	10.58	22.1	0.0003	0.88
Adult non-ECC	19	Slope	1.0	2.36	-3.96	5.97	0.67	0.1

SUPPLEMENTARY FIGURES

Figure S1:

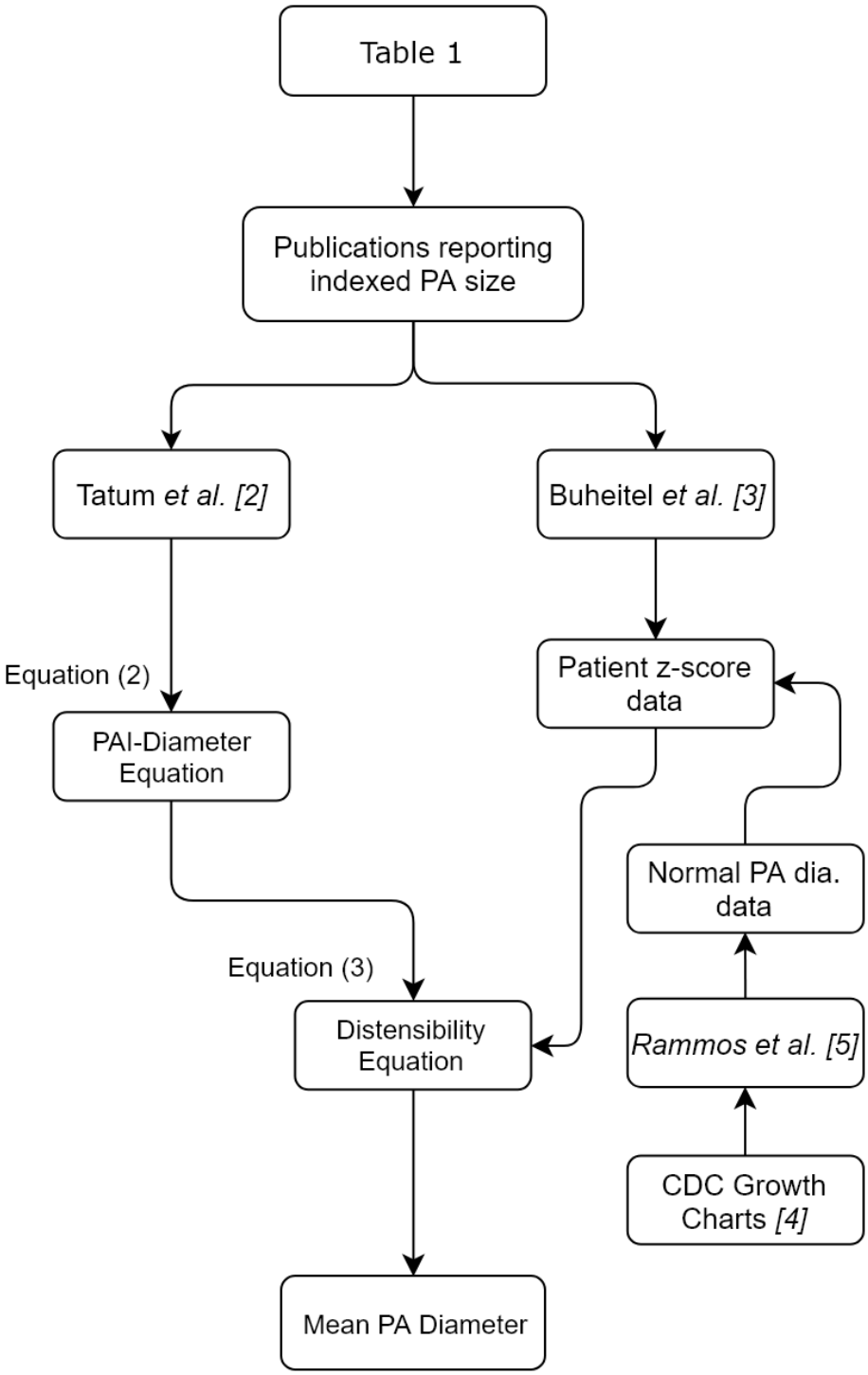


Figure S2:

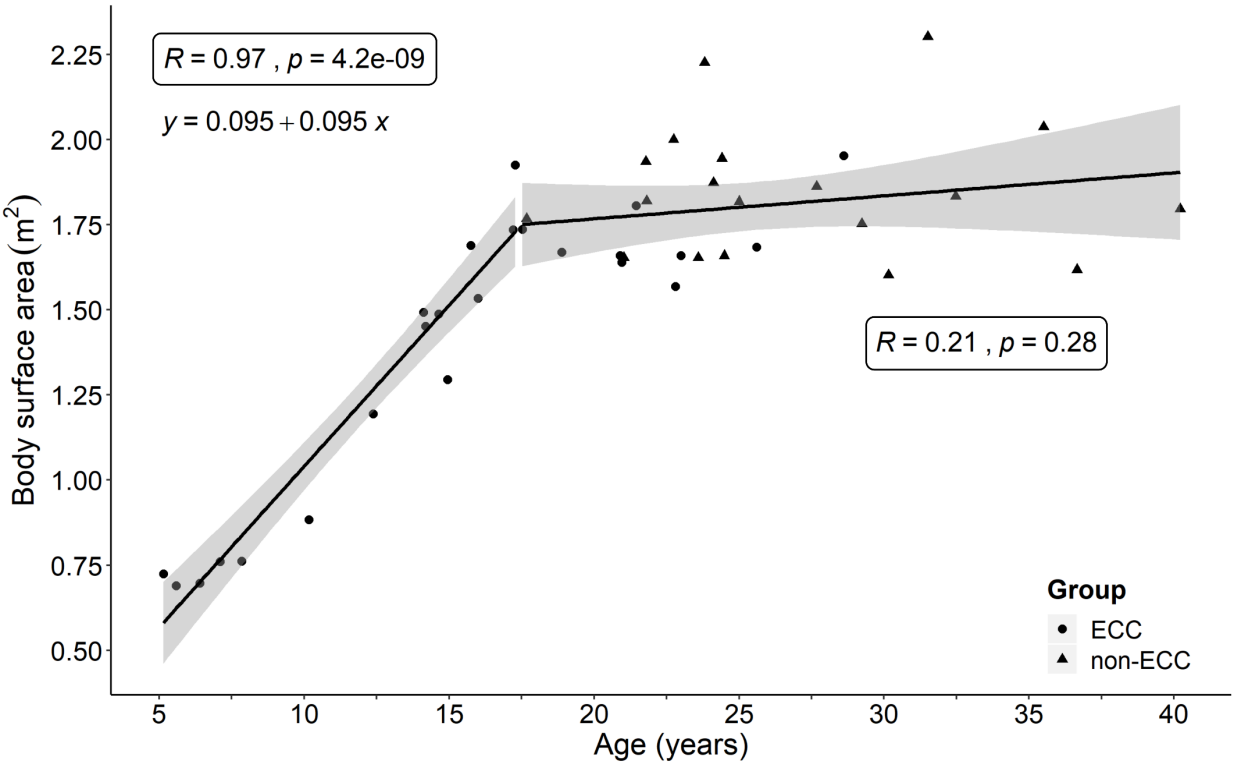
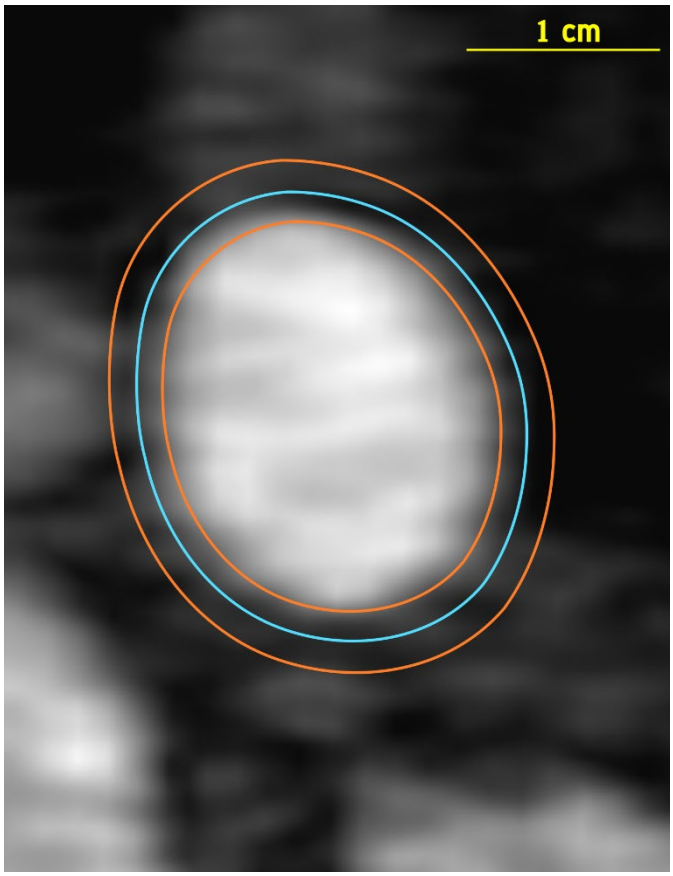

R = 0.97 , p = 4.2e-09
y = 0.095 + 0.095 x
R = 0.21 , p = 0.28
Body surface area (m2)
Age (years)
Group
ECC
non-ECC

Figure S3:



SUPPLEMENTARY FIGURE LEGENDS:

Figure S1: Literature data extraction and compilation workflow. PA, pulmonary artery ; BSA, body surface area; PAI, Pulmonary Artery Index.

Figure S2: Correlations between the body surface area and age for the entire cohort and the corresponding 95% confidence intervals (shaded regions). The breakpoint was determined to be 17.5 years (standard error = 1.1 years).

Figure S3: Section view of the PA of a representative Fontan patient. The size of the PA predicted by Model-BSA is shown in blue and the 95% confidence interval for the prediction is shown in orange.