A pediatric echocardiographic Z-score nomogram for a developing country: Indian pediatric echocardiography study – The Z-score

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ABSTRACT

Background : **Almost all presently available pediatric echocardiography Z-score nomograms are based on Western data. They may not be a suitable reference standard for assessing the sizes of cardiac structures of children from developing countries.**

Objective : **This study's objective was to collect normative data of 21 commonly measured cardiovascular structures using M-mode and two-dimensional echocardiography in Indian children aged between 4 and 15 years and to derive Z-score nomograms for each.**

Subjects and Methods : **The study was conducted at two centers in India - Ajmer, Rajasthan, and Mohali, Punjab. We studied a community-based sample involving healthy school going children. After excluding children with cardiovascular abnormalities on the screening echocardiogram, 746 children were included in the final analysis. Echocardiographic assessment was performed using a Philips iE33 system.**

Results and Analysis : **For each parameter measured, seven models were evaluated to assess the relationship of that parameter with the body surface area and the one with the best fit was used to plot the Z-score chart for that parameter. Z score charts were thus derived.**

Conclusions : **The Z-score nomograms derived by this study may be better alternatives to the Western nomograms for use in India and other developing countries for preprocedural decision making in the pediatric population. However, they will require validation in large-scale studies before they can become clinically applicable.**

Keywords : Developing country, echocardiography, pediatric, Z-score

INTRODUCTION

Description of the sizes of cardiac chambers, valves, and great vessels in terms of Z-score is an important step in quantifying abnormal findings and planning pediatric cardiac interventions and cardiac surgeries. Currently used nomograms are based on the Western studies and may be inappropriate for use in developing countries.

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One of the methods to depict the deviation of a specified structure's measured value from the population mean is the Z-score. It provides a way to record and compare serial measurements in children undergoing sequential echocardiographic measurements over time. By definition, $Z = (x - \mu)/\sigma$, where x is the child's

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measured value for the specified structure, μ is the mean of the population the child hails from, and σ is their standard deviation. Studies providing Z-scores for various cardiac structures are available, and it is with the help of these references that current day practitioners of pediatric cardiology derive Z-scores for their patients.

For the assessment of acquired and congenital heart disease (CHD) in children, quantification of cardiac chambers, valves, and great vessels is of absolute importance since major decisions regarding the need for and timing of intervention is made on the basis of these values. The Z-score for each measured parameter is assessed from nomograms or Z-score charts, which are available on dedicated websites and as smartphone applications. The routine practice world over is to use one of these sources to get the individual patient's Z-score for the measured parameter. Almost all of these nomograms are derived from studies done in developed countries. Thus, key decisions like necessity for and timing of intervention in children with CHD hailing from developing countries are made based on Western standards. Since biological parameters often vary between populations due to differences in ethnicity and environmental influences, Western data may not serve as a suitable reference standard for the developing countries. A detailed search on the available pediatric echocardiographic Z-score studies from countries in Asia and the Middle East (our search included India, Bangladesh, Nepal, Myanmar, Bhutan, Pakistan, China, Singapore, Taiwan, North and South Korea, Hong Kong, Japan, and Saudi Arabia) revealed only two published studies, both of which had focused on coronary artery diameter z scores.[1,2] Therefore, the primary objective of our study was to derive echocardiographic nomograms .for the commonly measured cardiac structures in healthy Indian children (early childhood to adolescence).

MATERIALS AND METHODS

The study was conducted at two centers in India with the objective of collecting normative data for the measurements of the various cardiac structures using M-mode and two-dimensional (2D) echocardiography in normal children aged between 4 and 15 years and to calculate Z-scores for each measured parameter. Seven hundred and forty-eight children were enrolled at Ajmer, Rajasthan, and thirty at Mohali, Punjab. Children were recruited from three different schools of Ajmer. In the Mohali center, children accompanying patients attending an adult cardiology facility were enrolled. Children with any chronic underlying disease or a CHD were excluded from the study. After obtaining written informed consent from the parents, the children were evaluated clinically followed by echocardiographic screening. Echocardiographic evaluation was performed using a Philips iE33 system (Philips Medical Systems, Bothell,WA, USA). The 2D and M-mode measurements of 21 cardiovascular structures were obtained for each subject. Age-appropriate transducers (4–12, 2–7, 2–5 MHz) were used. Echocardiograms were obtained at the standard precordial positions. We followed the recommendations for standardizing measurements made from M-mode and 2D quantification echocardiograms as described by Lopez *et al.*[3] The views utilized and the methods employed for measuring the 2D echocardiographic parameters are shown in Table 1. Two operators (one in the Ajmer center and the other in Mohali) were involved in the acquisition of echocardiographic measurements. Since only thirty subjects were evaluated at the Mohali center, a formal inter/intra-observer variability analysis was not performed. The measurements acquired by fellows in training were reassessed by the senior consultant (offline), and when found nonsatisfactory, repeat evaluation was done subsequently. The

Table 1: Methods and views employed in two-dimensional echocardiographic measurements

Measured parameter	View	Description
Ao An	Parasternal long axis	Inter hinge point distance during systole
SoV	Parasternal long axis	Maximum dimension in systole
STJ	Parasternal long axis	Maximum dimension in systole
Asc aorta	Parasternal long axis	Maximum dimension in systole as it crosses in front of the right pulmonary artery
MVA	Apical four chamber	Inter hinge point distance during diastole
TVA	Apical four chamber	Inter hinge point distance during diastole
LA minor axis diameter	Apical four chamber	Point to point distance at end-systole
LA major axis length	Apical four chamber	Point to point distance at end-systole
RA minor axis diameter	Apical four chamber	Point to point distance at end-systole
RA major axis length	Apical four chamber	Point to point distance at end-systole
RV basal diameter	Apical four chamber	Maximum dimension in diastole; point to point distance
RV mid cavity diameter	Apical four chamber	Maximum dimension in diastole; point to point distance
RV long axis length	Apical four chamber	Point to point distance

Ao An: Aortic valve annulus, SoV: Sinuses of Valsalva, STJ: Sino tubular junction, Asc aorta: Ascending aorta, MVA: Mitral valve annulus, TVA: Tricuspid valve annulus, LA minor: Left atrial dimension along the minor axis, LA major: Left atrial dimension along the major axis, RA minor: Right atrial dimension along the minor axis, RA major: Right atrial dimension along the major axis, RV basal: Right ventricular dimension at the basal level, RV mid: Right ventricular dimension at the mid cavity level, RV long: Right ventricular dimension along the long axis data obtained were expressed in relation to body surface area (BSA) calculated by Haycock's formula (BSA = weight$^{0.5378}$ × height$^{0.3964}$ × 0.024265).[4]

Calculation of sample size

For sample size calculation, we followed the method used by Cantinotti *et al.*[5] The population of interest was divided age-wise into four sections (section 1, 4–6 years; section 2, 73 months - 8 years; section 3, 97 months - 10 years; and section 4, 121 months - 15 years). The standard deviation of the population was assumed as 0.5 and distribution of the variables as normal.[6,7] A minimum of 100 subjects per age section would be needed to reach a 95% confidence interval at a margin of error of 0.1. All the 21 measurements might not be available in the echocardiographic examination of every subject. Giving allowance for this fact, a higher number of subjects were deemed necessary in each study section. We assumed that at least 70% examinations would be complete, containing all the 21 measurements. This meant we needed a minimum of 140 subjects per section to reach the 95% confidence interval. Thus, we arrived at the final sample size of ≥560 subjects.

Seven hundred and forty-eight children were evaluated at Ajmer, Rajasthan, and thirty at Mohali, Punjab. After excluding children who had CHD in the screening echocardiogram and incomplete examinations, the final number of subjects included in the analysis was 720 from Ajmer and 26 from Mohali [Figure 1].

Statistical analysis

To assess the relationship of a parameter with the BSA, regression equations were used. We chose seven different models of regression namely;- (1) linear: y = a + bx, logarithmic: (2) y = a + b ln[x], (3) ln[y] = a + bx), exponential: (4) ln[y] = a + b ln[x]) and square root: (5) y = a + b√ x, (6) √ y = a + bx, (7) √ y = a + b√ x, which were applied to each measured parameter. As one of the assumptions of regression analysis is that the residuals should be normally distributed, Shapiro–Wilk and Kolmogorov–Smirnov tests were employed for assessment of normality of residuals. The regression equation which had the highest R^2 (goodness-of-fit) was selected. Thus, for each measured parameter, we came up with one best regression equation out of the seven. Z-score charts for all the studied parameters were then derived [Figures 2-11]. The parameters, the best fit model for each, and the respective R^2 values are shown in Table 2. The regression equations are provided in Table 3. The analysis was done using Stata version 14.1 for Windows;Stata Statistical Software Release 14. College Station Tx:StataCorp, LP.

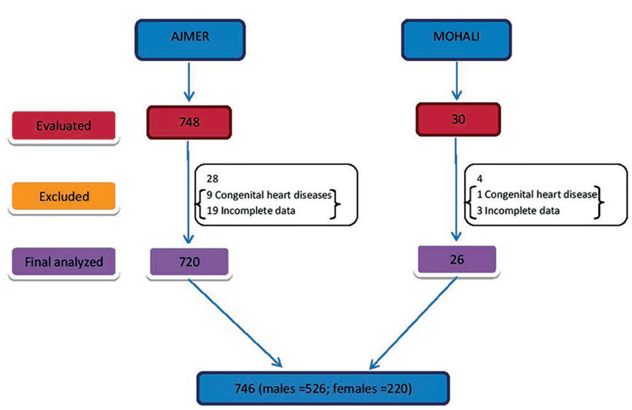

Figure 1: Screening and recruitment of children at the two centers

To calculate the Z-score for a subject using these regression equations in Table 3, the user has to substitute the subject's BSA and the measurement for the concerned parameter and the other values as provided in the table. The other way is to directly plot the measurement in the Z-score charts provided and directly arrive at the Z-score. Due to space constraints, the Z-score charts are provided only for ten parameters. The authors would be happy to provide interested users with the Z-score charts for the other parameters on request.

Table 2: Parameters assessed, the regression equation which provided the best fit model and corresponding R^2 values for each

Category	Parameter assessed	Model with best fit	R^2
M mode	IVSd	y=a+b√x	0.188
M mode	LVIDd	y=a+bx	0.355
M mode	LVPWD	y=a+bx	0.218
M mode	IVSs	y=a+bx	0.316
M mode	LVIDs	y=a+bx	0.114
M mode	LVPWS	y=a+bx	0.323
M mode	AoR	y=a+bxln (x)	0.346
M mode	AoVCS	√y=a+b√x	0.203
2D echo	Ao An	√y=a+bx	0.288
2D echo	SoV	y=a+bx	0.372
2D echo	STJ	√y=a+bx	0.32
2D echo	Asc aorta	y=a+bxln (x)	0.35
2D echo	MVA	y=a+bx	0.36
2D echo	TVA	y=a+bx	0.346
2D echo	LA minor	y=a+bx	0.244
2D echo	LA major	y=a+bx	0.177
2D echo	RA minor	y=a+bxln (x)	0.263
2D echo	RA major	y=a+bx	0.338
2D echo	RV basal	y=a+bx	0.366
2D echo	RV mid	y=a+bxln (x)	0.254
2D echo	RV long	y=a+bx	0.288

IVSd: Interventricular septal thickness in diastole, LVIDd: Left ventricular cavity internal dimension in diastole, LVPWD: Left ventricular posterior wall thickness in diastole, IVSs: Interventricular septal thickness in systole, LVIDs: Left ventricular cavity internal dimension in systole, LVPWS: Left ventricular posterior wall thickness in systole, AoR: Aortic root, AoVCS: Aortic valve cusp separation, Ao An: Aortic valve annulus, SoV: Sinuses of Valsalva, STJ: Sino tubular junction, Asc aorta: Ascending aorta, MVA: Mitral valve annulus, TVA: Tricuspid valve annulus, LA minor: Left atrial dimension along the minor axis, LA major: Left atrial dimension along the major axis, RA minor: Right atrial dimension along the minor axis, RA major: Right atrial dimension along the major axis, RV basal: Right ventricular dimension at the basal level, RV mid: Right ventricular dimension at the mid cavity level, RV long: Right ventricular dimension along the long axis, 2D: Two-dimensional

Table 3: Coefficients for regression equations for the measured echocardiographic parameters

Parameter assessed	Intercept	B	SEE (√MSE)	Kolmogorov–Smirnov	Shapiro–Wilk
Parameters with best fit with y=a+bx		**Z=(measurement – [intercept + B × BSA])/√MSE**			
LVIDd	22.450	12.807	3.660	0.040	0.992
LVPWD	4.990	2.242	0.917	0.087	0.972
IVSs	6.685	4.301	1.445	0.074	0.983
LVIDs	14.763	6.561	3.759	0.040	0.988
LVPWS	6.583	4.234	0.362	0.077	0.981
SoV	12.492	8.404	2.398	0.060	0.977
MVA	13.540	9.250	2.690	2.690	0.992
TVA	15.319	9.087	3.250	0.036	0.973
LA minor	16.023	9.621	3.610	0.066	0.979
LA major	21.464	12.063	5.410	0.038	0.038
RA major	17.659	12.716	3.831	0.069	0.986
RV basal	16.822	11.355	3.440	0.065	0.968
RV long	29.944	20.981	7.810	0.033	0.980
y=a + b X ln (x)		**Z=(measurement – [intercept + B × ln BSA])/√MSE**			
RA minor	17.290	9.791	3.560	0.049	0.981
RV mid	14.376	9.188	3.600	0.044	0.970
Asc Aorta	9.576	6.329	1.896	0.076	0.982
AoR	12.799	8.176	2.450	0.051	0.993
√y=a+bx		**Z=(√measurement – [intercept + B × BSA])/√MSE**			
STJ	9.917	6.967	2.225	0.067	0.934
Ao An	8.470	5.690	2.010	0.064	0.904
y=a+b√x		**Z=(measurement – [intercept + B × √BSA])/√MSE**			
IVSd	5.187	2.237	0.972	0.077	0.987
√y=a+b√x		**Z=(√measurement – [intercept + B × √BSA])/√MSE**			
AoVCS	10.703	5.197	2.388	0.093	0.793

Normality test: Shapiro–Wilk and Kolmogorov–Smirnov. B: Coefficient, IVSd: Interventricular septal thickness in diastole, LVIDd: Left ventricular cavity internal dimension in diastole, LVPWD: Left ventricular posterior wall thickness in diastole, IVSs: Interventricular septal thickness in systole, LVIDs: Left ventricular cavity internal dimension in systole, LVPWS: Left ventricular posterior wall thickness in systole, AoR: Aortic root, AoVCS: Aortic valve cusp separation, Ao An: Aortic valve annulus, SoV: Sinuses of Valsalva, STJ: Sino tubular junction, Asc aorta: Ascending aorta, MVA: Mitral valve annulus, TVA: Tricuspid valve annulus, LA minor: Left atrial dimension along the minor axis, LA major: Left atrial dimension along the major axis, RA minor: Right atrial dimension along the minor axis, RA major: Right atrial dimension along the major axis, RV basal: Right ventricular dimension at the basal level, RV mid: Right ventricular dimension at the mid cavity level, RV long: Right ventricular dimension along the long axis, BSA: Body surface area, MSE: Mean square error, SEE: Standard error of estimate

RESULTS

The study included 746 healthy children, age ranging from 4 to 15 years. Seventy-one percent were boys and 29% were girls. The BSA ranged from 0.57 cm^2 to 1.88 cm^2, median of 0.95 cm^2, and interquartile range (IQR) of 0.8–1.12 cm^2. The weight ranged from 11 kg to 77 kg, median of 25 kg, and IQR of 20–33 kg. The height ranged from 95 cm to 180 cm, median of 131 cm, and IQR of 119–143 cm. The distribution of BSA in the study subjects is shown in Table 4.

Table 4: Distribution of the body surface area in the study subjects

BSA (m^2)	*n* (%)
0.57–0.8	175 (24.1)
0.81–1	235 (32.36)
1.01–1.2	188 (25.9)
1.21–1.88	128 (17.6)

BSA: Body surface area

DISCUSSION

The World Health Organization growth charts[8] based on Western data[9-12] were found to grossly underestimate growth in Indian children.[13] The current day under-5 growth charts[14] were designed after elaborate studies in developing countries. On the same lines, utilizing Western Z-score standards for deriving Z-score values in Indian children or children from any other developing country might lead to erroneous judgments and faulty decisions.

Almost all published data on Z-scores of various heart structures have been based on studies conducted in the West. All pediatric centers in India and other developing countries have depended on these Western data till date for Z-score calculations for their young patients. Although there is no direct proof that growth parameters and dimensions of the heart vary between Western and Indian children, reasons exist to believe they do.[13] Therefore, separate Z-scores charts based on indigenous studies are needed in developing countries. There have been multiple studies for calculating Z-scores of various cardiac structures.[15] The most recent publications in this area[5,16-20] reveal that none of the latest Z-score research has come from any developing country.

Almost all these studies[5,16-20] have been done on hospital-based samples. Hospital-based samples have

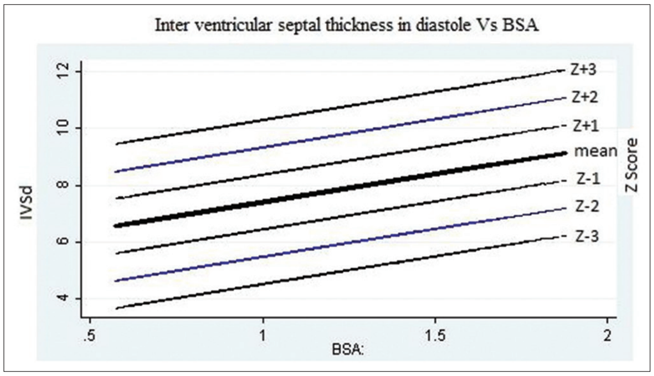

Figure 2: Z-score chart plot obtained by plotting the interventricular septal thickness in diastole (in millimeters [mm]) against the body surface area (m^2)

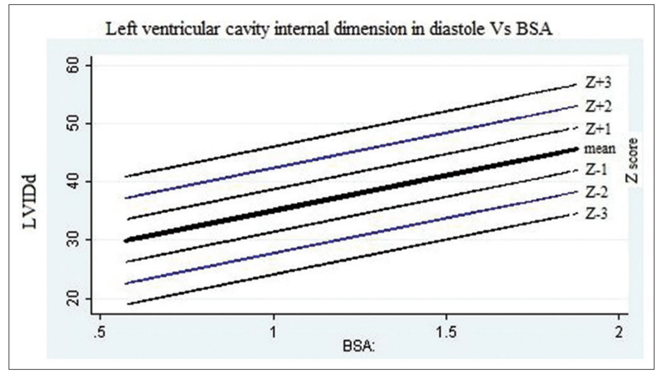

Figure 3: Z-score chart plot obtained by plotting the left ventricular cavity internal dimension in diastole (in millimeters [mm]) against the body surface area (m^2)

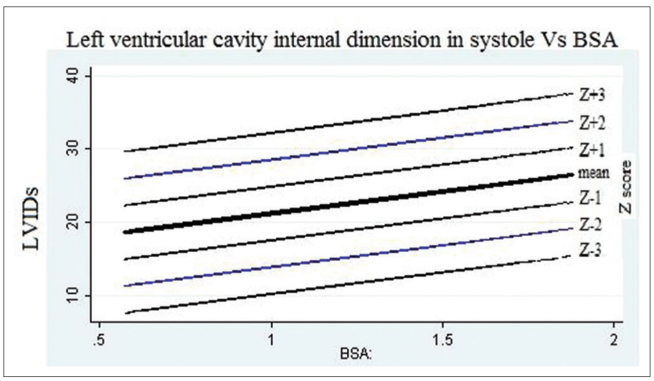

Figure 4: Z-score chart plot obtained by plotting the left ventricular cavity internal dimension in systole (in millimeters [mm]) against the body surface area (m^2)

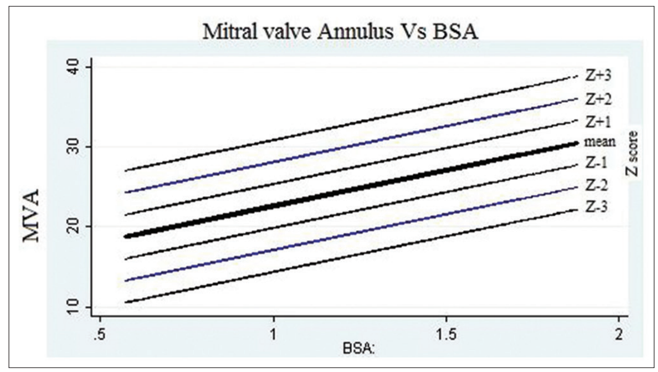

Figure 5: Z-score chart plot obtained by plotting mitral valve annulus measurement (two-dimensional echo) in millimeters [mm]) against the body surface area (m^2)

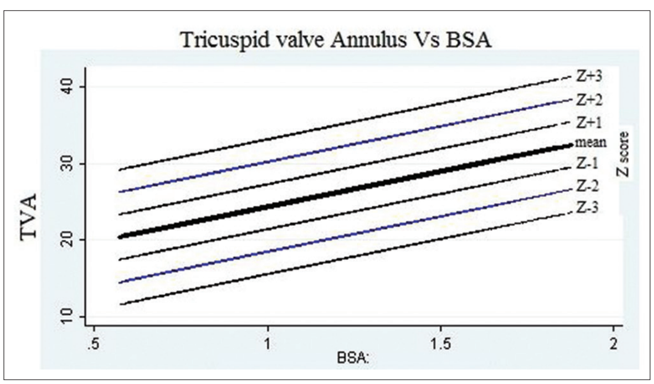

Figure 6: Z-score chart plot obtained by plotting tricuspid valve annulus measurement (two-dimensional echo) in millimeters [mm]) against the body surface area (m^2)

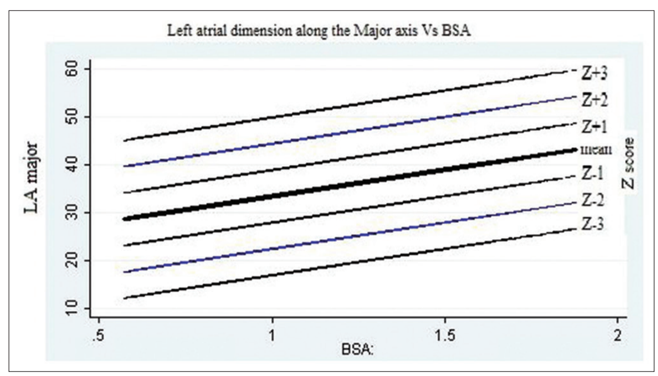

Figure 7: Z-score chart plot obtained by plotting the left atrial-major axis dimension (two-dimensional echo) in millimeters [mm]) against the body surface area (m^2)

their inherent disadvantages including selection bias. We studied healthy school going children. To the best of our knowledge, ours is the first study on such a large sample of children from the community. One of the schools included in our study was run by a private organization with the majority of children from an affluent background. The second was also a private institution with children from less affluent families. The third school was a non-governmental organization funded institution with children hailing from less privileged sections of the society. Majority of children from this school were undernourished. We did not exclude children based on malnutrition, obesity, or stunting. Malnutrition has an impact on cardiac growth. Studies uniformly agree that left ventricular (LV) mass decreases in severe malnutrition.[21] LV posterior wall and interventricular septal thickness have been found to fall below the 5th centile in proportion to the decrease in body size in majority of children with established kwashiorkor.[22]

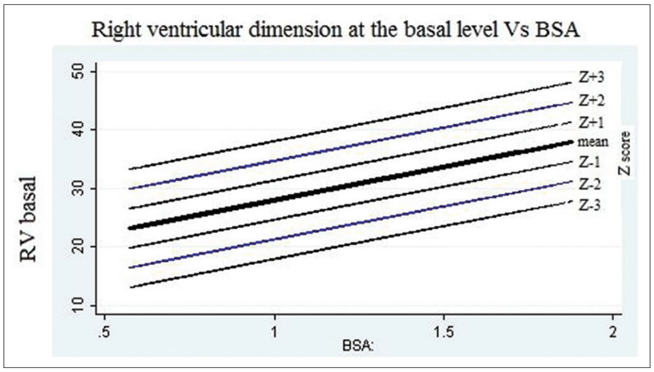

Figure 8: Z-score chart plot obtained by plotting the right ventricular cavity dimension measurement at the basal level (two-dimensional echo) in millimeters [mm]) against the body surface area (m^2)

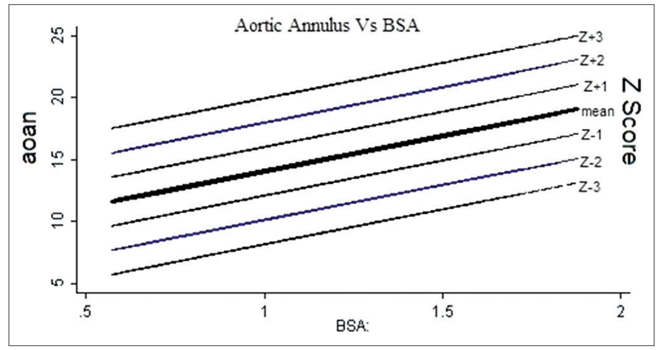

Figure 9: Z-score chart plot obtained by plotting the aortic annulus measurements (two-dimensional echo) in millimeters [mm]) against the body surface area (m^2)

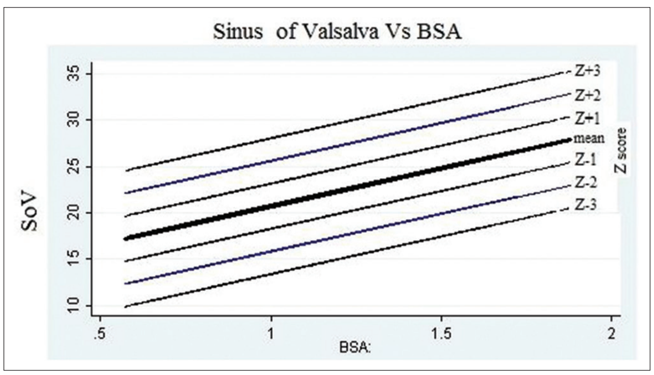

Figure 10: Z-score chart plot obtained by plotting aortic measurements at the sinuses of Valsalva (two-dimensional echo) in millimeters [mm]) against the body surface area (m^2)

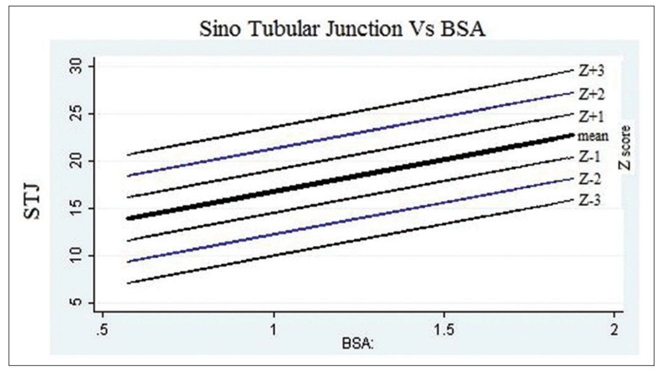

Figure 11: Z-score chart plot obtained by plotting aortic measurements at the sinotubular junction (two-dimensional echo) in millimeters [mm]) against the body surface area (m^2)

However, what happens in lesser degrees of malnutrition is unclear. We hypothesize that cardiac wall thickness and dimensions are maintained till a critical level of nutritional imbalance is reached. Including children with lesser degrees of malnutrition who had lower BSA but preserved cardiac dimensions may have resulted in the low R^2 values in our study. We compared the measurements of selected cardiac structures from our study with existing nomograms [Table 5].[5,23]

As seen in Table 5, the majority of parameters had values, which were uniformly lower in comparison to the Western standards. This reinstates our emphasis on the need for an indigenously developed Z-score nomogram for use in developing countries.

Strength and limitations of the study

This study has attempted to derive Z-scores for various 2D Echo and M-mode parameters in Indian children. The study subjects have been chosen from school going children. This community-based sampling adds to the strength of the study. Children included in the study represent multiple socioeconomic strata in our society. While this increases

Table 5: Comparison of the present study's measurements with previously published Western nomograms for a child with a body surface area of 1 m^2 (selected parameters)

Cardiac structure	Mean±2SD		
	Our study (mm)	Cantinotti *et al.* (mm)[5]	Pettersen *et al.* (mm)[23]
RA minor	27.72 (19.18–33.71)	31.50 (25.53–38.86)	
RA major	30.01 (18.90–37.92)	34.06 (27.83–41.68)	
RV basal	28.72 (21.36–35.32)	31.34 (25–39.29)	
RV long	49.77 (36.11–63.11)	51.11 (42.01–62.18)	
LA minor	26.04 (18.52–32.72)	30.02 (24.83–36.31)	
LVIDd	35.02 (27.82–42.04)		39.09 (32.06–48.79)
LVIDs	21.62 (14.36–27.6)		24.96 (18.92–31.80)

RA minor: Right atrial dimension along the minor axis, RA major: Right atrial dimension along the major axis, RV basal: Right ventricular dimension at the basal level, RV mid: Right ventricular dimension at the mid cavity level, RV long: Right ventricular dimension along the long axis, LVIDd: Left ventricular cavity internal dimension in diastole, LVIDs: Left ventricular cavity internal dimension in systole, SD: Standard deviation the external validity of our findings, the effects of varying nutrition and hence body weight and BSA may explain the relatively low R^2 values. Z-score nomograms for main and branch pulmonary arteries, aortic isthmus, and transverse aortic arch were not included as they were planned as a part of a subsequent study.

CONCLUSION

The Z-score nomograms derived by this study might serve as better alternatives to the Western nomograms for use in India and other developing countries for preprocedural decision making in the pediatric population. However, they will need to be validated in large-scale studies before they can become clinically applicable.

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Conflicts of interest

There are no conflicts of interest.

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