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Original Research Article

Coronary artery diameter measurement and Z-score regression equation calculation: a comparative study between Indian children between one to five years residing in and around Kolkata with children of South-East Asia and Western population

Satyaki Das[1], Swapan Kumar Ray[2], Sukanta Bhattacharya[1], Kripasindhu Chatterjee[2], Pradyut Kumar Mandal[2], Sukanta Sen[3]*

[1]Department of Pediatrics, Institute of Child Health, Dr Biresh Guha Street, Park Circus, Ballygunge, Kolkata, West Bengal, India
[2]Department of Pediatrics, [3]Department of Pharmacology, ICARE Institute of Medical Sciences and Research, Banbishnupur, P.O.- Balughata, Purba Medinipur, Haldia, West Bengal, India

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***Correspondence:**
Dr. Sukanta Sen,
E-mail: drsukant@gmail.com

ABSTRACT

Background: Congenital coronary anomalies may be isolated, or they may accompany other congenital heart defects, such as Fallot's tetralogy, transposition of the great arteries or pulmonary atresia. The most common cause of acquired abnormalities of the coronary vessels in children is kawasaki disease (KD). The aim of this study was to find the best model to obtain valid and normally distributed Z-scores for coronary artery (CA) diameters in a large, heterogeneous population of healthy children.
Methods: Echocardiography was performed on 300 healthy children. Linear regression models were tested with height, weight, body surface area, and aortic valve diameter. The computed Z scores were tested for normal distribution and stability.
Results: CA diameter was best predicted using regression with the body surface area and age in month. The weighted least squares method yielded normally distributed and very stable Z-score estimates for 3 principal CAs.
Conclusions: This study showed valid methods to estimate Z scores for CA size in children of all ages. Such Z scores are important for risk stratification in patients with Kawasaki disease.

Keywords: Coronary arteries, Echocardiography, Kawasaki, Normal value, Z-scores

INTRODUCTION

Anomalies of the coronary arteries in children can occur in many diseases. Congenital coronary anomalies may be isolated, or they may accompany other congenital heart defects, such as Fallot's tetralogy, transposition of the great arteries or pulmonary atresia. The most common cause of acquired abnormalities of the coronary vessels in children is kawasaki disease (KD).[1] The major consequence of this disease is coronary artery (CA) aneurysmal dilatation which occurs about 15-25% of untreated children and may lead to ischemic heart disease.[2] Even the transitory dilatation of the CA remains essential in the diagnosis, management, and follow-up of children with KD. In fact, the identification of CA dilatation upon the onset of KD has become central to support the diagnosis and guide therapy.[3] Weyman et al.

first visualized left main coronary artery by cross-sectional echocardiography.[4] Since then measurement of coronary artery diameter by non-invasive techniques like echocardiography has been widely used. There have been estimates of normal coronary artery size during childhood during past few years but the data have been reported to be arbitrary and a standard and generalized data were missing. Commonly used definitions of coronary involvement have relied on the Japanese Ministry of Health dichotomous criteria. This criteria defines abnormalities as having a maximum internal diameter >3 mm in children <5years of age, or >4 mm in children 5 years or older, or a segment 1.5 times greater than an adjacent segments or presence of luminal irregularities.[5] However, regression equations based on measurements from normal children have been used to calculate z-score based on BSA, thus allowing a continuous rather than a dichotomous measurements of coronary artery measurement.

The categorization of aneurysm size seemed to represent a prognostic value.[6] Since then, equations have been published, and both linear and exponential functions with body surface area (BSA) were proposed.[7-10] Normal distribution and stability of a Z score with growth are crucial for its validity, but such information was not available in previously published studies. In this prospective study it will be attempted to establish data for normal coronary artery diameter during childhood by using echocardiography and also to calculate z-score equation from patient's age, sex and BSA.

The aim was to propose accurate and validated Z-score and regression equations by testing several different models to ensure not only appropriate goodness of fit but also adequate distribution of the Z scores obtained.

METHODS

Randomly selected sample of 300 children attending in and out patient department of Institute of Child Health, Kolkata between one to five years of age from urban, suburban and rural areas in and around Kolkata from May 2015 - April 2016 were included in our study population. Patients were enrolled if they had normal physical examination results and their chest x-ray, ECG and echocardiogram were interpreted as normal by the attending cardiologist. Exclusion criteria consists of presence of structural heart disease, cardiac manifestation of a systemic disease, kawasaki disease, ventricular hypertrophy, abnormal ECG, abnormal CXR, abnormal echocardiogram. The height, weight, age and gender of all patients were recorded and the body surface area (BSA) for each patient was estimated using the formula of Dubois and Dubois.[11]

Echocardiography

All children were examined by complete 2-D echocardiographic study with colour flow and spectral Doppler examination. Studies are performed using PHILIPS HD7XE ultrasound system.

Coronary artery measurements

Left main coronary artery (LMCA) will be measured midway between ostia and bifurcation of left anterior descending (LAD) and LMCA from para-sternal short axis view. LAD and right coronary artery (RCA) will be measured 3 mm to 5mm distal to the origins in para-sternal short axis view. Each measurement will be performed by one reviewer and for a randomly selected 10% of the subjects a second reviewer who is blinded to the first readings will measure independently the coronary artery diameter. The inter-observer variability will be tested by using intra-class correlation coefficient and comparing readings of the 1st and 2nd reviewer. A p-value smaller than 0.05 is considered statistically significant.

Data were analyzed for echocardiographic findings and coronary artery diameter regression equations and Z-score was calculated by using Statistica version 6 (Tulsa, Oklahoma: StatSoft Inc., 2001) and MedCalc version 11.6 (Mariakerke, Belgium: MedCalc Software 2011).

Coronary artery measurements of 300 LMCA, 300 RCA and 300 LAD were enrolled for modelling. Coronary diameters were then modelled with BSA. Linear models were fitted, and outlier data were then eliminated and the model parameters were recalculated based on the measurements of 300 LMCA, 300 RCA and 300 LAD. Parameter estimates, r^2 (squared correlation coefficient) and Kolmogorov-Smirnoff statistical tests for the final models are presented in Table 6 (Appendix).

Calculation and goodness of fit of Z-score

To obtain the Z-score for a given coronary measurement, the mean values of LMCA, LAD and RCA corresponding to the examined coronary segment were used. The Z-score value was then calculated from the following equation: Z-score = (CAobs- CAmean)/standard deviation. The Kolmogorov-Smirnov statistical tests were applied to measure the goodness of fit of the calculated Z-score for a normal distribution. The P values for coronary diameters of LMCA, RCA and LAD were > 0.05 in each case, which indicated no significant departure from normal distribution.

RESULTS

From May 2015 to April 2016; about 300 children, attending Institute of Child Health, Kolkata, who fulfilled the inclusion criteria laid down by us were chosen for the study, amongst which 56% were male. The median age of the study population was 36.5 months with a SD of 14.821 months. The weight ranged from 11.7 to 19.1 kg (mean: 15.4 kg: standard deviation (SD): 2.168 kg], and the body surface area (BSA) of the children ranged from

0.50 - 0.79 m^2 with a mean of 0.64 m^2 (SD: 0.087 m^2) (Table 1).

In the male population, the median age was 36.5 months with a SD of 14.833 months. The weight ranged from 11.7 to 19.1 kg (mean: 15.4 kg: standard deviation (SD): 2.168 kg], and the body surface area (BSA) of the children ranged from 0.50 - 0.79 m2 with a mean of 0.65 m2 (SD: 0.087 m^2).

In the female population, the median age was 36.5 months with a SD of 14.860 months. The weight ranged from 11.7 to 19.1 kg (mean: 15.4 kg: standard deviation (SD): 2.177 kg), and the body surface area (BSA) of the children ranged from 0.50 - 0.79 m^2 with a mean of 0.64 m^2 (SD: 0.087 m^2).

The distribution of age and body surface area (BSA) of enrolled subjects is shown in Figure 1 and 2, respectively.

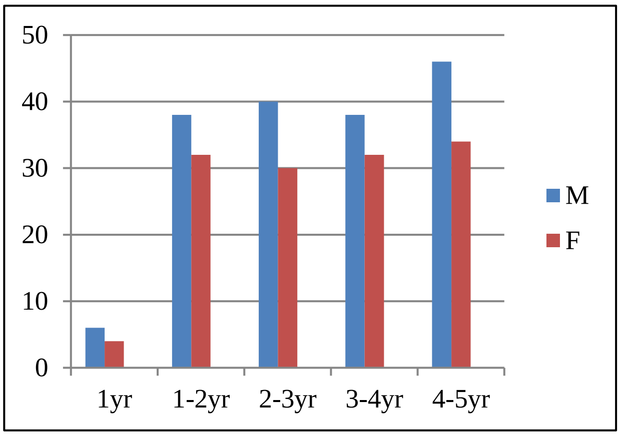

Figure 1: The distribution of age of enrolled subjects.

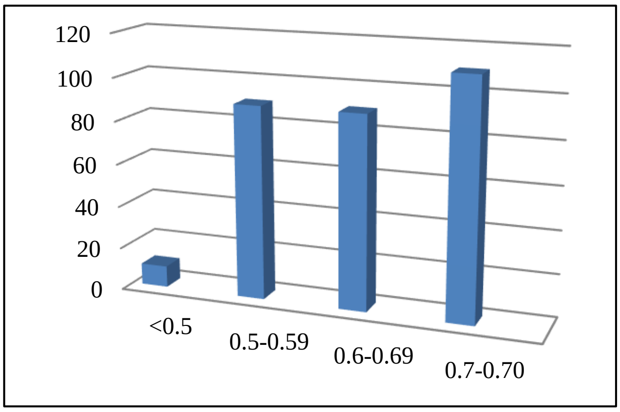

Figure 2: The distribution of body surface area (BSA in m^2) of enrolled subjects.

Gender effect

No significant difference of BSA between gender groups (p = 0.87) in unpaired student's t test. Consequently, gender-specific models were not further developed to avoid statistical complications.

Effect of BSA-estimation formula

Although the original BSA estimation proposed by Bois Du et al.[11] is widely used, other enhanced formulas, like Mosteller's formula have been developed for infants and younger children.[12] In previously published studies, Regression results from LMCA were compared when using different BSA-estimation methods, Mosteller's equation and Du Bois and Du Bois's method. The Z-scores obtained were very similar and misclassification was observed for only 0.2% of subjects classified as abnormal (Z > 2.5) for BSA using the Du Bois & Du Bois's method, but normal with BSA from Mosteller's equation12. Here, Du Bois and Du Bois formula was used for calculating BSA.

Correlation matrix depicting Pearson's r value

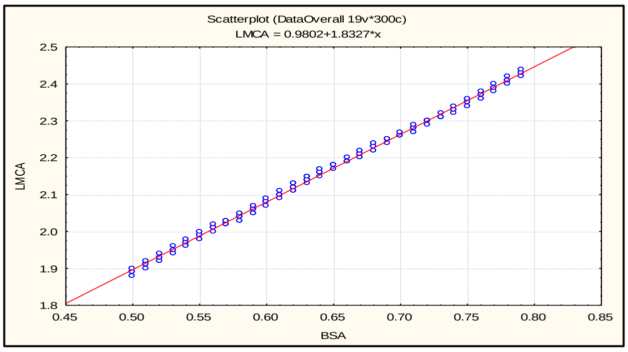

Figure 3: Correlation between LMCA diameter (in mm) and BSA (in m^2).

Table 1: Multiple regression equation for LMCA based on BSA in m^2 and age in months.

Dependent Y			LMCA	
Sample size			300	
Coefficient of determination R^2			0.9982	
R2-adjusted			0.9982	
Multiple correlation coefficient			0.9991	
Residual standard deviation			0.006778	
Regression equation				
Independent variables	**Coefficient**	**Std. error**	**t**	**P**
(Constant)	1.2117			
BSA	1.2913	0.1001	12.905	<0.0001
Age(m)	0.003170	0.0005853	5.416	<0.0001
Zero order correlation coefficients				
Variable	**r**			
BSA	0.9990			
Age_m	0.9986			

The r-values were approaching 1 in both cases. Hence, BSA (in m^2) and age in month correlating strongly with LMCA diameter (in mm).

The final regression equation obtained is as follows: LMCA = 1.212 + 1.291 X BSA + 0.003 X Age (m).

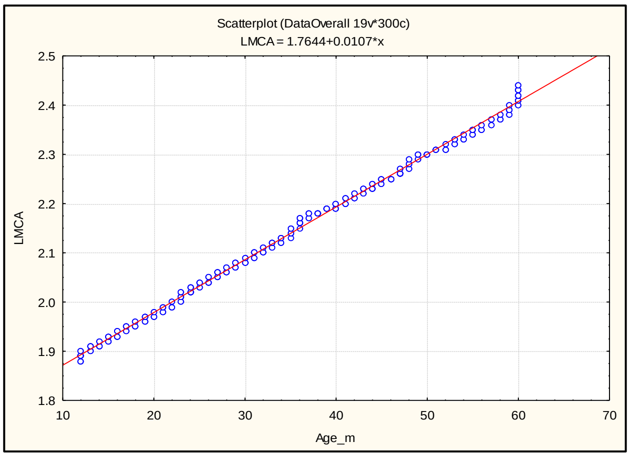

Figure 4: Multiple regression equation for LMCA based on BSA in m^2 and age in month.

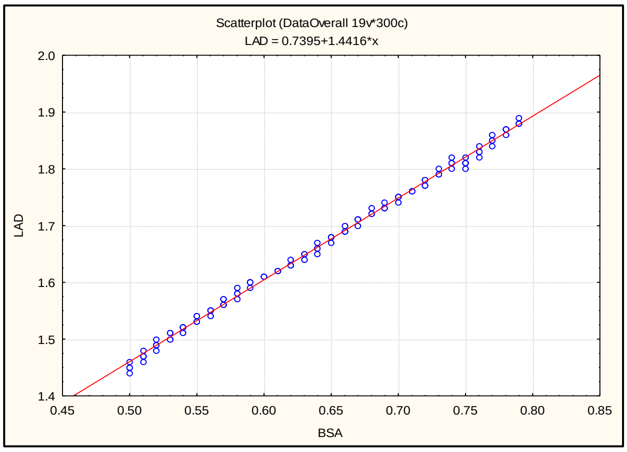

Figure 5: Correlation between LAD diameter (in mm) and BSA (in m^2).

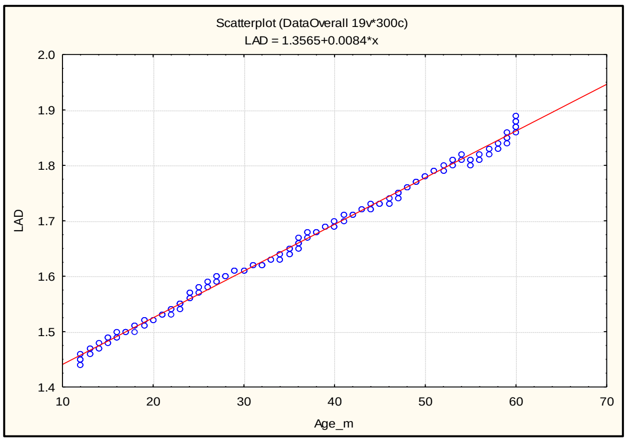

Figure 6: Correlation between LAD diameter (in mm) and age (in month).

Multiple regression equation for LAD based on BSA in m^2 and age in months.

Table 2: Multiple regression equation for LAD based on BSA in m^2 and age in months.

Dependent Y		LAD		
Sample size		300		
Coefficient of determination R^2		0.9975		
R2-adjusted		0.9975		
Multiple correlation coefficient		0.9988		
Residual standard deviation		0.006242		
Regression equation				
Independent variables	**Coefficient**	**Std. Error**	**t**	**P**
(Constant)	0.8196			
BSA	1.2542	0.09215	13.611	<0.0001
Age(m)	0.001097	0.0005391	2.035	0.0427
Zero order correlation coefficients				
Variable	**r**			
BSA	0.9987			
Age(m)	0.9980			

The r-values were approaching 1 in both cases. Hence, BSA (in m^2) and age in month correlating strongly with LMCA diameter (in mm).

The final regression equation obtained is as follows:
LAD = 0.820 + 1.254 X BSA + 0.001X Age (m)

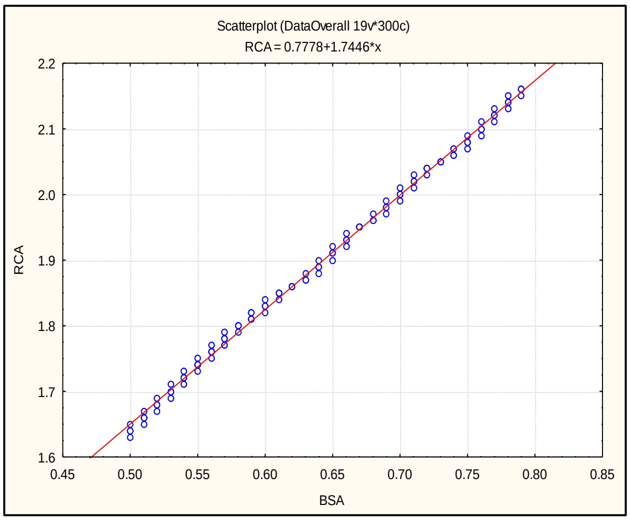

Figure 7: Correlation between RCA diameter (in mm) and BSA (in m^2).

Data were summarized by routine descriptive statistics and Kolmogrov-smirnov goodness of fit was applied to assess the normality of numerical variables. These variables were compared between gender subgroups using student independent sample t-test. To tailed, p-value<0.05 was considered statistically significant. Association between coronary artery diameter and BSA or age were explored through scatter-plot and quantified by calculation of Pearson correlation coefficient r.

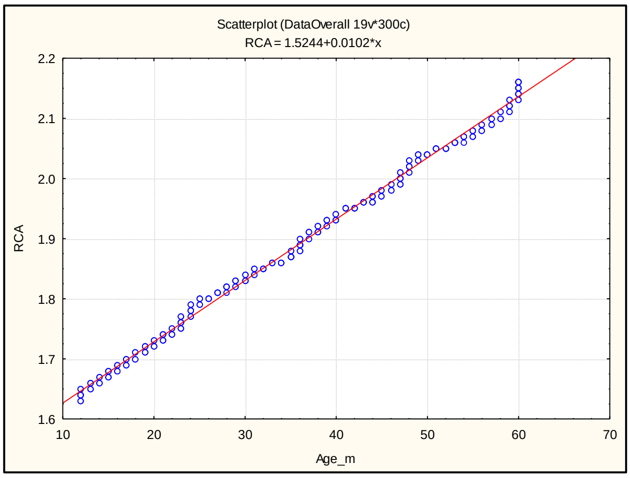

Figure 8: Correlation between RCA diameter (in mm) and age (in month).

As strong correlation were observed, a multiple linear regression model was fitted to obtain a predictive equation for individual coronary artery diameter on the basis of BSA (in m2) and age (in month). All numerical variables below (Table 1) were normally distributed by Kolmogorov-Smirnov goodness-of-fit test other than age in months (ignored since age in months having normal distribution in male and female subgroups

Multiple regression equation for RCA based on BSA in m^2 and age in months.

Table 3: Multiple regression equation for RCA based on BSA in m^2 and age in months.

Dependent Y	RCA			
Sample size	300			
Coefficient of determination R^2	0.9978			
R^2-adjusted	0.9978			
Multiple correlation coefficient	0.9989			
Residual standard deviation	0.007135			
Regression equation				
Independent variables	**Coefficient**	**Std. Error**	**t**	**P**
(Constant)	0.9021			
BSA	1.4541	0.1053	13.805	<0.0 001
Age_m	0.001701	0.0006 162	2.761	0.0061
Zero order correlation coefficients				
Variable	**r**			
BSA	0.9989			
Age_m	0.9982			

The r-values were approaching 1 in both cases. Hence, BSA (in m^2) and age in month correlating strongly with LMCA diameter (in mm).

The final regression equation obtained is as follows:

RCA = 0.902 + 1.454 X BSA + 0.002 X Age (m).

Table 4: Descriptive statistics of numerical variables: whole cohort (n = 300).

	N	Mean	Median	Min	Max	Lower quartile	Upper quartile	Std. Dev.
BSA	300	0.645	0.645	0.50	0.79	0.57	0.72	0.0867
Weight (kg)	300	15.400	15.400	11.70	19.10	13.50	17.30	2.1685
Height (cm)	300	100.458	100.400	82.500	117.700	91.500	109.500	10.2378
Age (months)	300	37.133	36.500	12.000	60.000	24.000	49.500	14.8205
LMCA	300	2.162	2.170	1.880	2.440	2.020	2.300	0.1590
LMCAp	300	2.156	2.154	1.894	2.412	2.020	2.290	0.1564
LMCAz	300	0.002	0.050	-1.774	1.748	-0.893	0.868	1.0003
LAD	300	1.669	1.670	1.440	1.890	1.560	1.775	0.1251
LADp	300	1.666	1.665	1.459	1.871	1.559	1.772	0.1235
LADz	300	0.003	0.008	-1.832	1.768	-0.872	0.848	1.0011
RCA	300	1.903	1.900	1.630	2.160	1.780	2.040	0.1514
RCAp	300	1.914	1.913	1.653	2.171	1.779	2.048	0.1557
RCAz	300	0.001	-0.020	-1.808	1.702	-0.815	0.907	1.0029

DISCUSSION

The current data closely correlates with the published equations from the Washington and Boston study groups.[9,13] However, this data showed greater dispersion, possibly because, the Singapore study group consisted of 390 Asians aged 2 months to 8 years and our group consisted of 300 Indian children aged 1 year to 5 years. In addition, the current data showed no difference in the RCA, LMCA and LAD coronary artery diameter between male and female children.[7] Therefore, the reference data we provide can be considered suitable for the daily clinical practice. The study provides a detailed analysis of multiple statistical models and concludes that a linear approximation incorporating BSA as the independent variable provides a better fit than other models, including those using polynomial and square approximation with BSA and those using height and weight as dependent variables.[14,15]

Accurate coronary artery measurement is important in the management of coronary disease in children, especially those with Kawasaki disease, in which coronary artery involvement is the principal complication. Because the coronary arteries grow throughout childhood, interpretation of coronary artery measurements must take into account the patient's body size, which is commonly performed by the calculation of z scores for the coronary artery measurement adjusted for BSA. Several pediatric echocardiography laboratories have developed their own normal reference data as part of their clinical decision making.[7,8,13,16,17] In this context, the case definition of CA dilatation has clearly improved during the past few years but remains imperfect. The Z score's principal utility is to determine the proportion of the population that lies beyond a given value of Z. Individuals with Z scores > 2 are often clinically defined as being ‘‘abnormal.’’ When Z scores are computed, it is critical that their distribution be normal and that these proportions be respected across the entire population. Our final regression model was tested for the goodness of fit to a normal distribution and yielded minimal asymmetry around the mean. Information on such a validation of Z scores was lacking in previously published equations, especially for India.

Pediatric coronary Z-scores are critical for managing children with KD. It has been increasingly recognized that dichotomous criteria based on absolute size is not always reliable and classification of coronary abnormalities on the basis of Z-score has already been proposed.[3,18] In the study of Dallaire et al, the square root model was also demonstrated to be good for the development of the Z-score calculator.[16] The data from our study correlated closely with those of McCrindle et al only in the RCA diameters, and with Dallaire et al only in the LMCA diameters. These results suggest that we do need our own Z-score calculators to accurately reflect the Indian population.[9,16]

In 2004, Sluysmans and Colan proposed a theoretical model of optimal cardiovascular allometry that predicted a linear relationship of vascular diameter with the square root of BSA.[19] They then have shown that many vascular diameters, including those of the CAs, indeed follows that rule. They suggested that indexing CA with the square root of BSA was adequate because no residual heteroscedasticity was observed. Our results were in accordance with the square root relationship with BSA. This precludes the use of a simple diameter indexing with BSA, at least for CAs. Although we acknowledge that this would be a much simpler way to report normal values, failure to fully account for heteroscedasticity could introduce significant bias. Such concern on indexing cardiac structures has also been issued by the American Society of Echocardiography in the recent recommendations for quantification methods in pediatric echocardiography.

To handle heteroscedasticity, Olivieri et al used logarithmic transformation, while McCrindle et al computed a linear regression of the residuals in addition of the logarithmic transformation.[13,9] Although previous models from Olivieri et al. and McCrindle et al. have greatly improved CA evaluation in children, we feel that the linear model with the weighted least squares approach was best to account for both heteroscedasticity and the behavior of coronary size at low BSA. We acknowledge that we ourselves propose a mathematic transformation of the BSA for our model.

The CA/aorta ratios suggested by Tan et al represent a valid modelization and have simplified the evaluation of coronary dilatation.[7] However, our regression results were substantially different. Tan et al. obtained lower ratios and lower intercepts. Consequently, Z scores computed were significantly higher to that yielded by our equation. Simple linear regression with aortic valve diameter simplifies the calculation of Z scores, and we believe that the equations shown above are valid ways to estimate Z scores with aortic valve annular diameter. In most cases, however, this method offers little benefit compared with the model with BSA, especially because it does not include adolescents and very small children.

Previous studies used computed tomography (CT) to establish reference curve and linear formulas for the coronary diameters in infants and children. The results appeared satisfactory and also demonstrated no significant difference in the coronary arterial size between the genders.[20,21] However, patient exposure to radiation and contrast media during CT examinations are issues of ongoing concern. Furthermore, coronary artery examinations and measurements should be repeated at the acute stage and 2 weeks, 6-8 weeks, 6 months and 12 months after onset of KD. One dose of CT radiation in KD children may be unremarkable, but the repeated and accumulated exposure of radiation and contrast medium may be harmful. Echocardiography is currently a preferred tool to do the biometrical measurements for all cardiac structures, especially in children.

The main utility for pediatric CA Z scores is in KD. It is being increasingly recognized that the case definition of CA dilatation in KD must not rely on dichotomous criteria based on absolute size. Classification of CA abnormalities on the basis of Z scores has already been proposed by others.[15] If Z scores become the basis of the CA dilatation definition, they must be derived from rigorous models with appropriate validation to avoid misclassification. Our results can be used in three ways to determine whether a given coronary artery is dilated. First, the approximate corresponding Z score for a specific BSA can be determined using the Z score graph. Second, the Z score can be directly and more precisely calculated using our regression equation. Third, the Z score range for a particular BSA range can be determined using the Z score boundaries.

However there are some limitations in our study. First, the number of echocardiographies done were relatively small. Therefore, the small number of cases may result in the deviation of statistical assumption. Second, the great majority of the CA measurements were done by a single echocardiographer. We did not assess intra-observer and inter-observer variation. The population included in this study was selected from a single referral center serving mostly Indian children between one to five years age group residing in and around Kolkata. Information on race was not available, and potential race-specific differences were not tested.

CONCLUSION

In conclusion, reference ranges were established for coronary artery diameters in normal Indian children between one to five years age group residing in and around Kolkata- the largest metropolitan city in the country with an ethnically heterogeneous population. The regression equations and Z-score calculators for the LMCA, LAD and RCA provide an objective determination of coronary dilatation, which is important in patients with Kawasaki disease. Our regression equation and Z-score equation may be useful in clinical decision-making for pediatric patients with congenital or acquired cardiac disease.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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