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A comparative study of established *z* score models for coronary artery diameters in 181 healthy Korean children

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Purpose: The aim of this study was to investigate the statistical properties of four previously developed pediatric coronary artery *z* score models in healthy Korean children.
Methods: The study subjects were 181 healthy Korean children, whose age ranged from 1 month to 15 years. The diameter of each coronary artery was measured using 2-dimensional echocardiography and converted to the *z* score in the four models (McCrindle, Olivieri, Dallaire, and Japanese model). Descriptive statistical analyses and 1-sample *t* tests were performed.
Results: All calculated *z* scores had *P* values of ≥0.050 using the Kolmogorov-Smirnov test. The one sample *t* test showed that the mean *z* scores did not converge to zero except in 1 model, and the mean right coronary artery (RCA) *z* score was less than zero in all 4 models. The smaller RCA diameter in this study could be associated with the more distal measuring point used to avoid the conal branch. The percentage of subjects with extreme *z* score values (≥2.0 and ≥2.5) for the left main coronary artery (LMCA) seems to be higher in the Dallaire (4.9% and 3.3%) and Japanese models (7.1% and 3.8%).
Conclusion: All 4 models showed statistical feasibility of normal distribution. More precise instructions would be needed for the measurement of the RCA. The higher percentage of extreme *z* scores for the LMCA is compatible with the basic understanding of anatomic variation in the LMCA.

Key words: *z* score, Coronary artery diameters, Korean children, Kawasaki disease

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Introduction

Kawasaki disease (KD) is an acute, self-limiting febrile illness of unknown cause that affects the coronary arteries, predominantly occurring in children aged ≤5 years. KD was first described by Kawasaki in 1967[1] and is now known as the most common cause of acquired heart disease in children in developed countries[2]. The appropriate initiation of treatment with intravenous immunoglobulin reduces the incidence of coronary artery aneurysms from 25% to 4%[3-6].

A quantitative assessment of the dimensions of the coronary artery using echocardiography is an important practice in the management of patients with KD. The criteria for coronary artery aneurysm, set by the Japanese Ministry of Health and Welfare in 1984, was a maximum internal diameter of ≥3 mm in children aged <5 years and ≥4 mm in children aged ≥5 years, a segment 1.5 times greater than the adjacent segment, and the presence of luminal irregularity[7]. Until recently, these criteria were widely used as they were easy to memorize and use. However, an underestimation of the incidence of coronary arterial lesions and an inability to reflect children's body growth in the application of these criteria have been pointed out[8]. A standardized score (*z* score) for assessing cardiovascular structures has been developed for use in pediatric clinical environments as children undergo rapid changes in their physical development with resultant variations in their body size[9]. Several coronary artery *z* score models have been subsequently proposed[8,10-15]; a relatively large number of subjects was included, and nonlinear regression methods were adopted in four of models[12-15]. In a recently published practice guideline by the American Heart Association, the classification of coronary arterial lesions is based on the *z* score of coronary artery diameter[2]. The previously reported *z* score model for Korean children has two major limitations: firstly, the number of subjects included in the study for the model was too small and secondly, a linear regression was adopted for model fitting of the body surface area[16]. The *z* score model by Kobayashi et al.[15], which was derived from the lambda-mu-sigma method in 3,851 Japanese children, holds promise for use in Korean children due to its large sample size and the racial similarity between the Japanese and Korean populations.

In this study, an investigation of the statistical properties of 4 previously developed pediatric coronary artery *z* score models, including the Japanese model, was performed in relation to 181 healthy Korean children. We expected the results of this investigation to present useful information on the selection of *z* score models in clinical practice in Korea.

Materials and methods

1. Subjects

The study subjects were 181 healthy Korean children, whose ages ranged from one month to 15 years (Fig. 1), and who presented at the Asan Medical Center for an evaluation of a cardiac murmur, abnormal findings on chest radiography (e.g., borderline heart size), syncope, or transient chest pain. Echocardiographic studies showed no significant anatomical and functional abnormalities in the subjects. The subjects' demographic characteristics were evaluated through a review of their medical records. A body surface area was estimated using the Haycock formula[17].

This study was approved by the Institutional Review Board of Asan Medical Center (2017-0853), and the requirement for informed patient consent was waived.

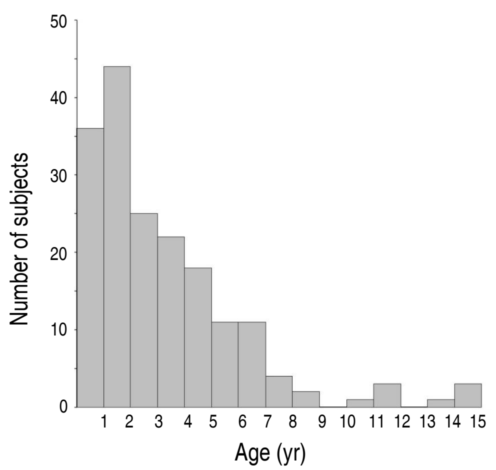

Fig. 1. Number of subjects according to age.

2. Echocardiography and coronary measurements

The standard method of measuring the diameter of coronary arteries in a pediatric population was applied according to the recommendation by the American Society of Echocardiography[18]. The intraluminal diameter of the coronary artery segments was measured from the inner to inner edges. The left main coronary artery (LMCA) was measured midway between the ostium and the bifurcation of the circumflex artery and the left anterior descending coronary artery (LAD) in the parasternal short-axis view. The LAD was measured distally to the bifurcation and before the start of the first marginal branch. A measurement for the right coronary artery (RCA) was obtained in the relatively straight section, just after the initial rightward turn from the anterior-facing sinus of the Valsalva. In a case with a visible origination of the conal branch, the RCA segment distal to the conal branch was measured (Fig. 2). The offline measurement of coronary artery diameters was performed by one author (JJY). The reproducibility of coronary artery diameter measurements has already been reported in another study which was performed by same echocardiographers[19] (an intraobserver variability in the measurement of the LMCA, LAD, and RCA as 5.4%, 8.7%, and 5.1%, respectively, and the interobserver variability as 5.8 %, 10.4%, and 7.0%, respectively).

3. Statistical analysis

The diameters of each coronary artery were measured and converted to the *z* score using the previously reported regression equations or spreadsheet file for calculation[12-15]. The results of the *z* score of coronary artery diameter were analyzed using the Kolmogorov-Smirnov test on a normal distribution and using the 1-sample *t* test on a convergence of the average value to zero. Statistical analysis

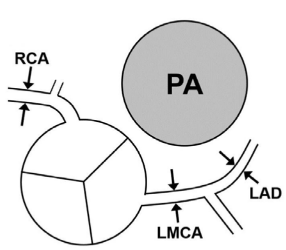

Fig. 2. Schematic representation of the locations used for coronary artery diameter measurement. RCA, right coronary artery; LMCA, left main coronary artery; LAD, Left anterior descending coronary artery; PA, pulmonary artery.

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was performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). Statistical significance was defined as $P<0.05$.

Results

One hundred eighty-one children were included in the study, 47% of whom were male (Table 1). The age of subjects was median 2.34 years (range, 1 month to 15 years; Fig. 1). The weight of the subjects was median 12.6 kg (range, 2.9–73.9 kg) and the height was median 89.0 cm (range, 48.7–176.6 cm). The body surface area was median 0.559 cm^2 (range, 0.201–1.909 cm^2). The median diameter of LMCA, LAD, and RCA was 2.13 mm (range, 1.35–4.01 mm), 1.65 mm (range, 1.10–3.26 mm), and 1.60 mm (range, 0.82–3.65 mm), respectively (Table 1).

Table 1. Demographic characteristics and the diameter of coronary arteries in 181 subjects

Characteristic	Value
Age (yr)	2.36 (0.03–15.0)
Male sex	85 (47)
Body weight (kg)	12.7 (2.9–74.0)
Height (cm)	89.3 (48.7–176.6)
Body surface area (m^2)	0.56 (0.20–1.91)
LMCA (mm)	2.13 (1.35–4.01)
LAD (mm)	1.65 (1.10–3.26)
RCA (mm)	1.60 (0.82–3.65)

Values are presented as median (range) or number (%).
LMCA, left main coronary artery; LAD, left anterior descending coronary artery; RCA, right coronary artery.

Table 2. Descriptive statistical characteristics of the *z* scores of coronary artery diameter in four models and results of the Kolmogorov-Smirnov test to determine the normal distribution of *z* score values

Coronary artery	Model	Mean±SD	Skewness	Kurtosis	*P* value*
LMCA	McCrindle	-0.41±0.918	1.046	2.315	0.252
	Olivieri	-0.15±0.961	0.404	0.923	0.861
	Dallaire	0.279±1.022	1.113	2.740	0.067
	Japanese	0.4±1.08	0.796	1.839	0.319
LAD	McCrindle	-0.652±0.906	0.120	-0.072	0.995
	Olivieri	-0.387±0.809	-0.252	0.026	0.808
	Dallaire	0.236±0.72	-0.003	-0.063	0.990
	Japanese	-0.034±0.839	-0.191	0.017	0.959
RCA	McCrindle	-0.653±0.898	0.423	0.231	0.725
	Olivieri	-0.894±0.95	-0.040	0.048	0.724
	Dallaire	-0.504±0.803	0.269	-0.043	0.732
	Japanese	-0.509±1.011	-0.014	-0.153	0.854

LMCA, left main coronary artery; LAD, left anterior descending coronary artery; RCA, right coronary artery; SD, standard deviation.
*Results of Kolmogorov-Smirnov test.

1. The descriptive statistical properties of *z* score value

By definition, the *z* score values must be normally distributed and the mean value should converge to zero, the standard deviation to 1, the skewness to zero, and the kurtosis to zero. The descriptive statistical characteristics of the *z* score value is presented in Table 2 and plotted as a histogram in Figs. 3-5. The mean value of the *z* score of the RCA was less than zero in all 4 models. The values of skewness and kurtosis of the LMCA were above zero in all models. The *P* value on the Kolmogorov-Smirnov test for the *z* score value was ≥0.050 in three coronary arteries in all four models, which suggests the statistical feasibility of normal distribution. One sample *t* test showed that the mean z score value was significantly different from zero (Table 3); the only exception was a *z* score of the LAD in the Japanese model ($P=0.582$).

2. The proportion of *z* scores with extreme value

The percentage of subjects with a *z* score of the LMCA ≥2.0 in the Dallaire and Japanese models appears higher (4.9% and 7.1%, respectively) than 2.3% which is the proportion of the *z* score ≥2.0 in standard normal distribution (Table 4). Moreover, the percentage of

Table 3. Results of one-sample *t* test for convergence of mean *z* scores of coronary artery diameters to zero in 4 models

Coronary artery	Model	Mean difference	95% CI	*P* value*
LMCA	McCrindle	-0.410	-0.545 to -0.274	0.000
	Olivieri	-0.150	-0.292 to -0.008	0.038
	Dallaire	0.279	0.128 to 0.430	0.000
	Japanese	0.400	0.240 to 0.559	0.000
LAD	McCrindle	-0.652	-0.785 to -0.519	0.000
	Olivieri	-0.387	-0.506 to -0.268	0.000
	Dallaire	0.236	0.131 to 0.342	0.000
	Japanese	-0.034	-0.157 to 0.088	0.582
RCA	McCrindle	-0.653	-0.785 to -0.521	0.000
	Olivieri	-0.894	-1.034 to -0.754	0.000
	Dallaire	-0.504	-0.622 to -0.386	0.000
	Japanese	-0.509	-0.658 to -0.361	0.000

LMCA, left main coronary artery; LAD, left anterior descending coronary artery; RCA, right coronary artery; CI, confidence interval.

Table 4. Number of *z* scores with extreme values for each coronary artery (n=181)

Coronary artery	*z* score	McCrindle	Olivieri	Dallaire	Japanese
LMCA	≥2.0	4 (2.2)	4 (2.2)	9 (4.9)	13 (7.1)
	≥2.5	3 (1.6)	3 (1.6)	6 (3.3)	7 (3.8)
LAD	≥2.0	0 (0)	0 (0)	0 (0)	0 (0)
RCA	≥2.0	2 (1.1)	0 (0)	0 (0)	1 (0.5)
	≥2.5	0 (0)	0 (0)	0 (0)	0 (0)

Values are presented as number (%).
LMCA, left main coronary artery; LAD, left anterior descending coronary artery; RCA, right coronary artery.

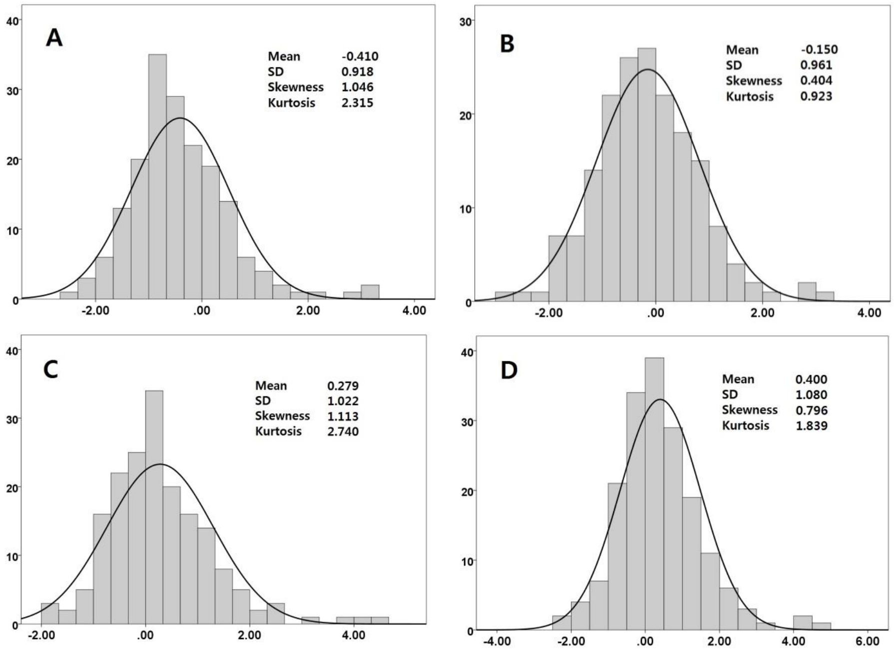

Fig. 3. Histograms for left main coronary artery *z* scores. (A) McCrindle model, (B) Olivieri model, (C) Dallaire model, and (D) Japanese model. SD, standard deviation.

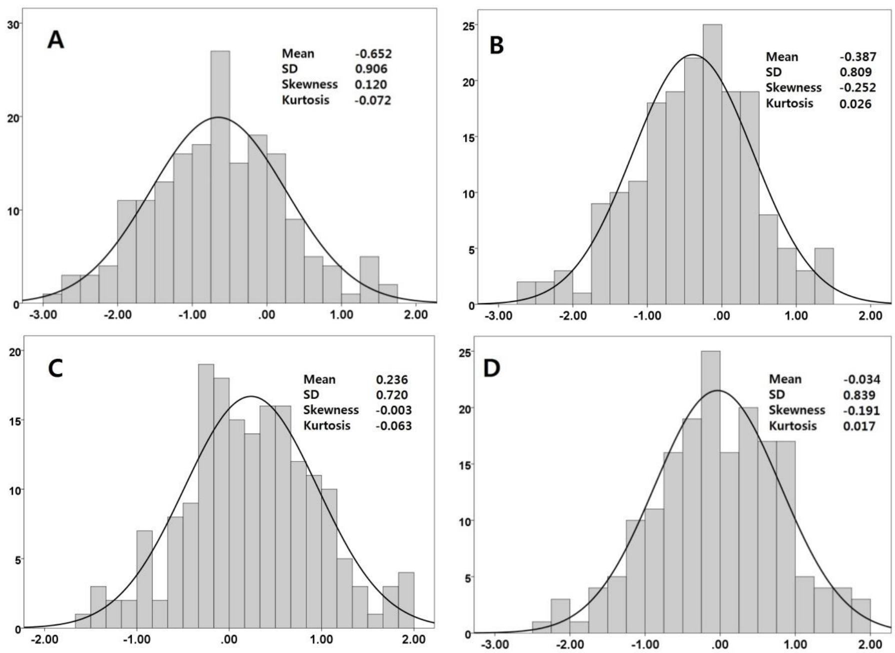

Fig. 4. Histograms for left anterior descending coronary artery *z* scores. (A) McCrindle model, (B) Olivieri model, (C) Dallaire model, and (D) Japanese model. SD, standard deviation.

the *z* score of the LMCA ≥2.5 also appears higher (3.3% and 3.8%, respectively) than 0.6% which is the proportion of the *z* score ≥2.5 in standard normal distribution in those 2 models. The extremely high *z* score of the LMCA seems to be more frequent in the Dallaire and Japanese models than in the other 2 models.

Discussion

In this study, the descriptive statistical analyses of coronary artery diameter *z* scores in 181 normal children were performed using four frequently used *z* score models (Table 5)[12-15]. As all models are designed to represent a normal population, we expected that the

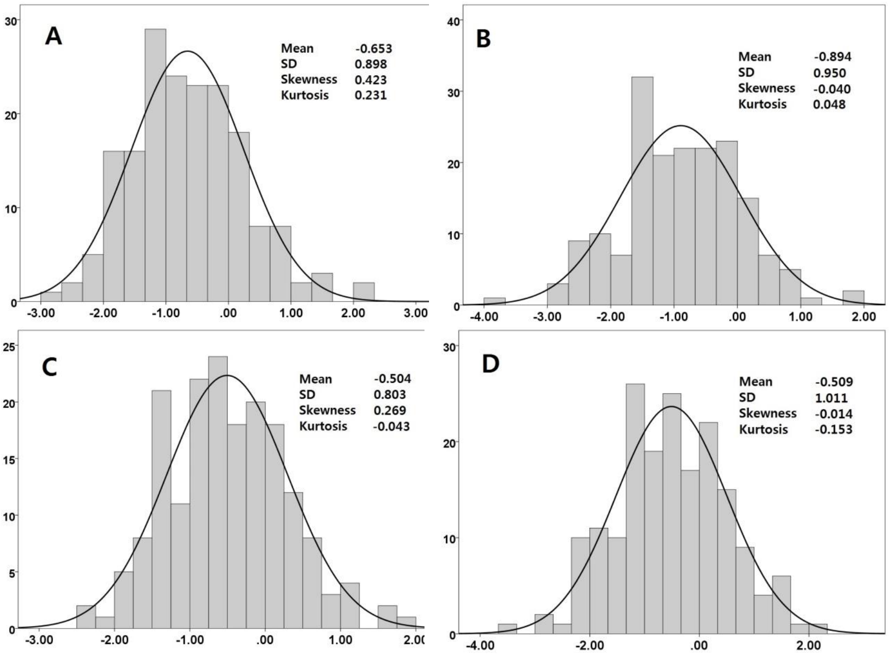

Fig. 5. Histograms for right coronary artery *z* scores. (A) McCrindle model, (B) Olivieri model, (C) Dallaire model, and (D) Japanese model.

Table 5. Comparison of four *z* score models in children

Variable	McCrindle	Olivieri	Dallaire	Japanese
Location	Boston, USA	Washington, USA	Quebec, Canada	Japan
Study period (yr)	1987–2000	2007	2001–2008	2010–2011
Age (yr)	0–18	0–20	-	0–18
No. of participants	221	432	1,033	3,851
Statistical model	Nonlinear regression	Nonlinear regression	Nonlinear regression	Lambda-Mu-Sigma model
	Exponential model with BSA	Exponential model with BSA	Square root model with BSA	

The range of participants' ages in the Dallaire model is not specified in the reference article.
BSA, body surface area.

calculated *z* scores for healthy children would also follow a normal distribution. The Kolmogorov-Smirnov test showed $P\geq0.050$ in three coronary arteries in all 4 models, implying the statistical feasibility of normal distribution. Therefore, it was consequently estimated that the four *z* score models would be distributed normally, which justifies the application of these models to Korean pediatric populations.

We additionally expected that the mean value of the *z* score should converge to zero since the subjects were normal healthy children. However, the mean *z* score value of the 3 coronary arteries was significantly different from zero in each of the four models, except for one of the LADs in the Japanese model. The limited number of subjects in this study could be one of causes. Another explanation for this difference could be the subtle differences in the measuring points. In this study, the mean *z* score of the RCA was consistently less than zero in all models, which implies that the measured RCA diameters were smaller than the reference values of the *z* score models. It is reported in the *z* score model reference papers that the RCA measurements were obtained 2–5 mm distal to its origin in the parasternal short-axis view[13-15]. In this study, the RCA segment distal to the conal branch was measured in a case with a visible origination of the conal branch to avoid an exaggerated measurement on the branching point. In addition, the measurement point was more distal to 5 mm from the origin of the RCA in some of such cases. As a result, the RCA diameters in this study would have been smaller accordingly. We think that more precise instructions are needed for an accurate and reproducible measurement of the RCA proximal diameter on the issue of the conal branch.

Among the four *z* score models, the Dallaire and Japanese models were more favorably recommended for use in recent American Heart Association guidelines because they included a relatively larger number of subjects and provide normative data on the left circumflex branch[2]. Incidentally, the percentage of subjects with an extreme *z* score of the LMCA appears to be higher in the Dallaire and Japanese models in this study than the expected level under normal distribution. This higher percentage could be due to anatomic variation in several cases, which can be seen in the histograms for the LMCA (Fig. 3). The positive skewness and kurtosis in the distribution of the LMCA *z* score would not impact on the higher percentage of subjects with extreme *z* scores of the LMCA. It is well known that anatomic variations are frequent in the LMCA[2]. Additionally, caution in the interpretation of the LMCA *z* score was also recommended in recent guideline[2]. For the other branches of coronary arteries, all four *z* score models could reasonably be used for the evaluation of vascular dilatation.

The relatively small number of subjects is a limitation of this study.

In conclusion, all 4 models showed statistical feasibility of normal distribution. More precise instructions are needed for RCA measurement. A higher percentage of extreme *z* scores of the LMCA is compatible with a commonsense understanding of anatomic variations of the LMCA.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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