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Newly Developed Sex-Specific Z Score Model for Coronary Artery Diameter in a Pediatric Population

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ABSTRACT

Background: This study aimed to generate a Z score calculation model for coronary artery diameter of normal children and adolescents to be adopted as the standard calculation method with consensus in clinical practice.
Methods: This study was a retrospective, multicenter study that collected data from multiple institutions across South Korea. Data were analyzed to determine the model that best fit the relationship between the diameter of coronary arteries and independent demographic parameters. Linear, power, logarithmic, exponential, and square root polynomial models were tested for best fit.
Results: Data of 2,030 subjects were collected from 16 institutions. Separate calculation models for each sex were developed because the impact of demographic variables on the diameter of coronary arteries differs according to sex. The final model was the polynomial formula with an exponential relationship between the diameter of coronary arteries and body surface area using the DuBois formula.
Conclusion: A new coronary artery diameter Z score model was developed and is anticipated to be applicable in clinical practice. The new model will help establish a consensus-based Z score model.

Keywords: Coronary Artery; Children; Kawasaki Disease; Z Score

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INTRODUCTION

The size of coronary arteries in the early phases of Kawasaki disease is the most important prognostic factor for future outcomes and determining management policies.[1-4] The definition of coronary artery aneurysm, a major complication of Kawasaki disease, was originally defined according to the criteria established by the Japanese Ministry of Health in 1984[5] and is still widely used today. However, after de Zorzi et al.[6] proposed the classification of coronary artery aneurysms based on Z scores in 1998, the use of the Z score has become prevalent in defining and categorizing the severity of coronary artery aneurysms. In recently published clinical guidelines on Kawasaki disease in the United States and Japan, the use of Z score is recommended for assessing the severity of coronary artery complications and providing prognostic counseling.[7,8]

There are currently five commonly used models for calculating the Z score of coronary artery diameter,[9-13] however, the most clinically useful has not been determined. Hence, no single method has been established as the preferred choice in clinical practice. The possibility for confusion in the diagnosis and classification of coronary artery aneurysms is also inevitable depending on the method used.[14,15] In Korea, there were studies on the normal range of coronary artery diameter,[16,17] but the limited number of subjects has hindered the utilization of their results in clinical practice.

The purpose of this study was to generate a Z score calculation model for coronary artery diameter in Kawasaki disease that could be adopted as the standard calculation method in Korean clinical practice. The study began with the gathering of coronary artery diameter data from multiple domestic institutions to create a large sample size.

METHODS

Study design and population

This study was a retrospective, multicenter study that collected coronary artery diameter measurement data of normal children and adolescents from various medical institutions across South Korea. Subjects included in the study were children and adolescents under the age of 18 who did not have extensive cardiovascular problems and who possessed clear echocardiographic images for precise measurement of the diameter of coronary arteries. The eligible subjects underwent echocardiographic examinations to assess cardiac murmurs, non-specific chest pain, palpitations, or abnormalities in cardiac shape on chest radiography. Individuals with clinically significant congenital or acquired cardiovascular issues were excluded from the study. Additionally, those with conditions such as fever of unknown origin, malignancies, hypertension, renal insufficiency, obesity, and those with a history of Kawasaki disease, treatment for malignancy, or prematurity were also excluded. Finally, subjects with musculoskeletal disorders, genetic abnormalities, or metabolic disorders or a family history of them were excluded. Subjects with trivial valvar regurgitation, patent oval foramen, and hemodynamically insignificant minor anomalies like aberrant subclavian artery, brachiocephalic artery, and right aortic arch were included. The responsible researcher (Yu JJ) collected anonymized demographic variables and measurements of the diameter of coronary arteries from participating institutions.

To evaluate the usefulness of the newly developed Z score calculation model, data on patients with Kawasaki disease in Asan Medical Center with more than 2 years of follow-up who had coronary artery stenosis with positive stress imaging or major adverse cardiovascular events (including death), were additionally collected.

Echocardiographic examination

The guidelines for echocardiography and the measurement of coronary artery diameter were as follows: 1) The use of sedation can be considered based on the age of the subjects. 2) During the examination, the default position is the left decubitus position, but the supine or right decubitus may be employed as needed. 3) When examining the coronary arteries, utilize the parasternal window and employ an ultrasound probe with a frequency of ≥ 5 MHz. 4) When setting up the diameter measurement screen, lower the 2-dimensional gain and dynamic range appropriately. 5) The measurer should enhance temporal resolution using the zoom function and measure the diameter in a segmental area where the shape of the vessel becomes stabilized, typically 2–3 mm beyond the origin site. Hence, for the left main coronary artery (LMCA), measurement of diameter was taken at the mid portion, and for the other three major coronary arteries, diameter was measured at the proximal segment. The participants who provided the data were all experienced pediatric cardiologists and confirmed their measurements to adhere to the guidelines outlined above. Each participant randomly selected 15 subjects and conducted re-measurements after an interval of 1 week or more. These additional data sets were utilized for intra-observer reproducibility.

Statistical analyses

All continuous variables are described as the mean ± standard deviation (SD). The frequency of sex is described as a percentage.

To explore the sex differences, comparisons between sexes were performed using Student's *t*-test. The interaction effect between sex and demographic variables in the linear regression model was also evaluated.

A one-sample *t*-test was performed to determine whether the Z scores for coronary artery diameter obtained using the previously published five models[9-13] converged to a mean of zero. Body surface area (BSA) was separately calculated using the Haycock and DuBois methods.[18,19] Data were analyzed to determine the model that best fit the relationship between the diameter of coronary arteries and independent demographic parameters. Linear, power, logarithmic, exponential, and square root polynomial models were tested for best fit. Adjusted R^2, Akaike information criterion (AIC), and Bayesian information criterion (BIC) values were used to determine the model that best fit the data. That is, the model with the lowest AIC and BIC values and the highest adjusted R^2.

All statistical analyses were performed using SPSS version 21 (IBM Co., Armonk, NY, USA). *P* values of < 0.05 were considered to indicate statistical significance in two-sided tests.

Ethics statement

This study was reviewed and approved by the Institutional Review Board of Asan Medical Center (2019-1511), with the requirement for informed consent waived.

RESULTS

Collection and characteristics of data

Data of 2,030 subjects were collected from 16 institutions across Korea (**Table 1**). The age distribution of the subjects differed across all age groups (**Fig. 1**). The number of subjects aged < 2 years was 634 (31.2%). Demographic data were complete for all subjects. However, some cases had missing coronary artery diameter measurements: the number of measured values was 2,017 in LMCA, 1,810 in the left anterior descending coronary artery (LAD), 1,661 in the left circumflex coronary artery (LCx), and 2,012 in the right coronary artery (RCA). In the intra-observer reproducibility test on the measurement of diameter conducted at each institution, the intra-class correlation coefficient was mean 0.971 ± 0.027 in the LMCA, 0.934 ± 0.074 in the LAD, 0.893 ± 0.161 in the LCx, and 0.960 ± 0.038 in the RCA.

The results of the calculated Z scores using five previously published calculation models[9-13] for the collected data on coronary artery diameter are presented in **Table 2**. Most Z scores did not converge to the average of zero, except that of RCA in the McCrindle ($P = 0.141$) and Lopez

Table 1. Demographics and diameter of coronary arteries

Variables	Total	Male (n = 1,105)	Female (n = 925)	*P* value
Age, yr	5.84 ± 5.01	6.03 ± 5.14	5.61 ± 4.85	0.065
Height, cm	109.1 ± 34.6	111.8 ± 36.4	107.4 ± 32.6	0.004
Body weight, kg	24.0 ± 18.4	26.1 ± 20.3	22.2 ± 16.1	< 0.001
Haycock BSA, m^2	0.84 ± 0.45	0.88 ± 0.48	0.80 ± 0.40	< 0.001
DuBois BSA, m^2	0.84 ± 0.45	0.87 ± 0.49	0.79 ± 0.41	< 0.001
LMCA, mm	2.50 ± 0.62	2.59 ± 0.70	2.42 ± 0.64	< 0.001
LAD, mm	2.03 ± 0.57	2.11 ± 0.58	1.97 ± 0.56	< 0.001
LCx, mm	1.79 ± 0.55	1.85 ± 0.56	1.75 ± 0.54	< 0.001
RCA, mm	2.07 ± 0.62	2.16 ± 0.65	1.99 ± 0.57	< 0.001

Values are mean ± standard deviation.
BSA = body surface area, LMCA = left main coronary artery, LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery.

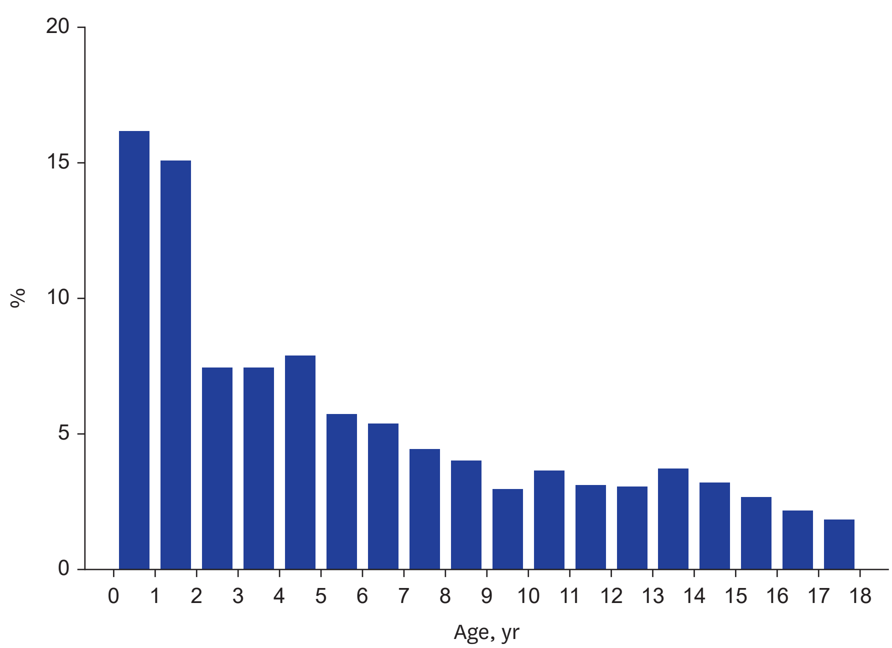

Fig. 1. Distribution of frequencies according to age of patients.

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Table 2. Calculations of Z score based on previously presented formulae and the results of one-sample *t*-test. And the number of data with Z score ≥ 2.0 in each coronary artery

Variables	McCrindle et al.[9]			Olivieri et al.[10]			Dallaire et al.[11]			Kobayashi et al.[12]			Lopez et al.[13]		
	Z score	*P* value	No. (%)	Z score	*P* value	No. (%)	Z score	*P* value	No. (%)	Z score	*P* value	No. (%)	Z score	*P* value	No. (%)
LMCA	−0.21 ± 0.85	< 0.001	27 (1.34)	0.08 ± 0.94	< 0.001	33 (1.64)	0.30 ± 0.96	< 0.001	79 (3.92)	0.48 ± 1.02	< 0.001	112 (5.55)	−0.24 ± 0.74	< 0.001	13 (0.64)
LAD	−0.25 ± 1.04	< 0.001	27 (1.49)	−0.04 ± 0.92	0.047	12 (0.66)	0.41 ± 0.88	< 0.001	48 (2.65)	0.20 ± 0.97	< 0.001	40 (2.21)	1.02 ± 1.06	< 0.001	303 (16.74)
LCx							−0.09 ± 0.89	< 0.001	8 (0.48)	0.07 ± 1.01	0.003	37 (2.23)			
RCA	−0.03 ± 0.88	0.141	32 (1.59)	−0.19 ± 0.86	< 0.001	4 (0.20)	−0.10 ± 0.82	< 0.001	13 (0.65)	0.07 ± 0.94	0.001	30 (1.49)	−0.01 ± 0.68	0.477	10 (0.50)

Values are mean ± standard deviation, or number of frequency with percentage.
LMCA = left main coronary artery, LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery.

Table 3. *P* values for interaction effect between sex and other parameters in the linear regression model

Variables	Age	Height	Weight	BSA Haycock	BSA DuBois
LMCA	0.0329	0.9398	0.0005	0.0305	0.0398
LAD	0.4149	0.5566	< 0.0001	0.0070	0.0100
LCx	0.2409	0.8766	0.0162	0.1319	0.1517
RCA	0.0026	0.2622	0.0546	0.4889	0.4944

BSA = body surface area, LMCA = left main coronary artery, LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery.

models ($P = 0.477$). The Lopez model calculated a high mean Z score value of 1.02 for the LAD ($P < 0.001$) and Z score value ≥ 2.0 in 16.74% of subjects. The mean Z score calculated through the Kobayashi model was significantly greater than zero for all 4 coronary arteries ($P < 0.001$ in LMCA and LAD, $P = 0.003$ in LCx, and $P = 0.001$ in RCA).

Among all subjects, 1,105 (54.4%) were male. During the sex comparison, values in males were significantly larger than in females for demographic variables other than age ($P = 0.065$) and diameter of coronary arteries. The interaction effect between sex and demographic variables (except height) showed statistical significance in ≥ 2 coronary arteries (**Table 3**). The significance of this interaction effect indicates that the impact of demographic variables on the diameter of coronary arteries varies according to sex. Therefore, it was deemed appropriate to construct separate calculation models for each sex.

Developing the model

Linear, power, logarithmic, exponential, and square root polynomial models were fitted to the diameter of the coronary arteries. Parameters in the models and statistical results for model fit are presented in **Supplementary Tables 1-4**. Across all four coronary arteries, the highest adjusted R^2 value was observed among the models with an exponential relationship. From the perspective of the parameters used, the exponential model utilizing BSA through the DuBois method exhibited the highest adjusted R^2 value in the LAD ($R^2 = 0.6771$ in males, $R^2 = 0.6234$ in females), RCA ($R^2 = 0.7245$ in males, $R^2 = 0.7000$ in females), and LCx ($R^2 = 0.5213$ in females). In the LMCA ($R^2 = 0.7147$ in males, $R^2 = 0.6936$ in females) and LCx of males ($R^2 = 0.5546$), the adjusted R^2 of the exponential model utilizing BSA through the DuBois method was similar to the adjusted R^2 of the best-fit model with other parameters–height in the LMCA ($R^2 = 0.7206$ in males, $R^2 = 0.6938$ in females) and BSA through the Haycock method in the LCx of males ($R^2 = 0.5552$). The lowest value of AIC and BIC also exhibited a pattern identical to that of the highest adjusted R^2 value described above.

The final model was the polynomial formula with an exponential relationship between the diameter of coronary arteries and BSA through the DuBois method (**Table 4**, **Fig. 2**).

$$\text{Z} - \text{score} = \frac{\ln(M) - \alpha - \beta 1 \cdot \ln(BSA)}{\sqrt{MSE}}$$

(ln, log natural; M, measured value [mm]; BSA, body surface area by DuBois method [m^2]).

Validation of the usefulness of the new model

Among patients with Kawasaki disease followed for more than 2 years at Asan Medical Center, data from 16 patients with coronary artery stenosis and positive stress imaging, in addition to two patients (17, 18 in **Table 5**) who died suddenly, were additionally investigated. These 18 additional patients were consecutive patients who met the above inclusion criteria

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Table 4. Final model using exponential formula

Variables	Male			Female		
	a	β_1	MSE	a	β_1	MSE
LMCA	1.0372	0.4169	0.0227	1.0096	0.4347	0.0231
LAD	0.8134	0.4226	0.0240	0.7868	0.4567	0.0302
LCx	0.6663	0.4179	0.0401	0.6495	0.4420	0.0436
RCA	0.8556	0.4569	0.0259	0.8179	0.4664	0.0258

a, intercept in **Supplementary Tables 1-4**; β_1, β_1 in **Supplementary Tables 1-4**.
MSE = mean squared error, LMCA = left main coronary artery, LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery.

among all patients who had been followed at Asan Medical Center since 1989. Two patients (7, 15 in **Table 5**) were managed at another hospital before the chronic phase and their demographic data at the time of echocardiography were unknown. The largest coronary artery diameter in the echocardiography performed in the subacute or convalescent phase was calculated according to the new model, and the Z score was ≥ 5.0 across all 18 patients. According to the American Heart Association (AHA) guidelines,[7] five were classified as having a medium-sized aneurysm and the others as having a giant aneurysm.

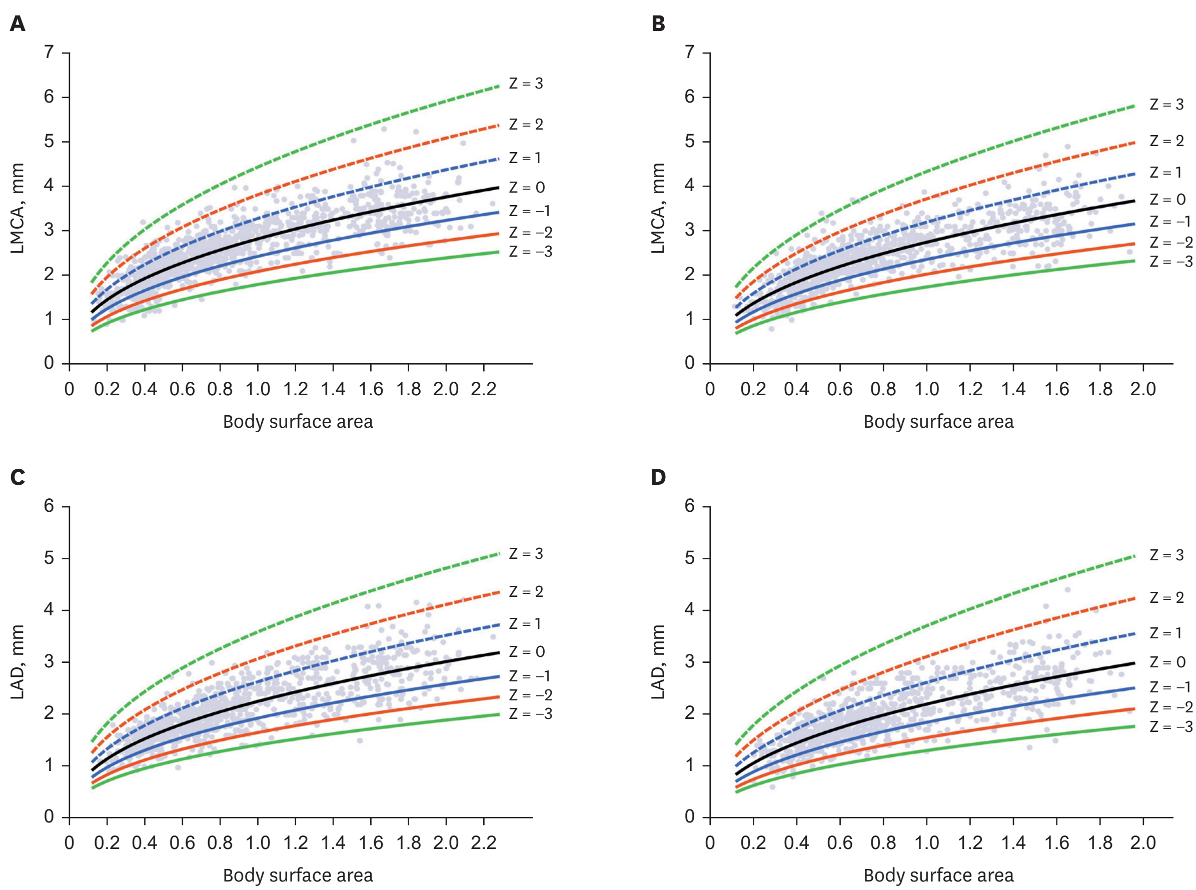

Fig. 2. Scatter plot of measured value and sex-specific Z score boundaries based on the new model for the diameter of coronary arteries against BSA. LMCA: (**A**) males, (**B**) females; LAD: (**C**) males, (**D**) females; LCx: (**E**) males, (**F**) females; and RCA: (**G**) males, (**H**) females.
BSA = body surface area, LMCA = left main coronary artery, LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery.

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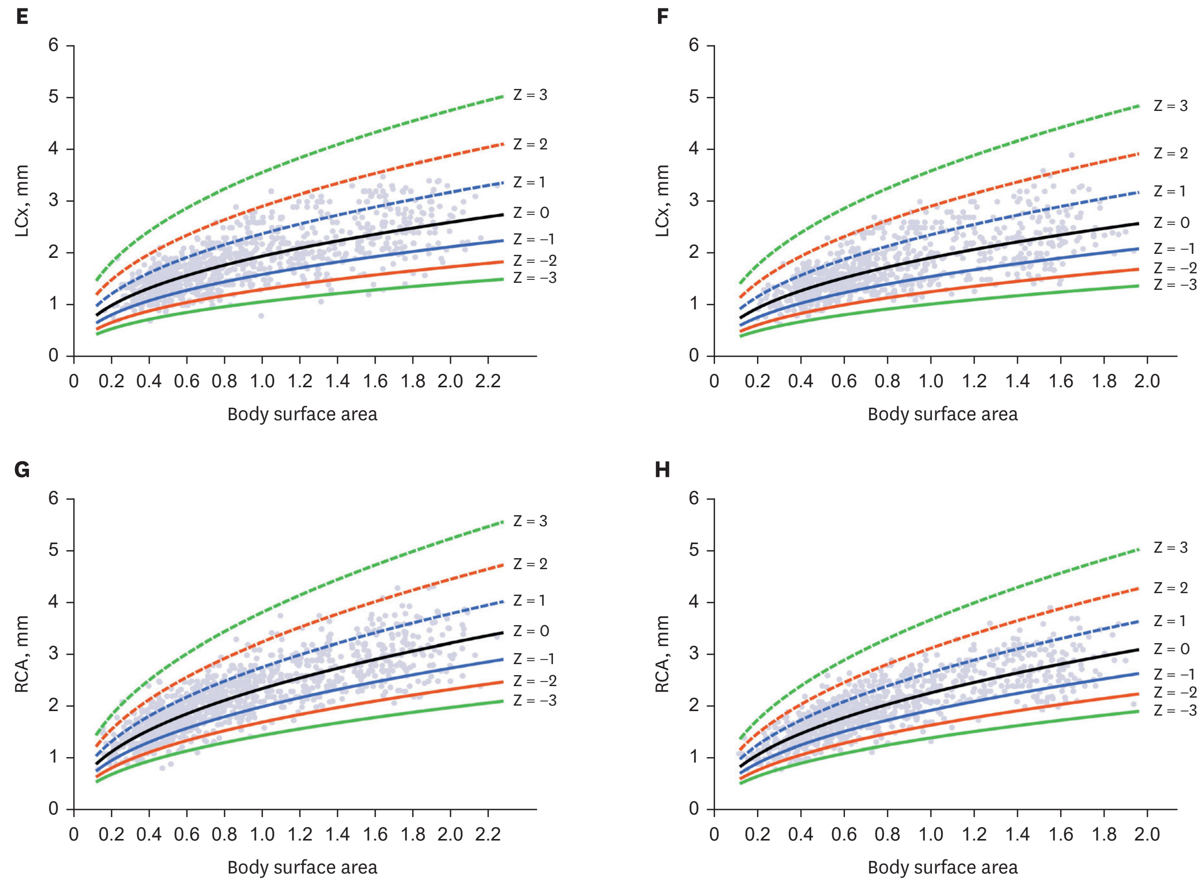

Fig. 2. (Continued) Scatter plot of measured value and sex-specific Z score boundaries based on the new model for the diameter of coronary arteries against BSA. LMCA: (**A**) males, (**B**) females; LAD: (**C**) males, (**D**) females; LCx: (**E**) males, (**F**) females; and RCA: (**G**) males, (**H**) females.
BSA = body surface area, LMCA = left main coronary artery, LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery.

Table 5. Classification of coronary artery aneurysm by Z score of maximum diameter of coronary artery measured during subacute or convalescent phase by a new model in 18 patients in whom significant stenosis of coronary artery developed or sudden death occurred during long-term follow-up

Number	Sex	Age at onset, yr	BSA, m^2	Coronary artery	Diameter, mm	Z score	Classification of aneurysm
1	M	7.26	0.949	RCA	9.0	8.49	Giant
2	M	0.25	0.416	RCA	8.5	10.47	Giant
3	M	1.98	0.651	LAD	5.0	6.31	Medium
4	M	4.69	0.725	LAD	5.3	6.39	Medium
5	M	3.45	0.820	RCA	8.8	8.76	Giant
6	M	9.28	1.001	LAD	7.6	7.84	Medium
7	M	0.21	?	RCA	12.5		Giant
8	M	3.46	0.678	RCA	7.4	8.22	Medium
9	M	4.75	0.834	RCA	14.0	11.60	Giant
10	M	4.17	0.709	RCA	7.3	8.01	Medium
11	M	4.97	1.124	RCA	8.0	7.27	Giant
12	M	4.13	0.685	RCA	15.0	12.58	Giant
13	M	0.68	0.716	RCA	9.0	9.28	Giant
14	M	2.25	0.588	RCA	12.5	11.88	Giant
15	F	0.83	?	LAD	10.0		Giant
16	M	2.53	0.711	RCA	12.0	11.12	Giant
17	M	3.29	0.606	RCA	17.0	13.71	Giant
18	M	0.70	0.440	LAD	8.9	11.10	Giant

BSA = body surface area, M = male, F = female, RCA = right coronary artery, LAD = left coronary artery.

DISCUSSION

This study developed a new model for calculating Z scores for coronary artery diameter. The new model calculates the Z score of ≥ 5.0 in patients with substantial coronary artery complications requiring long-term observation and is expected to be valuable in clinical practice. In addition, separate models were constructed according to sex owing to significant interaction, contrary to the expectations at the beginning of the study.

Following de Zorzi's report, introducing the Z score instead of the absolute value of coronary artery diameter in patients with Kawasaki disease allows for greater sensitivity in the detection of coronary artery abnormalities.[6] Although several disadvantages in the use of Z score have been highlighted—the lack of established normal values for all locations of coronary arteries, the impracticality of memorizing the calculation formula in a practice setting, and the potential for amplifying measurement errors during the calculation process, the advantage of incorporating body size appears to be receiving more attention. There have been recent reports on the utility of using Z score in long-term prognosis prediction.[2,4] Among reports from Japan on long-term prognosis prediction, there have been reports that include additional predictive factor reflecting the small body size of infants, in addition to the Japanese Ministry of Health criteria.[20,21]

However, the question of which calculation model to select for computing the Z score of measured coronary artery diameter remains a problem in clinical practice. As multiple calculation models are being used interchangeably, it is inevitable that there should be numerous non-consistent Z score results. Furthermore, it has been reported that such discrepancies become more pronounced, particularly with severe coronary artery dilatation.[15,22] In Korea, five previously published Z score models[9-13] and the Japanese Ministry of Health criteria[5] have been widely used to assess coronary artery complications, according to individual preferences. Korean society places a high level of awareness on Kawasaki disease, and it is common for the same patient to visit multiple medical institutions. As a result, differences in Z score values according to the model used have created confusion in patient consultations on outcomes and insurance benefits.

In the 2017 AHA guidelines,[7] the calculation models proposed by Dallaire et al.[11] and Kobayashi et al.[12] were recommended given they had been investigated in a relatively large number of subjects and provided a reference value for LCx. However, in another study conducted on normal children, it was noted that the proportion of cases with Z score calculated according to the two above models ≥ 2.0 was 4.9% and 7.1%, respectively.[23] The values in the results of this study were 3.92% and 5.55% (**Table 2**), which still looks higher than the expected percentage of 2.28% for normal subjects in a normal distribution. In this study, data from 2,030 subjects were collected from 16 nationwide institutions, which is deemed to represent normal values within the pediatric age group in Korea. Z score calculations using previously published models for the subjects were not centered around an average of zero (**Table 2**) serves as evidence for the need for a new calculation model.

We suspected that the most recently published Lopez model[13] was calculating high value of Z score for LAD, which we consistently confirmed when applying the existing models to the study subjects (**Table 2**). The Kobayashi model has been frequently used in Korea due to its similar racial background of subjects. Considering the application of the existing models to the study subjects (**Table 2**), our newly developed model is expected to yield Z score results somewhat lower than the Kobayashi model, owing to the required mean of 0.0 and SD of 1.0 across subjects. Therefore, it is expected that the newly developed model may have higher specificity in the diagnosis of coronary artery lesions compared to the Kobayashi model.

This study was initiated with the motivation to develop a coronary artery Z score calculation model that could be used with consensus in Korea. However, the lack of such consensus and the resulting confusion are presumed to be applicable in countries other than Korea as well. We anticipate that the result of this study could provide meaningful support in the selection of coronary artery diameter Z score calculation model.

The limitations of this study are in the nature of its design. Since conducting an inter-observer reproducibility assessment for measurement data from multiple institutions was not feasible, we proceeded by collecting the measured data. The intra-observer reproducibility results for each institution appeared satisfactory; however, the reproducibility of LCx was lower compared with other coronary arteries.

The non-uniform distribution of frequencies across age groups of all subjects is a limitation of the retrospective design, in addition to the missing values of coronary artery diameter in some subjects.

Validation of the newly developed model was conducted in 18 patients with significant complications associated with the coronary arteries; however, further evaluation of its validity with a larger patient population in the future is warranted.

In this study, a new coronary artery diameter Z score model was developed and is anticipated to be applicable in clinical practice. In addition, the new model will contribute to the establishment of a consensus-based Z score model.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Regression results for the left main coronary artery (N = 2,017)

Supplementary Table 2
Regression results for the left anterior descending coronary artery (N = 1,810)

Supplementary Table 3
Regression results for the left circumflex coronary artery (N = 1,661)

Supplementary Table 4
Regression results for the right coronary artery (N = 2,012)

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