A New *Z*-Score Curve of the Coronary Arterial Internal Diameter Using the Lambda-Mu-Sigma Method in a Pediatric Population

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Background: Several coronary artery *Z*-score models have been developed. However, a *Z*-score model derived by the lambda-mu-sigma (LMS) method has not been established.

Methods: Echocardiographic measurements of the proximal right coronary artery, left main coronary artery, proximal left anterior descending coronary artery, and proximal left circumflex artery were prospectively collected in 3,851 healthy children ≤18 years of age and divided into developmental and validation data sets. In the developmental data set, smooth curves were fitted for each coronary artery using linear, logarithmic, square-root, and LMS methods for both sexes. The relative goodness of fit of these models was compared using the Bayesian information criterion. The best-fitting model was tested for reproducibility using the validation data set. The goodness of fit of the selected model was visually compared with that of the previously reported regression models using a Q-Q plot.

Results: Because the internal diameter of each coronary artery was not similar between sexes, sex-specific *Z*-score models were developed. The LMS model with body surface area as the independent variable showed the best goodness of fit; therefore, the internal diameter of each coronary artery was transformed into a sex-specific *Z*-score on the basis of body surface area using the LMS method. In the validation data set, a Q-Q plot of each model indicated that the distribution of *Z*-scores in the LMS models was closer to the normal distribution compared with previously reported regression models. Finally, the final models for each coronary artery in both sexes were developed using the developmental and validation data sets. A Microsoft Excel–based *Z*-score calculator was also created, which is freely available online (http://raise.umin.jp/zsp/calculator/).

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Abbreviations

BIC = Bayesian information criterion

BSA = Body surface area

CAA = Coronary artery abnormality

e.d.f. = Equivalence of degrees of freedom

KD = Kawasaki disease

LAD = Proximal left anterior descending coronary artery

LCX = Proximal left circumflex coronary artery

LMCA = Proximal left main coronary artery

LMS = Lambda-mu-sigma

RCA = Proximal right coronary artery

Conclusions: Novel LMS models with which to estimate the sex-specific *Z*-score of each internal coronary artery diameter were generated and validated using a large pediatric population. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: *Z*-score, Lambda-mu-sigma method, Pediatric, Coronary artery abnormality, Kawasaki disease

Kawasaki disease (KD)[1] is a childhood systemic vasculitis syndrome that mainly affects the coronary arteries. Although recent progress in the treatment of KD has decreased the incidence of echocardiographically detectable coronary artery abnormalities (CAAs) to <3% at 28 days after onset,[2] KD remains the most common cause of pediatric acquired heart disease in developed countries. The occurrence of giant aneurysms is indeed the most severe outcome in KD; however, recognition of mild or transient dilatation of the coronary arteries is generally agreed as important in the diagnosis, management, and long-term follow-up of patients with KD.[3]

Two-dimensional echocardiography is commonly used to identify the presence of CAAs. The initial definition of CAA was given in the Japanese Ministry of Health criteria,[4] which dichotomously define abnormalities as a maximum absolute internal diameter of ≥3 mm in children <5 years of age, a segment 1.5 times greater than an adjacent segment, or the presence of luminal irregularity. The Japanese Ministry of Health criteria were widely used because of their simple and quick assessment of CAA formation. However, the criteria have several flaws, such as a lack of adjustment for body size and a lack of a standard specific for each major coronary artery.

Quantitative assessment of cardiac and vascular dimensions is essential for the evaluation and management of cardiovascular disorders. However, the estimation of accurate standard values for the pediatric population remains a substantial challenge because the dimensions of the heart and vessels depend on body size.[5] To adjust for these differences in body size, a standardized score (*Z*-score) was proposed and is now widely used in the clinical setting.[6-11] Regrettably, recent critical and systematic reviews have pointed out that echocardiographic nomograms or reference values of cardiovascular structures in the pediatric population have many problems, including a limited number of healthy subjects, poor differentiation among age subgroups, and methodologic flaws.[12,13] The previously reported *Z*-score for each coronary artery also reflected these limitations; especially, these models did not have validated accuracy.

In 1992, Cole and Green[14] proposed the lambda-mu-sigma (LMS) method with penalized likelihood to generate accurate normal references, which is extremely flexible and widely applicable. The LMS method has been increasingly used in recent years in standards such as the Centers for Disease Control and Prevention's growth charts in the United States and the World Health Organization's worldwide child growth standards.[15] *Z*-score curves for pediatric coronary arteries derived using the LMS method might provide more accurate standard values.

Against this background, this study was undertaken to develop a new pediatric *Z*-score for coronary arterial internal diameter on the basis of a large sample using a statistical approach based on the LMS method. We also validated the reproducibility of the LMS models and compared the LMS models with previously reported models.

METHODS

This was a multicenter, prospective, observational study in which 82 pediatric cardiologists and sonographers at 43 institutes participated. At each center, children referred for echocardiography were assessed for eligibility for this study. Inclusion criteria were (1) age ≤ 18 years, (2) benign symptoms or asymptomatic electrocardiographic abnormalities without anatomic or functional abnormalities (i.e., functional murmur, chest pain or syncope without cardiac cause, abnormal electrocardiographic results without symptoms, etc), and (3) mild cardiac valvular insufficiency without hemodynamic effects (i.e., trivial aortic or mitral valve regurgitation, mitral valve prolapse, mild aortic or pulmonary valve stenosis with flow velocity < 2.0 m/sec, or mild mitral or tricuspid valve stenosis with flow velocity < 1.5 m/sec). Exclusion criteria were (1) congenital heart defects, (2) history of KD or surgical or catheter intervention for heart disease, (3) myocardial disease, (4) chromosomal disorders (i.e., trisomy 21, Turner syndrome, Noonan syndrome, Marfan syndrome, Williams syndrome, 22q11.2 deletion, etc), (5) birth weight < 1,500 g, and (6) significant underlying disease (i.e., malignant tumor, leukemia, metabolic or endocrine disease, neuromuscular disease, etc.). We collected anonymous data regarding age, sex, body height, body weight, and coronary arterial internal diameter. From May 2010 to April 2011, we enrolled 2,567 participants who underwent echocardiographic studies. These data (developmental data set) were used to develop the LMS models. From May 2011 to December 2011, an additional 1,284 patients were collected to test the accuracy of the LMS and previously reported models; these data represented the validation data set. This prospective observational study was approved by the institutional review board of NTT East Japan Sapporo Hospital on March 16, 2010.

Echocardiography

Echocardiographic studies were performed at each center using the standard measurement methods for pediatric coronary arteries recommended by the Japanese Society of Kawasaki Disease.[16] Briefly, the patient is examined in the supine or right decubitus position using a sector probe with a ≥5-MHz frequency. The focus depth should be set to the coronary artery, and the frame rate should be increased to raise the time resolution. The coronary artery is observed at the center of the monitor screen and zoomed in two to three times before the measurement. During the coronary artery diameter measurement, the gain should be lowered as much as possible to minimize the trailing echo from the intima-lumen interface (minimal gain setting). The coronary