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ORIGINAL ARTICLE
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Echocardiographic Left Ventricular Z-Score Utility in Predicting Pulmonary-Systemic Flow Ratio in Children With Ventricular Septal Defect or Patent Ductus Arteriosus

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Background: The correlation between the Z-score of the left ventricular (LV) diameter and the LV volume-overload due to pulmonary over-circulation in children with ventricular septal defect (VSD) or patent ductus arteriosus (PDA) remains unclear.

Methods and Results: The present, retrospective study enrolled 70 children (aged 0.3–16.8 years; 33 males, 37 females) with a diagnosis of isolated VSD and/or PDA who underwent cardiac catheterization (CC) between 2015 and 2019. Patients with chromosomal/genetic anomalies, growth disorder, right-ventricular enlargement or other conditions causing LV enlargement were excluded. Echocardiographic parameters were retrospectively evaluated from the medical records, converted to a Z-score, then compared with CC data. The pulmonary-systemic flow ratio on CC (cQp/Qs) correlated significantly with the Z-score of both the LV end-diastolic diameter (Zd) (r=0.698, P<0.0001) and LV end-systolic diameter (r=0.593, P<0.0001). Regression analysis and curve-fitting were used to predict the cQp/Qs based on the Zd, and a significant regression equation was found on cubic regression (R^2 of 0.524, P<0.0001) showing a strong correlation with the cQp/Qs (r=0.724, P<0.0001).

Conclusions: The Z-score of the LV diameter can be a useful, non-invasive marker for evaluating LV volume overload and determining the surgical indications in children with VSD or PDA because of its strong correlation with the cQp/Qs.

Key Words: Children; Congenital heart disease; Echocardiography; Left ventricular volume over-load; Z-score

It is well-known that volume overload of the left ventricle (LV) in various heart diseases causes left ventricular chamber enlargement. In adults, acquired valve insufficiency, such as mitral valve regurgitation (MR) or aortic valve regurgitation (AR), is the principal cause. In these cases, the indications for surgical valve repair rely on LV diameter measurements using transthoracic echocardiography (TTE).[1–4] In pediatric patients, most cases of LV volume overload result from congenital heart diseases (CHD) with increased pulmonary circulation due to left-to-right shunt, such as ventricular septal defect (VSD) and patent ductus arteriosus (PDA). In such cases, the LV becomes enlarged as in adults,[5] but its size varies according to the patient's body size.

In the past, the degree of LV volume overload in children with VSD or PDA was evaluated by cardiac catheterization (CC), which can assess LV volume angiographically,[6] as well as demonstrate the pulmonary-systemic flow ratio (Qp/Qs). Although CC is currently the gold standard for

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evaluating the Qp/Qs and pulmonary vascular resistance in patients with VSD or PDA, it can be replaced by other imaging modalities, such as TTE and magnetic resonance imaging (MRI), as a means of evaluating LV volume overload.[7] Two-dimensional (2D) and three-dimensional TTE are frequently used to evaluate LV volume. MRI is sometimes used for this purpose as well,[7] and these imaging modalities are known to correlate well with LV volume measurements in healthy children.[8] Despite the recent development of such assessment methods, there are still no studies using any imaging modality to determine if there is a precise correlation between the degree of LV volume overload and LV volume size in children with VSD or PDA.

Some recent studies discussed the standardization of children's echocardiographic measurements based on the Z-score, which is useful for evaluating both congenital and

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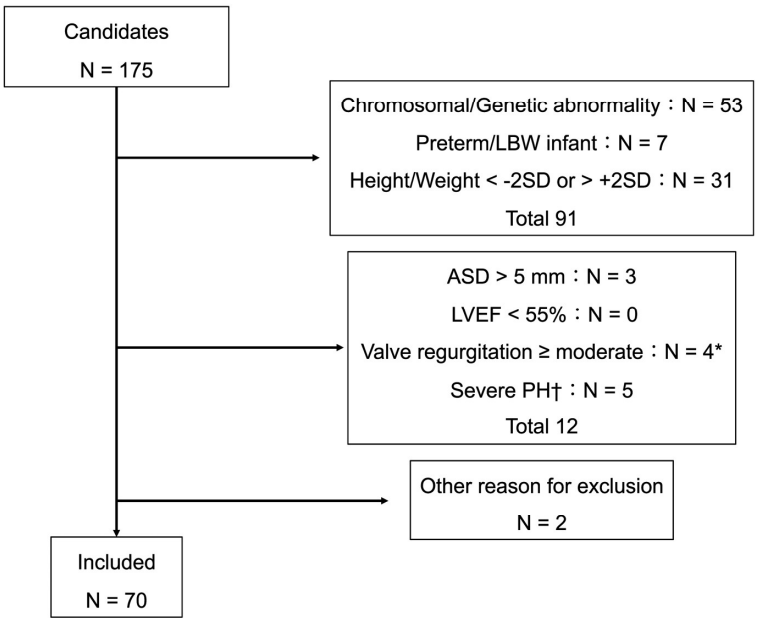


Figure 1. Number of candidate patients, excluded patients, and enrollees in the present study. ASD, atrial septal defect; LBW, low birth weight infant; LVEF, left ventricular ejection fraction; PH, pulmonary hypertension. *Includes 2 patients with moderate aortic valve regurgitation and 2 patients with moderate mitral valve regurgitation. †Severe pulmonary hypertension is defined by a mean pulmonary artery pressure >40 mmHg or right ventricular systolic pressure >70% of the left ventricular systolic pressure on cardiac catheterization.

acquired cardiac diseases.[9,10] The hemodynamic abnormalities in CHD affect the heart's structure and size. Thus, the echocardiographic Z-score is useful because it reflects the cardiac hemodynamic status.[10] Although children with VSD and PDA are known to have increased echocardiographic Z-scores of the LV dimensions,[11,12] no studies have described the relationship between increased pulmonary circulation and the Z-score of the echocardiographic LV dimensions precisely. We conducted the present study to test our hypothesis that the Z-score of the LV diameter correlates with LV volume overload caused by pulmonary over-circulation in children with VSD or PDA.

Methods

Inclusion and Exclusion Criteria

Children aged 0 to 18 years with the diagnosis of VSD and/or PDA without any other CHD who underwent CC between 2015 and 2019 at Keio University Hospital (KUH) or Tokyo Metropolitan Children's Medical Center (TMCMC) were enrolled. At these facilities, CC studies for VSD were performed routinely in patients with clinical findings of pulmonary over-circulation, including infants aged >6 months at KUH and <6 months at TMCMC to evaluate their Qp/Qs, and in some cases, pulmonary vascular resistance. Catheter closure for VSD is still not practiced in Japan. The main purpose of CC in PDA cases was catheter closure for patients with various levels of pulmonary blood flow. Some of these patients had undergone surgical or catheter closure after CC, whereas others had undergone neither. Also included were patients with atrial septal defect (ASD) ≤5 mm and trivial/mild valve regurgitation, including MR, AR, tricuspid valve regurgitation (TR), and pulmonary valve regurgitation (PR), because these diseases are often associated with VSD and PDA and were considered to have less impact on the LV size.

The following patients were excluded due to having an unsuitable Z-score: patients with (1) a history of cardiac surgery or catheter intervention; (2) a chromosomal abnormality, including 21 trisomy, genetic abnormality or multiple malformation syndrome; (3) birth weight <2,500 g or gestational age <37 weeks; (4) age <1 month or body weight <2,500 g at CC; and (5) height or weight <−2 SD or >+2 SD at CC, including poor growth due to left-to-right shunt, because in cases of extreme failure-to-thrive with a weight <−2 SD, the Z-score might be inaccurate owing to the deviation from the reference group norms. Also excluded were patients with: (6) severe pulmonary hypertension (PH), defined as a mean pulmonary artery pressure >40 mmHg or right ventricular systolic pressure >70 percent of the LV systolic pressure on CC; and (7) the following TTE findings: LV ejection fraction (LVEF) <55 %, ASD >5 mm or moderate/severe valve regurgitation, including MR, AR, TR, PR, because these are considered to have a significant impact on LV size independent of the Qp/Qs.

Study Design and Methods

The present, retrospective, cohort study was conducted at 2 hospitals in Japan. Candidates for enrollment were identified by their catheterization records. Demographic, clinical, TTE, CC, and surgical data were extracted from their medical records. The CC data, including the volume of pulmonary circulation (Qp), volume of systemic circulation (Qs), right ventricle (RV) systolic pressure, LV systolic pressure, and pulmonary artery pressure, were extracted from the catheterization records. The Qp and Qs values were calculated using Fick's principle. Pulmonary hypertension was defined as a mean pulmonary artery pressure of ≥20 mmHg on CC. We used data from TTE performed within 1 week prior to CC for infants and 1 month prior to CC for children aged >1 year, which included the left ventricular end-diastolic dimension (LVEDd), left ventricular end-systolic dimension (LVEDs), and Qp/Qs estimates based on measurements of the cardiac output at the respec-

Table. Patient Characteristics

	VSD* (n=47) (67.1%)	PDA† (n=23) (32.9%)	Total (n=70)
Median age in years (range)	1.7 (0.3–16.9)	3.2 (0.8–16.3)	2.3 (0.3–16.9)
Male sex	26 (55.3)	7 (30.4)	33 (47.1)
PH‡	9 (19.1)	1 (4.3)	8 (11.4)
ASD ≤5 mm	7 (14.9)	0	7 (10.0)
Surgical closure	34 (72.3)	1 (4.3)	35 (50.0)
Catheter closure	0	20 (87.0)	20 (28.6)

Data are presented as n (%) unless otherwise stated. *Includes one patient with both VSD and PDA. †Does not include the patient with both VSD and PDA. ‡Pulmonary hypertension was defined as a mean pulmonary artery pressure of ≥20 mmHg on cardiac catheterization. ASD, atrial septal defect; PDA, patent ductus arteriosus; PH, pulmonary hypertension; VSD, ventricular septal defect.

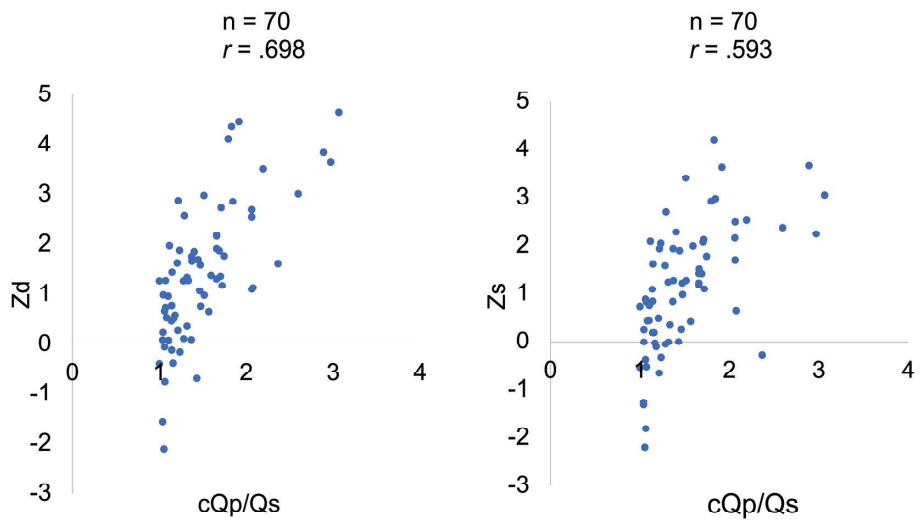


Figure 2. Pearson's correlation between the pulmonary-systemic flow ratio on cardiac catheterization and the Z-score of the left ventricular diameter. cQp/Qs, pulmonary-systemic flow ratio measured according to Fick's principle via cardiac catheterization; Zd, echocardiographic Z-score of the left ventricular end-diastolic diameter; Zs, echocardiographic Z-score of the left ventricular end-systolic diameter.

tive cardiac outflow tract using 2D echocardiography and pulse-wave Doppler (eQp/Qs),[13] whenever available. The parasternal LV long axis view on 2D-guided M-mode echocardiography immediately below the level of the mitral valve leaflet tips was used to assess the LVEDd and LVEDs,[14] and the images of all the patients were re-assessed by a single observer blinded to the CC data. The measurements were then converted to a Z-score using the formula described by Pattersen et al, as follows: Z-score of the LVEDd (Zd) = (ln (measured LVEDd (cm)) − 0.105 − 2.859 × body surface area (BSA) + 2.119 × BSA^2 − 0.552 × BSA^3) × 10, Z score of the LVEDs (Zs) = (ln (measured LVEDs (cm)) + 0.371 − 2.833 × BSA + 2.081 × BSA^2 − 0.538 × BSA^3) / $0.016^{0.5}$.[9] The BSA was calculated using Haycock's formula.[15] With regard to the eQp/Qs in patients with PDA, the flow across the outflow tract of the RV was calculated as a systemic flow measurement whereas the actual pulmonary flow was treated as the flow across the LV outflow tract, as previously reported.[16] We also assessed for the presence of valve regurgitation, and cases of moderate or higher valve regurgitation found via qualitative evaluation were excluded after adding a quantitative evaluation.

To examine the reliability of the echocardiographic measurements at the study centers, inter- and intra-observer variability were evaluated with blinding, and 2 repeated measurements of the LVEDd and LVEDs were taken in 20 subjects by 4 physicians who performed echocardiography at KUH or TMCMC between 2015 and 2019. The measurements' reliability was tested using the intraclass correlation coefficient.

Statistical Analysis

The relationship between the Qp/Qs on CC (cQp/Qs) and the TTE parameters was assessed using the Pearson's correlation coefficient. To investigate the effects of a small ASD, the above correlation was also analyzed except in patients with an ASD ≤5 mm. For TTE parameters with a strong correlation with the cQp/Qs, regression analysis and curve fitting were used to provide a formula for the line of best fit for predicting the cQp/Qs. Receiver operating char-

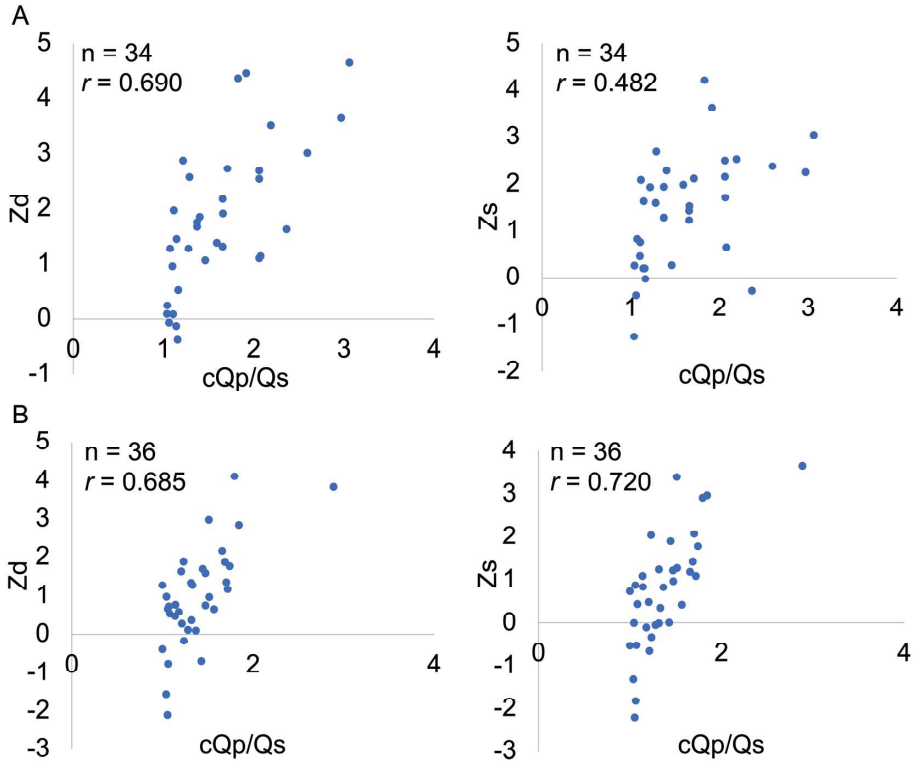


Figure 3. Pearson's correlation between the pulmonary-systemic flow ratio on cardiac catheterization and echocardiographic parameters of the young and older patients. (**A**) patients aged <2 years. (**B**) Patients aged ≥2 years. cQp/Qs, pulmonary-systemic flow ratio measured according to Fick's principle via cardiac catheterization; Zd, echocardiographic Z-score of the left ventricular end-diastolic diameter; Zs, echocardiographic Z-score of the left ventricular end-systolic diameter.

acteristic (ROC) analysis was performed to determine the threshold of the echocardiographic parameters to determine whether cQp/Qs was ≥1.5, and the area under the curve (AUC) was measured using a non-parametric method. To examine the difference in results by patient age, the patients were divided into those aged <2 years and those aged ≥2 years, and the same analyses as above, except for regression analysis, were performed. All statistical analyses were performed using IBM SPSS Statistics (version 25). P<0.05 was considered to indicate statistical significance.

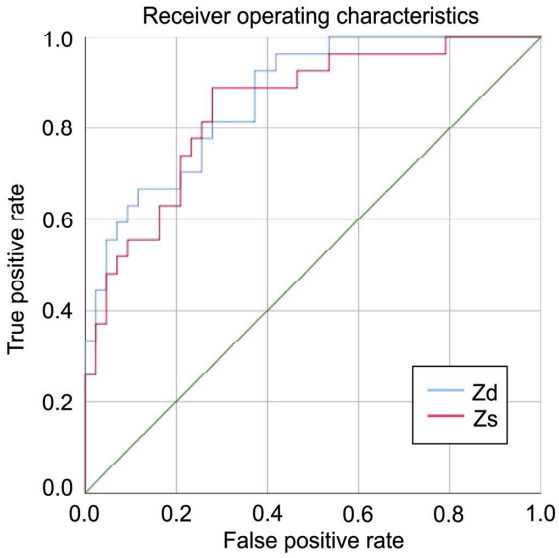
Ethics

All the procedures in this study were conducted in accordance with the Declaration of Helsinki. The present study was approved by the institutional review board of each participating facility (the approval number for KUH and TMCMC is 20190333 and 2019b-177, respectively). Written informed consent was waived because of the study's retrospective design.

Results

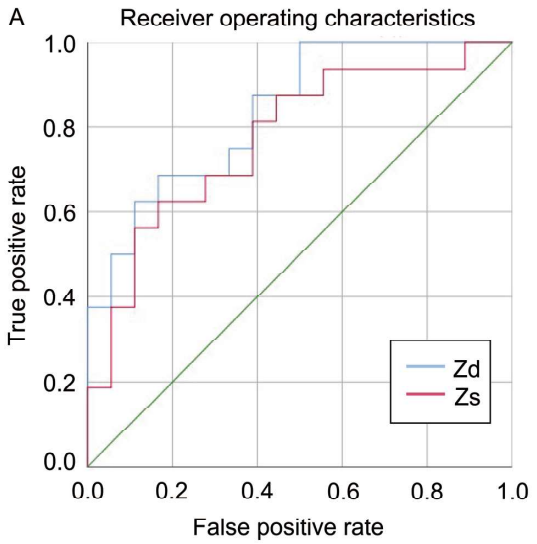
In total, 175 patients had VSD or PDA without any other CHD and underwent CC between 2015 and 2019 (**Figure 1**). All the patients were Japanese. Of these patients, 105 were excluded because they met the exclusion criteria described above, and 70 were finally enrolled. The most common cause of exclusion was a chromosomal or other genetic abnormality. The second most common cause was a growth disorder. Two patients each with moderate MR and moderate AR were excluded. Two more patients were deemed inappropriate for this study; 1 patient had inaccurate TTE data because the M-mode cursor on the 2D view was not aligned perpendicularly to the LV wall, and the remaining patient had congenital tracheal stenosis and right lung hypoplasia. Among the 70 patients enrolled, approximately two-thirds had VSD, and the remaining one-third had PDA (**Table**). Only one patient had both VSD and PDA. In the patients with VSD, 19% had PH, and 72% underwent surgical closure. In the patients with PDA, only 1 had PH, and 87% underwent catheter closure.

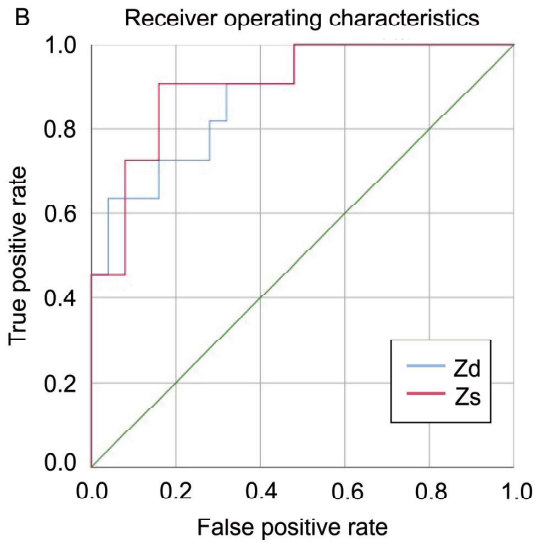
Pearson's correlation coefficient between the cQp/Qs and echocardiographic parameters in all patients, including the Zd, Zs, and eQp/Qs, was as follows: Zd: r=0.698, P<0.0001; Zs: r=0.593, P<0.0001; eQp/Qs: r=0.655, P<0.0001. All 3 echocardiographic parameters correlated with the cQp/Qs, with the Zd showing the strongest correlation. The Zd and Zs were able to be obtained from all patients, whereas the eQp/Qs was available from 45 patients. **Figure 2** shows the correlation between the cQp/Qs and echocardiographic parameters of the Zd and Zs. Similar analysis was also performed in all but 7 patients with ASD ≤5 mm, and no change was observed in the correlation tendency (Zd: r=0.670, P<0.0001; Zs: r=0.586, P<0.0001; eQp/Qs: r=0.572, P<0.0001). The correlation between cQp/Qs and echocardiographic parameters in patients aged <age 2 years and in



	AUC	*p*	SE	95% CI	Cut-off value	Sensitivity	Specificity
Zd	.868	< .0001	.042	.787 - .950	1.76	66.7%	88.4%
Zs	.846	< .0001	.047	.753 - .938	1.10	88.9%	72.1%

Figure 4. Receiver operating characteristics for calculating the threshold by echocardiographic parameters to determine whether the pulmonary-systemic flow ratio on cardiac catheterization was ≥1.5. AUC, area under the curve; CI, confidence interval; SE, standard error; Zd, echocardiographic Z-score of the left ventricular end-diastolic diameter; Zs, echocardiographic Z-score of the left ventricular end-systolic diameter.

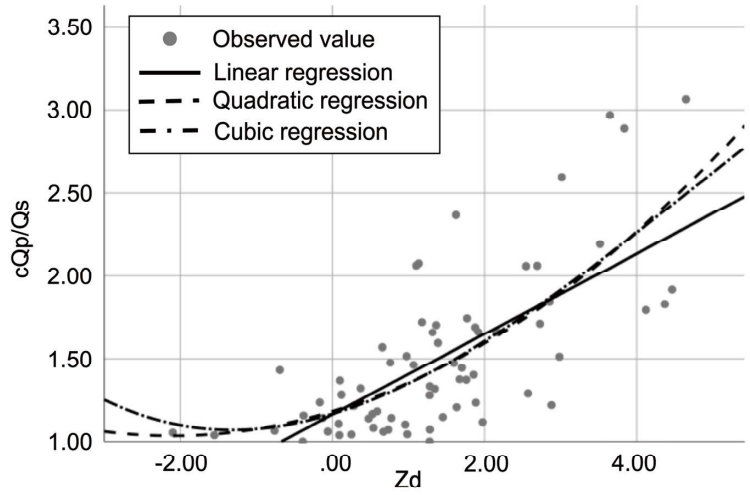




	AUC	*p*	Cut-off value	Sensitivity	Specificity
Zd	.837	.001	1.89	68.8 %	83.3 %
Zs	.774	.006	1.96	62.5 %	83.3 %

	AUC	*p*	Cut-off value	Sensitivity	Specificity
Zd	.880	< .0001	1.74	63.6 %	96.0 %
Zs	.905	< .0001	1.10	90.9 %	84.0 %

Figure 5. Receiver operating characteristics for calculating the threshold by echocardiographic parameters to determine whether the pulmonary-systemic flow ratio on cardiac catheterization was ≥1.5 in the young and older patients. (**A**) Patients aged <2 years. (**B**) Patients aged >2 years. AUC, area under the curve; Zd, echocardiographic Z-score of the left ventricular end-diastolic diameter; Zs, echocardiographic Z-score of the left ventricular end-systolic diameter.



Equation	R^2	F	df1	df2	*p*	Constant	β1	β2	β3
Linear	.487	64.645	1	68	<.0001	1.163	.243		
Quadratic	.523	36.692	2	67	<.0001	1.181	.139	.33	
Cubic	.524	24.212	3	66	<.0001	1.166	.139	.46	-.003

Figure 6. Regression analysis and curve fitting to predict the pulmonary-systemic flow ratio on cardiac catheterization based on the echocardiographic Z-score of the left ventricular end-diastolic diameter (Zd). cQp/Qs, pulmonary-systemic flow ratio measured according to Fick's principle via cardiac catheterization; df, degrees of freedom; Zd, echocardiographic Z-score of left ventricular end-diastolic diameter.

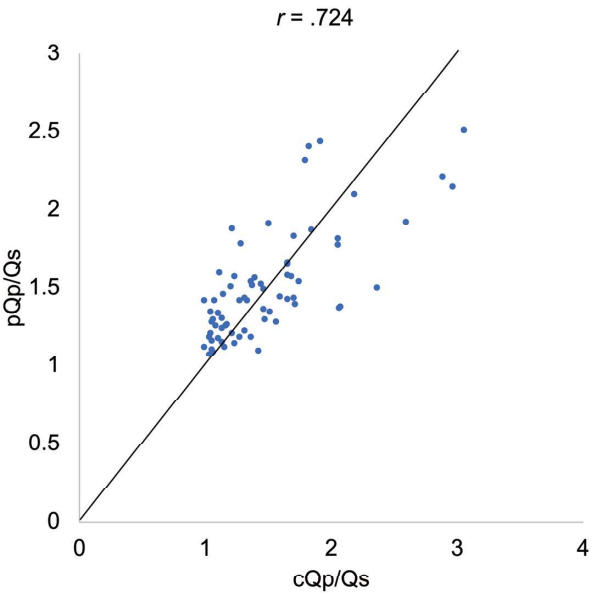


Figure 7. Pearson's correlation between the pulmonary-systemic flow ratio on cardiac catheterization and predicted pulmonary-systemic flow ratio calculated by a cubic equation obtained by regression analysis. cQp/Qs, pulmonary-systemic flow ratio measured according to Fick's principle via cardiac catheterization; pQp/Qs, predicted pulmonary-systemic flow ratio based on cubic equation obtained from regression analysis.

patients aged ≥2 years was as follows: age <2 years: Zd: r=0.690, P<0.0001; Zs: r=0.482, P=0.004; eQp/Qs: r=0.632, P=0.001; age ≥2 years: Zd: r=0.685, P<0.0001; Zs: r=0.720, P<0.0001; eQp/Qs: r=0.785, P<0.0001. Each echocardiographic parameter correlated with the cQp/Qs, except for Zs, in patients aged <2 years. **Figure 3A**,**B** show the correlation between cQp/Qs and Z-score of the LV diameter in both age groups. Inter-observer and intra-observer variability with respect to LV diameter measurements was low, with the interclass correlation coefficients ranging from 0.980 to 0.984 and 0.987 to 0.997, respectively.

In all patients, ROC analysis revealed a Zd cut-off value of 1.76 for determining whether the cQp/Qs was ≥1.5 (sensitivity: 66.7 %; specificity: 88.4 %; AUC: 0.868). Furthermore, the cut-off value for the Zs was 1.10 (sensitivity: 88.9 %; specificity: 72.1 %; AUC: 0.846) (**Figure 4**). When the patients were divided into those aged < 2 years and those aged ≥2 years, the ROC curves showed a higher AUC for the older group (**Figure 5A**,**B**).

Regression analysis and curve fitting for all patients were conducted to predict the cQp/Qs based on the Zd, and a significant regression equation was found on cubic regression (F=24.212, P<0.0001) with an R^2 of 0.524 (**Figure 6**). The participants' predicted cQp/Qs (pQp/Qs) was equal to $1.166+(0.139\times Zd)+(0.046\times Zd^2)-(0.003\times Zd^3)$. **Figure 7** shows Pearson's correlation between the pQp/QS and cQp/Qs. There was a strong correlation between the 2 variables (r=0.724, P<0.0001).

Discussion

The present study is the first to examine the relationship between the echocardiographic Z-score and LV volume overload due to pulmonary over-circulation in children with VSD or PDA. The study found a strong correlation in

children of all ages between the Zd and the cQp/Qs, which were found to be the best predictors of the quantity of LV volume overload independent of the patients' age and physique. In addition, the Zs also correlated well with the cQp/Qs in the older group and was also considered a good predictor of the quantity of LV volume overload. The ROC curve for determining whether the cQp/Qs was ≥1.5 was found to be highly accurate for all ages, especially for the older group. The LV diameter can be measured readily using TTE and does not require proficiency in the use of the technology. Moreover, TTE is less invasive and costly than CC and MRI and can be used in an outpatient setting.

In this study, both Zd and Zs correlated well with cQp/Qs, and the ROC curve for the older group also demonstrated high accuracy. Because patients with significant left-to-right shunt often present with obvious symptoms and echocardiographic findings of significant LV enlargement and pulmonary hypertension, the indications for closure in infants can be determined relatively easily without relying on detailed evaluation of the LV diameter. In contrast, in older children, the symptoms may be inadequate, even with a certain amount of shunt as in adults,[17] to make this determination, so that it is more important to assess the precise LV volume overload from the degree of LV enlargement by echocardiography. For these reasons, the Z-score of the LV diameter is considered more useful in assessing the indications for closure in older children rather than infants.

Our study found that the cut-off values for Zd and Zs for determining whether cQp/Qs was ≥1.5, were <+2.0; that is, they were within the normal range regardless of the child's age. This was an unexpected result because patients normally have significant left-to-right shunt even if their LV diameter is within the normal range. However, previous studies have also reported that the median Z-score of the LVEDd was <+2.0 due to pulmonary over-circulation in patients with VSD or PDA and was considered to be an indication for closure.[11,12] These findings may be problematic due to the low number of cases in previous reports, including ours; however, in some patients with a LV diameter within the normal range, closure is necessary if the measurements are near the upper limit. More data from further studies are needed to clarify this issue. The present study also showed a weak correlation between the Zs and cQp/Qs in the younger group. Left ventricular afterload in patients with VSD or PDA is considered relatively low due to the connection to pulmonary circulation so that Zs may not be as useful as Zd in assessing the LV volume overload in this population.

The present study also estimated the cQp/Qs by echocardiography using spectral Doppler measurements, which presented some problems despite widespread use of the method in assessing pulmonary over-circulation in patients with CHD. For example, spectral Doppler measurements require laminar flow at each semilunar valve, but in cases of VSD, high-flow shunting tends to generate a turbulent flow in the outflow tract of the RV,[18] leading to incorrect estimates of the pulmonary blood flow.[13] In PDA, the eQp/Qs is considered to be less reliable than the Qp/Qs on CC due to erroneous measurements of the outflow tract area,[16] and is even more difficult to evaluate in patients who have both VSD and PDA. In contrast, the echocardiographic Z-score of the LV diameter is unaffected by turbulent flow in the outflow tract of the RV, including the left-to-right shunt produced by PDA, and can be used for a wide range of patients, including those with VSD and PDA.

Predicting the pulmonary blood flow based on the Z-score also presents some problems. First, a dilated RV, such as is seen in ASD, TR, PR, and severe PH, depresses the LV volume, potentially leading to underestimation of the Z-score of the LV dimensions. The r and P values were similar between patients with and without a small ASD (≤5 mm), suggesting that this method might be applicable to both types of patient. However, it may be premature to state that cQp/Qs can be predicted with equal accuracy in patients with or without an ASD ≤5 mm based on the Z-score of the LV diameter. Further research is needed to clarify this question. Another problem is that the presence of a LV dysfunction or the amount of AR and MR may lead to overestimating the volume of pulmonary circulation using the Z-score because each increases the LV dimensions. The impact of these factors on the Z-score of the LV diameter was not examined in this study. In addition, some of our patients had a Zs of ≥3.0 despite having a cQp/Qs <2.0, suggesting a latent LV dysfunction, which might have affected the results. Furthermore, it is unclear whether predictions based on the Z-score can be applied to patients with a chromosomal or other genetic anomaly who often have CHD because they were excluded from the present study due to lacking normal TTE measurements. A similar problem is encountered in patients with preterm gestational age, low birth weight or growth failure.

A previous report demonstrated that the LV diameter as a percentage of the normal LV diameter (%normal LV diameter) can be treated as a value related to the surgical indications in patients with neonatal PDA,[19] but the precise relationship between %normal value and cQp/Qs has not yet been clarified. In the present study, the Z-score and %normal value had a 1 : 1 correspondence because they are expressed using the following equations: $Zd = \ln(\%\text{normal LVEDd}/100)/0.010^{0.5}$ and $Zs = \ln(\%\text{normal LVEDs}/100)/0.016^{0.5}$. The %normal LV diameter is the ratio of the measured LV diameter to the normal LV diameter, whereas the Z-score reflects the deviation of the LV diameter from the normal LV diameter in terms of the standard deviation. Because the numerical characteristics of the 2 parameters differ, determining which is more suitable for predicting cQp/Qs is difficult; the %normal LV diameter might be able to be used to predict cQp/Qs as well as the Z-score of the LV diameter. The Z-score has the advantages of allowing the deviation from the population to be determined statistically and having global recognition as a standard index in clinical research.

The present study has some limitations. At first, this study does not include patients with markedly poor weight gain due to left-to-right shunt and patients with small VSD who did not undergo CC due to having few clinical findings of pulmonary over-circulation; therefore, this study was not able to consider all cases of VSD and PDA. Moreover, LV size measurements were obtained only by using M-mode echocardiographic imaging, whereas 2D measurements, which can also be converted to a Z-score,[10] were not included. In addition, the data on TTE used in this study were derived from measurements performed by multiple physicians whereas in previous studies, TTE was performed by pediatric cardiovascular experts in the manner recommended by the guidelines.[20] However, the measurements used in the present study were reviewed and found to have low variability. Another limitation is the lack of data; 36% of the patients (25 of 70 patients) lacked

data on the eQp/Qs, making it impossible to use spectral Doppler measurements to assess the volume of pulmonary flow in all the patients. Moreover, because the subjects were all Japanese, it is unclear whether the findings are generalizable to other ethnicities, although a recent study showed that the Z-score itself is relatively unaffected by ethnicity.[10] Finally, due to the small sample size of patients, including both VSD and PDA, further research involving each disease enrolling larger patient cohorts is necessary to verify the findings of this study.

In conclusion, the Zd value in children of all ages and the Zs value in older children are readily obtainable and extremely useful markers for precisely evaluating the LV volume overload and predicting pulmonary over-circulation. They may also provide non-invasive means of determining the surgical indications for VSD or PDA with pulmonary over-circulation. Further research is required to confirm the relationship between the echocardiographic Z-score and hemodynamic characteristics in pediatric patients.

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Disclosures

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IRB Information

All the procedures in this study were conducted in accordance with the Declaration of Helsinki. The present study was approved by the institutional review board of Keio University Hospital and the institutional review board of Tokyo Metropolitan Children's Medical Center (the approval number for each facility is 20190333 and 2019b-177, respectively).

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