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Pulmonary artery diameter ratio as a prognostic indicator of congenital diaphragmatic hernia

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ABSTRACT

Background Following on from an earlier study published in 2008 about left pulmonary artery (LPA) flow measured on serial echocardiography being strongly prognostic in left-sided congenital diaphragmatic hernia (CDH) and the ratio of LPA to right pulmonary artery (RPA) diameters being a simple and reliable indicator for commencing nitric oxide (NO) therapy, the ratio of LPA:RPA diameters (PA ratio or PAR) was hypothesized to possibly reflect cardiopulmonary stresses accompanying CDH better.

Methods Subjects with isolated left-sided CDH treated between 2007 and 2020 at a single pediatric surgical center were recruited and classified according to survival. Data obtained retrospectively for subject demographics, clinical course, LPA/RPA diameters, and PAR were compared between survivors and non-survivors. The value of PAR for optimizing the prognostic value of PA diameter data in CDH were analyzed with receiver operating characteristic (ROC) curve analysis.

Results Of 65 subjects, there were 54 survivors (82.3%) and 11 non-survivors (17.7%); 7 of 11 non-survivors died before surgical repair could be performed. Mean PAR for survivors (0.851±0.152) was significantly higher than for non-survivors (0.672±0.108) (p=0.0003). Mean PAR for non-survivors was not affected by surgical repair. Characteristics of survivors were: LPA ≥2 mm (n=52 of 54; mean PAR=0.866±0.146) and RPA ≥3 mm (n=46 of 54; mean PAR=0.857±0.152). Non-survivors with similar LPA and RPA diameters to survivors had significantly lower mean PAR. ROC curve cut-off for PAR was 0.762. Subjects with high PAR (≥0.762) required high-frequency oscillatory ventilation/NO less than subjects with low PAR (<0.762) (p=0.0244 and p=0.0485, respectively) and subjects with high PAR stabilized significantly earlier than subjects with low PAR (1.71±0.68 days vs 3.20±0.87 days) (p<0.0001).

Conclusions PAR would appear to be strongly correlated with clinical outcome in CDH and be useful for planning management of cardiopulmonary instability in CDH.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Congenital diaphragmatic hernia causes changes in lung vasculature, with reduction in size of the pulmonary vascular bed.
⇒ Pulmonary artery diameters reflect physical stresses associated with pulmonary hypertension.

WHAT THIS STUDY ADDS

⇒ Mean pulmonary artery ratio (PAR) was significantly higher in survivors than non-survivors. PAR could be prognostic as clinical stabilization was significantly earlier when PAR was high.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Choice of ventilatory support and prognosis could be indicated by PAR, influencing surgical planning and contributing to optimizing resources for managing congenital diaphragmatic hernia.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is characterized by incomplete development of the diaphragm with herniation of abdominal organs into the chest that affects lung development. Sokol *et al* reported that fetal pulmonary artery (PA) diameters reflect pulmonary hypoplasia in CDH,[1] and O'Toole *et al* reported lung vasculature changes, with reduced size of the pulmonary vascular bed in patients with CDH.[2] PA becomes hypertrophied with more abundant contractile vascular smooth muscle cells and thicker media and adventitia related to the severity of pulmonary hypertension (PH).[1 3–8] PA diameters may also reflect the capacity and function of the side of the chest that is unaffected by CDH[9]; that is, right PA (RPA) diameter correlates more with severity in left-sided CDH than left PA (LPA) diameter.

Lung development is thus unbalanced in CDH because of physical obstruction and structural differences that combine to induce changes affecting PA diameters. An earlier study from the same institute on PA diameters and LPA flow measured on serial echocardiography found LPA diameter and LPA flow were strongly prognostic in left-sided CDH with the ratio of LPA to RPA diameters being a simple and reliable indicator for nitric oxide (NO) therapy.[10] In the present study, the

LPA:RPA ratio or PAR was hypothesized to better reflect physical changes that might be clinically prognostic and have potential as a marker for overall clinical severity as some cases of CDH can develop significant PH associated with severe pulmonary hypoplasia contributing to poor prognosis and high mortality with good PA diameters.[11 12] Thus, while PAR may reflect physical responses to stresses associated with pulmonary hypoplasia or PH, specific correlations between PAR and pulmonary hypoplasia or PAR and PH require more extensive research such as measuring the lowest partial pressure of carbon dioxide (pCO_2) achieved in the first 12–24 hours of life on conventional mechanical ventilation (CMV) or inability to achieve acceptable pCO2 levels. Here, PAR was investigated for optimizing the prognostic value of PA diameter data for managing CDH as a marker for cardiopulmonary stability.

METHODS

Subjects

The medical records of 65 Japanese patients with isolated left-sided CDH treated at a single center between 2007 and 2020 were reviewed retrospectively. Patients with right-sided CDH, chromosomal anomalies, congenital cardiac conditions, and incomplete echocardiographic assessment were excluded. Patient demographics, clinical course, LPA diameter, RPA diameter, and PAR were compared between survivors and non-survivors to identify etiologic/prognostic factors influencing survival.

Standard CDH management

Accurate echocardiography is fundamental to several decision-making steps in the standardized protocol used for CDH management, and a skilled neonatologist or pediatric cardiologist was consulted frequently to evaluate the pulmonary circulation and PH. Specific details of the protocol are described elsewhere.[10 13] All subjects were managed according to this protocol which did not include use of extracorporeal membrane oxygenation (ECMO) or pulmonary vasodilators other than NO. Briefly, the baby was intubated in the operating room after being delivered and transferred to the neonatal intensive care unit (NICU) for stabilization and high-frequency oscillatory ventilation (HFOV) commenced at maximum mean airway pressure (MAP)=25 cmH_2O and maximum stroke volume (SV)=10 mL/kg. Both RPA and LPA diameters were measured after clinical stabilization in NICU at the point of their bifurcation from the pulmonary trunk during systole, ideally within 2 hours of birth. PAR was calculated by dividing the diameter of the LPA by the diameter of the RPA. HFOV settings were reduced gradually to fraction of inspired oxygen (FiO_2)=0.6, SV=5 mL/kg, and MAP=15 cmH_2O or less to maintain post-ductal oxygen saturation (SpO_2) at more than 75%, aiming to convert HFOV to CMV, if possible. Initial settings for CMV were FiO_2=0.4–0.6; peak inspiratory pressure=15–20 mm Hg; positive end-expiratory pressure=3–5 mm Hg; and respiratory rate=35–40 breaths/min. NO was introduced when post-ductal SpO_2 was less than 75% or if echocardiography was typical of PH. Fentanyl (5–10 µg/kg/hour) was used for continuous deep sedation and vasopressors (dopamine 5 µg/kg/min and dobutamine 5–10 µg/kg/min) were used to maintain systolic blood pressure above 50 mm Hg.

Surgical intervention for CDH was performed once cardiopulmonary status was stabilized. Stabilization was defined as spontaneous closure or marked narrowing of a patent ductus arteriosus (PDA), dominant left-to-right flow through a PDA, marked increase in PA blood flow on the affected side, and tricuspid regurgitation velocity under 2.5 m/s. Patients who stabilized were indicated for thoracoscopic repair (TR) or open repair (OR) in an operating room. For TR, patients must satisfy two selection criteria: (1) stable cardiopulmonary status in the decubitus position during CMV or HFOV with/without NO for more than 10 min in NICU, and (2) tolerate manual ventilation with/without NO to allow transfer to the operating room. Patients who could not be stabilized had OR in NICU.

Statistical analysis

Categorical data were analyzed using the X^2 test and continuous data for PA diameters or PAR were analyzed using the Student's t-test. A p value of less than 0.05 was considered statistically significant. The logistic regression model and receiver operating characteristic (ROC) curve were used to evaluate the clinical usefulness of PAR.

Patient and public involvement

Parents or the public were not involved in this research's design, conduct or plans for the dissemination of our research.

RESULTS

There were 54 of 65 survivors (82.3%) and 11 of 65 non-survivors (17.7%). Of the non-survivors, 7 of 11 (63.6%) died before undergoing surgery. Data for survivors and non-survivors were: sex distribution (male: 48.1% vs 54.5%), birth weight (2801.3±430.6 g vs 2887.9±465.4 g) (p=0.54), gestational age at birth, (37.88±1.13 vs 37.52±1.08 weeks) (p=0.95), and prenatal diagnosis (75.9% vs 90.9%) (p=0.27). Data for fetal evaluations in prenatally diagnosed subjects were not available consistently and were not included. Postnatal MRI, lung-to-head ratio, and total fetal lung volume were not performed.

Mean LPA diameter, mean RPA diameter and PAR were significantly larger in survivors compared with non-survivors (LPA: 2.97±0.60 vs 2.02±0.46 (p<0.0001), RPA: 3.49±0.63 vs 3.01±0.55 (p=0.0227) and PAR: 0.852±0.151 vs 0.672±0.108) (p=0.0003), respectively). See table 1 for a summary of subject data. For reference, data from Katayama *et al* who measured fetal PA diameters in 175 normal

Table 1 Demographic and clinical characteristics of subjects

	Survivors (*n*=54)	Non-survivors (*n*=11)	*P* value
Gender (male/female)	26/28	6/5	0.70
Prenatal diagnosis (yes/no)	41/13 (75.9%)	10/1 (90.9%)	0.27
Mean birth weight (g)	2801.3±430.6	2887.9±465.4	0.54
Mean gestational age (weeks)	37.88±1.13	37.52±1.08	0.95
Mean LPA diameter (mm)	2.97±0.60	2.02±0.46	<0.0001
Mean RPA diameter (mm)	3.49±0.63	3.01±0.55	0.0227
Mean PAR	0.852±0.151	0.672±0.108	0.0003

LPA, left pulmonary artery; PAR, pulmonary artery ratio; RPA, right pulmonary artery.

infants and reported the normal range for both LPA and RPA as approximately 4.0 mm after 36 weeks' gestation are presented for comparison. They also measured LPA and RPA diameters in patients with left CDH who died and reported they were smaller than patients who survived.[14] From the earlier paper published by the same institute, mean LPA and RPA in patients who died were 2.13 mm and 2.90 mm, respectively,[10] while non-survivors in the present study series had mean LPA and RPA of 2.02 mm and 3.01 mm, respectively, suggesting there are PA diameters above which outcome may be better. Thus, LPA of 2.02 mm and RPA of 3.01 mm may be useful as cut-off values for predicting survival. Using these values, 52 of 54 survivors had LPA ≥2 mm and 46 of 54 survivors had RPA ≥3 mm.

Upon calculating PAR, 52 of 54 survivors with LPA ≥2 mm had mean PAR of 0.873±0.140, while 8 of 11 non-survivors with LPA ≥2 mm had mean PAR of 0.696±0.098 (p=0.0013) (figure 1A) and 46 of 54 survivors with RPA ≥3 mm had mean PAR of 0.857±0.152, while 8 of 11 non-survivors with RPA ≥3 mm and mean PAR of 0.696±0.098 (p=0.0064) (figure 1B). On the other hand, 2 of 54 survivors with LPA <2 mm had mean PAR of 0.529±0.029, while 3 of 11 non-survivors with LPA <2 mm had mean PAR of

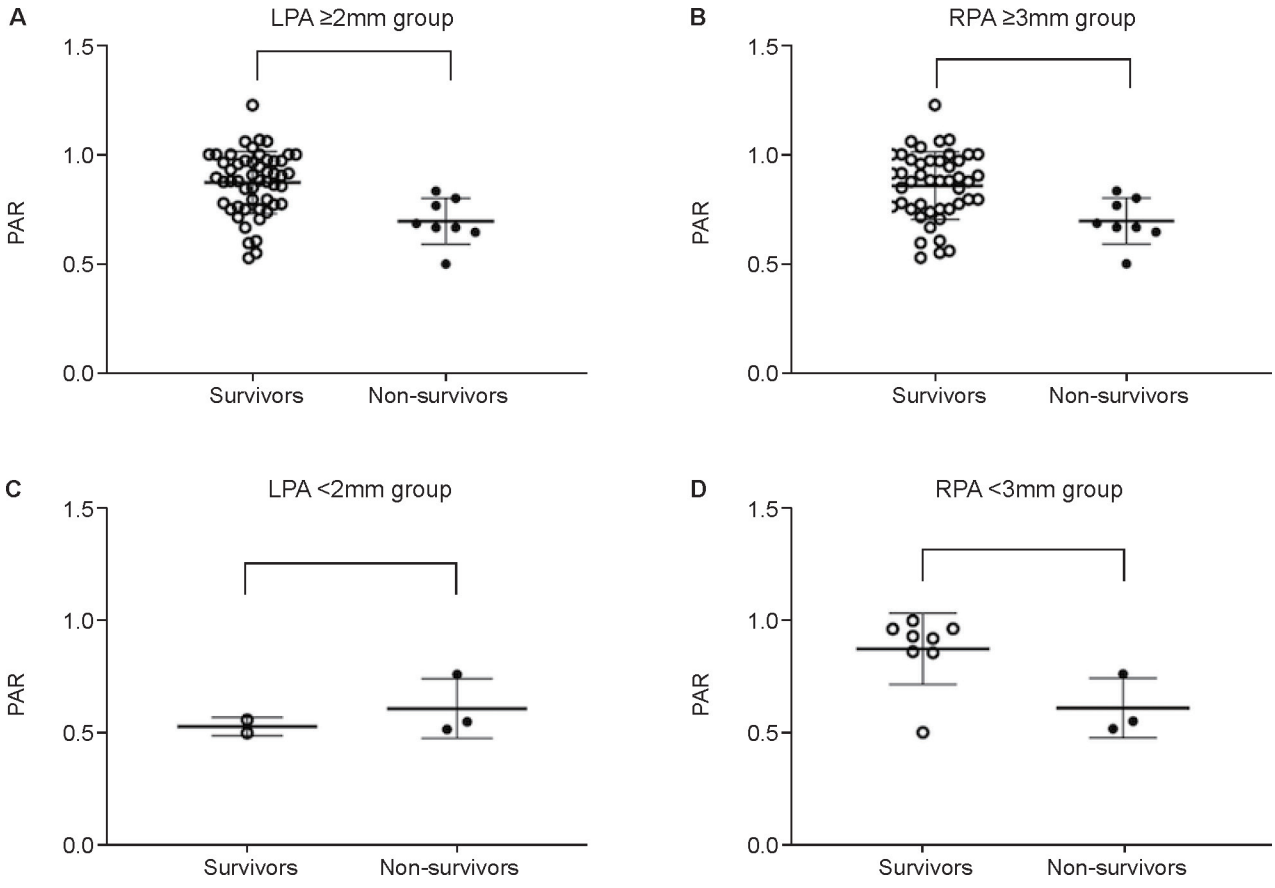

Figure 1 Comparison of pulmonary artery ratios (PARs) between survivors and non-survivors (mean±SD). (A) LPA ≥2 mm group, (B) RPA ≥3 mm group, (C) LPA <2 mm group, (D) RPA <3 mm group. LPA, left pulmonary artery; RPA, right pulmonary artery.

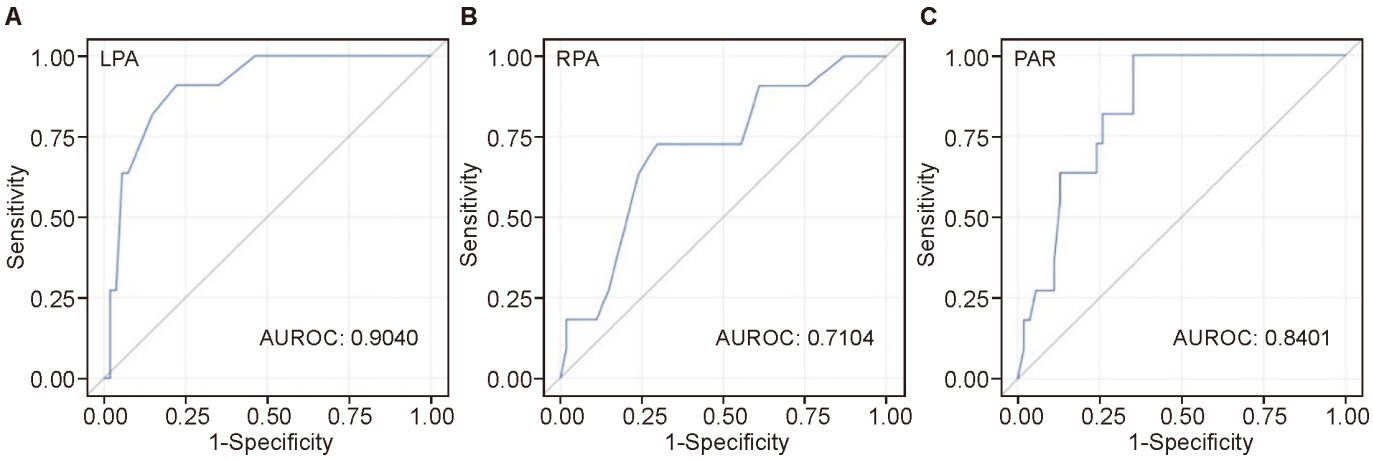

Figure 2 Receiver operating characteristic analysis according to clinical outcome: (A) left pulmonary artery (LPA), (B) right pulmonary artery (RPA) and (C) pulmonary artery ratio (PAR). AUROC, area under receiver operating characteristic curve.

0.610±0.108 (p=0.487) (figure 1C) and 8 of 54 survivors with RPA <3 mm had mean PAR of 0.875±0.115 and 3 of 11 non-survivors with RPA <3 mm had mean PAR of 0.610±0.108 (p=0.0315) (figure 1D). When published PA diameters from CDH cases who died were expressed as PAR according to the protocol used in the present study, mean PAR for non-survivors was also significantly less than mean PAR for survivors. PAR would appear to be consistently prognostic.

The largest area under ROC (AUROC) curve of 0.9040 was obtained for LPA, and the next largest AUROC of 0.8401 was obtained for PAR. The smallest AUROC of 0.7104 was obtained for RPA (figure 2). The cut-off value for PAR derived from the ROC curve was 0.762. However, PAR of 0.762 was considered useful as a cut-off value when management decisions (for example, requirement for HFOV and NO) were required. Subjects with high PAR (PAR ≥0.762) required HFOV and NO for more than 24 hours less than subjects with low PAR (PAR <0.762) (p=0.0244 and p=0.0485, respectively) (table 2). Similarly, when PAR and stabilization were assessed, subjects with high PAR stabilized significantly earlier than subjects with low PAR (1.71±0.68 days vs 3.22±0.92 days) (p<0.0001) (figure 3). In other words, subjects with low PAR had surgical intervention later.

Defect sizes in CDH diaphragms were compared using the Congenital Diaphragmatic Hernia Study Group Classification[15] and PAR of 0.762. The most common defect in high PAR subjects was B at 73.2% and in low PAR subjects was also B at 53.8%. A and B together comprised 61.5% of low PAR subjects. These differences were not significant but low PAR subjects had slightly larger defects (table 3).

DISCUSSION

By calculating PAR in this study, differences between survivors and non-survivors were significant even when PA diameters were comparable. In other words, the clinical relevance of PAR was strongly reflected by differences in outcome. In fact, while 8 of 11 non-survivors actually had favorable PA diameters of >2 mm, all had significantly lower PAR. Thus, PAR was found to be strongly correlated with clinical outcome in subjects with good prognosis by optimizing PA diameter data with potential for other practical/prognostic applications. Although AUROC of 0.9040 was obtained for LPA diameter alone, indicating that LPA was statistically the most prognostic in the subjects investigated in the present study, PAR was considered to reflect clinical status more comprehensively by identifying subjects who did poorly with good LPA (8 of 11 non-survivors with LPA ≥2 mm) and subjects with bad LPA (2 of 54 survivors with LPA <2 mm) who did well. LPA alone would not have identified these subjects. In other words, in the present study, low PAR was correlated with cardiopulmonary instability and high PAR with cardiopulmonary stability as reflected by PAR being useful for discriminating between subjects who needed NO and HFOV. The current management protocol uses post-ductal SpO_2 less than 75% or echocardiography typical of PH as indicators for NO, but PAR over 0.762

Table 2 Comparison of clinical course according to pulmonary artery ratio (PAR)

	PAR ≥0.762 (n=41)	PAR <0.762 (n=13)	P value
NO requirement*	24/41 (58.5%)	12/13 (92.3%)	0.0244
HFOV requirement*	31/41 (75.6%)	13/13 (100%)	0.0485

*For more than 24 hours.
HFOV, high-frequency oscillatory ventilation; NO, nitric oxide.

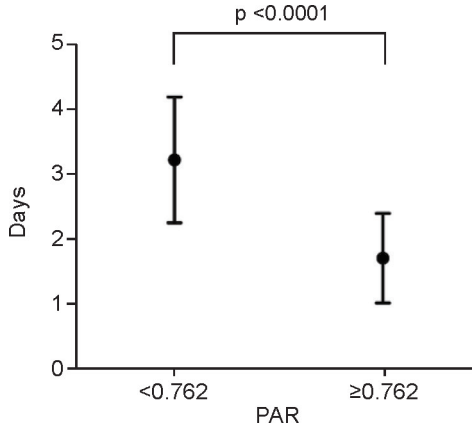

Figure 3 Comparison of duration until stabilization according to pulmonary artery ratio (PAR) (mean±SD).

could also be adopted as an indication for commencing NO as high PAR survivors required HFOV and NO less than low PAR survivors.

In the present study, PAR also correlated with time required for stabilization as high PAR subjects were stabilized significantly quicker than low PAR subjects. As pulmonary blood flow is crucial for effective postnatal gas exchange,[16] in CDH with low PAR, blood flow to the opposite lung is predominant with poor reserve to increase pulmonary blood flow on the side of the CDH. If blood flow to the PA on the side of the CDH cannot be increased, it would be difficult to improve hypoxemia, leading to a vicious cycle in which the PA does not dilate. One reason for pulmonary blood flow on the side of the CDH to increase poorly would be because one PA is larger, that is, low PAR. In other words, when PAR is low, it might be difficult to resolve PH requiring more intensive management. Severe PH in CDH can be avoided with optimal lung management, which often requires ECMO, and if ECMO is not available, strict avoidance of high ventilation pressures. As a result, by calculating PAR at the time of initial clinical assessment, management of CDH could be enhanced by having a simple way of predicting whether cardiopulmonary function can be stabilized preoperatively, an important factor when planning surgery.

This study has limitations, that is, that it is retrospective, performed at one center, is relatively small as a series, and echocardiography was not repeated postoperatively. However, PAR appeared to better reflect the severity of PH in CDH by optimizing the predictive value of PA diameter size. In other words, because non-survivors were similar to survivors demographically in the current study and there were non-survivors with PA diameters consistent with survival according to PA diameter criteria, PAR would appear to be valuable as an objective, non-invasive, readily assessable prognostic indicator that has potential because it is clinically relevant and applicable for enhancing management. One of the challenges with using PA diameter alone is that PA diameter is fixed, a fact that was demonstrated by serial echocardiography in a published paper from the same institute.[10] Despite this, PH is known to be dynamic during the early postnatal course, and the hemodynamic consequences of PH often depend on other factors including systemic blood pressure, reversibility of pulmonary vascular resistance and ventricular function. It is an oversimplification to suggest that PAR in isolation reflects PH severity. However, differences in hemodynamic variables such as need for one or more inotropes, use of pulmonary vasodilators, or presence of right-to-left ductal shunting were related to PAR when comparing survivors with non-survivors; PAR could be considered valid as a marker for assessing cardiopulmonary stability provided that the limitation of a static measurement accurately predicting a dynamic clinical course is understood.

Further studies are planned to confirm the prognostic value of PAR over time and to compare it with a control group without CDH, and to add other variable data such as PA trunk and aortic artery trunk, lung-to-head ratio, and total fetal lung volume. The present study would suggest that calculation of PAR from careful echocardiographic measurement of PA diameters soon after birth may be valuable for obtaining a more clinically relevant assessment of cardiopulmonary stability in patients with CDH.

Table 3 Comparison of defect size according to pulmonary artery ratio (PAR)

	PAR ≥0.762 (*n*=41)	PAR <0.762 (*n*=13)
A (<10%)	1 (2.4%)	1 (7.7%)
B (<50%)	30 (73.2%)	7 (53.8%)
C (>50%)	5 (12.2%)	4 (30.8%)
D (>90%)	1 (2.4%)	0 (0.0%)
Unknown	4 (9.8%)	1 (7.7%)

Contributors YM, HK, AY and TO designed the study. YM, HK, SN, SY, TO and GM collected and analyzed data. YM, HK, and GJL wrote the manuscript. AY and TO gave conceptual advice. HK is responsible for the overall content as guarantor. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Ethics approval This study involves human participants, was approved by the Institutional Review Board at Juntendo University School of Medicine (approval number: 16-257), and complies with the Helsinki Declaration of 1975 (revised 1983). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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