ORIGINAL RESEARCH

Preoperative cerebral and renal oxygen saturation and clinical outcomes in pediatric patients with congenital heart disease

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Abstract
We examined the predictability of preoperative cerebral and renal rSO_2 values for outcomes in pediatric patients undergoing cardiac surgery under cardiopulmonary bypass (CPB). Patients who underwent pediatric cardiac surgery under CPB between September 2015 and September 2017 were enrolled in this study. Patients monitored with both cerebral and renal rSO_2 at the beginning of surgery were included. The primary outcome was the prediction of outcomes after pediatric cardiac surgery. Outcome was defined as any of: (1) death within 30 days after surgery, or the need for (2) renal replacement therapy or (3) extracorporeal membrane oxygenation, (4) shorten mechanical ventilator-free day,(5) shorten ICU-free survival day. We included 59 patients: cyanotic n = 31; non-cyanotic n = 28. Among all patients, 15 (25%) had poor outcomes, including three deaths. The cerebral and renal rSO_2 values were significantly lower in the cyanotic patients with poor outcomes compared to those without poor outcomes (cerebral: 59 ± 11 vs. 50 ± 5, p = 0.021; renal: 59 ± 15 vs. 51 ± 14, p = 0.015) but only the renal rSO_2 value was significantly lower in the non-cyanotic patients (77 ± 10 vs. 61 ± 14, p = 0.011). The cut-off value (51%) of cerebral rSO_2 were associated with risk of mechanical ventilator-free day and ICU-free survival day [ORs of 22.8 (95% CI 2.21–235.0, p = 0.0087) and 15.8 (95% CI 1.53–164.0, p = 0.0204), respectively] in the cyanotic patients. The cut-off value (66%) of cerebral rSO_2 value was associated with risk of mechanical ventilator-free day [OR of 11.3 (95% CI 1.05–25.3, p = 0.0456)] and the cut-off value (66%) of renal rSO_2 value was associated with risk of ICU-free survival day [ORs of 33.0 (95% CI 2.25–484.0, p = 0.0107)] in the noncyanotic patients. The preoperative low rSO_2 values were associated with outcomes including 30-day mortality and might be reflective of the severity of cardiopulmonary function. Further studies are needed to confirm our results.

Keywords Congenital heart disease · Regional oxygen saturation · Cardiopulmonary dysfunction · Cerebrovascular autoregulation

1 Introduction

Near-infrared spectroscopy uses an infrared light source to measure regional oxyhemoglobin saturation (rSO_2) noninvasively into the tissue bed. Cerebral rSO_2 values are correlated with the invasive venous oxygen saturation ($ScvO_2$) values obtained after a patient's congenital heart surgery [1]. Low cerebral rSO_2 values have been associated with

an increased risk of hypoxic-ischemic brain injury [2, 3] and low renal rSO_2 values can be a good predictor of acute kidney injury after cardiac surgery in both adult and pediatric patients [4–7]. It was reported that in adult cardiac patients, the preoperative rSO_2 value may reflect the severity of cardiopulmonary dysfunction and be associated with short- and long-term mortality and morbidity [8]. However, the question of whether preoperative rSO_2 values could be used to predict poor outcomes in patients undergoing congenital heart surgery has not been well determined due to the complicated cardiac physiology and impaired cerebral blood flow in infants with congenital heart disease [9–11]. We conducted the present study to evaluate whether preoperative cerebral and renal rSO_2 values could have association

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with each outcome in pediatric patients undergoing cardiac surgery under cardiopulmonary bypass (CPB).

2 Methods

2.1 Study design

This retrospective observational study was approved by the Medical Ethics Committee of our hospital (Permission No. 2017-1110). Electronic medical and anesthesia records of patients who underwent pediatric cardiac surgery under CPB at our hospital between September 2015 and September 2017 were reviewed. Patients whose cerebral and renal rSO_2 values were monitored at the beginning of surgery were included. Monitoring of rSO_2 values was continued until the end of the surgery. Patients who had required extracorporeal membrane oxygenation (ECMO) preoperatively were excluded, because ECMO has a strong effect on rSO_2 values [12]. In the operating room, after the induction of anesthesia, pediatric-sized oximetry sensors were placed on the patient's forehead and the right flank below the costovertebral angle overlying the right kidney. An INVOS 5100B oximeter (Somanetics, Troy, MI) was used to monitor both the cerebral and renal rSO_2 values. We recorded the rSO_2 values at the time point of the initiation of surgical procedures because rSO_2 values are considered relatively stable at that time.

2.2 Outcome measurement

The primary outcome in this study was the prediction of each outcome including death after pediatric cardiac surgery. We defined outcome as any of the following: (1) death within 30 days after surgery, or the need for (2) renal replacement therapy (RRT) or (3) ECMO, (4) mechanical ventilator-free days (<lower quartile: < 23 days in all patients, < 22days in cyanotic patients and < 27 days in non-cyanotic patients), or (5) shorten intensive care unit (ICU)-free survival day (< lower quartile: < 21 days in all patients, < 19 days in cyanotic patients and < 24 days in non-cyanotic patients). The mechanical ventilator-free days and ICU-free days were calculated as 28 minus the number of days or part-days spent with mechanical ventilation or in the ICU during the first 28 days after surgery (excluding any days of ICU readmission); patients who died were assigned the worst possible outcome of zero mechanical ventilator-free days and ICU-free days. The criteria for extubation in the ICU include spontaneous ventilation, manageable airway secretion, $F_IO_2 \leq 0.4$, hemodynamic stability (dobutamine/dopamine ≤ 5 µg/kg/min), adequate cough reflex and spontaneous body movement. No patients after congenital heart disease were extubated in the

operating room, even if the patients had Fontan circulation or Glenn circulation.

2.3 Statistical analysis

The statistical analysis was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Comparisons between the groups' demographic and surgical data were assessed using the unpaired Student's t test or the Mann–Whitney U test. A subgroup analysis was also performed in patients with cyanotic and non-cyanotic congenital heart disease. To determine an optimal cutoff value for rSO_2 for the diagnosis of each outcome over time, we conducted a receiver operating characteristic (ROC) curve analysis. Optimal cutoff values were determined by using the Youden index. We estimated odds ratios (ORs) with their 95% confidence intervals (95% CIs) using Chi-square test to evaluate the risk of poor outcomes for rSO_2 values below the optimal cutoff obtained from the ROC curve. Due to the small sample size that limited our ability to perform multi-variable analyses, unadjusted odd ratios are presented. All data are presented as mean ± SD or median (25th to 75th percentile). A p-value < 0.05 was considered significant.

3 Results

We included 59 patients: 31 patients had cyanotic heart disease, and 28 patients had non-cyanotic heart disease. Diagnosis of the patients was shown in Table 1. Among all of the patients, 15 (25%) patients were eligible for outcomes, including three deaths. None of the non-cyanotic heart patients died or needed RRT or ECMO. The rSO_2 values were significantly lower in the patients with poor outcomes compared to those without poor outcomes (Table 2).

3.1 Preoperative rSO_2 and each outcome

The ROC curves in all patients are shown Fig. 1. The ROC curves analysis revealed that both cerebral and renal rSO_2 were good predictors of each outcomes in all patients (Table 3). The cerebral and renal rSO_2 values were a good predictor for 30-day mortality after surgery in all patients. In addition, cerebral rSO_2 showed better performance as a predictor of each type of outcome compared to renal rSO_2 in all patients. The best cut-off cerebral and renal rSO_2 values for each outcome in all patients were shown in Table 3 and the cut-off rSO_2 values were associated with risk of mechanical ventilation-free day and ICU-free survival day [cerebral rSO_2: ORs of 6.87 (95% CI 1.34–35.3, p = 0.0211) and 6.87 (95% CI 1.81–26.1, p = 0.0046), and

Table 1 Cardiac physiology groups

Group	Diagnosis
1: No cyanosis, no mixing	RVOT repair (2)
	Valve replacement/repair (1)
2: No cyanosis with L → R	VSD (15)
	ASD (5)
	cAVSD (4)
	Other (1)
3: Cyanosis without L → R shunt	Fontan (1)
4: Cyanosis with L → R shunt	TOF (5)
	TGA (4)
	Single ventricle, stage 1 (5)
	Single ventricle, stage 2 (2)
	TAPVR (2)
	CoA complex (3)
	DORV (3)
	PA/VSD (2)
	HLHS (1)
	Other (3)

L → R shunt left-to-right, *RVOT* right ventricular outflow tract, *VSD* ventricular septal defect, *ASD* arterial septal defect, *cAVSD* complete atrioventricular septal defect, *TOF* tetralogy of Fallot, *TGA* transposition of the great arteries, *CoA* coarctation of aorta, DORV double-outlet right ventricle, *PA* pulmonary atresia, *HLHS* hypoplastic left heart syndrome

renal rSO_2: ORs of 7.50 (95% CI 1.46–38.7, p = 0.016) and 12.0 (95% CI 2.37–60.6, p = 0.0027), respectively] in all patients.

3.2 Subgroup analysis

The ROC curves of cerebral and renal rSO_2 cut-off values that could be useful to identify patients with each type of outcome (Tables 4, 5) revealed that the cerebral rSO_2 value was a good predictor for 30-day mortality after surgery in the cyanotic patients (Table 4). The best cut-off cerebral and renal rSO_2 values for each outcome in cyanotic patients were shown in Table 4 and the cut-off rSO_2 values of cerebral rSO_2 were associated with risk of ventilator-free day and ICU-free survival day [ORs of 22.8 (95% CI 2.21–235.0, p = 0.0087) and 15.8 (95% CI 1.53–164.0, p = 0.0204), respectively] in the cyanotic patients.

However, in the non-cyanotic patients, the renal rSO_2 value was a better predictor of each outcome than the cerebral rSO_2 value (Table 5). The best cut-off cerebral and renal rSO_2 values for each outcome in non-cyanotic patients were shown in Table 5. The cut-off cerebral rSO_2 value was associated with risk of ventilator-free day [ORs of 11.3 (95% CI 1.05–25.3, p = 0.0456)] and the cut-off renal rSO_2 value was associated with risk of ICU-free survival day [ORs of 33.0 (95% CI 2.25–484.0, p = 0.0107)] in the non-cyanotic patients.

4 Discussion

This retrospective study revealed that the cerebral rSO_2 value obtained at the beginning of a pediatric patient's surgery could predict outcomes including death. This is in agreement with a large cohort study in which the preoperative rSO_2 value was observed to be an independent predictor of short-and long-term mortality in adult cardiac patients [8]: the rSO_2 value and 30-day mortality showed an AUC of 0.71 (95% CI 0.68–0.73; p < 0.0001) and a cutoff value of ≤ 51%. In addition, a recent retrospective study revealed that the baseline cerebral rSO_2 value was associated with 30-day mortality after left ventricular assist device surgery [13]. In addition, some studies have examined the utility of rSO_2 values to predict poor outcomes in patients with congenital heart disease [9, 10]. The pathophysiology and the surgery procedures for congenital heart disease are complex, and thus risk evaluations in congenital heart disease are difficult. However, the low baseline cerebral rSO_2 value, especially less than 50%, was associated with poor outcome in congenital heart disease pediatric patients and, interestingly, pediatric patients with left-to-right shunting rather than cyanotic had lower baseline cerebral rSO_2 [9]. Our results were in-line of these previous studies and a preoperative rSO_2 value might be useful for predicting the risk of outcome in congenital heart patients.

Our present findings suggest that rSO_2 values are reflective of the severity of cardiopulmonary function. This may be due to the correlation (r = 0.93, p < 0.0001) between the cerebral rSO_2 and the O_2 value obtained from the superior caval vein ($ScvO_2$) in pediatric cardiac patients [1]. It was also reported that changes in rSO_2 reflected those in mixed venous oxygen saturation in adult cardiac patients [14]. BNP [8, 15] and left ventricular ejection fraction [16, 17] were described as factors that are significantly associated with baseline rSO_2 values in cardiac patients. Additionally, multivariable regression analysis revealed that arterial saturation was significantly correlated with baseline cerebral rSO_2 value (r = 0.63, p < 0.001) [10]. Cardiopulmonary dysfunction before cardiac surgery increases the risk of low cardiac output syndrome, which is associated with morbidity and mortality. Considering the previous and present results, since low rSO_2 values represent cardiopulmonary dysfunction in congenital heart patients, strict perioperative management must be used to prevent potentially life-threatening cardiopulmonary complications.

The present data suggest that renal rSO_2 values were associated with outcomes in both cyanotic and non-cyanotic patients, whereas cerebral rSO_2 values were associated with outcomes only in the present cyanotic patients. This difference might be due to the impairment

Table 2 Patient characteristics and perioperative data

	All patients, n = 59			Cyanotic patients, n = 31			Non-cyanotic patients, n = 28		
	Poor outcomes		p	Poor outcomes		p	Poor outcomes		p
	(−)	(+)		(−)	(+)		(−)	(+)	
Male/female (n)	27/17	9/6	1.000	14/7	6/4	1.000	14/9	2/3	0.231
Age (months)	15 (5, 33)	3 (0, 9)	0.005	7 (1, 15)	6 (0, 9)	0.594	27 (11, 55)	7 (4, 21)	0.016
Height (cm)	77 (19)	57 (12)	0.001	64 (11)	58 (13)	0.205	86 (20)	69 (18)	0.096
Body weight (kg)	9.7 (5.5)	4.9 (3.0)	0.002	6.2 (3.0)	5.5 (3.5)	0.531	12.2 (6.0)	7.1 (4.4)	0.087
Body surface area (m^2)	0.47 (0.18)	0.31 (0.12)	0.002	0.36 (0.11)	0.30 (0.13)	0.240	0.54 (0.18)	0.37 (0.15)	0.067
F_IO_2	0.4 (0.3, 0.4)	0.4 (0.21, 0.6)	0.893	0.4 (0.4, 0.6)	0.4 (0.21, 0.6)	0.307	0.4 (0.3, 0.4)	0.4 (0.3, 0.4)	0.770
SpO_2 (%)	99 (90, 100)	86 (79, 94)	0.003	86 (77, 92)	85 (79, 91)	0.966	99 (1)	98 (2)	0.065
HR (bpm)	113 (21)	121 (14)	0.161	126 (18)	121 (16)	0.435	105 (18)	104 (18)	0.893
MAP (mmHg)	61 (16)	52 (13)	0.062	52 (12)	51 (12)	0.890	68 (15)	53 (10)	0.048
Cerebral rSO_2 (%)	65 (12)	54 (9)	0.001	59 (11)	50 (5)	0.021	70 (9)	62 (13)	0.105
Renal rSO_2 (%)	69 (13)	53 (12)	<0.001	59 (15)	51 (14)	0.015	77 (10)	61 (14)	0.011
Renal-cerebral rSO_2 (%)	3.9 (12.1)	−1.0 (11.0)	0.176	−0.2 (12.6)	0.9 (11.6)	0.812	7 (11)	0 (12)	0.250
Preoperative BNP (pg/mL)	31 (17, 66)	140 (94, 750)	0.001	68 (21, 506)	114 (94, 541)	0.163	30 (18, 52)	63 (51, 492)	0.141
Preoperative Cre (mg/dL)	0.30 (0.23,0.34)	0.38 (0.24, 0.52)	0.102	0.31 (0.23, 0.36)	0.40 (0.26, 0.66)	0.095	0.32 (0.21)	0.29 (0.09)	0.652
Preoperative Hb (g/dL)	11.5 (2.0)	12.0 (1.4)	0.364	12.3 (2.4)	12.4 (0.9)	0.931	11.0 (1.1)	10.2 (4.7)	0.286
Preoperative mechanical ventilation (n)	4	9	0.001	6	6	0.127	0	1	0.179
Preoperative inotropic support (n)	1	4	0.013	0	3	0.027	0	2	0.026
RACHS-1 (n)									
1	6	0	0.088	0	0	0.420	5	1	0.763
2	23	5		7	2		16	3	
3	11	7		9	6		2	1	
4	4	2		5	1		0	0	
6	0	1		0	1		0	0	
Duration of surgery (min)	237 (74)	334 (194)	0.007	279 (71)	377(244)	0.098	210 (63)	238 (66)	0.378
Duration of CPB	99 (69, 127)	144 (95, 239)	0.017	116 (88, 173)	165 (92, 307)	0.170	94 (61, 114)	92 (9, 157)	0.384
Duration of aortic clamp	49 (15, 63)	18 (0, 69)	0.208	35 (80, 100)	9 (0, 34)	0.520	55 (32, 62)	47 (20, 52)	0.401
Duration of anesthesia (min)	330 (87)	458 (217)	0.003	385 (88)	482 (259)	0.130	296 (71)	341 (104)	0.245

Mean (SD) median (interquartile range), *HR* heart rate, *MAP* mean arterial pressure, *rSO₂* regional oxyhemoglobin saturation, *BNP* brain natriuretic peptide, *Cre* serum creatinine, *RACHS-1* Risk Adjusted Classification for Congenital Heart Surgery-1

of cerebrovascular autoregulation in the cyanotic patients. In normal infants, the renal rSO_2 value is higher compared to the cerebral rSO_2 value, and the cerebral rSO_2 value remains unchanged due to the cerebrovascular autoregulation even though the renal rSO_2 value decreases when the hemodynamic status is unstable [18]. Impaired cerebrovascular autoregulation was found in approx. 40% of preterm infants [19]. Impaired cerebrovascular

Fig. 1 Receiver-operating characteristic curves comparing the ability of regional oxygen saturation to predict each outcome in all patients. **a** Renal replacement therapy; **b** extracorporeal membrane oxygenation; **c** intensive care unit-free survival day; **d** mechanical ventilator-free day, rSO_2 regional oxyhemoglobin saturation
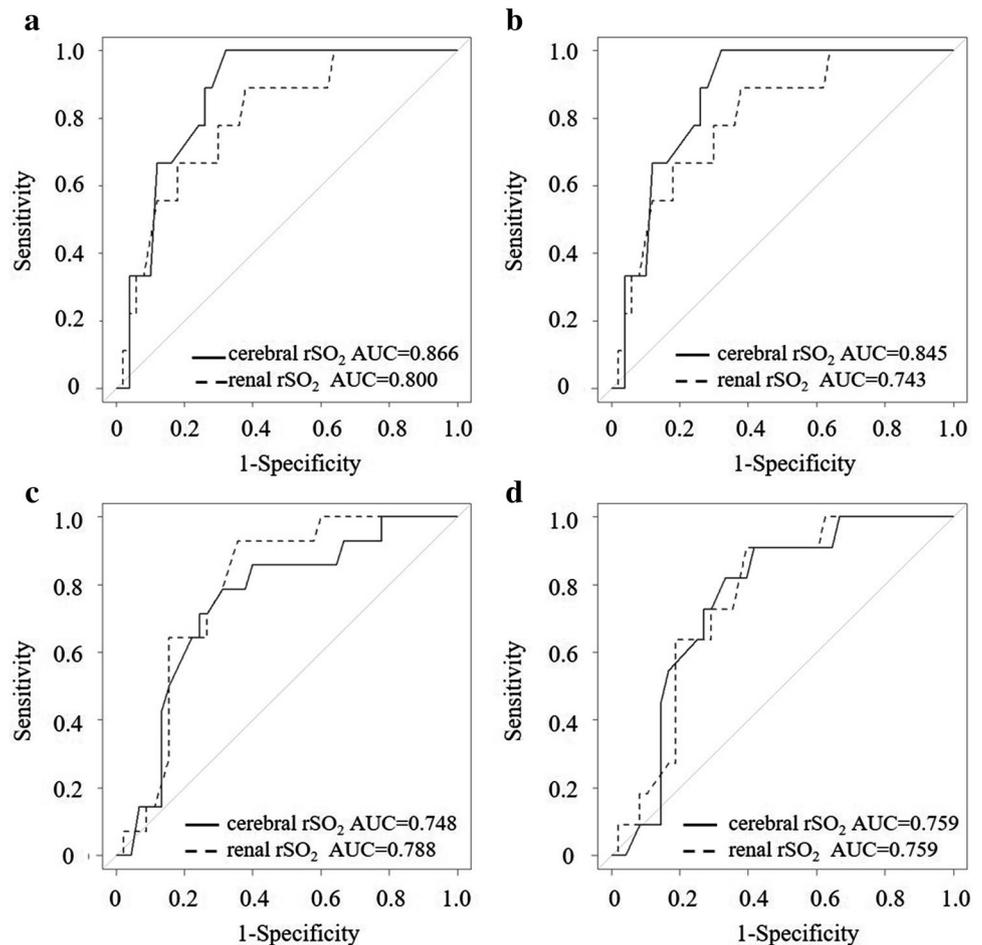

Table 3 Optimal cut-off values of rSO_2 for the prediction of poor outcomes in all patients (n = 59)

	n	rSO_2	Cut-off (%)	AUC (95% CI)	Sensitivity	Specificity
RRT	9	Cerebral	58	0.866 (0.770–0.961)	1.000	0.680
		Renal	66	0.800 (0.652–0.948)	0.889	0.620
ECMO	7	Cerebral	58	0.845 (0.733–0.956)	1.000	0.654
		Renal	66	0.743 (0.565–0.921)	0.857	0.596
Mechanical ventilator-free day (< 23 days)	11	Cerebral	61	0.759 (0.623–0.894)	0.909	0.583
		Renal	67	0.759 (0.627–0.892)	0.909	0.604
ICU-free survival day (< 21 days)	14	Cerebral	58	0.748 (0.606–0.891)	0.786	0.689
		Renal	67	0.788 (0.670–0.906)	0.929	0.644
Death within 30 days	3	Cerebral	51	0.887 (0.794–0.980)	1.000	0.839
		Renal	66	0.777 (0.537–1.000)	1.000	0.571

ECMO extracorporeal membrane oxygenation, *RRT* renal replacement therapy

autoregulation was also detected in patients with congenital heart disease and was associated with abnormal prenatal neurologic development [20]. In addition, the absence of cerebrovascular autoregulation was associated with adverse outcomes in preterm infants [21]. These findings suggest that impaired cerebrovascular autoregulation caused parallel changes in both cerebral and renal rSO_2 in cyanotic patients. Therefore, prompt intervention: red blood cell transfusion; administration of inotropic drugs; and changing mechanical ventilation setting; to lower the cerebral rSO_2 value may be required to improve the clinical outcomes of cyanotic patients.

Table 4 Optimal cut-off values of rSO$_2$ for the prediction of poor outcomes in the cyanotic patients (n = 31)

	n	rSO$_2$	Cut-off (%)	AUC (95% CI)	Sensitivity	Specificity
RRT	9	Cerebral	58	0.747 (0.572–0.923)	1.000	0.500
		Renal	53	0.672 (0.451–0.892)	0.667	0.682
ECMO	7	Cerebral	51	0.717 (0.524–0.911)	0.714	0.750
		Renal	53	0.586 (0.331–0.841)	0.571	0.625
Mechanical ventilator-free day (< 22 days)	6	Cerebral	51	0.757 (0.590–0.923)	0.833	0.760
		Renal	53	0.570 (0.299–0.841)	0.667	0.640
ICU -free survival day (< 19 days)	7	Cerebral	51	0.801 (0.646–0.955)	0.857	0.792
		Renal	53	0.607 (0.362–0.852)	0.714	0.667
Death within 30 days	3	Cerebral	51	0.798 (0.637–0.958)	1.000	0.714
		Renal	66	0.631 (0.249–1.000)	1.000	0.321

ECMO extracorporeal membrane oxygenation, *RRT* renal replacement therapy

Table 5 Optimal cut-off values of rSO$_2$ for the prediction of poor outcomes in the non-cyanotic patients (n = 28)

	n	rSO$_2$	Cut-off (%)	AUC (95% CI)	Sensitivity	Specificity
Mechanical ventilator-free day (< 27 days)	5	Cerebral	66	0.809 (0.616–1.000)	0.800	0.739
		Renal	71	0.845 (0.682–1.000)	1.000	0.696
ICU-free survival day (< 24 days)	4	Cerebral	70	0.536 (0.149–0.923)	0.750	0.583
		Renal	66	0.833 (0.551–1.000)	0.750	0.917

In the present analyses, not only the rSO$_2$ values but also the patients' age, physique (height, body weight, and body surface area), SpO$_2$, and the duration of surgery and anesthesia differed significantly between the patients with poor outcomes and those without poor outcomes in all patients and in the non-cyanotic patients. In contrast, only the rSO$_2$ value was different in the cyanotic patients. The following may explain the differences in our findings between all patients, non-cyanotic patients, and cyanotic patients. The severity of the heart disease was different between the cyanotic and non-cyanotic patients. In general, cyanotic congenital heart disease is more severe compared to non-cyanotic congenital heart disease, and it requires surgical repair during the neonatal period. The surgical repair of cyanotic heart disease is more complicated and takes longer compared to the surgery for non-cyanotic congenital heart disease. Thus, patient age, physique, SpO$_2$ and the duration of surgery and anesthesia were significantly different between our patients with or without poor outcomes in the total patient series.

Limitations of this study should be considered. First, as the study was retrospective with a small sample size, we could not perform multivariable analyses, and confounding factors might thus have affected the results. Additionally, due to a small sample size, the 95% confidence intervals of the AUC of ROC curve for prediction of some of poor outcomes were relatively wide. Further studies with larger numbers of patients are needed to test our findings. Second, we classified the patients into cyanotic and non-cyanotic patients, however the classification is difficult. Tetralogy of Fallot is usually classified into cyanotic congenital heart disease but in some cases, patients with mild right ventricular outflow tract (RVOT) obstruction do not show cyanosis. In our study, all patients with tetralogy of Fallot have moderate to severe RVOT obstruction so we classified these patients into the cyanotic congenital heart disease. Third, rSO$_2$ was measured at one point in time in this study. The trend of rSO$_2$ values might be a better predictor of poor outcomes. The utility of a rSO$_2$ desaturation score was reported by Slater and colleagues, and which was associated with an increased risk of cognitive decline and prolonged hospital stay [22]. The intraoperative rSO$_2$ desaturation score was also a predictor of postoperative low cardiac output state [23]. We should pay attention not only absolute value but also trend of rSO$_2$ values to prevent or reduce the severity of life-threatening complication. Fourth, the rSO$_2$ values at the beginning of each surgery were measured under general anesthesia and mechanical ventilation with different fraction of inspired oxygen (F$_I$O$_2$) levels and hemoglobin concentration. These might have impact on rSO$_2$ values, but F$_I$O$_2$ and hemoglobin concentration were no significantly different between patients with and without poor outcomes. Additionally, the measurement of a pediatric patient's rSO$_2$ value in the fully awake condition is difficult, and we want to avoid the misregistration of erroneous values by artifact and crying which increases the oxygen consumption leading to lower rSO$_2$. Thus, we decided to measure the rSO$_2$ under

a stable condition with general anesthesia and mechanical ventilation, which may reflect cardiopulmonary function.

The mortality and morbidity after congenital heart surgery are usually dependent on not only the patient's preoperative cardiopulmonary function but also the surgical procedure, the anesthetic management, the postoperative care and other factors. Nevertheless, our analyses revealed that the rSO$_2$ value (which reflects preoperative cardiopulmonary function) can be a predictor of outcomes, and this indicates that preoperative cardiopulmonary function is a major factor associated with outcomes after congenital cardiac disease surgery.

In conclusion, despite of the small sample size in this study, the preoperative low rSO$_2$ value was associated with outcomes including 30-day mortality and might be reflective of the severity of cardiopulmonary function. Further studies are needed to confirm our positive results.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest. All authors read and approved the final manuscript and attest to the integrity of the original data and the analysis reported in this manuscript.

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