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# Association of the central venous-to-arterial carbon dioxide difference with low cardiac output-related outcomes after cardiac surgery in children: a prospective cohort study

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**Introduction:** Low-cardiac-output syndrome (LCOS) after cardiac surgery may lead to poor postoperative outcomes. The venous-to-arterial carbon dioxide partial pressure difference (VACO<sub>2</sub>) showed association with poor outcomes in adults with cardiac surgery, but its validity in pediatric population is uncertain. We evaluated the association of VACO<sub>2</sub> with LCOS-related outcomes and the correlation with other surrogate markers such as lactate levels and oxygen extraction ratio.

**Methods:** This prospective cohort study was conducted at an intensive care unit in a tertiary academic hospital. Children aged 1 day–18 years old undergoing elective cardiac surgery with cardiopulmonary bypass between August 2021 and December 2023 were included. Arterial and venous blood gases were collected at intensive care unit admission and at 6, 12, and 24 h postoperatively. The LCOS-related outcomes were defined as at least two of the following criteria being met within 24 h postoperatively: vasopressor-inotropic score  $\geq 20$ , ejection fraction  $< 50\%$  on echocardiography, need for serious post-operative intervention, and death.

**Results:** Of the 127 included patients (median age: 44.4 months), 37 (29.1%) had a Risk Adjustment for Congenital Heart Surgery score  $\geq 3$ , and 26 (20.4%) had LCOS-related outcomes. Linear mixed model regression analysis revealed that the VACO<sub>2</sub> did not significantly differ between patients with and without LCOS-related outcomes at all four time points. VACO<sub>2</sub> showed a fair-to-weak correlation with the oxygen extraction ratio ( $R^2 = 0.58$ ;  $p < 0.001$ ,  $R^2 = 0.22$ ;  $p = 0.015$ , and  $R^2 = 0.19$ ;  $p = 0.045$ , at 6, 12, and 24 h postoperatively, respectively) but showed no correlation with lactate levels. A persistently high VACO<sub>2</sub> ( $\geq 6$  mmHg) at 6 h postoperatively was significantly associated with fewer 28-day inotrope-free and intensive care unit-free days.

**Discussion:** VACO<sub>2</sub> was not significantly associated with LCOS-related outcomes in children after cardiac surgery with cardiopulmonary bypass. A persistently high VACO<sub>2</sub> at 6 h postoperatively was correlated with prolonged inotrope use and a prolonged intensive care unit stay.

## KEYWORDS

cardiopulmonary bypass, carbon dioxide, congenital heart disease, post-operative period, cardiac surgery, venoarterial CO<sub>2</sub> difference, children

# 1 Introduction

Cardiopulmonary bypass (CPB) during open-heart surgery constitutes a potent stimulus that induces a systemic inflammatory response through the following mechanisms: blood contact with the CPB circuit, ischemia–reperfusion injury, heparin–protamine interaction, and surgical trauma (1). These mechanisms aggravate complement cascade activation, endotoxin release, and cytokine production, leading to low-cardiac-output (CO) syndrome (LCOS), which occurs in 5%–55% (2) of pediatric patients after cardiac surgery and frequently occurs 9–12 h postoperatively (3). Delayed recognition and treatment of LCOS can lead to multiorgan system failure and even death.

Serum lactate level, central venous oxygen saturation (ScvO<sub>2</sub>), and oxygen extraction ratio (O<sub>2</sub>ER) are commonly used to monitor LCOS after cardiac surgery, however, these parameters may be influenced by multiple factors that are unrelated to low CO. For example, hyperlactatemia can occur due to the stress response to surgery, use of beta-adrenergic agonists, hyperglycemia, or acute liver and renal failure (4); furthermore, normal or high ScvO<sub>2</sub> values may be observed in the presence of mitochondrial dysfunction or the peripheral shunting effect (5). Some studies in sepsis population demonstrated unclear benefits of lactate levels and ScvO<sub>2</sub> for guiding therapy (6, 7). Recently, a novel bedside biomarker, venous-to-arterial carbon dioxide (CO<sub>2</sub>) partial pressure difference (VACO<sub>2</sub>), has emerged, suggesting a potential utility as an adjunctive marker to facilitate the guidance of therapeutic interventions in sepsis (5, 8).

The VACO<sub>2</sub> theoretically measures the circulatory clearance of tissue CO<sub>2</sub> and is inversely correlated with CO (9). VACO<sub>2</sub> is a better surrogate indicator of stagnant dysoxia than of dysoxia caused by hypoxia, anemia, or cytopathic pathology (9). A high VACO<sub>2</sub> at the time of sepsis diagnosis in adult patients exhibited a significant correlation with both the cardiac index and other tissue perfusion parameters such as lactate levels and ScvO<sub>2</sub> (10). A recent meta-analysis of 21 studies with 2,155 critically ill adult patients with both surgical and medical conditions demonstrated an association between high VACO<sub>2</sub> and CO and linked this to mortality (11). However, only four of these 21 studies focused on cardiac surgery, and they all reported different associations with unfavorable outcomes. Chen et al. (12) conducted propensity-matched analysis in 228 individuals post cardiac surgery with CPB and reported a significant influence of high VACO<sub>2</sub> on adverse outcomes with superior discrimination power than arterial lactate. Furthermore, two prospective adult studies (13, 14) indicated that high VACO<sub>2</sub> is an independent predictor of major postoperative complication after multivariate analyses. Owing to the limited data on VACO<sub>2</sub> in pediatric patients after

cardiac surgery with CPB, the relevance of VACO<sub>2</sub> as a predictor of poor outcomes in this population remains unclear.

In this study, we aimed to evaluate the association between VACO<sub>2</sub> and LCOS-related outcomes in children undergoing cardiac surgery with CPB and determine its correlation with other bedside surrogate markers. The secondary objective was to examine the association between VACO<sub>2</sub> and postoperative outcomes.

# 2 Materials and methods

## 2.1 Study design, setting, and participants

This prospective cohort study was performed in an eight-bed pediatric intensive care unit (PICU) at Songklanagarind Hospital, Hat Yai, Songkhla. Children aged 1 day–18 years with congenital or acquired cardiac disease who underwent elective open cardiac surgery with CPB and were admitted to the PICU postoperatively were included in the study. The exclusion criteria were as follows: preterm infants (gestational age <37 weeks), weight <2 kg, inability to wean off CPB, requirement for extracorporeal membrane oxygenation (ECMO) before leaving the operating room, and absence of arterial and central lines postoperatively. This study was approved by the Institutional Review Board of the Faculty of Medicine, Prince of Songkla University (Institutional Review Board approval number 64-299-1-1; date of approval: August 3, 2021). The study was conducted in accordance with Good Clinical Practice and the Helsinki Declaration of 1975.

## 2.2 Surgical procedures

Anesthesia was initiated according to our standardized protocol. Following incision, heparin was administered intravenously at a dosage of 3 mg/kg to achieve an activated clotting time (ACT) exceeding 400 s. ACT was monitored at 30-min intervals throughout the procedure, with an additional heparin dose of 3 mg/kg provided if the ACT fell below 400 s. Intraoperative corticosteroids were administered intravenously, based on individual anesthesiologist preferences. The priming solution for the CPB circuit included either Ringer's lactate or normal saline with mannitol, along with 20% albumin for patients weighing less than 10 kg. Leukocyte-depleted packed red blood cells were utilized when the preoperative hematocrit was below 30%. CPB was performed using a CAPIOX<sup>®</sup> FX05 Oxygenator and Stockert S5 pump, following the  $\alpha$ -stat strategy at a target temperature of 28°C. Hypothermia was induced to varying degrees; depending on the surgical procedure. Antegrade cold blood cardioplegia was administered at a volume of 20 ml/kg to achieve cardiac arrest, with an additional 10 ml/kg given if aortic cross-clamp time exceeded 20 min. Pump flow rates were maintained between 100 and 150 ml/kg/min for infants and 2.5–3.0 L/m<sup>2</sup>/min for older patients; adjusted according to age-appropriate mean arterial pressure. Arteriovenous modified

### Abbreviations

AUC, area under the curve; CPB, cardiopulmonary bypass; CI, confidence interval; CO, cardiac output; CO<sub>2</sub>, carbon dioxide; ECMO, extracorporeal membrane oxygenation; IFDs, ICU-free days; IQR, interquartile range; LCOS, low-cardiac-output syndrome; O<sub>2</sub>ER, oxygen extraction ratio; PICU, pediatric intensive care unit; RACHS, Risk Adjustment for Congenital Heart Surgery; VACO<sub>2</sub>, venous-arterial carbon dioxide partial pressure difference; VFDs, ventilator-free days; VIS, vasoactive-inotropic score.

ultrafiltration was selectively applied, based on the consensus of the surgical team and perfusionist, and performed for 5 min after separating from CPB. At the conclusion of CPB intravenous protamine sulfate was administered to reverse heparin anticoagulation.

## 2.3 Data collection and measurement

After receiving written informed consent from the patients' parents or legal guardians before operation, 0.3 ml blood samples were simultaneously collected from both the arterial and internal jugular central lines. This sampling was repeated at four different time points after patient arrival in the PICU: at PICU arrival (T0), 6-h (T6), 12-h (T12), and 24-h (T24) post operation. Arterial and venous blood gas readings were accepted if the samples were collected within 5 min of each other. A 1 h time gap in the collection of blood samples from the research schedule was allowed owing to unpredictable intensive care unit occupancy. Blood samples were analyzed within 1 min of blood collection using an arterial blood gas analysis machine (ABL 800 Basic Radiometer; Copenhagen, Denmark) located within the PICU. The attending staff independently provided standard post-cardiac surgery care, including fluid resuscitation, vasopressor and inotropic medication, and steroid administration without the researcher's involvement. If either the central or arterial lines were displaced within 24 h postoperatively, the remaining data were recorded as missing.

Data, including general baseline characteristics, intraoperative parameters, postoperative interventions, and outcomes, were collected until the patient was discharged. The Risk Adjustment for Congenital Heart Surgery tool (15) was used to classify the risk of mortality after congenital cardiac surgery. The vasoactive-inotropic score (VIS) was calculated using the formula by Gaies et al. (16) as follows:

$$\begin{aligned} \text{VIS} = & \text{Dopamine dose } (\mu\text{g/kg/min}) \\ & + \text{dobutamine dose } (\mu\text{g/kg/min}) + 100 \\ & \times \text{epinephrine dose } (\mu\text{g/kg/min}) + 10 \\ & \times \text{milrinone dose } (\mu\text{g/kg/min}) + 100 \\ & \times \text{norepinephrine dose } (\mu\text{g/kg/min}) + 10000 \\ & \times \text{vasopressin dose } (\text{U/kg/min}) \end{aligned}$$

Acute kidney injury was diagnosed according to the Kidney Disease-Improving Global Outcomes guidelines, 2012 (17), based on the presence of any of the following: a  $>0.3$  g/dl increase in the serum creatinine level within 48 h,  $>1.5$  times increase in the serum creatinine level from a known baseline value or one recorded within the preceding 7 days, and urinary volume  $<0.5$  ml/kg/h for 6 h. The 28-day ventilator-free days (VFDs), 28-day inotrope-free days, and 28-day ICU-free days (IFDs) were defined as the number of days that the patient survived without invasive ventilation, inotropic drugs, or ICU admission during the first 28 days postoperatively, with the day after the first

postoperative night considered as day 1. These variables were counted as zero for non-survivors.

The independent variables studied included the bedside surrogate markers (VACO<sub>2</sub>, O<sub>2</sub>ER, and lactate level) that were measured postoperatively. ScvO<sub>2</sub> was not evaluated because the participants' single-ventricle physiology might have interfered with ScvO<sub>2</sub> interpretation. VACO<sub>2</sub> was calculated as the central venous minus arterial CO<sub>2</sub> level and O<sub>2</sub>ER as the ratio between the difference in arterial and central venous oxygen saturation divided by the arterial oxygen saturation.

The primary outcomes were LCOS-related outcomes, which was consisted of at least two of the following criteria within 24 h postoperatively: (1) VIS  $\geq 20$ ; (2) left ventricular ejection fraction  $<50\%$  on echocardiography; (3) any unplanned surgery or intervention, cardiac arrest, or utilization of ECMO; and (4) death. The secondary outcomes included: 28-day VFDs, 28-day inotrope-free days, 28-day IFDs, percentage of morbidities (reintubation, significant arrhythmic events requiring medication or intervention, acute kidney injury, renal replacement therapy, and neurological complications), and mortality rate.

## 2.4 Statistical analyses

Statistical analyses involved descriptive analysis of means (standard deviations) for normally distributed continuous data, medians (interquartile ranges) for non-normally distributed continuous data, and percentages for categorical data. The Student's *t*-test or Mann-Whitney *U* test was used for intergroup comparison of continuous data, depending on the pattern of data distribution. Categorical data were compared using the chi-squared or Fisher's exact test, as indicated. Correlation analysis between bedside parameters was performed using Pearson's and Spearman's correlation coefficients for parametric and non-parametric variables, respectively. Linear mixed-model regression was used to compare the postoperative laboratory (lactate, VACO<sub>2</sub>, and O<sub>2</sub>ER) values between the LCOS and no-LCOS groups over time with adjusted confounder variables that might affect outcome (age, RACHS, type of repair, CPB time, intraoperative corticosteroid, intraoperative fluid balance). Receiver operating characteristic curves were used to evaluate performance of VACO<sub>2</sub> on discriminating LCOS-related outcomes. Subgroup analysis was performed according to patient's age, type of repair, and RACHS score. Statistical significance was set at  $p < 0.05$ . All analyses were conducted using R version 4.3.1 (The R Foundation for Statistical Computing, Vienna, Austria).

## 2.5 Ethics statement

Ethical approval for this study was obtained from the Ethics Committee of the Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand.

## 3 Results

### 3.1 Baseline characteristics of participants

Between August 2021 and December 2023, 136 patients underwent open-heart surgery. Nine patients were excluded from the study, which included five patients who could not be weaned off CPB postoperatively and four patients who underwent emergency operations. The final analysis included 127 patients, of which 26 (20.4%) developed LCOS-related outcomes within 24 h postoperatively. Five patients (3.9%) required re-operation or reintervention, seven (5.5%) required ECMO, three (2.4%) developed cardiac arrest, and seven (5.5%) died. Factors significantly associated with LCOS-related outcomes included preoperative sepsis, a high Risk Adjustment for Congenital Heart Surgery score, long CPB time, long aortic clamp time, high amount of blood transfusion, and intraoperative corticosteroid administration (Table 1). The rates of postoperative intervention, including systemic steroid administration (60.4% vs. 24.3%,  $p < 0.01$ ), blood transfusion [19.6 [10.0–34.6] vs. 6.4 [0–13.5] ml/kg,  $p < 0.01$ ], and renal replacement therapy (13% vs. 0%,  $p = 0.002$ ), as well as those of end-organ dysfunction and death, were higher in the LCOS group than in the no-LCOS group (Supplementary Table 1).

TABLE 1 Comparison of baseline characteristics and intraoperative parameters between patients with and without LCOS-related outcomes ( $n = 127$ ).

| Characteristic                                         | LCOS-related outcomes ( $n = 26$ ) | No LCOS-related outcomes ( $n = 101$ ) | $p$ -value |
|--------------------------------------------------------|------------------------------------|----------------------------------------|------------|
| Age (months), median (IQR)                             | 5.4 (0.8–74.7)                     | 32.5 (11.9–69.7)                       | 0.053      |
| Genetic abnormalities, $n$ (%)                         | 2 (7.7)                            | 16 (15.8)                              | 0.363      |
| Preoperative sepsis, $n$ (%)                           | 12 (46.2)                          | 16 (15.8)                              | 0.002      |
| Previous cardiac surgery, $n$ (%)                      | 7 (26.9)                           | 32 (31.7)                              | 0.817      |
| Single-ventricle repair, $n$ (%)                       | 5 (19.2)                           | 18 (17.8)                              | 1.000      |
| RACHS score, $n$ (%)                                   |                                    |                                        | <0.001     |
| <3                                                     | 8 (30.8)                           | 82 (82.2)                              |            |
| $\geq 3$                                               | 18 (69.2)                          | 19 (17.8)                              |            |
| Cardiopulmonary bypass time (min), median (IQR)        | 152.0 (136.8, 244.2)               | 84.0 (52.0, 140.0)                     | <0.001     |
| Aortic clamp time (min), median (IQR)                  | 111.5 (77.2, 164.2)                | 47.0 (22.0, 82.8)                      | <0.001     |
| Intraoperative blood transfusion (ml/kg), median (IQR) | 60.4 (43.5, 91.9)                  | 37.0 (23.6, 54.7)                      | <0.001     |
| Intraoperative fluid balance (ml/kg), median (IQR)     | 21 (2.3, 38.4)                     | 18.2 (8.0, 37.7)                       | 0.998      |
| Intraoperative steroid use, $n$ (%)                    | 6 (23.1)                           | 6 (5.9)                                | 0.016      |

IQR, interquartile range; LCOS, low-cardiac-output syndrome; RACHS, Risk Adjustment for Congenital Heart Surgery.

### 3.2 Association between VACO<sub>2</sub> and outcomes after cardiac surgery

The patterns of laboratory values at the four time points are illustrated in Figure 1. The overall values of three parameters in the LCOS group were higher than those in the non-LCOS group at all four time points, with the exception for the VACO<sub>2</sub> at 24 h post operation. Univariate analysis performed to compare bedside surrogate marker values between patients with and without poor LCOS-related outcomes revealed that the LCOS group had significantly higher VACO<sub>2</sub> values at 12 h postoperatively, higher lactate levels at all four time points, and higher O<sub>2</sub>ER values at PICU admission and at 6 h postoperatively than the no-LCOS group. Analysis of the overall unadjusted area under the curve (AUC) of VACO<sub>2</sub> was 0.58–0.64 which was inferior to serum lactate levels in predicting LCOS events (Table 2).

After performing linear mixed-model regression analysis, the relationship between lactate change and the LCOS occurrence was significantly at 6 h and 12 h postoperatively ( $p < 0.05$ ), whereas the VACO<sub>2</sub> change was significant at 24 h postoperatively ( $p = 0.02$ ) and there was no relationship between O<sub>2</sub>ER change at all four time points (Figure 1).

To achieve the secondary study objective, we used a 6-mmHg cut-off, as described previously (9), to categorize the 6-h postoperative VACO<sub>2</sub> values into two groups. The results revealed significantly fewer 28-day inotrope-free days and 28-day IFDs in patients with a VACO<sub>2</sub>  $\geq 6$  mmHg than in patients with a VACO<sub>2</sub>  $< 6$  mmHg (24.0 [22.0–27.0] vs. 26.5 [23.0–28.0] days,  $p = 0.03$  and 23.0 [18.2–26.0] vs. 24.0 [22.0–27.0] days,  $p = 0.03$ , respectively) (Table 3). Subgroup analysis in patients with biventricular physiology and with aged more than one-month old revealed insignificant different outcomes (Supplementary Tables 2, 3).

### 3.3 Correlations between VACO<sub>2</sub> and other parameters

The correlations between VACO<sub>2</sub> and the other parameters (lactate level and O<sub>2</sub>ER) at the four time points are shown in Figures 2, 3. While VACO<sub>2</sub> did not show a significant correlation with lactate levels, it demonstrated a moderate correlation with O<sub>2</sub>ER at 6 h postoperatively ( $r = 0.58$ ;  $p < 0.001$ ) and a weak correlation with O<sub>2</sub>ER at 12 and 24 h postoperatively ( $r = 0.22$ ;  $p = 0.015$  and  $r = 0.19$ ;  $p = 0.045$ , respectively).

## 4 Discussion

This study explores the predictive value of VACO<sub>2</sub> in children undergoing cardiac surgery with CPB at four time points (PICU admission and 6, 12, and 24 h postoperatively) and compares it with that of other bedside indicators. The primary finding is that VACO<sub>2</sub> shows no association with LCOS-related outcomes and has lower predictive capability than arterial lactate levels.

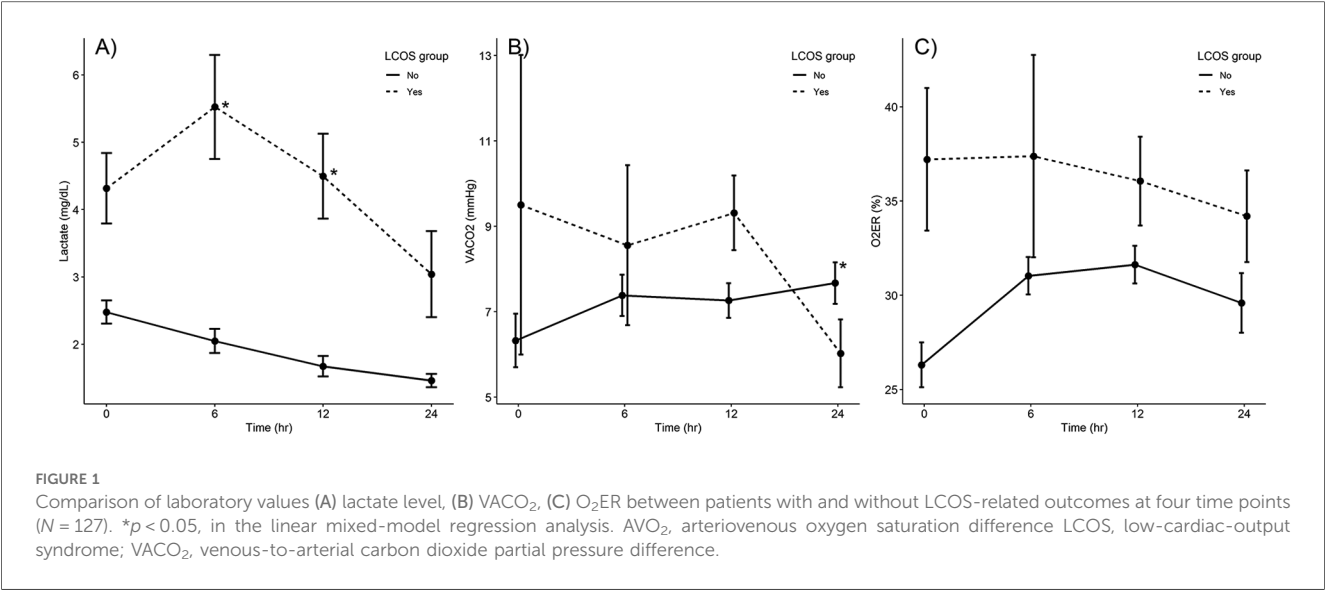


TABLE 2 Comparison of laboratory values between patients with and without LCOS-related outcomes (n = 127).

| Characteristic           | LCOS-related outcomes (n = 26) | No LCOS-related outcomes (n = 101) | p-value | AUC (95% CI)     |
|--------------------------|--------------------------------|------------------------------------|---------|------------------|
| VACO <sub>2</sub> (mmHg) |                                |                                    |         |                  |
| T0                       | 8.3 (3.2, 14.1)                | 6.8 (2.8, 10.2)                    | 0.240   | 0.58 (0.43–0.72) |
| T6                       | 9.4 (5.9, 12.0)                | 7.8 (5.3, 9.4)                     | 0.175   | 0.59 (0.44–0.74) |
| T12                      | 9.8 (6.4, 11.8)                | 7.2 (5.0, 9.8)                     | 0.027   | 0.64 (0.52–0.77) |
| T24                      | 5.8 (3.1, 11.8)                | 7.5 (5.8, 9.7)                     | 0.078   | 0.62 (0.48–0.77) |
| Lactate level (mmol/L)   |                                |                                    |         |                  |
| T0                       | 3.2 (2.2, 5.8)                 | 1.9 (1.4, 2.2)                     | <0.001  | 0.74 (0.63–0.84) |
| T6                       | 4.8 (2.5, 8.2)                 | 1.4 (1.1, 2.2)                     | <0.001  | 0.84 (0.75–0.93) |
| T12                      | 3.8 (2.4, 5.7)                 | 1.2 (0.8, 1.9)                     | <0.001  | 0.83 (0.73–0.93) |
| T24                      | 1.8 (1.3, 2.9)                 | 1.3 (0.9, 1.7)                     | 0.003   | 0.71 (0.58–0.83) |
| O <sub>2</sub> ER (%)    |                                |                                    |         |                  |
| T0                       | 33.7 (24.7, 52.0)              | 24.6 (19.7, 31.9)                  | 0.006   | 0.68 (0.54–0.81) |
| T6                       | 35.3 (28.5, 55.7)              | 30.4 (25.3, 37.6)                  | 0.017   | 0.66 (0.52–0.80) |
| T12                      | 36.1 (11.8)                    | 31.6 (10.0)                        | 0.058   | 0.61 (0.47–0.74) |
| T24                      | 31.8 (28.3, 40.0)              | 30.3 (24.1, 35.7)                  | 0.210   | 0.59 (0.45–0.73) |

Data are presented as means with standard deviations or medians with interquartile ranges. AUC, area under the curve; CI, confidence interval; LCOS, low-cardiac-output syndrome; O<sub>2</sub>ER, oxygen extraction ratio; ScvO<sub>2</sub>, central venous oxygen saturation; VACO<sub>2</sub>, venous-arterial carbon dioxide partial pressure difference.

Specifically, an elevated VACO<sub>2</sub> at 6 h postoperatively correlates with fewer 28-day inotrope-free days and IFDs.

Our negative findings were similar to Akamatsu et al. (18) regarding the correlation with other surrogates and the association between a VACO<sub>2</sub> ≥6 mmHg and unfavorable outcomes (prolonged extubation, duration of hospitalization, and mortality). That study was conducted retrospectively in 114 pediatric patients aged up to 18 years with single blood sampling of the VACO<sub>2</sub> at the time of admission. However, this is in contrast with the findings of Rhodes et al. (19), who found a high VACO<sub>2</sub> at PICU admission was linked to LCOS-related outcomes (high inotropic score, cardiac arrest, ECMO use, and unplanned surgical interventions within 48 h of PICU

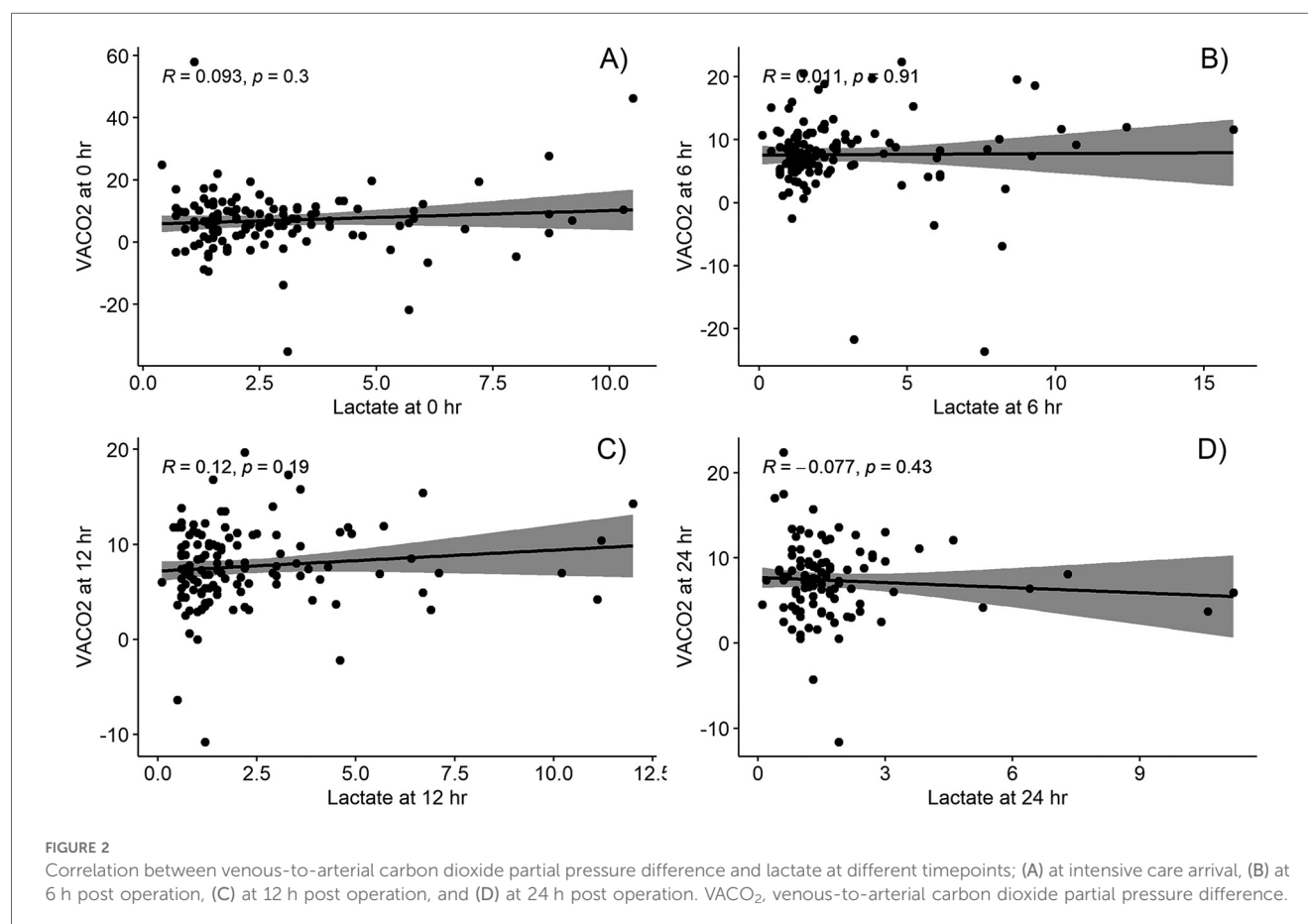
admission). They also found VACO<sub>2</sub> to have a predictive ability equal to that of lactate levels and superior to that observed in the present study (AUC for VACO<sub>2</sub>, 0.69 and AUC for lactate levels; 0.64). Another prospective study, conducted in 69 China infants, linked VACO<sub>2</sub> >12.3 mmHg within 42 h postoperatively to prolonged ventilator use and ICU stay (20). These contrast results could be attributed to different age groups within the targeted population, as these two studies were conducted in infants, whereas our study and that of Akamatsu et al. (18) were carried out in children aged up to 18 years. Studies in adults also reflect variability in the predictive power of VACO<sub>2</sub>. No association with outcomes was noted in some studies (21–23), while significant links to mortality were reported in others (12,

TABLE 3 Comparison of outcomes between patients with a  $VACO_2 < 6$  mmHg and  $\geq 6$  mmHg at 6 h after PICU admission ( $n = 124$ ).

| Characteristic                             | $VACO_2 < 6$ mmHg ( $n = 38$ ) | $VACO_2 \geq 6$ mmHg ( $n = 86$ ) | $p$ -value |
|--------------------------------------------|--------------------------------|-----------------------------------|------------|
| LCOS-related poor outcomes, $n$ (%)        | 7 (18.4)                       | 18 (20.9)                         | 0.938      |
| VIS $> 20$                                 | 18 (47.4)                      | 46 (53.5)                         | 0.664      |
| Reintervention                             | 3 (7.9)                        | 2 (2.3)                           | 0.167      |
| ECMO                                       | 1 (2.6)                        | 5 (5.8)                           | 0.666      |
| Cardiopulmonary arrest                     | 0 (0)                          | 3 (3.5)                           | 0.552      |
| Reintubation, $n$ (%)                      | 3 (7.9)                        | 9 (10.5)                          | 0.754      |
| 28-day ventilation-free days, median (IQR) | 27.0 (25.2–28.0)               | 27.0 (24.0–28.0)                  | 0.085      |
| 28-day inotrope-free days, median (IQR)    | 26.5 (23.0–28.0)               | 24.0 (22.0–27.0)                  | 0.027      |
| 28-day ICU-free days, median (IQR)         | 24.0 (22.0–27.0)               | 23.0 (18.2–26.0)                  | 0.031      |
| Significant arrhythmias, $n$ (%)           | 7 (18.4)                       | 18 (20.9)                         | 0.938      |
| Acute kidney injury, $n$ (%)               | 2 (5.3)                        | 16 (18.8)                         | 0.091      |
| Renal replacement therapy, $n$ (%)         | 1 (2.6)                        | 6 (7.0)                           | 0.437      |
| Neurological complication, $n$ (%)         | 1 (2.6)                        | 4 (4.7)                           | 1.000      |
| Death, $n$ (%)                             | 1 (2.6)                        | 6 (7.0)                           | 0.437      |

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; LCOS, low cardiac output syndrome; PICU, pediatric intensive care unit;  $VACO_2$ , venous-to-arterial carbon dioxide partial pressure difference; VIS, vasoactive-inotropic score.

$N = 124$  because three patients required ECMO or died at 6 h after PICU admission.



14, 24, 25). Overall, the discriminatory performance of  $VACO_2$  in adults ranges widely, from 0.52 to 0.83; this is similar to our findings.

The lack of significant association between  $VACO_2$  and LCOS-related outcomes in this study may be attributed to several factors. First, circulatory dynamics differ between children and adult's

cardiac condition for operation. This study included all pediatric patients across a wide range of ages and congenital cardiac anomalies, encompassing both uni- and biventricular systems. Although subgroup analysis was performed in biventricular physiology group, residual lesion did not take into account. Residual cardiac lesions following total correction or staged

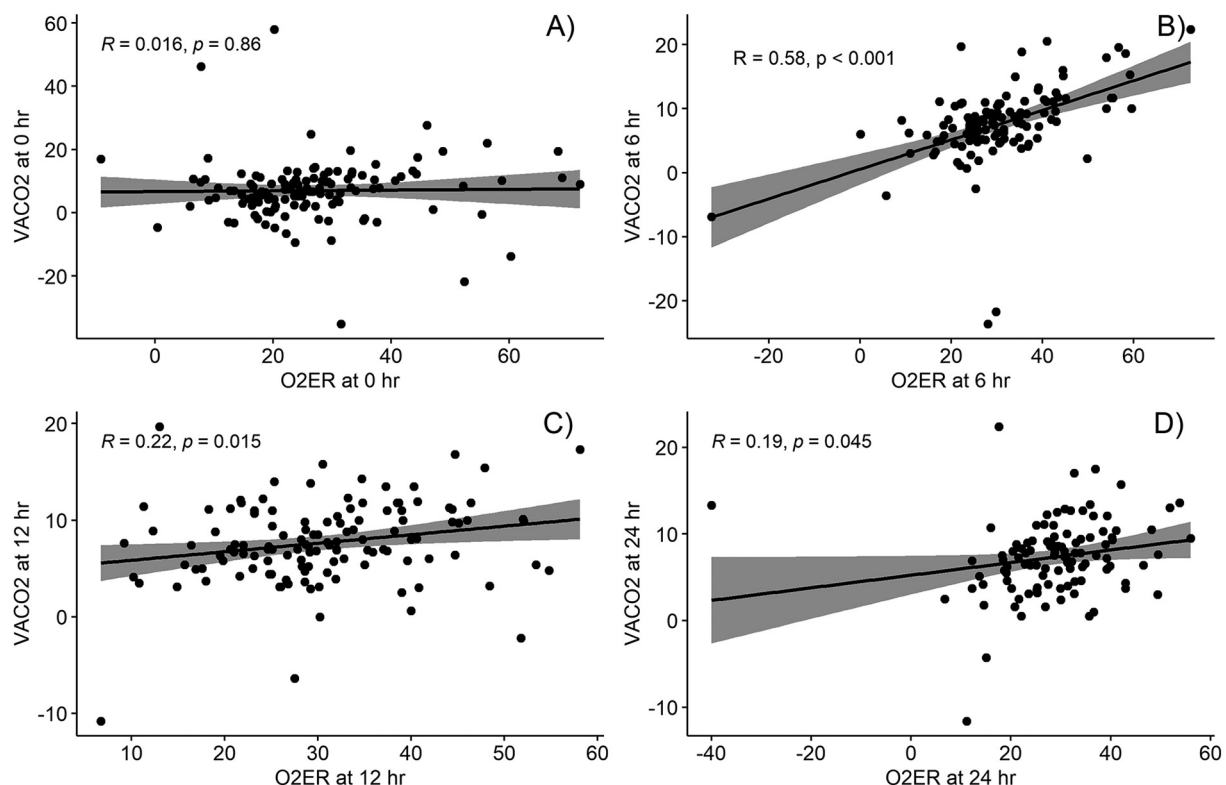


FIGURE 3

Correlation between venous-to-arterial carbon dioxide partial pressure difference and oxygen extraction ratio at different timepoints; (A) at intensive care arrival, (B) at 6 h post operation, (C) at 12 h post operation, and (D) at 24 h post operation. O<sub>2</sub>ER, oxygen extraction ratio; VACO<sub>2</sub>, venous-to-arterial carbon dioxide partial pressure difference.

reconstruction surgeries in children could influence VACO<sub>2</sub> while most cardiac surgery in adults are performed within the biventricular system which do not interfere with mixing cardiac lesions. This was supported by a study on pediatric participants with sepsis who had biventricular systems demonstrated a significant association between VACO<sub>2</sub>  $\geq 6$  mmHg and mortality (10).

Second, VACO<sub>2</sub> measurements may be influenced by conditions such as hyperventilation and hyperoxia in the post-cardiac surgery setting. This might transiently widen the CO<sub>2</sub> gap through acute decreases in arterial CO<sub>2</sub> levels and increased venous CO<sub>2</sub> levels (26, 27), potentially limiting the utility of VACO<sub>2</sub> as a reliable marker for predicting LCOS-related outcomes.

Third, the clinical outcomes following pediatric cardiac surgery are multifaceted and not solely attributable to low CO. Factors such as anemia due to intraoperative blood loss or mitochondrial dysfunction due to CPB effects may not necessarily result in an abnormal VACO<sub>2</sub>, although they can significantly impact poor outcomes (9). Fourth, the timing of the VACO<sub>2</sub> evaluation in previous studies differed from that in this study. Most of the adult and pediatric studies in cardiac surgery assessed VACO<sub>2</sub> values at the time of admission. In this study, we hypothesized that the evaluation time point at the 6-h postoperative is appropriate for identifying the consequences of LCOS after

patients received initial stabilization without the effect of anesthetic in the operating room. Moreover, the inflammatory response that leads to LCOS reaches peak effect at 9–12 h postoperatively (2). Because of the rapid responsiveness of VACO<sub>2</sub> to a low circulatory flow state, persistently high VACO<sub>2</sub> in a specific period might be better indicate outcomes than single values at admission time.

Our findings for the correlation between VACO<sub>2</sub> and other parameters are similar to those of Rhodes et al. and Singh et al. (19, 28); we observed a moderate correlation of VACO<sub>2</sub> with O<sub>2</sub>ER but no significant correlation with lactate levels. Similarly, the results of two studies of post cardiac surgery in adults concur with the findings in that VACO<sub>2</sub> had weak or no correlation with lactate levels (21, 29), despite there being a strong correlation with CO (12, 20). Although Castanuela et al. (30) reported a moderate correlation of VACO<sub>2</sub> with lactate levels at 12 h postoperatively ( $R^2 = 0.59$ ,  $p < 0.001$ ), the correlation became weaker when analyzing the total number of sample collected ( $R^2 = 0.25$ ,  $p < 0.001$ ). The moderate correlation of VACO<sub>2</sub> with O<sub>2</sub>ER but not with lactate levels could be because O<sub>2</sub>ER and VACO<sub>2</sub> change faster than lactate levels in response to circulatory flow changes.

To our knowledge, this is the first prospective study involving rigorous VACO<sub>2</sub>, O<sub>2</sub>ER, and lactate level assessment at multiple

time points following open-heart surgery in a pediatric population. Although this study involved only 127 pediatric patients, the sample size was larger than previous studies. However, it has some limitations. First, the study encompassed a wide variety of patients in terms of age, cardiac abnormalities, and surgical procedures, potentially diluting the significance of the results. Subgroup analysis was performed and remained insignificant different outcomes. The power could be enhanced by increasing the sample size to perform subgroup analyses. Second, the applicability of the gold standard method such as thermodilution method via Swan–Ganz catheterization or transesophageal echocardiography for diagnosing LCOS is limited to children, especially in postoperative states. There has been no consensus on the diagnostic criteria for LCOS in the pediatric population yet. The composite criteria we had set would identify the closest consequences from LCOS. Therefore, we are unable to endorse utilizing the VACO<sub>2</sub> as the bedside parameter in children who have undergone cardiac surgery with CPB, as there has not been strong evidence from the prospective study.

## 5 Conclusions

High level of VACO<sub>2</sub> was not significantly associated with LCOS-related outcomes in children who underwent cardiac surgery with CPB. However, a persistently high VACO<sub>2</sub> at 6 h postoperatively was related to prolonged inotropic use and a prolonged ICU stay. Further research on VACO<sub>2</sub> as an adjunctive diagnostic parameter by combining with lactate level might improve diagnostic accuracy.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Human Research Ethics Unit, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

## Author contributions

PC: Data curation, Writing – original draft, Writing – review & editing. JJ: Writing – review & editing. KS: Supervision, Writing –

review & editing. PD: Writing – review & editing. PV: Formal analysis, Methodology, Writing – review & editing. PP: Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Generative AI statement

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fped.2025.1536089/full#supplementary-material>

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