

Analysis of the Relationship Between Preoperative Arterial Oxygen Partial Pressure and Acute Kidney Injury after Surgery for Tetralogy of Fallot and Explore the Related Risk Factors

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Abstract

Background: Acute kidney injury (AKI) is a severe complication of pediatric cardiothoracic surgery (CTS). It is debatable whether patients with the low preoperative arterial partial pressure of oxygen (PaO₂) are more likely to develop AKI after surgery. The study aims to investigate the incidence and possible influencing factors of AKI in patients undergoing the radical operation of tetralogy of Fallot (TOF) with different preoperative oxygen partial pressure.

Methods: In this retrospective clinical study, 36 pediatric patients who underwent CTS were enrolled in this study. The patients were divided into 4 groups according to preoperative PaO₂. We examined the baseline data and outcomes of the study population among groups.

Results: Of the 36 patients, 17 developed AKI. Compared with the high preoperative PaO₂ group, the low preoperative PaO₂ group mostly had severe AKI and persistent, but there was no significant difference in AKI among groups ($P \geq 0.05$). In the 48-hour continuous monitoring after surgery, the oxygen metabolism indexes (Pv-aCO₂/Ca-vO₂) were correlated with AKI and there were significant differences among the groups.

Conclusions: Low preoperative PaO₂ does not significantly increase the incidence of AKI and Pv-aCO₂/Ca-vO₂ is associated with postoperative AKI and persistent.

Background

Acute kidney injury (AKI) is a severe complication of pediatric cardiothoracic surgery (CTS). Previous literature has reported that the incidence of postoperative AKI is as high as 20–30% and it is associated with markedly increased mortality and adverse outcomes after CTS (1–4). In the long run, AKI after congenital heart disease (CHD) will not only affect the prognosis but also increase the overall medical burden, which is an urgent problem to be solved (5). Previous researches found that cyanotic heart disease (C-CHD) was the independent risk factor for the development of AKI after CTS (6–7). And a study indicated that Tetralogy of Fallot (TOF) was a severe and most common C-CHD for which the outcomes were more unfavourable than other types of simple congenital heart diseases (8). But a recent study showed that there was no difference in postoperative AKI incidence between patients with higher haematocrit (Hct) and those without (9). The view was expressed that C-CHD patients had adaptive changes due to chronic hypoxia and these changes might be beneficial to the protection of postoperative renal function (10). Evidence from basic studies, repetitive hypoxic preconditioning increases renal hypoxia-inducible factor 1- α mRNA and protein levels and decreases mitochondrial Bax translocation, cytochrome c release, and tubular apoptosis, which has supported that idea (11). This study aimed to explore the relationship between the degree of hypoxia before CTS and postoperative AKI and analyze the risk factors of postoperative AKI.

Methods

A flowchart of our study is included in Fig. 1. This retrospective, single-center study enrolled 46 patients with TOF aged between 1-month and 12-month, who underwent CTS from July 1, 2017, to September 30, 2019. The study was in strict accordance with the Declaration of Helsinki and International Ethical Guidelines for Health-related Research Involving Humans. Demographic and clinical data were retrieved from the patients' medical records.

Inclusion criteria for patients were: (1) age from 1-month to 12-month; (2) TOF was confirmed by preoperative echocardiography and intraoperative findings. TOF consists of a tetrad, or a group of 4 defects, which are ventricular septal defect, pulmonary stenosis, overriding aorta, and right ventricular hypertrophy (12); (3) the first time to receive CTS treatment and undergo complete surgical repair. Complete surgical repair includes closing the ventricular septal defect, resecting muscle bundles within the right ventricular outflow tract with or without patch augmentation (13); (4) complete clinical information such as history and laboratory examination.

The exclusion criteria were: (1) preexisting renal dysfunction (RD) or requirement of renal replacement therapy before surgery. RD was defined as kidney injury denoted by pathological changes, or other indicators such as abnormal blood, urine, or imaging findings or an estimated glomerular filtration rate (eGFR) of less than $60 \text{ ml/min} \times 1.73 \text{ m}^2$ for more than 3 months (14); (2) a history of nephrotoxic drug use within 7 days before surgery; (3) a lack of postoperative renal data; (4) delayed sternal closure or reoperation was required due to bleeding and other reasons.

Finally, 36 patients were included in the study, of which 17 had AKI. Diagnosis and staging of AKI were performed according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guidelines (15). Patients scheduled for CTS should have preoperative tests including the complete history, transthoracic echocardiography, and blood test. Venous blood used for the preoperative blood test was collected via scalp vein needle from scalp vein or femoral vein. The radial artery catheter was needed to obtain a sample of arterial blood for gas analysis and invasive monitoring. A central venous catheter (CVC) was placed through the femoral venous or jugular vein and central venous pressure (CVP) was measured hourly.

All postoperative children were admitted to the pediatric intensive care unit (PICU) and had real-time monitoring, which included measurement of vital signs (temperature, blood pressure, pulse, and respiration rate), quantification of all fluid intake and output. Blood used for routine postoperative test were collected from indwelling arterial lines after CTS, and simultaneous blood samples were obtained from a central venous catheter and an arterial catheter at 48 hours after surgery. Echocardiographic reexamination was performed on the 7th day after the operation. Postoperative management, systematic monitor and programmatic therapy were performed based on Handbook of Pediatric Cardiac Surgical Intensive Care (16).

Baseline data including demographics, clinical manifestation, and laboratory data were extracted and analyzed. Preoperative data included weight, height, age, sex, serum creatinine (SCr), eGFR, arterial oxygen pressure (PaO₂), Hct, hemoglobin (Hb), McGoon ratio, Nakata index, pulmonary arterial pressure (PAP), left ventricular ejection fraction (LVEF) and fractional shortening (LVFS); surgical characteristics were CTS time, cardiopulmonary bypass (CPB) time and American Society of Anesthesiologists grade (ASA). Postoperative data including temperature, heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), lactic acid, arterial oxygen saturation (SaO₂), PaO₂ and urine output were recorded up to the first and second 24 hours after admission to PICU. Simultaneous monitoring of venous blood gas at 48 hours after CTS. The highest vasoactive inotrope score (VIS) within postoperative 48 hours was used to reflect the application of vasoactive drugs after CTS (17). Lengths of PICU and hospital stay were also recorded. To better show the oxygen metabolism in tissues, we calculated central venous-to-arterial carbon dioxide difference (Pv-aCO₂), central arterial-to-venous oxygen saturation difference (Sa-vO₂), central arterial-to-venous oxygen pressure difference (Pa-vO₂), arterial-to-venous oxygen content difference (Ca-vO₂), the rate of Pv-aCO₂/Ca-vO₂, and oxygen extraction ratio (O₂ ER) according to the following formulas (18–20):

- $CaO_2 = (1.34 \times SaO_2 \times Hb) + (0.003 \times PaO_2)$
- $CcvO_2 = (1.34 \times ScvO_2 \times Hb) + (0.003 \times PcvO_2)$
- $Ca - vO_2 = CaO_2 - CcvO_2$
- $Pv-aCO_2 = PcvCO_2 - PaCO_2$
- $Pv-aCO_2 / Ca - vO_2 \text{ ratio} = Pv-aCO_2 / Ca - vO_2$
- $Pa - vO_2 = PaO_2 - PcvO_2$
- $Sa - vO_2 = SaO_2 - ScvO_2$
- $O_2 \text{ ER} = Ca-vO_2 / CaO_2$

Shapiro-Wilk test was used to check the normality of the data; continuous variables with normal distribution were expressed in terms of mean and standard deviation. Group comparisons were analyzed by independent sample t-tests or ANOVA test. The continuous variables with the non-normal distribution were expressed as median (P25 and P75) and were compared using non-parametric factorial Kruskal-Wallis sum-rank test. Frequencies and proportions were estimated for categorical variables and were compared using the chi-squared test or Fisher's test. Odds ratios (ORs) with 95% confidence intervals (CIs) for the development of AKI in each group were calculated using a logistic regression model. Persistent AKI was defined as a continuance of AKI according to the KDIGO criteria beyond 48 h according to the consensus report of the ADQI 16 workgroup (21). Transient AKI was defined as AKI of less than 48 h duration. To investigate the relationship between preoperative PaO₂ and postoperative AKI, Univariate analysis was performed on the general preoperative data, hemodynamic indexes and oxygen metabolism indexes of the 4 groups at 24 and 48 hours after operation and the incidence, severity, and duration of AKI in the 4 groups were compared. Subgroup analysis was performed to explore the relationship between oxygen metabolism index (Sa-vO₂, Pa-vO₂, Pv-aCO₂, Ca-vO₂, Pv-aCO₂/Ca-vO₂, O₂ER) and persistent AKI. Single-factor regression analysis was performed to explore the risk factors with certain significance in univariate analysis (P < 0.05) of postoperative AKI and persistent AKI. All statistical analyses were performed with SPSS version 23 (IBM Corp. Released (2015) IBM SPSS Statistics for Windows. IBM Corp., Armonk, NY). The difference was considered significant when the two-tailed P-value was less than 0.05.

Results

Among the 36 patients, 21 were males and 15 were females. The median age was 6-month (range, 4–12 months). The median height was 67.0 cm (range, 55.0–80.0 cm) and the weight was 8.0 kg (range, 5.4–12.5 kg). Seventeen patients (47.2%) developed AKI. For the present analyses, patients were categorized by preoperative PaO₂ quartiles: Group 1, PaO₂ of >94.0 mmHg (n = 9); Group 2, PaO₂ of >70.5 to ≤ 94.0 mmHg (n = 9); Group 3, PaO₂ of >70.5 to ≤ 40.6 mmHg (n = 9); Group 4, PaO₂ of ≤ 40.6 mmHg (n = 9). The baseline values, clinical status, and surgical characteristics of all 36 patients were shown in Table 1.

Table 1
Study population characteristics (n = 36)

Characteristics	Preoperative PaO ₂ (mmHg)				Statistic	P value
	Group 1 >94.0 (n = 9)	Group 2 >70.5, ≤94.0 (n = 9)	Group 3 >40.6, ≤70.5 (n = 9)	Group 4 ≤ 40.6 (n = 9)		
Demographics						
Gender (male,%)	7 (19.4)	5 (13.9)	3 (8.3)	6 (16.7)	$\chi^2 = 3.842$	0.343
Age (month)	10.0 (6.0, 12.0)	6.0 (6.0, 7.0)	6.0 (5.0, 6.0) ^a	6.0 (6.0, 8.0)	$H = 7.815$	0.050
Height (cm)	73.1 ± 5.0	66.5 ± 3.0	66.0 ± 4.0	66.1 ± 6.2	$F = 4.852$	0.007
Weight (kg)	8.0 (7.5, 9.3)	7.6 (7.0, 9.0)	8.0 (7.0, 8.0)	8.0 (7.0, 9.0)	$H = 1.501$	0.682
Body mass index (kg/m ²)	16.0 ± 1.9	18.7 ± 2.7	17.5 ± 3.6	18.2 ± 4.8	$F = 1.069$	0.376
Preoperative testing						
SCr(umol/L)	23.8 ± 3.7	22.8 ± 4.3	23.2 ± 2.8	23.2 ± 5.0	$F = 0.093$	0.963
eGFR(ml/min/1.73 m ³)	101.4 ± 13.2	98.5 ± 23.2	93.6 ± 14.3	96.3 ± 22.7	$F = 0.272$	0.845
PaO ₂ (mmHg)	125.5 ± 17.7	80.8 ± 8.1	59.6 ± 9.1	34.8 ± 3.1	$F = 112.982$	<0.001
Hb(g/L)	115.0 (98.0, 141.0)	125.0 (118.0, 132.0)	144.0 (130.0, 153.0)	132.0 (124.0, 144.0)	$H = 6.228$	0.101
Hct(%)	34.6 (30.4, 41.20)	36.7 (34.5, 41.3)	42.8 (37.8, 45.7)	40.5 (37.4, 34.0)	$H = 7.512$	0.057
Preoperative echocardiography						
LVEF (%)	68.1 ± 7.1	65.7 ± 3.1	68.4 ± 6.8	65.8 ± 6.3	$F = 0.539$	0.659
LVFS (%)	36.1 ± 6.7	35.7 ± 2.6	36.2 ± 5.3	34.4 ± 4.8	$F = 0.232$	0.873

A two-tailed P value of < 0.05 was considered statistically significant; Compared with group 1, ^aP<0.05

PaO₂ = Arterial Partial Pressure of Oxygen; CTS = Cardiothoracic Surgery; CPB = Cardiopulmonary Bypass; SCr = Serum Creatinine; eGFR = estimated Glomerular Filtration Rate; PICU = Pediatric Intensive Care Unit; Hct = Hematocrit; Hb = Hemoglobin; ASA = American Society of Anesthesiologists; PAP = Pulmonary Artery Pressure; LVEF = Left Ventricular Ejection Fraction; LVFS = Left Ventricular Fraction Shortening

Characteristics	Preoperative PaO ₂ (mmHg)				Statistic	P value
	Group 1	Group 2	Group 3	Group 4		
	>94.0	>70.5,≤94.0	>40.6,≤70.5	≤ 40.6		
	(n = 9)	(n = 9)	(n = 9)	(n = 9)		
PAP (mmHg)	71.2 ± 21.9	79.3 ± 31.6	79.4 ± 26.9	81.4 ± 27.2	<i>F</i> = 0.250	0.860
Nakata index(mm ² /m ²)	128.3 (127.3, 138.7)	127.2 (118.9, 138.6)	122.8 (114.5, 127.3)	115.1 (107.2, 123.2)	<i>H</i> = 6.087	0.107
McGoon	1.5 (1.3, 1.7)	1.4 (1.3, 1.7)	1.3 (1.3, 1.4)	1.3 (1.3, 1.3)	<i>H</i> = 3.126	0.373
Surgical characteristics						
CTS time (min)	119.0 (109.0, 125.0)	148.0 (130.0, 163.0)	164.0 (135.0, 175.0)	165.0 (164.0, 220.0) ^a	<i>H</i> = 13.958	0.003
CPB time (min)	53.0 (48.0, 58.0)	65.0 (60.0, 69.0)	82.0 (64.0, 88.0)	86.0 (77.0, 112.0) ^a	<i>H</i> = 12.740	0.005
ASA grade						
≤2(%)	2 (5.6)	0	1 (2.8)	2 (5.6)	<i>χ</i> ² = 2.603	0.722
≥3(%)	7 (19.4)	9 (25.0)	8 (22.2)	7 (19.4)		
Prognosis						
PICU stay (days)	3.0 (3.0, 4.0)	4.0 (2.0, 5.0)	5.0 (4.0, 7.0) ^a	4.0 (3.0, 5.0)	<i>H</i> = 9.529	0.023
Hospital stay (days)	14.0 (11.0, 16.0)	13.0 (11.0, 15.0)	16.0 (15.0, 21.0)	16.0 (13.0, 18.0)	<i>H</i> = 4.549	0.208
Total hospitalization expenses (yuan)	55113.3 (53474.3, 60633.3)	68372.6 (61148.9, 76046.8) ^a	74039.3 (71326.8, 78707.4) ^a	70783.0 (66522.5, 74624.0) ^a	<i>H</i> = 17.543	0.001
A two-tailed P value of < 0.05 was considered statistically significant;Compared with group 1, ^a P<0.05						
PaO ₂ = Arterial Partial Pressure of Oxygen; CTS = Cardiothoracic Surgery; CPB = Cardiopulmonary Bypass; SCr = Serum Creatinine; eGFR = estimated Glomerular Filtration Rate; PICU = Pediatric Intensive Care Unit; Hct = Hematocrit; Hb = Hemoglobin; ASA = American Society of Anesthesiologists; PAP = Pulmonary Artery Pressure; LVEF = Left Ventricular Ejection Fraction; LVFS = Left Ventricular Fraction Shortening						

Table 2
Comparison of hemodynamic index and oxygen metabolism index among groups (n = 36)

Characteristics	Preoperative PaO ₂ (mmHg)				Statistic	P value
	Group 1	Group 2	Group 3	Group 4		
	>94.0 (n = 9)	>70.5, ≤94.0 (n = 9)	>40.6, ≤70.5 (n = 9)	≤ 40.6 (n = 9)		
<i>Temperature (°C)</i>						
Admission to PICU	36.5 (36.0, 36.8)	36.3 (36.0, 36.7)	36.4 (36.2, 36.8)	36.0 (36.0, 36.4)	H = 3.583	0.310
Postoperative 24 h	37.5 ± 0.5	37.5 ± 0.4	37.0 ± 0.7	37.2 ± 0.5	F = 0.167	0.686
Postoperative 48 h	37.6 ± 0.8	37.0 ± 0.7	37.3 ± 0.8	37.1 ± 0.6	F = 0.019	0.892
<i>Heart rate(beats/min)</i>						
Admission to PICU	148.6 ± 21.1	157.7 ± 15.4	163.9 ± 11.9	154.3 ± 15.3	F = 3.049	0.090
Postoperative 24 h	130.6 ± 15.0	151.0 ± 13.1	148.1 ± 8.7	145.9 ± 9.4	F = 1.016	0.321
Postoperative 48 h	133.9 ± 18.5	154.1 ± 22.2	158.8 ± 14.6	148.3 ± 14.7	F = 1.320	0.259
<i>MAP(mmHg)</i>						
Admission to PICU	67.4 ± 8.0	59.6 ± 8.9	66.3 ± 7.3	63.4 ± 6.6	F = 0.457	0.504
Postoperative 24 h	69.9 ± 9.0	60.6 ± 6.8	65.3 ± 8.7	66.4 ± 8.9	F = 1.378	0.249
Postoperative 48 h	62.7 (60.3, 74.0)	60.3 (57.3, 63.7)	61.7 (53.3, 62.0)	66.7 (60.3, 69.0)	H = 4.615	0.202
<i>CVP(mmHg)</i>						
Admission to PICU	11.0 (8.0, 11.0)	9.0 (9.0, 10.0)	10.0 (8.0, 11.0)	10.0 (8.0, 10.0)	H = 1.067	0.785
Postoperative 24 h	9.3 ± 1.4	8.4 ± 1.6	10.6 ± 1.9	9.9 ± 1.9	F = 1.315	0.287

A two-tailed P value of < 0.05 was considered statistically significant; Compared with group 1, ^aP<0.05; Compared with group 2, ^bP<0.05

PICU = Pediatric Intensive Care Unit; PaO₂ = Arterial Partial Pressure of Oxygen; MAP = Mean Arterial Pressure; CVP = Central Venous Pressure; SaO₂ = Arterial Oxygen Saturation; P_{v-a}CO₂/C_{a-v}O₂ = the ratio of central venous-to-arterial carbon dioxide difference (Pv-aCO₂) to arterial-to-central venous O₂ content difference (Ca-vO₂) ; O₂ER = Oxygen Extraction Ratio; PAP = Pulmonary Artery Pressure; LVEF = Left Ventricular Ejection Fraction; LVFS = Left Ventricular Fraction Shortening; VIS = Vasoactive Inotrope Score

Characteristics	Preoperative PaO ₂ (mmHg)				Statistic	P value
	Group 1	Group 2	Group 3	Group 4		
	>94.0	>70.5,≤94.0	>40.6,≤70.5	≤ 40.6		
	(n = 9)	(n = 9)	(n = 9)	(n = 9)		
Postoperative 48 h	9.1 ± 1.7	10.3 ± 1.9	9.9 ± 2.0	9.9 ± 2.1	F = 0.333	0.568
<i>Lactic acid (mmol/L)</i>						
Admission to PICU	1.3 (0.7, 1.5)	1.3 (1.2, 1.7)	1.9 (1.1, 2.2)	1.5 (1.0, 1.7)	H = 3.230	0.357
Postoperative 24 h	0.7 (0.5, 0.9)	0.9 (0.7, 1.2)	1.0 (0.7, 1.2)	0.9 (0.8, 1.2)	H = 3.236	0.357
Postoperative 48 h	0.6 (0.6, 0.7)	0.7 (0.6, 0.8)	0.8 (0.6, 0.9)	0.7 (0.6, 0.8)	H = 1.003	0.800
<i>SaO₂(%)</i>						
Admission to PICU	99.7 (99.4, 99.9)	99.6 (99.4, 100.1)	99.9 (99.7, 100.0)	99.7 (99.4, 100.3)	H = 0.783	0.854
Postoperative 24 h	99.9 (99.6, 100.1)	99.9 (97.9, 100.0)	98.5 (96.8, 99.5)	99.3 (99.2, 99.9)	H = 6.736	0.081
Postoperative 48 h	99.7 (99.6, 100.0)	99.9 (99.5, 100.3)	98.6 (96.7, 100.0)	99.0 (98.1, 99.7)	H = 5.790	0.122
<i>PaO₂(mmHg)</i>						
Admission to PICU	186.3 ± 30.9	177.4 ± 55.3	161.4 ± 55.8	155.0 ± 57.3	H = 0.716	0.550
Postoperative 24 h	175.2 ± 57.9	175.4 ± 86.0	129.9 ± 60.1	127.3 ± 66.0	H = 1.402	0.260
Postoperative 48 h	169.0 ± 26.5	157.7 ± 45.5	121.4 ± 64.7	94.1 ± 83.9	H = 3.030	0.044
<i>Oxygen metabolism index(Postoperative 48h)</i>						
Sa-vO ₂ (mmHg)	3.5 ± 1.9	5.9 ± 2.2	9.4 ± 4.0	19.1 ± 9.0	F = 1.076	0.373

A two-tailed P value of < 0.05 was considered statistically significant; Compared with group 1, ^aP<0.05; Compared with group 2, ^bP<0.05

PICU = Pediatric Intensive Care Unit; PaO₂ = Arterial Partial Pressure of Oxygen; MAP = Mean Arterial Pressure; CVP = Central Venous Pressure; SaO₂ = Arterial Oxygen Saturation; P_{v-a}CO₂/C_{a-v}O₂ = the ratio of central venous-to-arterial carbon dioxide difference (Pv-aCO₂) to arterial-to-central venous O₂ content difference (Ca-vO₂) ; O₂ER = Oxygen Extraction Ratio; PAP = Pulmonary Artery Pressure; LVEF = Left Ventricular Ejection Fraction; LVFS = Left Ventricular Fraction Shortening; VIS = Vasoactive Inotrope Score

Characteristics	Preoperative PaO ₂ (mmHg)				Statistic	P value
	Group 1	Group 2	Group 3	Group 4		
	>94.0	>70.5, ≤94.0	>40.6, ≤70.5	≤ 40.6		
	(n = 9)	(n = 9)	(n = 9)	(n = 9)		
Pa-vO ₂ (mmHg)	31.0 (24.0, 61.0)	41.9 (35.4, 68.4)	25.6 (16.2, 41.7)	69.7 (16.4, 91.9)	H = 3.141	0.370
Pv-aCO ₂ (mmHg)	0.6 (0.1, 3.1)	5.3 (1.0, 7.1)	11.8 (9.0, 15.6) a	23.4 (18.8, 28.1) ab	H = 25.681	<0.001
Ca-vO ₂ (mL/dL)	5.8 (4.3, 6.4)	9.2 (6.2, 10.1)	13.4 (11.8, 16.8) a	29.8 (20.8, 34.0) ab	H = 20.353	<0.001
Pv-aCO ₂ /Ca-vO ₂	0.2 (0.05, 0.48)	0.6 (0.4, 0.7)	0.7 (0.6, 1.3)	0.8 (0.7, 0.9) a	H = 12.566	<0.001
O ₂ ER	0.04 (0.03, 0.04)	0.06 (0.05, 0.07)	0.09 (0.07, 0.12) a	0.24 (0.14, 0.26) ab	H = 24.142	<0.001
<i>Echocardiography</i> (Postoperative 7th day)						
LVEF (%)	67.9 ± 5.9	68.0 ± 7.8	68.2 ± 7.2	65.9 ± 4.3	F = 0.255	0.857
LVFS (%)	36.9 ± 4.7	36.1 ± 5.9	37.1 ± 6.2	35.0 ± 3.2	F = 0.312	0.817
PAP (mmHg)	11.8 (11.0, 19.7)	19.0 (7.2, 23.8)	19.0 (16.3, 20.3)	13.0 (7.8, 17.6)	H = 1.707	0.635
Nakata index(mm ² /m ²)	145.2 (140.3, 157.3)	135.3 (135.0, 157.6)	141.2 (138.7, 147.1)	139.3 (123.1, 145.0)	H = 1.331	0.722
McGoon	1.6 (1.5, 1.9)	1.6 (1.5, 1.7)	1.6 (1.5, 1.6)	1.4 (1.4, 1.5)	H = 1.372	0.712
VIS (highest within 48 hours after CTS)	15.0 (14.0, 15.0)	13.0 (10.0, 15.0)	16.0 (15.0, 18.0)	18.0 (12.0, 20.0)	H = 4.914	0.178
A two-tailed P value of < 0.05 was considered statistically significant; Compared with group 1, ^a P<0.05; Compared with group 2, ^b P<0.05						
PICU = Pediatric Intensive Care Unit; PaO ₂ = Arterial Partial Pressure of Oxygen; MAP = Mean Arterial Pressure; CVP = Central Venous Pressure; SaO ₂ = Arterial Oxygen Saturation; P _{v-a} CO ₂ /C _{a-v} O ₂ = the ratio of central venous-to-arterial carbon dioxide difference (Pv-aCO ₂) to arterial-to-central venous O ₂ content difference (Ca-vO ₂) ; O ₂ ER = Oxygen Extraction Ratio; PAP = Pulmonary Artery Pressure; LVEF = Left Ventricular Ejection Fraction; LVFS = Left Ventricular Fraction Shortening; VIS = Vasoactive Inotrope Score						

The oldest group is group 1 and there was a significant difference between group 1 and 3 (P<0.05). Similarly, group 1 was the tallest among the groups. There was a significant difference in CTS time and CPB time between group 1 and 4; CTS time and CPB time were gradually increased (P<0.05). The children in group 1 had average total hospitalization expenses of RMB 56140.6 (US\$8536.0) and length of stay in PICU of 2.9 days compared

with the children in group 3 with expenses of RMB83770.8 (US\$12737.1) and PICU stays of 6.8 days ($P < 0.05$). The results showed that there were no significant differences in weight, sex, body mass index, preoperative SCr, preoperative eGFR, and preoperative echocardiography among groups (all $P > 0.05$).

The changes of hemodynamic indexes and oxygen metabolism indexes of the 4 groups at PICU, 24 hours and 48 hours after CTS were shown in Table 3. There were no statistically significant changes in the preoperative and 24, 48 hours postoperative records for temperature, HR, MAP, CVP lactic acid and SaO₂ ($P > 0.05$). PaO₂ decreased gradually over time, but no significant differences were found between the values of preoperative and 24 hours after CTS among the groups. Patients in group 4 tended to have lower PaO₂ at preoperative and 24, 48 hours after CTS, and compared with group 1, patient in group 4 had higher Pv-aCO₂ (23.4 vs 0.6, $P < 0.05$), Ca-vO₂ (29.8 vs 5.8, $P < 0.05$), Pv-aCO₂/Ca-vO₂ ratios (0.8 vs 0.2, $P < 0.05$) and O₂ ER (0.24 vs 0.04, $P < 0.05$) at 48 hours after CTS that met statistical significance (Table 3). There was no statistically significant difference in echocardiography (Postoperative 7th day) and VIS (highest within 48 hours after CTS).

Table 3
The occurrence and improvement of AKI in patients with congenital heart disease (n = 36)

Characteristics	Preoperative PaO ₂ (mmHg)				Statistic	P value
	Group 1	Group 2	Group 3	Group 4		
	>94.0 (n = 9)	>70.5, ≤94.0 (n = 9)	>40.6, ≤70.5 (n = 9)	≤ 40.6 (n = 9)		
AKI (%)						
During hospitalization	1 (2.8)	6 (16.7)	5 (13.9)	5 (13.9)	$\chi^2 = 6.597$	0.079
Admission to PICU	1 (5.9)	5 (29.4)	3 (17.6)	2 (11.8)	$\chi^2 = 2.792$	0.475
Duration of AKI ≥ 48 h	0	2 (11.8)	4 (23.5)	4 (23.5)	$\chi^2 = 4.460$	0.213
AKI severity (%)						
Stage 1	1 (5.9)	4 (23.5)	3 (17.6)	1 (5.9)	$\chi^2 = 5.439$	0.658
Stage 2	0	2 (11.8)	1 (5.9)	2 (11.8)		
Stage 3	0	0	1 (5.9)	2 (11.8)		
A two-tailed P value of < 0.05 was considered statistically significant; AKI = Acute Kidney Injury; PICU = Pediatric Intensive Care Unit; PaO ₂ = Arterial Partial Pressure of Oxygen						

The total incidence of acute kidney injury was 47.2% (n = 36) and the incidence of AKI was significantly lower in group 1 (n = 1, 2.8%). Most patients developed postoperative AKI in the early period after CTS (n = 11, 64%), and patients with low PaO₂ (group 3 and 4) tended to have persistent AKI (n = 8, 80%), however it was not statistically significant ($P > 0.05$).

Subgroup analysis was performed based on whether the patients were persistent or short AKI which was shown in Table 4. Patients with persistent AKI had significantly higher Pv-aCO₂, Ca-vO₂, Pv-aCO₂/Ca-vO₂ and O₂ER

than those with short AKI ($P > 0.05$). Even after grouping by PaO₂, this phenomenon persisted and those values of group 3 and 4 were higher than group 1 and 2.

Table 4
Comparison of oxygen metabolism index among groups (n = 17)

Characteristics	Short AKI (n = 7)	Persistent AKI (n = 10)	Statistic	P value	Group 1 and 2		Group 3 and 4	
					Short AKI (n = 5)	Persistent AKI (n = 2)	Short AKI (n = 2)	Persistent AKI (n = 8)
<i>Oxygen metabolism index</i>								
<i>(Postoperative 48h)</i>								
Sa-vO ₂ (mmHg)	5.6 (4.8, 7.7)	10.9 (7.2, 15.2)	H = 0.586	0.061	5.0 (4.8, 6.0)	6.9 (5.8, 7.9)	6.7 (5.6, 7.7)	10.1 (7.7, 15.2)
Pa-vO ₂ (mmHg)	41.2 ± 37.8	50.2 ± 31.7	F = 0.107	0.600	54.0 ± 37.5	39.8 ± 40.5	19.1 ± 10.0	52.8 ± 32.0
Pv-aCO ₂ (mmHg)	3.0 (1.3, 12.0)	12.6 (5.9, 23.1)	H = 1.807	0.070	2.2 (1.3, 3.0)	1.5 (1.3, 1.6)	13.4 (12.0, 14.7)	15.8 (11.7, 23.2)
Ca-vO ₂ (mL/dL)	8.2 (7.7, 10.5)	16.7 (10.8, 51.3)	H = 2.830	0.003	8.2 (7.7, 8.3)	10.0 (8.7, 11.4)	9.1 (7.4, 10.5)	33.3 (13.3, 55.3)
Pv-aCO ₂ /Ca-vO ₂	0.3 (0.2, 0.7)	0.4 (0.3, 1.4)	H = 2.537	0.040	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	0.5 (0.4, 0.9)	1.5 (1.4, 1.6)
O ₂ ER	0.06 (0.05, 0.08)	0.11 (0.07, 0.36)	H = 2.205	0.025	0.05 (0.05, 0.06)	0.07 (0.06, 0.08)	0.08 (0.05, 0.08)	0.24 (0.08, 0.38)
A two-tailed P value of < 0.05 was considered statistically significant; AKI = Acute Kidney Injury; PaO ₂ = Arterial Partial Pressure of Oxygen; SaO ₂ = Arterial Oxygen Saturation; P _{v-a} CO ₂ /C _{a-v} O ₂ = the ratio of central venous-to-arterial carbon dioxide difference (Pv-aCO ₂) to arterial-to-central venous O ₂ content difference (Ca-vO ₂) ; O ₂ ER = Oxygen Extraction Ratio								

Predictors of AKI and persistent AKI in single-factor logistic regression were shown in Fig. 2 and Fig. 3, respectively. Single-factor logistic regression analysis revealed a significant correlation between the occurrence of an AKI with age, height, Hb, Hct, PICU stay days, total hospitalization expenses, VIS, Pv-aCO₂ and Pv-aCO₂/Ca-vO₂, while only Pv-aCO₂/Ca-vO₂ showed a significant correlation with persistent AKI.

Discussion

AKI is one of the common and serious complications after CPB operation, which has a negative impact on the prognosis of patients and increases the fatality rate (21). Most studies believe that chronic hypoxia has a great effect on the organism, especially for the kidney and even put forward the concept of cyanotic nephropathy (CN) (22). Studies have indicated that CN occurs in about 30–50% of the patients with C-CHD. The incidence of AKI after CTS was as high as 47.2% in this study and 10 patients had persistent AKI according to the definition. Hence it is important to identify patients who are at risk of developing AKI after CTS. Preoperative symptoms, surgical interventions, and postoperative management are related to the postoperative AKI. Previous studies have clearly demonstrated that prolonged CTS time and CPB time were associated with the development of AKI (23–24), however, it was not the case in our study. We considered that this is because the advances in surgical techniques and perioperative management that the CTS time (range, 99 to 282 minutes) and CPB time (range, 40 to 127 minutes) were controlled within a relatively safe range and had led to dramatic improvements in survival outcomes for children with TOF. We also analyzed the hemodynamic indicators and oxygen metabolism indicators at the time of PICU admission, postoperative 24 h and 48 h. The arterial blood and venous blood gas analysis were measured simultaneously after the 48 hours CTS, and oxygen transport data ($Sa - vO_2$, $Pa - vO_2$, $Ca - vO_2$, $Pv-aCO_2$, $O_2 ER$ and $Pv-aCO_2 / Ca - vO_2$) were calculated. Due to the lack of echocardiographic data in the study population at 48 hours after surgery, we were unable to directly calculate oxygen delivery and oxygen consumption, which was a major flaw of this study.

MAP, CVP and SO_2 are commonly used as the indices of adequate tissue perfusion and oxygenation in patients, but tissue hypoxia may still exist even when these indices are within the normal range (25). And in this study, normalization of SO_2 and PO_2 does not exclude the persistence of tissue hypoperfusion and tissue hypoxia. Some studies have found out that $Sa-vO_2$ is an excellent indicator of adequacy of cellular oxygenation, and it has shown a good correlation with oxygen delivery (26); $Ca - vO_2$ can to some extent reflect poor tissue perfusion (27); In this study, $Pv-aCO_2 / Ca - vO_2$ and $Pv-aCO_2$ were independent risk factors for acute kidney injury, and $Pv-aCO_2 / Ca - vO_2$ was associated with persistent AKI. These results are consistent with previous studies. Mekontso-Dessap A et al. found that the $Pv-aCO_2 / Ca - vO_2$ ratio could detect global anaerobic metabolism in critically ill patients (28). As an index of the presence of anaerobic metabolism, its basic theory is: during anaerobic metabolism carbon dioxide production decreases less than oxygen consumption. The present study showed that a high $Pv-aCO_2 / Ca-vO_2$ ratio was associated with low survival rates at day 28 ($P < 0.005$) (29). Mukai A et al. found that $Pv-aCO_2$ and $Pv-aCO_2 / Ca-vO_2$ at the end of surgery had a superior ability for predicting postoperative complications (30)

The patients in this study were divided into 4 groups according to preoperative PaO_2 and patients with low PaO_2 had higher Hb and Hct due to chronic hypoxia. Multiple studies have shown that high Hb and Hct are associated with low cardiac output, increased blood viscosity, increased platelet aggregation, and impaired blood flow (31). Although there was no significant difference between the Hb and Hct among groups in this study, patients with higher Hb and Hct had longer CTS time and CPB times, longer postoperative PICU stays, higher VIS scores, and higher expenditures. However, there was no significant difference in the incidence of postoperative AKI among the 4 groups, several hypotheses might be used to justify this observed discrepancy between lung tissue and systemic responses: (1) following CTS, all patients were admitted to the PICU and received routine mechanical ventilation, vasoactive drugs, moderate rehydration, therefore, the mature surgical technique and rational postoperative management strategies were closely associated with the decreased of the incidence of AKI. (2) the

short follow-up time and the small number of patients involved, it was necessary to extend the follow-up time and increase the number of patients included. Overall, patients in group 1 had less kidney damage among the groups, and patients in group 3 and 4 were more likely to have severe AKI and persistent AKI.

During chronic hypoxia, increases in red blood cell number or formation of new vasculature occur, adapting an organism to decreased oxygen conditions. In this study, we found that there was not a significant increase in postoperative AKI of patients with low PaO₂ (group 3 and 4) during the early period after CTS. We hypothesized that it might be related to these adapt changes. The animal study suggested that hypoxic preconditioning of animals in vivo increased hypoxic tolerance (32). Alexander Zarbock et al. found that among high-risk patients undergoing cardiac surgery, remote ischemic preconditioning compared with no ischemic preconditioning significantly reduced the rate of AKI and use of renal replacement therapy (33).

The limitation of this study includes the following aspects. First, the relatively small sample may have lacked the power to detect significant interactions. Second, Hemodynamic indexes which the study collected cannot directly represent renal perfusion. Third, the evaluation criteria of microcirculation and oxygen metabolism are still controversial at present, and the indexes we adopted in this paper need to be further verified.

Conclusions

In conclusion, low preoperative PaO₂ did not significantly increase the incidence of AKI, but patients with low PaO₂ were more likely to have severe AKI and persistent AKI. Pv-aCO₂/Ca-vO₂ and Pv-aCO₂ are independent risk factors for postoperative AKI and Pv-aCO₂/Ca-vO₂ is an independent risk factor for persistent AKI. Monitoring Pv-aCO₂/Ca-vO₂ may offer some help for guiding AKI treatment.

Abbreviations

AKI, Acute Kidney Injury

CTS, Cardiothoracic Surgery

TOF, Tetralogy of Fallot

SCr, Serum Creatinine

KDIGO, Kidney Disease: Improving Global Outcomes

CVC, Central Venous Catheter

PICU, Pediatric Intensive Care Unit

RD, Renal Dysfunction

eGFR, Estimated Glomerular Filtration Rate

CPB, Cardiopulmonary Bypass

PaO₂, Arterial Partial Pressure of Oxygen

Pa-vO₂, Central Arterial-to-Venous Oxygen Pressure Difference

O₂ ER, Oxygen Extraction Ratio

Hct, Hematocrit

Hb, Hemoglobin

PAP, Pulmonary Arterial Pressure

LVEF, Left Ventricular Ejection Fraction

LVFS, Fractional Shortening

ASA, American Society of Anesthesiologists grade

HR, Heart Rate

MAP, Mean Arterial Pressure

CVP, Central Venous Pressure

SaO₂, Arterial Oxygen Saturation

Sa-vO₂, Central Arterial-to-Venous Oxygen Saturation Difference

Pv-aCO₂, Central Venous-to-Arterial Carbon Dioxide Difference

Ca-vO₂, Arterial-to-Central Venous O₂ Content Difference

VIS, Vasoactive Inotrope Score

CHD, Congenital Heart Disease

A-CHD, Acyanosis Congenital Heart Disease

C-CHD, Cyanosis Congenital Heart Disease

CN, Cyanotic Nephropathy

CI, Confidence Interval

N, Number

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all participants, where participants are children (under 16 years old) from their parent or guardian. This permits the researchers to engage in research, the use of identifiable

biospecimens and identifiable data during the peri-operative period and future follow-up without the requirement to obtain additional consent for the future storage, maintenance, or research uses, so long as the future activities are within the scope of the broad consent. The study protocols as well as the application form were fully reviewed, and we certify that this study did not raise any issues of patient risk or cause any harm to patients. We also certify that the study was strictly in accordance with the Declaration of Helsinki and International Ethical Guidelines for Health-related Research Involving Humans. This study was approved by the Ethics Committee of Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (Approval No. XHEC-D-2020-016).

Consent for publication

Written informed consent for publication was obtained from all participants

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no conflicts of interest.

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Authors' Contributions

YX contributed towards the study design, data collection and writing of the manuscript; YZ contributed towards the study design and literature search; ZL contributed towards the data collection and statistical analyses; LX contributed towards the statistical analyses; LC contributed towards data interpretation; WX contributed towards data interpretation and XZ contributed towards data interpretation and writing of the manuscript. All authors approved the final version of the manuscript.

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Figures

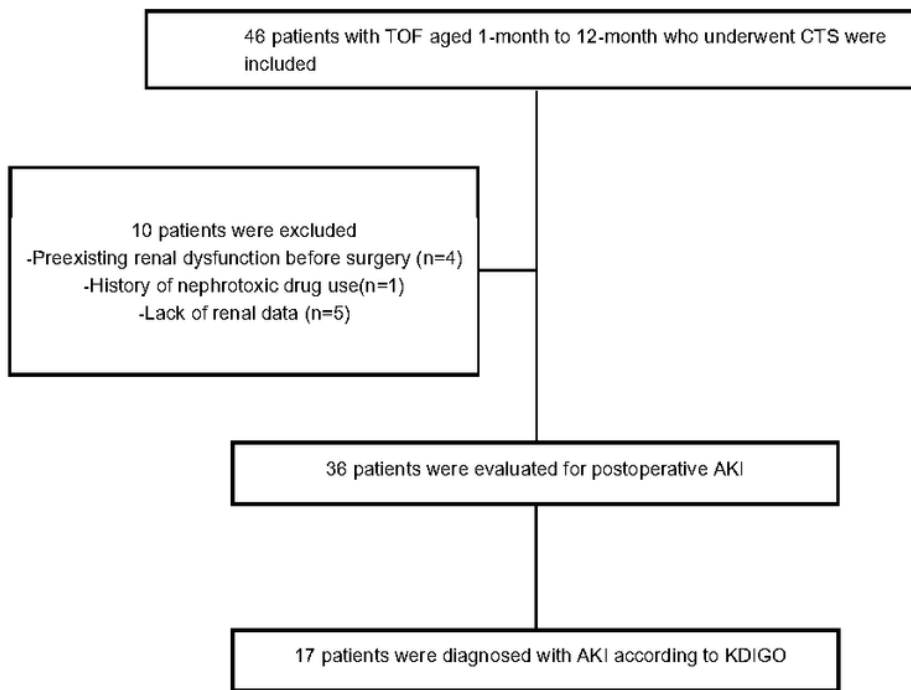


Figure 1

Flow diagram of the study participants TOF= Tetralogy of Fallot; CTS=cardiothoracic surgery; AKI=acute kidney injury; KDIGO=Kidney Disease: Improving Global Outcomes

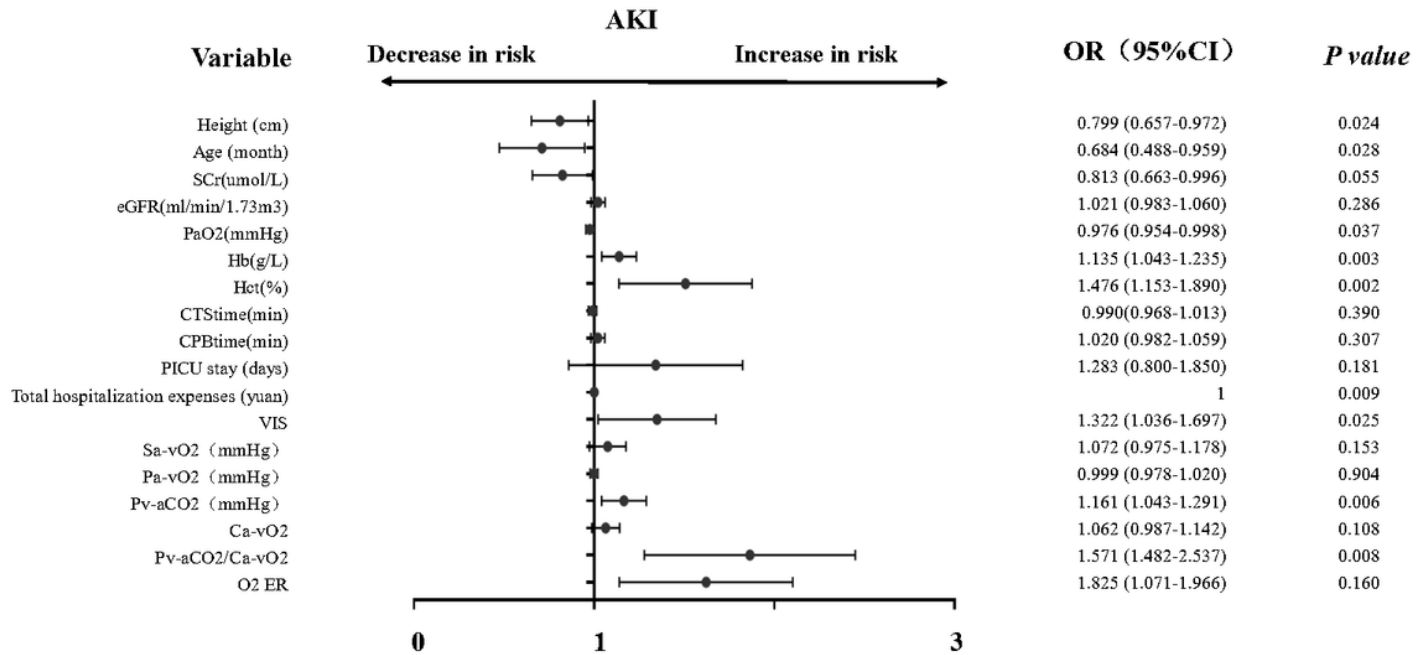


Figure 2

Logistic regression analysis for AKI AKI=Acute Kidney Injury; OR= Odds Ratio; CI= Confidence Interval; PaO₂=Arterial Partial Pressure of Oxygen; CTS = Cardiothoracic Surgery; CPB=Cardiopulmonary Bypass; SCr=Serum Creatinine; eGFR=estimated Glomerular Filtration Rate; PICU=Pediatric Intensive Care Unit; Hct=Hematocrit; Hb= Hemoglobin; VIS= Vasoactive Inotrope Score; SaO₂= Arterial Oxygen Saturation; Pv-aCO₂/Ca-vO₂= the ratio of central venous-to-arterial carbon dioxide difference (Pv-aCO₂) to arterial-to-central venous O₂ content difference (Ca-vO₂) ; O₂ER=Oxygen Extraction Ratio

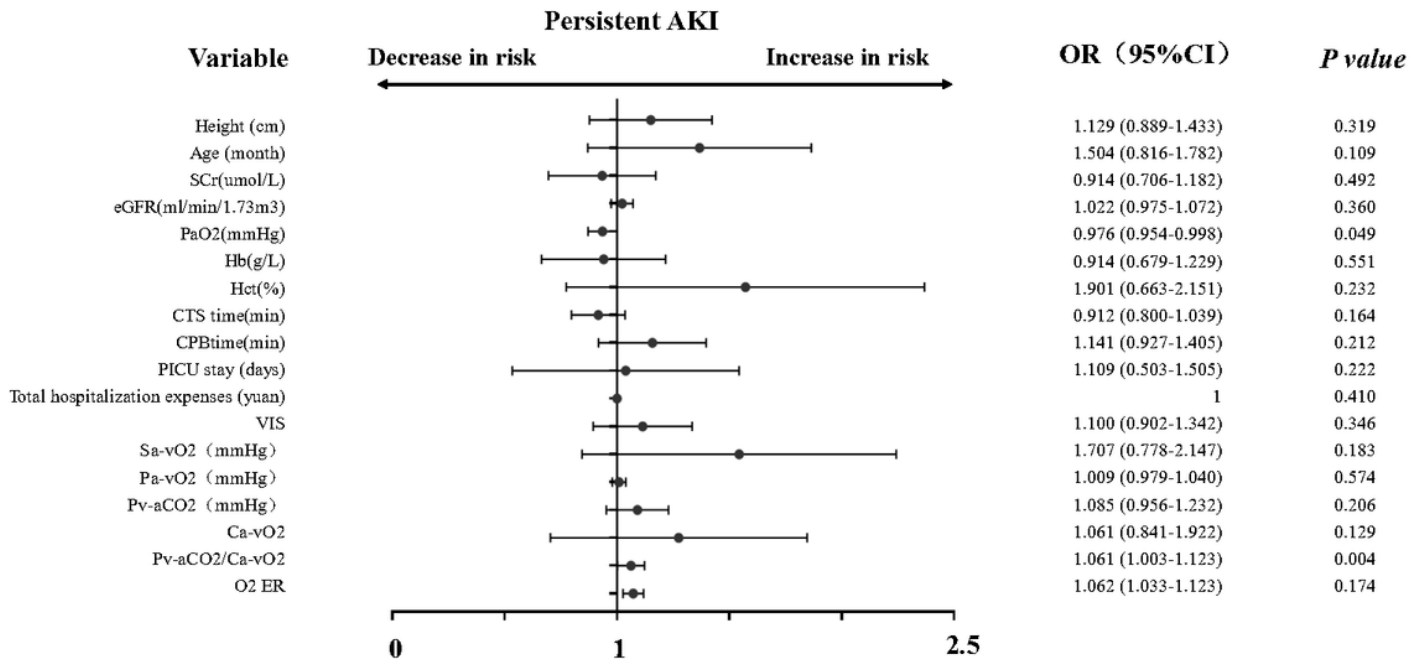


Figure 3

Logistic regression analysis for persistent AKI AKI=Acute Kidney Injury; OR= Odds Ratio; CI= Confidence Interval; PaO2=Arterial Partial Pressure of Oxygen; CTS = Cardiothoracic Surgery; CPB=Cardiopulmonary Bypass; SCr=Serum Creatinine; eGFR=estimated Glomerular Filtration Rate; PICU=Pediatric Intensive Care Unit; Hct=Hematocrit; Hb= Hemoglobin; VIS= Vasoactive Inotrope Score; SaO2= Arterial Oxygen Saturation; Pv-aCO2/Ca-vO2= the ratio of central venous-to-arterial carbon dioxide difference (Pv-aCO2) to arterial-to-central venous O2 content difference (Ca-vO2) ; O2ER=Oxygen Extraction Ratio.

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