Cardiology in the Young

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Early post-operative $P_{V\text{-}A}CO_2/C_{A\text{-}V}O_2$ predicts subsequent acute kidney injury after complete repair of tetralogy of Fallot

Yaya Xu, Xiaodong Zhu, Lili Xu and Zhen Li

Department of Pediatric Critical Care Medicine, Xinhua Hospital, Affiliated to the Medical School of Shanghai Jiaotong University, 1665 Kongjiang Road, Yangpu District, Shanghai 200092, China

Original Article

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Author for correspondence:
Xiaodong Zhu, MS, Department of Pediatric Critical Care Medicine, Xinhua Hospital Affiliated to the Medical School of Shanghai Jiaotong University, 1665 Kongjiang Road, Yangpu District, Shanghai 200092, China.
Tel: +86-13651727806.
E-mail: xinhuaxiaodong@126.com

Abstract

Background: Acute kidney injury is a severe complication following complete repair of tetralogy of Fallot. Anaerobic metabolism is believed to contribute to the development of acute kidney injury. The ratio of central venous to arterial carbon dioxide tension to arterio-venous oxygen content ($P_{V\text{-}A}CO_2/C_{A\text{-}V}O_2$) has been proposed as a surrogate for respiratory quotient and an indicator of tissue oxygenation. We hypothesised that a small increase of $P_{V\text{-}A}CO_2/C_{A\text{-}V}O_2$ might have superior discrimination ability in subsequent acute kidney injury prediction. *Methods:* This study is retrospective and single-centre design study. The study population consisted of 61 children with tetralogy of Fallot that underwent a complete surgical repair between July 2017 and January 2021. Baseline characteristics and intra-operative parameters were collected through a retrospective chart review. $P_{V\text{-}A}CO_2/C_{A\text{-}V}O_2$ was collected within 12 hours of surgical completion. Acute kidney injury was defined according to the criteria established by the Kidney Disease: Improving Global Outcomes group. Univariate and logistic regression analyses were performed to determine risk factors for acute kidney injury. *Results:* Of the 61 patients, 20 (32.8%) developed acute kidney injury. Multivariate logistic analyses showed that age, height, haematocrit, and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ were independently associated with the development of acute kidney injury. The addition of $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ to the model significantly increased model discrimination [AUROC 0.939 (95% CI 0.894–0.984) and AUROC 0.922 (95% CI 0.869–0.975), respectively]. *Conclusions:* The increase of $P_{V\text{-}A}CO_2/C_{A\text{-}V}O_2$ could improve the predictive ability for subsequent development of acute kidney injury in children with tetralogy of Fallot.

Acute kidney injury is a severe complication of paediatric cardiothoracic surgery associated with increased morbidity and mortality.[1,2] The presence of acute kidney injury is associated with a poor prognosis and increases the overall burden.[3] Tetralogy of Fallot is the most common congenital cyanotic heart disease in children. A retrospective study of 56 adult patients with complete repair of tetralogy of Fallot compared patients with and without renal dysfunction to identify risk factors for renal impairment, and[4] they showed that renal dysfunction is common at late follow-up evaluation after repair of tetralogy of Fallot (54 % of the patients had at least stage 2 chronic renal disease).

Mechanisms of cardiac surgery-associated acute kidney injury include renal ischaemia, haemodynamic instability, inflammation, generation of reactive oxygen species, and haemolysis.[5] Renal tissue hypoxia is one of the most important mechanisms leading to acute kidney injury and may also promote progression from acute injury to chronic kidney disease.[6] Furthermore, animal experiments have shown that acute kidney injury is associated with dramatic changes in cardiac metabolism, cardiac adenosine triphosphate depletion, and diastolic dysfunction.[7] The ratio of central venous to arterial carbon dioxide tension to arterio-venous oxygen content ($P_{V\text{-}A}CO_2/C_{A\text{-}V}O_2$) has been proposed as a tool for monitoring changes in tissue oxygenation status.[8] Some studies have found that high $P_{V\text{-}A}CO_2/C_{A\text{-}V}O_2$ has been associated with oxygen supply dependence and worse outcome.[9] However, the suggestion that $P_{V\text{-}A}CO_2/C_{A\text{-}V}O_2$ may be effective for predicting outcome, hyperlactataemia, microvascular abnormalities, and oxygen supply dependency has been controversial. Some studies indicated that $P_{V\text{-}A}CO_2/C_{A\text{-}V}O_2$ is useless as a goal of resuscitation.[10] Moreover, there has been little research on the effect of $P_{V\text{-}A}CO_2/C_{A\text{-}V}O_2$ on the post-operative acute kidney injury prediction.

Based on the existing literature, we hypothesise that $P_{V\text{-}A}CO_2/C_{A\text{-}V}O_2$ may have a superior tendency to predict acute kidney injury after cardiothoracic surgery among children with tetralogy of Fallot. The following were the aims of the current study: to determine the incidence of acute kidney injury according to the Kidney Disease Improving Global Outcomes criteria and to elucidate acute kidney injury risk factors and to determine whether the $P_{V\text{-}A}CO_2/C_{A\text{-}V}O_2$ may accurately predict subsequent acute kidney injury among children with tetralogy of Fallot.

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Materials and methods

We conducted a retrospective study of patients who underwent primary complete repair of tetralogy of Fallot with cardiopulmonary bypass from July 2017 to January 2021. This study was performed with the approval of the Ethics Committee of Xin Hua Hospital affiliated to Shanghai Jiaotong University School of Medicine. As it was a retrospective study using data obtained from medical records, informed consent was exempted by the Institutional Review Board.

Inclusion criteria for patients were aged 1–12 months; confirmed tetralogy of Fallot diagnosis by pre-operative echocardiography and intra-operative findings[11]; and underwent complete surgical repair for the first time for tetralogy of Fallot. The exclusion criteria were pre-existing renal dysfunction or requirement of renal replacement therapy before surgery[12]; lack of post-operative renal data; and delayed sternal closure or reoperation required due to bleeding and other reasons.

Study variables

Demographic and clinical data were retrieved from the patients' medical records. Pre-operative data included weight, height, age, sex, serum creatinine, estimated glomerular filtration rate, haematocrit, haemoglobin, McGoon ratio, Nakata index, pulmonary arterial pressure, left ventricular ejection fraction, and fractional shortening. Fasting venous blood samples were collected from all patients within 3 days after admission and were immediately sent for analysis. A cardiac ultrasound examination was performed within 7 days before cardiothoracic surgery.

Intra-operative data including duration of cardiothoracic surgery time, duration of cardiopulmonary bypass time, and American Society of Anesthesiologists grade were collected.[13] Complete surgical repair was defined as ventricular septal defect closure with or without right ventricular outflow tract intervention (transannular patch or right ventricle to pulmonary artery conduit).[14]

Central vein catheterisation was performed routinely during surgery, and an arterial catheter via the radial artery was used for the measurement of arterial blood pressure and to obtain blood samples for blood gas analysis. All post-operative children were admitted to the paediatric ICU.

Post-operative data including lactic acid, arterial oxygen saturation (S_aO_2), venous oxygen saturation (S_vO_2), arterial partial pressure of oxygen (P_aO_2), venous partial pressure of oxygen (P_vO_2), arterial partial pressure of carbon dioxide (P_aCO_2), and venous partial pressure of carbon dioxide (P_vCO_2) were collected. Post-operative arterial and venous blood gas was collected early (within 12 hours of surgery) after cardiothoracic surgery. We calculate oxygen metabolism index according to the following formulas[15–17]:

$$C_aO_2 = (1.34 \times S_aO_2 \times \text{haemoglobin}) + (0.003 \times P_aO_2)$$
$$C_vO_2 = (1.34 \times S_vO_2 \times \text{haemoglobin}) + (0.003 \times P_vO_2)$$
$$C_{a-v}O_2 = CaO_2 - C_{cv}O_2$$
$$P_{v\text{-}a}CO_2 = P_{cv}CO_2 - P_aCO_2$$
$$P_{v\text{-}a}CO_2/C_{a-v}O_2 \text{ ratio} = P_{v\text{-}a}CO_2/C_{a-v}O_2$$
$$P_{a-v}O_2 = P_aO_2 - P_{cv}O_2$$
$$S_{a-v}O_2 = S_aO_2 - S_{cv}O_2$$
$$O_2 \text{ ER} = C_{a\text{-}v}O_2/C_aO_2$$

Outcome variables

Diagnosis and staging of acute kidney injury were performed according to the Kidney Disease Improving Global Outcomes criteria[18]: an increase in serum creatinine value by 0.3 mg/dL (26.5 mumol/L) within 48 h or percentage by ≥50% from baseline within 1 week; or urine output <0.5 ml/kg/h for at least 6 hours. Lengths of paediatric ICU and hospital stay were also recorded.

Statistical analysis

The Shapiro–Wilk test was used to check the normality of the data. Continuous variables with normal distribution were expressed in terms of mean ± standard deviation, and group comparisons were analysed by independent sample t-tests. The continuous variables with the non-normal distribution were expressed as median (P_{25} and P_{75}), and comparisons among groups were carried out using the Mann–Whitney U-test. Frequencies and proportions were estimated for categorical variables and were compared using the chi-squared test or Fisher's test. Univariate logistic analysis was performed to determine predictive factors on acute kidney injury. Subsequently, significant predictors for univariate analysis were further included in the multivariable forward stepwise logistic analysis to confirm independent risk factors for acute kidney injury and to evaluate the predictive value of $P_{V\text{-}A}CO_2/C_{A\text{-}V}O_2$. The significance level for the removal of variables from the model was 0.1; otherwise, the significance level was set at 0.05.

Receiver operating characteristic curves were employed to evaluate the diagnostic accuracy of $P_{V\text{-}A}CO_2/C_{A\text{-}V}O_2$ in patients with acute kidney injury. All statistical analyses were performed with SPSS version 23 (IBM Corp. Released (2015) IBM SPSS Statistics for Windows. IBM Corp., Armonk, New York, United States of America). The difference was considered significant when the two-tailed P-value was <0.05.

Results

Basic characteristic

Among the 61 patients, 35 were males and 26 were females. The median age was 6 months (range, 4–12 months). The median serum creatinine level was 23.0 μmol/L, and estimated glomerular filtration rate was 111.7 ml/min/1.73 m^3 at baseline. Twenty patients (32.8%) developed acute kidney injury. The baseline values, clinical status, and surgical characteristics of all 61 patients are shown in Table 1.

The acute kidney injury group was younger than the non-acute kidney injury group and thus had lower pre-operative creatinine; however, no significant statistical difference was observed in pre-operative renal function (serum creatinine and estimated glomerular filtration rate) between the two groups ($P > 0.05$). We observed statistically significant differences in haematocrit between groups ($P > 0.05$). Although haemoglobin values for acute kidney injury group were higher than for non-acute kidney injury group, the difference was not statistically significant. Prior to surgery, differences of pre-operative echocardiography of the two groups were not statistically significant ($P > 0.05$). There was not any significant difference between two groups in terms of length of hospital stay and length of paediatric ICU stay. Due to poor effect of clinical treatment and continuous deterioration of the condition, through clinical evaluation, five patients in the acute kidney injury group chose to be automatically discharged from hospital.

Post-operative oxygen metabolism

Compared with the non-acute kidney injury groups, the acute kidney injury group showed decreased P_aO_2 and S_aO_2 levels. $P_{v\text{-}a}CO_2$, $C_{a\text{-}v}O_2$, $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$, and O_2 ER were significantly higher in the

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Table 1. Study population characteristics (n = 61).

Characteristics	Non-AKI (n = 41)	AKI (n = 20)	*P* value
Demographics			
Gender [male (%)]	26 (63.4)	9 (45.0)	0.270
Age (months)	7.0 (6.0, 11.0)	6.0 (5.0, 7.0)	0.085
Height (cm)	68.0 (65.5, 73.5)	66.0 (63.0, 68.0)	0.032
Weight (kg)	8.2 ± 1.9	7.7 ± 2.4	0.030
Body mass index (kg/m^2)	17.2 ± 3.0	17.5 ± 2.9	0.728
Pre-operative testing			
SCr (umol/L)	24.0 (21.0, 26.0)	21.0 (17.0, 24.0)	0.059
eGFR (ml/min/1.73 m^3)	109.1 ± 27.4	118.3 ± 21.5	0.218
Hb (g/L)	116.0 (97.0, 143.0)	133.0 (123.0, 147.0)	0.053
Hct (%)	34.5 (30.3, 42.1)	40.8 (37.3, 35.1)	0.035
Pre-operative echocardiography			
LVEF (%)	67.0 (64.0, 69.5)	67.0 (65.0, 68.0)	0.802
LVFS (%)	36.0 ± 7.2	35.4 ± 5.0	0.671
PAP (mmHg)	68.5 (44.5, 82.5)	80.0 (64.0, 100.0)	0.050
Nakata index (mm^2/m^2)	174.8 (134.9, 211.4)	165.5 (133.1, 215.0)	0.974
McGoon	2.0 (1.7, 2.3)	2.1 (1.7, 2.3)	0.723
Surgical characteristics			
CTS time (min)	155.0 (118.0, 188.0)	175.0 (150.0, 185.0)	0.041
CPB time (min)	68.0 (42.0, 90.5)	94.0 (84.0, 106.0)	0.001
ASA grade			
−≤2 [n (%)]	10 (16.4)	2 (3.3)	0.512
−≥3 [n (%)]	31 (50.8)	18 (29.5)	
Prognosis			
PICU stay (days)	5.0 (3.0, 6.0)	4.0 (3.0, 6.0)	0.524
Hospital stay (days)	16.1 ± 4.6	15.8 ± 4.5	0.829

AKI = acute kidney injury; ASA = American Society of Anesthesiologists; CPB = cardiopulmonary bypass; CTS = cardiothoracic surgery; eGFR = estimated glomerular filtration rate; Hb = haemoglobin; Hct = haematocrit; LVEF = left ventricular ejection fraction; LVFS = left ventricular fraction shortening; PaO_2 = Arterial Partial Pressure of Oxygen; PAP = Pulmonary Artery Pressure; PICU = Paediatric ICU; SCr = serum creatinine.
A two-tailed P value of < 0.05 was considered statistically significant.

Table 2. Comparison of oxygen metabolism index among groups (n = 61).

Characteristics	Non-AKI (n = 41)	AKI (n = 20)	Statistic	*P* value
SaO_2(%)	99.5 (99.2, 100.0)	96.1 (94.1, 100)	*H = 5.650*	0.118
PaO_2(mmHg)	168.0 ± 23.7	97.1 ± 33.0	*H = 3.510*	0.049
Sa-vO_2(%)	3.6 ± 1.7	19.3 ± 8.7	*F = 1.066*	0.284
Pa-vO_2(mmHg)	32.5 (23.0, 61.5)	69.0 (15.8, 92.0)	*H = 3.205*	0.410
Pv-aCO_2(mmHg)	0.7 (0.1, 3.8)	23.5 (18.7, 28.9)	*H = 29.210*	<0.001
Ca-vO_2 (mL/dL)	5.7 (4.2, 6.9)	29.6 (20.9, 35.9)	*H = 27.520*	<0.001
Pv-aCO_2/Ca-vO_2	0.2 (0.05, 0.6)	0.8 (0.1, 0.9)	*H = 13.471*	<0.001
O_2 ER	0.05 (0.03, 0.07)	0.28 (0.13, 0.32)	*H = 28.510*	<0.001

O_2ER = oxygen extraction ratio; PaO_2 = arterial partial pressure of oxygen; $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ = 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); SaO_2 = arterial oxygen saturation.
A two-tailed P value of < 0.05 was considered statistically significant.

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acute kidney injury group than in the non-acute kidney injury group ($P < 0.05$) (Table 2).

Baseline predictors for acute kidney injury

On univariate logistic analysis, factors strongly associated with acute kidney injury occurrence were age, height, haemoglobin, haematocrit, P_aO_2, $P_{v\text{-}a}CO_2$, and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ (Table 3). Multivariate logistic analyses showed that age, height, haematocrit, and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ were independently associated with acute kidney injury.

Sensitivity analyses

Model 1 adjusted for demographic factors (age, height, haematocrit) and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ were added to model 1 to form model 2 (Table 4). The addition of $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ to the model significantly increased model discrimination [AUROC 0.939 (95% CI 0.894–0.984) and AUROC 0.922 (95% CI 0.869–0.975), respectively], Fig 1.

Discussion

Acute kidney injury is a common but serious complication following cardiopulmonary bypass and cardiac surgeries and carries a poor prognosis.[19] Some studies believe that acute kidney injury can occur because children with congenital heart disorders, especially cyanotic, can be more prone to toxic agents due to chronic hypoxia leading to increase viscosity and increases in renal vascular resistance and higher intra-glomerular pressures.[20] In this study, acute kidney injury was a common complication after complete repair of tetralogy of Fallot. Studies have indicated that cyanotic nephropathy is seen in 30–50% of patients with congenital cyanotic heart disease.[21,22] Therefore, it is important to identify patients who are at risk of developing acute kidney injury post-cardiothoracic surgery. Previous studies have reported that younger age, longer surgery, and cardiopulmonary bypass times were associated with post-operative acute kidney injury.[23] However, our univariate analysis suggested no significant relationship between increased surgery and cardiopulmonary bypass times and acute kidney injury. Owing to advancements in surgical techniques, interventional procedures, and perioperative management, the outcomes of children with tetralogy of Fallot have dramatically improved. In our study, surgery and cardiopulmonary bypass times are tightly controlled to be within the safe range for a significant duration of time.

Our findings suggest that patients in the acute kidney injury group had higher haemoglobin and haematocrit than those in the non-acute kidney injury group. A multivariate regression analysis demonstrated that haematocrit was an independent risk factors for acute kidney injury. However, some studies suggested that the nadir haematocrit on cardiopulmonary bypass is widely recognised as a risk factor for post-operative acute kidney injury.[24] This might be due to the fact that haematocrit in our study was measured before surgery and higher haematocrit values decrease blood flow as a result of an increase in whole blood viscosity.

The limitation in renal tissue oxygen supply renders the kidney susceptible to hypoxia and has long been recognised as an important factor in the pathogenesis of acute kidney injury.[25] PO_2 and SO_2 are commonly used as the indices of oxygen metabolism, but tissue hypoxia may still exist even when PO_2 and SO_2 are within the normal range.[26] Although PO_2 and SO_2 were lower in the acute kidney injury group, they were not significant in a multivariate regression. Parameters obtained by central venous and arterial blood gas analyses were used to calculate the oxygen metabolism indices. The result showed that acute kidney injury was correlated with $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ using univariate and multivariate regression analysis. $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ measured early after the operation had been proven to improve subsequent acute kidney

Table 3. Univariate analyses with AKI as the outcome variable (n = 61).

Characteristics	OR (95% CI)	*P* value
Demographics		
Man sex (present)	1.132 (0.891–1.443)	0.402
Age (per 1 month month)	0.683 (0.485–0.960)	0.031
Height (per 1 cm increase)	0.798 (0.655–0.982)	0.022
Weight (per 1 kg increase)	1.022 (0.975–1.072)	0.360
Body mass index (per 1 kg/m^2 increase)	0.920 (0.708–1.179)	0.488
Pre-operative testing		
SCr (per 1 umol/L increase)	1.085 (0.956–1.232)	0.206
eGFR (per 1 ml/min/1.73 m^3 increase)	1.021 (0.983–1.060)	0.286
Hb (per 1 g/L increased)	1.138 (1.042–1.244)	0.048
Hct (per 1% increased)	1.478 (1.148–1.895)	0.003
Pre-operative echocardiography		
LVEF (per 1% increase)	1.106 (0.903–1.348)	0.540
LVFS (per 1% increase)	1.008 (0.980–1.043)	0.671
PAP (per 1 mmHg increase)	1.070 (1.038–1.143)	0.082
Nakata index (per 1 mm^2/m^{2}increase)	1.053 (0.852–1.933)	0.278
McGoon (per 1 unit increase)	0.923 (0.680–1.2321)	0.624
Surgical characteristics		
CTS time (per 1 min increase)	1.000 (0.997–1.013)	0.288
CPB time (per 1 min increase)	1.019 (0.991–1.058)	0.311
ASA grade 3 present	0.913 (0.789–1.041)	0.284
Prognosis		
PICU stay (per 1 day increase)	0.883 (0.782–1.853)	0.782
Hospital stay (per 1 day increase)	0.901 (0.526–2.352)	0.522
SaO_2(%)	1.505 (0.817–1.784)	0.111
PaO_2(mmHg)	0.977 (0.948–0.999)	0.048
Sa-vO_2(%)	1.073 (0.976–1.182)	0.164
Pa-vO_2(mmHg)	1.002 (0.992–1.022)	0.912
Pv-aCO_2(mmHg)	1.162 (1.044–1.293)	0.012
Ca-vO_2 (mL/dL)	1.063 (0.988–1.145)	0.110
Pv-aCO_2/Ca-vO_2	1.573 (1.483–2.541)	0.004
O_2 ER	1.830 (1.072–1.968)	0.152

ASA = American Society of Anesthesiologists; CPB = cardiopulmonary bypass; CTS = cardiothoracic surgery; eGFR = estimated glomerular filtration rate; Hb = haemoglobin; Hct = haematocrit; LVEF = left ventricular ejection fraction; LVFS = left ventricular fraction shortening; O_2ER = oxygen extraction ratio; PaO_2 = arterial partial pressure of oxygen; PAP = pulmonary artery pressure; PICU = paediatric ICU; $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ = 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); SaO_2 = arterial oxygen saturation; SCr = serum creatinine.
A two-tailed P value of < 0.05 was considered statistically significant.

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Table 4. Associations in model fit and discrimination across different models based on confirmative predictors for AKI (n = 61).

Models and variables	OR (95% CI)	*P* value	AUROC (95% CI)
Model 1			
Age	0.948 (0.911, 0.978)	0.042	0.922 (0.869–0.975)
Height	0.973 (0.954–0.995)	0.009	
Hct	1.458 (1.155–1.882)	0.012	
Model 2			
Age	0.999 (0.993–1.008)	0.047	0.939 (0.894–0.984)
Height	0.998 (0.993–1.003)	0.013	
Hct	1.482 (1.166–1.890)	0.013	
Pv-aCO_2/Ca-vO_2	1.575 (1.501–2.548)	0.038	

Hct = Haematocrit; $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ = 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).
A two-tailed P value of < 0.05 was considered statistically significant.

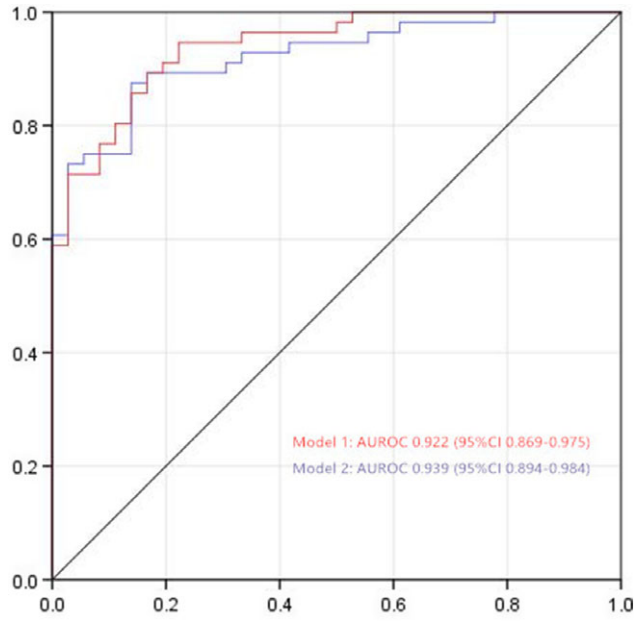

Figure 1. Receiver operating characteristic (ROC) curve analysed by the logistic regression model for the prediction of post-operative acute kidney injury (AKI). A two-tailed *P*-value < 0.05 was considered statistically significant. Model 1, an AKI risk prediction model in our study, was adjusted for age, height, and haematocrit (Hct). Model 2, an AKI risk prediction model in our study, was adjusted for age, height, Hct, and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$.

injury prediction. Some observational studies have suggested that $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ might be a good surrogate for the respiratory quotient. Increased carbon dioxide production, relative to oxygen consumption, occurs under conditions of tissue hypoxia, and the presence of anaerobic metabolism may be inferred when the $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ rises.[8] Mukai et al found that $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ at the end of surgery had a superior ability for predicting post-operative complications.[27] Regarding the optimal cut-off value of the $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$, there have been some controversies among different studies. Mekontso-Dessap et al demonstrated that a $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2 > 1.4$ was superior to $P_{v\text{-}a}CO$, S_vO_2, and $C_{a\text{-}v}O_2$, in predicting hyperlactataemia in a cohort of critically ill patients.[8] However, He et al suggested that the $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2 \geq 1.6$ was associated with ICU mortality in septic shock patients.[28]

The limitations of this study must be considered when interpreting our findings. First, this was a small, single-centre, retrospective study of patients who underwent cardiothoracic surgery. The generalisability of our results may, therefore, be limited. Second, the diagnosis of acute kidney injury was underestimated because we mainly used the serum creatinine criteria of the KDIGO guidelines. Our study did not use urine output to determine acute kidney injury because urine volume data were not available in our hospital information system for most patients. However, urine output criteria have been criticised due to inaccurate reflection of glomerular filtration rate, insensitivity to detect acute change in renal function, and being influenced by many factors including use of diuretics and volume status. Third, although we rigorously adjusted for some known confounders that affect renal function, the effect of measured and/or unmeasured residual confounders cannot be eliminated in our study. The evaluation criteria of microcirculation and oxygen metabolism are still controversial at present, and the applicability of the model proposed in this paper needs to be further verified.

Conclusions

We demonstrated that $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ measured after cardiothoracic surgery was significantly associated with subsequent acute kidney injury. Moreover, we showed that $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ significantly improved the risk prediction model for acute kidney injury after cardiothoracic surgery. We believe that early increased $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ could be one of the indicators for subsequent acute kidney injury prediction and will draw clinicians' attention to prevent or ameliorate acute kidney injury.

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Authors' contributions. Study Design: Yaya Xu; Data Collection: Yaya Xu; Zhen Li; Statistical Analysis: Lili Xu; Zhen Li; Data Interpretation: Xiaodong Zhu; Manuscript Preparation: Yaya Xu; Literature Search: Zhen Li.

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Conflicts of interest. None.

Ethical standards. This study was approved by the Ethics Committee of Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine

Availability of data and material (data transparency). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability (software application or custom code). All code generated or used during the study appears in the submitted article.

Consent to participate and publication. As our study was a retrospective study using data obtained from medical records, informed consent was exempted by the Institutional Review Board.

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