Oxygen delivery in pediatric cardiac surgery and its association with acute kidney injury using machine learning

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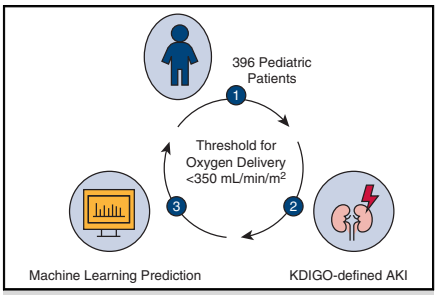
ABSTRACT

Objective: Acute kidney injury (AKI) after pediatric cardiac surgery with cardiopulmonary bypass (CPB) is a frequently reported complication. In this study we aimed to determine the oxygen delivery indexed to body surface area (Do_2i) threshold associated with postoperative AKI in pediatric patients during CPB, and whether it remains clinically important in the context of other known independent risk factors.

Methods: A single-institution, retrospective study, encompassing 396 pediatric patients, who underwent heart surgery between April 2019 and April 2021 was undertaken. Time spent below Do_2i thresholds were compared to determine the critical value for all stages of AKI occurring within 48 hours of surgery. Do_2i threshold was then included in a classification analysis with known risk factors including nephrotoxic drug usage, surgical complexity, intraoperative data, comorbidities and ventricular function data, and vasoactive inotrope requirement to determine Do_2i predictive importance.

Results: Logistic regression models showed cumulative time spent below a Do_2i value of 350 mL/min/m^2 was associated with AKI. Random forest models, incorporating established risk factors, showed Do_2i threshold still maintained predictive importance. Patients who developed post-CPB AKI were younger, had longer CPB and ischemic times, and required higher inotrope support postsurgery.

Conclusions: The present data support previous findings that Do_2i during CPB is an independent risk factor for AKI development in pediatric patients. Furthermore, the data support previous suggestions of a higher threshold value in children compared with that in adults and indicate that adjustments in Do_2i management might reduce incidence of postoperative AKI in the pediatric cardiac surgery population. (J Thorac Cardiovasc Surg 2023;165:1505-16)



Oxygen delivery <350 mL/min/m² is independently associated with acute kidney injury.

CENTRAL MESSAGE

Time spent on cardiopulmonary bypass with oxygen delivery <350 mL/min/m^2 is independently associated with acute kidney injury in pediatric patients undergoing cardiac surgery.

PERSPECTIVE

Goal-directed perfusion, through patient-specific intraoperative management, is a successful strategy for improving outcomes. However, current best practice centers on results of multiple adult investigations, with limited pediatric evidence. Our findings show a requirement for greater oxygen delivery during cardiopulmonary bypass than previously described to avoid acute kidney injury in children.

See Commentary on page 1517.

Acute kidney injury (AKI) is common after pediatric cardiac surgery, with recorded incidence up to 50%, due to factors directly related to cardiopulmonary bypass (CPB) and multifactorial perioperative components.[1-3] There remains very little evidence surrounding the best intervention to

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CONG

Abbreviations and Acronyms

AKI = acute kidney injury
AUC = area under the curve
BSA = body surface area
CPB = cardiopulmonary bypass
Do_2i = oxygen delivery indexed to body surface area
KDIGO = Kidney Disease Improving Global Outcomes
LVEF = left ventricular ejection fraction
ROC = receiver operating characteristic
sCr = serum creatinine
VIS = vasoactive inotrope score

prevent AKI and, alongside discrepancies in the definition used for its diagnosis, has meant improvements in management have been limited. Do_2i is the amount of oxygen delivered to the tissues in the body per minute, indexed to body surface area (BSA). It is a product of CPB pump flow, hemoglobin, oxygen saturation, and arterial oxygen tension, all variables that can be monitored and adjusted by the perfusionist.[4] It is hypothesized that when Do_2i decreases, organ dysoxia provokes tissue acidosis and hyperlactatemia through anaerobic respiration, which is detrimental to postoperative kidney function.[5] Although Do_2i is modifiable through pump flow adjustments, it is not routinely measured. Evidence from adult studies have suggested a critical threshold of 260 to 300 mL/min/m^2, below which patients are at an increased risk of AKI development, although little work has shown a delineated benefit of improved outcomes with increased time above this threshold.[6,7] Inconsistencies lie within study protocols, with initial studies measuring nadir Do_2i values as markers of suboptimal perfusion, whereas more recent publications suggest that measuring duration and severity below a critical threshold better reflects the dynamic variable.[8,9] Furthermore, pediatric evidence is sparse. Higher metabolic rates and oxygen demand in children would suggest adult Do_2i reference ranges cannot be used to guide practice. In this retrospective, single-center analysis we aimed to determine whether Do_2i is associated with postoperative AKI in pediatric patients, and whether its predictive value remains clinically important in the context of other known independent risk factors. Ultimately, this would determine whether Do_2i measurement should be used during CPB to improve patient outcomes.

METHODS

Study Design and Patient Selection

This was a retrospective analysis of patients aged younger than 18 years (maximum age treated at the institution), who underwent cardiac surgery with CPB for congenital heart disease at Great Ormond Street Hospital, London. The cohort was selected using a National Institute for Cardiovascular Outcomes Research (NICOR) validated data set for patients operated on between April 2019 and April 2021. Patients with preexisting kidney failure (defined as a serum creatinine level >1.5 times the normal for age, or requiring presurgical dialysis) or univentricular anatomy, born preterm (before 34 weeks), or whose surgical procedure involved deep hypothermic circulatory arrest or selective cerebral perfusion were excluded from this study, as were patients with missing data. Furthermore, only patients who had primary sternotomy, and did not receive a reoperation within 48 hours were included. All clinical data were collated in a research platform within the hospital's governance structure and deidentified before analysis. Institutional approval was given for the undertaking of this research (audit number 2970; November 20, 2020). Individual consent was not required because only routinely collected deidentified hospital data were evaluated within the secure digital research environment as part of an existing research database approval (17/LO/0008).

Data Collection

Routine clinical information was extracted from the institution's electronic health record system using a custom structured query language script. These data included patient demographic information, laboratory results, intraoperative, CPB, and medication administration data, and intensive care requirements. Comorbidities and outcomes were defined using Association for European Paediatric and Congenital Cardiology coding as part of the institution's NICOR data submission. Intraoperative data from the heart-lung and anesthetic machines were captured every minute throughout surgery. Presence of an antenatal diagnosis was used as a surrogate for lesion complexity (Online Data Supplement). Left ventricular ejection fraction (LVEF) and right ventricular ejection fraction were defined in accordance with the National Congenital Heart Disease Audit data manual and derived from imaging studies preprocedure. Ventricular functions were classed as good if the ejection fraction was >50%, moderate if between 30% and 50%, and poor <30%. Ventricular functions were used as a surrogate of patient condition presurgery. Baseline serum creatinine levels were taken within the 24 hours preceding surgery.

AKI

Postoperative AKI was defined on the basis of the consensus definition of AKI developed in 2012 by the Kidney Disease Improving Global Outcome (KDIGO) group, which categorizes AKI into 3 severity stages, according to serum creatinine elevation compared with baseline value or duration of decreased urine output (Table 1).[10] Patients were assigned the highest AKI grouping on the basis of their results. The primary end point was then attributed to a binary outcome variable with AKI confirmed if KDIGO stage was ≥1 in the first 48 hours after return to the intensive care unit after surgery.

Oxygen Delivery Thresholds

Oxygen delivery was defined as previously described and indexed to BSA[11]:

$$Do_2i = \frac{CO \times 10 \times \left(\left(1.36 \times \frac{HCT}{2.94} \times Sao_2\right) + \left(po_2 \times 0.0226\right)\right)}{BSA}$$

Where CO = cardiac output (L/min), HCT = hematocrit (%), Sao_2 = arterial oxygen saturation (%), and po_2 = partial pressure of oxygen (kPa). These variables were extracted from the heart-lung machine and Do_2i then calculated from these data every minute throughout the duration of CPB. Variable data were taken from the in-line blood gas monitoring system (CDI 550; Terumo Corp) which was calibrated every 20 minutes using laboratory measurements. Oxygen delivery thresholds were set every 10 mL/min/m^2 increment between 260 mL/min/m^2 and 400 mL/min/m^2,

TABLE 1. Neonatal KDIGO diagnostic definitions for postoperative AKI

Stage	sCr	Urine output
0	No change in sCr or increase <0.3 mg/dL	>0.5 mL/kg/h
1	>0.3 mg/dL within 48 h or >1.5-1.9 times baseline within 7 d	<0.5 mL/kg/h for 6-12 h
2	>2.0-2.9 times baseline	<0.5 mL/kg/h for >12 h
3	Initiation of dialysis or >3 times baseline or sCr >4.0 mg/dL (>2.5 mg/dL for neonates)	<0.3 mL/kg/h for >24 h or anuria for >12 h

KDIGO, Kidney Disease Improving Global Outcomes; *AKI*, acute kidney injury; *sCr*, serum creatinine.

with the sum of the CPB time when the lungs were deflated (defined as an absence of end-tidal CO_2 measurement) used to calculate the time under the Do_2i threshold. Where more than 1 bypass run was required, the data were combined into a single value for that patient.

Vasoactive Inotrope Score

Vasoactive inotrope score (VIS) was calculated as previously described to quantify the amount of cardiovascular support required postoperatively[12,13]:

$$VIS = DA + Dob + (100 \times Eph) + 10 \times Mil + 10,000 \times ADH + 100 \times NE$$

where DA = dopamine dose ($\mu gkg^{-1}min^{-1}$), Dob = dobutamine dose ($\mu gkg^{-1}min^{-1}$), Eph = epinephrine dose ($\mu gkg^{-1}min^{-1}$), Mil = milrinone dose ($\mu gkg^{-1}min^{-1}$), ADH = vasopressin ($ukg^{-1}min^{-1}$), and NE = norepinephrine dose ($\mu gkg^{-1}min^{-1}$) using the maximum dosing rates within the first 48 hours postsurgery.

Anesthesia

Anesthesia was induced by inhalation of sevoflurane in oxygen and, after induction, fentanyl 5 μg/kg and pancuronium 100 μg/kg were given and anesthesia was maintained with isoflurane 1.0% in oxygen and air. After tracheal intubation, arterial and central venous lines were inserted. Further incremental doses of fentanyl, up to 25 μg/kg, were given during the procedure.

CPB

The CPB circuit consisted of FX oxygenators with integrated arterial-line filter and hard-shell venous reservoir (Terumo Corp) with either 3/16 × 1/4, 1/4 × 1/4, 1/4 × 3/8, 3/8 × 3/8, or 3/8 × 1/2 tubing sets, dependent on patient size. The Stöcket S5 (Stöckert, LivaNova) heart-lung machine with pole-mounted roller pumps was used with a 3T heater/chiller (Stöckert, LivaNova). The total base prime volume was 330 mL, 350 mL, 500 mL, 800 mL, or 1000 mL depending on circuit size. When the predicted initial CPB hematocrit was <27% the prime consisted of packed red blood cells of the patient's blood group (120-200 mL), a synthetic colloid (Gelofusine; B Braun Melsungen AG), heparin 1000 U/mL, 1.5 mL (Heparin Sodium; Wockhardt), and mannitol 20% wt/vol (Baxter) at 2.5 mL/kg, added at the perfusionist's discretion. Blood primed circuits were then washed with 1000 mL of balanced crystalloid solution (Plasmalyte 7.4; Baxter) by performing prebypass ultrafiltration, carried out as previously described, to ensure an initial on-CPB hematocrit of 30%.[14] Biochemical compatibility was then attained using sodium bicarbonate as a buffering agent. Patients requiring a clear prime received crystalloid and colloid volumes in a 40:60 mix, with 10 mL sodium bicarbonate and 2 to 5 mL heparin. All patients were systemically cooled to nasopharyngeal temperatures between 28 and 35°C and myocardial protection was achieved with 30 mL/kg of cold blood cardioplegia (4:1 blood:cardioplegia to a final concentration of 20 mmol) of St Thomas's Solution (IVEX Pharmaceuticals). During the rewarming phase of CPB, a gradient no greater than 10°C between the patient's nasopharyngeal temperature probe and the heater/chiller (maximum arterial blood temperature 37.5°C) was maintained until a maximum nasopharyngeal temperature of 36°C was achieved.

Statistical Analysis

Data are expressed as median and interquartile range (IQR; continuous variables) or as counts and percentages (categorical variables). Proportional testing of groups was undertaken using a 2-sample (χ^2) test for equality of proportions, or Fisher exact test. Analysis of differences between groups was undertaken using 2-tailed t tests or Wilcoxon–Mann–Whitney tests according to the variables' distribution. The association of Do_2i with AKI were examined using univariable logistic regression. Before analysis, data were divided into training and test sets (75%/25%) using 10-fold cross validation. Final thresholds were selected on the basis of the largest area under the curve (AUC). Best performing models were then compared using receiver operating characteristic (ROC) curves to assess the diagnostic accuracy, sensitivity, and specificity of the models. Determination of critical Do_2i threshold importance in the presence of independent risk factors for AKI was assessed using a random forest analysis. Variables were tested for multicollinearity to avoid redundancy using Pearson correlation. In cases of intercorrelation, the best independent variable was chosen for further analysis. Random forest models were built after 10-fold cross validation of the data and using 500 decision trees to determine the best performing model for AKI prediction assessed according to predictive accuracy and AUC. Hyperparameter tuning of complexity and maximum tree depth parameters was undertaken using a grid search technique. The effect of Do_2i threshold was assessed by interrogation of the random forest's variable importance plot. Statistical differences between random forest and logistic regression models were assessed using Delong test of ROC AUC. Data analyses was performed using the R language and environment for statistical computing, version 4.1.0 (R Foundation for Statistical Computing) using the tidyverse suite of packages (v1.3.1).[15,16] Machine learning pipelines were undertaken using the broom (v0.7.10) and tidymodels (v0.1.4) packages.[17,18]

RESULTS

Demographic Characteristics and Operative Data

A total of 396 patients were included in the analysis (Figure 1). Postoperative AKI within 48 hours occurred in 102 (25.8%) patients (75 [18.9%] met urine output criteria first, whereas 27 [6.9%] met creatinine criteria first). All 102 patients exhibited reduced urine output, whereas 97 (95%) exhibited serum creatinine changes. Those who developed AKI were younger than those who did not (4 [IQR, 2-11] vs 7 [IQR, 3-27] months; $P = .025$; Table 2). Both groups displayed similar proportions of males and females ($P = .8$). There was a greater proportion of White patients who developed postoperative AKI ($P = .046$), and a greater proportion of patients who developed AKI had an antenatal diagnosis ($P = .002$). There was no difference in AKI incidence in relation to preexisting comorbid

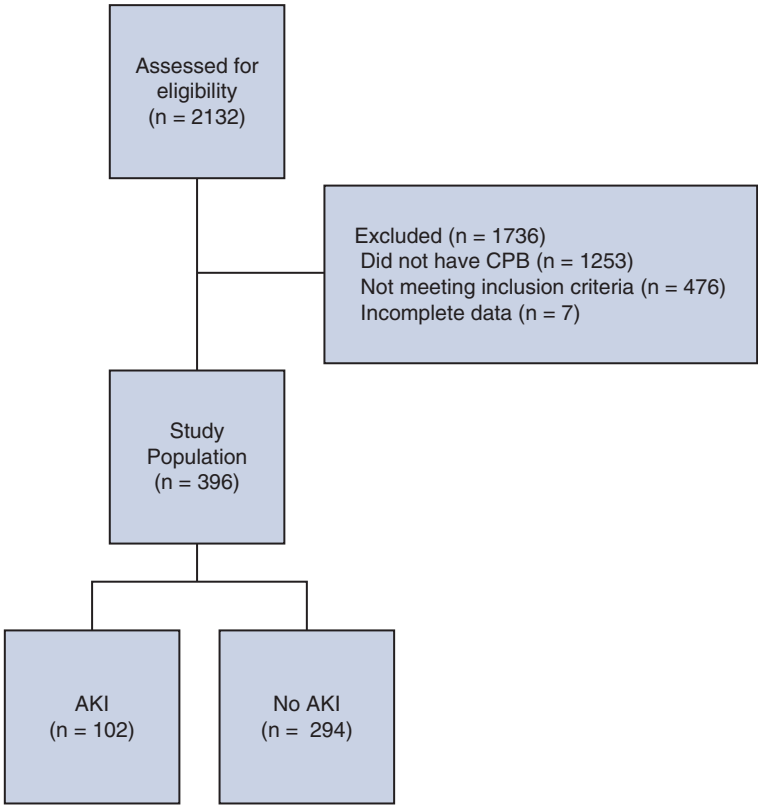


FIGURE 1. Study flow diagram. *CPB*, Cardiopulmonary bypass; *AKI*, acute kidney injury.

conditions ($P = .07$), required increased operative urgency ($P = .3$), or preoperative cyanotic diagnosis ($P = .10$). However, patients who developed AKI had worse preoperative ventricular function (LVEF $P = .025$; right ventricular ejection fraction $P = .028$). No patients required extracorporeal membrane oxygenation support after surgery.

Patients who developed AKI had longer ischemic durations ($P = .003$), CPB times ($P = .003$), and increased intra/postoperative inotrope requirement ($P < .01$). Fewer patients developed AKI who were administered furosemide ($P = .006$), whereas albumin administration was higher in those who developed AKI ($P = .01$). There were no differences in antifibrinolytic administration or antibiotic usage ($P > .8$), and no difference in mortality between those who developed AKI and those who did not (0 vs 2; $P = .11$; Table 3).

Critical Do_2i Threshold

Time under Do_2i thresholds were calculated for all patients (Figure 2) and used to model postoperative AKI association within 48 hours after surgery using logistic regression. Models were assessed using accuracy and AUC metrics from ROC curves. The best performing critical threshold identified was time under 350 mL/min/m^2 with an AUC of 60% and accuracy of 65% (Figure 3). A comparison of AKI and no AKI patients showed a longer time under the 350 mL/min/m^2 threshold (20 [IQR, 9-36] minutes vs 14 [IQR, 6-28] minutes; $P = .012$; Table 4). Investigation of the contributing factors to oxygen delivery showed similar median values between patients who developed AKI and those who did not, other than in mean arterial blood pressure, which was higher in the AKI group (43 [IQR, 39-48] vs 41 [IQR, 36-46]; $P = .009$). Subanalysis of Do_2i according to KDIGO stages showed similar median Do_2i values, and length of time under the 350 mL/min/m^2 threshold ($P = .4$ and .076, respectively; Table 5).

Oxygen Delivery Importance

The 350 mL/min/m^2 threshold data were taken together with preoperative and perioperative factors (Table 2) to determine its relative importance with other previously described independent risk factors for AKI. Testing for multicollinearity led to the removal of BSA and weight because of a high correlation with age ($r = 0.95$ and 0.98, respectively). Using a random forest method, 500 decision trees were ensembled to create the final model with highest accuracy and AUC. The final model required a tree depth of 7 and cost complexity of $1e^{-10}$, achieved through a hyperparameter grid search, and resulted in an AUC of 67%

TABLE 2. Patient demographic data

	No AKI	AKI	*P* value
Number of patients	294 (74.2)	102 (25.8)	
Age, mo	7[3-27]	4[2-11]	.025
Range	0.1-187	0-204	
BSA, m^2	0.39 [0.27-0.53]	0.32 [0.24-0.47]	.01
Weight, kg	7[4-12]	6[4-10]	.025
Cyanotic			.1
Yes	43 (15)	22 (22)	
No	251 (85)	80 (78)	
Sex			.8
Male	169 (57)	60 (59)	
Female	125 (43)	42 (41)	
Ethnicity			.046
White	181 (62)	74 (73)	
BAME	113 (38)	28 (27)	
Antenatal diagnosis			.002
Yes	89 (30)	48 (47)	
No	205 (70)	54 (53)	
Comorbidity			.07
Yes	128 (44)	55 (54)	
No	166 (56)	47 (46)	
LVEF			.025
Mild (40%-49%)	290 (98)	96 (94)	
Moderate (30%-39%)	2 (1)	2 (2)	
Severe (<30%)	2 (1)	4 (4)	
RVEF			.028
Mild (40%-49%)	290 (99)	96 (94)	
Moderate (30%-39%)	3 (0.7)	5 (5)	
Severe (<30%)	1 (0.3)	1 (1)	
Urgency			.3
Elective	291 (99)	100 (98)	
Urgent	3 (1)	1 (1)	
Emergency	0 (0)	1 (1)	

Data are presented as median [interquartile range] or n (%). *AKI*, Acute kidney injury; *BSA*, body surface area; *BAME*, Black, Asian, and minority ethnic; *LVEF*, left ventricular ejection fraction; *RVEF*, right ventricular ejection fraction.

TABLE 3. Operative characteristics

	No AKI	AKI	*P* value
CPB time, min	69 [48-104]	87 [60-118]	.003
X-clamp time, min	41 [26-62]	50 [32-81]	.003
Drug			
Tranexamic acid	246 (84)	85 (83)	>.9
Mannitol	34 (12)	11 (11)	.8
Furosemide	273 (93)	102 (100)	.006
Aprotinin	41 (14)	13 (13)	.8
Albumin	17 (5.8)	14 (14)	.01
Gentamicin	2 (0.7)	0 (0)	>.9
Vancomycin	2 (0.7)	0 (0)	>.9
VIS	6 [0-12]	12[7-16]	<.001
Deceased	0 (0)	2 (1.9)	.11

Data are presented as median [interquartile range] or n (percentage). *AKI*, Acute kidney injury; *CPB*, cardiopulmonary bypass; *X-clamp*, aortic crossclamp; *VIS*, vasoactive inotrope score.

with accuracy of 66%. An example decision tree from the random forest is given in Figure 4. Investigation of the model's variable importance plot (in which random noise is used to determine the variable predictive accuracy) showed that the critical Do_2i threshold of 350 mL/min/m^2 had not been removed by other independent predictor variables of AKI within the random forest model (all of which were positively associated with the outcome; Figure 5). This positive importance shows that mis-specification of Do_2i detracts from the predictive accuracy of the random forest model. However, compared with the top-ranking variable importance factors (the age at surgery and length of CPB), Do_2i <350 mL/min/m^2 contributes only a small amount to the predictive accuracy. Although the random forest model had a larger AUC compared with the Do_2i logistic regression model, the Delong test showed little improvement ($P = .294$). Similarly, using a multivariable logistic regression showed no improvement in predictive accuracy compared with Do_2i alone (Delong test $P = .557$).

DISCUSSION

Delivery of adequate oxygenation is fundamental to CPB. Imbalances between oxygen supply and demand lead to cellular injury causing profound adenosine triphosphate depletion and nitric oxide generation, which in turn induces a number of oxidative and apoptotic mechanisms.[3] However, data determining the critical level of oxygen to prevent a supply–demand mismatch, and thereby mitigate AKI, are lacking in pediatric practice. Because of the higher basal metabolic rate in children, it is reasonable to assume their Do_2i requirements and standards of care would be different to adults, requiring a higher rate of oxygen delivery to attenuate kidney injury. Our findings in a 2-year cohort of pediatric patients at a single institution to determine the critical Do_2i threshold associated with AKI shows that children require >350 mL/min/m^2 of oxygen delivered, with increasing time below this threshold, rather than median oxygen delivered during the CPB period, associated with an increased risk of postoperative AKI. This is a higher Do_2i threshold than previously reported for adults (260-300 mL/min/m^2). When integrated into a random forest analysis of multiple independent risk factors for AKI, Do_2i remains an important, although low-impact, variable in development of AKI. Figure 6 highlights the key findings of this study with corresponding narration in Video 1.

Determining the Critical Do_2i Threshold

Early work on the influence of Do_2i on AKI in adult patients used nadir values as the key predictor variable, with

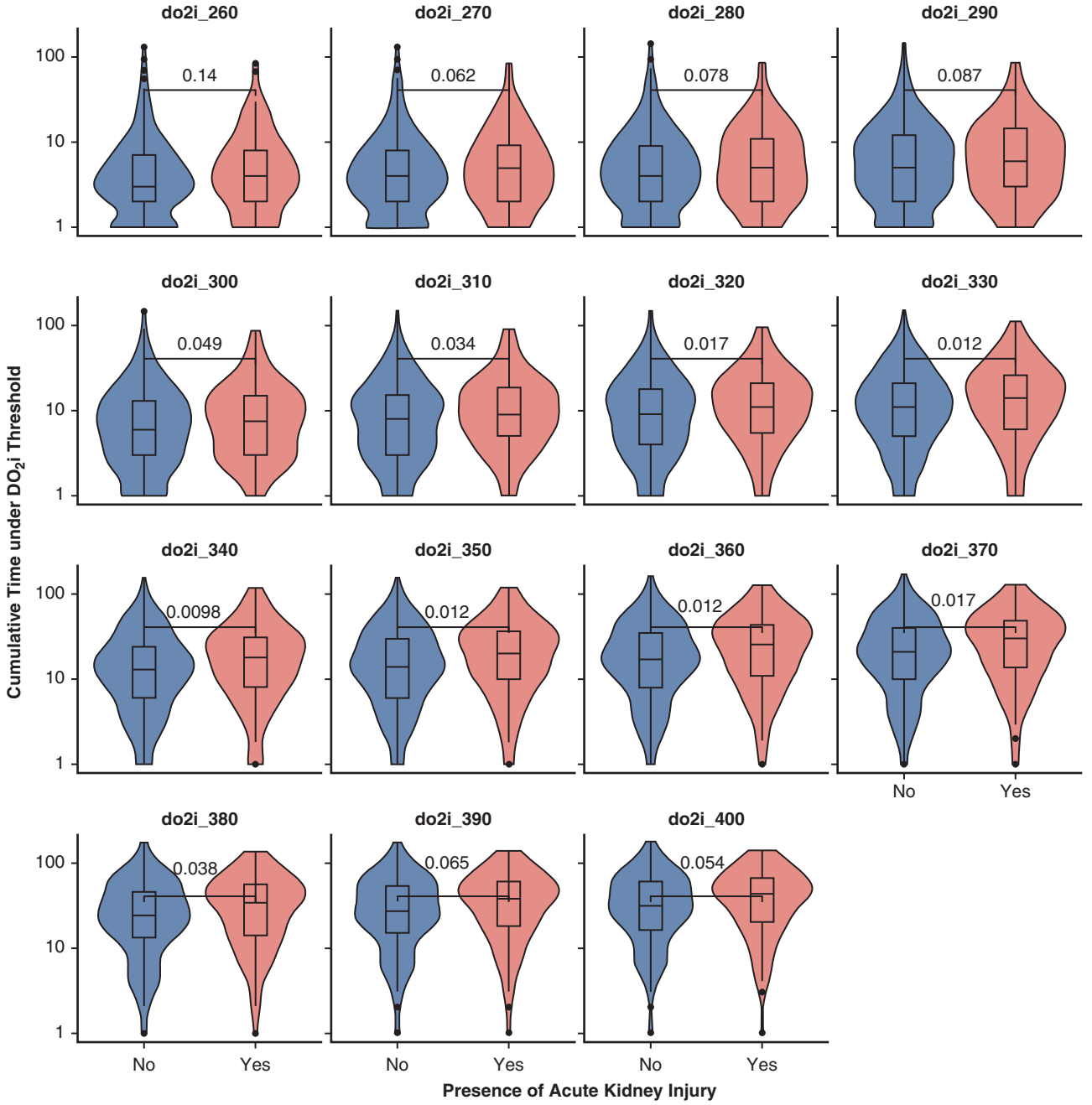


FIGURE 2. Violin plot of oxygen delivery indexed to body surface area (Do_2i) time under threshold. Data representing cumulative time below Do_2i threshold during cardiopulmonary bypass (CPB) when lung deflation occurred. *Red* indicates no acute kidney injury (AKI), and *blue* indicates AKI. Data are split according to the presence of AKI within 48 hours of CPB.

suggested critical values of 272, 262, and 225 mL/min/m^2.[6,7,19] A recent study in children reported a nadir value of 353 mL/min/m^2 as associated with AKI, indicating the increased metabolic requirement of children.[20] However, nadir Do_2i only considers the lowest point of oxygen delivery during CPB and not the duration of exposure to low Do_2i values, failing to reflect the conditions between sampling points. AUC, which represents the duration of cumulative oxygen debt, might be a better predictor of AKI because oxygen delivery is a dynamic variable, fluctuating throughout CPB. Maintenance of Do_2i values >300 mL/min/m^2 were suggested as most effective at reducing postoperative AKI compared with conventional management in a randomized controlled trial of 300 adults.[8] This highlights that measuring duration and severity of Do_2i below a critical threshold is more useful than a single low measurement

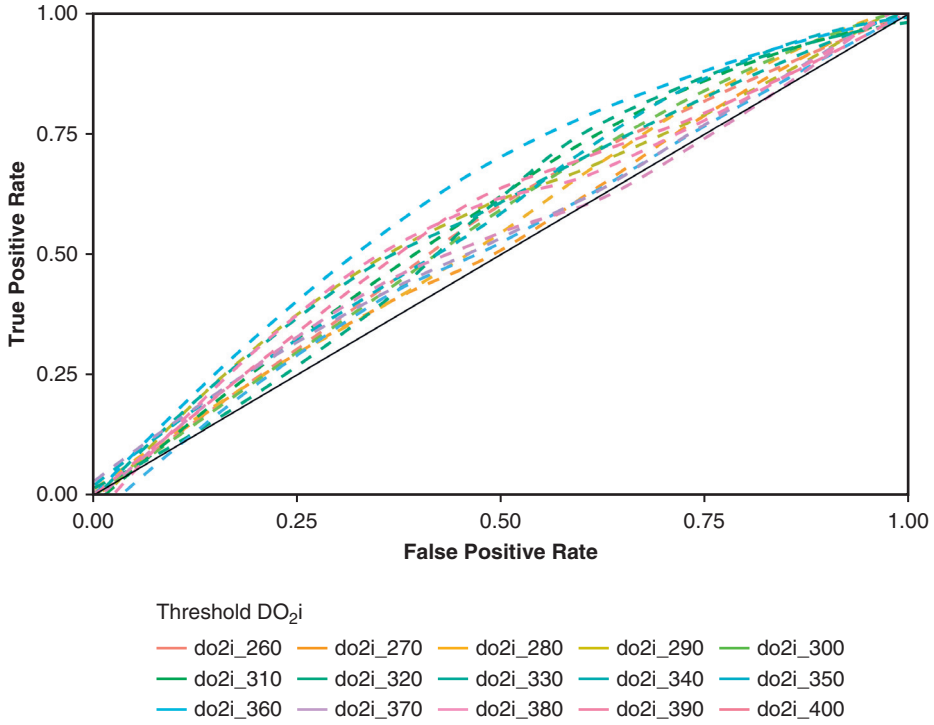


FIGURE 3. Comparison of oxygen delivery indexed to body surface area (*Do_2i*) thresholds for predicting postoperative AKI receiver operating characteristic curves. Models were assessed with logistical regression analyses and compared using area under the curve (AUC) and model accuracy. Best performing threshold was 350 mL/min/m^2 with 0.60 AUC. *Lines* represent cumulative time under threshold value.

used in other studies. Similarly, in 112 adult patients, it was shown that an AUC below a Do_2i threshold of 300 mL/min/m^2 was a more sensitive predictor of postoperative AKI compared with nadir Do_2i, with a cumulative AUC exceeding 15 minutes providing the greatest risk.[21] AUC measurements therefore might be particularly beneficial for predicting outcomes in pediatric surgery, in which Do_2i levels are dynamic due to surgical complexity. For this reason, we chose to calculate cumulative times under thresholds ranging from 260 mL/min/m^2 to 400 mL/min/m^2, to determine which threshold had the highest association with postoperative AKI. On the basis of logistic regression analyses, increasing time under a critical threshold of 350 mL/min/m^2 was identified as having the best association with AKI. However, it should be noted that an AUC of 0.6 suggests a weak discriminatory ability. Further prospective work has been proposed to determine whether the implementation of maintaining a threshold of

TABLE 4. Oxygen delivery contribution data

	No AKI	AKI	*P* value
Do_2i <350 mL/min/m^2, minutes	14 [6-28]	20 [9-36]	.012
Temperature, °C	33.1 [31.3-34.2]	33 [30.6-33.7]	1
Cardiac index, L/min/m^2	2.8 [2.65-2.95]	2.76 [2.61-2.92]	1
Mean arterial blood pressure, mm Hg	41 [36-46]	43 [39-48]	.009
Hematocrit, %	30 [28.5-32]	31 [29-32]	1
Hemoglobin, g/L	100 [94.2-106]	102 [96-106]	1
Do_2i, mL/min/m^2	392 [357-439]	403 [364-437]	1
Pao_2, mm Hg	22.4 [19.4-25.6]	22.2 [16.7-24.9]	1
Sao_2, %	99 [99-99]	99 [98-99]	.17
Svo_2, %	76 [73-81]	77 [74-83]	1

Data are presented as median [interquartile range]. *Do_2i*, Body surface area-indexed oxygen delivery; *Do_2*, oxygen delivery; *Sao_2*, arterial oxygen saturation; *Svo_2*, venous oxygen saturation.

TABLE 5. Oxygen delivery stratified according to KDIGO stage

	No AKI	AKI stage 1	AKI stage 2	AKI stage 3	*P* value
Total	294 (74.2)	66 (16.7)	6 (1.5)	30 (7.6)	
Do_2i, mL/min/m^2	392 [357-439]	393 [357-428]	382 [335-431]	417 [377-448]	.4
Do_2i <350 mL/min/m^2, min	14[6-28]	18.5 [8.5-37.8]	39 [11.8-54.2]	19.5 [10.2-27.8]	.076
Number below threshold	279 (94.9)	64 (97)	6 (100)	30 (100)	

Data are presented as median [interquartile range] or n (%). Number of patients under threshold was defined as all patients with >1 minute of Do_2i <350 mL/min/m^2. *KDIGO*, Kidney Disease Improving Global Outcomes; *AKI*, acute kidney injury; *Do_2i*, body surface area-indexed oxygen delivery.

>350 mL/min/m^2 would reduce the rate of AKI and improve clinical outcome.[22]

Assessing the Importance of Do_2i

Pediatric AKI is a complex diagnosis, with >35 different definitions being used in recent decades.[23] Disparity between official definitions has led to interstudy heterogeneity in detection and identification of risk factors. Three frequently used AKI definitions have been developed for pediatric use, pediatric risk, injury, failure, loss of kidney function and end-stage kidney disease model (pRIFLE), Acute Kidney Injury Network (AKIN), and KDIGO. These modern definitions have lower creatinine thresholds and are more sensitive to subtle elevations compared with the traditional worsening kidney function approach, allowing identification of more severe AKI.[24] The KDIGO method was used in this study because it has been shown to prevent bias toward classifying critically ill young infants and neonates in terms of presence of AKI using other definitions.[10] Prolonged CPB and aortic crossclamp duration have

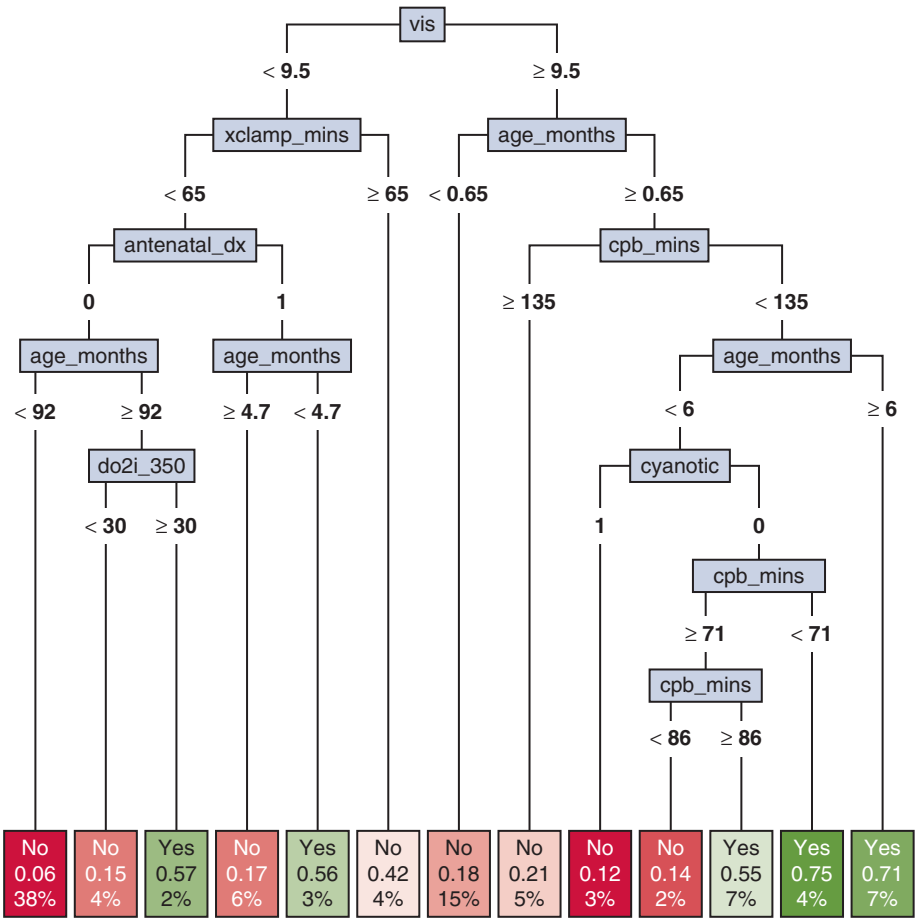


FIGURE 4. Decision tree model for acute kidney injury (AKI) prediction. Data on the basis of the example decision tree from the random forest modeling, with predictions made against this finalized decision tree. Nodes represent (from *top* to *bottom*) whether patients grouped are considered to develop AKI, the probability of developing AKI in that node, and the percentage of the study population captured in that node. *vis*, Vasoactive inotrope score; *xclamp_mins*, aortic crossclamp duration in minutes; *age_months*, patient's age in months; *antenatal_dx*, antenatal diagnosis; *cpb_mins*, cardiopulmonary bypass duration in minutes; *do2i_350*, duration under an oxygen delivery value of 350 mL/min/m^2.

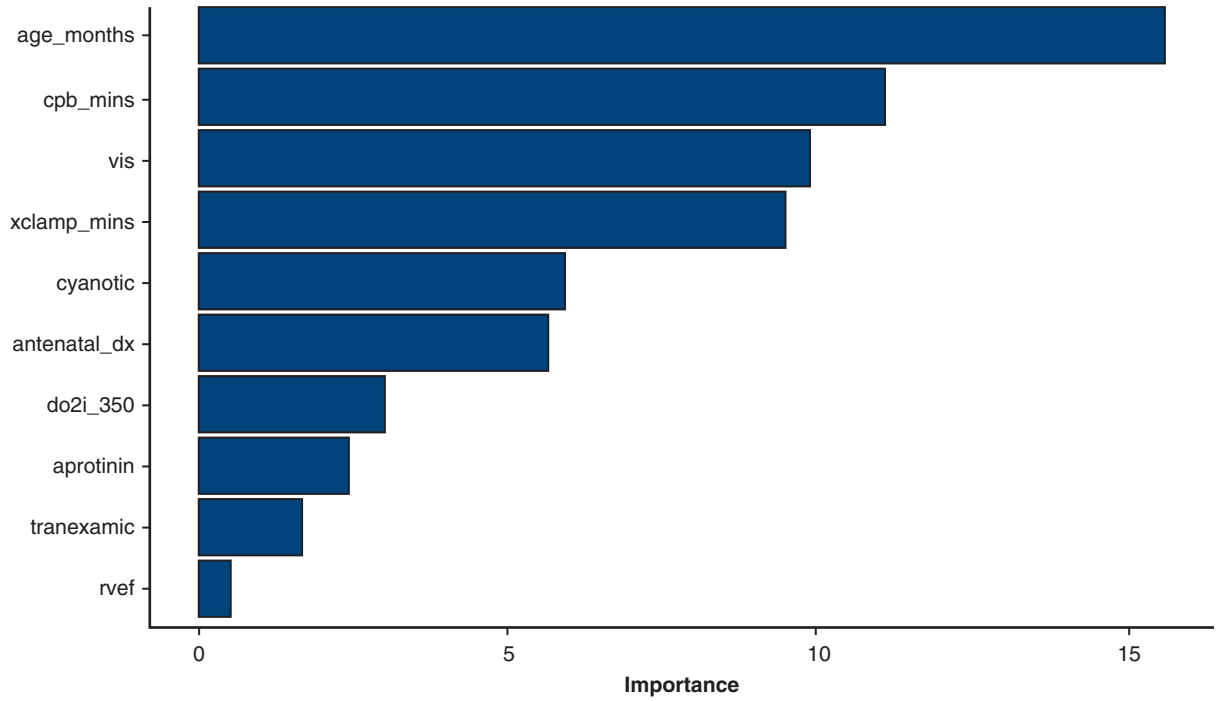


FIGURE 5. Variable importance plot. Data are presented on the 10 most impactful variables in the random forest. Importance level considered arbitrary and used to compare multiple predictor variables to evaluate relative effect size within the model. *age_months*, Patient's age in months; *cpb_mins*, cardiopulmonary bypass duration in minutes; *vis*, vasoactive inotrope score; *xclamp_mins*, aortic crossclamp duration in minutes; *antenatal_dx*, antenatal diagnosis; *do2i_350*, duration under an oxygen delivery value of 350 mL/min/m^2; *tranexamic*, tranexamic acid; *rvef*, right ventricular ejection fraction.

been reported as significant risk factors among pediatric publications.[25,26] For this reason, a random forest was created with known independent risk factors and the length of time under the 350 mL/min/m^2 threshold identified previously, to determine the relative effect that oxygen delivery has on AKI development. Interrogation of the model's variable importance plot showed that oxygen delivery was included in the predictors and therefore its effect was not removed by the inclusion of other risk factors. We did not investigate the need for a patient-specific management approach to CPB with individualized Do_2i goals. Further investigation, for example, should be given to comparing cyanotic and acyanotic infants. It is possible that cyanotic patients cope with lower Do_2i thresholds because they have been exposed to longstanding hypoxemia before surgery and have compensated with mechanisms such as polycythemia, to increase oxygen-carrying capacity.[27] Furthermore, hyperoxia might also be deleterious for these patients. Future research should seek to establish whether there is a maximum Do_2i threshold, prolonged time above which patients are also at risk of adverse outcomes (and this might explain why we observed a higher Do_2i in the AKI stage 3 patients compared with patients who did not develop AKI). Moreover, we observed more patients with an antenatal diagnosis (used here as a surrogate of lesion complexity), in the AKI group. Therefore, further research is required using a more appropriate indicator of lesion and surgical complexity to disentangle this effect. A further interesting observation is that patients who developed AKI had higher mean arterial pressures during CPB. CPB has well-established effects on hemodynamic changes and vasoconstriction, and although hypotension during noncardiac surgery is associated with AKI, it might be possible that hypertension in this group played a role in AKI development.[28] Unfortunately data on vasoconstrictor use by the perfusionist during CPB were not collected but future studies should include such data to elucidate the effect that this might have.

Limitations and Strengths

First, data were obtained from a single institution, which might not be generalizable to other centers. Second, the study design was retrospective, hence causal relationships cannot be inferred because the study did not explore the underlying mechanisms involved. Furthermore, using a retrospective design with data from electronic records collected by medical professionals, means variable measurements might have been inconsistent, however, it limits the influence of investigator bias. The generated models must be validated at multiple centers before they can be broadly applied to clinical scenarios and guide the design of future protocols for care.

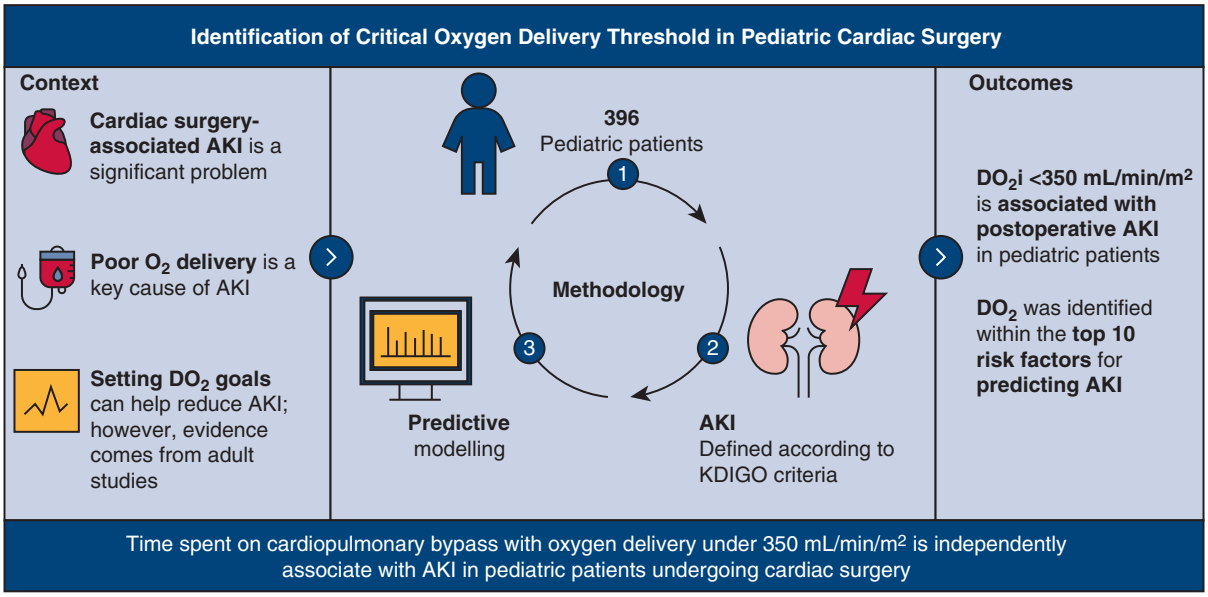
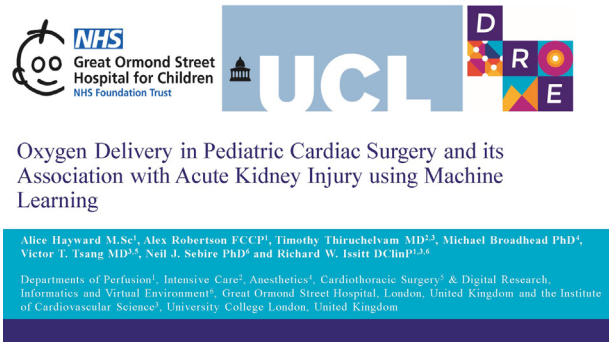


FIGURE 6. Identification of critical oxygen delivery (*Do_2i*) threshold in pediatric cardiac surgery. Three hundred ninety-six patients younger than 18 years old underwent cardiac surgery with cardiopulmonary bypass. Data relating to Do_2i were gathered at 1-minute intervals during the surgery, while the lungs were deflated. Data were analyzed to determine a critical threshold for Do_2i below which acute kidney injury occurred. Logistic regression identified a threshold of 350 mL/min/m^2 of Do_2i as most accurately classifying patients developing postoperative acute kidney injury (*AKI*). Inclusion of this threshold with other independent risk factors in a random forest classification model showed Do_2i had predictive importance and therefore remains an important risk factor in development of AKI. Awareness of Do_2i alongside the reduction of other known independent risk factors for AKI, such as prolonged cardiopulmonary bypass duration, will likely lead to improvement in patient outcomes in the future. *KDIGO*, Kidney Disease Improving Global Outcomes; *Do_2i*, oxygen delivery indexed to body surface area.

Furthermore, an issue in all pediatric AKI research relates to AKI definition. Using a standardized definition increases replicability for future research. However, the study only included clinical changes in the first 48 hours after bypass. This time period might have been too short to identify significant effects or severe AKI. Although one might argue the meaningfulness of this, especially because there are so many factors that can contribute to creatinine elevation without tubular injury, limiting data to 48 hours postsurgery minimized the potential effect of factors linked to intensive care treatment in the postsurgical period and focused on the intraoperative factors and effect of CPB. Moreover, the use of serum creatinine (sCr) to define AKI is flawed. First, nonkidney factors can influence sCr concentration, for example muscle mass, age, sex, and nutritional status.[29] Small children and particularly those with congenital heart disease might have low muscle mass and therefore very low baseline sCr values, which could have led to underestimation of AKI. Similarly, kidneys have significant functional reserve and there is usually a lag period after kidney insult, before the sCr increases significantly, therefore, small changes in sCr might lead to missed diagnosis of more severe AKI.[29] The search for novel biomarkers for early detection of AKI is ongoing and might provide better diagnostic potential in the future.[30] Within this study, AKI was defined as a binary outcome variable whereas the KDIGO definitions are on an ordinal scale. We did not attempt to determine whether Do_2i could aid the separation of AKI stages, but this remains an important question that should be addressed in future research.

The exclusion of circulatory arrest and hypothermic patients in this study can also be challenged, because it is likely that there are different critical limits for Do_2i at lower



VIDEO 1. Narration of the graphical abstract. Video available at: https://www.jtcvs.org/article/S0022-5223(22)00642-0/fulltext.

temperatures because of the decrease in metabolic rate and subsequent oxygen demand. This step was taken to minimize confounding sources of kidney impairment (for example, lower temperature as well as ischemia/reperfusion injury to the kidney) to ensure a population as homogenous as possible. Furthermore, the maintenance of high pump flow to achieve a Do_2i threshold is not always possible, for example when there is low venous return. It is also worth noting that the VIS calculations were designed to take maximum inotrope dosages into account, regardless of whether or not these occurred together or their temporality with the onset of AKI. Further investigation is required to explore and validate modifications to VIS that might provide superior methods for AKI prediction.[13]

Despite limitations, this study used a larger cohort than previous research in this area with well-defined exclusion criteria. Hyperparameters were tuned using crossvalidation to avoid overfitting of the random forest model and multicollinearity analysis was performed to remove numerical instability, strengthening conclusions. Further research will help validate the models generated in this study.

CONCLUSIONS

The present data support previous findings that global oxygen delivery during CPB is an independent risk factor for AKI development, supporting the concept of goal directed perfusion for improving patient outcomes. Further work is required to determine if a strategy of maintaining Do_2i >350 mL/min/m^2 can aid in reducing the incidence of pediatric AKI after CPB. Awareness of Do_2i alongside the reduction of other known independent risk factors for AKI, such as prolonged CPB duration, will likely lead to improvement in patient outcomes in the future.

Conflict of Interest Statement

Dr Sebire receives GOSHCC research grants, and Elsevier textbook royalties. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: cardiopulmonary bypass, acute kidney injury, goal-directed perfusion, oxygen delivery, machine learning