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Association between intraoperative lactate levels and acute kidney injury after on-pump cardiac surgery: a retrospective cohort study across two centers

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Abstract

Background Hyperlactatemia and acute kidney injury (AKI) represent significant perioperative complications in cardiac surgery. This study investigated their relationship by analyzing multiple lactate parameters during on-pump cardiac procedures.

Methods In this dual-center retrospective analysis of 5255 cardiac surgery patients, we evaluated the relationship between AKI and four distinct lactate parameters: baseline, mean, peak, and time-weighted average (TWA) concentrations. The association between lactate levels and outcomes was evaluated using restricted cubic spline functions with five knots in our retrospective statistical modeling approach. Concurrently, optimal lactate thresholds were determined through the application of a classification and regression tree algorithm.

Results Among the 5255 patients analyzed, 931 (17.72%) developed acute kidney injury. Statistical analysis revealed distinct patterns of association between lactate parameters and AKI risk. We identified an L-shaped relationship for mean, peak, and TWA lactate levels, contrasting with a linear association for baseline values. The study established critical thresholds for AKI risk prediction: mean lactate (2.96 mmol/L), peak lactate (4.50 mmol/L), and TWA lactate (2.33 mmol/L). Risk stratification demonstrated that patients in higher lactate quintiles faced substantially increased AKI risk, with odds ratios ranging from 1.34 to 4.37 across different lactate parameters.

Conclusion These findings established specific lactate thresholds as valuable predictive markers for AKI risk in cardiac surgery, offering clinically applicable parameters for perioperative risk assessment and management. This data supported the implementation of targeted lactate monitoring strategies during cardiac procedures.

Trial registration The study was registered at www.chictr.org.cn (Registration number: ChiCTR2200057320, Data of Registration: 2022-03-08).

Keywords Acute kidney injury, Lactate, Cardiac surgery, Cardiopulmonary bypass

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Introduction

Acute kidney injury (AKI) is a frequently observed type of organ injury following surgery, with a prevalence ranging from 13 to 43% in cardiac surgical patients [1, 2]. In addition to the heightened risk of mortality, regardless of the need for dialysis [1, 3], AKI also contributes to increased morbidity, healthcare expenses, and a significant reduction in quality of life [4]. Furthermore, AKI was also associated with multiple long-term morbidities, including worsened renal dysfunction [5, 6]. These complications significantly impact the long-term survival and healthcare costs of cardiac surgical patients, making AKI prevention a crucial clinical priority.

Prior studies have identified some important risk factors of AKI, such as advanced age [1], increasing level of serum creatinine (Scr) [1, 2], previous cardiac surgery or emergency procedures [2]. Elevated lactate levels can arise through two distinct mechanisms: type A and type B lactic acidosis. Type A lactic acidosis occurs due to tissue hypoperfusion and inadequate oxygen delivery, leading to anaerobic metabolism. This is commonly observed during cardiac surgery, particularly during CPB. In contrast, type B lactic acidosis develops without apparent tissue hypoxia and can result from impaired lactate clearance, often associated with hepatic or renal dysfunction. Understanding these mechanisms is crucial as AKI may both result from and contribute to lactate elevation - tissue hypoperfusion (type A) can cause kidney injury, while reduced renal function may impair lactate clearance (type B), creating a potential vicious cycle [7]. During cardiac surgery, particularly those involving cardiopulmonary bypass (CPB), tissue hypoperfusion and subsequent cellular hypoxia often occur, leading to increased anaerobic metabolism. This metabolic shift results in elevated lactate levels, which serve as a key indicator of tissue hypoperfusion and cellular oxygen debt [8]. Hyperlactatemia is observed in nearly two-third of individuals undergoing cardiac surgery [9]. Given that the kidneys are highly sensitive to perfusion changes and metabolic disturbances, monitoring lactate levels during cardiac surgery has emerged as a potentially valuable tool for assessing the risk of postoperative complications, including AKI. However, despite the established association between elevated lactate levels and AKI [10, 11], the predictive value of intraoperative lactate as a biomarker for AKI risk remains inconclusive. Several investigations have identified specific lactate thresholds associated with adverse outcomes, with cut-off values ranging from 2.0 to 4.0 mmol/L, based on both clinical observations and statistical analyses [12, 13]. Additionally, previous investigations have predominantly focused on measuring lactate levels at specific time points - upon intensive care unit admission and at 6, 12, and 24 h postoperatively - while intraoperative lactate dynamics remain largely unexplored [14, 15]. The existing literature strongly advocates for timely hemodynamic optimization during surgery to significantly enhance patient outcomes.

Despite the well-documented occurrence of hyperlactatemia in cardiac surgery, its intraoperative monitoring and predictive value for AKI remain poorly characterized. This study aimed to explored intraoperative lactate dynamics and identifying critical thresholds for AKI risk in a large, multicenter cohort.

Materials and methods

Study design

This study, initiated at West China Hospital of Sichuan University in 2022 (data collection: July 2019 to March 2022) and later including the Affiliated Hospital of Guizhou Medical University (data collection: January 2021 to March 2022), was approved by the respective Institutional Review Boards (West China Hospital: No. 869–2021; Guizhou Medical University: No. 2022019 K) with informed consent waived. It adhered to the Helsinki Declaration.

The primary outcome and several sub-analysis from the original cohort study have been published, all focused on examining the impact of intraoperative glucose and lactate levels on postoperative outcomes, particularly infections and AKI [16–18]. While our research group has previously published studies examining various cardiac surgery outcomes, it is important to note that those earlier works differed in their data sources. Specifically, previous studies were single-center investigations conducted at West China Hospital of Sichuan University, while the current analysis represents a more comprehensive dual-center approach, incorporating data from both institutions. Current data analysis expanded to include the Affiliated Hospital of Guizhou Medical University, focusing on the predictive value of lactate levels for organ perfusion and potential kidney damage. This expanded, dual-center approach not only increased our sample size but also enhanced the generalizability of our findings compared to our previous single-center studies. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to guarantee its quality [19].

Participants

The study population included adults over 18 years undergoing cardiac surgery with CPB at both institutions. Exclusions were made for those with preoperative renal dysfunction (Scr before surgery greater than 353.6 μmol/L or a requirement for renal replacement therapy), intraoperative death, heart transplant, or incomplete data (Fig. 1). Furthermore, if any patients had undergone multiple cardiac procedures during the study period, only the

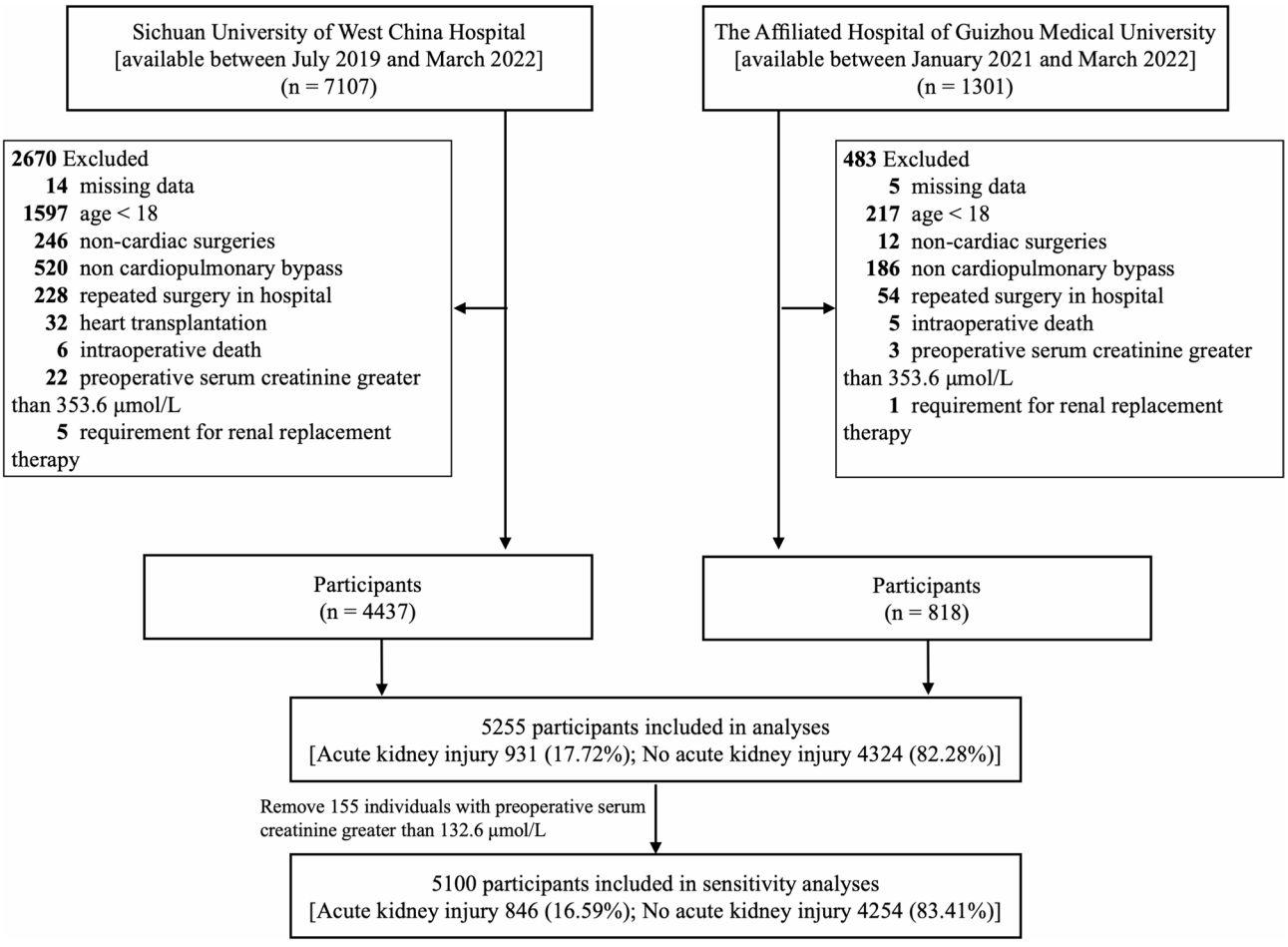


Fig. 1 Flow chart of participants' enrollment

first procedure was considered as the index procedure for the study.

CPB management and blood lactate concentration

The same protocol for CPB, transfusion strategy, and cell saver were applied in two hospitals and have described it in detail in previous published studies [16–18]. Briefly, The CPB system comprised a Sarns 8000 roller pump, Medtronic membrane oxygenator, and standard filtration system. The circuit was primed with 1000 mL of 4% succinylated gelatin and 500 mL crystalloid solution. CPB flow was maintained at 2.0–2.4 L/m²/min (mean arterial pressure > 50 mmHg). Myocardial protection was achieved using cold 4:1 blood cardioplegia, with nasopharyngeal temperature at 32–34 °C. Systemic anticoagulation was managed with heparin (initial dose 375 U/kg, targeting activated clotting time > 480 s) and reversed with protamine upon CPB weaning. Transfusion thresholds were set at hemoglobin < 7 g/dL during CPB and < 8 g/dL during non-CPB phases. Blood conservation included intraoperative salvage and post-CPB circuit blood reinfusion.

Arterial blood gas samples were obtained through arterial catheter placements for lactate concentration measurements. These samples were collected periodically from the extracorporeal circuit during CPB. Initial lactate levels were measured before anesthesia induction, setting the baseline, and subsequently intermittent test according to clinical conditions during CPB using the Roche cobas b 123 system. All patients included in the study had a minimum of three blood gas results recorded.

The study focused on several lactate measurements: baseline preoperative lactate, mean lactate, peak lactate levels during surgery, and the time-weighted average (TWA) lactate. TWA lactate was calculated as an index of intraoperative lactate control, derived from the area under the lactate-time curve divided by the observation period (defined as the interval between initial and final arterial blood gas measurements). This metric offers advantages over conventional measures such as mean or median lactate values, as it incorporates both the temporal distribution and magnitude of lactate variations throughout the surgical procedure. A minimum of three

lactate measurements per patient ensured comprehensive data for analysis.

Definition of the variables and the outcome

Postoperative AKI was identified according to the Kidney Disease: Improving Global Outcomes (KDIGO), focusing on serum creatinine changes [20]. The evaluation of AKI was limited to the first 7 days post-operation, excluding extended hospital stay data due to the unavailability of urine output data, as well as it is widely accepted and deemed satisfactory [21]. Regarding creatinine measurements, the inclusion criteria required that all patients had documented preoperative baseline creatinine values and underwent at least one creatinine measurement within 7 days postoperatively. All measurements were performed as part of routine clinical care.

Statistical analysis

Baseline characteristics and surgical data were analyzed for the entire cohort and stratified by AKI status. For categorical variables, data were presented as frequencies and percentages, with comparisons performed using either chi-square tests or Fisher's exact tests as appropriate. Continuous variables were first assessed for normality of distribution; normally distributed data were expressed as mean ± standard deviation and compared using Student's t-tests, while non-normally distributed data were presented as median with interquartile range (IQR) and analyzed using Mann-Whitney U tests.

Intraoperative lactate levels, including baseline, mean, peak, and TWA, were categorized into quintiles based on their distribution. The relationship between these lactate categories and the likelihood of developing AKI was assessed through odds ratios (ORs) and 95% confidence intervals (CI), calculated using logistic regression. Partly (models 1–4) or fully (model 5) adjusted for age (as a continuous variable), sex (male or female), and body mass index (BMI; as a continuous variable); preoperative comorbidities, including age-adjusted Charlson comorbidity index (0, 1, 2, or ≥ 3), American Society of Anesthesiologists physical status classification (ASA: ≤ III or > III), euroSCORE II (0, 1, 2, 3, or ≥ 4), New York Heart Association classification (NYHA: I, II, III, or IV); surgery-related variables, including emergency (yes or no), duration of surgery (≤ 240, 240 ~ 300, or ≥ 300 min), duration of cardiopulmonary bypass (≤ 120, 120 ~ 180, or ≥ 180 min), type of surgery (as categorical variables), and anesthesia method (as categorical variables); preoperative laboratory examination, including hemoglobin (as a continuous variable), N-terminal pro-brain natriuretic peptide (as a continuous variable), cardiac troponin T (as a continuous variable), albumin (as a continuous variable), serum creatinine (as a continuous variable), glomerular filtration rate (as a continuous variable), and cystatin C (as a continuous variable); intraoperative fluid management and vasoactive agents, including epinephrine (yes or no), norepinephrine (yes or no), milrinone (yes or no), dopamine (yes or no), nitroglycerin (yes or no), intraoperative blood transfusion (yes or no), autotransfusion (as a continuous variable), crystalloid (as a continuous variable), and colloid, and urine (as a continuous variable). Age-adjusted Charlson comorbidity index was calculated, as a proxy of baseline somatic fitness, summarizing the presence of 18 medical conditions and age. Also, euroSCORE II was calculated, as a proxy of baseline somatic fitness, summarizing the presence of 18 medical conditions or characteristics. ASA physical status classification and NYHA classification serve as measures of patients' general physical health and cardiac function. Consequently, it is important to note that this section does not encompass specific sub-categories of complications for analysis, such as hypertension, diabetes, or past occurrences of myocardial infarction, among others. To assess potential multicollinearity among covariates, we conducted a generalized variance inflation factor analysis. The threshold for the adjusted generalized standard error inflation factor was set at 1.6, with values below this threshold considered acceptable [22]. In the present study, all GSIF values approximated 1, demonstrating the absence of significant multicollinearity among the potential confounding variables.

A test for trend was conducted by treating the categorical lactate measurements as continuous variables, assigning median values to each category within the logistic regression framework. To explore potential nonlinear relationships between lactate changes and AKI risk, we employed logistic regression models with restricted cubic splines, setting five knots at predetermined percentiles (5th, 27.5th, 50th, 72.5th, 95th) [23]. If restricted cubic splines indicated nonlinear patterns (U-shaped, inverted U-shaped, or L-shaped), we identified inflection points to segment the data. Segmented logistic regression analyses were then applied to each segment to discern different associations between intraoperative lactate changes and AKI across varying lactate levels. As a measure of robustness, a sensitivity analysis excluded participants with preoperative mild renal impairment (Scr > 1.5 mg/dL or 132.6 μmol/L).

To determine the optimal cutoff values of intraoperative lactate (non-linearity association measurement, including mean, peak, and TWA lactate) to predict AKI incidence, a classification and regression tree (CART) algorithm of recursive partitioning and maximally selected rank statistics with the smallest P value ('caret' and 'maxstat' R package) [24, 25]. The prognostic cutoff point was determined by evaluating every possible cutoff point classifying all patients into two groups according to their level and selecting the most discriminant threshold

for AKI, corresponding to the smallest P value according to the test.

Multiple testing for stratified analysis increases the risk of type I error, but we did not correct for multiplicity. All analyses were performed with R software, version 4.0 (The R Foundation for Statistical Computing, https://www.r-project.org/). A two-sided $P < 0.05$ was considered statistically significant.

Sample size considerations

We conducted a *post hoc* power calculation using univariable logistic regression to estimate the strength of association that we could detect with 90% power at the 0.05 significance level with the given data. Considering 5255 patients available for this analysis, with an overall 17.72% incidence of the AKI and an estimated mean (SD) intraoperative mean lactate of 2.15 (1.17) mmol/L, we had 90% power to detect an odds ratio as small as 1.25 per SD increase in the mean lactate.

Results

Baseline characteristics and AKI incidence

A total of 5255 adult patients who underwent on-pump cardiac surgery were included in the analysis (Sichuan University of West China Hospital, $n = 4437$; The affiliated Hospital of Guizhou Medical University, $n = 818$; Fig. 1). Table 1 shows the baseline characteristics of patients according the presence of AKI (yes or no). The mean age of the patients was 52 years (SD 12.75) with a predominant proportion of females (2667/5255, 50.75%). The most common procedures were isolated cardiac valve surgery (26.91%) and aortic surgery (13.24%) (Table S1).

The overall incidence of AKI was 17.72% (931/5255) among qualified patients. Nearly all demographic, medical history, procedural, medicine, preoperative, and intraoperative factors were associated with AKI (Table 1 and Table S1). Descriptive statistics for AKI and all lactate exposures (i.e., baseline, mean, peak, and TWA) are displayed in Table S2. Baseline lactate was based on a mean of 1.40 ± 0.71 values per patient before surgery. Intraoperative mean lactate was 2.15 ± 1.17 mmol/L, peak lactate averaged was 3.34 ± 2.27 mmol/L, and intraoperative TWA lactate was 2.01 ± 1.05 mmol/L. Univariable analyses showed that patients having postoperative AKI had higher baseline, mean, peak, and TWA lactate compared to those with no evidence of AKI (all $P < 0.05$; Table S2).

Association between different lactate parameters and AKI

A multivariable adjusted model showed a positive association between intraoperative baseline, mean, peak, and TWA lactate baseline lactate and AKI. Compared with those in the lowest fifth of baseline lactate, patients in the highest fifth had a OR of 1.61 (95% CI 1.18 to 2.18; Table 2) for AKI. Compared with those in the lowest fifth of mean lactate, patients in the second to fourth fifths had 1.34–3.62 folds higher ORs of AKI (P for trend < 0.001). In the association analyses regard to the peak, TWA lactate and AKI, we consistently observed a strong association between the peak (ORs = 1.48 to 4.37; P for trend < 0.001) and TWA lactate (ORs = 1.83 to 3.40; P for trend < 0.001) and AKI. Similar ORs were derived from models with different adjustment strategies (Table 2).

In Fig. 2, we employed restricted cubic splines to model and visualize the association between intraoperative lactate and AKI. Baseline lactate demonstrated a near-linear relationship with AKI (P for non-linearity = 0.712). Statistical analysis revealed a significant non-linear association between mean lactate and AKI (P for non-linearity = 0.011), with an OR of 1.82 (95% CI: 1.65–2.02) per SD increase above the median value of 1.84 mmol/L (Fig. 2 and Table S3). Peak lactate and TWA lactate exhibited strong L-shaped relationships with AKI (P for non-linearity < 0.05). For peak lactate values exceeding 2.70 mmol/L, the OR was 1.83 (95% CI: 1.67-2.00) per SD increase. Similarly, for TWA lactate above 1.73 mmol/L, the OR was 1.79 (95% CI: 1.62–1.98) per SD increase. Sensitivity analyses excluding patients with preoperative mild renal impairment confirmed the robustness of these associations (Figure S1, Table S3 and Table S4).

Threshold analysis and risk stratification

To predict AKI incidence, tree-structured analysis using CART of a recursive partitioning algorithm demonstrated that intraoperative mean lactate cutoffs of 2.94 mmol/L and 4.53 mmol/L, 4.50 mmol/L and 10.90 mmol/L for peak lactate, 2.33 mmol/L and 3.71 mmol/L for TWA lactate were found to be optimal. When the patients were grouped according to the best cutoff values, patients with mean lactate 2.94–4.53 mmol/L and greater than 4.53 mmol/L had significantly higher AKI incidence rates of 34.27% and 62.50%, respectively, compared to those with mean lactate less than 2.94 mmol/L, who had a 13.95% AKI incidence (ORs = 2.29–4.63; P for trend < 0.001; Fig. 3). Besides, derived peak lactate cutoffs of 4.50 mmol/L and 10.90 mmol/L by CART to predict AKI showed a wide separation of the AKI incidence (ORs = 2.16–8.59; P for trend < 0.001). The result pattern was largely similar for different cutoffs of TWA lactate (ORs = 2.00-4.34; P for trend < 0.001).

Discussion

In this investigation, we evaluated the association between intraoperative lactate parameters and the risk of postoperative AKI among patients undergoing CPB surgery. Our analyses revealed a significant linear correlation between baseline lactate concentrations and AKI risk. Notably, mean, peak, and TWA lactate levels

Table 1 Baseline characteristics of patients, stratified by the presence of acute kidney injury

Characteristic	All	AKI	No AKI	*P*
No. of participants	5255	931	4324	
Age, yrs				
Median (IQR)	53 (45, 61)	56 (49, 64)	52 (44, 60)	< 0.001
Mean (SD)	52 ± 12.75	55 ± 11.60	51 ± 12.85	< 0.001
Age group, yrs, n (%)				< 0.001
≤ 45	1333 (25.37)	164 (17.62)	1169 (27.04)	
46 ~ 50	803 (15.28)	124 (13.32)	679 (15.70)	
51 ~ 60	1768 (33.64)	314 (33.73)	1454 (33.63)	
>60	1351 (25.71)	329 (35.34)	1022 (23.64)	
Sex, n (%)				< 0.001
Male	2588 (49.25)	607 (65.20)	1981 (45.81)	
Female	2667 (50.75)	324 (34.80)	2343 (54.19)	
Body-mass index, kg/m^2				
Median (IQR)	23.22 (21.03, 25.51)	23.93 (21.49, 26.44)	23.06 (20.96, 25.28)	< 0.001
Mean (SD)	23.40 ± 3.48	24.11 ± 3.67	23.25 ± 3.41	< 0.001
Body-mass index, kg/m^2, n (%)				< 0.001
≤24	3119 (59.35)	473 (50.81)	2646 (61.19)	
24 ~ 28	1637 (31.15)	321 (34.48)	1316 (30.43)	
≥28	499 (9.50)	137 (14.72)	362 (8.37)	
Comorbidity				
Aged-adjusted charlson comorbidity				
Median (IQR)	1.00 (0.00, 2.00)	1.00 (0.00, 2.50)	1.00 (0.00, 2.00)	< 0.001
Mean (SD)	1.33 ± 1.33	1.63 ± 1.51	1.26 ± 1.28	< 0.001
Aged-adjusted charlson comorbidity, n (%)				< 0.001
0	1748 (33.26)	250 (26.85)	1498 (34.64)	
1	1517 (28.87)	252 (27.07)	1265 (29.26)	
2	1062 (20.21)	196 (21.05)	866 (20.03)	
≥ 3	928 (17.66)	233 (25.03)	695 (16.07)	
EuroSCORE II				
Median (IQR)	2.00 (1.00, 4.00)	3.00 (1.00, 6.00)	1.00 (1.00, 4.00)	< 0.001
Mean (SD)	2.69 ± 2.73	4.02 ± 3.33	2.41 ± 2.50	0.001
EuroSCORE II, n (%)				< 0.001
0	1122 (21.35)	133 (14.29)	989 (22.87)	
1	1319 (25.10)	128 (13.75)	1191 (27.54)	
2	493 (9.38)	72 (7.73)	421 (9.74)	
3	767 (14.60)	144 (15.47)	623 (14.41)	
≥ 4	1554 (29.57)	454 (48.76)	1100 (25.44)	
NYHA, n (%)				< 0.001
I	336 (6.39)	34 (3.65)	302 (6.98)	
II	2772 (52.75)	449 (48.23)	2323 (53.72)	
III	2005 (38.15)	404 (43.39)	1601 (37.03)	
IV	142 (2.70)	44 (4.73)	98 (2.27)	
ASA class, n (%)				< 0.001
≤ III	4508 (85.78)	652 (70.03)	3856 (89.18)	
>III	747 (14.22)	279 (29.97)	468 (10.82)	
Diabetes, n (%)	308 (5.86)	83 (8.92)	225 (5.20)	< 0.001
Chronic obstructive lung disease history, n (%)	230 (4.38)	56 (6.02)	174 (4.02)	0.009
Congestive heart failure history, n (%)	485 (9.23)	122 (13.10)	363 (8.40)	< 0.001
Pulmonary hypertension[†], n (%)				0.066
None	4905 (93.34)	853 (91.62)	4052 (93.71)	
Moderate	246 (4.68)	54 (5.80)	192 (4.44)	
Severe	104 (1.98)	24 (2.58)	80 (1.85)	
Unstable angina, n (%)	100 (1.90)	33 (3.54)	67 (1.55)	< 0.001

Table 1 (continued)

Characteristic	All	AKI	No AKI	*P*
Recent myocardial infarct[‡], n (%)	87 (1.66)	37 (3.97)	50 (1.16)	< 0.001
Previous cardiac surgery, n (%)	376 (7.16)	90 (9.67)	286 (6.61)	0.001
Ejection fraction, n (%)				0.009
≥ 50%	4727 (89.95)	814 (87.43)	3913 (90.49)	
30 ~ 50%	494 (9.40)	112 (12.03)	382 (8.83)	
<30%	34 (0.65)	5 (0.54)	29 (0.67)	
Laboratory parameters				
Hemoglobin, g/L				
Median (IQR)	135.00 (123.00, 147.00)	134.00 (119.00, 146.00)	135.00 (123.00, 147.00)	< 0.001
Mean (SD)	134.23 ± 19.91	132.23 ± 21.83	134.66 ± 19.45	0.002
Albumin, g/L				
Median (IQR)	43.00 (40.20, 45.70)	41.80 (38.60, 44.50)	43.20 (40.50, 45.90)	< 0.001
Mean (SD)	42.70 ± 4.61	41.36 ± 4.76	42.98 ± 4.52	< 0.001
N-terminal fragment brain natriuretic peptides, pg/mL				
Median (IQR)	529.00 (139.00, 1446.00)	843.00 (252.00, 2309.00)	477.00 (125.00, 1306.00)	< 0.001
Mean (SD)	1229.52 ± 2214.00	1884.18 ± 3159.25	1087.79 ± 1921.29	< 0.001
Cardiac troponins T, μg/L				
Median (IQR)	9.70 (6.00, 16.60)	13.50 (7.10, 25.20)	9.20 (5.90, 15.15)	< 0.001
Mean (SD)	27.70 ± 226.04	66.29 ± 506.89	19.36 ± 79.07	0.005
Glomerular filtration rate, ml/min				
Median (IQR)	90.12 (74.83, 101.84)	83.06 (64.14, 95.68)	91.38 (77.25, 102.78)	< 0.001
Mean (SD)	89.16 ± 64.54	79.45 ± 22.96	91.21 ± 70.04	< 0.001
Serum creatinine, μmol/L				
Median (IQR)	75.00 (64.00, 88.00)	83.00 (69.00, 101.00)	74.00 (63.00, 85.00)	< 0.001
Mean (SD)	78.85 ± 25.16	90.97 ± 36.43	76.24 ± 21.11	< 0.001
Cystatin C, mg/L				
Median (IQR)	1.01 (0.88, 1.18)	1.13 (0.97, 1.40)	0.99 (0.86, 1.14)	< 0.001
Mean (SD)	1.08 ± 0.35	1.26 ± 0.46	1.04 ± 0.31	< 0.001
Medications, n (%)				
β-adrenergic receptor blocker	691 (13.15)	158 (16.97)	533 (12.33)	< 0.001
Aspirin	226 (4.30)	61 (6.55)	165 (3.82)	0.001
Low-molecular-weight heparins	296 (5.63)	66 (7.09)	230 (5.32)	< 0.001
Surgery related				
Emergency, n (%)	454 (8.64)	170 (18.26)	284 (6.57)	< 0.001
Type of surgery[#], n (%)				< 0.001
Isolated valve	1414 (26.91)	222 (23.85)	1192 (27.57)	
Complex valves	329 (6.26)	72 (7.73)	257 (5.94)	
Isolated CABG	353 (6.72)	95 (10.20)	258 (5.97)	
Aortic procedure	696 (13.24)	232 (24.92)	464 (10.73)	
Congenital heart disease	428 (8.14)	34 (3.65)	394 (9.11)	
Mixed	1672 (31.82)	240 (25.78)	1432 (33.12)	
Others	363 (6.91)	36 (3.87)	327 (7.56)	
Anesthesia, n (%)				0.149
Total intravenous or volatile	641 (12.20)	100 (10.74)	541 (12.51)	
Intravenous-inhalation combined	4614 (87.80)	831 (89.26)	3783 (87.49)	
Duration of cardiopulmonary bypass, min				
Median (IQR)	124.00 (92.00, 164.00)	164.00 (120.00, 211.00)	117.00 (89.00, 152.00)	< 0.001
Mean (SD)	134.99 ± 61.19	174.76 ± 76.29	126.43 ± 53.71	< 0.001
Duration of cardiopulmonary bypass group, min, n (%)				< 0.001
≤120	2520 (47.95)	240 (25.78)	2280 (52.73)	
120 ~ 180	1728 (32.88)	320 (34.37)	1408 (32.56)	
≥180	1007 (19.16)	371 (39.85)	636 (14.71)	
Duration of surgery, min				

Table 1 (continued)

Characteristic	All	AKI	No AKI	*P*
Median (IQR)	250.00 (210.00, 310.00)	310.00 (241.50, 402.50)	241.00 (204.00, 295.00)	< 0.001
Mean (SD)	271.38 ± 95.15	335.94 ± 123.14	257.48 ± 81.55	< 0.001
Duration of surgery group, min, n (%)				< 0.001
≤240	2387 (45.42)	232 (24.92)	2155 (49.84)	
240 ~ 300	1409 (26.81)	207 (22.23)	1202 (27.80)	
≥300	1459 (27.76)	492 (52.85)	967 (22.36)	

Data are present in n (%), mean (SD) or median (IQR)

†Recent myocardial infarction is defined as any diagnosed myocardial infarction in past 90 days before the operation

‡Pulmonary hypertension is defined as pulmonary artery systolic pressure equal or more than 31 mmHg. Moderate pulmonary hypertension defined as 31 ~ 55 mmHg and more than 55 mmHg were considered as severe pulmonary hypertension

#For operation type: mixed operations are referred to operations combined with CABG, and/or valve, and/or congenital heart disease, and/or others; others are referred to operations that could not be included in the types above (i.e., cardiac myxoma, pulmonary endarterectomy, MAZE, etc.)

AKI, Acute kidney injury; ASA, American Society of Anesthesiologists classification; NYHA, New York Heart Association classification

Table 2 Associations of intraoperative lactate and subsequent risk of acute kidney injury

Measurement	Lactate, mmol/L, mean (SD)	Incidence rate of AKI, *n* (%)	Odds ratio, (95% confidence interval)				
			Model 1	Model 2	Model 3	Model 4	Model 5
Fifth of preoperative lactate							
1 (lowest)	0.94 ± 0.14	174 (16.52)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
2	1.15 ± 0.05	261 (16.96)	0.98 (0.79, 1.22)	1.05 (0.84, 1.32)	1.26 (0.95, 1.66)	1.27 (0.95, 1.68)	1.15 (0.86, 1.53)
3	1.30 ± 0.00	86 (15.09)	0.83 (0.63, 1.11)	0.88 (0.65, 1.18)	1.07 (0.75, 1.53)	1.05 (0.73, 1.52)	0.94 (0.65, 1.36)
4	1.48 ± 0.08	187 (16.62)	0.90 (0.71, 1.13)	1.00 (0.79, 1.27)	1.23 (0.92, 1.66)	1.27 (0.94, 1.72)	1.10 (0.81, 1.50)
5 (highest)	2.28 ± 1.27	223 (23.04)	1.33 (1.06, 1.67)	1.41 (1.11, 1.78)	1.92 (1.43, 2.57)	1.86 (1.38, 2.50)	1.61 (1.18, 2.18)
P value for trend[*]			0.002	0.001	< 0.001	< 0.001	< 0.001
Fifth of intraoperative mean lactate							
1 (lowest)	1.24 ± 0.14	97 (9.18)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
2	1.56 ± 0.09	128 (11.34)	1.23 (0.93, 1.63)	1.24 (0.93, 1.65)	1.45 (1.03, 2.03)	1.33 (0.94, 1.88)	1.34 (0.95, 1.89)
3	1.86 ± 0.09	132 (13.50)	1.49 (1.12, 1.97)	1.45 (1.09, 1.93)	1.64 (1.16, 2.32)	1.43 (1.01, 2.04)	1.45 (1.01, 2.08)
4	2.29 ± 0.17	203 (19.39)	2.17 (1.67, 2.83)	1.99 (1.52, 2.60)	2.41 (1.74, 3.33)	1.97 (1.41, 2.74)	1.91 (1.34, 2.68)
5 (highest)	3.82 ± 1.66	371 (35.54)	5.01 (3.90, 6.43)	3.73 (2.88, 4.82)	5.17 (3.76, 7.09)	3.80 (2.72, 5.30)	3.62 (2.58, 5.10)
P value for trend[*]			< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Fifth of intraoperative peak lactate							
1 (lowest)	1.52 ± 0.22	90 (8.07)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
2	2.14 ± 0.17	128 (11.55)	1.47 (1.10, 1.96)	1.45 (1.09, 1.94)	1.61 (1.14, 2.27)	1.51 (1.06, 2.13)	1.48 (1.05, 2.11)
3	2.78 ± 0.20	139 (13.79)	1.74 (1.31, 2.32)	1.63 (1.22, 2.18)	1.86 (1.32, 2.62)	1.66 (1.17, 2.35)	1.65 (1.15, 2.35)
4	3.67 ± 0.34	195 (19.82)	2.68 (2.04, 3.51)	2.37 (1.80, 3.12)	2.82 (2.03, 3.92)	2.28 (1.63, 3.21)	2.31 (1.63, 3.26)
5 (highest)	6.78 ± 2.92	379 (36.44)	6.16 (4.77, 7.95)	4.56 (3.50, 5.93)	5.94 (4.34, 8.15)	4.38 (3.14, 6.13)	4.37 (3.10, 6.17)
P value for trend[*]			< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Fifth of intraoperative time-weighted average lactate							
1 (lowest)	1.20 ± 0.13	98 (9.34)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
2	1.48 ± 0.07	110 (10.46)	1.11 (0.83, 1.48)	1.09 (0.82, 1.47)	1.25 (0.88, 1.76)	1.14 (0.81, 1.61)	1.15 (0.81, 1.63)
3	1.74 ± 0.09	143 (13.59)	1.44 (1.09, 1.90)	1.40 (1.06, 1.85)	1.52 (1.08, 2.12)	1.32 (0.93, 1.85)	1.29 (0.91, 1.83)
4	2.13 ± 0.15	209 (19.81)	2.19 (1.69, 2.84)	2.03 (1.56, 2.65)	2.32 (1.69, 3.18)	1.91 (1.38, 2.65)	1.83 (1.32, 2.56)
5 (highest)	3.48 ± 1.51	370 (35.41)	4.87 (3.80, 6.24)	3.58 (2.77, 4.63)	4.94 (3.62, 6.73)	3.63 (2.62, 5.02)	3.40 (2.43, 4.74)
P value for trend[*]			< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

ORs (95% CI) were derived from logistic regression models, adjusted for Model 1: Age, sex, and body mass index; Model 2: Model 1 + preoperative comorbidities, including age-adjusted Charlson comorbidity index, American Society of Anesthesiologists physical status classification, euroSCORE II, New York Heart Association classification; Model 3: Model 2 + surgery-related variables, including emergency, duration of surgery, duration of cardiopulmonary bypass, type of surgery, and anesthesia method; Model 4: Model 3 + preoperative laboratory examination, including hemoglobin, N-terminal pro-brain natriuretic peptide, cardiac troponin T, albumin, serum creatinine, glomerular filtration rate, and cystatin C; Model 5: Model 4 + intraoperative fluid management and vasoactive agents, including epinephrine, norepinephrine, million, dopamine, nitroglycerin, intraoperative blood transfusion, autotransfusion, crystalloid, and colloid, and urine

[*]Test for trend based on variable containing median value for each quintile

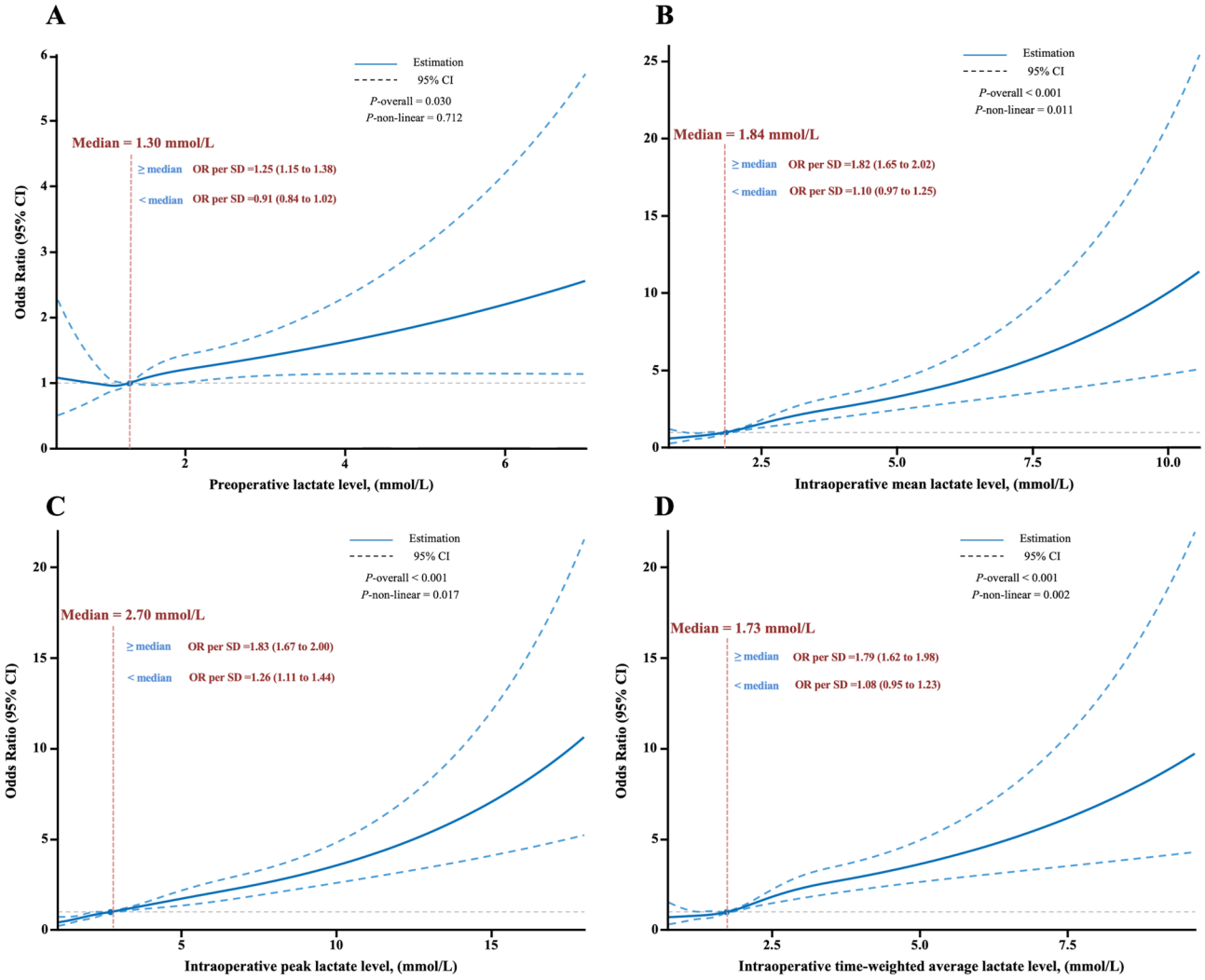
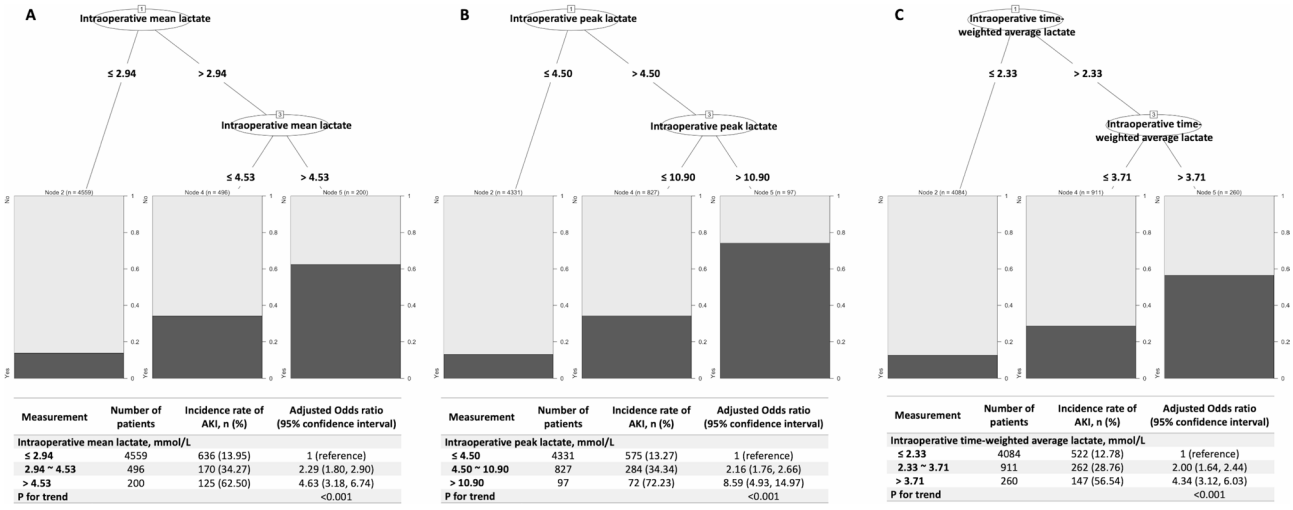


Fig. 2 Association of intraoperative lactate levels with acute kidney injury.**A**: preoperative (i.e., baseline); **B**: mean; **C**: peak; **D**: time-weighted average Odds ratios are indicated by solid lines and 95% CIs by dashed areas. reference point is lowest value for each of lactate, with five knots placed at 5th, 27.5th, 50th, 72.5th, and 95th centiles of each lactate distribution. Y-axis represents the odds ratio to present AKI for any value of lactate. The reference value was set depending on the restricted cubic splines shape All models were adjusted for cofounders in Table 1

demonstrated distinct L-shaped relationships with AKI incidence. Through statistical modeling, we identified clinically relevant threshold values associated with increased AKI risk: mean lactate at 2.94 mmol/L, peak lactate at 4.50 mmol/L, and TWA lactate at 2.33 mmol/L. The robustness of our findings is supported by several methodological strengths: a substantial cohort size, adherence to standardized KDIGO criteria for AKI classification, and comprehensive statistical methodology. Furthermore, the consistency of associations across multiple lactate parameters and sensitivity analyses substantiates the validity of our conclusions.

Consistent with our findings, numerous studies have revealed an association between intraoperative lactate levels and AKI. Pablo et al. enrolled 810 patients who underwent cardiac surgery with CPB and reported an increased risk of AKI in patients with higher lactate levels at ICU arrival, while no difference in lactate during the surgery [26]. Similar conclusions were drawn in studies focusing on lactate levels at the end of surgery, immediately after intensive care unit admission (0 h), 6 h, and 12 h after admission [27]. In current study, our attempted to clarify intraoperative lactate through a comprehensive measurement (i.e., baseline, mean, peak, and TWA) were important, which described changes in lactate in the perioperative period from various angles. Consequently, our shaped-focused analyses elucidated the association of lactate (including baseline, mean, peak, and TWA) on AKI, such as linear or non-linearity association. Our research has shown a discovery regarding the relationship between mean, peak, and TWA of lactate levels and the occurrence of AKI. These findings



Measurement	Number of patients	Incidence rate of AKI, n (%)	Adjusted Odds ratio (95% confidence interval)
Intraoperative mean lactate, mmol/L			
≤ 2.94	4559	636 (13.95)	1 (reference)
2.94 ~ 4.53	496	170 (34.27)	2.29 (1.80, 2.90)
> 4.53	200	125 (62.50)	4.63 (3.18, 6.74)
P for trend			<0.001

Measurement	Number of patients	Incidence rate of AKI, n (%)	Adjusted Odds ratio (95% confidence interval)
Intraoperative peak lactate, mmol/L			
≤ 4.50	4331	575 (13.27)	1 (reference)
4.50 ~ 10.90	827	284 (34.34)	2.16 (1.76, 2.66)
> 10.90	97	72 (72.23)	8.59 (4.93, 14.97)
P for trend			<0.001

Measurement	Number of patients	Incidence rate of AKI, n (%)	Adjusted Odds ratio (95% confidence interval)
Intraoperative time-weighted average lactate, mmol/L			
≤ 2.33	4084	522 (12.78)	1 (reference)
2.33 ~ 3.71	911	262 (28.76)	2.00 (1.64, 2.44)
> 3.71	260	147 (56.54)	4.34 (3.12, 6.03)
P for trend			<0.001

Fig. 3 Decision tree diagram for acute kidney injury. AKI, acute kidney injury. All models were adjusted for cofounders in Table 1.

highlight the significance of utilizing multiple parameters when analyzing intraoperative lactate levels, particularly in high-risk populations. By employing this approach, it becomes possible to identify individuals who may benefit from personalized interventions for AKI management. Patients with elevated lactate concentrations may benefit from targeted perioperative interventions. These include enhanced monitoring and comprehensive diagnostic evaluation, judicious avoidance of nephrotoxic agents, and timely fluid resuscitation to prevent acute kidney injury progression [28]. Implementation of protocol-driven glycemic management is particularly crucial for diabetic patients [16]. Intraoperatively, strategies such as minimizing CPB duration, reducing overall procedural time, employing meticulous blood conservation techniques, and goal-directed oxygen delivery on CPB may confer additional protective benefits in this high-risk population [28]. Our findings regarding lactate dynamics suggest the need for future studies to investigate whether targeted hemodynamic optimization strategies, including monitoring of various perfusion parameters, could help reduce AKI incidence in cardiac surgery patients [8, 11]. It is important to note that while the kidneys possess robust autoregulatory mechanisms that help maintain stable perfusion despite blood pressure variations recent evidence suggests that fluctuations in cardiac output [29], particularly in the immediate post-CPB period, may play a crucial role in AKI development [30]. Although the kidneys can compensate for moderate pressure changes, sustained low cardiac output after CPB may overwhelm these protective mechanism. This is particularly relevant as post-CPB low cardiac output syndrome, occurring in up to 20% of cardiac surgical patients [31], can create a state of persistent tissue hypoperfusion, leading to ongoing lactate production (type A lactic acidosis) despite apparently adequate blood pressure. This relationship may partly explain our findings of the association between elevated lactate levels and AKI, as lactate could serve as a marker of inadequate tissue perfusion even in the setting of seemingly adequate blood pressure. Furthermore, the combination of low cardiac output and elevated lactate levels may identify patients at particularly high risk for AKI, suggesting the need for careful hemodynamic optimization in the immediate post-CPB period, beyond just blood pressure management [32].

The characteristics and prognostic value of lactate in testing depend significantly on various factors. These factors include the specific patient population being studied, the timing of the lactate measurement, the chosen cutoff point, and the outcome of interest. It is worth noting that there is no clear definition of what constitutes a 'normal' lactate level. In a study conducted by Svenmarker et al. [33], a retrospective analysis was performed on a cohort of 5121 patients who underwent cardiac surgery. The focus of this study was to determine the normal lactate value at the time of weaning from CPB. The researchers identified an abnormal lactate value as anything above the 90th percentile, which equated to a lactate value of 2 mmol/L [33]. However, it is unclear whether this definition accurately represents a normal value and whether these findings can be applied to other healthcare centers. Additional research has utilized different cutoff points to define abnormal lactate levels, including values greater than 2 mmol/L, 3 mmol/L, or 4 mmol/L [8]. Some studies have categorized lactate values between 2 and 4 mmol/L as moderately elevated, while values equal to or exceeding 4 mmol/L are considered high lactate levels [8]. It is important to consider the variations in cutoff points used across different studies when interpreting and comparing results. In the present investigation, we estimated the optimal level of intraoperative lactate administration was determined based on the risk of AKI,

which covering baseline, mean, peak, and TWA of lactate measures. However, baseline characteristics differed significantly between AKI and non-AKI groups, with AKI patients showing higher rates of comorbidities (e.g., diabetes mellitus, chronic obstructive lung disease, and poor heart function). These differences present important considerations for our findings. The comorbidities may confound the lactate-AKI relationship, as conditions like diabetes can affect both metabolic responses and renal reserve [34]. Additionally, these patients' higher-risk profile might amplify the effects of intraoperative physiological disturbances. While our multivariate analysis adjusted for these baseline characteristics, residual confounding remains possible. Furthermore, the impact of comorbidities on lactate metabolism (e.g., altered lactate clearance in diabetic patients) [35] may influence our identified threshold values. Although our study recorded vasoactive medication use as a binary variable, the relationship between medication doses and AKI is noteworthy [16]. High-dose vasopressor requirements have been independently associated with increased AKI risk in cardiac surgery patients. This association may reflect both the severity of underlying hemodynamic instability and potential direct effects on renal perfusion. Future studies incorporating detailed dosing data could help establish threshold doses associated with increased AKI risk [36].

The underlying mechanisms linking higher lactate levels during surgery to increased AKI incidence can be explained by the insufficient supply of oxygen and the impairment of tissue oxygen utilization. Other researchers have suggested that increased aerobic lactate production may be a result of adrenergic stimulation [29]. This occurs during CPB when diminished blood flow can trigger the release of stress hormones and cytokines, leading to insulin resistance and excess glucose. The excessive glucose is then converted to lactate through the glycolytic pathway, resulting in elevated levels of lactate production [37]. The elevated lactate is often a marker of underlying illness severity rather than simply a cause of complications. These factors can have harmful consequences on different organs, particularly the kidneys, in the immediate postoperative period [38]. The kidneys play a crucial role in metabolizing lactate, contributing to about 30% of its breakdown through processes like gluconeogenesis or complete oxidation. Unlike the liver, the kidneys possess an enhanced ability to eliminate lactate in the presence of acidosis [29]. Furthermore, pre-existing conditions such as heart failure or diabetes that may affect tissue perfusion and metabolism. Therefore, the association between lactate and AKI may partially reflect that patients with higher lactate levels are generally more critically ill and at higher risk for various complications, including AKI. The relationship between lactate and AKI is likely bidirectional - tissue hypoperfusion can lead to both lactate elevation and kidney injury, while impaired renal function may affect lactate clearance. Finally, the duration of CPB can be indicative of the procedure's complexity or any unforeseen complications encountered during surgery. Prolonged CPB, combined with the occurrence of AKI, increases the likelihood of developing hyperlactatemia [39].

Limitations of study

Several significant limitations were identified in this study. One notable constraint is the retrospective approach adopted, which increases the potential for undetected bias and residual confounding. Since the study was conducted retrospectively, there was no established protocol to guide the timing of lactic acid sampling for serial measurements. Consequently, there is a possibility that the impact of persistent or late onset lactic acidosis, known to be a crucial predictor of outcome, might have been underestimated. Furthermore, on-pump cardiac surgery encompasses complex procedural variations across institutions, including differences in transfusion protocols, cardiopulmonary bypass management, pharmacological support strategies, postoperative fluid management protocols. However, data of postoperative fluid management were not systematically recorded in the hospital information systems. It is worth noting that this study did not investigate or account for potential confounders such as hepatic dysfunction, inborn errors of metabolism, pharmacological agents, and associated toxins [40], which could all contribute to elevated lactic acid levels. Our study is also limited by the lack of detailed data regarding volatile anesthetic administration during CPB. Given that volatile anesthetics may provide organ protection through ischemic preconditioning, this information could be relevant for outcome interpretation [41]. Although we excluded 19 patients (0.1%) due to missing data, this small proportion suggests minimal impact of selection bias on our findings. Given this extremely low missing rate, we performed complete case analysis rather than multiple imputation. Due to the retrospective study design, creatinine measurements were not conducted at standardized intervals, as the timing was dictated by clinical necessity rather than a predefined research protocol. This methodology resulted in heterogeneous measurement intervals among patients, with some individuals receiving more frequent monitoring than others. Consequently, the precise timing of peak creatinine levels may not have been accurately documented in all cases. Another limitation is related to the potential confounding effect of epinephrine on lactate levels. As epinephrine was our first-line vasopressor, its known effect of causing mild lactate elevation through β2-adrenergic stimulation might have influenced our lactate measurements [29]. Future studies might benefit from considering alternative

markers of tissue perfusion or adjusting for epinephrine-induced lactate elevation when evaluating the relationship between perfusion and outcomes. Furthermore, it is important to consider that this investigation took place at two large tertiary referral hospitals characterized by a high level of complexity. This complexity is evident in the patients' higher preoperative and postoperative scores, comorbidities, and outcomes. Another limitation of our study relates to multiple hypothesis testing. Although we obtained more than 5000 patients in two centers, we conducted multiple analyses including different lactate measurements (baseline, mean, peak, and time-weighted average lactate) and comparisons across AKI quintiles. While these analyses provided comprehensive insights into the lactate-AKI relationship, they also increased the risk of Type I errors. Our findings should be interpreted with caution until validated in independent cohorts with more stringent statistical approaches.

Conclusion

In conclusion, the measurement of intraoperative lactate, including baseline, mean, peak, and TWA levels during the surgical procedure, has been found to be a predictor of AKI in patients undergoing cardiac surgery with CPB. The findings of this extensive cohort study focusing on the determination of cutoff levels of intraoperative lactate levels revealed that patients with a mean lactate level over 2.96 mmol/L, a peak lactate level of 4.50 mmol/L, and a TWA lactate level of 2.33 mmol/L during the cardiac surgical process demonstrated a significantly heightened risk of AKI. While our analysis suggests potential lactate thresholds for risk stratification, these cutoff values require external and prospective validation before clinical implementation.

Abbreviations

ASA	American society of anesthesiologists
AKI	Acute kidney injury
AIMS	Anesthesia information management system
CI	Confidence intervals
CPB	Cardiopulmonary bypass
CART	Classification and regression tree
EMR	Electronic medical record
ICU	Intensive care unit
KDIGO	Kidney disease: Improving global outcomes
NYHA	New York heart association classification
OR	Odds ratio
Scr	Serum creatinine
TWA	Time-weighted average

Supplementary Information

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Supplementary Material 1

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Author contributions

DX C, YY Z, XX L, LZ and JS made the conception/design of the study. All authors participated the provision of study material or patients. YY Z and XX L participated in the collection and/or assembly of data. DX C performed the data analysis and interpretation. DX C, YY Z and XL X wrote the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets generated during the current study will be available from the corresponding author on reasonable request after the publication of the main findings.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. This study, initiated at West China Hospital of Sichuan University in 2022 and later including the Affiliated Hospital of Guizhou Medical University, was approved by the respective Institutional Review Boards (West China Hospital: No. 869–2021; Guizhou Medical University: No. 2022019 K) with informed consent waived.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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