SERUM LACTATE AS RELIABLE BIOMARKER OF ACUTE KIDNEY INJURY IN LOW-RISK CARDIAC SURGERY PATIENTS

SERUMSKI LAKTAT KAO POUZDAN BIOMARKER AKUTNOG OŠTEĆENJA BUBREGA KOD NISKORIZIČNIH KARDIOHIRURŠKIH BOLESNIKA

Mina Radovic[1], Suzana Bojic[2,3], Jelena Kotur-Stevuljevic[4], Visnja Lezaic[2,5], Biljana Milicic[6], Milos Velinovic[2,7], Radmila Karan[1,2], Sanja Simic-Ogrizovic[2,5]

[1]Department of Anaesthesiology and Intensive Care, Clinic for Cardiac Surgery, Clinical Centre of Serbia, Belgrade, Serbia
[2]School of Medicine, University of Belgrade, Belgrade, Serbia
[3]Department of Anaesthesiology and Intensive Care, CHC Bezanijska kosa, Belgrade, Serbia
[4]Department of Medical Biochemistry, Faculty of Pharmacy, Belgrade, Serbia
[5]Department of Nephrology, Institute for Nephrology, Clinical Centre of Serbia, Belgrade, Serbia
[6]Department of Statistics, Faculty of Stomatology, University of Belgrade, Belgrade, Serbia
[7]Department of Cardiac Surgery, Clinic for Cardiac Surgery, Clinical Centre of Serbia, Belgrade, Serbia

Summary

Background: Cardiac surgery-associated acute kidney injury (CSA-AKI) frequently occurs in patients assessed as low-risk for developing CSA-AKI. Neutrophil Gelatinase-Associated Lipocalin (NGAL), Kidney Injury Molecule-1 (KIM-1) and lactate are promising biomarkers of CSA-AKI but have not yet been explored in low-risk patients.
Aim: To evaluate urinary NGAL (uNGAL), KIM-1 and lactate as biomarkers of CSA-AKI in patients with low-risk for developing CSA-AKI.
Methods: This prospective, observational study included 100 adult elective cardiac surgery patients assessed as low-risk for developing CSA-AKI. UNGAL, KIM-1 and lactate were measured preoperatively, at the end of cardiopulmonary bypass (CPB) and 3, 12, 24 and 48 h later.
Results: Fifteen patients developed CSA-AKI. Patients with CSA-AKI had significantly higher lactate but similar uNGAL and KIM-1 levels compared to patients without CSA-AKI. Unlike uNGAL and KIM-1, postoperative lactate was good biomarker of CSA-AKI with the highest odds ratio (OR) 2.7 [1.4–4.9] 24 h after CPB. Peak lactate concentration ≥ 4

Kratak sadržaj

Uvod: Akutno oštećenje bubrega nakon kardiohirurških procedura (KH-AOB) nastaje često i kod bolesnika koji su ocenjeni kao niskorizični za nastanak KH-AOB. Neutrofilna želatinaza udružena sa lipokalinom (NGAL), bubrežni štetni molekul-1 (KIM-1) i laktat su novi biomarkeri KH-AOB ali do sada nisu ispitivani kod niskorizičnih bolesnika.
Cilj: Ispitati urinarni NGAL (uNGAL), KIM-1 i laktat kao biomarkere KH-AOB kod bolesnika koji su ocenjeni kao niskorizični za nastanak KH-AOB.
Metode: Ovom prospektivnom opservacionom studijom obuhvaćeno je 100 odraslih elektivnih kardiohirurških bolesnika koji su ocenjeni kao niskorizični za razvoj KH-AOB. UNGAL, KIM-1 i laktat su određivani preoperativno, na kraju kardiopulmonalnog bajpasa (KPB) kao i 3, 12, 24 i 48 sati kasnije.
Rezultati: KH-AOB se razvilo kod 15 bolesnika. Bolesnici sa KH-AOB su imali značajno više vrednosti lakatata ali slične vrednosti uNGAL i KIM-1 u poređenju sa bolesnicima bez KH-AOB. Za razliku od uNGAL i KIM-1, vrednost lakatata posle operacije se pokazala kao pouzdan biomarker KH-AOB sa najvišim OR 2.7 [1,4–4,9] 24 sata nakon završetka KPB.

Address for correspondence:

Suzana Bojic
CHC Bezanijska kosa, Bezanijska kosa bb,
11000 Belgrade, Serbia
e-mail: subojic@yahoo.com

List of abbreviations: BMI, Body mass index; CABG, Coronary artery bypass graft; CPB, Cardiopulmonary bypass; CSA-AKI, Cardiac surgery-associated cute kidney injury; KIM-1, Kidney Injury Molecule-1; uNGAL, Urinary Neutrophil Gelatinase-Associated Lipocalin.

mmol/L carried dramatically higher risk for developing CSA-AKI (OR 6.3 [1.9–20.5]).
Conclusions: Unlike uNGAL and KIM-1, postoperative lactate was significant independent predictor of CSA-AKI with the highest odds ratio 24 h after CPB.

Keywords: acute kidney injury, cardiac surgery, Kidney Injury Molecule-1, lactate, Neutrophil Gelatinase-Associated Lipocalin

Vrednosti lakatata ≥ 4 mmol/L su bile povezane sa dramatično povišenim rizikom za nastanak KH-AOB (OR 6,3 [1,9–20,5]).
Zaključak: Za razliku od uNGAL i KIM-1, vrednosti lakata posle operacije su bile značajan nezavisni prediktor razvoja KH-AOB sa najboljom prediktivnom vrednošću 24 sata nakon završetka KPB.

Ključne reči: akutno oštećenje bubrega, kardiohirurgija, bubrežni štetni molekul-1, laktat, neutrofilna želatinaza udružena sa lipokalinom

Introduction

Cardiac surgery carries a greater risk for perioperative acute kidney injury (AKI) than any other type of surgery (1). Cardiac surgery-associated AKI (CSA-AKI) occurs in approximately 22% of cardiac surgery patients and is linked to a 5-fold increase in mortality (2–4). Given the limited prevention and treatment strategies, recognition of patients at risk for development of CSA-AKI is of paramount importance. Risk assessment has, so far, been restricted to risk scores, and, arguably, novel biomarkers of AKI.

The best validated risk scores (5–7) are focused on predicting severe CSA-AKI requiring dialysis although mild CSA-AKI is far more likely to occur (3). The only scoring system designed to predict all stage CSA-AKI is Leicester Cardiac Surgery Research AKI Risk Score (8) but it still needs an external validation. It is very important to acknowledge that CSA-AKI could also occur in patients that are assessed as low-risk by available scores.

Novel biomarkers such as Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Kidney Injury Molecule-1 (KIM-1) have been studied as potential biomarkers of CSA-AKI with conflicting results (9, 10). High costs, absence of clear recommendations as well as difficult interpretation are preventing their routine use.

Lactate is routinely measured biomarker of tissue hypoperfusion. Hyperlactatemia is common in cardiac surgery especially if cardiopulmonary bypass (CPB) is employed (11). Its association with increased morbidity and mortality is well known (12–15) but only few recent studies suggested that it might be linked to development of CSA-AKI (13, 14, 16, 17).

We aimed to evaluate urinary NGAL (uNGAL), KIM-1 and lactate concentrations as biomarkers of CSA-AKI in patients undergoing elective cardiac surgery that are assessed as low-risk for development of CSA-AKI.

Materials and Methods

This prospective observational study was conducted at the tertiary level adult cardiac surgery university hospital. The study was approved by the institutional Ethical Committee and performed in conformance with the Declaration of Helsinki ethical guidelines. All patients included in this study signed an informed consent form.

Patients

A total of 100 adult consecutive consenting patients fulfilling study criteria were recruited. Inclusion criteria were age ≥ 18 years, elective cardiac surgery with cardiopulmonary CPB including coronary artery bypass grafting (CABG), valve surgery or combined CABG and valve surgery, normal preoperative kidney function and low risk for developing CSA-AKI. Exclusion criteria were age < 18 years, emergency or redo surgery, preoperative AKI or chronic kidney disease and medium or high risk for developing of CSA-AKI. Kidney function was considered normal if eGFR estimated by Modification of Diet in Renal Disease (MDRD) study equation (18) was > 60 ml/min per $1.73m^2$ (19). Risk for developing of CSA-AKI was assessed according to Cleveland Clinic Score (5). Patients with Cleveland Clinic Score ≤ 5 are considered to be at low risk for developing CSA-AKI. CSA-AKI was diagnosed according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria (20). Rapid reversal CSA-AKI was defined by an episode of AKI that lasts ≤ 48 h or less and acute kidney disease (AKD) by duration of AKI ≥ 7 days (21). All patients received routine perioperative care.

Age, gender, type of surgery, duration of CPB, duration of aortic cross-clamping, intraoperative blood loss and intraoperative blood transfusion were recorded. Body mass index (BMI) was calculated based on anthropometric evaluation (weight, height). Leicester Cardiac Surgery Research AKI Risk Score in which percent value presents probability for CSA-AKI development was also calculated (8).

Samples

Arterial blood and urine samples were collected simultaneously at predetermined time-points: preoperatively (before the induction of anaesthesia), immediately after the end of CPB and 3, 12, 24 and 48 hours after the end of CPB. Lactate levels were meas-

ured immediately after collection using blood gas analyzer Gem Premier 3000, Instrumentation Laboratory, Milano, Italy. Serum creatinine levels were measured on the day of collection employing routine laboratory method (AU680, Beckman Coulter, USA). Urine samples were centrifuged and stored at -80C until further analysis. Urine NGAL and KIM-1 levels were measured using Enzyme-linked Immunosorbent Assay (ELISA) method (ABBOTT Diagnostics, IL, USA and R&D Systems Inc, MN, USA, respectively).

Statistical analysis

Statistical analysis was performed in SPSS Statistics Version 25 software (SPSS Inc., Chicago, IL, USA). The normality of data was assessed with Kolmogorov-Smirnov test. The data are presented as median and 25th to 75th quartile or frequencies. The differences between the groups were compared using the Mann-Whitney U or Chi square test, where appropriate. The within-group variations were analyzed using the Friedman's test. A univariate binary logistic regression analysis was employed to test possible predictors of CSA-AKI. The significance level for all statistical tests was set at 0.05.

Results

In our study, 15 out of 100 low-risk cardiac surgery patients developed CSA-AKI. Twelve of CSA-AKI patients had rapid reversal AKI (stage 1 according to KDIGO definition) and 3 had AKD (stage 2 according to KDIGO definition).

Baseline characteristics of the patient groups are shown in *Table I*. Statistically significant difference between patients with and without CSA-AKI in age, gender, BMI, type of surgery, intraoperative blood loss and transfusion was not found. As expected from the study design, patients with and without CSA-AKI had similar Cleveland Clinic Scores but patients with CSA-AKI had significantly higher risk for developing CSA-

Table I Comparison of the baseline characteristics of the patients with and without CSA-AKI.

	Overall (n = 100)	Without CSA-AKI (n = 85)	With CSA-AKI (n = 15)	p
Age (years)	63.0 [56.25 – 69.0]	63.0 [57.0 – 68.5]	68.0 [60.0 – 73.0]	0.087
Gender (male/female)	77 / 23	66 / 19	11 / 4	0.714
BMI (kg/m^2)	27.5 [25.4 – 29.4]	27.3 [25.4 – 29.4]	28.1 [26.0 – 29.3]	0.612
Surgery (valve/CABG/valve + CABG)	21 / 75 / 4	18 /65 /2	3 / 10 / 2	0.134
Duration of CPB (min)	80.0 [64.0 – 97.7]	75.0 [59.5 – 93.0]	101.0 [74.0 – 110.0]	0.012
Duration of aortic cross-clamping (min)	44.5 [30.0 – 60.0]	40 [29.5 – 52.0]	55.0 [39.0 – 71.0]	0.024
Intraoperative blood loss (mL)	1200 [1000 – 1575]	1200 [1000 – 1500]	1400 [1200 – 2000]	0.052
Intraoperative transfusion (mL)	470 [415 – 590]	450 [405 – 565]	576 [430 – 714]	0.082
Hospitalisation (days)	6 [5 – 7]	6 [6 – 7]	7 [6 – 12]	0.017
Cleveland Clinic Score (0 /1 / 2)	39 / 22 / 19	35 /17 /17	4 / 4 / 3	0.514
Leicester Cardiac Surgery Research AKI Risk Score (%)	11.51 [8.44 – 15.96]	11.41 [7.41 – 15.23]	15.17 [11.24 – 19.10]	0.018
Baseline creatinine (μmol/L)	74.0 [65.0 – 83.0]	71.0 [64.5 – 80.5]	89.0 [70.0 – 96.0]	0.025
Baseline eGFR (mL/min/1.73 m^2)	93.3 [81.3 – 109.8]	95.6 [85.1 – 110.2]	76.4 [64.5 – 90.5]	0.002
Lactate (mmol/L)	1.30 [1.00 – 1.70]	1.3 [1.0 – 1.6]	1.2 [0.9 – 1.8]	0.656
uNGAL (ng/mL)	3.12 [0.39 – 11.78]	3.52 [0.51 – 12.36]	2.36 [0.25 – 6.02]	0.457
KIM-1 (pg/mL)	382.0 [123.5 – 936.0]	437.5 [136.0 – 946.2]	256.5 [86.0 – 760.5]	0.231

Data are presented as median and interquartile range or frequencies. Mann-Whitney U test, Chi-squire test. CSA-AKI – Cardiac surgery-associated cute kidney injury; BMI – Body mass index; eGFR – Estimated glomerular filtration rate; uNGAL – Urinary Neutrophil Gelatinase-Associated Lipocalin; KIM-1 – Kidney Injury Molecule-1; CABG – Coronary artery bypass graft; CPB – Cardiopulmonary bypass.
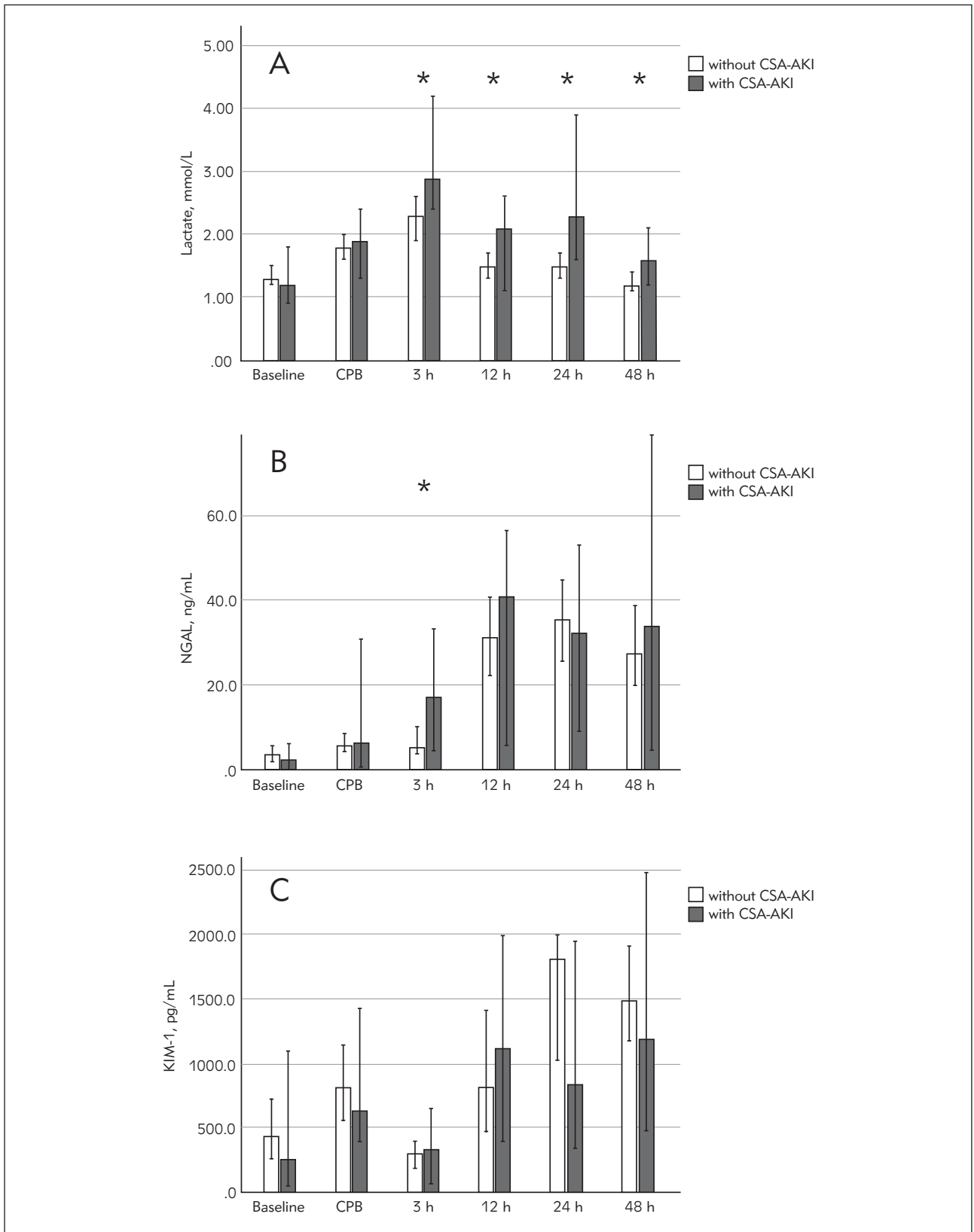
Figure 1 Serial (A) lactate, (B) uNGAL and (C) KIM-1 measurements in patients with and without CSA-AKI.

Data are presented as median and 95% C.I. *Statistically significant difference (p < 0.05) between patients with and without CSA-AKI at specified time point, Mann-Whitney U test. CSA-AKI – Cardiac surgery-associated acute kidney injury; uNGAL – Urinary Neutrophil Gelatinase-Associated Lipocalin; KIM-1 – Kidney Injury Molecule-1; CPB – Cardiopulmonary bypass.

Table II A univariate binary logistic regression for prediction of CSA-AKI.

	Odds Ratio [95% C.I.]	p
Creatinine (baseline)	1.056 [0.1.013 – 0.101]	0.009
eGFR (baseline)	0.947 [0.910 – 0.984]	0.006
Cleveland Clinic Score	1.164 [0.600 – 2.258]	0.653
Leicester Cardiac Surgery Research AKI Risk Score	1.047 [0.986 – 1.113]	0.135
Duration of CPB	1.016 [1.000 – 1.032]	0.048
Duration of aortic cross-clamping	1.022 [1.002 – 1.043]	0.030
Lactate (baseline)	0.664 [0.204 – 2.159]	0.496
Lactate (CPB)	1.540 [0.831 – 2.852]	0.170
Lactate (3 h)	1.410 [1.022 – 1.944]	0.036
Lactate (12 h)	1.470 [1.007 – 2.146]	0.046
Lactate (24 h)	2.721 [1.485 – 4.986]	0.001
Lactate (48 h)	2.436 [1.227 – 4.837]	0.011
Lactate (CPB – baseline)	1.936 [0.981 – 3.821]	0.057
Lactate (3h – baseline)	1.443 [1.034 – 2.015]	0.031
Lactate (12 h – baseline)	1.501 [1.026 – 2.195]	0.036
Lactate (24 h – baseline)	2.569 [1.460 – 4.546]	0.001
Lactate (48 h – baseline)	2.031 [1.109 – 3.719]	0.022
Lactate (3h – CPB)	1.503 [1.013 – 2.230]	0.043
Lactate (12 h – CPB)	1.457 [0.930 – 2.283]	0.100
Lactate (24 h – CPB)	2.173 [1.224 – 3.585]	0.008
Lactate (48 h – CPB)	1.369 [0.773 – 2.422]	0.281
Lactate (12 h – 3h)	0.891 [0.604 – 1.313]	0.559
Lactate (24 h – 3h)	1.003 [0.683 – 1.475]	0.986
Lactate (48 h – 3h)	0.861 [0.627 – 1.181]	0.352
Lactate (24 h – 12h)	1.310 [0.725 – 2.368]	0.371
Lactate (48 h – 12 h)	0.890 [0.598 – 1.325]	0.566
Lactate (48 h – 24 h)	0.596 [0.331 – 1.074]	0.085
Peak lactate	1.067 [0.939 – 1.212]	0.009
Peak lactate ≥ 4 mmol/L	6.330 [1.957 – 20.472]	0.001

Data are presented as odds ratio and 95% C.I. Univariate binary logistic regression. CSA-AKI – Cardiac surgery-associated acute kidney injury; eGFR – Estimated glomerular filtration rate; CPB – Cardiopulmonary bypass.

AKI according to Leicester Cardiac Surgery Research AKI Risk Score. Although only patients with normal kidney function were included, patients that developed CSA-AKI had significantly higher creatinine levels but similar uNGAL and KIM-1 levels compared to patients without CSA-AKI. CSA-AKI patients also had longer hospitalization, CPB and aortic cross-clamping duration.

Figure 1 depicts serial measurements of lactate (A), urinary NGAL (B) and KIM-1 (C) in patients with and without CSA-AKI. After the end of CPB, a significant increase in concentrations of all three biomarkers was noted ($p < 0.05$ for all timepoints, except for lactate at 48 h and uNGAL after completion of CPB). Compared to patients without CSA-AKI, patients with CSA-AKI had significantly higher lactate levels at all

time point except at the CPB end. A significant difference in uNGAL and KIM-1 levels between patients with and without CSA-AKI was not found except for uNGAL 3 h after CPB.

A univariate binary logistic regression was performed in order to identify independent predictors of CSA-AKI (*Table II*). As expected, absolute lactate levels at 3, 12, 24 and 48 h after the end of CPB were independent predictors of CSA-AKI with highest odds ratio of 2.72 for lactate levels at 24 h after the end of CPB. Interestingly, the differences in lactate concentrations between various time points as well as peak lactate concentration had lower prediction value then the absolute lactate concentration. However, peak lactate ≥ 4 mmol/L was associated with 6.33 times higher probability for developing CSA-AKI. Baseline creatinine and eGFR as well as duration of CPB and aortic cross-clamping were also independent predictors of CSA-AKI.

Discussion

Most of the research on prediction of CSA-AKI is focused on identifying high-risk patients. However, CSA-AKI also occurs in patients that are classified as low-risk so it is reasonable to assume that certain risk factors are missed by available risk scores. To identify low-risk patients we used Cleveland Clinic Score. Cleveland Clinic Score is best validated but, effectively, predicts only severe CSA-AKI that requires dialysis (5). On the other hand, Leicester Cardiac Surgery Research Acute Kidney Injury Risk Score predicts any stage CSA-AKI but has debatable application outside UK healthcare system (8). It is therefore not surprising that our patients with CSA-AKI had similar both Cleveland Clinic scores to patients without CSA-AKI (*Table I*).

As expected, a significant increase of uNGAL and KIM-1 levels after CPB was observed (*Figure 1B* and *1C*). An increase in uNGAL levels after CPB was already demonstrated in patients without CSA-AKI (22, 23) and could be a consequence of systemic inflammation caused by CPB. A significant difference in either uNGAL or KIM-1 levels between patients with and without CSA-AKI was not found which implies that both biomarkers have poor diagnostic and predictive value as previously reported (9, 10, 24–27). Bulluck at al. (28) demonstarted that pre-existing chronic kidney disease (CKD) could also alter NGAL and KIM-1 levels and, consequently, affect their levels during and after surgery. Patients with pre-existing CKD were excluded from our study.

In our study lactate concentrations significantly increased after the end of CPB and were significantly higher in patients with CSA-AKI (*Figure 1A*). Consequently, postoperative lactate was good predictor of CSA-AKI with the highest OR 2.7 for levels at 24 h after the end of CPB, close to previously reported (13). To our surprise, the differences in lactate concentrations between various time points had lower prediction value then the absolute lactate concentration (*Table II*). Mak et al. (13) found that persistent hyperlactatemia is more important determinant of postoperative outcome than the absolute lactate concentration but their study included patients at high risk for developing CSA-AKI and only those with lactate ≥ 3 mmol/L. According to our results (*Table II*), low-risk patients with peak lactate concentration ≥ 4 mmol/L were 6.3 times more likely to develop CSA-AKI similarly to findings of Naik et al. (14) although their study population included high-risk patients. Normalized lactate load (16), although more comprehensive, is labour intensive and, therefore, not very likely used by clinicians.

This study has numerous limitations including small number of patients, short observational period, infrequent sampling etc. Our results need to be confirmed by other researches with larger patient cohorts, patients with high risk for developing CSA-AKI and also pediatric cardiac surgery patients.

Conclusions

Our results suggest that, as opposed to uNGAL and KIM-a, absolute lactate levels could serve as reliable biomarkers of CSA-AKI even in cardiac surgery patients with low risk for developing CSA-AKI. Given the dramatic increase in CSA-AKI risk, a high level of vigilance for lactate concentrations ≥ 4 mmol/L should be maintained. Further investigations are needed to backup these conclusions.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

References

1. Grams ME, Sang Y, Coresh J, Ballew S, Matsushita K, Molnar MZ, et al. Acute Kidney Injury After Major Surgery: A Retrospective Analysis of Veterans Health Administration Data. American journal of kidney diseases: the Official Journal of the National Kidney Foundation 2016; 67(6): 872–80.

2. Goren O, Matot I. Perioperative acute kidney injury. British Journal of Anaesthesia 2015; 115: Suppl 2: ii3–14.

3. Hoste EAJ, Vandenberghe W. Epidemiology of cardiac surgery-associated acute kidney injury. Best practice & research Clinical Anaesthesiology 2017; 31(3): 299–303.

4. O'Neal JB, Shaw AD, Billings FTT. Acute kidney injury following cardiac surgery: current understanding and future directions. Critical care (London, England) 2016; 20(1): 187.

5. Gungor BZ, Sipahioglu N, Sonmez H, Ekmekci H, Toprak S, Ayaz G, Gurel CB, Mutlu T, Ulutin T, Sipahioglu F, Ilerigelen B. Endothelial dysfunction markers in low cardiovascular risk individuals: comparison of males and females. J Med Biochem 2017; 36: 62–72.

6. Panjeta M, Tahirović I, Sofić E, Ćorić J, Dervišević A. Interpretation of erythropoietin and haemoglobin levels in patients with various stages of chronic kidney disease. J Med Biochem 2017; 36: 145–52.

7. Englberger L, Suri RM, Li Z, Dearani JA, Park SJ, Sundt TM, 3rd, et al. Validation of clinical scores predicting severe acute kidney injury after cardiac surgery. American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation 2010; 56(4): 623–31.

8. Birnie K, Verheyden V, Pagano D, Bhabra M, Tilling K, Sterne JA, et al. Predictive models for kidney disease: improving global outcomes (KDIGO) defined acute kidney injury in UK cardiac surgery. Critical Care (London, England) 2014; 18(6): 606.

9. Ho J, Tangri N, Komenda P, Kaushal A, Sood M, Brar R, et al. Urinary, Plasma, and Serum Biomarkers' Utility for Predicting Acute Kidney Injury Associated With Cardiac Surgery in Adults: A Meta-analysis. American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation 2015; 66(6): 993–1005.

10. Zhou F, Luo Q, Wang L, Han L. Diagnostic value of neutrophil gelatinase-associated lipocalin for early diagnosis of cardiac surgery-associated acute kidney injury: a meta-analysis. European Journal of Cardio-thoracic Surgery: Official Journal of the European Association for Cardio-Thoracic Surgery 2016; 49(3): 746–55.

11. Minton J, Sidebotham DA. Hyperlactatemia and Cardiac Surgery. The Journal of Extra-corporeal Technology 2017; 49(1): 7–15.

12. Song Y, Soh S, Shim JK, Park KU, Kwak YL. Skin perfusion pressure as an indicator of tissue perfusion in valvular heart surgery: Preliminary results from a prospective, observational study 2017; 12(9): e0184555.

13. Mak NT, Iqbal S, de Varennes B, Khwaja K. Outcomes of post-cardiac surgery patients with persistent hyperlactatemia in the intensive care unit: a matched cohort study. Journal of Cardiothoracic Surgery 2016; 11: 33.

14. Naik R, George G, Karuppiah S, Philip MA. Hyperlactatemia in patients undergoing adult cardiac surgery under cardiopulmonary bypass: Causative factors and its effect on surgical outcome. Annals of Cardiac Anaesthesia 2016; 19(4): 668–75.

15. Hajjar LA, Almeida JP, Fukushima JT, Rhodes A, Vincent JL, Osawa EA, et al. High lactate levels are predictors of major complications after cardiac surgery. The Journal of Thoracic and Cardiovascular Surgery 2013; 146(2): 455–60.

16. Zhang Z, Ni H. Normalized lactate load is associated with development of acute kidney injury in patients who underwent cardiopulmonary bypass surgery. PloS one 2015; 10(3): e0120466.

17. Jorge-Monjas P, Bustamante-Munguira J, Lorenzo M, Heredia-Rodriguez M, Fierro I, Gomez-Sanchez E, et al. Predicting cardiac surgery-associated acute kidney injury: The CRATE score. Journal of Critical Care 2016; 31(1): 130–8.

18. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Annals of Internal Medicine 2006; 145(4): 247–54.

19. Zavada J, Hoste E, Cartin-Ceba R, Calzavacca P, Gajic O, Clermont G, et al. A comparison of three methods to estimate baseline creatinine for RIFLE classification. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association – European Renal Association 2010; 25(12): 3911–8.

20. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clinical Practice 2012; 120(4): c179–84.

21. Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED, Bagshaw SM, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. Nature Reviews Nephrology 2017; 13(4): 241–57.

22. Bataille A, Tiepolo A, Robert T, Boutten A, Longrois D, Dehoux M, et al. Reference change values of plasma and urine NGAL in cardiac surgery with cardiopulmonary bypass. Clinical Biochemistry 2017; 50(18): 1098–103.

23. de Geus HR, Ronco C, Haase M, Jacob L, Lewington A, Vincent JL. The cardiac surgery-associated neutrophil gelatinase-associated lipocalin (CSA-NGAL) score: A potential tool to monitor acute tubular damage. The Journal of Thoracic and Cardiovascular Surgery 2016; 151(6): 1476–81.

24. Friedrich MG, Bougioukas I, Kolle J, Bireta C, Jebran FA, Placzek M, et al. NGAL expression during cardiopulmonary bypass does not predict severity of postoperative acute kidney injury. BMC Nephrology 2017; 18(1): 73.

25. De Loor J, Herck I, Francois K, Van Wesemael A, Nuytinck L, Meyer E, et al. Diagnosis of cardiac surgery-associated acute kidney injury: differential roles of creatinine, chitinase 3-like protein 1 and neutrophil gelatinase-associated lipocalin: a prospective cohort study. Annals of Intensive Care 2017; 7(1): 24.

26. Metzger J, Mullen W, Husi H, Stalmach A, Herget-Rosenthal S, Groesdonk HV, et al. Acute kidney injury prediction in cardiac surgery patients by a urinary peptide pattern: a case-control validation study. Critical Care (London, England) 2016; 20(1): 157.

27. Vandenberghe W, De Loor J, Hoste EA. Diagnosis of cardiac surgery-associated acute kidney injury from functional to damage biomarkers. Current opinion in anaesthesiology 2017; 30(1): 66-75.

28. Bulluck H, Maiti R, Chakraborty B, Candilio L, Clayton T, Evans R, et al. Neutrophil gelatinase-associated lipocalin prior to cardiac surgery predicts acute kidney injury and mortality. Heart (British Cardiac Society) 2017; doi: 10.1136/heartjnl-2017-311760.