Early rise in postoperative creatinine for identification of acute kidney injury after cardiac surgery

L'augmentation précoce de la créatinine postopératoire, un outil pour l'identification d'une insuffisance rénale aiguë après une chirurgie cardiaque

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Abstract

Purpose Acute kidney injury (AKI) is a potentially serious complication of cardiac surgery. Treatment strategies are unlikely to prove efficacious unless patients are identified and treated soon after the onset of injury. In this observational study, we determined and validated the ability of an early rise in postoperative serum creatinine to identify patients who suffer AKI during cardiac surgery.

Methods The relationship between an early rise in creatinine (immediate postoperative / preoperative creatinine) and AKI (> 50% increase in creatinine by postoperative calendar days 1 or 2) was determined by

logistic regression modelling. Existing databases were used for model development ($n = 4,820$; one institution) and validation ($n = 6,553$; 12 institutions).

Results Acute kidney injury occurred in 9.1% ($n = 437$) and 9.8% ($n = 645$) of patients in the development and validation sets, respectively. An early rise in creatinine was related to AKI ($P < 0.001$), with an area under the receiver operating characteristic curve of 0.78 (95% confidence interval [CI], 0.75 to 0.80) in the development set and 0.77 (95% CI, 0.75 to 0.79) in the validation set. Using a threshold ratio of > 1.30 ($n = 127$), the sensitivity, specificity, positive, and negative predictive values for AKI in the development set were 20% (95% CI, 16 to 24), 99% (95% CI, 99 to 99), 68% (95% CI, 59 to 76), and 93% (95% CI, 92 to 93), respectively.

Conclusion In patients undergoing cardiac surgery with cardiopulmonary bypass, an early rise in postoperative creatinine is a useful marker for the early identification of AKI patients. This could allow inclusion of such patients in clinical trials of promising therapeutic strategies that need to be initiated soon after the onset of injury.

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Résumé

Objectif L'insuffisance rénale aiguë (IRA) est une complication potentiellement grave de la chirurgie cardiaque. Les stratégies de traitement ont peu de chances d'être efficaces, à moins que l'on parvienne à identifier et traiter rapidement les patients après l'amorce de l'insuffisance. Dans cette étude observationnelle, nous avons déterminé et validé qu'une augmentation précoce de la créatinine sérique postopératoire était utile pour identifier les patients souffrant d'une IRA pendant la chirurgie cardiaque.

Méthode La relation entre une augmentation précoce de la créatinine (créatinine postopératoire / préopératoire immédiate) et l'IRA (augmentation > 50 % de la créatinine au jour postopératoire 1 ou 2) a été déterminée à l'aide d'un modèle de régression logistique. Les bases de données existantes ont été utilisées pour la mise au point ($n = 4820$; une seule institution) et la validation ($n = 6553$; 12 institutions) de notre modèle.

Résultats Une insuffisance rénale aiguë est survenue chez 9,1 % ($n = 437$) et 9,8 % ($n = 645$) des patients dans les groupes mise au point et validation, respectivement. Une augmentation précoce de la créatinine a été liée à l'IRA ($P < 0,001$), avec une surface sous la courbe de fonction d'efficacité de l'observateur de 0,78 (intervalle de confiance [IC] 95 %, 0,75 à 0,80) dans la cohorte mise au point, et de 0,77 (IC 95 %, 0,75 à 0,79) dans la cohorte validation. À l'aide d'un seuil de ratio > 1,30 ($n = 127$), la sensibilité, la spécificité, les valeurs prédictives positives et négatives d'une IRA dans la cohorte mise au point étaient de 20 % (IC 95 %, 16 à 24), 99 % (IC 95 %, 99 à 99), 68 % (IC 95 %, 59 à 76) et 93 % (IC 95 %, 92 à 93), respectivement.

Conclusion Chez les patients subissant une chirurgie cardiaque avec circulation extracorporelle, l'augmentation précoce de la créatinine postopératoire est un marqueur utile qui permet d'identifier précocement les patients atteints d'IRA. Cette découverte pourrait permettre d'inclure ces patients dans des études cliniques examinant des stratégies thérapeutiques prometteuses qui doivent être rapidement amorcées après le début de l'insuffisance.

Acute kidney injury (AKI), defined as a rapid decrease in the glomerular filtration rate such that the rate of metabolic waste production exceeds the rate of renal excretion and results in increased serum creatinine levels,¹ carries a heavy burden of illness in cardiac surgery. It occurs in up to 30% of patients,^{2,3} and even small increases in creatinine are directly linked to increased morbidity and mortality.⁴⁻⁹

To mitigate the burden of AKI in cardiac surgery, numerous therapies with positive pre-clinical data have been clinically studied, but none have proved efficacious.^{7,10,11} These interventions may have failed in part because they were instituted at the time of a clinical diagnosis of AKI rather than soon after the onset of renal injury. A formal diagnosis of AKI typically relies on serum creatinine levels reaching the consensus threshold of > 50% above baseline levels,¹² which does not occur for up to 48 hr after renal injury due to the rate-limiting step of creatinine production and release from skeletal muscles.¹³ It may be futile to institute therapies that long after injury because data from animal studies indicate that the

therapeutic window for renal injury is limited to the first few (< 24) hours after the onset of injury.¹³⁻¹⁵ Thus, early recognition of renal injury is critical for evaluation of promising therapies.

To facilitate the early identification of renal injury in cardiac surgery, several biomarkers of AKI have been studied (e.g., neutrophil gelatinase-associated lipocalin and cystatin C).¹³ To date, however, none have been shown to predict AKI with great accuracy.¹³ Moreover, these biomarker assays are costly and not widely available for clinical use¹²; thus, better alternatives are needed.

Recent evidence suggests that, in cardiac surgical patients who develop AKI, serum creatinine starts to rise soon after surgery and may therefore be useful for early identification of patients with AKI.¹⁶ Given the advantages (i.e., general availability and low cost) of serum creatinine over other biomarker assays, if an early rise in postoperative serum creatinine can accurately identify patients who suffer perioperative AKI, then it would be ideal for the early identification of at-risk patients for inclusion in clinical trials evaluating novel therapies to address this common problem.

The objective of this observational study was to determine the ability of an early rise in serum creatinine after cardiac surgery to identify patients who suffer perioperative AKI.

Methods

Study setting and population

Following Institutional Ethics Board approval (University Health Network; July 26, 2016), which waived the need for informed consent, we used data from two registries. Our objectives were first to determine the predictive value of an early rise in creatinine after cardiac surgery for subsequent AKI and then to validate the findings. The development dataset was prospectively collected for institutional purposes and included consecutive patients who underwent cardiac surgery with cardiopulmonary bypass (CPB) from January 1, 2012 to December 31, 2015 at the Toronto General Hospital. A full range of adult cardiac surgical procedures are performed at this university-affiliated hospital. All patients are admitted to the intensive care unit (ICU) after surgery where their creatinine measurements are taken daily. For patients who underwent multiple eligible procedures during the study period, only data from their first procedure were used. Full-time research personnel blinded to the details of this study adjudicated all patient outcomes.

The validation dataset was from a recently completed multicentre cluster randomized clinical trial of a point-of-

care-based coagulation management algorithm. The trial included consecutive patients who had cardiac surgery with CPB from October 6, 2014 to May 1, 2015 at 12 Canadian hospitals.¹⁷

Patients were excluded from analysis if they did not have creatinine measured at *all* the following time points: (i) before surgery, (ii) upon admission to the ICU after surgery, and (iii) on postoperative calendar days 1 and 2. Patients were also excluded if they underwent heart transplantation.

Outcome

Acute kidney injury was defined based on the consensus recommendations of the AKI Network (AKIN) for serum creatinine criteria,¹⁸ measured from before surgery to the highest creatinine concentration on postoperative calendar days 1 or 2 (corresponding to AKIN's 48-hr time constraint). Stage I AKI (> 1.5-fold increase in creatinine levels) was the primary outcome, but stage II (> 2.0-fold increase) and stage III (> 3.0-fold increase) AKI were also assessed. Acute Kidney Injury Network's absolute increase in creatinine was not used. Moreover, since the timing of dialysis was not recorded, patients who required dialysis were included in the outcomes only if they met the creatinine criteria. Dialysis itself was assessed as a separate outcome.

Primary exposure

The primary exposure of interest was the immediate postoperative change in serum creatinine ($\Delta\text{Creat}^{\text{ratio}}$), measured as the ratio of postoperative creatinine (measured within 30 min of arrival to the ICU) to preoperative creatinine, which was the last available measure before surgery. Creatinine was routinely measured within two weeks before surgery, upon arrival to the ICU immediately after surgery, and at least once daily thereafter until discharge from the ICU. Patient demographics and other variables related to AKI after cardiac surgery were also collected.^{2,7,19–21}

Statistical analyses

Using the development dataset, categorical variables were summarized as frequencies and percentages, and continuous variables were summarized as medians and interquartile ranges. Fisher's exact, Chi square, and Wilcoxon two-sample tests were used to compare patient characteristics, risk status, and outcomes between patients with and without AKI. The unadjusted relationship between $\Delta\text{Creat}^{\text{ratio}}$ and AKI was assessed using cubic

spline functions.²² Univariate logistic regression modelling was used to determine the unadjusted relationship of $\Delta\text{Creat}^{\text{ratio}}$ with AKI as well as to generate receiver operating characteristic (ROC) curves to identify the optimal cutoff based on the proportion of correctly classified observations. To compare the predictive value of $\Delta\text{Creat}^{\text{ratio}}$ with clinical predictors of AKI, we conducted multivariable logistic modelling that adjusted for preoperative factors (using the Cleveland risk score)²⁰ and other previously identified perioperative risk factors for AKI (i.e., preoperative hemoglobin, CPB duration, need for mechanical support after CPB, and red blood cell transfusions on the day of surgery).^{2,7,23} Covariates were categorized if they did not meet the linearity assumptions of logistic regression.²⁴ Model overoptimism (internal validation) was assessed using bootstrap resampling.²⁴ One hundred computer-generated samples (same size as the original sample) were derived using random sampling with replacement; the model was refitted for each sample, and the corrected area under the ROC (AUROC) curve was obtained.

For sensitivity analysis, univariate logistic regression modelling was repeated in the following subgroups: patients who did not require dialysis after surgery (since the initiation date was not known, we could not be sure that surgery was the instigating event of the renal failure); patients who underwent elective and non-elective surgery (as non-elective cases may have already suffered renal injury before surgery and their creatinine may not be at steady state); patients without severe preoperative renal dysfunction (an estimated glomerular filtration rate of $\leq 30 \text{ mL}\cdot\text{min}^{-1}$ as calculated by the Cockcroft-Gault equation,²⁵ as they may develop AKI without meeting the change in creatinine thresholds); and excluding patients who met the definition of AKI immediately after surgery (i.e., $\Delta\text{Creat}^{\text{ratio}} > 1.5$).

For validation, modelling was repeated on the entire validation set as well as on the subgroups noted above. In addition, the sensitivity and specificity of $\Delta\text{Creat}^{\text{ratio}}$, at the identified optimal cutoff, were also calculated in the validation dataset.

No formal sample size calculations were conducted as the samples were ones of convenience; however, based on the anticipated incidence of AKI, the study was deemed to be adequately powered to allow for the planned multivariable analyses. SASTM version 9.3 (SAS Institute, Inc., Cary, NC, USA) was used for the statistical analyses.

Results

The development dataset included 5,070 patients who underwent cardiac surgery with CPB. The following

patients were excluded in order: 79 who were on dialysis before surgery, 47 who had no creatinine measured before surgery, 99 who had no creatinine measure immediately after surgery, and 15 who did not have any creatinine measured on postoperative days 1 or 2. After excluding these patients, 4,820 patients remained in the study. Of these remaining patients, 437 (9.1%) developed stage I AKI, 129 (2.7%) developed stage II, and 27 (0.6%) developed stage III AKI. Dialysis was initiated in 93 (1.9%) patients, 35 of whom did not meet any of the AKI criteria. Compared with patients without AKI, those with AKI had more severe comorbidities and underwent higher-risk surgeries (Tables 1 and 2). Patients with AKI had

significantly higher creatinine levels throughout the study period, including upon arrival in the ICU (Fig. 1).

The unadjusted mathematical relationship between $\Delta\text{Creat}^{\text{ratio}}$ and the probability and log odds of AKI are shown in Fig. 2. The AUROC curve of this relationship was 0.78 (95% confidence interval [CI], 0.75 to 0.80). The ROC curve, along with the incidence, sensitivity, specificity, and predictive value of several $\Delta\text{Creat}^{\text{ratio}}$ thresholds, are shown in Fig. 3. The $\Delta\text{Creat}^{\text{ratio}}$ threshold that resulted in the greatest proportion of correctly classified observations was 1.30, with an incidence of 2.6% ($n = 127$), sensitivity of 20% (95% CI, 16 to 24), specificity of 99% (95% CI, 99 to 99), positive predictive

Table 1 Patient characteristics and clinical status before surgery

	No AKI ($n = 4,383$)	AKI (Stage I) ($n = 437$)	<i>P</i> value
Sex (female)	1,325 (30.2%)	106 (24.2%)	0.01
Age (yr)	64 [54-73]	66 [56-74]	0.02
Weight (kg) (18 missing)	79 [68-91]	82 [71-96]	<0.001
Hypertension (15 missing)	2,856 (65.3%)	319 (73.3%)	<0.001
Diabetes (type I or II) (7 missing)	1,203 (27.5%)	124 (28.5%)	0.65
History of stroke or transient ischemic event	420 (9.6%)	70 (16.0%)	<0.001
Peripheral vascular disease (18 missing)	413 (9.5%)	70 (16.1%)	<0.001
Atrial fibrillation	439 (10.0%)	83 (19.0%)	<0.001
Endocarditis	46 (1.1%)	17 (3.9%)	<0.001
Left ventricular ejection fraction <40%	487 (11.1%)	98 (22.4%)	<0.001
Intra-aortic balloon pump	35 (0.8%)	11 (2.5%)	<0.001
Creatinine ($\mu\text{Mol}\cdot\text{L}^{-1}$)	81 [71-96]	89 [73-110]	<0.001
Hemoglobin ($\text{g}\cdot\text{L}^{-1}$) (38 missing)	141 [130-151]	134 [118-147]	<0.001

Values shown as n (%) or median [interquartile range]. AKI = acute kidney injury

Table 2 Surgical parameters

	No AKI ($n = 4,383$)	AKI (Stage I) ($n = 437$)	<i>P</i> value
Prior heart surgery	476 (10.8%)	76 (17.4%)	<0.001
Elective procedure	3,022 (69.0%)	232 (53.1%)	<0.001
Procedure type			<0.001
- Isolated CABG	1,617 (36.9%)	117 (26.8%)	
- Valve repair or replacement	1,159 (26.5%)	97 (22.2%)	
- Other procedures	1,606 (36.7%)	223 (51.0%)	
Cardiopulmonary bypass duration (min) (19 missing)	93 [72-120]	122 [89-169]	<0.001
Hypothermic circulatory arrest	218 (5.0%)	32 (7.3%)	0.03
Mechanical support off CPB	66 (1.5%)	39 (8.9%)	<0.001
Red blood cell transfusions on the day of surgery (units)	0 [0-1]	1 [0-4]	<0.001

Values shown as n (%) or median [interquartile range]. AKI = acute kidney injury; CABG = coronary artery bypass surgery; CPB = cardiopulmonary bypass

Fig. 1 Creatinine ($\mu\text{g}\cdot\text{mL}^{-1}$) measures during the study period in patients without acute kidney injury (AKI) (black circles) and with AKI (white circles). Error bars represent the interquartile ranges. While the differences were significant ($P < 0.001$) at all time points, the Z-scores were markedly higher postoperatively: $Z = 4.9$ at baseline, 17.1 in the intensive care unit (ICU), 26.2 on postoperative day 1, and 27.9 on postoperative day 2

Fig. 3 Receiver operating characteristic curve for the predictive value of the perioperative change in serum creatinine ($\Delta\text{Creat}^{\text{ratio}}$) for acute kidney injury (AKI). The predictive capacity of several thresholds is shown. In = incidence; PPV = positive predictive value; NPV = negative predictive value; $R = \Delta\text{Creat}^{\text{ratio}}$; Sn = sensitivity; Sp = specificity

Figs 2 The relationship between the perioperative change in serum creatinine ($\Delta\text{Creat}^{\text{ratio}}$; see text for definition) and the probability (a) and log-odds (b) of acute kidney injury (AKI)

value (PPV) of 68% (95% CI, 59 to 76), and negative predictive value (NPV) of 93% (95% CI, 92 to 93). In logistic regression analysis, each percent increase in $\Delta\text{Creat}^{\text{ratio}}$ was associated with a 6.6% (95% CI, 6.0 to 7.3) increase in the odds of AKI ($P < 0.001$) (Table 3). When other perioperative predictors of AKI were included in the model, the AUROC curve increased to 0.81 (95% CI, 0.78 to 0.83), but the $\Delta\text{Creat}^{\text{ratio}}$ was the most predictive variable in the model (Table 3).

The AUROC curves of the relationships between $\Delta\text{Creat}^{\text{ratio}}$ and AKI stages II and III were 0.81 (95% CI, 0.77 to 0.85) and 0.88 (95% CI, 0.80 to 0.97), respectively. When other perioperative predictors of AKI were included in the models, the AUROC was 0.83 (95% CI, 0.79 to 0.87) for AKI stage II and 0.90 (95% CI, 0.83 to 0.98) for AKI stage III. The $\Delta\text{Creat}^{\text{ratio}}$ remained the strongest predictor for both thresholds. The AUROC curve between $\Delta\text{Creat}^{\text{ratio}}$ and dialysis was 0.73 (95%, CI 0.67 to 0.79) without the inclusion of predictors, and 0.86 (95% CI, 0.82 to 0.90) with the inclusion of predictors.

In the validation set, $\Delta\text{Creat}^{\text{ratio}} > 1.30$ occurred in 280 (4.3%) patients, with a sensitivity of 24% (95% CI, 21 to 27), specificity of 98% (95% CI, 97 to 98), PPV of 55% (95% CI, 49 to 61), and NPV of 92% (95% CI, 91 to 93). Among patients with AKI, the primary difference between those with and without $\Delta\text{Creat}^{\text{ratio}} > 1.30$ was that the former more frequently underwent redo (22% vs 11%, respectively; $P < 0.001$) and complex procedures (60% vs 43%, respectively; $P < 0.001$) with longer median [interquartile range (IQR)] CPB times (167 [116-230] min vs 118 [88-163] min, respectively; $P < 0.001$) and

Table 3 Multivariable logistic regression models for AKI stage I

Model	AUROC (95% CI)	AUROC Optimism Corrected	Variables in the model (units or classification)	Wald χ^2	P value	Odds Ratio (95% CI)
Model 1: Including only $\Delta\text{Creat}^{\text{ratio}}$	0.78 (0.75 to 0.80)	0.78				
			$\Delta\text{Creat}^{\text{ratio}}$ (%)	404	< 0.001	1.07 (1.06 to 1.07)
Model 2: Including $\Delta\text{Creat}^{\text{ratio}}$ and other predictors	0.81 (0.78 to 0.83)	0.81				
			$\Delta\text{Creat}^{\text{ratio}}$ (%)	260	<0.001	1.06 (1.05 to 1.06)
			Preoperative hemoglobin (per 10 g·L ⁻¹)	23.2	<0.001	0.86 (0.81 to 0.92)
			Cleveland Score (< 3 baseline)	14.3	<0.001	
			3-5			1.3 (1.0 to 1.7)
			> 5			2.1 (1.4 to 3.0)
			RBC transfusion on day of surgery (≥ 5 vs 0-4 units)	4.9	0.03	1.5 (1.0 to 2.2)
			CPB duration (min)	16.4	<0.001	1.005 (1.002 to 1.007)
			Mechanical support off CPB	10.9	0.001	2.4 (1.4 to 4.0)

Where:

AUROC Area under the receiver operating characteristic curve

Wald χ^2 : Variable's $|\beta \text{ coefficient}| / \text{standard error}$. The higher the Wald χ^2 , the higher the predictive value of the variable. (β coefficient is the mathematical weighing of the variable)

P value: The probability value obtained by comparing the Wald χ^2 with the Chi square distribution with 1 degree of freedom

Odds ratio: The change in the odds of acute kidney injury for each unit change of the variable while controlling for other variables in the model

95% CI: 95% confidence interval

$\Delta\text{Creat}^{\text{ratio}}$ The change in serum creatinine (see text for definition)

AKI = acute kidney injury; CPB = cardiopulmonary bypass; RBC = red blood cells

more severe AKI, as measured by the percent increase in creatinine from before surgery to 48 hours after surgery (96 [71-136]% vs 72 [59-95]%, respectively; $P < 0.001$).

The results were similar in the subgroups analyzed in both the derivation and validation datasets (Table 4).

Discussion

In this observational study in patients undergoing cardiac surgery with CPB, we found that an early rise in postoperative creatinine, as measured by the ratio of postoperative creatinine within 30 min of arrival in the ICU to preoperative creatinine ($\Delta\text{Creat}^{\text{ratio}}$), can identify a large proportion of patients who suffer perioperative AKI—

defined as a $> 50\%$ increase in creatinine levels within 48 hr of surgery.¹⁸ The AUROC curve of the relationship between $\Delta\text{Creat}^{\text{ratio}}$ and AKI was 0.78 (95% CI, 0.75 to 0.80) in the development sample and 0.77 (95% CI, 0.75 to 0.79) in the validation sample. Using a $\Delta\text{Creat}^{\text{ratio}} > 1.3$ threshold for identification of AKI, the PPV and NPV in the development sample were 68% and 93%, respectively, and in the validation sample, they were 55% and 92%, respectively.

Thus, the ability of $\Delta\text{Creat}^{\text{ratio}}$ to facilitate early identification of patients who suffer perioperative AKI seems to be as good as or better than the urine or plasma biomarkers that have been evaluated as potential early indicators of AKI. In a recent meta-analysis that included 28 prospective observational studies, the AUROC curves

Table 4 Sensitivity analysis: relationship of $\Delta\text{Creat}^{\text{ratio}}$ with AKI stage I in the development and validation sets

Model	Development Dataset		Validation Dataset	
	<i>n</i> (AKI / no AKI)	AUROC (95% CI)	<i>n</i> (AKI / no AKI)	AUROC (95% CI)
Entire sample	437 / 4,383	0.78 (0.75 to 0.80)	645 / 5,908	0.77 (0.75 to 0.79)
Excluding non-elective cases	232 / 3,022	0.75 (0.71 to 0.79)	374 / 3,714	0.78 (0.76 to 0.81)
Excluding patients who required dialysis after surgery	379 / 4,348	0.77 (0.74 to 0.80)	596 / 5,863	0.77 (0.75 to 0.79)
Excluding patients with severe preoperative renal dysfunction	429 / 4,296	0.78 (0.75 to 0.80)	636 / 5,741	0.77 (0.75 to 0.79)
Excluding patients with $\Delta\text{Creat}^{\text{ratio}} > 1.5$ (i.e., met the definition of AKI immediately after surgery)	404 / 4,377	0.76 (0.73 to 0.79)	577 / 5,887	0.75 (0.72 to 0.77)

AKI = acute kidney injury; $\Delta\text{Creat}^{\text{ratio}}$ = change in serum creatinine (see text for definition); AUROC = area under the receiver operating characteristic curve

of the relationship of 12 such biomarkers (measured during or up to 24 hr after surgery) with AKI were < 0.70 for most and < 0.75 for all.¹³ These values are comparable with the values we observed for $\Delta\text{Creat}^{\text{ratio}}$.

While a few studies have evaluated the prognostic value for mortality based on an early (< 48 hr after surgery) rise in creatinine after cardiac surgery,^{4,26} only one study has assessed its ability for early identification of patients with AKI.¹⁶ That study included 350 adult patients who underwent elective valve or coronary artery bypass grafting at a single institution. Serum creatinine was measured within six hours after surgery, and the change in creatinine was categorized into three levels ($> 10\%$ decrease from baseline, within 10% of baseline, and $> 10\%$ increase from baseline). In a multivariable model that included an early rise in creatinine as well as other predictors of AKI, the AUROC was 0.78 (95% CI, 0.71 to 0.85), which was similar to our findings. Compared with this study, the strengths of our study include its larger sample size, earlier measurement of creatinine after surgery, inclusion of all types of cardiac surgeries requiring CPB, and validation of the results on a separate multicentre dataset.

The primary limitation of our study is that it is a retrospective investigation, which precludes a direct comparison of the predictive value of an early rise in creatinine with other biomarkers. We also used the last available creatinine measurement before surgery as the baseline measure, but this may not represent a steady-state value in some patients, e.g., those undergoing non-elective surgery. Nevertheless, our findings were similar when we excluded non-elective patients (Table 4). Our definition of AKI did not include the urine output parameter of AKIN because it was not available in the databases. Furthermore, we did not use the AKIN criterion of an absolute increase

in creatinine threshold ($\geq 26.5 \mu\text{mol}\cdot\text{L}^{-1}$) in our definition. Given that the glomerular filtration rate is linearly related to the inverse of serum creatinine concentration,²⁷ it reflects a variable drop in glomerular filtration rate depending on patients' baseline creatinine concentration. Another potential limitation is that, on arrival in the ICU, some patients who had reached the $\Delta\text{Creat}^{\text{ratio}}$ threshold used for early identification of AKI ($> 30\%$ increase) already had AKI according to the definition used in the study ($> 50\%$ increase in creatinine). Nevertheless, excluding these patients did not have a material effect on the results (Table 4).

Finally, with a sensitivity of 20%, the selected $\Delta\text{Creat}^{\text{ratio}}$ threshold of > 1.3 would detect only one in five cases of AKI, with those identified being at the more severe spectrum of AKI. In our opinion, the misclassification rate of $\Delta\text{Creat}^{\text{ratio}}$ is too high for it to be used as a clinical tool; however, it could prove useful as an early indicator of AKI in clinical trials of novel therapies for AKI, particularly if it is combined with other variables such as baseline hemoglobin and post-CPB clinical status.

In conclusion, this study confirms that, in patients undergoing cardiac surgery with CPB, an early rise in postoperative creatinine is a useful marker for early identification of patients who suffer perioperative AKI. As such, these patients are candidates for inclusion in clinical trials evaluating novel therapies to address this common problem.

Conflicts of interest None declared.

Editorial responsibility This submission was handled by Dr. Philip M. Jones, Associate Editor, *Canadian Journal of Anesthesia*.

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to the interpretation of data and revisions to the article. *Keyvan Karkouti* was primarily responsible for data acquisition and analysis and prepared the first draft of the article.

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