

Original Article

Identification of risk factors for renal failure after cardiac surgery by RFILE classification

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Abstract: Objective: Acute kidney injury (AKI) is a major complication after cardiovascular surgery. The unclear etiology of this highly complex event challenges definition, diagnosis and prediction of AKI, and hence hampers adequate patient management. Identification of associated risk factors have the potential to overcome this limitation. Methods: This retrospective study comprised 3574 patients who underwent cardiac surgery in a hospital in Germany. The patient cohort was interrogated for risk factors for AKI. Results: The analysis identified risk factors for AKI development, such as type of surgery (particularly bypass surgery) ($P = 0.02$), previous coronary surgeries ($P < 0.01$), the application of intra-aortic balloon pump in surgery ($P < 0.01$), and blood loss during surgery ($P < 0.01$). In addition, old age, duration of surgery as well as ischemia, perfusion and reperfusion times contributed to AKI development ($P < 0.01$). Further, perioperative hypothermia also appeared as putative risk factor in the analysis ($P < 0.01$). Conclusions: This study identified several risk factors for the development of AKI after cardiac surgery. Further validation of these risk factors could allow the implementation of adequate patient management, and the appropriate implementation of risk-adverse interventions in cardiovascular surgery.

Keywords: Acute kidney injury, extracorporeal circulation, RIFLE classification, continuous veno-venous hemodialysis, cardiac surgery, risk factors, KDIGO criteria, AKIN category

Introduction

Cardiovascular surgery still entails the risk for severe complications despite revolutionary advancements such as the heart-lung machine. A notable complication is acute kidney injury (AKI), which is associated with a high incidence of morbidity and mortality [1]. Moreover, AKI requires renal replacement therapy (RRT) in 2% to 5% of the affected patients, and thus increases mortality even further [2].

Prediction of the incidence of AKI is a major challenge due to the lack of consensus on the definition of AKI [3]. Therefore, the global incidence of AKI after cardiovascular surgery ranges considerably (i.e., 0.7% to 34%) depending on study population and definition [4]. Currently, a number of established risk scores attempt to predict AKI: (i) RIFLE (Risk, Injury, Failure, Loss, End-stage renal disease), which is based on serum creatinine, urine output and/or glomerular filtration rate (GFR) [5]; (ii) AKIN (Acute

Kidney Injury Network), which is based on serum creatinine, irrespective of GFR changes) [6]; (iii) KDIGO (Kidney Disease: Improving Global Outcomes), which combines the differences of RIFLE and AKIN [7].

The complex etiology of AKI and the diversity of the established risk scores hamper timely identification of the acute event before loss of organ function occurs [8]. According to a meta-analysis, serum biomarkers demonstrate only limited predictive power for AKI in the early period after cardiac surgery, whereas the traditional functional biomarkers, e.g. urine output and serum creatinine, provide only delayed diagnostic capability [9]. Consequently, these limitations render the currently established set of risk factors ineffective in the case of an acute event. In order to develop adequate prediction tools for routine clinical practice, and to provide optimal care for the patients, identification of the relevant risk factors for AKI is crucial.

Risk factors for acute kidney injury after cardiac surgery

In this retrospective study, we sought out to identify reliable risk factors for the incidence of AKI in 3574 patients after cardiac surgery in a hospital in Germany. We assessed the incidence rates for AKI using the RIFLE classification.

Materials and methods

Study design

This retrospective study included 3574 patients who underwent open-heart surgery with extracorporeal circulation from January 2000 to December 2005. Data collection of patient was performed via the GISI and GISI-OP database from the Göttingen University Hospital as described previously [10]. Briefly, the records included patient characteristics and medical records as well as information on the performed intervention, including the type of cardiac surgery, such as isolated bypass grafting, isolated aortic or mitral valve reparation or replacement, combined bypass grafting and valve surgery or interventions without bypass or without heart valve surgery. The inclusion criteria for this retrospective study was a minimum age of 18 years. The local ethics committee (No. 16-4-10) of the University Hospital of Göttingen, Germany approved this study.

Definition of acute kidney injury

Renal function after surgery was defined as stage 3 by the RIFLE classification, which is based on serum creatinine and urine output [5]. The RIFLE criteria for serum creatinine are the following: (i) a 3-fold elevation of serum creatinine or (ii) a maximum creatinine level of 4.0 mg/dL or (iii) a 75% decrease of the GFR compared to the preoperative value. The RIFLE criteria for urine output are (i) urine output below 0.3 mL/kg/h for 24 h or (ii) anuria for 12 h. Serum creatinine level (in mg/dL) were estimated with the Cockcroft-Gault equation for GFR in mL/min/1.73 m², and reads: $GFR = [(150 - \text{age}) \times \text{body weight (kg)} / \text{serum creatinine } (\mu\text{mol/L})] - \text{gender factor (10\% males, 15\% females)}$ [11].

Statistical analysis

The data sets were statistically analyzed with Statistica software version 7.0 (StatSoft Europe GmbH, Berikon, Switzerland) as mentioned previously [10]. Metric variables were patient age, serum creatinine level (evaluated immediately

after surgery, i.e. "creatinine A" or 24 h after surgery, i.e. "creatinine B"), duration of surgery, duration of ischemia, (re) perfusion time, bleeding (blood loss), and body temperature. Categorical parameters were gender, type of surgical intervention, use of an intra-aortic balloon pump (IABP), centrifugal or roller blood pump, cardioplegia (blood cardioplegia or Bretschneider), intraoperative body temperature (normothermia: > 33°C, mild hypothermia: ≤ 33°C to > 27°C, deep hypothermia: ≤ 27°C). Metric variables were compared using the Wilcoxon-Mann-Whitney-test, whereas categorical parameters were compared using the Wilcoxon-test. Longitudinal analysis of the metric variable "blood loss" was performed via the non-parametric Kruskal-Wallis-test. A chi-squared-test was employed for the comparison of categorical proportions. A logistic regression was performed with those factors that yielded significance in the bivariate analysis. For the model building a stepwise selection procedure was applied to the factors. A value of $\alpha = 5\%$ ($P < 0.05$) was deemed as statistically significant.

Results

Patient characteristics

The 3574 patients in this retrospective study underwent open-heart surgery with extracorporeal circulation (**Table 1**). The overall mortality among the study population was 6.4% ($n = 230$). According to the RIFLE criteria, 251 patients (7%) showed postoperative AKI, and the mortality rate in this subset was 22.7% ($n = 57$ patients). An overwhelming majority of the patients were male ($n = 2522$; 71%) with less than a third patients being female ($n = 1052$; 29%). The sex of the patient did not correlate with the incidence for AKI ($P = 0.62$) (**Table 1**). The median age of the patients was 68 years, ranging from 18 years to 92 years. The mean age of the male patients was 63.5 years, whereas the female patients were in average 69.3 years. Notably, patients who developed AKI had a median age of 71 (65 to 76.5) years, and hence were older than patients without AKI, and who had a median age of 68 (61 to 74) years ($P < 0.01$) (**Figure 1**).

Type of surgical intervention

The analysis of the study population showed that almost two third of the patients underwent

Risk factors for acute kidney injury after cardiac surgery

Table 1. Demographic and clinical categorical parameters of the study group

Parameter	AKI according to RIFLE		p-value (chi-squared test)
	No n = 3323	Yes n = 251	
Sex			0.62
Male	2341 (70%)	181 (72%)	
Female	981 (30%)	70 (28%)	
Bypass surgery			0.02
Yes	2520 (76%)	207 (82%)	
No	803 (24%)	44 (18%)	
Valve surgery			0.10
Yes	1157 (35%)	94 (37%)	
No	2166 (65%)	157 (63%)	
Surgery			< 0.01
Others	245 (7%)	18 (7%)	
Bypass	2037 (61%)	153 (61%)	
Valve	596 (18%)	30 (12%)	
Bypass + valve	445 (13%)	50 (20%)	
Previous surgery			< 0.01
Yes	172 (5%)	31 (12%)	
No	3151 (95%)	220 (88%)	
Intra-aortic balloon pump			< 0.01
Yes	83 (2%)	15 (6%)	
No	3240 (98%)	236 (94%)	
Pump			0.45
Centrifugal	2784 (84%)	215 (86%)	
Peristaltic	491 (15%)	31 (12%)	
none	48 (1%)	6 (2%)	
Cardioplegia			0.74
Bretschneider	1462 (44%)	116 (46%)	
Blood cardioplegia	1758 (53%)	129 (51%)	
none	103 (3%)	6 (2%)	
Temperature			< 0.01
Normothermia	2524 (76%)	177 (71%)	
Mild hypothermia	734 (22%)	63 (25%)	
Deep hypothermia	65 (2%)	11 (4%)	

coronary artery bypass graft surgery (61%), followed by aortic valve replacement (20%), and aortic valve replacement in combination with coronary surgery (15%) (**Table 1**). Moreover, the type of cardiac surgery was associated with an increased incidence for AKI (**Figure 2**). Bypass grafting increased the incidence rate ($P = 0.02$) by a statistical significant margin, whereas valve surgery had no statistical effect ($P = 0.10$). A logistic regression analysis confirmed that bypass grafting is a risk factor for AKI development ($P = 0.034$) (**Table 2**). A combination of both interventions did further increase

the incidence rate for AKI ($P < 0.01$). Other surgeries apart from bypass and valve surgery are also associated with an increased risk for the development of AKI ($P < 0.01$); however, no detailed analysis of these types of surgical interventions were performed due to a lack of sufficient information in the available patient records.

The data analysis deemed the application of an IABP during surgical intervention as risk factor for AKI as well ($P < 0.01$) (**Table 1**). Furthermore, the analysis also showed that previous coronary interventions are a significant risk factor for the development of AKI ($P < 0.01$). Logistic regression analysis confirmed this finding ($P < 0.001$) (**Table 2**). In contrast, the type of pump ($P = 0.45$), and the type of cardioplegia ($P = 0.74$) were not identified as risk factors for AKI.

Intraoperative parameters

The evaluation of Intraoperative parameters showed that duration of surgery, ischemia time, perfusion and reperfusion time increased the risk for AKI ($P < 0.01$) (**Table 3**). The duration of surgery was 274 (229 to 320) min for non-AKI patients, and hence was shorter than the time for AKI patients who underwent surgery for 303 (251 to 366) min. The ischemia time was also shorter for non-AKI patients than for AKI-patients (79 (60 to 103) min vs. 85 (64 to 114.5) min). The analysis showed a similar pattern for both perfusion and reperfusion time. The former one differed between

126 (98 to 160) min and 138 (110.5 to 185) min, whereas the latter one differed between 37 (28 to 49) and 43 (33 to 59) min. Logistic regression analysis on selected parameters (i.e., reperfusion time) confirmed their role as risk factors for AKI development ($P < 0.001$) (**Table 2**).

Perioperative body temperature

The analysis suggested that the perioperative body temperature of the patients is a risk factor for the development of AKI (**Table 1**). The analy-

Risk factors for acute kidney injury after cardiac surgery

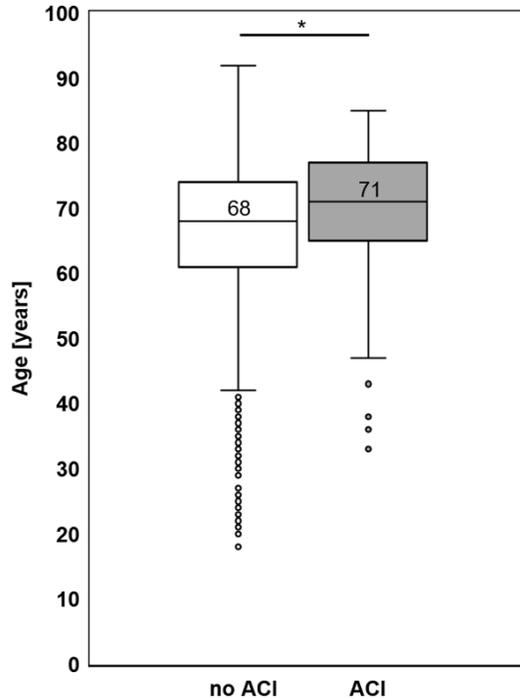


Figure 1. Old age is a risk factor for the development of acute kidney injury. The numbers in the box plots indicate the median age of the subset. Statistical significance was evaluated via a Wilcoxon-Mann-Whitney-test (* for p -value < 0.01).

sis of the categorical parameters showed that patients with deep hypothermia (i.e., $\leq 27^{\circ}\text{C}$) and mild hypothermia (i.e., $\leq 33^{\circ}\text{C}$ to $> 27^{\circ}\text{C}$) were at a higher risk for developing AKI than patients with normothermia (i.e., $> 33^{\circ}\text{C}$) ($P < 0.01$). Nevertheless, analysis of the metrical body temperature did not produced a statistical significance (**Table 3**). In this case, the median temperature of AKI patients was 34.0 (32.7 to 35.9) $^{\circ}\text{C}$, whereas the non-AKI patients showed a slightly higher median temperature of 34.3 (33.1 to 35.9) $^{\circ}\text{C}$ ($P = 0.19$).

Postoperative blood loss

Our analysis showed a statistically significant difference in the overall blood loss between patients with AKI and patients without AKI ($P < 0.01$) (**Figure 3A**). The median blood loss among AKI patients was 1540 mL, whereas non-AKI patients showed with 800 mL approximately half the loss. We also analyzed the blood loss dynamically over the course of 6 days, and compared the results among the patients with and without AKI. The analysis con-

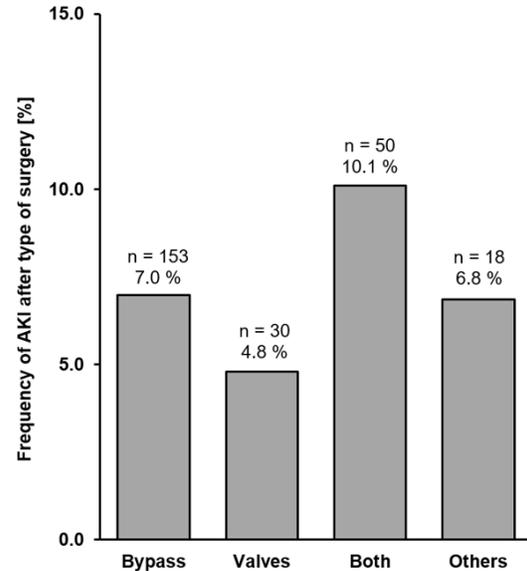


Figure 2. Frequency of patients with AKI varies among the different types of surgical procedures.

firmed that postoperative blood loss correlates with the risk of developing AKI ($P < 0.01$) (**Figure 3B**).

Discussion

AKI is a major complication of heart surgery, and is associated with systemic inflammation and multiple organ dysfunction, which eventually leads to increased mortality. Nevertheless, the real impact of AKI is difficult to assess due to the variety of definitions and diagnostic criteria [3]. Past efforts attempted to address this limitation, and to provide an international standard.

The first standardized definition of AKI was the RIFLE classification in May 2004, comprising five stages of kidney impairments of which three are severity classes and two are outcome classes [5]. RIFLE is based on the serum creatinine levels and urine output, and has been validated in a large portion of patients over the years [12]. AKIN, a modified version of the RIFLE criteria, followed in March 2007, and relies on serum creatinine levels and not on GFR changes [13]. The AKIN classification removed the two outcome classes (i.e., loss of kidney function and end-stage kidney disease) from the RIFLE predecessor, and defines only three stages. The KDIGO criteria attempt to combine both parallel classification systems

Risk factors for acute kidney injury after cardiac surgery

Table 2. Logistic regression analysis ^a of selected risk factors for AKI development

Parameter	Odds ratio (95% CI)	p-value
Bypass surgery	1.462 (1.029-2.077)	0.034
Previous surgery	2.394 (1.552-3.693)	< 0.001
Reperfusion time [min]	1.010 (1.006-1.014)	< 0.001

^aNagelkerke's R² = 0.029 (poor). CI, confidence interval.

into a uniform definition of AKI [7]. KDIGO utilizes creatinine levels, GFR and urine output in order to define three stages of AKI. In addition to these universal classification systems, there are also local SOP in individual hospitals for the definition of AKI. In this retrospective study, we focused on the RIFLE classification, because this system has been applied and validated in a number of clinical settings [12].

The use of a different classification system might change the outcome of this study, illustrating the challenges of identifying the incidence of AKI, and the associated risk factors. For instance, literature reports an incidence range of 0.7% to 34% after cardiovascular surgery [4, 14, 15]. In line with this very broad incidence range, the mortality rates vary from 1.3% to 22.3%, and from 25% to 90% if dialysis is required [4, 16, 17]. In our study, the incidence rate for AKI was 7%, whereas the mortality rate for patients with AKI was 22%. Hence, the mortality is in the upper range of the reported rates for AKI patients; however, since the analysis does not consider dialysis, the mortality rate likely falls within the expected range. The incidence rate for AKI, however, is on the higher end of the reported range. For instance, a large study of more than 30,000 patients who underwent open-heart surgery reported a substantially lower incidence rate of 1.7% [18]. The relative high incidence rate in our study can be attributed to the different surgical interventions, and the different composition of the patient cohort.

Notably, the age composition of our study appears to share the highest degree of similarity to the age composition of an earlier study that reported a similar, higher incidence rate of 9.3% for AKI after cardiac surgery [19]. In line with this reasoning, our study identified old age as a risk factor for the development of AKI. This is in excellent agreement with previous trials that identified old age as independent risk fac-

tor for AKI [20]. The ageing process is associated with a loss of renal mass, including tubules, and sclerotic changes of the kidney. This process causes a reduction of renal blood flow and a decline of GFR at a rate of 6.3 mL/min/1.73 m² per decade [21]. Therefore, the diminished physiological capacity of the kidney increased the risk for AKI. Additional physiological changes associated with ageing are likely to negatively affect renal function as well.

Another important aspect with respect to the composition of the study population is the gender distribution. Our study did not produce statistical evidence for the contribution of the patients' sex to the development of AKI. A previously reported study contradicts our finding and showed that gender-associated effects for cardiac surgery-associated AKI [9]. However, another study showed a higher incidence for AKI in male patients [22]. This illustrates the conflicting evidence on the role of sex in AKI development, and our study remains neutral on this aspect.

The surgical intervention itself can be a risk factor for AKI. The results of our study show that the type of cardiac surgery is a critical parameter to assess the risk for AKI development. Notably, our study showed that bypass surgery poses a higher risk for the development of AKI. This contradicts previous research that demonstrated that valve surgery is associated with a higher risk for AKI [23, 24]. A reason for this discrepancy between the reported literature is the highly complex nature of AKI development, and the contribution of multiple factor to this event. Nonetheless, literature and our study agree that the combination of coronary artery bypass grafting and valve surgery synergistically increase the risk for AKI development [9]. Furthermore, the results of this study show that repeated coronary interventions are another risk factor the AKI development, which is in agreement with previous studies [6, 25]. Another intraoperative risk factor in our study was the application of IABP, which is in agreement with recent studies [10, 26, 27]. One interpretation is the common application of IABP in patients who are in critical condition with low cardiac output. Low cardiac output is linked to hypoperfusion and functional loss of the kidney, which are both indicators for the development of AKI. In contrast, a study sh-

Risk factors for acute kidney injury after cardiac surgery

Table 3. Intraoperative metric variables of the study group

Parameter	AKI according to RIFLE						p-value (Wilcoxon)
	No n = 3323			Yes n = 251			
	25%	50%	75%	25%	50%	75%	
Duration of surgery [min]	229.0	274.0	329.0	251.0	303.0	366.0	< 0.01
Ischemia [min]	60.0	79.0	103.0	64.0	85.0	114.5	< 0.01
Perfusion [min]	98.0	126.0	160.0	110.5	138.0	185.0	< 0.01
Reperfusion [min]	28.0	37.0	49.0	33.0	43.0	59.0	< 0.01
Min. temperature [°C]	33.1	34.3	35.9	32.7	34.0	35.9	0.19

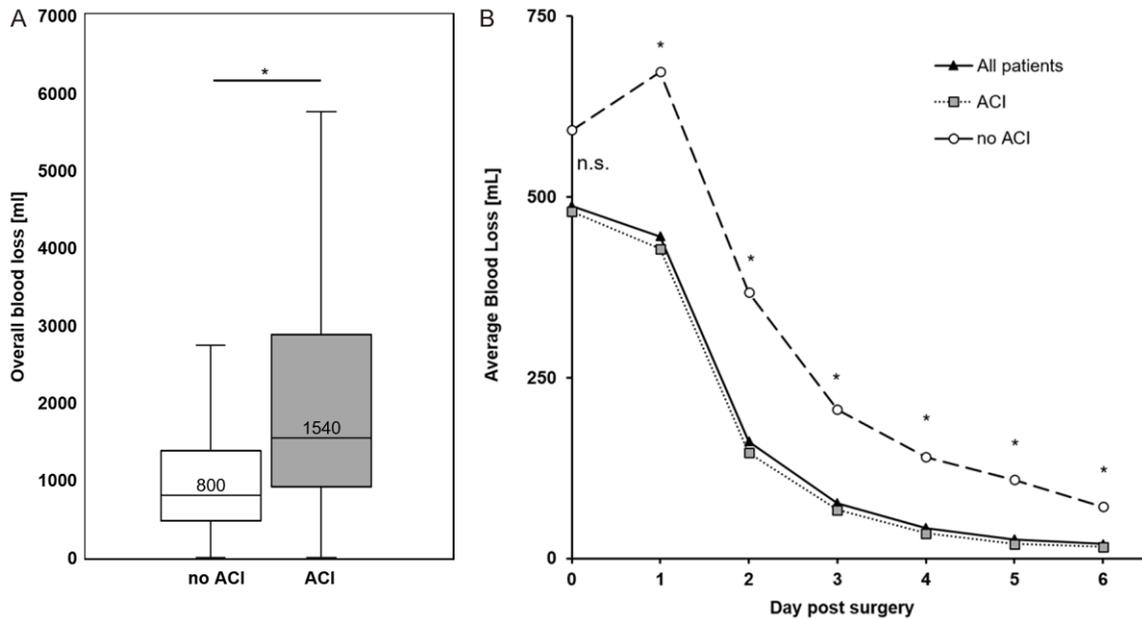


Figure 3. Intraoperative blood loss is a risk factor for the development of AKI. A. Overall blood loss is presented as box plots. The numbers indicate the median blood loss of the subset. Statistical significance was evaluated via a Wilcoxon-Mann-Whitney-test (* for p -value < 0.01). B. Mean values of postoperative blood loss over 6 days post-surgery. Statistical significance was evaluated via a non-parametric Kruskal-Wallis-test (* for $P < 0.01$; n.s. for not significant).

owed that the application of IABP has clinical benefits for the patients [28]. Furthermore, preoperative use of IABP is associated with a reduction in the incidence for AKI among high-risk patients [29]. Despite the promising body of data provided by our study and others, additional research is required to assess the risk-benefit balance of such preoperative application of IABP.

Other perioperative parameters identified as risk factors by this study are the duration of the surgical intervention as well as ischemia, perfusion and reperfusion times. These observations are in excellent agreement with literature

[30, 31]. Similarly, the blood loss after the surgery strongly correlated with AKI development in our retrospective study. This is in line with literature that reported this relationship earlier for cardiac surgery [32, 33] but also in different surgical settings, for instance pancreas or neurological interventions [34, 35].

In contrast, the identification of perioperative body temperature as risk factor for AKI is not entirely clear. The body temperature itself does not show any statistical effect on the AKI incidence; however, classifying the temperature according to normothermia or hypothermia does show a strong statistical effect on the

development of AKI. Previous studies either support [36] or contradict [37] classifying hypothermia as risk factor; hence, we call for additional studies to further elucidate this parameter in the context of cardiac surgery and AKI development.

Taken together, our study identified risk factors for the development of AKI, such as intraoperative body temperature, duration of surgery, duration of ischemia, and perfusion and reperfusion time. The results also demonstrate that several parameters, e.g. the medical history of the patient and the experience of the surgeon, influence the impact of a putative risk factor, which further highlights the complex process of AKI development. Hence, without further evaluation, the presented study does not allow drawing a final conclusion; instead, this work provides additional data for improved assessment and prediction of AKI after cardiac surgery in the future.

Conclusion

A number of perioperative risk factors for the development of AKI after cardiac surgery have been identified, such as old age, application of IABP, repeated surgical interventions, and bypass surgery. To reduce complication and mortality rate due to AKI, the role of the associated risk factors need to be clearly defined, and patient surveillance, risk assessment and risk prevention need to be improved. After major vascular surgery, in particular, the incidence for AKI is increased, and hence a clinical consensus should provide necessary guidelines for the risk-benefit balance of a surgical intervention. This could allow adequate patient management and the appropriate implementation of risk-adverse interventions. In addition, real-time monitoring of biomarkers for kidney function could reduce the time to recognize the onset of AKI and enables timely clinical intervention to mitigate the consequences.

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Disclosure of conflict of interest

None.

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Risk factors for acute kidney injury after cardiac surgery

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Risk factors for acute kidney injury after cardiac surgery

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