Acute Kidney Injury After Cardiac Surgery

Focus on Modifiable Risk Factors

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Background—Acute kidney injury (AKI) after cardiac surgery is a major health issue. Lacking effective therapies, risk factor modification may offer a means of preventing this complication. The objective of the present study was to identify and determine the prognostic importance of such risk factors.

Methods and Results—Data from a multicenter cohort of 3500 adult patients who underwent cardiac surgery at 7 hospitals during 2004 were analyzed (using multivariable logistic regression modeling) to determine the independent relationships between 3 thresholds of AKI (>25%, >50%, and >75% decrease in estimated glomerular filtration rate within 1 week of surgery or need for postoperative dialysis) with death rates, as well as to identify modifiable risk factors for AKI. The 3 thresholds of AKI occurred in 24% (n=829), 7% (n=228), and 3% (n=119) of the cohort, respectively. All 3 thresholds were independently associated with a >4-fold increase in the odds of death and could be predicted with several perioperative variables, including preoperative intra-aortic balloon pump use, urgent surgery, and prolonged cardiopulmonary bypass. In particular, 3 potentially modifiable variables were also independently and strongly associated with AKI. These were preoperative anemia, perioperative red blood cell transfusions, and surgical reexploration.

Conclusions—AKI after cardiac surgery is highly prevalent and prognostically important. Therapies aimed at mitigating preoperative anemia, perioperative red blood cell transfusions, and surgical reexploration may offer protection against this complication. (Circulation. 2009;119:495-502.)

Key Words: surgery ■ cardiopulmonary bypass ■ kidney ■ risk factors

Acute kidney injury (AKI) is a highly prevalent and prognostically important complication of cardiac surgery. By most estimates, up to 30% of cardiac surgery patients develop clinically relevant kidney injury.1 When the injury is severe enough to necessitate dialysis, which is the case for approximately 1% to 2% of patients,1 it confers an ~8-fold increase in the odds of death.2 Even when the injury is relatively modest, it is independently associated with markedly increased morbidity and mortality.3

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To mitigate the burden of AKI after cardiac surgery, numerous interventions have been tested, but none has proved efficacious.1 In the absence of proven interventions, a reasonable strategy would be to identify modifiable risk factors for AKI in this setting. These modifiable risk factors might, in turn, serve as therapeutic targets for preventing AKI. Previous studies have identified several
The primary purpose of most of these studies, however, was to identify risk stratification rather than risk modification; hence, they focused on patient comorbidities and nonmodifiable surgical factors. Consequently, we undertook this prospective observational multicenter study to examine the prognostic importance of modifiable risk factors for AKI after cardiac surgery.

Methods

Study Cohort

Data from a previously described multicenter cohort were used for the present study. The cohort consisted of 3500 adult (>18 years of age) patients who underwent cardiac surgery with cardiopulmonary bypass (CPB) at 7 academic Canadian hospitals during 2004. Each hospital contributed 500 consecutive patients, excluding infrequent procedures (heart transplantation, ventricular assist device placement, and complex congenital abnormalities). Additionally, exclusion criteria for the present study were preoperative dialysis dependence and missing preoperative or postoperative creatinine values. For patients who underwent more than 1 relevant procedure during the study period, only data on their initial surgery were collected.

After research board approval at each hospital was received, detailed perioperative data were collected retrospectively on patients from clinical databases and hospital charts. Data were entered into a computerized database, which was programmed to accept only matching double-entry data that fell within prespecified ranges. All queries were resolved by reference to the patients’ original records.

Dependent Variable

The primary dependent variable was AKI. Three thresholds for injury, taken from the consensus-based RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria, were examined: (1) >25% decrease in estimated glomerular filtration rate (eGFR); (2) >50% decrease in eGFR; and (3) >75% decrease in eGFR. All thresholds also included any patient who required dialysis during their postoperative hospital stay. Glomerular filtration rate was estimated with the Cockcroft-Gault equation, using preoperative creatinine and highest creatinine concentration during the first week after surgery.

Independent Variables

Measured preoperative and intraoperative variables known to be or that could potentially be associated with AKI or other adverse outcomes were examined.
After the exclusion criteria were applied, 3460 patients were included in the study. Of these, 829 (24%) met the first, 228 (7%) met the second, and 119 (3%) met the third threshold of AKI. As can be seen in Table 1, all 3 thresholds of AKI were associated with increased length of stay and death. The lowest threshold of \( \geq 25\% \) decrease in eGFR, for example, was associated with a 4-fold increase in the risk-adjusted odds of death.

The Figure shows the unadjusted relationships (using spline function curves) of selected continuous independent variables with a \( \geq 50\% \) decrease in eGFR (other thresholds had similar relationships; results not shown). The bivariate associations of patient- and procedure-related variables with AKI are shown in Table 2 (associations with other thresholds were similar; results not shown); variables with \( P < 0.3 \) were included in the multivariable analyses. No 2 variables had a Pearson correlation coefficient \( \geq 0.45 \), which suggests that collinearity was not an issue in the logistic regression analyses. Nine patients with missing values were excluded from the multivariable analyses.

The results of the multivariable analyses for the 3 thresholds of AKI are presented in Table 3. The models demonstrated good discrimination and calibration; furthermore, they remained stable during bootstrap resampling. The addition of interaction terms or of the center did not influence the models significantly. Accounting for clustering also did not have a significant effect on the models.

Although the most predictive risk factors in the models were CPB duration and intra-aortic balloon pump before surgery, 3 potentially modifiable and interrelated risk factors (preoperative anemia, perioperative red blood cell [RBC] transfusions, and the need for reexploration) were strongly associated with AKI in all 3 models. The Pearson correlation coefficients among these variables were \( \approx 0.3 \) (\( P < 0.0001 \)).

**Discussion**

In the present multicenter cohort, AKI occurred commonly and, even when mild, was independently associated with increased mortality rates. This shows that the burden of AKI in modern cardiac surgery remains high. Furthermore, it provides a multicenter validation of the clinical relevance of the RIFLE classification in cardiac surgery.\(^\text{17}\)

As in previous studies,\(^\text{1,4–14,24–27}\) we found several independent risk factors for AKI. Some of the risk factors, such as the comorbidities diabetes mellitus, preexisting kidney disease, and left ventricular dysfunction, are clearly nonmodifiable. Others, such as the presence of an intra-aortic balloon pump and CPB duration, may be modifiable, but not readily and only in selected cases. For example, in patients with intra-aortic balloon pumps, it may at times be possible to
Table 2. Characteristics of the Study Cohort

<table>
<thead>
<tr>
<th>Variables</th>
<th>≤25% Decrease in eGFR (n=2631)</th>
<th>&gt;25% Decrease in eGFR or Dialysis (n=829)</th>
<th>&gt;50% Decrease in eGFR or Dialysis (n=228)</th>
<th>&gt;75% Decrease in eGFR or Dialysis (n=119)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-related variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>628 (24)</td>
<td>229 (28)</td>
<td>61 (27)</td>
<td>31 (26)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age, y</td>
<td>65±11</td>
<td>66±11</td>
<td>68±12</td>
<td>69±11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81±16</td>
<td>83±19</td>
<td>83±19</td>
<td>82±19</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diabetes (type 1 or 2), n (%)</td>
<td>719 (27)</td>
<td>310 (37)</td>
<td>87 (38)</td>
<td>44 (37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1724 (66)</td>
<td>580 (70)</td>
<td>162 (71)</td>
<td>83 (70)</td>
<td>0.02</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n (%)</td>
<td>253 (10)</td>
<td>107 (13)</td>
<td>28 (12)</td>
<td>17 (14)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cerebrovascular disease, n (%)</td>
<td>253 (10)</td>
<td>97 (12)</td>
<td>30 (13)</td>
<td>16 (13)</td>
<td>0.08</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>290 (11)</td>
<td>103 (12)</td>
<td>20 (9)</td>
<td>11 (9)</td>
<td></td>
</tr>
<tr>
<td>Preoperative atrial fibrillation, n (%)</td>
<td>206 (8)</td>
<td>120 (14)</td>
<td>45 (20)</td>
<td>26 (22)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Recent (&lt;30 days) myocardial infarction, n (%)</td>
<td>465 (18)</td>
<td>171 (21)</td>
<td>58 (25)</td>
<td>34 (29)</td>
<td>0.06</td>
</tr>
<tr>
<td>Left ventricular dysfunction (ejection fraction &lt;40%), n (%)</td>
<td>371 (14)</td>
<td>175 (21)</td>
<td>57 (25)</td>
<td>35 (29)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preoperative intra-aortic balloon pump, n (%)</td>
<td>49 (2)</td>
<td>76 (9)</td>
<td>32 (14)</td>
<td>22 (18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preoperative hemoglobin, g/dL</td>
<td>13.6±1.6</td>
<td>13.0±1.9</td>
<td>12.5±2.1</td>
<td>12.3±2.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preexisting renal insufficiency (eGFR &lt;60 mL/min), n (%)</td>
<td>698 (27)</td>
<td>264 (32)</td>
<td>103 (45)</td>
<td>70 (59)</td>
<td>0.003</td>
</tr>
<tr>
<td>Preexisting coagulopathy (INR &gt;1.5), n (%)</td>
<td>76 (3)</td>
<td>52 (6)</td>
<td>22 (10)</td>
<td>11 (9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preexisting thrombocytopenia (platelet count &lt;150×10⁹/L), n (%)</td>
<td>165 (6)</td>
<td>91 (11)</td>
<td>35 (15)</td>
<td>22 (18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Use of ACE inhibitor or receptor blocker before surgery, n (%)</td>
<td>1541 (59)</td>
<td>462 (56)</td>
<td>121 (54)</td>
<td>67 (57)</td>
<td>0.2</td>
</tr>
<tr>
<td>Procedure-related variables</td>
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<td></td>
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<tr>
<td>Hospital, n (%)</td>
<td>0.005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>387 (15)</td>
<td>103 (12)</td>
<td>26 (11)</td>
<td>17 (14)</td>
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</tr>
<tr>
<td>2</td>
<td>365 (14)</td>
<td>129 (16)</td>
<td>31 (14)</td>
<td>18 (15)</td>
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<tr>
<td>3</td>
<td>374 (14)</td>
<td>120 (14)</td>
<td>53 (23)</td>
<td>30 (25)</td>
<td></td>
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<tr>
<td>4</td>
<td>385 (15)</td>
<td>112 (14)</td>
<td>19 (8)</td>
<td>11 (9)</td>
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</tr>
<tr>
<td>5</td>
<td>400 (15)</td>
<td>92 (11)</td>
<td>30 (13)</td>
<td>20 (17)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>364 (14)</td>
<td>133 (16)</td>
<td>43 (19)</td>
<td>17 (14)</td>
<td></td>
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<tr>
<td>7</td>
<td>356 (14)</td>
<td>140 (17)</td>
<td>26 (11)</td>
<td>6 (5)</td>
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</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Isolated aortocoronary bypass surgery, n (%)</td>
<td>1860 (71)</td>
<td>480 (58)</td>
<td>113 (50)</td>
<td>58 (49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Single valve surgery, n (%)</td>
<td>234 (9)</td>
<td>66 (8)</td>
<td>19 (8)</td>
<td>11 (9)</td>
<td></td>
</tr>
<tr>
<td>Other surgery, n (%)</td>
<td>537 (20)</td>
<td>283 (34)</td>
<td>96 (42)</td>
<td>50 (42)</td>
<td></td>
</tr>
<tr>
<td>Urgent surgery, n (%)</td>
<td>367 (14)</td>
<td>187 (23)</td>
<td>65 (29)</td>
<td>39 (33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Redo surgery, n (%)</td>
<td>175 (7)</td>
<td>90 (11)</td>
<td>33 (14)</td>
<td>22 (18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CPB duration, min</td>
<td>103±42</td>
<td>129±65</td>
<td>151±87</td>
<td>155±88</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Deep hypothermic circulatory arrest, n (%)</td>
<td>61 (2)</td>
<td>28 (3)</td>
<td>12 (5)</td>
<td>7 (6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Received aprotinin, n (%)</td>
<td>704 (27)</td>
<td>283 (34)</td>
<td>95 (42)</td>
<td>55 (46)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lowest hematocrit during CPB, %</td>
<td>24±3</td>
<td>23±4</td>
<td>23±4</td>
<td>22±4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median perioperative (day 0 or 1) RBC transfusion, U (Q1, Q3)</td>
<td>0 (0, 2)</td>
<td>2 (0, 4)</td>
<td>3 (1, 6)</td>
<td>4 (1, 7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Postoperative reexploration, n (%)</td>
<td>111 (4)</td>
<td>109 (13)</td>
<td>47 (21)</td>
<td>31 (26)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

INR indicates international normalized ratio of the prothrombin time; eGFR, estimated glomerular filtration rate.

*Comparisons between patients with ≤25% in eGFR and >25% in eGFR or on dialysis.
Continuous variables are shown as mean±SD unless otherwise stated.
delay the surgery until after the pump is explanted, and in high-risk patients who are anticipated to require prolonged CPB support, it may be possible to perform a less extensive surgery to reduce CPB duration. Use of aprotinin, a recently withdrawn antifibrinolytic drug that previously has been shown to be linked with renal dysfunction, was also independently but not strongly associated with AKI in the present study. Of note, we identified 3 potentially modifiable and interrelated variables that were independently and strongly associated with AKI. These variables were preoperative anemia, perioperative RBC transfusions, and postoperative reexploration. Before we explore the possible mechanisms by which these variables may contribute to kidney injury after cardiac surgery or the strategies by which they may be modified, it is first necessary to provide an overview of the pathogenesis of AKI in this setting.

Pathogenesis of AKI in Cardiac Surgery

An important cause of AKI in cardiac surgery, as well as in other settings, is cellular ischemia, which results in tubular epithelial and vascular endothelial injury and activation. Cardiac surgery heightens the risk of ischemic kidney injury by several processes. Normally, kidney perfusion is autoregulated such that glomerular filtration rate is maintained until the mean arterial blood pressure falls below 80 mm Hg. Mean arterial blood pressure during cardiac surgery is often at the lower limits or below the limits of autoregulation, especially during periods of hemodynamic instability. In addition, many cardiac surgery patients have impaired autoregulation due to existing comorbidities (eg, advanced age, atherosclerosis, chronic hypertension, or chronic kidney disease), administration of drugs that impact kidney autoregulation (eg, nonsteroidal antiinflammatory drugs, ACE inhibitors, angiotensin receptor blockers, and radiocontrast agents), or a proinflammatory state (see below). In patients with impaired autoregulation, kidney function may deteriorate even when the mean arterial blood pressure is within the normal range.

Another process by which cardiac surgery may contribute to ischemic kidney injury is by inciting a strong systemic inflammatory response. Proinflammatory events during cardiac surgery include operative trauma, contact of the blood components with the artificial surface of the CPB circuit,
ischemia-reperfusion injury, and endotoxemia.\textsuperscript{1,36,37} Inflammation plays a central role in the development of ischemic kidney injury,\textsuperscript{34,35} and it is thought that the systemic inflammatory response caused by cardiac surgery is similarly deleterious.\textsuperscript{1} Finally, cardiac surgery may further predispose patients to ischemic kidney injury through the generation of free hemoglobin and iron from hemolysis that occurs during CPB.\textsuperscript{1}

The present findings, as well as those of others, support the importance of these processes. Specifically, variables associated with impaired kidney perfusion, CPB duration, and hemodynamic instability have repeatedly (including in the present study) been shown to be associated with kidney injury after cardiac surgery.\textsuperscript{1}

Role of Anemia, RBC Transfusion, and Reexploration

The kidney can generally tolerate isolated insults such as hypoperfusion extremely well; for kidney injury to occur, a combination of several insults or risk factors, or multiple hits, is thought to be necessary.\textsuperscript{38} In cardiac surgery, anemia, RBC transfusion, and reexploration may represent the additional insults that culminate in AKI.

Anemia

We, and others, have shown that perioperative anemia in cardiac surgery is independently associated with various adverse outcomes, including kidney injury.\textsuperscript{15,39} Anemia may contribute to kidney injury by reducing renal oxygen delivery, worsening oxidative stress, and impairing hemostasis.

Tissue oxygen delivery is directly related to arterial oxygen content, which is primarily dependent on the hemoglobin concentration.\textsuperscript{40} Anemia would therefore decrease oxygen delivery to the kidneys, especially to the vulnerable renal medulla, where the normal partial pressure of oxygen in the renal tissue is very low.\textsuperscript{40} The adverse consequences of anemia are likely enhanced further during cardiac surgery, during which, for reasons outlined earlier, the kidney is more prone to renal hypoperfusion.\textsuperscript{35}

Anemia may enhance renal oxidative stress, because RBCs serve important antioxidant functions.\textsuperscript{40} Anemia impairs hemostasis because normal platelet function is dependent on the presence of an adequate (but as yet undetermined) hemoglobin concentration.\textsuperscript{41,42} In cardiac surgery, during which patients are already at increased risk for bleeding due to CPB-related hemostatic defects,\textsuperscript{43} the added burden of anemia-induced platelet dysfunction may lead to excessive bleeding, which in turn may necessitate multiple RBC transfusions and reexploration, both of which are associated with AKI.

RBC Transfusion

Although the intended therapeutic effect of RBC transfusion is to improve organ function by increasing tissue oxygen delivery, there is increasing evidence that transfused RBCs may actually contribute to organ injury in susceptible patients, likely because of changes that occur to RBCs during storage.\textsuperscript{44} During storage, RBCs become less deformable, undergo ATP and 2,3-diphosphoglycerate depletion, lose their ability to generate nitric oxide, have increased adhesive ness to vascular endothelium, release procoagulant phospholipids, and accumulate proinflammatory molecules, as well as free iron and hemoglobin.\textsuperscript{45–48} As a result, transfused stored RBCs may impair tissue oxygen delivery, promote a proinflammatory state, exacerbate tissue oxidative stress, and activate leukocytes and the coagulation cascade.\textsuperscript{45,46,48} In susceptible patients, such as those undergoing cardiac surgery, these changes can lead to organ dysfunction, with the kidney seemingly at particularly high risk for injury.\textsuperscript{44}

Reexploration

Surgical reexploration after cardiac surgery is independently associated with various adverse outcomes, including kidney injury.\textsuperscript{49} Although the mechanisms by which reexploration can cause kidney injury have not been fully elucidated, it is likely a safe assumption that they involve exacerbation of many of the factors outlined above, such as hemodynamic instability and operative trauma. Surgical reexploration is also inextricably linked to both anemia and RBC transfusion, because the principal reason for reexploration after cardiac surgery is coagulopathy (which is exacerbated by anemia), which leads to excessive blood loss (and massive RBC transfusion).\textsuperscript{43}

Clinical and Research Implications

If the observed association between these 3 factors—anemia, transfusion of stored RBCs, and coagulopathy requiring surgical reexploration—and AKI after cardiac surgery is causal, then it would follow that treating or avoiding these factors would reduce AKI after cardiac surgery. Several low-risk, low-cost, perioperative measures that can be readily implemented to help mitigate the occurrence or effects of these factors include preoperative discontinuation of drugs that impair coagulation, minimization of bloodletting and hemodilution, expedient surgery, administration of anti fibrinolytic drugs, and aggressive investigation and treatment of excessive blood loss. Other potential measures include use of intravenous iron or erythropoietin-stimulating agents to treat anemia before surgery, limiting RBC transfusions to units that have been stored for short durations, or administering hemostatic agents such as recombinant activated factor VII early in the course of blood loss. Because of their high costs, unproven effectiveness, possible risks, and logistical issues related to their implementation, however, the safety, efficacy, and cost-effectiveness of these measures must be assessed before their routine use can be considered.

Study Limitations

There are several limitations to be considered when interpreting the present study. First, postoperative renal function was estimated with the Cockcroft-Gault equation, which uses serum creatinine and weight (as a measure of muscle mass) to estimate renal function after surgery.\textsuperscript{18} During the postoperative period, however, these estimates may not be accurate because of imbalances between creatinine production and elimination, which can be caused by various factors, including changing renal function, muscle breakdown and injury, liver dysfunction, and various medications.\textsuperscript{50} Second, because only patients undergoing cardiac surgery with CPB were included in the present study, our results cannot be
generalized to other populations. Third, because this was a retrospective observational study, causality could not be determined. Thus, it is quite possible that AKI does not increase the risk of death but is simply associated with death. It is also possible that modifying any of the identified risk factors for AKI will not influence the risk of AKI. Fourth, the effects of unknown or unmeasured confounders on the observed associations between the risk factors and AKI (eg, perioperative use of nephrotoxic drugs), as well as between AKI and death (eg, liver dysfunction), cannot be ruled out. Fifth, neither the cause nor the duration of preoperative anemia, each of which has prognostic implications, was known. Sixth, the duration of follow-up was limited to the period of hospitalization. Thus, postdischarge complications could not be accounted for in the present analysis.

Conclusions
This multicenter, retrospective study found 3 potentially modifiable, interrelated risk factors—preoperative anemia, perioperative RBC transfusions, and postoperative reexploration—that were independently associated with AKI after cardiac surgery. Future studies should determine the benefits of therapies aimed at mitigating these factors.

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Disclosures
None.

References
Acute kidney injury (AKI) after cardiac surgery is a serious complication that is closely associated with postoperative death. In previous studies that evaluated risk factors for AKI, most of the identified risk factors were not modifiable (e.g., diabetes mellitus, preexisting kidney disease). In the present multicenter study of 3500 adult patients undergoing cardiac surgery in 2004, we focused on identifying potentially modifiable risk factors for postoperative AKI. We found that AKI, as defined by consensus-based criteria (≥25%, ≥50%, and ≥75% decrease in estimated glomerular filtration rate or need for dialysis within 1 week of surgery), was independently associated with a >4-fold increase in death rates. Three common and potentially modifiable variables (preoperative anemia, red blood cell transfusions, and surgical reexploration) were highly associated with AKI, even after adjustment for other perioperative risk factors (e.g., preoperative intra-aortic balloon pump, cardiopulmonary bypass duration). Given these results, we propose that randomized trials are now needed to determine whether interventions that modify these risk factors might also prevent AKI after cardiac surgery.
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