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***Original Article** / Özgün Makale*

Mitral and aortic valve surgery-related acute kidney injury: affecting factors and its one year follow-up

Mitral ve aort kapak cerrahisi ile ilişkili akut böbrek hasarı: Etkileyen faktörler ve bir yıllık sonuçları

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ABSTRACT

Background: This study aims to investigate the prevalence of acute kidney injury after isolated cardiac valve surgery, and to identify risk factors and one-year follow-up results.

Methods: Between January 2008 and December 2014, a total of 220 patients (106 males, 114 females; mean age 50.6±14.7 years; range 14 to 79 years) who underwent aortic and mitral valve surgery were retrospectively reviewed. Baseline characteristics of the patients, comorbidities, operative variables, and postoperative outcomes were recorded. The patients were divided into two groups as those with and without acute kidney injury, as assessed by preoperative and postoperative creatinine levels using the Acute Kidney Injury Network Criteria.

Results: Of all patients, 57 developed acute kidney injury. Of these, 12 patients required hemodialysis (stage 1, n=40; stage 2, n=12; stage 3, n=5). The patients with acute kidney injury tended to be older with a higher rate of diabetes mellitus. These patients also had higher rates of postoperative sepsis, bleeding revision, atrial fibrillation, and need for intra-aortic balloon pump with longer intensive care unit and hospital stay. A higher number of patients with acute kidney injury needed packed red blood cell transfusion, compared to those without.

Conclusion: Our study results show that acute kidney injury which is diagnosed with mild postoperative creatinine changes according to the Acute Kidney Injury Network criteria is a prognostically important complication. Age, diabetes mellitus, and blood transfusion are the main risk factors of postoperative acute kidney injury. Therefore, patients should be analyzed carefully preoperatively to prevent short- and long-term results of cardiac surgery-related acute kidney injury.

Keywords: Acute kidney injury; cardiac valve surgery; postoperative morbidity.

ÖZ

Amaç: Bu çalışmada izole kalp kapak cerrahisi sonrası akut böbrek hasarının prevalansı araştırıldı ve risk faktörleri ve bir yıllık takip sonuçları belirlendi.

Çalışma planı: Ocak 2008 - Aralık 2014 tarihleri arasında aort ve mitral kapak cerrahisi yapılan toplam 220 hasta (106 erkek, 114 kadın; ort. yaş 50.6±14.7 yıl; dağılım 14-79 yıl) retrospektif olarak incelendi. Hastaların başlangıç özellikleri, eşlik eden hastalıkları, cerrahi parametreleri ve cerrahi sonrası sonuçları kaydedildi. Hastalar Akut Böbrek Hasarı Ağı Kriterleri kullanılarak cerrahi öncesi ve sonrası kreatinin değerleri ile değerlendirildiği üzere, akut böbrek hasarı olanlar ve olmayanlar olarak iki gruba ayrıldı.

Bulgular: Tüm hastaların 57'sinde akut böbrek hasarı gelişti. Bu hastaların 12'sinde hemodiyaliz ihtiyacı oldu (evre 1, n=40; evre 2, n=12; evre 3, n=5). Akut böbrek hasarı gelişen hastalar, daha yüksek diabetes mellitus oranı ile daha yaşlı olma eğilimindeydi. Bu hastalarda cerrahi sonrası sepsis, kanama revizyonu, atriyal fibrilasyon ve intraaortik balon pompası ihtiyacı oranları daha yüksek ve yoğun bakım ünitesinde ve hastanede kalış süresi daha uzundu. Akut böbrek hasarı gelişmeyen hastalara kıyasla, gelişen hastalarda, daha fazla eritrosit transfüzyonu gerekli oldu.

Sonuç: Çalışma sonuçlarımız, Akut Böbrek Hasarı Ağı kriterlerine göre cerrahi sonrası hafif düzeyde kreatinin değişiklikleri ile tanılanan akut böbrek hasarının prognoz açısından önemli bir komplikasyon olduğunu göstermektedir. Yaş, diabetes mellitus ve kan transfüzyonu cerrahi sonrası akut böbrek hasarının başlıca risk faktörleridir. Kalp cerrahisi ile ilişkili akut böbrek hasarının erken ve geç dönem sonuçlarının önlenmesi için hastalar cerrahi öncesinde dikkatlice değerlendirilmelidir.

Anahtar sözcükler: Akut böbrek hasarı; kalp kapak cerrahisi; cerrahi sonrası morbidite.

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Acute kidney injury (AKI), which is associated with a high rate of short-term mortality, morbidity, and prolonged length of hospital stay, is an important complication after cardiac surgery.[1,2] Its incidence varies from 5 to 30% after cardiothoracic surgery.[3] There is little interest on the postoperative incidence and perioperative factors to be considered to prevent this complication in the literature.

There are many indicators which show kidney injury such as cystatin-C, N-acetyl-beta-D-glucosaminidase, neutrophil gelatinase-associated lipocalin, and serum creatinine (sCr); however, the latter is the most common indicator of the kidney injury.[4] Acute kidney injury may occur in a range from minimal elevation in sCr to anuria. Currently, many studies have shown that mild changes in sCr levels can be associated with high morbidity and mortality rates in the early and late postoperative period, and even after discharge from hospital with cardiac and renal recovery.[3,5] In recent years, several studies have addressed to the definition of AKI and certain criteria have been developed to define AKI and to monitor the severity of the disease, including Renal Risk, Injury, Failure, Loss of Kidney Function, End-stage Renal Disease (RIFLE) and the latest Acute Kidney Injury Network Criteria (AKIN), which focuses on mild sCr changes, have been shown to be more sensitive and specific, compared to the RIFLE.[6-8]

Although coronary artery bypass grafting (CABG) is a risk factor for AKI, cardiac valve surgery has a higher risk for postoperative AKI.[9] However, there is a limited number of studies in the literature investigating AKI in patients undergoing isolated cardiac valve surgery. In this study, we aimed to investigate the prevalence of AKI after isolated cardiac valve surgery, and to identify risk factors and one-year follow-up results.

PATIENTS AND METHODS

A total of 220 patients (106 males, 114 females; mean age 50.6±14.7 years; range 14 to 79 years) undergoing isolated mitral and aortic valve replacement between January 2008 and December 2014 were retrospectively analyzed. All patients met standard indications for surgery due to mitral valve and aortic valve diseases. The study protocol was approved by the Izmir Katip Celebi University Local Ethics Committee (IKCU, 199/17.09.2015). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Baseline demographic characteristics of the patients, body mass index, comorbidities, operative variables (i.e., cross-clamp time, total bypass time), preoperative ejection fraction, preoperative and postoperative hematological and biochemical profiles (i.e., sCr, hemoglobin), the amount of intra- and postoperative packed red blood cell transfusions, and postoperative outcomes were recorded.

The primary endpoints were as follows: development of AKI and one-year renal function following cardiac valve surgery. Acute kidney injury was defined by AKIN criteria,[7] as follows: stage 1: an increased postoperative sCr level of ≥1.5, but <2 times, compared to baseline; stage 2: an increased postoperative sCr level of ≥2, but <3 times, compared to baseline; and stage 3: an increased postoperative sCr level of ≥3 times, compared to baseline. The patients were, then, divided into two groups as those with AKI [AKI (+)] and without AKI [AKI (-)], based on the development of AKI within the first five days of surgery using the highest postoperative sCr levels.

Estimated glomerular filtration rate (eGFR) was also used to assess one-year follow-up of renal function and the eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[10] The eGFR was identified using postoperative fifth day, first, third, and sixth month, and first year sCr levels for survivors within this time period. The patients who were preoperatively on dialysis and patients who underwent an additional surgical intervention with mitral or aortic valve surgery such as CABG, tricuspid valve repair, left atrial ablation, combined aortic and mitral valve surgery or infective endocarditis were excluded from the study.

Postoperative complications including atrial fibrillation, intra-aortic balloon pump catheter placement, or bleeding revision, the length of stay in the intensive care unit and hospital, and in-hospital mortality were also evaluated.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean and standard deviation, median, frequency, and percentage. The Kolmogorov-Smirnov test was used to analyze the distribution of the variables. Baseline, operative, and postoperative characteristics and outcomes were compared between AKI (+) and AKI (-) patients using the Mann-Whitney U and chi-square tests. The Wilcoxon tests and Mann-Whitney U test were used to compare the difference between pre and post measurements of creatinine and eGFR levels, intraoperative and postoperative red packed cell transfusion amounts, and preoperative and postoperative hemoglobin levels between the groups. Chi-square test or Fisher's test was used for analyzing of the qualitative data. A p value of <0.05 was considered statistically significant.

RESULTS

Of all patients, 110 (50%) underwent aortic valve replacement and 110 (50%) underwent mitral valve replacement. Of all patients, 52% were females. The mean cross-clamp time was 59.8±16.4 min, while the mean total bypass time was 89.2±19.6 min. The baseline characteristics of the patients are summarized in Table 1.

Of 220 patients, 57 (26%) developed AKI, of which 12 (21%) required renal replacement therapy. Forty patients (18%) had stage 1 AKI, 12 (5%) had stage 2 AKI, and five (2%) had stage 3 AKI. There were no significant differences in the prevalence of AKI between patients who had aortic valve replacement and mitral valve replacement. However, the patients with AKI tended to be older than those without AKI (57.9±12.9 years vs 48.1±14.5 years; p=0.000). There was no significant difference in the gender, preoperative ejection fraction values, body mass index, cross-clamp time, total bypass time, pre- and postoperative lowest hemoglobin levels, and body temperature during cardiopulmonary bypass between the groups (p>0.05). However, the patients with AKI had a higher rate of diabetes mellitus (p=0.042), although AKI was not found to be associated with other preoperative risk factors such as peripheral and cerebrovascular disease, chronic pulmonary disease, and prior history of cardiac catheterization (Table 2).

There were no significant differences in preoperative creatinine levels between the two groups. In AKI (+) patients, postoperative creatinine levels were significantly higher, compared to AKI (-) patients. In AKI (-) patients, postoperative creatinine levels were significantly higher, compared to baseline levels; however, there was no significant difference at one, three, and six months, and one year, compared to baseline levels. On the other hand, in AKI (+) patients, sCr levels increased at one, three, and six months, and one year, compared to baseline levels (Table 3).

In addition, in AKI (+) group, eGFR values decreased at one, three, and six months, and one year, compared to baseline levels (p<0.05). In AKI (-) patients, postoperative eGFR values decreased, compared to baseline eGFR; however, there was no significant

Table 1. Baseline characteristics of the patients

	n	%	Mean±SD	Median	Min.-Max.
Age (years)			50.6±14.7	49.5	14.0-79.0
Gender					
Female	114	52			
Male	106	48			
Cross-clamp time			59.8±16.4	58.0	25.0-114.0
Cardiopulmonary bypass time			89.2±19.6	88.0	46.0-162.0
Temperature			28.4±0.8	28.0	26.0-30.0
Body mass index			27.1±5.7	27.0	17.0-41.0
Ejection fraction			56.7±8.5	60.0	15.0-70.0
Intraoperative hemoglobin			24.2±3.7	24.0	15.0-32.0
Length of stay in intensive care unit			3.4±2.6	3.0	0.0-25.0
Length of stay in hospital			9.2±5.3	7.0	0.0-43.0
In hospital mortality	20	9			
Operation					
Aortic valve replacement	110	50			
Mitral valve replacement	110	50			
Acute kidney injury					
Negative	163	74			
Positive	57	26			
Stage					
1	40	18			
2	12	5			
3	5	2			

SD: Standard deviation; Min.: Minimum; Max.: Maximum.

Table 2. Patient's operative characteristics and postoperative outcomes

	AKI (-)				AKI (+)				
	n-%	Mean±SD	Median	Min.-Max.	n-%	Mean±SD	Median	Min.-Max.	*p*
Age (years)		48.1±14.5	47	14-79		57.9±12.9	60	19-78	0.000
Gender									
Female	86-53				28-49				0.636
Male	77-47				29-51				
Cross-clamp time		59.1±16.7	58	29-114		61.6±15.2	60	25-101	0.204
Cardiopulmonary bypass time		87.6±19.3	87	46-162		93.9±19.9	90	57-149	0.051
Temperature		28.5±0.9	28	26-30		28.3±0.7	28	27-30	0.136
Body mass index		27.1±5.5	27	16-41		27.2±6.3	27	2-39	0.524
Ejection fraction		57.0±8.0	60	25-70		55.8±9.8	60	15-65	0.706
Intraoperative hemoglobin		24.4±3.6	24	16-32		23.5±4.0	23	15-31	0.203
Length of stay in intensive care unit		3.0±1.8	3	0-18		4.6±4.1	3	0-26	0.004
Length of stay in hospital		9.0±5.2	7	0-43		9.7±5.4	9	0-27	0.217
In hospital mortality									
Negative	159-97				41-72				0.000
Positive	4-3				16-28				
Operation									
Aortic valve replacement	83-51				27-47				0.644
Mitral valve replacement	80-49				30-53				
Mechanical valve	135-83				37-65				0.005
Need for dialysis	3-2				12-21				0.000
Diabetes mellitus	15-9				11-19				0.042
Peripheral arterial disease	7-4				2-4				0.797
Cerebrovascular disease	18-11				7-12				0.800
COPD	40-25				15-26				0.790
Cardiac catheterization	12-7				5-9				0.731
Sternal infection	0-0				1-2				0.059
Stroke	3-2				2-4				0.606
Sepsis	12-7				14-25				0.001
Bleeding revision	17-10				19-33				0.000
Postoperative AF	17-10				15-26				0.003
Intra-aortic balloon pump	4-2				11-19				0.000

AKI: Acute kidney injury; SD: Standard deviation; Min.: Minimum; Max.: Maximum; COPD: Chronic obstructive pulmonary disease; AF: Postoperative atrial fibrillation; Mann-Whitney U test/Chi-square test (Fisher test).

difference at one, three, and six months, and one year, compared to baseline values (Table 3). One-year eGFR follow-up results of the patients are shown in Figure 1.

The patients with AKI also had more complicated postoperative course. They had higher postoperative sepsis rates, bleeding revision, postoperative atrial fibrillation, need for intra-aortic balloon pump, and renal replacement therapy. These patients had also longer intensive care unit stay compared to those without (4.6±4.1 days vs 3.0±1.8 days; p=0.004); however, there was no significant difference in the in-hospital stay length between the groups. In addition, AKI (+) group also had higher in-hospital mortality rates (p=0.000). Considering the intra- and postoperative blood transfusion rates, the amount of transfused packed red blood cells was higher in AKI (-) group, than AKI (+) group (0.7±1.2 in AKI (-) vs 2.3±1.7 in AKI (+) group; p=0.000, for total transfusion values) (Table 4).

DISCUSSION

Acute kidney injury, which is associated with even mild changes in sCr in the postoperative period, is a significant risk factor for short- and long-term mortality.[11] Despite its significance, mild changes in sCr may be commonly overlooked by surgeons in the postoperative period. Patients who develop AKI and fully recover during the postoperative period have also an increased mortality risk during 10-year follow-up.[3] In a study investigating AKI after all types of cardiac surgery showed that 44% of patients with AKI survived, compared to 63% of patients without AKI at 10 years.[3,11]

Acute kidney injury risk after cardiac surgery is also higher due to high inflammatory potential during cardiac surgery.[3] However, it varies among surgical

Tablo 3. The comparison of the creatinine and estimated glomerular filtration rate levels between acute kidney injury (-) and acute kidney injury (+) patients

	AKI (-)			AKI (+)			
	Mean±SD	Median	Min.-Max.	Mean±SD	Median	Min.-Max.	*p*
Creatinine							
Preoperative	0.9±0.5	0.8	0.5-6.0	1.0±0.5	0.8	0.5-3.2	0.797
Postoperative	1.0±0.7*	0.9	0.6-3.9	2.1±1.6*	1.6	0.8-10.9	0.000
Month 1	0.9±0.5	0.8	0.5-5.0	1.2±0.8*	1.0	0.6-5.3	0.000
Months 3	0.9±0.3	0.8	0.5-4.0	1.1±0.7*	1.0	0.6-4.6	0.004
Months 6	0.9±0.4	0.8	0.5-5.0	1.0±0.5*	1.0	0.5-3.5	0.014
Year 1	0.9±0.5	0.8	0.6-5.5	1.0±0.5*	0.9	0.6-3.5	0.005
eGFR							
Preoperative	91.9±23.5	96	12-145	84.1±24.2	84	16-131	0.022
Postoperative	83.9±25.1*	85	15-136	40.3±17.3*	40	5-78	0.000
Month 1	93.2±24.3	97	14-139	69.6±24.9*	69	10-124	0.000
Months 3	93.8±23.3	98	19-139	74.8±22.6*	78	12-128	0.000
Months 6	93.6±23.4	96	14-138	77.8±22.1*	83	18-134	0.000
Year 1	93.2±23.5	97	13-138	77.8±19.9*	82	17-128	0.000

AKI: Acute kidney injury; SD: Standard deviation; Min.: Minimum; Max.: Maximum; * The difference according preoperative level; eGFR: Estimated glomerular filtration rate; Mann-Whitney U test/Wilcoxon test.

interventions in cardiac surgery. Several studies have shown that cardiac valve surgery has a higher AKI risk than CABG and aortic surgery.[3,12] Some authors have claimed that this high risk may be explained with high congestive heart failure risk during pre- and postoperative period due to valve disease.[3,9] In our study, we only analyzed AKI risk after aortic and mitral valve replacement and we excluded combined CABG and valve surgery, combined valve surgery,

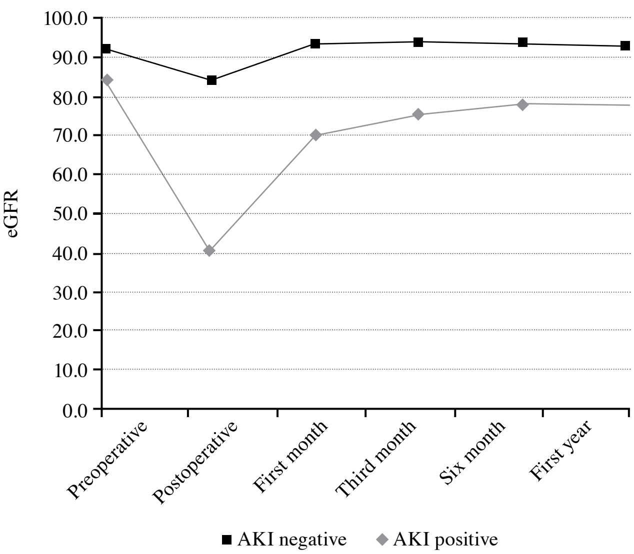

Figure 1. One year estimated glomerular filtration rate (eGFR) follow-up results between acute kidney injury (-) and acute kidney injury (+) patients.

aortic surgery, and left atrial ablation due to extra-inflammatory capacity of these interventions in the pre- and postoperative period. Therefore, we had a homogeneous pre- and postoperative risk potential.

The studies which investigated AKI risk after CABG showed an AKI incidence of 10 to 14%.[13-15] Several studies investigated AKI after all types of cardiac surgery interventions, such as CABG, valve surgery, and combined surgery reported an AKI incidence ranging from 30 to 43%.[16,17] Mao et al.[18] investigated 209 patients who underwent aortic, mitral, tricuspid, and combined valve operations. The authors reported the AKI risk to be 46%. In another study, Najjar et al.[19] investigated a total of 2,169 patients who underwent aortic valve replacement. In their study population, AKI occurred in 8.5% of patients (stage 1: 67%; stage 2: 23%; stage 3: 10%). In our study, we found an AKI incidence of 26% (stage 1: 70%; stage 2: 21%; and stage 3: 9% of the AKI (+) patients). These results show that isolated CABG has the lowest AKI risk. If the rate of combined cardiac surgery increases, AKI risk may also increase. Isolated valve surgery has the lower AKI risk, compared to combined valve intervention.

Furthermore, AKI risk is closely associated with preoperative risk factors.[4] Preoperative comorbidities and intraoperative factors are of utmost importance and they may be modifiable factors for developing AKI.[5] Karkouti et al.[16] described major risk factors of AKI as follows: intraoperative mean arterial pressure, pre- and intraoperative anemia, need for intraoperative

Tablo 4. The comparison of the preoperative/postoperative hemoglobin levels and number of intraoperative/postoperative transfused packed red blood cell

	AKI (-)			AKI (+)			
	Mean±SD	Median	Min.-Max.	Mean±SD	Median	Min.-Max.	*p*
Preoperative hemoglobin	12.8±1.6	13	9-18	12.3±1.8	12	9-17	0.073
Postoperative hemoglobin	10.2±1.4*	10	7-14	10.1±1.6*	10	7-14	0.509
Intraoperative transfusion	0.1±0.4	0.0	0.0-2.0	0.3±0.6	0.0	0.0-2.0	0.008
Postoperative transfusion	0.6±1.1	0.0	0.0-6.0	2.0±1.6	2.0	0.0-7.0	0.000
Total transfusion	0.7±1.2	0.0	0.0-6.0	2.3±1.7	2.0	0.0-7.0	0.000

AKI: Acute kidney injury; SD: Standard deviation; Min.: Minimum; Max.: Maximum; * The difference according preoperative level; Mann-Whitney U test/Wilcoxon test.

red blood cell transfusion, and pre- and intraoperative proinflammatory activity due to other organic diseases. Considering the comorbidities, there is a number of studies showing that diabetes mellitus, chronic obstructive pulmonary disease, high body mass index, congestive heart failure, and cardiopulmonary bypass time are important factors for AKI development.[16,19] In our study, we found a higher rate of diabetes mellitus in AKI (+) group with an older age. Other preoperative comorbidities were not related with AKI in our study. We also observed no significant difference in preoperative hemoglobin levels between the groups; however, intra- and postoperative amount of packed red blood cell transfusion were higher in AKI (+) patients, compared to AKI (-) patients. These results are also consistent with the literature data.[16,17,19]

Furthermore, cardiac surgery and cardiopulmonary bypass are significant factors which increase inflammatory activity due to artificial surface and ischemia reperfusion injury.[20] In patients with other active organic problems in addition to this inflammatory activity, such as AKI, lung injury, or sepsis and in patients with a high blood transfusion rate, prolonged ventilation time, and re-exploration in the postoperative period, postoperative morbidity and mortality increase.[20,21] There are several studies showing that postoperative AKI is associated with worse postoperative early and late outcomes.[3] Patients with AKI in the postoperative period have a higher infection and sepsis rate with longer intensive care unit stay and higher mortality rate, while they need more intra-aortic balloon pump and inotropic support.[19,22-25] Consistent with the previous findings, we found higher sepsis and postoperative atrial fibrillation rates in AKI (+) patients. Our patients with AKI also needed more intra-aortic balloon pump and renal replacement therapy during the postoperative course. They had also longer intensive care unit stay and higher in-hospital mortality rates. However, length of in-hospital stay did not significantly differ between the groups. In addition, a higher number of patients with AKI underwent postoperative bleeding revision.

Acute kidney injury occurs even with mild changes in the postoperative sCr and sCr normalizes in the short-term follow-up.[11] Despite early normalization of sCr, some studies have shown that renal blood flow and clearance function can remain impaired.[3] This can explain high morbidity and mortality rates in the long-term follow-up and may be the reason of developing chronic kidney disease.[3,16] Thakar et al.[26] investigated the effects of renal dysfunction on mortality in patients with renal dysfunction after cardiac surgery, but not requiring dialysis during the postoperative period. The authors reported equal to or more than 30% decline in the postoperative GFR values, compared to baseline. This decline in the GFR was found to be associated with a six-time higher mortality risk during long-term follow-up. In our study, we retrospectively analyzed survivors for one year. We found a decline in the eGFR values both in the AKI (-) and AKI (+) groups in the postoperative period. Nevertheless, this decline was not so prominent to cause AKI in -as the name implies- AKI (-) group. No significant changes were observed at the one, three, and six months, and one year, compared to baseline values. In AKI (+) group, eGFR values were always significantly lower, compared to previous time points, suggesting that postoperative AKI is a progressive disorder.

In conclusion, isolated cardiac valve surgery has higher acute kidney injury risk than isolated coronary artery bypass grafting; however, it did not significantly differ, compared to combined cardiac surgical interventions. Diabetes mellitus is a significant preoperative risk factor for isolated cardiac valve replacement. Age, diabetes mellitus, and blood transfusion are the main risk factors of postoperative acute kidney injury. Therefore, patients should be analyzed carefully preoperatively to prevent short- and long-term results of cardiac surgery-related acute kidney injury. Finally, it must be kept in mind by surgeons that even mild changes in serum creatinine levels may indicate acute kidney injury in the postoperative period and its effect may be progressive or even irreversible.

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