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Risk Factors and Hospital Outcomes of Acute Kidney Injury in Patients Operated on for an acquired Valvular Heart Disease

Aim	To determine predictors of acute kidney injury (AKI) related with surgeries for correction of acquired valvular heart disease (HD) and to evaluate the incidence of in-hospital complications in patients with postoperative AKI.
Material and Methods	This study included 62 patients after surgery for correction of acquired valvular HD (mean age, 61±10.9 years) with a disease duration of 11±5.3 years. NYHA functional class (FC) 1 chronic heart failure (CHF) was observed in 1.6% of patients, FC 2 in 64.5%, and FC 3 in 33.9%.17.7% of patients had chronic kidney disease (CKD). Coronary lesions of ≥50% of vascular lumen were detected in 27.4% of patients. Surgical correction of mitral valvular disease was performed in 32 cases, aortic valvular disease in 36 cases, tricuspid valvular disease in 8 cases, and combined operations for correction of valvular disease and coronary bypass in 8 cases. Creatinine concentrations were measured according to the Jaffe method; glomerular filtration rate (GFR) was estimated with the CKD-EPI equation. AKI was diagnosed based on KDIGO (2012) criteria.
Results	The AKI incidence related with surgeries for correction of valvular HD was 16.1% (8.1% of patients had stage 1 AKI, 3.2% had stage 2 AKI, and 4.8% had stage 3 AKI), and 3.2% required kidney replacement therapy. AKI was associated with the presence of CKD at baseline (p=0.044), development of hemopericardium requiring drainage (p=0.012), more pronounced coronary lesions (in the AKI group: stenoses from 50 to 70% in 20% of patients, from 70 to 90% in 30% of patients, and ≥90% in 0%; without AKI: from 50 to 70% in 13.4% of patients, from 70 to 90% in 3.8%, and ≥90% in 5.8% of patients, respectively; p=0.032). Probability of postoperative AKI significantly increased with the development of hemopericardium requiring drainage. Patients with postoperative AKI compared to persons without AKI had higher mortality (20% and 0%; p=0.001), greater incidence of decompensated CHF (40 and 9.6%; p=0.012) and hemopericardium requiring drainage (30 and 1.9%; p=0.012).
Conclusion	The development of postoperative AKI is associated with CKD at baseline, more pronounced coronary injury, and hemopericardium requiring drainage.

Keywords	Surgical correction of valvular heart diseases; acute kidney injury; postoperative in-hospital complications
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Open-heart surgery remains the leading treatment method for severe heart valve disease despite the introduction of mini-invasive endovascular techniques into clinical practice. Cardiac surgery may be accompanied by complications, such as acute kidney injury (AKI).

AKI associated with cardiac surgery has long been known. It has been shown that even a small transient decrease in kidney function in the early postoperative period is associated with an unfavorable prognosis, namely an increased risk of hospital and long-term complications, including death [1–3].

In 2012, the KDIGO (Kidney Disease Improving Out – comes) experts developed a clinical guideline for the evaluation and management of AKI [4]. The guideline outlines the main risk factors (RFs), leading pathophysiological mechanisms, prevention and management strategy for patients with AKI. The question is whether the use of new knowledge has significantly reduced the number of cases and hospital outcomes of AKI associated with cardiac surgery. It is also important to identify new factors that can cause AKI in patients who have undergone cardiac surgery.

Objective

Identify predictors of AKI associated with surgeries performed to correct acquired heart valve disease and assess the incidence of hospital complications in patients with postoperative AKI.

Material and methods

The study included patients with acquired heart valve disease of various origin who were hospitalized for surgical treatment. Indications for surgical correction of heart valve disease were determined in accordance with the 2017 ESC/EACT guideline [5].

The exclusion criteria were the age of 80 years and more, a less than 2-month history of myocardial infarction (MI) and stroke, repeat valve replacement, required replacement of the ascending aorta, erosive gastritis and exacerbation of peptic ulcer disease, elevated glucose levels (more than 12–14 mmol/L) in patients with diabetes mellitus (DM), acute or exacerbated chronic inflammatory diseases, severe liver, kidney, lung diseases, chronic kidney disease (CKD) stage IV–V, terminal chronic heart failure (CHF).

The study included 62 hospitalized patients who underwent surgical correction of acquired heart valve disease. There were 29 male (46.8%) and 33 female (53.2%) patients. The mean patient age was 61±10.9 years, the duration of the disease was 11±5.3 years. The causes of heart valve disease were rheumatic heart disease in 19 (30.6%) patients, infectious endocarditis in 4 (6.5%) patients, degenerative process 39 (63%) patients including 4 patients with a bicuspid aortic valve (AV).

Patients were examined before surgery (complete blood count and urinalysis, biochemical blood test, electrocardiography, echocardiogram, esophagogastroduodenoscopy, ultrasound examination of the brachiocephalic arteries and lower limb arteries and veins, coronary artery angiography (CAG) using a Philips Polidiagnos C angiographic device following the Judkins technique (1967).

Angioplasty and coronary artery stenting had been previously performed in 3 (4.8%) patients. According to the preoperative CT data, hemodynamically significant CA involvement (>70% of the vessel lumen) and ≥50% of the vessel lumen, were found in 8 (12.9%) and 17 (27.4%) patients, respectively. A history of MI was established in 4 (6.5%) patients. CHF (NYHA) FC I was present in 1 (1.6%) patient, FC II in 40 (64.5%) patients, FC III in 21 (33.9%) patients. Arterial hypertension (AH) was detected in 50 (80.6%) patients, carbohydrate metabolism disorders – 8 (12.9%), including DM – 5 (glycated hemoglobin 6.3±0.61%), obesity grade I–II – 21 (32.9%) patients. There were 4 (7.8%) smokers.

CKD (glomerular filtration rate (GFR) <60 mL/min/1.73 m^2) was detected in 11 (17.7%) patients. The causes of CKD were diabetic nephropathy (n=1), chronic glomerulonephritis (n=2), shrunken kidney in renal artery stenosis (n=2), primary shrunken kidney in AH (n=3), urolithiasis (n=3). Patients with CKD had creatinine levels 100±11.4 mkmol/L and GFR 53.6±4.98 mL/min/1.73 m^2. Permanent and paroxysmal atrial fibrillation (AF) was registered in 13 (21%) and 7 (11.3%) patients, respectively.

The dimensions of the heart chambers shown by echocardiography were the following: left atrium – 4.8±0.92 cm, right ventricle – 2.4±0.51 cm, left ventricular (LV) end-diastolic dimension – 5.5±0.90 cm, LV end-diastolic volume – 154±57 mL, LV end-systolic volume 61±33 mL, interventricular septal thickness – 1.2±0.3, LV posterior wall thickness –1.1±0.2 cm. Left ventricular ejection fraction (LVEF) was 61±9.4% (Simpson method).

Before surgery, beta-blockers were administered by 42 (67.7%) patients, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers by 38 (61.3%) patients, calcium channel blockers by 5 (8.1%), and statins by 20 (32.2%) patients.

Mitral valve, aortic valve, and tricuspid valve surgeries were performed in 32, 36, and 8 cases, respectively. Single valve correction was performed in 49 (79%) patients, double valve correction in 12 (19.4%) patients, triple valve correction in 1 (1.6%) patient, simultaneous surgery for heart valve disease and coronary artery bypass surgery (CABG) in 8 (12.9%) patients. Heart valve replacement was conducted in 59 (95.2%) patients, and combined valve replacement and plasty was performed in 3 (4.8%) patients. Mechanical valve prostheses (mainly On-X, On-X Life Technologies, USA; MedtronicHall, Medtronic, USA; SJM Regent, St Jude Medical, USA; MedInj, Russia) were implanted in 32 (51.6%) cases and biologicalvalve prostheses (mainly Biocor, St Jude Medical, USA) in 30 (48.4%) cases.

The surgery was performed with general anesthesia via median sternotomy and using cardiopulmonary bypass and mechanical ventilation with cold cardioplegia. The surgery lasted for 239±56 min, the duration of cardiopulmonary bypass and aortic occlusion was 125±44 min and 89±32 min, respectively. Mean intraoperative blood loss was 258±163 mL. On day 1 after surgery, glycemia was 11.2±3.3 mmol/L. Vasopressor and inotropic drugs were administered to 44 (70.9%) patients to maintain normal hemodynamics during surgery and in the early postoperative period.

Blood levels of creatinine were determined on the Synchron CX Systems device using the Jaffen technique, at baseline, daily in the first 7 days after surgery, and later, if necessary. GFR was calculated using the CKD-EPI formula. CKD was diagnosed if GFR was <60 mL/min/1.73 m^2 [6]. AKI onset and severity were assessed following the KDIGO criteria (2012) by an increase in creatinine levels after surgery compared with the baseline values [4]. The difference between the

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highest creatinine level after surgery and the baseline value was calculated for each patient. AKI stage I was diagnosed if creatinine increased after surgery by more than 26.5 mkmol/L

or 1.5–1.9-fold from the baseline, AKI stage II with creatinine levels 2–2.9 times higher than at baseline, AKI stage III with creatinine levels elevated by 353.6 mkmol/L or more or 3 times and more above the baseline levels. Glucose blood levels were was determined electrochemically using chip sensors on the BIOSEN C-line Clinic device at baseline, repeatedly on day 1 after surgery, and later, if necessary. Electrocardiogram was registered at baseline and daily after surgery. Continuous ECG monitoring was performed while patients stayed in intensive care unit.

The following hospital complications were registered: AKI, all-cause death, paroxysmal AF, stroke, decompensated CHF, pericardial drainage for hemopericardium. Decompensated CHF was established by the need for intravenous or intramuscular administration of furosemide. The incidence of in-hospital outcomes was assessed by the composite endpoint, which included death, decompensated CHF, paroxysmal AF, and required pericardial drainage for hemopericardium.

The study protocol was approved by the ethics committee of the Tyumen State Medical University. All patients signed the informed consent to participate in the study.

Statistical processing of the data obtained was carried out using the SPSS software suite. Depending on the type of data distribution, the results were presented as M±SD, where M is the arithmetic mean and SD is the standard deviation, or as the median (Me) and the values of the 25th and 75th percentiles. The Kolmogorov-Smirnov test was used to assess the normality of the data distribution. The level of the Kolmogorov-Smirnov test >0.05 corresponded to the normal distribution of variables and <0.05 to the non-normal distribution. Depending on the type of data distribution, the two-tailed Student's test or the Mann-Whitney test was used to assess the statistical significance of the inter-group differences. Qualitative data were compared using the chi-square test and the Fisher exact test. The Wilcoxon test was used to assess the differences between the pretreatment and post-treatment values. When CAG results were entered into the database, the severity of coronary artery stenosis were evaluated: 50–70% stenosis was scored 1, 70–90% stenosis – 2, stenosis of 90% and more – 3. The number of coronary arteries with ≥50% stenosis and the severity of coronary involvement were estimated. Logistic regression analysis was used to identify predictors of AKI. First, a univariate analysis was performed to identify indicators associated with AKI. The indicators with statistically significant differences were included in a stepwise logistic regression analysis, an odds ratio (OR) with a 95% confidence interval (CI) was evaluated. Differences between the indicators were considered statistically significant with $p<0.05$.

Results

According to the KDIGO criteria (2012) [4], AKI developed in 10 (16.1%) of 62 patients who underwent surgery to correct acquired heart valve disease, with AKI stage I in 5 (8.1%) patients, AKI stage II in 2 (3.2%) patients, and AKI stage III in 3 (4.8%) patients. Mean creatinine blood levels did not change significantly after surgery compared to the baseline levels, 87±13.4 mkmol/L and 84.0 [69.3; 99.4] mkmol/L, respectively (p=0.877). Creatinine blood levels increased statistically significantly in patients with AKI after the intervention compared to the baseline, 95±12.7 mkmol/L and 246±153 mkmol/L, respectively (p=0.005). Renal replacement therapy (RRT, hemofiltration) was required in 2 (3.2%) patients with severe AKI, the others had transient AKI, creatinine blood levels returned to the baseline values before discharge from the hospital.

The main RFs of AKI associated with cardiac surgery are elderly age, female sex, reduced LVEF, CHF FC III–IV, DM, CKD, combined surgical operations (heart valve correction and CABG), duration of cardiopulmonary bypass and aortic occlusion, acute heart failure, blood loss, hyperglycemia, and some others [7]. Stepwise multivariate logistic regression analysis was performed to identify predictors of postoperative AKI. First, a univariate regression analysis was carried out. The entire sample of patients was divided into two groups: Group 1 with postoperative AKI (n=10), Group 2 without AKI (n=52). The statistical significance of differences was assessed between these groups of patients in clinical, biochemical, echocardiographic, angiographic characteristics, surgical intervention indicators, glycemia levels on day 1 after surgery, pharmacotherapy, including the frequency of the administration of vasopressor and inotropic drugs to stabilize hemodynamics. The analysis included 68 indicators. The parameters with statistically significant differences between the analyzed groups are presented in Table1.

According to the results obtained, the presence of background CKD (GFR<60 mL/min/1.73 m^2), hemopericardium requiring drainage, more severe coronary artery lesions were the factors associated with the development of postoperative AKI. The volume of the pericardial fluid in the group of patients with AKI (n=3)

and without AKI (n=1) was 400 [250; 400] mL and 250 mL, respectively (p=0.317).

The indicators with statistically significant differences found by the univariate analysis were included in the stepwise multivariate regression analysis. The results of the analysis are provided in Table[2].

The multivariate logistic regression analysis showed that hemopericardium requiring drainage was the most significant factor contributing to the onset of postoperative AKI. The development of a hemopericardium requiring drainage increased a mean of 21-fold the probability of postoperative AKI.

We analyzed the incidence of in-hospital complications in patients who underwent surgical correction of acquired heart valve disease. There were 2 (3.2%) cases of death (on day 10 and day 14 after surgery due to multiple organ failure; extracorporeal membrane oxygenation was performed in one case, RRT in both cases), 9 (14.5%) cases of decompensated CHF, pericardial drainage for hemopericardium in 4 (6.4%) cases, and paroxysmal AF in 19 (30.6%) patients. Pericardial drainage was performed on day 1–3 after surgery, the volume of pericardial effusion was 325 [250; 400] mL. The percentage of patients with in-hospital outcomes (death, decompensated CHF, pericardial drainage for hemopericardium, paroxysmal AF) was 45.2% (n=28).

The incidence of postoperative complications was also analyzed in the groups of patients with and without AKI. The results are presented in Table.3.

As seen in Table[3], mortality was higher (p=0.001) and there was a higher percentage of patients with decompensated CHF (p=0.012) and hemopericardium requiring drainage (p=0.012) in the group of patients with postoperative AKI compared with patients without AKI. The percentages of patients with postoperative paroxysmal AF did not differ significantly (p=0.961). There were no cases of stroke in our study. The cumulative incidence of postoperative complications, including cases of death, paroxysmal AF, decompensated CHF and hemopericardium requiring drainage, was statistically significantly higher in the group of patients with AKI (p=0.016).

Table 1. Indicators associated with AKI developing after with surgical correction of acquired heart valve disease based on the results of the univariate regression analysis

Parameter	Group		p
	Patients with AKI (n=10)	Patients without AKI (n=52)	
Hemopericardium requiring drainage	3 (30%)	1 (1.9%)	0.012
The number of coronary arteries with stenosis according to CAG:			
• from 50 % to 70 %	2 (20%)	3 (30%)	
• from 70 % to 90 %	7 (13.4%)	2 (3.8%)	0.032
• 90 % and more	0	3 (5.8%)	
Background CKD	4 (40%)	7 (13.5%)	0.044

AKI, acute kidney injury; CAG, coronary angiography; CKD, chronic kidney disease.

Table 2. Predictors of AKI associated with surgical correction of acquired heart valve disease

Predictor	β	Wald	OR	95% CI	p
Hemopericardium requiring drainage	3.045	6.083	21	1.868–236	0.014

β is a coefficient reflecting the strength and direction of the connection; Wald is a criterion that characterizes the contribution of the predictor to the predictive ability of the model; OR is the odds ratio; CI is the confidence interval.

Table 3. In-hospital postoperative complications in patients with AKI associated with surgical correction of acquired heart valve disease and patients without AKI

Parameter	Patients with AKI (n=10)	Patients without AKI (n=52)	p
Decompensated CHF	4 (40 %)	5 (9.6 %)	0.012
Deaths	2 (20 %)	0	0.001
Paroxysmal AF after cardiac surgery	3 (30 %)	16 (30.8 %)	0.961
Hemopericardium requiring drainage	3 (30 %)	1 (1.9 %)	0.012
Death, paroxysmal AF, decompensated CHF, pericardial drainage	8 (80 %)	20 (38.5 %)	0.016

AKI, acute kidney injury.

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Discussion

AKI is a common complication of cardiac surgery with unfavorable short-term and long-term prognosis [1–3]. There are quite a lot of known RFs of AKI associated with cardiac surgery (age, female sex, AH, DM, duration of cardiopulmonary bypass and aortic occlusion, blood loss, etc.) [7]. We obtained no data on the relationship of these RFs with the development of AKI after surgical correction of acquired heart valve disease. According to the results of our study, background CKD, more severe coronary artery lesions and hemopericardium requiring drainage the factors associated with postoperative AKI.

CKD is one of the most significant RFs of AKI [6]. Even if kidney function is recovered after AKI, patients face an increased risk of the development and progression of CKD and cardiovascular diseases [6]. Thus, our findings on higher incidence of postoperative AKI among patients with previous CKD fully are quite consistent with the literature.

According to the KDIGO guideline (2012), the presence of chronic heart diseases is another RF contributing to the development of AKI [6]. This provision of the KDIGO guideline (2012) is confirmed by the association of postoperative AKI with more severe coronary artery lesions shown by CAG, which was identified in our study.

As for the relation of postoperative AKI with hemopericardium requiring drainage, it was revealed by us for the first time. There are no reports in the available literature that hemopericardium may be a RF predisposing to postoperative AKI.

According to the results of logistic regression analysis, among all the identified factors associated with postoperative AKI, the cases of hemopericardium requiring drainage were most significant. At the same time, the probability of postoperative AKI increased a mean of 21-fold if hemopericardium requiring drainage developed.

The revealed relationships between postoperative AKI and cases of hemopericardium requiring drainage can be interpreted in two ways. On the one hand, severe hemopericardium can cause a decrease in cardiac output and blood pressure, hemodynamic instability, hypoperfusion and hypoxia of organs and tissues, including kidneys, and thus the development of AKI. On the other hand, hemopericardium may be a consequence of AKI, since the incidence of hemorrhagic complications is well known to be higher in patients with renal dysfunction [8]. It is not possible to identify causal relationships in this case due to the fact that the diagnosis of AKI was based in our study on changes in creatinine levels, which increases rather late during the development of this complication.

In our small study, the number of cases of AKI associated with surgeries for heart valve correction was 16.1%, and the need for RRT was 3.2%. The data on the need for RRT due to the development of AKI after the CWC obtained in this work are quite consistent with the results of other authors (from 0.3 to 5.7%), including major foreign studies [1, 2, 9, 10]. The data we obtained on the frequency of AKI associated with CWC also correspond to the literature data. For example, in large studies by K. Karkouti et al. (2009), A. M. Robert et al. (2010), M. Che et al. (2011), which included 3500, 25086, and 1056 patients, respectively, the incidence of AKI after cardiac surgery was 10%, 30%, and 31%, respectively [11–13]. At the same time, there is an opinion that the incidence of postoperative AKI probably not only did not decrease but even slightly increased in the period from 2012 (after the publication of the KDIGO guideline) to 2021 due to higher age and prevalence of concomitant pathology in patients undergoing surgery.

The analysis of hospital complications in patients who underwent surgery to correct acquired heart valve disease showed that mortality was 3.2%, and AKI (16.1%), paroxysmal AF (30.6%), and decompensated CHF (14.5%) were the most frequent complications.

It should be noted that mortality was low in the group of patients who underwent surgery for acquired heart valve disease (3.2%), but it was 20% in patients with postoperative AKI, i.e., 6.3 times higher. Other researchers [2, 3] report similar data on a multiple increase in 30 day mortality (3–18 times) in patients with AKI after surgical correction of heart valve disease; and the higher the severity of AKI, the higher was the risk of death. A. Lassnigg et al. [2] showed that a slight postoperative increase in creatinine levels up to 0.5 mg/dL was associated with 3 times higher 30 day mortality and a more than 0.5 mg/dL increase with 18 times higher 30 day mortality. In the study by M. Che et al. [13], hospital mortality was 4.9% in AKI stage I, 12.1% in AKI stage II, and 48.7% in AKI stage III.

Cases of decompensated CHF and hemopericardium requiring drainage were statistically significantly more frequent among patients with postoperative AKI than those without AKI. The mechanism of decompensated CHF in AKI is well known: AKI-associated oligouria and anuria lead to the retention of sodium and fluid in the body, volume overload of the heart, and decompensated CHF [4].

We have identified for the first time a higher frequency of cases of hemopericardium requiring drainage among patients with AKI that developed after surgical correction of heart valve disease. Possible mechanisms of the

relationship between postoperative AKI and cases of hemopericardium have been described above.

According to our findings, cardiac arrhythmias, such as paroxysmal AF, were a frequent postoperative complication. There were no statistically significant differences between the groups of patients with and without postoperative AKI (p=0.961), although there are data in the literature on a higher incidence of paroxysmal AF among patients with AKI developed after cardiac surgery. For example, M.J. Albarani et al. [14] and R.R. Ng et al. [15] established a higher frequency of paroxysmal AF in patients with postoperative AKI. The mechanisms of the relationship between postoperative AKI and paroxysmal AF remain understudied. The authors suggest that this fact may be associated with a more severe inflammatory reaction (high production of cytokines, complement components) and oxidative stress, lower activity of the antioxidant system in patients with postoperative AKI [15].

It seems important that postoperative AKI increases the risk of cardiovascular complications. In our study, the composite endpoint (death, paroxysmal AF, decompensated CHF, hemopericardium requiring drainage) was almost 2 times higher in patients with postoperative AKI than those without AKI (80% and 38.5%, respectively; p=0.016). Our findings are quite consistent with the literature data evidencing an unfavorable hospital prognosis, namely, an increased risk of cardiovascular and hemorrhagic complications and fatal outcomes in patients with postoperative AKI associated with cardiac surgery [1–3].

There is still a long way to go in completely solving the problem of AKI associated with cardiac surgery. We fully agree in this regard with Y. Wang и R. Bellomo [16] who say that the existing prevention and treatment strategies for postoperative AKI are immature and require further development.

Conclusion

Acute kidney injury (according to the 2012 KDIGO criteria) developed after surgical correction of acquired valvular heart disease in 16.1% of patients, and the need for renal replacement therapy appeared in 3.2% of patients. The development of postoperative acute kidney injury is associated with background chronic kidney disease, more severe coronary artery lesions, and hemopericardium requiring drainage. The probability of postoperative acute kidney injury increases statistically significantly with the development of hemopericardium requiring drainage. Patients with postoperative acute kidney injury had higher mortality, higher incidence of decompensated chronic heart failure and hemopericardium requiring drainage.

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