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Acute Renal Injury in Cardiac Surgery Patients

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BACKGROUND Acute kidney injury following cardiac surgery remains a common and serious complication.

AIM OF STUDY To identify risk factors for the development and morphological features of acute renal injury, to assess the use of renal replacement therapy in patients after cardiac surgery.

MATERIAL AND METHODS The study involved 66 patients who were treated in the Department of Cardiac Resuscitation of the N.V. Sklifosovsky Research Institute for Emergency Medicine from 2009 to 2018. Of these, 45 men (68.2%) and 21 women (31.8%). The mean age of the patients was 56.3±13.2 years. Clinical and anatomical analysis of material from 19 deceased patients was carried out. Depending on the use of methods of renal replacement therapy, patients were divided into two groups: Group 1 included 23 patients with acute renal injury (ARI) requiring the use of renal replacement therapy; Group 2 included 43 patients where methods of renal replacement therapy were not used.

RESULTS Hospital mortality in Group 1 was lower (34.8 and 41.9%, respectively), however, the differences were statistically insignificant (p=0.372). To identify the factors in the development of acute renal damage, a stepwise regression analysis was performed by constructing a regression model of Cox proportional hazards. Age, history of chronic kidney disease, serum creatinine level on the first day after surgery, severity of the condition according to the APACHE-II scale, increased lactate level on day 2 of the postoperative period, decreased urine output on the first day after surgery were statistically significant.

Conclusion Risk factors for the development of ARI after cardiac surgery under cardiopulmonary bypass are advanced age, CKD in history, the severity of the patient's condition, assessed by the APACHE-II scale, increased serum creatinine on the first day after surgery, increased lactate on day 2 of the postoperative period, a decreased diuresis on day 1 after surgery. The use of RRT in patients after surgery under the conditions of AC was accompanied by a tendency to improve treatment results: in-hospital mortality in the group of patients who underwent RRT was 34.8% versus 41.9% in the group without RRT methods. Morphological and functional features of renal failure in patients with ARI were preceding chronic renal pathological processes of different etiology, mainly affecting the glomeruli, vessels and stroma, as well as acute pathological processes aggravating ARI (dyscirculatory disorder, degenerative changes, necrosis and necrobiosis tubular epithelium).

Keywords: acute kidney damage, risk factors, cardiac surgery, renal replacement therapy, morphology

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CABG – coronary artery bypass grafting
RRT – renal replacement therapy
AC – artificial circulation
K-M – analysis of patient survival using the Kaplan-Meier method
AKI – Acute Kidney Injury
CKD – Chronic Kidney Disease
EuroSCORE – European Score for Cardiac Operative Risk Evaluation
U – nonparametric Mann-Whitney test
NGAL – lipocalin associated with neutrophil gelatinase

INTRODUCTION

Acute kidney injury (AKI) after cardiac surgery remains a common and serious complication. According to the literature, the incidence of AKI varies from 5.0 to 7.5% in hospitalized patients receiving emergency care, and can reach 22–47% in patients in the intensive care unit. AKI is associated with significant mortality (23–41%), especially in patients requiring renal replacement therapy (RRT), and often leads to the development of chronic kidney disease (CKD) [1–5]. Identification of risk factors for AKI is necessary to improve early diagnosis and development of methods for the prevention of AKI in patients after cardiac surgery.

Purpose of the study: identification of risk factors for the development and morphological features of AKI, assessment of the use of RRT methods in patients after cardiac surgery.

MATERIAL AND RESEARCH METHODS

The study involved 66 patients (45 men (68.2%) and 21 women (31.8%)) who were treated in the Cardiac Resuscitation Department of the N.V. Sklifosovsky Research Institute for Emergency Medicine from 2009 to 2018. The average age of the patients was 56.3 ± 13.2 years. The patients underwent the following operations (Table 1): 4 patients underwent coronary artery bypass grafting (CABG), 20 – isolated heart valve replacement, 9 – combined operations– heart valve replacement and CABG; 3 – operations for thoracic aorta dissection, 30 – heart transplantation.

Table 1
Distribution of studied patients by type of surgery

Operation	The number of patients, n (%)	Mortality, n (%)
Coronary artery bypass grafting	4 (6.1%)	1 (25%)
Isolated heart valve replacement	20 (30.3%)	15 (75%)
Combined surgeries: prosthetics of heart valves and coronary artery bypass grafting	9 (13.6%)	9 (100%)
Surgery for thoracic aortic dissection	3 (7.6%)	2 (66.7%)
Heart transplantation	30 (46.9%)	0
Total	66	27 (40.9)

In the postoperative period, all the studied patients underwent prolonged artificial lung ventilation, infusion of catecholamines, 3 patients needed extracorporeal membrane oxygenation.

Depending on the need for RRT in the postoperative period, patients are divided into groups:

Group 1 (n = 23) – patients with AKI requiring RRT;

Group 2 (n = 43) – patients in whom RRT methods did not used.

Twenty three patients of the 1st group underwent 57 procedures of permanent RRT. The method was carried out in the modes of prolonged and long-term hemodiafiltration, hemodialysis, hemofiltration on Aquarius devices from Nikkiso, Japan [6, 7]. The duration of the procedures was 41.0 (16.0; 82.0) hours, the dose of permanent RRT was 35.0 (27.7; 45.4) ml / kg / h. Laboratory blood tests included biochemical parameters (urea, creatinine, electrolytes, blood gases) [8]. Blood samples were taken before and after surgical treatment, as well as on the 1st, 2nd, 3rd and 5th days.

All studies were performed in clinical diagnostic laboratories using unified methods. The assessment of the severity of the patient's condition was carried out using scale APACHE-II [9], using the worst indicators within 24 hours from the moment of the operation, the operational risk was assessed according to the operational risk scale EuroSCORE-II (European Score for Cardiac Operative Risk Evaluation) [10]. Using these scales, the likelihood of death was also assessed.

Additionally, a clinical and anatomical analysis of sectional material from 19 deceased patients was carried out. For histological examination, well-known methods were used, in a number of observations, in addition, staining for fibrin was used.

The results were statistically processed using the SPSS 19.0 (SPSS, Inc.) and STATISTIKA 12.0 (Stat.Soft, Inc.) programs. All samples were checked for normal distribution using the Kolmogorov-Smirnov test. The median and interquartile range, mean value and standard deviation were calculated. To compare variables with normal distribution, we used the paired Student's t-test (for independent samples). With a distribution other than normal, the nonparametric Mann – Whitney test was used for unconnected samples (U). Для анализа выживаемости больных использовали метод Каплана-Майера (K-M). Chi-square (χ2) test was used to compare nominative data. Particular importance was attached to the calculation of the relative risk of death (OR), for which the Cox regression model with proportional risks was used. The results obtained were considered statistically significant at the level $p < 0,05$.

RESULTS

Comparison of groups in terms of clinical indicators is given in table. 2.

Table 2

Comparison of studied groups

Indicators	Group 1 (n=23)	Group 2 (n=43)	p	Criterion
Age, years	60.0 (54; 63)	55.0 (47; 67)	0.014	U
Gender, m/f	17/6	28/15	0.465	χ2
APACHE-II, score	22.0 (19; 25)	18.5 (14; 22)	0.0025	U
Predicted mortality,%	42.4 (32.2; 53.0)	30.7 (18.6; 42.4)	0.0027	U
EuroSCORE-II, score	14.0 (11; 17)	14.0 (12; 15)	0.66	U
28-day mortality, n (%)	8 (34.8 %)	15.0 (34.9 %)	0.812	K-M
Hospital mortality, n (%)	8 (34.8%)	18 (41.9%)	0.372	K-M
Length of stay of surviving patients in the hospital, days	40 (31; 60)	24 (21; 34)	0.0132	U

Note: Data are presented as median and interquartile range (25th and 75th percentiles), χ2 – chi-square test, K-M – Kaplan-Meier method, n – number of patients, U – nonparametric Mann-Whitney test

As you can see from the table. 2, the groups did not differ statistically significantly by gender. The age of patients in group 1 was statistically significantly higher than in group 2 - 60.0 (54; 63) and 55.0 (47; 67) years, respectively. Also in group 1, the severity of the condition according to the APACHE-II scale was statistically significantly higher - 22.0 (19; 25) and 18.5 (14; 22) points. The assessment of operational risk on the EuroSCORE-II scale did not differ statistically significantly in both groups, the median was 14 points. Despite the fact that in the 1st group the predicted mortality was 42.4%, the 28-day mortality was 34.8%, in the 2nd group the predicted mortality was lower than the 28-day: 30.7% and 34, 9% respectively. The differences in 28-day mortality were statistically insignificant (Fig. 1).

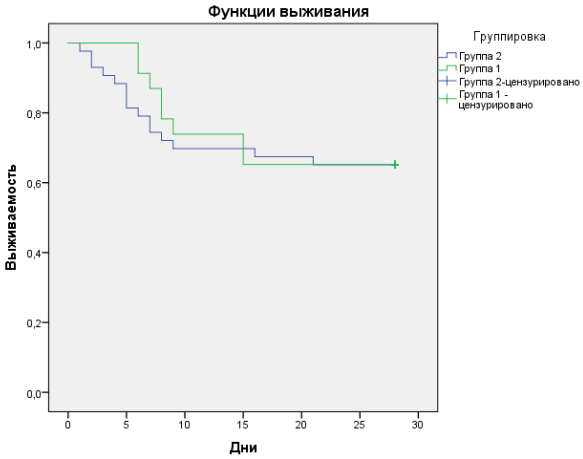

Fig. 1. The function of survival (28 days) depending on the use of RRT

When comparing hospital mortality in both groups, statistically insignificant differences were revealed in the 1st and 2nd groups: 34.8% and 41.9%, respectively (p=0,372). Thus, the use of RRT in patients after cardiac surgery was accompanied by a tendency to improve treatment results, in particular in the group of initially more severe patients. RRT makes it possible to maintain an adequate water-electrolyte balance and the level of catabolism, contributes to the correction of systemic inflammation, which ultimately, possibly, contributes to the improvement of treatment results.

In order to identify risk factors for the development of AKI requiring RRT, an intergroup analysis of the effect of CKD, arterial hypertension and type 2 diabetes mellitus, the use of X-ray contrast agents before surgery, the duration of surgery, the duration of artificial circulation, the duration of aortic clamping and the volume of intraoperative blood loss was carried out (Table. 3).

Table 3

Comparison of the studied groups by risk factors for ARI development

Indicators	Group 1 (n=23)	Group 2 (n=43)	p	Criterion
Surgery duration, minutes *	**345.0 (280; 378)**	**315 (270; 360)**	**0.821**	**U**
AC duration, minutes *	**170.0 (121; 215)**	**167.0 (137; 208)**	**0.994**	**U**
Duration of aortic clamping, minutes *	**97.0 (78; 168)**	**134.0 (82; 186)**	**0.379**	**U**
Blood loss volume, ml *	**2000 (1300; 2800)**	**2000 (1500; 2500)**	**0.469**	**U**
Diabetes mellitus, n (%)	**11 (47.8%)**	**10 (23.3%)**	**0.041**	**χ2**
X-ray contrast study before surgery, n (%)	**14 (60.9%)**	**20 (46.5%)**	**0.266**	**χ2**
Arterial hypertension degree 3, stage 3, n (%)	**19 (82.6%)**	**29 (67.4%)**	**0.187**	**χ2**
CKD, n (%)	**15 (65.2%)**	**17 (39.5%)**	**0.047**	**χ2**

Note: * Data are presented as median and interquartile range (25% and 75% percentiles), χ2 – chi-square test, n – number of patients, U – nonparametric Mann-Whitney test

It has been established that diabetes mellitus and history of CKD are statistically significant predictors of AKI with the need for RRT. Moreover, as can be seen from the table. 3, the groups did not differ statistically significantly in the duration of the operation, AC, the duration of aortic clamping and the volume of intraoperative blood loss. В 1-й группе чаще выполняли рентгенконтрастные исследования (60,9% и 46,5% соответственно), однако различия были статистически незначимыми.

To identify statistically significant factors in the development of AKI, a step-by-step regression analysis was carried out by constructing a regression model of Cox proportional hazards (Table. 4). As you can see from the table. 4, the statistically significant risk factors were age - (OR = 1.096), history of CKD - (OR = 3.225), serum creatinine level on the first day after surgery (OR = 1.012), severity of the condition on the APACHE-II scale (OR = 1.171), an increase in blood lactate levels on the 2nd day of the postoperative period (OR = 1.221) and a decrease in the rate of diuresis on the first day after surgery (OR = 0.999). According to the regression analysis, diabetes mellitus was not a statistically significant predictor of AKI.

Table 4

Multivariate analysis of risk factors for ARI development: Cox proportional hazards regression model

Variables	Coefficient	R	Odds ratio (OR)	95% CI
Patient age	0.036	0.035	1,096	(1.003-1.073)
Duration of surgery	0.003	0.180	1.003	(0.999-1.007)
Duration of mechanical ventilation	0.023	0.414	1.023	(0.969-1.081)
AC duration	- 0.01	0.852	0.999	(0.992-1.006)
Duration of aortic clamping	- 0.06	0.057	0.994	(0.987-1.000)
The volume of intraoperative blood loss	0.000	0.170	1,000	(1,000-1,001)
Serum creatinine level before surgery	0.004	0.511	1.004	(0.992-1.016)
Serum creatinine levels after surgery	0.012	0.023	1.012	(1.002-1.023)
History of type 2 diabetes mellitus	0.725	0.093	2,064	(0.887-4.804)
History of CKD	1.171	0.013	3.225	(1,286-8,085)
X-ray contrast examination before surgery	- 0.290	0.504	0.748	(0.319-1.752)
Risk level according to APACHE-II	0.158	0.003	1.171	(1.055-1.300)
Risk level according to EuroSCORE - II	- 0.008	0.926	0.992	(0.845-1.166)
Preoperative urea levels	0.26	0.613	1.026	(0.928-1.135)
Postoperative urea levels	0.088	0.064	1.092	(0.995-1.198)
Lactate level 1 day after surgery	0.054	0.291	1.055	(0.955-1.166)
Lactate level 1 day after surgery	0.200	0.032	1.221	(1.018-1.465)
Oxygenation index	- 0.003	0.076	0.997	(0.995-1.000)

Diuresis on day 1	- 0.001	0.001	0.999	(0.999-1.000)
Diuresis on day 2	0.000	0.038	1.000	(0.999-1.000)
Intravenous infusion volume per day	0.000	0.511	1.000	(1.000-1.000)

Динамика клинико-лабораторных показателей у пациентов до операции и на 1-е, 2-е, 3-и и 5-е сутки послеоперационного периода представлена в табл. 5.

Table 5

Dynamics of clinical and laboratory parameters depending on the groups of patients with ARI

Indicators	Group	Research stages				
		Initially	Day 1	Day 2	Day 3	Day 5
Creatinine in serum (mmol / L) **	1	118.9 (95; 135)	144.5 * (128; 176)	208.3 * (172; 279)	218 * (175; 319)	184.5 (167; 209)
	2	97.5 (84; 121)	126.5 (95; 149)	122.0 (93; 178)	130 (89; 189)	133 (87; 232)
Diuresis (ml / day) **	1	-	1695 * (1250; 2450)	1300 * (720; 2600)	1250 * (450; 2500)	700 (150; 2910)
	2	-	2625 (1750; 4000)	2500 (1690; 3300)	2300 (1900; 3420)	2100 (1350; 2700)
Blood potassium (mmol / L) **	1	-	4.27 ± 1.12	4.59 ± 1.02	4.70 ± 0.92 *	4.5 ± 0.71
	2	-	4.17 ± 1.01	4.17 ± 0.64	4.05 ± 0.85	4.1 ± 0.61
Urea (mmol / L) **	1	9.8 ± 5.3	12.5 ± 4.7 *	15.7 ± 7.2 *	19.0 ± 8.7	24.8 ± 12.5
	2	7.6 ± 2.7	8.6 ± 2.7	11.8 ± 4.7	14.7 ± 6.3	18.3 ± 9.8

Note:

* statistically significant differences compared with the second group ($p < 0.05$);

** with normal distribution, the values are presented as $M \pm \sigma$, t- test was used for independent samples; with a distribution other than normal, the median and interquartile range were used (25 % and 75 % percentiles)

As you can see from the Table 5, the level of creatinine in the blood before the operation compared with normal values was increased in both groups: by 48.6% in the 1st group and by 21.8% in the 2nd group. In the postoperative period, an increase in the level of creatinine in the blood serum was noted in patients of both groups, which reflected the development of AKI against the background of CKD.

In the 1st group, an increase in the level of creatinine in the blood was noted within 24 hours by 22.5%, and within 48 hours – by 75.0% of the initial, while by the end of the 2nd day, 95% of patients had already undergone RRT.

In patients of the 2nd group, an increase in the level of creatinine in the blood was noted by 29.7% and 25.1%, respectively. By the 3rd day, the median was 130.0 μmol / L.

Despite the RRT, the groups differed statistically significantly in the level of creatinine in the blood on the 1st, 2nd and 3rd days, which remained higher in the 1st group. By the 5th day, the creatinine level decreased in the 1st group, while the median was 184.5 μmol / L.

On the 3rd day of the postoperative period, the groups differed statistically significantly in the rate of urine output, the level of potassium in the blood plasma and the concentration of urea in the blood.

Clinical and anatomical analysis of the sectional material of 19 deceased patients after cardiac surgery revealed the following changes in the glomeruli: glomerulosclerosis – in 11 patients (57.9%), a secondary contracted kidney – in 4 (21.5%), minor changes – in 4 (21, 5 %); and changes in tubules: necronephrosis – in 16 (59.3%), dilatation – in 15 (55.6%), degenerative changes in nephrocytes – in 11 (40.7%). In 8 out of 9 deceased patients with type 2 diabetes mellitus, changes in the glomeruli were found in the form of focal thickening of the basement membranes of glomerular capillaries, proliferation of the mesangium, as well as nodular glomerulosclerosis and lipo-hyaline calyxes in individual glomeruli, pathognomonic for diabetes mellitus.

In 3 cases out of 9, against the background of a chronic pathological process in patients with type 2 diabetes mellitus, gross discirculatory processes with fibrin thrombi in glomerular capillaries were noted and in one of them - with a small form of cortical necrosis (Fig. 2).

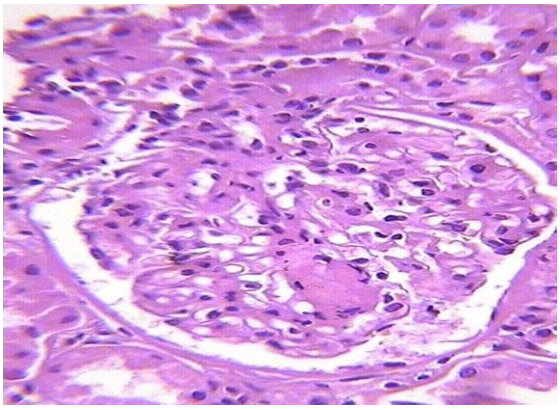

Fig. 2. Mixed diffuse-nodular form of glomerulosclerosis. Magnification x200. Stained with hematoxylin and eosin

In other deceased patients, sclerosis and glomerular hyalinosis, expressed in varying degrees, sectoral sclerosis and signs of chronic pyelonephritis were also noted (Fig. 3). Дистрофические изменения нефроцитов, как очагового, так и диффузного характера, были отмечены у всех умерших. Also, morphological signs of acute renal failure were identified: dilatation of nephrons, partial and widespread necrosis of the cytoplasm of nephrocytes with sequestration into the lumen and flattening of the epithelium, dyscirculatory disorders. Autopsy revealed in 2 deceased ischemic necrosis of the skeletal muscles of the back and pigment casts in the lumen of a small part of the nephrons (myoglobinuric nephrosis).

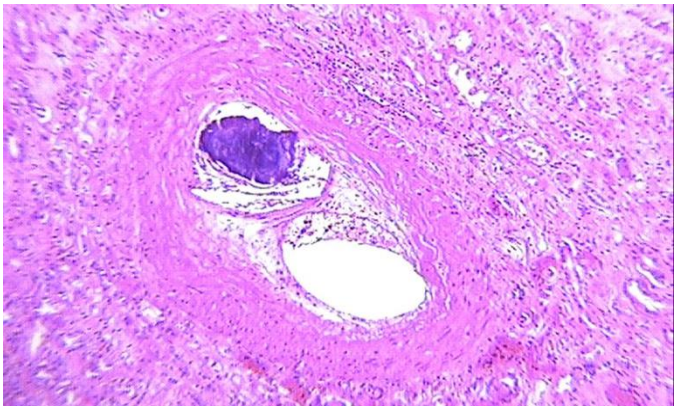

Fig. 3. Sclerotic vascular changes. Magnification x100. Stained with hematoxylin and eosin

DISCUSSION

In studies published in recent years, the incidence of AKI in patients after heart surgery with the use of infrared is from 5 to 42% and is accompanied by an increase in the risk of death by 3–8 times, an extension of the time spent in the intensive care unit and hospital, as well as a significant increase in the cost treatment [11]. Thus, in a meta-analysis published in 2016, among 3521 patients who underwent cardiac surgery under conditions of cardiopulmonary bypass, AKI developed in 27.8% of cases, accompanied by a statistically significant increase in the relative risk of an unfavorable outcome [12]. According to a study conducted in Finland, AKI was diagnosed in 28.7% of patients on the 1st day after cardiac surgery under conditions of cardiopulmonary bypass, in the first 3 days, AKI was noted in more than 80%, and 2.8% of patients needed OST [13].

The first stage of AKI is associated with an increase in the relative risk of death in regression analysis in 3.3% (1.8–6.1%), stage 2 – in 5.8% (2.7–12.1%), 3 stage – in 7.9% (3.5-17.6%). In multivariate regression analysis, the risk factors for AKI are advanced age, a history of CKD, the use of furosemide and vasopressors in the postoperative period, and a body mass index of more than 30 kg / m2.

A number of studies have shown that even a slight increase in serum creatinine (as a surrogate marker for a decrease in glomerular filtration rate) from normal values is reliably accompanied by an increase in mortality [14].

One of the main problems in the early diagnosis of AKI is the absence of a highly sensitive and, first of all, specific biomarker of renal damage – "renal troponin". Serum creatinine only measures changes in kidney function and is influenced by age, gender, race, muscle size, catabolism, and hydration levels. This marker poorly predicts the degree of renal damage in the early stages of the disease due to the fact that its value begins to increase only after dysfunction of more than 50% of the nephrons, and changes in plasma concentration may be significant only after 48 hours.

Today, the following AKI biomarkers are most commonly used in scientific and clinical practice:

— Neutrophil Gelatinase Associated Lipocalin (NGAL). As AKI develops, NGAL is filtered but not reabsorbed in the proximal tubules and collecting ducts. A meta-analysis published in 2016 showed that NGAL is not an effective marker of AKI in sepsis [15];

— cystatin C is a 13 kDa protein. Studies in patients undergoing cardiac surgery under cardiopulmonary bypass have shown that a 50% increase in cystatin C levels can predict AKI 48 hours before an increase in serum creatinine;

— interleukin-18 (IL-18) - biomarker of AKI after cardiopulmonary bypass, acute pulmonary injury and kidney transplantation in pediatric practice;

— issue inhibitor of metalloprotease-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP7), determined in urine. The meta-analysis noted a low specificity of biomarkers contained in plasma and urine for the diagnosis of AKI in cardiac patients operated on under cardiopulmonary bypass, especially after 24 hours after surgery [16].

As you can see, today there is no single biomarker that would prove its effectiveness in clinical practice. Existing biomarkers are located in different parts of the nephron, due to which different mechanisms of kidney damage are accompanied by different changes in their concentration [17].

CONCLUSION

The results obtained confirm the need to take into account the risk factors for the development of acute renal damage in patients undergoing cardiac surgery under extracorporeal circulation, constant monitoring of the serum creatinine level in the blood and the rate of urine output in order to detect early signs of the development of acute renal damage and to make a timely decision on the initiation of renal replacement. therapy. It is advisable to use biomarkers of acute renal injury to identify the risk group in patients planned for surgical treatment in conditions of artificial circulation, to predict the severity of acute renal injury and the need for renal replacement therapy.

FINDINGS

1. Risk factors for the development of acute renal injury after cardiac surgery under cardiopulmonary bypass are: old age, a history of chronic kidney disease, the severity of the patient's condition, assessed by the APACHE-II scale, an increased level of serum creatinine on the first day after surgery, an increase in blood lactate on the 2nd day of the postoperative period and a decrease in the rate of urine output on the first day after surgery.

2. The use of renal replacement therapy in patients after surgery under cardiopulmonary bypass is accompanied by a tendency to improve treatment results: hospital mortality in the group of patients who received renal replacement therapy was 34.8% versus 41.9% in the group without renal replacement therapy.

3. The morphological and functional features of renal failure in patients with acute renal injury were previous chronic pathological processes in the kidneys of various etiologies with a predominant lesion of the glomeruli, blood vessels and stroma, as well as acute pathological processes that aggravate acute renal damage (dyscirculatory disorders, degenerative changes, necrosis and necrobiosis of the epithelium).

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