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DIFFERENTIAL APPROACH OF CONTINUOUS AND INTERMITTENT RENAL REPLACEMENT THERAPY APPLYING IN CARDIAC SURGERY ACUTE KIDNEY INJURY

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ДИФЕРЕНЦІЙОВАНИЙ ПІДХІД ДО ЗАСТОСУВАННЯ ТРИВАЛОЇ АБО ІНТЕРМІТУЮЧОЇ НИРКОВОЇ ЗАМІСНОЇ ТЕРАПІЇ КАРДІОХІРУРГІЧНИХ ПАЦІЄНТІВ З ГОСТРИМ ПОШКОДЖЕННЯМ НИРОК

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Keywords: *acute kidney injury, cardiac surgery, continuous renal replacement therapy, intermittent renal replacement therapy, multiorgan failure.*

Ключові слова: *гостре пошкодження нирок, тривала ниркова замісна терапія, інтермітуюча ниркова замісна терапія, синдром поліорганної недостатності.*

Abstract. *Background: In-hospital mortality of cardiac surgery patients with AKI is 3-7 times higher than those without AKI. This prospective observational study was dedicated to evaluate a differential approach of applying continuous and intermittent modalities of RRT in cardiac surgery patients.*

Methods. One hundred and six adult cardiac surgery patients admitted hospital in 2008-2011 years, who had AKI and met inclusion criteria were allocated in CRRT or IRRT group.

Results. Observed in-hospital mortality of CRRT patients was significantly lower than predicted by APACHE II (p=0,01), in contrast with IRRT group. The in-hospital mortality of cardiac surgery patients with AKI and multiorgan dysfunction treated with CRRT was significantly lower than in patients treated with IRRT (32,5% vs 67,6%, p=0,012) and lower than predicted by APACHE II (32,5% vs 50%, p=0,025), while in IRRT group observed in-hospital mortality was significantly higher (67,6% vs 46%, p=0,012) than predicted.

Discussion. The complexity of the treatment of cardiac surgery patients with AKI and, especially, the subset with critical illness, could explain the lack of association between RRT modality and renal recovery and the in-hospital mortality of whole cohort, as well. This is a basis for differential and complementary applying of different RRT modalities according to the specific clinical situation.

Conclusions. Differential applying of continuous RRT modalities for the treatment of cardiac surgery patients with AKI, as a component of MOF, and intermittent RRT for the patients, who have not multiorgan dysfunction, could contribute to reducing in-hospital mortality in this cohort.

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Резюме. *Госпітальна летальність пацієнтів кардіохірургічного профілю з ГПН в 3-7 разів вища ніж у пацієнтів без ГПН. Це проспективне оглядове дослі-*

дження присвячено диференційному застосуванню тривалої (ТНЗТ) та інтермітуючої ниркової замісної терапії (ІНЗТ) у пацієнтів кардіохірургічного профілю.

Методи. 106 кардіохірургічних пацієнтів, госпіталізованих в 2008-2011 роках та які мали ГПН та критерії включення, були розподілені у групи ТНЗТ та ІНЗТ.

Результати. Госпітальна летальність, що спостерігали у пацієнтів в групі ТНЗТ, була достовірно нижчою за очікувану за шкалою APACHE II (p=0,01), на відміну від групи ІНЗТ. Госпітальна летальність кардіохірургічних пацієнтів з ГПН та СПОН, яких лікували ТНЗТ була достовірно нижчою ніж серед пацієнтів, яких лікували ІНЗТ (32,5% vs 67,6%, p=0,012) та нижчою за очікувану за шкалою APACHE II (32,5% vs 50%, p=0,025), в той час як госпітальна летальність в групі ІНЗТ була достовірно вищою (67,6% vs 46%, p=0,012) ніж очікувана.

Обговорення. Брак зв'язку між видом НЗТ та госпітальною летальністю лікування кардіохірургічних хворих з ГПН, особливо у критичному стані, можна пояснити його комплексністю. Це є основою для застосування диференційованого та комплементарного підходу у виборі виду НЗТ з урахуванням конкретної клінічної ситуації.

Висновки. Диференційований підхід до вибору тривалої НЗТ для лікування кардіохірургічних пацієнтів з ГПН, як складовою СПОН, та інтермітуючої НЗТ для пацієнтів без СПОН може сприяти зменшенню госпітальної летальності цих пацієнтів.

INTRODUCTION. Incidence of acute kidney injury (AKI) is growing and associated with adverse outcomes, particularly in critically ill patients. Depending on the definition frequency of AKI can reach 30% of patients after cardiac surgery [8] with renal replacement therapy (RRT) requirement of 2.6% of all patients or up to 22.5% of patients with AKI [4].

In-hospital mortality of cardiac surgery patients with AKI is 3-7 times higher than those without AKI [2, 4]. In case of AKI that needs RRT further deterioration of in-hospital mortality is observed with figures as high as 47-76% [3, 8].

Today, several modalities of RRT could be applied for AKI treatment and include continuous or intermittent extra-corporeal methods (hemodialysis, hemofiltration and hemodiafiltration) and peritoneal dialysis. Numerous clinical trials conducted last years could not demonstrate clear benefit of specific RRT modality in treatment of AKI in terms of in-hospital mortality.

This clinically-based prospective observational study was dedicated to evaluate a differential approach of applying continuous and intermittent modalities of RRT in cardiac surgery patients.

MATERIALS AND METHODS. Adult patients admitted National Institute of Cardio-Vascular Surgery NAMS of Ukraine for cardiac surgery during 2008-2011 years and met inclusion criteria were allocated in group of continuous modalities (CRRT) or in group of intermittent modalities (IRRT) of renal replacement therapy (RRT). Inclusion criteria: age ≥ 18 years old, cardiac illness with indications for surgical intervention and AKI, which needed RRT before or after surgical operation. Exclusion criteria: age < 18 years old; chronic kidney disease (CKD) V.

AKI was defined and staged according with RIFLE criteria ascribed by Bellomo et al., as well as complete and partial recovery of renal function [1]. Defining and staging of CKD was performed according with K/DOQI Guideline (2002) [7]. Glomerular filtration rate (GFR) was calculated using MDRD equation [6].

Sepsis, severe sepsis and septic shock were diagnosed according and multiple organ failure (MOF) was defined according to Consensus Conference (1991) as the presence of altered organ functions of two or more organs systems in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Surgical intervention, management before and after surgical treatment were conducted according to the local protocols of National Institute of Cardio-Vascular Surgery NAMS of Ukraine. Indications for RRT were determined according to the local protocol of Institute of Nephrology NAMS of Ukraine.

IHD was conducted with Innova (Gambro Dasco S.p.A., Italy) and AK-200 Ultra S (Gambro Lundia AB, Sweden) dialysis machines and Polyflux 17L (Gambro Dialyzatoren GmbH, Germany) dialyzers. Bicarbonate dialysis fluid was used with flow rate 500 ml/min and blood flow rate - 250 — 350 ml/min. The duration of sessions was 4-8 hours.

CVVH was performed in pre-dilution mode with Prisma machine (Gambro Dasco S.p.A., Italy) throughout 24 hours per day. HF1000 sets and Gambrosol 2 and Gambrosol 4 solutions were used (Gambro Dasco S.p.A., Italy). Blood flow rate was set up at 180 ml/min and prescribed substitution fluid rate was 35 ml/kg/hr.

SLEDD was performed with with Innova (Gambro Dasco S.p.A., Italy) and AK-200 Ultra S (Gambro Lundia AB, Sweden) dialysis machines and Polyflux 17L (Gambro Dialyzatoren GmbH, Germany) dialyzers. Sessions` duration was 8-12 hours and blood flow rate was 100 ml/min, meanwhile dialysis fluid rate was 350 ml/min.

HVHF was carried out in pre-dilution mode with AK-200 Ultra S (Gambro Lundia AB, Sweden) machine, Polyflux 14S (Gambro Dialyzatoren GmbH, Germany) hemofilters and durability 4-8 hours. Bicarbonate substitution fluid was used with flow rate 75-100 ml/kg/hr and blood flow rate was set up at 250 ml/min.

Vascular access in all cases was central venous catheter for hemodialysis 12 Fr, 20 cm (Arrow International Inc., USA), which was introduced in right jugular or subclavian vein or left subclavian vein. For anticoagulation unfractioned heparin was used in loading dose 10-25 IU/kg and maintain dose 10-20 IU/kg/hr (IHD and

HVHF) or 3-20 IU/kg/hr (CVVH and SLEDD). RRT for patients with active bleeding, INR ≥ 4 or APTT ≥ 120 sec was performed without anticoagulation.

Patients treated with CRRT could be switched to the intermittent HD after three days of treatment and in the case all of followed: vasopressors withdrawal, weaning from mechanical ventilation and urine output about 1 ml/kg/hr, which provides zero or negative water balance.

Statistical analysis included descriptive statistics and non-parametric tests (Mann-Whitney) for comparison. Kaplan-Mayer estimator was used for survival analysis). Preliminary correlation analysis was performed using Kendall tau-b and factors statistically significantly associated with outcome were included in Cox proportional hazards model for investigation of hospital mortality risk factors. All calculations were performed with SPSS for Windows v. 17.0 software.

RESULTS. One hundred and six adult cardiac surgery patients (74 males and 32 females), who needed RRT due to AKI development in perioperative period were prospectively included in the study. Forty nine patients were treated with continuous RRT modalities (CVVH - 43, SLEDD - 6) were allocated in the group of continuous RRT (CRRT), meanwhile 57 patients assigned group of intermittent RRT (IRRT) (IHD - 40, HVHF – 17). The patients' characteristics are summarized in Table 1 and 2.

Table 1

Baseline clinical patients' characteristic at RRT initiation

	Continuous RRT (n=49)	Intermittent RRT (n=57)	P
Male, n (%) Female, n (%)	39 (79.6) 10 (20.4)	35 (61.4) 22 (38.6)	0.043
Age, years (Mean±SD)	51.9±15.4	57±13.3	0.085
CKD-I, n (%)	2 (4.1)	1 (1.8)	0.292
CKD-II, n (%)	6 (12.2)	3 (5.3)	0.292
CKD-III, n (%)	2 (4.1)	11 (19.3)	0.292
Diabetes mellitus, n (%)	8 (16.3)	7 (12.3)	0.499
MOF, n (%)	40 (81.6)	34 (59.6)	0.014
Sepsis, n (%)	17 (34.7)	8 (14)	0.013
Oligouric, n (%)	40 (81.6)	40 (70.2)	0.174
Mechanical ventilation, n (%)	26 (53.1)	18 (31.6)	0.026

Table 2

Baseline laboratory patients' characteristic at RRT initiation

	Continuous RRT (n=49)	Intermittent RRT (n=57)	P
	(Mean±SD)		
Weight, kg	79.4±19.8	78.1±15	0.934
Height, cm	171.6±8.7	169.7±10.3	0.393
BMI	26.7±5.6	26.9±4.4	0.577
BSA, м2	1.9±0.3	1.92±0.22	0.967
APACHE II	23.2±6	20.8±5.6	0.041
MODS	7±3.4	5.8±3.3	0.045
SOFA	8.8±3.9	6.9±4.1	0.007
GFR (MDRD)	15.6±6.3	14.2±4.9	0.378
Blood urea, mmol/l	30.7±11.1	31.2±10.5	0.738
Blood creatinine, µmol/l	378.7±136.6	407.1±222.6	0.938
Urine output, ml/kg/hr	0.4±1.6	0.5±2.4	0.061

There were no significant differences between groups in types of cardiac surgery, but initiation of RRT before surgery was higher among IRRT patients (28. 6% vs 47.4%, $p=0.049$).

On the whole, observed hospital mortality of cardiac surgery patients with AKI who were treated with RRT was 35.8% and do not differ statistically with predicted by APACHE II - 42% ($p=0.192$).

There were no differences in the in-hospital mortality (28.6% vs 42.1%, respectively, $p=0.249$) and causes of death between CRRT and IRRT groups (fig. 1). However, observed in-hospital mortality of CRRT patients was significantly lower than predicted by APACHE II (28.6 vs 46%, respectively, $p=0.01$), in contrast with IRRT group (39% vs 41%, respectively, p=NS).

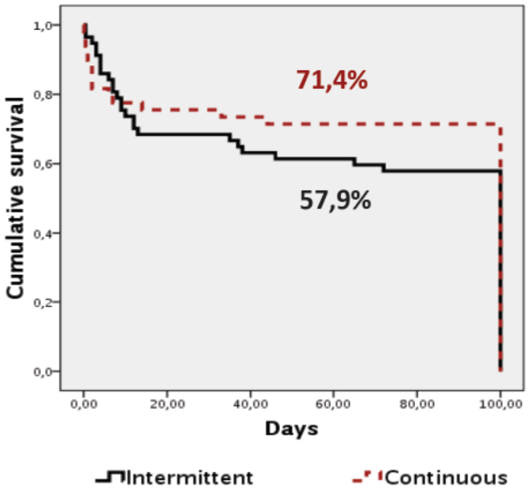

Fig. 1. The in-hospital survival of cardiac surgery patients treated with CRRT or IRRT ($p=0.249$).

Statistically significant difference in the in-hospital mortality of cardiac surgery patients with AKI and MOF treated with RRT (AKI-MOF) and those without MOF (AKI-w/oMOF) was observed (48.6% vs 6.3%, respectively, $p<0.001$) (fig. 2).

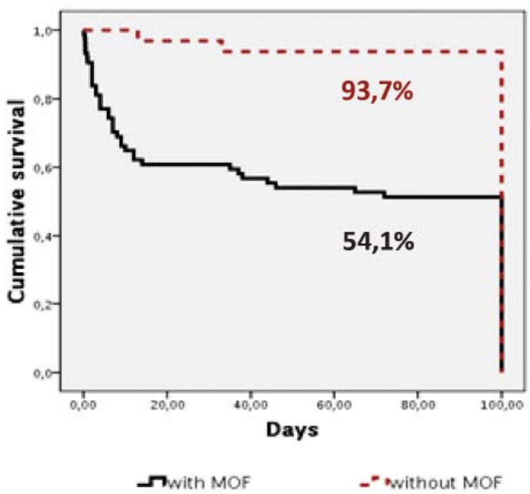

Fig. 2. The in-hospital survival of cardiac surgery patients with AKI-MOF and AKI-w/oMOF ($p<0.001$).

The in-hospital mortality of cardiac surgery patients with AKI-MOF treated with CRRT was statistically significantly lower than in patients treated with IRRT (32.5% vs 67.6%, respectively, $p=0.012$) (fig. 3). Moreover, observed in-hospital mortality in CRRT group was significantly lower than predicted by APACHE II (32.5% vs 50%, respectively, $p=0.025$), while in IRRT group observed in-hospital mortality was significantly higher (67.6% vs 46%, respectively, $p=0.012$).

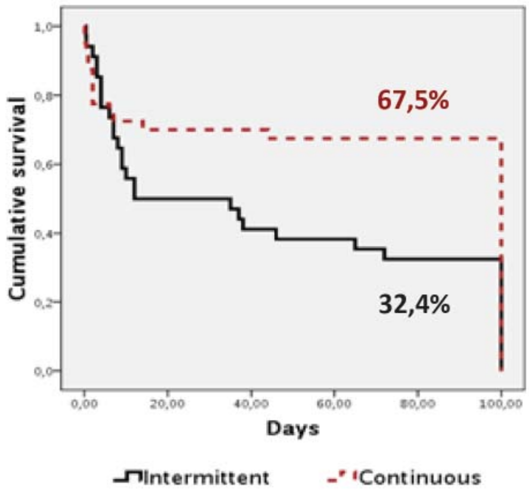

Fig. 3. The in-hospital survival of cardiac surgery patients with AKI-MOF treated with CRRT and IRRT ($p=0.012$).

The in-hospital mortality of cardiac surgery patients with AKI-w/oMOF did not differ significantly between CRRT and IRRT group (11% vs 4.3%, respectively, $p=0.504$) (fig. 4). However, observed in-hospital mortality of patients with AKI-w/oMOF treated with IRRT was significantly lower than predicated by APACE II (4.3% vs 29.1%, respectively, $p<0.001$), in contrast to CRRT group, where statistical significance was not demonstrated in (11.1% vs 29.1%, respectively, $p=0.144$).

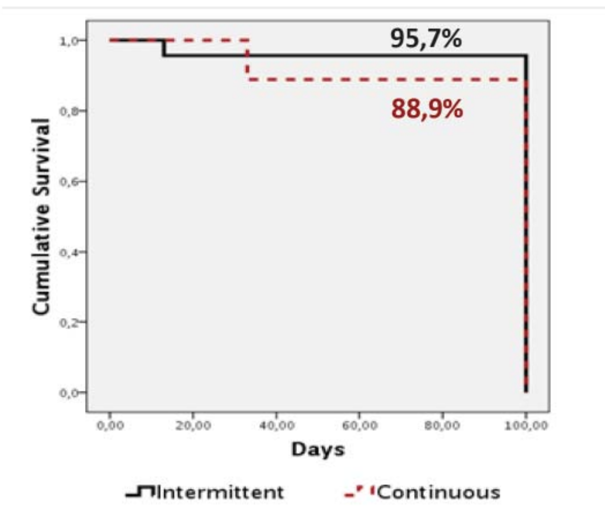

Fig. 4. The in-hospital survive of cardiac surgery patients with AKI-w/oMOF treated with CRRT and IRRT ($p=0.504$).

Presence of CKD-III was the only factor influenced on risk of in-hospital death of cardiac surgery patients with AKI treated with RRT (RR 3.45; 95% CI 1.14 – 10.46, p=0.029). Other parameters (ultrafiltration rate, presence of MOF, CKD-I, CKD-II, dopamine dose at RRT start, number of organ system with failure, presence of heart failure, respiratory failure, consciousness deficiency, mechanical ventilation, APACHE II scores, mean Kt/V and fluid balance, urine output at RRT start and on day 1, 2 and 3 and fluid balance on day 1) included in the Cox proportional hazards model were not statistically significant.

Cox proportional hazards model did not reveal statistically significant risk factors of the in-hospital mortality of cardiac surgery patients with AKI-w/oMOF. Meanwhile, continuance of RRT during the first 3 days after initiation, ultrafiltration rate, presence of CKD– III, MODS score and mean water balance of first 3 days of RRT were significantly associated with hospital mortality of cardiac surgery patients with AKI and MOF (table 4).

Table 4

Relative risk of hospital mortality of cardiac surgery patients with AKI and MOF treated with RRT

	P	Exp(B)	95.0% CI for Exp(B)	
			Lower	Upper
Continuance of RRT during the first 3 days after RRT initiation (hour)	0.015	0.954	0.919	0.991
Initiation of RRT before surgical intervention	0.884	0.896	0.204	3.934
Ultrafiltration rate (ml/kg/hrs.)	0.008	1.580	1.127	2.214
IHD	0.082	0.241	0.049	1.195
CVVH	0.874	1.116	0.287	4.344
CKD	0.212			
CKD - I	0.340	3.671	0.253	53.199
CKD - II	0.453	0.557	0.120	2.571
CKD– III	0.045	8.135	1.046	63.266
Urine output at RRT initiation (mlkg/hrs.)	0.362	1.000	0.998	1.001
Dopamine dose at RRT initiation (mcg/kg/min.)	0.250	1.661	0.700	3.941
Mechanical ventilation	0.852	1.144	0.279	4.699
Number. of organs system with failure	0.447	1.308	0.655	2.609
Dysfunction of CNS	0.616	0.735	0.221	2.445
MODS. score	0.018	1.321	1.049	1.662
Mean water balance (ml/kg)	0.005	1.001	1.000	1.002
Re-operation	0.387	1.798	0.476	6.788
BSA. m2	0.060	7.412	0.921	59.644
Oliguria duration (days)	0.560	0.984	0.934	1.038

DISCUSSION. The major limitations of our study are conducted with its observational nature and relatively small population size. On the other hand, the aim of this study was to evaluate in real-life environment hypothesis, that differential applying of RRT modalities may have beneficial effects on cardiac surgery patients with AKI.

In our study the in-hospital mortality was 35.8% with the highest figure – 48.6% - in patients with multiorgan dysfunction and the lowest (6.3%) in patients. who had not any signs of organs failure except kidney. This result corresponds to several studies of RRT treated cardiac surgery patients with AKI, that demonstrated in-hospital mortality at 47-65.5% [3. 8]. The in-hospital mortality of our study was at the lowest level of previously reported trials and could be related to differences in population enrolled. Management of patients besides RRT performing and. probably. absence of hard cut-off time value (for example 28 days) to define in-hospital mortality in our study. Meanwhile our data is in agreement with the previously reported work of M. Ostermann i R. W. Chang (2009). whether increase of in-hospital mortality of AKI patients was associated with increasing number of other organs systems failure [5].

Meanwhile lot of studies showed advantage of specific RRT method was conducted. Most of them had important limitations and their results were not confirmed in further trials. Recently published meta-analysis results (which included RCTs above) also confirmed the lack of benefits "more intensive" approach to RRT on the "less intensive" [9].

The main limitation of studies of RRT applying in treatment of AKI comes from hypothesis that "gold" RRT method exists and one size could fit all. Another concern is related to difficulties in separation of the modality effect from the dose effect or even timing effect. First of all, it is well recognized, that population of AKI patients is very heterogeneous not only regarding cause of AKI. But also patient-related factors (age, co-morbidities, etc.) and disease-related (localization of infection in sepsis, severity of disease, and so on). Thus, it is barely possible. that the specific RRT modality will be equally effective in cardiac surgery patient with cardiogenic shock due to myocardial infarction or in infective endocarditis patient with septic shock and heart failure or in a stable patients with contrast-induced AKI. That is why. we should be careful in extrapolation of results of different AKI studies and be aware about the population enrolled in. It is clearly demonstrated in our study. While in the whole cohort of cardiac surgery patients CRRT and IRRT were equally effective regarding in-hospital mortality and renal recovery. CRRT was beneficial in a subset of patients with multiorgan dysfunction. In contrast to patients with renal failure alone in which IRRT had benefit.

This finding could be explained by differences in clinical situations and. as a consequence. different goals of RRT. Since the in-hospital mortality of cardiac surgery patients is associated with continuance of RRT during the first and three days after RRT initiation. Mean water balance of first three days of RRT and ultrafiltration rate. the beneficial effect of CRRT in patients with MOF is related to its ability to provide smooth correction of volume status and solute removal. It is well elucidated, that patients with compromised cardiac function is extremely susceptible to large fluid and solute shifts and the beneficial effect of CRRT was noted mainly in patients with unstable hemodynamics. Cardiac surgery patients with AKI-MOF, who remained alive had highest duration RRT for the first three days of RRT in comparison with those who died (28.4±17.2 h vs 19.3±11.6 h, respectively, p=0.037). had lower ultrafiltration rate (1.18±1.01 ml/kg/h vs 1.94±1.88 ml/kg/h, respectively, p=0.05) and negative fluid balance for the first three days of RRT (-6.1±11.1 ml/kg i -0.7±10.8 ml/kg, respectively, p=0.026). It is important, that net ultrafiltration volume did not differ significantly between AKI-MOF patients who survived or died (27.8±28.6 ml/kg vs 38.45±37.02 ml/kg, respectively, p=0.333). Taken together, this may underline importance of ultrafiltration rate as a factor of morbidity and mortality of cardiac surgery patients. On the other hand, it could be the reflection of casual more restrictive approach in fluid management of survived patients.

It is not surprising that severity of disease affects outcome. Survived patients with AKI-MOF had lower MODS score at the RRT start than those who died (6.1±2.4 vs 8.9±3.8. respectively. p<0.001). CKD-III was associated with mortality of AKI-MOF patients and the only risk factor of whole cohort of cardiac surgery patients with AKI (RR 3. 45; 95% CI 1.14 – 10.46; p=0.029). Several studies elucidated the importance of CKD as a mortality risk factor of cardiac surgery patients.

The complexity of the treatment of cardiac surgery patients with AKI, and especially, the subset with critical illness could explain the lack of association between RRT modality and renal recovery and the in-hospital mortality of whole cohort, as well. Because other treatment points (such as surgery-related, conjunct with use of vasopressors. inotropes or specific type of mechanical support of cardiac and/or respiratory function. antimicrobial agents used, etc.) affected outcome are extremely important. Prescribed modality and parameters of RRT should take into account not only specific goals of renal support (i.e. fluid status correction or solute removal). But also above-mentioned and others treatment-related issues. This is a basis for differential and complementary applying of different RRT modalities according to the specific clinical situation.

CONCLUSION. Differential applying of continuous RRT modalities for the treatment of cardiac surgery patients with AKI as a component of MOF, and intermittent RRT for the patients, who have not multiorgan dysfunction could contribute to reducing in-hospital mortality in this cohort.

Beneficial effect of CRRT on mortality of cardiac surgery patients with MOF is related to the ability to provide negative fluid balance with slow ultrafiltration rate and without large fluctuations in intravascular volume and. possibly. solutes concentrations – factors to which patients with compromised cardiac function very susceptible are.

Pre-existed CKD-III is important risk factor of in-hospital mortality of cardiac surgery patients with AKI and severity of critical illness is additional factor contributes to mortality in patients with multiorgan dysfunction.

Despite the fact, that the development of multiorgan dysfunction worsens survival. This does not lead to worse renal prognosis in comparison with AKI patients without multiorgan failure, which is likely dependent from factors besides RRT modality.

REFERENCES:

1. *Bellomo R.* Acute renal failure - definition. outcome measures. animal models. fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group / Bellomo R., Ronco C., Kellum J. A., [et al.] // Crit Care – 2004. – № 8(4). – *P. 204*-212.
2. *Elahi M. M.* Early hemofiltration improves survival in post-cardiotomy patients with acute renal failure / Elahi M. M., Lim M. Y., Joseph R. N., [et al.] // Eur J Cardiothorac Surg – 2004. – № 26. – P. 1027-1231.
3. *Haase M.* A comparison of the RIFLE and Acute Kidney Injury Network classification for cardiac

surgery-associated acute kidney injury: A prospective cohort study / Haase M., Bellomo R., Matalanis G., [et al.] // J Thorac Cardiovasc Surg – 2009. – № 138. – P. 1370-1376.
4. *Jyrala A.* Effect of mild renal dysfunction (s-creat 1.2-2.2 mg/dl) on presentation characteristics and short- and long-term outcomes of on-pump cardiac surgery patients / Jyrala A., Weiss R. E., Jeffries R. A., [et al.] // Interactive Cardiovascular and Thoracic Surgery – 2010. – № 10. – P. 777-782.
5. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int. – 2012. – Suppl. 2. – 138 p.
6. *Kuan Y.* GFR prediction using the MDRD and Cockcroft and Gault equations in patients with end-stage renal disease / Kuan Y., Hossain M., Surman J., [et al.] // Nephrol Dial Transplant – 2005. – № 20. – P. 2394-2401.
7. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation. Classification and Stratification. – Am J Kidney Dis – 2002. – Suppl 1. – 266 p.
8. *Perez-Valdivieso J. R.* Cardiac-surgery associated acute kidney injury requiring renal replacement therapy. A Spanish retrospective case-cohort study / Perez-Valdivieso J. R., Monedero P., Vives M., [et al.] // BMC Nephrology – 2009. – № 10. – P. 27-31.
9. *Van Wert R.* High-dose renal replacement therapy for acute kidney injury: Systematic review and meta-analysis / Van Wert R., Friedrich J. O., Scales D. C., [et al.] // Crit Care Med – 2010. – № 38. – P. 57-65.

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