Early initiation of renal replacement therapy improves survival in patients with acute kidney injury

Rani početak primene metoda zamene funkcije bubrega poboljšava preživljavanje bolesnika sa akutnim oštećenjem bubrega

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Abstract

Background/Aim. Defining renal replacement therapy (RRT) initiation in critically ill patients with acute kidney injury (AKI) has become an imperative for nephrologists and intensivists. The aim of this study was to determine 28-day survival and the renal function recovery in patients with AKI. **Methods.** A single-center retrospective study included 385 surgical and non-surgical patients with AKI and episode of AKI in chronic kidney disease who were admitted to the Emergency Center of Clinical Center of Vojvodina (Novi Sad, Serbia) between 2014 and 2017 and received RRT. Patients with the Kidney Disease Improving Global Outcomes (KDIGO) stage 2 AKI and/or volume overload were assigned to the "early" group with RRT (dialysis) start within 24 h of the diagnosis; patients with poor response to conservative treatment or evidence of clinical complications associated with AKI were assigned to the "late" RRT group. **Results.** Based on the retrospective analysis we found that 241 patients (62.6%) received "early" RRT within 24 h. Patients in the "early" RRT group had significantly higher survival compared to the "late" RRT group (63.9% vs. 36.1%; $p = 0.001$). The "early" RRT group had more patients with renal function recovery (56.8%), but without statistical significance ($p = 0.514$). The patients who started RRT within 24 hours with the Sequential Organ Failure Assessment (SOFA) score of 1–3 were twice likely to recover renal function in relation to the patients with the SOFA score of 4 or higher [odds ratio (OR) = 2.01; 95% confidence interval (CI): 1.37–2.95; $p < 0.001$], while septic patients had a 62% lower chance of renal function recovery in relation to non-septic patients (OR = 0.38; 95% CI: 0.18–0.82; $p = 0.013$). In the "late" RRT group, it was found that non-diabetic patients had 3.8 times greater chance for renal function recovery compared to diabetic patients (OR = 3.53; 95% CI: 1.27–9.83; $p = 0.016$). **Conclusions.** Patients with the early initiation of RRT had significantly improved 28-day survival.

Key words:
acute kidney injury; renal dialysis; mortality; risk assessment; survival; time factors.

Apstrakt

Uvod/Cilj. Definisanje početka primene metoda zamene funkcije bubrega kod kritično obolelih sa akutnim oštećenjem bubrega postaje imperativ nefrolozima i intezivistima. Primarni cilj studije je bio ustanoviti preživljavanje bolesnika 28-og dana od prijema, a sekundarni cilj oporavak funkcije bubrega. **Metode.** U Urgentnom centru Kliničkog centra Vojvodine (Novi Sad, Srbija) sprovedeno je retrospektivno ispitivanje koje je uključilo 385 hiruških i nehiruških bolesnika sa akutnim oštećenjem bubrega i akutizacijom hronične bubrežne insuficijencije u periodu od 2014. do 2017. godine, kojima su primenjene metode zamene funkcije bubrega. Bolesnici sa *Kidney Disease Improving Global Outcomes* (KDIGO) stadijumom 2 i/ili hipervolemijom unutar 24 h od potvrđenog akutnog oštećenja bubrega imali su "rani" početak dijalize, dok su "kasni" početak imali bolesnici sa slabijim odgovorom na konzervativnu terapiju ili kliničkim komplikacijama povezanim sa akutnim oštećenjem bubrega. **Rezultati.** Retrospektivnom analizom je utvrđeno da je kod 241 bolesnika (62,6%) dijaliza rano započeta, unutar 24 h. Bolesnici koji su „rano" započeli dijalizu imali su značajno bolje preživljavanje u poređenju sa bolesnicima koji su imali „kasni" početak dijalize (63.9% vs. 36.1%; $p = 0.001$). Kod nešto većeg broja bolesnika sa „ranim" početkom dijalize došlo je do oporavka funkcije bubrega (56,8%), ali razlike nisu bile značajne ($p = 0.514$). Bolesnici sa „ranim" početkom

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dijalize i *Sequential Organ Failure Assessment* (SOFA) skorom 1–3 imali su 2 puta veću šansu da oporave funkciju bubrega u odnosu na bolesnike sa SOFA skorom ≥ 4 [*odds ratio* (OR) = 2,01; 95% *confidence interval* (CI): 1,37–2,95; *p* < 0,001], dok su bolesnici sa sepsom imali za 62% manju šansu oporavka funkcije bubrega u odnosu na bolesnike bez sepse (OR = 0,38; 95% CI: 0,18–0,82; *p* = 0,013). U grupi sa „kasnim" početkom dijalize utvrđeno je da bolesnici koji nemaju dijabetes imaju 3,8 puta veću šansu

za oporavak funkcije bubrega u odnosu na obolele od dijabetesa (OR = 3,53; 95% CI: 1,27–9,83; *p* = 0,016). **Zaključak.** Značajno bolje preživljavanje 28-dana imali su bolesnici kojima je zamena funkcije bubrega dijalizom „rano" započeta.

Ključne reči:
bubreg, akutna insuficijencija; bubreg, dijaliza; mortalitet; rizik, procena; preživljavanje; vreme, faktor.

Introduction

In the past decade, acute kidney injury (AKI) has become a well-recognized global occurrence that affects developed and developing countries alike, with initiatives like the Saving Young Lives and the International Society for Nephrology's 0by25 Initiative aiming at reducing the economic, social and healthcare burden imposed by AKI [1]. AKI frequently occurs in critically ill patients and severe AKI is associated with hospital mortality in 60% of the cases [2]. Those that survive the initially high mortality rate associated with dialysis-requiring AKI, mostly become independent of renal replacement therapy (RRT) within a year, but some of them do go on to develop chronic kidney disease (CKD) and even progress to end-stage renal disease [3]. The fundamental principle in the treatment of AKI is to correct the underlying cause, but besides hemodynamic resuscitation and removal of nephrotoxins, we lack any established pharmacotherapy. Although drugs are tested for the prevention and/or treatment of AKI, RRT appears to be our only efficacious option at the time. Thus, the management of AKI is largely limited to preventing further deterioration and the loss of function with the use of temporizing actions in severe cases until RRT is established [4]. Dialysis as the method of RRT, along with mechanical ventilation, vasoactive therapy and nutritional support, is one of the defined life-sustaining technologies in the current treatment of the critically ill. A recent trend suggests an increasing use of RRT in critically ill patients with AKI [5]. Despite the research and growing clinical experience in dialysis, the optimal time to start RRT in a critical disease complicated with AKI is unclear [2]. Heterogeneity in operational definitions of "time", "threshold" or "criteria" in individual observational data (often with variable designs and methodological qualities) have probably interfered with clear conclusions that could guide clinical practice on this issue [6]. It is unclear whether a preventive/early strategy of the initiation of RRT in order to avoid complications associated with AKI leads to better patient outcomes and the use of health services, or a more conservative strategy, in which RRT is started as a response to the development of complications, provides better results. Neither the standard clinical parameters, nor the new biomarkers that have been introduced to clarify the definitive ideal time more precisely, nor the clinical picture have optimized patient outcomes [2]. The primary objective of this study was 28-day patient survival and the secondary objective was renal function recovery in patients with "early" RRT compared with those with "late" RRT.

Methods

We performed a single-center retrospective study of 385 surgical and non-surgical adult patients with AKI and episode of AKI in CKD who were admitted to the Intensive Care Unit (ICU) and Intensive Internal Medicine Unit at the Emergency Center (Clinical Center of Vojvodina, Novi Sad, Serbia) between 2014 and 2017 and received RRT (dialysis). Patients with the Kidney Disease Improving Global Outcomes (KDIGO) stage 2 AKI (serum creatinine 2–2.9 times baseline and urine output < 0.5 mL/kg/h for 12 h) and/or volume overload were assigned to the "early" group with RRT start within 24 h of the diagnosis; patients with a poor response to the conservative treatment or evidence of clinical complications associated with AKI were assigned to the "late" RRT group. Although the condition of certain patients called for the start of RRT in the first 12 hours, they were denied this request at that time due to the organization of the team for starting RRT at weekends or at night, the unavailability of the apparatus and/or difficulty in placing the dialysis catheter. Other reasons for postponement were surgical interventions or radiological tests that were to be performed before the start of the RRT. Some patients started the treatment with intermittent dialysis at the time of hemodynamic stability or the unavailability of the apparatus since "more severe" patients and/or the ones who were occasionally dialyzed with it had the need for it. Patients with an immediate RRT indication having at least one of the following conditions from the beginning were excluded: laboratory analysis at the admission urea > 50 mmol/L, K > 6.5 mmol/L, pH < 7.15 in the context of either pure metabolic acidosis or mixed acidosis despite medical treatment; acute pulmonary edema due to fluid overload causing severe hypoxemia, as well as patients treated with conservative therapy. We analyzed: demographic data, comorbidities, laboratory and clinical data in confirmed AKI [urea, creatinine, C-reactive protein (CRP), procalcitonin (PCT), oliguria/anuria] and before continuous RRT (CRRT) initiation (urea, creatinine, 24 h diuresis (mL); the use of vasopressor therapy and mechanical ventilation; hospital length of stay (days); CRRT modalities: continuous venovenous hemodiafiltration (CVVHDF), continuous venovenous hemofiltration (CVVHF), continuous venovenous hemodialysis (CVVHD), CVVHD combined with CVVHDF; and those achieved ultrafiltration (UF). The choice of RRT modalities (intermittent or continuous) was at the discretion of clinicians, and based on international guidelines [7]. The RRT regimen was daily or every second day, de-

pending on clinical, laboratory parameters and response to the therapy. CRRT was done on the Multifilter and the Prismaflex; standard high-flux filters and membranes/adsorbers were used in septic patient: EMiC2 hemofilter (Fresenius Medical Care, Bad Homburg, Germany, 1.8 m² surface area), oXiris [Gambro, AN-69 based membrane, surface treated by polyethyleneimine (PEI) and grafted with heparin] and CytoSorb (total surface of > 40,000 square meters). The CRRT prescription included: treatment modality, blood flow, dilution mode, replacement and dialysis fluid flow, and the patient's weight and heparin anticoagulation, according to clinical practice guideline [7]. Organ dysfunction was quantified using the Sequential Organ Failure Assessment (SOFA) score.

Statistical methods

Descriptive and inferential statistical methods were used for the data analysis. Numerical characteristics are presented by the arithmetic mean, the median with interquartile range (IQR, 25–75 percentiles) and the standard deviation, while the attributive characteristics are expressed by frequency and percentage. The χ^2 test was used to compare the differences between different groups, and the Cox regression model was used to test the predictor of recovery and failure of the renal function, as well as to calculate survival with respect to the selected indicators. Three Cox regression models were made. In the first model, renal function recovery over a period of one month was used for the outcome variable, and the following: gender, age, CRRT 24 h, UF, urea at admission, urea at the start of CRRT, creatinine at admission, creatinine at the start of CRRT, CRP, PCT, surgical patients, sepsis, cardiovascular, cerebrovascular, pulmonary, digestive and other diseases and diabetes mellitus were used as independent indicators. For the formation of the other two models, the sample was selected with regard to the onset of CRRT. The outcome variable in both models is non-recovery of renal function selected with regard to the onset of CRRT (CRRT > 24 h and CRRT < 24 h) over a period of one month, and the independent indicators were the same as in the first model,

with the exception of CRRT 24 h. There was a statistical significance if $p < 0.05$, and a high statistical significance if $p < 0.001$. The IBM SPSS Statistical Package for Social Sciences 21 software package was used for statistical data processing.

Results

We found that 241 (62.6%) patients (male 65.4%), mean age 60.6 received "early" RRT within 24 h, and 144 (37.4%) patients (male 70.8%) mean age 63.5 received late RRT after 24 h. All studied comorbidities were more prevalent in "early" RRT, and cardiovascular diseases were the most prevalent comorbidity in both groups of patients. Patients in the "early" RRT group had a higher rate of sepsis and less frequent use of mechanical ventilation and vasopressor therapy compared to the "late" RRT group (54.7% vs 41.7%; 58.3% vs 70.8%; 56.7% vs 75.7%, respectively). The presence of adsorptive membrane/adsorbers according to the type and the number of procedures in both groups was similar. Over 50% in both groups had the SOFA score ≥ 4. Median diuresis (mL) before RRT was smaller in the "early" group compared to the "late" group (150 vs 400, respectively); median urea (mmoL) and creatinine (µmoL) were similar in both groups (25.1 vs 25 and 449 vs 458, respectively). The most common treatment modality in both groups was CVVHDF and the achieved UF was higher in "early" RRT compared to "late" RRT (2,279 vs 2,017 mL). Mean length of hospital stay was similar in both groups (8 vs 7 days) (Table 1). The patients in whom CRRT started within 24 hours had significantly better survival ($p < 0.001$) and better recovery of renal function, but without statistical significance ($p = 0.551$) compared to the patients in whom RRT started after 24 h (Figures 1 and 2). The SOFA score and sepsis were differentiated as predictors of renal function recovery. The patients with the SOFA score 1–3 had 1.7 times higher chance for renal recovery in relation to the patients with the SOFA score ≥ 4 [odds ratio (OR) = 1.79; 95% confidence interval (CI): 1.31–2.46; $p < 0.001$], while septic patients had a 53% lower chance to recover their renal function in relation to the patients with no sepsis (OR = 0.47; 95% CI: 0.24–
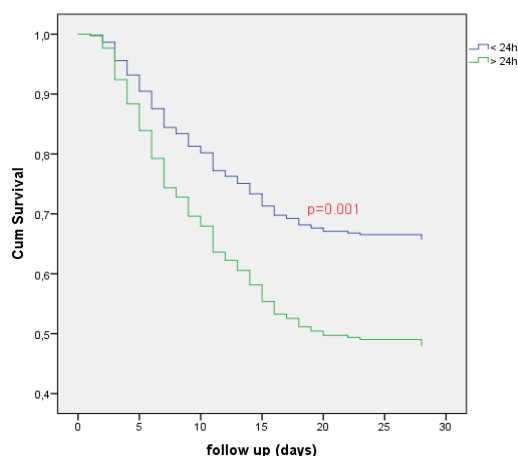

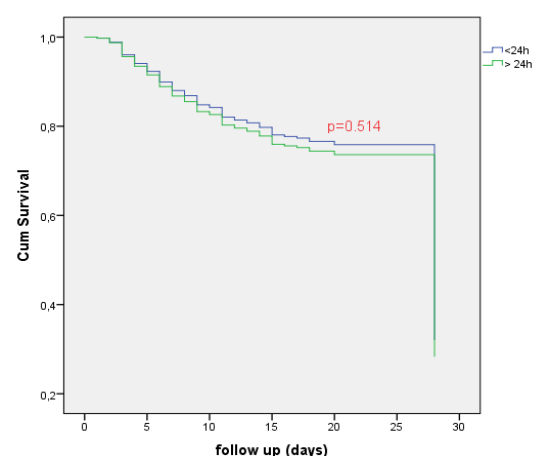**Fig. 1 – Patient survival depending on the time of renal replacement therapy initiation.**

Fig. 2 – Recovery of renal function depending on the time of renal replacement therapy initiation.

Table 1

Demographic and clinical data of patients treated with renal replacement therapy (RRT)

Variable	RRT < 24 h (n = 241) n (%)	RRT > 24 h (n = 144) n (%)
Sex		
male	157 (65.4)	102 (70.8)
female	83 (34.6)	42 (29.2)
Age (years), mean (SD)	60.06 (13.6)	63.5 (13.4)
CRRT modality, n (%)		
CVVHDF	92 (38.3)	57 (39.6)
CVVHD	84 (35.0)	54 (37.5)
CVVH	15 (6.3)	7 (4.9)
CVVHD+CVVHDF	49 (20.4)	26 (18.1)
Comorbidities, n (%)		
cardiovascular diseases	154 (64.2)	69 (47.9)
pulmonary diseases	24 (10.0)	13 (9.0)
gastrointestinal diseases	30 (12.5)	17 (11.8)
diabetes mellitus	56 (23.3)	22 (15.3)
cerebrovascular diseases	23 (9.6)	9 (6.3)
chronic kidney disease	29 (12.1)	6 (4.2)
other	64 (26.7)	41 (28.5)
without comorbidities	29 (12.1)	13 (9.0)
Recovery of renal function, n (%)	137 (56.8)	68 (47.2)
Nonsurvivors, n (%)	87 (57.6)	83 (57.6)
Septic patients, n (%)	131 (54.6)	60 (41.7)
Surgical patients, n (%)	63 (26.3)	43 (29.9)
Oliguric/anuric patients, n (%)	105 (43.3)	47 (32.6)
Diuresis (mL), median (IQR)	150 (0–750)	400 (0–1015)
Physiological support, n (%)		
invasive mechanical ventilation	140 (58.3)	102 (70.8)
vasopressors	136 (56.7)	109 (75.7)
Number of procedures with adsorptive membrane/adsorber, n (%)		
1–2	64 (26.3)	34 (23.9)
≥ 3	31 (12.8)	16 (11.3)
0	148 (60.9)	92 (64.8)
Type adsorptive membrane/adsorber, n (%)		
EMiC2	81 (33.3)	42 (29.6)
oXiris	3 (1.2)	2 (1.4)
CytoSorb	1 (0.4)	-
EMiC2 + oXiris	7 (2.9)	6 (4.2)
oXiris + CytoSorb	1 (0.4)	-
SOFA score, n (%)		
0	2 (0.8)	1 (0.7)
1	32 (13.2)	7 (4.9)
2	25 (10.3)	23 (16.2)
3	35 (14.4)	12 (8.5)
≥ 4	149 (61.3)	99 (69.7)
UF (mL), median (IQR)	2279 (1360 - 2983)	2017 (1310–2734)
Urea at admission (mmoL), median (IQR)	25.1 (18.8–36.7)	25 (18.3–35.2)
Urea at the start of RRT (mmoL), median (IQR)	29.2 (22.2–40.8)	29.05 (20.4–40.0)
Creatinine at admission (µmoL)-median (IQR)	421 (228–585)	330 (222–500)
Creatinine at the start of RRT (µmoL)-median (IQR)	449 (284–603)	458 (278–631)
CRP (mg/L), median (IQR)	120 (37.3–253.8)	121.5 (55.9–244.4)
PCT (ng/L), median (IQR)	4.7 (0.9–22)	5.2 (1.2–19.5)
Length of hospital stay (days), median (IQR)	8 (4.0–13)	7 (5.0–12)

CRRT – continuous renal replacement therapy; CVVHDF – continuous venovenous hemodiafiltration; CVVHD – continuous venovenous hemodialysis; CVVH – continuous venovenous hemofiltration; CVVHD+CVVHDF – CVVHD combined with CVVHDF; UF – ultrafiltration; CRP – C-reactive protein; PCT – procalcitonin; SOFA – Sequential Organ Failure Assessment; SD – standard deviation; IQR – interquartile range.

0.90; $p = 0.024$) (Table 2). The patients who started RRT within 24 hours with the SOFA score of 1–3 were twice likely to recover renal function in relation to the patients with the SOFA score of 4 or higher (OR = 2.01; 95% CI: 1.37–2.95; $p < 0.001$), while septic patients had a 62% lower chance of renal function recovery in relation to non-septic patients (OR = 0.38; 95% CI: 0.18–0.82; $p = 0.013$). In the "late" RRT group, it was found that non-diabetic patients had 3.8 times higher chance for the renal function recovery com-

pared to diabetic patients (OR = 3.81; 95% CI: 1.35–10.76; $p = 0.012$) (Table 3).

Discussion

Numerous organizations have published their studies and guides in order to better inform the clinical practice [8]. Each organization has recognized the limitations of the present evidence and the associated clinical uncertainty, there-

Table 2
Predictors of renal function recovery regardless of the time of renal replacement therapy (RRT) initiation

Variable	B	p
Sex	-0.177	0.260
Age	-0.005	0.350
Ultrafiltration	0.000	0.695
Urea at admission	0.003	0.692
Urea at the start of RRT	-0.005	0.544
Creatinine at admission	0.000	0.631
Creatinine at the start of RRT	0.000	0.833
C-reactive protein	0.000	0.859
Procalcitonin	0.001	0.415
Surgical patients	0.072	0.677
Septic patients	0.761	0.024
Cardiovascular diseases	0.188	0.282
Pulmonary diseases	0.221	0.418
Gastrointestinal diseases	0.338	0.165
Diabetes mellitus	0.294	0.140
Cerebrovascular diseases	-0.275	0.314
Other	-0.012	0.941
Number procedures with adsorptive membrane/adsorber	0.518/ -0.038	0.264/ 0.875
Type adsorptive membrane/adsorber	0.228	0.533
SOFA score	0.586	0.000

SOFA – Sequential Organ Failure Assessment.

Table 3
Predictors of renal function recovery depending on the time of renal replacement therapy (RRT) initiation

Variable	RRT < 24 h		RRT > 24 h	
	B	p	B	p
Sex	-0.241	0.222	-0.258	0.402
Age	-0.005	0.420	0.000	0.995
Ultrafiltration	0.000	0.926	0.000	0.432
Urea at admission	0.008	0.426	-0.002	0.885
Urea at the start of RRT	-0.005	0.609	-0.020	0.129
Creatinine at admission	0.001	0.441	-0.001	0.129
Creatinine at the start of RRT	0.001	0.431	-0.001	0.448
C-reactive protein	0.000	0.659	0.000	0.873
Procalcitonin	-0.001	0.658	0.005	0.119
Surgical patients	0.150	0.511	-0.050	0.866
Septic patients	0.944	0.013	-0.356	0.745
Cardiovascular diseases	0.374	0.096	0.190	0.554
Pulmonary diseases	0.277	0.382	0.095	0.866
Gastrointestinal diseases	0.382	0.199	0.399	0.415
Diabetes mellitus	0.133	0.559	1.337	0.012
Cerebrovascular diseases	-0.220	0.492	-0.172	0.764
Other	-0.037	0.858	-0.074	0.808
Number procedures with adsorptive membrane/adsorber	0.573 -0.038	0.296 0.903	-0.992 -0.307	0.438 0.533
Type adsorptive membrane/adsorber	0.370	0.397	0.348	0.617
SOFA score	0.698	0.000	0.503	0.097

SOFA – Sequential Organ Failure Assessment.

fore each of them recommended that additional high-quality studies should be carried out [9].

Previous studies have shown different results regarding heterogeneity of the population, the definition of the criteria for starting RRT, primary and secondary outcomes. In most studies, for the purpose of analyzing all causes of mortality, clinical indications and AKI classification have been used more frequently than biochemical parameters in order to define "early" and "late" RRT [10]. Our mixed population of predominantly non-surgical ICU patients started "early" RRT, according to the KDIGO practice guides that include statements about the time to start RRT in critically ill patients in the KDIGO 2 stage and/or hypervolemia within 24 hours. On the other hand, "late" RRT started in patients with developed complications related to AKI or the ones who had not responded to the conservative treatment. At the early onset of CRRT there was a higher percentage of oliguric/anuric, septic patients with comorbidities and a lower need for mechanical ventilation and vasoactive support, which were contributory indicators for a faster response in a clinical decision about supportive therapy. In comparison with the patients with "late" RRT, diuresis median was lower and the median of the achieved UF during RRT was higher, which, along with a better recovery of the renal function, indirectly indicates hypervolemia as an important additional criterion for starting RRT. The authors of two previously conducted meta-analyses, which included a total of 38 studies predominantly retrospective and of different quality, came to similar conclusions as ours, reporting a significant improvement in the 28-day mortality with "early" RRT [11, 12]. Other three studies have been conducted. Two of them [the multicenter randomized controlled trial (RCT) and the retrospective study] included septic patients and used different criteria of AKI classification for starting RRT in relation to our study design, but at the same RRT initiation time, showed a significant reduction in mortality in "early" RRT groups, while the third multicenter RCT conducted three years later found that there was no difference in mortality between the "early" and the "late" onset of RRT in 224 postoperative cardiosurgical patients [13–15].

In fact, since 2012, the majority of the published studies have not supported the benefit of "early" RRT in critically ill patients. Conducting a meta-analysis of 36 predominantly retrospective studies, it was established that the early initiation of RRT in critical patients did not improve survival for 28 or 30 days, nor did it reduce the length of stay in the ICU or the overall length of hospitalization. In the abovementioned studies, biochemical markers according to the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification, Acute Kidney Injury Network (AKIN) stages and time-based cut-offs were used (e.g. within the defined admission time or the development of the biochemical "start time") for defining the early start of RRT. However, the "early" RRT according to one author was the "late" RRT according to another author, which made it difficult to interpret the results. The "late" onset included classical indications of RRT that did not respond to conservative treatment [16].

A meta-analysis which included both the Artificial Kidney Initiation in Kidney Injury trial (AKIKI) and Effect of Early *vs* Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury trial (ELAIN) was subsequently published, including a total of 10 RCT with 1,672 participants combined. As the authors concluded, there appeared to be no added benefit of an early start of RRT on 30-, 60- and 90-day mortality "with respect to all-cause mortality, dialysis dependence, and recovery of renal functions or hospital stay". It was also found that there was no difference in reported complications: catheter-related infections, bleeding, hypotension, electrolyte disorders, thrombocytopenia, arrhythmias. It should be noted that the ELAIN single-center study analyzed 231 predominantly surgical patients with AKI and the episode of AKI in CKD in which the early criterion was the KDIGO 2 within 8h. It was established that there was no difference between the early and the late onset of RRT compared to the 28-day mortality (30.4 vs. 40.3%, respectively; $p = 0.11$). The exclusion of patients with urgent indications for RRT, as well as the fact that only 3.4% of the patients did not start RRT in the "early" group, were probably some of the reasons for the difference in reducing the 90-day mortality by comparing the "early" and "late" RRTs (39.3% vs. 54.7%, respectively; $p = 0.03$).

Meta-analysis of four RCTs showed similar results, except that a higher risk of catheter-related infections was reported at the early onset of RRT [17, 18]. A meta-analysis with six RCT that provided similar conclusions was conducted the same year, after which 4 additional RCT and 41 observational studies were included (a total of 51 studies) whose results showed that the "early" RRT was associated with a reduced risk of all causes of mortality, although the results were taken with caution, given the variety of design studies.

In our study of the early onset of RRT, we established a better 28-day renal function recovery, although the differences between the groups were not statistically significant. The ELAIN study indicated significant benefit since the early onset of RRT in renal function recovery (53.6% vs. 38.7%, $p = 0.02$), and the last meta-analysis also showed significant renal function recovery in 14 studies with 2,570 patients [10]. When we established a better renal function recovery, we tried to determine which predictors could affect this outcome. By applying multivariate Cox regression analysis in the total sample as well as in patients who started RRT early, SOFA score and sepsis stood out as significant predictors or renal function recovery. Namely, the patients with the 1–3 SOFA score who started RRT early, were two times more likely to recover from renal function in comparison to patients with the SOFA score 4 and above, while septic patients had a 62% lower chance to recover their renal function compared to non-septic patients. Contrary to our results, in a large retrospective study of the critically ill with AKI, older age, heart conditions and admission to ICU were significantly linked to a lower rate of renal function recovery 60–120 days after discharging from ICU [19]. However, in another retrospective study, Pistolesi et al. [20], concluded that older age, oliguria, sepsis and a higher SOFA score in 264 cardio-

surgical patients with severe AKI within the first week of CRRT start were independent prognostic indicators for non-recovery of renal function. However, in the late RRT group it was found that the patients without diabetes had a 3.8 times higher chance of recovering renal function compared to the patients with diabetes. Patschan and Müller [21] suggested that diabetes mellitus potentially increases AKI risk and long-term mortality/morbidity of AKI. Thakar et al. [22] showed that AKI episodes are associated with a cumulative risk of developing progressive CKD in diabetic patients, independently of other risk factors of progression. Unlike our results, the results of Johnson et al. [23] showed that AKI was diagnosed in 403 patients, 20.5% of whom were diabetic patients. Short-term renal function recovery was greater in diabetic patients (87% vs. 63%, $p = 0.001$) and the development of advanced CKD was lower (14%) in comparison with the non-diabetic ones [23]. In our study, a better renal function recovery at the late onset of RRT in non-diabetic patients requires additional testing of long-term renal recovery and the number of episodes of AKI in these patients compared to the patients at the risk of diabetes and the diabetics.

Also, it should be noted that in the studies similar to ours, the predictors of primary and secondary outcomes were less examined, because the main focus was on finding criteria for early/late start of RRT and predicting the outcomes.

Since each center has a limited number of patients for whom supportive therapy at the same time can be provided (in relation to resources, time, staff), the onset of RRT within 12 hours can lead to shortening the duration of RRT

initiation or to a delay in starting RRT for other patients. This comes to light if there is at the same time more than one urgent indication for patients of different age, comorbidity, etc. regardless of the defined criteria for the early onset of RRT. The current watchful waiting strategy (in the absence of urgent indications) allows for a greater impact of the doctor's clinical decision based on long-term experience and teamwork. However, if the "real" timing of the onset of RRT is not recognized, the ability to carry out RRT in already developed complications associated with AKI and renal function recovery is reduced.

There are some limitations associated with our study. We performed a single-center retrospective study. All our patients received RRT, there was no control group (due to the limited data availability), nor the possibility that delaying RRT could provide time for renal function recovery. Unlike other studies, we did not obtain the full data on "early" RRT-related complications, or the data on long-term outcomes [17, 18, 24].

Conclusion

The patients who had early started RRT had significantly better 28-day survival. A further prospective research of the primary and secondary outcome predictors is necessary.

Acknowledgements

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