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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Predictors of renal function non-recovery in critically ill patients with acute kidney injury treated with continuous renal replacement therapy

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SUMMARY

Introduction/Objective Acute kidney injury (AKI) is a highly prevalent complication among the critically ill individuals who are admitted to the intensive care unit (ICU). This study deals with identifying the frequency and predictors of the lack of renal function recovery in non-renal functions among critically ill patients requiring dialysis for AKI (AKI-D).

Methods The study included 440 ICU patients from the University Clinical Center of Vojvodina in the period from 2014 to 2018. The patients required Continuous Renal Replacement Therapy (CRRT). In this study, we analyzed various factors including demographic features, clinical characteristics, laboratory parameters, comorbidities, as well as the need for vasopressor therapy and mechanical ventilation on the day when AKI was confirmed. Additionally, we examined the different modalities of CRRT, which were used.

Results A retrospective analysis of the results included discovered that out of 440 patients with AKI-D, 242 (55%), average age 63.14, did not recover renal function. Significant predictors of renal function non-recovery in critically ill patients with AKI-D were: the patients age over 65 ($p = 0.044$), starting time of CRRT ($p = 0.043$), mechanical ventilation ($p = 0.044$) and previous kidney disease ($p = 0.005$). Significant predictors of renal function non-recovery in critically ill septic patients with AKI-D were: the patients age over 65 ($p = 0.002$), diabetes mellitus ($p = 0.023$), previous kidney disease ($p = 0.045$), CRP values < 100 mg/l ($p = 0.033$) and procalcitonin ($p = 0.010$), while in non-septic patients, the significant predictors of renal function non-recovery includes previous kidney disease ($p = 0.035$).

Conclusion Out of all examined predictors, both in septic and non-septic patients, previous kidney damage presents the greatest risk for renal function non-recovery in critically ill patients with AKI-D.

Keywords: acute kidney injury; recovery of renal function; critically ill; sepsis

INTRODUCTION

The development of acute kidney injury (AKI) is associated with various adverse outcomes such as prolonged intensive care unit (ICU) stay, development of chronic kidney disease (CKD), increased the mortality rate along with the increased treatment costs [1, 2].

The reported prevalence of AKI in ICUs varies from study to study and runs the gamut from 5% to 67% [3]. According to Opgenorth et al. [4] about 5–10% of these patients require renal replacement therapy (RRT).

In patients with AKI requiring RRT, the recovery of renal function occurs in only 20–60% of patients and patients' survival without the need for RRT is considered successful [4, 5]. Only 1–6% recovery of renal function occurs after 90 days of starting RRT [6]. AKI stage and time required for renal function recovery significantly influence morbidity/mortality rates after an acute episode of patients requiring dialysis for AKI (AKI-D) [7].

The results so far have indicated numerous predictors of renal function recovery and include those related to patients (age, CKD, proteinuria, comorbidity, etiology, stage, and duration of AKI, exposure to nephro-toxic drugs and/or diagnostic contrast agents, multi organ dysfunction), as well as potential predictors related to dialysis procedures itself (modalities, membrane, dose intensity, lasting and frequency of procedures) [5, 7, 8].

The aim of this study is to determine the prevalence and predictors of renal function non-recovery in critically ill patients with AKI-D.

METHODS

This retrospective study was conducted between 2014 and 2018 at the University Clinical Center of Vojvodina. The study included 440 adult surgical and non-surgical patients at the ICU and Emergency Room suffering from AKI and AKI on CKD who required continuous RRT (CRRT).

The study analyzed various parameters, including demographic features, comorbidities, laboratory and clinical analyses such as urea, creatinine, C-reactive protein (CRP), procalcitonin (PCT), quick sequential organ failure

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assessment score (qSOFA) score, the need for vasopressor therapy, and mechanical ventilation (MV) on the day when AKI was confirmed.

Different modalities of CRRT were utilized, including continuous veno-venous hemodiafiltration (CVVHDF), continuous veno-venous hemofiltration, continuous veno-venous hemodialysis (CVVHD), and CVVHD combined with CVVHDF. Discontinuation of CRRT was guided by the establishment of diuresis of 1000–1500 ml/day without diuretics. The recovery of renal function after AKI-D was defined independently from CRRT within 90 days of starting RRT. The criteria for early start of CRRT were stages II or III AKI according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines and/or hypervolemia with poor response to conservative treatment within 24 hours of AKI diagnosis, while manifested clinical complications related to AKI were criteria for i.e., late start of CRRT after 24 hours.

The choice of CRRT modalities was determined by the clinicians, guided by international guidelines. The CRRT prescription included specific details such as treatment modality, circulation, dilution mode, replacement and dialysis fluid flow, patient weight, and heparin anticoagulation.

The study also highlights the reasons for delayed initiation of RRT, such as organizational issues, unavailability of equipment, difficulty of catheter placement, or the need for surgical interventions or radiological tests before starting RRT. Some patients received intermittent dialysis initially based on factors like hemodynamic stability or equipment availability.

Certain exclusion criteria were applied to patients with urgent need for RRT, including specific laboratory abnormalities (urea > 50 mmol/l, K > 6.5 mmol/l, pH < 7.15) and acute pulmonary edema, and those treated with conservative therapy.

Table 1. Demographic and clinical parameters in critically ill patients and its association with renal recovery function

Variables	Renal function non-recovery n (%)	Renal function recovery n (%)	p
	242 (55)	198 (45)	
Sex Male Female	138/69.7 60/30.3%	156/64.5 86/35.5	p = 0.264
Mean age in years	63.14	60.93	
Comorbidities			
Hypertension	86 (43.4)	103 (42.6)	p = 0.923
Chronic pulmonary disease	25 (12.5)	25 (10.3)	p = 0.455
Diabetes mellitus	43 (21.7)	51 (21.1)	p = 0.907
Cerebrovascular disease	15 (7.6)	23 (9.5)	p = 0.500
Digestive disease	26 (13.1)	29 (12.0)	p = 0.773
Previous kidney disease	16 (8.1)	4 (1.7)	**p = 0.002***
MV support	61 (69.3)	65 (64.4)	p = 0.537
Vasopressor support	138 (69.7)	139 (57.4)	**p = 0.010***
Start of CRRT ≤ 24 hours	121 (61.1)	170 (70.2)	**p = 0.050***
qSOFA score			
0	47(23.7)	76 (31.4)	p = 0.296
1	53 (26.8)	64 (26.4)	
2	26 (13.1)	25 (10.3)	
3	72 (36.4)	77 (31.8)	
Types of CRRT modalities			
CVVHDF	81 (40.9)	88 (36.4)	p = 0.282
CVVHD	72 (36.4)	91 (37.6)	
CVVH	8 (4)	14 (5.8)	
CVVHD + CVVHDF	37 (18.7)	49 (20.2)	
Urea (mmol) + (Mean, SD)	26.32 ± 15.306	26.33 ± 13.962	p = 0.995
Creatinine (μmol) (Mean, SD)	401.43 ± 203.56	373.70 ± 191.51	p = 0.145
CRP (mg/L) (Mean, SD)	153.99 ± 121.44	154.62 ± 126.79	p = 0.966
PCT (ng/l) (Mean, SD)	42.80 ± 68.88	42.59 ± 94.32	p = 0.987
Ultrafiltration (ml) (Mean, SD)	3367.88 ± 5066.81	2592.8 ± 2946.46	**p = 0.046***

CRRT – continuous renal replacement therapy; CVVHDF – continuous veno-venous hemodiafiltration; CVVH – continuous veno-venous hemofiltration; CVVHD – continuous veno-venous hemodialysis; CRP – C-reactive protein; PCT – procalcitonin; MV – mechanical ventilation; qSOFA score – quick sequential organ failure assessment score

CRRT was performed on the Multifilter and the Prismaflex System (Baxter, Deerfield, IL, USA); standard high-flux filters and membranes/adsorbers were used in septic patients. 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 guidelines [9].

The study was carried out according to the principles of the Helsinki Declaration and it was approved by the local Ethics Committee, decision number 00-116.

Statistical analysis

SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical data processing. The obtained data were analyzed using the χ^2 test and t test of independent samples (when examining individual underlying possible predictors) and binomial logistic regression analysis (when examining individual continuous potential predictors, as well as when analyzing the association of all possible predictors along with no renal function recovery). The statistical significance of the influence of potential risk factors for the absence of renal function recovery was examined in the course of the study. The Box–Tidwell test was previously applied in order to confirm that the correlation between each continuous predictor and the corresponding logarithm of the odds ratio is linear.

RESULTS

Out of 440 patients with AKI-D, 242 (55%), average age 63.14, did not recover renal function. In patients who did not recover kidney function, earlier kidney diseases (p = 0.002) and vasopressor therapy (p = 0.010) were significantly more prevalent, and those patients also had a significantly higher average ultrafiltration (ml) (p = 0.046) and a significantly lower percentage of patients started earlier CRRT ≤ 24 hours (p = 0.050). There were more male patients in the group who did not recover their renal function in comparison to the patients who did (69.7% *vs.* 64.5%) (Table 1).

Significant predictors such as age (p = 0.044), CRRT start time (p = 0.043), lung MV (p = 0.044), and previous kidney disease (p = 0.005) were singled out in the entire sample of critically ill patients. CRRT start within 24 hours of AKI diagnosis was associated with a 1.353 times higher risk (95% CI 1.009–1.814) for non-recovery of kidney function, age was associated with a 1.437 times higher risk (95% CI 1.010–2.043), MV was associated with a 1.63 times higher risk (95% CI 1.013–2.633) and previous renal disease with a 5.49 times higher risk for renal function non-recovery (95% CI 1.661–18.148) (Table 2).

In the septic patient group, age (p = 0.002), CRP (p = 0.033), PCT (p = 0.010), diabetes mellitus (DM) (p = 0.023), and previous renal disease (p = 0.045) were significant predictors of renal function non-recovery. The patients over 65 years of age were associated with a 1.63 times higher risk of renal function non-recovery (95% CI 1.063–2.504). The patients over 65 years of age were at three times higher risk (95% CI 1.486–5.760), the ones with CRP higher than 100 mg/l were associated with 2.49 times higher risk (95% CI 1.077–5.748), DM with 2.71 times higher risk (95% CI 1.144–6.414), PCT with 2.84 times higher risk (95% CI 1.279–6.308) and previous kidney disease with 7.08 times higher risk of renal function non-recovery (95% CI 1.046–47.884) (Table 3). In the non-septic group of patients, previous kidney disease was associated with a 6.25 times greater risk of renal function non-recovery (p = 0.035, 95% CI 1.14–34.273) (Table 4).

Table 2. Predictors of renal function non-recovery in critically ill patients requiring dialysis for acute kidney injury with demographic, laboratory and clinical parameters

Parameters	Exp(B)	95% CI for EXP(B)		
		Lower	Upper	Sig.
Sex	1.472	0.940	2.304	0.091
Age	1.437	1.010	2.043	**0.044***
Ultrafiltration	1.081	0.767	1.524	0.657
Modalities of CRRT	0.950	0.787	1.147	0.595
Urea at admission	1.079	0.860	1.353	0.512
Creatinine at admission	1.004	0.979	1.031	0.739
CRP	1.424	0.880	2.304	0.150
PCT	0.620	0.371	1.038	0.069
Length of hospitalization	1.070	0.763	1.502	0.694
Oliguria/anuria	0.649	0.414	1.018	0.060
Start of CRRT ≤ 24 hours	1.353	1.009	1.814	**0.043***
Vasopressors support	0.958	0.507	1.808	0.894
MV support	1.633	1.013	2.633	**0.044***
Sepsis	0.247	0.732	0.431	1.242
CVD	0.886	0.560	1.402	0.606
Pulmonary diseases	1.306	0.850	2.007	0.223
Digestive disease	1.191	0.629	2.254	0.592
Diabetes mellitus	1.299	0.766	2.201	0.331
CD	0.753	0.355	1.599	0.460
Previous kidney disease	5.490	1.661	18.148	**0.005***
Other comorbidities	0.901	0.563	1.443	0.664
qSOFA score	1.111	0.699	1.763	0.657
Constant	0.173			0.167

Exp(B) – odds ratio; CRRT – continuous renal replacement therapy; CRP – C-reactive protein; PCT – procalcitonin; MV – mechanical ventilation; CD – cerebrovascular diseases; CVD – cardiovascular disease; qSOFA score – quick sequential organ failure assessment score

DISCUSSION

Although CRRT has been used for many years in critically ill hemodynamically unstable patients with AKI, the prognosis and recovery of renal function are still uncertain.

A retrospective analysis of the results found that out of a total of 440 patients with AKI, 198 (45%) did not recover their kidney function, which corresponds with previous results [4]. Having analyzed the entire sample, we found that age, the starting time of CRRT, MV, and previous kidney disease play a significant predictive role in the outcome of renal function. The subgroup analysis has also shown that these results were consistent after adjustment for multiple variables. Namely, patients over 65 have a 1.63 times greater risk of renal function non-recovery. In a retrospective study by Jiang et al. [10] that included cardiac surgery patients with AKI, multivariate analysis showed that age was an independent prognostic factor for renal function non-recovery during the first week of CRRT treatment. The authors of previous studies investigated outcomes in patients with AKI treated with CRRT and their results, as well as ours, indicate that older age has a significant prediction for renal function non-recovery [11]. It is highly likely that the reason for such results is the higher frequency of comorbidities in the elderly population, but also the structural and functional changes in the kidney that occur with aging [12]. In critically ill patients, AKI is manifested by varying degrees of uremia, volemia, acid-base status disorders, physiological and non-renal

Table 3. Association between non-recovery of renal function in septic critically ill patients and critically ill patients requiring dialysis for acute kidney injury with demographic, laboratory and clinical parameters

Parameters	Exp(B)	95% C.I. for Exp(B)		
		Lower	Upper	Sig.
Sex	1.728	0.833	3.582	0.142
Age	2.551	1.422	4.579	**0.002***
Ultrafiltration	1.128	0.616	2.066	0.696
Modalities of CRRT	0.997	0.701	1.417	0.986
Urea at admission	1.137	0.749	1.726	0.547
Creatinine at admission	1.012	0.965	1.063	0.616
CRP	2.488	1.077	5.748	**0.033***
PCT	2.841	1.279	6.308	**0.010***
Length of hospitalization	1.234	0.760	2.002	0.395
Oliguria/anuria	0.818	0.380	1.759	0.607
Start of CRRT ≤ 24 hours	1.522	0.926	2.501	0.098
Vasopressors support	0.999	0.296	3.374	0.999
MV support	1.572	0.577	4.284	0.377
CVD	1.391	0.626	3.088	0.418
Pulmonary diseases	1.904	0.776	4.670	0.159
Digestive disease	2.604	0.874	7.757	0.086
Diabetes mellitus	2.709	1.144	6.414	**0.023***
CD	1.562	0.371	6.583	0.543
Previous kidney disease	7.077	1.046	47.894	**0.045***
Other comorbidities	1.522	0.699	3.314	0.290
qSOFA score	0.763	0.354	1.645	0.489
Constant				

Exp(B) – odds ratio; CRRT – continuous renal replacement therapy; CRP – C-reactive protein; PCT – procalcitonin; MV – mechanical ventilation; CD – cerebrovascular diseases; CVD – cardiovascular diseases; qSOFA score – quick sequential organ failure assessment score

Table 4. Association between non-recovery of renal function in non-septic critically ill patients requiring dialysis for acute kidney injury with demographic, laboratory and clinical parameters

Parameters	Exp(B)	95% C.I. for Exp(B)		
		Lower	Upper	Sig.
Sex	1.541	0.816	2.911	0.183
Age	0.981	0.604	1.594	0.939
Ultrafiltration	0.852	0.531	1.367	0.507
Modalities of CRRT	0.938	0.735	1.197	0.608
Urea at admission	1.040	0.776	1.394	0.794
Creatinine at admission	1.002	0.969	1.037	0.887
CRP	1.093	0.578	2.070	0.784
Length of hospitalization	0.776	0.420	1.435	0.419
Oliguria/anuria	1.985	1.053	3.743	**0.034***
Start of CRRT ≤ 24 hours	1.321	0.872	2.002	0.189
Vasopressors support	0.814	0.402	1.647	0.567
MV support	1.423	0.749	2.702	0.282
CVD	0.640	0.338	1.211	0.170
Pulmonary diseases	0.756	0.310	1.843	0.538
Digestive disease	0.840	0.344	2.052	0.702
Diabetes mellitus	0.822	0.389	1.737	0.607
CD	0.621	0.238	1.619	0.330
Previous kidney disease	6.251	1.140	34.273	**0.035***
Other comorbidities	0.632	0.322	1.242	0.183
qSOFA score	1.440	0.746	2.780	0.277
Constant	0.524			0.703

Exp(B) – odds ratio; CRRT – continuous renal replacement therapy; CRP – C-reactive protein; MV – mechanical ventilation; CD – cerebrovascular diseases; CVD – cardiovascular diseases; qSOFA score – quick sequential organ failure assessment score

disorders, and often has a variable course. The decision to start RRT in these patients may depend on numerous factors and it represents a very complex process [13]. In relation to that, the start time of RRT has been difficult to study and has shown considerable variations of clinicians and institutions [14]. Due to its changeable clinical course of AKI, constant monitoring of patients is necessary to ensure that RRT starts timely, i.e., before the appearance of uremic and metabolic complications, but when there are signs of general improvement in the clinical condition and spontaneous recovery of renal function. The results of our study indicate that "early" initiation of RRT in critically ill patients with AKI significantly affects the rate of renal function non-recovery. Contrary to our results, Lin et al. [15] have concluded that the "early" start of RRT does not significantly affect the recovery of kidney function. The aforementioned results correspond to the meta-analysis published by Ponce et al. [16], where it was found that "early" initiation of RRT increases the chance of recovery of renal function by 30% compared to the "late" one. Our previous study, which aimed to identify predictors of kidney function recovery, with the very same criteria used both for "early" and "late" CRRT start time just like in this study, did not find any predictors of recovery of renal function in the "early" group, while in the "late" CRRT group, non-diabetic patients were found to have a 3.5 times higher chance of function recovery compared to patients with DM [17]. Completely different results were published in research by Castro et al. [18] and indicated that "early" initiation of RRT has no significant effect on the recovery of renal function. However, the studies included in this analysis were highly prone to be biased due to the study design itself, mixed cases, definition of timing of RRT initiation and variation in outcome determination [18]. MV, while essential in providing respiratory support for critically ill patients, can potentially exacerbate pre-existing lung injury or lead to the development of new lung injury, commonly known as ventilator-associated lung injury [19]. According to the available literature, we have observed that the majority of studies investigated the impact of MV on the development of AKI in critically ill patients, but we have not found any research on whether MV has an impact on the recovery of renal function. In our study, we found that MV was associated with a 1.63 times higher risk for failure to recover renal function. In a randomized clinical study, Yang et al. [20] found that protective MV compared to conventional MV had no significant effect on AKI progression, although AKI progression occurred in both groups of patients. Ostermann and Lumlertgul [21] performed a murine model of ventilator-associated lung injury and concluded that a short period of MV with high tidal volumes (17 mL/kg) causes increased lung permeability and liver and kidney inflammation. As pulmonary MV affects both the onset and progression of AKI, it probably has an effect on the recovery of renal function as well, which needs to be determined in future prospective randomized trials.

In the subgroup of septic patients, DM was linked to a 2.71 times higher risk and previous kidney disease with a 7.08 times higher risk of renal function non-recovery. Various studies indicate that DM potentially increases morbidity and mortality in patients with AKI [22]. In a multicenter study by Chung et al. [23], DM did not increase the risk of developing AKI, but significantly decreased the probability of renal function recovery. Regarding previous kidney conditions and renal function recovery, our results correlate with most studies, one of which was conducted by Vijayan et al. [24], which included patients with previous kidney diseases were significantly less likely to recover renal function after AKI. However, we must take into account that the aforementioned authors followed the long-term effects of comorbidities on the recovery of renal function.

In a cohort analysis of the 131 critically ill patients with AKI who underwent the CRRT, along with the older age, two other determined predictors that we did not examine (coronary artery disease and admission to the ICU) were associated with a lower rate of renal function recovery [11].

While our study provides valuable insights, it is important to acknowledge the limitations associated with it. Firstly, this study was conducted retrospectively in a single center, which may limit the generalizability of the findings to other settings or patient populations.

Additionally, we lacked specific data on the etiology of AKI-D, diuresis, and the use of diuretics. These factors could potentially influence the recovery of renal function and should be considered in future studies for a more comprehensive analysis.

Furthermore, we did not have detailed information on the parameters of the CRRT procedure. Factors such as the specific modality of CRRT, dialysis dose, choice of dialysis membrane, and duration of dialysis could potentially impact the chances of renal function recovery. Although there is no definitive evidence linking these factors to the recovery of renal function, their potential influence cannot be entirely ruled out.

Despite these limitations, our study contributes valuable information on the predictors of renal function non-recovery in critically ill patients with dialysis-dependent AKI. It underscores the importance of individual consideration of potential predictors and highlights the need for further research to address the limitations and expand our knowledge in this area [25. 26, 27].

CONCLUSION

After conducting both group and subgroup analyses, it was found that among all the predictors investigated, previous kidney conditions pose the highest risk for the failure to recover kidney function in critically ill patients with dialysis-dependent AKI. It is important to look at individual and overall predictors so that clinicians can assess the potential for recovery of kidney function and implement appropriate interventions to improve outcomes.

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Предиктори неопоравка функције бубрега код критично оболелих болесника са акутним оштећењем бубрега лечених континуираном дијализом

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САЖЕТАК

Увод/Циљ Акутно оштећење бубрега (АОБ) честа је компликација код критично оболелих болесника хоспитализованих у одељењима интензивног лечења. Циљ ове студије је утврђивање преваленције и предиктора неопоравка функције бубрега код критично оболелих болесника са АОБ зависним од дијализе (АОБ-Д).

Методе Студијом је било обухваћено 440 болесника лечених на одељењу интензивног лечења Универзитетског клиничког центра Војводине у периоду од 2014. до 2018. године који су захтевали континуирану замену функције бубрега. Анализирани су демографски, клинички и лабораторијски параметри, коморбидитети, потреба за вазопресорном терапијом и механичком вентилацијом у дану потврђеног АОБ и модалитети замене функције бубрега.

Резултати Ретроспективном анализом резултата установљено је да од укупно 440 болесника са АОБ-Д, 242 (55%) болесника, просечне старости 63,14 година, нису опоравила функцију бубрега. Значајни предиктори неопоравка функције бубрега код критично оболелих са АОБ-Д били су: старост изнад 65 година ($p = 0,044$), време почетка терапије замене функције бубрега ($p = 0,043$), механичка вентилација ($p = 0,044$) и претходне болести бубрега ($p = 0,005$). Значајни предиктори неопоравка функције бубрега код септичних болесника са АОБ-Д били су: старост изнад 65 година ($p = 0,002$), дијабетес мелитус ($p = 0,023$), претходне болести бубрега ($p = 0,045$), *CRP* вредности < 100 *mg/l* ($p = 0,033$) и прокалцитонин ($p = 0,010$), док су значајан предиктор неопоравка функције бубрега код критично оболелих болесника без сепсе биле претходне болести бубрега ($p = 0,035$).

Закључак Од свих испитиваних предиктора на укупном узорку, и код септичних и код несептичних болесника, претходне бубрежне болести представљају највећи ризик за неопоравак функције бубрега код критично оболелих болесника са АОБ-Д.

Кључне речи: акутно оштећење бубрега; опоравак бубрежне функције; критично оболели; сепса