

Differences in CVVH vs. CVVHDF in the management of sepsis-induced acute kidney injury in critically ill patients

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Abstract We hypothesized that patients with sepsis and AKI, especially patients without preserved renal function, and treated with continuous veno-venous hemodiafiltration (CVVHDF), have lower risk for mortality than patients treated with continuous veno-venous hemofiltration (CVVH). Patients were included if they fulfilled the diagnosis of severe sepsis or septic shock, suffered AKI and received continuous renal replacement therapy (CRRT) in intensive care unit. There were 62 patients treated by CVVH and 75 treated by CVVHDF. Mean survival time was longer in CVVHDF group with oliguric/anuric patients than in CVVH group. CVVH, and not classic risk factors, was associated with higher overall mortality in oliguric/anuric patients. In the linear regression model, hourly urine output was the strongest and positive predictor of longer survival. CVVHDF is according to our results a CRRT modality of choice for the treatment and lower mortality of septic patients with AKI where renal function is no longer preserved. CRRT has been associated with improved renal recovery, but it should be started earlier in AKI evolution with still preserved hourly urine output which is the most sensitive and prognostic marker of survival in septic patients with AKI.

Keywords Sepsis · Acute kidney injury · Survival · Continuous renal replacement therapy

Introduction

Sepsis is a serious medical condition characterized by a whole-body inflammatory state (systemic inflammatory-response syndrome, SIRS) and the presence of a known or suspected infection that has severe consequences, including multiple organ failure (MOF). The clinical diagnosis of sepsis requires finding a focus of infection as well as at least two signs of SIRS that comprise abnormal body temperature (higher than 38 °C or less than 36 °C), heart rate >90 beats/min, respiration >20 breaths/min or arterial partial pressure of CO₂ <32 mmHg, and deranged white blood cell counts (greater than $12 \times 10^3/\text{mm}^3$, less than $4 \times 10^3/\text{mm}^3$, or greater than 10% immature bands [1]). The progress of sepsis in severe sepsis is characterized by failure of organ systems and can be identified as an acute change in total Sequential Organ Failure Assessment (SOFA) score ≥ 2 points consequent to the infection. Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mmHg and having a serum lactate level >2 mmol/L despite adequate volume resuscitation [2, 3].

Acute kidney injury (AKI) is a frequent and serious complication of sepsis in intensive care unit (ICU) patients, in all age groups [4]. Moreover, there is strong evidence that sepsis and septic shock are the most important causes of AKI in critically ill patients, account for 50% or more of cases of AKI in ICUs, and associate with a very high mortality [5, 6].

The pathophysiology of AKI in sepsis is complex and multi-factorial and includes intrarenal hemodynamic changes, endothelial dysfunction, infiltration of

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inflammatory cells in the renal parenchyma, intraglomerular thrombosis, and obstruction of tubules with necrotic cells and debris [5]. A growing body of evidence now suggests that the sepsis-induced immune responses involve the activation, in a sequential manner, of both pro- and anti-inflammatory mechanisms [7].

Some studies suggest that continuous renal replacement therapy (CRRT) is associated with increased ability to clear inflammatory mediators [5, 6] from septic patients with AKI. There are two methods of clearance in continuous veno-venous hemodiafiltration (CVVHDF), diffusion and convection, while only convection in continuous veno-venous hemofiltration (CVVH). Convective modalities (hemofiltration) may provide better clearance of middle molecular weight solutes like cytokines compared with diffusive modalities [7]. Nevertheless, there are only few studies examining the impact of different CRRT modalities, especially CVVH and CVVHDF on survival in septic patients with AKI.

As sepsis associated with AKI has an increased short-term mortality and increased circulating cytokines mediate the development of septic shock and sepsis-associated AKI, we hypothesized that patients with sepsis and AKI and treated with CVVHDF have lower risk for mortality than other patients treated with CVVH. Additionally, because there are no present data on possible differences in survival of oligoanuric and non-oliguric septic patients with AKI, we hypothesized that CVVHDF, a combination of two methods, is a CRRT modality of choice for the treatment and lower mortality of septic patients with AKI where renal function is no longer preserved. To test this hypotheses, we analyzed clinical course of the patients through the hospitalization and survival rate after follow-up.

Materials and methods

This was a retrospective, longitudinal follow-up study for 12 months duration. In total, 137 patients were recruited from the ICUs in University Hospital Center Zagreb, Croatia.

Patients were included if they fulfilled the diagnosis of severe sepsis or septic shock, suffered AKI and received CRRT in ICU. Sepsis was defined as the presence of suspected or documented infection together with systemic inflammatory response syndrome while septic shock was defined as a status of sepsis with acute circulatory failure according to the American College of Chest Physicians/Society of Critical Care Medicine/European Society of Intensive Care Medicine criteria [1]. Other inclusion criteria included renal dysfunction (defined on the basis of an estimated creatinine clearance—eGFR, mL/min was

calculated daily using the simplified Modification of Diet in Renal Disease (MDRD) equation [8]. Acute kidney injury was defined by a modified definition of the Kidney Disease: Improving Global Outcomes (KDIGO) AKI Workgroup, harmonizing differences between the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) and the Acute Kidney Injury Network (AKIN) definitions [9]. Those with age less than 18 years old, presence of chronic kidney disease stage 5 (GFR <15 mL/min per 1.73/m²), end-stage renal failure on long-term dialysis or those treated with RRT before ICU admission were excluded.

Hourly fluid input and urine output data were extracted from ICU charts. At admission and after each treatment documented body weight was used. Patient follow-up continued until the last enrolled patient reached the 365-day time point. Each patient underwent a complete clinical and laboratory examination at the time of admission and during hospitalization. Selection of CVVH and CVVHDF as the primary treatment method was the choice of the involved nephrologist. Generally, patients with lower eGFR levels and a need of diffusion for reduction of serum creatinine and blood urea nitrogen (BUN) or potassium levels were referred for CVVHDF. Both modalities, CVVH and CVVHDF, were performed for each patient using the Prismaflex[®] CRRT and M100 membrane filters (Baxter Int., Deerfield, Illinois, USA). The patients have been followed by telemetry unit. A patient to nurse ratio was 2:1. Forty-five percent of patients were treated with CVVH and 55% with CVVHDF. Data for each patient concerning UF rates, duration of each treatment, blood, dialysate and replacement fluid pump flows and total number of treatments were obtained. Blood flow rate was maintained at between 200 and 250 mL/min, according to blood-access function and desired UF rates. Anti-coagulation was performed according to patient condition, either with low-molecular weight heparin or heparin-free anti-coagulation. The hemofilter and the extracorporeal circuit were replaced every 72 h. Ultrafiltration rates were prescribed depending on patients cardiac status, fluid overload and hourly urine output. The rates of reinfusion and dialysate were prescribed aiming at the dose of dialysis >35 mL/kg/h.

Discontinuation of treatment and discharge has been done by the treating intensive care physician (after consultation with nephrologist), based on clinically assessed volume status, symptoms, and objective data (including laboratory values). Plasma creatinine, blood urea nitrogen (BUN), serum sodium and potassium, C-reactive protein, serum albumin and white cell blood count were analyzed from blood samples at start and at the end of each treatment. Systolic and diastolic blood pressure were measured before, during and after each treatment (and in the

meantime, as it was indicated). A direct measurement of volume overload has been performed using central venous catheter (CVP, expressed in mmHg).

Ethical approval: All subjects enrolled in this research have given their informed consent, which has been approved by my institutional committee on human research, and this protocol has been found acceptable by them.

Statistical analysis was performed using SPSS version 23.0 (IBM Corp., USA). Normality of data distribution was tested using Kolmogorov–Smirnov test. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity. Descriptive characteristics were expressed as numbers and frequencies. Correlations were obtained using Pearson's test for normally distributed variables and Spearman rank correlation for non-normally distributed variables. Normally distributed variables were presented as means + standard deviations and Student's *t* test for independent samples was used for comparisons between two groups. Non-normally distributed data were presented as median and interquartile range and Mann–Whitney *U* test was used in comparison between two groups. Baseline-to-follow-up comparisons were done using Student's *t* test for paired samples and Wilcoxon test. Categorical variables were compared using χ^2 test. Survival analysis was done with Kaplan–Meier curves which were tested with log-rank test while hazard ratios were estimated with Cox proportional hazards regression. Multiple linear regression was used to explore the influence of different variables on survival, while logistic regression was used for categorical dependent variables. We constructed three regression models to assess independent associations of multiple independent variables with patients survival. In Model 1, we included variables known to be associated with increased mortality and related to dialysis: age, body weight at baseline and the end of the treatment, duration of dialysis, hourly urine output, sex and the presence of diabetes and hypertension (yes/no). Model 2 included, in addition to all variables in Model 1 those further related to the dialysis: serum creatinine, BUN, ultrafiltration rate and central venous pressure at baseline and end of the treatment. Model 3 was additionally adjusted for established laboratory parameters of sepsis and chronic disease: c-reactive protein and serum albumins. A *p* value <0.05 (two-sided tests) was considered significant.

Results

There were 62 patients treated by CVVH (37/59.6%/males) and 75 CVVHDF-treated patients (42/56.0%/males) at the beginning of the study. The follow-up completed 44

CVVH-treated patients and 45 CVVHDF-treated patients. Demographic, laboratory and clinical characteristics of patients treated with CVVH and CVVHDF at start and end of the treatments are demonstrated in Table 1. There were no differences in age and gender between CVVH and CVVHDF groups and with no differences in percentage of arterial hypertension or diabetes. No significant differences were observed in body weight, duration of hospitalization and number of dialysis treatments both at start and end of the treatments. Patients treated with CVVH had bigger reinfusion and ultrafiltration rates (UFR) than CVVHDF patients ($p < 0.05$). The standard dialysate flow rate for patients treated with CVVHDF was 1309 mL/h. The initialization of treatments was at significantly higher values of serum creatinine and BUN in CVVHDF patients while there was no difference in hourly urine output between two groups of patients. As shown in Table 1 at start and at the end of the treatments, there were no differences in brachial BP values and CVP values as well as in laboratory markers of sepsis, CRP, WBC and albumins. There was no difference in survival between two groups of patients. When patients were divided by hourly urine output on oliguric/anuric and non-oliguric, we did not find any significant differences between two groups of patients except longer survival in non-oliguric group. On univariate analysis survival was in all patients negatively correlated with age ($r = -0.329$; $p < 0.001$), duration of dialysis ($r = -0.193$; $p = 0.024$) and serum creatinine ($r = -0.209$; $p = 0.014$) at the end of the treatments and positively with hourly urine output ($r = 0.573$; $p < 0.001$) and serum albumins ($r = 0.172$; $p = 0.044$). In oliguric/anuric patients, we did not find any significant correlations between survival and other variables. In all three linear regression models hourly urine output was the strongest and positive predictor of longer survival ($\beta = 0.492$, $\beta = 0.496$ and $\beta = 0.492$, all $p < 0.001$) (see Table 2). Additionally, in Model 1 (adjusted $R^2 = 0.395$) age ($\beta = -0.282$, $p < 0.001$) and duration of dialysis ($\beta = -0.188$, $p = 0.007$) showed negative association with survival. In Model 2 (adjusted $R^2 = 0.413$) age ($\beta = -0.266$, $p < 0.001$) and duration of dialysis ($\beta = -0.217$, $p = 0.003$) were negatively associated with survival. Model 3 (adjusted $R^2 = 0.403$) showed negative significant associations of survival with age ($\beta = -0.266$, $p < 0.001$) and duration of dialysis ($\beta = 0.0216$, $p = 0.004$). The patients were followed for 12 months, 21 CVVH and 27 CVVHDF patients survived. Thirty-one patients have died from multi-organ failure caused by sepsis and ten patients have died from heart failure in the CVVH group while 33 patients have died from multi-organ failure caused by sepsis and 15 patients have died from heart failure in the CVVHDF group of patients. There was no difference in mean survival time between CVVH and

Table 1 Demographic, clinical and laboratory data of enrolled patients

	CVVH	CVVHDF	<i>p</i>
No. of patients	62	75	
Age (years)	62.5 (42.8–81.4)	62.9 (42.6–82.2)	0.87
Sex (male) <i>N</i> (%)	37 (59.6%)	42 (56.0%)	0.57
Body weight (kg) baseline	81.5 ± 10.5	80.5 ± 10.4	0.57
Body weight (kg) end of treatments	80 (55–116)	79 (54–112)	0.48
Duration of hospitalization (days)	32.8 (7.4–58.6)	34.5 (8.2–59.8)	0.64
Hypertension (yes) <i>N</i> (%)	42 (67.7%)	49 (65.3%)	0.34
Diabetes (yes) <i>N</i> (%)	18 (29.0%)	20 (26.6%)	0.31
Duration of dialysis (h)	18 (12–25)	17 (11–23)	0.45
Blood pump flow (mL/h)	216 (158–278)	222 (164–286)	0.29
Reinfusion pump flow (mL/h)	1887 (1324–2292)	1281 (892–1706)	<0.001
UFR (mL/h)	149 (130–161)	124 (102–148)	0.01
Total days of dialysis	15.7 (12.0–19.2)	17.4 (13.1–21.3)	0.59
eGFR (mL/min) baseline	21.0 (14.8–27.2)	15.2 (10.6–19.8)	<0.001
Serum creatinine (μmol/L) baseline	284 (226–352)	388 (320–456)	<0.001
eGFR (mL/min) end of treatments	29.1 (23.3–35.4)	32.4 (26.8–38.1)	0.36
Serum creatinine (μmol/L) end of treatments	211 (154–273)	197 (135–260)	0.43
BUN (nmol/L) baseline	25.8 (21.6–32.0)	27.8 (23.2–33.6)	0.30
BUN (nmol/L) end of treatments+	19.9 ± 2.1	15.1 ± 2.9	0.04
Sodium (mmol/L) baseline	135 (127–144)	135 (125–143)	0.95
Sodium (mmol/L) end of treatments	135 (126–143)	134 (123–144)	0.23
Potassium (mmol/L) baseline	4.3 (3.9–4.8)	4.4 (3.9–4.8)	<0.001
Potassium (mmol/L) end of treatments	4.0 (3.6–4.5)	4.1 (3.6–4.6)	0.05
C-reactive protein (mg/L)	173.3 (102.6–258.4)	173.2 (104.2–254.6)	0.99
WBC (×10 ⁹ /L)	16.3 (12.4–20.8)	16.9 (12.8–21.2)	0.62
Serum albumin (g/L)	39.1 (26.8–52.6)	39.4 (26.2–52.9)	0.86
Systolic blood pressure (mmHg) baseline	133 (112–154)	132 (110–152)	0.34
Systolic blood pressure (mmHg) end of treatments	121 (104–138)	122 (106–140)	0.55
Diastolic blood pressure (mmHg) baseline	84 (70–94)	84 (72–96)	0.58
Diastolic blood pressure (mmHg) end of treatments	72 (64–82)	72 (62–81)	0.78
Central venous pressure (mmHg) baseline+	21 (5–30)	20 (4–28)	0.18
Central venous pressure (mmHg) end of treatments	14.5 ± 3.4	14.1 ± 3.2	0.52
Hourly urine output (mL/h)	10.3 ± 0.4	9.5 ± 0.5	0.22
Survival (days)	189 (120–258)	177 (102–256)	0.64

CVVH continuous veno-venous hemofiltration, CVVHDF continuous veno-venous hemodiafiltration, UFR ultrafiltration rate; eGFR estimated glomerular filtration rate, BUN blood urea nitrogen; WBC white blood count; results are shown as mean ± SD or median (interquartile range)

CVVHDF patients [280.1 (95% CI 249.9, 311.6) vs. 274.7 (95% CI 239.9, 310.6) days] (Fig. 1). Demographic, laboratory and clinical characteristics of oliguric/anuric patients with treated with CVVH and CVVHDF are demonstrated in Table 3. There were no differences in age, gender and percentage of arterial hypertension and diabetes between CVVH and CVVHDF groups. There were no differences in dialysis parameters between two groups. The initialization of treatments was at significantly higher values of serum creatinine in CVVHDF patients (*p* = 0.03). Mean survival

time was longer in CVVHDF group with oliguric/anuric patients than in CVVH group [110.4 (95% CI 53.8, 167.1) vs. 22.9 (95% CI 0.9, 51.2) days, log-rank *p* = 0.006] (Fig. 2). All non-oliguric patients had a significantly longer survival time compared to oliguric/anuric patients group [229.5 (95% CI 199.9, 259.1) vs. 74.2 (95% CI 36.7, 111.6) days, log-rank *p* < 0.001]. Non-oliguric patients treated with CVVH had significant longer survival than oliguric/anuric patients as well as patients treated with CVVHDF modality (both log-rank *p* < 0.001). CVVH [HR 2.06

Table 2 Linear regression model

BetaModel	Unstandardized coefficients	Standardized coefficients	<i>t</i>	Sig.	
Coefficients ^a					
IB SE					
(constant)	111.419	146.097	0.763	0.447	
Age	−2.862	0.757	−0.266	−3.783	0.000
Body weight baseline	7.877	4.296	0.521	1.833	0.069
Body weight end of treatments	−7.827	4.513	−0.492	−1.735	0.085
Duration of dialysis	−6.413	2.201	−0.216	−2.914	0.004
Hourly urine output	20.428	2.959	0.492	6.904	0.000
Sex $m = 0 \quad \bar{z} = 1$	24.293	24.808	0.071	0.979	0.329
Hypertension $da = 0 \quad ne = 1$	7.892	23.682	0.024	0.333	0.740
Diabetes $da = 0 \quad ne = 1$	37.030	31.366	0.089	1.181	0.240
Ultrafiltration	−0.035	0.205	−0.013	−0.172	0.863
Creatinine baseline	−0.033	0.082	−0.034	−0.397	0.692
Creatinine end of treatments	−0.033	0.125	−0.022	−0.264	0.792
CVP baseline	−0.674	3.334	−0.022	−0.202	0.840
CVP end of treatments	8.211	4.614	0.194	1.780	0.078
C-reactive protein	0.111	0.141	0.055	0.788	0.432
Albumins	0.771	1.843	0.052	0.418	0.676

CVP central venous pressure

^a Dependent variable: survival in days

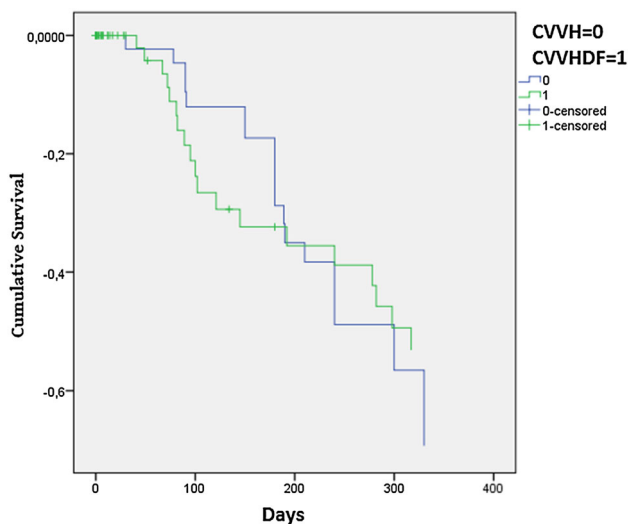


Fig. 1 Outcome for 1-year survival in all patients subdivided by CVVH or CVVHDF treatment at the end of follow-up. CVVH continuous veno-venous hemofiltration, CVVHDF continuous veno-venous hemodiafiltration

(0.98, 4.32)] and not classic risk factors as age, dialysis parameters and inflammatory marker levels were associated with higher overall mortality in oliguric/anuric patients while in all groups of patients only age [HR 1.04 (1.02, 1.06)] was associated with higher overall mortality.

We have not find significant differences in survival time in non-oliguric patients treated with CVVH and CVVHDF (Fig. 3) as well when patients were divided by different dose of dialysis and hourly urine output. There were no differences in renal survival between CVVH and CVVHDF in survived patients. Renal outcome transitioned to chronic hemodialysis in four patients in CVVH group and three patients in CVVHDF group.

Discussion

Sepsis and septic shock remain the most important cause of AKI in critically ill patients and septic-associated AKI. They account for approximately 50% of cases of AKI in the ICU [10–12], complicate between 15 and 20% of all ICU admissions with severe septic-associated AKI, and are responsible for triggering renal replacement therapy in 2–3% of all ICU admission [13, 14]. Mortality in patients with sepsis and AKI is still very high (between 40 and 55%), as it was demonstrated by two recent large studies [15, 16]. When compared with AKI of nonseptic origin, septic AKI patients have a significantly and unacceptably high mortality [17]. Unlike to previous reviews, AKI is a relatively common cause of long-term mortality and development of chronic renal failure (including end-stage

Table 3 Demographic, clinical and laboratory data in oliguric/anuric patients

	CVVH	CVVHDF	<i>p</i>
No. of patients	17	24	
Age (years)	65.7 (44.2–80.1)	63.0 (42.0–79.8)	0.52
Sex (men) <i>N</i> (%)	7 (41.1%)	10 (41.6%)	0.39
Body weight (kg) baseline	78.8 ± 10.5	80.8 ± 9.5	0.54
Body weight (kg) end of treatments	79 (48–106)	78 (46–100)	0.92
Duration of hospitalization (days)	26.0 (8.2–47.1)	28.8 (9.4–49.2)	0.60
Hypertension (yes) <i>N</i> (%)	6 (35.3%)	10 (41.6%)	0.09
Diabetes (yes) <i>N</i> (%)	5 (29.4%)	7 (29.1%)	0.59
Duration of dialysis (h)	18.1 (13.4–23.7)	17.7 (12.2–21.8)	0.81
Blood pump flow (mL/h)	240 (218–272)	227 (201–259)	0.16
UFR (mL/h)	165 (142–182)	133 (111–159)	0.12
Total days of dialysis	13.4 (11.4–15.7)	14.9 (12.8–16.5)	0.77
eGFR (mL/min) baseline	22.3 (16.1–28.2)	14.2 (8.1–20.3)	0.02
Serum creatinine (μmol/L) baseline	272 (210–341)	394 (331–460)	0.03
eGFR (mL/min) end of treatments	27.5 (21.2–33.8)	29.5 (23.1–35.8)	0.61
Serum creatinine (μmol/L) end of treatments	227 (160–289)	214 (151–279)	0.72
BUN (nmol/L) baseline	24.2 (20.1–27.9)	25.0 (21.2–29.2)	0.79
BUN (nmol/L) end of treatments	18.9 (14.1–23.8)	16.0 (12.3–21.8)	0.29
Sodium (mmol/L) baseline	135 (124–146)	135 (123–147)	0.29
Sodium (mmol/L) end of treatments	134 (121–144)	134 (120–144)	0.41
Potassium (mmol/L) baseline	4.3 ± 0.1	4.5 ± 0.1	0.005
Potassium (mmol/L) end of treatments	4.0 ± 0.1	4.2 ± 0.1	0.05
C-reactive protein (mg/L)	179.9 (112.2–250.1)	177.7 (110.8–246.6)	0.94
WBC (×10 ⁹ /L)	17.8 (12.7–23.2)	17.0 (12.2–22.9)	0.15
Serum albumins (g/L)	38.4 (21.4–54.4)	33.3 (16.3–50.1)	0.68
Systolic blood pressure (mmHg) baseline	134 (114–152)	130 (108–156)	0.14
Systolic blood pressure (mmHg) end of treatments	124 (105–140)	122 (107–139)	0.53
Diastolic blood pressure (mmHg) baseline	84 (70–96)	83 (71–94)	0.47
Diastolic blood pressure (mmHg) end of treatments	71 (63–80)	72 (62–82)	0.45
Central venous pressure (mmHg) baseline	23 (6–31)	20 (4–29)	0.07
Central venous pressure (mmHg) end of treatments	15.1 ± 2.5	13.7 ± 2.2	0.22
Survival (days)	23 (8–39)	110 (87–138)	0.01

CVVH continuous veno-venous hemofiltration, CVVHDF continuous veno-venous hemodiafiltration, UFR ultrafiltration rate, eGFR estimated glomerular filtration rate, BUN blood urea nitrogen, WBC white blood count; results are shown as mean ± SD or median (interquartile range)

renal failure, ESRD). There are only few present data comparing different CRRT modalities, namely CVVH and CVVHDF for treatment of septic patients with associated AKI.

In this study, we did not find significant difference in survival between septic patients with associated AKI treated with CVVH and CVVHDF at the end of the follow-up period (Fig. 1). To our knowledge, this is in agreement with only one present study [18]. Although patients treated with CVVH had higher reinfusion and UF rates than CVVHDF patients, treatments were initiated at significantly higher values of serum creatinine and BUN in CVVHDF patients with no difference in hourly urine

output between two groups of patients (Table 1). Treatment was initiated at similar levels of sepsis parameters in both groups of patients. Patients treated with CVVHDF had a significant decrease in serum creatinine and BUN levels at the end of the follow-up compared to CVVH patients as a sign of combination of two basic principles of dialysis, convection and diffusion.

Hourly urine output is a sensitive and specific biomarker that provides an early warning signal for AKI and higher mortality [19, 20]. The hourly urine output in our study was a significant and independent predictor of longer survival in all patients with the same association present when they were divided by hourly urine output in non-oliguric

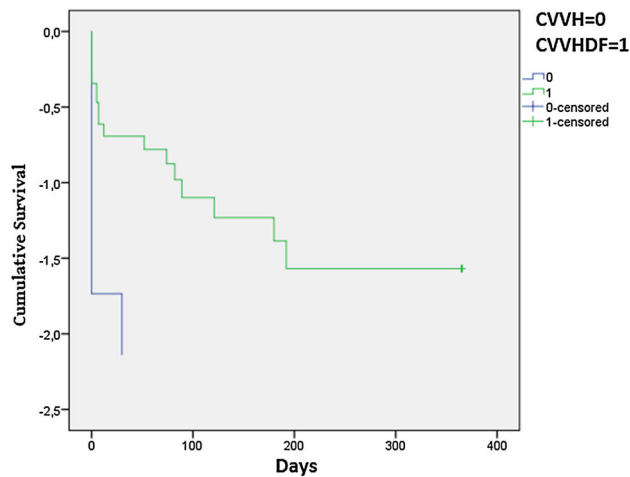


Fig. 2 Outcome for 1-year survival in oliguric/anuric patients subdivided by CVVH or CVVHDF treatment at the end of follow-up. CVVH continuous veno-venous hemofiltration, CVVHDF continuous veno-venous hemodiafiltration

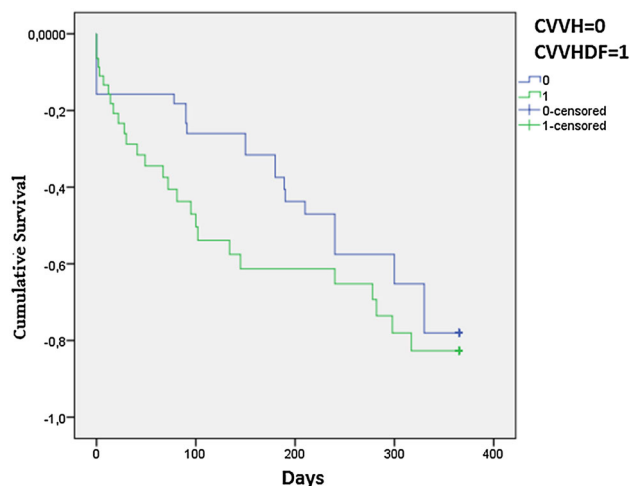


Fig. 3 Outcome for 1-year survival in non-oliguric patients subdivided by CVVH or CVVHDF treatment at the end of follow-up. CVVH continuous veno-venous hemofiltration, CVVHDF continuous veno-venous hemodiafiltration

subgroup. Regarding our results, serum creatinine and BUN were not significant predictors of better survival. When divided only by hourly urine output, patients with urine output <10 mL/h did not survive longer compared to patients with urine output >10 mL/h.

Although CRRT removes pro- and anti-inflammatory cytokines, outcomes do not seem to be affected regardless of the dose applied [21, 22] which was the same as the results in our study.

When divided on subgroups by hourly urine output and different CRRT modality, significantly higher number of patients with oliguria/anuria treated with CVVHDF survived compared to patients treated with CVVH (Fig. 2).

Interestingly, there was no difference in survival in non-oliguric patients treated with different CRRT modalities (Fig. 3).

Sepsis is characterized by release of excessive amounts of pro-inflammatory cytokines in the circulation which could be downregulated with the CRRT by nonspecific extracorporeal removal of cytokines and other mediators [21–23]. Some studies indicate that cytokine removal with current CRRT methods and synthetic membranes is more convective than diffusive [24, 25] which is in contrast to our findings. The results from Graziani et al. [26] suggested that in septic patients with preserved diuresis some pro-inflammatory cytokines were removed from the plasma and non-oliguric patients had a better prognosis than oliguric/anuric patients. No difference in survival between non-oliguric septic patients treated with CVVH and CVVHDF could be observed through the cytokine removal from the plasma due to still preserved diuresis while in the other group of patients, kidneys lost the function of cytokine removal. It is possible that cytokine accumulation was better controlled with the combination of convection and diffusion, which is in contrast with previous results, especially when taking into account the fact that the improvement of eGFR and, therefore, renal function was more pronounced in CVVHDF patients. Furthermore, CVVH and not CVVHDF was associated with higher overall mortality in oliguric/anuric patients. However, this hypothesis needs further investigations.

When we compared patients with different hourly urine output, all oliguric/anuric patients and those treated with different CRRT methods survived significantly shorter compared to non-oliguric patients. This is an additional argument for our hypothesis of cytokine removal by still preserved renal hourly urine output in septic patients with AKI.

This is the first study which analyzed the impact of different CRRT modalities (CVVH vs. CVVHDF) and hourly urine output on survival of septic patients with AKI. Our results on better survival of septic oliguric/anuric patients treated with CVVHDF are in line with our hypothesis that CVVHDF, a combination of two methods, is a CRRT modality of choice for the treatment and lower mortality of septic patients with AKI where renal function is no longer preserved. The present study suggests that the use of CVVHDF in septic non-oliguric patients is not associated with improved survival when compared with CVVH. Furthermore, the cytokine reduction in septic patients could not be only achieved by CRRT, especially when renal function is still preserved and kidneys have the ability of cytokine removal from plasma. Based on our results, hourly urine output is the most sensitive and prognostic marker of survival in septic patients with AKI.

Our work has several limitations. First, the study was an observational, non-randomised performed in a single centre and it could be limited by a relatively small sample size. Second, cytokine levels were not measured in this study. Plasma levels of TNF alpha, IL-1b, IL-6 and IL-8, related to pro-inflammatory state have a greater accuracy than clinical signs for the diagnosis of sepsis. The effect of cytokine removal by CVVHDF, especially in oliguric/anuric patients, could not be assessed directly but only by clinical signs and better survival compared to patients treated with CVVH. Third, all the included patients already had a presence of AKI. Some could argue why we did not include patients treated with CVVHD and, therefore, analyzed the impact on survival of three different CRRT modalities. In patients with AKI and a clinical signs of sepsis, convection, and not diffusion, has been considered a method of choice [27, 28] and we wanted to analyze only the addition of diffusion to convection. Furthermore, most patients treated with CVVHD had a presence of previous chronic kidney disease so they were not eligible for this study. Fourth, patient selection bias may play a role in choosing the dialysis mode in which patients with higher serum creatinine levels received CVVHDF.

Conclusion: The identification of high-risk patients is crucial in influencing outcome of the patients with sepsis-induced AKI. CVVHDF, a combination of two methods, is according to our results a CRRT modality of choice for the treatment and lower mortality of septic patients with AKI where renal function is no longer preserved. Although rare, nonspecific treatments for septic AKI, early antibiotic administration, avoidance of hypotension (through fluid administration or vasopressors), nephrotoxic agents and fluid overload can minimize AKI risk. Continuous renal replacement therapy, based on our results, should be started earlier in AKI evolution with still preserved hourly urine output which is the most sensitive and prognostic marker of survival in septic patients with AKI. Future trials should be designed to identify high-risk patients with early injury and focus on targeted therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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