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### Mortality predictors in acute kidney injury patients who underwent continuous venovenous hemodiafiltration: A retrospective, single-center study

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**Abstract.** *Continuous renal replacement therapy (CRRT) is an increasingly preferred treatment that is easier to use in patients with hemodynamic impairment and can be applied in critical care settings. There are various subtypes of CRRT, one of which is continuous venovenous hemodiafiltration (CVVHDF). In this study, we examined the general characteristics of intensive care patients who underwent CVVHDF.*

**Methods.** *The clinical and biochemical data of 123 patients who underwent CVVHDF in the intensive care units of our center between February 2012 and November 2014 were analyzed retrospectively. Patients who died during the course of therapy were compared with those who survived.*

**Results.** *The study included 123 patients, 73 males (59.3%) and 50 females (40.7%). The mean age was 64.4 years. Eighty-eight patients (71.5%) died during CVVHDF while 35 patients survived (28.5%). Hemodynamic parameters such as systolic and diastolic arterial blood pressure, mean arterial pressure, and pulse pressure were significantly lower in patients who died compared to survivors ( $p < 0.001$ ). Mean lactic acid level was significantly higher in the deceased group than in the surviving group (8.54 mmol/L vs. 3.68 mmol/L,  $p < 0.001$ , chi-square test).*

**Conclusions.** *Low bicarbonate level, low systolic arterial blood pressure, and older age were significant independent predictors of mortality in this study. Mortality rates were significantly higher among patients with lactic acidosis and those over 66 years of age. Lactic acid levels can be used to predict mortality in patients undergoing CVVHDF.*

**Key words:** *intensive care, acute kidney injury, renal replacement therapies, continuous venovenous hemodiafiltration.*

**Conflict of interest statement.** The authors declare no competing interest.

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## Предиктори смертності у пацієнтів з гострим пошкодженням нирок, які лікувались безперервною вено-венозною гемодіалізацією: ретроспективне одноцентрове дослідження

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**Резюме.** Безперервна вено-венозна гемодіалізація (БВВГДФ) часто застосовується для лікування гострого пошкодження нирок у критичнохворих пацієнтів із порушеннями гемодинаміки. У цьому дослідженні ми проаналізували загальні характеристики пацієнтів інтенсивної терапії, які лікувались БВВГДФ з метою визначення можливих предикторів смертності.

**Методи.** Демографічні, клінічні та біохімічні дані 123 пацієнтів, які лікувались БВВГДФ у відділеннях інтенсивної терапії нашого центру в період з лютого 2012 року по листопад 2014 року, були проаналізовані ретроспективно. Дані пацієнтів, які померли під час перебування у відділенні інтенсивної терапії (ВІТ), порівнювали з тими, хто вижив.

**Результати.** У дослідженні проаналізовано медичну документацію 123 пацієнтів, з яких 73 чоловіки (59,3%) та 50 жінок (40,7%). Середній вік становив 64,4 року. Вісімдесят вісім пацієнтів (71,5%) померли під час лікування, тоді як 35 пацієнтів вижили (28,5%). Гемодинамічні показники, такі як систолічний та діастолічний артеріальний тиск, середній артеріальний тиск та пульсовий тиск, були значно нижчими у пацієнтів, які померли порівняно з тими, що вижили ( $p < 0,001$ ). Середній рівень молочної кислоти був значно вищим у групі померлих, ніж у групі, що вижила (8,54 ммоль/л проти 3,68 ммоль/л,  $p < 0,001$ ).

**Висновки.** Низький рівень бікарбонату, низький систолічний артеріальний тиск та старший вік були важливими незалежними предикторами смертності в цьому дослідженні. Рівень смертності був значно вищим серед пацієнтів з лактним ацидозом та осіб старше 66 років. Рівні молочної кислоти можуть бути використані для прогнозування смертності у пацієнтів, які лікуються БВВГДФ.

**Ключові слова:** інтенсивна терапія, гостре пошкодження нирок, ниркова замісна терапія, безперервна вено-венозна гемодіалізація.

**Introduction.** Acute kidney injury (AKI) is an increasingly common complication in intensive care patients and is a major cause of mortality, morbidity, and high costs. In addition to hemodynamic stability, sepsis control, and effective fluid therapy, continuous renal replacement therapy (CRRT) is currently used in the management of AKI. Because CRRT is slow and prolonged, it is more effective than conventional hemodialysis in the clearance of endogenous and exogenous solutes while maintaining fluid balance close to physiologically normal limits. This feature allows CRRT to be better tolerated by hemodynamically unstable patients. Unfortunately, AKI in intensive care patients is still associated with high mortality despite these new treatment modalities. One of the main reasons for this is the critical condition of these patients when treatment

is initiated [1]. Although there is a growing body of research examining the indications and timing of CRRT, clinical and laboratory follow-up, and predictive markers, no clear consensus has been reached.

**Aim.** In this study, we retrospectively examined the clinical and biochemical characteristics of patients who underwent CVVHDF in our center and evaluated patient-related factors that may affect outcomes.

**Patients & Methods.** This was a retrospective, single-center study. Initially, 143 patients who underwent CVVHDF therapy were evaluated for the study. A total of 123 patients aged 18 years and over who had complete clinical records were included in the study. Patient follow-up forms prepared for the study were completed for patients in the Adnan Menderes University Medical Faculty Hospital intensive care units (Emergency, Anesthesia, Internal Medicine, Cardiovascular Surgery, and Cardiology ICUs) who had indications for CVVHDF. AKI was identified using the Acute Kidney Injury Network (AKIN) criteria [2]. The patients' medical history, clinical and biochemical features at ICU admission, findings at the time of CVVHDF initiation (urine volume, central venous pressure, arterial blood

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pressure, heart rate, presence of sepsis, use of diuretics, inotropic types, mechanical ventilation) were obtained from the hospital records system. Clinical and laboratory follow-up was performed daily. Other patient data were retrospectively collected from patients' charts.

The decision to initiate CVVHDF therapy was made by nephrologists based on hemodynamic status, reduced urine output, hypervolemia, electrolyte and acid-base imbalance (hyperkalemia, severe metabolic acidosis) and uremic status. Trained nurses performed technical monitoring. For each patient, the diagnosis related to the most prominent clinical or laboratory disruption was entered as the sole indication. Parameters such as hemogram, serum creatinine, albumin, bicarbonate, lactate, potassium, sodium, calcium, phosphorus, and C-reactive protein (CRP) levels were measured when CVVHDF was initiated. During follow-up, phosphorus levels and platelet counts were also analyzed to monitor for complications. CVVHDF was performed using the femoral, internal jugular, and subclavian veins for vascular access and a MultiFiltrate® device (Fresenius Medical Care, Bad Homburg, Germany).

CVVHDF therapy was started at a blood flow rate of 100 mL/min and was gradually increased to 150 mL/min. A standard dose (20–25 mL/kg/h) was used in all cases. The ultrafiltration rate was standardized according to the patient's volume status. Although chronic RRT (PD, HD) has been defined as an exclusion criterion in similar clinical studies, we included these patients in our study because our aim was to highlight the general characteristics of all patients who underwent CVVHDF. Anticoagulation was performed with unfractionated heparin in all patients. In accordance with the algorithmic recommendations in the literature, heparin was started with a 10 IU/kg bolus and 10 IU/kg/h maintenance dose, then titrated for an activated partial thromboplastin time ratio (aPTTr)  $\leq 2$  [3]. If clotting occurred during dialysis, the set was replaced and therapy continued. Indications for discontinuation of CVVHDF therapy were determined by a nephrologist; no definitive algorithm was used. The study endpoint was mortality during CVVHDF therapy. The effects of standard-dose therapy versus intensive therapy on mor-

tality remain unclear [4]. Therefore, the present study was based on a standard treatment approach. Due to the retrospective design and nature of the study, no ethics committee approval was received. The procedures followed were in accordance with the amended Declaration of Helsinki. All statistical analyses were done using SPSS 18.0 software. The Kolmogorov-Smirnov test was used to determine whether quantitative data showed normal distribution. Parametric data were expressed as mean  $\pm$  standard deviation, non-parametric data as median (minimum and maximum), and qualitative data as number (n) and percentage (%) values. For comparisons between groups, a t-test was used for parametric data and the Mann-Whitney U test was used for non-parametric data. The Chi-square test was used in comparisons of categorical data. Pearson and Spearman's methods were used in correlation analyses, and multiple linear regression with backward elimination was done to identify associated factors. In all analyses, p-value  $< 0.05$  was considered statistically significant.

**Results.** The study included 123 patients aged 18–88 years; the mean age was 64.4 years. Eighty-eight patients (71.5%) died during CVVHDF while 35 patients survived (28.5%). Of the 88 patients who died, 52 were male (59.1%) and 36 were female (40.9%). Mean age was significantly higher among deceased patients compared to survivors (66.02 vs. 60.42 years,  $p = 0.042$ ). Serum creatinine, urea, albumin, C-reactive protein, potassium, phosphorus, leukocyte, hemoglobin and platelet count, indications for ICU admission, frequency of comorbidities were similar between the two groups. Hemodynamic parameters such as systolic and diastolic arterial blood pressure, mean arterial pressure, and pulse pressure were significantly lower in patients who died compared to survivors ( $p < 0.001$ ). In the deceased and surviving groups, initial creatinine levels were  $2.87 \pm 1.34$  vs.  $3.0 \pm 1.20$  mg/dL ( $p = 0.625$ ), mean arterial pressure was  $57.09 \pm 14.83$  vs.  $70.6 \pm 17.14$  mmHg ( $p < 0.001$ ), and frequency of mechanical ventilation was 79.5% vs. 57.1% ( $p = 0.011$ ), respectively. Serum pH and bicarbonate levels were significantly lower in the deceased group. There was no difference between the two groups in terms of the AKI stage (Table 1).

Table 1

Initial characteristics features of the groups

	DECEASED (n = 88)	SURVIVED (n = 35)	p
♂/♀ (v, %)	52/36	21/14	0.926
Age (years)	66.02 $\pm$ 13.18	60.42 $\pm$ 14.62	0.042
Creatinine (mg/dL)	2.87 $\pm$ 1.34	3.00 $\pm$ 1.20	0.625
Urea (mg/dL)	140.81 $\pm$ 61.73	127.80 $\pm$ 52.15	0.273
Leukocyte (x10 <sup>9</sup> /L)	16.09 $\pm$ 12.43	15.83 $\pm$ 9.32	0.913
Hemoglobin (g/dL)	9.80 $\pm$ 1.91	10.02 $\pm$ 1.72	0.553
Platelet (x10 <sup>9</sup> /L)	186.97 $\pm$ 121.14	204.34 $\pm$ 107.95	0.461
Albumin (g/dL)	2.40 $\pm$ 0.63	2.56 $\pm$ 0.62	0.207
C-Reactive Protein (mg/dL)	144.78 $\pm$ 112.92	163.48 $\pm$ 108.20	0.403

Continuation of Table 1

	<b>DECEASED (n = 88)</b>	<b>SURVIVED (n = 35)</b>	<b>p</b>
Potassium (mmol/L)	4.58±1.22	4.41±0.95	0.471
Phosphorus (mg/dL)	6.13±2.71	5.27±1.72	0.083
SBP (mmHg)	82.98±22.26	105.60±25.11	<0.001
DBP (mmHg)	44.14±12.68	53.77±15.04	<0.001
MAP (mmHg)	57.09±14.83	70.60±17.14	<0.001
PP (mmHg)	38.95±15.35	51.82±17.99	<0.001
CVP (mmHg)	9.60±5.70	11.7±5.17	0.053
pH	7.20±0.18	7.33±0.13	<0.001
HCO <sub>3</sub> (mmol/L)	16.20±5.17	20.69±5.76	<0.001
Mechanical ventilation (n, %)	70 (79.5%)	20 (57.1%)	0.011
AKIN (n, %)			
- Stage ≤ 2	28	9	0.505
- Stage = 3	60	26	
ICU admission indication (n, %)			
- Respiratory failure	22 (25%)	6 (17.1%)	0.262
- Post-cardiovascular surgery	19 (21.6%)	5 (14.3%)	
- Poor general condition	16 (18.2%)	5 (14.3%)	
- Cardiogenic problem	14 (15.9%)	6 (17.1%)	
- Post-abdominal surgery	3 (3.4%)	9 (25.7%)	
- Septic shock	9 (10.2%)	1 (2.9%)	
- Other	5 (5.7%)	8 (6.5%)	
Comorbid disease (n, %)			
- Diabetes Mellitus	35 (39.8%)	10 (28.6%)	0.245
- Coronary Artery Disease	40 (45.5%)	12 (34.3%)	0.258
- Hypertension	38 (43.2%)	12 (34.3%)	0.365
Admission to ICU from (n, %)			
- Emergency department	38 (70.4%)	16 (13.0%)	0.477
- Outpatient clinic	21 (17.1%)	5 (4.1%)	
- Referral/transplantation	29 (23.6%)	14 (11.4%)	

Abbreviations: CVP, central venous pressure; DBP, Diastolic blood pressure; ICU, Intensive care unit; MAP, Mean arterial pressure; PP, Pulse pressure; SBP, Systolic blood pressure.

Initial lactic acid levels were 6.35 (0.17-25.80) mmol/L in deceased group and 2.15 (0.27-22.40) mmol/L in survived group ( $p < 0.001$ ) (Fig.1).

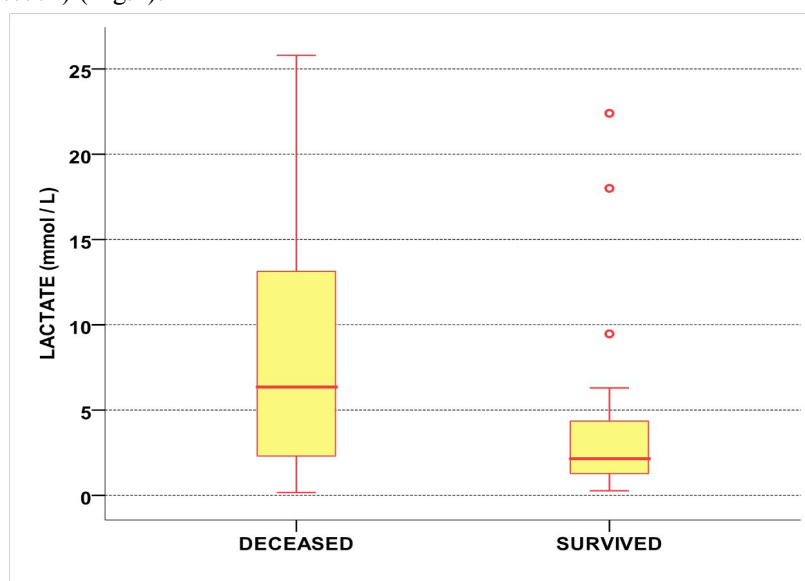


Fig. 1. Lactic acid levels according to the analyzed groups.

The most common care settings for patients in the deceased group were Nephrology (23.9%), Cardiovascular Surgery (22.7%), and Cardiology (11.4%) ICUs; for the survivors, the most common were Nephrology (22.9%), General Surgery (22.9%), and Cardiovascular Surgery (20%) ICUs. Overall, the most common indications for CVVHDF were anuria/oliguria (39%), metabolic/lactic acidosis (32.5%), and hypervolemia (17.1%). The most common indications in the deceased and surviving patients were metabolic/lactic acidosis and anuria/oliguria, respectively.

The mean CVVHDF duration was 2785.71 minutes overall, with significantly longer in the survived group compared to the deceased group ( $p < 0.001$ ). In the deceased group median total ultrafiltration, and total hospital stay were significantly lower. During the CVVHDF the incidence of hypophosphatemia ( $< 2.3$  mg/dL), one of the metabolic complications of CVVHDF, was 26.8%. This rate was 17% in deceased patients and 51.4% among survivors. Post-CVVHDF treatment, phosphorus levels were found to be  $3.25 \pm 1.80$  vs.  $2.12 \pm 1.23$  mg/dl in the deceased and survived group, respectively ( $p = 0.008$ ) (Table 2).

Table 2

#### Data of continuous venovenous hemodiafiltration

	DECEASED (n = 88)	SURVIVED (n = 35)	p
Total CVVHDF time (min)	1280 (54-16450)	3297 (841-10190)	<0.001
Total UF (mL)	2750 (0-61570)	9200 (550-36760)	<0.001
Hospital stay (days)	11 (0.63-154)	24.37 (6-119)	<0.001
Hypophosphatemia (n, %)	15 (17.0%)	18 (51.4%)	<0.001
Post-CVVHDF Phosphorus (mg/dL)	$3.25 \pm 1.80$	$2.12 \pm 1.23$	0.008

Abbreviation: CVVHDF, Continuous venovenous hemodiafiltration; UF, Ultrafiltration.

Post-CVVHDF phosphorus levels significantly negatively correlated with total CVVHF time ( $p < 0.001$ ,  $r = -0.481$ ), total ultrafiltration ( $p = 0.001$ ,  $r = -0.387$ ), and hospital stay days ( $p < 0.001$ ,  $r = -0.323$ ).

In regression analysis, low bicarbonate level, low systolic arterial blood pressure, and older age emerged as significant independent predictors of mortality (Table 3).

Table 3

#### Multiple linear regression analysis of mortality

Parameters	Regression Coefficient	Standard Error	Beta	P
SBP (mmHg)	0.006	0.001	0.312	$p < 0.001$
HCO <sub>3</sub> (mmol/L)	0.024	0.007	0.308	$p < 0.001$
Age (years)	-0.008	0.003	-0.231	$P = 0.005$

Abbreviation: SBP, Systolic blood pressure

**Discussion.** CRRT has partly solved the high mortality and morbidity afflicting the growing numbers of patients with AKI in intensive care. However, the decrease in mortality is still well below expectations. Nevertheless, CRRT is currently considered the best option, particularly for patients with hemodynamic impairment. CVVHDF has been more widely adopted because it can provide a combination of diffusion and convection. Studies are suggesting that CVVHDF is especially beneficial for septic patients due to its potential clearance of cytokines in addition to small- and medium-molecular-weight substances [5]. It is also the most commonly used form of CRRT in the ICUs in our center. In this study, we investigated the general characteristics of patients who underwent CVVHDF in our center and the factors affecting their outcome measures.

The geriatric patient population in critical care facilities is steadily growing. The risk of developing AKI while in intensive care is higher for geriatric patients. Multiple comorbidities, age-related physiological and structural changes in the kidney, and polypharmacy are factors contributing to this increased risk. The reduced sensitivity of serum creatinine level in the diagnosis of AKI in older patients is also an important factor. When we compared patients according to age ( $> 66$  years,  $n = 63$ ;  $\leq 66$  years,  $n = 60$ ), overall mortality was significantly higher in the patients over 66 years of age (77.7%). This high mortality rate may be attributed to the presence of complex comorbid conditions in this patient group. A detailed geriatric nephrological evaluation is appropriate to evaluate the efficacy and indications of CRRT in elderly patients. More detailed clinical studies are needed in this population.

In our study, the Nephrology department was consulted for all patients being treated in other wards. In patients treated in wards other than Nephrology, evaluation of the timing of the consultation request relative to the development of AKI revealed no significant differences in mortality or CVVHDF complication rates between patients whose consultation took place within the first 12 hours or more than 12 hours after AKI development ( $p=0.086$  and  $p=0.67$ , respectively). Costa e Silva et al. evaluated 115 patients who were treated in ICU and had RRT (intermittent HD/CVVHD) due to AKI and reported that the early (first 48 hours) nephrology consultation group had a significantly lower mortality rate compared to the late group [6]. In their study, the mean ages of patients in the late and early consultation groups were  $58\pm 18.4$  and  $57\pm 18.3$  years, respectively. The mean age was higher in our study and mortality was especially high in patients over the age of 66 years. However, a recent study by Li et al. of AKI patients over 75 years old showed that early or late consultation had no effect on mortality [7]. This suggests that clinical outcomes in the literature favoring early nephrology consultation in this group of patients may not be consistent in the geriatric population.

An association between hypervolemia and mortality was shown in some studies of patients with chronic kidney disease who underwent CRRT in the ICU. Raurich et al. found that intensive care mortality was higher in patients with positive fluid balance [8]. In a study of 208 male patients who underwent CVVHDF, Rhee et al. reported a higher in-hospital mortality rate among those with increased total body water (TBW/H<sub>2</sub>) determined by multi-frequency bioimpedance analysis before treatment [9]. In our study, central venous pressure at the start of therapy was not significantly associated with mortality but tended to be lower in deceased patients compared to survivors (mean 9.6 vs. 11.7 mmHg,  $p=0.053$ ). The high number of septic patients in our sample may have led to this clinical outcome. Although the mean 12-h urine volume was lower among patients who died, the difference was not statistically significant (146.98 mL vs. 182.28 mL,  $p=0.9$ ).

Hypophosphatemia is a common complication of CRRT and should be managed with phosphate replacement therapy when detected, despite the lack of a consensus replacement protocol. Some studies have associated hypophosphatemia with a poorer prognosis [10]. In our study, hypophosphatemia was detected in only 17% of deceased patients, and it was quite common among survivors (51.4%). This may be due to the shorter duration of CVVHDF time and therefore lower doses of CRRT in the deceased patients. Similarly, thrombocytopenia is one of the most common hematologic complications of CRRT. Incidence rates have been reported as 18.1% in CVVHDF and 59.1% in patients with CVVHD/CVVHF [11, 12]. The overall incidence of thrombocytopenia in our study was 17.8%, with no significant difference between the groups.

The most common indication for CVVHDF among deceased patients was metabolic/lactic acidosis (42%), whereas the most common indication for survivors was anuria/oliguria (48.6%). Acidosis may be more informative than oliguria/anuria in terms of mortality prediction in this patient group. In our study, mortality was significantly higher in patients with lactic acidosis ( $p<0.001$ , chi-square test). In a study evaluating patients who underwent CVVHDF, Santos et al. emphasized that reduced urine output was an independent predictor of mortality [13]. Other studies with similar results also showed this effect was not associated with creatinine level [14]. In a study examining septic patients with AKI who underwent CVVHDF, Passos et al. found that lactic acid levels at the start of treatment were higher in patients who died, although the difference was not significant. However, lactic acid levels measured 3 days after starting CVVHDF therapy were significantly higher in the deceased group [15]. A similar study reported that lactic acidosis may be an indicator of early mortality in patients undergoing CRRT [16]. In our study, lactate levels were mean:  $3.68\pm 4.64$ , median: 2.15 (maximum 22.4 and minimum 0.27) mmol/L in the surviving group and mean:  $8.54\pm 7.34$ , median: 6.35 (maximum 25.8, minimum 0.17) mmol/L in the deceased group ( $p<0.0001$ ). The median lactate level for all patients was 4.2 mmol/L. The mortality rate was significantly higher above this threshold (52 deceased, 9 survived,  $p=0.001$ ).

The most common reasons for discontinuing therapy in our study were death (64.2%), followed by hemodynamic improvement (25.2%), complications (8.9%), and hemodynamic deterioration (1.6%).

Relationships between several hemogram subparameters and mortality and complication rates were evaluated in this study, but none of the parameters were significant. Although previous studies have suggested that some hemogram parameters might be useful in predicting mortality in patients undergoing CRRT, we did not observe such results in our study [17]. There was no significant association between outcome measures and ratios such as mean platelet volume (MPV)-to-lymphocyte, red cell distribution weight (RDW)-to-platelet, lymphocyte-to-monocyte, platelet-to-lymphocyte, and neutrophil-to-lymphocyte ratio. The heterogeneity of the patient group may have obscured the clinical and laboratory effects of these indicators.

Long-term follow-up data for the 35 patients in the surviving group indicated that 15 patients later died while under hemodialysis therapy, 5 died during follow-up without RRT, 2 were discharged without treatment, 4 were discharged with a prescription for chronic hemodialysis, 5 underwent a period of hemodialysis followed by discharge with no further RRT, and 4 underwent a period of hemodialysis and later died during follow-up without RRT.

When we evaluated indications for CVVHDF in our study, we observed that uremia alone was not the primary reason for starting therapy. Mean creatinine level was 2.87 mg/dL in deceased patients and 3.0 mg/

dL in survivors ( $p=0.625$ ). The complex group of patients, most of whom had clinical sepsis, multiple comorbidities, and heterogeneous diseases raise the question of whether clinical findings or biochemical markers other than creatinine should be considered first when initiating CVVHDF therapy in AKI patients in the ICU. In particular, refractory or severe metabolic/lactic acidosis (due to its association with mortality) may be a higher priority indication than creatinine alone. There has been frequent discussion in recent years regarding when and how CRRT should be initiated in ICU patients with AKI, yet no clear algorithm has been determined. There are conflicting views on whether early treatment decreases mortality [18, 19]. The persistently high mortality (>50%) in patients undergoing RRT in ICUs has led to more in-depth and analytical thinking. An algorithmic approach that can be implemented quickly and incorporates emergency risk scoring and indication evaluation may offer a suitable approach to patients being considered for CRRT.

**Limitations.** Our study has several limitations. Firstly, it was a retrospective study. There was no specific algorithm for initiating CVVHDF, and the decision was based on evaluation by the nephrology de-

partment. The prescribed order varied according to the patient's clinical condition. The study population was heterogeneous and included patients who received short-term CVVHDF therapy. Due to inconsistencies in the patients' medical records, scores such as SOFA and APACHE could not be included in the study.

**Conclusions.** Low bicarbonate level, low systolic arterial blood pressure, and older age were significant independent predictors of mortality in this study. Mortality rates were significantly higher among patients with lactic acidosis and those over 66 years of age. Lactic acid levels can be used to predict mortality in patients undergoing CVVHDF.

**Conflict of interest:** The authors declare no competing interest.

**Authors' contributions and participation:**

**AA:** conceptualized the work, literature search, draft and data collecting;

**HA:** conceptualized the work, data analysis.

**YY:** revised and approved the final manuscript.

**All authors approved the final version of the manuscript.**

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