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Hyperlactatemia in critically ill patients with acute kidney injury treated with renal replacement therapy in the intensive care unit

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Abstract

Background Hyperlactatemia is common in intensive care unit (ICU) patients. The aim of our retrospective observational study was to analyse the impact of serum lactate on admission on mortality in patients with acute kidney injury (AKI) treated with renal replacement therapy (RRT).

Methods During the study period of 4 years, 2939 patients were admitted to the ICU, 503 patients were diagnosed with AKI and 209 of them required RRT. After excluding patients on chronic dialysis and with known malignant disease, we retrospectively analysed 154 patients. Hyperlactatemia was defined as a serum lactate concentration above 4 mmol/L on admission to the ICU.

Results The mean age of patients was 62.8 years, and 69.5% were men. The mean Charlson Comorbidity Index (CCI) on admission to the ICU was 3.7 and fifty-six (36.4%) patients had acute hyperlactatemia. All included patients had AKI stage 3 and were treated with RRT, 125 (81.2%) with continuous RRT and 29 (18.8%) with intermittent hemodialysis. The mean length of stay in the ICU was 15.7 ± 13 days and 118 (76.6%) patients died during the 60-day observation period. A Kaplan-Meier survival analysis showed that the survival rate was statistically significantly lower in the group of patients with hyperlactatemia (log-rank; $p = 0.032$). The univariate Cox regression analysis showed that serum lactate on admission to the ICU significantly predict 60-day survival (HR 1.075; 95%CI 1.015–1.140; $p = 0.014$). In the multivariate Cox regression analysis, which included age, gender, diabetes, hypertension, chronic kidney disease, estimated glomerular filtration rate, serum lactate, CCI and C-reactive protein, only age (HR 1.031; 95%CI 1.007–1.056; $p = 0.011$) and serum lactate (HR 1.067; 95%CI 1.004–1.134; $p = 0.035$) were independent predictors of mortality.

Conclusion Our study underscores the independent association between hyperlactatemia of more than 4 mmol/L on admission to the ICU and increased 60-day mortality in patients with AKI treated with RRT. These findings, which have significant implications for the management and prognosis of critically ill patients with AKI, provide a new understanding of the role of serum lactate in patient outcomes.

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Keywords Acute kidney injury, Lactate, Acidosis, Survival

Introduction

Patients with acute kidney injury (AKI) who are treated in the intensive care unit (ICU) with renal replacement therapy (RRT) are among the sickest patients in the ICU. The prevalence of patients with AKI requiring RRT in the ICU is between 5% and 6% [1]. Despite technical improvements in dialysis in recent decades, mortality in critically ill patients with AKI remains high, exceeding 40–60% [2]. A variety of factors have been associated with increased mortality, including male gender, ethnicity, older age, oliguria, sepsis, respiratory or liver failure, cerebrovascular events and, most importantly, overall disease severity [3].

Serum lactate is widely recognised as an important biomarker for assessing the hemodynamic status of critically ill patients. It reflects the balance between lactate production and excretion [4, 5]. Lactate metabolism via the liver and kidney has a remarkable physiological reserve under resting conditions. Renal excretion normally accounts for less than 2% under resting conditions, but increases in hyperlactatemia and especially in acidemia [5, 6]. Hyperlactatemia occurs when lactate production exceeds lactate excretion in the body, resulting in a serum lactate concentration above 2 mmol/L [7]. However, hyperlactatemia can progress to lactic acidosis (LA), which is characterised by elevated lactate levels (>4 mmol/L) and subsequent acidemia (pH<7.35) [7, 8]. Severe LA deteriorates the function of various organs and has a significant impact on outcome. Although lactate is a non-toxic molecule, the increase in concentration indicates important alterations in homeostasis and is therefore associated with increased mortality [4, 9]. Some studies have suggested that serum lactate is a useful biomarker for risk stratification, particularly in septic patients [10–12]. Studies on the use of serum lactate to predict outcome in patients with AKI receiving RRT in the ICU are lacking.

The aim of our study was to investigate the impact of serum lactate on ICU admission on mortality in critically ill patients with AKI treated with RRT.

Materials and methods

Study design and participants

We conducted a retrospective clinical study over a 4-year period (January 2017 to December 2020) in the 12-bed medical intensive care unit at the tertiary University Medical Centre Maribor, Slovenia. We wanted to exclude the influence of the Covid pandemic and for this reason we did not include patients treated in the ICU in 2021–2023.

Inclusion criteria were: (i) age>18 years, (ii) presence of AKI, stage 3 according to KDIGO criteria [13], (iii) treatment with RRT and (iv) laboratory data of serum lactate at admission.

Exclusion criteria were: (i) patients with chronic kidney disease (CKD) receiving chronic RRT, (ii) previously known malignancy.

All patients were treated with either continuous RRT (CRRT) or intermittent hemodialysis (IHD). We did not treat any patient in the acute phase with peritoneal dialysis. The indications for RRT as well as the modality, anticoagulation and all dialysis parameters, including the selected ultrafiltration, were determined by consensus between the treating intensivists and the nephrologist. It should be emphasised that each patient received an appropriate form of treatment depending on the indication and clinical condition, which complied with all relevant recommendations and guidelines.

Data collection

Patient and clinical data, data on comorbidity and diagnostic categories were collected from the electronic hospital database "Medis", the medical records in the intensive care unit and in the dialysis department in paper form as well as laboratory data from the laboratory database.

The severity of the disease was determined at the time of admission to the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score [14], the parameters of organ dysfunction (Sepsis-related Organ Failure Assessment - SOFA score) [15] and comorbidity using the Charlson Comorbidity Index (CCI) [16].

All patients were followed up during their ICU stay and the primary outcome considered was all-cause ICU mortality. Mortality status was determined from the medical record. Survival time was counted from ICU admission to death or 60 days after ICU admission.

The study protocol was reviewed and approved by the ethics committees of the University Medical Centre Maribor under the number UKC-MB-KME-65/22 and was conducted in accordance with the Declaration of Helsinki. Upon admission to the hospital, patients or their relatives signed an informed consent form for the entire treatment, including RRT. Given the nature of the research, additional patient consent was not expected.

Serum lactate

We analysed only serum lactate data at ICU admission. Hyperlactatemia was defined as a serum lactate concentration above 4 mmol/L on admission to the ICU. Due to the retrospective nature of the study, it was not possible to obtain data on serial measurements of serum lactate during ICU treatment and serum lactate levels immediately before the start of RRT.

RRT procedure

RRT was performed in the ICU according to the indications and consensus between the attending intensivists and nephrologists. All CRRT sessions were performed using the Monitor Multifiltrate (Fresenius Medical Care, Bad Homburg, Germany) equipped with a highly permeable polysulfone hemofilter (AV1000 or filter of the same series, Fresenius Medical Care). All IHD sessions were performed with the Fresenius 5008 monitor and a highly permeable polysulfone or polyamide hemofilter. Commercially available bicarbonate exchange/infusion fluid bags (Fresenius Medical Care) were used for all CRRT sessions.

Dialysis sessions were performed as continuous, prolonged (>6 h) or standard dialysis (<6 h), hemodiafiltration or hemodialysis. The duration of sessions, prescribed dialysis dose and net fluid removal were based on patients' clinical needs and best practise recommendations. Patients received unfractionated heparin or sodium citrate for anticoagulation in the extracorporeal circuit.

Statistical analysis

Descriptive statistics for continuous variables were calculated using mean ± SD (normally distributed) or median (interquartile range, IQR) (not normally distributed). Normality of continuous variables was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests. For categorical variables, the frequency and proportion (n, %) were used. Student's T-test for independent samples was used to compare two groups. The chi-square test was used to analyse categorical variables. The time-dependent receiver operating characteristic (ROC) curve was used to analyse the diagnostic accuracy of a single continuous variable measured at baseline in relation to the occurrence of an outcome. The risk factors for 60-day mortality were analysed using univariate and multivariate Cox regression models and presented as hazard ratios (HR) and the associated 95% confidence interval (CI). The estimated survival probability of the patients was analysed using the log-rank test and presented using the Kaplan-Meier curve. Statistical significance was considered as $p < 0.05$, and all reported probability tests were two-sided. Statistical analysis was performed using IBM SPSS software, version 29.0.0.0 (IBM, Armonk, NY, USA).

Results

In the period between 1 January 2017 and 31 December 2020, a total of 2939 patients were admitted to our medical intensive care unit. Of these, 503 patients had a diagnosis of AKI. After excluding patients undergoing chronic dialysis, patients with known malignancy or insufficient data for analysis, a total of 154 critically ill patients with stage 3 AKI who received RRT were included in the final study cohort. The flowchart of study participants is shown in Fig. 1.

The demographic, clinical and laboratory data of the entire study population and the two groups after 60-day survival from ICU admission are shown in Table 1. One

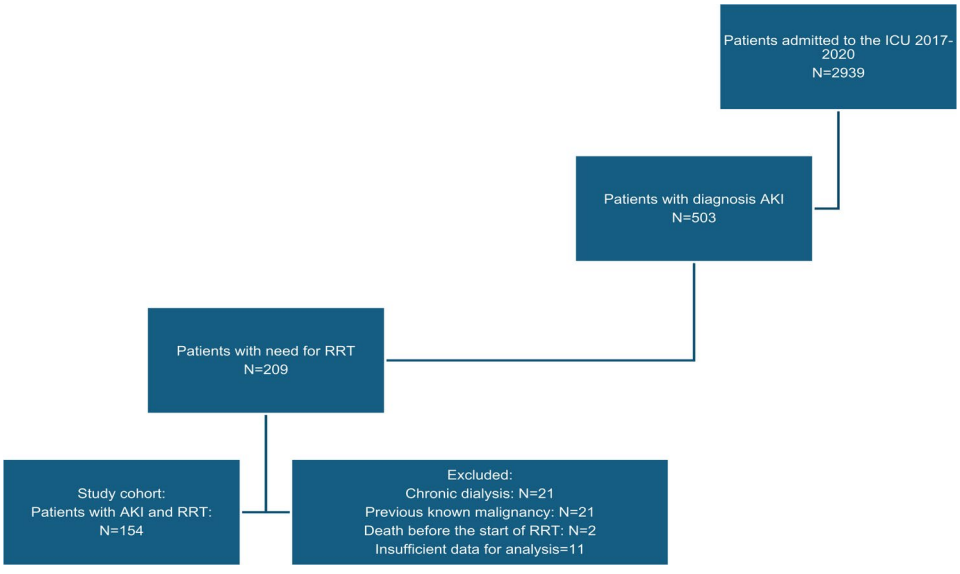


Fig. 1 Patient flow chart. N = number; AKI = acute kidney injury; RRT = renal replacement therapy

Table 1 Baseline characteristics of the study population

Characteristics	Total cohort *N* = 154	Survivors *N* = 36	Non-survivors *N* = 118	*p*-value
Age (years); mean; (median, IQR)	62.8; (64,19)	53.4; (54,19)	65.7; (68,17)	**< 0.001**
Male, N (%)	107 (69.5)	24 (66.7%)	83 (70.3)	0.683
BMI (kg/m^2), mean; (median, IQR)	30.1; (29.4,7.9)	29.9; (29.4,9.3)	30.1; (29.3,7.6)	0.845
Underlying diseases				
Diabetes mellitus, N (%)	66 (42.9)	10 (27.8)	56 (47.5)	0.053
Hypertension, N (%)	105 (68.2)	22 (61.1)	83 (70.3)	0.313
CKD, N (%)	33 (21.4)	6 (16.7)	27 (22.9)	0.494
Heart failure, N (%)	44 (28.6)	4 (11.1)	40 (33.9)	**0.01**
Coronary artery disesase, N(%)	36 (23.4)	5 (13.9)	31 (26.3)	0.177
COPD, N (%)	18 (11.7)	1 (2.8)	17 (14.4)	0.075
Liver cirrhosis, N (%)	6 (3.9)	0 (0)	6 (5.1)	0.337
Laboratory tests at ICU admission				
Serum creatinine (µmol/L); mean; (median, IQR)	290; (190,292)	344; (239,474)	274; (177,254)	0.150
BUN (mmol/L); mean; (median, IQR)	20; (16,18)	21; (18,19)	20; (15,17)	0.716
eGFR (mL/min/1.73m2); mean; (median, IQR)	36; (28,48)	34; (21,51)	37; (32,47)	0.627
Hemoglobin (g/L); mean ± SD	119 ± 28	117 ± 28	119 ± 28	0.702
CRP (mg/L); mean; (median, IQR)	121; (91,147)	147; (115,284)	114; (87,132)	0.146
Procalcitonin (µg/L); mean; (median, IQR)	12.7; (1.7,10.2)	20.7; (2,27.8)	10.3; (1.6,6.4)	**0.027**
pH; mean ± SD	7.24 ± 0.14	7.26 ± 0.16	7.24 ± 0.13	0.424
Bicarbonate (mmol/L); mean ± SD	19 ± 6	17 ± 6	19 ± 6	0.212
Lactate (mmol/L); mean; (median, IQR)	3.8; (2.5,3.3)	3.2; (2.2,3.1)	4; (2.6,3.6)	0.179
Sodium (mmol/L); mean; (median, IQR)	138; (139,7)	137; (136,6)	139; (139,7)	0.066
Potassium (mmol/L); mean; (median, IQR)	4.7; (4.4,1.4)	4.6; (4.4,1.8)	4.8; (4.4,1.3)	0.485
Calcium (mmol/L); mean; (median, IQR)	1.91; (1.93,0.24)	1.85; (1.87,0.32)	1.92; (1.94,0.21)	0.086
Serum albumin (g/L); mean; (median, IQR)	26; (26,7)	26; (27,9)	26; (26,7)	0.826
Disease severity				
APACHE II score; mean; (median, IQR)*	27; (29,14)	25; (28,20)	28; (29,13)	0.110
SOFA score; mean; (median, IQR) **	11; (11,4)	11; (11,5)	11; (11,4)	0.786
CCI; mean; (median, IQR)	3.7; (4,3)	2.1; (2,3)	4.2; (4,4)	**< 0.001**
Mechanical ventilation, N (%)	136 (88.3)	30 (83.3)	106 (89.8)	0.372

*$N = 144$

**$N = 149$

Abbreviations: APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; BMI, body mass index; BUN, blood urea nitrogen; CCI, Charlton morbidity index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; SOFA Sepsis-related Organ Failure Assessment

Bold values are statistically significant with the value < 0.05

hundred and seven patients (69.5%) were men and 47 (30.5%) women with a mean age of 62.8 ± 12.9 years. The most frequent indications for admission to the ICU were: acute respiratory failure (56 (36.4%) patients), cardiopulmonary resuscitation (25 (16.2%) patients), shock (17 (11%9 patients), acute coronary syndrome (11 (7.1%) patients) and sepsis (7 (4.5%) patients). In terms of major comorbidities, sixty-six (42.9%) participants had diabetes mellitus (DM), 105 (68.2%) had hypertension, 33 (21.4%) had chronic kidney disease (CKD), 44 (28.6%) had heart failure, and 36 patients (23.4%) had a history of coronary artery disease. Sixty-six (41.6%) patients were current or former smokers. One hundred and twenty-five (81.2%) patients received CRRT and 29 (18.8%) received IHD as their first RRT modality. Fourteen (9.1%) patients had been prescribed metformin prior to ICU admission. In our cohort, six (3.9%) patients had liver cirrhosis and none of these patients were prescribed metformin.

Of the patients studied, 36.4% ($n = 56$) had hyperlactatemia prior to ICU admission. Compared to patients without hyperlactatemia, these patients had a lower pH (7.16 vs. 7.29; $p < 0.001$), higher serum potassium (5.05 vs. 4.54 mmol/L; $p = 0.012$) and a shorter time from ICU admission to the start of RRT (88 vs. 128 h; $p = 0.046$). Age, CCI, eGFR, CRP, serum albumin and serum creatinine showed no significant differences between the groups.

Clinical profile and characteristics of the RRT sessions

Most patients (81.2%) were treated with CRRT, the main reason being hemodynamic (in)stability. During the ICU stay, one hundred and forty-five (94.2%) were treated with noradrenaline, seventeen (11%) with adrenaline, forty-five

(29.2%) with dobutamine and five (3.2%) with dopamine. Unfortunately, we found no data on treatment with vasopressor drugs in three patients. At the start of RRT, all patients were either uremic with metabolic acidosis (mean creatinine and pH were 477 µmol/L and 7.23, respectively; Table 2) or hypervolemic. The time interval between ICU admission and the start of RRT was 114 h, with a median duration of RRT of 43 h. The chronological time between ICU admission and the start of RRT was not significantly associated with 60-day mortality in the univariable Cox regression analysis (HR 0.99, 95% CI 0.997–1.00, $p = 0.126$). Low molecular weight heparin (LMWH) (56 patients), sodium citrate (38 patients) and unfractionated heparin (10 patients) were the most commonly used anticoagulants, while the remaining patients received a combination of LWMH, unfractionated heparin and citrate during the RRT sessions (some details in Table 2). Lactate levels on ICU admission were higher in patients anticoagulated with sodium citrate than with LWMH during RRT (4.65±3.27 vs. 3.14±2.5 mmol/L; $p = 0.013$).

Patient outcome

During the observation period of 60 days after admission to the ICU, 118 (76.6%) patients died. Most patients died during treatment in the ICU (108 patients, 70.1%). The average duration of treatment of patients in the ICU was 15.7 ± 12.7 days (1–72 days). Patients who died were older ($p < 0.001$), more likely to have known heart failure ($p = 0.01$) and had a higher severity of illness on ICU admission as shown by CCI ($p < 0.001$), while the SOFA score and APACHE II showed no statistically significant difference between survivors and non-survivors (Table 1). Using ROC curves comparing all three predictors, we found that only the CCI had predictive value (area under the curve 0.768, $p < 0.0001$) (Fig. 2).

It is interesting to note that only 4 patients required dialysis after 30 days of observation. To investigate the association between risk factors and mortality 60 days after ICU admission, age, serum lactate and CCI were significantly associated with a higher risk of 60-day mortality in a univariate Cox regression model (Table 3).

In a multivariable Cox regression model that included age, previous CKD, serum lactate and CCI at admission, only age (HR 1.023; 95% CI 1–1.047; $p = 0.048$) and serum lactate (HR 1.065; 95% CI 1.005–1.127; $p = 0.033$) were found to be independent predictors of death (Table 3). We also performed a separate analysis for the type of RRT using univariate and multivariate Cox regression analysis (Tables 4 and 5). Unfortunately, we did not find the same results as for the entire cohort, regardless of whether it was IHD or CRRT.

Kaplan-Meier analysis showed that patients with a serum lactate above 4 mmol/L on admission to the ICU had a worse outcome at 60 days (log rank (Mantel Cox) = 4.587; $p = 0.032$) (Fig. 3).

Discussion

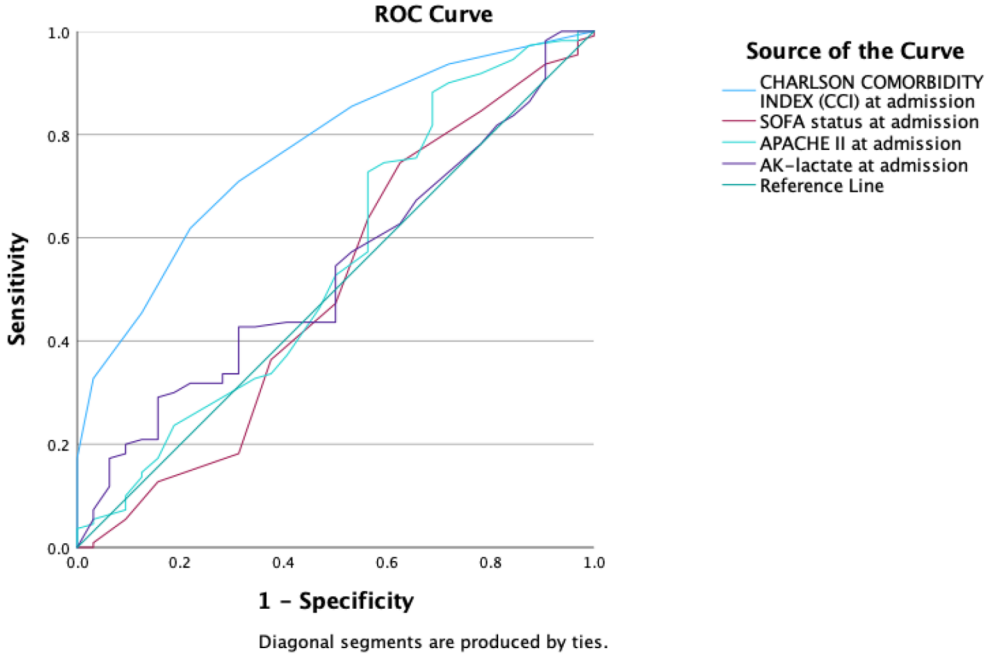
Based on our research results, we found that patients admitted to the ICU who require RRT due to AKI have a very high mortality rate. Two thirds of the patients died during the observation period of 60 days after admission to the ICU. It has been shown that the serum lactate determined on admission to the ICU is an important prognostic factor for survival, and that patients with

Table 2 Biochemical data and dialytic parameters for RRT patients in ICU

Parameter	Total cohort *N* = 154	Survivors *N* = 36	Non-survivors *N* = 118	*p*-value
At RRT start				
BUN (mmol/L), mean; (median, IQR)	40; (36,28)	39; (35,28)	40; (36,29)	0.687
Serum creatinine (µmol/L); mean ± SD	477 ± 233	547 ± 261	455 ± 220	**0.037**
eGFR (mL/min/1.73m2); mean; (median, IQR)	15; (10,9)	16; (8,9)	14; (10,10)	0.511
Potassium (mmol/L); mean; (median, IQR)	4.98; (4.82,1.59)	5.01; (5.06,1.38)	4.97; (4.78,1.65)	0.874
CRP (mg/L); mean; (median, IQR)	167; (123,200)	177; (159,200)	165; (123,199)	0.638
pH; mean; (median, IQR)	7.23; (7.23,0.12)	7.27; (7.27,0.13)	7.22; (7.22,0.13)	**0.02**
Bicarbonate (mmol/L), mean ± SD	18.7 ± 5.3	18.2 ± 6.2	18.9 ± 5.1	0.511
RRT clinical data and parameters				
Anticoagulation only with 4% sodium citrate (Number (%))	38 (24.7)	7 (19.4)	31 (26.3)	
Anticoagulation only with LWMH (Number (%))	56 (36.4)	7 (19.4)	49 (41.5)	
Anticoagulation only with unfractionated heparin (Number (%))	10 (6.5)	3 (8.3)	7 (5.9)	
Whole duration of RRT (hours); mean; (median, IQR)	42.9; (33,45)	55.3; (33,44)	39.3; (33,45)	0.087
Number of RRT sessions; mean; (median, IQR)	3.3; (2,3)	4.3; (3,6)	3; (2,3)	**0.022**
Cumulative ultrafitration (ml); mean; (median, IQR)	6202; (3575,7200)	7420;(4590,7688)	5839; (3420,7180)	0.363
CRRT / IHD as first RRT modality	125 / 29	100 / 18	25 / 11	

Abbreviations: BUN, blood urea nitrogen; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LWMH, low molecular weight heparin; RRT, renal replacement therapy; CRRT, continuous RRT; IHD, intermittent hemodialysis

Bold values are statistically significant with the value < 0.05



Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
CHARLSON COMORBIDITY INDEX (CCI) at admission	.768	.044	.000	.681	.855
SOFA status at admission	.505	.063	.938	.380	.629
APACHE II at admission	.552	.063	.370	.429	.675
AK-lactate at admission	.536	.056	.532	.427	.646

The test result variable(s): CHARLSON COMORBIDITY INDEX (CCI) OB SPREJEMU, SOFA status ob sprejemu, APACHE II ob sprejemu, AK-laktat ob sprejemu has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

Fig. 2 Receiver operating characteristic curves for prediction of 60 days mortality after ICU admission. **a**. Under the nonparametric assumption. **b**. Null hypothesis: true area = 0.5

serum lactate levels below 4 mmol/L have a better survival rate.

Similar to the study by De Corte et al. [4], in our study, lactate on admission did not differ between those who died and those who survived (Table 1). However, an important difference between these two studies must be emphasised: In our study, we analysed mortality 60 days after the patient was admitted to the ICU, whereas in the study by De Corte et al. mortality was only analysed within 24 h after the start of RRT. The high mortality in our patients could also be due to a higher severity of disease and organ dysfunction, which we can confirm with the highest CCI in the group of deceased patients. The study by Kim et al. also found a significant association between hyperlactatemia and mortality, but their observation time was only until discharge with a median of 10 days [17].

Lactate has a molecular weight of 90 Da, similar to that of urea (60 Da), and can therefore be easily removed by RRT. However, data on the clearance of lactate through the hemodialysis membrane are sparse and contradictory. It has been suggested that the beneficial effect of RRT on hyperlactatemia may be due to the improvement in acid-base and metabolic status, leading to improved lactate

Table 3 Association between risk factors and 60-day mortality in ICU patients with AKI and RRT using univariate and multivariate Cox-regression analysis

Risk factors		60-day mortality		
	Univariate		**Multivariate**	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age	1.036 (1.020–1.053)	**< 0.001**	1.023 (1-1.047)	**0.048**
Gender	1.093 (0.736–1.624)	0.658	-	-
Diabetes	0.797 (0.555–1.146)	0.220	-	-
Serum lactate (mmol/L)	1.075 (1.015–1.140)	**0.014**	1.065 (1.005–1.127)	**0.033**
Hypertension	0.841 (0.566–1.251)	0.393	-	-
CKD	0.639 (0.414–0.985)	**0.042**	0.719 (0.434–1.193)	0.202
CRP (mg/L)	0.999 (0.997-1.000)	0.096	-	**-**
eGFR (mL/min/1.73m^2)	0.998 (0.992–1.005)	0.596	-	-
CCI	1.214 (1.121–1.315)	**< 0.001**	1.089 (0.959–1.287)	0.236
SOFA	0.995 (0.934–1.059)	0.875	-	-
APACHE II	1.014 (0.994–1.033)	0.165	-	-

Abbreviations: APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; CCI, Charlton morbidity index; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; SOFA Sepsis-related Organ Failure Assessment;

Bold values are statistically significant with the value < 0.05

Table 4 Association between risk factors and 60-day mortality in ICU patients with AKI and CRRT (*N* = 125) using univariate and multivariate Cox-regression analysis

Risk factors		60-day mortality		
	Univariate		**Multivariate**	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age	1.028 (1.011–1.044)	**< 0.001**	1.022 (0.996–1.047)	0.096
Gender	1.147 (0.747–1.760)	0.531	-	-
Hypertension	0.808 (0.530–1.233)	0.324	-	-
Diabetes	0.845 (0.569–1.254)	0.403	-	-
CKD	0.568 (0.351–0.919)	**0.021**	0.619 (0.353–1.088)	0.096
Serum lactate (mmol/L)	1.057 (0.992–1.127)	0.089	1.050 (0.986–1.118)	0.125
CRP (mg/L)	0.998 (0.997-1.000)	0.063	-	-
eGFR (mL/min/1.73m^2)	0.999 (0.993–1.006)	0.876	-	-
CCI	1.171(1.073–1.279)	**< 0.001**	1.042 (0.898–1.208)	0.590
SOFA	0.991 (0.924–1.063)	0.800	-	-
APACHE II	1.012 (0.990–1.034)	0.295	-	-

Abbreviations: APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; CCI, Charlton morbidity index; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; SOFA Sepsis-related Organ Failure Assessment

Bold values are statistically significant with the value < 0.05

Table 5 Association between risk factors and 60-day mortality in ICU patients with AKI and IHD (*N* = 29) using univariate and multivariate Cox-regression analysis

Risk factors		60-day mortality		
	Univariate		**Multivariate**	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age	1.142 (1.058–1.234)	**< 0.001**	1.094 (1.001–1.195)	**0.047**
Gender	0.902 (0.321–2.535)	0.846	-	-
Hypertension	0.729 (0.211–2.523)	0.618	-	-
Diabetes	0.535 (0.207–1.386)	0.198	-	-
CKD	0.788 (0.280–2.218)	0.652	1.746 (0.450–6.773)	0.450
Serum lactate (mmol/L)	1.158 (0.989–1.357)	0.069	1.003 (0.854–1.178)	0.973
CRP (mg/L)	0.999 (0.994–1.003)	0.559	-	-
eGFR (mL/min/1.73m^2)	0.990 (0.974–1.007)	0.259	-	-
CCI	1.671(1.304–2.140)	**< 0.001**	1.594 (1.141–2.228)	**0.006**
SOFA	1.002 (0.866–1.159)	0.977	-	-
APACHE II	1.040 (0.988–1.093)	0.132	-	-

Abbreviations: APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; CCI, Charlton morbidity index; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; SOFA Sepsis-related Organ Failure Assessment

Bold values are statistically significant with the value < 0.05

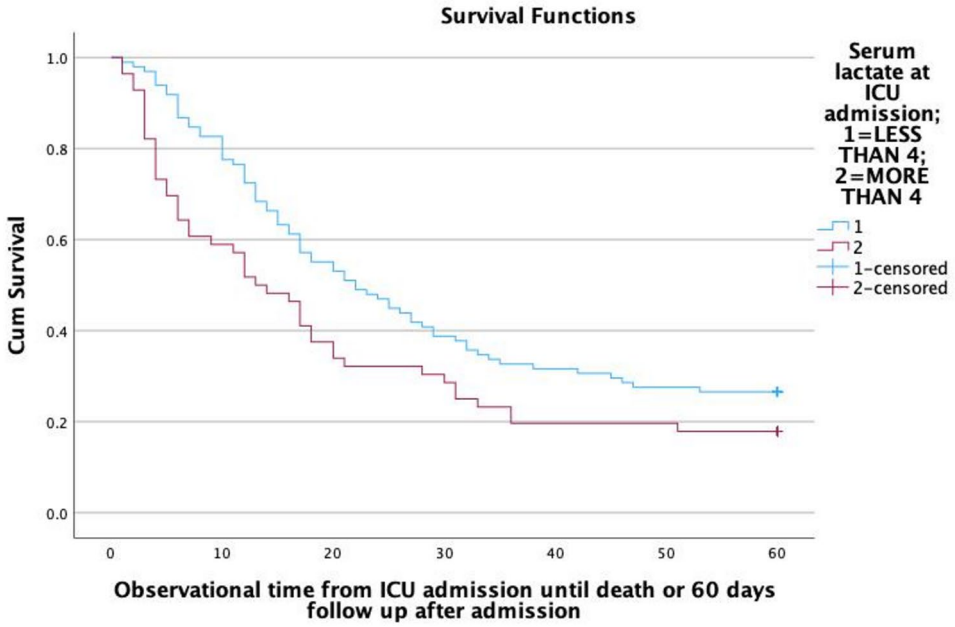


Fig. 3 Kaplan-Meier survival curves according to the serum lactate level at ICU admission

metabolism, rather than the direct removal of lactate by ultrafiltration and dialysis [17, 18]. Unfortunately, we did not measure the effects of RRT on lactate levels in our study, which is also one of the weaknesses of a retrospective study. As we know, we can only remove lactate with RRT, but we do not influence the cause or a disease that causes high lactate production. Bellomo assumes that lactate clearance during dialysis reaches 20% of endogenous clearance [6]. However, Levraut et al. conducted a study in 10 patients with AKI in the ICU in which lactate was measured in serum and ultrafiltrate samples of patients during CRRT and compared with endogenous clearance [19]. They found that lactate clearance through the hemodialysis filter was < 3% of total lactate clearance [19]. Acute LA in critically ill patients is associated with cellular dysfunction and increased mortality [20]. Elimination or control of the precipitating conditions remains the only effective therapy.

Serum creatinine prior to initiation of RRT was statistically significantly higher in patients who survived than in those who died. This indirectly indicates that the patients who survived had more muscle mass. Even on admission to the ICU, patients who survived more than 60 days had a higher serum creatinine than those who died, but this difference was not statistically significant. In the study by Gleeson et al. of 157 patients with AKI who required RRT, the authors also found that a higher serum creatinine level at the start of RRT was associated with better survival in the ICU [odds ratio (OR) 0.33, 95% CI 0.17–0.62; $p = 0.001$] [21].

The choice of anticoagulation during RRT was made by consensus between the attending intensive care physicians and the nephrologist. The main factor for the choice was the bleeding tendency and patients at risk of bleeding were anticoagulated with sodium citrate regardless of lactate levels on admission. It is known that impaired citrate metabolism can lead to citrate accumulation, exacerbating lactic acidosis and the anion gap [22]. In a retrospective study by Mariano et al. in 60 severely polytraumatised patients, early CRRT with citrate anticoagulation showed better safety and haemodynamic stability in the presence of low blood flow and circulatory citraemia, suggesting that citrate should be the anticoagulant of first choice in this patient group [22]. Survival analysis for the citrate and heparin groups showed a mortality rate of 43.5 and 57.1%, respectively, and the 90-day Kaplan-Meier curve showed a better survival trend for citrate ($p = 0.0957$) [22]. In our study, Kaplan-Meier analysis did not show better survival depending on the type of anticoagulation (sodium citrate vs. LWMH; $p = 0.739$; data not shown in Results).

An important aim of our retrospective study was to evaluate the outcome of dialysis treatment in critically ill patients in the ICU. These patients are usually in a severe condition on admission, so their prognosis is uncertain. Nevertheless, such a high mortality rate is too high even for those who treat these patients, so it would be necessary to investigate how we can improve the survival rate of patients in this area. We started dialysis treatment on average 114 h after admission to the ICU. The earliest a patient started dialysis treatment was one hour after admission and the latest was after almost 23 days (547 h after ICU admission) (data not shown in the results section). Due to the retrospective design of our study, we

cannot influence the timing of the start of RRT. Our patient cohort was very heterogeneous; nevertheless, this study reflects real-life practise in the ICU. We covered a period of four years and analysed all patients who underwent RRT in our ICU during this time.

At the same time, the question arises as to whether the patients outcome would have been different if they had started dialysis earlier. The optimal time to start RRT is still unclear and has yet to be determined. It is also controversial whether LA itself is a suitable indication for RRT. The ethics of a prospective, randomised study on this topic are questionable, making it difficult to find a clear answer.

The weakness of our study is the small number of patients included in the study and the fact that it is only a single centre study. Another shortcoming of our study is the lack and analysis of data on serial measurements of serum lactate before and after the start of RRT until discharge or death or until the end of the observation period of 60 days.

In conclusion, serum lactate levels above 4 mmol/L on admission to the ICU are an important indicator of patient survival and are associated with higher mortality. Lowering serum lactate below 4 mmol/L shortly after ICU admission may be beneficial, although this can be challenging due to the nature of the disease. Based on our data, the practical recommendation is to measure serum lactate at several points during the ICU stay: on admission, before starting RRT and regularly during and after RRT. Further studies are needed to determine whether initiation of RRT alone is effective in lowering serum lactate. Additional studies investigating the effects of lowering serum lactate on survival are warranted.

Abbreviations

AKI	Acute kidney injury
APACHE II	Acute Physiologic Assessment and Chronic Health Evaluation II
CCI	Charlson Comorbidity Index
CI	Confidence interval
CKD	Chronic kidney disease
CRRT	Continuous renal replacement therapy
DM	Diabetes mellitus
HR	Hazard ratio
ICU	Intensive care unit
IHD	Intermittent hemodialysis
LA	Lactic acidosis
ROC	Receiver operating characteristic
RRT	Renal replacement therapy
SOFA	Sepsis-related Organ Failure Assessment

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Author contributions
Study conception and design: RE Acqusition of data: BK and TK Analysis and interpretation the data: RE, SB and RH Drafting of manuscript: RE, FS, EJ, RH All authors read and approved the final manuscript.

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This research was no supported by any founding. The results presented in this paper have not been published previously in whole or part, except in an abstract format.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol was reviewed and approved by the Ethics Committees of the University Medical Centre Maribor under the number UKC-MB-KME-65/22 and was conducted in accordance with the Declaration of Helsinki. At admission to the hospital, patients or their relatives signed an informed consent form for all treatment, including RRT. Given the nature of the research, additional patient consent was not expected.

Consent for publication
Not appicable.

Competing interests
The authors declare no competing interests.

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