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Association of vasopressor use during renal replacement therapy and mortality

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ABSTRACT

Among critically ill patients with acute kidney injury (AKI) requiring renal replacement therapy (RRT) whether vasopressor use is associated with outcomes is unclear. We examined the association of vasopressor use following RRT initiation with in-hospital mortality in critically ill adults with AKI requiring different modalities of RRT. This observational study was conducted using the Premier Inc. (PINC) AI Healthcare Database of patients (n = 20,882) in U.S. hospitals with AKI requiring continuous RRT (n = 7660) and intermittent hemodialysis ([IHD], n = 13,222) with discharge from January 1, 2018, to June 30, 2021. Data on vasopressor use 3 days before and 3 days after RRT initiation were extracted. Exposure to vasopressors post-RRT initiation was significantly associated with risk-adjusted in-hospital mortality among patients treated with CRRT (risk-adjusted hazard ratio [aHR], 1.69 95 %CI: 1.55–1.85) and IHD (aHR, 1.72, 95 %CI: 1.61–1.84). There was an incremental risk of death associated with the number of vasopressors. Among CRRT patients, the risk of death were: 1 vasopressor (aHR, 1.50; 95 % CI: 1.36–1.65), 2 vasopressors (aHR, 1.94; 95 % CI: 1.76–2.14), and 3 vasopressors (aHR, 2.06; 95 % CI: 1.72–2.46). Similarly, for IHD patients, the aHRs were: 1 vasopressor (aHR, 1.57; 95 % CI: 1.47–1.68), 2 vasopressors (aHR, 2.20; 95 % CI: 2.02–2.40), and 3 vasopressors (aHR, 2.32; 95 % CI: 1.82–2.96). In summary, vasopressor use during the 3 days post-RRT initiation was independently and incrementally associated with higher in-hospital mortality in patients receiving either CRRT or IHD as the first modality.

1. Introduction

Acute kidney injury (AKI) is a frequent complication among critically ill patients in intensive care units (ICUs) and is associated with increased morbidity and mortality [1]. While the provision of acute renal replacement therapy (RRT) in patients with severe AKI can be life-saving, acute RRT use is also frequently associated with a high risk of hemodynamic instability [2,3]. This hemodynamic instability related to RRT (HIRRT) occurs through different mechanisms, including relative hypovolemia, rapid changes in extracellular osmolality, acid-base, and electrolytes [4]. In addition, patient factors also contribute to HIRRT, including sepsis, septic shock, systemic inflammation, myocardial infarction, etc. HIRRT is associated with further ischemic injury to the kidney, persistent AKI, and decreased likelihood of renal recovery [5].

HIRRT may also lead to multiorgan dysfunction, interfering with tissue perfusion and oxygen delivery, thereby increasing the risk of death [4,6,7]. A standardized definition of hemodynamic instability during acute RRT does not currently exist for critically ill patients [8]. Intravenous (IV) fluids and vasopressors are typically used to treat hemodynamic instability [9]. However, the impact of vasopressor use after RRT initiation on clinical outcomes is not fully known. This study aimed to examine the association of vasopressor use in the early period following RRT initiation with in-hospital mortality among critically ill adult patients with AKI.

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2. Material and methods

2.1. Study participants

Adult critically ill patients with AKI requiring RRT in U.S. hospitals providing continuous renal replacement therapy (CRRT) and intermittent hemodialysis (IHD) with discharge from January 1, 2018, to June 30, 2021, were analyzed using the Premier Inc. (PINC) AI Healthcare Database. This data source comprises inpatient and outpatient charge data from the past >20 years, taken from more than 1000 U.S. facilities, capturing about 20–25 % of U.S. hospital discharges. Similar inclusion and exclusion criteria and data extraction as in a previous study were used [10] (see method section of Supplement A). AKI was determined using ICD-10 diagnosis codes and first ICU RRT was defined by ICD-10 procedure codes CRRT: 5A1D90Z [performance of urinary filtration, continuous, >18 h per day] or IHD 5A1D70Z [performance of urinary filtration, intermittent, <6 h per day]) during the index ICU visit. Patients with other dialysis modalities (i.e., prolonged intermittent renal replacement therapy [PIRRT] and peritoneal dialysis) were excluded due to the low use as the first RRT modality in the current dataset (see method section of Supplement A). Only data from the first ICU admission for each patient were considered for analysis.

Determined by the ICD-10 procedure and diagnosis codes listed in Supplementary Table A1, patients who had end-stage renal disease, renal transplant, >1 dialysis-related procedure, or stage 5 chronic kidney disease (CKD) in the 12 months before admission were excluded. Patients without an AKI diagnosis (absence of ICD-10 diagnosis code for AKI) and from hospitals without continuous data submission during the study period were excluded as well. Inclusion criteria required that patients be in a facility that offered both CRRT and IHD as RRT modalities and remain hospitalized at least 3 days following RRT initiation to be able to characterize the vasopressor use after RRT initiation. In addition, IV fluid data had to be present to include the patient in the analysis.

2.2. Data collection and definitions

We extracted data on vasopressor and IV fluid use up to 3 days before and 3 days after RRT initiation. As we focused on vasopressor and IV fluid use while the patient was deemed critically ill, we truncated the pre-RRT data one day before ICU admission and the post-RRT data at ICU discharge. Specifically, we did not extract data from days following ICU discharge, even if those days would have been within the 3-day post-RRT initiation window, or from days more than one day before ICU admission, even if those would have been within the 3-day pre-RRT initiation window. A minimum of IV fluid data from one day pre- and one-day post-RRT initiation was required for inclusion. IV fluids included normal saline, lactated ringers, dextrose, dextrose + electrolytes, and balanced crystalloids. The use of mechanical ventilation and extracorporeal membrane oxygenation (ECMO) were collected for up to 3 days before RRT initiation, the day of RRT initiation, and 3 days after RRT initiation (see Supplementary Table A2 for ICD-10 Diagnosis Codes for clinical conditions, procedures, and comorbidities). Medicare Severity Diagnosis-related groups (MS-DRGs) were used to classify medical and surgical patients, while all patient-refined DRGs (APR-DRG) were used to classify the severity of illness. The APR-DRG accounts for age, procedures, and clinical severity of the primary diagnosis and all secondary diagnoses assigned during hospitalization, and is computed for each patient at the time of hospital discharge and has been validated in numerous studies [11–14]. The APR-DRG system categorizes a patient based on their reason for admission and the severity of illness into 4 levels: minor, moderate, major, and extreme, with extreme signifying the most critically ill patients.

2.3. Outcome measures

The primary outcome measure was in-hospital mortality. For patients still hospitalized, survival assessment was truncated at 90 days post-RRT initiation.

2.4. Statistical analysis

Multivariable Cox regression was used to examine the effects of post-RRT vasopressor exposure within 3 days of RRT initiation on in-hospital mortality, accounting for demographics (age, sex, and ethnicity), comorbidities, presence or absence of COVID, sepsis, acuity of illness, including APR-DRG, pre- and post-RRT IV fluid use and pre-RRT vasopressor exposure, and ICU care processes including ECMO, mechanical ventilation, MS-DRG category, and days in ICU before RRT initiation. Characteristics and outcomes were compared using descriptive statistics, with p-values from $\chi 2$ and Wilcoxon rank-sum tests. To compile the final model of in-hospital mortality as the dependent variable, the model was checked for potential interaction effects, including RRT modality by the number of vasopressors used post-RRT. RRT modality by the number of vasopressors used post-RRT was statistically significant, and therefore, the final model was stratified by the first RRT modality (IHD or CRRT). IV fluid use post-RRT and the number of vasopressors used post-RRT were included in the model as covariates. The independent variable analyzed was vasopressor use post-RRT initiation: Yes/No (see Supplementary material for definition). The use of vasopressors post-RRT initiation was further categorized according to the use of none, one, two, or three or more vasopressors.

A secondary analysis was performed on the effect of several vasopressor combinations on outcomes. To be included in the analysis, a vasopressor combination had to be present in at least 0.5 % of the patients receiving more than one vasopressor post-RRT. This resulted in 7 vasopressor combinations, plus an “Other Combinations” category that was an aggregate of any combinations that occurred in less than 0.5 % of patients receiving multiple vasopressors post-RRT.

2.4.1. Subgroup and sensitivity analyses

We examined pre-specified subgroups that included cardiac surgery patients and septic shock patients. Further, a sensitivity analysis excluding patients exposed to both CRRT and IHD during the study period was performed, followed by an assessment of the model in patients who received IHD in centers not offering CRRT. For the sensitivity analyses, only 0, 1, and 2+ vasopressor categories were considered because the 3+ vasopressor group was small and not significantly different from the 2+ group in the final model described above. More information about each sensitivity analysis can be found in the Sensitivity and subgroup analyses section of Supplement A. All analyses were completed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study cohort and baseline characteristics

A flowchart with the cohort selection is presented in Fig. 1. The final cohort included 20,882 critically ill adult patients. Of the final cohort, 7660 were treated with CRRT (37 %) and 13,222 (63 %) with IHD as the first RRT modality. The mean age (±SD) of the final cohort was 63 ± 14 years, 62 % of patients were male, and 62 % were white, non-Hispanic (Table 1). Among all patients, 16 % received vasopressors only pre-RRT, 21 % only post-RRT, 35 % both pre- and post-RRT, and 28 % did not receive vasopressor pre- or post-RRT (Supplementary Table A5). In both RRT cohorts, patients who used vasopressors post-RRT initiation had more sepsis, septic shock, COVID-19, and greater use of mechanical ventilation. Among the IHD cohort, patients who used vasopressors post-IHD initiation had greater use of ECMO. In both RRT cohorts, a greater

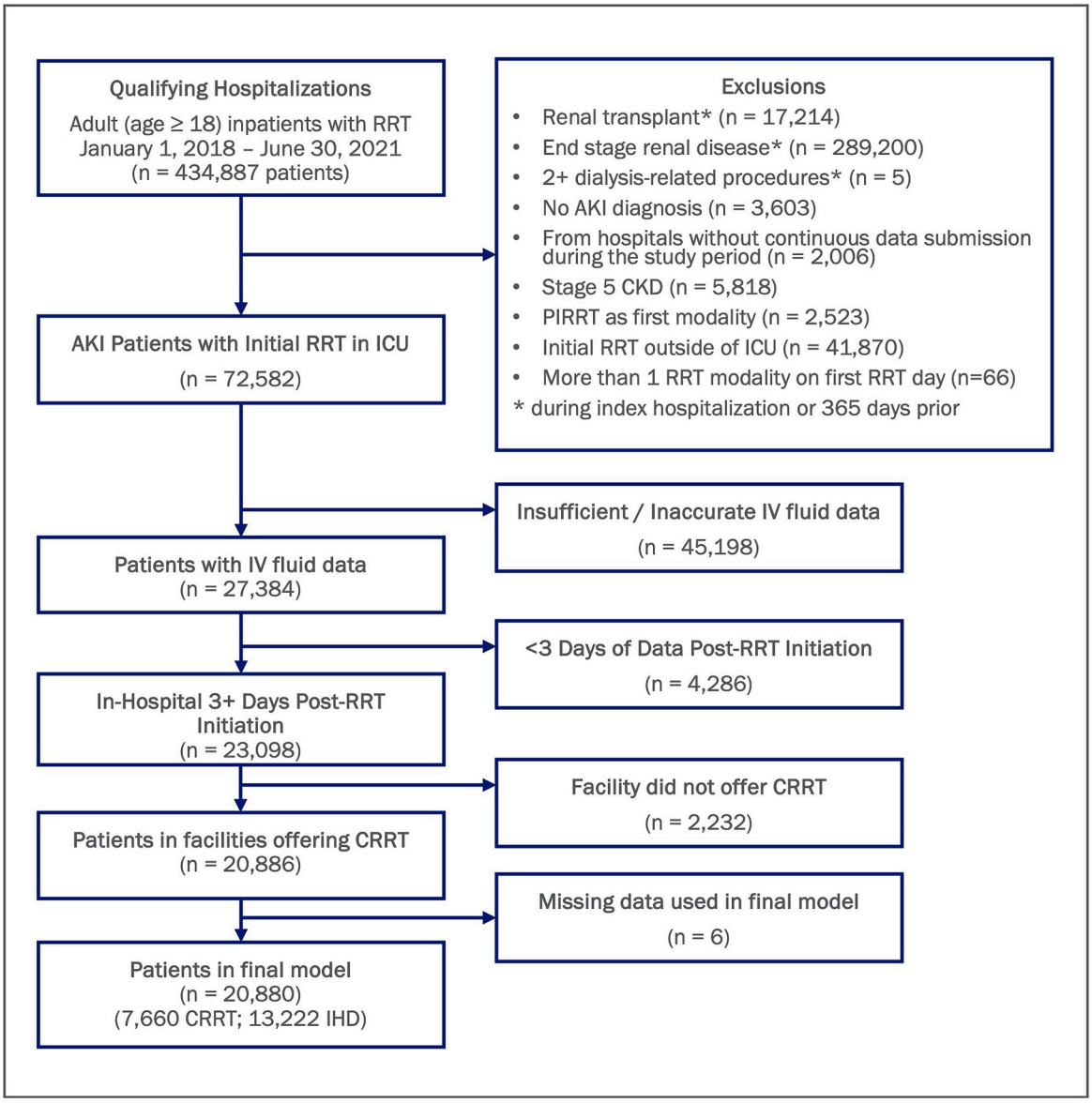

Fig. 1. Cohort selection flow chart. AKI: Acute Kidney Injury, CKD: Chronic Kidney Disease, CRRT: Continuous Renal Replacement Therapy, ICU: Intensive Care Unit, IV: Intravenous, PIRRT: Prolonged Intermittent Renal Replacement Therapy, RRT: Renal Replacement Therapy.

fluid requirement post-RRT initiation was observed in patients who used vasopressors post-RRT initiation. In the CRRT cohort, greater fluid requirements before RRT in patients who used vasopressors post-RRT was observed (Table 1).

Stratified by modality, 77 % of CRRT and 44 % of IHD patients received vasopressors post-RRT initiation. Exposure to vasopressors pre- vs. post-RRT dynamically changed in both the IHD and CRRT cohorts (Fig. 2). Among patients with no vasopressors use pre-RRT, a larger percentage of the CRRT patients compared to IHD patients received one or more vasopressors post-RRT. In general, very few switches were seen post-RRT initiation from no vasopressor use to the use of 2+ vasopressors and vice versa (Supplementary Fig. A3).

3.2. Primary analysis: effect of vasopressor use on outcomes

Patients with post-RRT vasopressor use were found to have similar in-hospital mortality rates as patients with both pre-RRT and post-RRT vasopressor use (both 21 % survival). Patients with neither pre- nor post-RRT vasopressor use had slightly lower, but not statistically different, survival rate than those with only pre-RRT vasopressor use (37 % and 44 % survival, respectively) (Fig. 3A). In adjusted models, pre-RRT vasopressor use did not impact in-hospital mortality ($p = 0.4$).

Patients with post-RRT vasopressor use had higher in-hospital mortality (90-day survival: 21 %, 95 % CI: 19 %, 24 %) compared to patients without post-RRT vasopressor use (90-day survival:39 %, 95 % CI: 34 %, 45 %; log-rank $p < 0.001$) (Fig. 3B). In both the CRRT and IHD cohort, in-hospital mortality was higher when patients received vasopressors post-RRT initiation. Among the IHD cohort, the length of stay in the ICU was longer for patients receiving vasopressors post-RRT initiation (Table 1). In the initial model, the adjusted hazard ratios (aHRs) for post-RRT vasopressor use on in-hospital mortality were 1.69 (95 % CI: 1.55, 1.85) for the CRRT cohort and 1.72 (95 % CI: 1.61, 1.84) for the IHD cohort (Supplementary Table A6).

3.3. Final model evaluation

After stratifying by RRT modality, the higher number of vasopressors used post-RRT and the higher average daily IV fluid use post-RRT were independently associated with increased risk of in-hospital mortality in both the CRRT and IHD cohorts. Older age, being male, having COVID,

Table 1
Patient characteristics by post-vasopressor use and renal replacement therapy cohort.

Characteristics	No. (%) CRRT-Cohort Vasopressor use post CRRT initiation			No. (%) IHD-Cohort Vasopressor use post IHD initiation		
	Yes	No	p-value	Yes	No	p-value
Total # of Patients	5.870	1.790		5.827	7.395	
% of Patients	77 %	23 %		44 %	56 %	
Demographics						
Age, years (mean, std. dev)	62 (14)	61 (15)	<0.001	64 (14)	62 (15)	<0.001
Male	3660 (62)	1114 (62)	0.93	3611 (62)	4539 (61)	0.49
Race / Ethnicity			0.002			<0.001
White, Non-Hispanic	3627 (62)	1120 (63)		3472 (60)	4626 (63)	
Black, Non-Hispanic	893 (15)	313 (17)		920 (16)	1330 (18)	
Hispanic	702 (12)	161 (9.0)		876 (15)	803 (11)	
Other / Unknown	648 (11)	196 (11)		559 (9.6)	636 (8.6)	
Clinical Characteristics						
MS-DRG	2559 (44)	688 (38)	<0.001	3071 (53)	3733 (50)	0.011
Sepsis, Any	4544 (77)	1076 (60)	<0.001	4539 (78)	4465 (60)	<0.001
Septic Shock	3970 (68)	806 (45)	<0.001	3886 (67)	2855 (39)	<0.001
COVID-19	1168 (20)	260 (15)	<0.001	1246 (21)	706 (9.5)	<0.001
APR-DRG Severity of Illness			<0.001			<0.001
Major	93 (1.6)	73 (4.1)		125 (2.1)	507 (6.9)	
Extreme	5775 (98)	1714 (96)		5700 (98)	6872 (93)	
Hypertension	3359 (57)	1086 (61)	0.01	3522 (60)	4869 (66)	<0.001
Diabetes	2814 (48)	918 (51)	0.013	3100 (53)	4047 (55)	0.081
Chronic Kidney Disease	2692 (46)	902 (50)	<0.001	2970 (51)	4229 (57)	<0.001
Charlson Comorbidities Index Category			0.02			<0.001
0	412 (7.0)	115 (6.4)		380 (6.5)	507 (6.9)	
1–2	1474 (25)	398 (22)		1364 (23)	1489 (20)	
3–4	1627 (28)	493 (28)		1570 (27)	1858 (25)	
5+	2357 (40)	784 (44)		2513 (43)	3541 (48)	
ECMO	344 (5.9)	87 (4.9)	0.11	70 (1.2)	32 (0.4)	<0.001
Mechanical Ventilation	5388 (92)	1462 (82)	<0.001	5060 (87)	4999 (68)	<0.001
Facility Characteristics						
Teaching Facility	3841 (65)	1293 (72)	<0.001	3061 (53)	4015 (54)	0.044
Urban Population	5535 (94)	1693 (95)	0.64	5343 (92)	6813 (92)	0.36
Bed Count			<0.001			<0.001
<300	942 (16)	248 (14)		1544 (27)	1724 (23)	
300–499	1616 (28)	437 (24)		1645 (28)	2174 (29)	
500+	3309 (56)	1105 (62)		2624 (45)	3489 (47)	
Outcomes						
In-hospital mortality	3307 (56)	599 (33)	<0.001	2841 (49)	1711 (23)	<0.001
Length of Stay, days (mean, std. dev)	25 (17)	28 (18)	<0.001	24 (16)	24 (16)	0.13
ICU Length of Stay, days (mean, std. dev)	19 (13)	20 (15)	0.86	17 (12)	15 (12)	<0.001
Average Daily IV Fluid Use						
Pre-RRT Initiation[a], median ml (IQR)	1750 (833; 3333)	1667 (750; 3163)	0.044	1517 (676; 3000)	1525 (667; 3000)	0.39
Post-RRT Initiation[a], median ml (IQR)	1883 (964; 3433)	1185 (500; 2315)	<0.001	1250 (583; 2327)	833 (333; 1583)	<0.001

Abbreviations: COVID-19: Coronavirus Disease 2019, CRRT: Continuous Renal Replacement Therapy, ECMO: Extracorporeal Membrane Oxygenation, ICU: Intensive Care Unit, IHD: Intermittent Hemodialysis, MS-DRG: Medicare Severity Diagnosis Related Groups: APR-DRG, All Patient Refined Diagnosis Related Group.

[a] Pre-RRT and Post-RRT: within 3 days before and after RRT initiation, respectively.

having septic shock, receiving mechanical ventilation, being a MS-DRG patient, and more days in the ICU before RRT initiation were associated with an increased risk of mortality in both the CRRT and IHD cohorts. Further, in the CRRT cohort only, ECMO was associated with an increased mortality risk, and extreme APR-DRG severity in the IHD cohort only (Table 2).

For the CRRT cohort, adjusted hazard ratios (aHR) for the number of vasopressors used were 1.50 (95 % CI: 1.36, 1.65, $p < 0.001$), 1.94 (95 % CI: 1.76, 2.14, $p < 0.001$), and 2.06 (95 % CI: 1.72, 2.46, $p < 0.001$) for 1, 2 and 3+ vasopressors respectively (Table 2). For the IHD cohort, aHR for the number of vasopressors used were 1.57 (95 % CI: 1.47, 1.68, $p < 0.001$), 2.20 (95 % CI: 2.02, 2.40, $p < 0.001$), and 2.32 (95 % CI: 1.82, 2.96, $p < 0.001$) for 1, 2 and 3+ vasopressors respectively (Table 2).

3.4. Secondary analysis: effect of vasopressor combination on outcomes

Of the population using 2+ vasopressors post-RRT initiation included in the final model, 95 % received either norepinephrine + vasopressin, norepinephrine + dopamine, or norepinephrine + vasopressin + dopamine (Supplementary Table A3). Patient characteristics for these and the other vasopressor combination used post-RRT are provided in Supplementary Table A8. Differences were observed between the patients included in each of the categories, including the presence of sepsis, septic shock, COVID-19, hypertension, comorbidities and RRT modality.

Although not all statistically significant, all the analyzed vasopressor

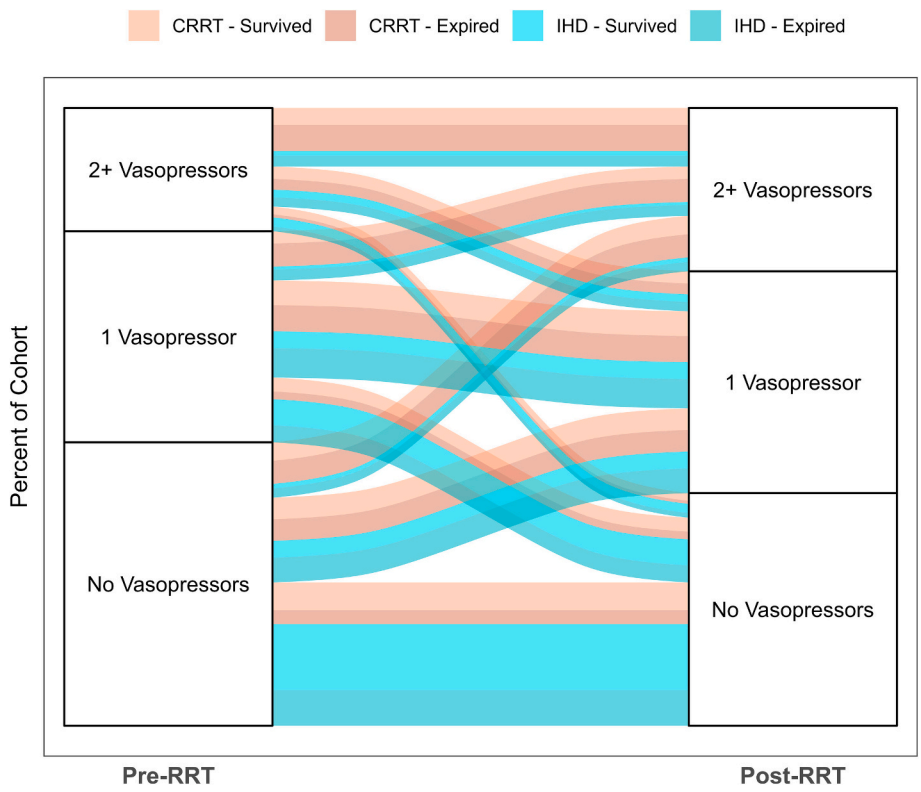

Fig. 2. Vasopressor use before and after renal replacement therapy initiation. Alluvial diagram assessing the transition of vasopressor use categories before and after RRT initiation according to RRT modality and 90-day outcome. Pre-RRT and Post-RRT: within 3 days before and after RRT initiation, respectively.

combinations were associated with increased risk of mortality compared to single vasopressor. Norepinephrine + vasopressin, the most used vasopressor combination (Supplementary Table A3), showed a significantly increased hazard ratio for both RRT cohorts (Supplementary Table A9; CRRT: HR 1.32, 95 %CI [1.22–1.42], $p < 0.001$; IHD: HR 1.46, 95 %CI [1.34–1.59], $P < 0.001$).

3.5. Subgroup and sensitivity analyses

Similar results as observed for the entire cohort were observed in subgroups of septic shock (Supplementary Table A11) and cardiac surgery (Supplementary Table A12). Sensitivity analyses including IHD patients from facilities that did not offer CRRT (Supplementary Table A14), and a model excluding patients exposed to both RRT modalities (CRRT and IHD) during the study period (Supplementary Table A15) were consistent with the primary results of the study.

4. Discussion

This study aimed to examine the effect of vasopressor use post-RRT initiation on in-hospital mortality. Key observations were that vasopressor exposure during the 3 days post-RRT initiation was independently associated, in a dose-response manner according to number of vasopressors, with higher in-hospital mortality in patients receiving either CRRT or IHD in the ICU as the first RRT modality. This association was independent of the severity of illness, and the magnitude of risk was greater in patients receiving multiple vasopressors and in those receiving different vasopressor combinations. Moreover, the risk appears greater in those receiving IHD vs. CRRT as the initial modality.

The presence, duration, and severity of hypotension have been identified as an independent risk factor for death and organ dysfunction in critically ill patients with AKI [1,15]. In addition, it has been shown that hypotension increases the risk of AKI progression [16], and the need for vasopressors can impact renal recovery [17,18]. Achieving hemodynamic stability and preserving renal perfusion is essential to improving AKI outcomes. This can be achieved by increasing cardiac output and renal blood flow through fluid resuscitation, inotropic drugs, renal vasodilators, or systemic vasopressors [1]. Indeed, in a secondary analysis of a randomized control trial, the use of Angiotensin II after RRT initiation was associated with lower mortality and greater independence from RRT [19].

Our study indicated that the adjusted mortality risk was greater in patients requiring vasopressors during the first three days after RRT initiation, independently from the use of vasopressors before RRT and IV fluids during RRT, and was particularly more remarkable in those receiving multiple vasopressors. A more precarious hemodynamic condition can explain a greater magnitude of mortality risk in patients receiving multiple vasopressors. Still, it can also be due to the insensitivity of critically ill patients to vasopressors, resulting in persistent hypotension and organ injury [1]. A retrospective study by Priyanka et al. showed that patients with vasopressor-resistant hypotension, defined as patients requiring greater than 0.2 μg/kg per minute of norepinephrine equivalents for more than 6 continuous hours, had increased risk-adjusted mortality [20]. In addition, although not a common mechanism, vasopressors may be cleared by RRT. In particular, when the venous port of a dialysis catheter lies within the same vein as the venous catheter being used for vasopressor infusion, it is possible that vasopressors are being cleared before they can exert systemic effects [8]. Further research is needed to define the underlying cause of higher mortality rates among patients receiving multiple vasopressors during RRT, and to develop new strategies of non-invasive hemodynamic monitoring and multi-modal pressor support.

Our study found a higher proportion of vasopressor use in patients that received CRRT as the initial modality as compared to IHD, and concordantly a larger percentage of 2+ vasopressor use in patients on CRRT, which aligns with the current preference for CRRT therapies for hemodynamically unstable patients [3,21]. However, for both modalities, mortality rates increased with the number of vasopressors used

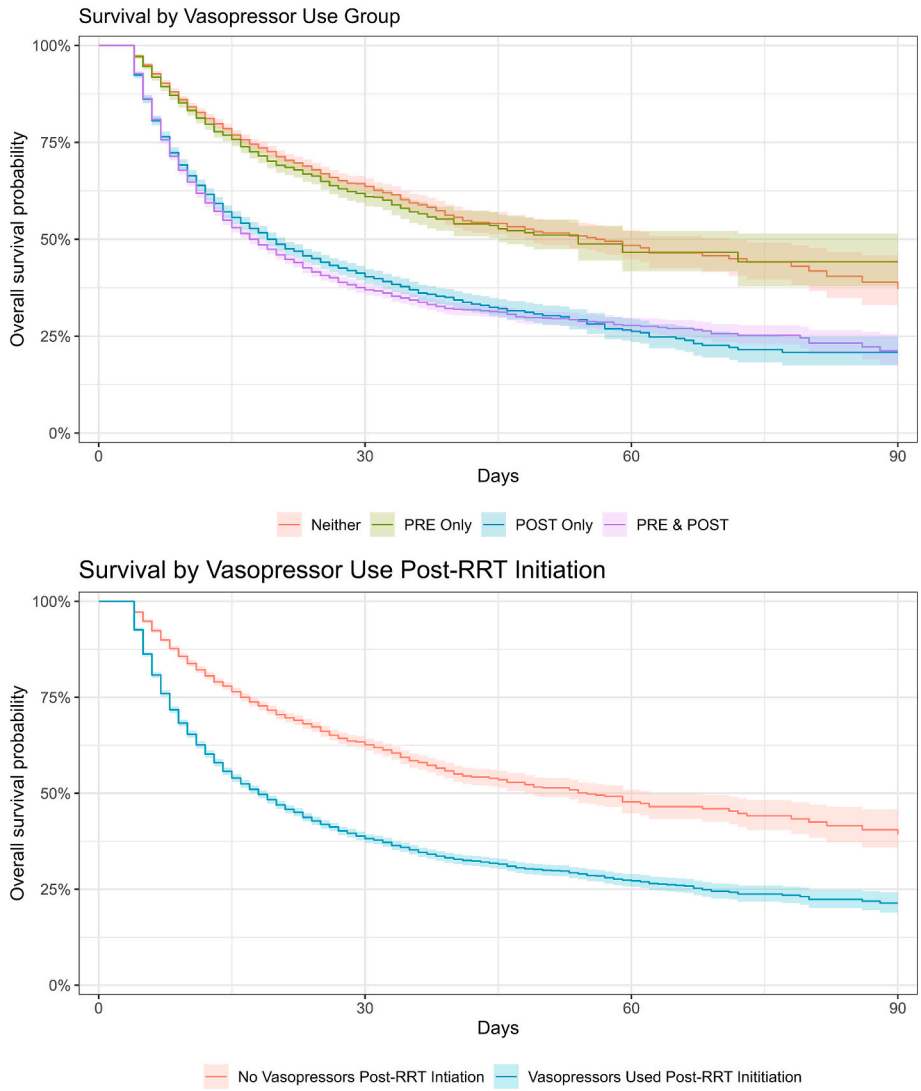

Fig. 3. Patient survival by vasopressor use. The Kaplan-Meier figures plots for the probability of crude in-hospital patient survival over 90 days post-RRT initiation, comparing patients by vasopressor use group (A) or by vasopressor use during the 3 days post-RRT initiation after consolidating the four vasopressor use groups into two groups (B). The shading in the figures denotes a 95 % CI. Patients with post-RRT vasopressor use had lower 90-day survival (21 %, 95 % CI: 19 %, 24 %) compared to patients without post-RRT vasopressor use (39 %, 95 % CI: 34 %, 45 %; (log-rank $p < 0.001$) (B). Patients with post-RRT vasopressor use were found to have similar 90-day survival rates regardless of pre-RRT vasopressor use (both 21 % survival), and likewise, patients without RRT vasopressor use had similar survival rates compared to patients with only pre-RRT vasopressor use (37 % and 44 % survival, respectively) (A).
Labels: Neither: no vasopressor use within 3 days of RRT initiation and those who only received vasopressors on the day of RRT initiation, PRE Only: patients with only pre-RRT initiation vasopressor use, POST Only: patients with only post-RRT initiation vasopressor use, PRE & POST: patients with both pre-and post-RRT initiation vasopressor use. The four vasopressor use categories (only pre-RRT initiation, only post-RRT initiation, both pre-and post-RRT initiation, and neither) were consolidated down into two categories: Vasopressor use post-RRT initiation Yes/No. The 'vasopressor use post-RRT initiation group' included the patients with only post-RRT initiation and patients with both pre-and post-RRT initiation. The 'no vasopressor use post-RRT initiation group' included the patients with only pre-RRT initiation, and patients with neither vasopressor use (no vasopressor use within 3 days of RRT initiation and those who only received vasopressors on the day of RRT initiation). RRT: Renal Replacement Therapy.

during the three days following RRT initiation. Furthermore, we found an interaction between modality and vasopressor-related outcomes, and the IHD cohort was more greatly impacted by the use of multiple vasopressors following RRT initiation. Given the window of evaluation was only 3 days post-RRT initiation, it is possible that some patients initially on IHD transitioned to CRRT later in the ICU course due to worsening hemodynamic status. Some advantages of CRRT over IHD have been shown, including improved cardiovascular stability, easier and greater fluid removal, better metabolic control, and removal of pro-inflammatory substances, whereas more hypotensive episodes have been observed with IHD as compared to CRRT in certain acutely ill patients [5,21–23].

The secondary analysis assessed vasopressor combinations. Combination vasopressor therapy has been hypothesized to raise MAP and treat vasodilatory shock more effectively than vasopressor monotherapy [20]. In our study, none of the vasopressor combinations proved to attenuate the risk of mortality but it has to be mentioned that several of these combinations were used in only a small number of patients.

Key strengths of this study are its large multicenter sample of diverse AKI patients requiring RRT who survived the first 3 days post-RRT initiation (n = 20,882) and the availability of relevant covariates including the demographics, comorbidity and acute illness indicators for adjustment in the models. Study limitations include the potential for confounding by unmeasured variables. First, vasopressor administration was limited to the initial 3 days post-initiation of RRT and does not encompass the entire RRT treatment; furthermore, there are insufficient

Table 2
Cox regression on patient survival by RRT modality.

	CRRT (n = 7660)			IHD (n = 13,222)		
	Hazard ratio	95 % CI	p-value	Hazard ratio	95 % CI	*p*-value
Age in Years	1.02	1.01, 1.02	<0.001	1.02	1.02, 1.02	<0.001
Sex						
Female	–	–		–	–	
Male	1.07	1.00, 1.14	0.046	1.17	1.10, 1.25	<0.001
White, Non-Hispanic	1.00	0.94, 1.07	>0.9	0.98	0.93, 1.04	0.600
MS-DRG Category						
Surgical	–	–		–	–	
Medical	2.33	2.16, 2.50	<0.001	2.34	2.19, 2.50	<0.001
APR-DRG Severity: Extreme vs Non Extreme	1.01	0.77, 1.32	>0.9	1.77	1.38, 2.28	<0.001
COVID	1.27	1.17, 1.37	<0.001	1.57	1.46, 1.68	<0.001
Septic Shock	1.09	1.02, 1.18	0.017	1.14	1.07, 1.22	<0.001
ECMO	1.49	1.31, 1.70	<0.001	1.32	0.98, 1.79	0.072
Mechanical Ventilation	1.25	1.11, 1.42	<0.001	1.62	1.48, 1.79	<0.001
Days in ICU before RRT Initiation						
0–1 days	–	–		–	–	
2–3 days	1.03	0.92, 1.15	0.600	0.98	0.87, 1.11	0.800
4–7 days	1.28	1.14, 1.45	<0.001	1.21	1.07, 1.37	0.002
8+ days	1.47	1.30, 1.66	<0.001	1.38	1.22, 1.56	<0.001
Number of Vasopressors, post-RRT						
0	–	–		–	–	
1	1.50	1.36, 1.65	<0.001	1.57	1.47, 1.68	<0.001
2	1.94	1.76, 2.14	<0.001	2.20	2.02, 2.40	<0.001
3+	2.06	1.72, 2.46	<0.001	2.32	1.82, 2.96	<0.001
Avg Total IV Fluid Use, post-RRT						
Bottom tertile	–	–		–	–	
Middle tertile	1.10	1.01, 1.21	0.038	1.15	1.07, 1.23	<0.001
Top tertile	1.17	1.07, 1.27	<0.001	1.13	1.04, 1.21	0.002

Abbreviations: COVID-19: Coronavirus Disease 2019, CRRT: Continuous Renal Replacement Therapy, ECMO: Extracorporeal Membrane Oxygenation, ICU: Intensive Care Unit, IHD: Intermittent Hemodialysis, MS-DRG: Medicare Severity Diagnosis Related Groups, APR-DRG: All Patient Refined Diagnosis Related Group.

data regarding dosing and titration details. In a previous retrospective study by Ramesh et al. [24], a time-dependent Cox proportional hazards model was employed, which adjusted for vasopressor doses and fluid balance, SOFA score, lactate and other markers of severity of illness, to investigate whether the use of a specific vasopressor was associated with increased mortality or adverse outcomes in patients with AKI receiving CRRT. Increasing doses of norepinephrine per 0.02 μg/min/kg and vasopressin per 0.02 unit/min during CRRT were associated with in-hospital mortality. Whereas our study lacked data regarding dosing and titration details, this study provided a detailed analysis of dosing and titration throughout CRRT, and provided evidence supporting the increased mortality risk associated with vasopressor use during CRRT after adjusting for clinical variables, fluid management, and demographic factors. Second, to compile the final model of in-hospital mortality as the dependent variable, the model was checked for potential interaction effects, including RRT modality by the number of vasopressors used following RRT inititiation. Patients were assigned according to the number of different vasopressors they received in the study period post-RRT initiation, meaning that patients receiving one vasopressor type for one day while being on another one for 2 days, as well as patients who received two types of vasopressors for 3 days, would both be classified as receiving 2 vasopressors. This method of classification could have led to some non-uniformity within the subgroups.

As expected, the CRRT cohort represented a larger percentage of patients requiring 2+ vasopressors post-RRT initiation and had higher mortality rates. This suggests that the CRRT cohort may have included patients with higher severity of illness than the IHD cohort. Therefore, and based on the significant statistical interaction between initial RRT modality (CRRT or IHD) and post-RRT vasopressor exposure for in-hospital mortality, the results of this study are presented stratified by initial RRT modality. Importantly, results were consistent when CRRT and IHD patients were analyzed separately and after several sensitivity analyses of specific subgroups such as patients with septic shock and cardiac surgery. In addition, there might have been some other biases. Only patients that remained hospitalized at least 3 days following RRT initiation were included. This inclusion criterium was set to allow for characterization of vasopressor use after RRT initiation, but this also resulted in exclusion of a small but key group of acute RRT patients, who died in the first 48-72 h of RRT initiation. Furthermore, the included patients were classified based on their initial RRT modality used, and crossover between modalities was not analyzed. Since there was a significant interaction between modality and the number of vasopressors used, the cross over between modalities might be relevant. In addition, it has been shown that patients who develop hemodynamic instability after transition from CRRT to IHD have a higher mortality than patients who do not transition to IHD [9]. However, since crossover typically occurs after 48 h of CRRT or at least 1 session of HD, the exposure period (post-RRT vasopressor use) of only 3 days limited the crossover probability.

While our analysis showed an apparent higher magnitude of risk of mortality associated with vasopressor use for IHD patients compared to those undergoing CRRT, even though CRRT patients generally had a higher severity of illness, it is important to interpret these findings cautiously due to the study limitations and observational design. Nevertheless, these results favor the need for further research on better approaches to vasopressor management during RRT, which could help develop better risk assessment tools and guide clinicians in choosing the most appropriate RRT modality for critically ill patients.

5. Conclusions

In conclusion, vasopressor use during the three days post-RRT initiation was independently and incrementally (according to higher number of vasopressors) associated with higher in-hospital mortality in patients first receiving either CRRT or IHD in the ICU.

Glossary

aHR	Adjusted Hazard Ratio
AKI	Acute Kidney Injury
CKD	Chronic Kidney Disease
CRRT	Continuous Renal Replacement Therapy
APR-DRG	All Patient-Refined Diagnosis-Related Group
ECMO	Extracorporeal Membrane Oxygenation
HIRRT	Hemodynamic Instability Related to Renal Replacement

	Therapy
ICU	Intensive Care Unit
IHD	Intermittent Hemodialysis
IV	Intravenous
MS-DRG	Medicare Severity Diagnosis-Related Group
PINC	Premier Inc
PIRRT	Prolonged Intermittent Renal Replacement Therapy
RRT	Renal Replacement Therapy
SLED	Sustained Low-Efficiency Dialysis

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CRediT authorship contribution statement

Javier A. Neyra: Writing – review & editing, Writing – original draft, Conceptualization. **Jorge Echeverri:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Daniel Bronson-Lowe:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Caio Plopper:** Writing – review & editing, Funding acquisition, Conceptualization. **Kai Harenski:** Writing – review & editing, Funding acquisition, Conceptualization. **Raghavan Murugan:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

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The present study has not been registered on clinical.trials.gov.

Appendix A. Supplementary data

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References

[1] Liang Z, Yue S, Zhong J, Wu J, Chen C. Associations of systolic blood pressure and in-hospital mortality in critically ill patients with acute kidney injury. Int Urol Nephrol 2023;55(8):2099–109.
[2] Rachoin JS, Weisberg LS. Renal replacement therapy in the ICU. Crit Care Med 2019;47(5):715–21.
[3] Douvris A, Malhi G, Hiremath S, et al. Interventions to prevent hemodynamic instability during renal replacement therapy in critically ill patients: a systematic review. Crit Care 2018;22(1):41.
[4] Douvris A, Zeid K, Hiremath S, et al. Mechanisms for hemodynamic instability related to renal replacement therapy: a narrative review. Intensive Care Med 2019;45(10):1333–46.
[5] Augustine JJ, Sandy D, Seifert TH, Paganini EP. A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. Am J Kidney Dis 2004;44(6):1000–7.
[6] Jordan M, Ortiz-Soriano V, Pruitt A, et al. Kidney recovery in patients with acute kidney injury treated in outpatient hemodialysis or rehabilitation facilities. Kidney Med 2021;3(6):916–24. e1.
[7] Shawwa K, Kompotiatis P, Jentzer JC, et al. Hypotension within one-hour from starting CRRT is associated with in-hospital mortality. J Crit Care 2019;54:7–13.
[8] Villa G, Husain-Syed F, Saitta T, et al. Hemodynamic instability during acute kidney injury and acute renal replacement therapy: pathophysiology and clinical implications. Blood Purif 2021;50(6):729–39.
[9] Beaubien-Souligny W, Yang Y, Burns KEA, et al. Intra-dialytic hypotension following the transition from continuous to intermittent renal replacement therapy. Ann Intensive Care 2021;11(1):96.
[10] Koyner JL, Mackey RH, Echeverri J, et al. Initial renal replacement therapy (RRT) modality associates with 90-day postdischarge RRT dependence in critically ill AKI survivors. J Crit Care 2024;82:154764.
[11] Averill R, Goldfield N, Hughes J. 3M APR DRG Classification System. 2008.
[12] Baram D, Daroowalla F, Garcia R, et al. Use of the all patient refined-diagnosis related group (APR-DRG) risk of mortality score as a severity adjustor in the medical ICU. Clin Med Circ Respirat Pulm Med 2008;2:19–25.
[13] Elgwairi E, Yang S, Nugent K. Association of the all-patient refined diagnosis-related groups severity of illness and risk of mortality classification with outcomes. South Med J 2021;114(10):668–74.
[14] McCormick PJ, Lin HM, Deiner SG, Levin MA. Validation of the all patient refined diagnosis related group (APR-DRG) risk of mortality and severity of illness modifiers as a measure of perioperative risk. J Med Syst 2018;42(5):81.
[15] Maheshwari K, Nathanson BH, Munson SH, et al. The relationship between ICU hypotension and in-hospital mortality and morbidity in septic patients. Intensive Care Med 2018;44(6):857–67.
[16] Izawa J, Kitamura T, Iwami T, et al. Early-phase cumulative hypotension duration and severe-stage progression in oliguric acute kidney injury with and without sepsis: an observational study. Crit Care 2016;20(1):405.
[17] Kellum JA, Sileanu FE, Bihorac A, Hoste EA, Chawla LS. Recovery after acute kidney injury. Am J Respir Crit Care Med 2017;195(6):784–91.
[18] Zhao Y, Wang W, Zhilong D. What is the real predictor of coronary artery calcification in patients with chronic kidney disease? Ren Fail 2022;44(1):269–71.
[19] Tumlin JA, Murugan R, Deane AM, et al. Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. Crit Care Med 2018;46(6):949–57.
[20] Priyanka P, Chang CH, Chawla LS, Kellum JA, Clermont G, Murugan R. Vasopressor-resistant hypotension, combination vasopressor therapy, and shock phenotypes in critically ill adults with vasodilatory shock. Shock 2022;58(4):260–8.
[21] John S, Griesbach D, Baumgärtel M, Weihprecht H, Schmieder RE, Geiger H. Effects of continuous haemofiltration vs intermittent haemodialysis on systemic haemodynamics and splanchnic regional perfusion in septic shock patients: a prospective, randomized clinical trial. Nephrol Dial Transplant 2001;16(2):320–7.
[22] Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1–38.
[23] Nadim MK, Forni LG, Bihorac A, et al. Cardiac and vascular surgery-associated acute kidney injury: the 20th international consensus conference of the ADQI (acute disease quality initiative) group. J Am Heart Assoc 2018;7(11).
[24] Ramesh A, Doddi A, Abbasi A, Al-Mamun MA, Sakhuja A, Shawwa K. Use of vasopressors in patients with acute kidney injury on continuous kidney replacement therapy. PloS One 2024;19(12):e0315643.