

Association of anticoagulation use during continuous kidney replacement therapy and 90-day outcomes: A multicentre study

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ABSTRACT

Introduction: Anticoagulation is recommended during continuous kidney replacement therapy (CKRT) to prolong the filter lifespan for optimal filter performance. We aimed to evaluate the effect of anticoagulation during CKRT on dialysis dependence and mortality within 90 days of intensive care unit (ICU) admission.

Method: Our retrospective observational study evaluated the first CKRT session in critically ill adults with acute kidney injury (AKI) in Singapore from April to September 2017. The primary outcome was a composite of dialysis dependence or death within 90 days of ICU admission; the main exposure variable was anticoagulation use (regional citrate anticoagulation [RCA] or systemic heparin). Multivariable logistic regression was performed to adjust for possible confounders: age, female sex, Acute Physiology and Chronic Health Evaluation (APACHE II) score, liver dysfunction, coagulopathy (international normalised ratio [INR] >1.5) and platelet counts of less than 100,000/uL).

Results: The study cohort included 276 patients from 14 participating adult ICUs, of whom 176 (63.8%) experienced dialysis dependence or death within 90 days of ICU admission (19 dialysis dependence, 157 death). Anticoagulation significantly reduced the odds of the primary outcome (adjusted odds ratio [AOR] 0.47, 95% confidence interval [CI] 0.27–0.83, $P=0.009$). Logistic regression analysis using anticoagulation as a 3-level indicator variable demonstrated that RCA was associated with mortality reduction (AOR 0.46, 95% CI 0.25–0.83, $P=0.011$), with heparin having a consistent trend (AOR 0.51, 95% CI 0.23–1.14, $P=0.102$).

Conclusion: Among critically ill patients with AKI, anticoagulation use during CKRT was associated with reduced dialysis or death at 90 days post-ICU admission, which was statistically significant for regional citrate anticoagulation and trended in the same direction of benefit for systemic heparin anticoagulation. Anticoagulation during CKRT should be considered whenever possible.

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CLINICAL IMPACT

What is New

- This is a large cohort study on continuous kidney replacement therapy (CKRT) practices in adult ICU patients.
- Two-thirds of patients with new onset acute kidney injury in ICU progress to develop chronic dialysis or death within 90 days of ICU admission.
- Mortality was highest amongst patients who did not receive anticoagulation with heparin or citrate.

Clinical Implications

- Anticoagulation during CKRT should be considered whenever possible.
- Future studies can be designed to look at the association of filter lifespan and efficiency with patient-centred outcomes, and the reasons for omitting anticoagulation.

INTRODUCTION

Acute kidney injury (AKI) affects 21.6% of critically ill adult patients,¹ with 5–7% requiring kidney replacement therapy (KRT).² AKI carries significant prognostic and socioeconomic implications—chronic kidney disease (CKD) progression over 1 year has been described in 21%, 30%, and 79% of initial survivors with septic AKI reversal, recovery and non-recovery, respectively.³ AKI also increases the risk of developing end-stage kidney disease⁴ leading to a significant healthcare and socioeconomic burden.⁵ With the increasing incidence of AKI⁶ and resultant end-stage kidney disease (ESKD), there has been increasing interest for effective treatment modalities, specifically therapies that might mitigate the rates of dialysis dependence.

Anticoagulation during continuous kidney replacement therapy (CKRT) prolongs the lifespan of the extra-corporeal circuit and optimal filter performance.⁷ Regional citrate anticoagulation (RCA) is preferred due to filter running times; reduces bleeding complications; allows effective control of acid–base status; and reduces adverse events like heparin-induced thrombocytopenia (HIT).⁸ The ideal anticoagulation strategy for CKRT remains debated,^{9–11} with limited data on patient-centred outcomes such as eventual dialysis dependence or ICU mortality.¹² Heparin

anticoagulation may not be feasible for patients who have ongoing bleeding manifestations or diathesis, or post-surgical patients in the early post-operative period.

Little is known about the contemporary KRT practices in Singapore.¹³ Leveraging the collaboration with the Society of Intensive Care Medicine Singapore-National Investigators for Clinical Epidemiology and Research (SICM-NICER), we embarked on this study aiming to evaluate current trends, and the association of anticoagulation use on patient-centred outcomes. The primary outcome was dialysis dependence or death within 90 days of ICU admission.

METHOD

Study design and setting

We conducted a nationwide study in Singapore, a diverse nation of 5.7 million people. With 16 restructured hospitals and a range of specialised ICUs—including medical, surgical and subspecialty units (neurosurgical, cardiology and cardiothoracic)—our study covered the critical care landscape. This retrospective observational study encompassed all critically ill patients in participating adult ICUs across these restructured hospitals.

Study population

We included patients who had AKI and received CKRT between 1 April 2017 and 30 September 2017, and patients with ESKD were excluded. ESKD and AKI was defined as per the Kidney Disease Improving Global Outcomes (KDIGO) criteria.¹⁴

Data sources and definitions

We extracted details of the patients' KRT regimen and disease progression from electronic and paper medical records. At each individual site, patient details were collected and de-identified before being compiled by the principal investigator. Our analysis focused on the initial KRT session; specifically, only sessions with complete data were included. We excluded non-continuous modes of KRT such as intermittent haemodialysis, sustained low-efficiency dialysis (SLED) and peritoneal dialysis. All patients who received RCA for CKRT, received calcium-free dialysate and replacement solutions. Details about filter lifespan and performance were not collected. To quantify the degree of haemodynamic support, we utilised an inotrope score.¹⁵ Liver dysfunction was defined as presence of liver cirrhosis or bilirubin ($>35 \mu\text{mol/L}$).¹⁶ Coagulopathy was defined as $\text{INR} > 1.5$, and thrombocytopenia was defined as platelet counts of $<100,000/\mu\text{L}$.

Statistical analysis

Continuous variables are presented as mean (standard deviation [SD]) and median (inter-quartile range [IQR]). Categorical variables are presented as number (%).

The initial KRT episode was analysed with multivariate logistic regression for factors associated with dialysis dependence or death at 90 days post-ICU (hyphen) admission. Logistic regression was done using key prognostic factors (i.e. age, female sex, APACHE II, liver dysfunction, coagulopathy, thrombocytopenia), and other possible confounders from Tables 1 and 2 with univariate *P* values of <0.05. Odds ratios were derived with 95% confidence intervals.

Ethics approval

Given the non-interventional nature of the study, waiver of informed consent was granted by the National Healthcare Group Domain Specific Review Board (DSRB reference 2017/01010) and mutually recognised by SingHealth Centralised Institutional Review Board (CIRB).

RESULTS

A total of 14 ICUs across 6 hospitals in Singapore contributed data to the study. The study population is described in Fig. 1. A total of 867 patients received KRT during the study period. The characteristics of 276 patients were analysed, and characteristics of their ICU stay, are described in Table 1. The most common cause of AKI was in association with sepsis, and the median ICU length of stay (LOS) was 7 days. In total, 176 patients (63.8%) experienced dialysis dependence or death within 90 days of ICU admission (19 dialysis dependence, 157 death).

Continuous veno-venous hemodiafiltration (CVVHDF) was the top choice for initial CKRT mode, accounting for 62% of sessions. Other modes included continuous veno-venous hemodialysis (CVVHD) (19.6%), continuous veno-venous hemofiltration (CVVH) (17.0%), and slow continuous ultrafiltration (SCUF) (1.1%). Table 2 provides further details on the characteristics of the CKRT sessions. The median time to first circuit change was 455.0 minutes (IQR 8.0–1192.0 minutes). Circuit changes were done for various reasons such as interruptions of CKRT for procedures, refractory haemodynamic instability, or circuit clotting or clogging.

Among the 276 patients receiving CKRT, anticoagulation during the first CKRT session during the ICU admission was associated with reduction of dialysis dependence and mortality at 90 days (adjusted OR [aOR] 0.47, 95% CI (0.27–0.83), *P*=0.009) (Table 3). Repeating the logistic regression analysis using anticoagulation as

a 3-level indicator variable, demonstrated that citrate anticoagulation was associated with mortality reduction (aOR 0.46, 95% CI 0.25–0.83, *P*=0.011) and with heparin having a consistent trend (aOR 0.51, 95% CI 0.23–1.14, *P*=0.102), compared to no anticoagulation use. In contrast, liver dysfunction, coagulopathy and thrombocytopenia did not have significant independent associations of dialysis dependence or death at 90 days.

DISCUSSION

This is the largest-ever observational study of AKI patients undergoing CKRT in Singapore. Among ICU patients who suffered AKI, 63.8% were left with dialysis dependence or died within 90 days. Mortality was highest in patients who did not receive anticoagulation with either heparin or citrate, and citrate anticoagulation was associated with reduced mortality. Heparin anticoagulation showed a consistent trend with the odds ratio in the same direction as citrate anticoagulation, but did not similarly reach significance, likely due to the smaller sample size for heparin (*n*=46), compared to citrate anticoagulation (*n*=100).

Sepsis was the leading cause of AKI in our study, in keeping with international data.² The 90-day mortality rate of 43.1% is consistent with international studies² as well and underscores the high mortality rate of AKI. The most common mode of CKRT in Singapore was CVVHDF, which is consistently favoured in published literature because of its lower failure rate compared to other modalities of CKRT.¹⁷ This is comparable with patients who had AKI who received SLED.¹⁸

Comparing between patients who had anticoagulation during KRT against those who did not (Table 1), there were more patients in the group that did not receive anticoagulation with platelet counts <100,000/ μ L. This could be a biomarker for bleeding risk. However, after adjusting for it during multivariable analysis, anticoagulation use retained a significant association with the primary outcome. There were differences in the prescribers who chose anticoagulation and those who omitted anticoagulation, but this may just reflect anticoagulation preference, rather than expertise with renal care. We therefore did not adjust for it in multivariable analysis.

Patients in the group receiving anticoagulation had higher numbers with hypokalemia and hypophosphataemia. This may be due to regional citrate anticoagulation, but we did not adjust for these as complications did not precede exposure to anticoagulation. The number of replacement or dialysate fluid bags were different between groups. However, we did not adjust for this as this did not precede exposure to anticoagulation.

Table 1. Patient demographics and ICU stay characteristics.

Variables	All patients n=276	Patients not on anticoagulation n=130	Patients on anticoagulation n=146	P value
Demographics				
Age, mean±SD, years	64.2±13.8	64.5±14.2	63.8±13.4	0.663
Female, n (%)	104 (37.7)	48 (36.9)	56 (38.4)	0.901
BMI mean±SD, kg/m ²	25.0±7.7	24.5±5.3	25.5±9.3	0.318
Comorbidities[^]				
Diabetes mellitus, n (%)	147 (53.3)	60 (46.2)	87 (59.6)	0.030
Hypertension, n (%)	191 (69.2)	87 (66.9)	104 (71.2)	0.514
Ischaemic heart disease, n (%)	96 (34.8)	44 (33.9)	52 (35.6)	0.801
Chronic kidney disease, n (%)	111 (40.2)	45 (34.6)	66 (45.2)	0.085
COPD, n (%)	15 (5.4)	8 (6.2)	7 (4.8)	0.791
Cancer, n (%)	38 (13.8)	20 (15.4)	18 (12.3)	0.488
Liver dysfunction,* n (%)	123 (44.6)	63 (48.5)	60 (41.1)	0.228
Coagulopathy,** n (%)	32 (11.6)	20 (15.4)	12 (8.2)	0.089
Thrombocytopenia,*** n (%)	78 (28.3)	45 (34.6)	33 (22.6)	0.032
Cause of AKI				
Sepsis, n (%)	151 (54.7)	67 (51.5)	84 (57.5)	0.151
Hypovolemia/ shock, n (%)	21 (7.6)	15 (11.5)	6 (4.1)	
Nephrotoxic agents, n (%)	4 (1.4)	2 (1.5)	2 (1.4)	
Major surgery, n (%)	16 (5.8)	7 (5.4)	9 (6.2)	
Hepatorenal syndrome, n (%)	10 (3.6)	8 (6.2)	2 (1.4)	
Cardiogenic shock, n (%)	55 (19.9)	24 (18.5)	31 (21.2)	
Post-obstructive, n (%)	2 (0.7)	1 (0.8)	1 (0.7)	
Others (e.g. rhabdomyolysis, pancreatitis), n (%)	17 (6.2)	7 (5.4)	10 (6.8)	
Admission source				
Emergency department, n (%)	118 (42.8)	55 (42.3)	63 (43.2)	0.199
General ward, n (%)	99 (35.9)	43 (33.1)	56 (38.4)	
Operating theatre, n (%)	29 (10.5)	13 (10.0)	16 (11.0)	
High dependency unit/ intermediate care unit, n (%)	19 (6.9)	14 (10.8)	5 (3.4)	
Others (e.g. endoscopy suite), n (%)	11 (4.0)	5 (3.8)	6 (4.1)	
APACHE II score, mean±SD				
	27.3±9.5	28.4±9.8	26.4±9.3	0.091
Vasopressor use, n (%)				
	221 (80.1)	109 (83.8)	112 (76.7)	0.181
Inotrope score, mean±SD				
	3.2±2.0	3.4±2.0	3.0±2.0	0.079
Respiratory support received before CKRT				
HFNC, n (%)	19 (6.9)	10 (7.7)	9 (6.2)	0.640
NIV, n (%)	34 (12.3)	20 (15.4)	14 (9.6)	0.479
Mechanical ventilation, n (%)	236 (85.5)	118 (90.8)	118 (80.8)	0.019
ICU LOS (days), median (IQR)				
	7 (3-16)	6.5 (3-16)	7 (3-17)	0.982
Survival				
Survived ICU stay, n (%)	152 (55.1)	56 (43.1)	96 (65.8)	<0.001
Survived at 30 days of ICU admission, n (%)	133 (48.2)	50 (38.5)	83 (56.9)	0.003
Survived at 90 days of ICU admission, n (%)	119 (43.1)	43 (33.1)	76 (52.1)	0.002
Mechanical ventilation free days up to 28 days, mean±SD				
	11.4±12.2	10.4±11.8	12.3±12.4	0.217
Fluid balance 24 hours prior to KRT (mL), median (IQR)				
	1291.2 (580.5-2258.0)	1321.50 (636.9- 2440.3)	1090.0 (434.8-2109.2)	0.479
Duration of oliguria before KRT, median (IQR)				
	10.0 (2.3-20)	12 (6-24)	10 (0-18)	0.381
Peak creatinine prior to KRT, µmol/L, median (IQR)				
	298 (214-489)	286.5 (200-465)	313 (219-514)	0.070

[^]Patients may have more than 1 comorbidity

AKI: acute kidney injury; CKRT: continuous kidney replacement therapy; COPD: chronic obstructive pulmonary disease; HFNC: high-flow nasal cannula; ICU: intensive care unit; INR: international normalised ratio; IQR: interquartile range; LOS: length of stay; NIV: non-invasive ventilation, PTT: partial thromboplastin time; SD: standard deviation

*Liver dysfunction (defined as presence of liver cirrhosis or bilirubin >35 µmol/L)

**INR>1.5

***Platelet <100,000/µL

Table 2. Characteristics of continuous kidney replacement therapy (CKRT) sessions.

Variables	All patients n=276	Patients not on anticoagulation n=130	Patients on anticoagulation n=146	P value
Type of anticoagulation, n(%)				NA
None	130 (47.1)	130	0	
Regional citrate	100 (36.2)	0	100	
Systemic heparin	46 (16.6)	0	46	
Prescription, n (%)				<0.001
Renal physician	108 (39.1)	81 (62.3)	27 (18.5)	
Intensivist	139 (50.3)	43 (33.1)	96 (65.8)	
Others	29 (10.5)	6 (4.6)	23 (15.7)	
Indication,[^] n (%)				
Routine / regular session	9 (3.3)	4 (3.1)	5 (3.6)	1.000
Clearance of toxins	3 (3.2)	2 (1.5)	1 (0.7)	0.603
Rhabdomyolysis	13 (4.7)	9 (6.9)	4 (2.7)	0.153
Hyperkalemia	96 (34.8)	47 (36.2)	49 (33.5)	0.705
Acidosis	200 (72.5)	92 (70.8)	108 (74.0)	0.591
Fluid overload	70 (25.4)	26 (20.0)	44 (30.1)	0.071
Uraemia	45 (16.3)	19 (14.6)	26 (17.8)	0.516
Oligo-anuria	206 (74.6)	87 (66.9)	119 (81.5)	0.006
Timing of KRT, n (%)				
After office hours	158 (57.2)	73 (56.2)	85 (58.2)	0.808
Duration of first CKRT (hours), median (IQR)	19.5 (8.3-35.0)	19.0 (6.0-34.0)	20.0 (10.0-34.0)	0.840
Time to first circuit change (min), median (IQR)	455.0 (8.0-1192.0)	585.0 (120.0-1475.0)	165.0 (0-879.8)	0.096
Complications after CKRT,[^] n (%)				
Hypokalemia	67 (24.3)	19 (14.6)	48 (32.9)	<0.001
Hypophosphataemia	64 (23.2)	21 (16.2)	43 (29.5)	0.017
Bleeding complications	38 (13.8)	15 (11.5)	23 (15.8)	0.382
Arrhythmia	103 (37.3)	51 (39.2)	52 (35.6)	0.553
Prescribed dose for CKRT (ml/kg/hour), median (IQR)	33.3 (30.0-35.0)	33.0 (30.0-35.0)	35.0 (30.0-35.0)	0.096
Number of replacement/dialysate fluid bags				
Bag 1, median (IQR)	6.0 (3.0-12.0)	5.0 (2.0-13.0)	7.0 (3.0-11.0)	0.067
Bag 2, median (IQR)	4.0 (2.0-7.0)	4.0 (1.0-5.0)	4.0 (2.0-7.0)	0.031

[^]May have more than 1 per session

KRT: Kidney replacement therapy; SD: standard deviation

There were more patients in the anticoagulation group with oligo-anuria than patients who did not receive anticoagulation, though the reason for this is unclear. Nonetheless, we adjusted for this and anticoagulation used remained significantly associated with the primary outcome. Oligo-anuria preceding CKRT was found to be an adverse prognostic factor (Table 3), consistent with a large series that showed it was an independent risk factor for death or end-stage kidney disease in AKD patients.¹⁹ These could be due to less morphologic and functional damage in non-oliguric compared with oliguric AKI (found in animal studies²⁰), and the absence of oliguria in AKI reflects less severe disease.²¹

Anticoagulation in some form is recommended during CKRT to prolong filter lifespan, because problems with filter clotting will lead to interruptions to CKRT and

may result in loss of blood which is in the circuit. Ideally, CKRT should be prescribed with anticoagulation. However, in critically ill patients, this is often contraindicated due to bleeding diathesis, recent surgery precluding use of heparin, or liver failure precluding the use of regional citrate anticoagulation, which will lead to metabolic acidosis and reduced ionised calcium. In severely critically ill patients, disease-induced coagulopathy or thrombocytopenia may also render anticoagulation unnecessary.

With regard to medical contraindications, patients in our study did not have statistically significant differences in the presence of liver dysfunction or coagulopathy, but there were more with thrombocytopenia (platelet counts <100,000/ μ L) in the group that did not receive anticoagulation.

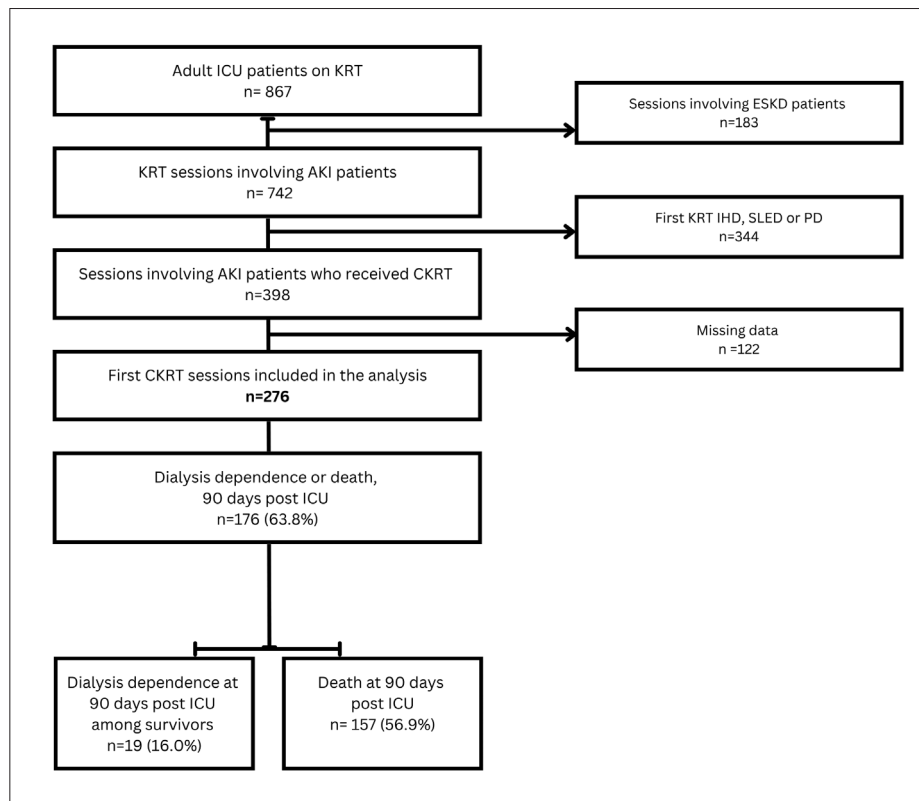


Figure 1. Study population flowchart.

AKI: acute kidney injury; KRT: kidney replacement therapy; CKRT: continuous kidney replacement therapy; ESKD: end stage kidney disease; IHD: Intermittent hemodialysis, SLED: slow low efficiency dialysis, PD: peritoneal dialysis

Table 3. Multivariable logistic regression of factors associated with dialysis dependence or death at 90 days post intensive care unit admission.

Dialysis dependence or death at 90 days	Odds ratio	95% CI of odds ratio	P value
Age	1.01	0.99-1.03	0.550
Female	1.19	0.69-2.05	0.539
APACHE II	1.03	1.00-1.07	0.034
Liver dysfunction*	1.30	0.76-2.21	0.340
Coagulopathy**	1.05	0.68-1.63	0.827
Thrombocytopenia***	0.86	0.47-1.57	0.626
Diabetes mellitus	0.96	0.72-1.28	0.777
Mechanical ventilation	1.90	0.89-4.06	0.097
Oliguria and anuria	2.95	1.59-5.50	0.001
Anticoagulation	0.47	0.27-0.83	0.009
Anticoagulation as a 3-level indicator variable			
No anticoagulation	Reference	Reference	Reference
Heparin anticoagulation	0.51	0.23-1.14	0.102
Citrate anticoagulation	0.46	0.25-0.83	0.011

APACHE II: Acute Physiology and Chronic Health Evaluation II; CI: confidence interval

*Liver dysfunction (defined as presence of liver cirrhosis or bilirubin >35 µmol/L)

** INR >1.5

*** Platelet <100,000/µL

We can postulate the reasons why prescribers omit anticoagulation in the initial KRT session. Patients are acutely ill with organ failure, thus the preference to avoid systemic anticoagulation to not increase bleeding risks and to avoid regional citrate anticoagulation to minimise pH and electrolyte changes (e.g. calcium, magnesium and phosphate). Regional citrate anticoagulation (RCA) also requires familiarity with the protocol and logistically poses more challenges.

Interruptions to CKRT impact on physiological stability, patient treatment, with added costs. The literature consistently shows RCA is beneficial for filter lifespan, with lower adverse events, compared to heparin anticoagulation.¹⁰ Despite this, the evidence for anticoagulation strategies and impact on mortality is not strong,²² and still being investigated. For instance, in one previous study, there was no difference in mortality, metabolic alkalosis, circuit loss and the amount of blood transfused between patients with heparin anticoagulation and RCA.²³

One of the postulated reasons for the findings is that anticoagulation had a beneficial impact on filter efficacy,²⁴ as delivered dose is reported to be highest in treatments where RCA was employed, with lower odds of death compared to CKRT with heparin anticoagulation.²⁴

However, we are unable to detect this association as this study did not collect data on filter efficacy by calculating effluent urea nitrogen/blood urea nitrogen ratios. We also did not specifically study filter lifespan or distinguish between interruptions to initial CKRT due to filter performance or extrinsic factors (such as need for interventions).

The strength of this study is that data were obtained from mixed, surgical, cardiac and medical units, which increases the generalisability of the data. This is also the first period prevalence study showing anticoagulation practices during CKRT in Singapore.

The limitations of this study are that it was a retrospective study, which was dependent on existing clinical databases, and thus there were missing or incomplete data. Not all units in Singapore participated in the study due to logistical reasons, but all tertiary hospitals are represented in this data. We also did not consider subsequent KRT sessions the patients received, which may have contributed to the prognosis. However, the initial KRT sessions early in AKI and critical illness may pose the highest risk, whereas subsequent sessions may be routine KRT while awaiting kidney recovery and have less prognostic impact. Other conditions that

contraindicate anticoagulation may have led to the primary outcome, but we have adjusted for illness severity, liver dysfunction and thrombocytopenia, and they were all not found to be associated with the primary outcome.

Anticoagulation during CKRT should be considered whenever possible. However, there are non-anticoagulant factors such as type and location of vascular access, blood flow rates and haematological conditions that influence filter efficiency and lifespan¹⁷; and anticoagulation is just one factor influencing filter performance. Future studies can consider studying specifically filter duration and efficiency and take into consideration all KRT sessions received by the patient. Future studies should also investigate other physician considerations for not using anticoagulation.

CONCLUSION

Among critically ill patients with AKI, anticoagulation use during CKRT was associated with reduced dialysis or death at 90 days post-ICU admission, which was statistically significant for regional citrate anticoagulation and trended in the same direction of benefit for systemic heparin anticoagulation. Anticoagulation during CKRT should be considered whenever possible.

Disclosure

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