

Regional citrate and systemic heparin are adequate to maintain filter half-life for COVID-19 patients on continuous renal replacement therapy

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Abstract

Introduction: The aim of our study is to compare clotting of CRRT filters in patients with COVID-19-associated AKI versus septic shock-associated AKI.

Methods: Retrospective study of adult ICU patients with COVID-19 compared to those with septic shock admitted to a tertiary hospital April–October 2020. Independent *t* test and chi-square test used to determine statistical significance of CRRT filter clotting between the two groups. Time-to-event data analyzed with Kaplan-Meier curves. Analyses performed on Microsoft Excel and MedCalc.

Results: Twenty-seven ICU patients with AKI requiring CRRT were included, 13 with COVID-19 and 14 non-COVID-19 patients with septic shock. The mean half-life of CRRT hemofilter was similar in COVID-19 patients compared to non-COVID-19 patients (27.4 vs. 27.5 h, $p = 0.79$). The number of CRRT hemofilter changes per day was similar in both groups (0.6 filter changes per day, $p = 0.84$). However, significantly more patients with COVID-19 were on systemic heparin (69% vs. 13%, $p = 0.02$).

Conclusion: We found that COVID-19 patients with AKI requiring CRRT had similar CRRT hemofilter half-life compared with sepsis-associated AKI patients with use of regional citrate and systemic heparin. Further studies are needed to find which methods of anticoagulation are optimal in patients with COVID-19 infection with AKI requiring CRRT.

1 | INTRODUCTION

Coronavirus-19 disease (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), results in a range of presentations varying from asymptomatic to severe critical illness characterized by cytokine storm, acute respiratory distress syndrome, respiratory failure, septic shock, and acute kidney injury (AKI).^{1–3} Coagulopathy manifested as pulmonary embolism, cerebral infarct, disseminated intravascular coagulopathy (DIC), or pulmonary microvascular thrombosis and hemorrhage is a major complication of severe disease in COVID-19 infection.^{4–6}

Patients with COVID-19 disease, multiorgan dysfunction, and severe AKI commonly require continuous renal replacement therapy (CRRT).¹ Anecdotal reports suggest that clotting of CRRT hemofilter resulting in decreased hemofilter half-life is more in COVID-19 patients compared to other critically ill patients with AKI requiring CRRT. Increased clotting of CRRT hemofilter leads to reduced time on CRRT and blood loss, worsening the anemia of critical illness and increasing need for blood transfusion.^{7,8} However, it is unknown if COVID-19 patients with AKI requiring CRRT have increased clotting of CRRT hemofilter compared to patients with septic shock with AKI requiring CRRT. The aim of our study was to compare the life of CRRT hemofilter in patients with COVID-19-associated AKI versus septic shock-associated AKI requiring CRRT.

Hilary Faust, MD, and Tripti Singh, MD, contributed equally to this work.

2 | MATERIALS AND METHODS

The study population included all patients with AKI requiring CRRT and confirmed COVID-19 infection or with septic shock using the Sepsis 3 guidelines with laboratory-confirmed negative COVID-19 admitted to the medical intensive care unit between April 2020 and October 2020 at our institution. COVID-19 infection was defined by a positive reverse transcription-polymerase chain reaction (RT-PCR) assay of a specimen collected on a nasopharyngeal swab or a tracheal aspirate. The University of Wisconsin-Madison Institutional Review Board and the Human Subjects Committee exempted the study.

Demographic data, laboratory data, CRRT administration data, and medications administered during ICU admission were obtained from the institution's electronic medical record. Nx Stage 505 filter was used with CRRT. All laboratory tests, CRRT administration, and medication use were at the discretion of the treating physician. Use of regional citrate for anticoagulation with CRRT is the standard of practice at our institution. However, initial start of CRRT is without citrate for all patients. If the filter clotted within 24 h after starting CRRT, then citrate was added for anticoagulation. Anticoagulant citrate compound 4% infusion was initiated at 100–350 ml/h and up-titrated per protocol based on postfilter ionized calcium goal of 1.5 mEq/dl. All replacement fluid was prefilter. There was no difference in replacement fluid for COVID-19 or non-COVID-19 patients.

If the patients were on systemic anticoagulation for other reasons during hospitalization, then citrate was not used with CRRT. However, for COVID-19 patients, citrate was used with CRRT regardless of systemic anticoagulation. Systemic heparin was part of protocol for management of severe COVID-19 patients. Therefore, COVID-19 patients without any other indication for systemic heparin like deep vein thrombosis, pulmonary embolism, or NSTEMI were still on heparin. Non-COVID-19 patients were not on systemic heparin unless there was an indication.

Patient data were censored at the time of data cutoff, which occurred on October 12, 2020. AKI was defined by KDIGO staging guidelines. Continuous variables were compared between the two groups (COVID-19 and non-COVID-19 patients) using independent *t* test. Categorical variables were compared between the two groups using chi-square test. Hemofilters were changed due to clotting. Per protocol, if there was no clotting, then the hemofilter was changed every 72 h. Time-to-event data of the life of the hemofilter was analyzed with Kaplan-Meier curve. Analyses were performed on Microsoft Excel and MedCalc. All *p* values <0.05 were considered statistically significant.

3 | RESULTS

A total of 27 patients with AKI requiring CRRT were included in the study, 13 with COVID-19 infection and 14 with septic shock. The mean age in the COVID-19 patients was 55.1 years, 10 (77%) were

male, mean BMI was 40.7, two (15%) had CKD, four (31%) had diabetes mellitus, five (39%) had hypertension, two (15%) had cardiovascular disease (CVD), and three (23%) were immunocompromised (from kidney transplant, asplenia, or use of biologic therapy). The mean age of non-COVID-19 patients was 59.6 years, nine (60%) were male, mean BMI was 35.1, five (33%) had CKD, three (20%) had diabetes mellitus, seven (47%) had hypertension, one (7%) had CVD, four (27%) had cirrhosis, and two (13%) were immunocompromised (both solid organ transplant patients on immunosuppressants). There were no significant differences between LDH and D-dimer between the two groups, both at admission and just prior to the start of CRRT (shown in Table 1).

The COVID-19 patients required CRRT at 5.9 days after admission compared to 6.1 days for non-COVID-19 patients (*p* = 0.94). Mean SOFA scores were similar between the two groups (12.3 for COVID-19 and 14.3 for non-COVID-19). Baseline serum creatinine was the same in both the groups. Admission serum creatinine was higher in the non-COVID-19 patients compared to the COVID-19 patients (3.5 vs. 1.8 mg/dl, *p* = 0.07). Admission serum BUN was significantly higher in the non-COVID-19 patients compared to the COVID-19 patients (51 vs. 32 mg/dl, *p* = 0.03). COVID-19 patients required CRRT for a mean of 8.4 days compared to 8.2 days for non-COVID-19 patients. Replacement fluid rates with CRRT were similar between the two groups (28.5 ml/kg/h for COVID-19 and 25 ml/kg/h for non-COVID-19).

Eight patients in each group (COVID-19 62% vs. non-COVID-19 53%) were on regional citrate for anticoagulation with CRRT as per institutional protocol. However, significantly more patients with COVID-19 were on systemic heparin compared to the non-COVID-19 patients (69% vs. 13%, *p* = 0.02). Requirement of packed red blood cell (pRBC) transfusion while on CRRT was similar in both groups. Seven (53%) of patients died in the COVID-19 group compared with eight (53%) of the patients in the non-COVID-19 group (*p* = 0.41) (shown in Table 1).

The mean half-life of CRRT hemofilter was similar in the COVID-19 patients compared to non-COVID-19 patients (27.4 vs. 27.5 h, *p* = 0.79) (shown in Table 2 and Figure 1). The number of CRRT hemofilter changes per day was also similar in both groups (0.6 filter changes per day for both groups, *p* = 0.84).

4 | DISCUSSION

We found that mean half-life of CRRT hemofilter in COVID-19 patients was similar to non-COVID-19 patients with septic shock and AKI requiring CRRT. The use of regional citrate with CRRT as an anticoagulant was similar in both groups. However, the use of systemic heparin was significantly higher in COVID-19 patients compared to non-COVID-19 patients (*p* = 0.02). These findings suggest that despite higher risk of coagulopathy in COVID-19 patients compared to other critically ill patients as seen in previous studies, use of regional citrate and systemic heparin are adequate in preventing clotting of CRRT hemofilters.

TABLE 1 Demographic and clinical data for COVID-19 and non-COVID-19 patients with AKI on CRRT

	COVID-19 N = 13	Non-COVID-19 N = 14	p value (95% CI)
Demographic data			
Age (years), mean (\pm SD)	55.1 (\pm 12.3)	59.6 (\pm 13.5)	0.37 (−5.6 to 14.61)
Male sex, n (%)	10 (77)	9 (60)	0.84
BMI (kg/m ²), mean (\pm SD)	40.7 (\pm 15.9)	35.1 (\pm 12.8)	0.31 (−16.7 to 5.6)
CKD, n (%)	2 (15)	5 (33)	
DM, n (%)	4 (31)	3 (20)	
HTN, n (%)	5 (39)	7 (47)	
CVD, n (%)	2 (15)	1 (7)	
Cirrhosis, n (%)	0	4 (27)	
Immunocompromised, n (%)	3 (23 ^a)	2 (13 ^b)	
Admission data			
Days to CRRT from admission, mean (\pm SD)	5.9 (\pm 6.1)	6.1 (\pm 8.8)	0.94 (−6.2 to 5.7)
SOFA score, mean (\pm SD)	12.3 (\pm 1.9)	14.3 (\pm 2.8)	0.03 (−3.9 to −0.15)
Baseline serum creatinine (mg/dl), mean (\pm SD)	1.0 (\pm 0.3)	1.0 (\pm 0.4)	0.61 (−0.2 to 0.3)
Admission creatinine (mg/dl), mean (\pm SD)	1.8 (\pm 1.4)	3.5 (\pm 3.0)	0.07 (−0.2 to 3.5)
Admission BUN (mg/dl), mean (\pm SD)	32 (\pm 19)	51 (\pm 27)	0.03 (1.2 to 37.9)
Admission LDH (U/L), mean (\pm SD)	670.8 (\pm 392)	678.6 (\pm 497)	0.97 (−368 to 384)
Admission D-dimer (mcg/ml), mean (\pm SD)	3.3 (\pm 3.4)	5.5 (\pm 2.3)	0.22 (−1.4 to 5.9)
Admission INR, mean (\pm SD)	1.2 (\pm 0.2)	1.6 (\pm 0.4)	0.004 (0.15 to 0.70)
Admission serum albumin (g/dl), mean (\pm SD)	2.8 (\pm 0.7)	2.5 (\pm 0.8)	0.50 (−0.8 to 0.4)
Days on CRRT, mean (\pm SD)	8.4 (\pm 5.9)	8.2 (\pm 6.1)	0.94 (−4.5 to 4.9)
CRRT replacement fluid rate (ml/kg/h), mean	28.5 (\pm 8.8)	25 (\pm 6.2)	0.22 (−9.4 to 2.3)
Citrate with CRRT, n (%)	8 (62)	8 (53)	0.73
Systemic heparin, n (%)	9 (69)	2 (13)	0.02
pRBC units transfused while on CRRT, mean (\pm SD)	1.9 (\pm 2.3)	2.5 (\pm 3.4)	0.59 (−1.7 to 2.9)
In-hospital HD requirement, n (%)	8 (62)	8 (53)	0.22
Mortality, n (%)	7 (53)	8 (53)	0.41

Abbreviations: BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; CVD, cardiovascular disease; HD, hemodialysis; HTN, hypertension; SOFA, Sequential Organ Failure Assessment; TPA, tissue plasminogen activator.

^aAsplenia, biologic therapy, and kidney transplant.

^bBoth solid organ transplant other than kidney.

Previous studies have shown that increased risk of clotting in COVID-19 is multifactorial. Comorbidities associated with vascular dysfunction such as hypertension, diabetes mellitus, obesity, and old age increase the risk for both COVID-19 infection and coagulopathy associated with severe COVID-19 disease.⁴ SARS-CoV-2 virus also contributes to coagulopathy on a cellular level by binding to cell surface ACE2 receptors (ACE2R) during cell entry.⁵ ACE2 has vasoprotective functions, offsetting the vasoconstrictive, pro-inflammatory, and pro-thrombotic effects of angiotensin II.⁴ Endothelial injury during SARS-CoV-2 infection compromises the endothelial monolayer, leading to up-regulation of tissue factors, thrombin, and fibrin deposition causing microvascular thrombosis.⁴ Clinically, a four-fold increase in D-dimer is predictive of mortality in COVID-19 patients, as it points to increased risk of venous thrombosis and cytokine storm.² The pro-inflammatory nature of severe COVID-19 infection may also drive coagulopathy in COVID-19, exhibited

TABLE 2 Details about CRRT in COVID-19 and non-COVID-19 patients with AKI

Filter changes per day (median, 25–75 P)		
COVID-19 (N = 13)	Non-COVID-19 (N = 14)	p value
0.6 (0.5 to 0.7)	0.6 (0.5 to 0.8)	0.84
Life of hemofilter (h) with CRRT (median, IQR)		
27.4 (16.8 to 25.9)	27.5 (19.5 to 32)	0.79

Note: Mean filter changes per day per group; mean life of the CRRT hemofilter in hours per group.

by GM-CSF and IL-6 both being increased in severe COVID-19 infection.

We found that increased use of anticoagulation is able to overcome the increased risk of CRRT filter clotting in patients with

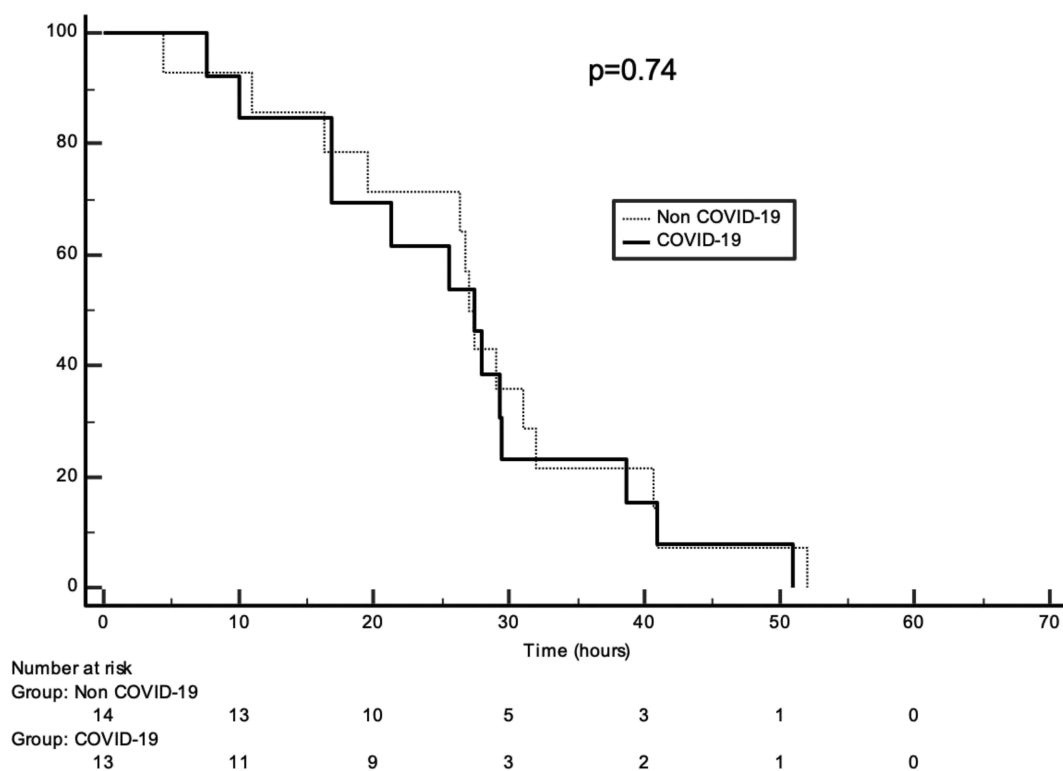


FIGURE 1 Half-life of CRRT filter in COVID-19 versus non-COVID-19 patients with AKI on CRRT

COVID-19, as hemofilter half-life was similar between COVID-19 and non-COVID-19 patients, while the use of systemic heparin was significantly higher in the COVID-19 group. These results indicate that while COVID-19 patients have increased incidence of coagulopathy compared to non-COVID-19 septic shock patients, the increased use of systemic heparin with regional citrate is adequate in preventing clotting of CRRT filters in COVID-19 patients. Having readily available tactics for clot prevention in CRRT hemofilters with regional citrate and systemic heparin may mitigate the well-known effects of COVID-19 on the kidney, namely, severe AKI often lasting up to 3 weeks and often requiring CRRT.⁹ Recent randomized clinical trial data from the ACTIV-4 trial demonstrated that ICU patients did not benefit from full-dose anticoagulation, but our findings indicate that COVID-19 patients requiring CRRT may constitute a subgroup in which the risk-benefit ratio may favor systemic heparin administration.¹⁰

Our study is limited by the small sample size and retrospective nature of its design. Larger studies are needed to better understand the burden of renal manifestations of coagulopathy in COVID-19 patients and confirm the potential therapeutic strategies of citrate and systemic heparin to prevent significant clotting of CRRT hemofilters in patients with COVID-19.

5 | CONCLUSION

In summary, COVID-19 patients with AKI requiring CRRT had similar CRRT hemofilter half-life compared with sepsis-associated AKI

patients with use of regional citrate anticoagulation and systemic heparin use. Further studies are needed to find which methods of anticoagulation are optimal in patients with COVID-19 infection with AKI requiring CRRT.

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CONFLICT OF INTEREST

No conflicts of interest reported by any of the authors.

ETHICS STATEMENT

The University of Wisconsin-Madison Institutional Review Board and the Human Subjects Committee exempted the study.

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