Continuous Renal Replacement Therapy in COVID-19-associated AKI: Adding Heparin to Citrate to Extend Filter Life – a Retrospective Cohort

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Abstract

Background: Coronavirus disease 2019 (COVID-19) may predispose patients to thrombotic events. The best anticoagulation strategy for continuous renal replacement therapy (CRRT) in such patients is still under debate. The purpose of this study was to evaluate the impact that different anticoagulation protocols have on filter clotting risk.

Methods: This was a retrospective observational study comparing two different anticoagulation strategies (citrate only and citrate plus intravenous infusion of unfractionated heparin) in patients with acute kidney injury (AKI), associated or not with COVID-19 (COV+ AKI and COV− AKI, respectively), submitted to CRRT. Filter clotting risks in the first 72 hours were compared between groups.

Results: Between January 2019 and July 2020, 248 patients were evaluated: 189 in the COV+ AKI group and 59 in the COV− AKI group. Filter clotting occurred during the first 72 hours of CRRT in 96 patients (38.7%). Heparin use conferred protection against filter clotting, resulting in longer filter survival. Bleeding events and the need for blood transfusion were similar between the citrate only and citrate plus unfractionated heparin strategies. In-hospital mortality was higher among the COV+ AKI patients than among the COV− AKI patients, although it was similar between the COV+ AKI patients who received heparin and those who did not. Filter clotting was more common in patients with D-dimer levels above the median (6086 ng/ml). In the multivariate analysis, the protective effect of heparin against filter clotting persisted, whereas an elevated D-dimer level, high platelet count, and high hemoglobin were found to be risk factors for circuit clotting. A diagnosis of COVID-19 was not a risk factor for filter clotting.

Conclusions: In COV+ AKI patients, adding systemic heparin to standard regional citrate anticoagulation may prolong CRRT filter patency by reducing clotting risk with low risk of complications.

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an extremely lethal agent that results in coronavirus disease 2019 (COVID-19), which has caused more than a million deaths worldwide (1) In the intensive care unit (ICU), up to 30% of COVID-19 patients develop acute kidney injury (AKI), renal replacement therapy (RRT) being required in such patients (2).

In patients with severe COVID-19, there have been reports of endothelial damage and subsequent thrombotic events, accompanied by elevated levels of fibrinogen and D-dimer, which are also predictors of a poor prognosis (3, 4). There have also been reports of multiple peripheral and cerebral infarcts, as well as myocardial infarction with ST-segment elevation, and an increased incidence of pulmonary embolism (5–7). Although some retrospective studies have suggested that anticoagulation with heparin is beneficial in patients with severe COVID-19 (8), that is still controversial and there is a need for more robust scientific evidence.

Hypercoagulability increases the risk of early clotting of the extracorporeal circuit in patients on continuous renal replacement therapy (CRRT). Some reports have suggested that the rates of premature filter change and dialysis downtime are higher in critically ill patients on CRRT (9, 10). At the *Hospital das Clínicas*, in the city of São Paulo, Brazil, a preliminary evaluation suggested that the life spans of dialysis filters and CRRT circuits are shorter in patients with COVID-19-associated AKI than in those with AKI from other causes (COV + AKI and COV − AKI, respectively).

The purpose of this study was to evaluate the impact that different anticoagulation strategies, namely regional citrate anticoagulation (RCA) only and RCA plus unfractionated heparin, have on the risk of CRRT circuit clotting.

Methods

Study Design and Population

This was a single-center, retrospective, observational study, involving critically ill patients treated at a large tertiary care hospital. From January 2019 to July 2020, all patients with AKI requiring CRRT were considered for inclusion in the study.

Until the end of 2019, before the COVID-19 pandemic, the standard of care for CRRT at our institution was continuous venovenous hemofiltration (CVVH), although continuous venovenous hemodialysis (CVVHD) or continuous venovenous hemodiafiltration (CVVHDF) was used in some patients. In January 2020, the CRRT standard became either CVVHD or CVVHDF. Given that there might be a higher risk of filter clotting in CVVH (11) and that all COVID-19 patients arrived at our institution in 2020, only patients receiving CVVHD or CVVHDF were included in this study..

We defined AKI on the basis of the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (12). We defined COV + AKI as AKI from any cause in SARS-CoV-2-positive patients, with diagnostic confirmation by real-time reverse transcriptase-polymerase chain reaction, or in patients who had symptoms of upper or lower respiratory tract infection and chest computed tomography findings suggestive of COVID-19. We defined COV − AKI as AKI from any cause in patients who did not have COVID-19.

CRRT Prescription

One of two machines was used for CRRT: Diapact (B. Braun Medical, Inc., Melsungen, Germany), with a 1.0-2.3 m^2 polysulfone high-flux filter (Diacap HI; B. Braun Medical, Inc.), for CVVHD; or Prisma (Gambro, Lund, Sweden), with a 0.9 m^2 membrane (AN69 M100 filter set; Gambro), for CVVHDF. Post-filter ionized calcium (iCa) was measured three times per day.

The decision to start CRRT was based on standard clinical guidelines. In all cases, bicarbonate-buffered solution was used. Filters were routinely changed after 72 hours, or sooner if any dysfunction was

detected. A pre-filter pressure > 270 mmHg was considered indicative of filter clotting. The prescribed dialysis dose was 30 ml/kg of body weight/hour.

Anticoagulation strategies

The main predictor of interest was the type of anticoagulation strategy employed. Before the COVID-19 pandemic, RCA for CRRT at our hospital was performed with anticoagulant citrate dextrose solution formula A (ACD-A; JP Indústria Farmacêutica, Ribeirão Preto, Brazil). Each 1000 ml of ACD-A contains 74.8 mmol trisodium citrate and 38.1 mmol citric acid (i.e., 112.9 mmol of citrate/L). The RCA was carried out with 3 mmol of ACD-A per liter of treated blood, with a target post-filter iCa concentration of 1.0-1.4 mg/dl. In April 2020, to counter the higher risk of RRT circuit clotting in COV + AKI patients, the standard RRT anticoagulation protocol was changed to include pre-filter infusion of unfractionated heparin in all COV + AKI patients, unless heparin use was contraindicated or the patient was already receiving systemic heparin for another reason. In addition, the ACD-A dose was increased to 4 mmol/L, with a target post-filter iCa concentration of < 1.0 mg/dl. Unfractionated heparin was infused pre-filter at a fixed rate of 10 U/kg of body weight/hour, which was not increased to reach a target activated partial thromboplastin time (aPTT), although it was decreased if that value was greater than 2.0 times the control value or discontinued if the patient experienced any anticoagulation-related adverse event. For patients receiving systemic heparin for indications other than RRT anticoagulation, the decision to alter the dose of or discontinue heparin was made by the ICU physician. We divided the sample into two groups, by the anticoagulation strategy employed: ACD-A only; and ACD-A plus unfractionated heparin (ACD-A + UH), which included patients receiving heparin via the protocol described for CRRT and those receiving systemic heparin for indications other than RRT anticoagulation.

Data Collection

At ICU admission, demographic and clinical data were recorded. Prior to CRRT, we collected physiological data, including vital signs, and biochemical data. In COVID-19 patients, pre-CRRT D-dimer levels were also determined.

During the first 72 hours of CRRT, clinical variables were evaluated, as were filter patency and any adverse events that could be related to the anticoagulation agent, such as bleeding (minor or major) and a low platelet count (< 100,000/mm^3). Major and minor bleeding were respectively defined as hemorrhagic events with and without clinical relevance or a drop in hemoglobin of ≥ or < 1 g/dl in 24 hours. In COV + AKI patients, the pre-CRRT serum D-dimer levels were determined and were used in order to stratify the patients.

Outcomes

The main outcome of interest was the first circuit clotting within the initial 72 hours of CRRT. Secondary outcomes included minor and major bleeding, as well as the need for blood transfusion and a drop in platelet count to < 100,000/mm^3, also within the initial 72 hours.

Ethical Aspects

The study was approved by the local institutional review board (Reference no. 33351120.0.0000.0068). This study was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement (13).

Statistical Analysis

Continuous variables are reported as mean ± SD or as median and interquartile range (IQR), as appropriate. Categorical variables are summarized as proportions. The ACD-A-only and ACD-A + UH groups were compared by t-test or Wilcoxon-Mann-Whitney test, as appropriate, for continuous variables and by chi-squared test or Fisher's exact test for categorical variables. Differences were considered statistically significant at $P < 0.05$. Filter survival was analyzed with Kaplan–Meier estimates. The *P*-values were calculated by log-rank test.

We used Cox proportional-hazards analysis to evaluate the association of each anticoagulation strategy with circuit clotting risk, adjusting for covariates. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were calculated. Reported *P*-values in the Cox model are based on the Wald test. Model 1 was based on the univariate association with the outcome, and variables were retained in the model by the Akaike information criterion with a stepwise approach. Models 2, 3, and 4 were based on variables of clinical relevance. Model 4 was restricted to the 179 patients in whom D-dimer levels were measured.

Statistical analyses were performed and graphics were generated with the R statistical software, version 4.0.2 (R Development Core Team, 2020).

Results

Of the 611 patients who underwent CRRT at our facility during the study period, 248 were included in this analysis (Fig. 1). Table 1 shows the baseline characteristics of the patients, by heparin use. In the ACD-A + UH group, the proportion of COVID-19 patients was higher than in the ACD-A-only group (100% versus 52.4%), whereas the median PaO_2/FiO_2 ratio was lower, vasopressor use was more common, the median platelet count was higher, and the median leukocyte count was higher, those differences potentially being consequences of the higher proportion of COVID-19 patients.

Table 1
Characteristics of patients undergoing continuous renal replacement therapy, by anticoagulation strategy

Characteristic	Anticoagulation strategy		*P*-value
	ACD-A + UH	ACD-A only	
	n = 124	*n* = 124	
Age, years	63.0 (53.0–70.2)	60.0 (48.0–68.0)	0.022
Male sex	68.5%	75.8%	0.339
White race	66.1%	63.7%	0.708
COVID-19 diagnosis	100.0%	52.4%	< 0.001
Class II or III obesity (BMI > 30 kg/m^2)	25.0%	16.9%	0.170
Hypertension	63.7%	59.7%	0.659
Diabetes	44.4%	36.3%	0.266
Mechanical ventilation*	95.2%	89.5%	0.147
PaO_2/FiO_2 ratio*,[a]	151 (99.0–188)	223 (152–308)	< 0.001
Vasopressor use*	92.7%	83.1%	0.030
Serum creatinine,[†] mg/dl	5.07 (3.52–6.73)	4.31 (3.26–6.54)	0.211
Serum BUN,[†] mg/dl	102 (76.2–121)	90.7 (61.2–111)	0.015
Total bilirubin,[†,b] mg/dl	0.52 (0.30–0.76)	0.52 (0.32–1.44)	0.203
Hemoglobin,[†,c] g/dl	9.90 (8.40–11.5)	8.90 (7.80–11.4)	0.087
Leukocytes,[†] $10^3/mm^3$	17.2 (13.0–25.5)	14.8 (10.1–21.0)	0.002
Platelet count,[†] $10^3/mm^3$	292 (195–373)	226 (93.8–334)	< 0.001
Peak D-dimer,[d] ng/ml	6215 (2294–16865)	5999 (2933–14789)	0.988
CRRT modality			0.319
CVVHD	90.3%	85.5%	
CVVHDF	9.7%	14.5%	
Catheter location			0.022
Right internal jugular vein	54.8%	43.5%	
Left internal jugular vein	4.0%	12.9%	

Characteristic	Anticoagulation strategy		*P*-value
	ACD-A + UH	ACD-A only	
	n = 124	*n* = 124	
Femoral vein	41.1%	43.5%	
Non-tunneled catheter	98.4%	97.6%	1.000
Subcutaneous heparin for VTE prophylaxis	34.7%	66.1%	< 0.001
Target citrate concentration			< 0.001
3 mmol/L	3.2%	49.2%	
4 mmol/L	96.8%	50.8%	

Data expressed as median (IQR) or percentage. ACD-A, anticoagulant citrate dextrose solution formula A; UH, unfractionated heparin; COVID-19, coronavirus disease 2019; BMI, body mass index; PaO_2/FiO_2, arterial oxygen tension/fraction of inspired oxygen; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; VTE, venous thromboembolism.

*At intensive care unit admission.

[†]At start of CRRT.

[a]*N*=228; [b]*N*=197; [c]*N*=242; [d]*N*=179.

Heparin, Filter Life, and Adverse Events

Of the 248 patients evaluated, 96 (38.7%) experienced clotting-censored filter loss within the first 72 hours. Figure 2 depicts Kaplan–Meier estimates showing longer filter survival in the ACD-A + UH group.

The median (95% CI) clotting-free filter survival was 45 hours (35–65) in the ACD-A-only group and could not be calculated for the ACD-A + UH group because it was longer than the 72-hour follow-up period. The 24-hour clotting-free filter survival probability (95% CI) was 83.9% (76.9–91.5) in the ACD-A + UH group, versus 72.5% (64.6–81.4) in the ACD-A-only group ($P < 0.001$). The 48-hour clotting-free filter survival probability (95% CI) was 71.6% (62.8–81.7) in the ACD-A + UH group, versus 45.7% (36.8–56.9) in the ACD-A-only group ($P < 0.001$), whereas the 72-hour clotting-free filter survival probability (95% CI) was 64.1% (54.5–75.5) in the ACD-A + UH group, versus 32.2% (23.4–44.3) in the ACD-A-only group ($P < 0.001$).

Among the 189 COV + AKI patients, filter clotting occurred within the first 72 hours of CRRT in 66 (34.9%)—in 35 (53.8%) of the 65 in the ACD-A-only group and in 31 (25.0%) of the 124 in the ACD-A + UH group ($P < 0.05$). Among the COV + AKI patients, the median clotting-free filter survival was 38 hours (95% CI, 31–63) in the ACD-A-only group and could not be calculated for the ACD-A + UH group because it was longer than the 72-hour follow-up period.

Evaluating just patients with COVID-19, the clotting-free filter survival probability at 24 hours was 83.9% (95% CI, 76.9 to 91.5%) in the ACD-A + UH group, versus 67.6% (95% CI, 56.3 to 81.2%) in the ACD-A-only group ($P < 0.001$). At 48 hours, the clotting-free filter survival probability was 71.6% (95% CI, 62.8 to 81.7%) in the ACD-A + UH group, versus 41.4% (95% CI, 29.8 to 57.5%) in the ACD-A-only group ($P < 0.001$), whereas at 72 hours it was 64.1% (95% CI, 54.5 to 75.5%) in the ACD-A + UH group, versus 29.2% (95% CI, 18.1 to 47.1%) in the ACD-A-only group ($P < 0.001$).

Of the 59 COV − AKI patients, 29 (49.1%) presented filter clotting in 72 hours, a proportion similar to that observed among the COV + AKI patients in ACD-A-only group.

The rate of heparin-related adverse events was relatively low in our patient sample (Table 2). The difference between ACD-A + UH and ACD-A only groups was not significant regarding bleeding episodes (minor and major) and the need for blood transfusion (Table 2). In-hospital mortality was higher in ACD-A + UH group (Table 2). To determine whether the excess mortality seen in the patients who received heparin was due to anticoagulation or to the higher proportion of COV + AKI patients in this group, we divided patients in three different groups for adverse-event analysis (Table 3): COV + AKI patients who received ACD-A + UH (ACD-A + UH-treated COV + AKI subgroup); COV + AKI patients who received ACD-A only (ACD-A-treated COV + AKI subgroup); and COV − AKI patients. That division allowed us to determine that COV − AKI patients were more likely to require a blood transfusion and to have a low platelet count, as well as to observe that in-hospital mortality was lower among the COV − AKI patients than among the COV + AKI patients. In-hospital mortality was similar between the ACD-A + UH-treated COV + AKI and ACD-A-treated COV + AKI subgroups (P: 0.611).

Table 2
Adverse events in patients undergoing continuous renal replacement therapy, by anticoagulation strategy

Variable	Anticoagulation strategy		*P*-value
	ACD-A + UH	ACD-A only	
	N = 124	*N* = 124	
Minor bleeding episode	4.24%	5.00%	1
Major bleeding episode	5.08%	7.50%	0.617
Blood transfusion	24.60%	35.00%	0.106
Platelet count < 100,000 /mm^3	14.40%	30.50%	0.006
Peak aPTT during the first 72 hours of CRRT[a]	2.42 (1.70–3.52)	1.25 (1.09–1.65)	< 0.001
In-hospital mortality[b]	87%	75%	0.025

Data expressed as median (IQR) or percentages. ACD-A, anticoagulant citrate dextrose solution formula A; UH, unfractionated heparin; aPTT, activated partial thromboplastin time, CRRT, continuous renal replacement therapy.

[a] *N*=201; [b] *N*=247.

Table 3
Adverse events in patients undergoing continuous renal replacement therapy, by coronavirus status and anticoagulation strategy

Variable	Anticoagulation strategy			*P*-value
	COV + AKI		COV − AKI	
	ACD-A + UH	ACD-A only	ACD-A only	
	n = 124	*n* = 65	*n* = 59	
Minor bleeding episode	4.24%	3.28%	6.78%	0.664
Major bleeding episode	5.08%	4.92%	10.20%	0.392
Blood transfusion	24.60%	24.60%	45.80%	0.009
Platelet count < 100,000/mm^3	14.40%	16.90%	44.10%	< 0.001
Peak aPTT during the first 72 hours of CRRT[a]	2.42 (1.70–3.52)	1.30 (1.10–1.67)	1.19 (1.02–1.64)	< 0.001
In-hospital mortality[b]	87.00%	83.10%	66.10%	0.003

Data expressed as median (IQR) or percentages. COV + AKI, coronavirus disease 2019-associated acute kidney injury; COV − AKI, acute kidney injury from causes other than coronavirus disease 2019; ACD-A, anticoagulant citrate dextrose solution formula A; UH, unfractionated heparin; aPTT, activated partial thromboplastin time, CRRT, continuous renal replacement therapy.

[a] *N*=201; [b] *N*=247.

It is worth pointing out that D-dimer levels did not differ between the ACD-A + UH-treated COV + AKI and ACD-A-treated COV + AKI subgroups (Table 1). In the COV − AKI patients, D-dimer levels were not measured.

Other Potential Contributors to Filter Clotting

The results of the univariate Cox proportional-hazards analysis are shown in Table 4. In the four multivariate Cox models (Table 5), the risk of filter clotting was lower in the ACD-A + UH group than in the ACD-A-only group, even after adjustment for other covariates. Elevated platelet counts and higher hemoglobin levels were associated with a higher risk of circuit clotting, as well as with high D-dimer levels. A D-dimer level above the median (6086 ng/ml) was associated with a 2.1 times higher risk of filter clotting (Table 5). Figure 3 shows the Kaplan–Meier estimates of filter survival, by D-dimer level.

Table 4
Cox univariate proportional-hazards analysis for filter clotting in the first 72 hours

Factor/comparison	Unadjusted HR (95% CI)	*P*-value
ACD-A + UH versus ACD-A only	0.42 (0.27–0.64)	< 0.001
COVID-19 diagnosis	0.73 (0.47–1.12)	0.2074
Target citrate concentration		
4 mmol/L versus 3 mmol/L	0.69 (0.45–1.06)	0.150
Age, per year increase	1.00 (0.98–1.01)	0.810
Catheter location		
FV versus RIJV	0.98 (0.64–1.50)	0.930
LIJV versus RIJV	0.90 (0.43–1.91)	0.788
Non-tunneled versus tunneled catheter	0.72 (0.18–2.92)	0.643
Male sex	1.25 (0.79–1.99)	0.343
CVVHDF versus CVVHD	0.49 (0.21–1.12)	0.092
Vasopressor use	0.58 (0.34–1.00)	0.049
Mechanical ventilation	0.81 (0.39–1.68)	0.579
Serum BUN, per unit increase	1.00 (0.99–1.00)	0.916
Platelet count, per 100,000 increase	1.00 (1.00–1.00)	0.200
Class II or III obesity	0.94 (0.58–1.53)	0.804
Hypertension	1.21 (0.79–1.83)	0.378
Diabetes mellitus	0.9 (0.60–1.37)	0.636
Subcutaneous heparin for VTE prophylaxis	1.88 (1.24–2.85)	0.003
D-dimer level		
Above versus below the median	1.77 (1.06–2.96)	0.028
Hemoglobin, per unit increase	1.09 (1.00–1.18)	0.057
Peak activated partial thromboplastin time	0.79 (0.65–0.96)	0.020

HR, hazard ratio; ACD-A, anticoagulant citrate dextrose solution formula A; UH, unfractionated heparin; COVID-19, Coronavirus disease 2019; FV, femoral vein; RIJV, right internal jugular vein; LIJV, left internal jugular vein; CVVHDF, continuous venovenous hemodiafiltration; CVVHD, continuous venovenous hemodialysis; BUN, blood urea nitrogen; VTE, venous thromboembolism.

Table 5
Multivariate Cox regression models for first continuous renal replacement therapy circuit clotting in 72 hours.

Factor	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Anticoagulation (ACD-A + UH versus ACD-A only)	0.36 (0.23–0.56)	< 0.001	0.32 (0.19–0.53)	< 0.001	0.39 (0.24–0.63)	< 0.001	0.33 (0.20–0.55)	< 0.001
Adjusted for								
CRRT modality (CVVHDF versus CVVHD)	0.50 (0.21–1.15)	0.102						
Vasopressor use	0.62 (0.36–1.09)	0.096						
Platelet count (per 100,000 increase)	1.00 (1.00–1.00)	0.015	1.00 (1.00–1.00)	0.012				
Hemoglobin level (per 1g/dl increase)	1.14 (1.04–1.25)	0.004	1.14 (1.04–1.26)	0.005				
Age (per year increase)			1.00 (0.98–1.02)	0.906				
Male sex			0.84 (0.50–1.40)	0.493				
BUN (per unit increase)			1.00 (0.99–1.00)	0.754				
COVID-19 diagnosis			1.02 (0.58–1.78)	0.956				
ACD-A dose (4 versus 3 mmol/L of treated blood)					1.17 (0.72–1.90)	0.520		

*For the D-dimer analysis, data were available for only 179 subjects.

HR, hazard ratio; ACD-A, anticoagulant citrate dextrose solution formula A; UH, unfractionated heparin; CRRT, continuous renal replacement therapy; CVVHDF, continuous venovenous hemodiafiltration; CVVHD, continuous venovenous hemodialysis; BUN, blood urea nitrogen; COVID-19, coronavirus disease 2019.

Factor	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Median D-dimer level (> versus ≤ 6086 ng/ml)*							2.08 (1.24–3.49)	0.006
*For the D-dimer analysis, data were available for only 179 subjects.								
HR, hazard ratio; ACD-A, anticoagulant citrate dextrose solution formula A; UH, unfractionated heparin; CRRT, continuous renal replacement therapy; CVVHDF, continuous venovenous hemodiafiltration; CVVHD, continuous venovenous hemodialysis; BUN, blood urea nitrogen; COVID-19, coronavirus disease 2019.								

In the multivariate Cox regression analysis, neither a diagnosis of COVID-19, nor the ACD-A dose level, nor the CRRT modality represented risk factors for filter clotting (Table 5).

Discussion

The key finding of this study is that RCA plus infusion of unfractionated heparin might be superior to RCA alone for prolonging circuit life and reducing filter losses during CRRT in COV + AKI patients, with similar rates of adverse events (bleeding or the need of blood transfusion).

In addition to the increased demand for dialysis, COVID-19 patients are especially predisposed to thrombotic events, theoretically increasing the propensity for filter clotting (9, 14–16). However, despite the initial impression that the life spans of dialysis filters are shorter in COV + AKI patients, a diagnosis of COVID-19 was not found to be a major risk factor for filter clotting in the present study. Nevertheless, CRRT filter clotting is still a major concern in critically ill patients because CRRT filter clotting not only can result in shortages of medical equipment and consumables but also may be associated with blood loss and shorter dialysis times. Therefore, it is crucial to maintain appropriate, effective anticoagulation during dialysis (17, 18).

Various anticoagulation strategies have been studied (19). Randomized controlled trials have shown RCA to be clearly superior to the use of heparin, with a better adverse-event profile (19–22). Unless contraindicated, citrate is also recommended as the first-line option in CRRT (12). However, none of those studies involved COV + AKI patients or other known prothrombotic factors. In addition, there have been no studies comparing the use of the combination of citrate and heparin with the use of either of those anticoagulation strategies, even in patients without COVID-19.

Our findings suggest that the use of systemic heparin plus RCA blunts the excessive prothrombotic effect that RRT has on filter patency in COVID-19 patients (9, 15, 16). Although some groups are already using this strategy informally in the management of CRRT in COVID-19 patients (9, 10, 14, 16), there have been few studies comparing different anticoagulation strategies in that context.

Our data are in agreement with the findings of Shankaranarayanan *et al.* (10), who showed that, in COVID-19 patients, the concomitant use of systemic heparin and citrate could lead to fewer thrombotic events in CRRT circuits when compared with other strategies, including citrate alone and heparin alone. Those authors reported a median filter life of just 21 hours for no anticoagulation, compared with 40 hours for citrate alone and > 72 hours for citrate plus heparin. Similarly, in the present study, in which no procedures were performed without anticoagulation, the median filter survival was 45 hours for citrate alone and > 72 hours for heparin associated with citrate. Wen *et al.* (16) also showed longer circuit life when heparin-based regimens were used in sustained low-efficiency dialysis.

In the present study, the adverse-event profile was similar between the ACD-A-only and ACD-A + UH groups. Heparin use was not found to be associated with lower platelet counts. We found a low incidence of bleeding episodes, so it is possible that they may not be sufficient to determine if adverse events rates are certainly different between groups. However, despite the relatively small number of patients studied, this is currently the greatest casuistic regarding anticoagulation in CRRT in patients with COVID-19 in the literature. To our knowledge, this is the first report of the safety profile of the heparin-citrate combination in CRRT. We also found that in-hospital mortality was similar to that previously reported for COV + AKI and COV – AKI (23, 24), the former being more lethal than the latter.

Another important aspect of the thrombotic potential of COVID-19 is related to D-dimer levels (1). In COVID-19 patients, an elevated D-dimer level has been shown to be predictive of thrombotic complications (25). In the present study, elevated D-dimer levels were found to predispose to higher rates of filter clotting in CRRT. That differs from the findings of a previous study comparing diverse anticoagulation strategies in COVID-19 (16), in which D-dimer levels had no apparent effect on circuit clotting. However, that study evaluated only sustained low-efficiency dialysis, with a median of < 36 hours per session in all groups, and the reported D-dimer levels were much lower. Therefore, it was not possible to draw comparisons with the present study.

To our knowledge, ours is the largest study comparing ACD-A alone and ACD-A plus unfractionated heparin in CRRT performed in COVID-19 patients. We believe that it is also the first study to address safety concerns regarding the use of the latter combination.

Our study has some limitations. To meet the challenge of the potential for clotting in CRRT performed in COVID-19 patients, we not only added systemic heparin to the regimen but also increased the ACD-A concentration and lowered the target post-filter iCa concentration. Therefore, in the ACD-A + UH group, the proportion of patients in whom the target citrate concentration was 4 mmol/L (rather than 3 mmol/L) was higher, and the outcome may in part be a consequence of the success of the anticoagulation with ACD-A, which may interfere in generalizability to other centers. That could have influenced our results, although a target citrate concentration of 4 mmol/L was not found to be a protective factor in the multivariate Cox analysis. However, the addition of heparin was found to be a consistent protective factor, and we believe that this combined strategy should be adopted in settings in which there is a high risk of clotting. In addition, because of the retrospective study design, data regarding D-dimer levels were not

available for the COV − AKI patients. It would have been interesting to determine whether higher D-dimer levels are associated with higher mortality. That would also have allowed us to investigate whether the supposed higher risk of filter clotting in COV + AKI patients is attributable solely to D-dimer levels. Furthermore, also because of the retrospective study design, our results might be attributable to other, unmeasured co-interventions. Moreover, our study reflects the experience of a single center in Brazil and therefore may not reflect the reality for all COV + AKI patients.

Conclusions

In conclusion, the combination of systemic heparin and RCA appears to extend filter Rodrigues reports life in COV + AKI patients. We hypothesize that this strategy would be useful in any patients who are prone to coagulation events. Prospective trials are needed in order to confirm or refute our findings.

Abbreviations

ACD-A
anticoagulant citrate dextrose solution formula A
AKI
acute kidney injury
aPTT
activated partial thromboplastin time
CI
confidence interval
COVID-19
coronavirus disease 2019
COV + AKI
acute kidney injury associated with coronavirus disease 2019
COV − AKI
acute kidney injury not associated with coronavirus disease 2019
CRRT
continuous renal replacement therapy (CRRT)
CVVH
continuous venovenous hemofiltration
CVVHD
continuous venovenous hemodialysis
CVVHDF
continuous venovenous hemodiafiltration
HR
Hazard ratio
iCa

ionized calcium
ICU
intensive care unit
IQR
interquartile range
KDIGO
Kidney Disease:Improving Global Outcomes
PaO_2/FiO_2
ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen
RCA
regional citrate anticoagulation
RRT
renal replacement therapy
SARS-CoV-2
severe acute respiratory syndrome coronavirus 2
SD
standard deviation
UH
unfractioned heparin

Declarations

Ethics approval and consent to participate

The study was approved by Hospital das Clínicas review board (Reference no. 33351120.0.0000.0068). As it was a retrospective analysis, consent to participate does not apply.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

C.E.R. received fees from Medtronic for providing instruction in catheter insertion. All remaining authors have nothing to disclose.

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Authors' contributions

E.O.V., C.P.S.C. and C.C.C.A. were responsible to the acquisition of the data,

G.V.S., M.F.A.O., G.T.M.S., I.S. and B.V.R. made substantial contributions to the design of the work,

V.F.S, P.R.G.L and C.E.R did the analysis and interpretation of data,

L.A., V.F.S, P.R.G.L and C.E.R were responsible for the conception and design of the work, and also for draft and review of the work.

All authors have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Figures

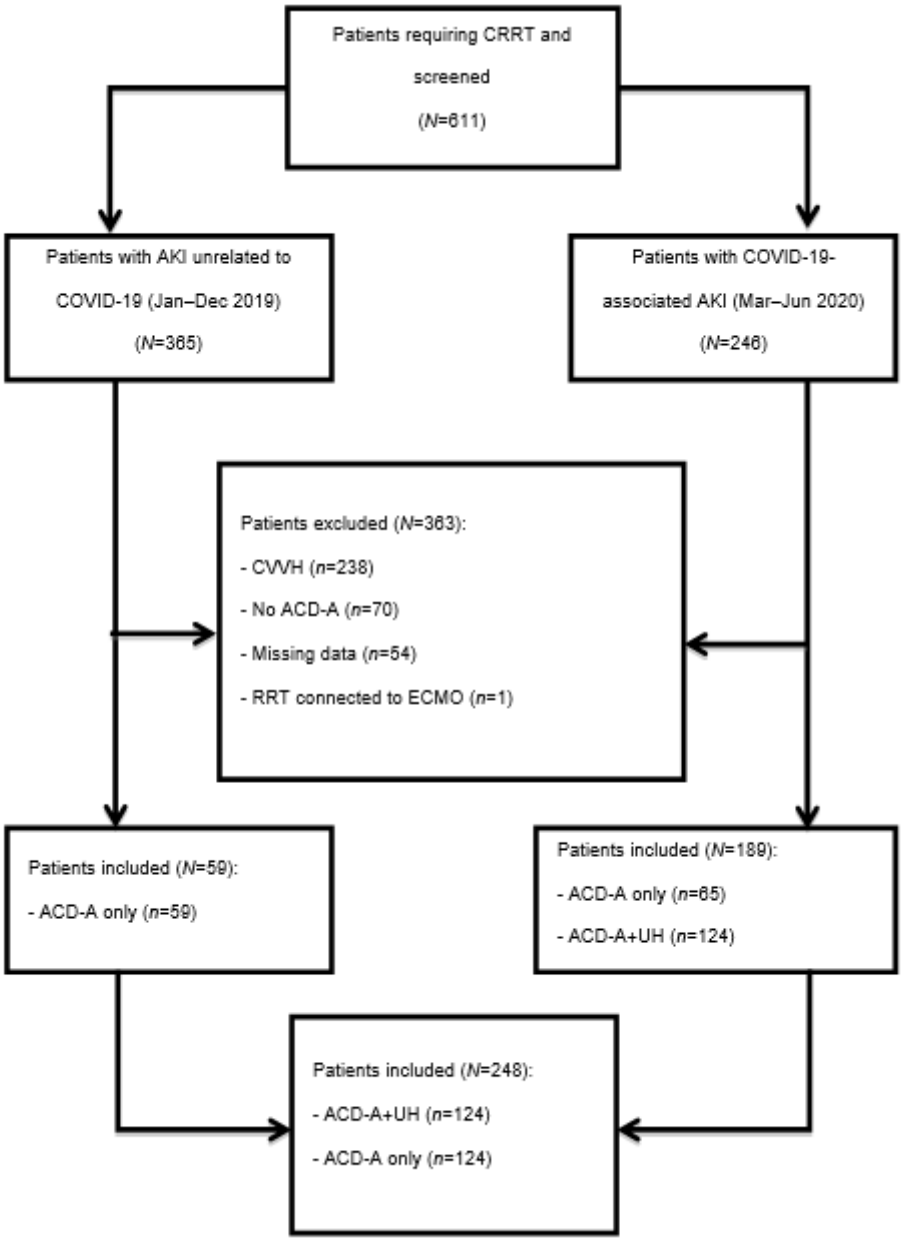

Figure 1

Flow chart of the study population selection process. CRRT, continuous renal replacement therapy; COVID-19, coronavirus disease 2019; AKI, acute kidney injury; CVVH, continuous venovenous hemofiltration; ACD-A, anticoagulant citrate dextrose solution formula A; ECMO, extracorporeal membrane oxygenation; UH, unfractionated heparin.

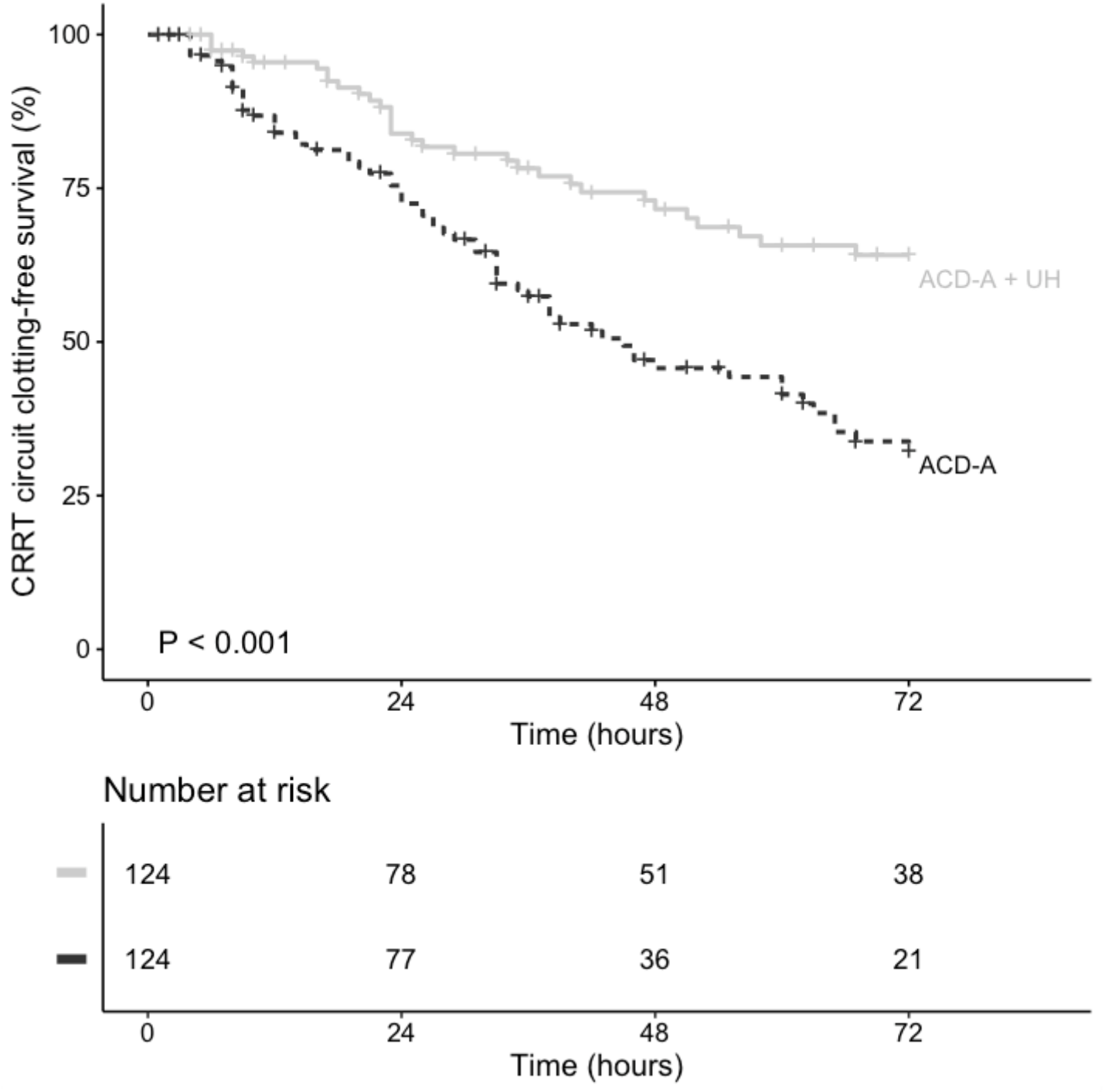

Figure 2

Kaplan–Meier estimate of filter clotting in the first 72 hours of continuous renal replacement therapy (CRRT). CRRT, continuous renal replacement therapy; ACD-A, anticoagulant citrate dextrose solution

formula A; UH, unfractionated heparin.

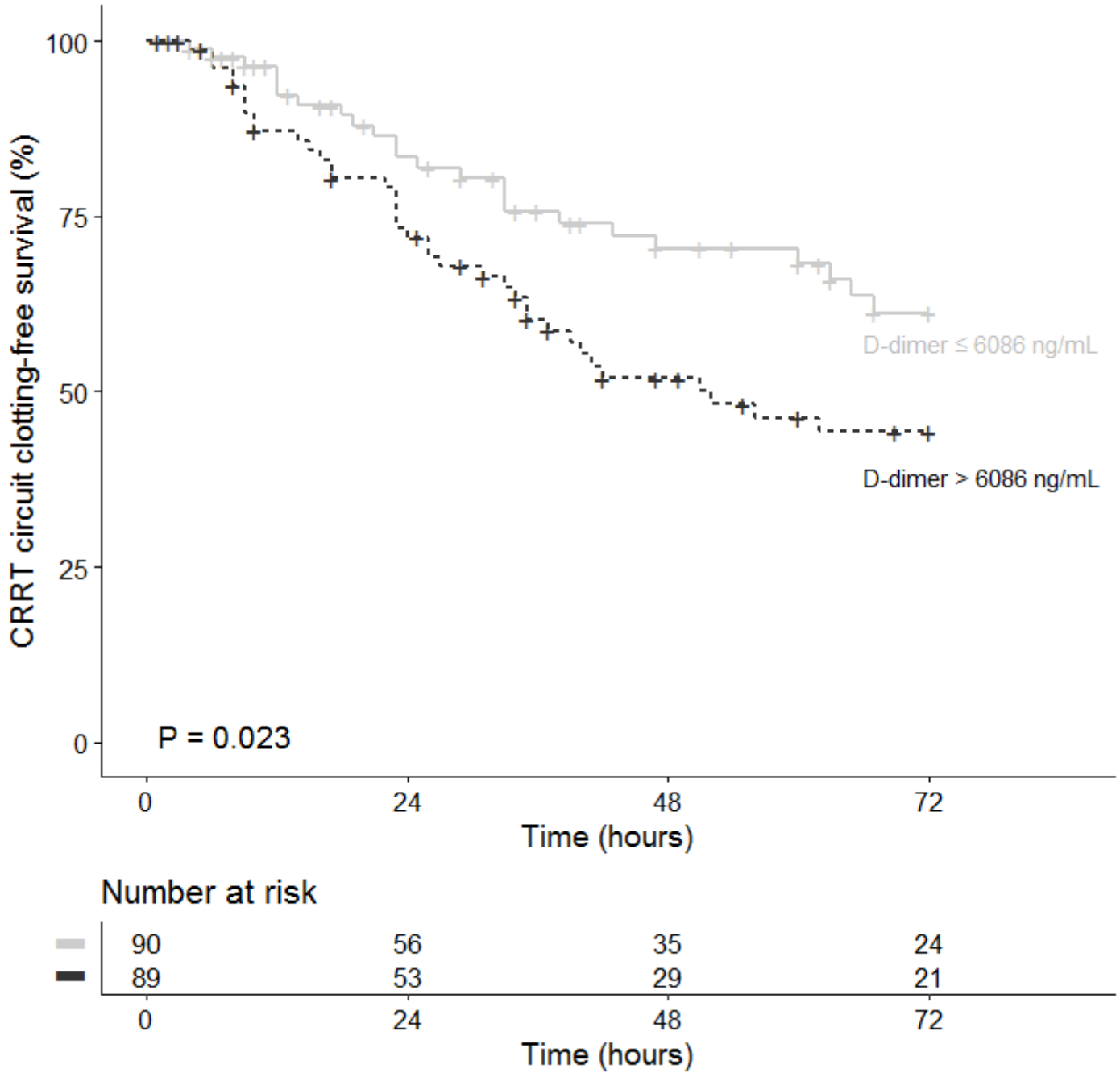

Figure 3

Kaplan–Meier estimate of filter clotting in the first 72 hours of continuous renal replacement therapy (CRRT), according to the D-Dimer median split.

Supplementary Files

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