Efficacy and Complications of Regional Citrate Anticoagulation During Continuous Renal Replacement Therapy in Critically Ill Patients with COVID-19

Dmytro Khadzhynov (dmytro.khadzhynov@charite.de)
Charite Universitatsmedizin Berlin https://orcid.org/0000-0001-5462-5776

Uwe von dem Berge
Charite Universitatsmedizin Berlin Campus Charite Mitte: Charite Universitatsmedizin Berlin

Frédéric Muench
Charite University Hospital Berlin: Charite Universitatsmedizin Berlin

Stoyan Karaivanov
Charite University Hospital Berlin: Charite Universitatsmedizin Berlin

Roland Koerner
Charite University Hospital Berlin: Charite Universitatsmedizin Berlin

Jan M. Kruse
Charité Universitätsmedizin Berlin: Charite Universitatsmedizin Berlin

Daniel Zickler
Charité Universitätsmedizin Berlin: Charite Universitatsmedizin Berlin

Klemens Budde
Charité Universitätsmedizin Berlin: Charite Universitatsmedizin Berlin

Kai-Uwe Eckardt
Charité Universitätsmedizin Berlin: Charite Universitatsmedizin Berlin

Lukas J. Lehner
Charité Universitätsmedizin Berlin: Charite Universitatsmedizin Berlin

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Abstract

Background: Enhanced coagulation in coronavirus disease 2019 (COVID-19) patients is considered a major obstacle for continuous renal replacement therapy (CRRT), but systematic analyses are sparse. We compared filter survival and citrate-induced complications during CRRT with regional citrate anticoagulation (RCA) in COVID-19 and Non-COVID-19 patients.

Methods: In this retrospective study we included all consecutive adult patients (n=97) with acute kidney injury (AKI) treated with RCA-CRRT at seven ICUs of a tertiary university hospital over the tree month period. Medical data were collected to compare the efficacy and complications of RCA-CRRT between COVID-19 (n=44) and Non-COVID-19 patients (n=53).

Results: There was no significant difference in the number of CRRT filters used per patient in COVID-19 vs. Non-COVID-19 patients (median 5 vs 3 filters, p=0.103). Mean filter run-time was significantly higher in COVID-19 patients compared to Non-COVID-19 patients (68.4 (95%CI 67.0-69.9) vs. 65.2 (95%CI 63.2-67.2) hours, respectively; log-rank 0.014). COVID-19 patients showed significantly higher activated partial thromboplastin time (aPTT) throughout the CRRT due to systemic anticoagulation compared to Non-COVID-19 patients (54 (IQR 45 – 61) vs. 47 (IQR 41 - 58) seconds, respectively; p<0.001). A significantly higher incidence of combined metabolic disturbances (metabolic alkalosis, hypercalcemia and hypernatremia), consistent with reduced filter patency and citrate overload during RCA, was observed in COVID-19 patients compared to Non-COVID-19 patients (19.1% vs. 12.7%, respectively; p=0.04). These metabolic disarrangements were resistant to per-protocol adjustments and disappeared after replacement of the CRRT-filter.

Conclusions: In contrast to initial concerns, adequate filter life-span can be achieved with RCA during CRRT in COVID-19 patients. However, close monitoring of the acid-base balance appears warranted, as these patients tend to develop reduced filter patency leading to a higher incidence of citrate overload and metabolic disturbances.

Trial Registration (local authority): EA1/285/20 (Ethikkommission der Charité - Universitätsmedizin Berlin); date of registration 08.10.2020.

Introduction:

The coronavirus disease 2019 (COVID-19) pandemic has created a surge in patients requiring intensive care worldwide [1]. A significant proportion of critically ill patients with severe respiratory distress syndrome due to SARS-CoV2 infection develop AKI and require renal replacement therapy (RRT) [2–5], compromising the capacity for delivering RRT in hotspots of disease outbreak [6–8]. Additionally, the incidence of filter clotting during RRT was reported to be very high despite the use of systemic anticoagulation, presumably due to an incompletely understood coagulopathy in patients with COVID-19

[9–11]. In combination with the rapid increase in the number of patients with AKI requiring CRRT the high incidence of unexpected treatment discontinuations due to shortened filter life-span may enhance the workload of medical staff and aggravate shortages of dialysis filters or other supplies. Consequently, there have been concerns about the optimal treatment strategy of COVID-19 patients requiring CRRT [6–8, 12]. Regional citrate anticoagulation for CRRT is generally recommended [13]. However, until now there is almost no evidence supporting the use of RCA during CRRT in COVID-19 patients with AKI [7]. In addition, nothing is known about the incidence and character of citrate related acid-base and electrolyte disturbances during RCA-CRRT in patients with COVID-19 as compared to other ICU patients. Regardless of therapy mode, in all RCA protocols citrate is partially infused into the patient and subsequently metabolized, potentially leading to alkalization [14]. In order to avoid development of metabolic alkalosis during treatment, sufficient RCA protocols usually include a dialysis solution with reduced sodium and bicarbonate concentration (Fig. 1A) [15, 16]. Due to increased coagulation tendency COVID-19 patients may be prone to an early loss of clearance at the filter level (so called filter-clogging), resulting in impaired citrate elimination and consequently excessive citrate load with metabolic alkalosis, hypernatremia and hypercalcemia. Strict protocol application normally allows to avoid those complications by adapting (reducing) the blood-to-dialysis flow ratio. However, in terms of irreversible filter patency loss due to filter-clogging, those metabolic complications could be resistant to per protocol adaptations and rapid replacement of the filter might be necessary (Fig. 1B).

In light of these considerations the aim of the actual study was 1) to determine the filter lifetime and 2) the frequency, extend, and time-course of acid-base and electrolyte disturbances indicative of reduced filter patency during CRRT with RCA in critically ill COVID-19 patients in comparison with Non-COVID-19 patients.

Methods:

Study design and study population

This retrospective study was conducted at the Charité Berlin, the largest university tertiary center in Germany. We included all consecutive adult patients with symptomatic COVID-19 disease and a positive reverse-transcriptase polymerase chain reaction (PCR) test result from an oropharyngeal swap, sputum, or bronchioalveolar lavage fluid, and AKI treated with the RCA-CRRT between March 1st, 2020 and May 31st, 2020. Patients were recruited from 7 different ICUs. During the study period in the first wave of the COVID-19 pandemic, the ICUs of our university hospital were separated into COVID-19 and Non-COVID-19 units. In both categories of ICUs diagnosis of AKI and indication for CRRT were determined in interdisciplinary consultation between intensivists and the renal consult service. There was no difference in the CRRT approach, materials used or medical staff involved in providing CRRT between COVID-19 and Non-COVID-19 patients. The study was approved by the local ethics review committee (Ethikkommission der Charité - Universitaetsmedizin Berlin; EA1/285/20) and was performed in accordance with the Declaration of Helsinki. The need for patient's informed consent was waived by the local ethics and data

safety committees due to retrospective character of the study and anonymization of all data sets before analysis.

Continuous renal replacement therapy with RCA

We used a previously published weight-adapted protocol for CVVHD [17] with RCA in all patients requiring CRRT and all patients received the same default settings at therapy start, aiming a therapy dose of 20 to 25 ml/kg/h. Briefly, CVVHD was conducted using high-flux dialyzers (AV1000, Fresenius Medical Care (FMC), Bad Homburg, Germany), calcium-free dialysis solution (Ci-Ca dialysate, FMC) and 4% trisodium citrate solution (FMC) with a starting dose of 4 mmol/L blood. Calcium substitution was started in a dose of 1.7 mmol per liter effluent flow. The initial ratio of blood flow was set accordingly to the chosen dialysate flow to maintain a ratio of 3:1. According to the published algorithm [17], dialysate flow was increased to a lower ratio of blood to dialysate flow in case of a high blood bicarbonate concentration and vice versa in case of a low blood bicarbonate concentration. Filters were changed routinely after 72 hours of treatment, as indicated by the manufacturer, with allowance of a tolerance ± 12 hours for practical reasons. A detailed description of this RCA-CVVHD protocol is presented in the *Supplement 1* (*Supplemental Digital Content*, Methods and Materials).

Routine check of metabolic and electrolyte parameters as well as postfilter ionized calcium measurement for anticoagulation monitoring was scheduled 3 times daily or more often if clinically required. The monitoring was started immediately after initiation of CRRT and every 8 hours thereafter. Systemic (typically from arterial line) and postfilter blood samples were analyzed on an automated blood gas analyzer (ABL900, Radiometer, Copenhagen, Denmark).

Filter clotting and filter capacity

Filter clotting was defined as a clotting or therapy stop to non-CRRT related reasons. Reduced filter clearance or filter-clogging was defined when patients developed 1) metabolic complications consistent with citrate overload (metabolic alkalosis, hypercalcemia (or reduced calcium infusion rate) and increasing sodium concentration), 2) those metabolic derangements were resistant to per protocol described adjustment algorithm and 3) those metabolic derangements were transient after the dialysis filter replacement.

Data collection

The following clinical data were extracted from electronic patient data management system: age, gender, reason for admission on ICU, acute physiology and chronic health evaluation score II (APACHE II) at admission, Sepsis-related Organ Failure Assessment score (SOFA) at admission, length of ICU stay, CRRT parameters (duration of RCA-CVVHD, reason for circuit discontinuation, filter run-time and flow rates of blood, citrate-, dialysate-, and calcium-solutions) as well as ICU mortality. The observation period was limited to ICU treatment.

Statistical analysis

Baseline demographics and laboratory data were described as mean ± standard deviation (SD) for normally distributed parameters and as median (interquartile range, i.e., 25–75 percentile range) for non-normally distributed values. Statistical significance of the differences between groups for continuous variables was tested using student's t-test or Mann-Whitney-U test in case of a non-parametric distribution. The Chi-squared test was used to assess the statistical difference between the groups for categorical variables. The over-all filter survival and cumulative risk of filter-clogging were calculated by using the Kaplan-Meier-Method. Significance level was set to $\alpha < 0.05$. All analyses were conducted using SPSS 23 for Windows (SPSS Inc., IBM, Armonk, USA).

Results:

Study population and demographics

During the study period there were 44 consecutive patients with COVID-19 and 53 Non-COVID-19 patients treated with RCA-CVVHD in the participating ICUs. Baseline patient characteristics and medical history of both COVID-19 and Non-COVID-19 patients are summarized in Table 1. Baseline characteristics were similar between both groups, with the exception of a significantly higher proportion of patients with hypertension and malignancies and a higher proportion of patients treated with extracorporeal membrane oxygenation in the COVID-19 group.

Table 1
Characteristics and Outcomes of COVID-19 and Non-COVID-19 patients treated with RCA-CRRT

	COVID-19 (n = 44)	**Non-COVID-19 (n = 53)**	***p-Value***
Age, y; mean (SD)	65 (10.7)	60 (15.8)	*0.062*
Male, n (%)	35 (79.5%)	38 (71.7%)	*0.373*
BMI, median (IQR)	29.1 (25.5–34)	27.8 (24.2–30.9)	*0.129*
Pre-existing comorbidities, n (%)			
Malignancies	7 (15.9%)	12 (22.6%)	0.012
Cardiovascular disease	10 (22.7%)	21 (39.6%)	*0.076*
Hypertension	36 (81.8%)	30 (56.6%)	0.008
Diabetes	16 (36.4%)	19 (35.8%)	*0.958*
Chronic renal disease	8 (18.2%)	18 (34.0%)	*0.069*
Chronic respiratory disease	15 (34.1%)	12 (22.6%)	*0.21*
Invasive mechanical ventilation, n (%)	38 (86.3%)	45 (84.9%)	*0.554*
Patients on ECMO, n (%)	14 (31.8%)	8 (15.1%)	0.042
Baseline APACHE II Score; mean (SD)	31 (10)	30 (11)	*0.611*
Baseline SAPS II Score; mean (SD)	49 (12)	54 (17)	*0.057*
Baseline SOFA Score; mean (SD)	10 (4)	10 (3)	*0.958*

Clinical outcome and CRRT Outcome

There was no significant difference in the ICU mortality rates between the groups (48% in COVID-19 patients vs 59% in Non-COVID-19 patients; p = 0.29). The median length of ICU stay was significantly higher in COVID-19 patients compared to Non-COVID-19 patients (42 days (IQR 22–69) vs 24 days (IQR 9–55), respectively; p = 0.045). Clinical outcomes of patients as well as CRRT outcomes are summarized in Table 2.

Table 2
Clinical Outcomes and Outcomes of RCA-CRRT

	COVID-19 (n = 44)	**Non-COVID-19 (n = 53)**	***p-Value***
ICU mortality; n (%)	21 (48%)	31 (59%)	*0.290*
28th day mortality	13 (30%)	20 (38%)	*0.397*
Length of ICU stay, days; median (IQR)	42 (22–69)	24 (9–55)	0.045
Duration of CRRT, hours; median (IQR)	348 (117–671)	186 (74–627)	*0.205*
Survivors on 28th day	407 (291–832)	*415 (101–790)*	*0.496*
Filters per Pts, n; median (IQR)	5 (3–11)	3 (1–10)	*0.103*
Pts with > 1 Filter clotting, n (%)	13 (30%)	14 (26%)	*0.722*
Pts with > 1 Filter clogging, n (%)	23 (52%)	12 (23%)	*0.002*

Filter life-span

Patients in the COVID-19 group used 293 circuits with a median total duration of RCA-CVVHD of 348 hours (IQR 117–671) compared to 314 circuits with a median total duration of 186 hours (IQR 74–627) of therapy in the Non-COVID-19 group (p = 0.205). There was no significant difference in filters used per patient between the groups (median 5 (IQR 3–11) vs. 3 (1–10) in COVID-19 and Non-COVID-19 patients respectively, p = 0.103). Reasons for filters discontinuation are shown in *Supplement 2* (*Supplemental Digital Content*, Table 1). Mean filter run-time of all hemofilters in COVID-19 patients was significantly higher than in Non-COVID-19 patients (68.4 (95%CI 67.0-69.9) vs. 65.2 (95%CI 63.2–67.2) hours, log-rank p = 0.014; Fig. 2). At the same time COVID-19 patients had significantly higher activated partial thromboplastin time (aPTT) throughout the CRRT due to intensified systemic anticoagulation therapy: median aPTT at the start of every circuit 54 (IQR 45–61) vs 47 (IQR 41–58) seconds in Non-COVID-19 patients (p < 0.001); and aPTT at the end of circuit running time 54 (IQR 45–61) vs 50 (IQR 42–60) seconds in Non-COVID-19 patients (p = 0.009).

Filter patency loss

There was a significantly higher incidence of combined metabolic disarrangements (metabolic alkalosis, hypercalcemia and increasing sodium concentration) consistent with reduced filter patency and citrate overload (filter clogging) during RCA in COVID-19 patients (19.1% vs. 12.7% filters in Non-COVID-19 patients, p = 0.04). The proportion of patients with at least one filter clogging episode was significantly higher in COVID-19 patients (52% vs. 23% patients in the Non-COVID-19 group, p = 0.002; Table 2). Characteristic metabolic disarrangements for filter clogging and the resistance to protocol-based CRRT adjustments as well as they time-course after filter replacement are shown in Fig. 3. The cumulative incidence of the filter clogging was time-dependent (Fig. 4).

Discussion:

To the best of our knowledge, this is the first study comparing filter survival and patency during RCA-CRRT in COVID-19 and Non-COVID-19 patients. The study revealed three main findings. First, a RCA protocol with the initial citrate dose of 4 mmol/L blood offers an effective anticoagulation strategy for CVVHD in COVID-19 patients with intensified anticoagulation, resulting in a mean circuit life-span of almost 70 hours. Second, despite initial concerns, the lifespan of CVVHD filters in COVID-19 patients in present study was not only non-inferior but, surprisingly, even superior compared to Non-COVID-19 patients. This unexpected finding can be partially explained by the fact that early during the evolution of the COVID-19 pandemic recommendations to start intensified anticoagulation in severely ill COVID-19 patients were implemented in clinical practice. Accordingly, in our study COVID-19 patients had significantly higher aPTT throughout the CVVHD treatment compared to Non-COVID-19 patients. Third, even in the presence of systemic anticoagulation we found evidence for enhanced filter clogging with reduced filter patency and consequent citrate overload during RCA-CVVHD in COVID-19 patients.

We are not aware of other studies comparing filter patency of RCA-CRRT between COVID-19 and Non-COVID-19 patients. Moreover, a systematic analysis of citrate-induced complications during RCA-CRRT in COVID-19 patients is lacking. The available evidence is solely based on a limited number of literature with small sample size and significant patient- and RRT-level heterogenity, comparing the anticoagulations strtegies during different modalities of RRT [18–20]. A recent retrospective and small study compared different anticoagulation strategies during RRT in COVID-19 patients [20]. Arnold et al reported a significantly longer circuit life-span of CRRT in the RCA group compared to patients treated with UFH alone, partially supporting the findings of the present study. Another retrospective study compared the anticoagulation strategies during CRRT [19]. In line with our results, Shankaranarayanan et al showed that most superior filter life was reached during combined regional citrate and systemic heparin anticoagulation. A prospective trial comparing regional citrate anticoagulation with systemic heparin anticoagulation during CRRT in patients with COVID-19 is ongoing and should provide results in the middle of 2021 [21].

Significantly higher frequency of combined metabolic disarrangements (metabolic alkalosis, hypercalcemia and increasing sodium concentration) consistent with reduced filter patency and citrate overload during RCA-CVVHD in COVID-19 patients could be explained by increased filter clogging, a well-known term from the early times of dialysis research [22]. This normally benign complication results in the reduced permeability of the filter. However, it gains apparent clinical significance when unphysiological solutions, such as citrate acid, are infused to the extracorporeal circuit. Filter sieving patency especially in terms of RCA-CRRT plays a crucial role regardless of the protocol used. All these protocols require pre-filter administration of a citrate solution, mostly in form of trisodium citrate. During treatment, after infusion of citrate solution into the extracorporeal circuit and formation of calcium-citrate complexes (CCC), a significant amount (approximately 50%) of CCCs is eliminated into the dialysate [16]. The clearance of CCC should be maintained as high as possible to reduce the administration of (sodium-) citrate to the patient. CCCs, which are not removed through the dialysis filter, return to the systemic

circulation and are further metabolized via the citric acid cycle, producing bicarbonate and releasing sodium and calcium. Thus, RCA leads to plasma alkalization due to bicarbonate generation and increases sodium load [16]. In order to avoid development of metabolic alkalosis during treatment, a sufficient RCA protocol has to compensate for alkalization of the blood from infused citrate by applying an adapted dialysis solution with the reduced bicarbonate and sodium concentration [23–26]. In case of the intact permeability and sieving patency of the hemofilter, quick correction of the metabolic alkalosis using the described RCA-CVVHD protocol could be simply reached by reducing the blood to dialysate ratio [15]. In case of reduced filter permeability due to early filter clogging citrate delivery increases and citrate overload might occur [16], resulting in metabolic alkalosis, hypernatremia and hypercalcemia. Clearly, those metabolic disarrangements are resistant to per protocol prescribed adjustments of the blood to dialysate ratio as the sieving of CCC is significantly reduced. Rapid filter replacement in this case is the only available option [16]. Not surprisingly, results of the present study showed that the cumulative incidence of filter clogging is increasing with the increasing treatment time, especially after 30 hours of filter run-time. This somewhat trivial finding is of pronounced importance because it underscores the importance of careful metabolic monitoring of filter patency and the efficacy of protocol adjustments, particularly for CRRT filters running longer than 48 hours.

The mechanisms leading to increase filter clogging in COVID-19 although not completely clear, are in line with the COVID-19 induced coagulopathy. Recently, several groups reported the association of thromboembolic complications with impaired fibrinolysis in critically ill COVID-19 patients [27, 28]. However, the extent of the influence of hypofibrinolysis as an important component of COVID-19 induced coagulopathy on increased filter clogging remains to be investigated.

Despite the fact that there is a generally accepted indication for therapeutic systemic anticoagulation in severely ill COVID-19 patients, we believe RCA should be the preferred option for CRRT in this group of patients, regardless of the systemic anticoagulation.

This study has some limitations. Although it includes patients with a wide spectrum of comorbidities and a variety of causes of critical illness in the Non-COVID-19 group, it focusses on patients with a high disease severity in a tertiary care center. The generalizability to other settings and patients with a less severe course and earlier stages of the disease needs to be tested. Second, due to the retrospective nature unidentified confounding factors might have been missed. Nevertheless, the relatively high number of patients and circuits used increases the validity of the comparison between COVID-19 and Non-COVID-19 patients. Moreover, there was no difference in the CRRT approach, materials or involved medical team for providing CRRT between COVID-19 positive and Non-COVID-19 patients, minimizing potential bias by diagnosis. Thirdly, we used a standardized RCA-Protocol with 4-mmol citrate per 1L blood flow and CVVHD as the CRRT-Mode; different protocols and especially different CRRT filters may show different performance. However, protocols using reduced citrate dose or those with a different CRRT-mode have been shown to be less effective in Non-COVID-19 patients [29, 30].

Conclusions:

Despite the initial concerns, CRRT combined with RCA allows to achieve an effective filter life-span in COVID-19 patients. However, due to significantly higher incidence of filter clogging leading to citrate overload and consecutive metabolic alkalosis, increasing sodium concentration and hypercalcemia, special attention should be paid to acid-base balance of COVID-19 patients on RCA-CRRT especially in CRRT-filters running for more than 48 hours, as they tend to develop reduced filter patency, which is resistant to CRRT-protocol adjustments.

Abbreviations

COVID-19, coronavirus disease 2019; RCA, regional citrate anticoagulation; CRRT, continuous renal replacement therapy; AKI, acute kidney injury; ICU, intensive care unit; CVVHD, continuous veno-venous hemodialysis; APACHE, acute physiology and chronic health evaluation score; SOFA, sequential organ failure assessment; aPTT, activated partial thromboplastin time; SD, standard deviation; CI, confidence interval; IQR, interquartile range; PCR, polymerase chain reaction; CCC, calcium-citrate complexes.

Declarations

Ethical Approval and Consent to participate

Ethical approval was granted by the local ethics review committee (Ethikkommission der Charité - Universitätsmedizin Berlin; EA1/285/20) on the 22nd October 2020, retrospectively registered. The study was performed in accordance with the Declaration of Helsinki. According to the local ethics review committee and data safety board no consent to participate was required due to the retrospective and anonymous character of this single center study.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the fndings of this study are available from the corresponding author upon reasonable request.

Competing interests

D.K., T.S., D.Z. and R.K. have received funds for speaking at symposia organized on behalf of Fresenius Medical Care, Germany. The other authors here have nothing to declare.

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Authors' contribution

All authors meet all authorship requirements. DK, LJL and TS conceived, designed and performed the study. UvB and DK performed data aquision. SK, UvB, RK, JMK, DZ, KUE, and KB contributed to conception and design as well as revised the manuscript for intellectual content and supported data interpretation. All authors participated in data analysis, read and approved the final manuscript.

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Figures

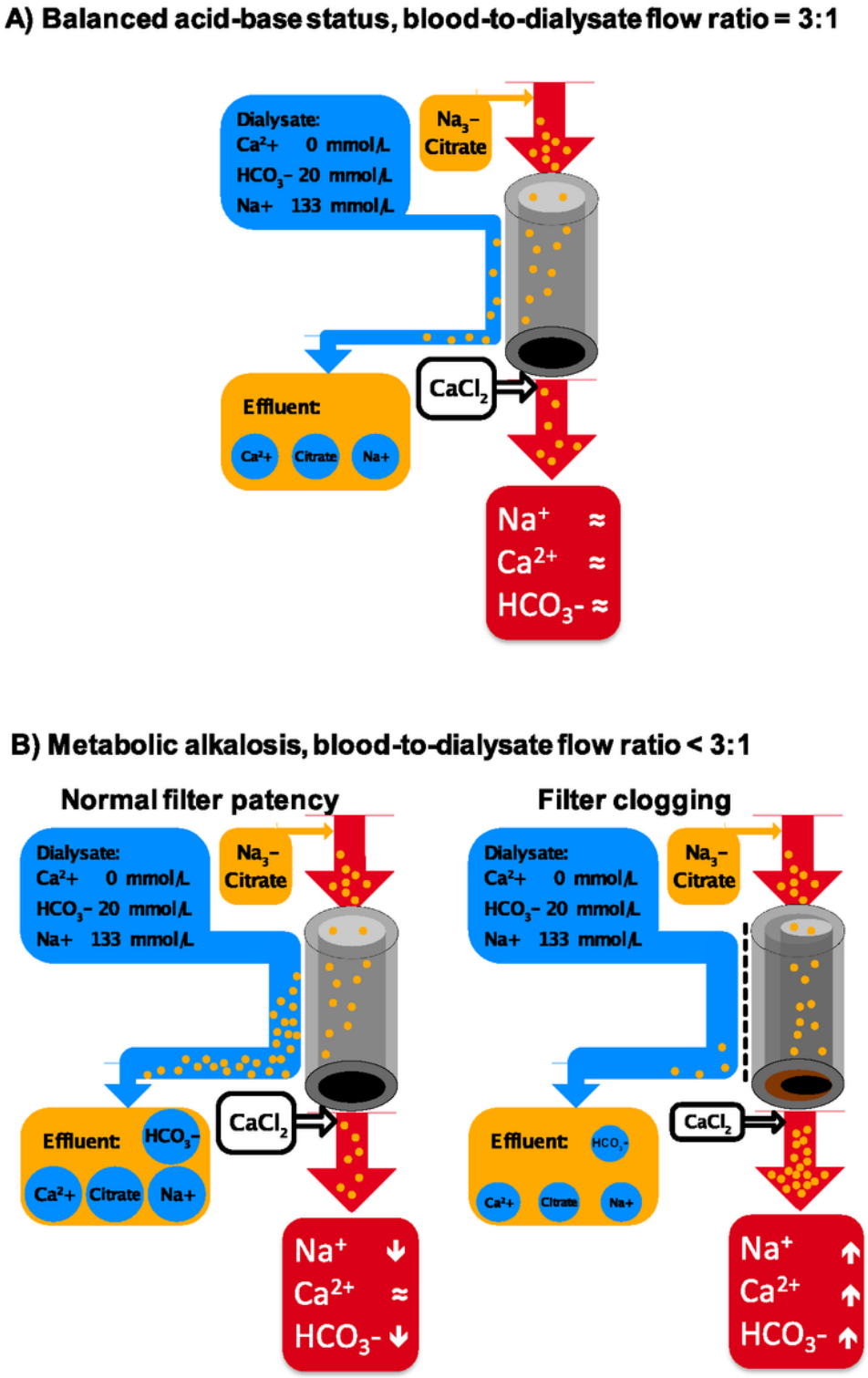

Figure 1

Schematic view of an extracorporeal circuit with regional citrate administration in CVVHD mode and usual per protocol adjustments during metabolic alkalosis. Citrate solution (often as a trisodium citrate) is administered in the arterial line of the CRRT circuit and forms citrate–calcium complexes (CCC, orange circles), which are largely removed from the blood through the CRRT filter and effluent. CCCs which are not removed from the extracorporeal circulation return to the patient's blood and are further metabolized,

producing bicarbonate and releasing calcium and sodium ions (A). In case of a metabolic alkalosis standard blood-to-dialysis ratio (3:1) is reduced by increasing the dialysate flow to enhance CCC removal (B, normal filter patency). In case of normal filter sieving patency, adjustment of blood-to-dialysis ratio leads to a decrease of systemic sodium load and bicarbonate generation. In terms of filter clogging the adjustment of the blood-to-dialysis is ineffective, as the sieving patency of the filter is reduced (B, filter clogging). Thus, filter clogging leads to metabolic alkalosis, hypernatremia and hypercalcemia, owing to increased CCC-substrate for bicarbonate generation and increased sodium and calcium load. Characteristically increasing systemic ionized calcium levels, resulting in lower calcium substitution rates are an early indicator of filter clogging.

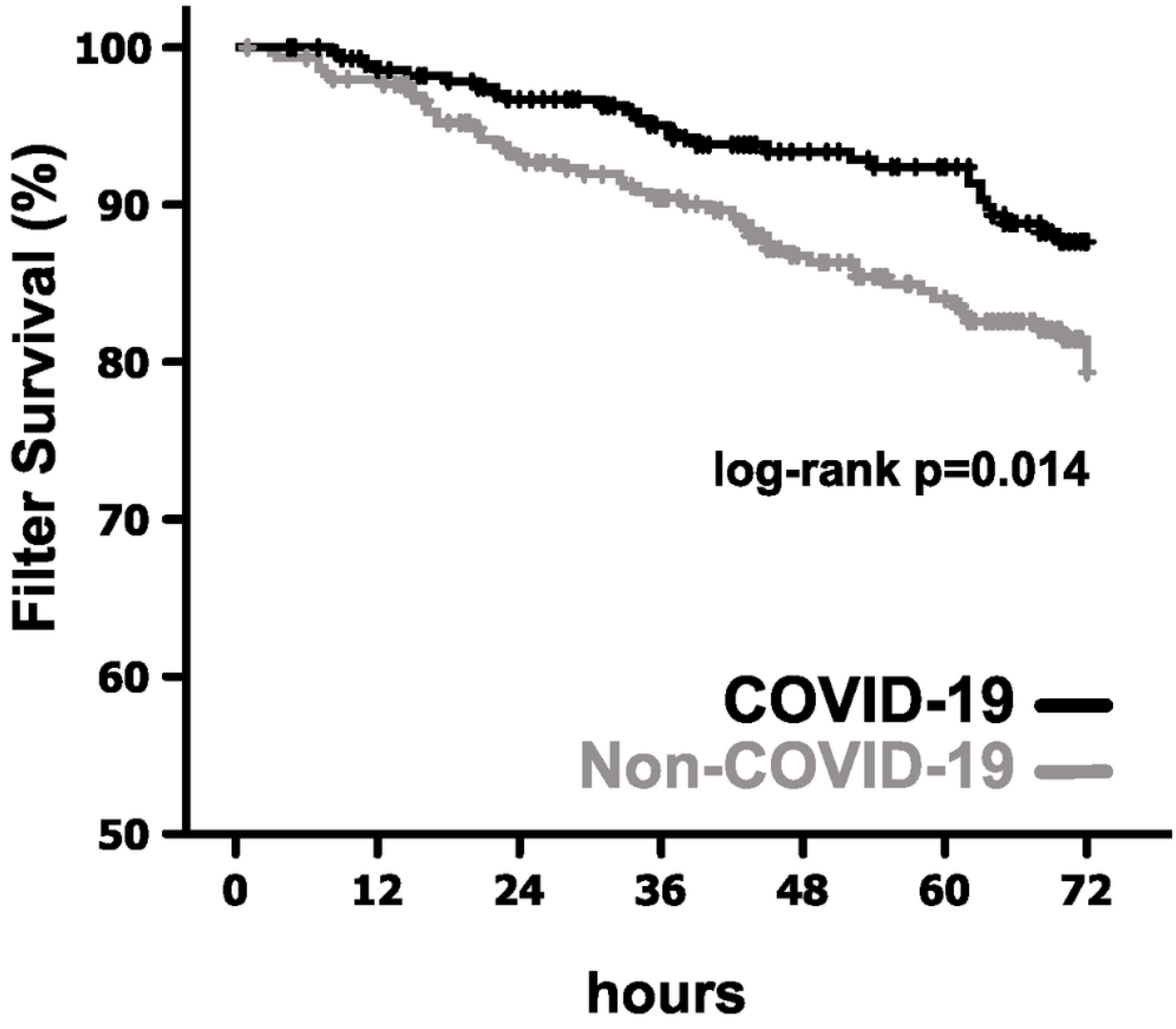

Figure 2

Cumulative CRRT filter survival

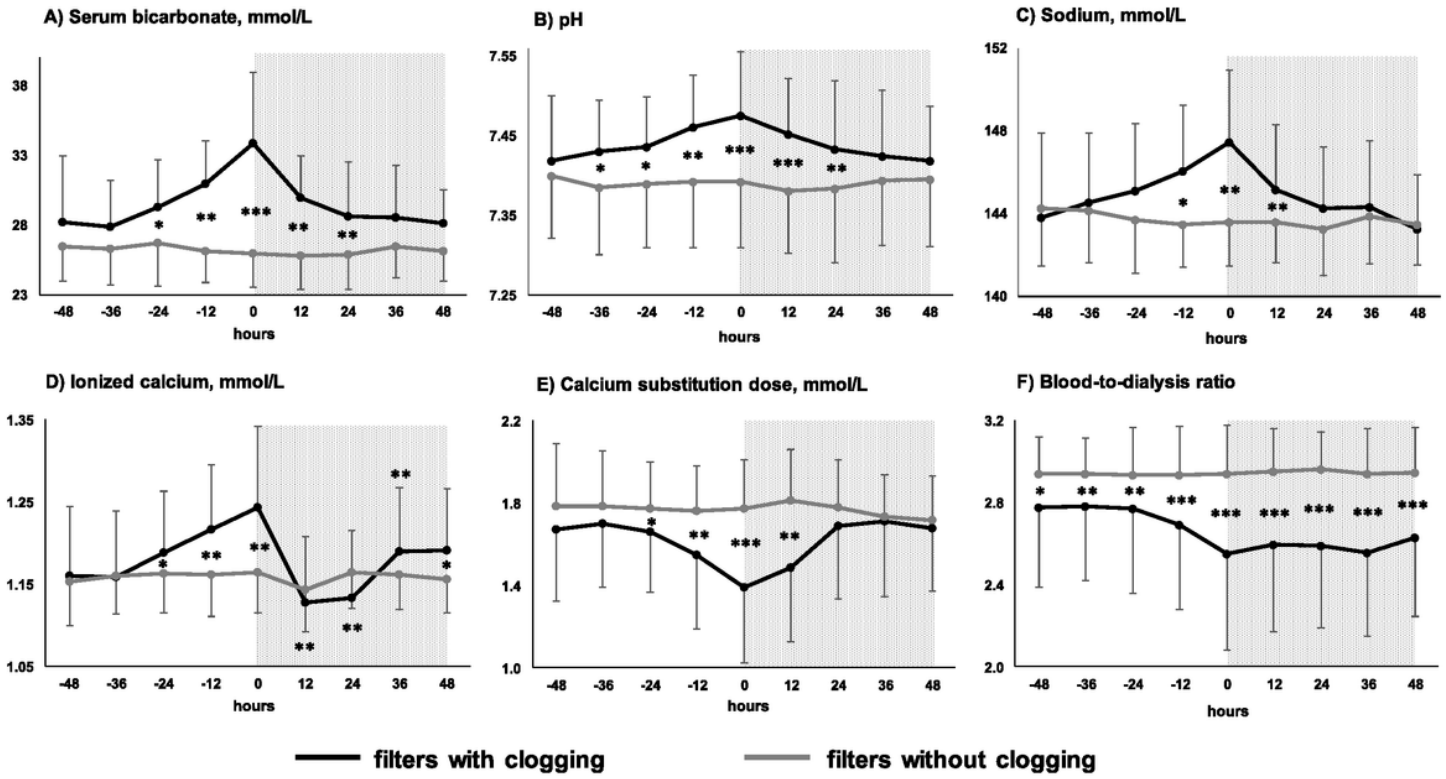

Figure 3

Time-course of characteristic metabolic derangements of COVID-19 patients treated with RCA-CVVHD due to filter clogging and consequent CRRT-protocol adaptations 48 hours before and after CRRT-filter exchange: (A) serum bicarbonate, (B) pH, (C) sodium, (D) ionized calcium, (E) calcium substitution dose, (F) blood-to-dialysis flow ratio. CRRT-filter was exchanged at time point 0. Data are present as mean ± SD. *p < 0.05, **p < 0.01, ***p < 0.001.

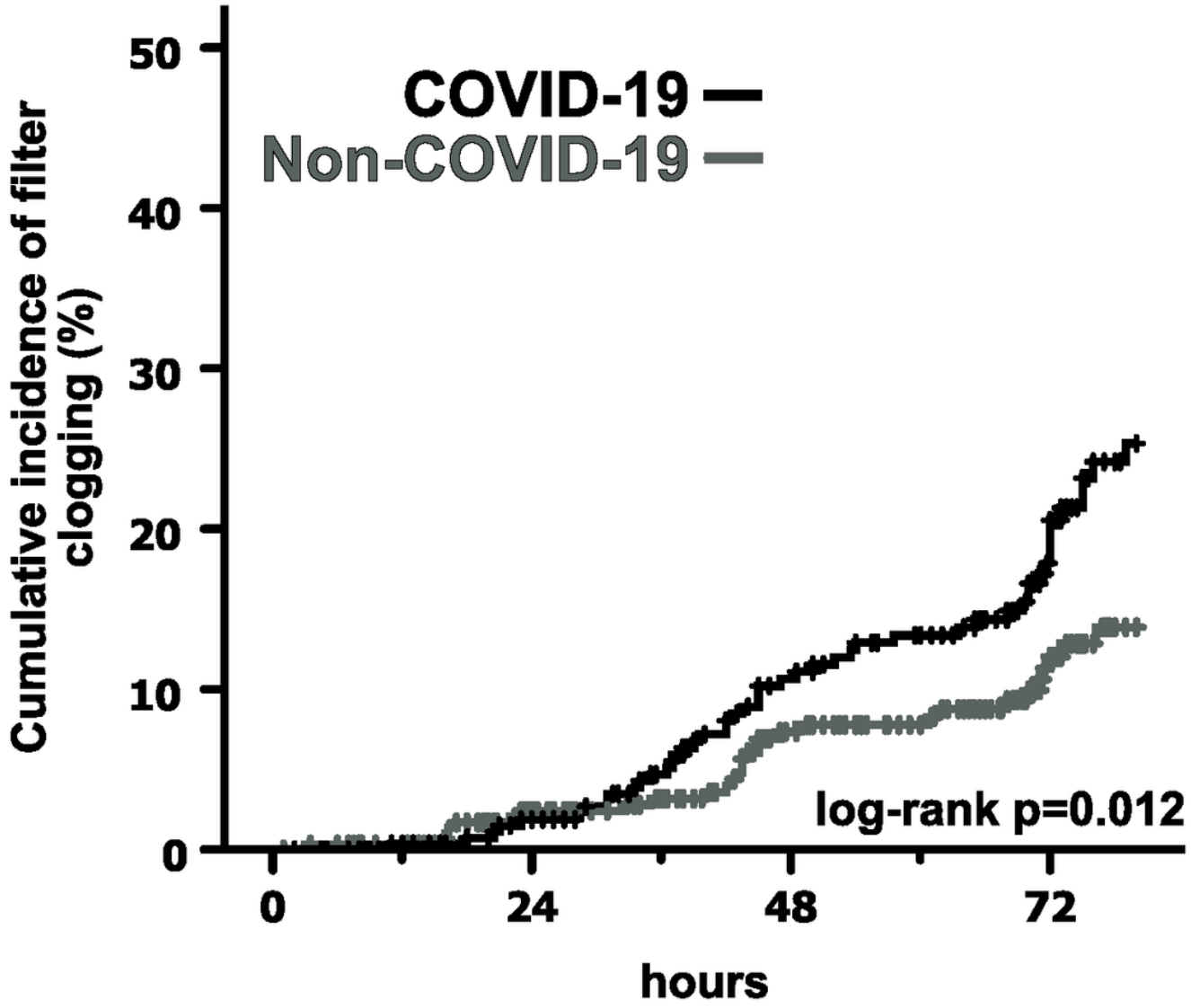

Figure 4

Cumulative incidence of reduced filter patency.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalDataFileSupplement1.docx
- SupplementalDataFileSupplement2final.docx
- visualabstractCOVID19CRRT.pptx