

## ORIGINAL ARTICLE

## Anticoagulation

# Increased risk of dialysis circuit clotting in hemodialysis patients with COVID-19 is associated with elevated FVIII, fibrinogen and D-dimers

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**Abstract**

**Introduction:** Severe COVID-19 infections increase the risk of thrombotic events and Intensive Care Units reported increased extracorporeal circuit clotting (ECC) in COVID-19 patients with acute kidney injury. We wished to determine whether hemodialysis (HD) patients with COVID-19 also have increased risk of circuit clotting.

**Methods:** We reviewed coagulation studies and HD records, 4 weeks before and after COVID-19 polymerase chain reaction detection in HD patients between April 2020 and June 2021.

**Findings:** Sixty-eight (33.5%) of 203 HD patients with COVID-19, 65% male, mean age  $64.9 \pm 15.3$  years, experienced some circuit clotting, and no clotting recorded prior to positive test results. In those who experienced ECC, prothrombin, activated partial thromboplastin or thrombin times were not different, whereas median factor VIII (273 [168–419] vs. 166 [139–225] IU/dl,  $p < 0.001$ ), D-dimers (2654 [1381–6019] vs. 1351 [786–2334] ng/ml,  $p < 0.05$ ), and fibrinogen ( $5.6 \pm 1.4$  vs.  $4.9 \pm 1.4$  g/L,  $p < 0.05$ ) were greater. Antithrombin (94 [83–112] vs. 89 [84–103] IU/dl), protein C (102 [80–130] vs. 86 [76–106] IU/dl), protein S (65 [61–75] vs. 65 [52–79] IU/dl) and platelet counts ( $193 [138–243]$  vs.  $174 [138–229] \times 10^9/L$ ) did not differ. On multivariable logistic analysis, circuit clotting was associated with log factor VIII (odds ratio [OR] 14.8 (95% confidence limits [95% CL] 1.12–19.6),  $p = 0.041$ ), fibrinogen (OR 1.57 [95% CL 1.14–21.7],  $p = 0.006$ ) and log D dimer (OR 4.8 [95% CL 1.16–12.5],  $p = 0.028$ ).

**Discussion:** Extracorporeal circuit clotting was increased within 4 weeks of testing positive for COVID-19. Clotting was associated with increased factor VIII, fibrinogen and D-dimer, suggesting that the risk of circuit clotting was related to the inflammatory response to COVID-19.

**KEYWORDS**

antithrombin, COVID-19, D-dimer, factor VIII, hemodialysis, heparin, protein C, protein S

## INTRODUCTION

Extracorporeal circuit clotting (ECC) is a well-recognized problem for hemodialysis (HD) patients [1]. This is thought to be due to the turbulent blood flow, shear stress, and contact of blood with the dialyzer membrane and other components of the extracorporeal circuit [2]. As blood passes through the extracorporeal circuit, platelets, leukocytes, and monocytes can be activated, along with the complement pathway leading to generation of thrombin, deposition of fibrin and platelets causing small clots within the dialyzer capillary fibers and venous air detector [3–5]. Therefore, in routine clinical practice most HD patients require anticoagulation with heparin to prevent clotting within the circuit [1,2].

In addition to the effects of the extracorporeal circuit on activation of the clotting cascades, patient factors, including sepsis, liver disease, and hematological malignancy can alter the risk of ECC [6,7], by affecting platelet numbers, increasing prothrombotic factors, and reducing natural anticoagulants [8,9]. Heparin, both unfractionated heparin (UFH) and low molecular weight heparin (LMWH) reduce thrombin generation by binding to the physiological anticoagulant anti-thrombin (AT), and reduced AT levels in acutely ill patients [10–12] can potentially result in inadequate anticoagulation.

Patients infected with COVID-19 have been reported to be at increased risk of thrombosis, with reports of pulmonary emboli and venous thrombosis [13,14], despite using prophylactic or therapeutic anticoagulation [15].

As with other centers we noted increased clotting, particularly in patients with COVID-19 admitted to the intensive care unit requiring continuous renal replacement therapy (CRRT) [14,16]. As AT levels have been reported to be lowered in critically ill patients admitted to the intensive care unit [17,18], we wished to determine whether HD patients who developed COVID-19 infections also had an increased risk of clotting of their extracorporeal circuits, and if this was predominantly due to an increase in procoagulant factors, or due to a reduction in natural anticoagulants, particularly AT.

## PATIENTS AND METHODS

This was a single center observational report from HD patients attending for intermittent HD treatments. Patients were routinely screened from April 2020 to June 2021 for COVID-19, using a United Kingdom (UK) approved nasal or nasopharyngeal COVID-19 real time reverse transcriptase-polymerase chain reaction (RT-PCR) test. Samples were collected for analysis of thrombophilia markers as part of service development in

response to the COVID-19 pandemic in HD dialysis patients with a positive RT-PCR. Blood samples were requested from the dialysis session after the positive COVID-19 test and collected into 0.109 M sodium citrate tubes (Becton Dickinson, Plymouth, Devon, UK) from the dialysis circuit prior to the start of dialysis. All samples were double centrifuged at 2000g for 12 min. Plasma was aliquoted and stored at  $-85^{\circ}\text{C}$ . Sample collection, handling, and processing were undertaken in accordance with the WHO COVID-19 laboratory guidance.

Samples were analyzed using an ACL TOP 700 analyzer (Werfen/IL, MA, USA), unless otherwise stated. Measurements of prothrombin time (PT) activated partial thromboplastin time (APTT) and Clauss fibrinogen were taken using HemosIL Recombiplastin 2G, SynthASIL APTT, and QFA Thrombin reagents (Werfen/IL, MA, USA) factor VIII (FVIII) levels were measured using standard one-stage APTT-based assays, as previously described [19]. Protein C and protein S levels were measured using HemosIL Prochrom and HemosIL free Protein S (PS free) reagents, respectively. All assays were performed, following manufacturer's instructions, and calibrated with reference plasma (Precision Biologic, Canada). The dilute Russell's viper venom time (dRVVT) test was used to screen for Lupus Anticoagulant using DVVTest reagent (BioMedica Diagnostics, Stanford, USA) and the silica clotting time test (HemosIL).

AT activity levels were measured using Berichrom chromogenic assays (Siemens Healthcare Diagnostics, Marburg, Germany) on a Sysmex CS-2000i system (Sysmex, Kobe, Japan), following manufacturer's instructions. Both assays were calibrated using a SHP calibrator (Siemens Healthineers, UK). Factor V Leiden and prothrombin 3' untranslated region (3' UTR) mutations were identified using a RT-PCR testing performed using a GeneExpert Dx (Cepheid, Sunnyvale, USA).

Standard hematological and biochemistry tests for C reactive protein (CRP), N-terminal brain natriuretic peptide (NTproBNP), and ferritin were also conducted by standard methods (XE-2100 Sysmex Corporation, Kobe, Japan; Roche Modular P, Burgess Hill, UK) [20,21].

In our center the low molecular weight heparin enoxaparin (Inhixa, Techdow Pharma England Ltd, Guilford, UK) was the standard anticoagulant for HD treatments and it is administered as a single bolus 2–3 min after the start of the dialysis treatment, into the arterial limb of the circuit. In keeping with UK national clinical guidelines, patients admitted to hospitals were given daily subcutaneous low molecular weight heparin as standard of care (tinzaparin, Leo Laboratories, Maidenhead, UK).

Patients were dialyzed with polysulfone high flux dialyzers (FX series) and 4008H dialysis machines (both

Fresenius Medical Care, Bad Homburg, Germany), with ultrapure quality dialysis water. Citra-lock™ (Dirinco AG, Wollerau, Switzerland) a 46.7% sodium citrate solution was used to lock central venous access catheters. Patient co-morbidity was assessed using the Charlson comorbidity score, adjusted for age [22]. Electronic dialysis records were reviewed for the 4 weeks prior to and then for the 4 weeks after the positive COVID-19 test for reports of clotting within the extracorporeal circuit or bleeding episodes. Clotting of extracorporeal circuits was defined as treatments prematurely terminated due to clotting in the circuit, or replacement of the venous blood line or dialyzer due to clotting.

## Statistical analysis

Results are expressed as mean  $\pm$  standard deviation, or median and interquartile range, or percentage. Standard statistical analyses were used: D'Agostino & Pearson normality test and the chi square test ( $\chi^2$ ) were used for categorical data, and ANOVA with appropriate post-hoc Bonferroni or Games-Howell correction for numerical data. Variables which were associated with clotting of dialysis circuits were entered into a stepwise backward logistic regression model, with log transformation of non-parametric variables, and then variables excluded if not statistically significant, unless they improved the model fit. Statistical analysis was performed using Graph Pad Prism (version 9.2, Graph Pad, San Diego, CA, USA), Statistical Package for Social Science version 26.0 (IBM Corporation, Armonk, New York, USA). Statistical significance was taken at or below the 5% level.

## RESULTS

Clotting studies were undertaken in 203 out of 206 (98.1%) HD patients, who tested positive for COVID-19, including 132 males (65.0%), with a mean age of  $64.9 \pm 15.3$  years. Sixty-eight patients had clotting of one or more of their extracorporeal circuits, with 16.2% experiencing clotting twice and 10.3% three or more. Clotting typically occurred during the first week following a positive COVID-19 test, although one patient had clotting in the third week. Standard dialysis was in post-dilution hemodiafiltration mode, although 12 patients (5.6% with no clotting and 7.4% who experienced clotting) had their circuits set up in pre-dilution mode ( $p > 0.05$ ). Although the majority of patients received anticoagulation with dialysis, 5.6% of patients with no clotting had 1 or more sessions with no anticoagulation, 7.4% of those experiencing clotting and 20% of those with excessive bleeding,  $p > 0.05$ . Blood flow

**TABLE 1** Clotting studies in dialysis patients tested positive for COVID-19

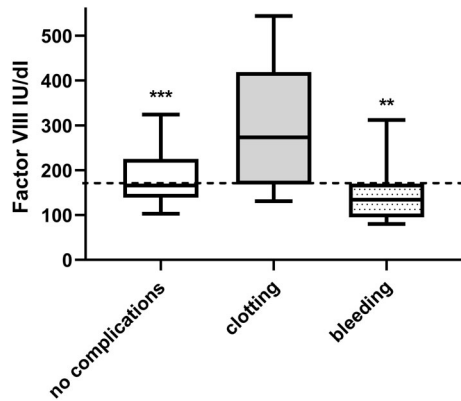
Variables	Values	Normal laboratory values
Prothrombin time (s)	11.6(10.9–12.9)	9–12
INR	1.0 (0.9–1.15)	0.9–1.12
APTT (s)	34.6 (30.8–40.8)	28–35
TT (s)	16.7 (14.5–20)	12–16
DRVVT ratio	1.03 $\pm$ 0.23	<1.15
Silica clotting time ratio	0.69 $\pm$ 0.2	<1.15
Lupus anticoagulant	2 positive	Negative
Factor V Leiden	2 homogeneous	Heterogenous Arg506Gln
Prothrombin 3'-UTR	All normal	Normal G/G
Antithrombin (IU/dl)	89 (83–103)	79–121
Protein C (IU/dl)	89 (76.3–109.8)	70–140
Protein S (IU/dl)	65 (55.3–81)	60–140
Factor VIII (IU/dl)	175 (142–270)	45–169
Fibrinogen (g/L)	5.0 $\pm$ 1.4	1.6–3.8
D-dimer (ng/ml)	1498 (866–3043)	< 400

Note: Data expressed as mean  $\pm$  standard deviation or median (interquartile range).

Abbreviations: INR, international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time; DRVVT, dilute Russell viper venom time.

during the first week after a positive COVID-19 test was lower in the group with clotting (300 [250–300] ml/min vs. 300 [294–300] ml/min,  $p = 0.021$ ). In addition, more patients with extracorporeal clotting dialyzed with catheters (54.4% vs. 30.9%,  $\chi^2 10.6$ ,  $p = 0.001$ ). Anti-platelet medications (aspirin/clopidogrel) were prescribed to 60% of those with no clotting of circuits, 51.7% of those with clotting and 50% of those with excessive bleeding,  $p > 0.05$ .

Although enoxaparin was the standard anticoagulant for HD, six patients were prescribed fondaparinux with a median dose of 2.5 mg (2.5–5.0) and five patients had warfarin. The results of clotting studies are detailed in Table 1, with the majority of patients having an increased thrombin time (TT), FVIII, D-dimer and fibrinogen. Natural anticoagulants: AT, proteins S and C were not reduced. Two patients (1%) tested positive for lupus anticoagulant (LA), which may have been due to the presence of low molecular weight heparin, as thrombin times were within the normal range, and two were heterogenous for factor V Leiden, and no patient had a prothrombin 3' UTR mutation.



**FIGURE 1** Factor VIII concentrations in hemodialysis patients with COVID-19 divided into those who had no clotting or bleeding complications with dialysis and those who experienced clotting or bleeding problems. \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$  versus clotting complications

To investigate whether these changes in clotting parameters had a clinical impact on dialysis, we divided patients into those who had clotting of their dialysis circuits during 4 weeks after a positive COVID-19 test, those with bleeding at vascular access sites, and those with no complications. None of the patients had any record of clotting of their dialysis circuit or excessive bleeding at needled sites post-dialysis in the month prior to the positive COVID-19 test. Sixty-three (31.0%) patients experienced clotting problems, and nine (4.4%) bleeding. There were no differences in patient demographics, age, gender, or co-morbidity between groups.

Patients who had ECC had higher plasma FVIII (Figure 1), D-dimers, fibrinogen, peripheral leukocytes, and lower protein C and hemoglobin (Table 2). Although CRP values were not statistically different, more patients with ECC had a raised CRP compared to those with no complications (96.8% vs. 80.9%,  $\chi^2 = 14.3$ ,  $p = 0.001$ ). One of the two patients who tested positive for factor V Leiden, experienced clotting of their dialysis circuit, whereas the other patient had no problems and neither patient tested positive for LA had any complications recorded during dialysis. One of the six patients prescribed fondaparinux had ECC, but none of the five patients prescribed warfarin. None of these patients experienced any problems with bleeding during dialysis. Although the dialysis sessional dose of enoxaparin did not differ (Table 2), patients admitted to hospital were routinely given prophylactic daily subcutaneous tinzaparin, and more patients who experienced ECC were admitted to hospital, although over-all mortality was similar.

In a logistic step-backward multivariable model of variables associated with ECC  $p < 0.1$  (factor V III, D-dimer, peripheral neutrophil count, hemoglobin, fibrinogen, total peripheral white blood cell count, protein C, CRP, catheter vs. fistula access, and blood pump speed), then ECC was

independently associated with increased FVIII, fibrinogen, and D-dimers (Table 3).

## DISCUSSION

Infection with COVID-19 has been reported to be associated with an increased risk of thrombotic events [13,14], and particularly for those admitted to the intensive care unit [23]. Several centers, including our own center experienced increase ECC in intensive care unit patients with COVID-19 who developed acute kidney injury and were treated with CRRT [14,16]. Although intermittent HD is a much shorter treatment than CRRT, just over 30% of our patients encountered clotting problems following infection with COVID-19, whereas they had not experienced any circuit or access clotting problems in the 4 weeks prior to infection.

In terms of routine laboratory coagulation testing, the majority of patients had a PT, INR, and APTT within the normal reference range and there were no differences between those with ECC, bleeding from fistula needle bleeding sites, or those without complications. The thrombin time, and the reptilase time, the latter only measured in a small subset, were prolonged in the majority of patients, but did not differ between groups. However, as the two patients who tested positive for LA had prolonged thrombin times, but normal reptilase times, this suggests an effect of low molecular weight heparin, rather than the development of a LA.

Heparin predominantly works by binding AT by preventing the formation of thrombin complexes [17]. Previous studies have reported that heparin anticoagulation is less effective when AT levels are reduced, with increased risk of ECC [24]. As the risk of clotting can be increased due to loss of, or reduction in the natural anticoagulants, we measured AT, and proteins S and C. These were normal in the majority of patients and did not differ between groups.

Inflammation, particularly inflammation driven by sepsis, leads not only to the initiation of coagulation, but also to the propagation of coagulation activity [25]. COVID-19 generates an inflammatory response [15], and although markers of inflammation including CRP, ferritin, and NTproBNP concentrations were not different between groups, more patients in the ECC group had raised CRP levels. Similarly, those with clotting complications had greater total peripheral white blood cell counts and leukocytes, and fibrinogen, which are also part of the acute phase response to inflammation. Although platelets play a key role in clotting in ECC [3,26], platelet counts were similar between groups.

D-dimer is a product of fibrinogen degradation, and a sensitive marker of fibrinolysis, but can also be

**TABLE 2** Dialysis patients divided according to whether there were clotting or bleeding complications with dialysis

	No complications	Clotting complications	Bleeding complications
Number	128	68	9
Male/female	89/42	39/24	4/5
Age years	65 ± 16	65 ± 14	67 ± 14.1
Charlson comorbidity	5 (4–7)	5 (2.5–6.5)	6.5 (4–9)
Outpatients (%)	67 (50.8)	16 (25.4)***	3 (33.3)
Mortality (%)	36 (27.3)	21 (33.3)	3 (33.3)
Hemoglobin (g/L)	107 ± 16	99 ± 19**	109 ± 16.3
WBC (×10 <sup>9</sup> /L)	6.64 ± 3.76	8.31 ± 5.1**	6.4 ± 3.55
PMN (×10 <sup>9</sup> /L)	4.91 ± 3.41	6.9 ± 4.99*	4.92 ± 3.34
PBL (×10 <sup>9</sup> /L)	0.93 ± 0.6	0.84 ± 0.53	0.82 ± 0.4
Platelets (×10 <sup>9</sup> /L)	174 (138–229)	193 (138–243)	200 (155–267)
C reactive protein (g/L)	33 (9–90)	52 (18–137)	9 (3–112)
Ferritin (µg/L)	916 (482–1654)	976 (627–2075)	1357(481–2340)
NTproBNP (ng/L)	4914 (2094–27,505)	13,330 (2535–32,395)	1687 (6500–32,842)
Prothrombin time (s)	12.9 ± 5.1	12.3 ± 2.6	11.8 ± 1.7
INR	1.2 ± 0.5	1.1 ± 0.2	1.2 ± 0.3
APTT (s)	37.4 ± 9.0	36.8 ± 9.5	37.0 ± 8.7
Thrombin time (s)	16 (14.3–19.2)	17.7 (15.3–20.6)	18.2 (14.9–19.9)
Antithrombin (IU/dl)	89 (84–103)	94 (83–112)	83 (75–91)
Protein C (IU/dl)	86 (76–106)	102 (80–130)	104 (91–109)
Protein S (IU/dl)	65 (52–79)	65 (61–75)	77 (75–79)
Fibrinogen (g/L)	5.1 (3.8–5.4)	5.4 (4.6–6.2)*	3.8 (1.8–4.4)
D-dimer (ng/ml)	1351 (786–2334)	2654 (1381–6019)*	885 (790–1205)*
Enoxaparin (mg)	20 (20–20)	20 (20–40)	20 (10–20)

Note: \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  versus no complications.

Abbreviations: INR, international normalized ratio; NTproBNP, N terminal probrain natriuretic peptide; PBL, lymphocytes; PMN, polymorphonuclear cells; WBC, total white blood cells.

**TABLE 3** Multivariable logistic model of factors independently associated with clotting of dialysis circuits in patients with COVID-19

Variable	$\beta$	StE $\beta$	Wald	Odds ratio	95% CL	$p$
Log factor VIII	2.7	1.3	4.2	18.8	1.12–19.6	0.041
Fibrinogen	0.45	0.16	7.6	1.57	1.14–21.7	0.006
Log D-dimer	1.32	0.61	34.8	3.8	1.12–12.5	0.028

Note: Nagelkerke  $r^2$  0.32.

Abbreviations: 95% CL, 95% confidence limit; StE, standard error.

increased by severe inflammation. Both fibrinogen and D-dimers were increased in patients with ECC, suggesting both increased fibrin production and degradation. However, as the levels of D-dimers can be very high, particularly in dialysis patients due to the reduced renal clearance, then there has been debate, particularly with COVID-19, as to whether fibrinolysis is actually impaired, with failure to clear the D-dimers [27,28].

Factor VIII is also an acute-phase factor that is released from the endothelium as part of the inflammatory response to infection, and other stimuli. Increased circulating FVIII levels are reported to be associated with both an increased risk of arterial and venous thrombosis and have been proposed to be a marker of prothrombotic risk in COVID-19 patients [29]. In keeping with these reports, our patients with ECC had higher FVIII levels, whether this represents a direct procoagulant effect of

FVIII increasing the risk of ECC, or part of a greater inflammatory response to COVID-19 which increases the risk of ECC remains to be determined.

Clotting may also occur due to an underlying pre-existing prothrombotic condition [30]. However, we only detected two patients with a factor V Leiden and no patients with the prothrombin PTR-3' UTR mutations. Only one patient with factor V Leiden had ECC after COVID-19, but there was no preceding record of problems with clotting of dialysis circuits. Two patients tested positive for LA, a phospholipid antibody, but neither patient was retested to determine whether this was pre-existing or secondary to inflammation caused by infection with COVID-19, or due to the presence of low molecular weight heparin [30], as neither patient subsequently developed ECC.

We found that the increased risk of clotting in extracorporeal circuits in patients with COVID-19, is not only limited to CRRT, but can also affect patients with chronic kidney disease treated by intermittent HD. Patients who experienced ECC had greater circulating levels of FVIII, D-dimers and fibrin suggesting hypercoagulability and increased clot turn over. Measurement of these variables could potentially identify those patients at greater risk of developing clotting of their dialysis circuit. As natural anticoagulants, in particular AT were not reduced, then appropriate anticoagulation with heparins should reduce the risk of clotting in the extracorporeal circuit.


## CONFLICT OF INTEREST

The authors have no conflict of interest.

## ETHICAL APPROVAL

This study complied with UK National Research Ethical standards for clinical practice development and audit, with all data appropriately anonymized and NHS ethics committee 20/SW/0077 approval.

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