The effect of SARS-Co-V2 infection on prothrombotic and anticoagulant factors in dialysis patients

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Abstract
Background: Patients with COVID-19 infection are at increased risk of thrombosis. We wished to determine whether this was due to an increase in prothrombotic or reduction in anticoagulant factors and whether heparin would be an appropriate anticoagulant.

Methods: We measured routine coagulation and prothrombotic factors in dialysis patients after a positive COVID-19 test between March 2020 –April 2021.

Results: Routine coagulation tests were measured in 227 dialysis patients, 148 males (65.2%), median age 67.5 (53.8–77.0) years. The international normalized ratio was prolonged in 11.5%, activated partial thromboplastin time in 48.5%, thrombin time in 57%. Factor VIII was increased in 59.1%, fibrinogen 73.8%, and D-dimer 95.5%. Protein C was reduced in 15.3%, protein S 28%, and antithrombin (AT) in 12.1%. Two patients were Lupus anticoagulant positive, and two Factor V Leiden positive. Factor VIII levels increased with clinical disease; outpatients 159 (136–179) IU/dl, hospitalized but not ventilated 228 (167–311) IU, ventilated 432 (368–488) IU/dl (p < 0.01). Overall 75% had an AT level ≥ 88 IU/dl (reference range 79–106), but only 11.7% of non-hospitalized patients compared to 45% of those who died, p < 0.01, fibrinogen, D-dimers, and protein S or C did not differ with clinical disease severity, whether patients required hospital admission or not and between survivors and those who died.

Conclusion: COVID-19 dialysis patients have increased levels of fibrinogen and D-Dimers, but only factor VIII levels in the clotting profile increased with clinical disease severity increasing systemic hypercoagulability. AT concentrations are maintained and as such should not compromise anticoagulation with heparins.

Keywords
antithrombin, D-dimer, factor VIII, hemodialysis, heparin, protein C, protein S, SARS-Co-V2

1 INTRODUCTION

Although patients with end-stage kidney disease (ESKD) may have prolonged bleeding times, once established on dialysis most patients are prothrombotic, and require anticoagulation to prevent clotting of their dialysis circuits.1 Several observational studies have reported that COVID-19 infection is associated with an increased risk of both arterial and venous thrombosis.2,3 The cause of this greater risk of thrombosis is not yet completely
elucidated. Autopsy studies have demonstrated primary infection of endothelial cells and risk of local coagulation, meta-analysis has shown both increased risk of thrombi forming in the pulmonary arteries and deep vein thrombosis, and so additionally with subsequent increased risk of emboli. Traditionally Virchow's triad of endothelial damage, venous stasis, and hypercoagulability is a helpful framework for investigation and to postulate potential mechanisms.4

Hemodialysis patients are at greater risk of contracting COVID-19, due to communal transport to and from dialysis centers, communal waiting areas in dialysis centers, and proximity to other patients and staff in buildings with inadequate ventilation while undergoing dialysis treatment.5 Although activation of the clotting cascades, platelets, and leukocytes occurs in the dialysis extracorporeal circuit with the generation of thrombin,6,7 most clotting in the dialysis circuit is sub-clinical.8 However, during the COVID-19 pandemic, we observed repeated clotting, particularly of continuous renal replacement circuits (CRRT) in the intensive care setting, but also reports of clotting of hemodialysis circuits.9

Our standard approach is to use unfractionated (UFH) and low molecular weight heparin (LMWH) anticoagulation for CRRT and hemodialysis circuits. Heparin predominantly works by binding antithrombin, but patients may develop resistance to anticoagulation with heparin anticoagulation due to reduced antithrombin levels.10 As such we wished to determine whether the coagulation effect in dialysis patients was due to increased prothrombotic factors, or reduced anticoagulants and whether anticoagulation with heparin remained the anticoagulant of choice.

2 | PATIENTS AND METHODS

From March 2020 to April 2021 coagulation samples were analyzed as part of care for chronic dialysis patients under the care of a single tertiary center who had a positive, United Kingdom (UK) approved nasal or nasopharyngeal, COVID-19 real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test. Patients attending dialysis outpatient treatments were routinely screened for COVID-19 whether symptomatic or not. Blood samples for coagulation testing were organized for the dialysis session following a positive COVID-19 RT-PCR result 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 −40°C until testing. Sample collection, handling, and processing were undertaken in accordance with the world health organization 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). D-dimers were measured using Innovan d-dimer test (Siemens Healthcare Diagnostics, Marburg, Germany) on a CS5100 (Sysmex, Kobe, Japan) Factor VIII (FVIII) levels were measured using standard one-stage APTT-based clotting factor assays. Protein C activity and protein S (PS) free levels were measured using HemosIL. Prochrom and HemosIL free protein S tests, respectively. All assays were performed, following the 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 (LA) using DVT test (BioMedica Diagnostics, Windsor, Canada) and the silica clotting time test (HemosIL).

Antithrombin (AT) activity levels were measured using Berichrom chromogenic assays (Siemens) on a Sysmex CS-2000i system (Sysmex), following the manufacturer’s instructions. Both assays were calibrated using an SHP calibrator (Siemens Healthineers, UK). Factor V Leiden and prothrombin 3’ untranslated region (PT 3’ UTR) mutations were identified using a real-time polymerase chain reaction (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 troponin T (TnT) were measured concurrently and analyzed in an accredited United Kingdom laboratory by standard methods (XE-2100 Sysmex Corporation, Kobe, Japan; ECLIA Roche Diagnostics, Mannheim, Germany).11,12

In keeping with UK clinical guidelines, patients admitted to hospital were given subcutaneous low molecular weight heparin, median dose 4500 IU/day (Tinzparin [Innohep®], Leo Pharma, UK) as standard of care.

2.1 | Statistical analysis

Results are expressed as mean ± standard deviation, or median and interquartile range, or percentage. Standard statistical analyses were used: D’Agostino & Pearson normality test, chi-square, and anova with appropriate post-hoc Bonferroni or Games-Howell correction. Statistical analysis was performed using Graph Pad Prism (version 9.0, 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.
3 | RESULTS

Routine coagulation screens including PT, INR, APTT, Clauss fibrinogen, and D-dimer part of the trust care bundle were measured in 223 out of 227 dialysis patients, 206 (90.7%) hemodialysis, and 17 peritoneal dialysis, who tested positive for Covid-19, 148 males (65.2%), median age 67.5 (53.8–77.0) year. Two patients voluntarily withdrew from dialysis, one patient with dementia received palliative care, and one peritoneal dialysis (PD) patient was quarantined at home. Ninety-three (41.7%) patients did not require hospital admission and 62 (27.8%) patients died. A full thrombophilia screen, including factor VIII levels were, available in 158 (69.6%) patients.

To analyze the data, we divided patients into four groups: those who survived and did not require hospital admission for their COVID-19 infection and were managed at home as outpatients (home survivors); those who survived but had more severe symptoms and required acute hospital admission but without ventilation (hospital survivors); and those who survived acute hospital admission but required ventilatory support (14 patients [6.2%]) (ventilated survived); and those who died (non-survivors) (Table 1). Non-survivors were older, and those who died had higher CRP, TnT, NTproBNP, and ferritin levels compared to those who survived and did not require hospital admission. PT, Clauss fibrinogen, TT, D-dimer measured as part of the routine coagulation screen did not differ between groups, apart from the APPT which was prolonged in the non-survivors (Table 1).

Results of full prothrombotic screens were available in 158 (69.6%) of patients, and there were no differences in the natural anticoagulants, proteins C, and S, but AT was lower in those patients who died. In terms of prothrombotic tendency, three patients were found to have factor VLeiden, and two patients tested positive for lupus anticoagulant (Table 2). FVIII levels increased with disease severity (Figure 1).

Dialysis patients with COVID-19 who required hospital admission had higher CRP values, along with ferritin, troponin, and NT-proBNP and total peripheral white blood cell counts, but lower lymphocytes. However, there were no differences in these blood tests in those who required ventilation and survived compared to those who died.

The majority of patients had a normal PT/INR, although more patients who died or required hospitalization for COVID-19 had an increased APTT and TT (Table 3). The majority of all patients had an increased

| TABLE 1 | Patient demographics and standard laboratory profiles taken after a positive polymerase chain reaction for SARS-CoV-2 result |
|----------------|-------------------------------------------------|------------------|------------------|------------------|
|               | Home survived | Hospital survived | Ventilated survived | Non-survivors |
| Number (%)    | 93 (58.1)     | 58 (67.2)         | 9 (64.3)          | 46 (74.2)      |
| Male (%)      | 54            | 39 (60)           | 9 (63)            | 46 (75)        |
| Age (years)   | 60 (50–75)***| 66 (50–77)**      | 61 (55–70)*       | 75 (65–82)     |
| Hb (g/dl)     | 11.9 (9.9–11.8)| 11.1 (9.7–11.7)  | 7.9 (7.8–9.9)     | 10.3 (9–11.6)  |
| WBC (x10^9/L) | 5.4 (4.2–7.0)* | 6.1 (4.7–8.2)    | 10.5 (3.7–12.1)   | 7.6 (5.4–9.7)  |
| PMN (x10^9/L) | 3.4 (2.6–4.8)** | 5.1 (3.3–6.9)   | 7.7 (2.9–10.5)    | 5.6 (4.2–8.3)  |
| PBL (x10^9/L) | 1.04 (0.68–1.46)** | 0.67 (0.5–0.95) | 0.69 (0.4–0.83) | 0.54 (0.32–0.81) |
| Plts (x10^9/L) | 187 (153–234) | 182 (152–250)    | 180 (133–255)    | 171 (118–226)  |
| CRP (mg/L)    | 14 (4–33)**   | 49 (22–107)*     | 63 (42–142)       | 127 (87–235)   |
| NT-proBNP (ng/L) | 3333 (1511–12071)** | 9982 (2348–45510) | 12059 (2819–36105) | 17092 (4929–34891) |
| TnT (ng/L)    | 60 (34–87)*   | 118 (65–178)     | 157 (140–363)    | 163 (111–313)  |
| Ferritin (ug/L) | 627 (342–1038)* | 1216 (648–2146) | 976 (657–2687) | 1444 (924–2665) |
| PT (s)        | 11.3 (10.7–12.1) | 11.9 (11–13.2) | 11.8 (10.5–13.2) | 11.8 (11.1–13.2) |
| INR           | 1.0 (1.0–1.1) | 1.1 (1.0–1.2)    | 1.0 (1–1.2)       | 1.1 (1.0–1.2)  |
| APTT (s)      | 32.8 (30.2–36.7)* | 36.4 (31–41)    | 32.1 (28.2 (39)  | 37.8 (32.1–43.6) |
| TT (s)        | 15.1 (14–17.6) | 18.3 (15.7–22.4) | 16.9 (14.4–19.5) | 19.7 (17.3–21.9) |
| Clauss fibrinogen (g/L) | 4.5 (3.5–5.5) | 5.4 (4.7–6.0) | 5.5 (4.6–6.1) | 5.4 (4.6–6.1) |
| D-dimer (ng/ml)| 1228 (632–1716) | 1400 (840–2634) | 5651 (2654–10216) | 2355 (1060–5779) |

Note: Data expressed as integer, percentage, median (interquartile range).
Abbreviations: APTT, activated partial thromboplastin time; CRP, C-reactive protein; Hb, hemoglobin; INR, international normalized ratio; NT-proBNP, N terminal probrain natriuretic peptide; PBL, lymphocytes; Plts, platelets; PMN, polymorphonuclear cells; PT, prothrombin time; TnT, troponin T; TT, thrombin time; WBC, total white blood cells.

*p < 0.05 versus non-survivors; **p < 0.01 versus non-survivors; ***p < 0.001 versus non-survivors.
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Clauss fibrinogen and D-dimer, and normal levels of the natural anticoagulants, AT, PS, and PC. Although there was a trend for more patients who died to have lower AT levels. The majority of patients admitted to hospital had increased FVIII and reduced peripheral lymphocyte counts, whereas there were no differences in the number of patients with thrombocytopenia (Table 1).

4 | DISCUSSION

Infection with COVID-19 has been reported to be associated with an increased risk of both arterial and venous thromboembolic events. In terms of routine laboratory coagulation testing, we found that although the PT/INR was within the normal reference range, the majority of our dialysis patients requiring hospital admission due to COVID-19 infection had prolonged APTT and TT times. Although this could reflect standard practice to administer prophylactic low molecular weight heparin to prevent deep venous thrombosis in hospitalized patients, around one third of non-hospitalized patients also had increased APTT and TT times. Nearly all patients had elevated D-dimers, and the majority had raised Clauss fibrinogen levels. It is well recognized that inflammation, particularly inflammation driven by sepsis, not only leads to the initiation but also the propagation of coagulation activity, as inflammation can result in prolongation of the APTT through cross talk with complement and activation of factors XII and XI. In addition, coagulation can equally influence the inflammatory reaction.

We noted that patients with more severe disease associated with COVID-19 had higher peripheral leukocyte counts, serum CRP, NT-proBNP, TNT, and ferritin, with lower peripheral lymphocyte counts, in keeping with a greater inflammatory reaction. Although NT-proBNP is often considered as a biomarker of heart failure, NT-proBNP has also been shown to be increased by inflammation. Similarly, troponins which are used to aid the diagnosis of acute myocardial ischemia have also been reported to be increased in cases of COVID-19, raising the question of viral associated myocarditis. However, TnT may also be increased in cases of sepsis and associated systemic inflammatory response, with a pro-coagulant tendency.

Patients may be at increased risk of thrombosis due to underlying pre-existing prothrombotic conditions. However, we only detected three patients with factor V Leiden and no patients with a PTR-3’UTR mutation. Two patients tested positive for lupus anticoagulant, but neither patient was retested to determine whether this was pre-existing or secondary to inflammation caused by COVID-19 infection could not be determined.

Inflammation can reduce the endothelial-associated anticoagulant pathways, in particular the protein C

### TABLE 2 Natural anticoagulants and prothrombotic screen results

|                  | Home survived | Hospital survived | Ventilated survived | Non-survivors |
|------------------|---------------|-------------------|---------------------|--------------|
| AT (IU/dl)       | 93 (85–103)*  | 94 (84–111)*      | 95 (83–120)         | 84 (71–89)   |
| PC (IU/dl)       | 88 (86–109)   | 92 (89–94)        | 99 (87–148)         | 85 (75–99)   |
| PS (IU/dl)       | 72 (59–84)    | 72 (59–86)        | 64 (55–73)          | 63 (49–76)   |
| Lupus anticoagulant | 1           | 0                 | 0                   | 1            |
| Factor V Leiden  | 1             | 1                 | 1                   | 0            |
| PTR-3’UTR        | 0             | 0                 | 0                   | 0            |

Note: Data expressed as integer, median (interquartile range).

Abbreviations: AT, Antithrombin; PC, protein C; PS, protein S; PTR 3’-UTR, prothrombin 3′ untranslated region.

*p < 0.05 versus non-survivors.
However, we found no differences in PC levels between those patients who did not require hospitalization, those hospitalized, and those who died. Similarly, we found no differences in PS-free levels, and although the majority of patients had AT levels within normal range, more patients who died had lower levels of AT compared to those who did not require hospitalization. This is in keeping with lower AT levels reported in patients with increasing severity of sepsis and sepsis syndrome. As heparins covalently bind to AT, then heparin may be a less effective systemic or extracorporeal anticoagulant in patients with reduced AT concentrations, which would be in keeping with increased circuit clotting in patients with acute kidney injury treated with continuous renal replacement therapy in patients with very low concentrations of AT. However, as 75% of our patients had an AT concentration of 88 IU/dl and above (reference range 79–106 IU/dl), then none of our patients had sufficiently low levels of AT to reduce the effectiveness of heparin anticoagulation. The great majority of our patients had normal levels of natural anticoagulants. Although there was a trend for an increasing number of patients to have lower levels of AT with increasing disease severity, the levels of AT were not sufficiently low to affect anticoagulation with heparins for dialysis.

Factor VIII levels were increased (>175 IU/dl) in just over 40% of non-hospitalized patients and increased in the majority of those hospitalized. Previous reports have also noted increased FVIII levels in patients with COVID-19. This would suggest that greater clinical severity of disease with COVID-19 is associated with greater systemic inflammation, but also endothelial inflammation, as demonstrated by the release of FVIII, and it is recognized that elevated FVIII levels are associated with an increased risk of thrombosis.

Whereas we found that the majority of or dialysis patients with COVID-19 had increased D-dimers and Clauss fibrinogen irrespective of clinical disease severity. Patients with the most severe disease and those who died had greater evidence of systemic inflammation with greater CRP, NTproBNP, and TnT, but also higher FVIII levels. This would suggest that the increasing severity of COVID-19 is associated with greater endothelial dysfunction, which predisposes to the increased risk of thrombotic disease.

Although endothelial dysfunction can explain an excess of venous thrombosis or de novo pulmonary thrombosis, more severe COVID-19 infections appear to result in systemic inflammation and hypercoagulability that potentially increases the risk of clotting in dialysis or continuous renal replacement circuits. However, as natural anticoagulants, in particular, AT were not suppressed, then anticoagulation with heparin should not be compromised.

**CONFLICT OF INTEREST**

The authors have no conflict of interest.

**AUTHOR CONTRIBUTIONS**

AR: laboratory sample analysis, critical revision, final approval. PC: design, data interpretation, critical revision, final approval. AD: data analysis, drafting article, final approval.
ETHICS APPROVAL
This study complied with UK National Research Ethical standards for clinical practice development and audit, with data collected as part of NHS ethics committee 20/SW/0077, with all data appropriately anonymized.

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