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ORIGINAL ARTICLE

Infection

Late thrombotic complications after SARS-CoV-2 infection in hemodialysis patients

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Abstract

Introduction: There is an increased risk of thrombotic complications in patients with COVID-19. Hemodialysis patients are already at an increased risk for thromboembolic events such as stroke and pulmonary embolism. The aim of our study was to determine the incidence of late thrombotic complications (deep vein thrombosis, pulmonary embolism, stroke, new-onset vascular access thrombosis) in maintenance hemodialysis patients after recovery from COVID-19.

Methods: We performed a retrospective cohort study of 200 prevalent hemodialysis patients in our center at the start of the pandemic. We excluded incident patients after the cohort entry date and those who required hemodialysis for acute kidney injury, and excluded patients with less than 1 month follow-up due to kidney transplantation or death from non-thrombotic causes.

Findings: One-hundred and eighty five prevalent hemodialysis patients finally met the inclusion criteria; 37 patients (17.6%) had SARS-CoV-2 infection, out of which 10 (27%) died during the acute phase of disease without evidence of thrombotic events. There was an increased risk of thrombotic events in COVID-19 survivors compared to the non-infected cohort (18.5% vs. 1.9%, $p = 0.002$) after a median follow-up of 7 months. Multivariate regression analysis showed that COVID-19 infection increased risk for late thrombotic events adjusted for age, sex, hypertension, diabetes, antithrombotic treatment, and previous thrombotic events (Odds Ratio (OR) 26.4, 95% confidence interval 2.5–280.6, $p = 0.01$). Clinical and laboratory markers did not predict thrombotic events.

Conclusions: There is an increased risk of late thrombotic complications in hemodialysis patients after infection with COVID-19. Further studies should

evaluate the benefit of prolonged prophylactic anticoagulation in hemodialysis patients after recovery from COVID-19.

KEYWORDS
chronic kidney disease, COVID-19, renal replacement therapy, stroke, thrombosis

INTRODUCTION

Since the emergence of the novel coronavirus SARS-CoV-2 in December 2019 in Wuhan, China,[1] it has been declared a pandemic by the World Health Organization and the European Centre for Disease Prevention and Control reports over 38 million cases of COVID-19 including over 1 million deaths worldwide as of October 15, 2020.[2] Spain has been one of the most affected countries by COVID-19, with over 900,000 reported cases including over 33,000 deaths as of the same date. The appearance of the pandemic has had a significant impact on patients with chronic kidney disease, particularly those on renal replacement therapy, with a high mortality rate especially in hemodialysis patients.[3] As of October 3, 2020, the COVID-19 Registry of the Spanish Society of Nephrology reported over 1090 cases infected by SARS-CoV-2 in patients on renal replacement therapy with hemodialysis, which would represent 5.2% of the total population on hemodialysis in Spain according to data from the 2018 Spanish registry for renal replacement therapy.[4]

Multiple studies have revealed an increased rate of thromboembolic complications in patients affected by SARS-CoV-2, including deep venous thrombosis, ischemic stroke, pulmonary embolism, and several cases reporting renal infarction.[5–11] Postmortem studies have revealed that in around 64%–86% of lung examinations had vascular damage and microthrombi.[12–14] It has been well established that a significant proportion of patients infected with SARS-CoV-2 suffer from several neurological manifestations.[15] Ischemic stroke is one of the main neurological manifestations that have been described in patients with COVID-19.[16]

It has been hypothesized that SARS-CoV-2 infection can activate the coagulation cascade and produce a hypercoagulable state through three mechanisms: (1) a direct endothelial infection produces endothelial dysfunction, (2) through immune activation that leads to the production of pro-inflammatory cytokines and complement activation that will further produce endothelial activation, and (3) through the downregulation of ACE2 receptors that will lead to an increased ANGII/ANG 1–7 ratio.[17]

The incidence of stroke[18,19] and pulmonary embolism[20] is already increased in patients receiving hemodialysis, with a high case-fatality rate. Therefore, we conducted a retrospective cohort study to determine the risk of thromboembolic events including ischemic stroke, deep venous thrombosis, and pulmonary embolism among prevalent hemodialysis patients after more than 6 months following infection with SARS-CoV-2, in comparison to those who did not get infected.

METHODS

Study population

This retrospective observational cohort study included all prevalent patients receiving hemodialysis attending Hospital Universitario Fundación Alcorcón Hemodialysis Unit and its satellite hemodialysis center Los Llanos, between February 25, 2020 and October 1, 2020, identified using the Hemodialysis Patient Record Registry of our center. Cohort entry was recorded as February 25, 2020 in patients already receiving hemodialysis (prevalent hemodialysis), since it was the date of the first case of COVID-19 reported in Madrid.

Patients who commenced maintenance hemodialysis after that date, patients temporally transferred from peritoneal dialysis, and patients treated with hemodialysis for acute kidney injury were all excluded. We also excluded those patients with <1 month of follow-up, due to either having received a kidney transplant or due to death from a non-thrombotic cause.

Clinical and demographic details at cohort entry were recorded, including presence of diabetes mellitus, hypertension, cause of kidney disease, past history of cardiovascular or cerebrovascular thrombotic events, and use of anticoagulant or antiplatelet treatment. We recorded those who had a positive nasopharyngeal swab test for SARS-CoV-2 by RT-PCR from the COVID-19 Registry and included clinical, laboratory, and radiological data during the infection. In the first week of May 2020 (May 4–8, 2020) we performed a serological screening (IgM and IgG) for SARS-CoV-2 to all patients in the hemodialysis unit. Those patients with positive IgG were considered to have passed the infection as asymptomatic and included in the infected cohort along those who had had positive RT-PCR.

After excluding those who died during the infective stage of COVID-19 without a documented thrombotic

complication, we then compared the surviving infected cohort to those who remained non-infected, recording any arterial or venous thrombotic complication (deep vein thrombosis, pulmonary embolism, acute ischemic attack, and stroke) during the following months from our electronic database, concluding the cohort study on October 1, 2020.

The study was conducted in accordance with the World Medical Association's Declaration of Helsinki; the Spanish Organic Law 3/2018, of December 5, 2018, on the Protection of Personal Data and Guarantee of Digital Rights. The Ethical Review Board of Hospital Universitario Fundacion Alcorcon approved the study and waived the requirement to obtain informed consent based on the observational design.

Outcomes

Thrombotic events are defined as the presence of a new clinical diagnosis of deep vein thrombosis, pulmonary embolism, acute ischemic attack or stroke during the study follow-up timeline. Imaging studies performed during the study period such as Doppler ultrasonography, chest and brain CT scans were reviewed for the presence of thrombotic complications, and included as thrombotic events. The time to first thrombotic complication in patients receiving hemodialysis was recorded from the time of diagnosis of SARS-CoV-2 in the case of infected patients, and from the time of onset of the study period (February 25, 2020) in the case of the non-infected cohort. Patients who developed vascular access thrombosis with a previous history of vascular access dysfunction (thrombosis or significant venous stenosis) were not considered as new thrombotic complications.

Statistical analysis

Baseline characteristics were compared using Student's t test, Mann-Whitney U test, chi-square test, or one-way ANOVA as appropriate. A multivariate logistic regression model was performed to identify significant independent risk factors for thrombotic events. Kaplan-Meier survival analysis was performed for time to first thrombotic event and for mortality in patients after excluding those who died during the infective stage of COVID-19. Follow-up data were available to October 1, 2020. Patient follow-up-was censored at renal transplantation or death from a non-thrombotic complication. All tests were two-sided, and a p value less than 0.05 was considered statistically significant. Data were analyzed with SPSS version 20 (IBM, Armonk, NY).

RESULTS

A total of 200 patients were prevalent in our maintenance hemodialysis program on February 25, 2020. During the first wave of the pandemic (from February 25, 2020 to May 10, 2020), 37 patients (17.6%) from our program were diagnosed with COVID-19. Twenty nine patients (78.4%) were diagnosed by a positive nasopharyngeal swab for SARS-CoV-2 by RT-PCR, performed due to the development of symptoms, out of whom 20 patients (69%) presented bilateral pneumonia and required hospitalization, and 9 patients developed mild symptoms without pneumonia and were managed as outpatients. Table S1 lists the demographic, clinical, laboratory, radiographic findings, and outcomes of hemodialysis patients with COVID-19. Eight additional patients (21.6%) were diagnosed by a positive serological test for IgG SARS-CoV-2 performed to the whole cohort of hemodialysis patients.

Of the 37 infected patients, 10 patients (27%) died from respiratory failure during the infective stage. None of the patients were documented to have any thrombotic complications. From the 163 remaining non-infected patients, 2 patients died from non-COVID related deaths (1 patient due to septicemia from soft tissue infection, 1 patient due to discontinuation of hemodialysis due to advanced dementia) and 3 patients received a kidney transplant during the first month of follow-up, and were excluded from the final analysis. Figure S1 shows a flow chart of the studied population. Median follow-up was 7 months.

Eight patients (4.3%) experienced 9 thrombotic events over a follow-up period of 104.2 patients-years; 7 patients had 8 episodes of ischemic stroke confirmed by brain imaging as part of the diagnostic evaluation, and 1 patient had pulmonary embolism. In the cohort of patients who had survived COVID-19, 6 thrombotic events occurred to 5 patients (18.5%) during the follow-up period, compared to 3 patients with thrombotic events (1.9%) in the non-infected cohort ($p = 0.002$). Stroke incidence was 38.9 episodes/1000 patient-years in patients infected with SARS-CoV-2, compared to an incidence of 2.8 episodes/1000 patient-years in non-infected patients during the follow-up period. The median time from diagnosis of SARS-CoV-2 to the first thrombotic event was 62 days (interquartile range 5–118 days). There were no differences in previous history of thromboembolic events nor in anticoagulant or antiplatelet treatments used between the two cohorts (see Table 1). Six patients in the non-infected cohort developed vascular access thrombosis, but they all had a previous history of vascular access dysfunction and were not included as new thrombotic events. Eight patients (4.3%) died during follow-up, with no differences

TABLE 1 Baseline characteristics of the total prevalent hemodialysis population and divided into those who got infected with SARS-CoV-2 and those who did not

	Whole cohort (n = 185)	COVID-infected (n = 27)	Non-infected (n = 158)	*p*
Age (years)	67.9 ± 14.1	74.0 ± 10.5	66.8 ± 14.4	0.003
Male sex (%)	117 (63.2%)	16 (59.3%)	101 (63.9%)	0.642
Hypertension (%)	134 (72.4%)	18 (66.7%)	116 (73.4%)	0.468
Diabetes mellitus (%)	70 (37.8%)	17 (63%)	53 (33.5%)	0.004
History of previous thromboembolic events	21 (11.4%)	4 (14.8%)	17 (10.8%)	0.367
History of vascular access thrombosis	39 (21.1%)	5 (18.5%)	34 (21.5%)	0.724
Vascular access thrombosis 6 months after pandemic	6 (3.2%)	0 (0%)	6 (3.8%)	0.383
Ongoing treatment				
Anticoagulants	43 (23.2%)	7 (25.9%)	36 (22.8%)	0.721
Antiplatelet drugs	75 (40.5%)	9 (33.3%)	66 (41.8%)	0.409
Thromboembolic complications	8 (4.3%)	5 (18.5%)	3 (1.9%)	0.002
Stroke	7 (3.8%)	4 (14.8%)	3 (1.9%)	0.009
Deep venous thrombosis	0 (0%)	0 (0%)	0 (0%)	—
Pulmonary embolism	1 (0.5%)	1 (3.7%)	0 (0%)	0.146
"Late" 6-month mortality	8 (4.3%)	3 (11.1%)	5 (3.2%)	0.094

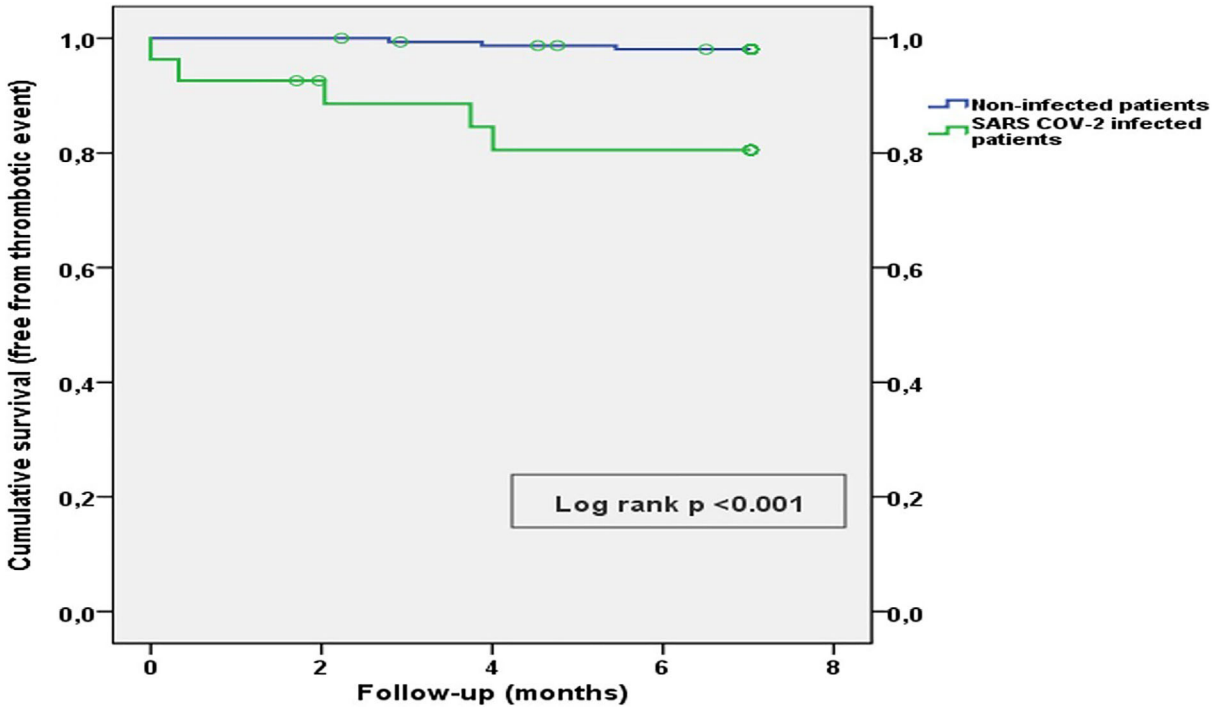

FIGURE 1 Kaplan-Meier survival curves for freedom from thrombotic events, stratified by COVID-19 infection status [Color figure can be viewed at wileyonlinelibrary.com]

between both groups. The patient who suffered two strokes in the COVID-infected cohort was the only one who died after a thrombotic event.

Survival analysis with Kaplan-Meier curves revealed an increase in the rate of thrombotic events after SARS-CoV-2 compared to non-infected patients (see Figure 1). Mean survival from thrombotic event was 6.1 ± 0.4 months in the COVID-infected group, compared to 6.97 ± 0.04 months in the non-infected group (Log rank χ^2 17.88, $p < 0.001$).

TABLE 2 Multivariate analysis for risk of developing thromboembolic events (ischemic stroke, pulmonary embolism)

		95% confidence interval		
	OR	Lower	Upper	*p*
SARS-CoV-2 infection	26.379	2.480	280.625	0.007
Male sex	1.932	0.235	15.901	0.540
Age	1.053	0.966	1.148	0.244
HTN	0.210	0.022	2.014	0.176
DM	1.125	0.112	11.314	0.921
Previous thrombotic events	47.211	4.389	507.8	0.001
Antiplatelet treatment	3.517	0.383	32.279	0.266

TABLE 3 Models for estimating risk of developing thromboembolic events following SARS-CoV-2 infection in hemodialysis patients

		95% confidence interval		
	OR	Lower	Upper	*p*
Crude	11.742	2.622	52.594	0.001
Model 1 (adjusted by age and sex)	9.823	2.133	45.238	0.003
Model 2 (adjusted by HTN and DM)	8.984	1.870	43.165	0.006
Model 3 (adjusted by previous thrombotic events and antiplatelet treatment)	27.864	3.543	219.161	0.002

A univariate analysis showed that patients with previous thrombotic events and those who had been infected with SARS-CoV-2 were at an increased risk of thrombotic events (Table S1). Multivariate regression analyses revealed that infections with SARS-CoV-2 (OR = 26.4, 95% confidence interval [CI] 2.5–280.6) and previous thromboembolic events (OR = 47.2, 95% CI 4.4–507.8) were significantly associated with the risk of developing a thrombotic event (Table 2). The association between SARS-CoV-2 and the risk of thrombosis persisted after adjusting in different models for variables such as age, sex, presence of hypertension, presence of diabetes, antiplatelet treatment, and previous thromboembolic events (see Table 3).

In the univariate analysis for risk factors predicting development of late thrombotic events after SARS-CoV-2, inflammatory markers such as LDH and C-reactive protein and procoagulant markers such as D-dimer and fibrinogen were not associated with an increased risk of developing a late thrombotic event. Antithrombotic treatment in SARS-CoV-2 infected patients was not associated with a decreased risk of thrombotic events (see Table 4).

DISCUSSION

COVID-19 increases the risk of microvascular and macrovascular thrombotic complications, and in its turn thrombotic events worsen the outcome of the disease.[21] Our study shows that there is an increased risk of thrombotic events in hemodialysis patients following infection with COVID-19 in the long run after resolution of the infection and hospital discharge.

Most of the studies that have reported thromboembolic events in patients with COVID-19 were in an inpatient setting, and usually critically ill patients were included. In most cases, these events occurred during the active phase. However, some articles have lately reported cases of venous thromboembolism after mild COVID-19, with some cases occurring in the convalescence phase after COVID-19 recovery, when the symptoms accompanying the acute illness have subsided. These cases are described usually after 15–20 days of remission of the acute illness.

Merkler et al. described that patients attending the emergency department or hospitalized for COVID-19 were seven times more prone to develop acute ischemic stroke than those attending the emergency department or hospitalized for influenza.[22] Yamakawa et al. reported that the average time for onset of stroke from the development of symptoms was 8 days, longer than that described in other respiratory tract infections[23] and more than half of the patients were diagnosed as having a cryptogenic stroke. Other studies corroborate the high incidence of cryptogenic stroke, with time to stroke ranging from 0 to 65 days after onset of symptoms.[24] In our study,

TABLE 4 Univariate analysis exploring predictive factors for developing a thromboembolic event after SARS-CoV-2 infection

	Thrombotic complication (n = 5)	No thrombotic complication (n = 22)	*p*
In-hospital admission	2 (40%)	11/22 (50%)	0.538
Pneumonia	1 (20%)	11/22 (50%)	0.240
Anticoagulant treatment	0 (0%)	7/22 (31.8%)	0.192
Antiplatelet treatment	3 (60%)	6/22 (27.3%)	0.189
Lymphocytes (/mcl)	720 ± 259	736 ± 531	0.921
Leukocytes (/mcl)	8880 ± 4281	5018 ± 2196	0.007
Fibrinogen (mg/dl)	645 ± 170	600 ± 110	0.581
D-Dimer (ng/ml)	5735.5 (1434.3–27128.5)	1341.5 (1010–1854.3)	0.127
LDH (U/L)	340 ± 161	283 ± 73	0.479
Hb (g/dl)	9.6 ± 1.8	10.4 ± 2.0	0.424
CRP (mg/l)	42 (27–269)	51.5 (16.3–111.5)	0.377
Ferritin (ng/ml)	711 (447.5–3611)	1272 (725.5–2378.5)	0.278

all cerebrovascular events occurred at a mean 46 days after diagnosis of COVID-19.

The pathogenesis of COVID-19-related hypercoagulable state is evolving. An intense and uncontrolled inflammatory response seen in some severe cases of COVID-19 appears to contribute to thrombosis, especially in the microvasculature due to thromboinflammation.[25] This inflammatory response causes damage to the vascular endothelium, compromising its thrombo-protective state.[26] Both, inflammation and endothelial injury activate the coagulation cascade, resulting in many of the coagulation abnormalities seen in SARS-CoV-2-infected patients.

However, in our study the classical laboratory features related to hyperinflammatory state such as elevated ferritin and LDH or procoagulant features such as elevated D-dimer and fibrinogen were not associated with an increased risk of thrombotic events.

COVID-19 coagulopathy is thought to be caused by the acute inflammatory systemic response to the virus and its products, characterized by an elevation of the inflammatory and coagulation markers previously described.[27] This is mediated by an increased production of cytokines and chemokines such as IL-1, IL-6, IL-10, IFN-γ and macrophage inflammatory proteins 1-α and 1-β.[28] In patients with additional predisposing factors, this coagulopathy could result in the development of in situ thrombotic complications such as pulmonary thrombosis or stroke. Recent findings in several studies agree in that hypercoagulability could explain the increased incidence of cryptogenic stroke of uncertain source.[29] Both microangiopathy and the activation of immune cells such as IL-1 and IL-6 are immune factors that are associated with respiratory distress syndrome, and may contribute synergistically to the risk of small and large vessel thrombosis both in early and late disease.

It has been reported that the nucleocapsid protein on several related coronaviruses, including SARS-CoV-2, can bind directly to MASP-2, a key protease in the lectin complement pathway.[30] This would explain complement activation found in some patients with COVID-19, regardless of whether they have a predisposition for abnormal complement responses.[31,32] The factors involved in the progression of SARS-CoV-2 infection into a spectrum of cytokine storm, microangiopathy, and respiratory distress syndrome might be both the viral load and the individual characteristics of the patient's immune response.[33,34]

Interestingly, none of the four patients who developed a stroke after COVID-19 had a history of atrial fibrillation or a cardioembolic cause was found, nor had they had previous thromboembolic complications, and the strokes were deemed to be cryptogenic. The patient who developed pulmonary embolism after COVID-19 did not present deep vein thrombosis. This would enforce the idea that in situ thrombosis caused by the procoagulant milieu induced by SARS-CoV-2 is the cause of the thrombotic events.

In view of the increased risk of thrombosis early in COVID-19 and the coagulation abnormalities, many studies have led to the consensus to start anticoagulation early in COVID-19 before the occurrence of thrombotic events. The risk-benefit ratio of this approach directed at treating presumed thrombosis as well as venous thromboembolisms detected by imaging studies is yet to be determined, and excessive bleeding might be an inevitable consequence of this approach. It has been previously described that anticoagulation with warfarin does not reduce the risk of stroke in hemodialysis patients with atrial fibrillation, while increasing the risk of bleeding complications.[35]

It is uncertain whether this excess hemorrhagic risk is surpassed by the increased patient survival associated with anticoagulation. We definitely believe that anticoagulation should not be the only treatment for these patients, and in some cases, coagulopathy develops when the disease progresses and it is too late to change the outcome. The close link between inflammation and thrombosis tends to indicate that a combined anti-inflammatory and anti-viral approach together with anticoagulation should be considered.

Klok et al. describe a subgroup of patients with COVID-19 who were on treatment with anticoagulant drugs at admission, and apparently were protected from developing thrombotic events, but on the other hand did not improve overall survival.[7] However, in our clinical experience there has been a proportion of patients who die after clinical improvement and discharge, and in our opinion this could be related to thrombotic events.

Limitations

This is a retrospective observational cohort study that is limited by the small number of events and hence, the results mainly indicate causal association of COVID-19 infection with acute thrombotic complications and cannot be ascertained. Further larger prospective studies should be conducted to confirm these results.

CONCLUSIONS

In our study, hemodialysis patients infected with SARS-CoV-2 are at an increased risk of developing late thrombotic events after recovery, in comparison to those patients who remain non-infected. Clinical and laboratory markers did not predict thrombotic events in these patients. Further studies should evaluate the benefit of a longer duration of prophylactic anticoagulation in hemodialysis patients even after recovery from COVID-19.

CONFLICT OF INTEREST

None declared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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