

Clotting of Hemodialysis Access in Patients with COVID-19 in an Inner-City Hospital

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Keywords

Coronavirus disease 2019 · Coronavirus · Hemodialysis · Access · Catheter · Clotting

Abstract

Background: An increased incidence of thrombotic complications in patients with coronavirus disease 2019 (COVID-19) has been reported. Severe acute kidney injury (AKI) is one of the major clinical manifestations of COVID-19 with the need for renal replacement therapy. It was observed that hemodialysis (HD) accesses tended to thrombose more often in the COVID-19 population than in non-COVID-19 patients. We hypothesize that the hypercoagulable state of COVID-19 is associated with higher incidence of access clotting. **Method:** In this retrospective single-centered study at Kings County Hospital in New York City, 1,075 patients with COVID-19 were screened, and 174 patients who received HD from January 3, 2021 to May 15, 2020 were enrolled to examine the risk factors of dialysis access clotting in patients with COVID-19. **Results:** Of the 174 patients, 109 (63%) were COVID-19 positive. 39 (22.6%) patients had dialysis access clotting at least once during their hospitalization, and they had significantly higher body mass index (BMI) ($p = 0.001$), high-

er rates of COVID-19 ($p = 0.015$), AKI ($p < 0.001$), higher platelet counts ($p = 0.029$), higher lactate dehydrogenase levels ($p = 0.009$), and lower albumin levels ($p = 0.001$) than those without access malfunctions. Low albumin levels ($p = 0.008$), AKI ($p = 0.008$), and high BMI ($p = 0.018$) were risk factors associated with HD access clotting among COVID-19 patients. **Conclusion:** Patients with COVID-19 who receive HD for AKI with high BMI are at a higher risk of clotting their HD access.

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Introduction

Early reports of complications in patients with coronavirus disease 2019 (COVID-19) suggested an increased incidence of thrombotic events [1, 2]; among such patients admitted to intensive care units (ICUs), thrombotic events were 31% higher than expected [3]. Multiple mechanisms were hypothesized, including endothelial injury [4], immunothrombosis [5], and coagulation abnormalities [6]. Although the precise mechanisms remain unclear, many studies of COVID-19 patients have observed a hypercoagulable state [7], which leads to increased incidence of both arterial and venous thromboses, as well as organ is-

chemia. Coagulopathy is independently associated with increased mortality in COVID-19 patients [6]. Cui et al. [8] noted that the incidence of venous thromboembolism (VTE) in patients with COVID-19 pneumonia was 25% ($n = 20/81$), with a high mortality in this subgroup. Most studies indicated some mortality benefit of heparin use in the patients with COVID-19, at least in those with more severe disease [6, 9, 10].

Acute kidney injury (AKI) is one of the major clinical manifestations of COVID-19. Patients with severe AKI require renal replacement therapy (RRT), typically through hemodialysis (HD) or continuous RRT; we noticed that the HD access tended to thrombose more often in the COVID-19 population in our practice, a finding that was also revealed recently by Karina et al. [11]. In order to understand this phenomenon, we present this study to assess the increased risk of clotting dialysis access in this population. We hypothesized that the hypercoagulable state of COVID-19 is associated with a higher incidence of HD access clotting. We expect to determine potential risk factors of hypercoagulability and the tendency of HD access clotting by examining variable characteristics of patients with and without COVID-19 who required RRT for either severe AKI or end-stage renal disease (ESRD) during the early phase of the COVID-19 pandemic.

Methods

This is a retrospective single-center study at Kings County Hospital (KCH), an inner-city hospital in New York City. KCH had 45 ICU beds that were expanded to approximately 150 ICU beds for COVID-19. This study was approved by the Institutional Review Board at SUNY Downstate Medical Center and New York City Health and Hospital Corporation.

3,665 patients were hospitalized in KCH between March 1st and May 15th, 2020, of whom 1,075 had laboratory-confirmed COVID-19 during their admission. We extracted medical record data from the charts of those who required HD because of either severe AKI or ESRD during this time period.

We identified potential study participants using the *Epic* EHR analytics platform *SlicerDicer*. The inclusion criteria were as follows: 1. Patients who were older than 18 years; 2. patients who were admitted to KCH from March 1st to May 15th; 3. patients who had received HD. Patients who met the inclusion criteria were automatically enrolled with a full waiver of written consent approved by both SUNY Downstate and New York City Health and Hospital Corporation institutional review boards.

These patients' charts were manually reviewed, including notes, medications, records of interventional procedures and HD, and laboratory results. We examined the incidence of HD access malfunction and patient characteristics to discover risk factors of dialysis access clotting. The primary outcome was the clotting of

HD access in those who were diagnosed with COVID-19 and those without COVID-19. The diagnosis of COVID-19 was by laboratory RNA polymerase chain reaction confirmation and/or clinical manifestation of viral pneumonia with high levels of inflammatory factors and severe hypoxia. HD access failure was diagnosed by persistent significant decrease in blood flow preventing continuing HD, regardless of repositioning, change of the tunneled or nontunneled catheter, or the use of tissue plasminogen activator in the catheter. Arteriovenous fistula (AVF) or graft (AVG) failure was diagnosed by a significant decrease in blood flow that led to HD cessation, a new tunneled/nontunneled catheter placement, or other clinical findings indicative of AVF/AVG malfunctioning. All malfunctioned dialysis accesses were examined and reported by dialysis nurses, confirmed by nephrology fellows, and attending physicians.

Statistical Analysis

We analyzed the descriptive statistics of the included patients' demographic features, medical history, in-hospital laboratory results, treatments administered, and outcomes during current admission. We compared these variables between patients with HD access clotting and those without using Fisher's exact test for categorical variables or Wilcoxon's rank-sum test for continuous variables. We chose these nonparametric tests as most groups of the dataset were not normally distributed.

To determine clotting risk factors within the COVID-19-positive patients' group, we selected variables that were significantly different in the 2 subgroups in Table 1 for the logistic regression test using the stepwise strategy. We removed D-dimer from the analysis in order to maximize the sample size due to a large number of missing data of D-dimer values. 109 patients with COVID-19 were included in this analysis. The statistical analysis was all conducted using R software (version 3.6.3).

Results

We compared data during the early phase of the pandemic to a historical control that was 2 months earlier in 2020 and noticed a significantly increased rate of AKI and incidence of dialysis access failure. From December 16th to February 29th, 2020, there were totally 97 admitted patients who received HD, with 3 patients (3.1%) being diagnosed with AKI that required HD, and 8 out of these 97 patients (8.2%) developed dialysis access malfunctioning. While 174 patients received HD from March 1st to May 15th, 2020, ninety-two patients received RRT (mostly intermittent HD) because of severe AKI (52.0%), and 122 patients (70.1%) received dialysis via tunneled or nontunneled catheters. Thirty-nine out of 174 patients (22.6%) experienced dialysis access clotting at least once during hospitalization. Eight of the 39 patients (20.5%) had ESRD, and 2 of them (25%) experienced AVF and AVG failure. Seventy-four patients (42.5%) had died by the time of data collection in July 2020.

Table 1. Characteristics of patients received hemodialysis between March 1 to May 15, 2020

	Total sample 174 (100%) <i>n</i> (%) / mean (SD)	Patients with access clotted 39 (22.4%) <i>n</i> (%) / mean (SD)	Patients without access clotted 135 (77.6%) <i>n</i> (%) / mean (SD)	<i>p</i> value	Missing numbers
Demographic					
African American	148 (85.1)	33 (84.6)	119 (85.2)	0.832	0
Male gender	108 (62.1)	24 (61.5)	84 (62.2)	1.000	0
Age	62.6 (12.7)	62.4 (11.6)	62.7 (13.0)	0.759	0
BMI	29.4 (7.7)	33.1 (8.6)	28.3 (7.1)	0.001	4
Medical history					
Diabetes	112 (64.4)	27 (69.2)	85 (63.0)	0.57	0
Hypertension	149 (85.6)	31 (79.5)	118 (87.4)	0.298	0
Asthma and/or COPD	24 (13.8)	3 (7.7)	21 (15.6)	0.294	0
Cancer	12 (6.9)	3 (7.7)	9 (6.7)	0.733	0
Antiplatelet or anticoagulant medication	67 (38.5)	16 (41.0)	51 (37.8)	0.713	0
Hospitalization					
COVID-19-positive laboratorial and clinical	109 (62.6)	31 (79.5)	78 (57.8)	0.015	0
AKI	91 (52.3)	31 (79.5)	60 (44.4)	<0.001	0
D-dimer levels (×1,000)	13.6 (2.0)	15.5 (1.9)	12.9 (2.0)	0.048	58
Lowest albumin levels	2.67 (0.76)	2.34 (0.62)	2.77 (0.78)	0.001	0
Platelet × 1,000	219.8 (104.4)	237.1 (86.7)	214.8 (108.8)	0.029	0
PT	14.23 (5.27)	13.29 (1.98)	14.54 (5.95)	0.2	29
INR	1.25 (0.46)	1.14 (0.21)	1.28 (0.51)	0.132	29
LDH	744 (543)	900 (540)	689 (536)	0.009	40
Ferritin × (100)	15.6 (7.7)	16.7 (8.8)	15.2 (7.2)	0.496	28
Mechanical ventilation	48 (27.6)	5 (12.8)	43 (31.9)	0.024	0
Received heparin therapy via any route	84 (48.3)	30 (76.9)	54 (40.0)	<0.001	0
Hydroxychloroquine therapy	96 (55.2)	28 (71.8)	68 (50.4)	0.019	0
Outcome					
Mortality	74 (42.5)	19 (48.7)	55 (40.7)	0.583	0

BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; PT, prothrombin time; INR, international normalized ratio; LDH, lactate dehydrogenase; AKI, acute kidney injury.

Bivariate correlation of all variables was analyzed. COVID-19 diagnosis and hydroxychloroquine use were strongly correlated as expected ($\rho = 0.713$, $p < 0.01$).

As shown in Table 1, the majority of the research subjects were African American (85.1%), male (62.1%), older (62.6 ± 12.7), and slightly overweighted (29.4 ± 7.7). The most common medical history included hypertension (85.6%) and diabetes mellitus (64.4%). 109 patients (62.6%) manifested COVID-19 infection. When those whose HD access clotted were compared to the patients who had no dialysis access failure, a higher body mass index (BMI) ($p = 0.001$), a higher rate of COVID-19 infection ($p = 0.015$), and more AKI cases ($p < 0.001$) were noticed. Higher D-dimer levels (although 58 patients had missing data) ($p = 0.048$), lower albumin levels ($p = 0.001$), higher platelet levels ($p = 0.029$), higher lactate hydroxylase levels ($p = 0.009$), less mechanical ventilation usage

Table 2. Correlations between AKI and lowest albumin levels

	Coefficient	<i>p</i> value
AKI and lowest albumin levels	-0.651	0.000

AKI, acute kidney injury.

($p = 0.024$), higher chance of heparin ($p < 0.001$), and hydroxychloroquine therapy ($p = 0.019$) were also associated with an increased risk of HD access failure. There was no significant difference of the mortality rate in these 2 groups.

In the COVID-19 patients' group, when the potential mechanisms of the hypercoagulable state of COVID-19 were examined, very interesting results were noticed in

Table 3. The potential risk factors for clotting in COVID-19 patients

	Coefficient	Adjusted odds	95% CI		p value
BMI	0.07	1.07	1.01	1.13	0.018
Hypertension	-1.17	0.31	0.10	0.99	0.046
Platelet*100	0.43	1.53	0.94	2.48	0.085
LDH*1,000	0.15	1.16	0.52	2.64	0.697
*AKI	1.55	4.72	1.60	16.30	0.008

AKI, acute kidney injury; LDH, lactate dehydrogenase; COVID-19, coronavirus disease 2019; BMI, body mass index. * When AKI is replaced by lowest albumin levels, the analysis yields the same statistically significant risk factors, and the p value for lowest albumin levels is also 0.008.

Tables 2 and 3. AKI and low albumin levels were significant risk factors when they fit in the model separately; however, they were not significant when both of them were included in the same model. Analysis confirmed significant correlation between AKI and low albumin levels, which explains this interesting finding. Meanwhile, higher BMI and history of hypertension remained significant, suggesting association with developing HD access clotting.

Discussion

This retrospective single-center study found a significantly increased rate of clotting of HD access in hospitalized patients who had COVID-19. Clotting was not only limited to catheters but also affected AVF and AVG. Strikingly, within the COVID-19 patients' group, severe AKI requiring HD as well as higher BMI were independent factors that strongly associated with access malfunction. Patients who presumably were on maintenance HD for ESRD via tunneled catheter or AVF/AVG had a lower rate of access complications; notably, only 2 patients with AVF and AVG had access malfunction (which ultimately required tunneled dialysis catheter placement after a failed intervention). These findings are consistent with other data in patients with COVID-19 and renal failure that have reported a high rate of clot formation in the extracorporeal circuit used for continuous RRT and a 50% shortened circuit patency [12, 13].

In critically ill patients with AKI requiring HD in prior studies before the pandemic, rates of thrombotic catheter malfunction were quite low. The incidence rate of non-tunneled HD access complications in our historical data is similar to that of these studies [14, 15]. Our analysis suggests that among all study participants who received HD, COVID-19 specifically but not AKI resulted in

thrombotic dialysis complications; Meanwhile, several prior studies [16, 17] investigating thrombotic events in COVID-19 patients did not report acute renal dysfunction as a significant risk factor; only one small study of large vessel thromboses in patients with COVID-19 found that 10 out of 21 such patients had AKI. Although the mechanism is not yet clarified, COVID-19 was a major risk factor for the access clotting in our analysis, which was also noted in other studies [6]. The reasons why COVID-19 patients with AKI required dialysis had a higher rate of access malfunction than ESRD patients with COVID-19 are unclear [18]. While studies investigated only native vessel thromboses, we had a more inclusive definition of clotting events effecting dialysis catheters. We speculate that the apparent hypercoagulable state in patients with COVID-19 may particularly effect intravascular foreign bodies such as dialysis catheters.

As we report 2 cases of AVF and AVG dysfunction in this time period, a survey of 255 ESRD patients with COVID-19 found 17 cases of AVF and AVG thromboses, suggesting that while the risk is reduced in ESRD patients, it is still quite substantial [19].

In our analysis, we noted a higher rate of administration of heparin including intra-catheter, intra-venous, and subcutaneous administration in the group of patients who had HD access clotting. It is more likely that the hyper-coagulopathy or HD access clotting was noticed before active anticoagulation therapy was initiated in this group.

Interestingly, a recent multicenter study noted that early initiation of anticoagulation did not improve survival in those critically ill patients with COVID-19 [20], although autopsy data suggest immune-thrombotic dysregulation with microthrombi formation in those with COVID 19 critical illness [5]. A possible explanation may be that the prophylactic dose of heparin might not be adequate.

Obesity has been associated with worse outcomes with AKI in critical illness [21–23], and it was included in a

COVID-19 scoring system for predicting worse outcomes [24]. In our analysis, higher BMI persisted in contributing to access clotting. It is unclear how it contributed to the worse outcome or hypercoagulability among patients on HD, yet it remains important to reveal the mechanism as it is a modifiable risk factor and a potential indication for aggressive anticoagulation therapy, which can possibly improve patient outcomes.

In our study, hypoalbuminemia is a factor being co-linear with AKI which was associated with HD access malfunction among patients with COVID-19. Hypoalbuminemia has been connected with worse outcomes in patients with COVID-19 in a meta-analysis [25] and in studies of critically ill patients prior to the pandemic. Low albumin may be predictive of development of mortality following AKI [26]. Studies have suggested that in the general population, hypoalbuminemia may be associated with increased risk for VTE [27, 28]. In Brosnahan et al.'s [16] investigation of patients with COVID-19, similar association between low albumin and increased risk for a thrombotic event was also noticed. A recent pilot study [29] also hypothesized albumin supplementation may be beneficial in reducing the risk of hypercoagulability in patients with COVID-19; unfortunately, no clear conclusions could be drawn due to the small sample size. These results and hypotheses suggest a research opportunity on the mechanism of hypercoagulability among COVID-19 patients, especially those who develop severe AKI, and a potential treatment by improving the albumin level.

This is one of the very few studies that evaluated increased incidence of HD access clotting in patients with COVID-19. The limitations of the presenting study include that the majority of enrolled patients are of a single race/ethnicity; it is a retrospective chart review from a single-center.

Conclusion

In conclusion, patients with COVID-19 are at a higher risk of clotting their HD access. Having a higher BMI is associated with a higher risk of HD access clotting regardless of COVID-19. Albumin played an important role in HD access clotting among patients with COVID-19. The incidence of access clotting is higher among patients who suffered from severe AKI caused by COVID-19. Further studies are needed to determine the mechanism of hypercoagulopathy in order to effectively prevent thromboses and decrease mortality of COVID-19.

Statement of Ethics

This is a retrospective study. All data were collected via chart review. A full waiver of written or oral consent was granted by SUNY Downstate Healthy Science University IRB and NYC Health + Hospital IRB.

Conflict of Interest Statement

None of the authors have any disclosures that are relevant to the study and manuscript.

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Author Contributions

All listed authors meet at least 4 of the following criteria for authorship: conception or design of the work, data collection, data analysis and interpretation, drafting the article, critical revision of the article, final approval of the version to be published, and ensuring the accuracy or integrity of the research work.

Data Availability Statement

The de-identified data used for analysis in this manuscript are saved in the NYCHHC KCH server. It will not be publicly available due to the NYCHHC IRB's requirement, but it can be provided via an encrypted email for review upon reasonable request. Further inquiries can be directed to the corresponding author.

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