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Malfunctioning temporary hemodialysis catheters in patients with novel coronavirus disease 2019

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ABSTRACT

Objective: The hypercoagulability seen in patients with novel coronavirus disease 2019 (COVID-19) likely contributes to the high temporary hemodialysis catheter (THDC) malfunction rate. We aim to evaluate prophylactic measures and their association with THDC patency.

Methods: A retrospective chart review of our institutions COVID-19 positive patients who required placement of a THDC between February 1 to April 30, 2020, was performed. The association between heparin locking, increased dosing of venous thromboembolism (VTE) prophylaxis and systemic anticoagulation on THDC patency was assessed. Proportional hazards modeling was used to perform a survival analysis to estimate the likelihood and timing of THDC malfunction with the three different prophylactic measures. We also determined the mortality, rate of THDC malfunction and its association with D-dimer levels.

Results: A total of 48 patients with a mortality rate of 71% were identified. THDC malfunction occurred in 31.3% of patients. Thirty-seven patients (77.1%) received heparin locking, 22 (45.8%) received systemic anticoagulation, and 38 (79.1%) received VTE prophylaxis. Overall, the rate of THDC malfunction was lower at a trend level of significance, with heparin vs saline locking (24.3% vs 54.6%; $P = .058$). The likelihood of THDC malfunction in the heparin locked group is lower than all other groups (hazard ratio [HR], 0.07; 95% confidence interval [CI], 0.01-0.45; $P = .005$). The rate of malfunction in patients with subcutaneous heparin (SQH) 7500 U three times daily is significantly lower than of the rate for patients receiving none (HR, 0.03; 95% CI, 0.001-0.74; $P = .032$). A trend level significant association was found for SQH 5000 U vs none ($P = .417$) and SQH 7500 vs 5000 U ($P = .059$). Systemic anticoagulation did not affect the THDC malfunction rate ($P = .240$). Higher D-dimer levels were related to greater mortality (HR, 3.28; 95% CI, 1.16-9.28; $P = .025$), but were not significantly associated with THDC malfunction (HR, 1.79; 95% CI, 0.42, 7.71; $P = .434$).

Conclusions: Locking THDCs with heparin is associated with a lower malfunction rate. Prospective randomized studies will be needed to confirm these findings to recommend locking THDC with heparin in patients with COVID-19. Increased VTE prophylaxis suggested a possible association with improved THDC patency, although the comparison lacked sufficient statistical power. (*J Vasc Surg* 2021;73:1881-8.)

Keywords: COVID-19; Coronavirus; Acute kidney injury; Heparin locking; Dialysis catheter

Since the emergence of the severe acute respiratory syndrome novel coronavirus 2 (COVID-19) in Wuhan China in December 2019, there has been a rapid focus throughout the medical community on its pathophysiology and management. Acute kidney injury (AKI) is present in about 0.5%¹ to 7.0%² of COVID-19 cases and in 23%³ to 29%⁴ of critically ill patients, with an increase in in-hospital mortality.⁵ In the 2003 severe acute

respiratory syndrome outbreak, from the same coronavirus family, AKI was found to be a fatal complication in 92% of the patients.⁶

A subset of patients with COVID-19 with AKI require acute hemodialysis (HD). Temporary HD catheters (THDC) are the mainstay in these patients given the acute requirement for HD. As many as 96% of patients with COVID-19 experience dialysis circuit clotting.⁷ Reports out of China and other nations confirmed a hypercoagulability in patients with COVID-19.^{7,8} The hypercoagulability is mediated by inflammation from the viral infection causing cytokine and tissue factor release, leading to an increase in the levels of circulating thrombin.⁹

Currently, there is a paucity of data and guidelines to address the problem of dialysis catheters clotting in patients with COVID-19. The following preventative and empiric treatments were employed at our institution to combat this problem: locking the catheters with heparin, systemic anticoagulation, and increasing doses of venous

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thromboembolism (VTE) prophylaxis. It is likely that many institutions treating patients with COVID-19 have encountered similar problems.

The primary aim of our study was to assess the association between different prophylactic interventions and the incidence of HD catheter malfunction. This information may have important implications for the care for these patients given the significant morbidity of failed HD. Additionally, we assessed the mortality rate in patients who experienced THDC malfunction. Finally, D-dimer and its association with THDC malfunction was analyzed.

METHODS

Study design, population, and primary predictors. We performed a retrospective cohort study via chart review at Ascension St. John Hospital and Medical Center, a large urban hospital in Detroit, Michigan. This study was conducted with approval by our institutional review board and the requirement for written consent was waived.

COVID-positive patients seen at our institution who required placement of a THDC between February 1, 2020, and April 30, 2020, were included. Follow-up for patient outcomes continued between May 1, 2020, and May 12, 2020, but no new patients were enrolled during this period. Patients who received THDC placement but never received HD through the temporary catheter were excluded. A THDC is defined as a 13F central venous catheter without a subcutaneous cuff. THDC were double or triple lumen and 16 to 24 cm in length.

At our institution, THDC were traditionally locked with 0.9% normal saline to decrease the complications of exposure to heparin. During the study period, the three prophylactic measures used were locking catheters with heparin, systemic anticoagulation, and increased dosing of VTE prophylaxis. Owing to a lack of guidelines and the disarray of the pandemic, the prophylactic measure chosen was based on physician discretion. Heparin locking was performed with 1.5 mL in each lumen with a concentration of 1000 U/mL. Catheters that were not locked with heparin were locked with 0.9% normal saline.

VTE prophylaxis was with subcutaneous unfractionated heparin (SQH). Systemic anticoagulation was either intravenous heparin, warfarin with an international normalized ratio of greater than 2.0 or novel oral anticoagulants.

To date, there is a lack of consensus regarding VTE prophylaxis regimens, although there are multiple clinical trials underway, leaving institutions to develop their own protocols.^{10,11} Our institutional guideline, which closely mimic the protocol put forth by Brigham and Women's Hospital,¹² was developed in mid-April 2020. It recommended that all patients with COVID-19 admitted to the hospital to be on high-intensity prophylactic anticoagulation (eg, SQH 7500 U three times daily

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, retrospective cohort study
- **Key Findings:** The likelihood of hemodialysis (HD) catheter malfunction was lower with heparin locking compared with saline locking (hazard ratio, 0.07; 95% confidence interval, 0.01-0.45; $P = .005$) and lower with subcutaneous heparin 7500 U three times daily compared with none (hazard ratio, 0.03, 95% confidence interval, 0.001-0.74; $P = .032$) in 48 patients with novel coronavirus disease 2019 requiring temporary HD catheter insertion.
- **Take Home Message:** Locking HD catheters with heparin and increased dosing of venous thromboembolism prophylaxis is associated with better HD catheter patency in patients with novel coronavirus disease 2019.

[TID]); a weight of 120 kg or greater qualifier was subsequently added. Systemic anticoagulation was recommended for patients with COVID-19 in the intensive care unit (ICU) or for D-dimer levels of more than 3000 ngFEU/mL with either the suspicion for thrombosis, a lymphocyte count of less than 5%,¹³ or increasing D-dimer levels. This D-dimer level is based on retrospective study by Tang et al,¹⁴ demonstrating a significant decrease in mortality with the use of heparin in patients with D-dimer that was more than 6-fold of the upper limit of normal. The rationale for the increased VTE prophylaxis dosing is an upwards of 30% VTE rate seen in patients with COVID-19 on standard prophylaxis.^{15,16} In ICU patients, a 3% to 85% VTE rate prompted the systemic anticoagulation recommendation.^{11,17,18} Owing to the timing of this protocol becoming available and the disarray caused by the pandemic, there were breaks in adhering to this protocol.

For this analysis, patients were recorded as receiving a prophylactic measure if they received it at any point during the study period. Because patients received various combinations of the three treatment modalities, it was not possible to identify each individual with a unique treatment arm. Instead, the analytic strategy used was to include three binary variables, each indicating whether or not each treatment was used with each patient (0 = treatment not used, 1 = treatment used). For the THDC malfunction analysis, the prophylactic treatments used for analysis were those received before death or the first catheter malfunction. Patients on SQH 5000 U twice daily and TID were combined for analysis. Increased VTE dosing group received SQH 7500 U TID.

Covariates and outcomes. Data extraction included demographics (age and sex), comorbidities (hypertension

[HTN], chronic kidney disease [CKD], end-stage renal disease (ESRD) on dialysis [HD or peritoneal dialysis], diabetes mellitus [DM] and chronic obstructive pulmonary disease [COPD]), home anticoagulation, and body mass index (BMI). CKD (all stages) and ESRD were combined for purposes of statistical analysis. Catheter covariates include THDC insertion site (femoral vs internal jugular [IJ]) and type of HD (conventional HD or continued renal replacement therapy).

The primary outcome is the incidence of THDC malfunction attributed the clotting requiring intervention (manual declotting, exchanging the catheter over a wire, instillation of alteplase, or HD catheter inserted at a new location) to reestablish flow. Clotting was diagnosed by visualization of the blood clot during catheter exchange or restoration of flow after manual declotting or alteplase administration.

The secondary outcome was the patients' final disposition: renal recovery, requiring dialysis at discharge (permanent dialysis), or mortality.

A proportional hazards regression analysis was performed based on the date of THDC insertion and number of days to outcome. Active inpatients and patients who did not experience THDC malfunction were not included in the analysis of catheter malfunction.

Statistical analysis. The primary analyses were conducted using proportional hazards modeling (Cox regression) with the outcome variable defined as time from line insertion to catheter malfunction. Using this method, the outcome variable is constructed using two elements: a binary variable indicating whether or not each patient experienced the outcome during the study period and a time variable representing the time at which the patient either experienced the event or exited the study for another reason (censoring). For each predictor, the proportional hazards model estimates an effect that can be expressed in terms of a hazard ratio (HR). The HR provides an estimate of the relative likelihood that the outcome will occur at any given point in time. Independent variables included as control predictors in the model include patient age, sex, comorbidities (HTN, high BMI, DM, CKD or ESRD, and COPD), prehospital anticoagulant therapy, and catheter insertion location (femoral vs IJ and right vs left side).

Additionally, two sets of sensitivity analyses were conducted to address two potential sources of ambiguity in the interpretation of the results. First, a competing risks analysis was conducted to examine how treating mortality as a competing risk for THDC malfunction may affect the results. Second, a time-varying analysis nesting treatment segments within patients (ie, a unique combination of treatment modalities and/or outcomes) was conducted to better control for differences in treatment timing and duration.

Additional analyses were conducted to examine the association between D-dimer levels and the outcomes in the subset of patients for whom D-dimer measurements were collected. The relationships between mean maximum D-dimer levels and outcomes were assessed using *t*-tests. The D-dimer levels in the proportional hazard model were transformed by the natural log to enhance the interpretability of the effect size estimates.

RESULTS

From February 1 to April 30, 2020, 49 patients with COVID required THDC placement. One patient was eliminated owing to mortality before the catheter being used, leaving 48 patients for statistical analysis. Forty-six were confirmed COVID-19 positive. Two patients tested negative; however, they had a clinical presentation compatible with COVID-19, were managed as false negatives, and therefore were included in the analysis. Forty-four patients (92%) were treated in the ICU. Throughout the study period, 37 patients (77.1%) received heparin locking, 22 (45.8%) received systemic anticoagulation, and 38 (79.2%) received VTE prophylaxis. Thirty-two patients (66.7%) received more than one prophylactic measure. A total of 24 patients received systemic anticoagulation throughout the study period; however, two were started on anticoagulation after the first THDC failure, so they were eliminated from the THDC failure analysis, leaving 22 for analysis. Of the 22 who received systemic anticoagulation, 17 had intravenous heparin and 5 had oral anticoagulants (2 argatroban, 2 apixaban, and 1 warfarin). Two patients had heparin-induced thrombocytopenia (HIT) and were treated with argatroban, one before THDC placement and the other while only receiving prophylactic systemic heparin. Neither experienced THDC malfunction. The initial indication for systemic anticoagulation in the 22 patients was 10 based on the institutional protocol discussed in the methods section, 6 for elevated D-dimer, 5 for atrial fibrillation, 3 for deep venous thrombosis and/or pulmonary embolism, and 1 for HIT. No hemorrhagic complications were seen.

A χ^2 analysis of patient variables (demographics, comorbidities, and dispositions) and their associations with treatment variables was performed to demonstrate which patient variables may act as confounders (Table I). Patient variables can be found in Table II. The χ^2 analysis presented in Table II compares the listed level of the predictor with other levels of the predictor for the corresponding outcome. For example, 24.3% of patients who were receiving heparin locking experienced HD failure, which is significantly lower than patients not receiving heparin locking who also experienced HD failure. Patients were in the study for a median of 7 days (range, 0-53 days; interquartile range [IQR], 2.5-14 days) before final disposition.

Table I. Patient demographics, comorbidities, disposition and their association with treatment variables

Patient variable	Treatment					
	Heparin locking		Systemic anticoagulation		Increased VTE prophylaxis	
	No, % (n = 11)	Yes, % (n = 37)	No, % (n = 26)	Yes, % (n = 22)	No, % (n = 33)	Yes, % (n = 15)
Demographics						
Age > 65	27.3	37.8	46.2	22.7 ^a	42.2	20.0
Female sex	54.5	46.0	57.7	36.4	51.5	40.0
Comorbidities						
DM	45.5	51.4	46.2	54.6	45.5	60.0
BMI > 40	45.5	35.1	34.6	40.9	33.3	46.7
CKD	36.4	16.2	30.8	9.1 ^a	18.2	26.7
ESRD	18.2	10.8	15.4	9.1	15.2	6.7
HTN	63.6	73.0	65.4	77.3	66.7	80.0
COPD	9.1	8.1	3.9	13.6	9.1	6.7
Prehospital anticoagulation	27.3	37.8	11.5	13.6	33.3	40.0
Catheter location						
Right IJ	18.2	13.5	50.0	18.2 ^a	21.2	0.0 ^a
Left IJ	54.6	18.9 ^b	30.8	22.7	27.7	26.7
Right femoral	0.0	18.9	46.2	40.9	18.2	6.7
Left femoral	27.3	48.7	3.9	27.3 ^b	33.3	66.7 ^b
Catheter length						
16 cm double lumen	36.4	13.5 ^a	26.9	9.1	15.2	26.7
16 cm triple lumen	36.4	8.1 ^b	7.7	22.7	21.2	0.0 ^a
20 cm double lumen	0.0	21.6 ^a	7.7	27.7 ^a	21.2	6.7
24 cm double lumen	27.3	56.8 ^a	57.7	40.9	42.4	66.7

BMI, Body mass index; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *ESRD*, end-stage renal disease; *HTN*, hypertension; *IJ*, internal jugular vein; *VTE*, venous thromboembolism.
Significance values represent results of χ^2 testing for patient variables by treatment. Percentages in treatment columns represent the percent of patients with the corresponding treatment.
^a $P < .10$.
^b $P < .05$.

Malfunction of the THDC occurred in 15 patients (31.3%). The median time to THDC malfunction from insertion date was 1 day (range, 0-17 days; IQR, 1-9 days). Among patients without malfunction, 24 died (median time to death, 4.5 days; range, 0-14 days; IQR, 1.5-7.5 days), 4 received permanent catheterization (median time, 21 days; range, 14-25 days; IQR, 16-24.5 days), 4 experienced renal recovery (median time, 13 days; range, 4-29 days; IQR, 6-23.5 days). All patients were censored at the time of any competing event (death, permanent catheterization, or renal recovery) or at the study end date if they did not experience failure or any competing outcome. The overall rate of THDC malfunction was lower with heparin vs saline locking (24.3% vs 54.6%; $P = .058$; Table II). Proportional hazards model results for time to first THDC malfunction are presented in Table III. This model demonstrates that, when all other variables are held equal, the rate of catheter malfunction at any given time undergoing heparin locking is estimated to be only 7% of the rate for catheters locked with normal saline ($P = .005$). Femoral insertion was associated with a greater HR (HR, 21.65; 95% CI, 1.75-267.65; $P = .017$) of catheter malfunction.

There was no difference in mortality rate between patients who experienced catheter malfunction and those who did not (66.7% vs 72.7%; $\chi^2 = 0.183$; $P = .669$).

Thirty-one patients (64.6%) were on VTE prophylaxis at the time of catheter insertion. Of the 17 (35.4%) not on VTE prophylaxis, 7 began VTE prophylaxis after line insertion (median, 2.5 days; IQR, 1-5 days) and 7 were on systemic anticoagulation, leaving 3 (6.3%) not on systemic or prophylactic anticoagulation during the study period. All three of these patients died within 1 day of line insertion. A majority of patients were on VTE prophylaxis; 23 (74.2%) received SQH 5000 U TID, followed by 7500 U TID (25.8%), and 1 patient (3.2%) received 5000 U twice daily. Dosing of VTE prophylaxis was increased from 5000 to 7500 U TID during the study period in seven patients (22.5%). Of the 15 patients on SQH 7500 U TID, the median weight was 119.1 kg (range, 59-214 kg; IQR, 86.4-150.2 kg) and all were ICU patients. According to the proportional hazards model (Table III), the rate of malfunction in patients with SQH 7500 U TID is estimated to be 3% of the rate for patients not receiving VTE prophylaxis ($P = .032$) and in patients receiving SQH 5000 U TID, 49% of the rate for patients not receiving VTE

Table II. Patient demographics, comorbidities, disposition and their association with mortality rate

	All patients	Outcomes			
	No. (%)	HD failure, %	Mortality, %	Permanent catheterization, %	Renal recovery, %
Total, n (%)	48 (100)	15 (31.3)	34 (70.8)	7 (14.6)	6 (12.5)
Treatment					
Heparin locking	37 (77.1)	24.3 ^a	64.9 ^a	16.2	16.2
Systemic anticoagulation	22 (45.8)	45.5 ^a	81.8	9.1	9.1
Increased VTE prophylaxis	15 (31.3)	33.3	66.7	13.3	20.0
Demographics					
Age > 65	17 (35.4)	17.7	76.5	11.8	5.9
Female sex	23 (47.9)	26.1	60.9	17.4	17.4
Comorbidities					
DM	24 (50.0)	37.5	83.3 ^a	8.3	8.3
BMI > 40	18 (37.5)	33.3	72.2	16.7	11.1
CKD	10 (20.8)	40.0	60.0	30.0	0.0
ESRD	6 (12.5)	16.7	66.7	16.7	16.7
HTN	34 (70.8)	32.4	70.6	14.7	14.7
COPD	4 (8.3)	50.0	75.0	0.0	25.0
Prehospital anticoagulation	17 (35.4)	29.4	64.7	17.7	17.7
Catheter location					
Right IJ	13 (27.1)	15.4	69.2	15.4	15.4
Left IJ	7 (14.6)	28.6	57.1	28.6	14.3
Right femoral	21 (43.8)	42.9	76.2	0.0	14.3
Left femoral	7 (14.6)	28.6	71.4	14.3	9.5
Catheter length					
16 cm double lumen	9 (18.8)	11.1	66.7	22.2	11.1
16 cm triple lumen	7 (14.6)	28.6	71.4	14.3	14.3
20 cm double lumen	8 (16.7)	25.0	75.0	12.5	12.5
24 cm double lumen	24 (50.0)	41.7	70.8	12.5	12.5

BMI, Body mass index; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *ESRD*, end-stage renal disease; *HTN*, hypertension; *IJ*, internal jugular vein; *VTE*, venous thromboembolism.
One patient was discharged to hospice and therefore was not included in the outcome data. Significance values represent results of χ^2 testing for the predictor group by outcome status. Percentages in outcome columns represent the percent of patients in the predictor group with the corresponding outcome.
^a $P < .10$.

prophylaxis ($P = .417$). No significant difference was observed between SQH 5000 TID and 7500 TID ($P = .059$).

Eighteen patients had D-dimer levels available for analysis. There was no difference in D-dimer levels between patients with THDC malfunction and without ($11,892 \pm 5901$ vs $10,154 \pm 5934$; $P = .560$). D-Dimer was significantly higher in patients who did not survive compared with those that did ($12,721 \pm 5376$ vs 5054 ± 2046 ; $P = .007$). Proportional hazards modeling indicated that higher D-dimer levels were related to greater hazards of mortality ($b = 1.19$; HR, 3.28; 95% CI, 1.16-9.28; $P = .025$), but were not significantly associated with hazards of THDC malfunction ($b = 0.58$; HR, 1.79; 95% CI, 0.42-7.71; $P = .434$).

Results of both sets of sensitivity analyses are presented in the [Appendix](#) (online only). The substance of the results was largely the same with respect to the key treatment variables, both in terms of significance and in

terms of the magnitude of the estimated model coefficients. The only exception was that the coefficient for the increased VTE prophylaxis dosage was only marginally significant in the competing risks model, although the magnitude of the estimate remained similar.

DISCUSSION

This retrospective cohort study was designed as a result of a high incidence of malfunctioning THDC seen in patients with COVID-19. Our institution was overwhelmed with patients with COVID-19 during the study period and patients could not be assigned to definitive study arms. During the study period, all modalities were used at physician discretion to prevent THDC malfunction. Locking HD catheters with heparin were independently associated with both a decreased malfunction rate and a longer time to malfunction.

Table III. Proportional hazards parameter estimates and hazard ratios (HR) for time to first hemodialysis (HD) catheter failure

Prophylactic treatments	b (SE)	HR	P value
Heparin locking	-2.63 (0.94)	0.07 [0.01-0.45]	.005
Systemic anticoagulation	1.44 (1.23)	4.24 [0.38-47.14]	.240
VTE prophylaxis			
5000 U TID ^a	-0.72 (0.88)	0.49 [0.09-2.77]	.417
7500 U TID ^a	-3.59 (1.65)	0.03 [0.001-0.74]	.032
Patient covariates			
Age	-0.02 (0.03)	0.98 [0.92-1.04]	.448
Female sex ^b	-1.23 (0.90)	0.28 [0.05-1.66]	.284
Comorbidities			
HTN	0.53 (0.95)	1.69 [0.26-10.99]	.582
BMI > 40	0.25 (0.76)	1.28 [0.29-5.67]	.746
DM	0.82 (1.12)	2.27 [0.25-20.44]	.464
CKD/ESRD	-1.88 (1.26)	0.15 [0.01-1.80]	.135
COPD	0.20 (1.74)	1.23 [0.26-37.35]	.908
Prehospital anticoagulants	1.24 (1.74)	3.47 [0.34-35.40]	.294
Treatment covariates			
Femoral insertion ^c	3.08 (1.28)	21.65 [1.75-267.65]	.017
Right side	1.66 (1.27)	5.28 [0.44-63.82]	.191

BMI, Body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HR, hazard ratio; HTN, hypertension; TID, three times per day; VTE, venous thromboembolism.
To test for a difference between subcutaneous heparin 5000 TID and 7500 TID, a supplementary model was run using and found no significant difference (b = -2.83; SE = 1.46; HR, 0.06; 95% confidence interval, 0.003-1.04; P = .059).
^aComparison group is no VTE prophylaxis.
^bComparison group is male.
^cComparison group is internal jugular insertion.

AKI is present in 0.5%¹ to 7%² of COVID-19 cases and in 23%³ to 29%⁴ that require intensive care admission. The cause is likely multifactorial: direct viral damage, systemic inflammation, hypoxemia, and iatrogenic hypovolemia during the management of acute respiratory distress syndrome.⁷ The binding affinity of the COVID-19 virus to angiotensin converting enzyme 2, which is highly expressed in the brush border of proximal tubular cells, induces AKI, and contributes to the dissemination of the virus.¹⁹⁻²³ As observed in acute respiratory distress syndrome, cytokine release syndrome may contribute to AKI via IL-6.^{20,24}

The previous literature is inconclusive on the best locking solution for central venous catheters.²⁵ A 2018 Cochrane review concluded that heparin may have little or no effect on catheter patency, but that most studies were of low-quality evidence.²⁶ Almost one-third (31.3%) of our THDC malfunctioned, highlighting the importance of identifying the most efficacious prophylactic modality.

Three prophylactic treatments were used at our institution to combat this high malfunction rate: locking the HD catheters with heparin, systemic heparin administration, and increasing the dose of VTE prophylaxis. In the current study, patients whose THDC were locked with heparin had a 92% lower chance of catheter malfunction, resulting in a longer time to malfunction and an overall lesser likelihood of malfunction. This potential

benefit of heparin locking may be reflective of the hypercoagulable patient population. The increased dose of VTE prophylaxis, SQH 7500 U, also showed some benefit. A significant improvement in THDC patency was seen in patients on SQH 7500 U TID compared with no VTE prophylaxis, which was not true for SQH 5000 U TID. A significant association was not seen between SQH 7500 and 5000 U TID, owing to the small sample size. However, this finding does suggest a possible benefit and the need for further study. Interestingly, systemic anticoagulation had no significant effect on the catheter malfunction rate.

We found that femoral insertion had significantly greater likelihood of catheter malfunction than IJ insertion, in contrast with the prior literature. A 2012 Cochrane review demonstrated fewer mechanical complications with femoral insertion for temporary HD than IJ, but similar thrombotic complications.²⁷ A 2015 *New England Journal of Medicine* randomized controlled trial demonstrated fewer mechanical complications with femoral than subclavian, but a nonsignificant difference between femoral and IJ insertion. Femoral insertion had higher symptomatic deep venous thrombosis complications than subclavian and IJ insertions.²⁸ Subclavian access for THDC is not used at our institution owing to concerns of central venous stenosis complicating future vascular access.^{29,30} In short, we demonstrated higher failure rates

with femoral insertion, although the literature seems to be heterogeneous on the ideal catheter insertion site.

The potential complications of locking THDC with heparin include HIT, incidental administration of a heparin bolus intended for heparin locking, and added expense. The Cochrane review did not demonstrate an increase in HIT with heparin locking, suggesting that this risk may be negligible.²⁶

The high malfunction rate is likely a result of the hypercoagulability that has been suggested in patients with COVID-19. Reports describe patients with COVID-19 without predisposing factors developing thromboembolic events.^{31,32} The etiology of these events is thought to be endothelial damage driven by the cytokine storm, leading to excess thrombin formation in addition to increased blood viscosity from hypoxemia.^{9,32}

We looked at the relationship between D-dimer levels and malfunctioning THDC to assess the possible usefulness of using D-dimer levels to predict which patients are more likely to experience a catheter malfunction. However, we found no difference in D-dimer levels between those with and without THDC malfunction. We did find that higher D-dimer levels are associated with higher mortality, which is consistent with prior literature.⁹ Only 18 of these 48 patients had D-dimer data. However, most of the patients with D-dimer data were at the end of our study period, likely a reflection of providers catching up with rapidly updating recommendations.

HTN and DM are the most common comorbidities associated with COVID-19, which is supported by our study.³³ CKD is seen in 1% to 3% of patients with COVID-19.³³ The Centers for Disease Control and Prevention states risk factors for severe illness from COVID-19 are age older than 65 years, COPD, heart conditions, immunocompromised, BMI of greater than 40, DM, CKD, and liver disease.³⁴ We did not find a difference in the mortality rate in patients with these comorbidities (Table II). However, the high mortality rate of our entire cohort likely obscures the impact of these comorbidities.

The incidence of AKI requiring HD in patients with COVID-19 is low. However, our study demonstrated a mortality rate of 71% in patients with COVID-19 who required a THDC. This finding is consistent with prior coronavirus infections, such as severe acute respiratory syndrome and Middle East respiratory syndrome where a 60% to 90% mortality rate was seen.³⁵ This finding has important implications for planning and resource delegation for future coronavirus infections.

The retrospective nature of the current study eliminated the ability to control the independent variables, resulting in most patients receiving multiple prophylactic measures at differing time points. This variability is due to the lack of guidelines, thus necessitating the need for this study. We controlled for these multiple measures on a single patient using proportional hazards

modeling. Our study reached statistical significance for heparin locking and increased dosing of VTE prophylaxis in decreasing the rates of THDC malfunction. The observational single institution design can affect this study's generalizability, but it would be difficult to randomize patients in an acute pandemic. Additionally, it was not possible to evaluate interactions between treatment modalities owing to the small numbers of patients who received each potential combination of treatments. Although the power is low ($n = 48$), this is the largest study to date addressing THDC malfunction in patients with COVID-19.

CONCLUSIONS

The hypercoagulability in patients with COVID-19 increases the malfunction rate of THDC. Heparin locking of THDC was associated with decreased malfunction rates. Prospective randomized studies will be needed to confirm these findings to recommend locking THDC with heparin in patients with COVID-19. Increased VTE prophylaxis suggested a possible association with improved THDC patency, although the comparison lacked sufficient statistical power. Additionally, the current study found a 71% mortality rate in patients with COVID-19 requiring acute HD, which has important implications for planning and resource delegation for future coronavirus infections.

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AUTHOR CONTRIBUTIONS

Conception and design: JK, JH, EE
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Critical revision of the article: JK, AP, RH, JH, EE
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APPENDIX (online only).

Sensitivity analyses

Sensitivity analyses were conducted to examine the robustness of our conclusions by addressing limitations of the main proportional hazards model. These are described separately herein. First, a competing risks analysis was conducted to evaluate the possibility that mortality acted as a competing risk for THDC failure, thus distorting the relationship between treatment modality and failure. Second, a nested time-varying proportional hazards analysis of treatment modality and time to THDC failure to control for differences in the timing and duration of the application of multiple combinations of treatment modalities within patients.

Sensitivity analysis 1: Competing risks. For the analysis of competing risks, patients were categorized by first outcome (0 = no THDC failure or mortality, 1 = THDC failure, 2 = mortality). There were 15 patients with THDC failure, 24 patients with mortality, and 9 patients with other outcomes. For the purposes of this analysis, success was defined as having an outcome other than THDC failure or mortality. Competing risks regression was implemented using Fine and Gray's method, which is based on modeling the cumulative incidence function.¹ This method differs from ordinary Cox regression in that it is models proportional subdistribution hazards, weighting cases with competing outcomes differently than censored cases, such that the weight of a case with a competing outcome decreases over time as a function of the likelihood that the event of interest would have occurred.²

The results of the competing risks model are presented in [Supplementary Table I](#), along with the corresponding results from the original proportional hazards model for purposes of comparison. There were two model coefficients that differed in significance between the two models: VTE prophylaxis (7500 TID vs none) and patient age. The coefficient for VTE prophylaxis was no longer significant after applying the competing risks analysis. This outcome implies that the relationship between VTE prophylaxis and failure rate may be partially accounted for by a disproportionate distribution of non-failure events in patients with mortality, leading to the estimate that a greater proportion of patients with the increased VTE prophylaxis dosage would have been likely to experience THDC failure if they had not died first. In mitigation, however, the CIs for the HRs overlapped substantially between the two models, and the

coefficient estimate remained marginally significant. Patient age, conversely, became a significant predictor of less likely THDC failure in the competing risks model. However, the CIs for the estimated HRs again overlapped substantially between the two models.

For the time-varying analysis, the data were restructured such that each unique combination of treatment modalities constituted an observation nested within patient. The purpose of this approach is to control for differences in the timing and duration of treatments (ie, to more accurately represent the relationship between treatment application and time to failure). This approach additionally allows for multiple outcomes for a single patient (ie, a patient may have had multiple THDC failures), and failure may be followed by another final outcome. Treatment in each time segment was represented with four binary variables corresponding with treatment conditions (use of heparin locking, systemic anticoagulation, VTE prophylaxis at 5000 U, and VTE prophylaxis at 7500 U) indicating whether or not the treatment had been applied in the current time segment or in an earlier time segment. There were a total of 130 time segments, nested within the 48 patients. The number of segments per patient ranged from 1 to 11, with a mean of 2.71 ± 1.92 , and a median of 2.0 segments (IQR, 1-4 segments). Among these 130 segments, 26 ended in THDC failure, 33 ended in mortality, and 75 were censored. Because time was indexed in days, four patients who experienced THDC failure followed by mortality in the same day had segments coded with two outcomes. Among the treatment modalities, 76 segments included heparin locking, 45 included systemic anticoagulation, 76 received VTE prophylaxis at 5000 U, and 37 received VTE prophylaxis at 7500 U.

The results are presented in [Supplementary Table II](#), along with the original time-invariant proportional hazards model for purposes of comparison. The results were substantially similar in the two models, with the exception of the coefficient for the comparison between DVT prophylaxis with 7500 U vs 5000 U, which had trend-level significance in the time-invariant model but not in the time-varying model. The significant coefficients in the original model remained significant in the time-varying model: treatment with heparin locking and VTE prophylaxis with 7500 U vs no prophylaxis were both associated with a lesser likelihood of THDC failure, whereas femoral artery insertion was associated with a greater likelihood of THDC failure. The 95% CIs for all of the key model variables overlapped between models.

Supplementary Table I (online only). Competing risks model compared with original proportional hazards model for temporary hemodialysis catheter (THDC) failure, sensitivity analysis 2: Time in treatment

Variable	Original model		Competing risks model	
	HR (95% CI)	P value	HR (95% CI)	P value
Heparin locking	0.08 (0.01-0.48)	.006	0.08 (0.01-0.59)	.013
Systemic anticoagulation	2.46 (0.32-18.91)	.388	5.48 (0.84-35.68)	.075
VTE prophylaxis				
7500 vs none	0.03 (0.001-0.70)	.029	0.14 (0.02-1.18)	.071
7500 vs 5000	0.08 (0.01-1.18)	.066	.20 (0.03-1.31)	.092
Age	0.97 (0.92-1.04)	.385	0.95 (0.92-0.99)	.008
Female sex	0.25 (0.04-1.61)	.144	0.55 (0.09-3.24)	.507
HTN	1.48 (0.22-10.00)	.685	1.17 (0.17-7.78)	.876
BMI > 40	1.75 (0.41-7.49)	.452	0.89 (0.28-2.83)	.850
DM	2.86 (0.32-25.46)	.347	1.79 (0.34-9.54)	.493
CKD/ESRD	0.15 (0.01-1.73)	.127	0.62 (0.12-3.14)	.875
COPD	1.69 (0.29-23.87)	.763	0.42 (0.001-150.13)	.775
Prehospital anticoagulants	2.64 (0.29-23.87)	.388	1.74 (0.39-7.70)	.464
Femoral insertion	15.15 (1.63-140.54)	.017	23.92 (2.16-264.54)	.010
Right side insertion	5.19 (0.44-61.51)	.192	1.00 (0.03-38.13)	.999

BMI, Body mass index; *CI*, confidence interval; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *ESRD*, end-stage renal disease; *HR*, hazard ratio; *HTN*, hypertension; *VTE*, venous thromboembolism.

Supplementary Table II (online only). Time-varying (nested) model compared with original proportional hazards model for temporary hemodialysis catheter (THDC) failure

Variable	Original model		Time-varying model	
	HR (95% CI)	P value	HR (95% CI)	P value
Heparin locking	0.08 (0.01-0.48)	.006	0.35 (0.12-0.99)	.049
Systemic anticoagulation	2.46 (0.32-18.91)	.388	1.13 (0.34-3.74)	.842
VTE prophylaxis				
7500 vs none	0.03 (0.001-0.70)	.029	0.11 (0.02-0.68)	.018
7500 vs 5000	0.08 (0.01-1.18)	.066	0.48 (0.15-1.54)	.213
Age	0.97 (0.92-1.04)	.385	0.96 (0.92-1.01)	.123
Female	0.25 (0.04-1.61)	.144	0.60 (0.20-1.78)	.354
HTN	1.48 (0.22-10.00)	.685	0.94 (0.27-3.31)	.928
BMI > 40	1.75 (0.41-7.49)	.452	0.79 (0.23-2.69)	.702
DM	2.86 (0.32-25.46)	.347	2.65 (0.66-10.71)	.172
CKD/ESRD	0.15 (0.01-1.73)	.127	0.84 (0.22-3.20)	.801
COPD	1.69 (0.29-23.87)	.763	3.02 (0.49-18.57)	.233
Prehospital anticoagulants	2.64 (0.29-23.87)	.388	0.75 (0.20-2.76)	.659
Femoral insertion	15.15 (1.63-140.54)	.017	5.33 (1.36-20.89)	.017
Right side insertion	5.19 (0.44-61.51)	.192	1.13 (0.31-4.05)	.855

BMI, Body mass index; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HR, hazard ratio; HTN, hypertension; VTE, venous thromboembolism.

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