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ORIGINAL ARTICLE

Management of therapeutic unfractionated heparin in COVID-19 patients: A retrospective cohort study

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Abstract

Background: Patients hospitalized with severe acute respiratory syndrome coronavirus 2 infection are at risk for thrombotic complications necessitating use of therapeutic unfractionated heparin (UFH). Full-dose anticoagulation limits requirements for organ support interventions in moderately ill patients with coronavirus disease 2019 (COVID-19). Given this benefit, it is important to evaluate response to therapeutic anticoagulation in this population.

Objectives: The aim of this study was to assess therapeutic UFH infusions and associated bleeding risk in patients with COVID-19.

Patients/Methods: This retrospective cohort study includes patients at Brigham and Women's Hospital, Boston, Massachusetts, receiving weight-based nursing-nomogram titrated UFH infusion during a 10-week surge in COVID-19 hospitalizations. Of 358 patients on therapeutic UFH during this interval, 97 (27.1%) had confirmed COVID-19. Patient characteristics, laboratory values, and information regarding UFH infusion and bleeding events were obtained from the electronic medical record.

Results: Patients who were COVID-19 positive had fewer therapeutic activatrd partial thromboplastin times (aPTTs) compared to COVID-19–negative patients (median rate, 40.0% vs 53.1%; $P < .0005$). Both major and clinically relevant nonmajor bleeding were increased in COVID-19–positive patients, with major bleeding observed in 10.3% (95% confidence interval [CI], 5.7%-17.9%) of patients who were COVID-19 positive and 3.1% (95% CI, 1.6%-5.9%) of patients who were COVID-19 negative ($P < .005$). In logistic regression, bleeding events were associated with receiving UFH for longer than 7 days, but not platelet count, coagulation, or inflammatory measurements.

Conclusions: Our data indicate a higher incidence of bleeding complications in patients with COVID-19 receiving weight-based nursing-nomogram titrated UFH infusions despite a higher prevalence of subtherapeutic aPTTs in this population. These data underscore the need for prospective studies aimed at improving the quality and safety of therapeutic anticoagulation in patients with COVID-19.

Jean M. Connors and Nathan T. Connell share co-senior authorship.

KEYWORDS
bleeding, coronavirus, coronavirus 2019, COVID-19, SARS-CoV-2, therapeutic anticoagulation, thromboembolism, thrombosis, unfractionated heparin

Essentials

- Intravenous blood thinners may be required in patients with coronavirus disease 2019 (COVID-19) who develop blood clots.
- We evaluated 358 patients receiving blood thinners during the COVID-19 surge in our hospital.
- Anticoagulant effect was often outside the therapeutic range in patients with COVID-19.
- Bleeding typically occurred in the first 3 days of anticoagulation or after 7 days of treatment.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), manifests as acute respiratory illness and is linked to significant coagulopathy and thrombosis.[1-11] While a recent report suggested that patients with COVID-19 have similar rates of thrombosis as patients with comparable degrees of severe illness and inflammation,[12] others have noted distinctions between coagulation profiles in COVID-19 and other severe pneumonias.[13]

In addition to venous thromboembolic disease, autopsies have demonstrated diffuse microthrombi in lung vasculature,[14,15] offering a possible explanation for the severely reduced lung compliance in COVID-19 compared to other viral pneumonias.[16] Early reports indicated a survival benefit with the use of prophylactic anticoagulation,[17] signaling an important contribution of thrombotic complications to COVID-19 mortality. It is hypothesized that hypercoagulability and enhanced thrombotic risk, reflected by a need for enhanced thromboprophylaxis, is related to a profound inflammatory syndrome in COVID-19 infections that underlies dramatic procoagulant profiles,[18,19] presence of antiphospholipid antibodies,[20-22] complement activation,[23] hyperviscocity,[24] and enhanced endothelial activation by overexpression of tissue factor in platelets, monocytes, and macrophages.[25-27] As there is increased incidence of thromboembolic complications—some of which occur despite appropriately dosed thromboprophylaxis[5]—and interim clinical trial data has shown that full-dose anticoagulation may limit need for mechanical ventilator support in moderately ill patients with COVID-19,[28] evaluating whether this population has a typical response to heparin-based anticoagulation is important.

Parenteral anticoagulation with heparins–both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH)–have advantages over oral anticoagulants for in-hospital use due to fewer drug-drug interactions with antivirals and other therapeutics. While LMWH use obviates the need for frequent monitoring and dosing adjustments, UFH remains a common anticoagulant for treating thromboembolic disease in hospitalized patients. UFH is relatively inexpensive, can be used in renal impairment, and is the predominant agent used in critical care indications such as extracorporeal membrane oxygenation (ECMO) due to its short half-life and reversibility.[29] However, known challenges with therapeutic UFH infusions include significant interindividual dose-response variability[30] driven by differences in clot burden, degrees of inflammation, and the presence of antiphospholipid antibodies. Nursing-driven-nomogram dosing of UFH is superior to individual dosing but requires familiarity with and adherence to the nomogram parameters.[31] The ability to safely administer and monitor UFH infusions may be further compromised by reports of heparin resistance[32-34] in patients with COVID-19 as well as health system stresses during surges in COVID-19 hospitalizations.

We evaluated the safety of UFH infusions during the 10-week surge in COVID-19 hospitalizations at our academic medical institution and report the real-world management and complications of weight-based nomogram titration of UFH infusions by nursing staff in hospitalized patients with and without COVID-19.

2 | METHODS

2.1 | Institutional Review Board approval

This study was approved by the Institutional Review Board of Partners Healthcare.

2.2 | Patients and data extraction from electronic medical records

All patients with an active order for therapeutic UFH infusion between March 1, 2020, and May 15, 2020, were reviewed. This 10-week period corresponded to the surge of patients with COVID-19 at our institution. A manual retrospective review of the electronic medical record (EMR) identified patients who were COVID-19 positive (defined as those with positive SARS-CoV-2 reverse transcriptase polymerase chain reaction [RT-PCR] result) and patients who were COVID-19 negative (defined as those with a negative SARS-CoV-2 RT-PCR and/or lacking clinical suspicion for COVID-19).

Patient data including demographics, reason for admission, location (ward vs intensive care unit [ICU]), laboratory values, indication for UFH infusion, duration of UFH infusion, and bleeding events were obtained by manual review of the EMR with a data cutoff date of May 31, 2020. When the indication for anticoagulation was deep vein

thrombosis (DVT) or pulmonary embolism (PE), we recorded whether the diagnosis was empiric or supported by radiographic confirmation.

2.3 | Anticoagulation therapy quality metrics

Patients received UFH infusion according to a weight-based nomogram titrated by nursing staff.[35] Our institutional protocol for therapeutic intensity or full-dose anticoagulation with UFH uses a goal activated partial thromboplastin time (aPTT) range of 60 to 80 seconds (1.5–2.0× baseline) based on our laboratory criteria. Low-intensity UFH infusions had a goal aPTT of 50 to 70 seconds and were used to treat acute coronary syndrome or when patients were deemed to have increased bleeding risk by providers, such as in postoperative patients. The nursing nomogram contained specific instructions for notifying the responsible clinician regarding out-of-range partial thromboplastin time values. We determined the percentage of therapeutic aPTTs during the UFH infusion observation period. Patients with subtherapeutic index aPTTs (first aPTT after UFH initiation) were evaluated for heparin resistance, defined as requiring ≥21 U/kg/h of heparin (≥35 000 U in 24 hours for a 70-kg person).

2.4 | Bleeding events and associated clinical factors

We used the Scientific and Standardization Committee of the ISTH criteria to classify patients who bled (identified from manual review of the EMR) while receiving an UFH infusion. Patients with suspected bleeding without an identified source were counted as having a bleeding event only if there was a documented drop in hemoglobin that was not explained by hemodilution or hemolysis. Major and clinically relevant nonmajor bleeding (CRNMB) was determined according to ISTH definitions.[36,37] Clinical factors associated with the number of supratherapeutic aPTTs, length of time receiving UFH and degree of inflammation were hypothesized to be associated with bleeding, and we evaluated the association of these parameters with bleeding in patients with and without COVID-19. The data are displayed in forest plots as odds ratios and 95% confidence intervals.

2.5 | Statistical analysis

R statistical software (R Foundation for Statistical Computing) was used for analysis. Figures were prepared using R software (R Foundation for Statistical Computing, Vienna, Austria) and Prism 7 (GraphPad Software, La Jolla, CA, USA). Continuous variables are presented as median and interquartile range (IQR). When used as continuous variables, laboratory values above the upper limit of detection were entered as 1 unit higher than the assay limit of detection. Missing data were not imputed. Proportions of categorical data were compared using Pearson's chi-square and Fisher's exact tests and continuous values were compared using the Mann-Whitney *U* test. A *P* value <.05 defined statistical significance.

3 | RESULTS

3.1 | Patient characteristics

Inclusion and exclusion criteria are illustrated in Figure 1. Our analysis included 358 patients, including 97 (27.1%) patients who were COVID-19 positive and 261 (72.9%) patients who were COVID-19 negative.

Table 1 lists patient baseline characteristics. Patients who were COVID-19 positive had a lower median age, but this was not significantly different from patients who were COVID-19 negative (63 years vs 67 years; *P* = .11). Black and Hispanic patients were

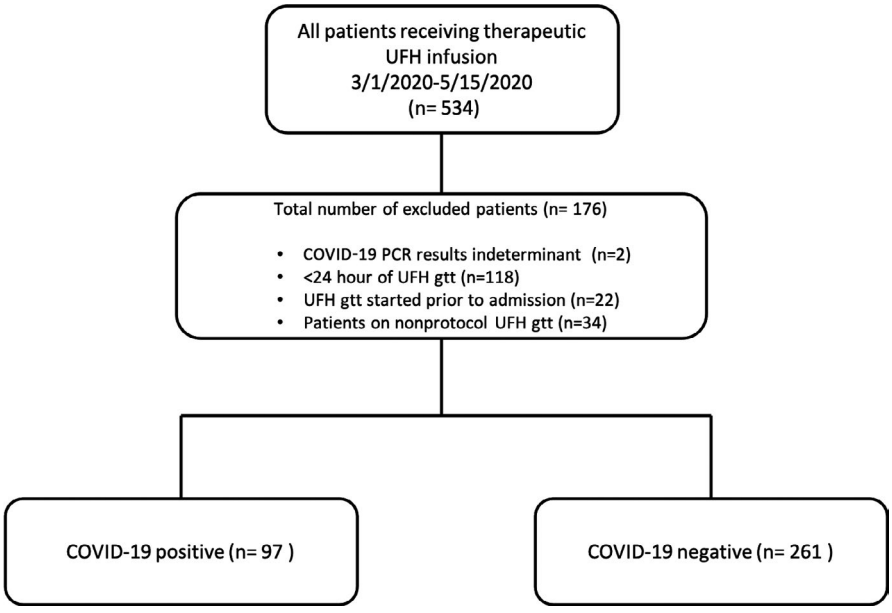

FIGURE 1 Project flow diagram. A total of 534 patients had orders for therapeutic unfractionated heparin (UFH) during the 10-week surge of coronavirus disease 2019 (COVID-19) cases at Brigham and Women's Hospital. Patients were excluded from analysis if they had inconclusive COVID-19 reverse transcriptase polymerase chain reaction (PCR) results, received <24 hours of therapeutic UFH, were started on therapeutic UFH before transfer from an outside institution and if they were receiving UFH infusion outside of nursing-driven protocol. Final cohorts include 97 patients who were COVID-19 positive and 261 patients who were COVID-19 negative

overrepresented among patients who were COVID-19 positive. A significantly higher proportion of patients on UFH who were COVID-19 positive were critically ill (ICU patients: 86.6% of patients who were COVID-19 positive vs 34.1% of patients who were COVID-19 negative; $P < .0001$) and more frequently admitted for respiratory illness. On the contrary, 47.5% of patients who were COVID-19 negative and only 4.1% of patients who were COVID-19 negative were admitted for cardiovascular indications.

Among patients who were COVID-19 positive, we observed significantly higher baseline aPTT ($P = .007$) as well as marked elevations in D-dimer ($P = .0002$), fibrinogen ($P < .0001$) and C-reactive protein (CRP; $P < 0.001$) compared to patients who were COVID-19 negative. No difference was observed in baseline platelet count for patients who were COVID-19 positive and patients who were COVID-19 negative (Table 1). When analysis was restricted to include only the subset of patients in the ICU at the time of UFH initiation, D-dimer, fibrinogen, and CRP remained significantly higher in patients who were COVID-19 positive compared to patients who were COVID-19 negative (Table S1).

3.2 | Heparin initiation and monitoring

UFH infusion indication and timing (hospital day on which infusion began) are summarized in Table 2. UFH infusions were initiated later in the hospital course for patients who were COVID-19 positive (hospital day 5; IQR, 1-7) compared to patients who were COVID-19 negative (hospital day 1; IQR, 0-4; $P <.0001$). Patients who were COVID-19 positive had a longer duration for UFH infusions compared to patients who were COVID-19 negative (median, 6 days vs 3 days; $P <.0001$) with UFH infusions lasting beyond 7 days noted for 50.5% versus 20.7% of patients who were COVID-19 positive versus patients who were COVID-19 negative, respectively.

UFH infusions were predominantly high intensity (91.8% of patients who were COVID-19 positive and 77.8% of patients who were COVID-19 negative), with a goal aPTT of 60 to 80 seconds. When ordered, low-therapeutic-intensity infusions were more commonly observed in patients who were COVID-19 negative. Treatment of confirmed or suspected DVT/PE was a common indication for UFH infusion but a significantly higher proportion of patients who were COVID-19 positive were treated for this indication (51.5% vs 37.2%; $P < .0001$). Both acute and chronic DVT/PE were managed (COVID-19 positive, 47 acute and 3 chronic; and COVID-19 negative, 68 acute and 29 chronic). Atrial fibrillation or atrial flutter was the second most common indication, and there was no significant difference in the proportion of patients who were COVID-19 positive and patients who were COVID-19 negative using UFH for this indication.

Titration outcomes for the first 3 aPTT values on the weight-based nomogram were used to evaluate aPTT monitoring in the first 18 to 24 hours of UFH infusion. Supratherapeutic median aPTT values were noted for the first 2 aPTT assessments in patients who were COVID-19 positive, whereas only the median value for the first aPTT was supratherapeutic in patients who were COVID-19 negative (Figure 2A). Therapeutic aPTT values were achieved by the third assessment (within 24 hours) for only 38% of patients who were COVID-19 positive compared to 50% of patients who were COVID-19 negative ($P = .004$; Figure 2B). While a higher percentage of patients who were COVID-19 positive had supratherapeutic third aPTT values (52% vs 31%; $P = .0003$), when values for the entire observation period were assessed, patients who were COVID-19 positive had more aPTT values in the subtherapeutic range compared to patients who were COVID-19 negative (25.9% [95% CI, 11.5-35.6] vs 18.2% [95% CI, 0-33.3; $P = .01$; Table 2). Overall, a lower percentage of therapeutic aPTT values was observed in patients who were COVID-19 positive (40.0% [95% CI, 30.4-57.7] vs 53.3% [95% CI, 38.0-66.7; $P = .0002$; Figure 2C).

3.3 | Assessment of heparin resistance

We next evaluated whether patients in our cohort who had subtherapeutic index aPTT values could be classified as heparin resistant. Subtherapeutic index aPTT values were documented for 34 patients (9.5% of the total cohort). This included 12 patients who were COVID-19 positive (12.4%) and 21 patients who were COVID-19 negative (8.0%) (Table S2). Of these patients, just two patients who were COVID-19 positive met criteria for heparin resistance, including one patient requiring 21 U/kg/h (40 360 total units in 24 hours) and another requiring 23 U/kg/h (44 980 total units in 24 hours).

3.4 | Bleeding events

A description of all bleeding events is provided in Table S3. Of the 358 patients receiving heparin, 54 (15.1%) had 59 independent bleeding events, corresponding to a bleeding rate of 0.03 bleeds per patient-day. Patients who bled did not have thrombocytopenia or laboratory evidence of disseminated intravascular coagulation (DIC; Table S4). Bleeding was more commonly observed in patients who were COVID-19 positive. A total of 34 bleeds were noted in 29 patients who were COVID-19 positive (29.9%), corresponding to a bleeding rate of 0.05 bleeds per patient-day. In contrast, 25 patients who were COVID-19 negative had 25 bleeds (9.6%; $P < .0001$) corresponding to a bleeding rate of 0.003 bleeds per patient-day. Major bleeding events occurred in 10.3% of patients who were COVID-19 positive compared to only 3.1% of patients who were COVID-19 negative ($P = .005$), and CRNMB events occurred in 20.6% of patients who were COVID-19 positive compared to only 6.5% of patients who were COVID-19 negative ($P < .0001$).

The median timing for bleeding was day 8 of UFH infusion for patients who were COVID-19 positive and day 4 for patients who were COVID-19 negative ($P = .05$). The timing of bleeding appeared to be bimodal for patients who were COVID-19 positive, with 11 (32.4%) of 34 bleeding events occurring on days 0 to 3 of UFH infusion and 21 (61.8%) of 34 bleeding events occurring at or beyond day 7 of UFH infusion for patients who were COVID-19 positive. In contrast,

TABLE 1 Characteristics of patients receiving therapeutic unfractionated heparin infusion

	All patients n = 358	COVID-19 positive n = 97	COVID-19 negative n = 261	*P* value
Age, y				
Median (IQR)	66 (55-74)	63 (53-73)	67 (56-75)	.11*
Sex, n (%)				
Male	220 (61.5)	60 (61.9)	160 (61.3)	.92†
Female	138 (38.5)	37 (38.1)	101 (38.7)	
Race, n (%)				
White	233 (65.1)	40 (41.2)	193 (73.9)	<.0001‡
Black	58 (16.2)	30 (30.9)	28 (10.7)	<.0001
Asian	16 (4.5)	3 (3.1)	13 (5.0)	.57
Other or unknown	51 (14.2)	24 (24.7)	27 (10.3)	.0005
Ethnicity, n (%)				
Hispanic	45 (12.6)	24 (24.7)	21 (8.0)	<.0001†
Non-Hispanic	313 (87.4)	73 (75.3)	240 (92.0)	
Location, n (%)				
Intensive care unit	173 (48.3)	84 (86.6)	89 (34.1)	<.0001†
Floor	185 (51.7)	13 (13.4)	172 (65.9)	
Reason for admission, n (%)				
Respiratory	111 (31.0)	86 (88.7)	25 (9.6)	<.0001‡
Cardiovascular	128 (35.8)	4 (4.1)	124 (47.5)	<.0001
Neurologic	21 (5.9)	4 (4.1)	17 (6.5)	.39
Oncologic	38 (10.6)	1 (1.1)	37 (14.2)	.003
Orthopedic/Trauma	10 (2.8)	1 (1.0)	9 (3.4)	.22
Obstetrics and gynecology	1 (0.3)	1 (1.0)	0	.10
Hematologic	6 (1.7)	0	6 (2.3)	.13
Renal and genitourinary	6 (1.7)	0	6 (2.3)	.13
Gastrointestinal/Hepatic	17 (4.7)	0	17 (6.5)	.10
Infectious (non-COVID)	19 (5.3)	0	19 (7.3)	.007
Endocrine/Metabolic	1 (0.3)	0	1 (0.4)	.10
Admission lab values				
Platelet count, K/μL[a]	219 (161-289)	228 (164-305)	215 (158-281)	.24*
aPTT, s[b]	34.1 (30.2-39.5)	35.7 (30.9-44.8)	33.9 (29.8-38.1)	.007*
D-Dimer, ng/mL[c]	3042 (1334-4001)	3396 (1942-4001)	1878 (790-3921)	.0002*
Fibrinogen, mg/dL[d]	524 (352-699)	624 (444-788)	392 (317-525)	<.0001*
C-reactive protein, mg/L[e]	114 (42.2-246.6)	186.9 (98-301)	51.1 (6.1-96)	<.0001*

Abbreviations: aPTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; IQR, interquartile range.

[a]Admission platelet count was available for all patients (n = 99 COVID-19 and n = 263 controls).

[b]Admission aPTT was available for 82 patients in the COVID-19 group and 145 patients in the control group.

[c]Admission D-dimer was available for 92 patients with COVID-19 and 51 control patients.

[d]Admission fibrinogen was available for 73 patients with COVID-19 and 48 control patients.

[e]Admission C-reactive protein was available for 87 patients with COVID-19 and 58 control patients.

*Mann-Whitney *U* test.

‡Pearson's chi-square test.

†Fisher's exact test.

12 (50%) of 24 bleeding events in patients with COVID-19 occurred on days 0 to 3 (Figure 3A). The bleeding distribution in patients who were COVID-19 positive remained bimodal when patients receiving ECMO were excluded from analysis. Overall, data evinced a higher 15-day cumulative incidence for all bleeding events in patients who were COVID-19 positive compared to patients who were COVID-19

TABLE 2 Therapeutic unfractionated heparin infusion timing and indication

	All patients n = 358	COVID-19 positive n = 97	COVID-19 negative n = 261	*P* value
Start time, hospital day				
Median (IQR)	2 (0–6)	5 (1–7)	1 (0–4)	<.0001§
0-6, n (%)	276 (77.1)	67 (69.1)	209 (80.1)	.028*
7-13, n (%)	49 (13.7)	23 (23.7)	26 (10.1)	.0008*
14-20, n (%)	16 (4.5)	4 (4.1)	12 (4.6)	.85*
21-27, n (%)	7 (2.0)	1 (1.0)	6 (2.3)	.44*
≥28, n (%)	10 (2.8)	2 (2.1)	8 (3.1)	.61*
Days of observed anticoagulation				
Median (IQR)	4 (2–7)	6 (3–13)	3 (2–6)	<0.0001§
0–3 days, n (%)	159 (44.4)	28 (28.9)	131 (50.2)	<0.0001*
4–6 days, n (%)	98 (27.4)	22 (22.7)	76 (29.1)	0.23*
7–9 days, n (%)	40 (11.2)	17 (17.5)	24 (9.2)	0.028*
≥10 days, n (%)	60 (17.0)	32 (33.0)	30 (11.5)	<0.0001*
Intensity,[a] n (%)				
High	292 (81.6)	89 (91.8)	203 (77.8)	.002‡
Low	66 (18.4)	8 (8.2)	58 (22.2)	
aPTT values, median, % (IQR)				
Frequency in therapeutic range	50 (33.3-66.7)	40.0 (30.4 -57.7)	53.3 (38.0-66.7)	.0002§
Frequency subtherapeutic	20 (5.3-33.3)	25.9 (11.5-35.6)	18.2 (0-33.3)	.01§
Frequency supratherapeutic	25 (14.3-38.6)	25.0 (16.3-41.4)	25.0 (14.3-31.5)	.22§
Indication for UFH infusion, n (%)				
DVT/PE[b]	147 (41.4)	50 (51.5)	97 (37.2)	<.0001*
Afib/flutter[c]	83 (23.2)	20 (20.6)	63 (24.1)	.48*
ECMO	14 (3.9)	9 (9.3)	5 (1.9)	.001*
CVVH	5 (1.4)	5 (4.1)	0	.0002*
Other thrombus[d]	3 (0.8)	2 (2.1)	1 (0.4)	.12*
ACS	47 (13.1)	4 (4.1)	43 (16.5)	.002*
CVA	11 (3.1)	2 (2.1)	9 (3.4)	.50*
Intracardiac device/mass and vascular surgery	46 (12.8)	4 (4.1)	42 (16.1)	.003*
Nephrotic syndrome	1 (0.3)	1 (1.0)	0	.10*
Hip fracture	1 (0.3)	0	1 (0.4)	0.54*
Patients with bleeding events, n (%)				
Any bleeding	54 (15.1)	29 (29.9)	25 (9.6)	<.0001*
Major bleeding	18 (5.0)	10 (10.3)	8 (3.1)	.005*
Clinically relevant non-major bleeding	37 (10.3)	20 (20.6)	17 (6.5)	<.0001*

Abbreviations: ACS, acute coronary syndrome; Afib/flutter, atrial fibrillation/flutter; aPTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; CVA, cerebrovascular accident; CVVH, continuous veno-venous hemofiltration; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; PE, pulmonary embolus; UFH, unfractionated heparin.

For all statistical tests, a *P* value of <.05 is considered significant.

[a]High intensity = goal PTT 60-80 seconds; low intensity = goal PTT 50-70 seconds.

[b]Acute and chronic DVT/PE.

[c]Acute and chronic Afib/flutter.

[d]Other thrombus includes arterial clots and concern for thrombotic microangiopathy.

§Mann-Whitney *U* test.

*Pearson's chi-square.

‡Fisher's exact test.

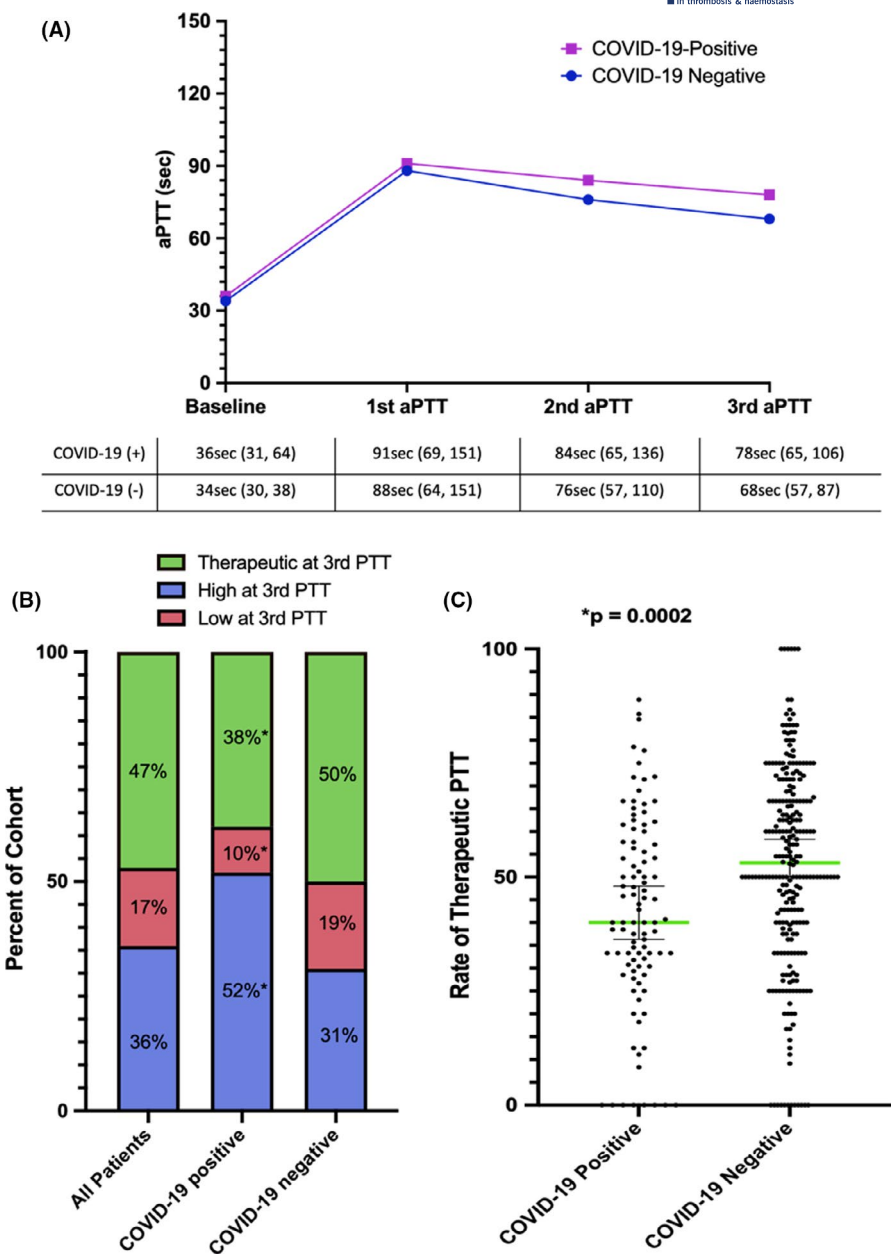

FIGURE 2 Heparin monitoring. A, Titration outcomes for patients who were coronavirus disease 2019 (COVID-19) positive (magenta) and COVID-19 negative (blue), median activated partial thromboplastin time (aPTT) values, and 95% confidence intervals are plotted. B, Frequency of therapeutic (green), supratherapeutic (blue), and subtherapeutic (red) aPTT in the total cohort, patients who were COVID-19 positive and patients who were COVID-19 negative. *Indicates percentages are significantly different between patients who were COVID-19 positive and patients who were COVID-19 negative by chi-square testing (P = .004, therapeutic aPTT; P = .005 for subtherapeutic aPTT; and P = .0003 for supratherapeutic aPTT). C, The percentage of therapeutic aPTT values during nomogram heparin monitoring for patients in our cohort by COVID-19 status. Green line represents median values (40.0% for COVID-19 positive and 53.1% for COVID-19 positive, Mann-Whitney U test; P = .0002)

negative (0.57 vs 0.34; P = 0.006; Figure 3B). Patients who bled were more commonly in the ICU (100% of patients who were COVID-19 positive and 60% of patients who were COVID-19 negative with bleeding) and were predominantly receiving UFH for DVT/PE (Table S3). Importantly, significantly higher 15-day cumulative incidence was observed for patients who were COVID-19 positive compared to patients who were COVID-19 negative (0.65 vs 0.41; P = .01; Table S1).

Patients receiving empiric UFH for management of venous thromboemboli and those receiving ECMO therapy are two special populations considered at potentially high risk for bleeding for whom published data are sparse. UFH infusion was used in 12 patients who were COVID-19 positive and 7 patients who were COVID-19 negative to manage suspected DVT/PE in the absence of radiographic confirmation. Major bleeding events occurred in 2 (16.7%) of the 12 patients who were COVID-19 positive and 1 (14.3%) of the 7 patients who were COVID-19 negative being treated with empiric UFH infusion. Additionally, CRNMB events occurred in 1 patient who was COVID-19 positive and 1 patient who was COVID-19 negative receiving empiric UFH (Table S3). ECMO was the UFH indication for 14 patients, and among these we observed 13 bleeding events in 10 (71%) patients. This included 10 events (3 major and 7 CRNMB) in 7 of the 9 patients who were COVID-19 positive on ECMO and 3 events (2 major and 1 CRNMB) in 3 of the 5 patients who were COVID-19 negative on ECMO. Of these bleeding events, 2 major bleeds in patients who were COVID-19 positive, 2 major bleeds in patients who were COVID-19 negative and 2 patients with CRNMB were associated with the ECMO cannulation insertion site (Table S3).

We next evaluated clinical parameters associated with bleeding. Importantly, a higher incidence of bleeding was observed in patients who were COVID-19 positive even when patients receiving low-intensity heparin infusions were excluded from the analysis.

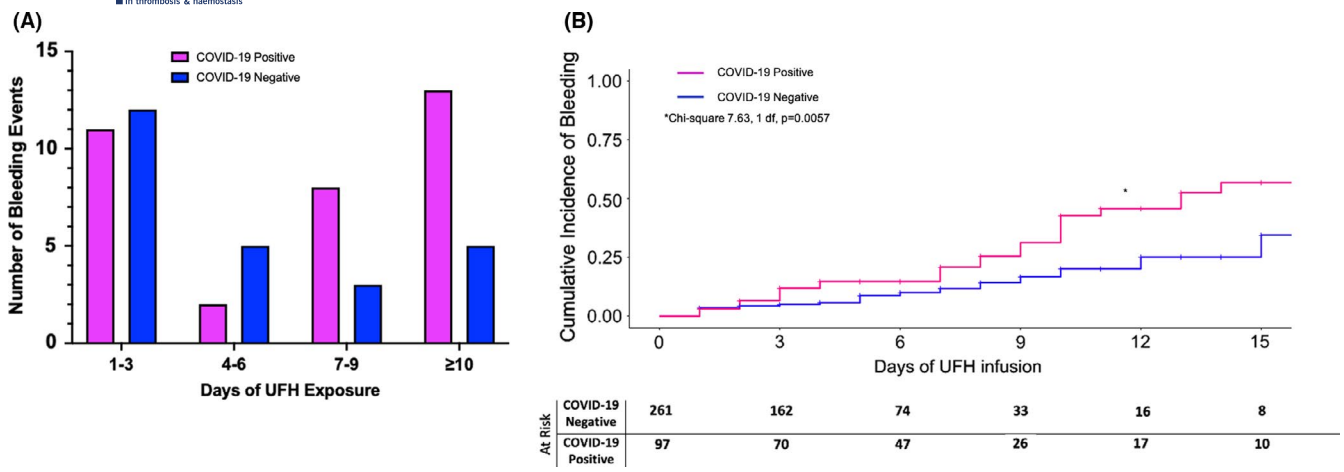

FIGURE 3 Bleeding events. A, Number of bleeding events by duration of unfractionated heparin (UFH) exposure (days) for coronavirus disease 2019 (COVID-19) positive and COVID-19 negative. B, Cumulative incidence curves for bleeding events. Fifteen-day cumulative incidence was 0.57 vs 0.34 in patients who were COVID-19 vs patients who were COVID-19 negative; $P = 0.006$, log-rank Mantel-Cox test

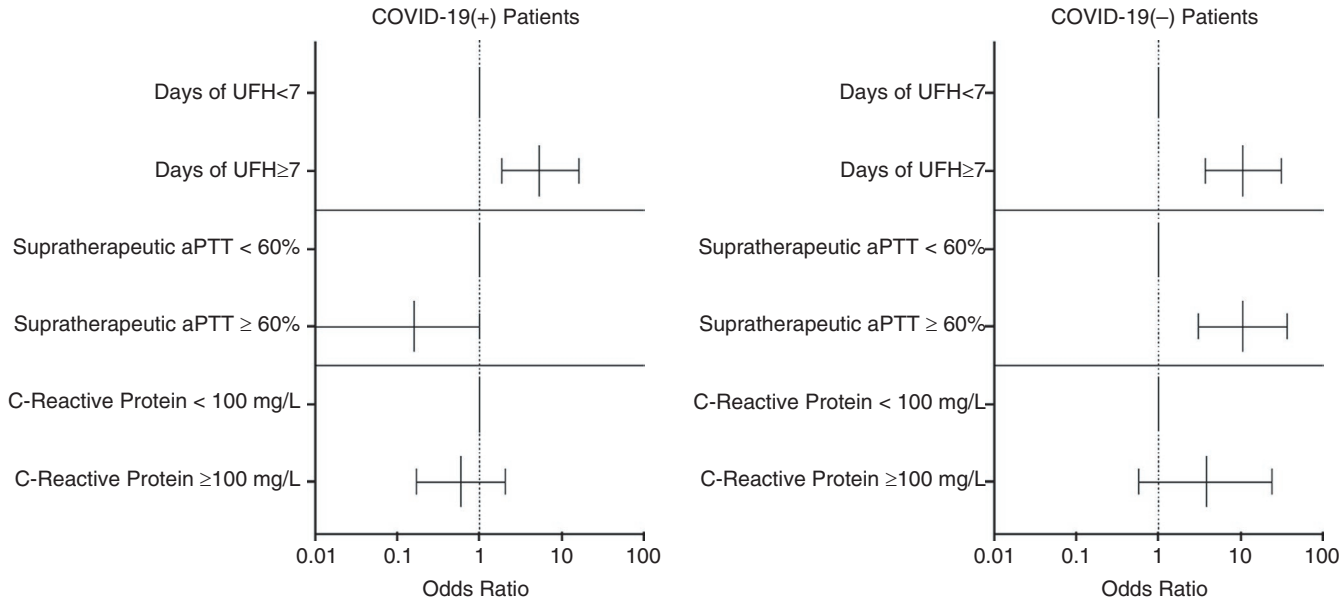

FIGURE 4 Predictors of bleeding. Forest plots showing results of multivariable regression analysis for patients who were coronavirus disease 2019 (COVID-19) positive (left panel) and patients who were COVID-19 negative (right panel). Values are in Table S2

Additionally, removal of patients on ECMO from analysis only mildly attenuated the overall rate of bleeding with a non-ECMO COVID-19–positive overall bleeding rate of 25% (95% CI, 17.1%-35%), including 24 events in 22 individuals or 0.04 bleeds per patient-day compared to a non-ECMO COVID-19–negative bleeding rate of 8.6% (95% CI, 5.7%-12.7%), including 22 bleeds in 22 individuals or 0.02 bleeds per patient-day ($P < .0001$; data not shown).

We hypothesized that a higher percentage of supratherapeutic aPTT values, a longer time exposed to heparin, and higher levels of systemic inflammation would be associated with bleeding while patients were receiving UFH infusion. In multivariable regression analysis, stratified by COVID-19 status and adjusted for age and patient location (ICU vs floor) as a proxy for illness severity, we observed that bleeding was associated with receiving UFH for >7 days in both patients who were COVID-19 positive and patients who were COVID-19 negative (Figure 4 and Table S5). Interestingly, CRP values >100 mg/L were not associated with bleeding in patients who were COVID-19 positive or patients who were COVID-19 negative, and having ≥60% supratherapeutic aPTT values was associated with bleeding in patients who were COVID-19 negative but not patients who were COVID-19 positive (Figure 4 and Table S5). Upon further review, all patients who were COVID-19 positive who bled were documented as having therapeutic-range aPTTs at the time of bleeding (Table S4) and only 1 of the patients who were 20 COVID-19 positive with ≥60% supratherapeutic aPTT values bled. We observed similar associations in multivariable regression analysis restricted to only ICU patients stratified by COVID-19 status (Table S5).

Given the observed difficulty maintaining aPTT within the therapeutic range, we evaluated the frequency of lupus anticoagulant testing and use of anti-Xa monitoring. Lupus anticoagulant testing was pursued in only 36 (10.1%) of 358 patients (24.7% of patients who were COVID positive and 4.6% of patients who were COVID negative). Lupus anticoagulants were detected in 75% of patients tested who were COVID-19 positive (18/24 tests) and 83.3% of patients tested who were COVID-19 negative (10/12 tests). Of the 41 individuals with >60% supratherapeutic aPTT values, lupus anticoagulant was detected in 4 of 5 patients tested who were COVID-19 positive and the 1 patient tested who was COVID-19 negative. Anti-Xa levels were used for UFH monitoring in 24 (9.3%) of 358 patients in our cohort, including 6 patients who were COVID-19 positive and 3 patients who were COVID-19 negative with >60% supratherapeutic aPTTs (Table S6).

4 | DISCUSSION

In this retrospective analysis of therapeutic anticoagulation in patients receiving weight-based nursing-nomogram titrated UFH infusions, we report our observation of high incidence of bleeding and atypical difficulty using aPTT monitoring to titrate UFH in patients who were COVID-19 positive.

Patients who were COVID-19 positive were infrequently within goal range for aPTT. The correlation between aPTT, UFH concentration, and antithrombotic effect may be less reliable in the context of COVID-19 infection.[19,27,38,39] Our data indicate a mild increase in baseline aPTT for patients who are COVID-19 positive compared to patients who are COVID-19 negative. Lupus anticoagulants were infrequently assayed in our cohort, but prior reports suggest that lupus anticoagulants are commonly detected in patients with COVID-19,[21,40,41] and this is a potential explanation for this observation. High levels of inflammation that increase serum CRP or other acute-phase reactants may also yield false-positive results for aPTT-based lupus anticoagulant testing, but should not alter the dilute Russell's viper venom test.[20,40]

Recent data have illustrated that both bleeding and thrombotic complications in COVID-19 are associated with marked increases in procoagulant profiles, particularly in critically ill patients with high degrees of systemic inflammation.[12] Management of confirmed or suspected DVT/PE was the predominant indication for UFH among patients who were COVID-19 positive, and the median timing of acute thrombotic event and UFH initiation of around day 5 in our study is consistent with a prior report from our institution.[11] Interestingly, while we observed that patients who were COVID-19 positive were predominantly supratherapeutic for the first 24 hours of UFH infusion, aPTT values were mostly in the subtherapeutic range for the duration of UFH exposure, which may reflect unmeasured increases in inflammation and thus procoagulability as illness progresses. Yet, while reports have demonstrated heparin resistance in patients with COVID-19,[32-34] only 2 patients who were COVID-19 positive in our study met criteria for heparin resistance. Prospective studies monitoring aPTT along with concomitant measurement of procoagulant and inflammatory profiles and including radiographic assessments of efficacy in DVT/PE propogation or resolution would help to clarify the clinical consequences of persistent subtherapeutic aPTT in patients who are COVID-19 positive on therapeutic anticoagulation.

Anti-Xa assays provide a reliable alternative to aPTT for UFH monitoring in patients with COVID-19 when available. A limitation of this retrospective study is that parallell anti-Xa monitoring was infrequent in our cohort, used primarily in cases of positive lupus anticoagulant testing or persistently supratherapeutic aPTT values. In patients without COVID-19, published aPTT and anti-Xa concordance rates vary from 35% to 60%.[42-44] Prospective investigations of the concordance of aPTT and anti-Xa assays in patients who are COVID-19 positive to determine the method of laboratory-based monitoring that enhances safety and efficacy of UFH infusion are warranted. Future prospective analyses using systematic data collection for multiple factors of interest, including factor VIII and lupus anticoagulants, are needed to determine the relationship between these factors and bleeding during the course of UFH infusion in patients with COVID-19.

We observed higher incidence of both major and CRNMB in patients who were COVID-19 positive compared to patients who were COVID-19 negative. This is consistent with published accounts indicating that while spontaneous bleeding events do occur in patients who are COVID-19 positive such as diffuse alveolar hemorrhage[45] and microthrombosis-associated[46] hemorrhage, bleeding in COVID-19 is most often in the context of prophylactic[12,47] and therapeutic[47,48] anticoagulation. Our results are also consistent with data from other centers that have noted high rates of bleeding among patients with COVID-19 receiving therapeutic anticoagulation.[49] In our experience, bleeding on heparin occurred within the first 3 days or after 7 days of UFH infusion in patients who are COVID-19 positive. This is consistent with recent data that showed major bleeding in patients with COVID-19 receiving intensive prophylaxis occurred after the first 10 to 14 days of therapy[49] and may be explained by worsening illness severity, higher likelihood of multiorgan failure, or need for procedures in patients with prolonged critical illness.

Patients who were COVID-19 positive bled in the absence of thrombocytopenia, hypofibrinogenemia, or DIC, contrary to earlier reports[17] but consistent with recent data.[12] Bleeding was not explained by supratherapeutic aPTT in patients who were COVID-19 positive, but was in patients who were COVID-19 negative. We do not interpret our data to suggest that prolonged aPTT is in any way protective against bleeding in COVID-19 infection. Rather, these data add credence to the unreliability of aPTT as a marker for bleeding risk in this population. Before COVID-19, reports indicated that a number of bleeding events may occur in the absence of critically high aPTT values.[50] Moreover, use of LMWH rather than UFH may decrease bleeding risk due to predictable pharmacologic dose-response properties[51] and a direct comparison of bleeding complications using full-dose LMWH and UFH in patients with COVID-19 is warranted.

Interim reports of clinical trials evaluating full-dose anticoagulation with heparin/LMWH compared to prophylaxis in patients with COVID-19 offer conflicting results. In moderately ill patients, full-dose heparin/LMWH was superior to prophylactic dose with a higher number of days free of organ support. However, in severely ill ICU patients, full-dose heparin/LMWH met predefined futility criteria, although there were fewer thrombotic events with the intervention in a secondary analysis.[28] Further results from these trials are needed to know how to apply this information to patients; however, management of therapeutic-dose UFH will not change. Two major bleeding events observed in patients who were COVID-19 positive were in the context of empiric anticoagulation to treat suspected DVT/PE without radiographic confirmation. In light of this and the overall high incidence of bleeding in patients who are COVID-19positive receiving therapeutic anticoagulation, we advise prudent consideration of the bleeding risks and benefits of anticoagulation and a higher risk of caution when therapeutic dosing is used outside of tradiational clinical indications in patients with COVID-19.

In conclusion, our data indicate significant management challenges in using therapeutically dosed UFH infusions in patients who are COVID-19 positive with standard weight-based nursing-nomogram titrated heparin infusions. Higher rates of major and non-major bleeding in patients with COVID-19 is strongly associated with the duration of UFH exposure. Future analyses of the efficacy of weight-based nomograms is warranted for patients with COVID-19 to better understand how to optimize the safety of full-dose anticoagulation. Larger-scale prospective analyses of UFH management and of bleeding incidence in special populations such as patients receiving ECMO and minoritized racial/ethnic groups, which are over-represented among patients with COVID-19, are needed.[52]

RELATIONSHIP DISCLOSURE

LDW, KWS, and NTC declare no conflicts of interest. JMC has received personal fees from Bristol-Myers Squibb, Abbott, Portola, and Pfizer, and research funding to her institution from CSL Behring.

AUTHOR CONTRIBUTIONS

LDW wrote the first draft of the manuscript, conceptualized and designed the study, extracted data from the electronic medical record, performed data analysis, created tables and figures, and made critical contributions to manuscript revision and final approval. KWS procured lists of patients from pharmacy records, made critical contributions to data analysis, and made manuscript revisions and final approval. JMC made critical contributions to study concept, design, data analysis, manuscript revision, and final approval. NTC made critical contributions to study concept, design, data analysis, manuscript revisions, and final approval.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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