




# Continuous Infusion Low-Dose Unfractionated Heparin for the Management of Hypercoagulability Associated With COVID-19

Journal of Pharmacy Practice  
2022, Vol. 35(2) 205–211  
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DOI: 10.1177/0897190020966207  
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## Abstract

**Introduction:** The Coronavirus Disease 2019 (COVID-19) is associated with severe hypercoagulability. There is currently limited evidence supporting the routine use of therapeutic anticoagulation in the setting of COVID-19. **Objectives:** The primary objective was to compare the incidence of thromboembolic events in adult patients with COVID-19 treated with an unfractionated heparin (UFH) infusion versus prophylactic dose anticoagulation. Secondary objectives included exploration of the efficacy and safety of an UFH infusion through the evaluation of organ function and incidence of minor and major bleeding. **Methods:** Retrospective observational cohort study with propensity score matching of COVID-19 patients who received an UFH infusion targeting an aPTT between 40 and 60 seconds. **Results:** Fifty-six patients were included in this study. There was no difference in the composite of thromboembolic events comprised of venous thromboembolism, arterial thrombosis, and catheter-related thrombosis between the UFH and control group (17.9% vs. 3.6%,  $P = 0.19$ ). There was a significant increase in median D-dimer concentrations from day 1 to day 7 in the control group (475 ng/mL [291-999] vs. 10820 ng/mL [606-21033],  $P = 0.04$ ). Patients treated with UFH had a higher incidence of minor bleeding (35.7% vs. 0%,  $P < 0.005$ ) and required more units of packed red blood cell transfusion (0.8 units  $\pm$  1.6 vs. 0 units,  $P = 0.01$ ). **Conclusion:** Continuous infusion of UFH for patients with COVID-19 infection did not decrease the overall incidence of thromboembolic complications. UFH was associated with stabilization of D-dimer concentrations and increased rates of minor bleeding and transfusions.

## Keywords

COVID-19, hypercoagulable, venous thromboembolism, pulmonary embolism, heparin

## Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to over 9 million confirmed cases worldwide with an estimated mortality rate of 5%.<sup>1</sup> Mortality of COVID-19 patients is often associated with multiple organ failure and pathological changes indicative of profound inflammation and hypercoagulation as opposed to respiratory distress alone.<sup>2-4</sup> The severe hypercoagulability induced by COVID-19 often manifests with elevated D-dimer concentrations and formation of microthrombi resulting in multi-organ dysfunction.<sup>4,5</sup> Venous and arterial thromboembolic events are estimated to occur up to 25% in hospitalized COVID-19 patients, with the incidence increasing up to 59% in critically ill patients.<sup>6</sup>

There is limited clinical data or guideline recommendations supporting the routine use of therapeutic anticoagulation in the

setting of COVID-19 hypercoagulability.<sup>3</sup> According to the American Society of Hematology, therapeutic anticoagulation should not be given without an alternative indication such as documented atrial fibrillation or venous thromboembolism (VTE).<sup>7</sup> Despite this, patients with severe COVID-19 disease are at high risk for thrombosis and many institutions have anecdotally initiated various doses of therapeutic anticoagulation.

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Unfractionated heparin (UFH) is a commonly used anticoagulant that has proven clinical efficacy in a variety of thrombotic disorders as well as immunomodulatory effects in-vitro.<sup>8</sup> In order to mitigate the systemic insult of the hypercoagulable state while ensuring frequent and reliable monitoring, COVID-19 patients presenting to our institution with elevated D-dimer concentrations were started on a low dose UFH infusion at 8 units/kg/hour with subsequent titration every 6 hours to a goal activated partial thromboplastin time (aPTT) between 40 to 60 seconds as opposed to our normal therapeutic range of 53 to 98 seconds. Due to the clinical urgency at the time of implementation, our practice was to initiate the UFH infusion for patients with a D-dimer concentration above 1500 ng/mL with daily monitoring of D-dimer concentrations for the duration of therapy despite the lack of concrete clinical guidance.<sup>9</sup> A lower aPTT range of 40 to 60 seconds was targeted based on expert opinion at our institution given the uncertain tolerability of full-dose therapeutic anticoagulation in these patients.

The primary goal of our study was to compare the incidence of thromboembolic events in patients treated with the low-dose UFH infusion versus those with routine prophylactic dosing. Further, we sought to explore the efficacy and safety of the UFH infusion through the evaluation of organ function, incidence of minor and major bleeding, length of stay, and mortality.

## Materials and Methods

### Patients

The study was determined to be exempt human research and received approval from the Icahn School of Medicine at Mount Sinai institutional review board. Adult patients 18 years and older with confirmed COVID-19 infection treated with an UFH infusion between March 1, 2020 and April 14, 2020 in a community teaching hospital in New York City were retrospectively identified through our institution's electronic health record and included in this study. Subjects were excluded if they were pregnant or incarcerated, had an ICU length of stay of less than 48 hours, UFH duration of less than 48 hours, transferred to another institution, or had an alternative indication for therapeutic anticoagulation. The decision to initiate the UFH infusion as opposed to standard prophylaxis dosing was left up to the treatment team as this clinical guidance was not mandated by our institution.

### Study Outcomes

The primary study outcome was a composite of documented thromboembolic events comprised of VTE, arterial thrombosis, and catheter-related thrombosis confirmed by imaging. In addition to the primary study outcome, we collected the following surrogates of organ function and data points as secondary outcomes: D-dimer, PaO<sub>2</sub>: FiO<sub>2</sub> (PF) ratio, serum creatinine, daily urine output, hepatic transaminases, fibrinogen, international normalized ratio (INR), aPTT, absolute lymphocyte count, lactate dehydrogenase (LDH), duration of mechanical

ventilation, intensive care unit (ICU) length of stay, and seven-day mortality. For our safety analysis, we collected the incidence of minor bleeding, major bleeding, and heparin-induced thrombocytopenia. Definitions of minor and major bleeding were based on the International Society of Thrombosis recommendations.<sup>10,11</sup>

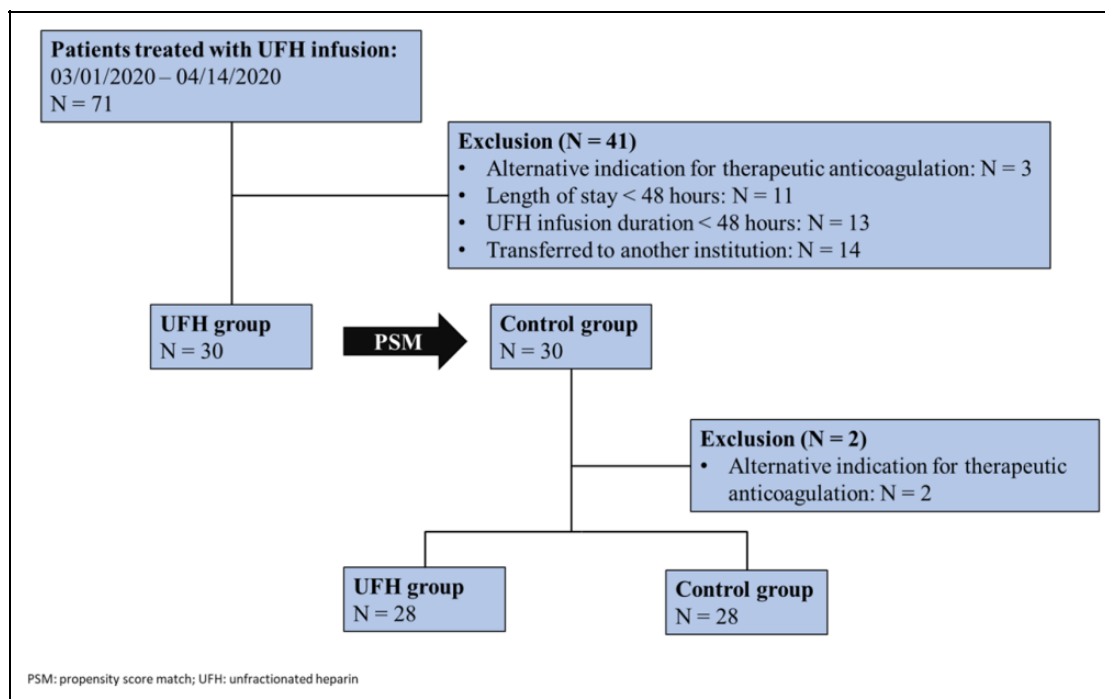
### Statistical Analysis

Statistical analysis was performed with SAS Studio (SAS Corporation, Cary, NC, USA) and GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA). A propensity score calculation was performed where treatment with an UFH infusion was the dependent variable and patient sex, age, and past medical history of diabetes mellitus, hypertension, and coronary artery disease were the independent variables. After propensity score calculation, global optimal matching was used to create a propensity score matched cohort. Dichotomous study outcomes were compared using the Fisher's Exact Test and continuous outcomes were compared using Student's T Test. Associations of changes in the secondary outcomes previously described and the use of UFH infusions were assessed with the use of linear regression.

## Results

A total of 71 COVID-19 confirmed patients treated with an UFH infusion were identified through our electronic health record. Figure 1 shows patients that were excluded and the eventual number of cases that were included in the propensity score matched cohort, 28 patients in the UFH group and 28 patients in the control group. Baseline characteristics for both groups are shown in Table 1. Severity of illness as assessed by the Sequential Organ Failure Assessment (SOFA) score was significantly higher in the UFH group as compared to the control group ( $5.8 \pm 3.8$  vs.  $3.2 \pm 2.7$ ,  $P = 0.007$ ).

The mean lowest UFH infusion rate was  $8.4 \pm 2.1$  units/kg/hour and the mean highest UFH infusion rate was  $15.1 \pm 4$  units/kg/hour. In the control group, 14 (50%) patients received standard prophylaxis with subcutaneous UFH 5000 units every 8 or 12 hours, 12 (42.9%) received standard prophylaxis with enoxaparin 40 mg every 24 hours, and 2 (7.1%) patients did not receive any pharmacologic prophylaxis. There was no statistically significant difference in the use of concomitant antiplatelet therapy and no patients received systemic thrombolytic agents. A comparison of laboratory values over time between the UFH group and control group is shown in Table 2. The median maximum aPTT values in the UFH group during the treatment duration were all considered to be within our institution's therapeutic range of 40-60 seconds (Figure 2). Patients in the control group had a statistically significant increase in daily median D-dimer concentrations whereas the UFH group's trend was not statistically significant (Figure 2). The UFH group's decrease in daily median aspartate transaminase (AST) level and increase in urine output was statistically significant. There was a statistically significant increase in daily median fibrinogen concentration in the UFH group. No significant



**Figure 1.** Patient identification and inclusion. PSM: propensity score match; UFH: unfractionated heparin.

differences were found regarding PF ratio, serum creatinine, alanine transaminase (ALT), INR, absolute lymphocyte count, or LDH.

There was no significant difference in the composite of thromboembolic complications between the UFH and control groups (17.9% vs. 3.6%,  $P = 0.19$ ) (Table 3). Patients in the UFH group required more renal replacement therapy (35.7% vs. 3.6%,  $P = 0.005$ ), more mechanical ventilation (75% vs. 25%,  $P < 0.005$ ), longer durations of mechanical ventilation (13.7 days  $\pm$  7.4 vs. 1.7 days  $\pm$  3.8,  $P < 0.005$ ), and ICU length of stay (12 days  $\pm$  9.2 vs. 1 day  $\pm$  7.4 2.9,  $P < 0.005$ ) as compared to the control group. Patients treated with UFH had a higher incidence of minor bleeding (35.7% vs. 0%,  $P < 0.005$ ) and required significantly more units of packed red blood cell transfusion (0.8 units  $\pm$  1.6 vs. 0 units,  $P = 0.01$ ). There was no difference in the incidence of major bleeding (7.1% vs. 0%,  $P = 0.49$ ). In addition, there were no documented cases of positive heparin induced platelet antibodies and positive serotonin release assays in either group.

## Discussion

In an observational cohort study of patients treated with low-dose continuous infusion UFH for management of COVID-19 hypercoagulability, we found that there was no difference in the primary composite of thromboembolic events.

Early anticoagulation may be needed for COVID-19 patients as organ failure is likely secondary to COVID-19 disease may be caused by hypercoagulation leading to systemic microthrombi.<sup>12,13</sup> In a case series of 4 critically ill patients with COVID-19, patients presented with markedly elevated

**Table 1.** Baseline Characteristics.

Characteristic	UFH (N = 28)	Control (N = 28)	P Value
Mean age, years	63.8 $\pm$ 13.6	65.3 $\pm$ 12.7	0.69
Sex, % male	18 (64%)	20 (71%)	0.78
Mean body mass index (kg/m <sup>2</sup> )	32.9 $\pm$ 9.2	27.1 $\pm$ 4.6	0.005
Asthma	2 (7%)	2 (7%)	1.0
Cancer	3 (11%)	3 (11%)	1.0
Chronic obstructive pulmonary disease	0 (0%)	1 (4%)	0.49
Coronary artery disease	3 (11%)	4 (14%)	1.0
Diabetes mellitus	18 (64%)	15 (54%)	0.80
End stage renal disease on dialysis	1 (4%)	3 (11%)	0.35
Hypertension	19 (68%)	23 (82%)	0.36
Mean baseline hemoglobin (g/dL) $\pm$ SD	12.9 $\pm$ 2.6	12.2 $\pm$ 2.1	0.28
Mean SOFA score	5.8 $\pm$ 3.8	3.2 $\pm$ 2.7	0.007
Concomitant antiplatelet therapy	2 (7%)	3 (11%)	0.67
Intensive care unit management	16 (57%)	8 (29%)	0.06

Abbreviations: SOFA: sequential organ failure assessment; UFH: unfractionated heparin.

D-dimers and respiratory failure which responded to systemic tissue plasminogen activator.<sup>12</sup> If therapeutic anticoagulation is initiated early in the disease course of COVID-19 patients, thrombotic complications may be prevented and thrombolysis would not be needed, potentially decreasing the risk for major bleeding complications and reducing cost of therapy.

The 17.9% incidence of thrombotic complications in this study was lower than the 20-30% described in earlier

**Table 2.** Comparison of Laboratory Values.

Variable	Group	Pre-treatment	Day 1	Day 3	Day 5	Day 7	Post-treatment	P Value	P Value
Median [IQR] D-dimer (ng/mL)	UFH	5243 [1239-32971]	6439 [2965-10660]	5527 [2868-8316]	4417 [3576-7936]	5027 [3546-7996]	5221 [3576-10768]	0.30	< 0.005
	Control	475 [291-999]	5000 [885-6394]	5500 [3440-7559]	10820 [606-21033]	10820 [606-21033]		0.04	
Median [IQR] PF ratio	UFH	156 [92-198]	149 [114-210]	142 [93-244]	159 [90-256]	147 [82-240]	167 [108-214]	0.46	0.45
	Control	243 [133-404]	200 [125-383]	263 [87-388]	263 [87-388]	196 [93-424]		0.69	
Median [IQR] daily urine output (mL)	UFH	562 [365-1000]	500 [150-1050]	300 [55-1200]	700 [260-1875]	1013 [550-2435]	1063 [400-1820]	0.04	0.19
	Control	741 [91-1500]	1350 [575-1975]	303 [95-700]	303 [95-700]	750 [213-1500]		0.69	
Median [IQR] serum creatinine (mg/dL)	UFH	2.25 [0.95-4.82]	3.83 [1.25-5.79]	3.88 [1.73-8.47]	1.84 [1.06-7.18]	2.46 [1.12-6.56]	1.82 [0.92-4.05]	0.29	0.27
	Control	1.34 [0.86-3.18]	1.66 [0.98-5.13]	1.66 [0.89-8.0]	1.87 [0.89-8.0]	2.42 [1.15-5.99]		0.11	
Median [IQR] ALT (units/L)	UFH	44 [30-71]	40 [24-137]	46 [20-79]	54 [33-65]	45 [29-79]	37 [34-90]	0.92	0.92
	Control	21 [12-43]	21 [12-43]	39 [24-62]	50 [38-83]	41 [18-66]		0.25	
Median [IQR] AST (units/L)	UFH	76 [51-132]	76 [41-157]	69 [46-91]	55 [30-88]	57 [40-69]	42 [36-52]	< 0.005	0.07
	Control	37 [28-69]	37 [28-69]	67 [43-103]	83 [45-143]	54 [46-144]		0.56	
Median [IQR] absolute lymphocyte count (10 <sup>3</sup> cells/mcL)	UFH	0.97 [0.62-1.39]	1 [0.48-3.0]	0.8 [0.44-2.94]	0.96 [0.5-1.7]	0.94 [0.64-1.95]	0.82 [0.63-1.78]	0.36	0.07
	Control	1.29 [0.74-1.86]	1.29 [0.74-1.86]	1.12 [0.78-1.91]	0.96 [0.69-1.8]	0.96 [0.74-2.04]		0.06	
Median [IQR] maximum aPTT (sec)	UFH	31 [27-37]	44 [27-37]	52 [38-63]	51 [45-72]	56 [38-81]	34 [26-71]	0.59	0.64
	Control	30 [25-33]	30 [25-33]	30 [30-36]	28 [24-47]	29 [26-33]		0.33	
Median [IQR] fibrinogen (mg/dL)	UFH	482 [396-538]	415 [282-598]	428 [385-798]	488 [382-674]	616 [411-674]	719 [452-770]	0.04	N/A
	Control	601 [508-693]	601 [508-693]	795				N/A	
Median [IQR] INR	UFH	1.1 [1.1-1.3]	1.1 [1.0-1.1]	1.1 [1.0-1.2]	1.1 [1.0-1.2]	1.1 [1.0-1.2]	1.2 [1.1-1.4]	0.20	0.48
	Control	1.2 [1.1-1.3]	1.2 [1.1-1.3]	1.3 [1.1-1.3]	1.3 [1.1-1.4]	1.3 [1.1-1.4]		0.23	
Median [IQR] LDH (units/L)	UFH	616 [521-886]	738 [562-900]	767 [537-839]	655 [517-870]	667 [502-900]	517 [172-750]	0.31	0.78
	Control	606 [560-666]	606 [560-666]	484 [474-576]	514 [428-600]			0.49	

ALT: alanine transaminase; aPTT: activated partial thromboplastin time; AST: aspartate transaminase; LDH: lactate dehydrogenase; PF: PaO<sub>2</sub>; FIO<sub>2</sub>; UFH: unfractionated heparin.

reports.<sup>9,14</sup> This difference in this observation may be attributable to the use of higher doses anticoagulants with an UFH infusion as opposed to routine prophylactic doses with UFH or a low molecular weight derivative. Although our study did not evaluate trends in inflammatory biomarkers, the use of UFH specifically as opposed to alternative agents may have its own set of benefits that may have affected our results such as inhibition of inflammatory mediators and cytokines which are implicated in the regulation of coagulation and fibrinolysis.<sup>8,15</sup>

The provider team-driven practice of initiating a low-dose UFH infusion with a target aPTT of 40 to 60 seconds began after we noticed many patients were experiencing catheter-related thromboses despite being on routine prophylactic regimens. UFH was chosen in preference to other anticoagulants because of in-vitro data demonstrating direct binding of the SARS-CoV-2 Spike protein to heparin causing significant structural changes as well as the direct downregulation of proinflammatory cytokines such as interleukin-6.<sup>16,17</sup> The decision to target a lower aPTT range instead of full therapeutic doses with a higher aPTT range was made balancing the benefit of anticoagulation with the risk of bleeding and tolerability in critically ill patients. Even with a lower aPTT target of 40 to 60 seconds, patients the UFH group had significantly more cases of minor bleeding and transfusion requirements than the control group. Interestingly, unlike disseminated intravascular coagulation, the fibrinogen levels in our cohort were significantly elevated as compared to baseline, which may indicate normal or increased coagulation activity.

D-dimer concentration has been reported as a strong single predictor of venous thromboembolic disease in patients with severe COVID-19 infection.<sup>9</sup> The increase in daily D-dimer concentrations seen in the control group despite prophylactic anticoagulation contrasted to stable D-dimer concentrations in the UFH group signifies that prophylaxis may not be enough for these patients. The absence of a statistically significant decrease in D-dimer concentrations in the UFH group is likely multifactorial. The first consideration that needs to be made as alluded to previously is the therapeutic target for anticoagulation and the potential benefit from increasing the dose to achieve higher aPTTs in established therapeutic ranges. The second consideration are the various factors that have been associated with increased D-dimer levels throughout the course of treatment such as age, concomitant infection, liver disease, and renal disease.<sup>18,19</sup>

The statistically significant differences in AST and urine output is hypothesis generating as they serve as surrogates for hepatic and renal function, respectively. It is plausible that organ function would improve with the initiation of UFH via prevention of microthrombi formation. However, the lack of statistical significance in other laboratory values and indices of organ function such as serum creatinine, ALT, and PF ratio suggest that these findings may not be clinically significant. Although the statistically significant differences in duration of mechanical ventilation, requirement for renal replacement therapy, and ICU length of stay are likely indicative of a higher

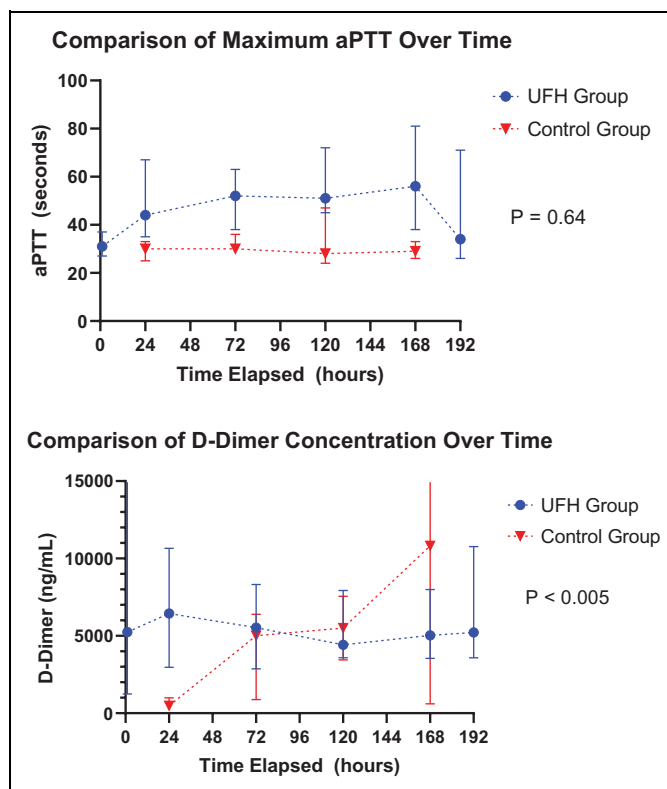


Figure 2. Comparison of aPTT and D-dimer over time.

Table 3. Subject Outcomes.

Outcome	UFH (N = 28)	Control (N = 28)	P Value
Thromboembolic complication	5 (17.9%)	1 (3.6%)	0.19
Arterial thromboembolism	2	1	–
Catheter-related thromboembolism	1	0	–
Venous thromboembolism	2	0	–
Patients requiring mechanical ventilation	21 (75%)	7 (25%)	<0.005
Duration of mechanical ventilation, days	13.7 ± 7.4	1.7 ± 3.8	<0.005
New renal replacement therapy requirement	10 (35.7%)	1 (3.6%)	0.005
Mean PRBC transfused, units	0.8 ± 1.6	0	0.01
Patients requiring PRBC transfusion	10 (35.7%)	0	<0.005
Major bleed	2 (7.1%)	0	0.49
Minor bleed	10 (35.7%)	0	<0.005
ICU length of stay, days	12 ± 9.2	1 ± 2.9	<0.005
Seven-day mortality	5 (17.9%)	9 (32.1%)	0.36

Abbreviations: PRBC: packed red blood cell; UFH: unfractionated heparin.

severity of illness in the treatment group, it may also represent longer hospital survival.

Since the completion of this study, additional guidance recommendations have been released regarding the management of hypercoagulability associated with COVID-19. The



International Society of Thrombosis and Haemostasis recommends monitoring of D-dimer concentrations as well as initiation of prophylactic dose low molecular weight heparin (LMWH) for all patients with COVID-19 infection in the absence of contraindications.<sup>20</sup> A literature review performed by Bikdeli and colleagues acknowledged the need for further investigation before routinely utilizing therapeutic anticoagulation in patients with COVID-19, although a minority of panel members considered intermediate-dose or therapeutic dose to be reasonable.<sup>21</sup> The National Institutes of Health COVID-19 treatment guidelines did not make recommendations for or against monitoring of D-dimer concentrations or initiation of therapeutic anticoagulation due to insufficient evidence.<sup>22</sup> The CHEST guideline and expert panel recommended standard prophylaxis dosing over full therapeutic dosing based on lack of evidence and use of LMWH over UFH to limit staff exposure.<sup>23</sup> The Anticoagulation Forum suggested against using biomarkers such as D-dimer to guide intensification of anticoagulation and recommended the use of standard dose VTE prophylaxis for non-critically ill patients and increased doses of VTE prophylaxis (subcutaneous heparin 7500 units 3 times daily, enoxaparin 40 mg twice daily, or low-intensity heparin infusion) for critically ill patients, recommendations based largely on expert opinion.<sup>24</sup> In addition to the above recommendations, there are currently a number of ongoing studies evaluating the effects of anticoagulation with alternative agents such as enoxaparin and rivaroxaban or different therapeutic targets such as anti-Xa levels or higher aPTT ranges in patients with COVID-19.<sup>25-29</sup>

Our study has several limitations that we acknowledge. First, given its retrospective design, we were unable to achieve a study with a large sample size with balanced severity of illness or account for missing data values in the electronic medical record. Although patient comorbidities were well matched, there was a significant difference in the SOFA scores between the 2 groups and potential for selection bias which were unable to be accounted for due to limitations in overall sample size and the retrospective nature of this study. Second, we were unable to report the trends of laboratory values and clinical endpoints over a longer period given logistical restrictions. The lack of statistical significance in our primary outcome may be attributed to the limited use of diagnostic ultrasonography and radiology; these procedures were limited at the time in an effort to minimize staff exposure performing unnecessary tests. Moreover, imaging studies were challenging in select patients with severe ARDS who required prone positioning. Furthermore, the diagnostic yield of those tests would have likely been low given the high incidence of microvascular as opposed to macrovascular thrombosis.

## Conclusion

In summary, the use of continuous infusion UFH targeting an aPTT of 40 to 60 seconds for patients with confirmed COVID-19 infection was not associated with a lower rate of thromboembolic complications. The use of an UFH infusion

may prevent increases in D-dimer concentrations but may also increase the risk of minor bleeding. Additional studies are needed to determine the precise indications for initiation of therapy, the optimal anticoagulant, and the therapeutic target for the management of hypercoagulability associated with COVID-19 infection.

## Acknowledgments

The authors would like to thank Brian L Altonen, MS, MPH for his statistical expertise during the analysis of this study.

## Declaration of Conflicting Interests


The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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