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# Heparin Resistance in SARS-CoV-2 Infected Patients with Venous Thromboembolism

**Terence Chau[1], Merlyn Joseph[2], Diana M. Solomon[1], Bryan Lee[3], and Lauren A. Igneri[1]**

## Abstract

**Introduction:** Heparin resistance has been reported in coronavirus disease 2019 (COVID-19) patients receiving intravenous unfractionated heparin (IV UFH). Anti-Xa monitoring of IV UFH has been suggested over activated partial thromboplastin times due to laboratory interference from elevated factor VIII and fibrinogen levels in COVID-19 patients. Information on heparin resistance with anti-Xa monitoring in COVID-19 patients with confirmed venous thromboembolism (VTE) is lacking. **Methods:** In this retrospective cohort study of patients with radiographically confirmed VTE, IV UFH dosage requirements in COVID-19 positive patients were compared with COVID-19 negative patients. The primary endpoint was the IV UFH dose needed to achieve a therapeutic anti-Xa level. Secondary endpoints included time to therapeutic anti-Xa, number of dose adjustments to achieve therapeutic anti-Xa, and bleeding. **Results:** Sixty-four patients with confirmed VTE were included (20 patients COVID-19 positive, 44 patients COVID-19 negative). Eighty-five percent (17 of 20) of COVID-19 positive patients achieved anti-Xa $\geq$0.3 units/mL with the first anti-Xa level drawn post-IV UFH infusion initiation. The median UFH dose needed to achieve first therapeutic anti-Xa was similar between COVID-19 positive and COVID-19 negative patients (median [IQR]: 18 units/kg/hour [18-18] vs 18 units/kg/hour [18-18], $P = .423$). The median number of dose adjustments and time to achieve therapeutic anti-Xa were also similar between the 2 groups. The frequency of patients receiving IV UFH of more 35 000 units/day did not differ between the 2 groups. Two cases of clinically significant heparin resistance in the COVID-19 positive group were identified. **Conclusions:** During the first wave of COVID-19, heparin dose and time to therapeutic anticoagulation appeared to be similar between COVID-19 positive and COVID-19 negative patients monitored by anti-Xa at our institution. More studies are required to evaluate clinically significant heparin resistance in the context of the wide range of viral variants which developed, and beyond the population observed in this single center retrospective study.

**Keywords**
anticoagulants, blood, COVID, critical care

## Background

Despite the use of standard venous thromboembolism (VTE) prophylaxis and therapeutic anticoagulation dosing strategies, anticoagulation failures including heparin resistance (ie, requiring heparin doses >35 000 units/day to achieve therapeutic anticoagulation), have been described in coronavirus disease 2019 (COVID-19) patients.[1-3] Potential mechanisms for anticoagulation failures have been proposed including severe inflammatory process, direct endovascular injury, elevated risk of thromboembolism in COVID-19, increased heparin-binding proteins, and altered pharmacokinetics (ie, augmented renal clearance, increased heparin clearance), or lower antithrombin levels.[4-6]

One concern with heparin resistance in COVID-19 patients may be due to the anticoagulation monitoring method. Heparin binds reversibly to antithrombin leading to inactivation of factors IIa and Xa. Thus, antithrombin deficiency will result in lower anti-Xa and activated partial thromboplastin times (aPTT) in patients on intravenous (IV) unfractionated heparin (UFH). Elevated levels of factor VIII and fibrinogen will affect aPTT, but not anti-Xa assays. Small observational, retrospective studies in COVID-19

[1]Cooper University Health Care, Camden, NJ, USA
[2]Texas A&M University, Irma Lerma Rangel College of Pharmacy, Houston, TX, USA
[3]Kaiser Permanente Oakland Medical Center, Oakland, CA, USA

**Corresponding Author:**
Terence Chau, Department of Pharmacy, Cooper University Hospital, One Cooper Plaza, Camden, NJ 08103, USA.
Email: chau-terence@cooperhealth.edu

patients showed these patients had normal antithrombin values, but elevated levels of factor VIII and fibrinogen. Therefore, it is suggested anti-Xa activity assays be utilized over aPTT monitoring in COVID-19 patients.[7,8]

We conducted a retrospective cohort study to determine if COVID-19 positive patients required more IV UFH to achieve therapeutic anticoagulation with anti-Xa monitoring compared to COVID-19 negative patients. We hypothesized the heparin dosage needed to achieve therapeutic anti-Xa levels between COVID-19 positive and COVID-19 negative patients would not differ significantly when using anti-Xa monitoring.

## Methods

This was an IRB-approved, retrospective medication use evaluation of IV UFH in adult patients with radiographically confirmed VTE during the first wave of the COVID-19 pandemic (March 2020 through June 2020). Exclusion criteria included: conditions which may alter heparin pharmacokinetics including pregnancy and targeted temperature management; acquired conditions which may increase risk for heparin resistance, including extracorporeal membrane oxygenation; less than 3 anti-Xa levels drawn or duration of IV UFH infusion of less than 24 hours; or received a direct oral anticoagulant (DOAC) prior to IV UFH initiation (to avoid DOAC influence on the heparin anti-Xa assay). Baseline and peak inflammatory markers, such as C-reactive protein, ferritin, fibrinogen, D-dimer, and lactate dehydrogenase were collected in the COVID-19 positive patients.

The primary outcome was to compare the IV UFH dose needed to achieve an anti-Xa $\geq$0.3 units/mL between COVID-19 positive and COVID-19 negative patients. Anti-Xa levels of $<$0.3, 0.3 to 0.7, and $>$0.7 units/mL were considered to be subtherapeutic, therapeutic, and supratherapeutic, respectively. Secondary outcomes included: time to anti-Xa $\geq$0.3 units/mL; number of dose adjustments needed to achieve anti-Xa $\geq$0.3 units/mL; IV UFH dose needed to achieve therapeutic anti-Xa (0.3-0.7 units/mL); number of dose adjustments needed to achieve therapeutic anti-Xa concentrations; time to therapeutic anti-Xa concentrations; and bleeding.

Data was analyzed with the Chi-Square/Fisher's exact test and Mann-Whitney *U*-test where appropriate. All laboratory analyses were performed using the same analyzer (ACL TOP 750 CTS; Werfen) and reagents (HemosIL Liquid Anti-Xa; Werfen).

Our institution's VTE protocol has an optional IV UFH bolus of 80 units/kg with an initial starting dose of 18 units/kg/hour. Doses were based upon actual body weight and dose-capping was at the provider discretion during the study timeframe. Anti-Xa levels are drawn 6 hours after initiation of the UFH infusion and every 6 hours thereafter until 2 consecutive anti-Xa levels are therapeutic, then anti-Xa levels are checked daily. For patients unable to achieve anti-Xa $\geq$0.3 units/mL within 24 hours of IV UFH protocol initiation, they were further evaluated for potential clinically significant heparin resistance. Heparin resistance was defined as either: (1) requirement $>$35 000 units of IV UFH per day to achieve anti-Xa $\geq$0.3 units/mL; or (2) $>$35 000 units of IV UFH per day and unable to achieve anti-Xa $\geq$0.3 units/mL.

## Results

A total of 321 patients were screened for eligibility. We included 64 patients with confirmed VTE in the analysis (20 patients COVID-19 positive, 44 patients COVID-19 negative). COVID-19 positive patients were more likely to be admitted or transferred to the intensive care unit (85% vs 52.3%, $P$=.014), receive mechanical ventilation (65% vs 31.8%, $P$=.013), and experience acute kidney injury (25% vs 2.3%, $P$=.010). There were no significant differences between age, weight, body mass index, or the use of UFH loading dose between the 2 groups (Table 1). The median duration of hospitalization was longer in COVID-19 positive patients (median [interquartile range (IQR)]: 18.5 days [7.3-27] vs 7 days [4-17.8], $P$=.006).

Eighty-five percent (17 of 20) of COVID-19 positive patients achieved anti-Xa $\geq$0.3 units/mL with the first anti-Xa level drawn post-IV UFH infusion initiation. In COVID-19 negative patients, 90.9% (40 of 44) achieved this value with the first anti-Xa lab draw. For the primary outcome (Table 2), the median UFH dose needed to achieve first anti-Xa $\geq$0.3 units/mL was similar between COVID-19 positive and COVID-19 negative patients (median [IQR]: 18 units/kg/hour [18-18] vs 18 units/kg/hour [18-18], $P$=.423). The median number of dose adjustments and time to achieve anti-Xa $\geq$0.3 units/mL were also similar between the 2 groups.

All patients achieved anti-Xa $\geq$0.3 units/mL with IV UFH. A total of 23 patients (7 COVID-19 positive and 16 COVID-19 negative) required more than 35 000 units/day to achieve or maintain anti-Xa $\geq$0.3 units/mL. There was no significant difference between the COVID-19 positive and COVID-19 negative patients in the frequency of IV UFH requirements greater than 35 000 units/day (35% vs 36.5%, $P$=.916). The median weight for these patients were 99.1 kg (IQR: 84.3-115.2). The median IV UFH dose required for first anti-Xa $\geq$0.3 units/mL achievement was 18 units/kg/hour (IQR: 18-18). The median time to anti-Xa $\geq$0.3 units/mL achievement was 6.7 hours (IQR: 6.2-12.5). There was no statistically significant difference between median weight, median IV UFH dose for first anti-Xa $\geq$0.3 units/mL, or median time to anti-Xa $\geq$0.3 units/mL between the COVID-19 positive and COVID-19 negative patients.

Three patients (2 COVID-19 positive patients and 1 COVID-19 negative patient) did not achieve anti-Xa $\geq$0.3 units/mL within 24 hours of UFH initiation. Of these 3 patients, we identified 2 cases of potentially clinically significant heparin resistance. Both cases were COVID-19

**Table 1.** Baseline Characteristics.

| Variable | COVID-19 positive n = 20 | COVID-19 negative n = 44 | *P*-value |
|---|---|---|---|
| Patient demographics | | | |
| Male, n (%) | 13 (65) | 24 (54.5) | .432 |
| Age, years | 62 (56.0-72.8) | 60 (48.0-73.8) | .755 |
| Diabetes mellitus, n (%) | 7 (35) | 7 (15.9) | .087 |
| Heart failure, n (%) | 0 (0) | 3 (6.8) | .546 |
| Chronic kidney disease or end-stage renal disease, n (%) | 3 (15) | 1 (2.3) | .087 |
| Malignancy, n (%) | 1 (5) | 6 (13.6) | .419 |
| Chronic obstructive pulmonary disease, n (%) | 0 (0) | 3 (6.8) | .546 |
| Hospital course | | | |
| Length of stay, days | 18.5 (7.3-27.0) | 7.0 (4.0-17.8) | .006 |
| ICU, n (%) | 17 (85) | 23 (52.3) | .014 |
| Mechanical ventilation, n (%) | 13 (65) | 14 (31.8) | .013 |
| Cardiac arrest, n (%) | 0 (0) | 4 (9.1) | .300 |
| Infection, other than COVID-19, n (%) | 7 (35) | 8 (18.2) | .141 |
| Acute kidney injury, n (%) | 5 (25) | 1 (2.3) | .010 |
| Heparin dosing characteristics | | | |
| BMI, mg/kg$^2$ | 29.9 (25.6-36.2) | 29.8 (23.5-37.0) | .696 |
| Height, inch | 69 (64.5-70.8) | 66.5 | .300 |
| Weight, kg | 92.1 (75.1-107.5) | 84.4 (68.0-104.6) | .434 |
| Deep vein thrombosis, n (%) | 14 (70) | 22 (50) | .453 |
| Pulmonary embolism, n (%) | 5 (25) | 18 (40.9) | |
| Other thrombus type, n (%) | 1 (5) | 4 (9.1) | |
| UFH loading dose, n (%) | 9 (45) | 16 (36.4) | .512 |
| UFH loading dose, unit/kg | 79.9 (65.8-80.2) | 79.6 (79.2-79.7) | .760 |
| Laboratory information | | | |
| Serum creatinine, mg/dL | | | |
| Initial | 1.3 (1.0-1.7) | 1.3 (0.9-1.6) | .456 |
| Peak | 2.8 (1.5-4.4) | 1.5 (1.0-1.9) | .003 |
| Albumin, g/dL[a] | | | |
| Initial | 3.1 (2.7-3.6) | 3.4 (2.8-3.7) | .245 |
| Nadir | 2.5 (2.0-2.8) | 2.7 (2.3-3.5) | .053 |
| Total bilirubin, mg/dL[a] | | | |
| Initial | 0.7 (0.4-1.0) | 0.6 (0.2-0.8) | .288 |
| Peak | 0.9 (0.6-1.5) | 0.7 (0.5-1.1) | .131 |
| AST, u/L[a] | | | |
| Initial | 50 (21-96) | 27.5 (15.5-57.5) | .239 |
| Peak | 81 (50-271) | 36.5 (19-135) | .056 |
| ALT, μ/L[a] | | | |
| Initial | 34 (14-52) | 22 (14.3-45.5) | .479 |
| Peak | 52 (31-98) | 36 (15.5-107.5) | .229 |
| Hemoglobin, g/dL | | | |
| Initial | 12.9 (10.9-14.4) | 11.2 (9.0-14.0) | .192 |
| Nadir | 8.2 (5.9-9.9) | 8.5 (6.7-11.1) | .235 |
| INR[b] | | | |
| Initial | 1.2 (1.1-1.3) | 1.2 (1.1-1.4) | .918 |
| Peak | 1.4 (1.2-2.2) | 1.4 (1.2-2.1) | .934 |
| aPTT, s[c] | | | |
| Initial | 31.4 (27.6-47.7) | 32.1 (27.5-43.3) | .933 |
| Peak | 50.6 (39.9-69.8) | 41.7 (30.6-120.0) | .516 |
| Platelet, $10^3/\mu L$ | | | |
| Initial | 243.5 (170.5-305.3) | 222 (172.5-360.0) | .873 |
| Nadir | 140 (63-228.5) | 170 (107-234.5) | .281 |
| Triglycerides, mg/dL[d] | | | |
| Initial | 249 (183.5-380.8) | 112 (91-266) | .071 |
| Peak | 355.5 (226.8-571.3) | 112 (103-266) | .021 |

*(continued)*

**Table 1. (continued)**

| Variable | COVID-19 positive n = 20 | COVID-19 negative n = 44 | *P*-value |
|---|---|---|---|
| Inflammatory markers[e] | | | |
| Initial C-reactive protein, mg/dL | 14.7 (8.0-24.6) | — | — |
| Peak C-reactive protein, mg/dL | 20.75 (10.3-27.2) | — | — |
| Initial ferritin, ng/mL | 1320.5 (924.3-1541) | — | — |
| Peak ferritin, ng/mL | 1967 (1538.3-2742.8) | — | — |
| Initial d-dimer, μg/mL | 3.7 (2-10.7) | — | — |
| Peak d-dimer, μg/mL | 7.4 (5.4-21.6) | — | — |
| Initial lactate dehydrogenase, unit/L | 517 (400.5-848.8) | — | — |
| Peak lactate dehydrogenase, unit/L | 819.5 (499-1016.5) | — | — |

*Note.* Median (IQR) unless otherwise specified. BMI = body mass index; ICU = intensive care unit; UFH = unfractionated heparin; AST = aspartate transaminase; ALT = alanine transaminase; PT = prothrombin time; INR = international normalized ratio; aPTT = activated partial thromboplastin time.
[a]Data available for 19 COVID-19 positive patients, 36 COVID-19 negative patients.
[b]Data available for 18 COVID-19 positive patients, 36 COVID-19 negative patients.
[c]Data available for 19 COVID-19 positive patients, 43 COVID-19 negative patients.
[d]Data available for 14 COVID-19 positive patients, 11 COVID-19 negative patients.
[e]Data available for 18 COVID-19 positive patients.

**Table 2.** Results.

| | COVID-19 positive n = 20 | COVID-19 negative n = 44 | *P*-value |
|---|---|---|---|
| Primary outcome | | | |
| UFH dose for first anti-Xa ≥ 0.3 units/mL, units/kg/h | 18 (18-18) | 18 (18-18) | .423 |
| UFH dose ranges for first anti-Xa ≥ 0.3 units/mL, units/kg/h, n (%) | | | |
| 18 | 17 (85) | 40 (90.9) | .448 |
| >18-22 | 1 (5) | 3 (6.8) | |
| >22-26 | 1 (5) | 1 (2.3) | |
| >26-30 | 0 (0) | 0 (0) | |
| >30 | 1 (5) | 0 (0) | |
| Other outcomes | | | |
| Time to first anti-Xa ≥ 0.3 units/mL, h | 6.13 (5.92-9.44) | 6.25 (6.03-7.29) | .317 |
| Number of dose adjustments to achieve ≥0.3 units/mL | 0 (0-0) | 0 (0-0) | .430 |
| Frequency of dose adjustments to achieve ≥0.3 units/mL, n (%) | | | |
| 0 | 17 (85) | 40 (90.9) | .173 |
| 1 | 1 (5) | 3 (6.8) | |
| 2 | 0 (0) | 1 (2.3) | |
| >2 | 2 (10) | 0 (0) | |
| First anti-Xa level post-UFH infusion ≥0.3 units/mL, n (%) | 17 (85) | 40 (90.9) | .483 |
| UFH dose for first therapeutic anti-Xa level range, unit/kg/h | 15 (12-18) | 15.5 (12.3-18) | .865 |
| Number of dose adjustments to achieve first therapeutic anti-Xa level range | 1.5 (0.25-3) | 1 (0-2) | .190 |
| Time to therapeutic target range attainment, h | 21.1 (7.8-32.7) | 15.8 (9.1-27.9) | .690 |
| High dose heparin infusions | | | |
| Received >35 000 units/day to achieve or maintain anti-Xa ≥ 0.3 units/mL | 7 (35) | 16 (36.4) | .916 |
| Clinically significant heparin resistance* | 2 (10) | 0 (0) | .094 |

*Note.* Median (IQR) unless otherwise specified. UFH = unfractionated heparin.
*In patients unable to achieve anti-Xa ≥ 0.3 units/mL within 24 hours; heparin resistance definition: (1) requirement >35 000 units of IV UFH per day to achieve anti-Xa ≥ 0.3 units/mL; or (2) >35 000 units of IV UFH per day and unable to achieve anti-Xa ≥ 0.3 units/mL).

positive, exhibited prolonged time to achieve anti-Xa ≥ 0.3 units/mL, and required over 50 000 units of IV UFH per day. The third patient was determined not to be heparin resistant as prolonged time to achieve anti-Xa ≥ 0.3 units/mL was attributed to IV access issues and required less than 35 000 units/day of UFH per day. Details of these 3 patients are described in Table 3.

Initial anti-Xa levels were frequently supratherapeutic (>0.7 units/mL) and occurred in 64.1% of our patients (70% in COVID-19 positive and 61.4% in COVID-19 negative

**Table 3.** Characteristics of Patients not Achieving Anti-Xa ≥ 0.3 units/mL at 24 hours.

| Patient | COVID-19 status | Indication for anticoagulation | ICU status | Weight, kg | UFH bolus, units/kg | Estimated UFH dose, units/day | Time to anti-Xa ≥ 0.3 units/mL, h | Heparin resistance* | Discharge status |
|---|---|---|---|---|---|---|---|---|---|
| 59 year old male | Positive | Deep vein thrombosis | ICU | 98.4 | None | 56 696 | 28.23 | Yes | Alive |
| 41 year old male | Positive | Pulmonary embolism | Floor | 77.6 | 80 | 59 577 | 53.62 | Yes | Alive |
| 87 year old female | Negative | Deep vein thrombosis | Floor | 59.2 | None | 28 393 | 27.52 | No | Alive |

*In patients unable to achieve anti-Xa > 0.3 units/mL within 24 hours; heparin resistance definition: (1) requirement >35 000 units of IV UFH per day to achieve anti-Xa ≥ 0.3 units/mL; or (2) >35 000 units of IV UFH per day and unable to achieve anti-Xa ≥ 0.3 units/mL)

patients, $P = .504$). There were no differences in the UFH dose needed to achieve therapeutic anti-Xa range concentrations (0.3-0.7 units/mL) between the COVID-19 positive and COVID-19 negative patients (median [IQR]: 15 units/kg/hour [12-18] vs 15.5 units/kg/hour [12.3-18], $P = .865$). The median number of dose adjustments needed to achieve therapeutic anti-Xa range was also similar ($P = .190$). Time to therapeutic target range attainment was longer in the COVID-19 group, but not statistically significant (median [IQR]: 21.1 hours [7.8-32.7] vs 15.8 hours [9.1-27.9], $P = .690$).

Hemoglobin decrease ≥2 g/dL from baseline occurred more frequently in COVID-19 patients (80% vs 47.7%, $P = .028$), but there was no difference in number of patients with hemoglobin <7 g/dL compared to COVID-19 negative patients (35% vs 29.5%, $P = .633$). Protamine administration occurred once in the COVID-19 negative group. No patients received ≥2 units of packed red blood cells during or immediately after IV UFH infusion. Full International Society of Thrombosis and Hemostasis Criteria for major bleeding and clinically relevant non-major bleeding was unable to be collected due to the retrospective nature of the study.

## Discussion

Heparin resistance has been traditionally defined as: (1) the need for IV UFH doses of >35 000 units/day to achieve target anticoagulation; or (2) the need for more than 500 units/kg to achieve target activated clotting time in patients undergoing cardiopulmonary bypass.[9,10] The mechanisms behind heparin resistance include: increased heparin-binding proteins; increased heparin clearance; antithrombin deficiency; and elevated levels of factor VIII and fibrinogen.[10]

In a patient with increased heparin-binding proteins, increased clearance, or antithrombin deficiency, the aPTT and anti-Xa values will be lower than expected while receiving IV UFH. Management of heparin resistance due to increased heparin-binding proteins and clearance include increasing the heparin dosage or consideration of an alternative anticoagulation (ie, direct thrombin inhibitor). If antithrombin deficiency is identified as the cause of heparin resistance, the patient may either be transitioned to a direct thrombin inhibitor or antithrombin may be increased by supplementation.

For IV UFH patients with elevated levels of factor VIII and fibrinogen, such as those seen with substantial systemic inflammation, aPTT values will be falsely low but anti-Xa values will not be affected. These cases have been referred to as heparin pseudo-resistance.[6,11] Management of these cases include changing the laboratory monitoring method of IV UFH from aPTT to anti-Xa. Alternatively, anticoagulation with low molecular weight heparin would be an acceptable option. Switching to a direct thrombin inhibitor would not be ideal as aPTT is typically used to monitor therapy.[12]

Any COVID-19 patient with suspected heparin resistance needs to be evaluated in the context of the laboratory test used to monitor IV UFH and the target anticoagulation goal. Small observational, retrospective studies in COVID-19 patients with heparin resistance have shown normal antithrombin values, but elevated levels of factor VIII and fibrinogen. Therefore, it is suggested anti-Xa activity assays be utilized over aPTT monitoring in COVID-19 patients as aPTT will be falsely low due to elevation of those factors.[7,8]

In our overall patient cohort, dosage requirements and time to anti-Xa ≥ 0.3 units/mL with an UFH anti-Xa monitoring strategy for VTE treatment were similar between COVID-19 positive and COVID-19 negative patients. While the incidence of heparin resistance outside of cardiac surgery is unknown, small retrospective studies reported potential heparin resistance in 75% to 80% of examined COVID-19 patients.[8,13] Notably, we identified 10% of our COVID-19 positive patients with potential clinically significant heparin resistance with anti-Xa monitoring. Our results suggest concerns for apparent heparin resistance in COVID-19 patients may potentially be mitigated with anti-Xa monitoring of IV UFH. While the COVID-19 group presumably had higher inflammatory markers, higher rates of acute renal failure and hypertriglyceridemia were also present. Renal failure and elevated triglycerides (>360 mg/dL) may impact anti-Xa levels through decreased heparin clearance and assay interference, respectively.[14] In this study,

only one patient received IV UFH with hypertriglyceridemia concomitantly. The significance of the interaction between these factors on anti-Xa achievement would need to be further evaluated in larger studies.

There are several limitations to this retrospective, single-center study. The small sample size could increase the risk of a Type II error. One reason for the small number of COVID-19 positive patients was our strict inclusion criteria of radiographically confirmed VTE with IV UFH treatment. Previous studies reporting heparin resistance in COVID-19 positive patients included patients on UFH or low molecular weight heparin with or without confirmed thrombosis.[7,8,13] Second, we included patients on UFH infusions for at least 24 hours. We may not have captured all heparin resistant patients as those with initial low anti-Xa levels may have transitioned to alternative anticoagulants. Third, inflammatory markers such as interleukin-6, C-reactive protein, ferritin, and D-dimer are not routinely obtained in our COVID-19 negative patients thus we were unable to make comparisons between the 2 study groups. It is assumed the COVID-19 positive group would have higher levels of inflammation than COVID-19 negative patients. Fourth, the impact of COVID-19 variants on heparin resistance and thrombotic complications is largely unknown. This study reviewed COVID-19 patients during the first wave in the northeastern United States (March through June 2020). The results of this study may not be generalizable to the current variant. Fifth, although doses and time to anti-Xa $\geq 0.3$ units/mL achievement was evaluated in our study, ongoing IV UFH doses required to maintain this therapeutic target was not evaluated. Heparin resistance was primarily screened during the acute phase of IV UFH initiation and there is a possibility of the development of heparin resistance later in the hospital stay. One final consideration is the definition of heparin resistance. While doses of $>35\,000$ units/day of IV UFH has been suggested,[9,10] this definition has not been validated in clinical trials. Additionally, patient body weight will significantly impact heparin resistance rates using this definition. Patients in our study had median weights of 92.1 and 84.4 kg in the COVID-19 positive and negative groups, respectively. Generally accepted doses for initial treatment of VTE (18 units/kg/hour) could easily exceed 35 000 units/day of IV UFH with these body weights. With strict application of this definition alone, 23 patients (median weight of 99.1 kg) would meet heparin resistance criteria (7 COVID-19 positive and 16 COVID-19 negative). By applying the definition of heparin resistance on patients unable to achieve anti-Xa $\geq 0.3$ units/mL within 24 hours of IV UFH initiation, we identified 2 potentially clinically significant cases of heparin resistance in COVID-19 positive patients with active VTE where delayed time to therapeutic goal may be detrimental.

Strengths of our study are the use of a control group and limiting therapeutic anticoagulation to IV UFH only. Any concerns about variation in heparin potency in the IV UFH were minimized both treatment groups were on IV UFH during the same timeframe. Another strength is the inclusion of patients only with radiographically confirmed VTE. Our study timeframe spanned the first wave of the COVID-19 pandemic when there was much discussion in both the public and medical media about thromboembolic events, whether macrovascular or microvascular, contributing to the complexity and severity of illness of patients diagnosed with COVID-19. During this first wave, some institutions adopted practices for empiric therapeutic-dose and intermediate-dose prophylactic anticoagulation. Our institution did not adopt these practices due to inadequate supporting evidence in the literature. Much data has since been published on the subject of therapeutic-dose and intermediate-prophylactic dose anticoagulation in COVID-19 in the 2 years the pandemic has impacted the United States.[15-19] While the authors' note the importance of VTE prophylaxis, our study is different as it only included patients with confirmed VTE and an indication for therapeutic-dose anticoagulation. At this time, empiric therapeutic anticoagulation in critically ill COVID-19 patients is not recommended.[20,21] The majority of our COVID-19 patients were critically ill and our results reflect a more realistic clinical situation where therapeutic anticoagulation would be utilized in the intensive care unit. To date, there is a lack of large studies examining the use of IV UFH for the treatment of VTE in COVID-19 patients as these studies utilized empiric anticoagulation or primarily low molecular weight heparins, such as enoxaparin.[15-19]

## Conclusion

Previous studies have suggested anti-Xa over aPTT monitoring of IV UFH may be advantageous in COVID-19 patients. Our study revealed heparin dosage and time to therapeutic anticoagulation appear to be similar between COVID-19 positive and COVID-19 negative patients with anti-Xa monitoring. COVID-19 patients may be successfully anticoagulated with IV UFH using an anti-Xa monitoring strategy; however concern for clinically significant heparin resistance in COVID-19 patients monitored with anti-Xa levels may still exist based on our findings. Future studies examining the use of anti-Xa for IV UFH in COVID-19 patients are needed to strengthen the recommendation to use an anti-Xa monitoring strategy over aPTT and to further define heparin resistance in this population.

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## ORCID iDs

Terence Chau https://orcid.org/0000-0002-3671-8394

Merlyn Joseph https://orcid.org/0000-0003-4190-8800


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