

# EFFECTS OF THERAPEUTIC ANTICOAGULATION FOR SARS-COV-2 COAGULOPATHY ON MARKERS OF INFLAMMATION AND MORTALITY

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## The Novel Virus and Anticoagulation

Thromboembolic events are a recognized and feared complication of the Novel 2019 SARS-CoV-2 virus responsible for the 2019 COVID pandemic<sup>1</sup>. Emerging data suggests that significant end organ damage occurs as a result of microthrombi formation within these organ systems<sup>2</sup>. Serum markers, namely C Reactive Protein (CRP), D-Dimer, Ferritin and Lactate Dehydrogenase (LDH) are used as surrogates to measure this process. Practitioners have been using therapeutic anticoagulation to treat and oftentimes prevent these occurrences with little data regarding their effects on these serum inflammatory markers. Furthermore, it was not well understood the effects that discreet patient variables would have on clinical outcomes of patients receiving therapeutic anticoagulation.

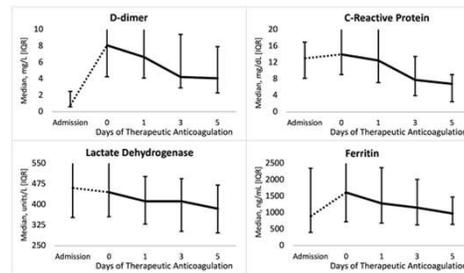
## The Formal Evaluation

In this single center, retrospective cohort study, we identified 145 COVID positive, adult patients admitted to the medical intensive care unit (ICU) between March 3, 2020, and April 12, 2020. Patients were initiated on parenteral therapeutic anticoagulation with unfractionated heparin (UFH) at the discretion of the care provider. Informal indications for initiation of anticoagulation, based on common practice, became D-Dimer greater than six times the upper limit of normal (>6x ULN), a Sepsis Induced Coagulopathy (SIC) score of greater than 4, or evidence of thrombotic disease. Demographic and laboratory data was collected on each of the subjects upon ICU admission and repeated on days one, three, five and seven of admission and at the conclusion of the follow up period when patient outcomes were also documented. Comparisons were made using two-sided Mann-Whitney U test. Multivariate analyses for predicting death were calculated using Cox proportional-hazards models. Survival analyses were conducted using Kaplan-Meier estimators for death, stratified by age, d-dimer, and BMI. Patients missing any of the variables used to stratify the population under survival analysis (e.g. age, final d-dimer, BMI) were excluded. Patients with time under anticoagulation therapy as less than 48 hours were also excluded. Patients were followed from initiation of anticoagulation therapy until censorship. Censorship criteria included death, discharge, discontinuation of parenteral anticoagulation, or change in anticoagulation strategy.

## Results

Of 145 subjects, 67 (46%) received therapeutic anticoagulation; 58 (87%) for COVID-19 coagulopathy and 12 (18%) for thrombotic events. Initial median [IQR] serum values were as follows: CRP 14 mg/dL (9-21), d-dimer 8.1 mg/L (4.3-18.6), ferritin 1,614 ng/mL (723-2526) and LDH 445 units/L (356-629). Five days after initiation of anticoagulation all patients had a decrease in all measured serum values: CRP 6.8 (2.5-9), LDH 385 (297-472), D-Dimer 4.1 (2.3-7.9) and Ferritin 975 (646-1483;  $P < 0.05$  for all). At the time of follow-up, 23 (34%) patients had been discharged alive, 20 (30%) patients had expired, and 24 (36%) patients remained in-hospital. Mortality was directly associated with age (HR 9.05; 95%CI 1.71-46) and post-anticoagulation d-dimer level (HR 9.78; 95%CI 1.81-52.9;  $P < 0.01$  for both), and inversely associated with obesity (HR 0.27, 95%CI 0.80-0.93;  $P < 0.05$  for all).

Figure 1. Change in Serum Laboratory Values After Initiation of Therapeutic Anticoagulation



Legend for Figure 1. This figure depicts the changes in d-dimer, c-reactive protein, lactate dehydrogenase and ferritin from the time of admission and then at days 1, 3 and 5 after starting therapeutic anticoagulation.

Figure 2. Kaplan-Meier Estimate of Mortality in Critically Ill Patients Undergoing Therapeutic Anticoagulation for COVID-19 Coagulopathy

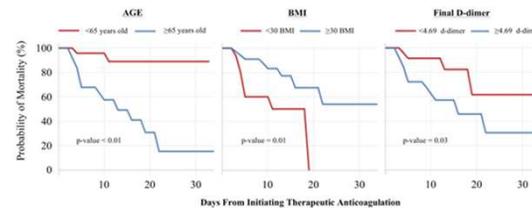


Figure 2 Legend. These Kaplan-Meier estimator curves depict the mortality of the patient sample according to (left-to-right) age > 65 years-old, BMI > 30 kg/m<sup>2</sup>, and final d-dimer\* >4.69 mg/L. Definitions: BMI, Body mass index.

\* Final D-dimer was defined as the last available serum d-dimer result measured after initiating therapeutic anticoagulation. D-dimer values were stratified by the median of the cohort (4.69 mg/L).

## Discussion

This study is the first report the effects of therapeutic anticoagulation on pro-inflammatory serum markers. In this population, the results show a statistically significant decrease in these markers which may suggest not only efficacy in prevention/treatment of thrombotic disease, but also may speak to the anti-inflammatory properties of UFH itself.

Older age and higher d-dimer levels were identified as risk factors for mortality in this study. Specifically, we found that age greater than 65 years-old and a increased d-dimer were associated with higher mortality rates.

The majority of this critically ill population was obese, consistent with prior data showing obesity to be a strong risk factor for clinically severe COVID-19 infection<sup>3</sup>. In contrast to prior studies, however, we found that BMI greater than 30 kg/m<sup>2</sup> conferred a lower risk of death in patients on therapeutic anticoagulation. UFH therapy in obese patients has unique attributes, including close monitoring of weight-based dosing, that may help obese patients achieve target dosing range more quickly. We also propose that therapeutic anticoagulation with UFH may also uniquely benefit obese patients by addressing the higher rates of thrombotic disease and the inflammatory state associated with obesity. The therapeutic roles of heparin in obese COVID positive patients will require further exploration.

## Conclusions

In this patient population, therapeutic anticoagulation was associated with a decrease in inflammatory markers, suggesting efficacy of treatment. Anticoagulation may have a particularly important role in obese patients, as obesity was associated with higher survival in patients placed on anticoagulation. This study provides important data for larger, prospective trials.

## References

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