Clinical Outcomes With the Use of Prophylactic Versus Therapeutic Anticoagulation in Coronavirus Disease 2019

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Objectives: To determine the impact of anticoagulation on inhospital mortality among coronavirus disease 2019-positive patients with the a priori hypothesis that there would be a lower risk of inhospital mortality with use of preemptive therapeutic over prophylactic dose enoxaparin or heparin.

Design Setting: Retrospective cohort study from April 1, 2020, to April 25, 2020. The date of final follow-up was June 12, 2020 Two large, acute-care hospitals in Western Connecticut.

Patients: Five hundred and one inpatients were identified after discharge as 18 years or older and positive for severe acute respiratory syndrome coronavirus 2. The final sample size included 374 patients after applying exclusion criteria. Demographic variables were collected via hospital billing inquiries, whereas the clinical variables were abstracted from patients' medical records.

Exposure: Preemptive enoxaparin or heparin at a therapeutic or prophylactic dose.

Main Results: When comparing treatments through multivariable analysis, risk of inhospital mortality was 2.3 times greater in patients receiving preemptive therapeutic anticoagulation (95% CI = 1.0–4.9; $p = 0.04$). Additionally, the average treatment effects were higher ($\beta = 0.11$, $p = 0.01$) in the therapeutic group.

Conclusions: An increase in inhospital mortality was observed among patients on preemptive therapeutic anticoagulation. Thus, in the management of coronavirus disease 2019 and its complications, we recommend further research and cautious use of preemptive therapeutic over prophylactic anticoagulation.

Key Words: anticoagulants; coronavirus; length of stay; mortality; pneumonia; thrombosis

Postmortem analyses of patients with severe acute respiratory syndrome (SARS) viruses revealed microthrombi in pulmonary microvasculature, deep vein thrombosis, and pulmonary embolisms (1, 2). There have also been reports of coronavirus disease 2019 (COVID-19)-induced chilblains and acute acroischemia in younger patients (3). Prior studies sought to determine possible benefits in treating COVID-19 patients with anticoagulation therapy. Shi et al (4) found that 42 patients had a significant decrease in the proportion of lymphocytes, D-dimer levels, and fibrinogen-degradation products among a small sample of patients that received prophylactic low-molecular weight heparin (LMWH), with no decrease in length of hospitalization. Tang et al (5) found no difference in 28-day mortality among a sample of 449 COVID-19 patients who did or did not receive prophylactic LMWH. However, a subgroup analysis among patients with markers for severe disease revealed a significantly lower rate of mortality among patients who received heparin (5). In two studies, Paranjpe et al (6) described an association between the use of prophylactic and therapeutic anticoagulation and decreased inhospital mortality compared with patients who did not receive anticoagulation, but no significant difference in mortality between patients who received therapeutic versus prophylactic dosing.

All of these findings support the hypothesis that COVID-19 can induce a prothrombotic state. Despite some evidence, additional research is needed to identify possible treatments to minimize

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the potential harm among patients who are at risk for thrombotic complications. This research is particularly relevant given several popular algorithms (such as MATH+) advocating use of therapeutic anticoagulation, as well as reports from a number of centers using more than standard prophylactic dosing (7). There is also potential for harm with therapeutic anticoagulation due to increased bleeding risk, and a study by Kvernland et al (8) even showed increased rates of hemorrhagic stroke in anticoagulated COVID patients. The primary objective of this study was to determine the impact of anticoagulation on mortality among patients who received a therapeutic versus prophylactic dose of enoxaparin or heparin. We hypothesize preemptive treatment with therapeutic anticoagulation can lower the risk of mortality.

The secondary objective was to perform a subgroup analysis of patients with a severe inflammatory response (peak C-reactive protein [CRP] ≥ 200 mg/L) to determine the difference between the two groups in inhospital mortality.

This study is the first of its kind to compare clinical outcomes of COVID-19 positive patients who received preemptive therapeutic versus prophylactic anticoagulation, started upon admission instead of the treatment of a thrombotic condition. Previous studies assessed the impact of any anticoagulation therapy compared with none. This study can provide guidance to clinicians on the appropriate utilization of anticoagulation in COVID-19 patients.

MATERIALS AND METHODS

Study Design, Setting, and Participants

We conducted a retrospective cohort study of patients from two large, acute care hospitals in Western Connecticut. Both hospitals are located in Fairfield County, which had the highest frequency of infection in Connecticut with more than 24,000 cases of the virus to date (9). The protocol and subsequent work were granted exempt status by the Biomedical Research Alliance of New York (BRANY) Institutional Review Board under category #4(iii), as detailed in 45 code of federal regulations 46.104(d) and the BRANY's Standard Operating Procedure.

The study included adult patients admitted with a diagnosis of COVID 19 (*International Classification of Diseases,* 10th Edition code B97.29, J12.89, J18.9, U07.1) between April 1, 2020, and April 25, 2020, and treated with anticoagulation during their inpatient stay. Anticoagulation was defined as the therapeutic or prophylactic use of enoxaparin or heparin; both regimens started preemptively upon admission. As we designed the study to assess preemptive anticoagulation utilization, we excluded patients if they did not take enoxaparin or heparin during their inpatient stay or if they were on other forms of anticoagulation prior to or during their hospitalization. Demographic variables were collected via hospital billing inquiries, whereas the clinical variables were abstracted from patients' medical records.

Variables

Main Outcomes and Predictors. The primary outcome measures were a dichotomous variable for death. The secondary outcome measure was mortality in patients with peak CRP greater than or equal to 200 mg/L.

The primary exposure variable was dose of anticoagulation. Therapeutic dosage for enoxaparin was defined as 1 mg/kg subcutaneously bid or 1.5 mg/kg subcutaneously daily or based on renal function, or higher doses titrated to anti-Factor Xa range of 0.6–1 international units (IU)/mL (for bid dosing) and 1–2 IU/mL (for daily dosing) (10). Prophylactic dosage for enoxaparin was defined as 30 or 40 mg subcutaneously every day. For heparin, therapeutic dosage was defined as IV heparin titrated to an activated partial thromboplastin time between 70 and 110 s, and prophylactic dosage was defined as 5,000 units given subcutaneously every 8 hours. Patients were assigned to the therapeutic group if they preemptively received a therapeutic dosage of either medication at any time or the prophylaxis group if they only received prophylaxis for the duration of their inpatient stay. We recognize that the dichotomization of a time-varying variable may introduce some bias to the analysis. Thus, we created an alternative exposure variable for sensitivity analyses that defined anticoagulation as prophylactic or therapeutic dosage at time of admission.

Covariates. Numerous patient and treatment-related variables were included as possible confounders given their potential association with the outcomes (**Table 1**). Demographic variables included age, gender, race, and ethnicity. Race was defined as White, Black, or African American, and others. Ethnicity was defined as either Hispanic or non-Hispanic. We also included body mass index, smoking status (never/ever), diabetes, and current immunosuppression, prior history of heart disease, pulmonary disease, kidney disease, cancer, and hyperlipidemia. History of heart disease was defined as a dichotomous variable for any of the following: hypertension, congestive heart failure, myocardial infarction, atrial fibrillation, and other heart disease. History of any pulmonary disease included asthma, chronic obstructive pulmonary disease, pulmonary embolism, obstructive sleep apnea, and other.

History of cancer and kidney disease was each a dichotomous variable reflecting either of these conditions. We included immunosuppression as a dichotomous variable that reflected diseases such as transplant, myelodysplasia, rheumatoid arthritis, psoriatic arthritis, and cancer. Cancer and immunosuppression had some overlap in patients. However, they were maintained as separate variables, because the correlation between the variables was less than 0.25.

Treatment-related variables included the need for ICU admission, mechanical ventilation, and treatment with antibiotics, tocilizumab, hydroxychloroquine, or lopinavir/ritonavir. We also included a dichotomous variable for peak CRP defined as less than 200 or greater than or equal to 200 mg/L to reflect a hyperinflammatory response. Additionally, we collected data on the outcome of receiving packed red blood cells (pRBC) transfusion and the occurrence of an arteriovenous occlusive event.

Statistical Methods

We performed all analyses with StateSE 16 (StataCorps LLC, College Station, TX) (11). We computed descriptive statistics as percentages of the total for dichotomous and categorical variables and mean with SD for continuous. We also used Independent Student's *t* test to assess group differences for each continuous covariate and chi-square

TABLE 1. Descriptive Statistics Among Coronavirus Disease 2019-Positive Patients From Two Hospitals in Western Connecticut in the Coronavirus-Anticoagulation Study

Characteristics	Full Sample	Prophylactic Anticoagulation	Therapeutic Anticoagulation	*p*
Number of subjects	374	299	75	
Length of stay, mean (SD)	6.5 (5.0)	5.6 (4.0)[a]	10.8 (8.5)[b]	< 0.01
Age, mean (SD)	64.7 (18.1)	64.2 (17.9)	66.9 (18.6)	0.23
Body mass index[c], mean (SD)	29.0 (7.6)	28.7 (7.0)	30.5 (9.3)	0.07
Expired, *n* (%)	72 (19.3)	43 (14.4)	29 (38.7)	< 0.01
Gender[d] (female), *n* (%)	154 (41.2)	122 (40.8)	32 (42.7)	0.76
Race[e], *n* (%)				
White	202 (54.0)	159 (53.2)	43 (57.3)	0.81
African American	37 (9.9)	30 (10.0)	7 (9.3)	
Other	30 (8.0)	25 (8.4)	5 (6.7)	
Ethnicity (Hispanic), *n* (%)	125 (33.4)	104 (34.8)	21 (28.0)	0.25
Smoking status (ever), *n* (%)	124 (33.2)	105 (35.1)	19 (25.3)	0.56
Diabetes[d] (yes), *n* (%)	118 (31.6)	98 (32.8)	20 (26.7)	0.37
Heart disease[c] (yes), *n* (%)	212 (56.7)	174 (58.2)	38 (50.7)	0.30
Pulmonary disease[d] (yes), *n* (%)	94 (25.1)	75 (25.1)	19 (25.3)	0.89
Cancer[d] (yes), *n* (%)	46 (12.3)	37 (12.4)	9 (12.0)	0.98
Kidney disease[d] (yes), *n* (%)	40 (10.7)	32 (10.7)	8 (10.7)	0.96
Hyperlipidemia[d] (yes), *n* (%)	137 (36.6)	108 (36.1)	29 (38.7)	0.59
Immunosuppressed[c] (yes), *n* (%)	11 (2.9)	10 (3.3)	1 (1.3)	0.36
Intensive care (yes), *n* (%)	63 (16.8)	36 (12.0)	27 (36.0)	< 0.01
Mechanically ventilated (yes), *n* (%)	44 (11.8)	21 (7.0)	23 (30.7)	< 0.01
Peak C-reactive protein (≥ 200), *n* (%)	112 (29.9)	76 (25.4)	36 (48.0)	< 0.01
Antibiotic[c] (yes), *n* (%)	217 (58.0)	160 (53.5)	57 (76.0)	< 0.01
Hydroxychloroquine[d] (yes), *n* (%)	219 (58.6)	181 (60.5)	38 (50.7)	0.13
Lopinavir/ritonavir[c] (yes), *n* (%)	190 (50.8)	162 (54.2)	28 (37.3)	0.01
Tocilizumab[c] (yes), *n* (%)	56 (15.0)	31 (10.4)	25 (33.3)	< 0.01
Transfusion (yes), *n* (%)	3 (0.8)	1 (0.3)	2 (2.7)	0.04
Occlusive event[d] (yes), *n* (%)	13 (3.5)	4 (1.3)	9 (12.0)	< 0.01
Elected comfort measures (yes), *n* (%)	47 (12.6)	31 (10.4)	16 (21.3)	< 0.01

[a]Among survivors only (*n* = 256).
[b]Among survivors only (*n* = 46).
[c]Missing data < 5%.
[d]Missing data < 1%.
[e]Missing data = 28.1%.

or Fisher exact test for dichotomous/categorical covariates. We accounted for missing data with listwise deletion and set the alpha for statistical hypothesis testing at 0.05.

We used a multivariable logistic regression model to determine risk differences in mortality given anticoagulation dosage. We developed the model according to a priori hypotheses on confounders that were both associated with our primary exposure and outcome and not in the causal pathway. We also verified model assumptions. We performed a sensitivity analysis and qualitatively assessed differences in effect size and direction with the alternative exposure variable. We used similar methods to assess differences in mortality among patients with CRP greater than or equal to 200 mg/L.

To further account for potential bias, we performed multivariable logistic regression using a propensity score-matched sample.

We calculated the propensity score using variables that suggest severe illness, including mechanical ventilation, treatment in the ICU, use of tocilizumab and antibiotics, and peak CRP greater than or equal to 200 mg/L. We used 1:1 nearest neighbor matching to generate the adjusted sample. We also calculated the average treatment effect using propensity score matching via augmented inverse probability weighting (12).

We performed a post hoc investigation of the cause of death among patients in our cohort to explore the reason for the increased risk of death among patients on therapeutic dosage of anticoagulant. We computed descriptive statistics on the primary cause of death and election of comfort measures (CMO) among all patients that expired.

Finally, we assessed the difference in receiving pRBC transfusion and frequency of occlusive events among all patients on therapeutic and prophylactic anticoagulation with univariate logistic regression.

RESULTS

Participants

A total of 501 inpatients were initially identified as 18 years or older and positive for SARS-coronavirus 2. A total of 374 patients were included in this study following the application of exclusion criteria (**Fig. 1**). Post hoc analysis of the sample size determined power to be 99.2%. There was limited missing data with most variables missing less than 1–5% (Table 1). Race had more than 20% missing data, because Hispanic was listed as race in some medical records. Thus, the race of the patient was unknown. Listwise deletion for the multivariable logistic model resulted in a final sample size of 351. The subgroup analysis to determine risk of mortality among patients with CRP greater than or equal to 200 mg/L included 104 patients.

We provide descriptive statistics in Table 1. The average age was 64.7 years old, more than half of the sample was male (58.6%), and the majority was White (54.0%) and non-Hispanic (63.6%). Nearly all patients in our sample took enoxaparin at some time during their inpatient stay (93.5%), whereas less than one-fifth took heparin (14.8%). Some patients took both medications at different times, depending on their treatment requirements. Seventy-five patients (20.1%) were on therapeutic anticoagulation, and seventy-two patients expired (19.2%). There were statistically significant treatment group differences on univariate analysis for intensive care, mechanical ventilation, peak CRP greater than or equal to 200 mg/L, and use of antibiotics, tocilizumab, and lopinavir/ritonavir ($p < 0.01$). There were no significant differences in the prevalence of diabetes, cancer, and cardiac, renal, or pulmonary disease between the groups.

Additionally, 1.3% of patients in the prophylactic group experienced an occlusive event (i.e., stroke and deep vein thrombosis), whereas 12.0% of patients in the therapeutic group experienced the same. Additionally, 0.3% of patients in the prophylactic group experienced a significant bleed requiring transfusion, whereas 2.7% of the therapeutic group experienced the same. Both comparisons were statistically significant upon chi-square analysis.

Risk Differences in Mortality

There was a statistically significant increase in the risk of mortality in the therapeutic anticoagulation group compared with the prophylactic anticoagulation group upon crude analysis (**Table 2**). The full logistic model included anticoagulation dosage, age, ethnicity, diabetes, history of cancer or heart disease, hyperlipidemia, peak CRP, intensive care, mechanical ventilation, and antibiotic use.

The risk of mortality was higher (absolute risk reduction [aRR] = 2.3; 95% CI = 1.0–4.9; $p = 0.04$) for patients on therapeutic anticoagulation when compared with prophylactic anticoagulation after controlling for all variables in the model (Table 2). The propensity score-matched logistic regression resulted in a similar point estimate (aRR 2.4; 95% CI = 0.9–6.6; $p = 0.09$). This result had a wider CI due to the reduced sample size ($n = 133$) using 1:1 nearest neighbor matching. The average treatment effect was $\beta = 0.11$ (95% CI = 0.02–0.2; $p = 0.01$). Thus, we can state with more certainty that the probability of death is higher among patients on therapeutic dose anticoagulation.

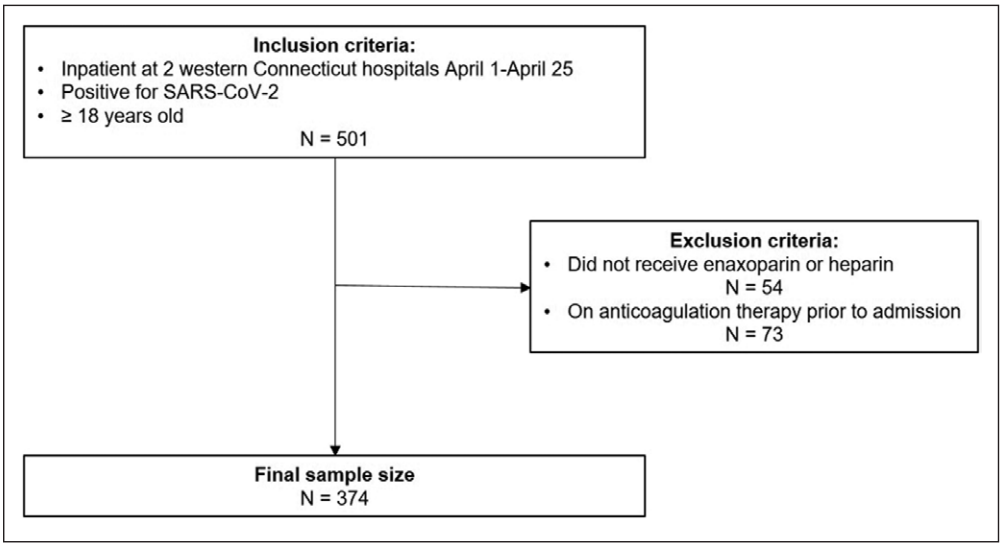

Figure 1. Sampling strategy with inclusion and exclusion criteria for the coronavirus disease anticoagulation study to assess differences in risk of in-hospital mortality and length of stay among given patient dosage of anticoagulation.

Subgroup Analyses

We performed a subgroup analysis of patients with a CRP greater than or equal to 200 mg/L to determine if there was a risk difference in mortality. We hypothesized that patients with evidence of severe inflammation may benefit from therapeutic anticoagulation. However, multivariable logistic regression that included anticoagulation dosage,

TABLE 2. Results From Multivariable Logistic Regression to Determine the Difference in Risk of Mortality Between Patients on Therapeutic Versus Prophylactic Doses of Anticoagulation in the Coronavirus-Antioagulation Full Sample and Among Patients With Peak C-Reactive Protein ≥ 200 ($\alpha = 0.05$)

Full Sample Analysis			
Outcome	**Prophylactic Anticoagulation[a]**	**Therapeutic Anticoagulation[b]**	***p***
Number of subjects	299	75	
Number of deaths	43	29	
Prevalence[c]	14.4	38.7	
Crude risk ratio, 95% CI ($n = 374$)	17	2.7 (1.8–4.0)	< 0.01
Adjusted risk ratio, 95% CI ($n = 350$)	(Reference)	2.3 (1.0–4.9)	0.04
Propensity score-adjusted risk ratio, 95% CI ($n = 133$)	(Reference)	2.4 (0.9–6.6)	0.09
Average treatment effect, 95% CI	0.16 (0.1–0.2)[d]	0.11 (0.02–0.2)	0.01
Subgroup analysis: C-reactive protein ≥ 200			
Number of subjects	76	36	
Number of deaths	27	17	
Prevalence[c]	35.5	47.2	
Crude risk ratio, 95% CI ($n = 104$)	(Reference)	1.3 (0.8–2.1)	0.24
Adjusted risk ratio, 95% CI ($n = 104$)	(Reference)	1.0 (0.2–4.5)	0.97

[a]Unexposed group.
[b]Exposed group.
[c]Per 100 persons.
[d]Potential outcome mean for the null treatment (prophylactic anticoagulation).

age, ethnicity, diabetes, history of cancer, history of any heart disease, intensive care, mechanical ventilation, and use of antibiotics, hydroxychloroquine, and tocilizumab demonstrated no difference in the risk of mortality between patients on therapeutic and prophylactic anticoagulations (aRR = 1.0; 95% CI = 0.2–4.5; $p = 0.97$) (Table 2).

Additionally, there was no difference found in the transfusion of pRBC or frequency of arteriovenous occlusive events across anticoagulation dosage on univariate analysis.

Sensitivity Analyses

Qualitatively, we found there was little difference in the risk ratios in the sensitivity analyses for risk of mortality. However, the CIs in the primary exposure variable were more precise (aRR = 2.25; 95% CI = 1.02–4.94) than the alternative exposure variable (aRR = 3.08; 95% CI = 1.13–8.44). The conclusions remain the same regardless of the definition for therapeutic anticoagulation.

Post Hoc Analyses

The main causes of death among patients that expired are provided in **Table 3**. The majority of patients expired due to worsening oxygenation (71.8%) and acute respiratory failure with hypoxia. Patients also expired due to shock and multiorgan failure. Approximately 8% of patients died from other causes, including anoxic brain injury due to hemorrhage ($n = 1$), kidney dysfunction with inability to access hemodialysis port ($n = 1$), and failure to thrive with encephalopathy ($n = 1$). Additionally, 47 of patients (12.6%) in the sample elected to receive CMO only for end-of-life care (Table 1). Among those who died, there was no significant difference in the number who received CMO between the groups ($p = 0.103$).

DISCUSSION

In mid-April 2020, the COVID-19 epidemic exploded in the New York, NJ, and Connecticut tristate area. Though aggressive efforts were underway to elucidate an effective antiviral or biologic agent against the virus, mortality rates remained high. As a result, clinicians at our institutions began adapting therapies based on preliminary scientific evidence. Several studies, including those by Giannis et al (1) and Mehta et al (13), describe the hyperinflammatory state and thromboembolic diseases found in COVID patients (2). We hypothesized systemic thromboses may be contributing to the clinical decline seen in these patients. Thus, we shifted from using standard prophylactic anticoagulation to full dose anticoagulation for virtually all hospitalized patients with COVID 19. Given the impression that "nothing was working," we conducted this observational study to determine if full-dose anticoagulation in COVID patients reduced the risk of mortality compared with patients on prophylactic anticoagulation. It is likely that the significantly higher rate of

TABLE 3. Causes of Death Among Coronavirus Disease 2019-Positive Patients From Two Hospitals in Western Connecticut in the Coronavirus-Antioagulation Study[a]

Event	Expired	Prophylactic Anticoagulation	Therapeutic Anticoagulation
Number of subjects	72	43	29
Acute respiratory failure with hypoxia, *n* (%)	51 (70.8)	31 (72.1)	20 (69.0)
Multiorgan failure and septic shock, *n* (%)	5 (6.9)	3 (7.0)	2 (6.9)
Cardiac arrest, *n* (%)	9 (12.5)	6 (14.0)	3 (10.3)
Anoxic brain injury due to hemorrhage, *n* (%)	1 (1.4)	0 (0.0)	1 (3.4)
Kidney injury and failure to access hemodialysis port, *n* (%)	1 (1.4)	1 (2.3)	0 (0.0)
Failure to thrive with encephalopathy, *n* (%)	1 (1.4)	0 (0.0)	1 (3.4)

[a]Causes of death are not mutually exclusive. Some patients died of multiple indications.

intubated patients in the therapeutic arm of our study was the effect of the timing of the changes in our treatment algorithm. Otherwise, the two cohorts were relatively evenly matched with respect to other significant comorbidities, such as preexisting cardiac disease, renal failure, pulmonary disease, and diabetes that have been shown to lead to a worse outcome from COVID (14).

Despite our hypothesis, we found the alternative: patients on preemptive therapeutic anticoagulation had 2.3 times higher risk of mortality than those on prophylactic anticoagulation after controlling for confounding factors. Our subgroup analysis of patients with greater severity of inflammation (CRP ≥ 200 mg/L) resulted in a null finding. Klok et al (15) reported a similar result among patients given therapeutic anticoagulation at baseline. These results were surprising and somewhat contrary to previous studies (6). Thus, it is important to communicate them to the medical community.

It is possible that therapeutic anticoagulation is an ineffective treatment for this syndrome. Indeed, the higher rate of occlusive events among patients receiving therapeutic anticoagulation may support this. We assessed cause of death among patients who expired and found that most patients expired due to refractory acute respiratory failure with hypoxia, shock, and multiorgan system failure. Although thrombosis may have played a role, mortality may be associated with reasons unrelated to thrombosis including direct end organ damage or to the systemic inflammatory response syndrome. Regardless, our analyses do not suggest that therapeutic dosing of anticoagulation prevented overall disease progression and may have contributed to a small but significant increase in bleeding risk. Of note, the high frequency of CMO in this study reflects a transition after other aggressive interventions failed and death was imminent. There were no patients in our study that entered the hospital on CMO (median time from admission to CMO designation = 5 d).

There were several limitations recognized in this study. First, this is an observational study that did not randomize patients to treatment groups. Group assignments may be biased by prescriber preferences (i.e., indication bias) or differences in unmeasured clinical variables. However, the decision to administer prophylactic or therapeutic anticoagulation to each patient was based more on changes in institutional COVID treatment algorithms as the pandemic evolved rather than individual physician preference. We used statistical methods recommended to account for nonrandomization in observational studies to address this bias (16, 17). The lack of efficacy in the hyperinflamed CRP subgroup may also decrease the concern that indication bias influenced our results and interpretation, as does the relatively even matching of our two cohorts with respect to other significant comorbidities that lead to a worse outcome from COVID. Of note, studies of this nature are often skewed by immortal time bias (18). Our study was less sensitive to immortal time bias given patients received treatment at time of admission. We did not collect data on treatment fidelity, and it is possible some patients did not complete a full course of treatment. However, both lovenox and heparin were titrated according to anti-Xa and partial thromboplastin time levels. Our anticoagulation protocols are diligently followed by nursing staff with medication and dosing oversight by pharmacists and physicians with a very low historic institutional frequency of missed doses. Second, mortality after the patients left the hospital was not captured in this study. Therefore, there may be some misclassification bias in the outcome. Additionally, we included variables in our model that we hypothesized would affect mortality among patients on anticoagulation. However, it is likely there is unmeasured confounding present in the model.

The patients in this sample were selected from two institutions in Western Connecticut and were predominantly older, non-Hispanic, and White. Additionally, we only included patients without a known history of thrombotic events. Interpretation of the results should only be generalized to similar patient populations. Future research should use a randomized control design and include additional factors related to mortality, bleeding, and complications of anticoagulation utilization.

CONCLUSIONS

Among hospitalized patients with COVID-19 and no prior history of thrombotic disease, an increase in the risk of mortality was observed in patients who preemptively received therapeutic anticoagulation when compared with those who received prophylactic anticoagulation. It is important to consider the risks and benefits for the patient, as well as the healthcare system, when using preemptive therapeutic anticoagulation in COVID-19. We recommend further research and cautious use of therapeutic

anticoagulation over standard prophylactic anticoagulation in the management of COVID-19 and its complications.

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