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Anticoagulation in COVID-19: a single-center retrospective study

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ABSTRACT

Introduction: COVID-19 induces a pro-thrombotic state as evidenced by microvascular thrombi in the renal and pulmonary vasculature. Therapeutic anticoagulation in COVID-19 has been debated and data remain anecdotal.

Hypothesis: We hypothesize that therapeutic anticoagulation is associated with a reduction in in-hospital mortality, upgrade to intensive care unit, invasive mechanical ventilation, and acute renal failure necessitating dialysis by decreasing the over-all clot burden.

Methods: A retrospective cohort study was done to determine the impact of therapeutic anticoagulation in hospitalized COVID-19 patients. Independent t-test and multivariate logistic regression analysis were performed to calculate mean differences and adjusted odds ratios (aOR) with its 95% confidence interval (CI) respectively.

Results: A total of 176 hospitalized COVID-19 patients were divided into two groups, therapeutic anticoagulation and prophylactic anticoagulation. The mean age, baseline comorbidities and other medications used during hospitalization were similar in both groups. The aOR for in-hospital mortality (OR 3.05, 95% CI 1.15–8.10, p = 0.04), upgrade to intensive care (OR 3.08, 95% CI 1.43–6.64, p = 0.006) and invasive mechanical ventilation (OR 4.27, 95% CI 1.95–9.34, p = 0.00) were significantly lower while there was no statistically significant difference in the rate of developing acute renal failure (OR 1.87 95% CI 0.46–7.63, p = 0.64) between two groups.

Conclusions: In patients with COVID-19, therapeutic anticoagulation offers a significant reduction in the rate of in-hospital mortality, upgrade to intensive medical care, and invasive mechanical ventilation. It should be preferred over prophylactic anticoagulation in COVID-19 patients unless randomized controlled trials prove otherwise.

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1. Introduction

The ongoing pandemic caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has led to unprecedented challenges for the global healthcare system. This novel coronavirus disease phenotype ranges from asymptomatic carriage to multi-organ dysfunction and as of July 2020 more than 500,000 deaths have been reported worldwide. Increasing social and economic devastation caused by COVID-19 has led the Federal Drug Administration (FDA) to issue Emergency use authorizations (EUA) for various drugs without proven benefits [1]. While randomized controlled studies are underway to find an effective treatment for COVID-19, hydroxychloroquine, azithromycin, tocilizumab, remdesivir, dexamethasone, convalescent plasma and steroids among others are being used all over the world based on either in-vitro evidence or extrapolated results of preliminary randomized control trials.COVID-19 has been found to be a prothrombotic state as evidenced by microvascular thrombi in pulmonary vasculature on autopsy studies and clinical observations of the increased rate of venous thromboembolism in hospitalized patients [2]. Initial evaluation of the Wuhan data suggests that the coagulopathy associated with COVID-19 is a result of the inflammatory response to viral particles resulting in thrombo-inflammation and driving thrombosis. Despite the significant overlap, it appears to be a distinct entity from disseminated intravascular coagulation (DIC) and some experts have termed it as COVID-19 associated coagulopathy (CAC) [3]. Approach to therapeutic anticoagulation in COVID-19 has evolved as data emerged with the course of pandemic and at present, most of the enterprises are following interim guidelines issued by the International Society on Thrombosis and Haemostasis [4,5].

Though the American Society of Hematology (ASH) states that all hospitalized patients with COVID-19 should receive pharmacologic thromboprophylaxis, the rising incidence of thrombotic complications in COVID-19 patients has led most hospitals to adopt the strategy of increasing the dose of anticoagulation for prophylaxis to 'intermediate intensity' doses such as 0.5 mg/kg twice a

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day of enoxaparin, using a risk-adapted strategy with increased doses based on levels of D-dimer, fibrinogen, ICU location and other factors associated with increased risk [6]. Regardless of institutional protocols and international societies' guidelines, clinicians have to weigh the benefits and risks of therapeutic anticoagulation in terms of thrombosis and major bleeding for individual patients. The purpose of this study is to evaluate the overall clinical effectiveness of therapeutic anticoagulation as compared to prophylactic anticoagulation in our hospital. We hypothesized that the therapeutic anticoagulation would be associated with a reduction in the end-points of in-hospital mortality, upgrade to ICU, need for IMV, AKI necessitating dialysis and reduction in D-dimer and C-reactive protein (CRP) level at the day-7 of hospitalization.

2. Methods

2.1. Study design and participants

This retrospective cohort study included adult patients (≥18 years old) with confirmed COVID-19 who were admitted at Abington Hospital – Jefferson Health between 1 March 2020, and 30 May 2020. Institutional Review Board approved the study and the Research Ethics Committee waived the requirement for informed consent.

2.2. Patient and public involvement

All the data were gathered from electronic medical records by chart review of the individual patients in a retrospective fashion. There was no direct patient interaction in the study. Common inpatient outcomes of hospitalized patients influenced the formation of the research question and the results of this study would not be directly conveyed to study participants.

2.3. Data collection

We used a data collection form to obtain data from electronic medical records by medical record numbers (MRNs) of the individual patients. Three authors gathered the data and one author reviewed differences in interpretation between the data extractors. A real-time qualitative polymerase chain reaction (RT-qPCR) method was used to detect the virus in respiratory specimens (nasopharyngeal or throat swabs). Other investigations on the day of presentation to the hospital and on day 7 of hospitalization, including but not limited to complete blood count, kidney and liver function tests, inflammatory markers, markers of coagulopathy and myocardial enzymes (troponin T, CK-MB) were performed on most of the patients. The most common coexisting comorbidities in most of the patients included hypertension (HTN), diabetes mellitus (DM), chronic kidney disease (CKD), chronic obstructive lung disease (COPD) and coronary artery disease (CAD). Patients were discharged from the hospital after they were free of symptoms for at least 48 hours.

2.4. Statistical analysis

Categorical data were analyzed using the chi-square and Fisher exact test. Continuous variables were reported as mean and standard deviations (SD) and were analyzed using the t-test analysis. An unadjusted odds ratio (OR) was calculated using a Cochran-Mantel-Haenszel test. To determine the impact of potential effect modifiers a logistic regression model was used to calculate the adjusted odds ratio. The measured impact of baseline comorbidities and demographics was controlled to determine the pooled estimates of in-hospital mortality, ICU upgrade, IMV, dialysis and inflammatory marker level. The patient demographics included age and sex while baseline comorbidities included DM, HTN, CAD, CKD and COPD. We also considered the anticoagulant use at home and use of other medications during hospitalization (HCQ, tocilizumab, remdesivir, steroid) while calculating the adjusted odds. A p-value of less than 0.05 was considered statistically significant and all values were reported with a 95% confidence interval (CI). Statistical analyses were performed using the SPSS software (version 25, windows).

3. Results

3.1. Demographics and baseline characteristics

Our study population consisted of 176 patients which were divided into two groups, therapeutic anticoagulation versus prophylactic anticoagulation (n = 34 vs n = 142). The mean age of patients was 62.5 and 64.2 years in the therapeutic anticoagulation arm and prophylactic anticoagulation arm of the study, respectively. There was a uniform distribution of underlying comorbidities in both of the arms of the study with no statistically significant difference as follows: diabetes (38% vs. 35% p = 0.84), hypertension (65% vs. 65% p = 0.85), chronic kidney disease (21% vs. 18% p = 0.88), coronary artery disease (15% vs 18%, p = 0.81), COPD (15% vs. 13%, p = 0.94). However, the use of hydroxychloroquine (HCQ), tocilizumab (TCZ) and steroids were significantly higher in the therapeutic anticoagulation arm compared to the prophylactic anticoagulation arm of the study as follows: HCQ (97% vs. 78%, p = 0.02), TCZ

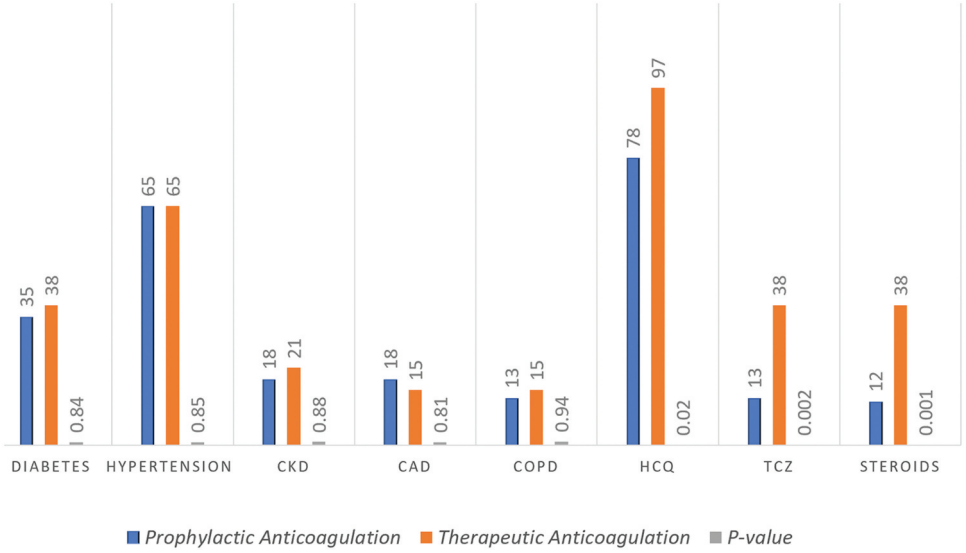

Figure 1. Bar Chart representing the number of patients and P-value of difference on the top of bars.

Table 1. Comorbidities and Medications used during hospitalization with P-value of difference.

Characteristics	Prophylactic Anticoagulation	Therapeutic Anticoagulation	P-value
Diabetes	35	38	0.84
Hypertension	65	65	0.85
CKD	18	21	0.88
CAD	18	15	0.81
COPD	13	15	0.94
HCQ	78	97	0.02
TCZ	13	38	0.002
Steroids	12	38	0.001

(38% vs. 13%, p = 0.002), steroids (38% vs. 12%, p = 0.001). (Figure 1, Table 1)

CKD: chronic kidney disease, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, HCQ: hydroxychloroquine TCZ: tocilizumab

3.2. Odds ratios of outcomes

All-cause mortality was lower in the therapeutic anticoagulation arm compared to the prophylactic anticoagulation arm with a statistically significant unadjusted odds ratio (OR 3.05 95% CI 1.15–8.10 p =.04). The unadjusted odds for patients requiring an upgrade to the ICU were significantly lower in patients in the therapeutic anticoagulation arm as compared to patients in the prophylactic anticoagulation arm (OR 3.08 95% CI 1.43–6.64, p = .006). Similarly, patients who received therapeutic doses of anticoagulation showed a significant reduction in the need for invasive mechanical ventilation (IMV) compared to the control group (OR 4.27 95% CI 1.95–9.34 p = .00). The D-dimer level at day 7 of hospitalization was also significantly lower in the therapeutic anticoagulation arm compared to the prophylactic anticoagulation arm. (OR 5.86 95% CI 1.67–20.57 p = .005). However, there was no significant difference in the odds of acute renal failure necessitating dialysis (OR 1.87 95%CI .46–7.63 p = .64) and reduction in C-reactive protein (CRP) level at day 7 of hospitalization (OR 1.01 95% CI .44–2.28 p = .84) between the two groups.

We used a multivariate regression model to adjust the observed odds for baseline comorbidities and medications, including DM, HTN, CAD, COPD, use of HCQ, TCZ, remdesivir and steroids. The adjusted odds were similar to the unadjusted odds for all the outcomes except for an upgrade to the medical ICU which was non-significantly different between the two groups. It implies that underlying comorbidities contributed to more ICU upgrades in the therapeutic anticoagulation arm and more frequent medication use in this group did not impact any of the hard outcomes of the study (Table 2, Figure 2).

4. Discussion

Our study reveals that therapeutic anticoagulation has a significant role in improving hard clinical outcomes in the treatment of COVID-19 patients. Compared to the patients in the control group, those who received therapeutic anticoagulation showed a significant reduction in the rate of all-cause in-hospital mortality, need for IMV and D dimer level on day 7 of hospitalization. Although the unadjusted rate of an upgrade to the medical ICU was lower in the therapeutic anticoagulation arm, this effect disappeared when the impact of underlying comorbidities and other medications used were taken into account as evident by non-significantly different adjusted odds ratio on multivariate analysis (Table 2)(Figure 2).

The preferred anticoagulation therapy in hospitalized COVID-19 patients is subcutaneous heparin or enoxaparin. Warfarin and Direct Oral Anticoagulants

Table 2. Odds ratio of outcomes with P-value of difference before and after adjustment with underlying comorbidities and medications used during hospitalization.

Outcomes	TA	PA	uOR	P-value	AOR	P-Value
ICU Upgrade	32	68	3.08(1.43–6.64)	0.006	2.09(0.87–5.03)	0.09
IVM	35.0	65.0	4.27(1.95–9.34)	0.00	3.33(1.33–8.33)	0.01
Dialysis	30	70	1.87(0.46–7.63)	0.64	2.77(0.42–18.39)	0.29
Mortality	38	62	3.05(1.15–8.10)	0.04	3.32(1.02–10.86)	0.05
Discharge	6	94	0.19(0.06–0.56)	0.002	0.19(0.05–0.70)	0.01
CRP day 7	21	79	1.01(0.44–2.28)	0.84	1.35(0.49–3.72)	0.56
D-dimer day 7	30	70	5.86(1.67–20.57)	0.005	5.64(1.40–22.63)	0.02
CRP day 1	23	77	1.56(0.72–3.40)	0.35	1.67(0.86–3.21)	0.31
D-Dimer day 1	26	74	1.98(0.91–4.33)	0.13	2.01(0.95–3.99)	0.11

TA: therapeutic anticoagulation, PA: prophylactic anticoagulation, uOR: unadjusted odds ratio, AOR: adjusted odds ratio, IVM: invasive mechanical ventilation

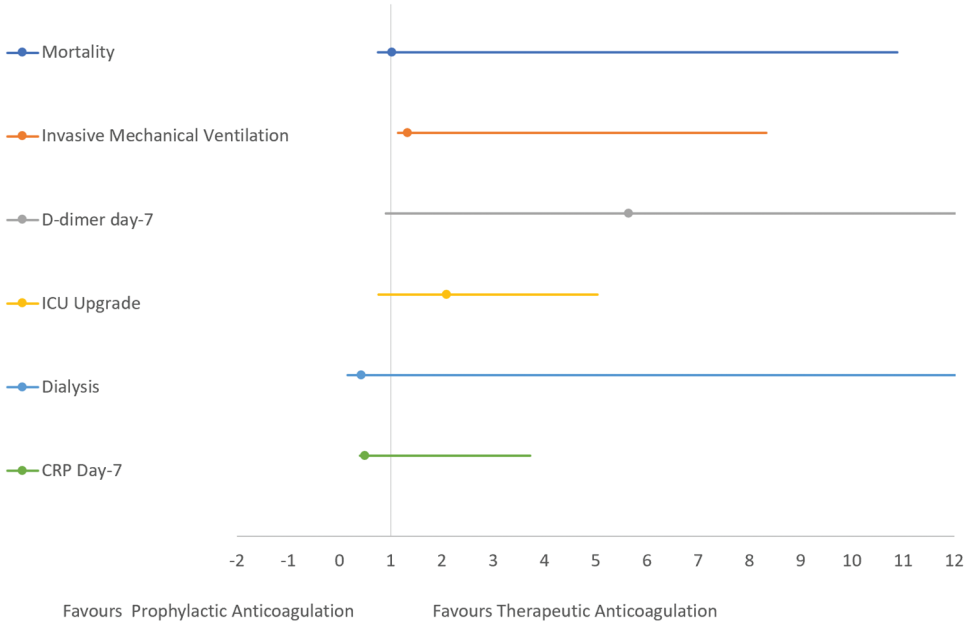

Figure 2. Forest plot representing the odds ratio of outcomes after adjustment with baseline comorbidities and medications used during hospitalization.

(DOACs) are less efficacious due to COVID 19-related hepatic dysfunction and reduced oral intake which may affect absorption or response to warfarin [7]. Enoxaparin has also shown to possess anti-viral properties in vitro and its anti-inflammatory characteristics are believed to circumvent the activation of coagulation cascade induced by inflammation in the setting of cytokine release syndrome and overall proinflammatory state of COVID-19 [8]. Our hospital, following the guidelines of its parent enterprise, advocated for therapeutic anticoagulation for all the COVID-19 patients who had an alternative indication for anticoagulation or those having high clinical suspicion of thrombosis without objective evidence as diagnostic testing was limited in COVID-19 patients. Very high inflammatory markers, particularly the D-dimer level, were also used as a surrogate marker for therapeutic anticoagulation in the right clinical settings. In our patient population, enoxaparin was used in both therapeutic anticoagulation and prophylactic anticoagulation arms. Heparin was used in renal insufficiency and DOACs were continued if a particular patient was already on them due to an alternative indication like atrial fibrillation or deep venous thrombosis, etc.

Our findings are in line with previous literature. A study by Klok et al. included 184 patients with confirmed COVID-19 infection who were admitted to ICU of different hospitals in the Netherland between 17 March and 5 April 2020 [9]. All patients received at least a standard dose of thromboprophylaxis according to their respective hospital protocol. The median duration of observation was 7 days and on 5 April 2023 patients had died, 22 recovered and discharged from the hospital while 139 patients were still in the ICU. The results were astonishing as 27% of the patients developed venous thromboembolism and 4% developed arterial thrombotic events. Klok et al. proposed that despite thromboembolism prophylaxis, 31% incidence of thrombotic complications in ICU patients with COVID-19 infection is remarkably high and that too with limited screening. Generally, COVID-19 patients are not screened extensively despite high clinical suspicion of thrombotic events.

However, this study has several limitations. Because patients were physically located in different hospitals so findings for the actual administered doses of anticoagulants and the effect of changes in doses on the patient outcome could not be measured. Actual thrombotic events might have been underreported on account of observation limited to only objective evidence of clotting. The patient population was observed only for a week and this might have led to underreporting of thrombotic events. Based on these observations, Klok et al. proposed increasing the prophylaxis towards high-prophylactic doses, e.g. going from enoxaparin 40 mg OD to 40 mg BID, even in the absence of randomized evidence and suggested that therapeutic dose of anticoagulation might be required for adequate control and treatment.

In another study, Tang et al. used the scoring system for sepsis-induced coagulopathy (SIC) proposed by the International Society of Thrombosis and Hemostasis (ISTH) [10]. This scoring system identifies the earlier phase of sepsis-associated DIC called sepsis-induced coagulopathy (SIC). In this study of 449 patients with severe COVID-19, 99 patients received heparin, mainly low molecular weight heparin (LMWH) for 7 days or more. The 28-day mortality between heparinized (hep+) and non-heparinized (hep−) patients was compared in different risk populations who were stratified by SIC score or D-dimer levels. Overall, no difference was observed in 28-day mortality between hep+ and hep− patients; however, the mortality of hep+ patients was lower than hep− patients with SIC score ≥4 or D-dimer >6-fold of the upper limit of normal. For SIC score description, the researchers concluded that anticoagulation appears to be associated with better prognosis in severe COVID-19 cases meeting SIC criteria or with markedly elevated D-dimer. Yin et al. used this previous cohort data to evaluate whether patients with elevated D-dimer could benefit from therapeutic anticoagulation. They found that the 28-day mortality of heparin users was lower than non-users in COVID-19 patients with D-dimer >3.0 μg/mL [11]. It implies that therapeutic anticoagulation improves clinical outcomes in this subset of COVID-19 patients and different hospitals use different criteria to identify that particular subset. In our study population, therapeutic anticoagulation was being given to the patients who had objective evidence of clotting on imaging or those who were deemed appropriate for therapeutic anticoagulation by treating physician based on overall laboratory (markers of inflammation and coagulation) and clinical-picture(unexplainedrise in oxygen requirement in the absence of Imaging evidence of clot). In terms of mortality, the results of our study are similar to the above-stated study by Yin et al. However, our study not only expands the mortality findings of previous studies but also identifies that therapeutic anticoagulation leads to a lower number of ICU upgrades and reduced need for IMV compared to prophylactic anticoagulation. Also, by adjusting the outcomes against patient demographics, underlying comorbidities, and other medications used during hospitalization, our study has addressed the impact of potential confounders on overall results.

The clinical benefits of therapeutic anticoagulation are clearly shown in our study by the drop in mortality rate and reduction in the need for invasive mechanical ventilation in the therapeutic anticoagulation arm compared to the prophylactic anticoagulation arm. At present, RCTs are underway which are evaluating the efficacy and complications of full-dose empiric anticoagulation without a diagnosed clinical condition needing anticoagulation in the management of COVID-19-related coagulopathies [12,13]. Based on the data available so far, some hospitals are therapeutically anticoagulating COVID-19 patients without objective evidence of thromboembolism, however, to reach a more reliable conclusion supporting therapeutic doses of anticoagulation, further studies need to be done and more data are required.

Disclosure statement

No potential conflict of interest was reported by the authors.

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