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Full Length Article

Anticoagulation and bleeding risk in patients with COVID-19

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ABSTRACT

Background: There is no current standardized approach to anticoagulation in patients with Coronavirus Disease 2019 (COVID-19) while potential bleeding risks remain. Our study characterizes the patterns of anticoagulation use in COVID-19 patients and the risk of related bleeding.

Methods: This is a single center retrospective analysis of 355 adult patients with confirmed diagnosis of COVID-19 from March 1 to May 31, 2020. Chi-square was used to analyze the relationship between degree of anticoagulant dose and bleeding events by site. Multivariable logistic regression was used to look at factors associated with inpatient death.

Results: 61% of patients were being treated with prophylactic doses of anticoagulation, while 7% and 29% were being treated with sub-therapeutic and therapeutic anticoagulation (TA) doses respectively. In 44% of patients, we found that the decision to escalate the dose of anticoagulation was based on laboratory values characterizing the severity of COVID-19 such as rising D-dimer levels. There were significantly higher rates of bleeding from non-CNS/non-GI sites ($p = 0.039$) and from any bleeding site overall ($p = 0.019$) with TA. TA was associated with significantly higher rates of inpatient death (41.6% vs 15.3% $p < 0.0001$) compared to those without. All patients who developed CNS hemorrhage died $p = 0.011$. After multivariable logistic regression, only age OR 1.04 95% CI (1.01 to 1.07) $p = 0.008$ and therapeutic anticoagulation was associated with inpatient mortality OR 6.16 95% CI (2.96 to 12.83) $p \leq 0.0001$.

Conclusion: The use of TA was significantly associated with increased risk of bleeding. Bleeding in turn exhibited trends towards higher inpatient death among patients with COVID-19. These findings should be interpreted with caution and larger more controlled studies are needed to verify the net effects of anticoagulation in patients with COVID-19.

1. Introduction

As the coronavirus disease 2019 (COVID-19) pandemic has continued to unfold, so has the level of understanding about the various implications of the disease. However, despite being several months into the pandemic, the uncertainty regarding management of severe disease continues to prevail. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been thought to be a predisposition to a hypercoagulable state with some thrombotic events resulting in fatal outcomes for the patients. Recent data have confirmed that these patients are at increased risk of venous and arterial thromboembolism [1]. The pathophysiological explanation behind this is thought to be related to several factors such as the severe inflammatory state presumed to be a cytokine release syndrome, characterized by the elevation of numerous inflammatory markers [2]. Furthermore, the profound hypoxia as well as the immobilized state of these patients has also been thought to contribute to this hypercoagulable state [3]. In many cases, the development of life threatening of thromboembolic events occurred despite prophylactic doses of anticoagulation [3]. There has been significant variability in medical decision making with regards to anticoagulation among patients with COVID-19. It is well known that anticoagulation is not without its risks of bleeding and is therefore a therapy that requires close clinical monitoring. The decision to escalate anticoagulation doses should therefore be carefully considered. Risks

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should be communicated and shared decision making is optimal in such clinical settings [4]. We therefore undertook a retrospective study to investigate the different doses of anticoagulation being used among patients with COVID-19 and the rates of bleeding events in these patients.

2. Patients and Methods

2.1. Study design, participants, and data collection

This study was a single center retrospective analysis of all patients > 18 years of age with a confirmed diagnosis of COVID-19 via reverse transcriptase–polymerase chain reaction assays (RT-PCR) performed on nasopharyngeal swab specimens from March 1 to May 31, 2020. We excluded 9 patients who were still admitted at the time of analysis, of these patients, 5 were on either Remdesivir or convalescent plasma as these were relatively newly introduced treatments at that time. Demographic and clinical factors including age, gender, race, and comorbidities were extracted from electronic medical records with a standardized data collection form. Prophylactic doses of anticoagulation were based on institutional protocols (heparin 5000 units subcutaneously 2–3 times/day or low molecular weight heparin (LMWH) 30-40 mg daily. Therapeutic anticoagulation was based on indication with VTE (80 units/kg IV bolus followed by 18 units/kg/h infusion) while for atrial fibrillation/flutter or acute coronary syndrome (12 units/kg/h infusion). For therapeutic LMWH dose was 1 mg/kg q12 hours. Any dose in between prophylactic and therapeutic was then considered as subtherapeutic. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria which was fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g L) or more, or leading to transfusion of two or more units of whole blood or red cells [5]. This study was approved by the institutional review board.

2.2. Statistical analysis

Demographic variables were presented using descriptive statistics and frequencies. Categorical variables were analyzed with chi-square testing. Demographic and clinical variables were tabulated. Chi-square was used to analyze the relationship between degree of anticoagulant dose and bleeding events by site. Chi square was also used to analyze rates of inpatient death in relation to site of bleeding. Bleeding events were classified as major bleeding and separate site-specific bleeding including: CNS bleeding, GI bleeding and bleeding on other sites. Mann-Whitney *U* test was used to identify differences with skewed variables. 95% confidence intervals were used and are presented when appropriate. All analyses were performed using IBM's SPSS Statistics for Windows, Version 23.0.

3. Results

3.1. Demographic and clinical profile of patients

A total of 389 patients were evaluated in our hospital and tested positive via RT-PCR for COVID-19. A total of thirty-four patients were excluded. 9 patients were still admitted at the time of analysis. 25 patients with missing clinical data to preclude analysis, including those who were transferred to other institutions were excluded, leaving a final sample of 355 patients (see Supplemental Fig. 1). In the final sample of 355 patients, the mean age (+/− SD) was 66.21 ± 14.21, 49% were female and 70% were African American. Chronic medical conditions of these patients included hypertension (77%), diabetes mellitus (47%), COPD (13%) and asthma (8%) (see Table 1).

Table 1
Clinical characteristic of the patients at baseline.

Characteristics	Patients (N = 355)
Age mean ± SD	66.21 ± 14.21
Female gender n (%)	174(49)
Ethnicity n (%)	
African American	249(70)
Caucasian	28(8)
Hispanic	39(11)
Other	39(11)
Comorbidities	
BMI (mean ± SD)	29.71 ± 9.11
COPD	45(13)
Asthma	27(8)
Heart failure	60(17)
Atrial fibrillation	39(11)
Liver cirrhosis	10(3)
Diabetes	166(47)
Chronic kidney disease all stages	101(18)
End stage renal disease on dialysis	41(12)
Coronary artery disease	77(22)
Hypertension	272(77)
HIV	7(2)
Medications used	
Antiplatelets	142(40)
NOAC	7(2)
Warfarin	4(1)
COVID-19 treatment	
Hydroxychloroquine	216 (61)
Steroids	103(29)
Tocilizumab	43(12)
Clinical outcomes	
Inpatient death	80(23)
Need for CRRT/HD	56(16)
Need for vasopressors	81(23)
Need for intubation	89(25)
Anticoagulation regimen	
Prophylactic dose for VTE	216(61)
Subtherapeutic dose	23(7)
Therapeutic dose	101(29)
Indications for anticoagulation	
COVID related reasons/d-dimer	54(44)
Venous thromboembolism	40(32)
Atrial fibrillation	23(19)
Others	7(5)
Any clinically significant bleeding	20(6)
GI bleeding	12(60)
Brain bleed	3(15)
Other site of bleeding	6(30)

3.2. Anticoagulation doses, indications and outcomes

61% of patients were on prophylactic doses of anticoagulation to prevent VTE. Seven percent were on subtherapeutic anticoagulation while 29% were on therapeutic anticoagulation doses. 44% of the non-prophylactic doses of anticoagulation were started for COVID-19 related reasons/rising D-dimer levels while 32% were used for VTE and 19% for atrial fibrillation (see Table 1). Other indications for therapeutic AC were acute limb ischemia and acute coronary syndromes (ACS). Patients on therapeutic anticoagulation had significantly higher rates of major bleeding compared to those without anticoagulation $p = 0.044$ while subtherapeutic doses and prophylactic doses did not have any significant differences in major bleeding outcomes compared to patients without anticoagulation (see Table 2). On the other hand, comparing doses of anticoagulation between each other, therapeutic AC had a significantly higher rate of major bleeding compared to prophylactic doses ($p = 0.04$). Seeing that 7 patients with prophylactic doses of anticoagulation also had bleeding (see Table 2), we looked at this specific subset and found that in all cases except 1, the patients had elevated D-dimer levels > 1500 ng/mL $p = 0.043$. Looking at a subgroup analysis, patients who were placed on therapeutic anticoagulation had significantly higher D-dimer $p < 0.006$, CRP

Table 2
Bleeding outcomes based on highest dose of Anticoagulation used.

	With anticoagulation	No anticoagulation	p-Value
Major bleeding comparing those with anticoagulation vs without			
Prophylactic dose	7/178 (4%)	1/55 (2%)	0.684
Subtherapeutic dose	1/20 (5%)	1/55 (2%)	0.465
Therapeutic dose	11/102 (11%)	1/55 (2%)	0.044
Major bleeding comparing doses of anticoagulation			
Therapeutic vs prophylactic	11/102(11%)	7/178 (4%)	0.04
Therapeutic vs sub-therapeutic	11/102 (11%)	1/20 (5%)	0.688
Subtherapeutic vs prophylactic	1/20 (5%)	7/178 (4%)	0.580

p = 0.016 and LDH p < 0.0001 (see Supplemental Tables 1–2). Patients placed on therapeutic anticoagulation also had significantly more atrial fibrillation (p < 0.0001) and had more venous thromboembolism (VTE) p < 0.0001 (see Supplemental Table 2).

3.3. Mortality and bleeding outcomes

The number of in hospital deaths was 80 (23%) with about 64% ICU mortality rate. 20 patients had documented bleeding events and 45% of these events were in ICU patients. 60% of these bleeds were from gastrointestinal sources, and 15% were from the CNS. Thirty percent of the bleeding events were in other sites such as intraabdominal, retroperitoneal and pulmonary. All patients who developed CNS hemorrhage died p = 0.011 (see Table 3). Major bleeding regardless of site showed trends towards association with inpatient death 40% vs 21.5% p = 0.054 (see Table 3) meanwhile GI bleeding was not significantly associated with in-patient death (16.7% vs those without GI bleed 22.7% p = 1.000). After multivariable logistic regression, only age OR 1.04 95% CI (1.01 to 1.07) p = 0.008, D-dimer ≥ 1500 ng/mL OR 5.89 95% CI (2.84 to 12.20) p < 0.0001 and the use of therapeutic anticoagulation were independently associated with higher inpatient mortality OR 6.16 95% CI (2.96 to 12.83) p ≤ 0.0001 (see Table 4).

4. Discussion

Our study investigated the bleeding rates in patients with therapeutic, subtherapeutic and prophylactic doses of anticoagulation. Therapeutic and subtherapeutic anticoagulation doses were most commonly indicated in our study by the degree of elevation in D-dimer levels. This approach clearly reflects the practice of anticoagulation in patients with COVID-19 due to severity of the infection. Patients who received therapeutic anticoagulation treatment showed significantly higher rates of major bleeding while In the other hand, subtherapeutic doses of anticoagulation was associated with less bleeding compared to therapeutic levels but was higher compared to those who received no anticoagulation although this was not statistically significant. This is consistent with a recent study done by Ishan Paranjpe et al., where 63% of the hospitalized patients with COVID-19 that were given systemic anticoagulation treatment were found to have major bleeding [6]. Additionally, in our study, all patients who experienced CNS bleeding did not survive. Although this was not statistically significant due to being underpowered from the small event rates, this reminds us of the most feared complication of anticoagulation that is intracerebral hemorrhage which has a high case fatality rate with potentially high long-term morbidity in those who survive [7–9]. These results caution against indiscriminate use of therapeutic anticoagulation without clear indication. Patient selection for therapeutic doses of AC should be based on a clear diagnosis of VTE, or high suspicion of pulmonary embolism in ICU or with the help of objective findings such as bedside ultrasound. The risks for bleeding should be carefully weighed in.

Table 3
Inpatient death in relation to bleeding.

	With bleeding	No bleeding	p-Value
Major bleeding	40%	21.5%	0.054
CNS bleeding	100%	21.9%	0.001
GI bleeding	16.7%	22.7%	1.000
Other site of bleeding	50%	22.1%	0.131

Table 4
Multivariate logistic regression looking at factors associated with inpatient death.

Characteristics	Odds ratio (95% CI)	p-Value
Age	1.04 (1.01 to 1.07)	0.008
Male	*Referrant*	
Female	1.37 (0.75 to 2.51)	0.305
BMI	0.99 (0.95 to 1.03)	0.509
African American	*Referrant*	
Caucasian	1.20 (0.38 to 3.77)	0.752
Hispanic	0.75 (0.22 to 2.52)	0.641
Others	1.31 (0.52 to 3.32)	0.564
Diabetes	1.49 (0.78 to 2.86)	0.227
CKD	1.30 (0.65 to 2.60)	0.466
Hypertension	1.14 (0.48 to 2.72)	0.762
COPD	0.97 (0.41 to 2.33)	0.950
D-dimer ≥ 1500 (ng/mL FEU)	5.89 (2.84 to 12.20)	< 0.0001
Atrial fibrillation	0.226 (0.074 to 0.687)	0.009
VTE	0.434 (0.155 to 1.22)	0.113
Major bleeding	1.32 (0.43 to 4.01)	0.628
Therapeutic AC	6.16 (2.96 to 12.83)	< 0.0001

Although associated with risks of bleeding, anticoagulation use has shown to increase survival in patients with severe COVID-19 infection. Recent data from a study on patients who are high risk for thrombosis conducted in Wuhan by Ning Tang et al. indicated that anticoagulation decreased mortality in patients with severe [10]. Paranjpe et al., also found that among patients hospitalized with COVID-19, longer duration of AC treatment was associated with a reduced risk of mortality (adjusted HR of 0.86 per day, 95% CI 0.82–0.89, p < 0.001) [6]. However, therapeutic anticoagulation dosing in our study was associated with higher in-patient mortality. A potential explanation to this is that our patient population may be sicker with a higher mortality rate especially for severe cases who needed ICU admission. This may also be a form of selection bias as patients with more severe disease with evidence of worsening D-dimer and associated high inflammatory marker levels were put on anticoagulation. In fact, when we looked at patients on low prophylactic doses of anticoagulation who developed major bleeding, all but 1 had their D-dimer levels significantly elevated > 1500 ng/mL p = 0.043. Elevated D-dimer levels may reflect extensive fibrinolysis and proteolytic activity of plasmin by the activation of matrix metalloproteinases which can contribute to inflammation and tissue injury [11]. The D-dimer elevation in patients with COVID-19 might not necessarily directly reflect thrombotic risk or burden but rather severity of disease. This severe disease or sepsis in itself from COVID-19 can dysregulate the coagulation pathway and can increase the risk of bleeding in these patients [12]. There can also be bias by indication as patients placed on therapeutic anticoagulation had more history of atrial fibrillation and development of VTE. This is where careful risk stratification like the use of CHA_2DS_2VASc for atrial fibrillation may potentially avoid the use of unnecessary anticoagulation and its risks. However, even after adjusting for these comorbidities including bleeding events, therapeutic anticoagulation was still independently associated with inpatient death. Major bleeding was not associated with mortality as the event rates were low and the effects were likely diluted by other stronger predictive factors. On the other hand, subtherapeutic doses of anticoagulation was associated with less

bleeding compared to therapeutic levels but was higher compared to those who received no anticoagulation although this was not statistically significant. Proper patient selection including identification of patients at higher risk for bleeding at the same time weighing this against the risk of thrombosis may help firmly establish the role of anticoagulation in patients with COVID-19. Since the current evidence regarding the benefits of anticoagulation in the management of COVID-19 are mixed, with some studies showing potential benefit while others such as ours showing risk of bleeding and mortality, we recommend that current guidelines in the management of VTE be followed appropriately [13]. As much as possible, objective evidence of VTE should be present before initiation of therapeutic levels of anticoagulation to properly balance out the potential risks and benefits. Larger prospective trials are needed to truly determine the degree of risks and benefits of anticoagulation in patients with COVID-19.

5. Limitations

This is a retrospective single center study of predominantly African American patients. This may limit generalizability. Our findings should be interpreted with caution as the bleeding event rates were also relatively low which may underestimate the actual effect. We could not account for other medications that may influence bleeding such as use of antiplatelet agents. Exact temporal relationships cannot be established between initiation of anticoagulation and bleeding events and mortality due to the retrospective nature. This study only looked at major bleeding events, other potentially relevant non-major bleeds were not investigated. There may be selection bias as patients with more severe disease were placed on anticoagulation. There can also be bias by indication as more patients with known atrial fibrillation and who developed VTE were also on anticoagulation. Although we adjusted for the use of antiplatelets and the possible effect of uremia on platelet function by including CKD in our multivariable model, other factors that may influence the risk of bleeding may not be fully accounted for. Patients on oral anticoagulants were switched to heparin/LMWH on admission but pre-existing anticoagulant use outpatient may influence subsequent outcomes. We also did not risk stratify our patients in detail according to bleeding risk and risk for venous thromboembolism which may have influenced clinical outcomes. Although there was significantly less bleeding associated with sub-therapeutic anticoagulation compared to therapeutic doses, efficacy and risk benefits cannot be determined due to the relatively low number of patients placed on these subtherapeutic doses. This study also cannot make recommendations based on the use of anticoagulation in the setting of atrial fibrillation and COVID-19 as this was outside the scope of the current study. Nevertheless, our study provides insight as to the potential harms of therapeutic anticoagulation especially when it comes to CNS bleeding and other sites of non-GI bleeding which may be associated with poor clinical outcomes. Perceived benefits or harms of anticoagulation may entirely depend on the delicate balance of identification of patients at higher risk for bleeding at the same time weighing this against the risk of thrombosis. Proper patient selection by risk stratification may help firmly establish the role of anticoagulation in patients with COVID-19.

6. Conclusion

Therapeutic anticoagulation is associated with increased risk of major bleeding. Bleeding in turn exhibited trends towards higher inpatient death among patients with COVID-19. The balance between risks and benefits of anticoagulation in patients with COVID-19 should be accounted for. Our findings should be interpreted with caution and larger more controlled studies are needed to verify the net effects of anticoagulation in patients with COVID-19.

Declaration of competing interest

No conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2020.08.035.

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