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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. Multivariable logistic regression was used to look at factors associated with inpatient death.

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
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, intrathoracic, intracardial, 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 the relationship between degree of anticoagulant dose and bleeding events by site. Chi-square was used to analyze the relationship between degree of anticoagulant dose and bleeding events by site. Chi-square was used to analyze the relationship between degree of anticoagulant dose and bleeding events by site. Chi-square was used to analyze the relationship between degree of anticoagulant dose and bleeding events by site. Chi-square was used to analyze the relationship between degree of anticoagulant dose and bleeding events by site. Chi-square was used to analyze the relationship between degree of anticoagulant dose and bleeding events by site. 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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 showed trends towards association with inpatient death 40% vs 21.5% OR 6.16 95% CI (2.96 to 12.83) p ≤ 0.0001 (see Table 4). 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. The risks for bleeding should be carefully weighed in.

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 CHA2DS2VASc 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

### Table 2

| Characteristics | Major bleeding | No anticoagulation | p-Value |
|-----------------|----------------|--------------------|---------|
| Prophylactic    | 7/178 (4%)     | 1/55 (2%)          | 0.684   |
| Subtherapeutic  | 1/20 (5%)      | 1/55 (2%)          | 0.465   |
| Therapeutic     | 11/102 (11%)   | 7/178 (4%)         | 0.04    |
| GI bleeding     | 16.7%          | 22.7%              | 1.000   |
| Other site of bleeding | 50%  | 22.1%              | 0.131   |

### Table 3

| Characteristics | 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   |
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 antplatelet 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 antplatelets 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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