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Original Article

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Incidence of Venous Thromboembolism and Effect of Anticoagulant Dosing in Hospitalized COVID-19 Patients

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is characterized by coagulopathy and thrombotic events. We examined factors associated with development of venous thromboembolism (VTE) in COVID-19 and to discern if higher dose of anticoagulation was beneficial in these patients.

Methods: This study involves an observational study of prospectively collected data in the setting of a large community hospital in a rural setting in Northeast Georgia with COVID-19 between March 1, 2020 and February 5, 2021. Anticoagulation dose (none, standard, intermediate, and therapeutic dosages) was studied in adult patients (≥ 18 years). We constructed multivariable logistic regression model to examine the association of clinical characteristics with VTE. To examine the effect of dose of anticoagulation in preventing VTE, we used inverse probability weighted regression adjustment.

Results: Of the 4,645 patients with COVID-19, 251 (5.4%) patients were found to have VTE. Of these, 91 had pulmonary embolism, 148 had deep venous thrombosis (DVT) and 12 had both. A total of 129 of VTE cases were diagnosed at admission. Of all admissions, 12.9% did not receive any DVT prophylaxis, 70.4% received prophylactic dose, 1.3% received intermediate dose and 15.5% received therapeutic dose. Male gender (odds ratio (OR): 1.55, 95% confidence interval (CI): 1.0 - 2.4, P = 0.04) and Black race (OR: 2.0, 95% CI: 1.2 - 3.4, P = 0.01), along with higher levels of lactate dehydrogenase (LDH) and D-dimer were associated with higher odds of developing VTE. Patients receiving steroids had lower rates of VTE (3.9% vs. 8.3%, P < 0.001). Use of intermediate or therapeutic anticoagulation was not associated with lower odds of developing VTE. However, patients on therapeutic anticoagulation had lower odds of in hospital mortality when compared to standard dose (OR: 0.47, 95% CI: 0.27 - 0.80, P = 0.006).

Conclusions: In COVID-19, D-dimer and LDH can be useful in predicting VTE. Steroids appear to have some protective role in development of VTE. Therapeutic anticoagulation did not result in lower rates of VTE but was associated with in-hospital mortality.

Keywords: COVID-19; Anticoagulation; Venous thromboembolism

Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may lead to dysfunction in the coagulation cascade resulting in arterial and venous thromboembolism (VTE) [1]. Coronavirus disease 19 (COVID-19) associated coagulopathy is multifactorial; possible mechanisms include imbalances in pro- and anticoagulant pathways, increased viscosity, and endothelial injury [2-4]. Jimenez et al reported a 17% pooled incidence of VTE (including distal deep venous thrombosis (DVT) and sub-segmental pulmonary embolism (PE)), although rates were higher if routine screening was used [5].

Plasma fibrinogen and D-dimer concentrations are often elevated in patient with COVID-19 [6, 7]. Though not supported by randomized control trial (RCT) evidence, in clinical practice elevated D-dimer levels have been incorporated into protocols to initiate intermediate and therapeutic dose anticoagulation in efforts to prevent VTE [8]. Whether this practice prevents VTE or has any clinical benefit is currently unknown. Data, mostly from observational cohorts are conflicting: studies have demonstrated benefit, harm and no effect of higher-dose anticoagulation as compared to standard VTE

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prophylaxis [9-13]. While a Cochrane meta-analysis found a reduction in all-cause mortality with therapeutic anticoagulation as compared to standard VTE prophylaxis, another found no differences in outcomes [14]. An expert panel from American College of Chest Physicians (ACCP) suggests using standard dose of anticoagulation over intermediate or therapeutic doses [15]. Our healthcare system followed anticoagulation for COVID-19 guidelines proposed by the Emory healthcare system, which stratified the use of anticoagulation according to levels of D-dimer [16].

The objectives of this retrospective study were to determine the risk factors associated with development of VTE in hospitalized COVID-19 patients and the association of anticoagulation strategies on outcomes. We tested the hypothesis that therapeutic dose anticoagulation as compared to intermediate or prophylactic doses would result in lower mortality in hospitalized COVID-19 patients.

Materials and Methods

Study design and data source

We performed a retrospective analysis of adult COVID-19 patients (age ≥ 18 years) admitted to a large community hospital in a rural setting in Northeast Georgia between March 1, 2020 to February 5, 2021. COVID-19 patients were identified from our Epic® electronic medical record (EMR) using International Classification of Disease, 10th Revision, Clinical Modification (ICD-10-CM) and/or Current Procedural Terminology (CPT) codes for COVID-19 infection and/or positive COVID-19 testing. We obtained clinical and demographical details of patients from Epic® Caboodle data warehouse and Cerner Acute Physiology and Chronic Health Enquiry Score (APACHE®) Outcomes. Systems integration was provided by IPC Global, and we leveraged their in-process data factory innovation running on an Amazon Web Services (AWS®) VPC. Readmissions of the patients with COVID-19 patients were excluded. The study was reviewed and found exempt by the Institutional Review Board (IRB) of the Northeast Georgia Health System; and this study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Definitions

We defined VTE if DVT was confirmed using Doppler ultrasound of the extremities, or acute PE was confirmed using computed tomography (CT) angiogram of chest. We collected clinical and demographic data including comorbidities, home anticoagulation, antiplatelet use, laboratory values, inflammatory markers (ferritin, C-reactive protein (CRP), lactate dehydrogenase (LDH), fibrinogen and D-dimer), presence of central venous catheters and medications given for COVID-19 infection (remdesivir, steroids, tocilizumab, convalescent plasma and hydroxychloroquine). We ascertained anticoagulation status prior to the diagnosis of acute VTE. We adjudicated that patients presenting with VTE on admission were not on anticoagulation unless they were on therapeutic anticoagulation at home. We classified the anticoagulation status of patients who developed VTE after in-hospital admission as follows: 1) standard prophylactic dose (heparin 5,000 U twice a day (BID)/three times a day (TID) or enoxaparin 0.5 mg/kg/day); 2) intermediate dosing (enoxaparin 1 mg/kg/day); and 3) therapeutic dosing (either one of enoxaparin 1 mg/kg/BID, heparin drip, direct oral anticoagulant agents, or warfarin) (Supplemental Material 1, www.thejh.org).

Definition of variables

Our primary dependent variable was the occurrence of VTE. The primary independent variable was the use of anticoagulation. Other adjustment variables included demographics, pertinent clinical characteristics, and laboratory values, use of medications for COVID-19, receipt of mechanical ventilation, vasopressor agents, renal replacement therapy and severity of illness scores. Secondary outcomes included bleeding complications. We used blood transfusions and intra cranial hemorrhage as markers of bleeding complications.

Inclusion criteria

All patients with a diagnosis of COVID-19 and with an age ≥ 18 years were included.

Exclusion criteria

Patients without COVID-19 and below 18 years of age were excluded from the study.

Statistical methods

We describe the categorical data using frequency count and percentages. We report means and standard deviation or medians and inter quartile ranges for continuous variables as appropriate for their distribution. For all analyses, we deemed P value < 0.05 to be of statistical significance.

We constructed multivariable logistic regression model to determine the independent association of variables resulting in VTE. We used the backward elimination method to finalize variables for our models, keeping variables that were significant at a P value of < 0.1. Variables previously known to be associated with development of VTE were kept in the model regardless of their significance. We log transformed (natural logs) markers of inflammation as they were not normally distributed. For D-dimer we used quartiles as we were unable to normalize its distribution. We imputed missing values of inflammatory markers using median values. We bootstrapped the final model using 2,000 bootstrap replicates and case resampling with replacement from the original dataset.

Model to examine treatment effect of therapeutic anticoagulation

To compare the three regimens of anticoagulation (prophylactic, intermediate and therapeutic), we used inverse probability weighted regression adjustment (IPRWA) to correct for potential bias brought about by higher dose of anticoagulation in sicker patients. We calculated the probability of receiving anticoagulation (propensity score model) by fitting a multivariable logistic regression model with anticoagulation dosing as the dependent variable and patient demographics, comorbidities, use of anticoagulants and antiplatelet agents prior to hospitalization, Sequential Organ Failure Assessment (SOFA) score on admission, invasive mechanical ventilation, intensive care unit (ICU) transfer before development of DVT, medications related to COVID-19 and initial inflammatory markers (ferritin, D-dimer, fibrinogen, LDH and CRP). These predictors were chosen based on clinical judgement and model fit. Inverse probability weights were obtained by using inverse of the predicted probability of anticoagulation from the propensity score model. Next, we fitted our outcome model using the inverse probability weights and adjusted this regression model for patient demographics, comorbidities, use of anticoagulants and antiplatelet agents prior to hospitalization, invasive mechanical ventilation, COVID-19 medications received before development of VTE and initial inflammatory markers (ferritin, D-dimer, fibrinogen, LDH and CRP). We made four comparisons: any dose to none, therapeutic dose to standard and intermediate dose to standard dose, and any intermediate/therapeutic dose to standard dose. We calculated the odds of developing acute VTE and death for each of these comparisons using the same multivariate techniques. We performed all statistical analysis using STATA MP 16.0 (StataCorp, College Station, TX).

Results

There were 4,645 COVID-19 admissions during the study period. A total of 1,072 venous Doppler ultrasounds and 1,345 pulmonary CT angiograms were performed. Overall, 251 (5.4%) patients had VTE, of which, 91 had PE, 148 had DVT and 12 had both. Of the 251 diagnosed with VTE, 129 patients were diagnosed within first 24 h of admission (on home anticoagulation (n = 12), and not on home anticoagulation (n = 117)), and 122 were diagnosed after 24 h of hospitalization (not on anticoagulation (n = 3), on standard dose (n = 103), intermediate dose (n = 3) and therapeutic dose (n = 13)). After hospitalization, 12.9% did not receive any DVT prophylaxis, 70.4% received prophylactic dose, 1.3% received intermediate dose and 15.5% received therapeutic dose.

Characteristics of patients with VTE

In unadjusted analysis, patients with DVT were more likely to be men, of Black race and have blood group O as compared to blood group A (Table 1). Patients experiencing VTE more often received therapies for COVID-19 (vitamin C, zinc, steroids, convalescent plasma, remdesivir, steroids, ivermectin and tocilizumab). In the cohort that developed VTE, both acute kidney injury (AKI) and AKI requiring hemodialysis were more common than in the cohort without VTE (Table 1, Supplemental Materials 2, 3, www.thejh.org).

Admission pulse and respiratory rates were higher in patients developing VTE. Patients who developed VTE had higher admission troponin, lactate, creatinine, bilirubin, and white blood cell (WBC) counts (Table 2). Use of blood transfusion was significantly higher in patients who received higher doses of anticoagulation (therapeutic 14.6%; intermediate 13.6% vs. standard 7.8%, P = 0.001, Table 3).

Patient who developed VTE were sicker than counterparts who did not develop VTE as adjudicated by higher rates of ICU admissions (53% vs. 23%, P < 0.001), ventilator use (62.4% vs. 46.9%, P = 0.001) and norepinephrine requirements (14.7% vs. 9%, P = 0.003) (Supplemental Material 4, www.thejh.org).

Unadjusted in hospital mortality was higher in patients who developed VTE (28.7% vs. 15%, P = 0.001). Rate of discharges to home (65.7% vs. 44.1%) and skilled nursing facility (SNF)/long-term acute care (LTAC, 12.5% vs. 24%) were significantly different in patients who developed VTE. Readmission rates (13.5% vs. 11.2%, P = 0.37) were not significantly different in patients with or without VTE (Table 1).

Inflammatory markers

Patients with VTE on average had higher levels of admission ferritin, CRP, LDH and D-dimer (Table 2). The rates of VTE rose significantly when D-dimer level was ≥ 4 µg/mL FEU, LDH level was > 400 U/L, CRP levels ≥ 20 mg/L and ferritin > 2,400 µg/L (Supplemental Material 5, www.thejh.org).

Results of multivariable analysis

After adjustment for potential confounders, male gender (OR 1.55, 95%CI 1.0-2.4, p = 0.04) and Black race (odds ratio (OR): 2.0, 95% confidence interval (CI): 1.2 - 3.4, P = 0.01) were associated with higher odds of developing VTE in COVID-19. Among inflammatory markers, higher levels of LDH and D-dimer were associated with higher odds of developing VTE (Table 4). Convalescent plasma use was associated with higher odds of VTE (OR: 2.52, 95% CI: 1.58 - 4.01, P < 0.001). Other COVID-19 medications (remdesivir, tocilizumab and steroids) and inflammatory markers (ferritin, CRP and fibrinogen) were not associated with VTE. Use of antiplatelet agents such as aspirin or Plavix was not associated with lower odds of VTE.

Standard dose vs. high dose heparin (rates of VTE and in-hospital mortality)

Use of any form of anticoagulation was associated with lower odds of developing VTE (OR: 0.05; 95% CI: 0.03 - 0.08, P < 0.001). However, there was no difference in odds for developing VTE when higher or intermediate dose was compared to

Table 1. Demographical, Clinical Characteristics and Outcomes of COVID-19 Patients With and Without Venous Thromboembolism (VTE)

	No VTE	VTE	P value
Total	4,394	251	
Age, median (IQR)*	66 (52 - 77)	64 (52 - 75)	0.81
Male (%)	51.9	61.4	0.003
Race (%)*			0.08
White	71	67.7	
Blacks	8.2	12.8	
Hispanic	16.7	14.7	
Asian	1.5	2.4	
Not disclosed	2.7	2.4	
BMI	30 (25.7 - 35.6)	31.3 (26.5 - 37.5)	0.81
Comorbidities (%)			
Hypertension	71.7	73.3	0.57
Congestive heart failure	29.4	33.5	0.17
Diabetes mellitus	44	47.4	0.28
Chronic obstructive pulmonary disease	35.7	29.4	0.22
End-stage renal disease	3.5	4.8	0.28
Cirrhosis	12.4	13.2	0.72
Cancer	13.1	11.6	0.47
History of VTE	5.6	10.0	0.004
COVID-19 medications (%)			
Tocilizumab	5.6	14.3	< 0.001
Steroids	66.5	47.0	< 0.001
Remdesivir	57.1	61.7	0.017
Died (%)	15.0	28.7	< 0.001
LOS in survivors, median (IQR)	5 (3 - 8)	8 (4 - 27)	< 0.001
Time to death, median (IQR)	10 (5 - 18)	14.5 (9 - 24)	< 0.001
Disposition (%)			< 0.001
Home	65.7	44.1	
Home with health	17.6	22.4	
SNF/LTAC/rehab	12.5	24.0	
Others	4.1	9.5	
Readmissions	13.5	11.2	0.37

*Median (inter quartile range), number of observations. COVID-19: coronavirus disease 2019; SNF: skilled nursing facility; LTAC: long-term acute care; LOS: length of stay; IQR: interquartile range.

standard dose (Table 5).

Therapeutic dose anticoagulation as compared to prophylactic doses was associated with improved survival (OR: 0.47, 95% CI: 0.27 - 0.80, P = 0.006, Table 5).

Discussion

The most important finding of our study is the low incidence of VTE in hospitalized patients with COVID-19. When we excluded patients, who were diagnosed with VTE on admission (129/251), just 2.7% (122/4,516) developed VTE during hospitalization. This is remarkable because most patients (83%) either received prophylactic dose anticoagulation or did receive any anticoagulation through the hospital stay. Additionally, we found no effect of anticoagulation dosing strategies on VTE occurrence; however therapeutic dose anticoagulation was associated with reduced likelihood of mortality compared to prophylactic dose.

Our rates of VTE are much lower than reported in literature

Table 2. Initial Labs and Inflammatory Markers of COVID-19 Patients With and Without Venous Thromboembolism (VTE)

	No VTE	VTE	P value
Initial clinical characteristics[a]			
SOFA score at admission	1 (0 - 2), 4,394	1 (0 - 2), 251	< 0.001
Mean arterial pressure (mm Hg)	90 (80 - 100), 4,383	92 (81 - 102), 249	0.25
Pulse	90 (78 - 104), 4,363	93 (80 - 110), 244	0.007
Respiratory rate	20 (18 - 24), 4,347	23 (19 - 26), 237	0.001
White blood cell count ($\times 10^3$)	7.7 (5.6 - 10.8), 4,375	9.6 (6.8 - 13.4), 250	0.001
Lymphocyte count ($\times 10^3$)	0.96 (0.66 - 1.41), 4,206	0.93 (0.61 - 1.33), 249	0.28
Hemoglobin (g/dL)	13.1 (11.6 - 14.4), 4,377	13.5 (12.4 - 14.9), 250	0.007
Platelets ($\times 10^3$)	205 (158 - 265), 4,367	221 (161 - 291), 250	0.02
Lactate (mmol/L)	1.1 (0.8 - 1.6), 2,449	1.3 (0.9 - 2.0), 200	0.001
Troponin (ng/mL)	0.02 (0.02 - 0.02), 2,216	0.02 (0.02 - 0.12), 138	< 0.001
aPTT	28.8 (26.3 - 31.9), 2,658	28 (25.2 - 31.5), 200	0.05
INR	1.17 (1.09 - 1.29), 3,877	1.21 (1.12 - 1.34), 246	0.02
BUN (mg/dL)	18 (12 - 27), 4,259	21 (15 - 32), 247	< 0.001
Creatinine (mg/dL)	1.08 (0.85 - 1.44), 4,257	1.21 (0.91 - 1.7), 246	< 0.001
ALT (IU/L)	32 (21 - 50), 4,220	37 (25 - 58), 248	< 0.001
Bilirubin (mg/dL)	0.5 (0.4 - 0.8), 4,150	0.6 (0.5 - 0.8), 248	< 0.001
ECHO findings[a]			
Lowest LVEF	60 (53 - 66), 1,297	60 (53 - 66), 163	0.89
Lowest TAPSE	2 (1.6 - 2.3), 1,460	2 (1.7 - 2.3), 176	0.72
Highest RVSP	35 (27 - 46), 954	36 (26 - 46), 116	0.87
Initial inflammatory markers during hospitalization[a]			
Ferritin (µg/L)	427 (200 - 874), 3,458	638 (311 - 1197), 232	< 0.001
CRP (mg/L)	7.4 (3.2 - 12.9), 3,474	11 (4.3 - 17.2), 234	< 0.001
LDH (U/L)	311 (238 - 407), 3,129	418 (310 - 582), 206	< 0.001
Fibrinogen (mg/dL)	540 (426 - 673), 3,188	564 (423 - 712), 221	0.46
D-dimer (µg/mL FEU)	0.8 (0.5 - 1.5), 3,433	1.97 (0.9 - 4), 237	< 0.001

[a]Median (inter quartile range), number of observations. COVID-19: coronavirus disease 2019; aPTT: activated partial thromboplastin time; SOFA: Sequential Organ Failure Assessment; INR: international normalized ratio; BUN: blood urea nitrogen; ALT: alanine transaminase; ECHO: echocardiogram; LVEF: left ventricular ejection fraction; TAPSE: tricuspid annular plane systolic excursion; RVSP: right ventricular systolic pressure; CRP: C-reactive protein; LDH: lactate dehydrogenase.

Table 3. Rate of Venous Thromboembolism (VTE) and Bleeding Complications of Anticoagulation According to Dose

	None (n = 598)	Standard (n = 3,269)	Intermediate (n = 59)	High (n = 719)	P
VTE at admission (%)	19.6	-	-	1.7	< 0.001
VTE during admission (%)	0.5	3.2	5.1	1.8	0.001
Acute intracranial hemorrhage (%)	2.3	1.0	1.7	1.7	0.03
Gastrointestinal bleeding	11.6	4.8	4.2	10.4	< 0.001
Blood transfusion (%)	11.0	7.8	13.6	14.6	< 0.001
Average units of blood transfusions	1.6	0.8	0.4	1.1	< 0.001
Fresh frozen plasma transfusion (%)	1.2	1.5	5.1	4.2	< 0.001
Cryoprecipitate transfusion (%)	1.2	0.5	0	0.6	0.21
Platelets transfusion (%)	2.0	1.1	0	1.4	0.26

Table 4. Factors Associated With Venous Thromboembolism in COVID-19 Patients

	Odds ratio	95% confidence interval	P
Age	0.83	0.55 - 1.25	0.37
Gender (male vs. female)	1.55	1.01 - 2.39	0.04*
Race (black vs. others)	2.00	1.19 - 3.35	0.01*
Diabetes mellitus	1.45	0.96 - 2.19	0.07
End-stage renal disease	1.30	0.50 - 3.37	0.58
Congestive heart failure	1.04	0.66 - 1.65	0.83
Cancer	0.54	0.23 - 1.29	0.16
Cirrhosis	1.07	0.56 - 2.02	0.84
Anticoagulants at home	0.52	0.12 - 2.27	0.39
NSAIDs	0.70	0.37 - 1.31	0.27
P2Y12 inhibitors	0.68	0.23 - 1.99	0.48
Steroid use	0.58	0.30 - 1.11	0.10
Convalescent plasma	2.52	1.58 - 4.01	< 0.001*
Remdesivir	1.22	0.67 - 2.20	0.51
LDH	2.53	1.70 - 3.78	< 0.001*
CRP	1.30	0.99 - 1.72	0.06
D-dimer	1.15	1.06 - 1.24	< 0.001*
SOFA score on admission	1.52	0.82 - 2.80	0.18

*P < 0.05. COVID-19: coronavirus disease 2019; NSAIDs: nonsteroidal anti-inflammatory drugs; CRP: C-reactive protein; LDH: lactate dehydrogenase; SOFA: Sequential Organ Failure Assessment.

despite similar rates of therapeutic anticoagulation. It is possible that selection bias leads to over-representation of VTE. Moreover, rates of VTE are likely dependent on frequency of screening. Routine periodic screening will increase the likelihood of discovering VTE, including clinically insignificant ones. For example, Jimenez et al reported pooled rates of VTE to be 17% which included distal DVT and sub-segmental PE [5]. However, rates were 33% if patients were screened routinely and 9.8% if based on clinical diagnosis. We screened for DVT only if clinically indicated. Further, 17% of our patients on therapeutic anticoagulation received it empirically and for presumed PE without undergoing definitive testing; this may have lowered the precision of our estimates of VTE (Supplemental Material 6, www.thejh.org). Our rates of VTE are comparable to the study of Cohen et al, who also reported overall VTE rate to be 2.9% in 9,407 patients in New York area [17].

Anticoagulation strategies especially in severe COVID-19 have generated considerable controversy. Rates of pulmonary micro-thrombi on autopsy appear to be significantly higher in COVID-19 illness as compared to equally severe influenza infection [18]. However, report of therapeutic anticoagulation to treat presumed hypercoagulable state has yielded conflicting results [19]. Nadkarni et al found that any form of anticoagulation (prophylactic or therapeutic) was associated with lower mortality and rates of intubation; however, they could not demonstrate improvements in mortality when using higher doses of anticoagulation [10]. Jonmarker et al reported lower death and VTE risk with high dose prophylaxis in critically ill patients [20]. In a multicenter study of 3,239 patients, Al-Samkari et al were unable to find improved mortality with early therapeutic anticoagulation [21]. Conversely, Meizlish et al reported lower in-hospital death with intermediate dose heparin and aspirin [22].

Table 5. Odds of Developing Venous Thromboembolism (VTE) and Odds of In-Hospital Mortality in COVID-19 Patients According to Anticoagulation (AC) Status

AC dose	For developing VTE		For in-hospital mortality	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
No AC vs. any	0.05 (0.03 - 0.08)	< 0.001	0.81 (0.49 - 1.32)	0.41
Standard vs. intermediate	1.15 (0.30 - 4.38)	0.83	1.62 (0.65 - 4.05)	0.29
Standard vs. therapeutic	1.30 (0.57 - 2.95)	0.52	0.47 (0.27 - 0.80)	0.006
Standard vs. intermediate/therapeutic	1.26 (0.60 - 2.63)	0.53	0.61 (0.34 - 1.07)	0.08

COVID-19: coronavirus disease 2019; CI: confidence interval.

In a small RCT with 10 patients in each arm, Lemos et al found that therapeutic as compared to prophylactic dose anticoagulation resulted in improved gas exchange and decreased need for mechanical ventilation in severe COVID-19 [12]. Recently, enrollment for National Institutes of Health (NIH) ACTIV trial of blood thinners in critically ill COVID-19 patients was halted as it did not reduce the need for organ support [23]. However, in another report by NIH, full dose anticoagulation was found superior to usual care prophylactic dose anticoagulation (proportional OR: 1.5; 1.1 - 2.2) in reducing the need for organ support, but not mortality in moderately ill hospitalized COVID-19 patients who did not require ICU level care [24]. Conflicting results are likely due to variable inclusion criteria, severity of illness, timing of anticoagulation and confounding from selection bias and other factors. Although therapeutic doses of anticoagulation as compared to prophylactic doses were associated with improved survival in our study, findings should be interpreted as hypothesis generating. Therapeutic doses of anticoagulation were predominantly used in the sicker cohort of COVID-19 patients. Discerning true effect of a therapy from observational data especially when sicker patients are targeted for treatment is challenging as other aspects of clinical care are not standardized. We observed higher rates of blood transfusion in patients receiving high dose heparin which has been reported in literature [25]. Use of escalating dose of anticoagulation in critically ill patients may be used after assessing risk and benefits [26, 27].

While we did not find any association of anticoagulation strategies with the occurrence of VTE, escalating levels of D-dimer, LDH and CRP were associated with higher likelihood of developing VTE. Previously, elevated D-dimer and fibrinogen levels have been demonstrated in VTE [28, 29]. It is possible that these known markers of inflammation and endothelial injury are reflective of a milieu that predisposes to VTE. Whether following these markers serially to either target sub-cohorts for screening for VTE and/or therapeutic anticoagulation are important questions that should be the focus of future investigations.

Steroid use was associated with significantly lower rates of VTE on univariate analysis, though it did not reach significance on multivariate analysis. Steroids have been used in COVID-19 to decrease the hyperinflammatory response. They have shown to improve mortality in sicker cohort of patients [30]. Their role in prevention of VTE in COVID-19 has not been studied. Steroids being protective for VTE may seem reasonable as inflammation is central to development of VTE.

We also found men and Black patients were more likely to develop VTE. Black population has shown to be more likely to develop thrombotic complications due to their biologic and environmental factors [31]. We found higher concentrations of inflammatory markers in Black population. Similarly, males have shown to have higher rates of proximal DVT [32].

The strength of our study is its large size; however, we acknowledge important limitations. First, its single center, observational and retrospective nature makes it susceptible to selection bias and prevents us from assigning causation. We attempted to mitigate this bias by including all hospitalized patients with COVID-19. Though we have attempted to minimize confounders in treatment outcomes through IPRWA modeling, residual confounding may still prevent capture of important unknown factors that affect differences in outcomes. There were about 25% missing values with respect to the inflammatory markers. These may have affected the precision of our estimates. Many of the sicker patients on the ventilator did not undergo CT angiogram for evaluation of PE, thus it is possible that VTE in our study is underrepresented. We could not ascertain whether the anticoagulation regimen changed during hospitalization depending on other indications such as atrial fibrillation, non-ST-elevation myocardial infarction (NSTEMI), bleeding issues, changing severity of illness, and changing inflammatory markers.

Conclusions

The incidence of VTE in COVID-19 appears to be low and therapeutic anticoagulation may be associated with improved mortality. Results of large RCTs are required to reliably provide guidance on timing and dosing and anticoagulation in COVID-19.

Supplementary Material

Suppl 1. Study design and definitions of VTE while on different anticoagulation dose.

Suppl 2. Demographical, clinical characteristics and outcomes of COVID-19 patients, with and without venous thromboembolism.

Suppl 3. Rates of VTE during admission according to demographical and clinical characteristics of COVID-19 patients.

Suppl 4. ICU characteristics in COVID 19 patients with and without venous thromboembolism.

Suppl 5. Rates of venous thromboembolism (%) at different levels of inflammatory markers on presentation.

Suppl 6. Reasons for therapeutic anticoagulation.

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Financial Disclosure

The authors declare that there was no funding for this study.

Conflict of Interest

None to declare.

Informed Consent

The IRB had reviewed this retrospective study and have waived the requirement of an informed consent. It was based on the following criteria: no patient identifying data is being

published, no patient interaction was involved and no patient intervention was done during the course of this retrospective study.

Author Contributions

Gagan Kumar, Rahul Nanchal, and Achuta Kumar Guddati: conception and design of study, acquisition, analysis, interpretation, drafting of manuscript, final approval of manuscript and agreement to be accountable for all aspects of the work. Dhaval Patel, Tariq Odeh, Erine Rojas, and Ankit Sakhuja: analysis, interpretation, drafting of manuscript, final approval of manuscript and agreement to be accountable for all aspects of the work. Mark Meersman and Drew Dalton: acquisition, analysis, interpretation, drafting of manuscript, final approval of manuscript and agreement to be accountable for all aspects of the work.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

PE: pulmonary embolism; DVT: deep venous thrombosis; VTE: venous thromboembolism; CI: confidence interval; OR: odds ratio; IPRWA: inverse probability weighted regression adjustment; AWS: Amazon Web Services; ICD-10-CM: International Classification of Disease, 10th Revision, Clinical Modification; CPT: Current Procedural Terminology; SIC: sepsis induced coagulopathy; ICU: intensive care unit; AKI: acute kidney injury; HD: hemodialysis; LDH: lactate dehydrogenase; CRP: C-reactive protein; DOACs: direct oral anticoagulants; SNF: skilled nursing facility; LTAC: long-term acute care; LOS: length of stay; SOFA: Sequential Organ Failure Assessment

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