Title: Clinical and Laboratory characteristics of patients with COVID-19 Infection and Deep Venous Thrombosis

Short Title: Deep Venous Thrombosis in COVID-19 Patients.

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ARTICLE HIGHLIGHTS:

Type of Research: Single Center, Retrospective, Non-Randomized Cohort study.

Key Findings: Seventy-one COVID-19 patients had 107 venous duplex examination studies. Presence of DVT was noted in 37 % of examinations. Majority of those who experienced DVT were male (67%) with proximal DVT and had a significantly elevated mean d-dimer (5447 ng/ml), Alkaline Phosphatase (Alk Po4, 110 IU/L). A d-dimer cutoff 2450 ng/ml provided a 70% and 59.5% sensitivity and specificity.

Take home Message: A model for calculating the probability of DVT in patients with severe COVID-19 can be developed that may help identify risk for DVT.

Based on our results, patients may need a higher dose of anticoagulation therapy as most of our patients diagnosed with DVT while on anticoagulation.

Table of Contents Summary:

Single Center, retrospective, non-randomized study investigating the relationship of COVID-19 and deep venous thrombosis (DVT). Seventy-one COVID-19 patients had 107 venous duplex examination studies with DVT noted in 37% of the examinations. The majority were male (67%)

with elevated d-dimer (mean,5447 ng/ml). Males with severe infection were at highest risk of developing DVT. A multivariable model can predict DVT risk.

Abstract:

Objective: Early reports suggest that patients with COVID-19 infection carry a significant risk of altered coagulation with an increased risk for venous thromboembolic events. This report investigates the relationship of significant COVID-19 infection and deep venous thrombosis (DVT) as reflected in the patient clinical/laboratory characteristics.

Methods: We reviewed demographics, clinical presentation, laboratory/radiological evaluations, results of venous duplex imaging and mortality of COVID-19 positive patients (18-89 years) admitted to the Indiana University Academic Health Center. Using oxygen saturation, radiological findings and need for advanced respiratory therapies; patients were classified into mild, moderate or severe categories of COVID-19 infection. Descriptive analysis was performed using univariate and bivariate Fisher's exact and Wilcoxon rank-sum tests to examine the distribution of patient characteristics and compare the DVT outcomes. A multivariable logistic regression model was used to estimate the Adjusted Odds Ratio of experiencing DVT while a Receiver Operating Curve (ROC)analysis to identify the optimal cutoff for d-dimer to predict DVT in this COVID-19 cohort. Time to the diagnosis of DVT from admission was analyzed using log-rank test and Kaplan Meier plots.

Results: Our study included 71 unique COVID-19 positive patients (mean age 61 years) categorized as having 3% mild, 14% moderate and 83% severe infection and evaluated with 107 venous duplex studies. DVT was identified in 47.8% of patients (37% examinations) at an average of 5.9 days post admission. Patients with DVT were predominantly male (67%, p =0.032) with proximal venous involvement. (29% upper and 39% in the lower extremities with 55% of the latter demonstrating bilateral involvement). Patients with DVT had a significantly higher mean d-dimer of 5447 ng/ml (SD 7032, p=0.0101), and Alkaline Phosphatase (Alk Po4) of 110 IU/L (p=0.0095) than those without DVT. On multivariable analysis, elevated d-dimer (p=0.038) & Alk Po4 (p=0.021) were associated with risk for DVT while age, gender, elevated CRP and ferritin levels were not. ROC analysis suggests an optimal d-dimer value of 2450 ng/ml cutoff with 70% sensitivity, 59.5% specificity, and 61% positive and 68.8% negative predictive values.

Conclusion: This study suggests that males with severe COVID-19 infection requiring hospitalization are at highest risk for developing DVT. Elevated d-dimers, Alk Po4 along with our multivariable model can alert the clinician to the increased risk of DVT requiring early evaluation and aggressive treatment

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Key Words: COVID-19, Venous Disease, Deep Venous Thrombosis, Hypercoagulable State, Anticoagulation, d-dimer

Introduction:

SARS-COV2 otherwise also known as COVID-19 is an infection due to a Novel Corona Virus-19. COVID-19 can present in mild, moderate or severe forms [1,2.] Patients who are admitted to either an inpatient facility or to an intensive care unit tend to have moderate to severe symptoms with shortness of breath progressing to pneumonia requiring supportive respiratory therapy with or without the need for multi organ supportive therapy [3]. In a small number of patients, COVID-19 infection leads to cytokine surge, endothelial dysfunction with an increase in acute phase reactants and inflammatory markers resulting in coagulopathy. Increases in d-Dimer, fibrinogen, C-reactive protein and ferritin levels indicate the combination of a prothrombotic and hyper-inflammatory state that may contribute to COVID-19 associated severity of illness, morbidity and mortality [4-7]

The objective of our report is to examine the select group of patients who were admitted to hospital with COVID-19 infection and had venous duplex ultrasonography imaging. We report their characteristics in the context of clinical severity and laboratory results. This report examines mortality outcome and comparisons between the two cohorts of patients who were positive for COVID-19 but differed in the presence or absence of DVT.

Methods: The study was conducted in accordance with the Declaration of Helsinki. The study was granted expedited review status by Indiana University School of Medicine -Institutional Review Board (IRB Protocol 2004249979).

Study Cohort:

All COVID-19 positive patients between age group of 18 to 89 years admitted to the Academic Health Center, Indiana University Health and who had a duplex examination of their venous system between March 15th and April 14th, 2020 were included in this study. These patients were admitted to either an inpatient or intensive care unit of the hospital depending on the level of the care required. Study patients were identified from In Record Time (In Record Time, LLC. Fenton, Michigan), our vascular lab database that records and maintains every non-invasive vascular imaging and interpretation in the facility. Appropriate annotation of COVID-19 status was made in the vascular database.

Patient & Laboratory Characteristics :Patient demographics consisted of age, gender, race, insurance status , body mass index (BMI), smoking status, renal function with need for renal replacement therapy, history of active or remote cancer, use of immune suppression medications, and history of any organ or hematopoietic transplantation were identified from patients records. Patients were classified as mild or moderate severity of infection depending on < or > 94% Oxygen Saturation respectively. Severe category patients had in addition respiratory rate of >30, $PaO_2/FiO_2 \leq 300$ mmHg or need for Mechanical Ventilation. Using medications charted in Cerner, the hospital electronic medical records, documentation was made of the use of angiotensin converting enzyme (ACE) inhibitors or angiotensin Receptor blockers (ARB), use and type of anticoagulation, hydroxychloroquine, antiviral medications per hospital protocol (Remdesivir, Lopinavir, Ritonavir) used in treatment. Laboratory variables in terms of serum hemoglobin in gm% (Hb%), hematocrit (Hct), C-reactive protein in mg/L (CRP), erythrocyte sedimentation rate mm/Hour (ESR), Platelet (Plt) per microliter, serum fibrinogen levels in mg/dl (fibrinogen), d-dimer in ng/ml, renal function test with blood Urea nitrogen (BUN), serum creatinine in mg/dl, liver function test results with aspartate aminotransferase (AST) Units/L) , alanine aminotransferase (ALT Units/L), alkaline phosphatase (Alk Po4 IU/L), serum ferritin in ng/ml, serum. Procalcitonin in ng/ml, and presence or absence of any abnormality on electrocardiography (EKG) were recorded. For the purposes of reporting the severity of COVID-19 infection and medication usage, they were recorded either less than or equal to 48 hours from the day of the venous duplex examination.

Venous Duplex Examinations: All patients had either upper and/or lower extremity venous duplex ultrasonography at the request of the treating physicians. Patients had imaging of either one or all four extremities. Patients were then categorized into two groups depending on the status of the venous duplex examination as either positive or negative for deep venous thrombosis (DVT). Extent (proximal versus distal) as well as the location (superficial venous thrombosis (SVT) and/or DVT) of the venous thrombus was considered for reporting. Time to diagnosis of the venous thrombosis from the time of admission was recorded using the admission date. All examinations were carried out by registered vascular technologists and interpreted by attending physicians in accordance with the protocols suggested by the Intersocietal Accreditation Commission (IAC)

Statistical Analysis: All the above-mentioned variables including the venous duplex examination results were entered into the REDCap database for analysis. REDCap (Research Electronic Data Capture) is a Health Insurance Portability and Accountability Act (HIPAA) compliant , highly secure and intuitive tool designed by Vanderbilt University, USA used by the participating institutions in developing databases to capture data for clinical and translational research.[8] . Descriptive analysis was performed to examine the distribution of patient characteristics and DVT outcomes in the COVID-19 positive patients using frequency distribution for categorical variables and mean (standard deviation, SD) and median (interquartile range IQR) for continuous variables. Bivariate analyses were conducted to investigate the socio-demographic, clinical and laboratory characteristics of patients with COVID-19 infection and the incidence of DVT using Fisher's exact test and Wilcoxon rank-sum test for categorical and continuous variables, respectively. Multivariable logistic regression was used to examine the Adjusted Odds Ratio (AOR) of DVT with 95% Confidence intervals (CI) of the AOR among COVID patients. The coefficients from the multivariable logistic model were used to define an equation to obtain the probability of developing DVT in male and female patients separately. Mathematically, the logistic regression model can be presented as $log\frac{p(x)}{1-p(x)} = \beta_0 + x.\beta$, which can be used to obtain probability or risk that an outcome=1 by using the formula $\frac{\exp(\beta_0+x.\beta)}{1+\exp(\beta_0+x.\beta)}$, where exp is the natural exponential function, β is the logistic regression coefficient and x is the covariate in the model.. All variables with $p<0.20$ in the bivariate analysis and those with $p>0.20$ (age, S.ferritin) otherwise considered clinically important were included in multivariable analysis Multicollinearity was assessed and any potential variables with variance inflation greater than 10 were excluded from the multivariable modeling. The multivariable model included gender, age, d-dimer, CRP, ferritin, and Alk Po4. Time to diagnosis of DVT from admission was analyzed using log-rank test to determine the time-to-event differences between different severity levels of COVID-19 and was displayed using Kaplan Meier plots. Receiver Operating Curve (ROC) analysis for d-dimer as a predictor of DVT was done to report the Area Under the Curve (AUC). Youden Index was used to identify the optimal cutoff for the d-dimer that would distinguish between DVT positive and DVT negative cases. Sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were reported for different levels of the cutoff based on an increment of 500 ng/ml. All analyses were performed at 0.05 level of significance using Stata SE/14.2 (StataCorp, L.P., and College Station, TX).

Results: This study includes 71 unique COVID-19 positive patients, who underwent 107 venous duplex examinations between March 15th to April 14th, 2020 at the Academic Health Center, Indiana University School of Medicine (IU-AHC). Mean age of the cohort were 61 years (± 14.56) with a majority male (54%) and African American patients (61%). Forty two percent of our patients were either ex-smokers or active smokers at the time of admission. Only 10% of the patients were uninsured. The majority of our patients were categorized into severe COVID-19 infections (83%) while 17% were with moderate (14%) to mild (2.8%) infections. Patient's demographics, comorbidities, use of medications was compared between the two patient groups consisting of those with or without any form of thrombotic event in the venous system. Among the 34 patients (48%) who had a positive venous duplex examination, we observed 23 patients were males (68%) (p= 0.032) and race was not found to be significant (p=0.329) for venous thrombotic events. Additional results are shown in **Table 1**.

Bi-variate analysis (**Online table 1)** evaluating the use of ACE (p= 0.665), ARB (p=0.599), hydroxychloroquine (p>0.99), hypoglycemic agents (p=0.315), statins (p >0.99) and antiviral medications (p=0.479) demonstrated no difference between groups. The majority of patients (99%) were on anticoagulation (84% on prophylactic and 16% on therapeutic dose) with either Unfractionated Heparin (UFH) or Low Molecular Weight Heparin (LMWH) at the time of DVT diagnosis. In the cohort of patients with DVT, laboratory levels of d-dimers (p=0.010),Alk Po4 (p=0.009) were found to be abnormally elevated and statistically significant while CRP (p=0.077) , AST (p=0.060) trended towards significance on bivariate analysis between those with and without DVT. **Table 2** provides additional information on laboratory parameters in patients with and without DVT.

There were no significant differences identified in abnormal chest x rays (p>0.99) in those patients (N=68) where the information was available. EKG changes with QT prolongation was see in 6 patients with no differences between the groups with and without DVT (p >0.99, 3 patients in each group).

Positive findings on the venous duplex examination for DVT were found in 37% (N=40) examinations. Patients had venous thrombotic events, either in isolation or in combination with a proximal or distal venous system in the upper and/or lower extremities. The majority of the venous duplex examinations included an evaluation of the lower extremities (70/107 exams). Fifty five percent of all the positive lower extremity examinations had a positive finding for venous thrombotic event in both lower extremities while 29% of the upper extremity venous examinations had a positive finding in both upper extremities. Proximal venous thrombosis was found in 39% of lower extremity examinations in the femoral and popliteal veins with 29% of upper extremity examinations having venous thrombosis in the proximal venous system including one or more of the brachial, axillary and subclavian veins. Isolated SVT was found in 17. 8% (N=19) examinations. SVT was most frequently found in the upper extremities, 54% of patients, and in association with proximal deep venous thrombosis. Details of venous thrombotic events are shown in **Online table 2**. There was no statistical difference in the probability of being diagnosed with DVT among moderate and severe COVID-19 cases (p=0.197), however the time to event analysis by severity of COVID-19 symptoms using Kaplan Meier plot shows (**Figure: 1)** that the likelihood of diagnosis of DVT for severe category of COVID-19 patients was higher and trending towards significance as was seen in the univariate Cox regression (HR=2.13, 95% CI: 0.64, 7.08) than that for mild to moderate patients. On an average, the days from admission to the diagnosis of DVT was 10.4 days for mild/moderate and 6.83 days for severe COVID-19 patients. This difference was not statistically significant as analyzed by Wilcoxon rank sum test (p-value=0.9416).

Based on the (ROC) analysis **(Figure:2A)**, the sensitivity, specificity and predictive values of d-dimers at 500 ng/ml units' intervals was analyzed and obtained an optimal cutoff of 2450 ng/ml. This cutoff was also validated using Youden Index after ROC analysis. **Table 3** shows d-dimer levels in increments of 500 ng/ml along with their specificity %, sensitivity %, PPV %and NPV %. At 2450 ng/ml, these values are 70.6%, 59.5%, 61.5% and 68.8% respectively

Our multivariable logistic regression model (**Figure:2B)** for predicting the odds of DVT gave us an AUC of 0.8214 which indicates that the model has a good predictive ability[11] and potential of clinical utility to discriminate DVT cases from non-DVT cases among COVID-19 patients. **Table 4** shows patient and laboratory characteristics with the adjusted odds ratio predicting their association with DVT amongst COVID-19 patients. Elevated d-dimers (p=0.038) and Alk Po4 (p=0.021) were significantly associated with the risk of diagnosing DVT. Based on this model, we propose equations for the probability of DVT occurrences in COVID-19 positive patients among male and female cases is as shown below.

Probability for DVT among female COVID-19 positive patients can be predicted by using

$$\Pr(DVT = 1) = \frac{e^{(-2.672+0.0002*ddimer-0.0013*CRP+0.0004*Ferritin+0.0269*AlkPO4-0.0042*Age-1.2947)}}{1 + e^{(-2.672+0.0002*ddimer-0.0013*CRP+0.0004*Ferritin+0.0269*AlkPO4-0.0042*Age-1.2947)}}$$

Similarly, for male COVID-19 positive patients the probability for DVT can be predicted by using

$$\Pr(DVT = 1) = \frac{e^{(-2.672+0.0002*ddimer-0.0013*CRP+0.0004*Ferritin+0.0269*AlkPO4-0.0042*Age)}}{1 + e^{(-2.672+0.0002*ddimer-0.0013*CRP+0.0004*Ferritin+0.0269*AlkPO4-0.0042*Age)}}$$

Here, e represents the natural exponential function, -2.672 is a constant in the logistic regression, and 0.0002, -0.0013, 0.0004, 0.0269, -0.0042, and -1.2947 are the coefficients respectively for the variables d-dimer, CRP, Ferritin, AlkPO4, Age and Female.

Mechanical ventilation were required in 77.5% patients in the entire cohort with 3 patients required ECMO. There were no differences in the use of either mechanical ventilation or ECMO in patients with and without DVT.

In this entire cohort, ten deaths (14%) occurred during the follow-up period of 13.4 ±7.1 days. All deaths were related to progressive sepsis with multi-organ dysfunction. The analysis of survival comparing the mild/moderate disease and severe disease patients did not reach statistical significance.

Discussion: At the time of this manuscript the United States accounted for both the highest number of patients as well as fatalities due to COVID-19 infections in the world We had a mortality of 14 % in our cohort which is similar to those reported for all COVID-19 related admissions to Intensive care units requiring advanced respiratory therapies and supportive care.[9-12] . Our results demonstrate similar observations with significant number of male COVID-19 positive patients with others reporting a high BMI as an additional risk.[13,14.] Similar to published reports our cohort is composed of approximately 60% African American patients. [15].

Similar to our results, venous thromboembolism (VTE) in critically ill patients with COVID-19 reportedly ranges from 25-31%.[16-18] Patients with severe and fatal COVID-19 are in a prothrombotic and hyper-inflammatory state with reportedly higher d-dimer levels [4-6,18,21-23]. Given the varying degrees of sensitivity (80-100%) , specificity (23-63%) d-dimer levels are not advised as a single definitive test for diagnosis [19-20] for VTE.Tang et al defined the high risk population as having a D-dimer elevation more than six times the upper limit of normal and Sepsis Induced Coagulopathy (SIC) score of more than or equal to 4 .[16]. In our study, the sensitivity of d-dimer of 2450g/ml was approximately 70% and specificity was approximately 60% and reflect the limitations of using d-dimer as a stand-alone trigger for treatment. It also must be noted that 99% of our patients were on anticoagulation (84% on prophylactic and 16% on therapeutic dose) at the time of diagnosis. Given the high percentage of patients who were diagnosed with DVT while on prophylactic anticoagulation, one might postulate that these patients need full anticoagulation to be reliably protected against experiencing DVT.

Mechanisms related to such high levels of d-dimer as well as the risk of DVT may be related to a cytokine surge, the upregulation of hypoxia induced transcription pathways [16], or potentially the use of continuous positive airway pressure (c-PAP) ventilator, thought to compress superficial or deep vessels of the upper limbs which might lead to thrombosis[24] . Our study provides no insights into the underlying pathophysiology.

The presence of liver abnormalities have been observed in the COVID population potentially due to various pathophysiological pathways.[25] Worsening transaminases such as, Alk-Po4 a sign of significant liver disease, is associated with heightened risk of VTE. based on our analysis. Cui et al [17] has suggested worsening transaminases is related to worse patient outcomes in COVID-19. Chen et al [26] similarly suggest an aspartate aminotransferase >40U/liter (HR: 2.2, 95% CI: 1.1-6.73) was an independent risk factor associated with fatal outcome.

Based on our multivariable analysis, d-dimer along with C- reactive protein, alkaline phosphatase, ferritin levels and gender would be helpful to assess the probability of underlying deep venous thrombosis. An absolute level of D dimer cannot be used to initiate a high dose anticoagulation in COVID-19 positive patients, we recommend calculating the probability of venous thromboembolism in these patients and then make decisions based on clinical needs of the patient. This model should help guide further treatment decisions. A larger cohort is needed to validate our observations.

Similar to sepsis induced coagulopathy, there are reports that suggest survival benefit in COIVD-19 patients with pneumonia and DVT when treated with anticoagulation [16,26]. Available algorithms take into consideration Well's pretest probability score [28,29] advising either prophylaxis, thrombostabilizing protocol, or therapeutic anticoagulation for DVT and PE. However, given the limitations [30-31] with varying degrees of sensitivity, specificity as well as age related challenges and ability to predict only the proximal venous thrombosis, it remains to be seen if the Well's score can be used to advise anticoagulation strategies for COVID-19 patients. To overcome some of these limitations age adjusted d-dimer along with Well's probability score [32] has been advised.

Based on initial observations, which forms the basis for this report, a high dose anticoagulant regimen was advised for DVT prophylaxis (Online **table 3**) in our health facility for ICU COVID-19 patients. Since both upper and lower extremities are often involved with DVT in our cohort, there appears to be little role for IVC filters in this patient population. Relatively low sensitivity of D-dimer amidst high DVT prevalence warrants consideration of empiric anticoagulation on admission. If the probability score is high based on our multivariate model, we postulate that patients will benefit a therapeutic dose to offer protection against DVT. Our observations are similar to Obi et al indicating H1N1 ARDS patients had 23.3-fold higher risk for pulmonary embolism and 17.9-fold increased risk for VTE. This led to authors concluding empirical systemic heparin anticoagulation in this cohort of patients significantly reduced VTE incidence without increased hemorrhagic complications [33]

Given the concerns for acquiring COVID-19 infection and to protect our health care providers, prudent and judicious use of the vascular lab resources is critical. Since anticoagulation will be provided no matter where the DVT is found, termination of extensive testing seems warranted when a major proximal DVT is found. In addition to the concerns expressed by Obi et al [28] we believe that an algorithm of who is at most risk based on gender and other factors from our multivariate model might eventually provide an answer on whom to study.

This report focuses on patients in the moderate to severe categories of COVID-19 infection requiring hospital admission. This study adds to the existing body of literature in that male patients are at highest risk for complications. The study has strengths in the fact that all patients included in the study had a venous duplex ultrasonography to provide confirmation of DVT. We have identified variables beyond those described to predict the probability of DVT in patients with COVID-19 infection. Besides a small sample size, weakness of the study is very similar to those inherent to any single center retrospective series and, limited by inherent biases related to patient selection, investigation, as well as treatments provided. The multivariable model proposed in this manuscript needs further validation and research. In addition, the study has also its weakness as we did not perform evaluations for the pulmonary embolism or investigating for the caval or iliac venous thrombosis.

Conclusions:

Male gender and patients admitted with severe category of COVID-19 infections are at high risk for DVT. Elevated d-dimer and Alk Po4 levels have the ability to predict DVT in our model. Our novel multivariate predictive model should provide guidance, as we consider high dose empiric anticoagulation in this high risk COVID-19 patients. To limit the risk of exposure to healthcare workers considerations should be given in judicious ordering of vascular lab imaging.

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Tables:

Table 1 : Patient Characteristics and bivariate relationship with DVT

Characteristics	In Sample (n=71)	DVT status		p-value
		Negative (n=37)	Positive (n=34)	
Age (n=71)				0.7478
Mean (SD)	61.06 (14.56)	61.11 (13.6)	61 (15.74)	
Median (IQR)	63 (20)	63 (14)	65 (20)	
Gender				0.032
Male	38 (54%)	15 ((41%)	23 (68%)	
Female	33 (46%)	22 (59%)	11 (32%)	
Race				0.329
Whites	22 (31%)	13 (35%)	9 ((27%)	
AA	43 (61%)	23 (62%)	20 (61%)	
Others	5 (7%)	1 (3%)	4 (12%)	
Missing	1 (1%)			
Smoking Status				0.934
Current Smokers	6 (8%)	3 (8%)	3 (10%)	
Former Smokers	24 (34%)	14 (38%)	10 ((32%)	
Never Smokers	38 (54%)	20 (54%)	18 (58%)	
Missing	3(4%)			
Active Cancer				>0.99
No	65 (92%)	35 (95%)	30 (94%)	
Yes	4 (6%)	2 (5%)	2 (6%)	
Missing	2 (2%)			
Remote Cancer				>0.99
No	64 (90%)	34 (92%)	30 (94%)	
Yes	5 ((7%)	3 (8%)	2 (6%)	
Missing	2 (3%)			
Insurance				0.442
Medicare	33 (46%)	19 (51%)	14 (41%)	
Medicaid	7 (10%)	5 (14%)	2 (6%)	
Private	22 (31%)	10 (27%)	12 (35%)	
Others	2 (3%)	0 (0)	2 (6%)	
Uninsured	7 (10%)	3 (8%)	4 (12%)	
CKD				0.088
No	55 (78%)	26 (70%)	29 (88%)	
Yes	15 (21%)	11 (30%)	4 (12%)	
Missing	1 (1%)			

RRT (Renal Replacement therapy)				0.479
No	70 (99%)	37 (100)	33 (97%)	
Yes	1 (1%)	0 (0)	1 (3%)	
				0.152
Immune Sup Med				>0.99
No	63	33 (89%)	30 (91%)	
Yes	7	4 (11%)	3 (9%)	
Missing	1			
HTN				0.795
No	21 (30%)	10 (27%)	11 (32%)	
Yes	50 (70%)	27 (73%)	23 (68%)	
CAD				>0.99
No	54 (76%)	28 (76%)	26 (76%)	
Yes	17 (24%)	9 (24%)	8 (24%)	
Diabetes				0.628
No	43 (61%)	21 (57%)	22 (65%)	
Yes	28 (39%)	16 (43%)	12 (35%)	
Hyperlipidemia				0.232
No	35 (49%)	21 (58%)	14 (42%)	
Yes	34 (48%)	15 (42%)	19 (58%)	
Missing	2 (3%)			
COPD				>0.99
No	64 (90%)	33 (89%)	31 (91%)	
Yes	7 (10%)	4 (11%)	3 (9%)	
BMI (n=70)				0.4727
Mean (SD)	33.62 (8.35)	34.61 (9.12)	32.54 (7.4)	
Median (IQR)	33 (10.2)	33 (12.9)	31 (8.9)	
COVID Severity				0.867
Mild	2 (3%)	1 (3%)	1 (3%)	
Moderate	10 (14%)	6 (16%)	4 (12%)	
Severe	59 (83%)	30 (81%)	29 (85%)	

Table 2: Bivariate Analysis of Lab Parameters comparing patients with and without Deep venous Thrombosis

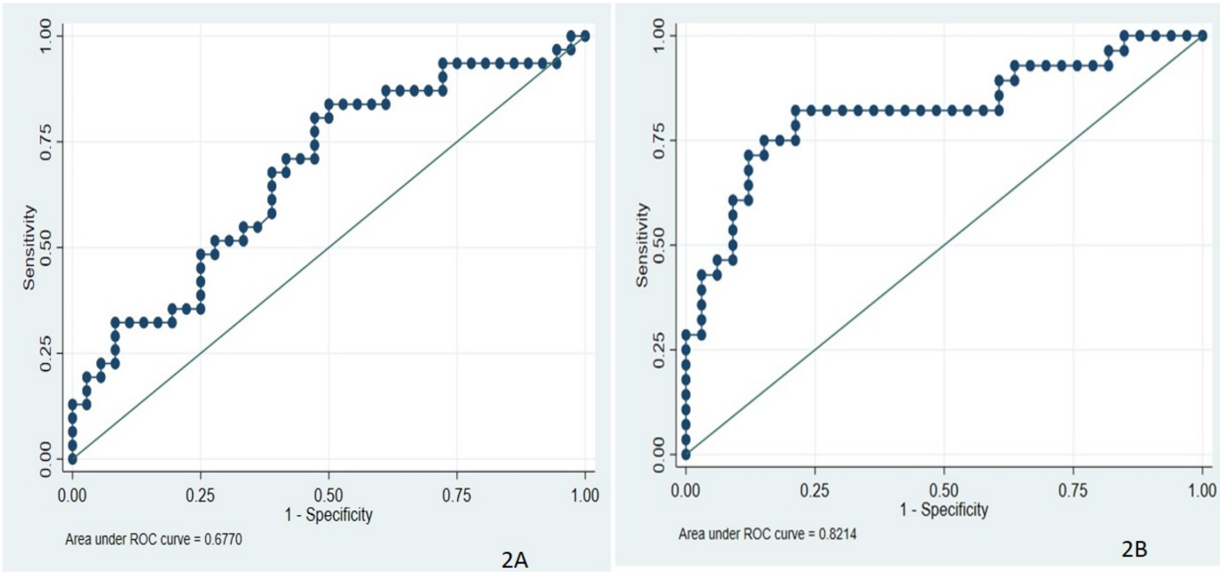
Lab Parameters (In Sample)	Results Mean (SD)	DVT Negative Mean (SD)	DVT Positive Mean (SD)	P Value
Hgb gm% (n=71)	10.72 (1.99)	10.47 (1.94)	11 (2.05)	0.4038
HCT (n=71)	32.48 (5.99)	31.78 (5.8)	33.25 (6.18)	0.4878
d-dimer ng/ml (n=67)	3941.21 (5240.36)	2644.03 (2378.77)	5447.61 (7032.01)	0.0101
Fibrinogen mg/dl (n=41)	664.66 (198.69)	655.57 (220.84)	676.28 (171.8)	0.8422
Platelets /microlit (n=71)	282.76 (98.91)	290.73 (107.67)	274.09 (89.2)	0.5313
CRP mg/L(n=67)	18.26 (17.35)	17.54 (21.83)	19.1 (10.26)	0.0772
ESR (n=11)	80.82 (25.33)	83 (31.84)	79 (21.51)	0.9361
Ferritin ng/ml (n=65)	1038.73 (1191.61)	820.83 (1001.94)	1277.7 (1346.15)	0.1295
Procalcitonin ng/ml (n=29)	2.18 (5.92)	2.38 (7.7)	1.94 (2.72)	0.1873
BUN mg/dl (n=70)	32.86 (25.95)	35.94 (28.67)	29.59 (22.7)	0.2841
Serum Creatinine mg/dl(n=70)	1.41 (1.65)	1.57 (1.91)	1.25 (1.32)	0.3222
Albumin mg/dl (n=68)	2.91 (0.58)	2.9 (0.44)	2.91 (0.71)	0.4015
AST Units /L (n=68)	59.16 (47.49)	47.72 (36.17)	72.03 (55.44)	0.0604
ALT Units/L (n=68)	50.49 (40.31)	45.25 (34.69)	56.38 (45.67)	0.3828
Alkaline PO4 IU/L(n=68)	89.56 (59.67)	71.39 (24.2)	110 (78.86)	0.0095

Table 3: Optimal cutoff of d-dimer values to predict DVT in patients with COVID-19 infection

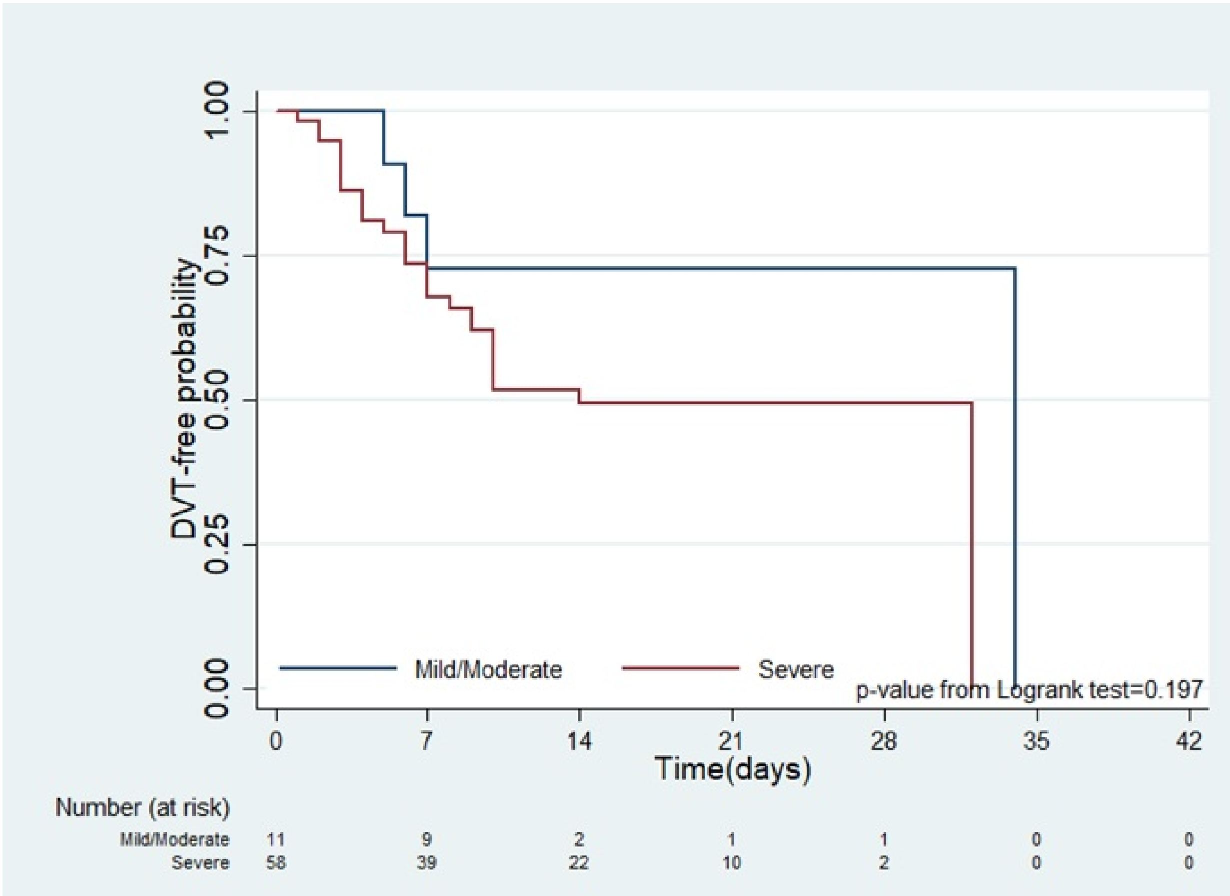
d-dimer ng/ml Cutoff	Prevalence, %	AUC	Sensitivity, %	Specificity, %	PPV, %	NPV, %
1450	47.9	0.63	85.3	40.5	56.9	75
1950	47.9	0.64	76.5	51.4	59.1	70.4
2450*	47.9	0.65	70.6	59.5	61.5	68.8
2950	47.9	0.6	58.8	62.2	58.8	62.2
3450	47.9	0.63	55.9	70.3	63.3	63.4
3950	47.9	0.59	44.1	73	60	58.7
*Optimal cutoff based on Youden Index for d-dimer to predict DVT						

Table 4 : Multivariable Analysis of DVT among COVID positive patients

Characteristics	Adj. Odds Ratio	95% CI		p-value
d-dimer	1.000243	1.000014	1.000472	0.038
CRP	0.9987068	0.9600632	1.038906	0.949
ferritin	1.000353	0.999747	1.000959	0.254
alkpo4	1.027308	1.003987	1.05117	0.021
Age	0.9958539	0.9517951	1.041952	0.857
Female	0.2739775	0.0701369	1.070246	0.063



Sensitivity
0.00
0.25
0.50
0.75
1.00
1 - Specificity
Area under ROC curve = 0.6770
2A
Sensitivity
1 - Specificity
Area under ROC curve = 0.8214
2B



DVT-free probability
1.00
0.75
0.50
0.25
0.00
Mild/Moderate
Severe
p-value from Logrank test=0.197
0
7
14
21
28
35
42
Time(days)
Number (at risk)
Mild/Moderate 11 9 2 1 1 0 0
Severe 58 39 22 10 2 0 0

Online Table 1 : Bivariate Analysis of patient's medications and status of deep venous thrombosis

Medications	In sample (N=71)	DVT Negative (N=37)	DVT Positive (N=34)	P Value
Aspirin				0.315
No	47 (66.2)	22 (59.46)	25 (73.53)	
Yes	24 (33.8)	15 (40.54)	9 (26.47)	
ACE				0.665
No	66 (92.96)	35 (94.59)	31 (91.18)	
Yes	5 (7.04)	2 (5.41)	3 (8.82)	
ARB				0.599
No	67 (94.37)	36 (97.3)	31 (93.94)	
Yes	3 (4.23)	1 (2.7)	2 (6.06)	
Missing	1 (1.41)			
Hydroxychloroquine				>0.99
No	28 (39.44)	15 (40.54)	13 (38.24)	
Yes	43 (60.56)	22 (59.46)	21 (61.76)	
Hypoglycemics				0.315
No	46 (64.79)	22 (59.46)	24 (72.73)	
Yes	24 (33.8)	15 (40.54)	9 (27.27)	
Missing	1 (1.41)			
Statins				>0.99
No	50 (70.42)	26 (70.27)	24 (70.59)	
Yes	21 (29.58)	11 (29.73)	10 (29.41)	
Antiviral Medications				0.479
No	61 (85.92)	30 (83.33)	31 (91.18)	
Yes	9 (12.68)	6 (16.67)	3 (8.82)	
Missing	1 (1.41)			
Anticoagulation Status at the time of Diagnosis				>0.99
No	1 (1.41)	1 (2.7)	0 (0)	
Yes	70 (98.59)	36 (97.3)	34 (100)	
If Yes, Types				0.515
Therapeutic	11 (15.71)	7 (19.44)	4 (11.76)	
Prophylactic	59 (84.29)	29 (80.56)	30 (88.24)	

Online Table 2: Description of location and extent of venous thrombotic events

Location and Extent of Venous Thrombosis (N=107 Examinations: 70 Lower extremity+37 Upper extremity)	% Positive Studies
Total number of venous thrombotic events	55% (N=59)
Total number of Deep venous thrombosis (DVT)	37.38% (N=40)
Total number of isolated Superficial venous Thrombosis	17.75% (N=19)
Bilateral Lower extremity DVT (of lower extremity examinations)	55%
Bilateral Upper extremity DVT (of upper extremity examinations)	29%
% Positive Proximal DVT in lower extremity examinations (Femoral , Popliteal Veins)	39%
% Positive Proximal DVT in upper extremity examinations (Axillary, Subclavian , Jugular veins)	29%

Online table 3 : Indiana University –Academic Health Center Protocol for Prophylactic dosing of anticoagulation in severe COVID-19 infections .

Creatinine Clearance	Weight - < 119kg	Weight 120-150kg	Weight > 150kg
>30ml/min	Enoxaparin 30mg Q12H	Enoxaparin 40mgQ12H	Enoxaparin 60mg Q12H
< 30ml/min, End stage renal disease	Heparin 5000Q8H	Heparin 7500Q8H	Heparin 7500Q8H

Figure Legends :

Figure 1: Time to event analysis for determining DVT-free probability using log rank test and KM plot

Figure 2A: Receiver Operating Curve for the model predicting DVT using d-dimer

2B: Receiver Operating Curve for the multivariable model predicting DVT

Table Legends :

Table 1 : Patient Characteristics and bivariate relationship with DVT

Online Table 1: Bivariate Analysis of patient's medications and status of deep venous thrombosis

Table 2: Bivariate Analysis of Lab Parameters comparing patients with and without Deep venous Thrombosis (*p<0.10, **p<0.05, ***p<0.01)

Table 3 : Optimal cutoff of d-dimer values to predict DVT in patients with COVID-19 infection

Online Table 2 : Online Table 2: Description of location and extent of venous thrombotic events

Table 4: Multivariable Analysis of DVT among COVID positive patients

Online table 3 : Indiana University –Academic Health Center Protocol for Prophylactic dosing of anticoagulation in severe COVID-19 infections