Predictors of acute deep venous thrombosis in patients hospitalized for COVID-19

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Abstract
Deep venous thrombosis (DVT) is associated with high mortality in coronavirus disease 2019 (COVID-19) but there remains uncertainty about the benefit of anti-coagulation prophylaxis and how to decide when ultrasound screening is indicated. We aimed to determine parameters predicting which COVID-19 patients are at risk of DVT and to assess the benefit of prophylactic anti-coagulation.

Adult hospitalized patients with positive severe acute respiratory syndrome coronavirus-2 reverse transcription-polymerase chain reaction (RT-PCR) undergoing venous duplex ultrasound for DVT assessment (n = 451) were retrospectively reviewed. Clinical and laboratory data within 72 hours of ultrasound were collected. Using split sampling and a 10-fold cross-validation, a random forest model was developed to find the most important variables for predicting DVT. Different d-dimer cutoffs were examined for classification of DVT. We also compared the rate of DVT between the patients going and not going under thromboprophylaxis.

DVT was found in 65 (14%) of 451 reverse transcription-polymerase chain reaction positive patients. The random forest model, trained and cross-validated on 2/3 of the original sample (n = 301), had area under the receiver operating characteristic curve = 0.91 (95% confidence interval [CI]: 0.85–0.97) for prediction of DVT in the test set (n = 150), with sensitivity = 93% (95%CI: 68%–99%) and specificity = 82% (95%CI: 75%–88%). The following variables had the highest importance: d-dimer, thromboprophylaxis, systolic blood pressure, admission to ultrasound interval, and platelets. Thromboprophylaxis reduced DVT risk 4-fold from 26% to 6% (P < .001), while anti-coagulation therapy led to hemorrhagic complications in 14 (22%) of 65 patients with DVT including 2 fatal intra-cranial hemorrhages. D-dimer was the most important predictor with area under curve = 0.79 (95%CI: 0.73–0.86) by itself, and a 5000 ng/mL threshold at 7 days postCOVID-19 symptom onset had 75% (95%CI: 53%–90%) sensitivity and 81% (95%CI: 72%–88%) specificity. In comparison with d-dimer alone, the random forest model showed 68% versus 32% specificity at 95% sensitivity, and 44% versus 23% sensitivity at 95% specificity.

D-dimer >5000 ng/mL predicts DVT with high accuracy suggesting regular monitoring with d-dimer in the early stages of COVID-19 may be useful. A random forest model improved the prediction of DVT. Thromboprophylaxis reduced DVT in COVID-19 patients and should be considered in all patients. Full anti-coagulation therapy has a risk of life-threatening hemorrhage.

Abbreviations: AUC = area under curve, BMI = body mass index, COVID-19 = coronavirus disease 2019, DVT = deep vein thrombosis, PE = pulmonary embolism, PT = prothrombin time, PTT = partial thromboplastin time, RT-PCR = reverse transcription-polymerase chain reaction, SBP = systolic blood pressure, VTE = venous thromboembolism.

Keywords: COVID-19, d-dimer, deep vein thrombosis, random forest, thromboprophylaxis, venous thromboembolism.
1. Introduction

A growing body of evidence shows coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus-2, is an independent risk factor for thromboembolic events, despite thromboprophylaxis. A recent meta-analysis has estimated a 31% prevalence of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and/or pulmonary embolism (PE) with estimated prevalence of 20% and 19%, respectively. These prevalence rates may underestimate VTE risk due to thromboprophylaxis and the limited number of studies systematically screening for DVT.

When all patients were screened for DVT, prevalence doubled to 41%. A growing body of evidence shows coronavirus disease 2019 (COVID-19) is an independent risk factor for VTE, and this risk is exacerbated when duplex US is performed portably. A reliable screening method for predicting DVT based upon laboratory and clinical parameters may identify COVID-19 patients with DVT allowing immediate prophylactic anti-coagulation while deferring ultrasound until they are no longer infectious.

While thromboprophylaxis was associated with reduced rate of VTE, there is no clear guideline for initiating prophylactic versus therapeutic dose anti-coagulation. Although lower extremity ultrasound is highly accurate for diagnosing DVT, performing the ultrasound requires extended patient contact frequently during the patient’s infectious period, and risks are exacerbated when duplex US is performed portably. A reliable screening method for predicting DVT based upon laboratory and clinical parameters may identify COVID-19 patients with DVT allowing immediate prophylactic anti-coagulation while deferring ultrasound until they are no longer infectious.

In this multicenter study analyzing patients admitted between March and June 2020 in 3 New York City hospitals, we identified risk factors for DVT at the time of duplex exam and developed a multivariable classification algorithm to predict DVT in hospitalized patients. We also assessed the effect of prophylactic anti-coagulation on the rate of DVT.

2. Materials and methods

2.1. Study population

COVID-19 patients admitted to New York-Presbyterian/Weill Cornell Medical Center, New York-Presbyterian/Lower Manhattan Hospital and NIH Medical Group/Queens, affiliated community hospitals, between March 3, 2020 and June 5, 2020 with the following criteria were included in this retrospective study: patients ≥18 years-old, COVID-19 diagnosis confirmed by a positive severe acute respiratory syndrome coronavirus-2 reverse transcription-polymerase chain reaction (RT-PCR) via nasopharyngeal swab and undergoing venous duplex ultrasound of upper and/or lower extremities for suspected DVT. We did not screen all patients for DVT, ultrasound examinations were performed based on the physicians suspecting DVT considering signs, symptoms, and lab findings. In case of a negative RT-PCR test in patients with high clinical suspicion for COVID-19, the RT-PCR test was repeated, and patients were included if the subsequent test was positive. The patients with DVT prior to the first RT-PCR test were excluded. Institutional review board of Weill Cornell Medical Center approved the study. The requirement of informed consent was waived.

Demographic, laboratory, medical history, medications, and clinical data were extracted from the patients' electronic medical records using the institution’s COVID-19 research data repository. Demographic, clinical and laboratory data, vital signs, oxygen supplementation methods, and arterial blood gas analysis within 72 hours of duplex ultrasound exam for diagnosis of DVT were used for the analysis. Demographic data included age, gender, race/ethnicity, body mass index (BMI), and inhalational tobacco use ("smoking"). Laboratory and clinical data included d-dimer, fibrinogen, ferritin, C-reactive protein, platelets, PT and activated partial thromboplastin time (APTT), heart rate, systolic blood pressure (SBP) and diastolic blood pressure, arterial %O2 saturation, duration and route of supplemental O2 administration (invasive or non-invasive mechanical ventilation), past medical history of chronic lung disease, cardiovascular disease and chronic kidney disease, hypercoagulability and DVT, diabetes mellitus, active cancer, human immunodeficiency virus, and anti-coagulation use at least 48 hours before duplex ultrasound evaluation.

2.2. Duplex ultrasound procedure

Upper and lower extremity ultrasound was performed using a 9 MHz linear probe and a 5 MHz curved linear probe for deeper penetration in the setting of obesity or lower extremity edema (General Electric Medical Systems Logic S8 Portable machines and GE E10, with the 9 Linear C1-5 curved linear probes). All technologists were credentialed as registered diagnostic medical sonographers. A minority also registered as vascular technologists ranging in experience from 1 to 13 years. All exams were performed either portably at the bedside or in the radiology ultrasound suite according to American Institute of Ultrasound in Medicine guidelines. Evaluation of the lower extremities included graded compression gray scale and color Doppler evaluation of the common femoral vein, femoral vein, deep femoral vein, and popliteal vein in all cases, with spectral duplex Doppler evaluation of the common femoral and popliteal veins, and, where possible, graded compression and color flow evaluation of greater saphenous, external iliac, peroneal, posterior tibial, and anterior tibial veins as recorded from the venous duplex ultrasound reports. DVT diagnosis was only considered positive for thigh DVT, from popliteal vein to the common femoral or external iliac veins. Findings of acute calf DVT and chronic DVT without evidence for acute thrombosis were considered negative.

2.3. Statistical analysis

2.3.1. Descriptive statistics. Continuous variables were reported as mean ± standard deviation (or median and interquartile range) and their difference between the groups with and without acute DVT were assessed using 2-tailed t test (or Mann-Whitney U test). Dichotomous variables were reported as frequency and percentage and between group difference was assessed using chi-squared test. The outcome of interest was recorded as a binary variable.

2.3.2. Prediction model development. Missing values were imputed in variables with less than 10% missing data points using the missForest method of imputation. The total study sample was randomly divided into a training set maintaining the

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**Note:** The text appears to be cut off or incomplete, but based on the visible content, it seems to be a medical research paper discussing the prevalence of COVID-19 and DVT, and the development of a predictive model for DVT.
outcome proportion, including 2/3 of the patients, and a test set (i.e., the remaining 1/3) for model building and validation, respectively. As acute DVT was a rare event, synthetic minority oversampling technique\cite{9} was applied in the training set to balance the data, by up-sampling the minority group. A random forest model was fitted on the balanced training set for prediction of acute DVT. The independent variables were age, gender, BMI, smoking, past medical history of chronic lung disease, cardiovascular disease, and hypercoagulability; COVID-19 symptoms to ultrasound interval (days), hospital stay (days), thromboprophylaxis 48 hours before ultrasound, days on ventilator, intubation, need for supplemental oxygen at arrival, non-invasive ventilation, heart rate, SBP, %O2 saturation, d-dimer, C-reactive protein, fibrinogen, ferritin, platelets, PT, and PTT. Variable importance was determined using mean decrease in Gini impurity index and permutation importance (i.e., mean decrease in accuracy). A 10-fold cross-validation was used to train the model on the training set. Predictions were then made using the random forest model on the test set. The area under the receiver operating characteristic curve (AUC) was calculated to assess the model performance on the validation set. Youden index was then used to threshold the predictions for diagnosis of acute DVT. The significance level was set to .05 and the statistical analysis was performed in R version 4.0.2 (R Core Team, Vienna, Austria, 2020).

2.3.3. Sensitivity analysis. Univariate logistic regression was used to assess the predictive performance of d-dimer as a continuous variable. Then, sensitivity analysis was performed at different d-dimer thresholds <500, <1000, <1500, <3000, <5000, <7500 ng/mL at different time points ≤7, ≤14, and ≤50 days from COVID-19 symptom onset.

3. Results

3.1. Patient characteristics

Figure 1 shows the number of patients meeting the inclusion criteria; their baseline characteristics are presented in Table 1. Of the 451 hospitalized patients with COVID-19 undergoing ultrasound evaluation, 65 (14%) were diagnosed with acute DVT.
DVT. The interval between COVID-19 symptom onset and duplex exam ranged from 0 to 62days (median [interquartile range]: 12 [5, 20]) which was significantly shorter in the DVT group (10days [1, 17] vs 12days [6, 21], \( P = .004 \), Table 1). Comparison of the patient characteristics between the groups with and without DVT showed significant difference in the past medical history of DVT/hypercoagulability, active cancer, human immunodeficiency virus, \%O2 saturation, D-dimer, fibrinogen level, PT and use of anti-coagulation prophylaxis (\( P < .05 \), Table 1). In the DVT group only 25% (16/65) of the patients were on thromboprophylaxis \( \geq 48 \) hours before the ultrasound evaluation, compared to 63% (245/386) of the patients without DVT (\( P < .001 \)).

Table 2 shows the comparison of complications and death between DVT and non-DVT patients. Hospital stay was significantly longer for the non-DVT group, while PE was significantly more prevalent in the DVT group (\( P < .001 \)). Acute respiratory distress syndrome (ARDS) was significantly more prevalent in non-DVT group in the ICU (92% vs 78%, \( P = .005 \), data not shown). Death rate was 25% (16/65) in the DVT group versus 17% (64/386) without DVT but this trend was not statistically significant, \( P = .15 \).

3.2. Random forest analysis

Figure 2 shows the importance of the predictor variables calculated by mean decrease in accuracy in the final random forest model trained on the training set (\( n = 301 \)), fit using a 10-fold cross-validation. In general, the higher the mean decrease in accuracy when omitting the variable from the model, the more important the variable. D-dimer, thromboprophylaxis \( \geq 48 \) hours before ultrasound, SBP, COVID-19 symptom onset/admission to ultrasound interval, platelets, age, ferritin, diastolic blood pressure, PTT, BMI, were the 10 most relatively important variables in the model, in descending magnitude of importance. The receiver operating characteristic curve analysis for the prediction of acute DVT among the 150 patients in the test sample revealed an AUC of 0.91 (95% CI: 0.85–0.97). Using the

### Table 1

|                       | No DVT 386 (86%) | DVT 65 (14%) | \( P \) value |
|-----------------------|------------------|--------------|--------------|
| Age                   | 65 ± 15.9        | 66.7 ± 13.3  | .41          |
| Female                | 142 (37%)        | 22 (34%)     | .648         |
| Race                  |                  |              | .087         |
| African American      | 48 (12%)         | 14 (22%)     |              |
| Asian                 | 65 (17%)         | 3 (5%)       |              |
| White                 | 88 (23%)         | 15 (23%)     |              |
| Other/unknown         | 185 (48%)        | 33 (50%)     |              |
| Body mass index (kg/m²) | 29 ± 7.2       | 28.8 ± 5.3   | .847         |
| History of DVT/hypercoagulability | 33 (9%)       | 12 (18%)     | .014         |
| Smoking               | 100 (26%)        | 21 (32%)     | .281         |
| Chronic lung disease  | 78 (20%)         | 12 (18%)     | .745         |
| Coronary artery disease | 62 (16%)      | 12 (18%)     | .629         |
| Hypertension          | 214 (55%)        | 41 (63%)     | .251         |
| Cerebrovascular accident | 23 (6%)        | 3 (5%)       | .667         |
| Diabetes mellitus     | 136 (33%)        | 24 (37%)     | .792         |
| Chronic kidney disease| 41 (11%)         | 9 (14%)      | .444         |
| Dialysis              | 69 (18%)         | 14 (22%)     | .462         |
| Active cancer         | 20 (5%)          | 8 (12%)      | .028         |
| Viral hepatitis       | 9 (2%)           | 2 (3%)       | .719         |
| HIV positive          | 6 (2%)           | 4 (6%)       | .020         |
| Non-invasive mechanical ventilation | 63 (16%) | 13 (20%) | .464 |
| Thromboprophylaxis    | 245 (63%)        | 16 (25%)     | <.001        |
| Need for supplemental O₂ at presentation† | 285 (74%) | 47 (72%) | .796 |
| Heart rate (bpm)      | 93.2 ± 19.9      | 96 ± 21.2    | .287         |
| Systolic blood pressure (mm Hg) | 126.7 ± 21.7 | 131.3 ± 23.4 | .122 |
| Diastolic blood pressure (mmHg) | 73.8 ± 13.9 | 76.1 ± 13.9 | .237 |
| Respiratory rate (bpm) | 23 ± 6          | 23.5 ± 6.3   | .607         |
| O₂ saturation (%)     | 94.6 ± 5         | 93 ± 8.1     | .033         |
| D-dimer (ng/mL)       | 3605.7 ± 5704.2  | 12432 ± 13897.6 | <.001 |
| Fibrinogen (mg/dL)    | 603 ± 198.3      | 508 ± 249.9  | .003         |
| Ferritin (ng/mL)      | 1449 ± 2098.4    | 1682 ± 2020.4 | .42  |
| C-reactive protein (mg/L) | 13.8 ± 10.1    | 14.3 ± 9.7   | .728         |
| Prothrombin time (s)  | 14.5 ± 3.6       | 15.6 ± 3.9   | .018         |
| Partial thromboplastin time (s) | 34.7 ± 11.3 | 33.4 ± 7.2   | .367         |
| Platelets (\( \times 10^3 \)) | 292 ± 131.6   | 282 ± 109    | .581         |
| COVID-19 symptom onset to ultrasound interval (days) | 12 (6.21) | 10 (1.17) | .004† |

COVID-19 = coronavirus disease 2019, DVT = deep vein thrombosis, HIV = human immunodeficiency virus, SD = standard deviation.

* Wilcoxon signed rank test.
† Within 3 hours of arrival to the emergency department.
Youden index, the model classified the patients into DVT and no DVT outcome with accuracy of 0.83 (95% CI: 0.76–0.89) and sensitivity and specificity = 0.93 (95% CI: 0.68–0.99) and 0.82 (95% CI: 0.75–0.88), respectively (Table 3). The specificity was 0.68 at the sensitivity of 0.95, and the sensitivity was 0.44 at the specificity of 0.95.

### 3.3. D-dimer

Since d-dimer was the dominant variable affecting DVT risk, we analyzed the utility of d-dimer alone for predicting DVT. The univariate logistic regression model showed AUC = 0.79 (95% CI: 0.73–0.86), sensitivity = 0.68 (95% CI: 0.54–0.80), specificity = 0.82 (95% CI: 0.78–0.86), and accuracy = 0.80 (95% CI: 0.76–0.84), using d-dimer as a continuous variable. The optimal cutoff point was 5390 ng/mL using the Youden index in the entire sample. Figure 3 shows the result of a sensitivity analysis for DVT classification using different d-dimer cutoffs at different time intervals since the COVID-19 symptom onset/admission. We found that sensitivity drops while specificity rises when d-dimer increases from 500 to 7500 ng/mL. The highest AUC was

### Table 2

|                     | No DVT 386 (86%) | DVT 65 (14%) | P value |
|---------------------|------------------|--------------|---------|
| Hospital stay (days)| 17 ±12.2         | 12 ±11.1     | .020    |
| Pulmonary embolism  | 32 (8%)          | 17 (26%)     | <.001   |
| Acute respiratory distress syndrome | 227 (59%) | 35 (55%)     | .506    |
| ICU admission       | 232 (60%)        | 40 (62%)     | .827    |
| Intubation          | 225 (58%)        | 37 (57%)     | .836    |
| Death               | 64 (17%)         | 16 (25%)     | .117    |

DVT = deep vein thrombosis, SD = standard deviation.
observed for 5000 ng/mL with sensitivity = 0.75 (95% CI: 0.53–0.90) and specificity = 0.81 (95% CI: 0.72–0.88) at 7 days post COVID-19 symptom onset. We also explored d-dimer cutoffs corresponding to 90% and 95% sensitivity and specificity. The sensitivity declined with increase in time interval beyond 2 weeks from the symptom onset. We found the d-dimer levels as low as 900 and 1100 ng/mL having 95% and 90% sensitivity with 32% and 40% specificity, respectively. The d-dimer levels as high as 9000 and 12,000 ng/mL showed 90% and 95% specificity, with 43% and 23% sensitivity, respectively.

### Table 3

| Predicted | DVT   | No DVT | Total |
|-----------|-------|--------|-------|
| Positive  | 14    | 24     | 38    |
| Negative  | 1     | 111    | 112   |
| Total     | 15    | 135    | 150   |

DVT = deep vein thrombosis.

3.4. Thrombophrophylaxis

Compared to the patients without prophylactic anti-coagulation, the patients on thromboprophylaxis were younger and had lower rates of DVT (6% vs 26%) and PE (6% vs 18%) with lower d-dimer levels; but also had longer hospital stays, higher rates of ICU admission, intubation, ARDS, and dialysis (Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A468), all indicators of greater illness severity. Subsequently, thromboprophylaxis showed 20% and 12% absolute risk reduction corresponding to 5 and 8 number needed to treat (number needed to treat = 1/absolute risk reduction) for DVT and PE, that is, 5 and 8 patients should undergo thromboprophylaxis in order to prevent 1 DVT and 1 PE, respectively. Figure 4 shows the comparison of the time interval between COVID-19 symptom onset/admission and ultrasound evaluation of DVT in patients with and without DVT and stratified by thromboprophylaxis. Subjects without thromboprophylaxis had their ultrasound exams earlier than those receiving thromboprophylaxis, mostly within a few days of admission.

There were 14 hemorrhagic complications in the 65 patients treated for DVT ranging from minor hemorrhage (e.g.,
hematoma, tracheal/oropharyngeal bleed) to major hemorrhage (e.g., gastrointestinal [GI] bleeding and fatal intra-cranial hemorrhage), with some patients having more than 1 type. There were 4 cases of tracheal/oropharyngeal bloody secretion, 2 cases of IV-line oozing, and 1 breast and 1 abdominal hematoma. Five patients experienced GI bleeding (3 of them upper GI bleed) and 1 patient had vaginal bleeding. There were 2 cases of fatal acute intra-cranial hemorrhage, 1 case of non-fatal hemorrhagic conversion of a subacute posterior cranial artery stroke, and a case of chronic petechial cortical hemorrhage.

4. Discussion

Although thrombosis is a protective mechanism, containing infection by reducing blood borne viral dissemination, excessive thrombosis including DVT, PE, and disseminated intra-vascular coagulation can be fatal.[10] Similarly, therapeutic anti-coagulation, in addition to thwarting the protective effects of local thrombosis, can lead to fatal intra-cranial hemorrhage. Since PE is usually a consequence of DVT, identifying acute PE and DVT in COVID-19 patients is important but may be impractical to perform on all patients given cost/risks of transportation to computed tomograph and the radiology personnel-related transmission risks of prolonged contact required for ultrasound. In this multi-institutional study of DVT in 451 hospitalized COVID-19 patients, we found a lower rate of DVT compared to the earlier reports from Asia, presumably due to lack of anti-coagulation therapy in the initial outbreak.[11] Further, we identify d-dimer, thromboprophylaxis initiated at least 48 hours before ultrasound, ferritin, SBP, platelets, PT, PTT, BMI, COVID-19 symptom onset/admission to ultrasound interval, and hospital stay to be important predictors for DVT. A multivariate model trained on 301 patients improved the DVT prediction compared to a model including only d-dimer, with AUC=0.91 and 95% sensitivity and 68% specificity in a test set of 150 different patients.

Although there were a multitude of risk factors, d-dimer was the most important predictor for acute DVT by a wide margin in our multivariable random forest model. D-dimer accounted for the highest average decrease in accuracy when omitted from the model based on the permutation importance, suggesting that d-dimer may be useful by itself especially for physicians who do not have access to complex machine-learning technology. But d-dimer, a fibrin breakdown product that increases in the setting of fibrinolysis following thrombosis, is elevated in nearly all COVID-19 patients gradually increasing as COVID-19 induces more and more thrombosis throughout the body.[11]

Accordingly, we explored multiple threshold levels for diagnosing DVT with d-dimer at different time points following COVID-19 symptom onset. In patients with time interval of ≤7 days, a d-dimer threshold of 5000 ng/mL had the best AUC in predicting DVT with 75% sensitivity and 80% specificity. This was similar to a tentatively recommended threshold d-dimer for initiating therapeutic anti-coagulation.[12]

D-dimer >1000 ng/mL has been reported to be associated with a 9 fold increase in DVT incidence,[4] and 18 times higher rate of mortality.[13] Our data show this d-dimer threshold level of 1000 ng/mL to have a sensitivity of 96% and specificity of 42% for DVT diagnosis at 7 days postCOVID-19 symptom onset. Others have proposed 1500 ng/mL as the cutoff with highest negative predictive value for ruling out DVT in asymptomatic patients.[14,15] We cannot compare to this 1500 ng/mL d-dimer cutoff level because our data include only symptomatic, hospitalized COVID-19 patients.

Our random forest analysis shows that combining d-dimer with multiple additional variables can further increase accuracy of DVT diagnosis by solely using d-dimer. At 95% sensitivity, our model had 68% specificity. That is, were the model applied to our
data set, 204 out of 301 patients would have been spared an unnecessary ultrasound (true negative), while only missing 3 out of 65 DVT (false negative). However, using d-dimer alone would have only spared 96 out of 301 patients, at 95% sensitivity. The anti-coagulation prophylaxis might also be safely discontinued in those patients predicted to be negative for DVT, although this recommendation would require further confirmation by prospective studies. Our results in 451 patients are similar to a multivariable model trained on a smaller Chinese cohort (n = 143), systematically screened for DVT, which showed d-dimer in combination with CURB-65 and Padua scores predict DVT with AUC = 0.82. However, their result was limited by lack of a validation sample.[4]

Thromboprophylaxis beginning ≥48 hours before duplex ultrasound decreased the rate of DVT 4-fold, however it did not completely prevent DVT. Patients who did not receive thromboprophylaxis before the ultrasound were also seen to develop DVT with high d-dimer levels, earlier in their disease course with short intervals between COVID-19 symptom onset/admission and US examination for DVT. Our results confirm the previous studies suggesting benefit from the routine prophylactic anti-coagulation protocols.[6,16] For patients at higher risk of DVT, however, it may be useful to consider anti-coagulation at higher doses and starting quickly after diagnosis, especially for those with d-dimer levels ≥5000 ng/mL. However, we found a 22% (14/65) rate of hemorrhagic complication including 2 cases of fatal intra-cranial hemorrhage among patients with DVT undergoing therapeutic anti-coagulation. Thus, close monitoring of anti-coagulation activity, such as anti-Xa factor assay, should be followed to prevent adverse bleeding in those with supra-therapeutic anti-coagulant activity. All the patients were switched to therapeutic dose at some point in their care when DVT was detected or suspected. A recent study found no survival benefit in early anti-coagulation therapy in critically ill COVID-19 patients.[17] As such, for patients with lower DVT risk, anti-coagulation may be an undesirable disruption of the local thrombotic protective mechanism preventing viral dissemination. In these patients mechanical DVT prophylaxis may be preferable, while waiting for the results of clinical trials to optimize anti-coagulation strategies in COVID-19.

A strength of our findings is that the prevalence of DVT in our sample was similar to other retrospective studies including a recent study in New York.[12,18] and we found a trend toward increased mortality rate in patients with DVT similar to other reports.[14,19] Limitations include the retrospective nature of the study and lack of systematic DVT screening for DVT in all hospitalized COVID-19 patients. We did not exclude patients with chronic COVID-19. Some of the patients were still hospitalized at the time of data collection and analysis. The comparison between low and intermediate dose prophylactic anti-coagulation was not possible, since it might have been influenced by changes in physicians ordering patterns since low dose was only used initially. Some of the laboratory data were not available and had to be imputed in as many as 10% of some patients for the machine learning analysis. A lack of external data limits the generalizability of the prediction model. Lastly, lack of repeated lab measurements prevented us from assessing variability. A prospective cohort would make it possible to control for these limitations.

In conclusion, a random forest model improved DVT prediction by combining clinical and laboratory features, however, the single parameter, d-dimer > 5000 ng/mL was nearly as accurate. Thus, regular monitoring with d-dimer in the early stages of COVID-19 may be useful. Thromboprophylaxis was also useful, reducing DVT incidence by 4-fold. In positive cases, therapeutic anti-coagulation should be monitored closely with plasma anti-coagulant activity to minimize hemorrhagic complications.

Author contributions

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References

[1] Chi G, Lee JJ, Jamil A, et al. Venous thromboembolism among hospitalized patients with COVID-19 undergoing thromboprophylaxis: a systematic review and meta-analysis. J Clin Med 2020;9:2489.
[2] Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and venous thromboembolism: a meta-analysis of literature studies. Semin Thromb Hemost 2020;46:763–71.
[3] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844–7.
[4] Zhang L, Feng X, Zhang D, et al. Deep vein thrombosis in hospitalized patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: prevalence, risk factors, and outcome. Circulation 2020;142:114–28.
[5] Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020;135:2033–40.
[6] Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:1094–9.
[7] Radiology, ACo. ACR-ALUM-SPR–SRU practice parameter for the performance of peripheral venous ultrasound examination. 39;2020: E49–E56.
[8] Stekhoven DJ, Bühlmann P. MissForest—non-parametric missing value imputation for mixed-type data. Bioinformatics 2012;28:112–8.
[9] Chawla NV, Bowyer KW, Hall LO, Kegelmeyer WP. SMOTE: synthetic minority over-sampling technique. J Artif Intell Res 2002;16:321–57.
[10] Malato A, Dentali F, Siragusa S, et al. The impact of deep vein thrombosis in critically ill patients: a meta-analysis of major clinical outcomes. Blood Transfus 2015;13:559.
[11] Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus pneumonia. Thromb Haemost 2020;120:876.
[12] Koleilat I, Galen B, Choinski K, et al. Clinical characteristics of acute lower extremity deep venous thrombosis diagnosed by duplex in patients hospitalized for coronavirus disease 2019. J Vasc Surg Venous Lymphat Disord 2021;9:36–46.
[13] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62.
[14] Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 2020;18:1421–4.

[15] Demelo-Rodríguez P, Cervilla-Muñoz E, Ordieres-Ortega L, et al. Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. Thromb Res 2020;192:23–6.

[16] Piazza G, Campia U, Hurwitz S, et al. Registry of arterial and venous thromboembolic complications in patients with COVID-19. J Am Coll Cardiol 2020;76:2060–72.

[17] Al-Samkari H, Gupta S, Leaf RK, et al. Thrombosis, bleeding, and the observational effect of early therapeutic anticoagulation on survival in critically ill patients with COVID-19. Ann Intern Med 2021;174:622–32.

[18] Choi JJ, Wehmeyer GT, Li HA, et al. D-dimer cut-off points and risk of venous thromboembolism in adult hospitalized patients with COVID-19. Thromb Res 2020;196:318–21.

[19] Wichmann D, Sperhake J-P, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Ann Intern Med 2020;173:268–327.