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Deep Vein Thrombosis in Hospitalized Patients with Coronavirus Disease 2019 (COVID-19) in Wuhan, China: Prevalence, Risk Factors, and Outcome

Running Title: *Zhang et al.; DVT in Hospitalized COVID-19 Patients*

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Abstract

Background: To investigate deep vein thrombosis (DVT) in hospitalized patients with coronavirus disease 2019 (COVID-19), we performed a single institutional study to evaluate its prevalence, risk factors, prognosis, and potential thromboprophylaxis strategies in a large referral and treatment center.

Methods: We studied a total of 143 patients with COVID-19 from January 29 to February 29, 2020. Demographic and clinical data, laboratory data, including ultrasound scans of the lower extremities, and outcome variables were obtained, comparisons were made between DVT and non-DVT groups.

Results: Of the 143 patients hospitalized with COVID-19 (aged 63 ± 14 years; 74 [51.7%] man), 66 patients developed lower extremity DVT (46.1%, included 23 [34.8%] with proximal DVT and 43 [65.2%] with distal DVT).Compared with patients who with no DVT, patients with DVT were older and had a lower oxygenation index, a higher rate of cardiac injury, and worse prognosis including an increased proportion of deaths (23 [34.8%] vs 9 [11.7%], $P = 0.001$) and a decreased proportion of patients discharged (32 [48.5%] vs 60 [77.9%], $P < 0.001$). Multivariant analysis only showed an association between CURB-65 score 3-5 (OR = 6.122, $P = 0.031$), Padua prediction score ≥ 4 (OR = 4.016, $P = 0.04$), and D-dimer >1.0 (μg/ml) (OR = 5.818, $P < 0.014$) and DVT in this cohort, respectively. The combination of a CURB-65 score 3-5, a Padua prediction score ≥ 4, and D-dimer > 1.0 (μg/ml) has a sensitivity of 88.52% and a specificity of 61.43% for screening for DVT. In the subgroup of patients with a Padua prediction score ≥ 4 and whose ultrasound scans were performed >72 hours after admission, DVT was present in 18 (34.0%) of the subgroup receiving venous thromboembolism prophylaxis vs 35 (63.3%) in the nonprophylaxis group ($P = 0.010$).

Conclusions: The prevalence of DVT is high and is associated with adverse outcomes in hospitalized patients with COVID-19. Prophylaxis for venous thromboembolism may be protective in patients with a Padua protection score ≥ 4 after admission. Our data seem to suggest that COVID-19 is probably an additional risk factor for DVT in the hospitalized patients.

Key Words: COVID-19; deep vein thrombosis; novel coronavirus

Non-standard Abbreviations and Acronyms

COVID-19: coronavirus disease 2019

CTPA: computed tomography pulmonary angiography

Clinical Perspective

What is new?

- What are the prevalence of deep vein thrombosis (DVT), risk factors, prognosis, and potential prophylaxis strategies for hospitalized patients with COVID-19?
- In this single-center observational study of 143 hospitalized patients confirmed to have COVID-19, DVT was found in a high percentage of patients: 66 (46.1%) of 143, associated with adverse outcome, and with CURB-65 score 3-5, Padua prediction score ≥ 4, and D-dimer > 1.0 (μg /ml), which in combination predict DVT with a sensitivity of 88.52%.
- Thromboprophylaxis was associated with lower DVT in a subgroup of patients with high Padua prediction score.

What are the clinical implications?

- DVT is more common in hospitalized patients with COVID-19; ultrasound screening of high-risk patients (CURB-65 score 3-5, Padua prediction score ≥ 4, and D-dimer > 1.0 (μg/ml) may be indicated.
- Prevention of DVT with low-molecular-weight heparin in high risk patients (high Padua prediction scores) may reduce DVT in hospitalized patients with COVID-19.

Background

Coronavirus disease 2019 (COVID-19) is a highly infectious disease that emerged in Wuhan, Hubei Province, China and has been reported globally.[1] As of February 29, 2020, the total number of patients had already risen to 79,394 in mainland China, with 2,838 deceased. The COVID-19 infection caused a severe respiratory illness similar to that caused by severe acute respiratory syndrome coronavirus and was associated with a high rate of intensive care unit (ICU) admissions and a high mortality rate;[2] other common complications included shock, acute cardiac injury, and secondary infection.[3,4] Previous studies demonstrated an increased risk of deep vein thrombosis (DVT), venous thromboembolism (VTE), and potential pulmonary embolism (PE) in respiratory and other intensive care settings and have suggested that individual thromboprophylaxis therapy be considered. COVID-19 can lead to respiratory and systemic viral infection, inflammatory response and a hypercoagulable state, noninvasive or invasive mechanical ventilation, intubation, immobility, ICU stay, and stasis in severe and critical cases. However, the prevalence of DVT, the pathophysiology, risk factors, prognosis, screening, and preventive strategies have not been investigated in this novel viral illness that can cause severe and critical disease and death.

We performed a single institutional study in patients with confirmed COVID-19 pneumonia to identify the prevalence, risk factors, and prognosis of DVT in a large cohort of hospitalized patients.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

This cross-sectional survey was performed at the West Branch of Union Hospital (Affiliated Tongji Medical College, Huazhong University of Science and Technology) Wuhan, China, one of the major designated referral and treatment hospitals for critically ill adult patients (≥18 years old) with COVID-19 from January 29 to February 29, 2020, in accordance with the World Health Organization's interim guidance.[5] Patients confirmed to have COVID-19 were admitted to our center and assigned to 16 wards. All patients in the 3 wards managed by the investigators were screened for DVT using lower extremity venous ultrasound scanning. If there was more than one ultrasound scan for a single patient, all the results were recorded. The study was approved by the ethics committee of the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. Oral consent was obtained from patients involved before enrollment.

Clinical Data

We analyzed the medical records of the subjects admitted to the 3 wards managed by the investigators at the West Branch of Union Hospital in Wuhan, China. Eligible subjects included those still under inpatient care for more than 3 days, subjects who were discharged from the hospital after treatment, and deceased patients. Data, which included demographic information, clinical (medical history, exposure history, underlying comorbidities, symptoms) history, vital signs, laboratory findings, treatment, complications, and outcomes of the participants during hospitalization, were collected and analyzed by 2 analysts. We evaluated our patients clinically for PE. If there was any clinical suspicion of PE, computed tomographic pulmonary angiography (CTPA) was considered and obtained, if possible. Clinical outcomes (i.e., in-hospital, discharge,

or death) were monitored through March 24, 2020, the final date of follow-up. The date of disease onset was defined as the day when the symptoms were noted.

Ultrasound Study

Bedside ultrasound examinations were performed using an ultrasound scanner (EPIQ 7C, Philips Medical Systems, Andover, MA, USA, equipped with an L12-5/S5-1 probe or a Mindray portable Ultrasound M9, GD, China, equipped with an L10-3 probe).The lower extremity venous ultrasound and echocardiographic data were obtained from the Picture Archiving and Communication System. The levels of DVT included the bilateral common femoral, deep, and superficial femoral, and the popliteal veins as well as the posterior tibial, peroneal, and calf muscle veins. Left ventricular and right ventricular function parameters were captured. The presence of pulmonary artery hypertension was evaluated by adding a tricuspid regurgitation pressure gradient to the estimated right atrial pressure.[6] The left ventricular ejection fraction was calculated using Simpson's biplane method.

Definitions

Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition.[7] Acute kidney injury was identified according to Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines: serum creatinine levels increased by ≥ 0.3 mg/dl (≥ 26.5 μmol/l) within 48 hours or by 1.5 times baseline.[8] Cardiac injury was defined as the serum levels of cardiac high-sensitivity troponin I above the upper limit of the reference. The illness severity of COVID-19 was defined according to the Chinese Management Guideline for COVID-19 (version 6.0) as follows: (1) General: fever and respiratory symptoms, with evidence of pneumonia on radiological imaging; (2) Severe: patients with any of the following symptoms and signs: respiratory distress with respiratory rate ≥ 30 breaths/min; SpO_2 ≤ 93% at rest; and

$PaO_2/FiO_2 \leq 300$mm Hg (1mm Hg = 0.133 kPa); (3) critical: patients with any of the following conditions: respiratory failure requiring mechanical ventilation, shock, and/or other organ failure requiring admission to the intensive care unit (ICU).[9] The durations from the onset of the disease to hospital admission, to diagnosis of DVT, and to ICU admission were recorded. The Padua prediction score was defined according to the Barbar model.[10] The Wells score for DVT, the simplified Wells score, and the revised Geneva score for PE were defined according to the Di Nisio model.[11]

Statistical Analyses

Categorical variables were described as number and percentage (%) and continuous variables, as mean, standard deviation, median, and interquartile range (IQR). The Shapiro-Wilk test was used to verify normality. Differences between DVT and non-DVT groups were assessed by a 2-sample *t* test for normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed continuous variables, and the χ^2 or Fisher exact test for categorical variables. Univariate and multivariate logistic regression models were used to examine the risk factors associated with DVT and the proximal and distal DVTs in patients with COVID-19 using the demographic, clinical, and laboratory variables. Due to the limited number of events and to avoid overfitting in the model, 7 significant variables in the univariable model, including the Padua prediction score, confusion status, urea, respiratory rate and blood pressure (CURB-65 score), the white blood cell count, C-reactive protein levels, procalcitonin, prothrombin time, and D-dimer with significant *P* values were entered into the multivariate logistic regression model. Odds ratios (OR) and corresponding 95% CIs were presented as effective measures. Receiver operating characteristic (ROC) analysis was performed to calculate the sensitivity and specificity of risk factors for screening for DVT. Survival curves were plotted using the Kaplan-Meier

method and compared between patients with or without DVT using the log rank test. All statistical analyses were performed using SPSS version 23.0 (Statistical Package for the Social Sciences, Chicago, IL USA). All tests were 2-tailed; $P < 0.05$ was considered statistically significant.

Results

From January 29 to February 29, 2020, a total of 745 patients confirmed to have COVID-19 were admitted to our center and assigned to 16 wards. A total of 159 consecutive patients were admitted to the 3 wards managed by the investigators. In this cohort of all patients in the 3 wards (n = 159), lower extremity venous ultrasound scanning was performed wherever feasible for 143 patients after initial findings of a possible high prevalence of distal and intramuscular DVT regardless of clinical symptoms of the lower limbs, except for 16 patients who were not studied because they died (n = 6) or were transferred to specialized shelter hospitals (n = 10) before they could be included in the ultrasound study. Therefore, the prevalence of DVT (n = 66) in our study population was 46.1% (66/143 studied), 41.5% (66/159 total patients in our 3 wards), and 8.8% (66/745 of all patients in our center).

Table 1 shows the clinical data for our cohort. The mean age was 63 ± 14 years; 74 (51.7%) patients were men. Comorbidities included hypertension, diabetes mellitus, coronary artery disease, malignancy, chronic liver disease, and chronic kidney disease. One (0.7%) patient had a history of VTE. The common symptoms at the onset of illness were fever, dry cough, fatigue, dyspnea, diarrhea, and headache. Duration from the first appearance of symptoms to hospitalization was 11 ± 6 days (Figure 1).

Table 2 shows laboratory data and abnormalities, including lymphopenia, leukopenia, thrombocytopenia, serum creatinine, high-sensitivity troponin I, prothrombin times, and activated partial thromboplastin time. All 143 patients studied had abnormal chest computed tomographic scan results. CTPA was performed in 3 patients with DVT, and 1 patient had a confirmed PE.

Treatments, complications, and prognoses of patients with COVID-19 are shown in Table 3. Of the 143 patients, 141 (98.6%) received antiviral therapy; 11 (7.7%) received angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy; 53 (37.1%) patients were given DVT prophylaxis; and 59 (41.3%) patients received low-molecular-weight heparin therapy after positive ultrasound studies for DVT. Most patients(134, 93.7%) received oxygen therapy, 23 (16.1%) patients with invasive mechanical ventilation; and 17 (11.9%) patients with noninvasive mechanical ventilation. There was no statistically significant difference between the DVT and non-DVT groups (22 [33.3%] vs 31[40.3%]; $P = 0.393$). Further subgroup analysis by Padua prediction scores (< 4 or ≥ 4) and by early or late ultrasound studies (≤ 72 or > 72 hours) is also provided in Table 3. In the subgroup of patients with a Padua prediction score ≥ 4 and whose ultrasound examination was performed >72 hours after admission, the DVT group had fewer patients with VTE prophylaxis (34.0% vs 63.3%) and more patients without VTE prophylaxis (66.0% vs 36.7%) ($P = 0.010$).

During hospitalization, the major complications included ARDS in 105 (73.5%) patients, acute kidney injury in 23 (24.0%) patients, acute cardiac injury in 18 (25.4%) patients, coagulation dysfunction in 52 (36.4%) patients, and deteriorated chronic obstructive pulmonary disease in 9 (6.3%) patients. Fifteen (10.5%) patients were admitted to the ICU. At this point, 92 (64.3%) patients had been discharged and 32 (22.4 %) patients had died. The duration from onset

of disease to death was 26 (19, 33) days; the median duration from ICU admission to death was 15 (5, 24) days. For the patients who died, the median hospitalization time was 15 (9, 26) days.

Compared with non-DVT patients, more DVT patients were older than 65 years (66.7% vs 41.6%); had a low oxygenation index, a higher proportion of leg pain, a higher proportion of bedridden time > 72 hours; and were critically ill (65.2% vs 28.6%). In addition, patients with DVT had a higher Well score, a higher Padua prediction score, a higher CURB-65 score, as well as lower lymphocyte count, higher values of inflammation-related indices (C-reactive protein and procalcitonin); and higher coagulation function indices (D-dimer and prothrombin time) than non-DVT patients.

Laboratory data were tracked from illness onset in the DVT and non-DVT groups (Figure 2). Patients with DVT had higher levels of D-dimer than the non-DVT patients, and the D-dimer value was the highest on day 19 after illness onset and gradually decreased during hospitalization in the DVT group, whereas the non-DVT patients had a relatively flat trend of D-dimer during the whole course of their hospitalization. The level of platelets first decreased and then tended to increase in these 2 groups during hospitalization. Table 3 shows that in the subgroup of patients with Padua prediction scores < 4 and whose ultrasound examination was performed > 72 hours after admission, those patients with and without DVT all had a lower proportion of low-molecular-weight heparin for VTE prophylaxis (33.3% vs 19.4%) and a higher proportion of non-prophylaxis (66.7% vs 80.6%) ($P = 0.593$). In the subgroup of patients with a Padua prediction score ≥ 4 and whose ultrasound examination was performed > 72 hours after admission, compared with patients without DVT, patients with DVT had a lower proportion of low-molecular-weight heparin for VTE prophylaxis (34.0% vs 63.3%) and a higher proportion of nonprophylaxis (66.0% vs 36.7%; $P = 0.010$). In addition, in the group of patients with DVT,

89.4% (59/66) of the patients had therapy with low-molecular-weight heparin after the ultrasound examination. Patients with DVT received more high-flow oxygen (68.2% vs 42.9%; $P = 0.002$) and more invasive mechanical ventilation (28.8% vs 5.2%; $P < 0.001$); had a higher proportion of ARDS (90.9% vs 58.5%; $P < 0.001$); had a higher proportion of cardiac injury (40.0% vs 15.0%; $P = 0.018$); and were more likely to be admitted to the ICU (18.2% vs 3.9%; $P = 0.005$) than non-DVT patients.

In the 66 patients with DVT, DVT of the lower limbs developed in 23 (34.8%) proximal veins (popliteal vein or more proximal), in 43 (65.2%) distal veins (calf muscle veins) and in at least 1 branch of the 3 pairs of deep calf veins (anterior tibial vein, posterior tibial vein, or peroneal vein) (Supplemental Figure I). The median number of ultrasound examinations of the 143 patients was 1 (range, 1- 4). The median duration from the onset of COVID-19 symptoms to DVT was 21(17, 24) days, and the median time from admission to detection of DVT was 9 days (IQR 6 -13 days).

A total of 79 (55.2%) patients had echocardiograms (Table 4). The right atrial and right ventricular diameters were larger in the DVT group than in the non-DVT group (36.2±4.0 vs 34.6±6.0, $P = 0.036$; 34.5±3.9 vs 32.8±4.5, $P = 0.036$). A higher proportion of patients with DVT had pulmonary artery hypertension (34.4% vs 12.8%; $P = 0.022$), and more patients with DVT had a higher right ventricular myocardial performance index (0.45 ± 0.10 vs 0.38 ± 0.13; $P = 0.011$). There was no significant difference in the left ventricular ejection fraction (58.2±11.6 vs 58.7±8.8; $P = 0.832$) in these 2 groups.

The results of univariate and multivariate logistic regression models are shown in Table 5. In univariate analysis, age; diastolic blood pressure; bedridden time; Padua prediction score; Wells score; CURB-65 score; disease severity status; leukocytosis; neutrophilia; lymphocyte count;

prothrombin time; and elevated serum D-dimer, C-reactive protein, procalcitonin, blood urea nitrogen, and lactic dehydrogenase levels were associated with DVT. In the multivariate logistic regression model, we found that a higher Padua prediction score (Padua prediction score ≥ 4, OR = 4.016, 95% CI = [1.069, 15.094]; *P* = 0.040), CURB-65 score (CURB-65 score 3-5, OR = 6.122, 95% CI = [1.190, 31.773]; *P* = 0.031), and D-dimer level at admission (D-dimer > 1.0 μg/ml, OR = 5.818, 95% CI = [1.422, 23.809]; *P* = 0.014) were associated with increased odds of DVT in patients confirmed to have COVID-19. The combination of the D-dimer level, CURB-65 score, and Padua prediction score for DVT showed the highest diagnostic accuracy for screening for DVT (area under the curve [AUC] = 0.817; 95% CI: 0.739 – 0.879, sensitivity: 88.52%, specificity: 61.43%), followed by the Padua prediction score alone (AUC = 0.700; 95% CI: 0.614 - 0.777, sensitivity: 89.39%, specificity: 54.55%), D-dimer alone (AUC = 0.708; 95% CI: 0.622 – 0.784, sensitivity: 88.52%, specificity: 52.86%), and CURB-65 score alone (AUC = 0.673; 95% CI: 0.586 – 0.752, sensitivity: 54.55%, specificity: 77.92%).

In addition, the multinomial logistic regression for identifying the risks for the proximal and distal DVT in patients with COVID-19 showed that the D-dimer level at admission (D-dimer > 1.0 μg/ml, OR = 13.506, 95% CI = [1.334, 136.741]; *P* = 0.028) was independently associated with the increased odds of proximal DVT and that both the D-dimer level (D-dimer > 1.0 μg/ml, OR= 3.564, 95% CI = [1.122, 11.323]; *P* = 0.031) and a higher CURB-65 score (CURB-65 score 3-5, OR = 6.585, 95% CI = [1.362, 31.848]; *P* = 0.019) were independently associated with an increased odds of distal DVT in patients with COVID-19 (Supplemental Table I).

Patients with DVT had a worse prognosis than patients without DVT, including more admissions to the ICU (12 [18.2] vs 3 [3.9]; *P* = 0.005), fewer discharges (32 [48.5] vs 60 [77.9]; *P* < 0.001), and more deaths (23 [34.8] vs 9 [11.7]; *P* = 0.001). Kaplan-Meier survival curves

showed that patients with DVT had significantly higher clinical adverse outcomes than those without DVT ($P = 0.004$; Figure 3). Patients with DVT who were bedridden for more than 72 hours had a worse prognosis than those bedridden for less than 72 hours ($P = 0.020$; Supplemental Table II). In addition, patients with both proximal and distal DVT had higher mortality rates than the non-DVT groups ($P < 0.05$), whereas there was no difference in the mortality rates between patients with proximal DVT and patients with distal-DVT (Supplemental Table III).

Discussion

In December 2019, Wuhan become the center of the outbreak of COVID-19. The virus has since reported in more than 25 countries within 1 month of its appearance in Wuhan.[12] Many patients were admitted to inpatient and ICU units for treatment of severe or critical disease. In this study, we performed a single institutional study of the patients with confirmed COVID-19 pneumonia and found from ultrasound scans a high prevalence of DVT and an association between DVT and CURB-65 scores (3-5), Padua scores, and D-dimer levels in hospitalized patients with COVID-19.

We studied 143 patients with confirmed COVID-19 infection and performed at least 1 ultrasound scan of the lower limb veins in all patients in the 3 wards we managed; 16 patients who died or were transferred before they could be included in the study were excluded. Therefore, the prevalence of DVT (n=66) in our study population was 46.1% (66/143 studied), 41.5% (66/159 total patients in our 3 wards), and 8.8% (66/745 of all patients in our center). The prevalence of 46.1% was appropriate for this study because this was the percentage that represented the true positive cases from all the cases we studied. The DVT status for the cases

we did not study was unknown and therefore could not be included in the prevalence calculation. This prevalence appears to be higher than that reported in the literature,[13-16] especially in the study by Greets et al.,[14] who reported that the rates of objectively confirmed DVT in 4 prospective studies ranged from 13% to 31% and who suggested a potential role for thromboprophylaxis in patients requiring critical care.

The prevalence is also higher than that among patients in the ICU in Singapore who had severe acute respiratory syndrome; in this group, 20.5% of the patients had DVT, and 11.4% showed clinical evidence of PE.[17] In a published necropsy series comprising a total of 8 patients with SARS, 4 patients had PTE and 3 (37.5%) had DVT. This rate was also higher than that reported for many other hospitalized patients,[18,19] and series of patients in ICUs (without COVID19) reported from China.[20]

Several reasons probably account for the high prevalence of DVT. First, our cohort represented a group of patients who were admitted later in the course of their disease and had more severe illness. Because a large number of patients presented at the hospital in a short period of time in Wuhan, China, bed resources were insufficient. The period from the first appearance of symptoms to hospitalization in our group was 11 ± 6 days; many of these patients were bedridden at home before admission. Our hospital was one of the major designated treatment hospitals for critically ill patients with COVID-19. Of the 143 patients studied, most (n = 106; 74.1%) were categorized as severe or critical. We recorded all levels of DVTs and found that 43 (65%) patients had thromboses only in the distal intramuscular veins. Asymptomatic isolated distal DVT can probably be identified only by screening ultrasound. Whether it is a case of simple association or a cause of the adverse outcome of COVID-19 is yet to be ascertained.

Our univariant analysis showed age ≥ 65 years, lower diastolic pressure, being bed-ridden > 72 hours, a Padua prediction score ≥ 4, a Well score ≥ 2, a CURB-65 score 3-5, disease severity status (severe and critical status), lymphopenia, neutrophilia, higher c-reactive protein level, procalcitonin, D-dimer, prothrombin time, blood urea nitrogen level, and lactate dehydrogenase level are associated with DVT in this group of patients, respectively. The findings suggested a multifactorial cause or the association of older age, more chronic and severe illness, stasis, viral infection, and high inflammatory and coagulopathic state with DVT in these hospitalized patients with COVID-19.

In contrast, our multivariant analysis only showed an association among CURB-65 score 3-5 (OR = 6.122, $P = 0.031$), Padua prediction score ≥ 4 (OR = 4.016, $P = 0.04$), and D-dimer > 1.0 (μg/ml) (OR = 5.818, $P < 0.014$) and DVT in this cohort, respectively. The CURB-65 score was developed as a prognostic model in immunocompetent patients with pneumonia.[21] In the current study, we found that 67.9% (36/53) of patients with a CURB-65 score ≥ 2 developed DVT and that a higher CURB-65 score on admission was associated with higher odds of DVT. The Padua prediction score assigns points to eleven common VTE risk factors and categorized hospitalized medical patients as low risk (4 points) or high risk (≥ 4 points) for VTE.[10] In the current study, we found that 62.8% (59/94) of patients with a Padua prediction score ≥ 4 had DVT, whereas 14.3% (7/49) of patients with a Padua prediction score < 4 had DVT. D-dimer is a molecular marker that results from the dissolution of cross-linked fibrin and is often elevated in thrombotic conditions. We also found that 54/87 (88.5%) of patients with a D-dimer > 1.0 (μg/ml) had DVT, whereas 7/44 (15.9%) with that D-dimer < 1.0 (μg/ml) had it. Using a receiver-operating characteristic analysis, a combination of a CURB-65 score 3-5, a Padua

prediction score ≥ 4, and a D-dimer > 1.0 (μg/ml) yielded a sensitivity of 88.52% and a specificity of 61.43% for DVT in these hospitalized patients with COVID-19.

Furthermore, the prevalence of DVT in this cohort of hospitalized patients with COVID-19 is higher than that in previous reports in similar patients who did not have COVID-19. Our uni- and multivariate analyses showed an association between DVT and multiple risk factors, especially the CURB-65 score, the Padua prediction score, and D-dimer, suggesting multifactorial causes of DVT in patients with COVID-19 that may include older age, more chronic and severe illness, stasis, viral infection, and high inflammatory and thrombotic and fibrinolytic abnormalities associated with DVT in these hospitalized patients with COVID-19. Because these risk factors are associated with other respiratory diseases or with other severe and critical patients who do not have COVID-19 but who have a lower prevalence of DVT, our findings seem to suggest that COVID-19 infection may be an additional risk factor for DVT, which would account for the higher prevalence of DVT in this cohort. Possible mechanisms for the connection between DVT and COVID-19 infection may include viral infection-induced release of cytokine, which is also thrombogenic, and the plausible role of angiotensin-converting enzyme receptors in vascular alterations,[22] but further study is needed to elucidate the pathophysiology of DVT in COVID-19 infection.

In addition, outcome analyses showed that DVT is associated with adverse outcomes, including more admissions to the ICU ($P = 0.005$), fewer hospital discharges ($P < 0.001$), more deaths ($P = 0.001$), and lower actuarial survival rates ($P = 0.026$) in the hospitalized patients with COVID-19. Although these findings are not surprising, given that our patient population represented older, severely ill patients at high risk for DVT, with respiratory and other organ-

related diseases, our data raised the question of screening for DVT, risk stratification, and potential VTE prophylaxis to improve outcomes in hospitalized patients with COVID-19.

Finally, prophylaxis for VTE[23,24] and for extended-duration VTE[25,26] has been investigated in clinical trials to improve clinical outcomes in severely or critically ill patients. In our cohort, 53 of 143 (37.1%) patients were given DVT prophylaxis. There was no statistically significant difference between the DVT and non-DVT groups (22 [33.3%] vs 31[40.3%]; $P = 0.393$). Further subgroup analysis by Padua prediction scores (< 4 or ≥ 4) and by early or late ultrasound studies (≤ 72 or > 72 hours) (Table 3) showed that DVT was present in 18 (34.0%) patients in the VTE prophylaxis subgroup vs 35 (63.3%) in the nonprophylaxis subgroup ($P = 0.010$). Our data suggest that there is a possible protective effect of prophylaxis for VTE in the higher risk and more chronically ill patients in this cohort. Because our sample size is limited, the effect of VTE prophylaxis on hospitalized patients with COVID-19 warrants further investigation.

One of the major limitations of this study was the lack of a control group with patients who did not have COVID-19. Such a control group could help to validate the prevalence, risk factors, prognosis, and thromboprophylaxis of DVT in patients with COVID-19. Unfortunately, a control group was not feasible in this referral and dedicated COVID-19 treatment center. Another limitation worth noting was that, due to the relative shortage of medical resources and the infectivity of the coronavirus, the median number of ultrasound examinations of the 143 patients was 1 (range, 1- 4), and a single ultrasound was done early in 14 patients; together, these factors may have led to an underestimation of the prevalence of DVT. Third, we evaluated our patients clinically for PE. If there was any clinical suspicion of PE, a CTPA would be considered and obtained, if possible. We had 3 patients who underwent CTPA, and 1 patient was diagnosed

with PE. Therefore, the true prevalence of PE and the clinical significance of DVT, without screening for PE by CTPA, was not validated in this cohort.

Conclusions

In hospitalized patients with COVID-19, the prevalence of DVT is high and is associated with adverse outcomes. We also found an association between DVT and multiple risk factors, especially a CURB-65 score 3-5, a Padua prediction score ≥ 4, and D-dimer > 1.0 (μg/ml). A combination of the CURB-65 score, the Padua prediction score, and the D-dimer provided a sensitivity of 88.52% and a specificity of 61.43% for screening for DVT. VTE prophylaxis may be protective in patients with a Padua ≥ 4 after admission. Because the prevalence of DVT is higher in this cohort than in other severe or critical respiratory or high-risk groups, we suspect that COVID-19 is an additional risk factor for DVT in the hospitalized patients.

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Supplemental Materials

Data Supplemental Tables I - III

Supplemental Figures I

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020; 382:727-733.
2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020;395:507-513.
3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061-1069.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395:497-506.
5. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. 2020. [WHO reference number: WHO/2019-nCoV/clinical/2020.4].Geneva: World Health Organization.
6. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr.* 2010;23:685-713; quiz 786-788.
7. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307:2526-2533.
8. Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco ALM, De Jong PE, Griffith KE, Hemmelgarn BR, Iseki K, Lamb EJ, et al. Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements. 2013;3:1-150. doi: org/10.1038/kisup.2012.73 .
9. National Health Commission of the People's Republic of China. Chinese management guideline for COVID-19 (version 6.0). Feb 19, 2020. http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2/files/b218cfeb1bc54639af227f922bf6b817.pdf.
10. Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, De Bon E, Tormene D, Pagnan A, Prandoni P. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost.* 2010;8:2450-2457.
11. Di Nisio M, van Es N, Buller HR. Deep vein thrombosis and pulmonary embolism. *Lancet*. 2016;388:3060-3073.
12. Zhang Y, Xu J, Li H, Cao B. A novel coronavirus (COVID-19) outbreak: A call for action. *Chest*. 2020;157:e99-e101.
13. Moser KM, LeMoine JR, Nachtwey FJ, Spragg RG. Deep venous thrombosis and pulmonary embolism. Frequency in a respiratory intensive care unit. *JAMA*. 1981;246:1422-1424.

14. Geerts W, Cook D, Selby R, Etchells E. Venous thromboembolism and its prevention in critical care. *J Crit Care*. 2002;17:95-104.
15. Wilasrusmee C, Kiranantawat K, Horsirimanont S, Lertsithichai P, Reodecha P, Soonthonkit Y, Boonbavonrutanakun A, Tangsakuntong P, Panichvisai S, Jirasirithum S, et al. Deep venous thrombosis in surgical intensive care unit: prevalence and risk factors. *Asian J Surg*. 2009;32:85-88.
16. Angral R, Islam MS, Kundan S. Incidence of deep vein thrombosis and justification of chemoprophylaxis in Indian patients: a prospective study. *Bangladesh Med Res Counc Bull.* 2012;38:67-71.
17. Chong PY, Chui P, Ling AE, Franks TJ, Tai DY, Leo YS, Kaw GJ, Wansaicheong G, Chan KP, Ean Oon LL, et al. Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: challenges in determining a SARS diagnosis. *Arch Pathol Lab Med*. 2004;128:195-204.
18. Dagadaki O, Birbas K, Mariolis T, Baltopoulos G, Myrianthefs P. Necessity of the periodical ultrasound assessment of the peripheral venous system in intensive care unit patients. *Ultrasound Med Biol.* 2019;45:367-373.
19. Boddi M, Peris A. Deep vein thrombosis in intensive care. *Adv Exp Med Biol.* 2017;906:167-181.
20. Zhang C, Zhang Z, Mi J, Wang X, Zou Y, Chen X, Nie Z, Luo X, Gan R. The cumulative venous thromboembolism incidence and risk factors in intensive care patients receiving the guideline-recommended thromboprophylaxis. *Medicine (Baltimore)*. 2019;98:e15833.
21. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, Cooley LA, Dean NC, Fine MJ, Flanders SA, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200:e45-e67.
22. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579:270-273.
23. Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation*. 2004;110:874-879.
24. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, Leizorovicz A, Nguyen H, Olsson CG, Turpie AG, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med*. 1999;341:793-800.
25. Cohen AT, Harrington RA, Goldhaber SZ, Hull RD, Wiens BL, Gold A, Hernandez AF, Gibson CM. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med*. 2016;375:534-544.
26. Cohen AT, Spiro TE, Buller HR, Haskell L, Hu D, Hull R, Mebazaa A, Merli G, Schellong S, Spyropoulos AC, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368:513-523.

Table 1. Demographic and Clinical Characteristics of 143 Patients with COVID-19

Variable	Total (N=143)	DVT (n=66)	Non-DVT (n=77)	*P* value
Age (years)	63 ± 14	67 ± 12	59 ± 16	0.003
Age group				0.005*
≤ 45 y, n (%)	19 (13.3)	4 (6.1)	15 (19.5)	
45-64 y, n (%)	48 (33.6)	18 (27.3)	30 (39.0)	
≥ 65 y, n (%)	76 (53.1)	44 (66.7)	32 (41.6)	
Male, n (%)	74 (51.7)	36 (54.5)	38 (49.4)	0.535
BMI †	23.6 ± 3.0	23.6 ± 2.9	23.6 ± 3.1	0.920
≤ 24.9, n (%)	70 (64.2)	33 (67.3)	37 (61.7)	0.538*
> 24.9, n (%)	39 (35.8)	16 (32.7)	23 (38.3)	
Onset of symptoms				
Fever, n (%)	125 (87.4)	58 (87.9)	67 (87.0)	0.876
Dry cough, n (%)	101 (70.6)	44 (66.7)	57 (74.0)	0.335
Fatigue, n (%)	94 (65.7)	48 (72.7)	46 (59.7)	0.103
Dyspnea, n (%)	86 (60.1)	41 (62.1)	45 (58.4)	0.654
Diarrhea, n (%)	22 (15.4)	13 (19.7)	9 (11.7)	0.186
Headache, n (%)	12 (8.4)	3 (4.5)	9 (11.7)	0.125
Vital signs				
Temperature (℃)	38.5 (37.8, 39.0)	38.6 (38.0, 39.0)	38.4 (37.8, 39.0)	0.086
Respiratory rate (breaths per min)	25.0 (20.0, 30.0)	25.0 (20.0, 30.0)	24.0 (20.0, 30.0)	0.591
Heart rate (beats per min)	89 (78, 99)	89 (84, 96)	88 (50, 102)	0.764
SBP (mmHg)	128 (120, 141)	130 (126, 139)	132 (119, 144)	0.506
DBP (mmHg)	76 (70, 84)	80 (79, 87)	82.0 (74, 90)	0.005
Oxygenation index	178 (98, 303)	108 (80, 195)	243 (131, 306)	< 0.001
Comorbidities				
Current smoker, n (%)	9 (6.3)	5 (7.6)	4 (5.2)	0.733
Hypertension, n (%)	56 (39.2）	28 (42.4)	28 (36.4)	0.459
Diabetes mellitus, n (%)	26 (18.2)	13 (19.7)	13 (16.9)	0.664
Coronary artery disease, n (%)	17 (11.9)	9 (13.6)	8 (10.4)	0.550
Cardiac mechanical valve replacement, n (%)	3 (2.1)	1 (1.3)	2 (2.6)	1.000
Cerebral infarction, n (%)	5 (3.5)	2 (3.0)	3 (3.9)	1.000
Malignancy, n (%)	7 (4.9)	3 (4.5)	4 (5.2)	1.000
Chronic liver disease, n (%)	5 (3.5)	1 (1.5)	4 (5.2)	0.374
Chronic kidney disease, n (%)	4 (2.8)	1 (1.5)	3 (3.9)	0.624
History of VTE, n (%)	1 (0.7)	0 (0.0)	1 (1.3)	1.000
Edema of lower extremity, n (%)	18 (12.6)	9 (13.6)	9 (11.7)	0.726
Leg pain, n (%)	4 (2.8)	4 (6.1)	0 (0.0)	0.043
Bedridden time				< 0.001*
> 72 hours, n (%)	79 (55.2)	49 (74.2)	30 (39)	
≤ 72 hours, n (%)	64 (44.8)	17 (25.8)	47 (61)	
Wells score	1 (0, 2)	2 (2, 2)	0 (0, 1)	< 0.001
< 2, n (%)	85 (59.4)	9 (13.6)	76 (98.7)	< 0.001*
= 2, n (%)	57 (39.9)	56 (84.8)	1 (1.3)	
> 2, n (%)	1 (0.7)	1 (1.5)	0 (0.0)	
Padua prediction score	5 (2, 6)	6 (5, 6)	3 (2, 5)	< 0.001
0-3, n (%)	49 (34.3)	7 (10.6)	42 (54.5)	< 0.001*

≥ 4, n (%)	94 (65.7)	59 (89.4)	35 (45.5)	
CURB-65 score	1 (1, 2)	2 (1, 2)	1 (0, 1)	< 0.001
0-1, n (%)	90 (62.9)	30 (45.5)	60 (77.9)	< 0.001*
= 2, n (%)	37 (25.9)	24 (36.4)	13 (16.9)	
3-5, n (%)	16 (11.2)	12 (18.2)	4 (5.2)	
Simplified Wells score	1.0 (0.0, 1.0)	1.0 (0.0, 2.0)	1.0 (0.0, 1.0)	0.091
0-1, n (%)	112 (78.3)	46 (69.7)	66 (85.7)	0.020*
≥ 2, n (%)	31 (21.7)	20 (30.3)	11 (14.3)	
Revised Geneva score	2.0 (1.0, 2.0)	2.0 (2.0, 3.0)	2.0 (1.0, 2.0)	0.008
0-1, n (%)	47 (32.9)	15 (22.7)	32 (41.6)	0.037*
2-4, n (%)	95 (66.4)	50 (75.8)	45 (58.4)	
≥ 5, n (%)	1 (0.7)	1 (1.5)	0	
Disease severity status				< 0.001*
General, n (%)	37 (25.9)	5 (7.6)	32 41.6)	
Severe, n (%)	41 (28.7)	18 (27.3)	23 (29.9)	
Critical, n (%)	65 (45.5)	43 (65.2)	22 (28.6)	
Symptom onset to hospital admission (days)	11 ± 6	10 ± 5	12 ± 6	0.093

BMI indicates body mass index; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; DVT, deep vein thrombosis; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation; VTE, venous thromboembolism. Data are mean ± SD, median (IQR), or n (%). *P* values comparing DVT and non-DVT were from the 2-sample *t* test, χ^2 test, Fisher's exact test, or Mann-Whitney U test. $P < 0.05$ was considered statistically significant.

* χ^2 test or Fisher's exact test comparing all subcategories.

† 76.2% (109/143) of patients for whom BMI data were available.

Table 2. Laboratory Data of DVT vs Non-DVT Patients with COVID-19

Variable	Total (N=143)	DVT (n=66)	Non-DVT (n=77)	*P* value
Hematological and infection-related indices				
White blood cells ($\times 10^9$/L)	7.6 (5.3, 10.5)	8.6 (6.4, 10.9)	6.4 (4.8, 9.3)	0.001
< 3.5, n (%)	3 (2.1)	1 (1.5)	2 (2.6)	0.049*
3.5-9.5, n (%)	95 (67.4)	38 (58.5)	57 (75.0)	
> 9.5, n (%)	43 (30.5)	26 (40.0)	17 (22.4)	
Lymphocytes ($\times 10^9$/L)	0.82 (0.53, 1.29)	0.68 (0.49, 1.14)	0.98 (0.68, 1.37)	0.009
< 1.1, n (%)	93 (66.4)	46 (71.9)	47 (61.8)	0.210
Neutrophil ($\times 10^9$/L)	6.1 (3.9, 9.3)	7.0 (5.5, 9.9)	4.4 (3.6, 7.7)	< 0.001
< 1.8, n (%)	3 (2.1)	1 (1.5)	2 (2.6)	0.001*
1.8-6.3, n (%)	70 (49.6)	22 (33.8)	48 (63.2)	
> 6.3, n (%)	68 (48.2)	42 (64.6)	26 (34.2)	
Neutrophils /Lymphocytes	7.3 (3.8, 14.3)	10.5 (5.3, 16.8)	5.1 (3.2, 11.4)	0.001
Platelets ($\times 10^9$/L)	221.0 (152.3, 287.5)	185.5 (140.3, 289.0)	229.0 (170.5, 285.8)	0.087
< 125, n (%)	18 (12.9)	12 (18.8)	6 (7.9)	0.056
Hemoglobin (g/L)	119.4 ± 30.0	118.4 ± 18.7	120.3 ± 22.8	0.606
C-reactive protein (mg/L)	44.1 (9.2, 84.3)	58.0 (21.9, 102.8)	34.0 (7.5, 65.7)	0.012
≤ 8, n (%)	30 (22.9)	12 (19.7)	18 (25.7)	0.007*
> 8-50, n (%)	40 (30.5)	12 (19.7)	28 (40.0)	
> 50, n (%)	61 (46.6)	37 (60.7)	24 (34.3)	
Procalcitonin, ng/mL	0.11 (0.06, 0.27)	0.18 (0.10, 0.38)	0.07 (0.05, 0.19)	< 0.001
≤ 0.05, n (%)	23 (17.4)	4 (6.5)	19 (27.1)	0.007*
0.05-0.5, n (%)	95 (72.0)	50 (80.6)	45 (64.3)	
> 0.5, n (%)	14 (10.6)	8 (13.9)	6 (8.6)	
Coagulation function index				
D-dimer (μg/ml)	2.7 (0.6, 8.0)	6.6 (2.5, 8.0)	0.9 (0.4, 3.5)	< 0.001
≤ 0.5, n (%)	26 (19.8)	4 (6.6)	22 (31.4)	< 0.001*
> 0.5-1.0, n (%)	18 (13.7)	3 (4.9)	15 (21.4)	
> 1.0, n (%)	87 (66.4)	54 (88.5)	33 (47.1)	
Prothrombin time (seconds)	13.6 (12.6, 14.8)	14.2 (13.3, 15.4)	12.9 (12.3, 14.0)	< 0.001
> 16, n (%)	15 (11.5)	10 (16.4)	5 (7.2)	0.103
Activated partial thromboplastin time (seconds)	34.8 (30.8, 39.3)	36.2 (31.2, 41.9)	34.4 (30.2, 38.0)	0.137
Liver function index				
Total protein (g/L)	62.0 ± 7.8	61.8 ± 7.9	62.1 ± 7.8	0.831
Albumin(g/L)	28.7 ± 5.5	27.9 ± 5.4	29.2 ± 5.5	0.140
Aspartate aminotransferase (U/L)	31.0 (22.5, 31.0)	33.0 (25.5, 50.8)	27.0 (20.5, 36.5)	0.008
> 40, n (%)	34 (25.6)	20 (33.37)	14 (19.2)	0.063
Alanine aminotransferase (U/L)	34.0 (24.0, 54.0)	39.0 (29.0, 64.0)	30.0 (19.5, 45.0)	0.004
> 35, n (%)	66 (49.6)	35 (58.3)	31 (42.5)	0.069
Total bilirubin (μmol/L)	12.1 (9.1, 16.8)	13.8 (9.2, 17.5)	11.5 (8.4, 15.7)	0.105
Direct bilirubin (μmol/L)	3.9 (2.8, 6.0)	4.6 (3.2, 6.6)	3.5 (2.6, 5.3)	0.013
> 6.8, n (%)	25 (18.8)	14 (23.3)	11 (15.1)	0.225

Lactic dehydrogenase (U/L)	310.0 (201.0, 472.5)	389.0 (255.5, 587.3)	248.0 (191.0, 387.0)	< 0.001
> 245, n (%)	84 (63.2)	47 (78.3)	37 (50.7)	0.001
Kidney function index				
Blood urea nitrogen (mmol/L)	5.7 (4.0, 9.0)	7.3 (4.2, 10.0)	5.0 (3.6, 7.0)	0.002
> 8.2, n (%)	37 (27.8)	25 (41.7)	12 (16.4)	0.001
Serum creatinine (μmol/L)	62.0 (53.0, 78.3)	62.3 (53.4, 78.3)	61.9 (52.1, 79.3)	0.585
K+ (mmol/L)	4.0 ± 0.6	4.0 ± 0.7	3.9 ± 0.6	0.579
Na+ (mmol/L)	139.5 (136.8, 142.2)	139.2 (137.1, 143.1)	139.6 (136.4, 142.0)	0.547
Cardiac injury index				
High-sensitivity troponin I, (ng/mL) [†]	5.4 (2.1, 44.1)	14.0 (3.1, 79.6)	3.5 (1.7, 13.8)	0.022
> 26.5, n (%)	18 (25.4)	12 (41.4)	6 (14.6)	0.012
Creatinine kinase-myocardial band (U/L)	10.0 (4.0, 15.0)	11.0 (6.8, 16.0)	9.0 (0.8, 13.0)	0.020
> 25, n (%)	27 (20.8)	16 (26.7)	11 (15.7)	0.125
B-type natriuretic peptide (pg/ml)	49.9 (24.5, 99.0)	65.4 (26.8, 122.4)	49.3 (20.5,79.3)	0.073

COVID-19 represents coronavirus disease 2019; DVT, deep vein thrombosis; IQR, interquartile range; SD, standard deviation
Data are mean ± SD, median (IQR), or n (%). *P* values comparing DVT and non-DVT were from a 2-sample *t* test, χ^2 test, Fisher's exact test, or Mann-Whitney U test. $P < 0.05$ was considered statistically significant.
*χ^2 test or Fisher's exact test comparing all subcategories.
[†]49.7% (71/143) of patients for whom complete clinical data were available.

Table 3. Treatments, Complications, and Prognosis of Patients with COVID-19

Variable, n (%)	Total (n=143)	DVT (n=66)	Non-DVT (n=77)	*P* value
Treatments				
Antiviral therapy, n (%)	141 (98.6)	65 (98.5)	76 (98.7)	1.000
Antibiotic therapy, n (%)	117 (81.8)	56 (84.8)	61 (79.2)	0.515
Glucocorticoid therapy, n (%)	63 (44.1)	34 (51.5)	29 (37.8)	0.096
ACEI/ARB, n (%)	11 (7.7)	5 (7.6)	6 (7.8)	0.961
Immunoglobulin, n (%)	59 (41.3)	37 (56.1)	22 (28.6)	0.001
LMWH after + ultrasound for DVT, n (%)	59 (41.3)	59 (89.4)	0 (0.0)	< 0.001
Oxygen therapy, n (%)	134 (93.7)	63 (95.5)	71 (92.2)	0.506
High-flow oxygen, n (%)	78 (54.5)	45 (68.2)	33 (42.9)	0.002
Invasive mechanical ventilation, n (%)	23 (16.1)	19 (28.8)	4 (5.2)	< 0.001
Noninvasive mechanical ventilation, n (%)	17 (11.9)	8 (12.1)	9 (11.7)	0.936
VTE prophylaxis				0.393
Low-molecular-weight heparin, n (%)	53 (37.1)	22 (33.3)	31 (40.3)	
Nonprophylaxis, n (%)	90 (62.9)	44 (66.7)	43 (59.7)	
Padua score < 4				
Time from admission to ultrasound† >72 hours				0.593
Low-molecular-weight heparin, n (%)	9 (21.4)	2 (33.3)	7 (19.4)	
Nonprophylaxis, n (%)	33 (78.6)	4 (66.7)	29 (80.6)	
Time from admission to ultrasound† ≤72 hours				0.429
Low-molecular-weight heparin, n (%)	3 (42.9)	1 (100)	2 (33.3)	
Nonprophylaxis, n (%)	4 (57.1)	0 (0.0)	4 (66.7)	
Padua ≥ 4				
Time from admission to ultrasound† >72 hours				0.010
Low-molecular-weight heparin, n (%)	37(44.6)	18(34.0)	19 (63.3)	
Nonprophylaxis, n (%)	46 (55.4)	35 (66.0)	11 (36.7)	
Time from admission to ultrasound† ≤72 hours				0.242
Low-molecular-weight heparin, n (%)	4 (36.4)	1 (16.7)	3 (60.0)	
Nonprophylaxis, n (%)	7 (63.6)	5 (83.3)	2 (40.0)	
Major complications				
ARDS, n (%)	105 (73.5)	60 (90.9)	45 (58.5)	< 0.001
Mild, n (%)	21 (14.7)	5 (7.6)	16 (20.8)	0.026
Moderate, n (%)	40 (28.0)	23 (34.8)	17 (22.1)	0.090
Severe, n (%)	44 (30.8)	32 (48.5)	12 (15.6)	< 0.001
Acute kidney injury‡, n (%)	23 (24.0)	9 (19.6)	14 (28.0)	0.333
Cardiac injury‖, n (%)	18 (25.4)	12 (40.0)	6 (15.0)	0.018
Coagulation dysfunction, n (%)	52 (36.4)	29 (43.9)	23 (29.9)	0.081
Deteriorated COPD, n (%)	9 (6.3)	5 (7.6)	4 (5.2)	0.559
Admission to ICU, n (%)	15 (10.5)	12 (18.2)	3 (3.9)	0.005
Prognosis				0.001*
Hospitalization, n (%)	19 (13.3)	11 (16.7)	8 (10.4)	0.270#
Discharge, n (%)	92 (64.3)	32 (48.5)	60 (77.9)	< 0.001#
Death, n (%)	32 (22.4)	23 (34.8)	9 (11.7)	0.001#

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; ICU, intensive care unit; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

Data are n (%). *P* values comparing DVT and non-DVT were from χ^2 test or Fisher's exact test. $P < 0.05$ was considered statistically significant.

* χ^2 test comparing all subcategories.

† lower extremity venous ultrasound.

‡67.1% (96/143) of patients for whom complete clinical data were available.

‖49.7% (71/143) of patients for whom complete clinical data were available.

χ^2 test comparing DVT and Non-DVT group.

Table 4. Echocardiographic Findings of Patients with COVID-19

Variable	Total (n=79)	DVT(n=32)	Non-DVT (n=47)	*P* value
LA diameter (mm)	34.6 ± 5.5	34.8 ± 4.2	34.5 ± 6.7	0.386
LV diameter (mm)	45.4 ± 4.9	45.0 ± 4.2	45.7 ± 5.3	0.526
LVESVI (mL/m^2)	21.7 (16.4, 33.2)	19.6 (14.2, 27.3)	22.2 (17.8, 34.1)	0.267
LVEDVI (mL/m^2)	54.7 (43.9, 69.8)	54.5 (41.5, 65.0)	56.1 (45.4, 72.8)	0.323
Simpson biplane EF (%)	58.5 ± 10.0	58.2 ± 11.6	58.7 ± 8.8	0.832
LV Tei index	0.43 ± 0.13	0.46 ± 0.13	0.41 ± 0.13	0.110
Mitral valve				
E/A	1.0 ± 0.4	0.9 ± 0.2	1.1 ± 0.4	0.012
DT (ms)	192 ± 55	200 ± 50	186 ± 57	0.271
E/e'	9.3 ± 3.4	9.5 ± 3.3	9.2 ± 3.5	0.720
RA diameter (mm)	35.3 ± 5.3	36.2 ± 4.0	34.6 ± 6.0	0.036
RV diameter (mm)	33.6 ± 4.3	34.5 ± 3.9	32.8 ± 4.5	0.036
PA diameter (mm)	23.8 ± 3.1	24.1 ± 3.0	23.6 ± 3.2	0.296
IVC (mm)	15.6 ± 3.7	15.1 ± 3.9	16.0 ± 3.6	0.318
>21, n (%)	6 (7.6)	3 (9.4)	3 (6.4)	1.000
TAPSE (mm)	24 ± 4	23 ± 4	24 ± 4	0.176
S' (cm/s)	14.9 ± 3.3	14.8 ± 2.8	14.9 ± 3.7	0.895
RV FAC (%)	46.2 ± 5.7	47.0 ± 6.2	45.6 ± 5.3	0.290
RV MPI	0.41 ± 0.12	0.45 ± 0.10	0.38 ± 0.13	0.011
PASP (mmHg)	33.8 ± 11.6	36.5 ± 10.1	31.3 ± 12.6	0.052
PAH, n (%)	17 (21.5)	11 (34.4)	6 (12.8)	0.022

A indicates late diastolic inflow velocity; COVID-19, coronavirus disease 2019; DT, deceleration time; DVT, deep vein thrombosis; E, early diastolic inflow velocity; EF, ejection fraction; FAC, fractional area change; IQR: interquartile range; IVC, inferior vena cava; LA, left atrial; LV, left ventricular; LVESVI, left ventricular end-systolic volume index; LVEDVI, left ventricular end-diastolic volume index; MPI, myocardial performance index; PA, pulmonary artery; PAH, pulmonary artery hypertension; PASP, pulmonary artery systolic pressure; RA, right atrial; RV, right ventricular; S', systolic tricuspid lateral annular tissue velocity; SD: standard deviation; TAPSE, tricuspid annulus systolic displacement. Data are mean ± SD, median (IQR), or n (%). *P* values comparing DVT and non-DVT were from 2-sample *t* test, χ^2 test, or Mann-Whitney U test. $P < 0.05$ was considered statistically significant.

Table 5. Risk Factors Associated with Patients with COVID-19 with DVT

Factor	Univariable OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Age group				
≤ 45 y	1 (ref)			
45-65 y	2.250 (0.646, 7.839)	0.203		
≥ 65 y	5.156 (1.564, 17.004)	0.007		
Gender				
Female	1 (ref)			
Male	1.232 (0.637, 2.381)	0.536		
BMI				
≤ 24.9	1 (ref)			
> 24.9	0.780 (0.353, 1.722)	0.539		
DBP *	0.960 (0.931, 0.989)	0.007		
Bedridden time				
≤ 72h	1 (ref)			
> 72h	4.516 (2.205, 9.250)	< 0.001		
Padua prediction score				
0-3	1 (ref)		1 (ref)	
≥ 4	10.114 (4.101, 24.948)	< 0.001	4.016 (1.069, 15.094)	0.040
Wells score				
< 2	1 (ref)			
≥ 2	34.306 (13.474, 87.347)	< 0.001		
CURB-65 score				
0-1	1 (ref)		1 (ref)	
= 2	3.692 (1.651, 8.257)	0.001	2.842 (0.918, 8.803)	0.070
3-5	6.000 (1.783, 20.191)	0.004	6.122 (1.190, 31.773)	0.031
Disease severity status				
General	1 (ref)			
Severe	5.009 (1.624, 15.449)	0.005		
Critical	12.509 (4.276, 36.595)	< 0.001		
White blood cells ($\times 10^9$/L)				
3.5-9.5	1 (ref)		1 (ref)	
< 3.5	0.750 (0.066, 8.564)	0.817	0.510 (0.011, 24.260)	0.733
> 9.5	2.294 (1.099, 4.791)	0.027	0.582 (0.195, 1.736)	0.332
Lymphocytes ($\times 10^9$/L) *	0.397 (0.194, 0.812)	0.011		
Neutrophil ($\times 10^9$/L)				
1.8-6.3	1 (ref)			
< 1.8	1.091 (0.094, 12.679)	0.945		
> 6.3	3.524 (1.745, 7.117)	< 0.001		
C-reactive protein (mg/L)				
8-50	1 (ref)		1 (ref)	
≤ 8	1.556 (0.575, 4.209)	0.384	1.197 (0.296, 4.839)	0.800
> 50	3.597 (1.539, 8.410)	0.003	1.429 (0.430, 4.753)	0.561
Procalcitonin, ng/mL				
≤ 0.05	1 (ref)		1 (ref)	

0.05-0.5	5.041 (1.601, 15.867)	0.006	2.950 (0.693, 12.555)	0.143
> 0.5	14.250 (2.069, 98.140)	0.007	1.212 (0.094, 15.574)	0.883
D-dimer (μg/ml)				
≤ 0.5	1 (ref)		1 (ref)	
0.5-1.0	1.100 (0.215, 5.640)	0.909	1.274 (0.190, 8.528)	0.803
> 1.0	9.000 (2.850, 28.424)	< 0.001	5.818 (1.422, 23.809)	0.014
Prothrombin time (s) *	1.329 (1.085, 1.628)	0.006	1.160 (0.946, 1.423)	0.154
Aspartate aminotransferase (U/L)				
≤ 40	1 (ref)			
> 40	2.107 (0.954, 4.653)	0.065		
Alanine aminotransferase (U/L)				
≤ 35	1 (ref)			
> 35	1.897 (0.950, 3.789)	0.070		
Blood urea nitrogen (mmol/L)				
≤ 8.2	1 (ref)			
> 8.2	3.631 (1.625, 8.114)	0.002		
Lactic dehydrogenase (U/L)				
≤ 245	1 (ref)			
> 245	3.518 (1.634, 7.572)	0.001		

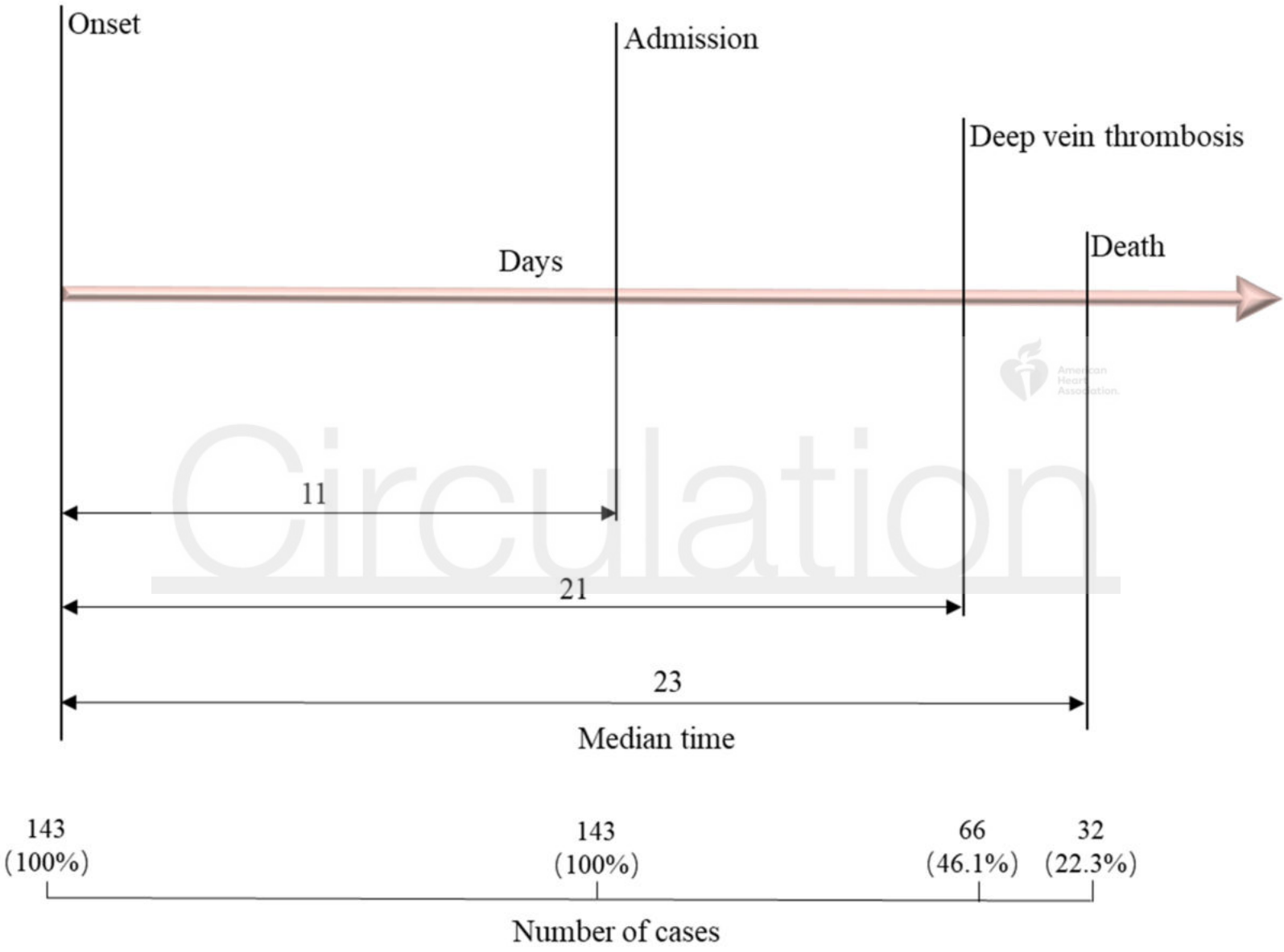
BMI indicates body mass index; CI, confidence interval; DBP, diastolic blood pressure; OR=odds ratio.
*Per 1-unit increase.

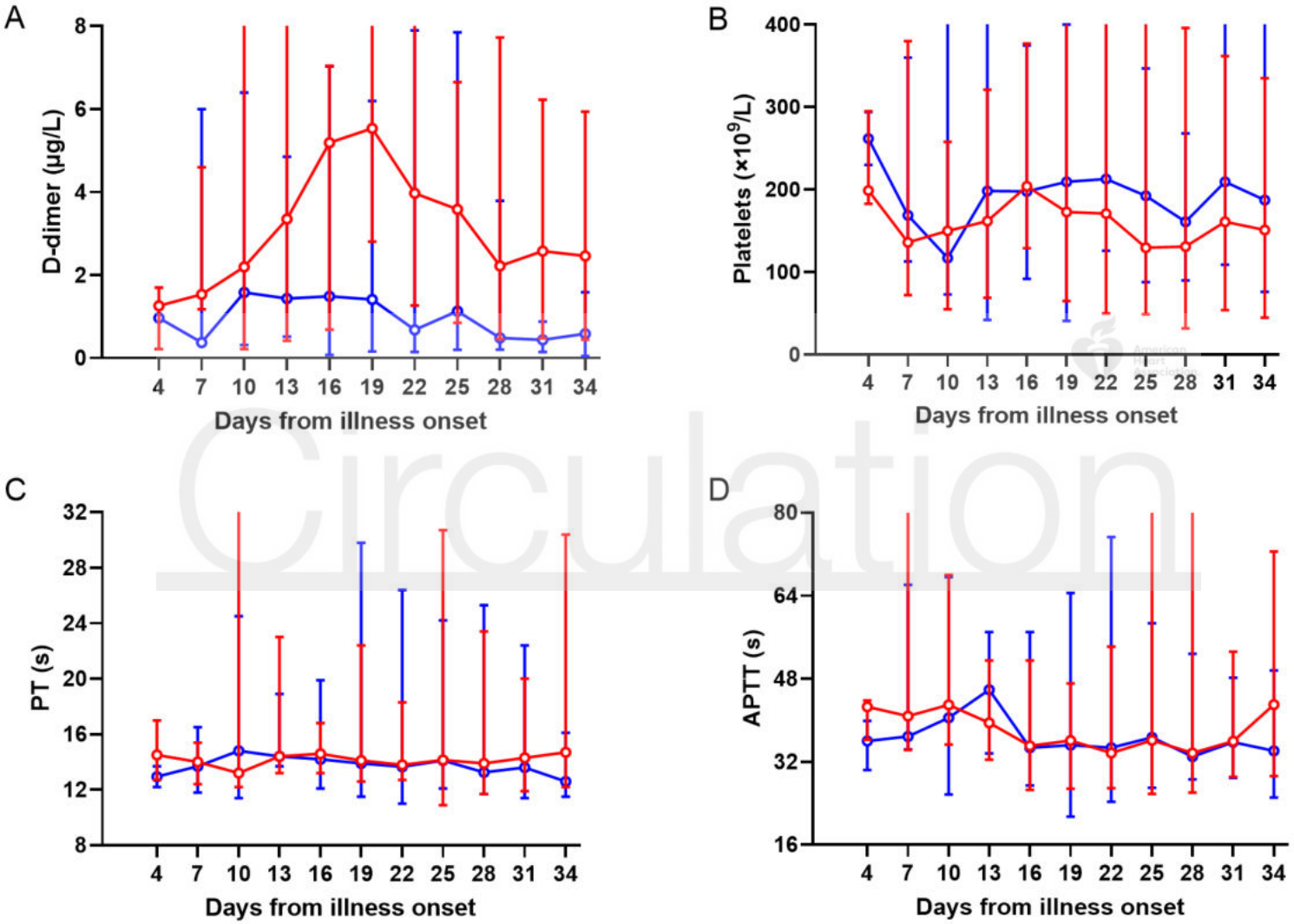
Figure Legends

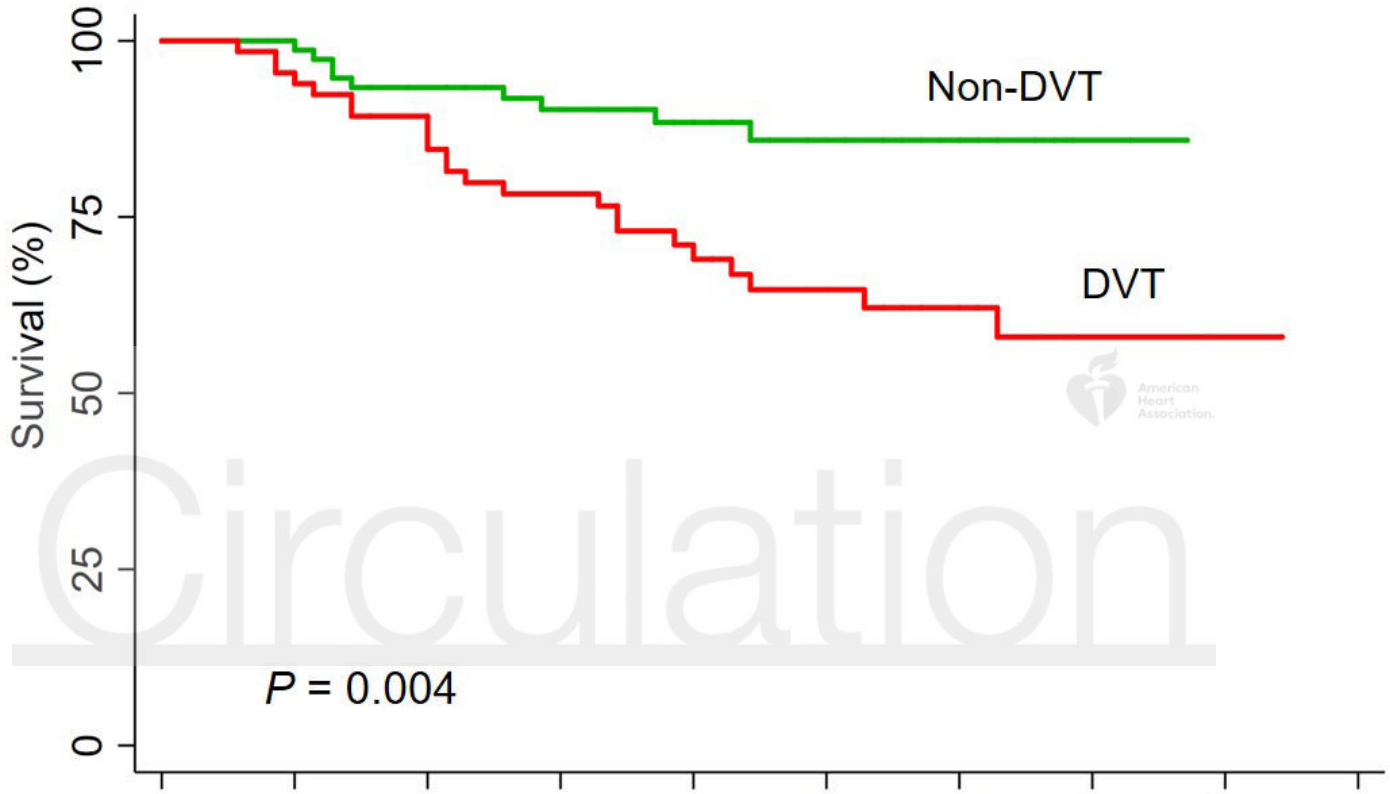
Figure 1. Timeline of COVID-19 cases after onset of illness. COVID-19 indicates coronavirus disease 2019.

Figure 2. Timeline charts for laboratory markers from illness onset in patients with COVID-19 with DVT and without DVT. Figure shows temporal changes in D-dimer **(A)**, platelets (**B**), PT (**C**), APTT (**D**). PT, prothrombin time. APTT indicates activated partial thromboplastin time; COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis.

Figure 3. Kaplan-Meier survival curves for patients with COVID-19 with DVT and without DVT. COVID-19 indicates coronavirus disease 2019; DVT, deep vein thrombosis.


Onset
Admission
Deep vein thrombosis
Death
Days
11
21
23
Median time
143
(100%)
143
(100%)
66
(46.1%)
32
(22.3%)
Number of cases





Number at risk

Non-DVT	77	76	65	55	43	28	11	4	0	0
DVT	66	62	57	48	35	27	17	5	1	0