

Deep Venous Thrombosis in COVID-19 Patients: A Cohort Analysis

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Abstract

Background

Deep venous thrombosis (DVT) is a severe complication of the coronavirus disease 2019 (COVID-19). It may interfere with COVID-19 treatment and delay the recovery, but there is less data about the anticoagulant therapy and sex difference of VTE in patients with COVID-19. The purpose of this study is to study the prevalence, risk factors, anticoagulant therapy and sex difference of deep venous thrombosis (DVT) in patients with COVID-19.

Methods

The enrolled 121 patients were confirmed positive for COVID-19. All suspected patients with a high Caprini index (≥ 4) or PADUA index (≥ 4) received color Doppler Ultrasound (US) to screen DVT in both lower extremities. Clinical characteristics of DVT-COVID-19 patients were analyzed. Multivariate logistic regression was performed to identify risk factors related to DVT in COVID-19 patients. The distribution of DVT locations, anticoagulation therapy with sex difference, and the outcomes were also analyzed.

Results

DVT was found in 48% asymptomatic COVID-19 patients with increased PAUDA index or Caprini index by US scanning. Multivariate logistic regression determined that age, CRP and baseline D-dimer were risk factors among COVID-19 patients. Although the most common DVT location was infrapopliteal (Class I and Class II), higher mortality in DVT-COVID-19 patients was confirmed. DVT-COVID-19 patients presented significant increases in the CRP, neutrophil count and D-dimer throughout the whole inpatient period compared to non-DVT-COVID-19 patients. Although anticoagulation therapy accelerated the recovery of lymphocytopenia condition in DVT patients, men DVT-COVID-19 patients showed higher CRP and neutrophil count vs. lymphocyte count (N/L) ratio but lower lymphocyte count compared to women DVT-COVID-19 patients.

Conclusions

DVT is common in COVID-19 patients with high risk factors, especially for older age, higher CRP and baseline D-dimer populations. It is important to consider sex differences in the anticoagulant therapy among DVT-COVID-19 patients.

Background

In December, 2019, coronavirus disease 2019 (COVID-19) was breaking out in China[1]. COVID-19 has become an international pandemic and there are more than 9.2 million patients worldwide with $> 479,133$ deaths reported to date[2]. Based on recent reported clinical experiences on COVID-19, severe COVID-19 patients are difficult to rescue not only because of the acute respiratory distress syndrome, but also susceptibility to complications linked to immunological system, renal system and circulation system [3–

5]. COVID-19 positive patients can present with hypercoagulability and higher susceptibility for DVT [6, 7]. But very little is known about the characteristics and prognosis of deep venous thrombosis (DVT) in COVID-19 patients, especially for the anticoagulant therapy and sex differences. The purpose of this single institutional study is to evaluate the risk factors, characteristics, prognosis and diversities of DVT among COVID-19 patients by conducting a retrospective cohort study with 121 confirmed COVID-19 patients.

Methods

Study Design and Patients

The medical records of 1419 hospitalized non-ventilator COVID-19 patients from January 25, 2020 to March 04, 2020 were retrospectively collected. In this retrospective cohort study, all COVID-19 patients were diagnosed at least by the laboratory SARS-CoV-2 qRT-PCR assay and/or pulmonary computed tomography (CT) scan according to World Health Organization guidance [8]. In total, 121 of 1419 COVID-19 patients with high Caprini index (≥ 4) or PADUA index (≥ 4) were enrolled (Fig. 1). PADUA index and Caprini index were evaluated following the standard protocol [9]. All suspected patients were scheduled color Doppler ultrasound (US) to screen DVT in both lower extremities. A diagnosis of DVT was confirmed with the presence of visible embolus, dilated incompressible vessel, or abnormal flow pattern[10]. Once DVT was detected, anticoagulant was administered including heparin injection, heparin (flush), danaparoid, enoxaparin or xarelto according to the revised DVT guideline [11]. Endpoints assessed were set as decease or discharge. The COVID-19 patients who suffered any clinical symptoms for pulmonary embolism were excluded in this study.

Data Collection

The demographic, epidemiological, DVT location, clinical, laboratory, treatment, and outcome data were collected from electronic medical records using a standardized data collection form by three investigators (Y.G., Y.Y., K.H.). Vital signs on admission were collected including heart rate, systolic blood pressure, diastolic blood pressure and initial oxygen saturation. Comorbidities included active cancer, hypertension, diabetes, cardiovascular disease, respiratory disease, chronic kidney disease, liver disease and recurrent DVT on admission. Primary outcome was defined as deceased, transfer to intensive care unit (ICU) or discharged. Laboratory examinations were extracted at two time points including initial admission and before final outcome. All data were checked by three physicians (Y.G., Y.Y., K.H.) and a fourth researcher (C.C.) adjudicated any differences in interpretation between the primary three reviewers.

Statistical Analysis

Continuous and categorical variables were described as means \pm SD and percentage (%), respectively. Characteristics of patients accompanied with DVT were compared to those without DVT using corresponding statistical methods. Mann–Whitney U-test was performed for numerical variables (age, anticoagulation days, and inpatient days). Fisher's exact test and Chi-squared test were applied for the

association of DVT and qualitative variables (sex, combined diseases, location of lesions, DVT classification, elevated baseline D-dimer). Kruskal–Wallis test was performed for ordinal variables, such as blood laboratory examinations. Some laboratory findings, including thromboelastography (TEG), protein C/S, IL-6, were unavailable in the current emergency circumstances. The anticoagulant therapy and sex difference were analyzed by a Two-way ANOVA with multiple comparisons followed by a post hoc Bonferroni's correction. Statistical significance was defined as $P < 0.05$. All statistical analysis was performed by R v3.5.3.

Results

Patient Characteristics

There were 121 COVID-19 patients enrolled in this study in total. The baseline clinical and laboratory characteristics were presented in **Table 1**. DVT was identified in 58 patients, corresponding to 48% of COVID-19 cases. The median age of DVT patients (53.45% men, 46.55% women) ranged in age from 40 to 96 years (69 ± 11 years old). Decreased lymphocyte count ($P = 0.004$) and eosinophil count ($P = 0.0056$) were common in DVT-COVID-19 patients compared to non-DVT-COVID-19 patients. There were significant increases in CRP ($P = 0.0310$), white blood cell count ($P = 0.0219$), neutrophil count ($P = 0.0094$), N/L ratio ($P = 0.0004$) of DVT-COVID-19 patients, respectively.

Risk Factors Of Dvt In Covid-19 Patients

Univariate and multivariable analyses were used to identify risk factors for DVT in COVID-19 patients. In the univariate analysis, using non-DVT as a reference group, the following factors were associated with increased risk for DVT in COVID-19 patients: age (OR 1.06; 95% CI, 1.03–1.10; $P = 0.0004$), PADUA index (OR 1.53; 95% CI, 1.07–2.32; $P = 0.0288$), Caprini index (OR 1.35; 95% CI, 1.07–1.75; $P = 0.0158$), hypertension (OR 2.14; 95% CI, 1.04–4.48; $P = 0.0406$), neutrophil count (OR 2.48; 95% CI, 1.25–5.11; $P = 0.0109$), N/L ratio (OR 1.09; 95% CI, 1.04–1.15; $P = 0.0024$), and baseline D-dimer (OR 2.40; 95% CI, 1.44–4.18; $P = 0.0012$) (Table 2).

Table 2
Univariate analysis of DVT risk factors in COVID-19 patients

	Univariable OR	95% CI	P value
Age	1.06	1.03 ± 1.10	0.0004
Woman sex	0.84	0.41 ± 1.72	0.6411
On admission O ₂ (%)	0.97	0.91 ± 1.02	0.2710
PADUA index	1.53	1.07 ± 2.32	0.0288
Caprini index	1.35	1.07 ± 1.75	0.0158
Cancer	0.90	0.25 ± 3.14	0.8630
Hypertension	2.14	1.04 ± 4.48	0.0406
Diabetes	0.64	0.25 ± 1.60	0.3498
Chronic kidney disease	1.66	0.27 ± 12.98	0.5848
Neutrophil count	2.48	1.25 ± 5.11	0.0109
Lymphocyte count	0.30	0.13 ± 0.68	0.0047
N/L ratio	1.09	1.04 ± 1.15	0.0024
FIB	0.90	0.44 ± 1.80	0.7583
CRP	0.36	0.14 ± 0.90	0.0338
Baseline D-dimer elevated	2.40	1.44 ± 4.18	0.0012

N/L ratio, neutrophil count vs. lymphocyte count; DVT, deep venous thrombosis; FIB, fibrinogen; CRP, C-reactive protein. The risk factors of DVT were analyzed by univariate logistic regression.

Next, all 121 DVT-COVID-19 patients with complete data were collected in the multivariable logistic regression model using age, sex, PADUA index, Caprini index, CRP, and baseline D-dimer. Older age (OR 1.05, 95% CI 1.00–1.10, P = 0.0306), woman sex (OR 3.39, 95% CI 0.99–11.63, P = 0.0521), higher CRP level (OR 1.02, 95% CI 1.01–1.04, P = 0.0040), and higher D-dimer on admission (OR 1.42, 95% CI 1.15–1.76, P = 0.0010) showed a higher likelihood of DVT among COVID-19 patients (Table 3).

Table 3
Multivariable analysis of DVT risk factors in COVID-19 patients

	Multivariable OR	95% CI	P value
Age	1.05	1.00 ± 1.10	0.0306
Woman sex	3.39	0.99 ± 11.63	0.0521
PADUA index	1.85	0.82 ± 4.20	0.1390
CRP	1.02	1.01 ± 1.04	0.0040
Baseline D-dimer elevated	1.42	1.15 ± 1.76	0.0010
CRP, C-reactive protein. We chose age, sex, PADUA index, Caprini index, Baseline D-dimer elevated, CRP for our multivariable logistic regression model to identify COVID-19 patient characteristics related to DVT.			

Characteristics Of Dvt Locations

Multiple reported studies determine that there are diversities in the locations of DVT patients [12, 13]. DVT-COVID-19 patients with unilateral- and those with bilateral-leg DVT were comparable in terms of baseline demographic data and risk factors in Table 4. Although there were no significant differences in sex, on admission oxygen saturation, active cancer, hypertension and diabetes comorbidities, younger age COVID-19 patients ($P = 0.0377$) presented more likely to suffer bilateral DVT. However, bilateral DVT patients showed lower Caprini index ($P = 0.0345$). This indicates the concealment of bilateral thrombotic diseases in COVID-19 patients. Besides the comparisons of demographic and risk factors, the distributions of DVT locations were analyzed in Table 5. Lower extremity thrombosis (LET) classification has been suggested by DVT guideline and widely used in clinic practices[11], and this classification stratifies DVT patients into four groups: class I, calf vein thrombosis; class II, popliteal and femoral vein thrombosis; class III, common femoral/iliac vein thrombosis; class IV, inferior vena cava thrombosis[14]. Fortunately, in both unilateral and bilateral DVT groups the majority DVT-COVID-19 patients were diagnosed as Class I grade DVT (unilateral DVT: 58.18%, bilateral DVT: 83.87%, Table 5).

Table 4
Clinical characteristics of unilateral and bilateral DVT-COVID-19 patients

	Unilateral DVT	Bilateral DVT	P value
Demographic data			
Age	71 ± 12	65 ± 10	0.0377
Man	12(54.55)	16(51.61)	-
Woman	10(45.45)	15(48.39)	-
Risk factors for DVT			
On admission oxygen saturation (%)	93 ± 5	93 ± 6	0.7208
Active cancer, N(%)	3(13.64)	2(6.45)	-
Hypertension, N(%)	8(36.36)	17(54.84)	0.2945
Diabetes, N(%)	2(9.09)	6(19.35)	-
PADUA index	5 ± 1	5 ± 1	0.8781
Caprini index	7 ± 2	6 ± 2	0.0345
Neutrophil count ($\times 10^9$ per L), N(%)	6.02 ± 3.45	7.47 ± 4.58	0.2828
Lymphocyte count ($\times 10^9$ per L), N(%)	0.73 ± 0.38	0.84 ± 0.54	0.6845
Baseline D-dimer elevated ($\mu\text{g/ml}$), N(%)	4.26 ± 3.46	4.19 ± 3.29	0.9903
Continuous variables are presented as means ± SD. Categorical variables are presented as percentage (%).			

Table 5
Distribution of DVT locations according to the side of DVT in COVID-19 patients

	Unilateral DVT	Bilateral DVT
Class I, N(%)	15(58.18%)	26(83.87%)
Class II, N(%)	3(13.64%)	5(16.13%)
Class III, N(%)	3(13.64%)	0(0%)
Class IV, N(%)	1(4.55%)	0(0%)
Categorical variables are presented as percentage (%). Class I, calf vein thrombosis; Class II, popliteal and femoral vein thrombosis; Class III, common femoral/iliac vein thrombosis; Class IV, inferior vena cava thrombosis.		

Treatment And Outcome For Dvt-covid-19 Patients

The treatment and outcome of DVT-COVID-19 patients were analyzed in Table 6. There was no significant difference of antibiotics administration between DVT and non-DVT patients. Only 31.75% non-DVT-COVID-19 patients received preventive anticoagulant treatment, while around 82.76% DVT-COVID-19 patients received anticoagulated therapy. There was a significant difference in the anticoagulant length between these non-DVT and DVT patients (DVT: 12 ± 10 days, non-DVT: 5 ± 10 days, $P < 0.0001$). There was a significant difference in the mortality between DVT and non-DVT-COVID-19 patients (DVT: 16(27.59%), non-DVT: 5(7.94%), $P = 0.0008$). There were more DVT-COVID-19 patients transferred to intensive care unit (ICU) during hospitalization (DVT: 9(15.52%), non-DVT: 3(4.76%), $P = 0.0943$), but less discharged DVT-COVID-19 patients compared to non-DVT-COVID-19 patients (DVT: 39(67.24%), non-DVT: 56(88.89%), $P = 0.0092$).

Table 6
Treatment and outcomes for DVT patients compared to non DVT patients

Variable	Without DVT	With DVT	P value
	(N = 63)	(N = 58)	
Antibiotics, N(%)	47(74.60%)	49(84.48%)	0.2643
Anticoagulant, N(%)	20(31.75%)	48(82.76%)	-
Anticoagulant length (days)	5 ± 10	12 ± 10	< 0.0001
Deceased, N(%)	5(7.94%)	16(27.59%)	0.0008
Transfer to ICU, N(%)	3(4.76%)	9(15.52%)	0.0943
Discharge, N(%)	56(88.89%)	39(67.24%)	0.0092
Inpatient stays (days)	33 ± 14	34 ± 14	0.7164

Continuous variables are presented as means \pm SD. Categorical variables are presented as percentage (%).

Anticoagulant Effect In The Covid-19 Therapy

The differences between DVT-COVID-19 patients received anticoagulants and non-DVT-COVID-19 patients absent of anticoagulants were analyzed. Expectedly, there were significant increases in the baseline CRP ($P = 0.0116$, Fig. 2A), neutrophil count ($P = 0.0094$, Fig. 2B), D-dimer assay ($P < 0.0001$, Fig. 2C) and lymphocyte count ($P = 0.0309$, Fig. 2D) of DVT patients compared to non-DVT controls. Additionally, after anticoagulant therapy DVT patients presented significantly continuous higher CRP ($P = 0.0204$, Fig. 2A); neutrophil count ($P = 0.0003$, Fig. 2B) and D-dimer ($P = 0.0288$, Fig. 2C). Although there was no difference in the use of antibiotics among DVT and non-DVT patients (DVT: 84.48% vs. non-DVT: 74.60%, Table 6), there was an unexpected no difference in the lymphocyte count by the end of the whole inpatient treatment (DVT: $1.18 \pm 0.73 \times 10^9/L$, non-DVT: $1.40 \pm 0.62 \times 10^9/L$, $P = 0.1865$, Fig. 2D). This

indicated that after anticoagulant therapy DVT patients presented accelerated recovery from the lymphocytopenia condition.

Sex Differences In Dvt-covid-19 Patients

Sex difference has been described in the prevalence of COVID-19 disease [15], but less information is known about DVT and anticoagulation in COVID-19 patients. All the DVT with anticoagulants and non-DVT without anticoagulants patients were divided into four subgroups based on presence of DVT and sex: women without DVT (25, average age: 55 ± 16 years), men without DVT (18, average age: 56 ± 12 years), women with DVT (23, average age: 66 ± 11 years) and men with DVT (25, average age: 69 ± 11 years). The laboratory characteristics are presented in Fig. 3. There were no significant sex differences in the baseline and final lab values in non-DVT patients (Figs. 3A-3J).

Next, the sex differences among DVT positive patients were analyzed. Firstly, there were no significant sex differences of the baseline laboratory assays in DVT-COVID-19 patients (Figs. 3A-3J). After anticoagulant therapy, there were no significant sex differences in the average FIB (Fig. 3A), D-dimer (Fig. 3B), neutrophil count (Fig. 3D), monocyte count (Fig. 3G), eosinophil count (Fig. 3H), WBC count (Fig. 3I), and PLT count (Fig. 3J). Interestingly, women-DVT patients presented significant decreases in the average CRP (women: 13.59 ± 19.94 mg/L vs. men: 77.97 ± 92.41 mg/L, average decrease: 83%, P = 0.0077, Fig. 3C) and N/L ratio (women: 7.00 ± 9.47 vs. men: 17.56 ± 20.26 , average decrease: 60%, P = 0.0291, Fig. 3F), with a significant increase in the lymphocyte count (women: $1.49 \pm 0.84 \times 10^9$ /L vs. men: $0.94 \pm 0.54 \times 10^9$ /L, average increase: 59%, P = 0.0183, Fig. 3E) compared to man-DVT patients. This indicated that women DVT-COVID-19 patients presented lower inflammatory parameters post anticoagulant therapy compared to men DVT-COVID-19 patients.

Discussion

The primary aims of this retrospective study were to identify the risk factors, characteristics, anticoagulant therapy and sex differences of DVT in COVID-19 patients. The overall DVT prevalence among COVID-19 inpatients in this study was 48%, obviously higher than that in general medical wards patients (9%-27.5%) and ICU inpatients (26%-32%) before this COVID-19 prevalence[16]. DVT-COVID-19 was associated with both infection and immobilization, and this may be the reason for the high morbidity in the present study. This morbidity could vary in different medical centers due to the limited medical resources, and not each COVID-19 patient was able to receive US screening.

This study demonstrated that COVID-19 patients who were older age, higher baseline CRP and D-dimer had elevated risk of DVT. Markel et al.[17] found evidences of at least 83% DVT patients involved in unilateral leg compared to 17% with bilateral legs. The results of this study suggested that COVID-19 infection is associated with an elevated risk of bilateral-sided DVT, especially in younger patients. It is

important to perform bilateral DVT examinations in asymptomatic limbs among severely infective patients.

Our data demonstrated that on admission there was a significant decrease in the lymphocyte count of DVT-COVID-19 patients compared to non-DVT-COVID-19 patients. However, after anticoagulant therapy there was an unexpected no difference in the lymphocyte count between DVT and non-DVT patients (Fig. 2D). This data implied that anticoagulant therapeutic DVT patients achieve a faster recovery out of the initial lymphocytopenia condition. This study provided direct human therapeutic support for the hypothesis that effective identification and appropriate anticoagulant therapy may benefit COVID-19 management[18]. Moreover, this is the first comparison regarding sex differences in the anticoagulation treatment among DVT positive COVID-19 patients. The average days of anticoagulant therapy for women and men were 14 ± 9 and 16 ± 10 , respectively. The average rates of antibiotics administration among women and men with DVT were 78% and 96%, respectively. After initiation of anticoagulation, women DVT patients had decreased CRP and N/L ratio as well as increased lymphocyte count compared to men DVT patients (Fig. 3). These data may help explain higher mortality rates in men with COVID-19 [19].

The present study has several limitations. First limitation is that this is a prospective study, which is inherent to observational studies. Second limitation is the lack of the comprehensive ultrasound evaluation of the DVT in asymptomatic patients with low PAUDA index or Caprini index, and a small number of patients with high prevalence of DVT enrollment. Third, the interval was not standardized between COVID-19 onset and US screening. The prevalence in the present study might be underestimated because US detection was performed beyond the acute phase in some cases. Four, certain confounders were unavailable, such as body mass index(BMI) and glucocorticoid usage, which are known as risk factors for DVT[20, 21]. Despite these limitations, the use of diagnosed COVID-19 patients without DVT as a control group alleviates confounding in the anticoagulant therapy and sex difference analyses.

Conclusion

This retrospective study demonstrated that COVID-19 patients had an increased risk for developing DVT. Although most of the DVT in COVID-19 patients were confirmed as infrapopliteal, the mortality was higher in DVT-COVID-19 patients compared to those absences of DVT patients. Therefore, it is important to identify the high risk COVID-19 patients and initiate thrombosis prophylaxis promptly. Comprehensive US screening in COVID-19 patients may be important and urgent. Although anticoagulant therapy presented beneficial effects in DVT patients, it is important to consider sex differences in the treatment of DVT-COVID-19 populations. Prolonged anticoagulant may be necessary in the anti COVID-19 therapy, especially for men COVID-19 patients.

Abbreviations

COVID-19

coronavirus disease 2019;

DVT
deep venous thrombosis;
CRP
C-reactive protein;
N/L ratio
neutrophil count vs. lymphocyte count ratio;
WBC
white blood cell;
FIB
fibrinogen;
PLT
platelet count.

Declarations

Ethics Approval

This study was approved by the Ethics Committee of Union hospital Wuhan, China. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Consent for Publication

Consent for publication was obtained for every individual person's data included in the study.

Availability of Data and Materials

All necessary data generated or analyzed during this study are included in this published article (results section, tables). Individual patient data that support the findings of this analysis are available upon request from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing of interests.

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Authors' Contributions

Y.G., Y.Y., K.H., F.C., L.Y., K.L., S.M., Y.L., W.W. and C.C. contributed to study design, data interpretation, manuscript writing and revising. Y.G., Y.Y., K.H. F.C., M.X., D.Y. contributed to patient's clinical information collection and follow-up. L.Y. contributed to the statistical analysis. All authors read and approved the final manuscript.

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22. Legend.

Tables

Variable	Total (N = 121)	Without DVT (N = 63)	With DVT (N = 58)	P value
Age (years)	64 ± 14	59 ± 15	69 ± 11	0.0004
Sex, N(%)				0.7102
Men	62(51.24)	31(49.21)	31(53.45)	0.7762
Women	59(48.76)	32(50.79)	27(46.55)	0.7762
Recurrent DVT, N(%)	4(3.31)	1(1.59)	3(5.17)	-
Comorbidity, N(%)				
Active cancer	11(9.09)	6(9.52)	5(8.62)	-
Hypertension	55(45.45)	23(36.51)	32(55.17)	0.0605
Diabetes	23(19.01)	14(22.22)	9(15.52)	0.4795
Cardiovascular disease	23(19.01)	9(14.29)	14(24.14)	0.2510
Respiratory disease	13(10.74)	6(9.52)	7(12.07)	0.8746
Chronic kidney disease	5(4.13)	2(3.17)	3(5.17)	-
Liver disease	8(6.61)	6(9.52)	2(3.45)	-
Others	32(26.45)	12(19.05)	20(34.48)	0.0860
Vital signs on admission				
Heart rate (beats/min)	91 ± 21	92 ± 18	91 ± 24	0.3229
Systolic blood pressure (mmHg)	136 ± 21	136 ± 19	136 ± 22	0.9011
Diastolic blood pressure (mmHg)	82 ± 13	83 ± 14	81 ± 12	0.5232
On admission oxygen saturation	96% ± 3%	94% ± 8%	93% ± 6%	0.0074
DVT risk score				
PADUA index	5 ± 1	5 ± 1	5 ± 1	0.0071
Caprini index	6 ± 2	6 ± 1	7 ± 2	0.0209
Laboratory assays on admission, N(%)				
CRP (mg/L)				0.0310

DVT, deep venous thrombosis; CRP, C-reactive protein; PLT, platelet count ; N/L ratio, neutrophil count vs. lymphocyte count; FIB, fibrinogen; PCT, procalcitonin. Continuous variables are presented as means ± SD. Categorical variables are presented as percentage (%).

Variable	Total (N = 121)	Without DVT (N = 63)	With DVT (N = 58)	P value
< 8	27(22.31%)	19(32.76%)	8(15.09%)	
> 8	84(69.42%)	39(67.24%)	45(84.91%)	
White blood cell count ($\times 10^9$ per L)				0.0219
< 3.5	10(8.26%)	6(9.68%)	4(6.90%)	-
3.5–9.5	77(63.64%)	45(72.58%)	32(55.17%)	-
> 9.5	33(27.27%)	11(17.74%)	22(37.93%)	-
PLT count ($\times 10^9$ per L)				0.712
< 100	7(5.79%)	4(6.56%)	3(5.17%)	-
100–300	93(76.86%)	46(75.41%)	47(81.03%)	-
> 300	19(15.70%)	11(18.03%)	8(13.79%)	-
Neutrophil count ($\times 10^9$ per L)				0.0094
< 1.8	4(3.31%)	3(4.84%)	1(1.72%)	-
1.8–6.3	70(57.85%)	42(67.74%)	28(48.28%)	-
> 6.3	46(38.02%)	17(27.42%)	29(50.00%)	-
Lymphocyte count ($\times 10^9$ per L)				0.004
< 1.1	82(67.77%)	35(56.45%)	47(81.03%)	-
1.1–3.2	38(31.40%)	27(43.55%)	11(18.97%)	-
> 3.2	NA	NA	NA	-
N/L ratio	10.43 \pm 11.80	6.9 \pm 6.66	14.33 \pm 14.74	0.0004
Monocyte count ($\times 10^9$ per L)				0.9142
< 0.1	1(0.83%)	1(1.61%)	0(0%)	-
0.1–0.6	97(80.17%)	49(79.03%)	48(82.76%)	-
> 0.6	22(18.18%)	12(19.35%)	10(17.24%)	-
Eosinophil count ($\times 10^9$ per L)				0.0056

DVT, deep venous thrombosis; CRP, C-reactive protein; PLT, platelet count ; N/L ratio, neutrophil count vs. lymphocyte count; FIB, fibrinogen; PCT, procalcitonin. Continuous variables are presented as means \pm SD. Categorical variables are presented as percentage (%).

Variable	Total (N = 121)	Without DVT (N = 63)	With DVT (N = 58)	P value
< 0.02	65(53.72%)	26(41.94%)	39(67.24%)	-
0.02–0.52	55(45.45%)	36(58.06%)	19(32.76%)	-
> 0.52	0(0%)	0(0%)	0(0%)	-
D-dimer (µg/ml)				0.0004
< 0.5	25(20.66%)	17(36.96%)	8(17.02%)	-
0.5-1.0	19(15.70%)	14(30.43%)	5(10.64%)	-
> 1.0	49(40.50%)	15(32.61%)	34(72.34%)	-
FIB (g/l)				0.9055
< 2.00	4(3.31%)	1(2.13%)	3(6%)	-
2.00–4.00	33(27.27%)	17(36.17%)	16(32%)	-
> 4.00	60(49.59%)	29(61.7%)	31(62%)	-
PCT (ng/ml)				0.0523
< 0.05	62(51.24%)	31(77.5%)	31(93.94%)	-
> 0.05	11(9.09%)	9(22.5%)	2(6.06%)	-

DVT, deep venous thrombosis; CRP, C-reactive protein; PLT, platelet count ; N/L ratio, neutrophil count vs. lymphocyte count; FIB, fibrinogen; PCT, procalcitonin. Continuous variables are presented as means ± SD. Categorical variables are presented as percentage (%).

Figures

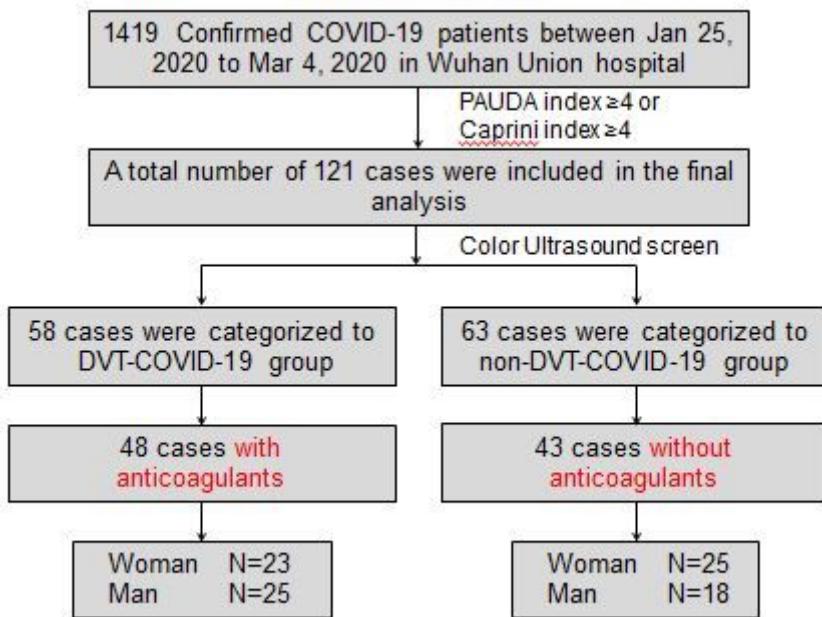


Figure 1

Flow chart illustrates this DVT-COVID-19 study.

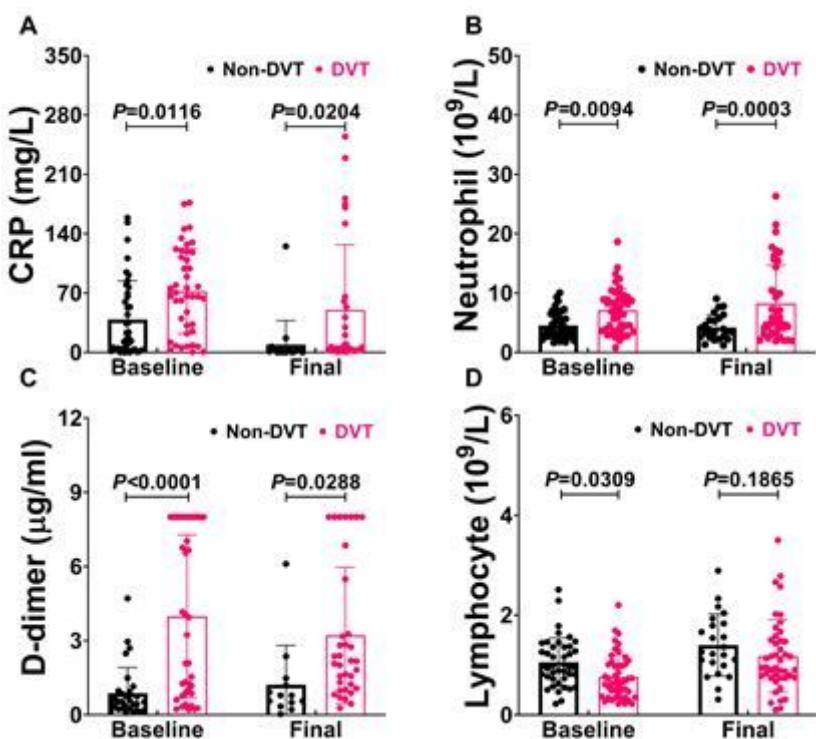


Figure 2

The therapeutic effect of anticoagulation in DVT-COVID-19 patients. (A-D) On admission DVT-COVID-19 patients showed significantly increased CRP, neutrophil count and D-dimer levels but decreased

lymphocyte count compared to the non-DVT-COVID-19 patients. At the end of the anticoagulant therapy, DVT patients continuously presented significant increases in the CRP (A), neutrophil count (B) and D-dimer level (C) compared to non-DVT patients, but there was no difference in lymphocyte count (D). Two-way ANOVA with multiple comparisons followed by a post hoc Bonferroni's correction was performed to analyze the continuous changes in the CRP, neutrophil count, D-dimer level and lymphocyte count between non-DVT-COVID-19 patients without anticoagulant therapy and DVT-COVID-19 patients received anticoagulant therapy.

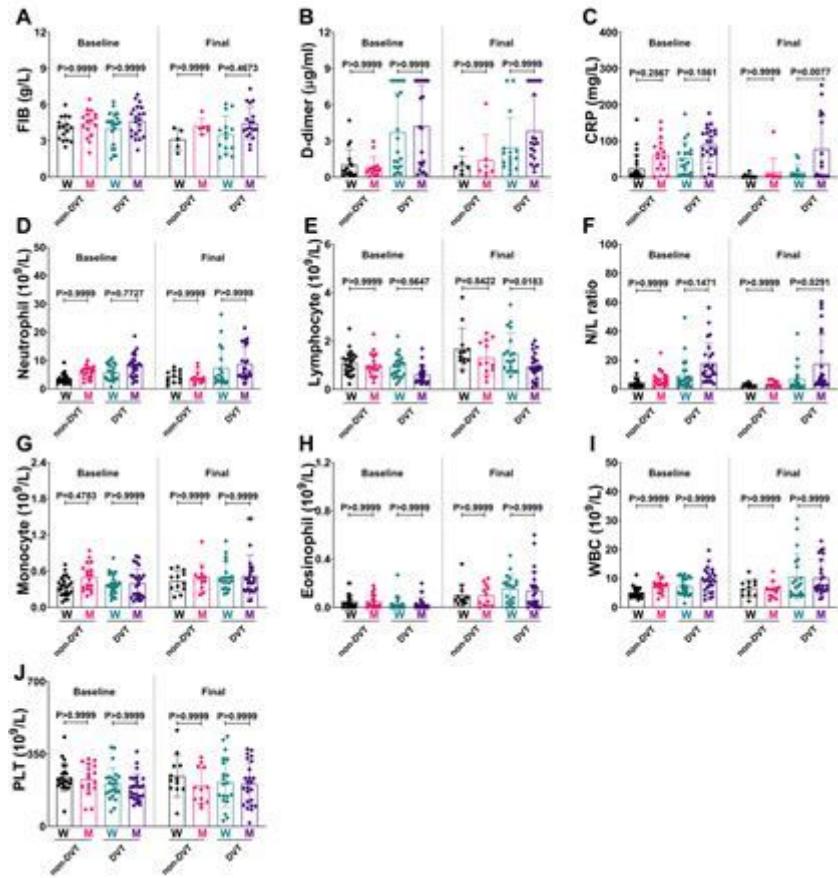


Figure 3

The sex differences of laboratory assays among COVID-19 patients. (A-J) On admission and discharge there were no sex differences in the average FIB (A), D-dimer (B), CRP (C), neutrophil count (D), lymphocyte count (E), N/L ratio (F), monocyte count (G), eosinophil count (H), WBC count (I) and PLT count (J) among non-DVT-COVID-19 patients (women: 25, men: 18), respectively. There were no sex differences of the baseline laboratory assays in DVT-COVID-19 patients (women: 23, men: 25). On discharge, women-DVT-COVID-19 patients showed significant increase in lymphocyte count (E), but significant decreases in CRP (C) and N/L ratio (F) compared to men-DVT-COVID-19 patients. Two-way ANOVA with multiple comparisons followed by a post hoc Bonferroni's correction was performed to analyze the continuous changes in the FIB, D-dimer, CRP, neutrophil count, lymphocyte count, N/L ratio, monocyte count, eosinophil count, WBC count and PLT count between non-DVT-COVID-19 patients without anticoagulant therapy and DVT-COVID-19 patients received anticoagulant therapy. W: woman; M:

man; FIB: fibrinogen; CRP: C-reactive protein; N/L: neutrophil count/lymphocyte count ratio; WBC: white blood cell count; PLT: platelet count.