**Clinical characteristics and risk factors for symptomatic venous thromboembolism in hospitalized COVID-19 patients: A multicentre retrospective study**

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**SUMMARY**

**Background**

High incidence of asymptomatic deep vein thrombosis has been observed in severe COVID-19 patient, but the prevalence, characteristics, risk factors, and reliable risk prediction for symptomatic venous thromboembolism (VTE) in general COVID-19 patients have not been well described.

**Methods**

This retrospective observational study enrolled all laboratory-confirmed COVID-19 patients with a subsequent VTE in 16 centers in China from January 1 to March 31, 2020. VTE risk associated with COVID-19 was compared with a historic cohort of 23,434 non-COVID-19 medical inpatients in 2018. Disease-severity matched COVID-19 patients without symptomatic VTE were enrolled as a disease control group at a 2:1 ratio.

**Findings**

A total of 2779 patients were confirmed with COVID-19 in three centers. In comparison with non-COVID-19 medical inpatients, the ORs for developing symptomatic VTE in severe and non-severe hospitalized COVID-19 patients were 5.94 (95%CI 3.91 to 10.09) and 2.79 (95%CI 1.43 to 5.60), respectively. When 104 VTE cases and 208 Non-VTE cases from 16 centers were compared, pulmonary embolism cases had a higher rate for in-hospital death (OR 6.74, 95%CI 2.18 to 20.81). Pharmacological thromboprophylaxis was employed in only 12.5% of VTE cases and 16.8% of Non-VTE cases with COVID-19. Symptomatic VTE developed at a median of 21 days (IQR 13.25 to 31) after COVID-19 onset and 11 days (IQR 8 to 20.75) after hospitalization. Independent factors for symptomatic VTE were advancing age, cancer, longer interval from onset to admission, thymosin injection, lower fibrinogen and higher D-dimer on admission, and D-dimer increment (DI) ≥ 1.5 fold; of these, DI ≥ 1.5 fold had the most significant association (OR 15.55, 95%CI 6.65 to 36.34). A newly defined simple “3-factor” model consisting of 3 coagulation variables (fibrinogen and D-dimer levels on admission, and DI ≥ 1.5 fold) showed very good prediction for symptomatic VTE (AUC 0.865, 95%CI 0.822 to 0.907, sensitivity 0.930, specificity 0.710).

**Interpretation**

There is an excess risk of symptomatic VTE in severe and non-severe hospitalized COVID-19 patients compared to non-COVID-19 medical inpatients. New-onset pulmonary embolism increased in-hospital deaths, and 3 coagulation variables (fibrinogen and D-dimer on admission, and DI ≥ 1.5 fold) predicted symptomatic VTE in hospitalized COVID-19 patients.

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**RESEARCH IN CONTEXT**

**Evidence before this study**

We searched PubMed on May 29, 2020, for articles that investigated the incidence or risk factors for symptomatic VTE in hospitalized patients with COVID-19, caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), using the search terms (“novel coronavirus” OR “SARS-CoV-2” OR “COVID-19” OR “coronavirus disease 2019”) AND (“symptomatic venous thromboembolism” OR “symptomatic venous thrombosis”) with no language or time restrictions. We found 4 citations reporting the incidence of symptomatic VTE: 2 focused on critical ill patients in ICU and 2 analyzed all the hospitalized patients. All of the 4 works were single center studies. No published works were found on risk factors, predictors, or risk prediction models for symptomatic VTE in COVID-19 patients.

**Added value of this study**

In this multicentre retrospective study, we demonstrate increasing ORs for developing symptomatic VTE in severe and moderately severe hospitalized COVID-19 patients were 5.94 (95%CI 3.91 to 10.09) and 2.79 (95%CI 1.43 to 5.60), respectively. Symptomatic VTE developed at a median of 21 days (IQR 13.25 to 31) after illness onset and 11 days (IQR 8 to 20.75) after hospitalization. Independent factors for symptomatic VTE were advancing age, cancer, longer interval from onset to admission, thymosin injection, lower fibrinogen and higher D-dimer on admission, and DI ≥ 1.5 fold; of these, DI ≥ 1.5 fold had the most significant association (OR 15.55, 95%CI 6.65 to 36.34). A newly defined “3-factor” model consisting of 3 coagulation variables (fibrinogen and D-dimer levels on admission, and DI ≥ 1.5 fold) showed good prediction for symptomatic VTE (AUC 0.865, 95%CI 0.822 to 0.907, sensitivity 0.930, specificity 0.710).

**Implications of all the available evidence**

We need to weigh the benefits against bleeding risks before prophylactic anticoagulation. The combination of D-dimer and fibrinogen levels on admission, and DI is a promising strategy for predicting symptomatic VTE in hospitalized COVID-19 patients. This “3-factor” model could help early identification of COVID-19 patients who are at high risk for VTE.

**INTRODUCTION**

Venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE), occurred in approximately 1 out of 1000 individuals in the general population, but is often secondary to other clinical conditions.1 During the Coronavirus disease 2019 (COVID-19) pandemic, high prevalence of DVT was observed in severe COVID-19 patients, especially in the Intensive Care Unit (ICU).2, 3 High prevalence of incident thrombosis in small and mid-sized pulmonary arteries have been demonstrated in clinicopathologic case series, despite anticoagulation.4, 5 Most VTE are asymptomatic and whether they are the cause of death or only concurrent events remains controversial.6 On the other hand, COVID-19 patients at high risk for VTE are also at high risk for bleeding, including catastrophic intracranial hemorrhage.7 Therefore, anticoagulation may potentially be harmful, and it would be important to distinguish those who will develop thrombosis in hospitalized COVID-19 patients.8

The prevalence, clinical characteristics, and risk factors for clinical relevant symptomatic VTE in hospitalized COVID-19 patients continue to be debated, and there remains a lack of satisfactory VTE risk prediction in these patients. Given this context, we performed a multicentre study to explore the prevalence, predictive risk factors and prediction models for symptomatic VTE in hospitalized COVID-19 patients.

**METHODS**

**Study design and participants**

The flowchart for the study is summarized in Figure S1. This multicentre, retrospective, observational study was conducted in 16 centers from Hubei Province including Wuhan city, China, the first epicenter of the COVID-19 pandemic in the world.

First, we investigated the absolute and relative risk for symptomatic VTE in hospitalized COVID-19 patients using a retrospective cohort study design. From January 1 to March 31, 2020, all laboratory-confirmed COVID-19 patients hospitalized in three of the 16 centers were included, who were compared with a historic cohort of 23,434 non-COVID-19 medical inpatients from January 1 to March 31, 2018. Data on age, gender, and symptomatic VTE event were extracted by the Lex Clinical Data Application 3.2 (Shanghai Lejiu Healthcare Technology Co., Ltd), a validated Big Data System designed to query clinical data warehouse and return tabular data for analysis and visualization. Second, we investigated the potential risk factors and predictors for symptomatic VTE in hospitalized COVID-19 patients using a case-control study design. From January 1 to March 31, 2020, those COVID-19 patients who had a subsequent symptomatic VTE event during hospitalization were included from 16 centers (‘cases’) and compared to disease-severity matched COVID-19 patients *without* symptomatic VTE (‘control group’) at an approximate 2:1 ratio (Figure S2).

This study was registered in Chinese Clinical Trial Registry (ChiCTR2000033055) and approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology. Informed consent was waived by the Ethics Commission.

**Data collection and definitions**

For the case-control study, data on demographic, clinical, laboratory, chest radiographs or CT scan, treatment, outcome, and VTE and bleeding events were extracted from electronic medical records of each center. Missing or uncertain records were clarified through communication with involved clinicians or patients. All data were checked by two investigators (LVT and HFW), and any diﬀerence in interpretation was adjudicated by a third clinician (ZPC).

COVID-19 was confirmed by the laboratory tests of SARS-CoV-2 RNA as described previously.9, 10 Severity of COVID-19 was divided into mild, moderate and severe categories, based on WHO guidelines (https://apps.who.int/iris/handle/10665/331446). Virus clearance was defined as at least two consecutive negative RNA tests for SARS-CoV-2. The time of follow-up was defined as the duration from illness onset of COVID-19 to outcomes (symptomatic VTE, discharge, or died) of patients. No cases were lost to follow-up in this study.

Symptomatic VTE was diagnosed based on clinical manifestations (such as swelling and pain of the lower extremities, superficial varicose veins, chest pain, and hemoptysis), elevated level of D-dimer, and was confirmed by objective imaging: color Doppler ultrasonography for deep vein thrombosis, CT pulmonary angiography for pulmonary embolism. According to the ISTH criteria, major bleeding following anticoagulation was defined as clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 20 g/L or transfusion of at least 2 U of packed red blood cells, occurring at a critical site (such as intracranial), or resulting in death. In this study, D-dimer increment (DI) was defined as D-dimer level on day 4 to day 6 divided by that on day 1 to day 3 following hospitalization.

**Risk prediction for VTE**

Three *clinical risk assessment models* (the Padua model, the Improve model and the Geneva model) for VTE in hospitalized medical patients were evaluated for each participant.11 A “7-factor model” was tentatively defined as the combination of 7 independent variables for VTE in the final logistic regression model: age, cancer, interval from COVID-19 onset to admission, thymosin injection, fibrinogen concentration and D-dimer level on admission, and D-dimer increment ≥ 1.5 fold. A simplified “3-factor model”, or “Wuhan score” was tentatively defined as the model consisted of the 3 coagulation variables (fibrinogen and D-dimer on admission, and DI ≥ 1.5 fold) that were significantly associated with symptomatic VTE in COVID-19 patients described in the analysis below.

**Statistical analysis**

Continuous and categorical variables were presented as median (IQR) and number (%), respectively. The Mann-Whitney U test, chi-squared, or Fisher’s exact test were employed to compare diﬀerences between VTE group and Non-VTE group where appropriate. To explore the risk factors associated with symptomatic VTE in-hospital, univariable and multivariable logistic regression analysis were performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs) adjusting for age, active cancer, venous catheterization, glucocorticoid, thymosin, days from COVID-19 onset to admission, D-dimer on admission, DI and Fibrinogen, as well as the Padua score, Improve score, and Geneva score. VTE-free survivals were estimated by the Kaplan-Meier method stratified by Padua score, Improve score, Geneva score and D-dimer increment, respectively. Any differences in VTE incidence were evaluated with a log-rank test.

Multivariable analysis with the Cox proportional-hazard model was employed to assess the simultaneous effects of related factors on symptomatic VTE. Receiver-operating- characteristic (ROC) analysis was performed to estimate the sensitivity, specificity, and overall accuracy of predictors for symptomatic VTE. Area under the curve (AUC) was calculated for each factors included. A two-sided P values < 0.05 was considered statistically significant. All statistical analyses were performed using with SPSS 13.0.

**Role of the funding source**

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**RESULTS**

From January 1 to March 31, 2020, a total of 2779 COVID-19 patients were enrolled from three centers: there were 1139 non-severe and 1640 severe COVID-19 patients. Of these, 42 of them developed symptomatic VTE during hospitalization.

A historical cohort of 23,434 non-COVID-19 medical inpatients was retrospectively enrolled from the same centers during the same month period in 2018 (Figure S1). Of these, 70 patients of the historical cohort developed symptomatic VTE. The crude rates of VTE were 1.95% in severe COVID-19 patients, 0.87% in non-severe COVID-19 patients, and 0.30% in non-COVID-19 medical patients, respectively (P = 4.26 × 10-16). After adjustment for age and gender, the ORs for developing symptomatic VTE were 5.94 (95%CI 3.91 to 10.09, P = 2.68 × 10-8) and 2.79 (95%CI 1.43 to 5.60, P = 0.012) in severe and non-severe hospitalized COVID-19 patients, when compared to non-COVID-19 ones (Figure 1).

**VTE vs non-VTE patients**

We compared 104 VTE cases and 208 disease-severity matched controls without symptomatic VTE from 16 centers (Figures S1-S2). The 104 VTE cases consisted of 88 DVT events and 16 PE events (also combined with DVT). During hospitalization of the DVT, PE, and Non-VTE groups, there were 9, 6, and 17 deaths, respectively (Figure S3). All other patients were discharged. The crude case-fatality rates in hospital were broadly comparable between COVID-19 patients with DVT (10.23%) and those without VTE (8.17%). Nevertheless, PE cases had a significantly higher rate for death compared with Non-VTE ones (OR 6.74, 95%CI 2.18 to 20.81, P = 0.001).

There were 64 and 120 severe cases in VTE group and Non-VTE group (61.5% vs 57.7%, P = 0.52) (Table 1). The median age of the VTE patients was 66.0 years (IQR 61.0 to 79.0), significantly higher than the non-VTE group (60.5, IQR 49 to 68). The most frequent used antiviral drug was arbidol, and more than 90% of cases were prescribed broad-spectrum antibiotics. Thymosin injection and systematic glucocorticoid use differed significantly between VTE cases and non-VTE cases (P = 0.001 and 0.003, respectively). On admission, the VTE group had significantly higher levels of median white blood cells, neutrophil count, C-reactive protein and D-dimer levels, and lower fibrinogen concentrations, when compared with Non-VTE group (Table 1).

**VTE prophylaxis and treatment**

Pharmacological thromboprophylaxis was employed in 13 (12.5%) VTE cases and 35 (16.8%) of non-VTE cases with COVID-19 (Table 2); Low-molecular-weight heparin (LMWH) was most commonly prescribed (95.8%), usually 4000 IU per day. One gastrointestinal major bleeding occurred in the VTE group, whereas one gastrointestinal major bleeding and one intra-abdominal fatal bleeding occurred in the non-VTE group. All the major and fatal bleeding events developed in patients receiving LMWH of 4000 IU per day.

For VTE treatment, the most frequent used anticoagulants were LMWH (41.4%), followed by LMWH conversion to rivaroxaban (40.4%), and rivaroxaban only (16.3%). 60 out of the 85 cases receiving LMWH were prescribed the usual dose of 4000-6000 IU twice a day, whereas half dose LMWH was prescribed in the other 25 cases (23.5%) due to the co-existing of high bleeding risk. In this subgroup, 4 gastrointestinal major bleeding occurred and no fatal bleeding was observed (Table S1).

The timeline for clinical outcomes from COVID-19 onset is summarized in Figure 2. Symptomatic VTE developed at a median of 21 days (IQR 13.25 to 31) after illness onset and 11 days (IQR 8 to 20.75) after hospitalization. Median time from illness onset to admission was longer in VTE cases than in non-VTE cases (10 days, IQR 6 to 14, vs 5 days, IQR 3 to 9, P = 7.86 × 10-10). The VTE group had a longer duration of hospitalization stay than that in non-VTE group (median 39 days, IQR 25.5 to 48, vs 22 days, IQR 18 to 28, 6.77 × 10-15). Median times from COVID-19 onset to virus clearance were similar in the two groups (P = 0.53).

**Risk prediction for VTE**

Possible factors and prediction models related to VTE in hospitalized COVID-19 patients were assessed (Table S2). The proportion of Padua score ≥ 4, Improve score ≥ 3, Geneva score ≥ 3, and D-dimer increment ≥ 1.5 fold were higher in the VTE cases than in non-VTE cases. Altogether 12 factors were associated with increased risk of developing VTE in univariable analysis (Table 3). The 12 factors from 255 COVID-19 patients (86 VTE cases and 169 Non-VTE cases) with complete data were further included into a logistic regression model.

On multivariable analysis, independent factors for symptomatic VTE were advancing age, cancer, longer interval from onset to admission, thymosin injection, lower fibrinogen and higher D-dimer on admission, and D-dimer increment ≥ 1.5 fold. Of these, D-dimer increment ≥ 1.5 fold had the most significant association (OR 15.55, 95%CI 6.65 to 36.34), followed by D-dimer level on admission (OR 1.34, 95%CI 1.18 to 1.52), and fibrinogen level on admission (OR 0.63, 95%CI 0.48 to 0.81). The three VTE risk assessment models (Padua, Improve, and Geneva) were not associated with symptomatic VTE occurrence.

Univariable Kaplan-Meier curves showed a higher cumulative symptomatic VTE incidence in hospitalized COVID-19 patients with Padua score ≥ 4, Improve score ≥ 3, Geneva score ≥ 3, and D-dimer increment ≥ 1.5 fold (Figure 3). Multivariable analysis using a Cox proportional-hazard model indicated that only D-dimer increment was independently associated with symptomatic VTE (Figure S4, HR 5.31, 95%CI 3.13 to 9.02).

ROC curve analysis was performed for the possible predicting factors (Figure 4). We tentatively defined the “7-factor model” as the combination of 7 independent variables for VTE in the final logistic regression model. We also defined a more simple “3-factor score”, (“Wuhan score”) as the model using the 3 coagulation variables significantly associated with symptomatic VTE: fibrinogen and D-dimer on admission, and DI ≥ 1.5 fold. The 7-factor model showed the highest prediction accuracy for symptomatic VTE (AUC 0.912, 95%CI 0.878 to 0.945), followed by the simple Wuhan score (AUC 0.865, 95%CI 0.822 to 0.907), DI ≥ 1.5 fold (AUC 0.751, 95%CI 0.686 to 0.816), D-dimer on admission (AUC 0.711, 95%CI 0.644 to 0.779), Geneva score, Improve score, and Padua model. The Wuhan score (3-factor model) had a sensitivity of 0.93 and a specificity of 0.71 for predicting symptomatic VTE in COVID-19 patients.

**DISCUSSION**

To our knowledge, this is the largest multicentre study that systematically investigated the risk of, and predicting factors for, symptomatic VTE in hospitalized COVID-19 patients. Our principal findings are as follows: (i) there is an excess risk of VTE in severe and non-severe hospitalized COVID-19 patients compared to non-COVID-19 medical inpatients; (ii) New-onset PE increased in-hospital deaths, and 7 factors predicted symptomatic VTE in hospitalized COVID-19 patients independent; and (iii) a simple “3-factor” model (Wuhan score) consisting of 3 coagulation variables (fibrinogen and D-dimer levels on admission, and DI ≥ 1.5 fold) showed very good prediction for symptomatic VTE.

Several other studies and case series on incidence of VTE in COVID-19 patients have been published.12-24 The reported incidence of VTE in these cohorts varied widely (4.1% to 85.4%) due to the different characteristics of study population, different diagnostic methods, and various thromboprophylaxis modalities. Most of the studies enrolled critical ill patients and employed a screening strategy with ultrasonography. Asymptomatic VTE events were also commonly included, which accounted for 65.2% to 87.8% of the total VTE events. Therefore, strikingly high rates of VTE in hospitalized COVID-19 patients were observed.

In contrast, we focused on symptomatic VTE which was more clinical relevant and has always been used as the primary outcome in clinical trials. Indeed, asymptomatic VTE is widely prevalent in special populations, such as patients suffering from acute infectious diseases, cancer and those are critical ill, even before hospitalization. The clinical importance and prognosis of asymptomatic VTE is uncertain and there is no consensus on the necessity of detection and treatment.25 Of note, less than 5% of the asymptomatic VTE could progress to a clinically symptomatic event. Thus, asymptomatic DVT is associated with a low risk of recurrence as well as a low risk of post-thrombotic syndrome, and long-term mortality in asymptomatic DVT is broadly comparable with that seen in non-DVT patients. Moreover, anticoagulant prophylaxis confers an absolute risk reduction in asymptomatic VTE events of only 2.6%, but results in significant increased risk in major bleeding.26

We report various risk factors for symptomatic VTE, but we found for the first time that thymosin injection was a novel risk factor for symptomatic VTE in hospitalized COVID-19 patients (Table 3). Thymosin is usually used as an immunomodulator for the treatment of hepatitis B and congenital immunodeficiency. One component of the thymosin extract, thymosin β4, plays an important role in wound healing, thrombosis, and platelet aggregation, including cross-linkage of thymosin beta4 to fibrin and collagen.27 During the current pandemic, thymosin was widely used in China, and was prescribed in our cohort to 72.1% VTE patients and 52.9% non-VTE patients with COVID-19, corresponding to a population attributable risk of as high as 34.6%.

In this study, 12.5% VTE cases and 16.8% Non-VTE cases with COVID-19 received pharmacological thromboprophylaxis (Table 2). Rate of thromboprophylaxis in VTE group did not significantly differ from that in Non-VTE cases and a considerable number of COVID-19 patients developed symptomatic VTE despite anticoagulation. COVID-19 patients who are at high risk for VTE may also be at high risk for bleeding.28 As shown in the current study, 3 out of the 48 COVID-19 patients (6.25%) receiving thromboprophylaxis developed major bleeding. A more precise method should be developed to recognize patents who are at real high risk for thrombosis and those who are at greater risk for major bleeding where caution is needed with full dose anticoagulation.29, 30

In early studies on COVID-19, the most typical finding was a higher D-dimer concentration on admission in patients with VTE than that in those without VTE.15, 18, 23 Therefore, D-dimer on admission was considered as a diagnostic marker for VTE in COVID-19. Nevertheless, D-dimer has a low specificity, and we have observed that many patients with a high D-dimer level would not necessarily develop a symptomatic VTE even if the level kept stable or increased slowly. In contrast, D-dimer would rise sharply within the first week after hospitalization in COVID-19 patients who would develop a symptomatic VTE.

Since the duration from admission to symptomatic VTE ranged from 8 to 20.75 (Figure 2), we proposed using a D-dimer increment of ≥ 1.5 fold increase, from day 1~3 to day 4~6 following hospitalization. Indeed, such a D-dimer increment was the most significant risk factor for developing symptomatic VTE using multivariable analysis. Additionally, D-dimer increment improved the specificity significantly, and predictive accuracy for VTE prediction when comparing single clinical or laboratory variables (Figure 4).

The Padua Score, the IMPROVE model, and the Geneva Risk Score are three robust risk assessment models evaluating VTE risk in hospitalized medical patients.11 Consistent with previous findings, the above 3 models were also important factors associated with symptomatic VTE in COVID-19 on univariable analysis, but the association was non- significant after adjusting for fibrinogen, D-dimer and D-dimer increment. This can be explained by the fact that those score were all clinical assessment models, which included only demographic and clinical characteristics. All these clinical variables will ultimately contribute to a hypercoagulate state and therefore are at best, *indirect* predictors. In contrast, coagulation variables such as D-dimer reflect the existence of a pathophysiological process of hemostasis and therefore are *direct* markers for thrombosis. Therefore, we proposed a 7-factor model which showed the highest prediction accuracy for symptomatic VTE (AUC 0.912), which followed by a simple “3-factor score” (Wuhan score) (AUC 0.865). The latter consisted of 3 independent coagulation predictors for VTE identified using multivariable analysis: lower fibrinogen on admission (coagulation consumption), higher D-dimer on admission (hyperfibrinolysis), and D-dimer increment ≥ 1.5 fold (persistent hyperfibrinolysis). The Wuhan model showed very good predictive accuracy for symptomatic VTE prediction, which was broadly comparable to the more complex 7-factor model (sensitivity 0.930 vs 0.965, specificity 0.710 vs 0.680).

*Strengths and Limitations*

This research has some strengthens. This was a multicentre study covering all hospitalized COVID-19 patients, with complete follow up. Therefore, the study population would be representative of the whole hospitalized COVID-19 population in China. In addition, we focused on symptomatic VTE which has more clinical relevance, and investigated the associated factors comprehensively. Moreover, we proposed a simple experimental model for symptomatic VTE prediction, which could more directly reflect the underlying hypercoagulable state.

This study also has several limitations. First, it was a retrospective study, with lack of regular dynamic clinical and laboratory data. Second, the sample size was not large enough to adjust for possible differences in patients’ characteristics across centers, and interpretation of our findings might be limited by the sample size. By including all patients with symptomatic VTE in the 16 major designated COVID-19 hospitals, we believe our study population is representative of cases managed in the epicenter of China. Third, genetic factors may play an important role in VTE, but these data were not available in this study. Lastly, follow-up after discharge were not conducted, and post-discharge VTE events were not analysed.

In conclusion, there is an excess risk of symptomatic VTE in severe and non-severe hospitalized COVID-19 patients compared to non-COVID-19 medical inpatients. New-onset PE increased in-hospital deaths, and 3 coagulation variables (fibrinogen and D-dimer on admission, and DI ≥ 1.5 fold) predicted symptomatic VTE in hospitalized COVID-19 patients.

**Authors’ contributions**

LVT and YH were the overall principal investigators in this study who conceived the study and obtained financial support, were responsible for the study design and supervised the entire study. LVT, HFW, DL, DLW, PP, WHW, LW, XWY, JYX, FZ, NX, FS, CXW, XT, HY, WJW, BDL, WZL, ZPC, YGW, and XRD recruited participants and collected the data. LVT, PY, DL, and WZL completed the statistical analyses. LVT, HFW, DLW, FS, CXW, WJW, BDL, ZPC, and YH completed data analysis. LVT, HFW, YXW, LQC, HS and GYHL drafted the paper. All authors participated in interpretation data, critically revised the manuscript for important intellectual content, and gave final approval for the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Declaration of interests**

GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.

The others declare no competing interests.

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**FIGURE LEGENDS**

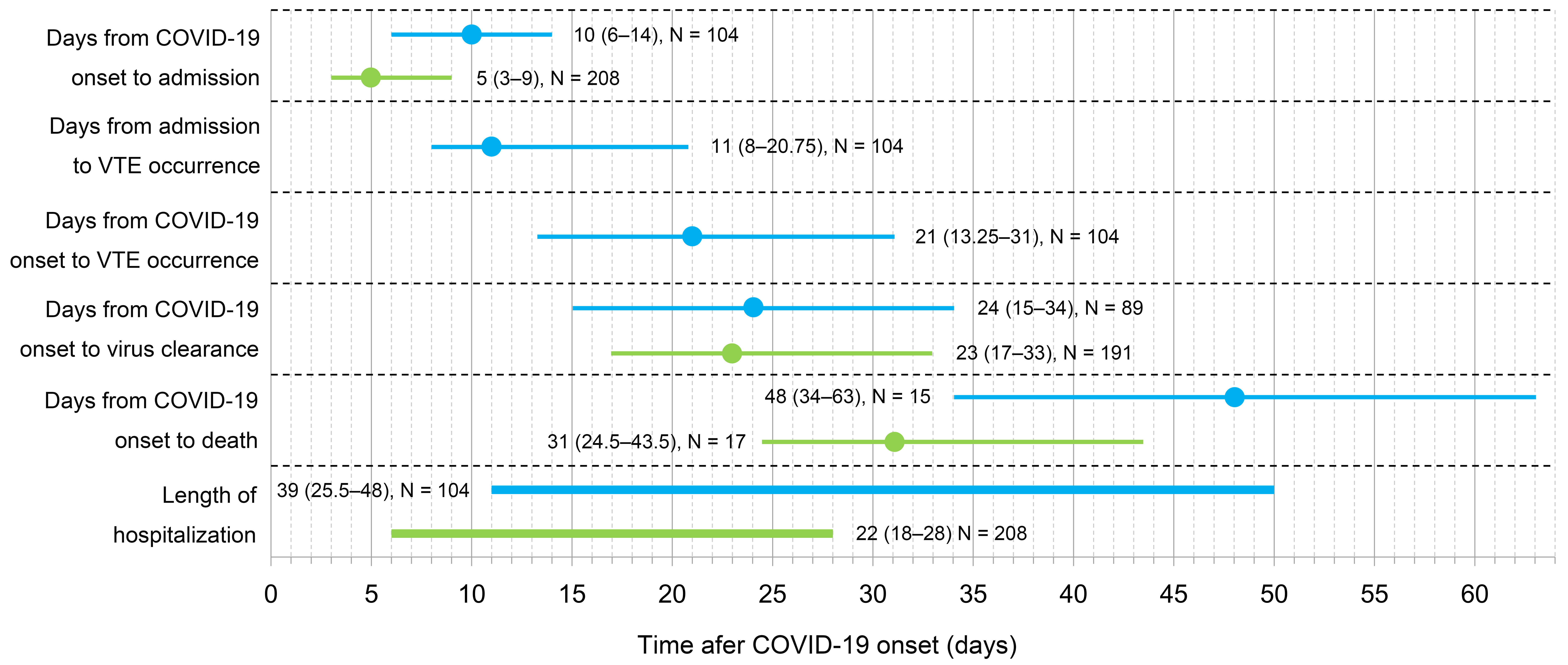
**Figure 1. Risk of symptomatic VTE in COVID-19 patients**

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Rates and odds ratios were calculated with data from COVID-19 patients and a historical non-COVID-19 cohort in three centers. OR was adjusted for age and gender.

**Figure 2. Timeline chart for clinical outcomes from COVID-19 onset**

Data were expressed as median (circle) and IQR (straight line); blue: VTE group; green: Non-VTE group; virus clearance was defined as at least two consecutive negative RNA tests for SARS-CoV-2.

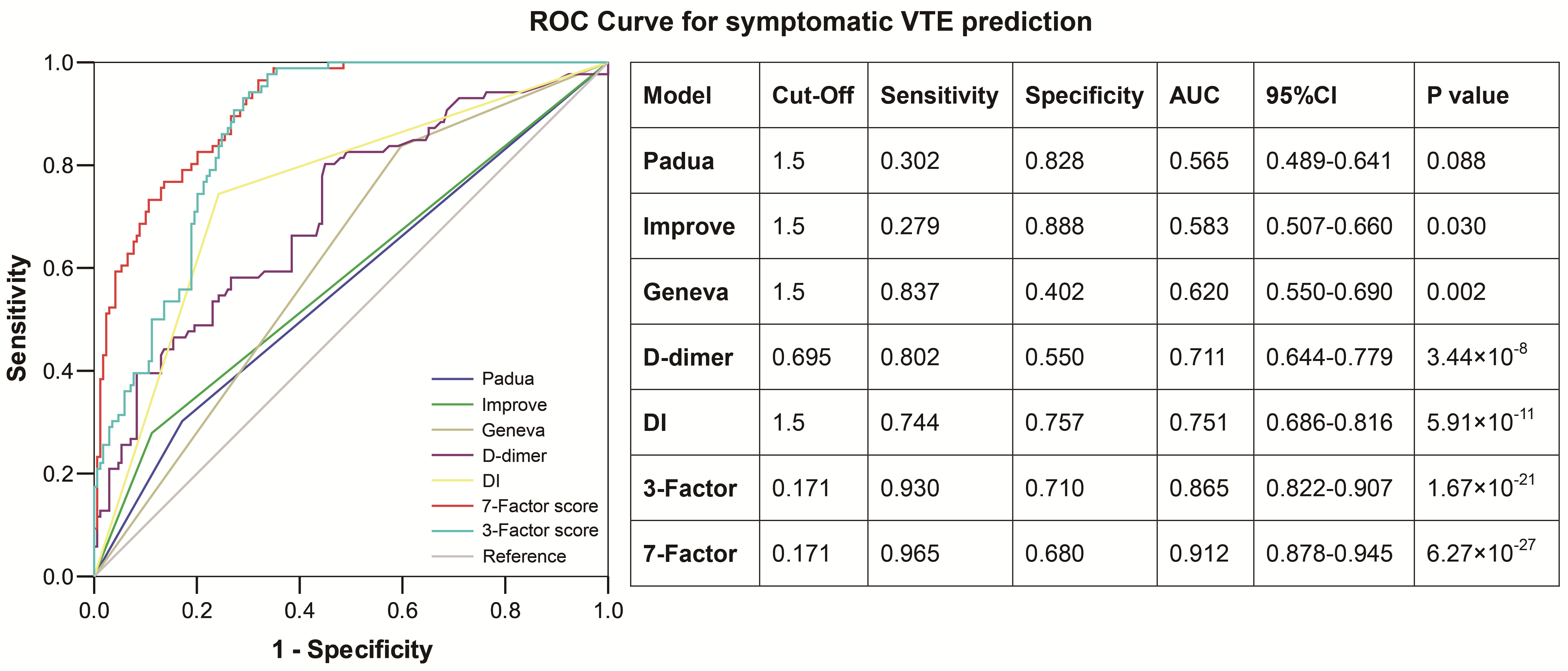


**Figure 3. Cumulative symptomatic VTE incidence in COVID-19 patients**

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VTE incidence was estimated by the Kaplan-Meier method. Any differences in the incidence were evaluated with a log-rank test; DI: D-dimer increment; DI values were available for 88 VTE cases and 169 Non-VTE ones.

**Figure 4. ROC curve of models predicting symptomatic VTE in COVID-19 patients**



AUC was estimated in 7 models; the Youden index was used to determine sensitivity and specificity; 255 COVID-19 patients (86 VTE cases and 169 Non-VTE cases) with complete data were included in this analysis; DI: D-dimer increment; AUC: area under ROC curve; 7-factor model: age, cancer, interval from COVID-19 onset to admission, thymosin injection, fibrinogen concentration, D-dimer level on admission, and D-dimer increment ≥ 1.5; 3-factor score (Wuhan score): fibrinogen, D-dimer on admission, and DI ≥ 1.5.

**Table 1. Demographic, clinical characteristics, and laboratory findings of COVID-19 patients with or without symptomatic VTE**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | VTE group  N = 104 | Non-VTE group  N = 208 | P |
| Severity of COVID-19 |  |  | 0.52 |
| Moderate | 40 (39.5%) | 88 (42.3%) |  |
| Severe | 64 (61.5%) | 120 (57.7%) |  |
| Age (year, median, IQR) | 66 (61–79) | 60.5 (49–68) | 6.77 × 10-7 |
| Male gender | 45 (43.3%) | 95 (45.7%) | 0.69 |
| Smoking | 8 (7.7%) | 8 (3.8%) | 0.18 |
| Top temperature |  |  | 0.69 |
| <37.5℃ | 29 (27.9%) | 68 (32.7%) |  |
| ≥37.5 and <39℃ | 48 (46.2%) | 90 (43.3%) |  |
| ≥39℃ | 27 (25.9%) | 50 (24.0%) |  |
| Cough | 87 (83.6%) | 155 (74.5%) | 0.08 |
| Dyspnea on admission | 33 (31.7%) | 61 (29.3%) | 0.70 |
| Pulmonary radiography on admission |  |  | 0.87 |
| Focal small patchy lesions | 48 (46.2%) | 94 (45.2%) |  |
| Extensive or diffuse lesions | 56 (53.8%) | 114 (54.8%) |  |
| Comorbidities |  |  |  |
| Coronary heart disease | 24 (23.1%) | 35 (16.8%) | 0.22 |
| Hypertension | 46 (44.2%) | 58 (27.9%) | 8.99 × 10-4 |
| Diabetes | 22 (21.2%) | 38 (18.3%) | 0.54 |
| Atrial fibrillation | 10 (9.6%) | 8 (3.8%) | 0.07 |
| COPD | 15 (14.4%) | 20 (9.6%) | 0.25 |
| Chronic heart failure | 19 (18.3%) | 23 (11.0%) | 0.11 |
| Active cancer | 12 (11.5%) | 5 (2.4%) | 0.001 |
| Autoimmune disease | 2 (1.9%) | 1 (0.5%) | 0.26 |
| Therapies |  |  |  |
| Arbidol | 71 (68.3%) | 155 (74.5%) | 0.24 |
| Hydroxychloroquine | 12 (11.5%) | 24 (11.5%) | 1.00 |
| Lopinavir-ritonavir | 20 (19.2%) | 44 (21.1%) | 0.77 |
| Remdesivir | 2 (1.9%) | 1 (0.5%) | 0.26 |
| Convalescent plasma | 2 (1.9%) | 2 (1.0%) | 0.60 |
| Antibiotics | 97 (93.3%) | 189 (90.9%) | 0.52 |
| Antifungal agents | 24 (23.1%) | 36 (17.3%) | 0.23 |
| Tocilizumab | 10 (9.6%) | 11 (5.3%) | 0.16 |
| Glucocorticoid | 44 (42.3%) | 54 (26.0%) | 0.003 |
| Immunoglobin | 50 (48.1%) | 82 (39.4%) | 0.14 |
| Thymosin injection | 75 (72.1%) | 110 (52.9%) | 0.001 |
| Mechanical ventilation | 18 (17.3%) | 24 (11.5%) | 0.16 |
| Laboratory findings on admission (median, IQR) |  |  |  |
| WBC count (109/L) | 6.33 (4.70–9.67) | 4.28 (2.96–6.56) | 8.08 × 10-10 |
| Neutrophil (109/L) | 4.51 (3.15–8.16) | 3.26 (2.20–5.46) | 3.02 × 10-6 |
| Lymphocyte (109/L) | 0.82 (0.54–1.33) | 1.19 (0.79–1.56) | 0.001 |
| Platelet count (109/L) | 205.5 (153.25–306) | 216 (156.2–278) | 0.73 |
| ALT (U/L) | 35 (20.8–50) | 26.5 (19–48.2) | 0.11 |
| AST (U/L) | 29.5 (21.8–49.2) | 28 (20–39) | 0.10 |
| CRP (mg/L) | 59.4 (32.9–83.4), n = 104 | 12.3 (4.4–49.2), n = 206 | 6.16 × 10-10 |
| IL-6 (pg/ml) | 14.09 (5.34–27.09), n = 81 | 9.47 (4.78–24.19), n = 164 | 0.28 |
| D-dimer (μg/mL) | 2.07 (0.8–6.57), n = 96 | 0.61 (0.29–1.46), n = 187 | 1.62 × 10-10 |
| Fibrinogen (g/L) | 4.12 (2.89–4.98), n = 94 | 4.47 (3.66–5.39), n =185 | 0.005 |

Cases (VTE group) and controls (Non-VTE group) were 1 to 2 matched by severity of COVID-19. Some laboratory tests were not performed on admission and comparisons were made by available data; WBC: white blood cell; CRP: C-reactive protein; IL-6: Interleukin 6; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; COPD: chronic obstructive pulmonary disease.

**Table 2. Thromboprophylaxis in the VTE group and non-VTE group**

|  |  |  |
| --- | --- | --- |
| Characteristics | VTE group (N = 13) a | non-VTE group (N = 35) b |
| Regimens |  |  |
| LMWH 4000 IU qd | 10 (76.9%) | 29 (82.9%) |
| LMWH 2000 IU qd c | 3 (23.1%) | 4 (11.4%) |
| Rivaroxaban 10 mg qd | 0 | 2 (5.7%) |
| Bleeding events |  |  |
| Major bleeding d | 1 (gastrointestinal bleeding) | 1 (gastrointestinal bleeding) |
| Fatal bleeding | 0 | 1 (intra-abdominal bleeding) |

a. VTE group: COVID-19 patients with a subsequent symptomatic VTE event; 13 of the 104 cases received pharmacological thromboprophylaxis;

b. Non-VTE group: COVID-19 patients without a subsequent symptomatic VTE event; 35 of the 208 cases received pharmacological thromboprophylaxis;

c. Half dose of LMWH (2000 IU) per day was prescribed for patients older than 70 years or blood platelet count less than 50 × 109/L;

d. All the major and fatal bleeding events occurred in patients receiving LMWH of 4000 IU per day.

**Table 3. Multivariable logistic regression analysis of factors associated with symptomatic VTE risk in COVID-19 patients**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Factors | Crude OR (95%CI) | P | Adjusted OR (95%CI) | P |
| Age | 1.05 (1.03–1.07) | 2.86 × 10-6 | 1.04 (1.01–1.07) | 0.008 |
| Days from COVID-19 onset to admission | 1.10 (1.05–1.16) | 2.07 × 10-4 | 1.12 (1.05–1.20) | 0.001 |
| Active cancer | 5.30 (1.81–15.46) | 0.001 | 5.80 (1.18–28.48) | 0.031 |
| Thymosin | 2.30 (1.39–3.83) | 0.001 | 2.61 (1.19–5.73) | 0.017 |
| D-dimer on admission | 1.26 (1.14–1.38) | 5.10 × 10-6 | 1.34 (1.18–1.52) | 7.38 × 10-6 |
| DI ≥ 1.5 fold | 8.32 (4.63–14.96) | 9.54 × 10-14 | 15.55 (6.65–36.34) | 2.38 × 10-10 |
| Fibrinogen | 0.72 (0.58–0.89) | 0.002 | 0.63 (0.48–0.81) | 4.74 × 10-4 |
| Glucocorticoid | 2.09 (1.27-3.44) | 0.004 | 1.95 (0.86–4.44) | 0.113 |
| Venous catheterization | 4.64 (2.20–9.76) | 5.36 × 10-5 | 2.10 (0.58–7.57) | 0.255 |
| Padua score ≥ 4 | 2.11 (1.23–3.60) | 0.007 | 1.71 (0.41–7.07) | 0.459 |
| Improve score ≥ 3 | 3.26 (1.78–5.98) | 1.81 × 10-4 | 0.19 (0.04–1.01) | 0.054 |
| Geneva score ≥ 3 | 3.33 (1.85–6.01) | 3.12 × 10-5 | 0.50 (0.14–1.76) | 0.28 |

DI: D-dimer increment, defined as D-dimer level on day 4 to day 6 divided by that on day 1 to day 3 following admission; DI values were available for 88 VTE cases and 169 Non-VTE ones; adjusted OR: odds ratio for symptomatic VTE was adjusted for age, active cancer, venous catheterization, glucocorticoid, thymosin, days from COVID-19 onset to admission, D-dimer on admission, DI, Fibrinogen, Padua score, Improve score, and Geneva score.

**Supplementary Appendix**

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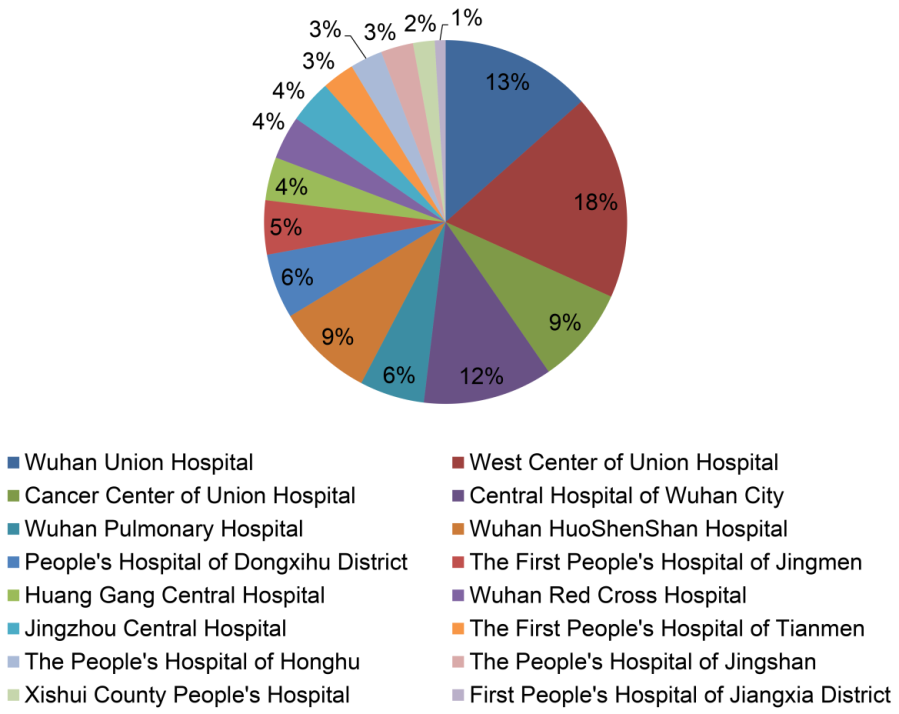
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**Figure 1. Flowchart of the study**

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Risk for symptomatic VTE in COVID-19 was assessed in the retrospective study, and VTE risk prediction was analyzed in the case-control study; RNA tests mean SARS-CoV-2 RNA determination using RT-PCR or sequencing. COVID-19: Coronavirus disease 2019; VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism.

**Figure S2. Distribution of the participants included in the case-control study across centers**

****

104 COVID-19 cases with symptomatic VTE and 208 controls without VTE were matched and enrolled in 16 centers from Wuhan and other cities from Hubei province, China

**Figure S3. Risk of death in COVID-19 patients with or without symptomatic VTE**

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Case-fatality rate means death events during hospitalization; VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; OR: crude odds ratio.

**Figure S4. Simultaneous effects of thrombosis factors on symptomatic VTE**

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Analysis was performed with the Cox proportional-hazard model adjusted for age, active cancer, venous catheterization, glucocorticoid, thymosin, days from COVID-19 onset to admission, D-dimer on admission, DI, Fibrinogen, Padua score, Improve score, and Geneva score; DI: D-dimer increment; 255 COVID-19 patients (86 VTE cases and 169 Non-VTE cases) with complete data were included.

**Table S1. Anticoagulation in COVID-19 patients with a subsequent symptomatic VTE event**

|  |  |
| --- | --- |
| Characteristics | COVID-19 patients with VTE (N = 104) |
| Anti-thrombotic therapy in-hospital |  |
| LMWH only | 43 (41.4%) |
| Rivaroxaban only | 17 (16.3%) |
| LMWH followed by rivaroxaban | 42 (40.4%) |
| AngioJet thrombectomy followed by rivaroxaban | 2 (1.9%) |
| LMWH doses |  |
| LMWH 4000 IU – 6000 IU bid | 60/85 |
| LMWH 4000 IU – 6000 IU qd a | 25/85 |
| Anti-thrombotic therapy following discharge (rivaroxaban) b | 85 out of 89 patients who are alive |
| Adverse events |  |
| Major bleeding c | 4 (4 gastrointestinal bleeding) |
| Death and possible causes | 15 |
|  | 7 Exacerbation of pneumonia |
|  | 7 Confirmed or Suspected PE |
|  | 1 Sepsis |

a. LMWH (4000 IU – 6000 IU) was prescribed only once daily for patients older than 70 years old or blood platelet count less than 50 × 109/L;

b. 89 patients with VTE discharged: 85 of them would continue anticoagulation using rivaroxaban for 90 days, and the other 4 would not because of the major bleeding events during hospitalization;

c. All the 4 major bleeding events were gastrointestinal bleeding: 3 for LMWH bid and 1 for rivaroxaban 10 mg qd.

**Table S2. Possible factors and prediction models related to VTE in COVID-19 patients**

|  |  |  |  |
| --- | --- | --- | --- |
| Factors | VTE group (n, %)  N = 104 | Non-VTE group (n, %)  N = 208 | P |
| Ischemic stroke within 1 month | 5 (4.8%) | 6 (2.9%) | 0.52 |
| Myocardial infarction within 1 month | 3 (2.9%) | 4 (1.9%) | 0.69 |
| Surgery or trauma within 1 month | 10 (9.6%) | 11 (5.3%) | 0.16 |
| Venous Catheterization | 23 (22.1%) | 12 (5.8%) | 3.75 × 10-5 |
| Thromboprophylaxis | 13 (12.5%) | 35 (16.8%) | 0.41 |
| Padua score ≥ 4 | 34 (32.7%) | 39 (18.8%) | 0.007 |
| Improve score ≥ 3 | 30 (28.8%) | 23 (11.0%) | 1.81 × 10-4 |
| Geneva score ≥ 3 | 87 (83.6%) | 126 (60.6%) | 3.12 × 10-5 |
| DI ≥ 1.5 fold a | 64 (61.5%), n = 88 | 41 (19.7%), n = 169 | 9.54 × 10-14 |

Thromboprophylaxis: defined as pharmacological anticoagulation for at least 7 days; DI: D-dimer increment, defined as D-dimer level on day 4 to day 6 divided by that on day 1 to day 3 following admission. D-dimer increment values were available for 88 VTE cases and 169 Non-VTE ones with COVID-19.