

Clinical characteristics and risk factors for symptomatic venous thromboembolism in hospitalized COVID-19 patients

A multicenter retrospective study

Li, Jun-Ying; Wang, Hong-Fei; Yin, Ping; Li, Di; Wang, Di-Le; Peng, Peng; Wang, Wei-Hua; Wang, Lan; Yuan, Xiao-Wei; Xie, Jin-Yuan; Zhou, Fan; Xiong, Nian; Shao, Feng; Wang, Chun-Xiu; Tong, Xiang; Ye, Hao; Wan, Wen-Jun; Liu, Ben-De; Li, Wen-Zhu; Li, Qian; Tang, Liang V; Hu, Yu; Lip, Gregory Yh; Thrombo-COVID-19 Collaborative

Published in:

Journal of Thrombosis and Haemostasis

DOI (link to publication from Publisher):

[10.1111/jth.15261](https://doi.org/10.1111/jth.15261)

Creative Commons License

CC BY-NC 4.0

Publication date:

2021

Document Version

Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

Citation for published version (APA):

Li, J.-Y., Wang, H.-F., Yin, P., Li, D., Wang, D.-L., Peng, P., Wang, W.-H., Wang, L., Yuan, X.-W., Xie, J.-Y., Zhou, F., Xiong, N., Shao, F., Wang, C.-X., Tong, X., Ye, H., Wan, W.-J., Liu, B.-D., Li, W.-Z., ... Thrombo-COVID-19 Collaborative (2021). Clinical characteristics and risk factors for symptomatic venous thromboembolism in hospitalized COVID-19 patients: A multicenter retrospective study. *Journal of Thrombosis and Haemostasis*, 19(4), 1038-1048. <https://doi.org/10.1111/jth.15261>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

Take down policy

If you believe that this document breaches copyright please contact us at vbn@aub.aau.dk providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from vbn.aau.dk on: December 06, 2025

DR LIANG V. TANG (Orcid ID : 0000-0002-3253-0220)

Article type : Original Article

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

Running Title: symptomatic VTE in COVID-19 patients

Jun-Ying Li^{1*}, Hong-Fei Wang^{2*}, Ping Yin³, Di Li⁴, Di-Le Wang⁵, Peng Peng⁶, Wei-Hua Wang^{6, 8}, Lan Wang^{7, 8}, Xiao-Wei Yuan⁹, Jin-Yuan Xie¹⁰, Fan Zhou¹¹, Nian Xiong^{12, 13}, Feng Shao¹⁴, Chun-Xiu Wang¹⁵, Xiang Tong¹⁶, Hao Ye¹⁷, Wen-Jun Wan¹⁸, Ben-De Liu¹⁹, Wen-Zhu Li^{20, 21}, Qian Li²², Liang V. Tang¹, Yu Hu¹, Gregory YH Lip^{23, 24}, The Thrombo-COVID-19 Collaborative

¹ Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

² Department of Cardiovascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

³ Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, China

⁴ Department of Medical Records Management and Statistics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

⁵ Department of Vascular Surgery, Central Hospital of Wuhan City, Wuhan, China

⁶ Wuhan Pulmonary Hospital, Wuhan, China

⁷ Blood Center of Wuhan City, Wuhan, China

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/JTH.15261](#)

This article is protected by copyright. All rights reserved

⁸ Wuhan HuoShenShan Hospital, Wuhan, China

⁹ Department of Otorhinolaryngology, People's Hospital of Dongxihu District, Wuhan, China

¹⁰ Department of Orthopedics Surgery, The First People's Hospital of Jingmen, Jingmen, China

¹¹ Department of Medicine, Huang Gang Central Hospital, Huanggang, China

¹² Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

¹³ Wuhan Red Cross Hospital, Wuhan, China

¹⁴ Department of Intensive Care Unit, Jingzhou Central Hospital, The Second Clinical Medical College, Yangtze University, Jingzhou, China

¹⁵ The First People's Hospital of Tianmen City, Tianmen, China

¹⁶ Department of Neurosurgery, The People's Hospital of Honghu, Honghu, China

¹⁷ Department of Infectious Diseases, The People's Hospital of Jingshan, Jingshan, China

¹⁸ Department of Hepatobiliary Surgery, Xishui County People's Hospital, Huanggang, China

¹⁹ Department of Emergency Medicine, First People's Hospital of Jiangxia District, Wuhan, China

²⁰ Department of Geriatrics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

²¹ Cardiovascular Research Center, Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

²² MOE Key Laboratory of Environment and Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

²³ Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom

²⁴ Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

***Contributed equally**

Address for correspondence

Yu Hu (dr_huyu@126.com) or Liang V. Tang (lancet.tang@qq.com), No. 1277 Jiefang Avenue, Union Hospital,

Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China; Tel.: +86 27 85726387; fax: +86 27 85726387

Word Count: 3278 (body), 250 (abstract)

Tables: 2

Figures: 4

Supplemental Material: 3 Figures and 5 Tables

Essentials

- There is an excess risk of VTE in severe and non-severe hospitalized COVID-19 patients.
- Risk factors are aging, cancer, longer duration of symptoms prior to admission, lower fibrinogen, higher D-dimer, and D-dimer Increment.
- D-dimer Increment ≥ 1.5 fold has the most significant association with VTE in hospitalized COVID-19 patients.
- A novel experimental model is a promising approach for symptomatic VTE prediction.

ABSTRACT

Background

High incidence of asymptomatic venous thromboembolism (VTE) has been observed in severe COVID-19 patients, but the characteristics of symptomatic VTE in general COVID-19 patients have not been described.

Objectives

To comprehensively explore the prevalence and reliable risk prediction for VTE in COVID-19 patients.

Methods/Results

This retrospective study enrolled all COVID-19 patients with a subsequent VTE in 16 centers in China from January 1 to March 31, 2020. A total of 2779 patients were confirmed with COVID-19. In comparison with 23,434 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 were compared, pulmonary embolism cases had a higher rate for in-hospital death (OR 6.74, 95%CI 2.18 to 20.81). VTE developed at a median of 21 days (IQR 13.25 to 31) since onset. Independent factors for VTE were advancing age, cancer, longer interval from symptom onset to admission, lower fibrinogen and higher D-dimer on admission, and D-dimer increment ($DI \geq 1.5$ fold; of these, $DI \geq 1.5$ fold had the most significant association (OR 14.18, 95%CI 6.25–32.18, $P = 2.23 \times 10^{-10}$). A novel model consisting of simple 3 coagulation variables (fibrinogen and D-dimer levels on admission, and $DI \geq 1.5$ fold) showed good prediction for symptomatic VTE (AUC 0.865, 95%CI 0.822 to 0.907, sensitivity 0.930, specificity 0.710).

Conclusions

There is an excess risk of VTE in hospitalized COVID-19 patients. The novel model can help early identification of patients who are at high risk for VTE.

Keywords

SARS-CoV-2; COVID-19; Thrombosis; Venous Thromboembolism; D-dimer Increment

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).²⁻⁴ High prevalence of incident thrombosis in small and mid-sized pulmonary arteries have been demonstrated in clinicopathologic case series, despite thromboprophylaxis.^{5, 6} Most VTE are asymptomatic and whether they are the cause of death or only concurrent events remains controversial.⁷ On the other hand, COVID-19 patients at high risk for VTE are also at high risk for bleeding, and sometimes catastrophic intracranial hemorrhage may occur.⁸ Therefore, anticoagulation may potentially be harmful, and it would be important to distinguish those who will develop thrombosis in hospitalized COVID-19 patients.⁹

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 multicenter study to explore the prevalence, risk factors and prediction models for symptomatic VTE in hospitalized COVID-19 patients.

MATERIALS AND METHODS

Study design and participants

The flowchart for the study is summarized in Figure S1. This multicenter, retrospective, observational study was conducted in 16 centers 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, with data from 3 of the 16 centers in

which a Big Data System was implanted. From January 1 to March 31, 2020, all laboratory-confirmed hospitalized COVID-19 patients 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 events 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.¹⁰ 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 (WZL).

COVID-19 was confirmed by the laboratory tests of SARS-CoV-2 RNA as described previously.^{11, 12} 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 both clinical manifestations and elevated level of

D-dimer ($> 0.5 \mu\text{g/mL}$), and was confirmed by objective imaging: compression ultrasonography for deep vein thrombosis, CT pulmonary angiography for pulmonary embolism. Clinical manifestations included swelling and pain of the lower extremities, superficial varicose veins, severe chest pain and hemoptysis under a stable disease state, worse $\text{PaO}_2/\text{FiO}_2$, hemodynamic impairment requiring fluid challenge, or dilated right ventricle. Catheter associated thrombosis and visceral VTE were not examined. 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.¹³ A “6-factor model” was tentatively defined as the combination of 6 independent variables for VTE in the final logistic regression model: age, cancer, interval from COVID-19 onset to admission, 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). There were 13 factors showed significant differences in univariable analysis (Table 1 and

Table S3). To avoid overfitting in the model, 3 factors (WBC count, Neutrophil, and Lymphocyte on admission) were excluded from further analysis because we think they would have colinearity with coagulation variables. Finally, 10 factors were included in multivariable analysis, including: age, hypertension, active cancer, venous catheterization, glucocorticoid, days from COVID-19 onset to admission, CRP, D-dimer on admission, DI and Fibrinogen.

Multivariable analysis with the Cox proportional-hazard model was employed to assess the simultaneous effects of related factors on symptomatic VTE. 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. 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 analyzes were performed using with SPSS 13.0.

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). The historical cohort consisted of non-COVID-19 patients hospitalized for a variety of medical conditions, all of whom were de-identified. The median age was 61.5 years (IQR 46-79.5 years) and 53.3% of the patients were male. 71.6% of the patients admitted mainly for cardiovascular diseases, hematological tumors, nervous system diseases, or respiratory diseases. 8.0% of them were transferred to intensive care unit. The following cases were excluded: receiving surgical procedures during hospitalization, hospital stay less than 3 days, age less than 14 years, or readmission due to transfer to another ward. Of these, 70 patients of the historical cohort developed symptomatic VTE. The crude rates of VTE were 1.95% (1.27% to 2.63%) in severe COVID-19 patients, 0.87%

(0.32% to 1.43%) in non-severe COVID-19 patients, and 0.30% (0.23% to 0.37%) in non-COVID-19 medical patients, respectively ($P = 4.26 \times 10^{-16}$). After adjustment for age and gender, the ORs for developing symptomatic VTE were 5.94 (95%CI 3.91 to 10.09) and 2.79 (95%CI 1.43 to 5.60) 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%, $P = 0.52$), respectively (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. Systematic glucocorticoid use was significantly higher in VTE cases compared to non-VTE cases ($P = 0.003$). 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 S1); 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. Treatment for VTE was shown in Table S2.

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, $P = 7.86 \times 10^{-10}$). 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 S3). 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.

On multivariable analysis (Table 2), independent factors for symptomatic VTE were advancing age, cancer, longer interval from onset to admission, 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 14.18, 95%CI 6.25–32.18, $P = 2.23 \times 10^{-10}$), followed by D-dimer level on admission (OR 1.33, 95%CI 1.17–1.50, $P = 7.46 \times 10^{-6}$), and fibrinogen level on admission (OR 0.64, 95%CI 0.49–0.83, $P = 7.56 \times 10^{-4}$).

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 also indicated that D-dimer increment ≥ 1.5 fold had the most significant association with symptomatic VTE (Table S4, HR 4.66, 95%CI 2.76–7.85, $P = 7.65 \times 10^{-9}$).

ROC curve analysis was performed for the possible predicting factors (Figure 4). We tentatively defined the “6-factor model” as the combination of 6 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 6-factor model showed the highest prediction accuracy for symptomatic VTE (AUC 0.905, 95%CI 0.870 to 0.940), followed by the

simple Wuhan score (AUC 0.865, 95%CI 0.822 to 0.907), $DI \geq 1.5$ fold (AUC 0.751, 95%CI 0.686 to 0.816), and D-dimer on admission (AUC 0.711, 95%CI 0.644 to 0.779). 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 multicenter 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 6 factors independent predicted symptomatic VTE in hospitalized COVID-19 patients; and (iii) a simple “3-factor” model (Wuhan score) consisting of 3 coagulation variables (fibrinogen and D-dimer levels on admission, and $DI \geq 1.5$ 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.¹⁵⁻²⁸ 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. Some studies suggested that 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.²⁹ 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.³⁰ In contrast, there is also evidence that asymptomatic DVT is associated with increased short-term mortality in medical patients.^{31,32} Therefore, the clinical importance and prognosis of asymptomatic VTE is still uncertain and there is no consensus on the necessity of detection and treatment.³³

In this study, 12.5% VTE cases and 16.8% Non-VTE cases with COVID-19 received pharmacological thromboprophylaxis (Table S1). 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.³⁴ 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 patients 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.³⁵⁻³⁹

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.^{18, 21, 26} Therefore, D-dimer on admission was considered as a diagnostic marker for VTE in COVID-19.⁴⁰ 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 if the level kept stable or increased slowly. In contrast, in COVID-19 patients who are likely to develop a symptomatic VTE, the D-dimer will rise sharply within the first week during hospitalization.

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 robust risk assessment models evaluating VTE risk in hospitalized medical patients (Table S5).¹² Consistent with previous findings, the above 3 models were also associated with developing symptomatic VTE in hospitalized COVID-19 patients. They are clinical assessment models which included various demographic and clinical characteristics. All these clinical variables will ultimately contribute to a hypercoagulate state which will be reflected by coagulation variables. Therefore, we proposed a simple “3-factor score” (Wuhan score) consisting of 3 independent coagulation predictors for VTE identified using multivariable analysis: lower fibrinogen on admission (coagulation consumption), higher D-dimer on admission (secondary hyperfibrinolysis), and D-dimer increment ≥ 1.5 fold (persistent hyperfibrinolysis). The Wuhan model showed very good predictive accuracy for symptomatic VTE, which was broadly comparable to the more complex 6-factor model (sensitivity 0.930 vs 0.907, specificity 0.710 vs 0.751).

Strengths and Limitations

This research has some strengths. This was a multicenter study covering all hospitalized COVID-19 patients with VTE, with complete follow-up. Therefore, the study population would be representative of the whole hospitalized COVID-19 population with VTE 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. Fourth, there is no internal or external validation done; because the COVID-19 outbreak was controlled rapidly in China. Fifth, other major VTE risk

factors of the historic cohort were not taken into account when predicting the OR for VTE. Fifth, in Western populations the majority of patients admitted with COVID-19 receive thromboprophylaxis. There is ethnic variation in risk of VTE and therefore the estimates of absolute and relative risk may not apply to other populations. There is also ethnic variation in D-dimer and fibrinogen, so the proposed model may not apply elsewhere. Sixth, in the Kaplan-Meier analyzes, the cumulative VTE incidences have not been adjusted for deaths. Therefore, the VTE incidence may have been overestimated. Lastly, follow-up after discharge were not conducted, and post-discharge VTE events were not analyzed.

Conclusions

There is an excess risk of symptomatic VTE in severe and non-severe hospitalized COVID-19 patients. New-onset PE increased in-hospital deaths, and 3 coagulation variables (fibrinogen and D-dimer on admission, and $DI \geq 1.5$ fold) predicted symptomatic VTE in hospitalized COVID-19 patients. This “3-factor” model can help early identification of COVID-19 patients who are at high risk for symptomatic VTE.

Acknowledgments

We wish to acknowledge the dedication, commitment, and sacrifice of the staff, providers and personnel in each center through the local COVID-19 crisis and express our profound sadness about the suffering and loss of our patients, their families, and our community. Special thanks go to the participants included in this report.

Conflict of interest

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.

Funding

This work was supported by Program for HUST Academic Frontier Youth Team (No.

2018QYTD14) and National Natural Science Foundation of China (No. 81973995 and No. 31620103909). The funder of the study had no role in study design, data collection, data analysis, data interpretation.

Author 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. JYL, LVT, HFW, DL, DLW, PP, WHW, LW, XWY, JYX, FZ, NX, FS, CXW, XT, HY, WJW, BDL, and WZL recruited participants and collected the data. JYL, LVT, PY, DL, QL, and WZL completed the statistical analyses. JYL, LVT, HFW, DLW, FS, CXW, WJW, BDL, QL, and YH completed data analysis. JYL, LVT, HFW, 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.

REFERENCES

1. Cohen AT, Tapson VF, Bergmann JF, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* 2008; **371**(9610): 387-94.
2. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *The Lancet Haematology* 2020.
3. Zhai Z, Li C, Chen Y, et al. Prevention and Treatment of Venous Thromboembolism Associated with Coronavirus Disease 2019 Infection: A Consensus Statement before Guidelines. *Thrombosis and haemostasis* 2020.
4. Bowles L, Platton S, Yartey N, et al. Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with Covid-19. *N Engl J Med*. 2020;NEJMc2013656. doi:10.1056/NEJMc2013656
5. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association?. *Eur Heart J*. 2020;41(19):1858.

6. Lax SF, Skok K, Zechner P, et al. Pulmonary Arterial Thrombosis in COVID-19 With Fatal Outcome: Results From a Prospective, Single-Center, Clinicopathologic Case Series. *Annals of internal medicine* 2020.
7. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. *Journal of the American College of Cardiology* 2020.
8. Carroll E, Lewis A. Catastrophic Intracranial Hemorrhage in Two Critically Ill Patients with COVID-19. *Neurocritical care* 2020.
9. Spyropoulos AC, Ageno W, Barnathan ES. Hospital-based use of thromboprophylaxis in patients with COVID-19. *Lancet* 2020; **395**(10234): e75.
10. Tang Y, Zhu C, Liu J, et al. Association of Intraoperative Hypotension with Acute Kidney Injury after Noncardiac Surgery in Patients Younger than 60 Years Old. *Kidney Blood Press Res.* 2019;44(2):211-221
11. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**(10229): 1054-62.
12. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA.* 2020;323(11):1061 - 1069
13. Stuck AK, Spirk D, Schaudt J, Kucher N. Risk assessment models for venous thromboembolism in acutely ill medical patients. A systematic review. *Thrombosis and haemostasis* 2017; **117**(4): 801-8.
14. Moumneh T, Riou J, Douillet D, Henni S, Mottier D, Tritschler T, et al. Validation of risk assessment models predicting venous thromboembolism in acutely ill medical inpatients: A cohort study. *J Thromb Haemost.* 2020;18(6):1398-1407
15. Leonard-Lorant I, Delabranche X, Severac F, et al. Acute Pulmonary Embolism in COVID-19 Patients on CT Angiography and Relationship to D-Dimer Levels. *Radiology* 2020: 201561.
16. Klok FA, Kruip M, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thrombosis research* 2020.
17. Garcia-Olive I, Sintes H, Radua J, Capa JA, Rosell A. D-dimer in patients infected with COVID-19

-
- and suspected pulmonary embolism. *Respiratory medicine* 2020: 106023.
18. Zhang L, Feng X, Zhang D, et al. Deep Vein Thrombosis in Hospitalized Patients with Coronavirus Disease 2019 (COVID-19) in Wuhan, China: Prevalence, Risk Factors, and Outcome. *Circulation* 2020.
 19. Ren B, Yan F, Deng Z, et al. Extremely High Incidence of Lower Extremity Deep Venous Thrombosis in 48 Patients with Severe COVID-19 in Wuhan. *Circulation* 2020.
 20. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *Journal of thrombosis and haemostasis : JTH* 2020.
 21. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive care medicine* 2020.
 22. Mei F, Fan J, Yuan J, Liang Z, Wang K, Sun J, Guan W, Huang M, Li Y, Zhang WW. Comparison of Venous Thromboembolism Risks Between COVID-19 Pneumonia and Community-Acquired Pneumonia Patients. *Arterioscler Thromb Vasc Biol.* 2020 Sep;40(9):2332-2337
 23. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis research* 2020.
 24. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *Journal of thrombosis and haemostasis : JTH* 2020.
 25. Bompard F, Monnier H, Saab I, et al. Pulmonary embolism in patients with Covid-19 pneumonia. *The European respiratory journal* 2020.
 26. Stoneham SM, Milne KM, Nuttal E, et al. Thrombotic risk in COVID-19: a case series and case-control study. *Clinical medicine* 2020.
 27. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thrombosis research* 2020; **191**: 9-14.
 28. Jiménez D, García-Sánchez A, Rali P, Muriel A, Bikdeli B, Ruiz-Artacho P, et al. Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. *Chest.* 2020 17:S0012 -3692(20)35146-1.

-
29. Yamashita Y, Shiomi H, Morimoto T, et al. Asymptomatic Lower Extremity Deep Vein Thrombosis-Clinical Characteristics, Management Strategies, and Long-Term Outcomes. *Circ J*. 2017;81(12):1936 - 1944
30. Lloyd NS, Douketis JD, Moinuddin I, Lim W, Crowther MA. Anticoagulant prophylaxis to prevent asymptomatic deep vein thrombosis in hospitalized medical patients: a systematic review and meta-analysis. *Journal of thrombosis and haemostasis : JTH* 2008; **6**(3): 405-14.
31. Kalayci A, Gibson CM, Chi G, Yee MK, Korjian S, Datta S, et al. Asymptomatic Deep Vein Thrombosis is Associated with an Increased Risk of Death: Insights from the APEX Trial. *Thromb Haemost*. 2018;118(12):2046-2052
32. Vaitkus PT, Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Goldhaber SZ; PREVENT Medical Thromboprophylaxis Study Group. Mortality rates and risk factors for asymptomatic deep vein thrombosis in medical patients. *Thromb Haemost*. 2005;93(1):76-9
33. Heidrich H, Konau E, Hesse P. Asymptomatic venous thrombosis in cancer patients--a problem often overlooked. Results of a retrospective and prospective study. *VASA* 2009; **38**(2): 160-6.
34. Wang T, Chen R, Liu C, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. *The Lancet Haematology* 2020; **7**(5): e362-e3.
35. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 2020.
36. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *Journal of thrombosis and haemostasis : JTH* 2020; **18**(5): 1094-9.
37. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19: CHEST Guideline and Expert Panel Report. *Chest*. 2020;S0012-3692(20)31625-1
38. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID and Coagulation: Bleeding and Thrombotic Manifestations of SARS-CoV2 Infection. *Blood*. 2020; doi:10.1182/blood.2020006520
39. Spyropoulos AC, Levy JH, Ageno W, et al. Scientific and Standardization Committee Communication: Clinical Guidance on the Diagnosis, Prevention and Treatment of VTE in Hospitalized Patients with

COVID-19. J Thromb Haemost. 2020;10.1111/jth.14

40. Choi JJ, Wehmeyer GT, Li HA, Alshak MN, Nahid M, Rajan M, et al. D-dimer cut-off points and risk of venous thromboembolism in adult hospitalized patients with COVID-19. Thromb Res. 2020;196:318-321

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

Rates and odds ratios were calculated with data from COVID-19 patients and a historical non-COVID-19 cohort in three centers. ORs were 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

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; 6-factor model: age, cancer, interval from COVID-19 onset to admission, fibrinogen concentration, D-dimer level on admission, and D-dimer increment ≥ 1.5 fold; 3-factor experimental score (Wuhan score): fibrinogen, D-dimer on admission, and DI ≥ 1.5 ; Equation: $\text{Logit}(P) = -3.954 + 0.304 \times \text{D-dimer} + 2.775 \times \text{DI (No=1, Yes=2)} - 0.385 \times \text{Fibrinogen}$.

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°C	29 (27.9%)	68 (32.7%)	
≥37.5 and <39°C	48 (46.2%)	90 (43.3%)	
≥39°C	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
Immunoglobulin	50 (48.1%)	82 (39.4%)	0.14
Mechanical ventilation	18 (17.3%)	24 (11.5%)	0.16
Laboratory findings on admission (median, IQR)			
WBC count (10 ⁹ /L)	6.33 (4.70–9.67)	4.28 (2.96–6.56)	8.08 × 10 ⁻¹⁰
Neutrophil (10 ⁹ /L)	4.51 (3.15–8.16)	3.26 (2.20–5.46)	3.02 × 10 ⁻⁶
Lymphocyte (10 ⁹ /L)	0.82 (0.54–1.33)	1.19 (0.79–1.56)	0.001
Platelet count (10 ⁹ /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

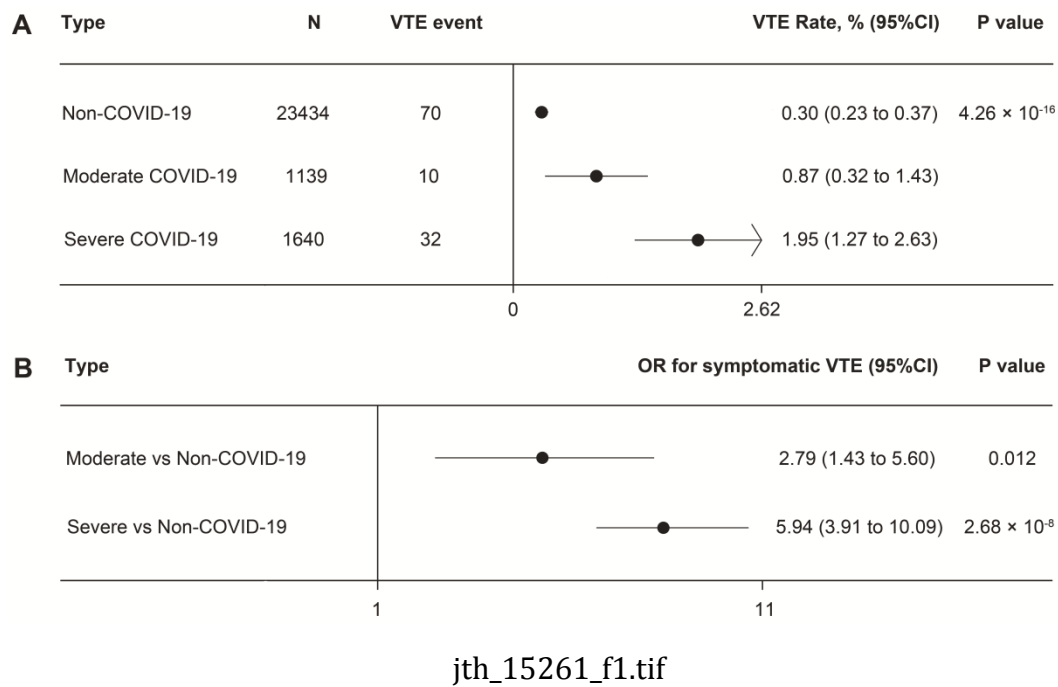
Cases (VTE group) and controls (Non-VTE group) were 1 to 2 matched by severity of COVID-19. Some laboratory tests were not performed on admission and comparisons were made by available data; WBC: white blood cell; CRP: C-reactive protein; IL-6: Interleukin 6; ALT: Alanine aminotransferase; AST: Aspartate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

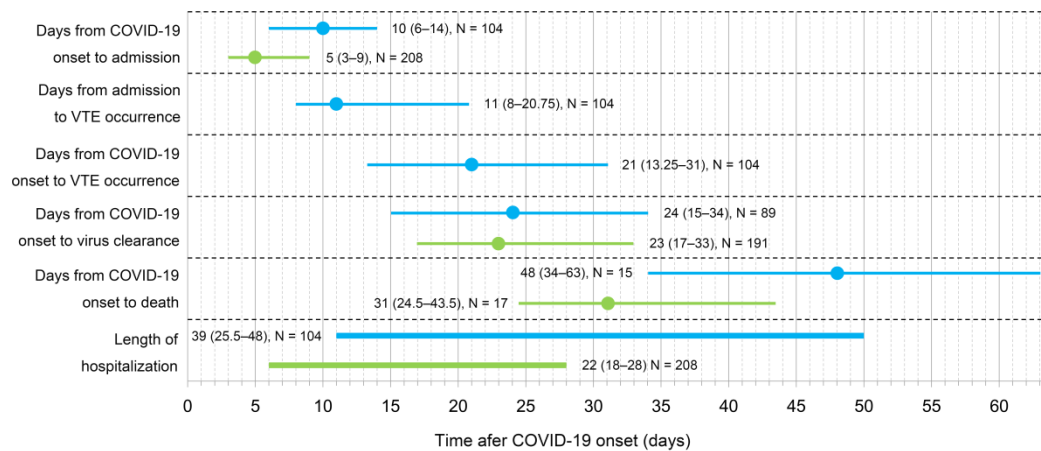
Table 2. Multivariable logistic regression analysis of factors associated with symptomatic VTE risk in COVID-19 patients

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
Hypertension	2.60 (1.60–4.21)	8.99×10^{-4}	1.62 (0.76–3.44)	0.208
Active cancer	5.30 (1.81–15.46)	0.001	6.14 (1.29–29.21)	0.022
CRP on admission	1.008 (1.000–1.015)	0.054	1.007 (0.996–1.014)	0.067
D-dimer on admission	1.26 (1.14–1.38)	5.10×10^{-6}	1.33 (1.17–1.50)	7.46×10^{-6}
DI ≥ 1.5 fold	8.32 (4.63–14.96)	9.54×10^{-14}	14.18 (6.25–32.18)	2.23×10^{-10}
Fibrinogen on admission	0.72 (0.58–0.89)	0.002	0.64 (0.49–0.83)	7.56×10^{-4}
Glucocorticoid	2.09 (1.27–3.44)	0.004	1.95 (0.86–4.44)	0.113
Central Venous Catheterization	4.64 (2.20–9.76)	5.36×10^{-5}	2.10 (0.58–7.57)	0.255

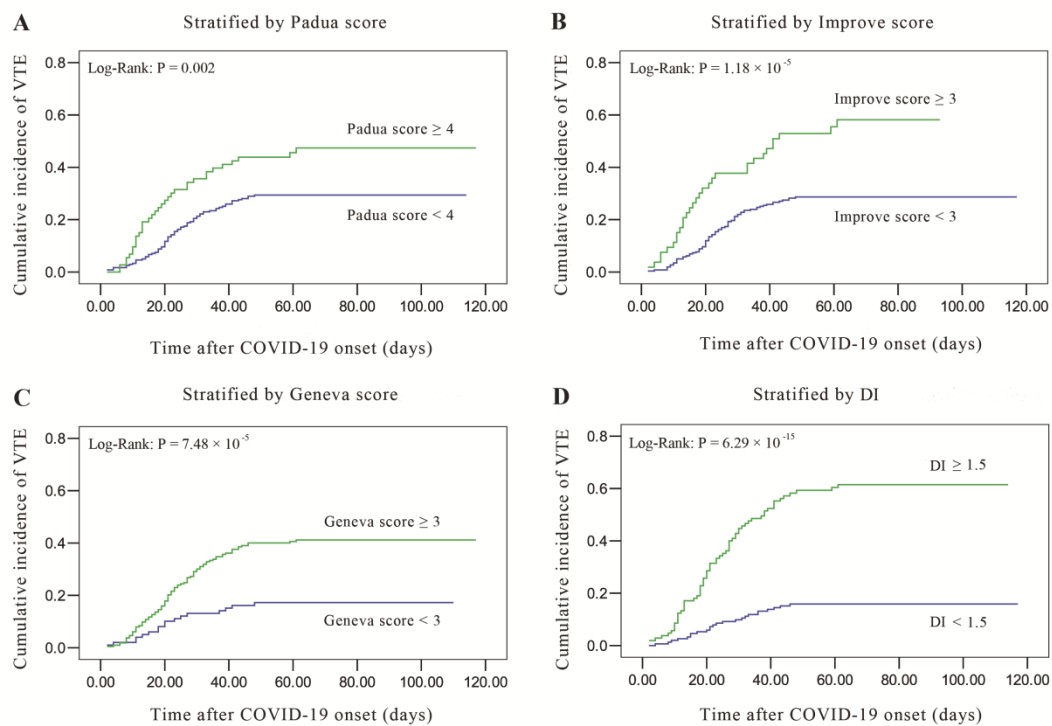
DI: D-dimer increment, defined as D-dimer level on day 4 to day 6 divided by that on day 1 to day 3 following

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, hypertension, active cancer, venous catheterization, glucocorticoid, days from COVID-19 onset to admission, CRP, D-dimer on admission, DI, Fibrinogen.

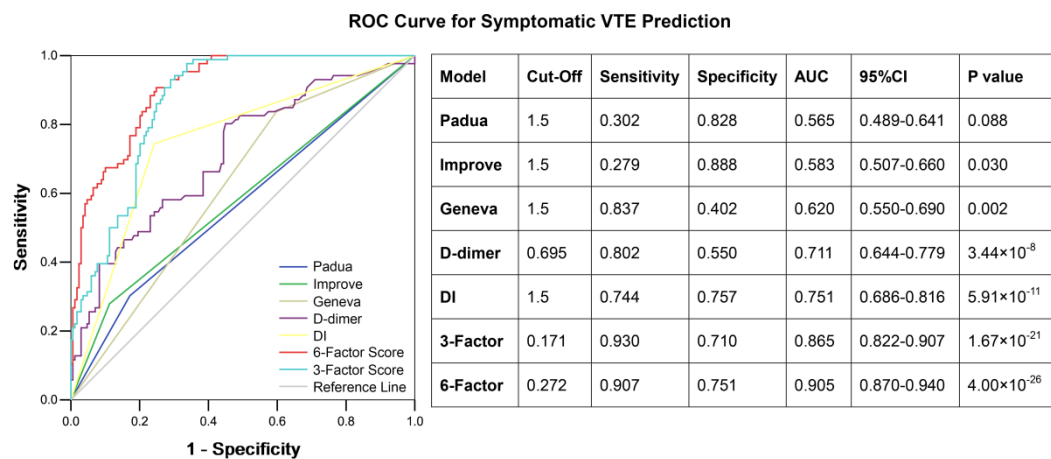




jth_15261_f2.tif



jth_15261_f3.tif



jth_15261_f4.tif