10.1161/CIRCULATIONAHA.120.047407

Extremely High Incidence of Lower Extremity Deep Venous Thrombosis in 48 Patients with Severe COVID-19 in Wuhan

Running Title: *Ren, Yan, Deng, Zhang, et al.; Incidence of DVT in Severe COVID-19*

Bin Ren, MD[1#]; Feifei Yan, PhD[1#]; Zhouming Deng, MD[1#]; Sheng Zhang, MD[1#]; Lingfei Xiao, MD[1]; Meng Wu, MD[2*]; Lin Cai, MD[1*]

[1]Department of Orthopedics, Zhongnan Hospital of Wuhan University, Wuhan, Hubei Province, China; [2] Department of Ultrasound, Zhongnan Hospital of Wuhan University, Wuhan, Hubei Province, China

[#]co-first authors

*co-corresponding authors

***Addresses for Correspondence:**
Meng Wu, MD
Department of Ultrasound
Zhongnan Hospital of Wuhan University
No.169, Donghu Road, Wuhan, Hubei Province, China
Tel: +86 027-67813127; Fax: +86 027-67813127
Email: wb000713@whu.edu.cn

Lin Cai, MD
Department of Orthopedics
Zhongnan Hospital of Wuhan University
No.169, Donghu Road, Wuhan, Hubei Province, China
Tel: +86 027- 67813116; Fax: +86 027-67813116
Email: orthopedics@whu.edu.cn

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

The COVID-19 pandemic has caused more than 4 million infections and 280000 deaths worldwide (as of May 13, 2020). The case fatality ratio (CFR) in China (as of Feb. 11, 2020) was 2.3% while that number among hospitalized critical cases was 49.0%.[1] The reason for the high CFR in critical COVID-19 patients is not completely clear. During the 2002 SARS pandemic，the incidences of deep vein thrombosis (DVT) and pulmonary embolism (PE) were 20.5% and 11.4% in autopsy cases.[2] Whether thrombosis contributes to the high mortality of COVID-19 remains unclear. As the global fight against COVID-19 continues, our study examined how prevalent thrombosis formation is for COVID-19 patients.

A cross-sectional study was carried out in two hospitals in Wuhan, China from Feb. 29, 2020 to Mar. 2, 2020. Patients were enrolled from the Intensive Care Unit (ICU) of Zhongnan Hospital of Wuhan University and Leishenshan Hospital, a newly constructed hospital designated for COVID-19 in Wuhan. Confirmed COVID-19 patients in ICU treatment (exclude patients with prior DVT or recent surgery) received compression ultrasound examinations in the lower extremities. The examinations were performed at least twice by the experienced sonographer team blinded to patient clinical history. Deep veins from the inguinal ligament to the ankle, including femoral vein, popliteal vein, posterior tibial vein, peroneal vein and intermuscular vein in the calf, were examined. Laboratory findings were gathered at the first assessment after patients were admitted to ICU. The study was approved by the Medical Ethical Committee of Zhongnan Hospital of Wuhan University (approval number 2020031). Oral consent was obtained from patients or direct relatives.

For enrolled 48 critically ill COVID-19 patients, the median age was 70 years (interquartile range IQR, 62-80) (*Table*). All but one (due to coagulation contradiction) patients received 30-40

mg of low molecular weight heparin (LMWH) (subcutaneous injection, qd) as anticoagulation. Lower extremity DVT were detected in 41 patients (85.4%), with 36 (75%) isolated distal DVT and 5 (10.4%) proximal DVT. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 16 (9-24). In terms of comorbidities, patients with hypertension, diabetes, prior cardiovascular disease and prior cerebrovascular disease were 19 (39.6%), 13 (27.1%), 11 (22.9%) and 7 (14.6%), respectively. All patients exhibited abnormal levels of inflammatory indicators, including an elevation of neutrophil count and a reduction of lymphocyte count. Of the 29 patients received mechanical ventilation, 18 had endotracheal intubation. The median level of D-dimer in no DVT, isolated distal DVT and proximal DVT patients were 0.90 (0.51-3.10), 5.31 (1.12-9.78) and 3.53 (1.87-11.64), respectively (P=0.09), which were above the superior limit. In terms of patient death, as of Apr. 16, 2020, 2 cases (28.6%) in no DVT group, 10 (27.8%) in isolated distal DVT group, and 3 (60%) in proximal DVT group died (P=0.43).

In our investigation, the overall rate of developing DVT in patients receiving ICU treatment due to COVID-19 was much higher than what was shown previously. A Prophylaxis for Thromboembolism in Critical Care Randomized Trial showed that the rates of lower extremity VTE for patients receiving dalteparin and heparin as anticoagulation were 5.1% (96/1873) and 5.8% (109/1873). Even in critically ill patients with H1N1 infection, the incidence of lower extremity DVT was 12.7% (9/71).[3]

Severe infection and inflammation might be important contributors to the development of DVT in patients with severe COVID-19. The high level of neutrophilia counts may be related to the cytokine storm induced by virus infection. Coagulation activation could also have been associated with a sustained inflammatory response.[4] Besides the infection itself, complete

bedrest, mechanical ventilation, and venous catheterization are also possible factors that contribute to the high risk of thrombosis observed in the critically ill COVID-19 patients.

We found in our study that the majority of the thrombi were detected in the distal part of the lower extremity, while only 10.4% in the proximal lower-limb deep veins. The low incidence of proximal DVT may be attributed to LMWH as prophylactic anticoagulation during hospitalization. Although the risk of PE caused by distal DVT is lower than of the proximal DVT, the literature also indicates that most of the thrombi originated from the calf tend to spread upward.[5] Therefore, the clinical relevance of distal DVT should not be ignored.

Our current study is limited by several factors. For one, we have a small sample size of critically ill COVID-19 patients. Furthermore, the cross-sectional study design limits the interpretation of a causal relation between COVID-19 and DVT.

In conclusion, we found an extremely high incidence of lower extremity DVT developed in critically ill COVID-19 patients. More attention should be paid to the prevention and clinical management of PE and DVT. Timely evaluation of DVT and preventive measures against PE are necessary for the treatment of patients with severe COVID-19.

Acknowledgments

Author Contributions:

Drs Ren and Cai had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Ren, Yan, Deng and Zhang contributed equally and share first authorship. Drs Wu and Cai contributed equally to this article.

Concept and design: F.Yan, B. Ren, M.Wu, L.Cai.

Data acquisition and analysis: S.Zhang, Z.Deng, L.Xiao.

Interpretation of the results: Z.Deng, S.Zhang

Statistical analysis: S.Zhang,L.Xiao.

Drafting of the manuscript: B. Ren, F.Yan, Z.Deng, S.Zhang

Critical revision of the manuscript and approval of the final version: B. Ren, F.Yan, Z.Deng,S.Zhang, M.Wu, L.Cai

Source of Funding

This study was supported by grant 2020YFC0845500 from the National Key Research and Development Plan of China and grant 2020020201010012 from the Wuhan Emergency Technology of COVID-19 epidemic.

Disclosures

None.

References

1. Wu Z and McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020. doi:10.1001/jama.2020.2648.[epub ahead of print].
2. Chong PY, Chui P, Ling AE, Franks TJ, Tai DYH, Leo YS, Kaw GJL, Wansaicheong G, Chan KP, Ean Oon LL, et al. Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: challenges in determining a SARS diagnosis. *Arch Pathol Lab Med*. 2004;128:195-204.
3. Obi AT, Tignanelli CJ, Jacobs BN, Arya S, Park PK, Wakefield TW, Henke PK and Napolitano LM. Empirical systemic anticoagulation is associated with decreased venous

thromboembolism in critically ill influenza A H1N1 acute respiratory distress syndrome patients. *J Vasc Surg Venous Lymphat Disord*. 2019;7:317-324.

4. Beristain-Covarrubias N, Perez-Toledo M, Thomas MR, Henderson IR, Watson SP and Cunningham AF. Understanding Infection-Induced Thrombosis: Lessons Learned From Animal Models. *Front Immunol*. 2019;10:2569.

5. Cogo A, Lensing AWA, Prandoni P and Hirsh J. Distribution of Thrombosis in Patients With Symptomatic Deep Vein Thrombosis: Implications for Simplifying the Diagnostic Process With Compression Ultrasound. *Arch Intern Med*. 1993;153:2777-2780.

Table. The results of DVT detection, clinical characteristics, comorbidities, laboratory findings and outcomes in severe COVID-19 patients.

	Total (n=48)	No DVT (n=7, 14.6%)	Isolated distal DVT* (n=36, 75%)	Proximal DVT† (n=5, 10.4%)	P value‡
Clinical characteristics, median (IQR)					
Age, y	70 (62-80)	66 (60-75)	71 (63-80)	66 (63-68)	0.59
Male, sex, n. (%)	26 (54.2)	2 (28.6)	21 (58.3)	3 (60)	0.45
BMI≥24, n. (%)	16 (33.3)	2 (28.6)	13 (36.1)	1 (20)	0.88
APACHE II	16 (9-24)	14 (7-16)	16 (10-25)	15 (9-22)	0.34
Mechanical ventilation, n. (%)	29 (60.4)	4 (57.1)	22 (61.1)	3 (60)	1.00
Endotracheal intubation, n. (%)	18 (37.5)	3 (42.9)	13 (36.1)	2 (40)	1.00
Patients with ipsilateral femoral venous catheters, n. (%)	7 (14.6)	1 (14.3)	5 (13.9)	1 (20)	0.82
Interval between COVID-19 diagnosis and DVT diagnosis, d	27 (19-34)	-	27 (21-34)	27 (19-29)	0.84
Interval between admission and DVT diagnosis, d	23 (15-29)	-	22 (15-30)	24 (15-26)	0.98
Interval between ICU admission and DVT diagnosis, d	12 (7-14)	-	12 (8-14)	7 (6-11)	0.39
Comorbidities, n. (%)					
Hypertension	19 (39.6)	3 (42.9)	13 (36.1)	3 (60)	0.70
Diabetes	13 (27.1)	2 (28.6)	10 (27.8)	1 (20)	1.00
Cardiovascular disease	11 (22.9)	1 (14.3)	8 (22.2)	2 (40)	0.71
Cerebrovascular disease	7 (14.6)	1 (14.3)	5 (13.9)	1 (20)	0.82
Laboratory findings, median (IQR)					
D-dimer, mg/L (NR:<0.55)	3.48 (0.83-9.23)	0.90 (0.51-3.10)	5.31 (1.12-9.78)	3.53 (1.87-11.64)	0.09
Fibrinogen, g/L (NR:2-4)	4.05 (3.50-4.55)	4.42 (3.93-4.89)	4.05 (3.45-4.55)	3.87 (3.50-4.23)	0.66
WBC count, ×109/L (NR:3.5-9)	8.55 (5.57-11.16)	8.97 (5.94-11.87)	7.55 (5.48-11.12)	10.40 (10.07-13.92)	0.49
Lymphocyte count, ×109/L (NR:1.1-3.2)	0.53 (0.40-0.90)	0.70 (0.36-0.90)	0.53 (0.40-0.90)	0.78 (0.51-0.85)	0.91
Neutrophil count, ×109/L (NR:1.8-6.3)	6.91 (4.00-9.78)	7.69 (4.96-9.89)	6.91 (3.83-9.53)	9.77 (8.63-12.36)	0.41

Hypersensitive troponin I, ng/mL (NR:<0.04)	0.031 (0.012-0.096)	0.020 (0.015-0.038)	0.040 (0.012-0.097)	0.030 (0.012-0.088)	0.78
Outcomes§, n. (%)					
Death	15 (31.3)	2 (28.6)	10 (27.8)	3 (60)	0.43

Abbreviation: BMI, Body Mass Index; APACHE II, Acute Physiology and Chronic Health Evaluation II; NR, normal range; WBC, white blood cell.

* Patients with thrombosis only in distal lower extremity (including posterior tibial vein, peroneal vein and intermuscular vein in the calf) were diagnosed as isolated distal DVT.

† Patients with thrombosis in femoral vein or popliteal vein were diagnosed as proximal DVT.

‡ P values indicated statistical difference between the no DVT, isolated distal DVT and proximal DVT groups. P values for categorical variables were calculated with Fisher exact test. P values for continuous variable were calculated with Kruskal-Wallis H test. P valve<0.05 was considered statistical different.

§ The outcomes were observed until Apr.16, 2020 since all the enrolled patients were either discharged or dead.