Applicability of bedside ultrasonography for the diagnosis of deep venous thrombosis in patients with COVID-19 and treatment with low molecular weight heparin

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Abstract
Purpose: The aim of this study was to evaluate the applicability of bedside ultrasonography for the diagnosis of deep venous thrombosis (DVT) in patients infected with corona virus disease 2019 (COVID-19) with and without treatment with low molecular weight heparin (LMWH).
Methods: We retrospectively analyzed the records of deceased and surviving patients in whom ultrasonography detected or not a DVT, and in whom LMWH was or not prescribed.
Results: The incidence of DVT is higher in the deceased (33/35) than in the surviving (22/46) patients. LMWH was administered in a larger proportion of surviving (18/22) than of deceased (18/33) patients. D-dimer concentrations decreased in patients who received LMWH in both groups.
Conclusions: There was a high incidence of DVT in patients who succumbed to COVID-19. Bedside ultrasonography can detect the presence of DVT as early as possible and help assessing the risk of venous thromboembolism, allowing early and reasonable use of LMWH.

KEYWORDS
bedside ultrasonography, COVID-19, deep venous thrombosis, low molecular weight heparin

1 | INTRODUCTION

Corona virus disease 2019 (COVID-19), which was first reported in Wuhan, China, in late December 2019, is currently spreading to other provinces in mainland China and to other countries around the globe, with major public health and economic consequences.1

Bedside ultrasonography can detect deep venous thrombosis (DVT) in a timely and accurate manner, which helps assessing the risk of venous thromboembolism. Bedside checks can be repeated in a short time span because there is no radiation, and can provide safe and important diagnostic information for patients with COVID-19.

Based on existing studies, the clinical manifestations and pathological results of COVID-19 infection are associated with acute respiratory distress syndrome (ARDS),2 characterized by respiratory distress and difficulty to correct hypoxemia, with a high mortality rate,3 due to excessive intra-alveolar fibrin deposition. The imbalance between activation of coagulation and inhibition of fibrinolysis in patients with ARDS leads to fibrin formation, which occurs both systemically and in the lungs and airspace.4 Nearly 20% of COVID-19 patients present severe coagulation abnormalities, which may occur in almost all of the severe and critical ill COVID-19 cases.5 The large amount of thrombin can induce the expression of E-selectin, P-selectin, and platelet-activating factors, promote the aggregation and adhesion of platelets and activated neutrophils, and strengthen the interaction between endothelial cells and neutrophils.6
ultimately promoting the further aggravation of inflammation. Therefore, the pathological setting of ARDS is the mutual promotion between hypocoagulability and inflammation. In the present study, we used bedside ultrasonographic examination to detect DVT and to assess the effect of low molecular weight heparin (LMWH), which possesses dual anticoagulant and anti-inflammatory effects.

2 | MATERIALS AND METHODS

2.1 | Patients

Our study was conducted in accordance with the principles of the Declaration of Helsinki. The locally appointed ethics committee has approved the research protocol, and informed consent has been obtained from all subjects.

Diagnosis of COVID-19 was based on a positive nucleic acid test of SARS-CoV-2, according to the Diagnosis and Treatment Plan of Novel Coronavirus Pneumonia (trial version 7th) issued by the National Health Commission of the People’s Republic of China. COVID-19 severity was assessed according to the following clinical classification: (a) light type: mild clinical symptoms, no pneumonia on imaging; (b) common type: fever, respiratory symptoms, pneumonia on imaging; (c) severe type: respiratory distress with respiratory rate ≥30/min and/or oxygen saturation ≤93% at rest and/or partial arterial pressure of oxygen/fraction of inspired oxygen ≤300 mm Hg (40 kPa); and (d) critical type: respiratory failure requiring mechanical ventilation and/or shock and/or other organ failure and admission to intensive care unit (ICU).

We performed the retrospective analysis of 81 severe and critical COVID-19 patients who had had an ultrasonographic examination performed in the ICU of Wuhan Jinyintan Hospital from January 1, 2020 to March 5, 2020. The total number of patients on ICU during the same time was 108. At the end-point date of March 5, 2020, the patients were divided into two groups: those who had succumbed to COVID-19, and the surviving patients. We did not report underlying diseases, since they have been reported to be absent in 47% of deceased patients.

2.2 | Instruments and methods

Bedside ultrasonographic examination in search of DVT was performed in patients showing lower limb swelling and/or increased D-dimer values, using a M9 ultrasound system (Mindray Medical...
International, Shenzhen, China) and a 3.0 to 13.0 MHz linear transducer. Patient’s both lower limbs were examined above and under the knee, and B-mode images were obtained in transverse and longitudinal sections. The extent of thrombosis was recorded and detailed in the patients’ medical records. The ultrasonic criteria of acute DVT were an enlarged vein, the presence of a hypoechoic intraluminal mass (Figure 1), absent or incomplete vein collapse at the compression test (Figure 2), and absence of detectable blood flow signal on color Doppler flow imaging (Figure 3). Patients with DVT were followed-up every 3 days, and administration of LMWH as well as D-dimer levels was recorded.

2.3 | Statistical analysis

SPSS 20.0 statistical software (IBM, New York, NY) was used for statistical analysis. Categorical data were expressed as number (percentage) and χ² test was used for comparisons. Continuous variables were expressed as mean ± SD and compared with paired student’s t-test. A P value <.05 was accepted as statistically significant.

3 | RESULTS

There was no difference in clinical data between deceased and surviving patients (Table 1). There were deceased 35 patients, among whom 33 had DVT of whom 18 received LMWH. There were 46 surviving patients, among whom 22 had DVT of whom 18 received LMWH. The incidence of DVT was higher in deceased than in surviving patients (P <.001). The proportion of DVT patients who did not receive LMWH was greater among deceased than among surviving patients (P <.034). DVT was detected 2.5 ± 1.5 days after admission and LMWH administrating started 4.5 ± 1.5 days after admission in the whole population sample.

D-dimer values were normally and similarly distributed in both groups. The concentration of D-dimer in the group of deceased patients with DVT treated with LMWH was 36.2 ± 4.5 and 23.9 ± 3.6 mg/L, respectively, before and after treatment (P <.05). In the group of surviving patients with DVT treated with LMWH, it was 28.4 ± 5.6 and 14.7 ± 3.0 mg/L, respectively, before and after treatment (P <.05) (Table 2).

4 | DISCUSSION

The main clinical manifestations of COVID-19 are fever, fatigue, and dry cough. Pneumonia of varying degrees may appear if the condition deteriorates. A considerable number of patients suffer from respiratory distress, with some requiring admission to the ICU due to respiratory or another other organ failure. Some patients suffer from a sudden deterioration, with significant increases in D-dimer values, and an increased risk of sudden death. Therefore, a rapid clinical alarm

| Table 2 | Deep venous thrombosis (DVT) in groups A and B |
| --- | --- | --- |
| Groups | Without DVT (n) | With DVT (n) |
| Group A (n = 35) | 2 | 33 * |
| Group B (n = 46) | 24 | 22 * |
*P < .05.

Table 1 | Patients’ clinical characteristics |
| --- | --- | --- | --- |
| N | Gender | Age (years) | Body mass index | Comorbidities | Range of deep venous thrombosis |
| --- | --- | --- | --- | --- | --- |
| | Male | Female | | | I | II | III |
| --- | n | % | n | % | n | % | n | % | n | % |
| Group A | 35 | 25 | 71.4 | 10 | 28.6 | 62.4 ± 10.2 | 22.3 ± 1.9 | 26 | 72.3 |
| Group B | 46 | 29 | 63.0 | 17 | 37.0 | 61.1 ± 14.1 | 21.8 ± 2.0 | 32 | 69.5 |
| Group A+ | 33 | 23 | 70.0 | 10 | 30.0 | 62.8 ± 10.3 | 22.6 ± 1.7 | 24 | 72.7 |
| Group B+ | 22 | 14 | 63.6 | 8 | 36.4 | 61.3 ± 13.3 | 22.0 ± 1.6 | 15 | 68.2 |

Note: Comorbidities—hypertension, hyperglycemia, coronary atherosclerotic heart disease, cerebral infarction, cerebral hemorrhage, malignant tumor, chronic obstructive pulmonary disease, etc. I: Intermuscular vein; II: Intermuscular vein, peroneal vein and posterior tibial vein; III: Intermuscular vein, peroneal vein, posterior tibial vein, popliteal vein and above.
Changes of D-dimer before and after low molecular weight heparin (LMWH) treatment in groups A+ and B+

| Groups | Before (mg/L) | After (mg/L) | Percentual decrease (%) |
|--------|---------------|--------------|-------------------------|
| The D-dimer of patients in group A+ treated with LMWH (n = 18) | 36.21 ± 4.48 | 23.87 ± 3.55 \* | 36.73 ± 8.24 |
| The D-dimer of patients in group B+ treated with LMWH (n = 18) | 28.35 ± 5.59 | 14.68 ± 2.97 \* | 43.15 ± 9.58 |

\* P < .05 compared with before treatment.
CONCLUSION
The prevention and early detection of DVP are particularly important for the comprehensive management of COVID-19 patients. Bedside ultrasonography can detect DVT early and help assessing the risk of pulmonary embolism. On this basis, prophylactic or therapeutic LMWH treatment should be administered generously.

CONFLICT OF INTEREST
The authors declare no conflicts of interest.

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