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DOI: 10.5582/bst.2022.01225

Heparin therapy in COVID-19: Call for randomized controlled trials (RCTs)

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SUMMARY Coronavirus disease 2019 (COVID-19) is associated with increases in abnormal coagulation, and particularly D-dimer (D-D) levels. Heparin therapy has been recommended as pharmacologic thromboprophylaxis in patients hospitalized with COVID-19; however, data on its efficacy are lacking. The current study retrospectively analyzed changes in blood coagulation and the impact of heparin therapy. Medical records of 593 patients with confirmed COVID-19 were collected. On admission, elevated fibrinogen (Fg) levels were noted in with 42.2% (250/593) of patients, followed by increases in D-D (28.5%) and a prolonged prothrombin time (PT) (23.9%). Patients with severe/critical COVID-19 had a higher proportion of abnormal coagulation parameters than patients with mild/ordinary COVID-19. Dynamic changes in coagulation parameters were plotted on timeline charts for 97 patients with COVID-19 after heparin treatment. These changes, when combined with Fg, PT, D-D, and other indicators, may provide a relatively comprehensive description of coagulation abnormalities. Heparin seems to be important in the treatment of patients with COVID-19 based on the current findings. The efficacy of heparin in the treatment of COVID-19 should be confirmed by randomized controlled trials (RCTs) as soon as possible.

Keywords coronavirus infection, COVID-19, blood coagulation, heparin, fibrin degradation products

Coronavirus disease 2019 (COVID-19) has been reported in Wuhan since December 2019 and has since spread throughout China and around the world (*1,2*). Despite this immense global burden, no pharmacologic therapies have definitively proven beneficial. Around the world, researchers have been trying to understand the disease manifestations in order to develop both prognostic and therapeutic tools.

Abnormal coagulation has been noted clinically in patients with COVID-19. A severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection might lead to an increased risk of both arterial and venous thrombosis, which may be attributed to the widespread endothelial cell damage caused either directly by the virus itself or indirectly by the burst of proinflammatory cytokines (*3-7*). Monitoring coagulation parameters in patients with COVID-19 is crucial to analyzing the overall severity of the disease. D-dimer (D-D) levels in particular are prognostically significant for mortality in COVID-19 (*6,7*). The degree of increased fibrin degradation products (FDP) and D-D in severe/critical ill patients is significantly higher than in patients with milder disease and who did not die (*8,9*). However, there is no consensus on the difference in coagulation in patients with COVID-19 of varying degrees of severity. Increased attention is being paid to the impact of heparin treatment on patients with COVID-19. Several studies have reported the use of higher doses of heparin to decrease mortality in patients with COVID-19 and additional risk factors. However, anticoagulant therapy mainly with low molecular weight heparin did not appear to improve clinical outcomes in several patients with severe COVID-19 (*10-14*) (Supplemental Table S1, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=105*). The American Society of Hematology recommended pharmacologic thromboprophylaxis in patients hospitalized with COVID-19 (unless contraindicated) and suggested the administration of therapeutic doses when thrombosis is proven or highly suspected based on clinical findings (*13*). Nonetheless, the optimal preventive strategy in terms of the intensity of anticoagulation for patients with COVID-19 remains to be determined.

In order to answer these questions, the current authors conducted a retrospective study to analyze the relationship between coagulation parameters in 593

patients with COVID-19 of varying severity. Moreover, the dynamic profile of coagulation parameters was determined in patients with COVID-19 receiving heparin therapy. Those parameters may have prognostic value and may indicate important therapeutic targets.

This study collected the medical records of patients (non-pregnant women, over the age of 18) with COVID-19 confirmed by RT-PCR seen at the Shanghai Public Health Clinical Center in Shanghai from January 20, 2020 to May 20, 2020. Patients were categorized into two groups according to disease severity: a group with mild/ordinary COVID-19 and a group with severe/critical COVID-19. The categorization of COVID-19 was according to the World Health Organization's interim guidance (*15*). This study was approved by the Ethics Committee of the Shanghai Public Health Clinical Center (approval no. YJ-2020-S131-01). Informed consent was obtained from all participants.

Patients with COVID-19 were treated with prophylactic doses of heparin depending on their D-D or FDP levels. Patients with D-D > 0.5 mg/L and FDP > 5 mg/L were given 3,000 – 5,000 U of low-molecular weight heparin by subcutaneous injections to prevent thrombosis. Patients with D-D > 5 mg/L were given 6,000 – 8,000 U of low-molecular weight heparin. Patients with D-D > 5 mg/L and FDP > 10 mg/L were given 12,500 – 20,000 U of unfractionated heparin daily by syringe pumps to alleviate abnormal coagulation. The heparin was administered daily for three to five days.

Demographic data, the medical history, clinical characteristics, and laboratory coagulation parameters of the patients on admission were obtained. The coagulation profile was assessed using the following parameters: fibrinogen (Fg), activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), D-D, and FDP. For patients who received heparin after admission, data on coagulation parameters (PT, APTT, FDP, D-D) were collected on the day that heparin treatment started to provide a baseline for comparison, and that point was designated Measuring Point 0 (MP 0). In addition, the endpoints at MP 3 were the measurements following heparin treatment. The two measuring points (MP 1 and MP2) were chosen in accordance with time and were evenly distributed between the two points above when blood was collected.

The study included 593 patients with confirmed COVID-19. Demographic characteristics of and coagulation parameters in the sample population are shown in Table 1. More than half of the patients were male (55,5%), and 103 (17.4%) received heparin. Mean age was 42.6-years old (± 16.9). In the 593 patients, increased Fg levels were noted in 42.2% (250/593), increased D-D levels were noted in 28.5%, and prolongation of PT was noted in 23.9%. A decreased platelet count was noted in only 3.2% (19/593) of patients. The APTT was prolonged in 108 patients (18.2%), and it was longer than 10 seconds in 10 of those patients.

Also shown in Table 1 are the differences in parameters between patients with severe/critical COVID-19 and those with mild/ordinary COVID-19. All of the median values for PLT, PT, APTT, FDP, D-D, and TT in the two groups were within the normal range. Coagulation parameters (APTT, Fg, FDP, D-D) except for TT differed significantly in the group with severe/critical COVID-19 and the group with mild/ordinary COVID-19 ($P < 0.05$). Patients with severe/critical COVID-19 had more abnormal coagulation parameters than patients with mild/ordinary COVID-19, including prolonged PT, prolonged APTT, Fg > 4g/L, FDP > 5 mg/

Table 1. Demographic characteristics of and coagulation parameters in patients with COVID-19 on admission

Parameters	Normal range	Total (n = 593)	Severe/Critical (n = 32)	Mild/Ordinary (n = 561)	P
Age (years)		42.6 ± 16.9	62.3 ± 15.7	41.4 ± 16.3	< 0.001
Sex (male/female)		329/264	25/7	304/257	0.008
Heparin treatment		103	29	68	< 0.001
On admission	125-350				
PLT	11-13.7	202 (157-251)	167.5 (130.5-203.3)	206 (160.5-253.0)	0.002
PT	31.5-42.5	13.3 (12.9-13.7)	13.7 (12.9-14.4)	13.3 (12.9-13.7)	0.036
APTT	2.0-4	38.2 (35.4-41.3)	42.1 (36.8-48.7)	38.1 (35.4-40.9)	< 0.001
Fg	0-5	3.7 (3.0-4.6)	4.62 (4.03-5.27)	3.68 (3.00-4.57)	< 0.001
FDP	0-0.5	0.65 (0.22-1.36)	1.96 (1.02-4.04)	0.62 (0.22-1.33)	< 0.001
D-D	14-21	0.35 (0.23-0.55)	0.87 (0.45-1.50)	0.33 (0.23-0.53)	< 0.001
TT		16.4 (15.7-17.1)	16.5 (15.9-18.1)	16.4 (15.7-17.1)	0.089
Coagulation					
PLT < 100×10^9/L		19 (3.2)	2 (6.2)	17 (3.0)	0.270
PT Increased		142 (23.9)	15 (46.9)	127 (22.6)	0.002
APTT Increased		110 (18.5)	15 (46.9)	95 (16.9)	< 0.001
Fg > 4 g/L		250 (42.2)	25 (78.1)	225 (40.1)	< 0.001
FDP > 5 mg/L		18 (3.0)	5 (15.6)	13 (2.3)	0.002
DD > 0.5 mg/L		169 (28.5)	22 (68.8)	147 (26.2)	< 0.001

PLT, platelet count; PT, prothrombin time; APTT, activated partial thromboplastin time; Fg, fibrinogen; FDP, fibrin degradation products; D-D, D-dimer; TT, thrombin time;

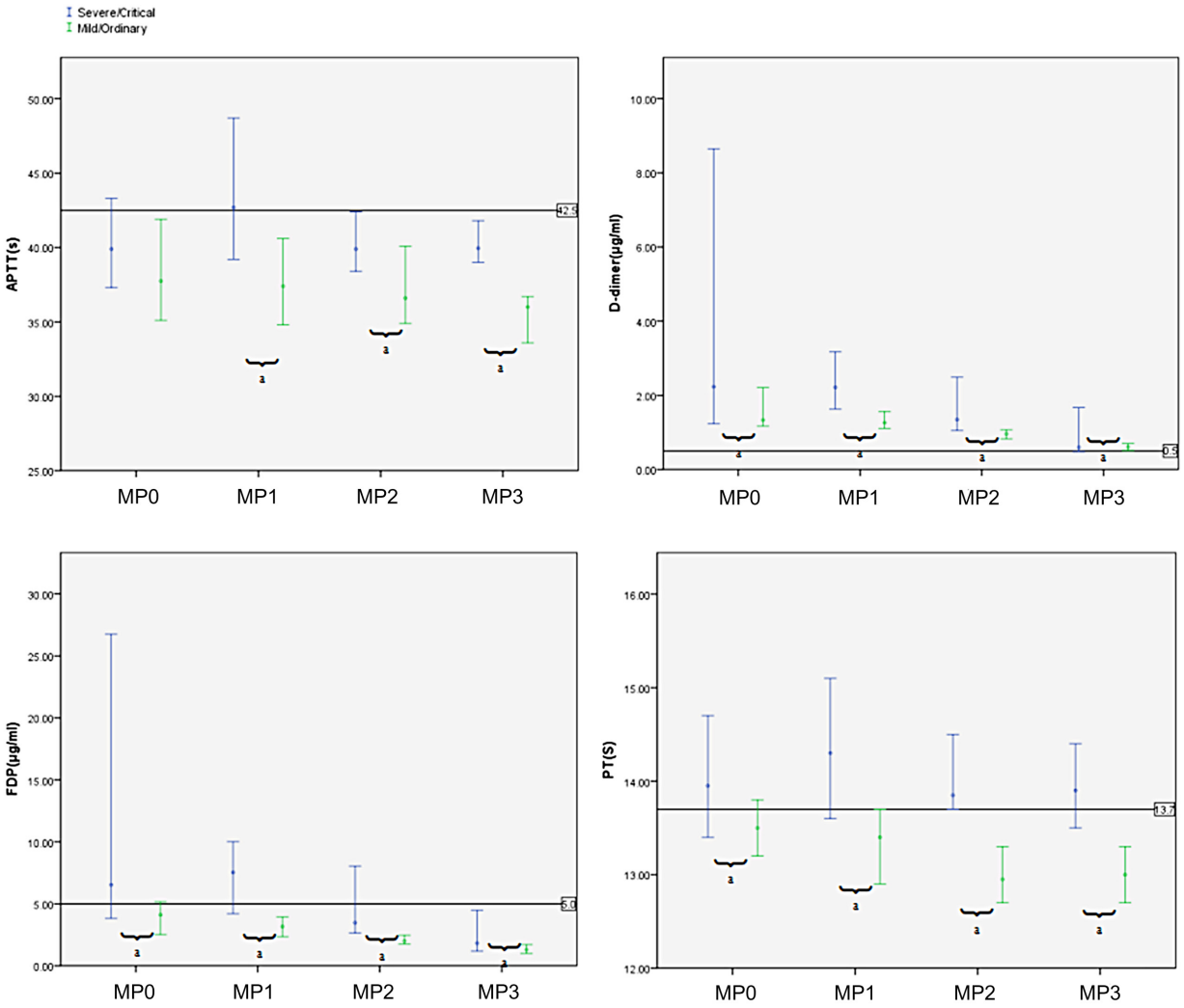

Figure 1. Dynamic profile of coagulation parameters in patients with COVID-19. Timeline charts illustrate changes in coagulation parameters in 97 patients with COVID-19 (29 patients with severe/critical COVID-19 and 68 patients with mild/ordinary COVID-19) after heparin treatment. The error bars indicate medians and 25% and 75% percentiles. The horizontal lines indicate the upper normal limits of PT, APTT, D-D, and FDP. [a]$P < 0.05$ for severe/critical versus mild/ordinary COVID-19.

L, and D-D > 0.5 mg/L.

A total of 103 patients (17.3%) received heparin therapy; 29 had severe/critical COVID-19 and 68 had mild/ordinary COVID-19. Timeline charts illustrate the dynamic changes in coagulation parameters in the 97 patients with COVID-19 after heparin treatment, as determined at 4 measuring points (MP 0, MP 1, MP 2, and MP 3) (Figure 1). As a result of heparin therapy, the coagulation parameters (D-D, FDP, PT, and APTT) decreased rapidly in both groups, including patients with severe/critical and those with mild/ordinary COVID-19, which indicated the effect of heparin therapy, despite increased coagulation parameters in patients with severe/critical COVID-19.

Patients with COVID-19 are prone to venous, cerebrovascular, and coronary thrombi, and this is particularly true in those with severe disease (*3,16*). Abnormalities in a given coagulation parameter might have limited ability to predict venous thrombosis in people infected with SARS-CoV-2. The complete coagulation parameters in patients with COVID-19 cases might have prognostic value and indicate important therapeutic targets.

An acute phase reactant protein, Fg is an important component of the coagulation cascade that can lead to hypercoagulability and thrombosis if increased. Moreover, it can significantly increase in patients with early-stage mild or critical COVID-19 and significantly decrease in patients with late-stage critical COVID-19 (*17*). In the patients in the current study, 42.2% had increased Fg levels upon admission. This was the most common abnormality. In line with previous studies, abnormal Fg levels were significantly higher in patients with severe/critical COVID-19 than in those with mild/ordinary COVID-19 (*4,17*).

In 28.5% of patients, levels of D-D were elevated on admission, suggesting that the fibrinolytic system and thrombogenesis were active. D-D levels are elevated in patients who are likely to have COVID-19, so clinicians need to be aware of the potential for thrombosis in these

patients. In addition, D-D levels were slightly elevated in most patients, and that level was over 5 mg/L in just 1.85%, suggesting that the likelihood of thrombosis formation is limited and that disseminated intravascular coagulation (DIC) did not develop. Alternatively, this complication might be self-limited by a timely diagnosis and treatment or by the body's own resistance. D-D levels differed significantly in patients with critical COVID-19 and patients with mild COVID-19; this indicated that conventional coagulation parameters during the course of COVID-19 were significantly associated with disease prognosis. Some patients with critical COVID-19 deteriorated suddenly during treatment, suggesting they may be at greater risk of thrombosis (*3,4*).Combining PT, APTT, and other indicators can provide a comprehensive description of coagulation abnormalities. Therefore, these factors closely need to be monitored closely. If a serious situation arises, medical personnel can immediately take appropriate measures.

Several studies have indicated that a therapeutic dose of heparin improves clinical outcomes in patients with mild or ordinary COVID-19 on hospital admission (*10,11,17*). However, use of anti-thrombotics to improve outcomes in patients with severe COVID-19 is controversial (*10,11,16*). In the current study, the four coagulation indicators (D-D, FDP, PT, and APTT) were significantly higher in patients with severe/critical COVID-19 than in patients with mild/ordinary COVID-19 at the same measuring point, possibly because tissue damage has already occurred. Patients with severe/critical COVID-19 were not able to recover to the same degree as those with mild/ordinary COVID-19 by the end of heparin treatment. To some extent, this finding reflects the importance of heparin in the early treatment of patients with COVID-19. Notably, the coagulation parameters in most patients returned to normal - D-D, FDP, PT, and APTT in particular - after the intervention with heparin. These parameters might have the potential to guide treatment and evaluate prognosis. Heparin treatment should be initiated as soon as possible in patients with COVID-19 who meet the corresponding criteria for receiving heparin. A limitation of the current retrospective study is that it was unable to establish a direct causal connection. Randomized controlled trials (RCTs) should be conducted as soon as possible to confirm the efficacy of heparin in treating COVID-19 and to explore its appropriate timing and dose.

Acknowledgements

The authors wish to thank all of the participants who participated in this study.

Funding: This study was supported by grants from the Shenzhen Project to Fund Medical and Health Care by Noted Physicians, Hospitals, and Clinics (grant number: SZSM201512029); the National Science Foundation of China (grant number: 92169119), the Program to Produce Academic Personnel of the Shanghai 3-year Action Plan to Create a Public Health System (2020-2022)-Health Education and Health Communication (grant number: GWV-10.1-XK02), the Wuxi Health Committee's Program to Fund Talented Young and Middle-aged Researchers (BJ2020091), and a Project funded by the Shenzhen Third People's Hospital (grant numbers: G2021027 and G2022062).

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received May 23, 2022; Revised July 13, 2022; Accepted July 27, 2022.

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Released online in J-STAGE as advance publication July 30, 2022.