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Prominent changes in blood coagulation of patients with SARS-CoV-2 infection

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Abstract

Background: As the number of patients increases, there is a growing understanding of the form of pneumonia sustained by the 2019 novel coronavirus (SARS-CoV-2), which has caused an outbreak in China. Up to now, clinical features and treatment of patients infected with SARS-CoV-2 have been reported in detail. However, the relationship between SARS-CoV-2 and coagulation has been scarcely addressed. Our aim is to investigate the blood coagulation function of patients with SARS-CoV-2 infection.

Methods: In our study, 94 patients with confirmed SARS-CoV-2 infection were admitted in Renmin Hospital of Wuhan University. We prospectively collect blood coagulation data in these patients and in 40 healthy controls during the same period.

Results: Antithrombin values in patients were lower than that in the control group ($p < 0.001$). The values of D-dimer, fibrin/fibrinogen degradation products (FDP), and fibrinogen (FIB) in all SARS-CoV-2 cases were substantially higher than those in healthy controls. Moreover, D-dimer and FDP values in patients with severe SARS-CoV-2 infection were higher than those in patients with milder forms. Compared with healthy controls, prothrombin time activity (PT-act) was lower in SARS-CoV-2 patients. Thrombin time in critical SARS-CoV-2 patients was also shorter than that in controls.

Conclusions: The coagulation function in patients with SARS-CoV-2 is significantly deranged compared with healthy people, but monitoring D-dimer and FDP values may be helpful for the early identification of severe cases.

Keywords: blood coagulation; Corona Virus Disease 2019; SARS-CoV-2.

Introduction

Since 2 months ago, a new type of pneumonia now defined as coronavirus disease 2019 (COVID-19) has been widely spreading in China and even in many foreign countries. In December 2019, it started with a cluster of patients with pneumonia of no identifiable cause connected to a seafood wholesale market in Wuhan, China [1]. This phenomenon immediately attracted the attention of experts all over the country. Rapidly, a novel coronavirus was isolated from human airway epithelial cells, and it was named severe acute respiratory syndrome (SARS)-CoV-2 [1]. In addition to SARS-CoV-2, there were six other coronaviruses that could generate human infections worldwide [2]. The growing number of infected patients in many Chinese cities, as well as in other countries around the world, clearly reflects the high risk of human-to-human transmission [3]. A recent article also reported that women infected with SARS-CoV-2 during late pregnancy are unlikely to promote vertical transmission [4]. After SARS-CoV [5–8] and Middle East respiratory syndrome coronavirus (MERS-CoV) [9, 10], SARS-CoV-2 is the third of such viruses to threat public health around the world during the past two decades [11, 12]. Compared with SARS and MERS, the disease severity seems relatively mild [13].

Albeit a good knowledge has been gained on clinical features of COVID-19, less clear information has been provided on laboratory abnormalities and, especially, on the potential derangement of hemostasis tests. Therefore,

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the aim of this study was to explore the significance of the difference among some blood coagulation parameters between patients with confirmed SARS-CoV-2 infection and healthy controls, further addressing their role in predicting disease progression.

Materials and methods

Patients

A total number of 94 patients diagnosed with SARS-CoV-2 in Renmin Hospital (Wuhan University, China) from January 31 to February 10, 2020, were included as the case group along with 40 healthy control people. All patients were diagnosed according to the "pneumonia diagnosis protocol for novel coronavirus infection (trial version 5)." The control group was subjected to the same tests as the experimental group, including clinical examination, computed tomography (CT), and real-time reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2, all tests resulting negative. The SARS-CoV-2 group was divided into three additional subgroups according to new pneumonia diagnosis and treatment of COVID-19 (trial version fifth).

Data collection

Data on coagulation parameters were obtained from all 94 confirmed SARS-CoV-2 infection patients as well as from 40 healthy controls. Coagulation tests, which included activated partial thromboplastin time (APTT), antithrombin (AT), fibrin/fibrinogen degradation products (FDP), fibrinogen (FIB), prothrombin time (PT), international normalized ratio (INR), prothrombin time activity (PT-act), and thrombin time (TT), were performed using a Sysmex CS5100 automatic coagulation analyzer (Japan) and proprietary reagents. These confirmed patients were subjected to a broad series of investigations, including clinical examination, laboratory tests, chest x-rays, and real-time reverse transcriptase polymerase chain reaction (rRT-PCR) for SARS-CoV-2 performed according to the World Health Organization guidelines [14, 15] and using a SARS-CoV-2 detection kit (Bioperfectus, Taizhou, China). Clinical and laboratory information was collected during routine clinical work, and the study was approved by the Ethics Committee and Institutional Review Board of the Renmin Hospital of Wuhan University (certificate no. WDRY2020-K066).

Statistical analysis

SPSS software version 25.0 was used for statistical analysis. All measurements were expressed as mean and standard deviation. Test or variance analyses were used to analyze differences among groups. According to the homogeneity of variance, multiple comparisons were conducted by using the Bonferroni test and the Tamhane test, respectively. In all tests, $p < 0.05$ was defined as statistically significant.

Results

Clinical characteristics

Among all COVID-19 patients, 48 (51%) were males and 46 (49%) were females. In the control group, 28 subjects (70%) were males and 12 (30%) females. The age was not significantly different among groups. None of the subjects of our study population was taking anticoagulant drugs before blood drawing.

Coagulation function of SARS-CoV-2 patients and control

The differences of hemostasis function between patients with SARS-CoV-2 and healthy controls encompassed the assessment of nine parameters, as earlier indicated. Compared with healthy controls, the AT values were found to be lower in COVID-19 patients (85% vs. 99%; $p < 0.001$). The PT-act was found to be lower in patients than that in controls (81% vs. 97%; $p < 0.001$), whereas the values of D-dimer (10.36 vs. 0.26 ng/L; $p < 0.001$) and FDP (33.83 vs. 1.55 mg/L; $p < 0.001$) were higher in patients than those in controls. Notably, FIB values in SARS-CoV-2 patients were also higher than those in the control group (5.02 vs. 2.90 g/L; $p < 0.001$). Unlike these tests, no other differences could be observed in values of APTT, PT, PT-INR, and TT between the two groups ($p > 0.05$) (Table 1).

Coagulation function of three subgroups patients and control

The entire cohort of SARS-CoV-2 patients was then divided into three groups, namely exhibiting an ordinary, severe, or critical clinical phenotype. The coagulation parameters in these three groups are shown in Table 2. No significant difference could be observed for APTT, PT, and PT-INR between three subgroups and the control group ($p > 0.05$). The values of AT in the three groups of patients were lower than those in the control group, but no significant difference could be found in the three COVID-19 subgroups. As concerns D-dimer, severe disease patients displayed considerably higher values than those in the control group. Multiple analyses allowed us to define that D-dimer values were significantly different between mild (i.e. ordinary) and severe disease groups. Similar findings emerged for FDP values, which were found to be higher in mild and severe patient groups than those in the healthy controls,

Table 1: Comparison of coagulation function between SARS-CoV-2 patients and control group ($\bar{x} \pm s$).

Parameters	SARS-CoV-2 patients (n = 94)	Controls (n = 40)	t-test	p-value
APTT, s	29.01 ± 2.93	28.65 ± 3.03	0.648	0.518
AT, %	85.46 ± 14.43	98.82 ± 12.91	−5.054	<0.001
D-dimer, mg/L	10.36 ± 25.31	0.26 ± 0.18	3.871	<0.001
FDP, mg/L	33.83 ± 82.28	1.55 ± 1.09	3.803	<0.001
FIB, g/L	5.02 ± 1.53	2.90 ± 0.53	11.88	<0.001
PT, s	12.43 ± 1.00	12.08 ± 5.28	0.419	0.678
PT-INR	1.07 ± 0.09	1.05 ± 0.49	0.244	0.809
PT-act, %	80.59 ± 12.77	96.86 ± 26.92	−3.651	0.001
TT, s	18.00 ± 1.80	18.34 ± 0.92	−1.495	0.137

The coagulation parameters were compared using Student's t-test. APTT, activated partial thromboplastin time; AT, antithrombin; FDP, fibrin/fibrinogen degradation products; FIB, fibrinogen; PT, prothrombin time; INR, international normalized ratio; PT-act, prothrombin time activity; TT, thrombin time.

Table 2: Comparison of coagulation function between different degree of SARS-CoV-2 patients and control group ($\bar{x} \pm s$).

Parameters	SARS-CoV-2 patients			Controls (n = 40)
	Ordinary (n = 49)	Severe (n = 35)	Critical (n = 10)	
APTT, s	28.56 ± 2.66	29.53 ± 3.48	29.41 ± 1.68	28.65 ± 3.03
AT, %	85.98 ± 13.03[c]	85.59 ± 16.13[c]	82.44 ± 15.89[b]	98.82 ± 12.91
D-dimer, mg/L	2.14 ± 2.88[c]	19.11 ± 35.48[b]	20.04 ± 32.39	0.26 ± 0.18
FDP, mg/L	7.92 ± 11.38[c]	60.01 ± 108.98[b]	69.15 ± 129.19	1.55 ± 1.09
FIB, g/L	5.10 ± 1.16[c]	4.76 ± 1.7301[c]	5.59 ± 2.26[b]	2.90 ± 0.53
PT, s	12.20 ± 0.88	12.65 ± 1.13	12.80 ± 0.87	12.08 ± 5.28
PT-INR	1.04 ± 0.08	1.09 ± 0.10	1.10 ± 0.08	1.05 ± 0.49
PT-act, %	83.56 ± 12.20[b]	77.90 ± 13.60[c]	75.5 ± 9.32[a]	96.86 ± 26.92
TT, s	17.93 ± 1.19	18.49 ± 2.35	16.54 ± 1.24[c]	18.34 ± 0.92

Multiple comparative analysis showed that D-dimer and FDP values were significantly different between ordinary and severe patients ($p < 0.05$ and $p < 0.05$, respectively). [a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$. APTT, activated partial thromboplastin time; AT, antithrombin; FDP, fibrin/fibrinogen degradation products; FIB, fibrinogen; PT, prothrombin time; INR, international normalized ratio; PT-act, prothrombin time activity; TT, thrombin time.

whereas severe diseased patients also exited higher values than patients with milder disease. Notably, all COVID-19 patients had also higher FIB values than healthy people, but FIB values did not differ in patients belonging to these three subgroups. The clotting time of PT-act was found to be lower in all three COVID-19 patient groups compared with healthy controls, but no significant differences were found among the three COVID-19 subgroups. Finally, TT values were significantly shorter in patients with critical COVID-19 compared with the control group.

Discussion

The number of patients with COVID-19 is unfortunately exhibiting a constant progression [1, 16, 17]. As more clinical information accumulates on SARS-CoV-2 infection, the feature of COVID-19 partially overlaps with that of SARS [13]. Although the mortality of this new syndrome seems relatively low, patients with severe or critical disease are at high risk of developing acute respiratory distress syndrome (ARDS) and to be admitted to the intensive care unit (ICU). Therefore, accurate diagnosis and monitoring of disease progression from the early stages is essential to improve the otherwise unfavorable clinical outcomes.

In our study, AT values in COVID-19 patients were found to be lower, whereas those of D-dimer, FDP, and FIB were found to be higher than in a control healthy population, thus confirming earlier similar findings [18]. This evidence would imply that routine hemostasis tests may be additional useful tools for improving early diagnosis. Even more importantly, the gradual progression

of disease severity was mirrored by increasing values of D-dimer and FDP. Altogether, these findings would support the notion that the development of consumption coagulopathy, especially of disseminated intravascular coagulation (DIC), may be not so rare in patients with SARS-CoV-2 infection and that its onset may then influence unfavorably the clinical course. We hence reinforce the suggestion that routine monitoring of hemostasis tests may be a useful aid for establishing an accurate therapeutic strategy and preventing disease progression, up to death [19].

Overall, our results are also in keeping with those of previous studies. It has in fact been reported that coagulation is activated and accelerated in response to several infections because this mechanism may enhance the physiological response [20–23]. Coagulation has also an immune function, which can be hence considered another line of defense against severe infections [24]. Therefore, although we find it reasonable that hemostasis is deranged in patients with COVID-19, an excessive consumption of coagulation factors then leads to the risk of developing DIC, which has an obvious negative impact on the prognosis [25, 26]. In conclusion, blood coagulation in COVID-19 patients seems to be clearly deranged compared with a healthy control population. More specifically, D-dimer, FDP, and FIB values were found to be significantly increased, whereas AT was found to be significantly lower. Even more importantly, D-dimer and FDP were found to be especially predictive of disease progression; hence, their routine monitoring would appear advisable in patients with COVID-19.

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