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A Retrospective Analysis of the Coagulation Dysfunction in COVID-19 Patients

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Abstract

To discuss the coagulation dysfunction in COVID-19 patients and to find new biomarkers to separate severe COVID-19 patients from mild ones. We use a retrospective analysis of 88 COVID-19 patients, and compare the coagulation function between severe and mild groups. We found the prothrombin time (PT), thrombin time (TT), D-dimer were significantly higher in the severe group ($P < 0.05$), and the highest area under the curve (AUC) is 0.91 for D-dimer, while the AUC of PT and TT were 0.80 and 0.61 respectively. We identified that D-dimer has a better value in predicting patients who are likely to develop into severe cases, with the sensitivity and specificity were 84.4% and 88.8%, respectively. D-dimer may be a good biomarker to separate the severe COVID-19 patients from the mild ones.

Keywords

biomarkers, coagulation, blood coagulation factors

Background

Since December 2019, an outbreak of coronavirus disease 2019 in Wuhan, has spread throughout the world.[1] Till now, about 19 million COVID-19 cases leading to 713,829 deaths have been reported worldwild, including 89,026 cases and 4,687 deaths in China. The pathogen has been identified as a β-coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and this virus can spread from human to human(SARS-CoV-2).[2] As a single-stranded RNA virus, SARS-CoV-2 infection may present with various manifestations, such as fever, dry coughing, fatigue, shortness of breath and some of patients may develop into respiratory failure or even death. Old-aged patients with underlying medical conditions such as hypertension, diabetes, cardiovascular and cerebrovascular diseases are more likely to develop into sever cases which are associated with worse outcome.[3-5] So far, neither specific therapeutic drug nor preventive vaccine is available and treatment has been limited to supportive measures.[4] Although fast and accurate identification of the patients who will develop into severe condition is important in patient management, no specific biomarker has been identified so far. SARS-CoV-2 infection may cause coagulation dysfunction but the results are quite varied. Results from a retrospective analysis of 99 COVID-19 patients revealed that 16% of the patients had an reduced activated partial thromboplastin time (APTT) while 6% showed an extended APTT, 30% presented with a shortened PT, and 5% of extended PT.[6] Another study showed that 4 of 7 COVID-19 patients had an extended PT and 4 were diagnosed with Disseminated Intravascular Coagulation (DIC).[7] Interestingly, D-dimer and extended PT were identified in 99 severe COVID-19 patients who received low molecular weight heparin treatment for 7 days or longer.[8] In line with this observation, 4 of 30 medical workers infected with SARS-CoV-2, D-dimer was also significantly increased.[9] COVID-19 patients with D-dimer levels $\geq$2.0 μg/ml had a higher incidence of mortality when compared to those with D-dimer levels <2.0 μg/ml.[10] A retrospective analysis also found that fibrinogen (Fib) and D-dimer

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were higher while PLT count, Alb were much lower in severe patients.[11] In this study, we performed a retrospective analysis on the coagulation function in mild and severe COVID-19 patients, trying to identify a biomarker that can be used to predict the severity of this pandemic disease.

Methods

We have retrospectively analyzed 58 mild and 30 severe COVID-19 patients who were confirmed to have SARS-CoV-2 infection by RNA detection and were enrolled in Jingzhou central hospital, Hubei Province from February 1 to March 6, 2020. The diagnosis and classification of COVID-19 were based on the guidelines on the novel coronavirus-infected pneumonia diagnosis and treatment (trial version 7) issued by the National Health Commission of China. COVID-19 patients who had one of the following conditions at the time of admission were classified as severe cases: (I) respiratory distress ($\geq$30 breaths/min); (II) oxygen saturation at rest $\leq$93%; (III) PaO2/FiO2 ratio $\leq$300 mmHg; (IV) lung imaging progress >50% during 24-48 hours.

The coagulation tests from plasma samples were performed on ACL TOP automatic coagulation analyzer (Instrumentation Laboratory, IL, USA) following manufacturer's recommended procedures. The test items include PT, APTT, FIB, TT, and D-dimer.

The Graphpad Prism 5.0 was used for statistical data analysis. The independent sample t-tests were used to compare the differences between the mild and severe groups. The receiver operating curve (ROC) and the area under the curve(AUC) were calculated to compare each parameter. A *P*-value of <0.05 was considered statistically significant.

Results

In this retrospective study, we analyzed and compared the coagulation function of COVID-19 mild (n = 58) and severe(n = 30) patients. As shown in Table 1, there was no statistical difference in APTT, Fibrinogen (Fib) between the 2 groups.

Table 1. Coagulation Parameters of COVID-19 Patients Between Mild and Severe Groups.

Parameters	Mild group	Severe group	*P* value
PT(S)	11.34 ± 1.35	13.98 ± 2.97	<0.001
APTT(S)	30.39 ± 4.29	32.34 ± 7.18	0.112
Fib(g/L)	4.56 ± 1.53	4.25 ± 1.28	0.46
TT(S)	16.04 ± 1.76	17.33 ± 3.00	0.015
D-dimer(ng/mL)	575.53 ± 845.85	3258.36 ± 3639.27	0.014

Abbreviations: PT, prothrombin time APTT, activated partial thromboplastin time; Fib, fibrinogen; TT, thrombin time; S, seconds.

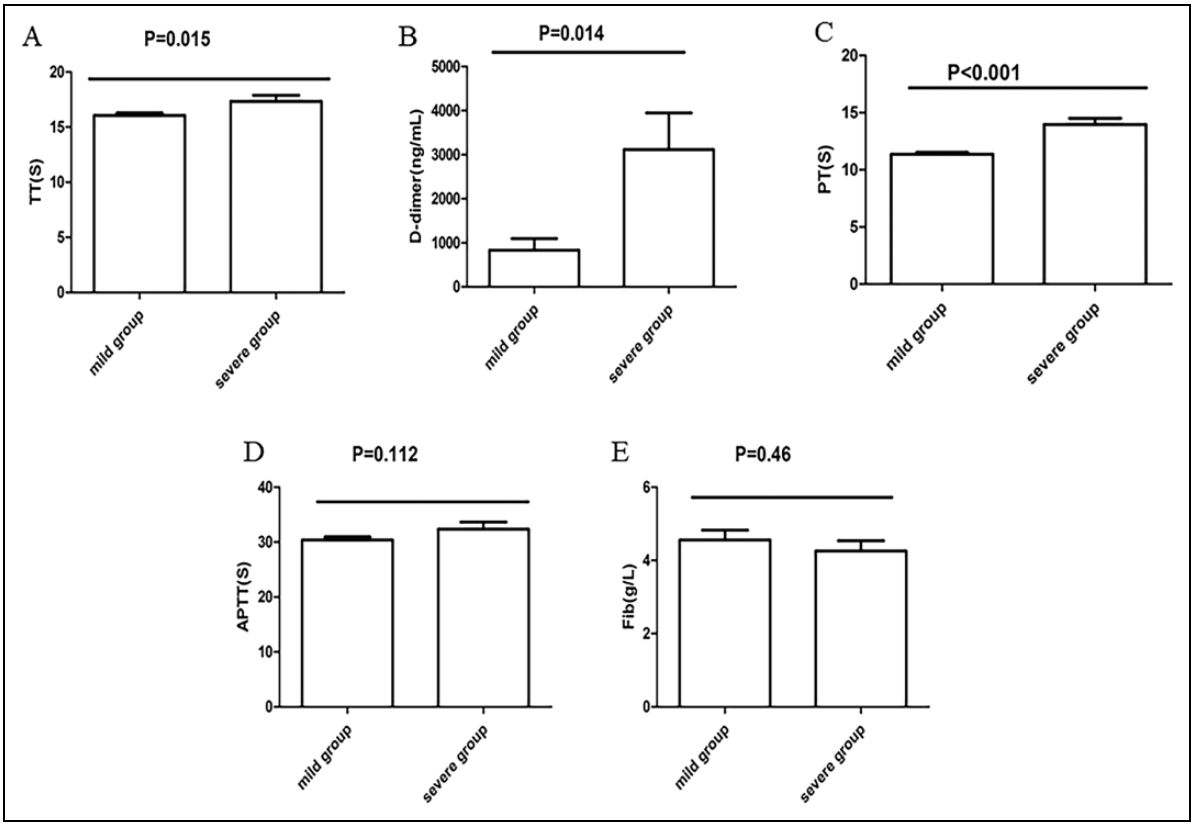

Figure 1. The coagulation parameters between mild and severe groups. TT(A), D-dimer(B), PT(C), APTT(D), Fib(E) between mild patients group and severe papients group, $P < 0.05$ as a statistic difference.

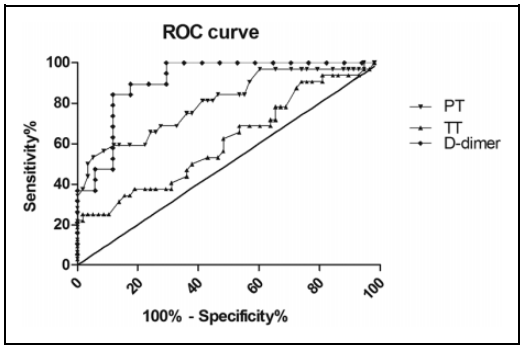

Figure 2. The receiver operation curve of hematological parameters for predicting the severity of COVID-19 patients. ROC analysis of PT, TT, D-dimer for discriminating 30 severe COVID-19 cases from 58 mild cases.

Table 2. The Predictive Value of PT, TT and D-Dimer in Mild and Severe COVID-19 Patients.

group	AUC	p	Cut off value	Sensitivity (%)	Specificity (%)	Positive predicitive value(%)	Negative predicitive value(%)
PT(S)	0.804	<0.001	13.35	50	92.9	80	76.8
TT(S)	0.613	<0.01	19.85	39.1	96.4	81.8	70.5
D-dimer	0.910	<0.01	821	84.2	88.2	88.9	88.2

Abbreviations: PT, prothrombin time; TT, thrombin time; S, seconds.

However, PT, TT, D-dimer were significantly higher in the severe group ($P < 0.05$, Figure 1).

Then we further analyzed PT, TT, D-dimer, and the receiver operation characteristic curve (ROC) and AUC were calculated for these 3 parameters. As shown in Figure 2, the highest AUC is D-dimer (0.91), and the AUC of PT and TT were 0.80 and 0.61 respectively. As shown in Table 2, D-dimer has a better predicting value for severe patients, with the sensitivity and specificity of 84.4% and 88.8%, respectively. In addition, the positive predictive value (PPV) and negative predictive value (NPV) is higher than the value of TT and PT.

Discussion

Since the outbreak of COVID-19 in Wuhan, this disease has been spreading all over the world and the WHO declares a pandemic which causes a Public Health Emergency of International Concern. SARS-CoV-2 was identified as the pathogen of the COVID-19 and the virus uses angiotensin-converting enzyme2(ACE2) as one of the receptors to enter into susceptible cells.[12] Belonging to the β-coronavirus genus, SARS-CoV-2 has a 85% homology with bat SARS-like coronavirus.[12]

Once infected, the disease progression and outcome of the patients vary. Although most patients infected by SARS-CoV-2 present with mild or even no symptoms, some will develop into severe cases leading to breath failure and death if not managed properly. Therefore, identification of the biomarkers that can be used to predict disease progression is of particular importance. D-dimer molecules are generated through the degradation of cross-linked fibrin during fibrinolysis.[13] The analysis of D-dimer is critical for the modern triage and diagnosis of disseminated intravascular coagulation (DIC).[14] In this retrospective study, we aim to identify possible biomarkers to differentiate the severe patients from the mild ones so that clinicians may make a quick response and provide a more suitable therapeutic scheme for severe patients. We analyzed the coagulation function of the mild and severe groups, and we found that PT, TT and D-dimer showed a higher level in the severe group, while no statistic difference in APTT and Fib in 2 groups (Table 1 and Figure 1). In the severe group, PT, TT and D-dimer were statistically higher when compared with those of mild group (P value was <0.001,<0.05,0.014 respectively). We further chose TT, PT and D-dimer for ROC test (Figure 2). We found that D-dimer has a larger area (0.91) than TT (0.613) and PT(0.804) (Table 2). Although PT and TT both have higher specificity(92.9% and 96.4%), their sensitivity (50% and 39.1%) were much lower than D-dimer. D-dimer has better sensitivity of 84.2% and specificity of 88.9% in predicting the severe COVID-19 cases. Furthermore, the optimum cut off value of D-dimer was 821ng/mL. COVID-19 patients with the D-dimer higher than 821ng/mL may develop into severe cases that need more carefully monitored.

However, there were only 88 cases, with 58 mild and 30 severe patients, respectively. Considering the relatively small patient population in this analysis, more clinical cases are needed to confirm our conclusion. Furthermore, we did not analyze the prognosis of the enrolled cases, and follow-up study is in progress.

In summary, our retrospective analysis of 50 mild and 38 severe COVID-19 patients indicated that the coagulation function between the mild and the severe patients are different, and D-dimer higher than 821ng/mL is a useful biomarker to predict the patient is likely to develop into severe case with a sensitivity of 84.2% and specificity of 88.9%.

Author Contributions

Xu Chen, Min Xu and Qinghua Wang were involved in the paper drafting; Xu Chen and Qinghua Wang were responsible for data collection and data analysis; Chengbin Li and Min Xu involved in the research desigh and revision of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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