

# Analysis of dynamic disturbance in blood coagulation function of 261 patients with Coronavirus Disease 2019

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Nian Chen  
the First Affiliated Hospital of Nanjing Medical

Yu-Wen Li  
the First Affiliated Hospital of Nanjing Medical

Hao-Zhi Fan  
Zhujia People's Hospital of Zhejiang Province

An-Ran Tian  
the First Affiliated Hospital of Nanjing Medical University

Hui Yuan  
the First Affiliated Hospital of Nanjing Medical University

Zheng-Yi Jiang  
The First Affiliated Hospital, College of Medicine, Zhejiang University

Yun-Xi Yu  
Huangshi Hospital of Traditional Chinese Medicine

Li-Li Ruan  
The Fifth Hospital of Huangshi

Ping-Ping Hu  
the First Affiliated Hospital of Nanjing Medical University

Ming Yue  
the First Affiliated Hospital of Nanjing Medical University

Jun Li  
the First Affiliated Hospital of Nanjing Medical University

Chuan-Long Zhu

the First Affiliated Hospital of Nanjing Medical University

✉ [chuanlong@yahoo.com](mailto:chuanlong@yahoo.com) *Corresponding Author*  
ORCID: <https://orcid.org/0000-0002-0657-828X>

**DOI:**

10.21203/rs.3.rs-21928/v1

**SUBJECT AREAS**

*Infectious Diseases*

**KEYWORDS**

*Coagulation function, D-dimer, Fibrin/fibrinogen degradation products (FDP), COVID-19, SARS-CoV-2*

## Abstract

**Background:** With the spread of SARS-CoV-2 around the world, a rising number of studies have been conducted on the epidemiological and clinical characteristics of COVID-19. However, studies about the effect of SARS-CoV-2 on coagulation function are rare. Hence, we aimed to assess the differences and dynamic changes of blood coagulation function in ordinary, severe and critical patients with COVID-19.

**Methods:** A retrospective study was conducted. Clinical information, including age, routine blood and blood coagulation function, was collected from medical records of COVID-19 patients from January 24 to March 25, 2020 in Huangshi, Hubei Province. According to new pneumonia diagnosis and treatment of COVID-19 (trial version seventh), the patients were divided into ordinary, severe and critical groups.

**Results:** 261 COVID-19 patients (186 ordinary, 45 severe and 30 critical ones) were enrolled. Average age in critical group ( $71.47 \pm 11.48$  years) was the oldest of three subgroups. At admission, statistically differences could be observed for D-dimer, FDP, Platelet and lymphocyte count among three subgroups ( $P < 0.05$ ). During hospitalization, the peak values of coagulation and valley values of blood routine were monitored, and there were significant differences among ordinary, severe and critical patients in D-dimer ( $0.26 \pm 0.46$ ,  $1.39 \pm 1.51$  and  $2.89 \pm 1.68$  mg/L), FDP ( $3.29 \pm 5.52$ ,  $23.68 \pm 39.07$  and  $56.11 \pm 49.94$   $\mu\text{g/ml}$ ), platelet [ $(164 \pm 55.53)$ ,  $(171 \pm 69.96)$  and  $(84 \pm 57.80) \times 10^9/\text{L}$ ] and lymphocyte counts [ $(1.10 \pm 0.46)$ ,  $(0.65 \pm 0.35)$  and  $(0.55 \pm 0.31) \times 10^9/\text{L}$ ], respectively ( $P < 0.001$ ). In the critical group, D-dimer and FDP were significantly increased, while platelet count and lymphocyte count were obviously decreased. D-dimer and FDP in the course of disease in severe/critical groups showed a first upward and then downward trend.

**Conclusions:** Close monitoring of coagulation function could help predict the severity of COVID-19, and guide treatment.

## Background

From December 2019, patients with pneumonia of unknown cause connected to seafood wholesale market in Wuhan, China, were discovered one after another<sup>1</sup>. Rapidly, a novel coronavirus named

severe acute respiratory syndrome coronavirus 2 (SARS-CoVA-2) isolated from the throat swab sample of patients was identified as the pathogen. Subsequently, this unique pneumonia was named as Coronavirus Disease-19 (COVID-19) by World Health Organization (WHO). With its high contagious capacity, over 37,0000 cases were confirmed, with 16231 deaths all over the world until 24, March, 2020<sup>2</sup>. COVID-19 is mainly transmitted through respiratory droplets and close contact. Fever, dry cough and fatigue are the main clinical manifestations of this disease. A few patients are accompanied by nasal congestion, runny nose, myalgia and diarrhea. Ordinary patients have a good prognosis, but severe patients can rapidly develop a range of complications such as acute respiratory distress syndrome (ARDS), coagulation dysfunction and multiple organ failure (MOF), which can eventually lead to death<sup>3</sup>.

Albeit a good knowledge has been obtained on the pathogenesis, clinical features and CT imaging changes of COVID-19, little is known about the derangement of blood coagulation. Our study aims to investigate the differences of fibrinogen (FIB), fibrin/fibrinogen degradation products(FDP), D-dimer and platelet count in different types of patients, as well as the dynamic changes of the above indexed in severe and critical patients, and further explore the relationship between coagulation indexes and COVID-19 progress.

## Methods

### **Patients**

The clinical data of 261 patients with COVID-19 confirmed in Huangshi Hospital of traditional Chinese medicine in Hubei Province from January 24 to March 25, 2020 were collected. According to the diagnosis and treatment scheme for COVID-19 of Chinese (trial version seventh), COVID-19 patients were confirmed by positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2, or the sequencing of virus, highly homologous with SARS-CoV-2, or detection of new coronavirus-specific antibody<sup>3</sup>. Clinical and laboratory information of enrolled patients could be complete without missing.

Patients infected with other common respiratory viruses, including influenza A and B virus, respiratory syncytial virus, parainfluenza virus, adenovirus were excluded from this study. At the same time,

patients with abnormal coagulation function caused by underlying conditions, recently taking anticoagulant and antiplatelet drugs, and pregnant or lactating women were excluded as well. The degrees of COVID-19 were categorized into ordinary, severe and critical, based on the diagnosis and treatment scheme for COVID-19 of Chinese (trial version seventh)<sup>3</sup>. In brief, ordinary patients exhibited mild clinical symptoms with or without imaging changes. Severe type was characterized by at least one of the following symptoms: respiratory frequency  $\geq 30$ /minute, blood oxygen saturation at rest  $\leq 93\%$ , PaO<sub>2</sub>/FiO<sub>2</sub> ratio  $< 300$ mmHg, and lung infiltrates  $> 50\%$  within 24–48 hours. Critical cases were those that exhibited respiratory failure with mechanical ventilation, septic shock, and/or multiple organ dysfunction/failure needed intensive care unit (ICU) monitoring.

### **Data collection**

Clinical information, such as age, gender, date of admission and course records, and laboratory information, especially blood coagulation parameters, of 261 SARS-CoV-2 infected patients at admission and during following hospitalization were obtained from medical records. Coagulation tests were consisted of fibrin/fibrinogen degradation products (FDP), fibrinogen (FIB) and D-dimer.

### **Statistical analysis**

SPSS (version 22.0) was used to perform statistical analyses. Continuous data were expressed as means  $\pm$  standard deviation (SD) or means  $\pm$  standard error of the mean (SEM), and were analyzed by one-way analysis or Welch analysis of variance, depending on the result of homogeneity of variance tests. Categorical data were expressed as numbers (%) and were compared by chi-squared test. In all tests,  $P \leq 0.05$  was considered as statistical significance.

## **Results**

### **Clinical characteristics of patients with COVID-19**

Among all the 261 COVID-19 patients, 186 (71.3%) were ordinary, 45 (17.2%) were severe, and 30 (11.5%) were critical. All patients included 128 (49%) males and 133 (51%) females, with an average age of 54.70 years old, and the majority of patients (65.1%) were over 50 years old. There were significant differences in age ( $P < 0.001$ ) among different subgroups, of which the mean age of the critical group was the oldest ( $71.47 \pm 11.48$  years), but not significant differences were found in

gender ( $P = 0.607$ ) among the subgroups. Notably, none of the subjects in our study was taking anticoagulant drugs before blood drawing. The distribution of age within each group is presented in Table 1.

Table 1  
The distribution of baseline characteristics of COVID-19 patients.

Clinical characteristics	All patients n= (261)	Subgroups			P-value
		Ordinary n= (186)	Severe n= (45)	Critical (n = 30)	
Age (mean $\pm$ SD), y	54.70 $\pm$ 15.65	50.22 $\pm$ 14.27	62.04 $\pm$ 13.18	71.47 $\pm$ 11.48	< 0.001
Age grouping, No. (%)					< 0.001
< 40 y	49 (18.8)	47 (25.3)	2 (4.4)	0 (0)	
40-49 y	42 (16.1)	36 (19.3)	5 (11.1)	1 (3.3)	
50-59 y	69 (26.5)	55 (29.6)	11 (24.5)	3 (10.0)	
60-69 y	57 (21.8)	35 (18.8)	13 (28.9)	9 (30.0)	
70-79 y	28 (10.7)	11 (5.9)	9 (20.0)	8 (26.7)	
> 80 y	16 (6.1)	2 (1.1)	5 (11.1)	9 (30.0)	
Gender, No. (%)					0.607
Male	128 (49.0)	88 (47.3)	23 (51.1)	17 (56.7)	
Female	133 (51.0)	98 (52.7)	22 (48.9)	13 (43.3)	

Comparison of coagulation function among different subgroups of COVID-19 at admission

At admission, significant differences for the values of D-dimer, FDP, platelet count and lymphocyte count among three subgroups were observed ( $P < 0.05$ ). Compared with ordinary and severe groups, the D-dimer and FDP values in critical patients (D-dimer:  $1.16 \pm 1.58$  mg/L) ; FDP:  $21.94 \pm 40.98$   $\mu$ g/ml) were found to be higher, while the platelet count [ $(117 \pm 38.31) \times 10^9/L$ ] was lower ( $P < 0.05$ ).

Notably, lymphocyte count in severe [ $(0.82 \pm 0.35) \times 10^9/L$ ] and critical groups [ $(0.75 \pm 0.39) \times 10^9/L$ ] was lower than that in the ordinary group [ $(1.18 \pm 0.46) \times 10^9/L$ ]( $P < 0.05$ ) (Table 2). Unlike the parameters mentioned above, no difference was observed in the value of FIB among three subgroups ( $P = 0.088$ ).

Table 2

Comparison of coagulation function among COVID-19 patients from different subgroups at admission

Variables	Normal range	All patients n= (261)	Subgroups			P_value
			Ordinary n= (186)	Severe n= (45)	Critical (n = 30)	
FIB(g/L)	2.00-4.00	4.77 ± 1.42	4.79 ± 1.41	4.96 ± 1.29 <sup>d</sup>	4.23 ± 1.53 <sup>d</sup>	0.088
D-dimer (mg/L)	0-0.50	0.36 ± 0.82	0.18 ± 0.33 <sup>b,c</sup>	0.63 ± 1.13 <sup>b,d</sup>	1.16 ± 1.58 <sup>c,d</sup>	0.001 <sup>a</sup>
FDP (µg/ml)	0-5.0	6.38 ± 18.33	3.11 ± 5.30 <sup>b,c</sup>	9.82 ± 23.91 <sup>b,d</sup>	21.94 ± 40.98 <sup>c,d</sup>	0.020 <sup>a</sup>
PLT (× 10 <sup>9</sup> /L)	125-350	168 ± 64.98	169 ± 62.85 <sup>c</sup>	188 ± 71.56 <sup>d</sup>	117 ± 38.31 <sup>c,d</sup>	< 0.001
LYM (× 10 <sup>9</sup> /L)	1.10-3.20	1.08 ± 0.47	1.18 ± 0.46 <sup>b,c</sup>	0.82 ± 0.35 <sup>b</sup>	0.75 ± 0.39 <sup>c</sup>	< 0.001

a represents the variance is not uniform in multiple groups, and Welch method is used to compare. b represents the significant difference between ordinary and severe group. c represents the significant difference between ordinary and critical group. d represents the significant difference between severe and critical group. FIB: fibrin/fibrinogen degradation products, FDP: antithrombin, PLT: platelet count, LYM: lymphocyte counts.

Comparison of coagulation function among different degrees of COVID-19 during hospitalization

During hospitalization, blood routine examination and coagulation function were carried out several times. The peak values of FIB, D-dimer and FDP, and the valley values of platelet and lymphocyte count were selected for further statistical analysis. Multiple analyses allowed us to define that the values of FIB, D-dimer, FDP, platelet count and lymphocyte count were significant different among three different groups of COVID-19 patients ( $P < 0.001$ ). In detail, compared to ordinary patients (D-dimer:  $0.26 \pm 0.46$  mg/L; FDP:  $3.29 \pm 5.52$  µg/ml), the values of D-dimer and FDP were higher in severe (D-dimer:  $1.39 \pm 1.51$  mg/L; FDP:  $23.68 \pm 39.07$  µg/ml) and critical patients (D-dimer:  $2.89 \pm 1.68$  mg/L; FDP:  $56.11 \pm 49.94$  µg/ml), but the opposite trend was observed in lymphocyte count ( $P < 0.05$ ). As concerns FIB, severe patients ( $6.43 \pm 4.62$  g/L) displayed considerably higher values than those in the other two groups ( $P < 0.05$ ). Notably, the mean value of platelet count in critical patients [ $(84 \pm 57.80) \times 10^9/L$ ] was significantly lower than the normal range, and was significantly different from that in ordinary [ $(164 \pm 55.53) \times 10^9/L$ ] and severe groups [ $(171 \pm 69.96) \times 10^9/L$ ], as shown in Table 3.

Table 3  
Comparison of coagulation function among different degrees of COVID-19 patients during hospitalization.

Variables	Normal range	All patients n= (261)	Subgroups			P_value
			Ordinary n= (186)	Severe n= (45)	Critical (n = 30)	
FIB (g/L)	2.00–4.00	5.15 ± 2.49	4.89 ± 1.57 <sup>b</sup>	6.43 ± 4.62 <sup>b,d</sup>	4.83 ± 2.01 <sup>d</sup>	0.001
D-dimer(mg/L)	0-0.50	0.76 ± 1.27	0.26 ± 0.46 <sup>b,c</sup>	1.39 ± 1.51 <sup>b,d</sup>	2.89 ± 1.68 <sup>c,d</sup>	< 0.001 <sup>a</sup>
FDP(μg/ml)	0-5.0	12.87 ± 29.32	3.29 ± 5.52 <sup>b,c</sup>	23.68 ± 39.07 <sup>b,d</sup>	56.11 ± 49.94 <sup>c,d</sup>	< 0.001 <sup>a</sup>
PLT(× 10 <sup>9</sup> /L)	125–350	156 ± 63.82	164 ± 55.53 <sup>c</sup>	171 ± 69.96 <sup>d</sup>	84 ± 57.80 <sup>c,d</sup>	< 0.001
LYM(× 10 <sup>9</sup> /L)	1.10–3.20	0.96 ± 0.48	1.10 ± 0.46 <sup>b,c</sup>	0.65 ± 0.35 <sup>b</sup>	0.55 ± 0.31 <sup>c</sup>	< 0.001 <sup>a</sup>

a represents the variance is not uniform in multiple groups, and Welch method is used to compare. b represents the significant difference between ordinary and severe group. c represents the significant difference between ordinary and critical group. d represents the significant difference between severe and critical group. FIB: fibrin/fibrinogen degradation products, FDP: antithrombin, PLT: platelet count, LYM: lymphocyte counts.

Dynamic changes of coagulation indexes during hospitalization in severe and critical patients

Blood routine examination and coagulation function were performed several times in severe and critical patients during hospitalization, depending on the needs of disease. We observed that the levels of D-dimer in these two groups showed a similar trend of first increasing and then decreasing as with FDP, and most of them were above the normal values. The platelet count and lymphocyte count of critical patients were always at a low level, and their rising trend was not obvious as shown in Fig. 1.

## Discussion

At present, COVID-19 has become a worldwide pandemic. The number of confirmed patients in Italy, the United States, Spain, Germany and other countries has already exceeded 60,000<sup>2,5</sup>. Although its mortality rate is lower than SARS, its stronger infectivity still puts enormous pressure on public health<sup>6</sup>. Studies have shown that the development of ARDS in critical patients is extremely rapid, and the mortality rate of patients at this stage is very high<sup>7</sup>. Therefore, it is of great importance to monitor the laboratory examination closely in the early stage of COVID-19 and prevent further deterioration.

The pathological results of new pneumonia diagnosis and treatment of COVID-19 (trial version seventh) indicate the existence of microthrombus in pulmonary vessels, liver and kidney of COVID-19 patients<sup>3</sup>. Microthrombus, also known as transparent thrombus, is mainly composed of fibrin, which is



common in disseminated intravascular coagulation (DIC). In physiological state, the fibrin produced by the body will be dissolved by the constantly activated fibrinolysis system. But when the infection leads to the damage of vascular endothelial cells and/or the activation of endogenous coagulation pathway, a large number of fibrin thrombosis will be generated. Patients with COVID-19 are characterized by a strong systemic inflammation as measured by high levels of inflammatory cytokines, which can cause 'cytokine storm' during the initial stage of disease, and thus promoting blood coagulation<sup>8</sup>.

Interestingly, we found that the platelet count in critical patients was at a low level at admission, and the decrease was more obvious at exacerbation, while the changes in ordinary and severe patients were relatively small. It is widely recognized that platelets not only play a role in coagulation, but also are an integral part in infection and inflammatory immune response<sup>9</sup>. Patients with severe thrombocytopenia have higher levels of proinflammatory cytokines than those with normal platelet counts<sup>10,11</sup>. Taken together, thrombocytopenia has a strong correlation with severe infection and increased risk of DIC. As an indicator of disease deterioration, the value of platelet count must be paid enough attention.

In the present study, the majority of patients were elderly, and 86.7% of critical patients are over 60 years old, indicating that elderly patients are easy to worsen, in line with other report<sup>12</sup>. This may be related to the decline of resistance caused by the decrease of immune cells in the elderly. Similar to the reports from Han H et al<sup>13</sup>, the FIB values of three subgroups were greater at admission compared to the normal range, but the differences within different subgroups were not significant. As for the values of D-dimer and FDP in severe and critical patients, they were much higher than normal range, and show significant difference to the ordinary group.

What is novel in this study is the dynamic analyses of FIB, D-dimer, FDP, platelet count and lymphocyte count in COVID-19 patients. The data in this study showed that the values of D-dimer and FDP increased significantly after admission, and then decreased gradually after reaching the peak. The dynamic changes were consistent with the progress and recovery of disease. Previous studies

have shown that severe acute respiratory syndrome (SARS)<sup>14</sup>, Middle East respiratory syndrome (MERS)<sup>15</sup> and community-acquired pneumonia (CAP)<sup>16</sup> have significantly abnormal coagulation function at the disease onset, mainly manifested as the increase of FIB, D-dimer and FDP, and the elevation degree will become more and more significant with the aggravation of the disease, which is similar to the results observed in this study. As a marker of DIC, secondary hyperfibrinolysis and thrombosis, D-dimer is of great significance in the diagnosis of hypercoagulability<sup>8</sup>. Recently, it has been found that compared with survival patients, dead COVID-19 patients have higher levels of D-dimer and FDP, as with the appearance of DIC<sup>8,12</sup>. Therefore, regular detection of coagulation index is of great importance in judging the severity and predicting prognosis of COVID-19.

This study still requires further refinement. As a single-center retrospective study, there might be some limitations because all the enrolled patients were from Huangshi Hospital of traditional Chinese medicine. And due to the relatively stable condition of ordinary patients, the number of coagulation function rechecks during hospitalization is less, thus the dynamic changes can't be observed. As the end point of observation was discharge, the changes of coagulation function post-discharge could not be further analyzed.

## Conclusions

With the progress of disease, the coagulation function of patients with COVID-19 will show different degrees of abnormality. As there is no specific antiviral treatment for COVID-19 at present, it is of great importance to find and correct the coagulation dysfunction in time to reduce the formation of DIC and improve the prognosis.

## Abbreviations

COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization; ARDS: Acute respiratory distress syndrome; MOF: Multiple organ failure; RT-PCR: Real-time reverse transcriptase polymerase chain reaction; SD: Standard deviation; SEM: Standard error of the mean; DIC: Disseminated intravascular coagulation; ICU: Intensive care unit; FIB: fibrinogen; FDP: fibrin/fibrinogen degradation products; PLT: platelet; LYM: lymphocyte

## Declarations

## **Ethics approval and consent to participate**

This study was approved by the Ethics Committee of the Huangshi Hospital of traditional Chinese medicine in Wuhan province (HSZYPJ-2020-021-01).

## **Consent for publication**

Not applicable.

## **Availability of data and materials**

All data generated or analysed during this study are included in this published article.

## **Competing interests**

The authors declare that they have no competing interests.

## **Funding**

This work was supported by the National Natural Science Foundation of China (grant no. 81770591, no.81800778), the Key Medical Talents Fund of Jiangsu Province (grant no. ZDRCA2016007).

## **Authors' contributions**

NC, YL and HF contributed equally to this article. CZ and NC designed the study. HF developed the statistical methods. NC, YL, AT, HY, YY, LR, PH, MY and JL were participated in the collection of clinical data. HY, CZ and ZJ wrote the initial draft of the manuscript. All authors read and approved the final manuscript.

## **Acknowledgements**

We thank all the front-line medical staffs in Hubei province for their bravery and efforts in COVID-19 prevention and control.

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## Figures

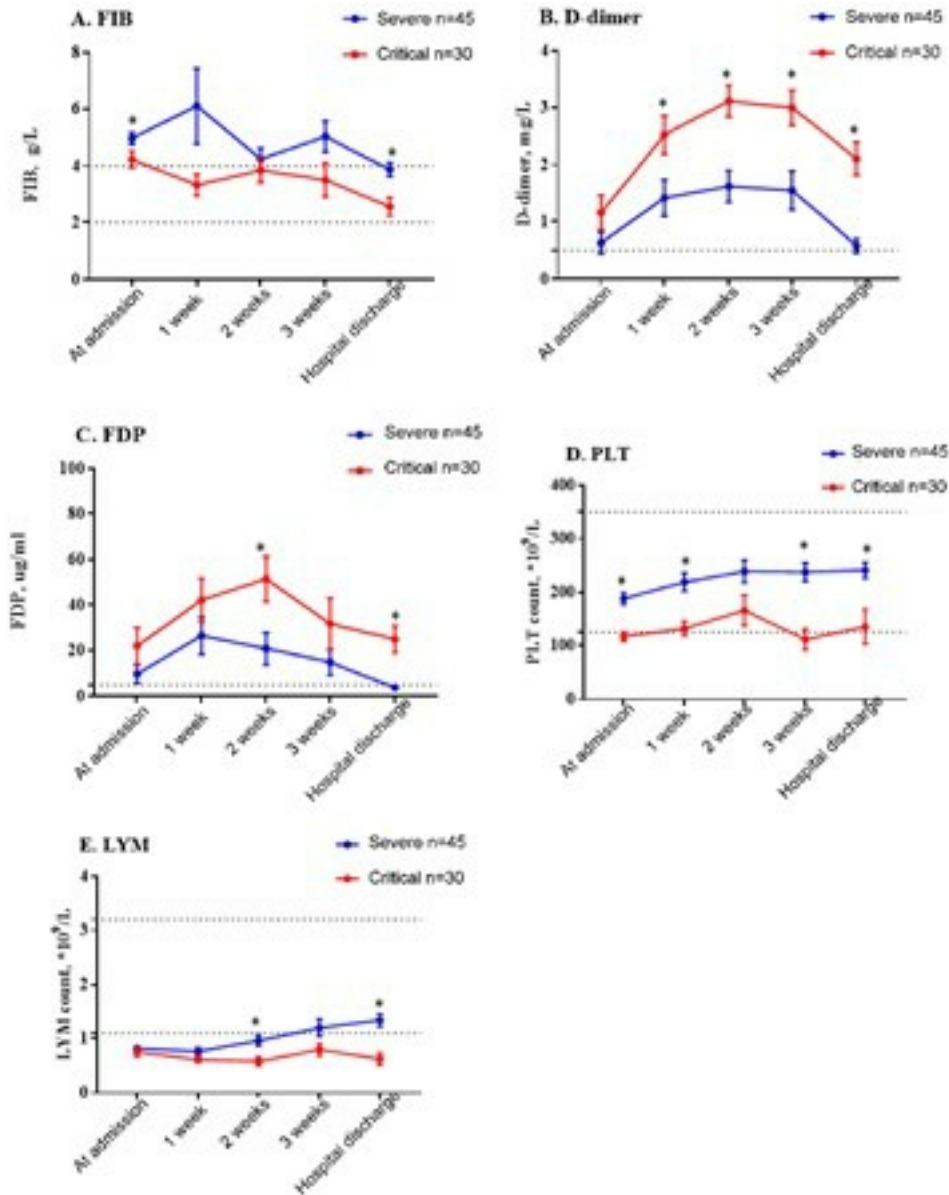


Figure 1

Line graph represents the dynamic changes of laboratory examination results during hospitalization. The data are shown as means  $\pm$  SEM. Dashes indicate the range of normal values. \* represents the significant difference between severe and critical group ( $P < 0.05$ ).

