Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
D-dimer level is associated with the severity of COVID-19

Hai-Han Yu 1, Chuan Qin 1, Man Chen, Wei Wang, Dai-Shi Tian*  
Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, PR China  

ARTICLE INFO
Keywords:  
COVID-19  
D-dimer  
Severity

ABSTRACT

Introduction: Abnormal coagulation function has been demonstrated to be involved in the disease progression of COVID-19. However, the association between D-dimer levels and the severity of COVID-19 is not clear. The study was aimed to investigate the association between D-dimer levels and the severity of COVID-19 based on a cohort study and meta-analysis.

Materials and methods: Demographic and clinical data of all confirmed cases with COVID-19 on admission to Tongji Hospital from January 27 to March 5, 2020, were collected and analyzed, and coagulation function parameters were described and compared between patients with severe infection and those with non-severe infection. Cohort studies reporting risk estimates for the D-dimer and severity of COVID-19 association were searched and included to perform a meta-analysis.

Results: In our cohort study, patients with severe disease were more likely to exhibit dysregulated coagulation function, and a significantly higher D-dimer level (median 1.8 μg/ml [interquartile range 0.9–4.6] vs 0.5 [0.3–1.1], p < 0.001) was found in severe cases than the mild ones, on admission. In the meta-analysis of 13 cohort studies (including the current study), patients with severe disease had an increase in mean D-dimer value by 0.91 (95% confidence interval, 0.51–1.31, p < 0.001) μg/ml compared to those with non-severe disease, and odds of severe infection was associated with D-dimer greater than 0.5 μg/ml (odds ratio = 5.78, 95% confidence interval, 2.16–15.44, p < 0.001) on admission.

Conclusions: Patients with severe COVID-19 have a higher level of D-dimer than those with non-severe disease, and D-dimer greater than 0.5 μg/ml is associated with severe infection in patients with COVID-19.

1. Introduction

In December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease it caused, now known as coronavirus disease 2019 (COVID-19), were initially reported in Wuhan, China and rapidly spread throughout the world [1]. As of June 25, 2020, more than 9 million laboratory-confirmed cases have been identified in 208 countries and areas, with more than 480,000 fatal cases, according to the data from World Health Organization (WHO) reports [2].

In recent studies documenting the clinical features of confirmed patients with COVID-19, it has been reported that most of them would present a type of mild infection of the COVID-19 disease [3,4]. However, a number of patients were observed to present with severe infection on admission with high mortality. Therefore, it is crucial to discriminate accurately among subjects with COVID-19 who have a high risk of severe infection and guide the use of different therapies at an early stage. Abnormal coagulation function, including elevated D-dimer, has been demonstrated to be more common in deceased patients with COVID-19, and increasing odds of in-hospital death was associated with D-dimer greater than 1 μg/ml [5,6]. However, the association between D-dimer and the severity of COVID-19 is not clear.

In our cohort study, epidemiological, clinical characteristics, and coagulation function parameters of patients with confirmed COVID-19 on admission were collected and compared, between patients with severe infection and those with non-severe infection. Further, a meta-analysis including our cohort study was then conducted to evaluate the association between D-dimer levels and severe COVID-19.

Abbreviations: COVID-19, coronavirus disease 2019; CI, confidence interval; OR, odds ratio; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; SD, standard deviation; WMD, weighted mean difference; IQR, interquartile range; SARS-CoV, severe acute respiratory syndrome coronavirus

* Corresponding author.
E-mail address: tiands@tjh.tjmu.edu.cn (D.-S. Tian).
Yu and Qin contributed equally to this work.

https://doi.org/10.1016/j.thromres.2020.07.047
Received 30 April 2020; Received in revised form 22 July 2020; Accepted 25 July 2020
Available online 27 July 2020
0049-3848/ © 2020 Elsevier Ltd. All rights reserved.
2. Materials and methods

2.1. Study design and participants recruited

Totally 1561 patients with COVID-19 were recruited retrospectively from January 27th to March 5th, 2020, at Tongji hospital, the largest comprehensive medical center in Wuhan and the specific hospital for the treatment of patients with severe COVID-19 in Wuhan designated by the Chinese government. Laboratory confirmation of COVID-19 was carried out by real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) using method described previously [4]. This study was approved by Tongji Hospital Ethics Committee (IRB ID: TJ-CC20200121). Written informed consent was waived by the Ethics Commission of Tongji hospital for emerging infectious diseases.

2.2. Data collection from electronic medical records

Epidemiological characteristics, comorbidities, coagulation function markers on admission and disease severity, were obtained from patients’ medical records. D-dimer were detected using a STA-R MAX Corporation, College Station, Texas, USA) was used for the data analysis. proportions were delineated as n (%) and compared by χ2 test and Fisher’s exact test. The association between clinical characteristics and the presence of severe infection were determined by multivariable logistic regression analysis. The results were expressed as odds ratio (OR), 95% confidence intervals (CI), and p values. For individual statistical tests on the coagulation function, we calculated a corrected critical P value of 0.0063 (0.05/8 where 8 = the eight tested parameters of coagulation function) using the Bonferroni correction method. For multivariable logistic regression analysis, Bonferroni-Holm (B-H) correction was used to adjust for multiple testing, and results were defined as significant if the p-value of the regression analysis was lower or equal as the B-H corrected p-value. For all other analyses, the statistical significance was set at 0.05. All tests were two-sided.

For meta-analysis, weighted mean difference (WMD) with 95% confidence interval (95% CI) and odds ratio (OR) with 95% CI, were pooled for differences of D-dimer value and odds of severe COVID-19, respectively. The heterogeneity was evaluated using I² and p value based on Chi-square test. I² ≤ 50% or p ≥ 0.1 demonstrated no significant heterogeneity, and a fixed-effects model was used. I² > 50% or p < 0.1 indicated a significant heterogeneity, and a random-effects model was applied. Funnel plot and the Egger’s test were performed to evaluate publication bias. STATA statistical version 12.0 (Stata Corporation, College Station, Texas, USA) was used for the data analyses.

3. Results

3.1. Clinical characteristics and coagulation function of patients with COVID-19 in our cohort

Comparison of characteristics between patients with severe disease and mild cases in our cohort study is shown in Table 1. Among the 1561 patients with confirmed COVID-19, 365 (23.4%) patients were clinically diagnosed with severe infection, and 1196 (76.6%) were diagnosed with mild infection. Older (median 67 years [interquartile range, IQR 58–73] vs 60 [47–68], p < 0.001) and male (204/365 [56%] vs 576/1196 [48%], p = 0.006) patients were more common in the severe group when compared with those with non-severe disease. More comorbidities, including hypertension (162/365[44%] vs 349/ 1196[29%], p < 0.001), diabetes (74/365[20%] vs 159/1196[13%], p = 0.001), chronic obstructive pulmonary disease (11/365[3%] vs 11/ 1196[1%], p = 0.006), and cardiovascular disease (47/365[13%] vs 108/1196[9%], p = 0.022), were found in patients with severe disease as compared to those with mild COVID-19. It should be interpreted with caution as the p-values were not adjusted for multiple testing.

Moreover, patients with severe COVID-19 were significantly more likely to exhibit dysregulated coagulation function. Elevated levels of prothrombin time (median 14.4 [IQR 13.7–15.4] vs 13.6 [13.1–14.2] s, p < 0.001), thrombin time (16.9 [15.8–18.2] vs 16.4 [15.7–17.3] s, p < 0.001), fibrinogen (5.3 [4.0–6.5] vs 4.3 [3.4–5.5] g/L, p < 0.001), fibrin(ogen) degradation products (6.5 [4.0–21.8] vs 4.0 [4.0–4.5] μg/ml, p < 0.001), and international normalized ratio (1.1 [1.1–1.2] vs 1.0 [1.0–1.1], p < 0.001), and decreased prothrombin activity (84.0 [74.0–92.5] vs 93.0 [86.0–101.0] %, p < 0.001) were observed in patients with severe disease when compared with non-severe group. Particularly, a significantly increased level of D-dimer (1.8 [0.9–4.6] vs 0.5 [0.3–1.1] μg/ml, p < 0.001) was found in patients with severe disease (Table 1, Fig. 1). Multivariable logistic regression analysis showed presence of severe COVID-19 was associated with prothrombin time longer than 14.5 s (2.71, 2.00–3.67; p < 0.001, B-H corrected significance level: p = 0.0029), fibrin(ogen) degradation products greater than 5.0 μg/ml (2.33, 1.74–3.12, p < 0.001, B-H corrected significance level: p = 0.0031), and D-dimer greater than 0.5 μg/ml (3.44, 2.29–5.17; p < 0.001, B-H corrected significance level: p = 0.0028), on admission, as shown in Table 2. These results suggested that the severity of COVID-19 was associated with coagulation dysfunction in Tongji Hospital.
3.2. Study selection for meta-analysis in patients with COVID-19

As shown in Fig. 2, a total of 699 articles were identified from electronic database after removal of duplicate studies. Finally, 13 studies (including our cohort study) were included for this meta-analysis. The characteristics of these 13 studies were shown in Table 3. Of the 12 studies other than our cohort study, 8 studies reported the absolute value of D-dimer in patients with severe disease and those with non-severe disease [10–17]. The odds ratio (OR) of severe infection in patients with D-dimer greater than 0.5 μg/ml were obtained directly or by calculation from our cohort study and 4 other studies [3,18–20].

3.3. Higher level of D-dimer in patients with severe COVID-19

For meta-analysis concerning the mean value of D-dimer, 9 studies (including our cohort study) were included, with 2574 patients in total. The mean value of D-dimer of all patients was 0.34 (standard deviation SD, 0.14) μg/ml, 0.30 (0.12) for patients with non-severe disease, and 0.89 (0.34) for severe patients. Differences of mean value of D-dimer between severe and non-severe group was 0.91 μg/ml (95% confidence interval CI, 0.51–1.31, \(p < 0.001, I^2 = 94.7\%\)), after pooling WMD for these studies, as shown in Fig. 3, suggesting a significant increase of D-dimer level in patients with severe disease than those with non-severe disease, on admission.

3.4. Odds of severe COVID-19 in patients with abnormal D-dimer

For meta-analysis concerning the odds of severe COVID-19, 4 studies and our cohort study were included. The odds ratio of severe COVID-19 associated with D-dimer greater than 0.5 μg/ml was 5.78
Table 2
Logistics regression of factors associated with severity of COVID-19.

| Characteristics                                      | Multivariate analysis | Bonferroni-Holm corrected p-value |
|-------------------------------------------------------|-----------------------|-----------------------------------|
|                                                       | OR   | 95% CI       | p value |                                     |
| Age, years, years                                     | 1.01 | (0.99, 1.02) | 0.07    | 0.0045                               |
| Sex (male vs female)                                  | 1.04 | (0.78, 1.37) | 0.80    | 0.025                                |
| Smokers vs non-smokers                                | 1.15 | (0.68, 1.96) | 0.61    | 0.01                                 |
| Comorbidities                                         |       |              |         |                                       |
| Chronic obstructive pulmonary disease                 | 2.17 | (0.82, 5.74) | 0.12    | 0.005                                |
| Hypertension                                          | 1.48 | (1.09, 1.99) | 0.01    | 0.0033                               |
| Cardiovascular disease                                | 0.87 | (0.57, 1.33) | 0.51    | 0.0083                               |
| Cerebrovascular disease                               | 0.61 | (0.27, 1.35) | 0.22    | 0.0063                               |
| Chronic liver disease                                 | 0.75 | (0.32, 2.44) | 0.63    | 0.0013                               |
| Diabetes                                              | 1.24 | (0.86, 1.78) | 0.24    | 0.0071                               |
| Tuberculosis                                          | 0.23 | (0.05, 1.09) | 0.06    | 0.0008                               |
| Malignant tumor                                        | 1.73 | (0.85, 3.49) | 0.13    | 0.0056                               |
| Chronic kidney disease                                | 0.90 | (0.39, 2.06) | 0.80    | 0.05                                 |
| Coagulation function                                  |       |              |         |                                       |
| Prothrombin time, s                                   |       |              |         |                                       |
| ≤14.5                                                  | Reference |            |         |                                       |
| > 14.5                                                 | 2.71 | (2.00, 3.67) | < 0.001 | 0.0029                               |
| Activated partial thromboplastin time, s              |       |              |         |                                       |
| ≤42.0                                                  | Reference |            |         |                                       |
| > 42.0                                                 | 1.06 | (0.79, 1.44) | 0.69    | 0.017                                |
| Thrombin time, s                                      |       |              |         |                                       |
| ≤19.0                                                  | Reference |            |         |                                       |
| > 19.0                                                 | 1.51 | (0.97, 2.35) | 0.07    | 0.0042                               |
| Fibrinogen, g/L                                       |       |              |         |                                       |
| ≤4.00                                                  | Reference |            |         |                                       |
| > 4.00                                                 | 1.48 | (1.08, 2.03) | 0.02    | 0.0036                               |
| Fibrinogen degradation products, μg/ml                |       |              |         |                                       |
| < 5.0                                                  | Reference |            |         |                                       |
| ≥5.0                                                   | 2.33 | (1.74, 3.12) | < 0.001 | 0.0031                               |
| D-dimer, μg/ml                                        |       |              |         |                                       |
| < 0.5                                                  | Reference |            |         |                                       |
| ≥0.5                                                   | 3.44 | (2.29, 5.17) | < 0.001 | 0.0028                               |

p values were calculated from logistic regression analysis to estimate the odds ratio of presence of severe infection in patients with COVID-19. COVID-19 = coronavirus disease 2019; OR = odds ratio; CI = confidence interval.

* Prothrombin time, international normalized ratio and prothrombin activity are three different expressions of the same laboratory parameter, and only prothrombin time was included in the multivariable logistic regression model.

(95% CI, 2.16–15.44, p < 0.001, \(I^2 = 87.2\%\), Fig. 4), indicating that the severe COVID-19 was associated with increased level of D-dimer on admission.

### 3.5. Publication bias

The funnel plots and the Egger’s test (p = 0.01) for the studies reporting the absolute value of D-dimer showed that a publication bias existed in these studies (Supplementary Fig. 1A). And no significant publication bias was detected among studies evaluating the odds of severe COVID-19 in patients with abnormal D-dimer, with Egger’s test showing p = 0.794 (Supplementary Fig. 1B).

### 4. Discussion

Abnormal coagulation function, including elevated D-dimer, has been demonstrated to be involved in the disease progression of COVID-19 [5,21]. In this study, we analyzed the association between elevated D-dimer levels and the disease severity of COVID-19 based on the evidence from our cohort study and meta-analysis. In our retrospective cohort study, the level of D-dimer was markedly increased in patients with severe COVID-19, and the meta-analysis further confirmed that odds of severe COVID-19 was associated with D-dimer greater than 0.5 μg/ml.

D-dimer assays are commonly used in clinical practice to exclude a diagnosis of deep vein thrombosis or pulmonary embolism, and elevated D-dimer indicates increased risk of abnormal blood clotting. Elevated levels of D-dimer were also found to be related with higher mortality rate of community-acquired pneumonia [22]. Patients with severe community-acquired pneumonia had significantly higher D-dimer levels, and D-dimer within normal range indicated low risk for complications [23]. Augmented activity of urokinase could cause hyperfibrinolysis, by increasing cleavage of plasminogen into the active plasmin, and finally led to diffuse alveolar damage and acute lung injury, in a mouse model of SARS-CoV disease [24]. In our cohort study, the level of coagulation function parameters, including prothrombin time, fibrinogen, fibrinogen degradation products, and D-dimer, were found elevated in patients with severe COVID-19. Presumably, the severity of COVID-19 might also be associated with coagulation dysfunction.

Recent studies documenting the laboratory changes of patients with confirmed COVID-19 have noted that elevated D-dimer might be found to be related with higher mortality rate of community-acquired pneumonia [22]. Patients with severe community-acquired pneumonia had significantly higher D-dimer levels, and D-dimer within normal range indicated low risk for complications [23]. Augmented activity of urokinase could cause hyperfibrinolysis, by increasing cleavage of plasminogen into the active plasmin, and finally led to diffuse alveolar damage and acute lung injury, in a mouse model of SARS-CoV disease [24]. In our cohort study, the level of coagulation function parameters, including prothrombin time, fibrinogen, fibrinogen degradation products, and D-dimer, were found elevated in patients with severe COVID-19. Presumably, the severity of COVID-19 might also be associated with coagulation dysfunction.

Recent studies documenting the laboratory changes of patients with confirmed COVID-19 have noted that elevated D-dimer might be associated with the disease progression of COVID-19. The level of D-dimer in patients with COVID-19 admitted to the ICU was reported significantly increased [25]. Clinical attention to venous thromboembolism risk should particularly be paid to those patients with severe COVID-19, who were often bedridden and presented with abnormal coagulation function [25,26]. Rapid deterioration was observed in cases with significantly increased D-dimer during the disease progression. In this regard, pulmonary embolism after deep vein thrombosis detachment should be considered and immediately on the alert, especially when patients presented clinical manifestations such as a rapid drop in blood pressure, sudden deterioration of oxygenation, and respiratory distress.
In addition to thrombosis and pulmonary embolism, D-dimer might be a manifestation of severe virus infection. A virus infection may develop into sepsis and induce coagulation dysfunction, which was common in serious disease progression. Moreover, the increase of D-dimer may be an indirect manifestation of inflammatory reaction, as inflammatory cytokines could cause the imbalance of coagulation and fibrinolysis in the alveoli, which may activate the fibrinolysis system, and then increase the level of D-dimer [27,28]. And D-dimer greater than 1 μg/ml was found a risk factor of poor prognosis for patients with COVID-19 [6]. Abnormal levels of D-dimer were also associated with 28-day mortality in patients with COVID-19, and low molecular weight heparin treatment might be beneficial to COVID-19 patients with markedly elevated D-dimer (i.e. over 3 μg/ml) with reduced mortality rate [27].

There were several limitations in our study. Firstly, a significant degree of heterogeneity and a publication bias were detected in the meta-analysis, because most of included studies were retrospective and non-randomized controlled trial. Secondly, converting non-normally distributed statistics (median and range) to normally distributed statistics (mean and SD) may cause a bias, when evaluating the changes of D-dimer value between severe patients and non-severe patients. Finally, the odds of severe COVID-19 associated with abnormal level of D-dimer, was based on univariable analysis or obtained by calculation in some studies [3,18–20]. Therefore, the bias may be inevitable.

Table 3
Characteristics of patients from 12 published studies and our cohort study included in the meta-analysis.

| Study          | All patients | Non-severe | Severe |
|----------------|--------------|------------|--------|
|                | Sample size  | D-dimer (μg/ml) | Sample size  | D-dimer (μg/ml) | No. of abnormal D-dimer | Sample size  | D-dimer (μg/ml) | No. of abnormal D-dimer |
| Cao M et al. [10] | 195         | 0.39(0.28–0.67) | 176       | 0.37(0.26–0.56) | NA            | 19           | 0.77(0.43–1.23) | NA            |
| Liu J et al. [11] | 40          | 0.6(0.3–0.9)    | 27        | 0.4(0.2–0.8)    | NA            | 13           | 0.9(0.7–1.5)    | NA            |
| Liu L et al. [12] | 51          | 0.28(0.19–0.51) | 44        | 0.28(0.18–0.46) | NA            | 7            | 0.6(0.28–1.4)   | NA            |
| Lu HZ et al. [13] | 265         | 0.42(0.29–0.8)  | 243       | 0.39(0.28–0.72) | NA            | 22           | 0.8(0.5–3.5)    | NA            |
| Qian GQ et al. [14] | 91          | 0.3(0.11–0.45)  | 82        | 0.3(0.11–0.4)   | NA            | 9            | 0.45(0.16–0.49) | NA            |
| Xu Y et al. [15] | 69          | 0.5(0.3–1.2)    | 44        | 0.5(0.3–0.9)    | NA            | 25           | 2.3(0.6–14.1)   | NA            |
| Zhang GQ et al. [16] | 221        | 0.23(0.13–0.49) | 166       | 0.18(0.12–0.32) | NA            | 55           | 0.44(0.21–1.30) | NA            |
| Zhang JJ et al. [17] | 81          | 0.2(0.1–0.5)    | 43        | 0.2(0.1–0.3)    | NA            | 38           | 0.4(0.2–2.4)    | NA            |
| Chen X et al. [18] | 254         | NA           | 209       | NA              | 199           | 45           | NA              | 44            |
| Guan W et al. [19] | 560         | NA           | 451       | NA              | 195           | 109          | NA              | 65            |
| Liu T et al. [19] | 80          | NA           | 11        | NA              | 0             | 69           | NA              | 45            |
| Qi D et al. [20] | 267         | NA           | 217       | NA              | 6             | 50           | NA              | 13            |
| Our study       | 1561        | 0.7(0.33–1.61) | 1196      | 0.52(0.28–1.13) | 621           | 365          | 1.77(0.86–4.55) | 327           |

Data of D-dimer value were shown in median (IQR). IQR = interquartile range.

Fig. 2. Flow chart presenting the process of literature search for this meta-analysis.
Nevertheless, our study demonstrated that the D-dimer level in patients with severe COVID-19 was higher than that in mild cases. Thus, the evidence that patients with elevated D-dimer levels might have a higher risk of severe infection from our cohort study and the meta-analysis, provided a timely reminder to physicians that those COVID-19 patients with higher D-dimer should attract more attention in early time.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2020.07.047.

Authorship contributions

Dai-Shi Tian and Wei Wang conceived and designed study. Hai-Han Yu, Chuan Qin and Man Chen collected data. Chuan Qin performed statistical analyses about the cohort study, and Hai-Han Yu for the meta-analysis. Dai-Shi Tian, Hai-Han Yu and Chuan Qin wrote the initial draft of the manuscript. Final approval was required by all authors.

Funding

This work was supported by the National Natural Science Foundation of China (81873743 to D.S. Tian, 81801223 to C. Qin).

Declaration of competing interest

None.

Acknowledgments

None.

References

[1] Q. Li, X. Guan, P. Wu, et al., Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia, New Engl. J. Med. 382 (13) (2020) 1199–1207, https://doi.org/10.1056/NEJMoa2001316.
[2] World Health Organization (WHO), Coronavirus disease 2019 (COVID-19) situation report – 51, https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10, (March 11 2020).
[3] W.J. Guan, Z.Y. Ni, Y. Hu, et al., Clinical characteristics of coronavirus disease 2019 in China, New Engl. J. Med. (2020), https://doi.org/10.1056/NEJMoa2002052.
[4] C. Qin, L. Zhou, Z. Hu, et al., Dysregulation of immune response in patients with COVID-19 in Wuhan, China, Clin. Infect. Dis. (2020), https://doi.org/10.1093/cid/ciaa246.
[5] N. Tang, D. Li, X. Wang, et al., Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, J. Thromb. Haemost. 18 (4) (2020) 844-847, https://doi.org/10.1111/jth.14768.
[6] F. Zhou, T. Yu, R. Du, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (10229) (2020) 1054–1062, https://doi.org/10.1016/s0140-6736(20)30566-3.
[7] WHO, 2019-nCoV/clinical/2020.4, https://www.who.int/publications-detail/
clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.

[8] S.P. Hozo, B. Djulbegovic, I. Hozo, Estimating the mean and variance from the median, range, and the size of a sample, BMC Med. Res. Methodol. 5 (2005) 13, https://doi.org/10.1186/1471-2288-5-13.

[9] T. Liu, G. Li, L. Li, et al., Association between C-reactive protein and recurrence of atrial fibrillation after successful electrical cardioversion: a meta-analysis, J. Am. Coll. Cardiol. 49 (15) (2007) 1642–1648, https://doi.org/10.1016/j.jacc.2006.12.042.

[10] M. Cao, D. Zhang, Y. Wang, et al., Clinical features of patients infected with the 2019 novel coronavirus (COVID-19) in Shanghai, medRxiv (2020), https://doi.org/10.1101/2020.03.04.20030395 2020.03.04.20030395.

[11] J. Liu, S. Li, J. Liu, et al., Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients, medRxiv (2020), https://doi.org/10.1101/2020.02.16.20023671 2020.02.16.20023671.

[12] L. Liu, J.Y. Gao, Clinical characteristics of 51 patients discharged from hospital with COVID-19 in Chongqing, China, medRxiv (2020), https://doi.org/10.1101/2020.02.20.20025536 2020.02.20.20025536.

[13] H. Lu, J. Ai, Y. Shen, et al., A descriptive study of the impact of diseases control and prevention on the epidemics dynamics and clinical features of SARS-CoV-2 outbreak in Shanghai, lessons learned for metropolis epidemics prevention, medRxiv (2020), https://doi.org/10.1101/2020.02.19.20025031 2020.02.19.20025031.

[14] G.-Q. Qian, N.-B. Yang, F. Ding, et al., Epidemiologic and clinical characteristics of 91 hospitalized patients with COVID-19 in Zhejiang, China: a retrospective, multicentre case series, medRxiv (2020), https://doi.org/10.1101/2020.02.23.20026856 2020.02.23.20026856.

[15] Y. Xu, Y.-r. Li, Q. Zeng, et al., Clinical characteristics of SARS-CoV-2 pneumonia compared to controls in Chinese Han population, medRxiv (2020), https://doi.org/10.1101/2020.03.08.20031658 2020.03.08.20031658.

[16] G. Zhang, C. Hu, L. Luo, et al., Clinical features and outcomes of 221 patients with COVID-19 in Wuhan, China, medRxiv (2020), https://doi.org/10.1101/2020.03.02.20030452 2020.03.02.20030452.

[17] J.J. Zhang, X. Dong, Y.Y. Cao, et al., Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China, Allergy (2020), https://doi.org/10.1111/all.14238.

[18] X. Chen, F. Zheng, Y. Qing, et al., Epidemiological and clinical features of 291 cases with coronavirus disease 2019 in areas adjacent to Hubei, China: a double-center observational study, medRxiv (2020), https://doi.org/10.1101/2020.03.03.20030353 2020.03.03.20030353.

[19] T. Liu, J. Zhang, Y. Yang, et al., The potential role of IL-6 in monitoring severe case of coronavirus disease 2019, medRxiv (2020), https://doi.org/10.1101/2020.03.01.20029769 2020.03.01.20029769.

[20] D. Qi, X. Yan, X. Tang, et al., Epidemiological and clinical features of 2019-nCoV acute respiratory disease cases in Chongqing municipality, China: a retrospective, descriptive, multi-center study, medRxiv (2020), https://doi.org/10.1101/2020.03.01.20029397 2020.03.01.20029397.

[21] H. Han, L. Yang, R. Liu, et al., Prominent changes in blood coagulation of patients with SARS-CoV-2 infection, Clin. Chem. Lab. Med. (2020), https://doi.org/10.1515/cclin-2020-0188.

[22] J.M. Querol-Ribelles, J.M. Tenias, E. Grau, et al., Plasma d-dimer levels correlate with outcomes in patients with community-acquired pneumonia, Chest 126 (4) (2004) 1087–1092, https://doi.org/10.1378/chest.126.4.1087.

[23] D. Snijders, M. Schoorl, M. Schoorl, et al., D-dimer levels in assessing severity and clinical outcome in patients with community-acquired pneumonia. A secondary analysis of a randomised clinical trial, Eur J Intern Med 23 (5) (2012) 436–441, https://doi.org/10.1016/j.ejim.2011.10.019.

[24] L.E. Gralinski, A. Bankhead 3rd, S. Jeng, et al., Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury, mBio 4 (4) (2013), https://doi.org/10.1128/mBio.00271-13.

[25] C. Huang, Y. Wang, X. Li, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506, https://doi.org/10.1016/s0140-6736(20)30183-5.

[26] N. Chen, M. Zhou, X. Dong, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (10223) (2020) 507–513, https://doi.org/10.1016/j.laneuo.2020.10.017.

[27] N. Tang, H. Bai, X. Chen, et al., Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy, J. Thromb. Haemost. (2020), https://doi.org/10.1111/jth.14817.

[28] X.Y. Li, B. Du, Y.S. Wang, et al., The keypoinst in treatment of the critical coronavirus disease 2019 patient, Zhonghua Jie He He Hu Xi Za Zhi 43 (0) (2020) E026, https://doi.org/10.15630/zjhar.43.0.20200224.00159.