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Original Article

Risk factors for disease severity in COVID-19 patients: A single-center retrospective study

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ABSTRACT

Background: The outbreak of coronavirus disease 2019 (COVID-19) has posed a huge threat to human health. However, little is known regarding the risk factors associated with COVID-19 severity. We aimed to explore early-stage disease risk factors associated with eventual disease severity.

Methods: This study enrolled 486 hospitalized, non-intensive care unit (ICU)-admitted adult patients with COVID-19 (age ≥ 18 years) treated at Wuhan Jinyintan Hospital, who were divided into three groups according to disease severity. The demographic, clinical, and laboratory data at admission and clinical outcomes were compared among severity groups, and the risk factors for disease severity were identified by multiple regression analysis.

Results: Of 486 patients with COVID-19, 405 (83.33%) were discharged, 33 (6.71%) died outside of the ICU, and 48 (7.20%) were still being treated in the ICU by the time the study period ended. Significant differences in age, lymphocyte counts, and the levels of procalcitonin, aspartate aminotransferase, and D-dimer ($P < 0.001$ for all) among the three groups. Further analysis showed that older age, decreased lymphocyte counts, and increased procalcitonin, aspartate aminotransferase, and D-dimer levels were significantly associated with disease progression.

Conclusion: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may impair the immune system, the blood coagulation system, and hepatic and cardiac function. Some clinical characteristics and laboratory findings can help identify patients with a high risk of disease severity, which can be significant for appropriate resource allocation during the COVID-19 pandemic.

Introduction

The coronavirus disease 2019 (COVID-19) outbreak presents a critical threat to global health and represents a huge challenge for the economic, medical, and public health infrastructure of China and the world. COVID-19 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The clinical characteristics, diagnosis, pathogenesis, and epidemiology of COVID-19 have been well-described in many studies [1–4]. These studies reported that older age, comorbidities, D-dimer levels greater than 1 μg/L, and high Sequential Organ Failure Assessment (SOFA) scores assessed during early-stage disease were potential risk factors for poor prognosis. The clinical spectrum of COVID-19 ranges from mild to critical. Yang et al. [3] analyzed

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52 critically ill patients who were admitted to the intensive care unit (ICU) of Wuhan Jinyintan Hospital and reported a mortality rate as high as 61.5%. Disease severity has been associated with clinical outcomes. However, little is known regarding the factors that contribute to COVID-19 disease severity.

Studies examining the detailed clinical features and the clinical outcomes of COVID-19 patients presenting with different disease severity are scarce. However, such studies will provide guidance for the efficient allocation of healthcare resources, which is crucial for reducing patient mortality. In this study, we compared the clinical and laboratory characteristics and outcomes among patients groups presenting with moderate, severe, and critical COVID-19 to explore the risk factors for increased disease severity. Our purpose was to establish a preliminary triage principle to quickly identify patients who were likely to become critically to provide a reasonable mechanism for resource allocation in situations in which the number of patients is rising rapidly and resources are scarce.

Methods

Study design and participants

This study was a single-center, retrospective study that included 486 hospitalized, non-ICU-admitted adult patients with COVID-19 (age ≥ 18 years) at Wuhan Jinyintan Hospital between February 1, 2020, and March 20, 2020 (**Clinical trial registration number:** NCT04292327). All of the adult patients enrolled in this study were diagnosed with COVID-19 and treated according to the Fifth version of the Protocol of the Diagnosis and Treatment for Novel Coronavirus Pneumonia (hereafter referred to as the Fifth Protocol), which was released by the National Health Commission and State Administration of Traditional Chinese Medicine of China on February 6, 2020 [5].

This study was approved by the Ethics Committee of the Jinyintan Hospital (KY-2020-24.01), and written informed consent was waived by the Ethics Committee.

Clinical classification

According to the Fifth Protocol, COVID-19 patients were categorized into four groups: mild, moderate, severe, and critical. Patients in the mild group presented with mild clinical symptoms and no signs of pneumonia on imaging. Patients in the moderate group presented with fever, cough, and other respiratory symptoms, with evidence of pneumonia on chest computed tomography. Patients were classified as severe if they met any of the following criteria: (1) respiratory distress and respiratory rate ≥ 30 breaths a minute; (2) oxygen saturation on room air ≤ 93% at rest; or (3) arterial partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ≤ 300 mmHg. Patients were categorized into the critical group if they met any of the following criteria: (1) required mechanical ventilation due to respiratory failure; (2) experienced shock; or (3) experienced organ failure, requiring ICU care.

Data collection

Data were extracted from electronic medical records. We collected baseline demographic variables, clinical symptoms at admission (fever, cough, tachypnea, sore throat, fatigue, and diarrhea), disease severity (mild, moderate, severe, and critical), time from symptom onset to diagnosis, time from diagnosis to hospital admission, the fastest respiratory rate and blood pressure values recorded on admission, laboratory variables (white blood cell counts, lymphocyte counts, platelet counts, and levels of creatinine, total bilirubin, and inflammatory cytokines), radiological findings, comorbidities (hypertension, coronary heart disease, diabetes, chronic hepatitis, and tumor), and clinical outcomes (death, admission to ICU, and discharge). All medical data were independently verified by two authors (J Xu and Q Li), and another author (Y Cai) made the final decision on any differences in data interpretation between the two authors.

We compared the clinical characteristics and laboratory findings among three of the four groups (moderate, severe, and critical). We set the upper and lower limits for each variable based on the normal limits of laboratory examinations and then counted the number of individuals in each group that were above or below those numbers. The time from symptom onset to diagnosis and the time from diagnosis to hospital admission were included due to the overwhelming number of patients with COVID-19 and the local limited medical resources in Wuhan during the early stages of the disease outbreak.

Statistical analysis

The Shapiro–Wilk normality test was used to examine the assumption of normality for all variables. Data are expressed as the mean ± standard deviation, median (interquartile range [IQR]), or frequencies and percentage, as indicated. Analysis of variance, Kruskal–Wallis test, Chi-square test, and Fisher's exact test were used to compare values among the three severity groups. A logistic regression model was built for each of the three groups, using the moderate severity group as the reference group, to examine the relationships between disease severity and predictor variables. To explore the prognostic risk factors, multiple regression analysis was used. The results are expressed as odds ratios with 95% confidence intervals (CIs). A value of $P < 0.05$ was considered significant. SPSS version 23.0 (IBM Corporation, Chicago, IL, USA) was used for data analysis.

Results

Patients characteristics

A total of 270, 124, and 92 patients were included in the moderate, severe, and critical groups, respectively [Table 1]. The average age for all included patients was 59.25 ± 13.69 years. Patients in the critical group were older than those in the severe and moderate groups ($P< 0.001$ for both). Only 2.06% of patients had any history of contact with the Huanan Seafood Wholesale Market (Huanan wet market). A total of 39.71% of patients had comorbidities, especially hypertension. More patients with comorbidities were categorized in the severe and critical groups than in the moderate group. The time from symptom onset to diagnosis was similar among the three groups. Compared with the moderate group, the wait time for admission among patients with severe and critical illness was shorter.

Table 1
Demographics and clinical characteristics of patients with COVID-19 according to disease severity.

Variable	Total patients	Disease severity			*P*-value
	(*n* = 486)	Moderate (*n* = 270)	Severe (*n* = 124)	Critical (*n* = 92)	
Age (years), mean±SD	59.25±13.69	56.66±13.25*, †	60.67±13.12*	64.89±13.87	<0.001
Sex					0.250
Female, *n* (%)	23 4 (48.15)	138 (51.11)	58 (46.77)	38 (41.30)	
Male, *n* (%)	252 (51.85)	132 (48.89)	66 (53.23)	54 (58.70)	
Exposure history to seafood market, *n* (%)	10 (2.06)	6 (2.22)	3 (2.42)	1 (1.09)	0.761
Comorbidity, *n* (%)	193 (39.71)	86 (31.85)*	53 (42.74)	54 (58.70)	<0.001
Hypertension	136 (27.98)	56 (20.74)*	42 (33.87)	38 (41.30)	<0.001
Coronary heart disease	25 (5.14)	10 (3.70)	7 (5.65)	8 (8.70)	0.160
Diabetes	48 (9.88)	24 (8.89)	13 (10.48)	11 (11.96)	0.672
Chronic hepatitis	11 (2.26)	7 (2.59)	2 (1.61)	2 (2.17)	0.917
Tumor	10 (2.06)	1 (0.37)*	3 (2.42)	6 (6.52)	0.001
First symptom, *n* (%)					
Fever	389 (80.04)	212 (78.52)	105 (84.68)	72 (78.26)	0.326
Cough	223 (45.88)	126 (46.67)	59 (47.58)	38 (41.30)	0.610
Tachypnea	137 (28.19)	75 (27.78)	25 (20.16)*	37 (40.22)	0.005
Sore throat	5 (1.03)	4 (1.48)	1 (0.81)	0 (0.00)	0.833
Fatigue	101 (20.78)	58 (21.48)	21 (16.94)	22 (23.91)	0.418
Diarrhea	24 (4.94)	12 (4.44)	6 (4.84)	6 (6.52)	0.728
Systolic pressure (mmHg), median (IQR)	123.00 (115.00, 132.00)	123.00 (114.75, 132.00)	123.00 (115.50, 130.50)	124.00 (110.00, 135.00)	0.909
Diastolic pressure (mmHg) median (IQR)	78.00 (70.00, 85.00)	77.00 (71.00, 85.00)	79.00 (69.50, 85.50)	78.00 (66.00, 86.00)	0.384
Time from symptom onset to diagnosis (days), median (IQR)	7.00 (5.00, 11.00)	7.00 (5.00, 11.00)	8.00 (6.00, 12.00)	7.00 (5.00, 10.75)	0.319
Time from diagnosis to hospital admission (days), median (IQR)	3.00 (1.00, 6.00)	3.00 (1.00, 7.00)*,†	2.00 (1.00, 5.00)	2.00 (1.00, 5.00)	0.004

SD: Standard deviation; IQR: Interquartile range.
*$P < 0.05$ and † $P < 0.05$. There are post-hoc comparisons.
* Comparison between critical group and moderate or severe group.
† Comparison between severe group and moderate group.

Laboratory findings on admission

The proportions of patients with abnormal white blood cell counts, neutrophil counts, and brain natriuretic peptide levels were the highest in the critical group [Table 2]. The critical group and the severe group contained more patients with high levels of serum ferritin and troponin I and low total lymphocyte counts than the moderate group, whereas the proportions of patients with abnormally high levels of procalcitonin, aspartate aminotransferase, and D-dimer were the highest in the critical group and the lowest in the moderate group. Compared with the moderate group, the critical group had a lower platelet count and a higher creatinine level.

Clinical outcomes

A total of 33 (35.87%) critically ill patients died in a non-ICU ward, and 38 (41.3%) critically ill patients were transferred to the ICU. A total of 97.78% of patients in the moderate group and 96.77% of patients in the severe group were successfully treated and discharged. More patients in the critical and severe groups presented with the positive detection of SARS-CoV-2 nucleic acids by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) after two consecutive negative results than those in the moderate group. No significant difference in the persistence of positive SARS-CoV-2 nucleic acid test results was observed among the three groups [Table 3].

Table 2
Laboratory findings of patients at the time of hospital admission.

Laboratory finding	Total patients	Disease severity			*P*-value
	(n = 486)	Moderate(n = 270)	Severe(n = 124)	Critical(n = 92)	
White blood cell count >10 × 10^9/L or <4 × 10^9/L	104 (21.40)	44 (16.30)*	25 (20.16)*	35 (38.04)	<0.001
Neutrophil count >6.3 × 10^9/L or <1.8 × 10^9/L	137 (28.19)	56 (20.74)*	35 (28.23)*	46 (50.00)	<0.001
Lymphocyte count <1.1 × 10^9/L	256 (52.67)	102 (37.78)*, †	82 (66.13)*	72 (78.26)	<0.001
Platelet count <125 × 10^9/L	45 (9.26)	15 (5.56)*	12 (9.68)	18 (19.57)	<0.001
Hematocrit >0.45 or <0.35	192 (39.51)	99 (36.67)	59 (47.58)	34 (36.96)	0.103
Inflammatory cytokines					
C-reactive protein >6 mg/L	84 (17.28)	64 (23.70)*, †	12 (9.68)	8 (8.70)	<0.001
Procalcitonin >0.05 ng/L	139 (28.60)	38 (14.07)*, †	45 (36.29)*	56 (60.87)	<0.001
Interleukin-6 >0.7 pg/L	279 (57.41)	147 (54.44)	72 (58.06)	60 (65.22)	0.193
Erythrocyte sedimentation rate>20 mm/H	325 (66.87)	159 (58.89)*, †	96 (77.42)	70 (76.09)	<0.001
Serum ferritin >274.66 ng/mL	271 (55.76)	127 (47.04)*, †	82 (66.13)	62 (67.39)	<0.001
Total bilirubin >21 μmol/L	42 (8.64)	19 (7.04)	9 (7.26)	14 (15.22)	0.045
ALT >40 μmol/L	172 (35.39)	91 (33.70)	46 (37.10)	35 (38.04)	0.682
AST >35 μmol/L	208 (42.80)	85 (31.48)*, †	58 (46.77)*	65 (70.65)	<0.001
Creatinine >81 μmol/L	117 (24.07)	54 (20.00)*	28 (22.58)	35 (38.04)	0.002
Amylase >135 U/L	14 (2.88)	7 (2.59)	4 (3.23)	3 (3.26)	0.914
Lipase >78 U/L	45 (9.26)	16 (5.93)†	17 (13.71)	12 (13.04)	0.018
PT >13.5 s	22 (4.53)	10 (3.70)	6 (4.84)	6 (6.52)	0.522
APTT >37 s	30 (6.17)	10 (3.70)	12 (9.68)	8 (8.70)	0.039
Fibrinogen >4 g/L	247 (50.82)	115 (42.59)†	82 (66.13)	50 (54.35)	<0.001
D-dimer >1.5 μg/mL	124 (25.51)	41 (15.19)*, †	35 (28.23)*	48 (52.17)	<0.001
BNP >100 pg/mL	48 (9.88)	17 (6.30)*	9 (7.26)*	22 (23.91)	<0.001
cTnI >0.1 ng/mL	52 (10.70)	43 (15.93)*, †	4 (3.23)	5 (5.43)	<0.001

Values are presented as n(%).
ALT: Alanine transaminase; AST: Aspartate aminotransferase; PT: Prothrombin time; APTT: Activated partial thromboplastin time; BNP: Brain natriuretic peptide; cTnI: Troponin I.
*$P < 0.05$ and † $P < 0.05$. There are post-hoc comparisons.
* Comparison between critical group and moderate or severe group.
† Comparison between severe group and moderate group.

Table 3
Clinical outcomes according to disease severity.

Variable	Total patients	Disease severity			*P*-value
	(n = 486)	Moderate (n = 270)	Severe (n = 124)	Critical (n = 92)	
Deaths, n(%)	33 (6.79)	0 (0.00)*	0 (0.00)*	33 (35.87)	<0.001
ICU admissions, n(%)	48 (7.20)	6 (2.22)*	4 (3.23)*	38 (41.30)	<0.001
Discharge, n(%)	405 (83.33)	264 (97.78)*	120 (96.77)*	21 (22.83)	<0.001
Hospital stay (days), median (IQR)	13.00 (10.00, 18.00)	13.00 (9.00, 17.00)†	14.00 (12.00, 20.00)	13.00 (9.00, 21.00)	0.006
RP, n(%)	55 (11.32)	20 (7.41)*, †	20 (16.13)	15 (16.30)	0.010
The duration of nucleic acid positive PCR(days), median (IQR)	9.00 (6.00, 13.00)	9.00 (5.00, 13.00)	10.00 (6.00, 13.00)	11.00 (7.00, 14.00)	0.403

IQR: Interquartile range; RP: Re-detectable SARS-CoV-2 nucleic acids by RT-PCR test after two consecutive negative results.
*$P < 0.05$ and † $P < 0.05$. There are post-hoc comparisons.
* Comparison between the critical group and the moderate or severe group.
† Comparison between the severe group and the moderate group.

Table 4
Logistic regression of factors associated with disease severity.

Variables	Moderate (n = 270)	Severe (n = 124)	Critical (n = 92)
Age	1.000	1.022 (1.001–1.044)	1.035 (1.008–1.063)
Lymphocyte count	1.000	2.268 (1.290–3.989)	3.585 (1.663–7.729)
Procalcitonin	1.000	1.857 (0.992–3.475)	3.207 (1.561–6.587)
Aspartate aminotransferase	1.000	1.242 (0.713–2.166)	4.081 (2.004–8.312)
D-dimer	1.000	1.678 (0.903–3.119)	3.336 (1.622–6.863)

Values are presented as odd ratio (95% confidence interval).

Risk factors for disease severity

Statistically significant indicators of univariate analysis were included in multiple regression analysis. As shown in Table 4, older age, decreased lymphocyte counts, and increased levels of procalcitonin, aspartate aminotransferase, and D-dimer were identified as risk factors for disease severity.

Discussion

The number of patients infected with SARS-CoV-2 continues to increase dramatically outside of China, such as in America, Europe, and Southeast Asia. Many healthcare workers in these regions are facing similar situations that the doctors and nurses in Wuhan have previously experienced, in which the sharp increase in the number of patients places tremendous pressure on medical staff and resource allocation. Therefore, the development of a reliable triage process that can be used to better classify COVID-19 patients remains necessary to allow for physicians to appropriately evaluate and treat suspected or confirmed COVID-19 patients, which will improve medical resource allocation and reduce mortality. We summarized the clinical characteristics, laboratory results, and outcomes among patients diagnosed with COVID-19 at the Jinyintan Hospital, which has been designated as a specific treatment center for patients who are positive for SARS-CoV-2, to explore the risk factors associated with disease severity.

Patients with COVID-19 were categorized into moderate, severe, and critical presentation groups according to the diagnostic criteria established by the Fifth Protocol. We found that the older patients tended to experience more serious disease presentations. Compared with the moderate group, severe and critically ill patients had more comorbidities, especially hypertension, which is similar to the findings reported by other groups [6]. No significant differences in the degree of hypertension were observed among the three groups. The median time from symptom onset to diagnosis was 7 days. The wait times between diagnosis and admission for severe and critically ill patients were shorter than that for the moderate group, which indicates that the medical system in Wuhan adopted an effective triage process. The results of this study showed that the wait time for admission did not affect patient prognosis, in contrast with the study reported by Liang et al. [7], which found that the duration from symptom onset to hospitalization was an independent risk factor for prognosis.

More abnormal laboratory test results were observed in the severe group and the critical group than in the moderate group, such as elevated levels of brain natriuretic peptide, procalcitonin, serum ferritin, total bilirubin, blood creatinine, aspartate aminotransferase, and D-dimer, increased white blood cell and neutrophil counts, prolonged prothrombin times, and decreased total lymphocyte and platelet counts. These findings suggested that COVID-19 could cause multiple organ dysfunction. Increasing research on the pathogenesis and pathophysiology of COVID-19 has identified angiotensin-converting enzyme 2 (ACE2) as the most likely primary receptor through which SARS-CoV-2 gains access to human cells [8]. Disease progression results in the activation of immune cells and coagulation pathways, which can lead to multiple organ failure [8,9].

The multiple regression analysis showed that older age, decreased lymphocyte count, and increased levels of procalcitonin, aspartate aminotransferase, and D-dimer were independent risk factors for disease severity. In addition, recent studies have indicated that increased procalcitonin levels in patients with COVID-19 pneumonia were associated with bacterial infections [10,11], suggesting that the increased severity of COVID-19 could be the result of concomitant bacterial infections, damaged cellular immunity, and impaired blood coagulation and liver functions. These results also remind us that the prevention of bacterial infections and appropriate immunotherapy may be key factors for delaying disease progression and reducing mortality. Many studies have shown that immunotherapy represents a promising therapeutic avenue for COVID-19 [12,13].

C-reactive protein (CRP) and interleukin (IL)-6 levels have previously been associated with COVID-19 disease severity, but our retrospective study did not support these findings [14–16]. Unlike previous studies, the present study compared the proportions of abnormal indicators among different disease severity groups rather than examining differences in the absolute values of these indicators. These differences between our study and the previous studies may also indicate that other factors are involved in disease progression. For example, recent studies have shown that coagulation system disorders could lead to microthrombosis [9,17]. More studies remain necessary to determine the pathophysiological mechanisms that lead to the exacerbation of COVID-19.

There are several limitations to our study. First, this study was a single-center retrospective study with a limited sample size, and the data we collected occurred during the early stages of the COVID-19 outbreak before some laboratory tests began to be ordered for COVID-19. Second, some information for patients who were transferred to the ICU was missing, which may be crucial for exploring further risk factors. Third, we only analyzed some of the clinical characteristics, laboratory findings, and final outcomes of patients. However, dynamic changes in computed tomography and other clinical symptoms and laboratory findings may also be crucial to predicting disease progression. Finally, we compared the proportion of patients with abnormal laboratory tests among different disease severity groups. However, the absolute values of these laboratory tests may also be related to disease progression.

In conclusion, based on our data and analyses, SARS-CoV-2 may attack the immune system, the blood coagulation system, and the livers and hearts of COVID-19 patients. More attention should be paid to patients with older age, decreased lymphocyte counts, and increased levels of procalcitonin, aspartate aminotransferase, and D-dimer.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

[1] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323(11):1061–9. doi:10.1001/jama.2020.1585.
[2] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8(4):420–2. doi:10.1016/S2213-2600(20)30076-X.
[3] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8(5):475–81. doi:10.1016/S2213-2600(20)30079-5.
[4] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054–62. doi:10.1016/S0140-6736(20)30566-3.
[5] http://www.nhc.gov.cn/yzygj/s7653p/202002/d4b895337e19445f8d728fcaf1e3e13a.shtml. February 2020.
[6] Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with different severities: a multicenter study of clinical features. Am J Respir Crit Care Med 2020;201(11):1380–8. doi:10.1164/rccm.202002-0445OC.
[7] Liang WH, Guan WJ, Li CC, Li YM, Liang HR, Zhao Y, et al. Clinical characteristics and outcomes of hospitalised patients with COVID-19 treated in Hubei (epicentre) and outside Hubei (non-epicentre): a nationwide analysis of China. Eur Respir J 2020;55(6). doi:10.1183/13993003.00562-2020.
[8] Datta PK, Liu F, Fischer T, Rappaport J, Qin X. SARS-CoV-2 pandemic and research gaps: understanding SARS-CoV-2 interaction with the ACE2 receptor and implications for therapy. Theranostics 2020;10(16):7448–64. doi:10.7150/thno.48076.
[9] Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020;18(5):1023–6. doi:10.1111/jth.14810.
[10] Tang ML, Li YQ, Chen X, Lin H, Jiang ZC, Gu DL, et al. Co-infection with common respiratory pathogens and SARS-CoV-2 in patients with COVID-19 pneumonia and laboratory biochemistry findings: a retrospective cross-sectional study of 78 patients from a single center in China. Med Sci Monit 2021;27:e929783. doi:10.12659/MSM.929783.
[11] Heesom L, Rehnberg L, Nasim-Mohi M, Jackson A, Celinski M, Dushianthan A, et al. Procalcitonin as an antibiotic stewardship tool in COVID-19 patients in the intensive care unit. J Glob Antimicrob Resist 2020;22:782–4. doi:10.1016/j.jgar.2020.07.017.
[12] AminJafari A, Ghasemi S. The possible of immunotherapy for COVID-19: a systematic review. Int Immunopharmacol 2020;83 106455. doi:10.1016/j.intimp.2020.106455.
[13] Kandikattu HK, Venkateshaiah SU, Kumar S, Mishra A. IL-15 immunotherapy is a viable strategy for COVID-19. Cytokine Growth Factor Rev 2020;54:24–31. doi:10.1016/j.cytogfr.2020.06.008.
[14] Potempa LA, Rajab IM, Hart PC, Bordon J, Fernandez-Botran R. Insights into the use of C-reactive protein as a diagnostic index of disease severity in COVID-19 infections. Am J Trop Med Hyg 2020;103(2):561–3. doi:10.4269/ajtmh.20-0473.
[15] Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, et al. Prognostic value of C-reactive protein in patients with Coronavirus 2019. Clin Infect Dis 2020;71(16):2174–9. doi:10.1093/cid/ciaa641.
[16] Chen X, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, et al. Detectable serum severe acute respiratory syndrome Coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 level in critically ill patients with Coronavirus disease 2019. Clin Infect Dis 2020;71(8):1937–42. doi:10.1093/cid/ciaa449.
[17] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18(4):844–7. doi:10.1111/jth.14768.