Research Article
iMedPub Journals
http: journals.imedpub.com
DOI: 10.36648/biology-medical-research.4.21
Journal of Biology and Medical Research
2020
Vol. 4 ISS. 2

The Values of Cytokines in Evaluating the Severity and Prognosis of COVID-19

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Citation: SJin X, Wang D, Liu Y, Peng D, Bao T, et al. (2020) The Values of Cytokines in Evaluating the Severity and Prognosis of COVID-19. Vol 4 No. 2:1. DOI: 10.36649/biology-medical-research.4.2.1.

Abstract

Background: Cytokine storms are the dominating cause of Coronavirus disease 2019 (COVID-19) patients death, and cytokines will be used as useful indicators of COVID-19 severity.

Methods: We retrospectively collected 205 COVID-19 patients at Wuhan Leishenshan Hospital of Hubei, China. We analyzed the relationship between the levels of the cytokines and COVID-19 patients through the data including interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-1β (IL-1β), interleukin-2 receptor (IL2R), interleukin-8 (IL-8), tumor necrosis factor α (TNF-α).

Results: There were significant difference in IL-6, IL-10, IL-2R, IL-8, and TNF-α among mild, severe and critical patients (all $p<0.05$), interestingly, although IL-1β was no significant difference, 99% patients with the higher level of IL-1β. Significantly, disease severity was associated with age, acute COVID-19, IL-6, IL-10 IL-2R, IL-8, and TNF-α. Logistic regression analysis showed that several factors as the risk factors for the development of severe and death, which included the acute COVID-19, IL-6, IL-2R, IL-8, and IL-10. However, age was not the risk factors for the death. Further, the receiver operating characteristic curves showed that the IL-6 is excellent predicting the mortality risk of COVID-19.

Conclusion: Cytokines is closely related to COVID-19 severity, dynamic monitoring of them, might be a key in the control of COVID-19 death.

Keywords: COVID-19; Cytokines; Predict

Received: July 13, 2020; **Accepted:** July 27, 2020; **Published:** August 03, 2020

Introduction

Coronavirus disease 2019 (COVID-19), a cluster of acute respiratory illness, now has been widely known as a global health threat [1-5]. The 2019 novel coronavirus (SARS-CoV-2) was identified in samples of alveolar lavage fluid from a patient in Wuhan and was confirmed as the cause of COVID-19. Coronavirus can cause multiple systemic infections and mainly respiratory tract infections in humans, such as severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) [6,7]. Although most of the COVID-19 patients have mild symptoms and good prognosis, some patients progressed rapidly with Acute Respiratory Distress Syndrome (ARDS), which was eventually followed by multiple organ failure, for the reason of the cytokine storms [8,9]. Cytokine storms, also termed Cytokine Release Syndrome (CRS), play an important role in the process of disease aggravation [10].

Cytokine storms, the excessive immune response produced by the body to external stimuli, the uncontrolled release of cytokines in large quantities in a short time can lead to systemic inflammatory damage, which can quickly cause hemodynamic instability and multiple organ failure. Cytokines, form a group of small-to-medium size (5-100 kDa) proteins or glycoproteins that act as intercellular communication signals. They are released by various cells, usually in response to an activating stimulus, and induce responses through binding to specific receptors. They have critical roles in haematopoiesis, inflammation, the development and maintenance of immune responses [11-13]. Aberrant release of multiple cytokines appears to trigger a cytokine storm that produces immunopathogenic damage to tissues and organs, even while the immune response seeks to suppress and eradicate the virus. Previous studies have suggested that IL-6 is an important channel and key cytokine to induce cytokine storms [14]. Effective and timely detection of cytokine storms is an important way to prevent the deterioration of patients with SARS-CoV-2 infection and save the patients' lives. Therefore, this study retrospectively analyzed cytokines among COVID-19 patients, which may help

to early identify the disease severity and predict the prognosis of COVID-19, to early perform clinical intervention and control the COVID-19 death.

3. Methods

3.1 Patients

205 consecutive patients confirmed COVID-19 admitted to Wuhan Leishenshan Hospital from February 20 to March 20 was enrolled. The patients were diagnosed and classified followed the New Coronavirus Pneumonia Prevention and Control Program (7th edition) published by the National Health Commission of China. The study was approved by the Ethics Committee of Zhongnan Hospital of Wuhan University. In this study, the acute COVID-19 was defined as the period after the onset of symptoms but before the peak of illness, usually within three weeks after the onset of symptoms; the convalescent COVID-19 was defined as the period immediately after the negative conversion of real-time RT-PCR, usually between two and five weeks after symptom onset.

Standard of severe patients

Severe patients should have any of the following items:

- Respiratory distress, respiratory rate (RR) ≥30 times/minute;
- Under the resting state, the oxygen saturation ≤93%;
- Oxygen partial pressure (PaO2)/oxygen concentration (FiO2) in arterial blood ≤

300 mmHg;

- Lung imaging showed obvious progression of the lesion >50% within 24-48 hours.

Standard of critical patients

Critical patients should have any of the following items:

- Have respiratory failure and mechanical ventilation required;
- Shock;
- Complications of other organ failure require treatment in the intensive care unit (ICU).

3.2 Examination

Examination was ordered at the discretion of the physicians and were measured using standard methods in our hospital. Fasting whole blood from every subject with more than infected 15 days was collected in an separation glue treated tube and analyzed within 30 minutes of collection. Plasma cytokines, interleukin-10 (IL-10), Interleukin-1β (IL-1β), interleukin-2 receptor (IL2R), interleukin-8 (IL-8), tumor necrosis factor α (TNF-α) were detected by Siemens chemiluminescence method and interleukin-6 (IL-6), were detected by Roche electrochemiluminescence method according to the manufacturer's instruction. The detection of SARS-CoV-2 by real-time RT-PCR assay was conducted by the viral nucleic acid detection kit according to the manufacturer's protocol (Daan Gene Co. Ltd.).

3.3 Statistical analysis

Statistical analysis was performed with SPSS version 25.0 software and Graphpad Prism (version 7.0). All the measurement data were tested for normality; non-normally distributed data were expressed as median (interquartile range), nonparametric Mann-Whitney test was used for comparison between the two groups, and Kruskal-Wallis H test was used for comparison between three groups. In correlation analysis, Spearman correlation coefficient was used for the variables of normal distribution, Pearson correlation coefficient for those of skewed distribution, and Kendall's correlation coefficient for ranked data. Logistic regression analysis: calculate the odds ratio and 95% confidence interval. The prediction of various indicators for prognosis COVID-19 patients were analyzed by the receiver operating characteristic (ROC) curves, the area under the ROC curve (AUC) was measured to evaluate the discriminative ability. P value <0.05 was considered statistically significant.

4. Results

4.1 Presenting characteristics

Among the 205 COVID-19 patients, 99 were males and 106 were females, the median age was 58 years

(Interquartile range (IQR), 50-67), as reported previously, older age was linked with severe disease (Table 1, P<0.05). There were 117 mild patients, 69 severe patients and 19 critical patients. 185 were convalescent COVID-19 and 20 were acute COVID-19 (Table 1).

	Total (n=205)	Mild (n=117)	Severe (n=69)	Critical (n=19)	p-value
Age, median (IQR), y	58 (50-67)	54 (48-62)	64 (52-71)	67 (58-77)	<0.001
Gender-No. (%)					[illegible]
Female	106/205 (51.70%)	65/117 (55.55%)	33/69 (47.82%)	8/19 (42.10%)	
Male	99/205 (48.29%)	52/117 (44.44%)	36/69 (52.17%)	11/19 (57.89%)	
Acute COVID-19	20/205 (9.76%)	7/117 (5.98%)	7/69 (10.14%)	6/19 (31.58%)	0.002
Convalescent COVID-19	185/205 (90.24%)	110/117 (94.02%)	62/69 (89.86%)	13/19 (68.42%)	
IL-6 (normal range <7 pg/mL)	151/205 (73.66%)	100/117 (85.47%)	50/69 (72.46%)	1/19 (5.26%)	<0.001
Increased	54/205 (26.34%)	17/117 (14.53%)	19/69 (27.54%)	18/19 (94.74%)	
IL-10 (normal range <9.1 pg/mL)	189/205 (92.20%)	114/117 (97.44%)	63/69 (91.30%)	10/19 (52.63%)	<0.001
Increased	16/205 (7.80%)	3/117 (2.56%)	6/69 (8.70%)	9/19 (47.37%)	
IL-1β (normal range <5 pg/mL)	2/205 (0.98%)	2/117 (1.71%)	0/69 (0.00%)	0/19 (0.00%)	0.148
Increased	203/205 (99.02%)	115/117 (98.29%)	69/69 (100.00%)	19/19 (100.00%)	
IL-2R (normal range 223-710 U/mL)	129/205 (62.93%)	75/117 (64.10%)	46/69 (66.67%)	8/19 (42.11%)	<0.001
Decrease	48/205 (23.41%)	36/117 (30.77%)	10/69 (14.49%)	2/19 (10.53%)	
Increased	28/205 (13.66%)	6/117 (5.13%)	13/69 (18.84%)	9/19 (47.37%)	
IL-8 (normal range <62 pg/mL)	200/205 (97.56%)	116/117 (99.15%)	68/69 (98.55%)	16/19 (84.21%)	<0.001
Increased	5/205 (2.44%)	1/117 (0.85%)	1/69 (1.45%)	3/19 (15.79%)	
TNF-α (normal range <8.1 pg/mL)	158/205 (77.07%)	96/117 (82.05%)	52/69 (75.36%)	10/19 (52.63%)	0.017
Increased	47/205 (22.93%)	21/117 (17.95%)	17/69 (24.64%)	9/19 (47.37%)	

Table 1: Baseline characteristics of 205 patients with COVID-19. The acute COVID-19 was defined as the period after the onset of symptoms but before the peak of illness, usually within two weeks after the onset of symptoms; the convalescent COVID-19 was defined as the period immediately after the negative conversion of real-time RT-PCR, usually between two and five weeks after symptom onset.
Abbreviations: IQR: Interquartile Range

	R	P
Age	0.354	<0.001
Disease course	-0.045	0.518
Acute COVID-19	0.187	0.007
IL-6	0.366	<0.001
IL-10	0.327	<0.001
IL-1β	-0.074	0.293
IL-2R	0.329	<0.001
IL-8	0.273	<0.001

Table 2: Correlation coefficient and P value between parameters and disease severity.

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	Odd Ratio (95% CI)	p value	Odd Ratio (95% CI)	p value
Age	1.054 (1.030-1.079)	<0.001	1.039 (0.980-1.100)	0.192
Gender	1.433 (0.822-2.497)	0.204	1.902 (0.341-10.621)	0.464
Disease course	1.004 (0.973-1.034)	0.778	0.952 (0.866-1.045)	0.299
Acute COVID-19	2.724 (1.038-7.148)	0.042	10.706 (2.004-57.19)	0.006
IL-6	1.037 (1.010-1.064)	0.006	1.001 (1.000-1.001)	0.001
IL-10	1.080 (1.004-1.162)	0.038	1.037 (1.009-1.107)	0.019
IL-1β	0.989 (0.969-1.010)	0.229	0.964 (0.924-1.006)	0.094
IL-2R	1.002 (1.001-1.004)	<0.001	1.002 (1.000-1.003)	<0.001
IL-8	1.035 (1.017-1.054)	0.004	1.049 (1.014-1.086)	0.007
TNF-α	1.000 (0.975-1.027)	0.734	1.033 (0.997-1.070)	0.072

Table 3: Logistic regression analyses of factors predictive for the severe development and death in the COVID-19.

	AUC	95%CI	Cut-of	Sensitivity	Specificit y
IL-6	0.931	0.922-0.991	43.10	1.000	0.899
IL-10	0.742	0.549-1.000	8.05	0.667	0.934
IL-2R	0.815	0.607-1.023	1836	0.600	0.984
IL-8	0.922	0.684-1.000	22.50	0.833	0.945

Table 4. ROC.

4.2 Cytokines parameters of three subgroups patients

The levels of cytokines at mild, severe and critical groups were demonstrated in Figure 1. IL-6, IL-10, IL-2R, IL-8, and TNF-α were significantly different among the three groups (all P<0.05), interestingly, although IL-1β was no significant difference among the groups, 99% patients with the level of IL-1β higher than the normal level (Table 1). As shown in Figure 2, the IL-6, IL-10, IL-2R, IL-8, and TNF-α levels were significantly different among three groups, and all IL-1β concentration was >5 pg/mL in severe and critical patients (Figure 2C). In addition, although the IL-8 reference range was <62 pg/mL, the IL-8 levels of most patients in the mild and the severe groups were <30 pg/mL, and just 15% critical patients in critical group were >62 pg/mL (Table 2). Showed the correlation analysis results between the parameters with disease severity. Significant correlations were found about age, the acute COVID-19, IL-6, IL-10, IL-2R, IL-8, and TNF-α, there was no significant correlation on IL-1β, gender and disease course. Further using logistic regression analysis also found that age, the acute COVID-19, IL-6, IL-10, IL-2R, IL-8 were the risk factors for severe disease in COVID-19 patients (Table 3). The AUC of IL-6, IL-10, IL-2R, IL-8 were 0.588, 0.544, 0.651, 0.592 in mild vs. severe group (Figure 3A). And, the AUC of IL-6, IL-10, IL-2R, and IL-8 were 0.896, 0.742, 0.674, and 0.729 in severe vs. critical group (Figure 3B). This shows that IL-6, IL-10, IL-2R, IL-8 are better in predicting the risk of severe to critical disease, especially the IL-6 increased, indicating worsen the disease.

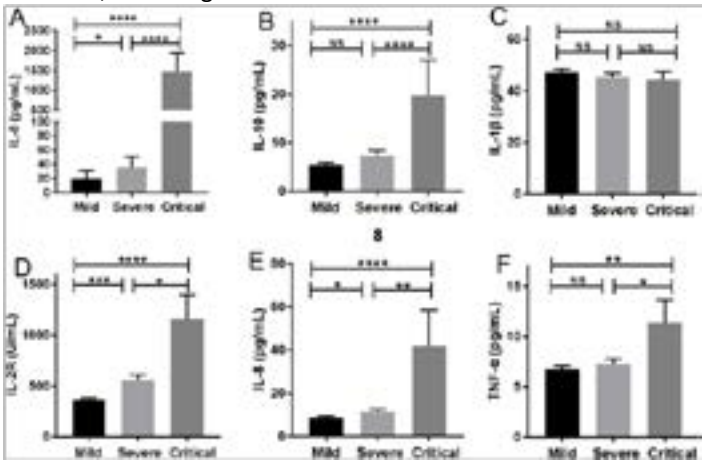

Figure 1: Characteristics of cytokines parameters among mild, severe and critical patients with COVID-19 pneumonia. (A) IL-6; (B) IL-10; (C)IL-1β, (D) IL2R; (E) IL-8; (F) TNF-α. *P<0.05; *P<0.05; ***P<0.001; ****P<0.0001; NS: P>0.05.

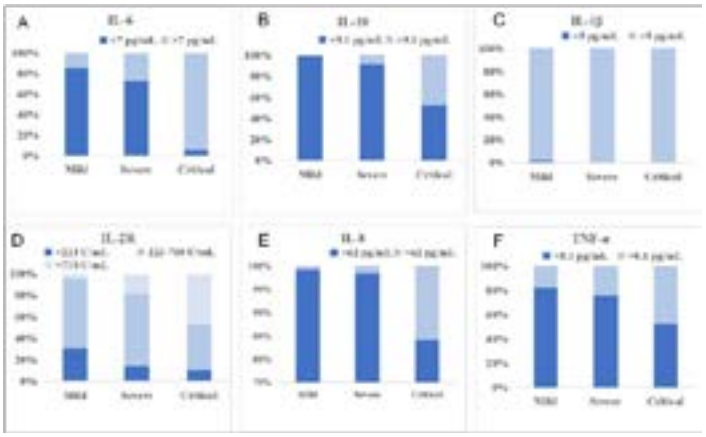

Figure 2: Comparison of cytokines parameters among mild, severe and critical patients with COVID-19 pneumonia. (A) IL-6; (B) IL-10; (C) IL-1β, (D) IL2R; (E) IL-8; (F) TNF-α.

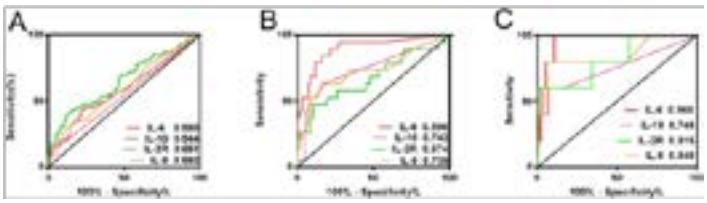

Figure 3: (A) Receiver operator characteristic curves for IL-6, IL-10, IL-2R, and IL-8 to predict the risk of severe illness in mild patients (B) Receiver operator characteristic curves for IL-6, IL-10, IL-2R, and IL-8 to predict the risk of critical illness in severe patients (C) Receiver operator characteristic curves for cytokines prediction of COVID-19 prognosis.

4.3 Cytokines of COVID-19 patients in death and survival group

The levels of cytokines at death and survival group were demonstrated in Figure 4. COVID-19 patients in the death group had significantly higher levels of IL-6, IL-10, IL-2R, IL-8, and TNF-α than the survival group, while there were no significant differences in levels of IL-1β. Logistic regression analysis found that the acute COVID-19, IL-6, IL-10, IL-2R, and IL-8 were the risk factors for death in COVID-19 patients (Table 3). The AUC of IL-6, IL-10, IL-2R, IL-8 were 0.956 [95% confidence interval (95%CI) =0.922-0.991], 0.785 [95%CI=0.549-1.000], 0.815

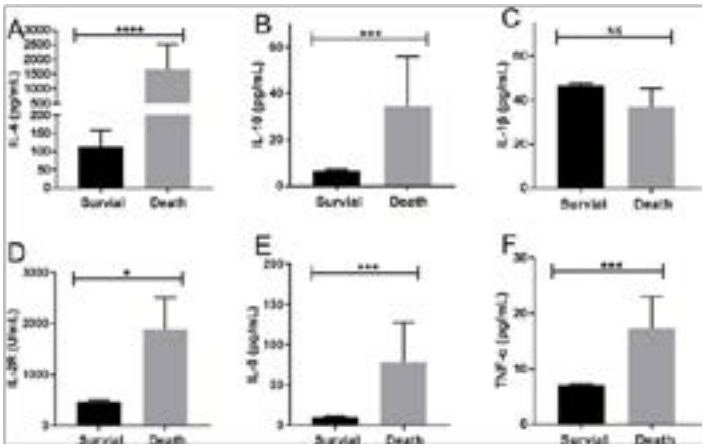

Figure 4: Characteristics of cytokines parameters in death and survival group. (A) IL-6; (B) IL-10; (C)IL-1β, (D) IL2R; (E) IL-8; (F) TNF-α. *P<0.05; ***P<0.001; ****P<0.0001; NS: P>0.05.

[95%CI=0.607-1.023], 0.866 [95%CI=0.684-1.000]. The sensitivity and specificity of IL-6 in predicting death respectively were 100% and 89.9% with the cut-off of greater than 43.10 pg/mL; and those for IL-10 were 66.7% and 93.4% with the cut-off of greater than 8.05 pg/mL; 60.0% and 98.4% for IL-2R with the cut-off of greater than 1836 U/mL; 83.3% and 94.5% for IL-8 with the cut-off of greater than 22.50 pg/mL (Table 4). The ROC curve was further found that the IL-6 showed a high value in prediction of COVID-19 prognosis (Figure 3C).

5. Discussion

This report is a study for cytokines of Wuhan Leishenshan hospitalized patients with COVID-19. COVID-19 caused by SARS-CoV-2 differs from pneumonia caused by bacteria. Its clinical manifestations include respiratory symptoms, fever, dry cough and panting. The disease seems to be self-limited, most patients having mild symptoms and complete recovery, while some patients may be affected by uncertainties such as the cytokine storms, which can lead to severe stages and even death [15-17]. The immune cells are over-activated, producing a large number of inflammatory cytokines, which form cytokines storms through a positive feedback loop mechanism. This process involves many different types of cytokines, such as interleukin, chemokine's, colony-stimulating factors, interferon's, and tumor necrosis factor.

Cytokines are signaling peptides, proteins, or glycoproteins that are secreted by many cell types, including immune cells, epithelial cells, endothelial cells, and smooth muscle cells. Cytokines allow context-dependent communication within the body [18,19]. If the communications that lead to cytokines production are destabilized, cytokine storms can result, producing unbridled inflammation within tissues and organs. In this study, a retrospective analysis was conducted about cytokines of 205 COVID-19 patients, IL-6, IL-10, IL-1β, IL-2R, IL-8 and TNF-α were expected to assess the inflammatory in patients and indicate the severity of the patients to provide clinical assistance.

We found that the concentrations of IL-6, IL-10, IL-2R, IL-8 and TNF-α in COVID-19 patients with different clinical types were inevitably changed featuring by the higher of cytokines concentrations with the more severe disease (all p<0.05), interestingly, although IL-1β was no significant difference among the groups, 99% patients with the higher level of IL-1β than normal level, similar to Gong's study [20]. The secretion of various cytokines was related to development of clinical symptoms, for instance, TNF-α can cause flu-like symptoms, fever, general malaise, and fatigue, also cause vascular leakage, cardiomyopathy, lung injury, and acute-phase protein synthesis [21]. IL-6 is an important target in CRS and can lead to vascular leakage, complement activation and the coagulation cascade, leading to the severe CRS, such as diffuse intravascular coagulation (DIC) [22,23]. The uncontrolled production of pro-inflammatory factors (IL-6, IL-8, IL-1β, and GM-CSF) and chemokine's (CCL2, CCL-5, IP-10, and CCL3) together with reactive oxygen species cause ARDS leading to pulmonary fibrosis and death [24,25]. In accordance with Wan S's [26] and Liu J's [27] Study, our study also found that the age, the acute COVID-19, IL-6, IL-10, IL-2R, IL-8, TNF-α were associated with the severity of COVID-19. Besides, we also found the 94.74% critical patients with higher IL-6 levels, and 100% severe and critical patients with higher IL-1β levels. More than 90% mild and severe patients with the normal levels of IL-8 and IL-10, for patients with IL-8 >62 pg/mL or IL-10 >9.1 pg/mL, more attention need to avoid the disease progression. In addition, logistic regression analysis showed that several risk factors related to the development of severe, which included age, the acute COVID-19, IL-6, IL-10, IL-2R, IL-8. Through the ROC curves, we found that IL-6, IL-10, IL-2R, IL-8, and TNF-α had lower accuracy in predicting the risk of COVID-19 patients from mild to severe. While, they were more effective in predicting the risk of COVID-19 patients from severe to critical. Among them, the IL-6 levels are more effective in predicting COVID-19 critical risk. IL-6 is the predominat inducer of the innate immune mechanism triggered by infection and inflammation during the acute-phase. After infection, TNF-α, IL-1β and IL-8 appeared in the early minutes for hours, followed by IL-6 with a more sustained increase. IL-10 appears somewhat later as an anti-inflammatory cytokine as the body attempts to control the acute systemic inflammatory response [28,29]. The above studies suggest that the cytokine storms were positively correlated with disease severity.

Further, our findings demonstrated that the IL-6, L-10, IL-2R, IL-8, and TNF-α showed differences in the survival and death groups, while the IL-1β was no significant difference. Logistic regression analysis found that the acute COVID-19, IL-6, IL-2R, IL-8, and IL-10 were the risk factors for death in COVID-19 patients. Based on clinical practice and ROC analysis between survival and death groups (Table 4), the AUC of IL-6 was 0.956, the sensitivity and specificity of IL-6 in predicting death respectively were 100% and 89.9% with the cut-of of greater than

43.10 pg/mL. The ROC curve was further found that the IL-6 showed a high value in prediction of COVID-19 prognosis. As reported previously, the IL-6 is the key cytokines to induce cytokine storms [14] and the most important index of cytokines for warning in our results (Table 4). Once the COVID-19 patients are the acute COVID-19, and their IL-6, IL-2R, IL-8, and IL-10 levels are significantly increased, it is necessary to be vigilant. In case the cytokine storms are formed, the immune system will kill both the SARS-CoV-2 and normal cells in the lung, and severely disrupt the warning of lung's ventilation function.

Taken together, our study conclude that cytokines were valuable in assessing severity and predict the prognosis of COVID-19, meanwhile, our study argue that the virus-induced immunopathological events play a crucial role in the fatal pneumonia observed after SARS-CoV-2 infections. Especially, IL-6 may be an ideal marker of the disease monitoring. Besides, we provide a laboratory reference index for clinical early warning of transition critical in COVID-19 patients, and reduce the death rate of COVID-19 patients by dynamic monitoring of cytokines. However, this study had some limitations and needs further supported. One defect of the study is the kinds of cytokine profiles tested were relatively small; Yang Y et al. also reported IP-10 and MCP-3 are valuable in COVID-19 [30].

Conclusion

In the next study, more patients and more kinds of cytokine profiles, basic diseases and medication of patients' needs to identify the critical disease factors.

Author Contributions

W X had the idea and designed the study. W X, X J and D W had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. W X contributed to critical revision of the report. X J, D W contributed to the statistical analysis. All authors contributed to data acquisition, data analysis, or data interpretation, and reviewed and approved the final version. X J and D W contributed equally and share first authorship.

Conflicts of Interest

The authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

We acknowledge all health-care workers involved in the diagnosis and treatment of patients in Wuhan.

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