

# Serum IL-6 and procalcitonin are two promising novel biomarkers for evaluating the severity of COVID-19 patients

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## Abstract

To evaluate the development of coronavirus disease 2019 (COVID-19), the roles of interleukin 6 (IL-6) and procalcitonin (PCT) were assessed to diagnose severe COVID-19.

Between January and February 2020, 100 consecutive patients with confirmed COVID-19 were included and divided into common (n=56), severe (n=28), and critical (n=16) groups.

IL-6 and PCT levels were assayed and compared among groups. IL-6 levels were significantly different among groups (common, 23.93±9.64 pg/mL; severe, 69.22±22.98 pg/mL; critical, 160.34±26.15 pg/mL;  $P < .05$ ), and there was also a significant difference in the levels of PCT among groups (common, 0.23±0.13 ng/mL; severe, 0.38±0.16 ng/mL; critical, 0.73±0.36 ng/mL;  $P < .05$ ). Further analysis showed that patients in the critical group had the highest levels of IL-6 and PCT, and those in the common group had the lowest levels (all  $P < .05$ ).

IL-6 and PCT are associated with the severity of COVID-19, and thus have potential value in the diagnosis of COVID-19.

**Abbreviations:** COVID-19 = coronavirus disease 2019, IL-6 = interleukin 6, PCT = procalcitonin.

**Keywords:** biomarker, coronavirus disease 2019, diagnosis, interleukin 6, procalcitonin, severity

## 1. Introduction

In December 2019, there was an outbreak of pneumonia of unknown cause in Wuhan, China. Consequently, the epidemic was reported by the World Health Organization.<sup>[1]</sup> Subsequently, the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was isolated from patients with

pneumonia and designated coronavirus disease 2019 (COVID-19) by the World Health Organization.<sup>[2,3]</sup> The clinical spectrum of COVID-19 ranges from asymptomatic infection and mild respiratory tract illness to severe progressive pneumonia and death.<sup>[4-6]</sup> Severe acute respiratory infection can occur in the early stages of COVID-19, followed by acute respiratory distress syndrome and other serious complications in a short time, and eventually multiple organ failure.<sup>[6]</sup> About 20% of patients develop severe respiratory illness, with an overall mortality of 2.3%.<sup>[6]</sup> Unfortunately, no specific therapeutic agents for coronavirus infections are available; therefore, the early identification and timely treatment of severe cases are very important for managing these patients. Interestingly, in recent studies, it has been demonstrated that increased serum levels of interleukin 6 (IL-6) are associated with the death of patients with severe COVID-19 (PMID: 32251717, PMID: 32234467). In addition, IL-6 level is positively correlated with the disease course (PMID: 32428990). These findings suggest that IL-6 may be useful for characterizing the progression of COVID-19.

Currently, the mechanism, prognosis, and treatment of severe COVID-19 remain unclear. In this study, we assessed the serum levels of IL-6 and procalcitonin (PCT) among COVID-19 patients divided into common, severe, and critical groups, and estimated their diagnostic ability for evaluating COVID-19 severity.

## 2. Materials and methods

### 2.1. Study design

The study was a cross-sectional prospective observational study.

### 2.2. Power of sample

The power of this study was calculated according to the following formula:  $N = Z^2 * [P * (1 - P)] / E^2$ , where N is the power of the

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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sample,  $Z$  is the statistic,  $E$  is the error value, and  $P$  is the probability value. The reliability of this study was 95% ( $Z=1.96$ ), the error value was 10%, the probability value was 0.5, and the sample size after calculation was 96.

### 2.3. Participants

The study followed the Declaration of Helsinki principles. Written consent was provided by all patients included in the study, and the study protocol was approved by the Ethics Committee of the Dalang Hospital of Dongguan City (Dongguan, China).

Between January and June 2020, consecutive patients who had a history of travel to Wuhan or contact with people from Wuhan and were admitted to our center due to corresponding symptoms (such as fever, cough, sore throat, and fatigue), were suspected to have COVID-19 and included for further investigation. Subsequently, COVID-19 patients were confirmed if their respiratory tract specimens tested positive by quantitative PCR. Then, according to the New Coronavirus Pneumonia Prevention and Control Program (6th edition) published by the National Health Commission of China,<sup>[7]</sup> patients were divided into common, severe, and critical groups. Severe cases of COVID-19 were diagnosed if patients met one of the following criteria: respiratory rate  $\geq 30$  times/min, oxygen saturation  $< 93\%$  in a resting state, or arterial partial pressure of oxygen (PaO<sub>2</sub>)/oxygen concentration (FiO<sub>2</sub>)  $\leq 300$  mmHg. Critical cases were diagnosed if patients met the following criteria: shock, required mechanical ventilation due to respiratory failure, or non-respiratory failure requiring intensive care unit care. Inclusion criteria were male and female patients, who consented to participate in the study and donate their biological samples. Exclusion criteria were inadequate samples, and those who were unable to or did not give consent. For IL-6 and PCT assays, blood samples were collected from enrolled participants in patients in the common group on admission, and were collected from severe and critical patients before their clinical diagnosis. The samples were centrifuged at 2000 rpm for 10 min. In addition, the comorbidities were collected from the electronic medical record and all comorbidities were reviewed and compared between groups.

### 2.4. IL-6 and PCT assays

A quantum dots immunofluorescence assay (Jinzhun, China) was used to evaluate the serum levels of IL-6 (reference, 0–7 pg/mL). The PCT assay (chemiluminescence method; reference, 0–0.5 ng/mL) produced by Shenzhen New Industry Biomedical Engineering Co., Ltd. (Shenzhen, China) was used for PCT analysis.

### 2.5. Statistical analyses

SPSS 22.0 software was used for statistical analyses. Categorical variables were expressed as percentage, and the chi-square test was used for comparisons between groups. All continuous variables were initially tested for normal distribution using the Kolmogorov–Smirnov test. The data with normal distribution are expressed as the mean  $\pm$  standard deviation, and the  $t$ -test was used to compare the mean differences. The data with non-normal distribution were described as the median (interquartile range), and the mean between groups was compared by the rank-sum test.

## 3. Results

### 3.1. Baseline characteristics

A total of 100 COVID-19 patients were included, aged 11 to 79 years old. The mean age was  $44.6 \pm 13.8$  years old, and the median was 46 years. Patients were divided into common ( $n=56$ ), severe ( $n=28$ ), and critical ( $n=16$ ) groups. Compared with patients with the common form, severe and critical patients were older in age ( $45.2 \pm 13.1/55.7 \pm 14.6$  years vs  $38.5 \pm 12.4$  years;  $P < .001$ ), and were more likely to have a history of hypertension ( $50.0\%/42.8\%$  vs.  $19.6\%$ ;  $P < .001$ ) and cerebrovascular diseases ( $10.7\%/18.8\%$  vs.  $3.6\%$ ;  $P < .001$ ), but there was no significant difference between males and females (both  $P > .05$ ). In addition, underlying diseases were more common in severe and critical patients than in those of the common type ( $P < .001$ ). Other variables such as contact history, onset symptoms, pulse, and respiratory rate were not significantly difference between the two groups (all  $P > .05$ ). The initial symptoms were as follows: fever ( $n=98, 98\%$ ), cough ( $n=71, 71\%$ ), dyspnea ( $n=62, 62\%$ ), fatigue ( $n=42, 42\%$ ), headache ( $n=9, 9\%$ ), and diarrhea ( $n=17, 17\%$ ). In addition, an abnormal respiratory rate ( $>24$  times/min) was observed in 26 cases (26%). The data are listed in Table 1.

All common forms of COVID-19 were diagnosed on the second day after admission. However, the mean period between admission and diagnosis of severe or critical COVID-19 was  $6.75 \pm 1.65$  days. All blood samples were collected on the second day after determination of COVID-19 type.

### 3.2. Serum levels of IL-6 and PCT

Statistical analysis showed that IL-6 and PCT data were normally distributed. The level of IL-6 was significantly different among groups (common,  $23.93 \pm 9.64$  pg/mL; severe,  $69.22 \pm 22.98$  pg/mL; critical,  $160.34 \pm 26.15$  pg/mL;  $P < .05$ ), and a significant difference also existed in the levels of PCT among groups (common,  $0.23 \pm 0.13$  ng/mL; severe,  $0.38 \pm 0.16$  ng/mL; critical,  $0.73 \pm 0.36$  ng/mL;  $P < .05$ ) (Table 2). Further analysis performed between two groups found that patients in the critical group had the highest levels of IL-6 and PCT, and those in the common group had the lowest levels (all  $P < .05$ ).

### 3.3. IL-6 and PCT positivity in COVID-19 patients

The levels of IL-6 and PCT were further categorised as positive or negative according to the reference ranges, and a comparison of positivities was performed among groups. The positivity of PCT was 10.7% in the common group, 25.0% in the severe group, and 62.5% in the critical group. At the same time, the positivities of IL-6 were 82.1% in the common group, 89.3% in the severe group, and 100% in the critical group. Statistical analysis showed that the positivities of PCT and IL-6 were significantly different among groups (all  $P < .05$ ). The highest positivity for each biomarker occurred in the critical group, and the lowest positivity occurred in the common group (all  $P < .05$ ). Twenty-three patients had positive PCT and IL-6 results, and 10.7%, 25.0%, and 62.5% of them were in the common, severe, and critical groups, respectively. A positive association between the severity of COVID-19 and PCT, or IL-6 was suggested due to the distribution of positive PCT and IL-6 results between groups. In addition, patients with high levels of PCT or IL-6 tended to have poor outcomes and longer hospital stays. patients with

**Table 1****Clinical characteristics of COVID-19 patients (common, severe, and critical).**

Groups	Total (n=100)	Common group (n=56)	Severe group (n=28)	Critical group (n=16)	P value <sup>*,#</sup>
Age (Mean, SD)	44.6 ± 13.8	38.5 ± 12.4	45.2 ± 13.1	55.7 ± 14.6	<.001 <.001
Gender (n, %)					
Male (n, %)	57 (57)	31 (55.4)	17 (60.7)	9 (56.3)	>.05 >.05
Contact history <sup>*</sup> (n, %)	100 (100)	56 (100)	28 (100)	16 (100)	>.05 >.05
Comorbidities (n, %)					
Hypertension (n, %)	31 (31)	11 (19.6)	12 (42.8)	8 (50.0)	<.001 >.05
Cerebrovascular diseases (n, %)	8 (8)	2 (3.6)	3 (10.7)	3 (18.8)	<.001 <.001
Diabetes (n, %)	11 (11)	6 (10.7)	3 (10.7)	2 (12.5)	>.05 >.05
Coronary heart disease (n, %)	3 (3)	0	2 (7.1)	1 (6.3)	>.05 >.05
Chronic liver disease (n, %)	3 (3)	2 (3.6)	1 (3.6)	0	>.05 >.05
Chronic kidney disease (n, %)	2 (2)	1 (1.8)	1 (3.6)	0	>.05 >.05
Malignant tumor (n, %)	0	0	0	0	>.05 >.05
COPD (n, %)	2 (2)	1 (1.8)	1 (3.6)	0	>.05 >.05
1 Comorbidity (n, %)	29 (29)	9 (16.1)	13 (46.4)	7 (43.8)	
2 Comorbidities (n, %)	8 (8)	4 (7.1)	3 (10.7)	1 (6.3)	
≥3 Comorbidities (n, %)	5 (5)	2 (3.6)	2 (7.1)	1 (6.3)	
Symptoms (n, %)					
Fever ≥ 37.3°C (n, %)	98 (98)	54 (96.4)	28 (100)	16 (100)	>.05 >.05
Cough (n, %)	71 (71)	40 (71.4)	20 (71.4)	11 (68.6)	>.05 >.05
Dyspnea (n, %)	62 (62)	35 (62.5)	17 (60.7)	10 (62.5)	>.05 >.05
Fatigue (n, %)	42 (42)	23 (41.1)	12 (42.3)	7 (43.8)	>.05 >.05
Headache (n, %)	9 (9)	5 (8.9)	3 (10.7)	1 (6.3)	>.05 >.05
Diarrhea (n, %)	17 (17)	10 (17.9)	5 (17.9)	2 (12.5)	>.05 >.05
Signs					
Respiratory rate [median (IQR)]	20 (18–26)	20 (19–25)	21 (18–26)	22 (19–26)	>.05 >.05
Pulse [median (IQR)]	85 (78–93)	86 (79–94)	83 (74–95)	82 (73–96)	>.05 >.05
Systolic pressure (Mean, SD)	122.5 ± 13.8	120.1 ± 9.7	134.7 ± 16.2	136.7 ± 14.4	<.001 >.05
Diastolic pressure (Mean, SD)	76.5 ± 10.6	73.9 ± 8.8	86.1 ± 13.4	87.2 ± 11.2	<.001 >.05
Blood oxygen saturation [median (IQR)]	96 (92–98)	96 (95–98)	90 (88–94)	85 (80–91)	<.001 <.001

IQR = interquartile range, SD = standard deviation.

<sup>\*</sup>exposure to Wuhan, or COVID-19 patients. <sup>\*</sup>Severe group vs common group.<sup>#</sup>Critical group vs severe group.

underlying diseases or of older age were more likely to have elevated levels of PCT and IL-6; however, age did not reach statistical significance in our dataset. This may be due to a relatively small sample size. In addition, gender had no significant impact on the results.

#### 4. Discussion

In the study, the levels of IL-6 and PCT among the common, severe, and critical groups of COVID-19 were investigated, and a significant difference in the two biomarkers was found. The finding may help to improve the management of patients with severe and critical types of COVID-19.

Pneumonia is the initial sign of COVID-19. However recently, gastrointestinal symptoms and asymptomatic infections have also

been described as onset symptoms in patients with this disease.<sup>[8,9]</sup> Some observational studies have found that the incubation period varies widely between 0 and 24 days, with a mean and median period of 5 and 3 days, respectively.<sup>[10,11]</sup> Usually, infection develops into severe disease in about 6.1% of patients.<sup>[11]</sup> Due to the lack of available therapeutic agents for coronavirus infections, early identification and timely treatment of severe cases are very important to manage patients with severe disease, in whom prominent laboratory abnormalities are common.<sup>[11]</sup> For example, lymphopenia and elevated inflammatory markers (c-reactive protein and cytokines) are found in most severe types of COVID-19. Therefore, monitoring biomarkers may be useful for the management of patients with severe disease. However, the usefulness of IL-6 and PCT remains unclear, which is the reason this prospective study was performed in our hospital.

**Table 2****Levels of IL-6, PCT, and corresponding positivity according to the reference ranges among groups.**

Groups	n	IL-6 (pg/mL)	IL-6 (+/-)	PCT (ng/mL)	PCT (+/-)
Common group	56	23.93 ± 9.64	46 (82.1%)	0.23 ± 0.13	6 (10.7%)
Severe group	28	69.22 ± 22.98 <sup>*</sup>	25 (89.3%)	0.38 ± 0.16 <sup>*</sup>	7 (25.0%)
Critical group	16	160.34 ± 26.15 <sup>#</sup>	16 (100%)	0.73 ± 0.36 <sup>#</sup>	10 (62.5%)
P		<.001		<.001	

IL-6 = interleukin 6, PCT = procalcitonin.

<sup>\*</sup>compare with common group, P < .001.<sup>#</sup>compare with severe group, P < .001.

Our study found that the levels of IL-6 among patients in the common, severe, and critical groups were significantly different, and further analysis showed that the severity of COVID-19 was associated with the level of IL-6. IL-6 is a non-specific inflammatory marker that is typically used to evaluate inflammation, as its level is expected to be elevated before the onset of symptoms. Usually, increasing levels of cytokines and chemokines occur in patients with severe infection, and the increase is considered to reflect the severity of the infectious disease.<sup>[12]</sup> Regarding COVID-19, infection with SARS-CoV-2 can activate specific T cells, and cytokines such as granulocyte-macrophage colony-stimulating factor and IL-6 are secreted within a short amount of time.<sup>[4,13]</sup> Moreover, granulocyte-macrophage colony-stimulating factor can further activate CD14+CD16+ monocytes, causing more cytokines to be produced and subsequently triggering a cytokine storm that causes multi-organ failure and often death. Accumulating evidence suggests that some patients with severe COVID-19 might have cytokine storm syndrome. The pathophysiology of cytokine storm during COVID-19 is closely related with high levels of IL-6.<sup>[14]</sup> In addition, we believe that the increase of IL-6 is positively correlated with TNF- $\alpha$  and IL-1 $\beta$ . A similar hyperactive inflammatory response also occurred during SARS-CoV and MERS-CoV infections, leading to severe lung fibrosis (often poor outcome).<sup>[14]</sup> IL-6 is considered a marker during coronavirus infection, and is also a key factor for the development of cytokine storm. The severity of COVID-19 disease is positively correlated with levels of inflammatory cytokines, and IL-6 is significantly increased in patients requiring ICU care.<sup>[14]</sup> The cytokine storm in the lungs is more likely to develop prior to the recruitment of inflammatory cells, especially in patients with allergic and other co-morbidities, leading to a high mortality rate.<sup>[15]</sup> Therefore, immunosuppression is likely to be beneficial for patients with severe disease. IL-6 is considered a key factor in the development of cytokine storm. Recently, tocilizumab, an IL-6 receptor agonist approved for the treatment of CAR-T cell-induced cytokine release syndrome, was studied in patients with COVID-19 in a large multi-centre randomised study (ChiCTR2000029765).<sup>[13]</sup> This promising agent may have a potential therapeutic role in severe and critical patients, reducing their mortality. Thus, our study demonstrated that the level of IL-6 may be used as a diagnostic biomarker for the evaluation of COVID-19 severity, which may provide a guide for the management of patients with COVID-19.

In most patients, IL-6 level was elevated but PCT level was normal. However, the level of PCT was also correlated with the severity of COVID-19. This finding showed that bacterial infection was more common in patients with severe and critical COVID-19. Although IL-6 is also correlated with bacterial infection, the increasing trend of IL-6 exists widely in infectious disease progression irrespective of the pathogen species.<sup>[16]</sup> However, PCT is relatively specific for bacterial infections.<sup>[17]</sup> Hence, use of a PCT assay may be helpful in controlling bacterial infection secondary to the pneumonia caused by SARS-CoV-2. In addition, several studies have shown that PCT can be used to distinguish Gram-negative from Gram-positive bacteria and fungal bloodstream infections.<sup>[18–20]</sup> This would allow the choice of antimicrobial agents empirically when microbiological results are not available, despite the lack of desirable precision. It may be taken as an additive diagnostic value of PCT when used for the evaluation of patients with COVID-19. In fact, considering the level of PCT among groups, bacterial infection may be common in patients with severe or critical forms of COVID-19. In fact,

patients with abnormal PCT in the severe and critical groups were treated with antibacterial drugs including moxifloxacin, levofloxacin, and cephaloperidone sulbactam.

This study had some limitations. First, due to the sample size, regression analysis was not performed to investigate the association between biomarker levels and severity of COVID-19 and corresponding risk factors of severe COVID-19 disease. Second, because of the limited financial support, sequential tests (IL-6 and PCT) for COVID-19 patients were not performed, which would have provided more information than that of a cross-sectional study. Third, further analysis is required to determine the correlation between cytokine storm and IL-6 in patients with COVID-19, which would be useful in accurately determining when the cytokine storm is initiated.

## 5. Conclusions

In conclusion, the results of our study showed a statistically significant difference in IL-6 and PCT levels among patients in the common, severe, and critical groups, and their levels were correlated with COVID-19 severity. Our findings suggest that these two promising biomarkers have a potential diagnostic value in COVID-19, and may help to improve the management of patients with severe and critical types of this disease.

## Author contributions

JT, JL, EZ, MZ, YL, YF, and YY contributed to conception and design of the study. YL and JT organized the database. YY and MZ performed the statistical analysis. JL, EZ and JT wrote the first draft of the manuscript. JT and YL wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version

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