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# Correlation between cytokines and coagulation-related parameters in patients with coronavirus disease 2019 admitted to ICU

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ABSTRACT

*Background:* The novel SARS-CoV-2 caused a large number of infections and deaths worldwide. Thus, new ideas for an appropriated assessment of patients' condition and clinical treatment are of utmost importance. Therefore, in this study, the laboratory parameters of patients with coronavirus disease 2019 (COVID-19) were evaluated to identify the correlation between cytokine expression and other laboratory parameters.

*Methods:* A retrospective and single-center study was performed in Wuhan, involving 83 severe or critical COVID-19 patients admitted to the intensive care unit (ICU). Laboratory parameters in ICU patients with laboratory-confirmed infection of SARS-CoV2 were collected. The association between parameters was assessed by Spearman's rank correlation.

*Results:* Patients' median age was 66 years (IQR, 57–73), and 55 (66%) were men. Among the 83 patients, 61 (73%) had 1 or more coexisting medical condition. The median concentration of IL-2R, IL-6, IL8, IL10, and TNFα were above the normal range, without IL-1β. A significant negative correlation between IL-6 and platelet count was discovered ($r^2 = -0.448$, $P < 0.001$) as well as a significant correlation between IL-6 and other platelet parameters. Finally, a correlation between multiple cytokines and coagulation indicators was found, pro-inflammatory factors were found to be more associated to coagulation parameters, with the highest correlation between IL-6 and the International normalized ratio (INR) ($r^2 = 0.444$, $P < 0.001$).

*Conclusions:* Our results suggested that cytokines play an important role in the pathogenesis of COVID-19. In addition, IL-6 seems more relevant in the evaluation of the condition of COVID-19 patients.

## 1. Introduction

At the end of 2019, a novel coronavirus (SARS-CoV-2) epidemic broke out in Wuhan, China causing a large number of infections and deaths all over the country. As of April 21, 2020, this new coronavirus spread in 216 countries and regions around the world due to uncontrollable and incompletely blocked international travels, causing a total of 2,356,414 confirmed cases and a confirmed death toll of 160,120. Therefore, on March 11, 2020, the SARS-CoV-2 was declared a pandemic by the World Health Organization. The novel coronavirus outbreak represents a global threat, thus, joint efforts by all countries around the world are undertaken to overcome this pandemic.

The clinical manifestations of COVID-19 patients include fever, nonproductive cough, dyspnea, myalgia, fatigue, normal or decreased leukocyte count, organ dysfunction (eg, shock, acute respiratory distress syndrome [ARDS], acute cardiac injury, and acute kidney injury), and radiographic evidence of pneumonia, ultimately leading to death in severe cases [1]. The pathogenesis of COVID-19 is still unclear. Most patients show mild or asymptomatic symptoms after being infected, while some patients are affected by serious clinical symptoms or even life-threatening ones. In a single-center case series of 138 hospitalized patients with confirmed COVID-19 in Wuhan, 26% of patients were admitted to ICU, and the mortality rate was 4.3% [2]. Some studies showed that the inflammatory response during SARS-CoV-2 infection

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**Table 1**
Demographics and baseline characteristics of ICU patients.

| Characteristic | Patients in ICU (n = 83) |
|---|---|
| Age, years | 66 (57–73) |
| Sex | |
| Men | 55(66%) |
| Women | 28(34%) |
| Any comorbidity | 61(73%) |
| Diabetes | 19(23%) |
| Hypertension | 43(52%) |
| Cardiovascular disease | 18(22%) |
| Cerebrovascular Disease | 10(12%) |
| Chronic obstructive pulmonary disease | 6(7%) |
| Malignancy | 3(4%) |
| Chronic liver disease | 3(4%) |
| Chronic kidney disease | 4(5%) |
| Signs and symptoms | |
| Fever | 76(92%) |
| Cough | 64(77%) |
| Myalgia or fatigue | 43(52%) |
| Sputum production | 41(49%) |
| Headache or dizziness | 11(13%) |
| Hemoptysis | 4(5%) |
| Diarrhea | 16(19%) |
| Dyspnoea | 56(67%) |
| Pharyngalgia | 9(11%) |
| Nausea | 14(17%) |
| Dizziness | 5(6%) |

Data are expressed as median (IQR), n (%).

may be the cause of uncontrolled pulmonary inflammation and lung injury, probably one of the main reasons of mortality [3]. Significantly high levels of cytokines and chemokines were detected in patients with COVID-19, including IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA [1]. Wan et al. [4] revealed that normal IL6 levels are associated with a higher survival and thus, this cytokine can be used as a biomarker of disease evolution. However, the protective or harmful role of cytokines in the occurrence of COVID-19 is still controversial.

In this work, the laboratory characteristics of 83 hospitalized patients with severe or critical COVID-19 and admitted to ICU were measured to explore the correlation between the concentration of cytokines and other laboratory parameters, since COVID-19 is often characterized by a pattern of coagulopathy correlated with a parallel rise in markers of inflammation. Our goal was to provide new ideas for an appropriate assessment of patients' condition.

## 2. Methods

### 2.1. Study design and participants

The present study was a retrospective and single-center study in which 83 ICU patients with confirmed severe or critical COVID-19 admitted to the Sino–French New City Branch of Tongji Hospital, Wuhan, China, were recruited. This hospital actually represents the center for treating COVID-19 patients, managed by a medical team from the Peking Union Medical College Hospital. All the participants of the present study were confirmed as SARS-CoV2 infected patients according to the Chinese Recommendations for Diagnosis and Treatment of SARS-CoV2 Infection. This study was approved by the Ethics Committee of Peking Union Medical College Hospital (ZS-2303) and the informed consent was obtained from each patient enrolled in this study, or patient family member.

**Table 2**
Laboratory parameters of ICU patients.

| | Normal range | Patients in ICU (n = 83) | No. of patients tested |
|---|---|---|---|
| IL-1β, pg/mL | <5 | 5.00(5.00–5.00) | 56 |
| IL-2R, U/mL | 223–710 | 1117.50(638.00–1602.00) | 56 |
| IL-6, pg/mL | <7.0 | 69.30(24.50–212.15) | 62 |
| IL-8, pg/mL | <62 | 34.65(15.70–86.15) | 56 |
| IL-10, pg/mL | <9.1 | 9.45(5.43–16.43) | 56 |
| TNFα, pg/mL | <8.1 | 11.70(6.63–19.43) | 56 |
| White blood cell count (WBC), ×109/L | 3.50–9.50 | 10.51(8.12–16.58) | 83 |
| Neutrophil count (NEU), ×109/L | 1.80–6.30 | 9.67(7.01–14.90) | 83 |
| Lymphocyte count (LYM), ×109/L | 1.10–3.20 | 0.52(0.28–0.81) | 83 |
| Red blood cell count (RBC), ×1012/L | 4.30–5.80<br>3.80–5.10 | 3.54(2.93–4.07) | 83 |
| Hemoglobin (HGB), g/L | 130.0–175.0<br>115.0–150.0 | 109.00(90.00–129.00) | 83 |
| Hematocrit (HCT), % | 40.0–50.0<br>35.0–45.0 | 32.90(27.00–38.10) | 83 |
| Mean corpuscular volume (MCV), fL | 82.0–100.0 | 93.00(89.70–96.90) | 83 |
| Mean corpuscular hemoglobin (MCH), pg | 27.0–34.0 | 31.00(29.80–32.40) | 83 |
| Mean corpuscular hemoglobin concentration (MCHC), g/L | 316–354 | 333.00(316.00–346.00) | 83 |
| Red blood cell distribution width CV (RDW-CV) | <14.9 | 14.10(12.90–15.40) | 83 |
| Red blood cell distribution width SD (RDW-SD), fL | 39.0–46.0 | 46.90(42.70–50.50) | 83 |
| Platelet count (PLT), ×109/L | 125.0–350.0 | 116.50(62.00–195.00) | 82 |
| Platelet distribution width (PDW), fL | 9.0–17.0 | 13.50(11.80–16.55) | 74 |
| Mean platelet volume (MPV), fL | 8.0–15.0 | 11.40(10.68–12.63) | 74 |
| Platelet larger cell ratio (P-LCR), % | 13.0–46.0 | 36.05(30.03–44.60) | 74 |
| Plateletcrit (PCT), % | 0.10–0.35 | 0.15(0.10–0.24) | 73 |
| Prothrombin time (PT), s | 11.5–14.5 | 16.20(15.00–17.80) | 83 |
| Prothrombin activity (PTA), % | 75.0–125.0 | 67.00(57.00–78.00) | 83 |
| International normalized ratio (INR) | 0.80–1.20 | 1.29(1.17–1.45) | 83 |
| Fibrinogen (FBI), g/L | 2.00–4.00 | 3.90(2.76–5.59) | 83 |
| Activated partial thromboplastin time (APTT), s | 29.0–42.0 | 43.10(38.00–50.50) | 83 |
| Thrombin time (TT), s | 14.0–19.0 | 16.70(15.30–18.80) | 83 |
| D-dimer, mg/L | <0.5 | 6.93(2.40–21.00) | 81 |
| Fibrin degradation products (FDP), ug/mL | <5.0 | 31.80(10.85–150.00) | 65 |
| Antithrombin (AT), % | 80–120 | 79.50(68.00–92.75) | 64 |

Data are expressed as median (IQR). Two reference intervals for male and female in RBC, HGB and HCT.

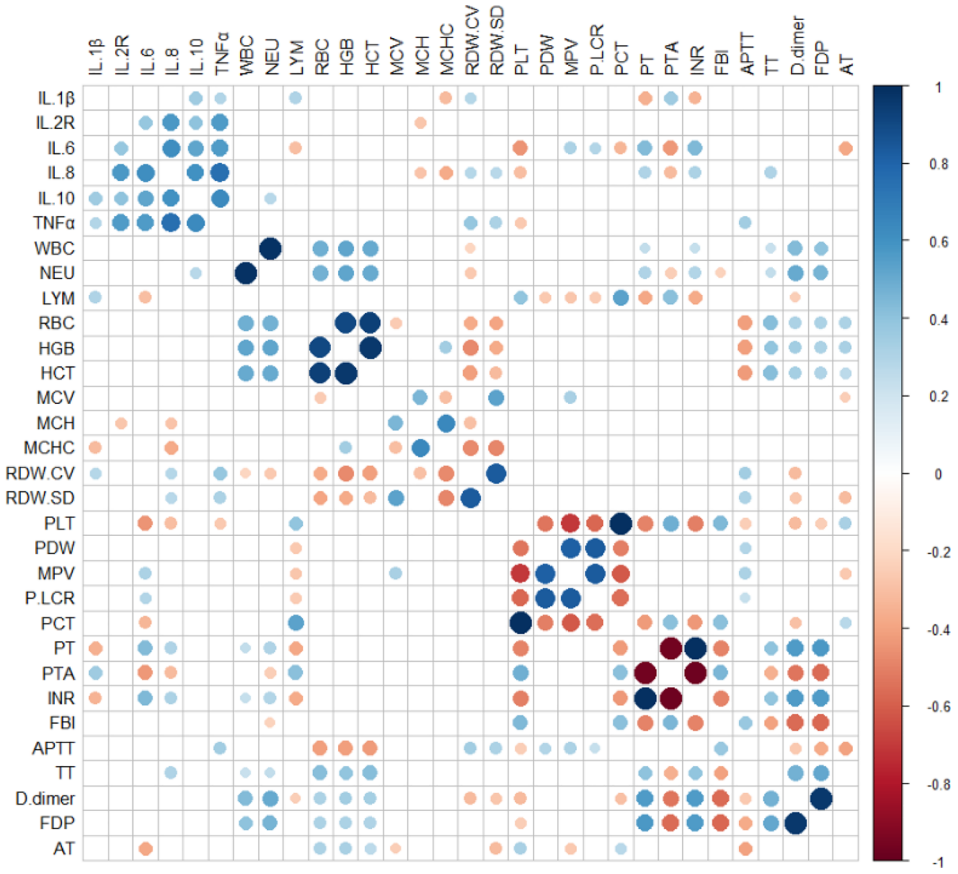


**Fig. 1.** Spearman correlation correlogram. The strength of the correlation between two variables is represented by the color of the circle at the intersection of those variables. Colors range from bright blue (strong positive correlation; i.e. $r^2 = 1.0$) to bright red (strong negative correlation; i.e. $r^2 = -1.0$). Results were not displayed if $P > 0.05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

### 2.2. Data collection

Clinical information, including cytokine type and concentration, blood count, and coagulation parameters of ICU patients with laboratory-confirmed infection of SARS-CoV2 were collected during the ICU stay. The cytokines tests were detected using the human Th1/2 cytokine kit II (BD Ltd., Franklin lakes, NJ, USA). The coagulation tests were detected using a STA-R MAX coagulation analyzer and original reagents (Diagnostica Stago, Saint-Denis, France). The data of each test performed were collected and grouped by type of test. Since this was a retrospective study, some results were incomplete. The number of patients tested was recorded in the "Results" section.

### 2.3. Statistical analysis

Statistical analysis was performed using SPSS 25.0 for Windows (SPSS, Inc.), while the figures were plotted using the R software (R Version 3.6.3). Frequency rates and percentages were used to describe the categorical variables, and median and interquartile range (IQR) values were used to describe continuous variables. The Spearman rank correlation coefficient was used to perform the linear correlation analysis between two groups with continuous variables. A two-sided α of less than 0.05 was considered statistically significant.

## 3. Results

### 3.1. Patient characteristics

The characteristics of the study population are described in Table 1. Among the 83 participants, the median age was 66 years (IQR, 57–73), 55 (66%) were men, and 61 (73%) had 1 or more coexisting medical conditions. Hypertension (43 [52%]), diabetes (19 [23%]), and cardiovascular disease (18 [22%]) were the most common conditions coexisting with COVID-19. The most common symptoms at the onset of the disease were fever (76 [92%]) and nonproductive cough (64 [77%]). More than half of the patients (56 [67%]) developed dyspnoea before being hospitalized.

### 3.2. Laboratory examinations

The results of the laboratory tests performed on the 83 patients are shown in Table 2, and they included cytokines (IL-1β, IL-2R, IL-6, IL-8, IL-10, TNFα), the count of many blood parameters and blood coagulation parameters. The number of patients tested was recorded. The results regarding the cytokines were relatively incomplete, while almost all the blood count results were complete, since blood count testing was more frequent. Among the six type of cytokines evaluated in ICU patients, the concentration of IL-1β (5.00 pg/mL [IQR, 5.00–5.00]) is within the normal range in most of the patients, while in 9% (five of 56) of the patients was above the normal range. The median concentration of IL-2R, IL-6, IL-8, IL-10, and TNFα was 1117.50 U/mL, 69.30 pg/mL, 34.65 pg/mL, 9.45 pg/mL, and 11.70 pg/mL, respectively, all above the normal range. The blood count revealed that the median white blood cell count and median neutrophil count were higher than the normal range, while the median lymphocyte count was less than the normal range ($0.52 \times 10^9$/L [IQR, 0.28–0.81]). The median red blood cell count, hemoglobin and platelet count were all below the normal range. In addition, the median of most the coagulation parameters (seven of 9) were also within an abnormal range.

### 3.3. Correlation analysis

The Spearman rank correlation coefficient was calculated (Fig. 1) and the association among the 31 markers was performed. Part of the results of the correlation analysis between cytokines and some indicators is shown in Table 3, while the complete results are shown in

**Table 3**
Correlation analysis between cytokines and coagulation-related parameters.

| | | NEU | LYM | MCH | MCHC | RDW-CV | RDW-SD | PLT | MPV | P-LCR | PCT | PT | PTA | INR | APTT | TT | AT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IL-1β | $r^2$ | −0.027 | 0.308* | −0.194 | −0.312* | 0.289* | 0.258 | −0.034 | 0.056 | −0.166 | 0.040 | −0.353** | 0.351** | −0.338* | 0.138 | −0.203 | −0.011 |
| | P | 0.844 | 0.021 | 0.152 | 0.019 | 0.031 | 0.055 | 0.808 | 0.692 | 0.239 | 0.779 | 0.008 | 0.008 | 0.011 | 0.310 | 0.134 | 0.943 |
| IL-2R | $r^2$ | 0.208 | −0.170 | −0.271* | −0.121 | 0.101 | 0.116 | −0.076 | −0.113 | −0.012 | −0.107 | 0.250 | −0.243 | 0.251 | 0.245 | 0.238 | −0.165 |
| | P | 0.124 | 0.209 | 0.044 | 0.374 | 0.458 | 0.394 | 0.581 | 0.424 | 0.933 | 0.456 | 0.063 | 0.071 | 0.062 | 0.068 | 0.077 | 0.278 |
| IL-6 | $r^2$ | 0.153 | −0.306* | 0.017 | −0.072 | 0.191 | 0.185 | −0.448** | 0.318* | 0.293* | −0.330* | 0.433** | −0.439** | 0.444** | 0.246 | 0.165 | −0.389** |
| | P | 0.236 | 0.015 | 0.898 | 0.578 | 0.137 | 0.150 | 0.000 | 0.016 | 0.027 | 0.013 | 0.000 | 0.000 | 0.000 | 0.054 | 0.201 | 0.007 |
| IL-8 | $r^2$ | 0.095 | −0.247 | −0.279* | −0.379** | 0.283* | 0.278* | −0.303* | 0.156 | 0.234 | −0.238 | 0.305* | −0.312* | 0.314* | 0.220 | 0.303* | −0.196 |
| | P | 0.486 | 0.067 | 0.037 | 0.004 | 0.035 | 0.038 | 0.025 | 0.269 | 0.095 | 0.093 | 0.022 | 0.019 | 0.018 | 0.103 | 0.023 | 0.196 |
| IL-10 | $r^2$ | 0.271* | −0.050 | −0.085 | −0.214 | 0.155 | 0.140 | −0.172 | 0.040 | 0.008 | −0.037 | 0.136 | −0.124 | 0.141 | 0.073 | 0.183 | −0.140 |
| | P | 0.044 | 0.716 | 0.532 | 0.113 | 0.254 | 0.303 | 0.210 | 0.779 | 0.955 | 0.794 | 0.318 | 0.361 | 0.299 | 0.592 | 0.176 | 0.361 |
| TNFα | $r^2$ | 0.114 | −0.096 | −0.244 | −0.245 | 0.385** | 0.318* | −0.266* | 0.031 | 0.034 | −0.165 | 0.152 | −0.160 | 0.170 | 0.349** | 0.234 | −0.148 |
| | P | 0.404 | 0.482 | 0.070 | 0.068 | 0.003 | 0.017 | 0.049 | 0.826 | 0.812 | 0.247 | 0.264 | 0.238 | 0.211 | 0.008 | 0.083 | 0.332 |

*$P < 0.05$; **$P < 0.01$. Partial correlation results with P values greater than 0.05 were not displayed.

the supplementary material. A significant correlation between cytokines, blood count and blood coagulation parameters was observed ($P < 0.05$). Among them, a significant negative correlation between IL-6 and platelet count was found ($r^2 = -0.448$, $P < 0.001$), as well as a significant correlation between IL-6 and other platelet parameters, including the mean platelet volume ($r^2 = 0.318$, $P = 0.016$), platelet larger cell ratio ($r^2 = 0.293$, $P = 0.027$), and plateletcrit ($r^2 = -0.303$, $P = 0.013$). In addition, results suggested a correlation between multiple cytokines and coagulation indicators, with the highest correlation between IL-6 and international normalized ratio ($r^2 = 0.444$, $P < 0.001$). There were correlations between pro-inflammatory factors (IL-1β, IL-6, IL-8, TNFα) and coagulation indicators (PT, PTA, AT, APTT, TT). However, there was no significant correlation between anti-inflammatory factor (IL-10) and coagulation parameters (Table 3). Furthermore, a significant negative correlation was found between IL-6 and lymphocyte count ($r^2 = -0.306$, $P = 0.015$).

### 3.4. Subgroup analysis

According to hypothesis proposed by Li et al, Viral sepsis is considered crucial to the disease mechanism of COVID-19 [5]. “Systemic inflammatory response syndrome” (SIRS) followed by “compensatory anti-inflammatory response syndrome” (CARS) is a conceptual framework to explain the immunologic trajectory that ICU patients with severe sepsis [6]. Increased levels of anti-inflammatory factors such as IL-10 are the main features of CARS. We performed subgroup correlation analysis based on whether the concentration of IL-10 exceeded the normal range (<9.1 pg/mL, Table 4) to distinguish potential patients with SIRS and CARS. The results showed that when the concentration of IL-10 was in the normal range, potential SIRS patients were mainly in the inflammatory response stage at this time, and pro-inflammatory factors (IL-6, IL-8) were related to coagulation indicators. But no correlation was observed between IL-6, IL-8 and coagulation indicators in potential CARS patients, who were in post inflammatory immune suppression stage.

## 4. Discussion

This study provided a detailed correlation analysis among several laboratory parameters of confirmed severe or critical COVID-19 ICU patient admitted to one hospital in Wuhan, China. Although relevant studies analyzing laboratory parameters in COVID-19 patients are already available, including diagnosis, condition assessment and prognosis, this was the first study analyzing the correlation between cytokines and coagulation-related parameters in severe or critical patients. A significant correlation among cytokines, coagulation indicators, and blood counts indicators was discovered, suggesting that cytokines might play a critical role in the pathogenesis of COVID-19.

Respiratory failure from ARDS is the leading cause of mortality in COVID-19 patients [7]. Previous studies on patients with SARS-CoV and MERS-CoV revealed that COVID-19-related ARDS may be induced by a massive cytokine release, with secondary hemophagocytic lymphohistiocytosis [8]. Ruan et al. [7] found that the mortality of COVID-19 patients may be due to virus-activated cytokine release or fulminant myocarditis. Chen et al. [9] showed that severe COVID-19 cases had remarkably higher levels of IL-2R, IL-6, IL-10, and TNF-α compared with moderate cases, and our present results are consistent with their results. In our study, IL-1β was also not significantly changed in COVID-19 patients, which might suggest that IL-1β did not play a significant role in the pathogenic mechanism of COVID-19. IL-6 and other inflammatory cytokines are activated and secreted by monocytes, macrophages, and dendritic cells due to the coronavirus infection, and IL-6 has relevant proinflammatory properties [8]. A systemic “cytokine storm” is activated through two main IL-6 pathways called cis signaling and trans signaling, resulting in vascular permeability and leakage, leading to hypotension and pulmonary dysfunction in ARDS [10,11].

**Table 4**
Subgroup correlation analysis between cytokines and coagulation-related parameters.

| | | NEU | LYM | MCH | MCHC | RDW-CV | RDW-SD | PLT | MPV | P-LCR | PCT | PT | PTA | INR | APTT | TT | FDP | AT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IL-1β | $r^2$# | | | | | | | | | | | | | | | | | |
| | P# | | | | | | | | | | | | | | | | | |
| | $r^2$ | −0.165 | 0.419* | −0.251 | −0.370* | 0.391* | 0.337 | 0.022 | 0.039 | −0.250 | 0.085 | −0.531** | 0.513** | −0.519** | 0.217 | −0.346 | −0.360 | 0.017 |
| | P | 0.391 | 0.024 | 0.189 | 0.048 | 0.036 | 0.074 | 0.911 | 0.853 | 0.227 | 0.693 | 0.003 | 0.004 | 0.004 | 0.259 | 0.066 | 0.092 | 0.939 |
| IL-2R | $r^2$# | 0.432* | −0.076 | −0.086 | 0.033 | 0.144 | 0.191 | 0.021 | −0.291 | −0.281 | −0.069 | 0.439* | −0.407* | 0.427* | 0.233 | 0.342 | 0.421 | −0.342 |
| | P# | 0.025 | 0.706 | 0.670 | 0.870 | 0.475 | 0.340 | 0.918 | 0.140 | 0.155 | 0.731 | 0.022 | 0.035 | 0.026 | 0.242 | 0.081 | 0.051 | 0.119 |
| | $r^2$ | −0.136 | −0.193 | −0.440* | −0.226 | 0.073 | 0.052 | −0.089 | 0.150 | 0.361 | −0.143 | 0.087 | −0.109 | 0.099 | 0.427* | 0.009 | −0.250 | −0.059 |
| | P | 0.481 | 0.315 | 0.017 | 0.238 | 0.705 | 0.790 | 0.652 | 0.474 | 0.076 | 0.505 | 0.653 | 0.573 | 0.609 | 0.021 | 0.964 | 0.251 | 0.790 |
| IL-6 | $r^2$# | 0.165 | −0.320 | 0.122 | 0.081 | 0.028 | 0.103 | −0.295 | 0.119 | 0.104 | −0.311 | 0.380 | −0.366 | 0.376 | 0.147 | 0.253 | 0.439* | −0.569** |
| | P# | 0.410 | 0.103 | 0.545 | 0.688 | 0.892 | 0.608 | 0.135 | 0.554 | 0.604 | 0.115 | 0.051 | 0.061 | 0.053 | 0.465 | 0.202 | 0.041 | 0.006 |
| | $r^2$ | −0.134 | −0.190 | −0.146 | −0.031 | 0.293 | 0.191 | −0.414* | 0.363 | 0.400* | −0.254 | 0.326 | −0.350 | 0.338 | 0.267 | 0.072 | −0.227 | −0.105 |
| | P | 0.490 | 0.324 | 0.451 | 0.875 | 0.123 | 0.322 | 0.028 | 0.074 | 0.047 | 0.230 | 0.084 | 0.062 | 0.073 | 0.161 | 0.712 | 0.297 | 0.632 |
| IL-8 | $r^2$# | 0.030 | −0.303 | −0.171 | −0.190 | 0.237 | 0.296 | −0.258 | 0.040 | 0.031 | −0.261 | 0.397* | −0.402* | 0.400* | 0.419* | 0.451* | 0.127 | −0.433* |
| | P# | 0.881 | 0.125 | 0.394 | 0.343 | 0.234 | 0.134 | 0.194 | 0.844 | 0.877 | 0.188 | 0.041 | 0.038 | 0.039 | 0.030 | 0.018 | 0.572 | 0.044 |
| | $r^2$ | −0.101 | −0.185 | −0.406* | −0.414* | 0.288 | 0.234 | −0.218 | 0.208 | 0.395 | −0.129 | 0.282 | −0.313 | 0.302 | 0.241 | 0.161 | 0.036 | 0.054 |
| | P | 0.600 | 0.335 | 0.029 | 0.026 | 0.130 | 0.222 | 0.265 | 0.318 | 0.051 | 0.548 | 0.138 | 0.099 | 0.112 | 0.208 | 0.404 | 0.869 | 0.807 |
| IL-10 | $r^2$# | 0.214 | 0.029 | −0.166 | −0.077 | 0.131 | 0.172 | 0.024 | −0.119 | −0.111 | 0.006 | 0.316 | −0.280 | 0.298 | 0.339 | 0.449* | 0.255 | −0.260 |
| | P# | 0.285 | 0.887 | 0.408 | 0.702 | 0.516 | 0.390 | 0.905 | 0.556 | 0.582 | 0.978 | 0.109 | 0.157 | 0.131 | 0.084 | 0.019 | 0.251 | 0.243 |
| | $r^2$ | −0.230 | 0.042 | −0.033 | −0.041 | 0.066 | −0.023 | −0.001 | −0.103 | 0.002 | 0.212 | −0.048 | 0.004 | −0.029 | 0.237 | −0.064 | −0.115 | 0.219 |
| | P | 0.231 | 0.827 | 0.864 | 0.833 | 0.734 | 0.905 | 0.998 | 0.624 | 0.991 | 0.320 | 0.806 | 0.982 | 0.883 | 0.216 | 0.741 | 0.602 | 0.316 |
| TNFα | $r^2$# | 0.031 | 0.018 | 0.126 | 0.149 | 0.378 | 0.371 | −0.255 | −0.106 | −0.125 | −0.260 | 0.241 | −0.237 | 0.256 | 0.292 | 0.457* | 0.172 | −0.410 |
| | P# | 0.878 | 0.928 | 0.533 | 0.458 | 0.052 | 0.057 | 0.199 | 0.598 | 0.535 | 0.191 | 0.226 | 0.234 | 0.198 | 0.139 | 0.016 | 0.445 | 0.058 |
| | $r^2$ | −0.104 | −0.107 | −0.445* | −0.320 | 0.315 | 0.234 | −0.158 | 0.141 | 0.228 | −0.030 | 0.115 | −0.161 | 0.135 | 0.501** | −0.012 | −0.268 | 0.141 |
| | P | 0.591 | 0.581 | 0.016 | 0.090 | 0.096 | 0.222 | 0.421 | 0.501 | 0.272 | 0.889 | 0.552 | 0.404 | 0.485 | 0.006 | 0.952 | 0.217 | 0.521 |

*$P < 0.05$; **$P < 0.01$. # Results from IL-10 normal range subgroup. The concentration of IL-1β in IL-10 normal range subgroup was less than the detection range, and the correlation coefficient cannot be obtained.

Chen et al. [12] showed that elevated IL-6 concentration was associated with Detectable serum SARS-Cov-2 RNA. In this study, IL6 concentration in severe or critical ICU patients was correlated to multiple parameters, suggesting that IL6 might have a potential role in the progression of COVID-19.

COVID-19 patients are also characterized by an abnormal coagulation, as demonstrated by many studies. Tang et al. [13] found that parameters associated with an abnormal coagulation are common in patients who died of COVID-19. The 71.4% of death with SARS-CoV2 shows disseminated intravascular coagulation, meaning that the coagulation function is very important in the prognosis of critical patients. Han et al. [14] discovered that the coagulation in patients with SARS-CoV-2 is significantly unbalanced. Tang et al. [15] found that an anticoagulant therapy mainly with low molecular weight heparin is associated, at least in part, with a better prognosis of severe SARS-CoV-2 patients. The coagulation cascade can be activated by the inflammatory response, which might explain the abnormal coagulation in patients with SARS-CoV-2. IL-6 and other inflammatory cytokines such as IL-8, TNF-α, IFN-γ and IL-1β induce tissue factor, which in turn promotes coagulation by stimulating the extrinsic coagulation pathway [16]. In this study, our results also showed a significant correlation between cytokines and coagulation indicators, in particular, a significant negative correlation between IL-6 and platelet count. This result might imply that the increase of cytokine expression resulted in the increase of platelet consumption or decrease of platelet production. Some studies show that the platelet function is not only to sense the injured vessel endothelium and initiate blood clotting for hemostasis, but it is also an integral part of the innate immune system due to their role as pro-inflammatory cells [17,18]. The relationship between platelet count and various viral infections is already previously reported [19–21]. Kim et al. [22] found that thrombocytopenia is detected in infections due to highly pathogenic influenza virus, but it is an aspect rarely observed under the infection by other human viruses, such as adenovirus, metapneumovirus, coronavirus or bocavirus. However, an evident thrombocytopenia was observed in severe or critical COVID-19 patients in this study and a systematic review indicated that platelet count showed significantly lower levels in severe patients compared to non-severe patients [23]. This might indicate that thrombocytopenia was related to the severity of viral infection and the body's inflammatory response. Interestingly, we also found that there were correlations between pro-inflammatory factors and coagulation parameters, but there was no correlation between anti-inflammatory factors and coagulation parameters. The results of the subsequent subgroup analysis showed that pro-inflammatory factors might play a greater role in coagulation dysfunction in the early stage, and in the later stage of the inflammatory, due to the antagonistic effect of IL-10 and other factors that inhibited the inflammatory response, the coagulation function of patients with COVID-19 was less affected by pro-inflammatory factors. This indicated that inflammation was critical in the pathogenesis of COVID-19 and more research is needed to elucidate the underlying mechanisms.

This study has some limitations. First, it was a single-center study, and bias could affect some results. Second, only data on severe or critical ICU patients were available, thus, they could not be compared with data on mild patients. Third, some patients have incomplete laboratory data because this was a retrospective study, and therefore, this aspect might have a potential impact on the results.

## 5. Conclusion

Our results indicate a significant correlation between cytokines and coagulation-related parameters. Pro-inflammatory factors may be more associated to coagulation parameters, especially in the early stage of COCID-19 inflammation. Within this correlation, IL-6 seems more relevant in the evaluation of the condition of COVID-19 patients. More high-evidence research is needed to further clarify the pathogenesis of SARS-CoV-2, to further improve the cure and reduce mortality.

## 6. Contributors

SZ and YL conceived and designed the study. DZ, XZ, HZ, HC, HZ, ZL, QL, YX, XY, and RT contributed to data collection. SY, LX, XD, and MX contributed to data analysis. SY and YC contributed to the figures. SY contributed to the writing of the article.

## CRediT authorship contribution statement

**Dong Zhang:** Resources, Data curation. **Xiang Zhou:** Resources, Data curation. **Songxin Yan:** Formal analysis, Methodology, Visualization, Writing - original draft. **Ran Tian:** Resources, Data curation. **Longxiang Su:** Formal analysis, Methodology. **Xin Ding:** Formal analysis, Methodology. **Meng Xiao:** Formal analysis, Methodology. **Yu Chen:** . **Hua Zhao:** Resources, Data curation. **Huan Chen:** Resources, Data curation. **Hongmin Zhang:** Resources, Data curation. **Zunzhu Li:** Resources, Data curation. **Qi Li:** Resources, Data curation. **Yingchun Xu:** Resources, Data curation. **Xiaowei Yan:** Resources, Data curation. **Yongzhe Li:** Project administration, Funding acquisition, Writing - review & editing. **Shuyang Zhang:** Project administration, Funding acquisition, Writing - review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2020.07.002.

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