# Risk factors and laboratory predictors of severe Coronavirus Disease 2019

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**Abstract**

A pandemic caused by SARS-CoV-2 has infected more than 2 million people and killed exceeding 150,000 people around the world as of April 19,2020. We obtained the clinical data of all diagnosed patients in Fuyang, Anhui province to investigate indicators that can be used to assess severity of COVID-19. Of the 155 patients, 87(56.13%) were males. The mean age was 41.95 (SD 15.34) years. Only 30(19.35%) patients had critical condition. Fever (84.52%) followed by cough (81.94%) were the most common symptoms, and short of breath was more common in severe patients (P<0.01). Lymphopenia was observed in most patients (74, 47.7%). It showed the elevation of C-reaction protein (CRP) in 100 (64.5%) patients and the elevation of serum amyloid protein A (SAA) in 104 (67.1%) patients. Interleukin 6 (IL-6) was above the normal range in 104 (67.1%) patients. The calculated cut-off value of CRP was 19.35 mg/mL, the AUC was 0.777, sensitivity was 73.3%, specificity was 69.6%; SAA was 73.55 mg/L, 0.679, 83.3%, 56.8% respectively; IL-6 was 18.85 pg/mL, 0.797, 83.3%, 64.8%; D-Dimer was 0.325 mg/L, 0.673, 66.7% and 68.8%. The combination of CRP, SAA, IL-6 and D-Dimer was 0.823 in AUC, 73.3% in sensitivity and 78.4% in specificity. Old age, co-existing disease and lymphopenia are related to severe COVID-19. Elevated CRP, SAA, IL-6 and D-Dimer can be predictors to severe COVID-19. The combination of these four indicators can improve the effectivity and specificity of assessing severe COVID-19.

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**Summary**

A pandemic caused by SARS-CoV-2 has infected more than 2 million people and killed exceeding 150,000 people around the world as of April 19,2020.

We obtained the clinical data of all diagnosed patients in Fuyang, Anhui province to investigate indicators that can be used to assess severity of COVID-19.

Of the 155 patients, 87(56.13%) were males. The mean age was 41.95 (SD 15.34) years. Only 30(19.35%) patients had critical condition. Fever (84.52%) followed by cough (81.94%) were the most common symptoms, and short of breath was more common in severe patients (P<0.01). Lymphopenia was observed in most patients (74, 47.7%). It showed the elevation of C-reaction protein (CRP) in 100 (64.5%) patients and the elevation of serum amyloid protein A (SAA) in 104 (67.1%) patients. Interleukin 6 (IL-6) was above the normal range in 104 (67.1%) patients. The calculated cut-off value of CRP was 19.35 mg/mL, the AUC was 0.777, sensitivity was 73.3%, specificity was 69.6%; SAA was 73.55 mg/L, 0.679, 83.3%, 56.8% respectively; IL-6 was 18.85 pg/mL, 0.797, 83.3%, 64.8%; D-Dimer was 0.325 mg/L, 0.673, 66.7% and 68.8%. The combination of CRP, SAA, IL-6 and D-Dimer was 0.823 in AUC, 73.3% in sensitivity and 78.4% in specificity.

Old age, co-existing disease and lymphopenia are related to severe COVID-19. Elevated CRP, SAA, IL-6 and D-Dimer can be predictors to severe COVID-19. The combination of these four indicators can improve the effectivity and specificity of assessing severe COVID-19.

**Key words:** COVID-19; SARS-CoV-2; Risk factors; predictors; ROC curve

**Introduction**

Coronavirus Disease 2019 (COVID-19), a highly contagious respiratory disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has created a worldwide pandemic at present(WHO, 2020c, 2020d). As of 3 April, 2020, the outbreak has spread to more than 200 countries globally with exceeding 1 million cumulative confirmed cases and 50,000 deaths(WHO, 2020a), which is a major threat to the health of people around the world. Initial studies suggest that the outbreak was closely linked to the Huanan seafood market in Wuhan, Hubei province, China, in which wildlife was sold illegally(Huang Chaolin, 2020). However, as the researches progressing and the global pandemic shows that Wuhan may not be the source of SARS-CoV-2, and that the virus may have started weaker transmission and constant mutation over a long period of time (before December 2019)(Andersen, Rambaut, Lipkin, Holmes, & Garry, 2020). Currently, the major thing is to control the global outbreak as quickly as possible. After taking strict

measures of containment and isolation, China has achieved a phased victory of controlling the epidemic, and more than 94% patients infected with SARA-CoV-2 have been cured as of 3 April(NHC).

Current studies still show that fever is the most common symptom in patients confirmed with COVID-19, and lower lymphocyte count and multiple ground-glass opacity in chest computed tomography are two means of screening suspected patients. For the dead patients, the main cause of death is still respiratory failure. Researchers performed autopsy to some deaths, it showed acute diffuse alveolar injury with extensive hyaline membrane formation with partial alveolar wall destruction(Yao et al., 2020). There were more exudative lesions and no obvious fibrosis compared with SARS(Liu Qian, 2020). In addition, there were varying degrees of degeneration and necrosis in other organs and transparent thrombosis was found in the capillaries of the lung and kidney, which may be related to systemic inflammatory storm(Yao et al., 2020). Therefore, patients infected with SARS-CoV-2 may have complications in the course of the disease, such as acute myocardial injury, venous thrombosis, acute renal injury, septic shock, the occurrence of these complications may indicate poor prognosis(Zhou et al., 2020). The abnormality in inflammatory indicators and coagulation function can provide early warning for the worsen condition. Due to bordering Hubei Province, the original center of the outbreak, there was also a serious epidemic in Anhui Province on February,2020. At present, the COVID-19 patients in Anhui Province have been cured, with no new confirmed cases. We obtained the data of patients in Fuyang city to explore the relationship between inflammatory indicators, coagulation function and the severity of disease, which can help the medical workers to identify critical patients as soon as possible and take appropriate measures to intervene earlier.

## Method

All the patients who was diagnosed with COVID-19 in Fuyang city as of April 8,2020 were enrolled in this study. All these patients were laboratory-confirmed cases, who were conducted SARS-CoV-2 nucleic acid detection by the second hospital of Fuyang city, Centers for Disease Control and Prevention in Fuyang and Anhui province.

We obtained epidemiological characteristics, clinical manifestations, laboratory results, radiologic data from the electronic medical record system of the hospital or by face-to-face interview with patients or their relatives. Epidemiological features included age, sex, occupation, chronic underlying disease, history of exposure and smoking. Laboratory examination mainly included blood routine, liver and kidney function, coagulation function, C-reactive protein, interleukin-6、serum amyloid protein A and other inflammatory indexes. Lung radiologic data of all patients was obtained by computed tomography. The severity of COVID-19 was defined depending on the diagnosis and treatment program of COVID-19 (trail seventh version). The data collection process has passed the oral consent of the patients themselves or their clients.

We denoted categorical variables by frequency (percentage) and compared the proportions of categorical variables by $\chi 2$ tests. For the continuous variables, a single sample Kolmogorov-Smirnov test was used to test whether it conforms to the normal distribution firstly. Then it was expressed by mean (standard deviation) or median (IQR) depending on whether the variables were normally distributed and the mean of continuous variables were compared by independent group t-test or Mann-Whitney U test as appropriate. Meanwhile, ROC curve was drawn to determine the best cut-off value of each index to evaluate the severity of COVID-19, and the sensitivity and specificity of the biomarkers were calculated to evaluate the clinical diagnostic efficacy. The difference was statistically significant when p value was less than 0.05. All statistical analyses were carried out by SPSS (social science statistical software package) version 25.0 software.

## Results

### Demographic and clinical features

Table 1 showed the demographic and clinical features. Of the 155 patients in Fuyang, Anhui province, 87(56.13%) were males, and 68(43.87%) were females. The range of age was from 1 year 4 months to 82 years. The mean age was 41.95 (SD 15.34) years. 7.09% of patients were aged below 18 years. Furthermore, there was significant difference (39.78 vs. 50.97, P=0.001) in the age between moderate and severe (critical)

group. 20(12.9%) patients had a history of smoking, there was no marked difference between the two groups (12.0% vs. 16.7%, P>0.05).

38(24.53%) patients had chronic underlying disorder, the most common of which was hypertension, diabetes. Moreover, chronic underlying disease was significantly more common in severe (critical) than non-critical group (50.0% vs. 18.4%, P<0.001). Majority of patients were moderate, only 30(19.35%) patients were severe or critically ill.

Fever (84.52%) followed by cough (81.94%) were the most common symptoms, and there were other symptoms, like fatigue (34.84%), short of breath (41.29%), which was shown in more than a third of patients. Some patients developed symptoms other than respiratory system, such as diarrhea, nausea (vomiting) and erythra. Severe patients had higher temperature (38.7 vs. 38.1, P=0.001) than the moderate group, and short of breath was more common in severe patients (P<0.01). Diarrhea was common in moderate group than severe group (39.2% vs. 20.0%, P=0.048). Other symptoms had no significant difference between the two groups (all P>0.05).

**Laboratory and computed tomography findings**

Table 2 and table 3 showed the laboratory findings of 155 patients. On admission, 24 (15.48%) patients had leukopenia, 7 (23.3%) developed into severe (critical) type during the course of disease. Lymphopenia was observed in 74 (47.7%) patients, with a significant difference (40.8% vs. 76.6%, P=0.001) between moderate and severe (critical) groups. In addition, the median of lymphocytes count in critical patients was lower than non-critical patients. Hemoglobin and platelet had no specific increase or decrease in confirmed patients.

Only a few patients had abnormity in prothrombin time and activated partial thromboplastin time. Fibrinogen and d-dimer were increased in 23(14.8%) and 34 (21.9%) patients respectively, with a higher percent in severe cases. In this study, few patients had liver or kidney impairment. Elevated levels of alanine aminotransferase, serum total bilirubin, creatinine and blood urea nitrogen were less. Lactate dehydrogenase was significantly elevated in severe patients (20/29, 69%), with a mean of 308.52 U/L.

In the 155 patients, there were significant elevations in some infection-related indicators, which showed the elevation of C-reaction protein (CRP) in 100 (64.5%) patients and the elevation of serum amyloid protein A (SAA) in 104 (67.1%) patients. And interleukin 6 (IL-6) was above the normal range in 104 (67.1%) patients. The elevation of procalcitonin (PCT) was less common. 54% patients had elevated erythrocyte sedimentation rate (ERS), with no significant difference between the two groups. Critical patients had more prominent abnormity in inflammatory indicators (e.g., CRP, SAA, IL-6) compared with non-critical patients (all P<0.05).

Table 4 showed the CT findings of 155 patients. Of all patients, 123 (79.4%) showed bilateral pneumonia. All the 30 severe (critical) patients had double pneumonia. At the time of admission, 9 patients presented normal results in CT, all of whom were non-critical patients. 50 (32.3%) patients were found ground-glass opacity in CT, with a higher proportion of severe (critical) patients.

**Clinical outcomes and length of stay**

In this study, all 155 patients were cured to discharge (table 1). None of patients was died. The length of stay was ranged from 8 to 43 days. The median time of LOS is 16 days (14˜22). There was no significant difference of the length of stay between the two groups (16 vs. 19.5, P>0.05).

**ROC curve and severe COVID-19**

ROC curve was drawn based on the test results of CRP, SAA, IL-6, D-Dimer alone and the combination of the four indicators (figure 1, table 5). The area under the ROC curve was 0.777, 0.679, 0.797, 0.673, 0.823 respectively. When the Youden index was maximum, we regarded the detected value as the cut-off value. The calculated cut-off value of CRP was 19.35 mg/mL, the AUC was 0.777, sensitivity was 73.3%, specificity was 69.6%; SAA was 73.55 mg/L, 0.679, 83.3%, 56.8% respectively; IL-6 was 18.85 pg/mL, 0.797,

83.3%, 64.8%; D-Dimer was 0.325 mg/L, 0.673, 66.7% and 68.8%. The combination of CRP, SAA, IL-6 and D-Dimer was 0.823 in AUC, 73.3% in sensitivity and 78.4% in specificity.

**Discussion**

We conducted a retrospective study of all confirmed patients in Fuyang city, Anhui province to describe the general features of patients infected with SARS-CoV-2 and the value of some laboratory indicators for assessing severe COVID-19.

SARS-CoV-2 is the third zoonotic human coronavirus we encountered in the 21st century. There is no doubt that COVID-19 has caused a great impact on the health of people and economic development all over the world. While the mortality rate of COVID-19 (about 6.8%)(WHO, 2020b) is lower than the severe acute respiratory syndrome (SARS) (9.6%)(WHO) or middle-eastern respiratory syndrome (MERS) (34.4%)(WHO) as of April 22,2020, its prevalence is much higher than that of SARS or MERS, with the result that number of deaths has far exceeded the sum of SARS and MERS so far. In particular, the situation has intensified in some countries in Europe and America, and the surge of confirmed cases made it a huge challenge to the health system of these countries.

Previous studies have shown angiotensin converting enzyme 2 (ACE2) is the receptor of SARS-CoV-2 which is identified as the receptor of SARS-CoV(Hamming et al., 2004; Lu et al., 2020). SARS-CoV-2 mainly binds to the ACE 2 on the surface of airway epithelial cells via S-spike after invading the body(Yan, Xiao, & Lin, 2020). Then the virus will replicate inside the cell until releasing from the cell to cause tissues injury and invade other cells. In addition, ACE2 expresses in vascular endothelial cells, renal tubular epithelium, smooth muscle cells and small intestinal epithelial cells(Hamming et al., 2004), which may explain that some confirmed patients showed elevated myocardial enzymes, abnormal renal function and diarrhea. Meanwhile, this distribution pattern of ACE2 suggested that the possibility of fecal-oral transmission(Zhang et al., 2020).

In this study, the youngest patient was only 1 year and 4 months old, and the oldest was 82 years old, which suggested that people in all age groups were susceptible to SARS-CoV-2. The mean age of the critically ill patients was older than that of the non-critical group. In the study of 1099 patients with COVID-19, the median age of severe group was 52 years old, non-severe group was 45 years old(W. Guan, 2020). In addition, it suggested that co-existing disorders, especially hypertension, diabetes, coronary heart disease and chronic obstructive pulmonary disease, and smoking history may be the risk factors of severe COVID-19. It may be related to the poor immunity of elderly patients and more chronic underlying diseases, which is more prone to multiple organ dysfunction. Recent study has shown that smoking can increase the expression of ACE2 in lung tissue to increase risk of coronavirus complication(Cai, 2020), so current smoking was found to be a significant predictor of COVID-19 severity(Liu et al., 2020). On the contrary, other studies have suggested that there was no significant relationship between smoking and worsen prognosis(Giuseppe Lippi 2020). The difference in smoking history between the two groups of patients was not statistically significant in our study either. Therefore, whether there is association between smoking history and the poor prognosis of the COVID-19 requires further studies to confirm.

Fever remained the most common symptom in these patients, with a higher peak temperature in critical patients than non-critical patients, while chest tightness was significantly different between the two groups as well, which was consistent with the previous study(W. Guan, 2020). Therefore, high fever or shortness of breath during the course may indicate progression of COVID-19.

Among laboratory indicators, lymphopenia was the most obvious change, which is different from the general viral infection that causes a reactive increase in lymphocyte count. The mechanism of SARS-CoV-2 induced lymphopenia remains unclear. But the pathological findings in patients who died of SARS may supposed that SARS-CoV-2 can affect T cells directly, but further studies are needed to confirm it(Gu et al., 2005; Li et al., 2020). In addition, D-dimer, fibrinogen was elevated in some patients; elevations of CRP, IL-6, and SAA were prominent in critical patients than non-critical patients. Most patients in our study had normal liver and kidney function and only showed elevated lactate dehydrogenase. Relevant studies have shown that severe cases had more obvious abnormality in laboratory indicators (e.g., CRP, IL-6, SAA, LDH, D-dimer,

etc.)(Arachchillage & Laffan, 2020; Huan Li 2020; Soraya, 2020; Wang, 2020). CRP is acute phase protein, which is an important indicator for the diagnosis and assessment of severe pulmonary infectious disease, with CRP levels positively correlating with lung lesions and severe presentation(Wang, 2020). D-dimer above 1mg/L is a risk factor for poor prognosis(Zhou et al., 2020),which may be associated with a high risk of venous thromboembolism, even pulmonary thromboembolism. Therefore, appropriate anticoagulant therapy should be based on the results of coagulation function(Zhai et al., 2020). Updated study suggested that the levels of inflammatory cytokines and chemokines are significantly elevated in COVID-19 patients, so it may infer that the possible presence of a cytokine storm in severe COVID-19(Li et al., 2020). Critical patients in our study had higher IL-6 levels than non-critical patients, and a cytokine storm can cause multi-organ injury, especially aggravating lung damage. Then it would develop into ARDS leading to death from respiratory failure(Chen, Zhang, Ju, & He, 2020). Consequently, immunotherapy, such as tolizumab, can be used in some patients with high cytokine levels to reduced blood cytokine levels, but further clinical trials are needed to confirm its effectiveness(Luo et al., 2020).

Through the ROC curve, we concluded that IL-6 has the best effect of evaluating severe COVID-19 and the sensitivity is higher. The combination of four indicators can improve the effect and specificity of assessing severe COVID-19, meanwhile it has a better sensitivity. A study from Zhong Nanshan suggested that it is the most important to protect early, identify early, diagnose early and isolate early to combat the COVID-19 outbreak(W. J. Guan, Chen, & Zhong, 2020). In addition, it is vital to identify and intervene early in severe patients with COVID-19.

There are several limitations in our study. First, although we included all confirmed patients in Fuyang City, the overall number of cases remains low, it may cause some deviations. Furthermore, some information, like exposure history, date of exposure was incomplete due to the busy clinic work. We cannot analyze the epidemiological characteristics in Fuyang city to know whether there was difference between different areas. In addition, with the efforts of the medical staff, all patients were discharged from the hospital, which gave us only a rough idea of the risk factors for critically ill patients. We will follow up these patients for a long time to understand the long-term prognosis of COVID-19.

**Conclusion**

Advanced age, comorbidities, chest tightness, lymphopenia and increased IL-6, SAA are risk factors for severe COVID-19. IL-6 is a better index to evaluate severe COVID-19. Combining multiple indexes can improve the effectiveness and specificity of assessing severe COVID-19.

**Conflicts of interest** : The authors declare that there are no conflicts of interest.

**Data availability statement** : All data generated or analyzed during this study are included in this paper and its Supporting Information.

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**Author contributions** : Xiaoyun Fan designed the study. Min Pan was responsible for processing the statistical data and writing the paper. The authors from the NO.2 People's Hospital of Fuyang City contributed to the treatment of patients and All the authors contributed to this paper.

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**Ethics Statement** : The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received.

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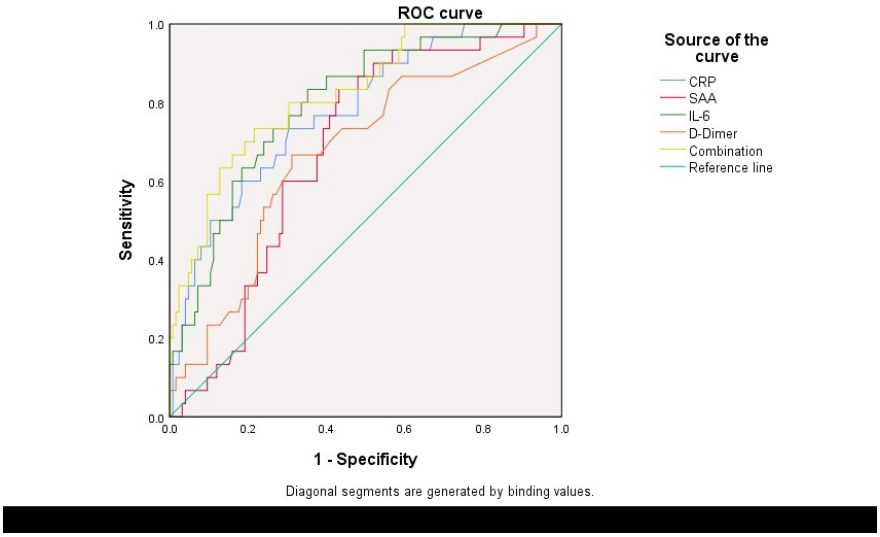


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