Risk factors for Coronavirus disease 2019 pneumonia after admission outside Wuhan, China

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Abstract
Coronavirus disease 2019 (COVID-19) has spread worldwide, causing significant stress on the medical system. We explored the risk factors for condition changes in COVID-19 pneumonia patients after admission.

The patients diagnosed with COVID-19 pneumonia at 2 medical centers in Hunan Province were studied, and those whose conditions changed after admission were compared. Their clinical characteristics and experimental indicators were compared using SPSS software and R language to build a disease risk prediction model.

Patients with condition changes after admission were older and had more blood cell abnormalities and impaired organ function (decreased albumin, elevated D-dimer) than normal patients. We found that age, neutrophil ratio, D-dimer, chest Computed tomography (CT) changes, and glucocorticoid use were risk factors for COVID-19 pneumonia after admission.

Elderly patients are more susceptible to disease changes after COVID-19 pneumonia; COVID-19 pneumonia patients who develop disease changes after admission have higher neutrophil ratios, increased D-dimer levels, chest imaging changes, and glucocorticoid usage. Additional research is needed.

Abbreviations: ACE2 = angiotensin-converting enzyme 2, APTT = activated partial thromboplastin time, ARDS = acute respiratory distress syndrome, AUC = area under the receiver operating characteristic curve, COVID-19 = Coronavirus Disease 2019, CRP = C-reactive protein, CT = computed tomography, DDI = D-dimer, FIO2 = oxygen absorption concentration, ICU = intensive care unit, LASSO = absolute contraction selection operator, PaO2 = arterial partial pressure of oxygen, PCT = procalcitonin, PT = prothrombin time, RAS = renin-angiotensin system, RR = respiratory rate.

Keywords: COVID-19, D-dimer, neutrophils, pneumonia, risk factors

1. Introduction
Coronavirus disease 2019 (COVID-19) is caused by SARS-COV-2, which invades host cells through human angiotensin-converting enzyme 2 (ACE2) and through the human CD147 pathway, causing pneumonia, acute respiratory distress syndrome (ARDS), coagulopathy and even death.[1,2] COVID-19 was first reported in Wuhan in December 2019 and has caused a pandemic in 187 countries and regions. As of 04:00 on March 23, 2020, 294,110 cases of COVID-19 pneumonia have been diagnosed worldwide, and a total of 12,944 deaths have been reported.[3] In the treatment of COVID-19 pneumonia, how to predict changes in a patients condition is extremely important. Current research has shown that patients requiring intensive care unit (ICU) care have increased inflammation levels.[4] Studies of critically ill patients have shown that patients older than 65 years of age with underlying disease have an increased risk of death.[5] An analysis of patients who progressed to ARDS and died after admission revealed that age, neutrophil count, organ dysfunction and coagulopathy were risk factors for disease progression.[6] However, most of these studies are single-center studies and concentrated in Wuhan, a city where only severe patients are hospitalized when medical resources are overwhelmed, resulting in possible selection bias. This study analyzed the clinical characteristics of patients with COVID-19 pneumonia who underwent changes after admission at 2 medical centers in Hunan Province to investigate the risk factors for the changes in the condition of patients and construct a risk prediction model...
predict the risk of condition changes of patients with pneumonia after admission to better help and guide clinical treatment.

2. Methods

2.1. Research subjects

This study was a retrospective database analysis approved by the research ethics committee of Xiangtan Central Hospital. Requirement for written informed patient consent was waived because all data were anonymous.

We retrospectively collected the medical data of 109 patients diagnosed with COVID-19 in Xiangtan city and Shaoyang city from January 2020 to March 2020, including their general condition, epidemiological history, signs and symptoms, laboratory examination and imaging findings, treatment and prognosis. According to the patients condition change, we divided the patients into normal patients and severe patients. Normal patients were those with few symptoms, cough, and other clinical symptoms accompanied by imaging showed pneumonia: 1. shortness of breath (respiratory rate (RR) ≥30 bpm); 2. oxygen saturation ≤93% in the resting state; 3. arterial partial pressure of oxygen (PaO2)/oxygen absorption concentration (FiO2) ≤300 mm Hg [1 mm Hg = 0.133 kPa] in high-altitude areas (over 1000 m above sea level), correction of PaO2/FiO2 should be made according to the following formula: PaO2/FiO2 ≤ [atmospheric pressure (mm Hg)/760] / 0.133 kPa; 4. lung imaging showed significant progression in 50% of lesions within 24 to 48 hours; 5. respiratory failure requiring mechanical ventilation; 6. shock; and, 7. patients with other failure requiring monitoring and treatment in the ICU. “Severe” patients refer to those who are admitted to the hospital as “normal” and have an aggravated condition during treatment with any of the following manifestations or any of the following conditions upon admission:

1. Shortness of breath (RR ≥30 bpm);
2. Oxygen saturation ≤93% in the resting state;
3. PaO2/FiO2 ≤ 300 mm Hg (1 mm Hg = 0.133 kPa) [in high-altitude areas (over 1000 m above sea level), correction of PaO2/FiO2 should be made according to the following formula: PaO2/FiO2 ≤ [atmospheric pressure (mm Hg)/760] / 0.133 kPa];
4. Lung imaging showed significant progression in 50% of the lesions within 24 to 48 hours;
5. Respiratory failure requiring mechanical ventilation;
6. Shock; and,
7. other organ failure requiring monitoring and treatment in the ICU.

The included children met the following criteria:

1. Shortness of breath (<2 months old, RR ≥60 times/minutes; 2–12 months old, RR ≥50 times/minutes; 1–5 years old, RR ≥40 times/minutes; 6–10 years old, RR ≥30 times/minutes), excluding the effects of fever and crying;
2. at rest, oxygen saturation ≤92%;
3. Assisted breathing (moaning, nasal wing agitation, 3 concave signs), cyanosis, or intermittent apnea; and
4. Lethargy and convulsion, with the condition gradually improving during hospitalization without aggravation.

2.2. Patient management and data collection

COVID-19 patients from Xiangtan city and Shaoyang city were admitted to Xiangtan Central Hospital and Shaoyang Central Hospital, respectively, which were designated COVID-19 hospitals. Both hospitals, as grade 3A hospitals, were approved by the National Centers for Disease Control and Prevention for reverse transcription-polymerase chain reaction (RT-PCR) detection. We performed RT-PCR tests on the body fluid samples of all patients, such as nasopharyngeal secretion, sputum, blood, and stool samples, to confirm that the patients were infected. The patients symptoms, signs and medical history were collected. Laboratory tests, such as routine blood, liver and kidney function, myocardial enzymology, coagulation function, D-dimer (DDI), C-reactive protein (CRP), procalcitonin (PCT), and lung computed tomography (CT) tests after admission were also performed. Hormone use history was also included in the collection.

2.3. Statistical methods

SPSS software and R language were used for statistical analysis. The continuous and categorical variables are described by the mean and standard deviation and by quantity and percentage, respectively. Univariate analysis of continuous variables was compared in patients with mild disease by the t-test, and categorical variables were compared by the Chi-Squared test. P < .05 was considered statistically significant. Independent predictors were selected by the absolute contraction selection operator (LASSO) regression model, and a prognostic nomogram was established to generate a comprehensive index to evaluate the aggravation of the condition of COVID-19 patients. A prediction curve was generated, and the discriminant of the nomogram was quantified by measuring the area under the receiver operating characteristic curve (AUC), sensitivity, specificity and accuracy.

3. Results

3.1. Clinical characteristics of COVID-19 patients

As of March 18, 2020, a total of 109 patients with COVID-19 pneumonia were diagnosed in Xiangtan and Shaoyang, 68 and 41 of whom were designated normal and severe, respectively (Table 1); their average age was 36.68 and 54.07 years, respectively. Severe patients were relatively older. There were 37 males and 31 females among the general patients and 21 males and 20 females among the severe patients. Regarding sex distribution, there was no significant difference between the 2 groups. The heart rate and blood pressure of severe patients displayed warning signs (87.51 vs 82.62, 125.71 vs 119.37, 79.83 vs 75.94, P < .05); there was no significant difference between the 2 groups regarding body temperature at admission (P = .112). One of the normal and severe patients had a smoking history. The time from onset to admission was shorter in severe patients (6.76 vs 8.96 days, P = .019). The common underlying diseases in patients with severe COVID-19 were hypertension and diabetes (13 vs 6, 8 vs 3, P < .05). In patients with COVID-19, fever was still the most common symptom, with approximately 78.3% of patients having a fever. Cough followed closely (73.39%), Diarrhea and headache were rare (2.73% and 2.73%). Most of the severe patients had imaging changes, and one of the common patients had exacerbation of imaging findings (19 vs 1, P < .001). Glucocorticoids were used only in severe patients, and approximately 56.10% of severe patients were administered glucocorticoids.
### Clinical Characteristics of COVID-19 pneumonia patients.

| T               | Normal | Changes | P-value |
|-----------------|--------|---------|---------|
| Numbers         | 68     | 41      |         |
| AGE, year       | 36.68±15.14 | 54.07±13.57 | <.001  |
| ONSET TO ADMISSION, days | 8.96±5.19   | 6.76±3.60   | .019    |
| SP02, %         | 97.33±1.53   | 96.07±2.57   | .002    |
| T, °C           | 36.80±0.44   | 36.98±0.68   | .112    |
| HR, beats per minute | 82.62±9.27   | 87.51±12.62  | .022    |
| SBP, mm Hg      | 119.37±13.48 | 125.71±14.09 | .021    |
| DBP, mm Hg      | 75.94±9.00   | 79.83±9.19   | .032    |
| GENDER. Female  | 31 (45.59%) | 21 (51.22%) | .715    |
| Male            | 37 (54.41%) | 20 (48.78%) |         |
| SMOKING. No     | 67 (98.53%) | 40 (97.56%) |         |
| Yes             | 1 (1.47%)   | 1 (2.44%)   |         |
| HYPERTENSION. No| 62 (91.18%) | 28 (68.29%) | .002    |
| Yes             | 6 (8.82%)   | 13 (31.71%) |         |
| DIABETES. No    | 65 (95.59%) | 33 (80.40%) | .011    |
| Yes             | 3 (4.41%)   | 8 (19.51%)  |         |
| COPD. No        | 66 (97.06%) | 36 (87.80%) | .056    |
| Yes             | 2 (2.94%)   | 5 (12.20%)  |         |
| CVD. No         | 67 (98.53%) | 40 (97.56%) | .715    |
| Yes             | 1 (1.47%)   | 1 (2.44%)   |         |
| CHD. No         | 65 (95.59%) | 39 (95.12%) | .910    |
| Yes             | 3 (4.41%)   | 2 (4.88%)   |         |
| LIVER.DISEASE. No| 67 (98.53%) | 39 (95.12%) | .292    |
| Yes             | 1 (1.47%)   | 2 (4.88%)   |         |
| OPERATION. No   | 64 (94.12%) | 35 (85.37%) | .125    |
| Yes             | 4 (5.88%)   | 6 (14.63%)  |         |
| FEVER. No       | 19 (27.94%) | 7 (17.07%)  | .197    |
| Yes             | 49 (72.06%) | 34 (82.93%) |         |
| COUGH. No       | 18 (26.47%) | 11 (26.83%) | .967    |
| Yes             | 50 (73.53%) | 30 (73.17%) |         |
| FATIGUE. No     | 48 (70.59%) | 25 (60.98%) | .301    |
| Yes             | 20 (29.41%) | 16 (39.02%) |         |
| SHORTNESS.BREATH. No | 58 (85.29%) | 29 (70.73%) | .067    |
| Yes             | 10 (14.71%) | 12 (29.27%) |         |
| HEADACHE. No    | 65 (95.59%) | 41 (100.00%)| .173    |
| Yes             | 3 (4.41%)   | 0 (0.00%)   |         |
| DIARRHEA. No    | 67 (98.53%) | 39 (95.12%) | .292    |
| Yes             | 1 (1.47%)   | 2 (4.88%)   |         |
| IMAGE CHANGE. No| 66 (98.51%) | 22 (53.66%) | <.001   |
| Yes             | 1 (1.49%)   | 19 (46.34%) |         |
| HORMONE. No     | 68 (100.00%)| 18 (43.90%) | .001    |
| Yes             | 0 (0.00%)   | 23 (56.10%) |         |
| TIME.TO.USE.TAMVRUS. day | 5.53±3.79   | 4.59±3.63   | .203    |

### Laboratory index of COVID-19 pneumonia patients.

| T               | Normal | Severe | P-value |
|-----------------|--------|--------|---------|
| Numbers         | 68     | 41     |         |
| WBC, 10^9/L     | 6.25±4.88 | 6.71±4.58 | .627    |
| NE, %           | 62.87±12.36 | 74.98±11.20 | <.001  |
| LYM, 10^9/L     | 1.35±0.70   | 0.87±0.33   | <.001   |
| PLT, 10^9/L     | 230.19±60.52 | 183.54±64.93 | <.001  |
| ALT, IU/L       | 26.77±18.98 | 27.10±17.04 | .927    |
| AST, IU/L       | 27.80±16.42 | 34.22±22.25 | .087    |
| ALB, g/L        | 42.59±5.76   | 38.86±7.68   | .005    |
| GLB, g/L        | 27.17±5.35   | 29.45±4.60   | .026    |
| CR, umol/L      | 63.60±18.13 | 68.86±21.73 | .463    |
| PT, seconds     | 11.38±1.48   | 11.43±1.25   | .973    |
| DDI, ug/ml      | 0.34±0.28   | 0.87±1.64   | .013    |
| APTT, seconds   | 32.64±8.34   | 34.45±9.01   | .304    |
| PCT, ug/L       | 0.07±0.06   | 0.12±0.18   | .063    |
| CRP, mg/L       | 11.55±23.02 | 40.42±51.24 | <.001   |

### Table 2

#### 3.2. Laboratory tests

The laboratory specifications are described in Table 2. Compared with that in normal patients, the neutrophil ratio was higher in severe patients, and the absolute count of lymphocytes was lower (74.98 vs 62.87, 0.87 vs 1.35, P < .001); the platelet count level in severe patients was also relatively lower (183.54 vs 230.19, P < .001). In the detection of liver function, no significant difference was found in transaminase levels between severe patients and normal patients, but the severe patients showed lower albumin levels and higher globulin levels (38.86 vs 42.59, 29.45 vs 23.02, P < .001). The detection of liver function, no significant difference in renal function and PCT content between normal and severe patients. Regarding the detection of blood coagulation indicators, we found that the severe patients had higher DDI values, which indicated that the severe patients had a tendency toward hypercoagulability, while activated partial thromboplastin time (APTT) and prothrombin time (PT) did not show abnormalities. CRP levels were significantly higher in the severe patients (40.42 vs 11.55, P < .001).

#### 3.3. Disease prediction model

As shown in Figure 1, we applied the LASSO Logit model to assess the exacerbation of COVID-19 disease. The penalty coefficient in the LASSO model was adjusted by 10-fold cross-validation and the minimum criterion, and 5 predictive factors related to the aggravation of COVID-19 were screened out of 41 related factors. These factors were age, neutrophil ratio, DDI content, imaging changes, and hormone use. For synthesizing the 5 main predictors in the above screening, we used R language to establish a COVID-19 exacerbation risk prediction model to predict a patient’s exacerbation risk (Fig. 2). As shown in Figure 3, the AUC of the predictor nomogram is 0.94 (0.94–0.99), the sensitivity is 0.82, the specificity is 0.889, and the accuracy is 0.862.

### 4. Discussion

We analyzed the clinical characteristics of 109 patients with COVID-19 pneumonia at 2 medical centers in Hunan Province.
(Xiangtan city and Shaoyang city) and analyzed the cases with changes in condition after admission. According to the results, elderly patients and patients with chest CT changes after admission were more likely to experience changes in condition, which suggests that we need to pay additional attention to elderly patients and imaging changes because they indicate increased risk of exacerbation. In addition, compared with normal patients, severe patients after admission were older, had potential health problems in the past (such as hypertension, diabetes, and other underlying complications) and had more organ functional impairment, which is consistent with previous studies.[6-8] However, due to possible bias, additional research is needed.

Patients with progression of COVID-19 pneumonia often showed an increase in neutrophil levels and a decrease in lymphocyte levels, which is consistent with the results observed in most current studies.[9-10] As an inflammatory activating factor, neutrophils are likely to cause overactivation of the body’s immune response and cytokine storms. Elevated neutrophil levels may herald an enhanced immune response. What is confusing is that monocyte and macrophage infiltration are more common under pathological microscopy in patients with fatal COVID-19 pneumonia than granulocyte infiltration.[11] Therefore, we hypothesize that neutrophils activate the immune response to fight against virus invasion, and this effect is one of the possible mechanisms by which SARS-CoV-2 causes damage to the body.

This study showed that patients with changes in COVID-19 pneumonia are more likely than stable patients to develop hypercoagulability, which is manifested by an increase in DDI content. Previous studies have found that SARS-CoV-2 infects humans and causes disease through human ACE2 in the same way as SARS. As ACE2 is an important participating member of the renin-angiotensin system (RAS), SARS-CoV-2 infection may also cause damage to vascular endothelial cells and trigger a medium-to-high coagulation state in the blood.[1] In addition, fever, being bedridden, and bacterial and fungal infections in patients with COVID-19 pneumonia all increase the risks of a hypercoagulable state.[12] Furthermore, the findings of vascular micro-thrombosis confirmed by pathological studies have confirmed our hypothesis.[13] Therefore, anticoagulation therapy for patients with high coagulation risk, such as patients with elevated DDI levels, may be more beneficial to patient prognosis and reduce patient complications. Additional research is needed to confirm this hypothesis.

The use of glucocorticoids in patients with COVID-19 pneumonia is controversial. Currently, the pathophysiological mechanism of SARS-CoV-2 infection in humans is not very clear.
Glucocorticoids have led to mixed outcomes in previous viral pneumonia cases, and there have been conflicting results, such as with the use of glucocorticoids in H1N1.[14,15] In the treatment of SARS patients, glucocorticoids played a substantial role, but some studies have found that the use of glucocorticoids prolonged virus clearance.[16,17] With the presence of a cytokine storm in COVID-19 pneumonia, studies have found that the use of glucocorticoids in patients who progress to ARDS is beneficial to their prognosis.[6–8] However, due to the difference in the condition of critically ill patients, research on hormone use is currently mainly retrospective, which may itself be biased. Additional research is still needed.

This study has some limitations. First, the study had a small sample size. Second, our data are not externally validated. The statistical results of possible bias and survivor bias need to be interpreted with caution. Therefore, more research is needed in the future to confirm the findings.

5. Conclusions
Elderly patients and those with hypertension and diabetes are more likely to develop condition changes after SARS-CoV-2 infection. During the treatment of COVID-19 pneumonia, changes in imaging findings suggest further condition changes.
We constructed a disease prediction model for age, neutrophil ratio, imaging finding changes, glucocorticoid use, and DDI levels to predict changes in the disease course. Additional research is needed to combat the COVID-19 pneumonia epidemic.

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Author contributions
LSJ, YY, JMY, ZJP, XXD and LP conceived and designed the study; LSJ and YY contributed major in writing original manuscript. ZJP, XXD, CXP and HC contributed to the statistical analysis; all authors contributed to data collection, data analysis and read and approved the final manuscript.

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Figure 3. The ROC curve of the predictor normogram.

| Model       | AUC (95%) | Sensitivity (%) | Specificity (%) | Accuracy (%) |
|-------------|-----------|-----------------|-----------------|--------------|
| Full model  | 0.94 (0.94-0.99) | 82%             | 88.9%           | 86.2%        |

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