Title: Development of a risk prediction score to identify high-risk groups for the critical coronavirus disease 2019 (COVID-19) in Japan

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Summary

Coronavirus disease 2019 (COVID-19) emerged in mid-December 2019 and rapidly spread worldwide. In order to construct a simple risk prediction score for implementation in prehospital settings, we conducted a retrospective analysis of data from patients with COVID-19. Patients were classified into critical and non-critical groups based on disease severity during hospitalization. Multivariate analysis was performed to identify independent risk factors and develop a risk prediction score. In total, 234 patients were included in this study. The median age of the critical group was significantly older than that of the non-critical group (68.0 and 44.0 years), and the percentage of males was higher in the critical group than in the non-critical group (90.2% and 60.6%). Multivariate analysis revealed that age ≥ 45 years, male sex, hypertension, and cancer, along with fever and dyspnea on admission, were independently associated with the critical group. No critical events were noted in the patients with total risk factors ≤ 2. In contrast, the patients with total risk factors ≥ 4 were highly related to the critical group. This risk prediction score may be useful to identify critical COVID-19.
Introduction

Patients with pneumonia associated with a novel coronavirus emerged first in Wuhan, Hubei, China, in mid-December 2019 (1). Thereafter, on February 11, 2020, the World Health Organization (WHO) announced a name for the novel disease—coronavirus disease 2019 (COVID-19). Genetic analysis revealed COVID-19 was caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 rapidly spread from a single city to the entire world. The Chinese Center for Disease Control and Prevention (CDC) published the largest case series of COVID-19 (2). The overall case-fatality rate (CFR) was 2.3%; however, it varied across populations, and the CFR among critical cases was quite high (49.0%).

The most frequent complication is acute respiratory distress syndrome (ARDS), and management of this illness is key to saving patients with COVID-19 (3). Although various treatment agents that effectively prevented viral increases in vitro have been used in clinical trials, no proven therapies for COVID-19 have yet been found (4). Previous literature in China has reported that older age and increased comorbidities, including hypertension, chronic lung disease, cardiovascular disease, and diabetes mellitus (DM), are risk factors for complications of COVID-19 (5, 6). Additionally, obesity, end-stage renal disease, liver disease, and immunocompromised hosts are considered potential risk factors (7). A higher Sequential Organ Failure Assessment score on admission is also a potential risk factor for a poor prognosis at an early stage (8). During an outbreak of COVID-19, medical facilities are required to deal with many patients, and clinicians must identify the high-risk groups quickly for careful monitoring. In this situation, simple risk prediction scores for the severity of COVID-19 would be quite useful. Some Chinese studies have reported the usefulness of risk prediction scores for death and severe cases of COVID-19 (9–11). These studies included
laboratory data or imaging findings and, therefore, are not useful for predicting risk in prehospital settings. Based on past literature, a simple and easy risk prediction score, especially one useful in prehospital settings, has not yet been fully investigated. We conducted a retrospective study on patients hospitalized with COVID-19 with the aim of developing a risk prediction score for use in prehospital settings using some fundamental information available.

**Materials and Methods**

**Setting and Patients**

This was a single-center, retrospective, observational study at Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital. The hospital is an 815-bed, tertiary care hospital specialized for patients with cancer and infectious diseases. All patients included in this study were diagnosed with a reverse transcription (RT)-PCR assay for SARS-CoV-2 from a pharyngeal or nasopharyngeal specimen (12). The patients were admitted to the hospital between January 31 and May 16, 2020. All of the patients who were diagnosed with COVID-19 during this period were included in this study. WHO guidelines show the following classification for the severity of COVID-19: “Asymptomatic,” “Mild,” “Moderate,” “Severe,” and “Critical” (13). Asymptomatic case means a patient who has evidence of SARS-CoV-2 infection without any symptoms of COVID-19. Mild case means a symptomatic patient with COVID-19 without evidence of pneumonia or hypoxia. Moderate case means the patient with clinical signs of pneumonia but no oxygen supplementation (SpO₂ ≥ 90% on room air). Severe case means the patient with clinical signs of pneumonia with respiratory frequency of ≥ 30/min, blood oxygen saturation < 90%, or severe respiratory distress. Critical case means the patient who develop
ARDS, sepsis or septic shock. According to this classification, we defined the severity of COVID-19 at the time of admission and the patient’s most severe state during hospitalization. We classified patients into either a critical or non-critical group, which includes asymptomatic, mild, moderate, and severe groups, based on the most severe state and compared variables between them. Fever was defined as an axillary temperature of at least 37.5 °C, and ARDS was diagnosed according to the Berlin Definition (14). During the study period, we followed the Japanese government’s criteria for discharging patients, which included the resolution of symptoms and two consecutive negative SARS-CoV-2 PCR tests for at least 24 hours apart. We collected data, including clinical characteristics, symptoms on admission, laboratory data on admission, treatment, and outcome data, from routine clinical electronic records. Informed consent was waived because all of the data was obtained retrospectively, and the participants can avoid being enrolled in the study with the opt-out method. This study was approved by an institutional committee on research ethics in the hospital (approval number: 2522). This work was supported by Japan Agency for Medical Research and Development (AMED) [grant number 20fk0108253].

**Statistical analysis**

Statistical data analysis was performed by R version 3.6.1. Categorical variables were described by percentages and analyzed using the chi-squared test or Fisher’s exact test. Continuous variables were described by medians and interquartile ranges (IQR) and analyzed using the Mann–Whitney U test. Statistical significance was defined as a 2-sided $P$-value of $<0.05$. Some continuous variables were analyzed by describing a receiver operating characteristics (ROC)
curve and area under the curve (AUC). We identified the cutoff value to associate with the critical group. In order to construct a risk prediction score, we selected significant variables from clinical characteristics, comorbidities, and symptoms on admission associated with the critical group. There were no missing values in the selected variables. We included them into multivariate logistic regression analysis and selected the most ideal model by a forward-backward stepwise selection method. The risk prediction score was constructed by significant variables, and the points were detected by efficient covariates of each variable. The Kaplan–Meier method and the Log-rank test were used for describing and analyzing the duration from the onset of the symptoms that appeared first to critical events (the timing of diagnosing the critical patients with COVID-19) by each risk group. We omitted four asymptomatic patients from the event-free survival analysis.

Results

During the study period, a total of 234 patients were diagnosed with COVID-19. Among these patients, 41 were classified into the critical group and 193 into the non-critical group. The median age in the critical group was significantly higher than that in the non-critical group (68.0 and 44.0 years, \( p < 0.001 \)) (Table 1). We found that severity was higher among those in the older age category (Fig. 1). Regarding sex, the percentage of male patients was higher in the critical group than in the non-critical group (90.2% and 60.6%, \( p = 0.001 \)). Fewer patients in the critical group had never smoked than in the non-critical group (29.3% and 59.1%, \( p = 0.001 \)). The percentage of some comorbidities was higher in the critical group as determined by univariate analysis (e.g., hypertension, DM, chronic obstructive pulmonary disease [COPD], cancer, and coronary
vascular disease [CVD]). The median number of days from the onset of the symptoms that appeared first to admission was similar between these two groups (9.00 and 9.00 days, \( p = 0.919 \)). Although no cases of mild pneumonia developed into a critical state, 5.4% (6/113) of moderate cases and 43.9% (29/66) of severe cases developed into a critical state.

Table 1 shows the differences in symptoms on admission by each group. Fever was more common in the critical group than in the non-critical group (73.2% and 24.4%, \( p < 0.001 \)), and the same was true for dyspnea (70.7% and 22.3%, \( p < 0.001 \)). In contrast, olfactory and taste disorders were less common in the critical group.

Laboratory findings on admission differed significantly between each group, with the exception of serum amylase (Table 2), indicating that patients in the critical group had significantly more prominent laboratory abnormalities on admission.

Table 2 also shows the treatments and outcomes of the patients. The median number of days from the onset of the symptoms that appeared first to a critical event was 12.0 days (IQR: 10.0–13.0), and median days from admission to a critical event was 3.0 days (IQR: 1.0–5.0). The condition of most patients in the critical group worsened rapidly after admission, and approximately half of the patients (46.3%) in the critical group died during hospitalization. We compared the number of days from the onset of the symptoms that appeared first to the first day of two consecutive negative PCR tests and the number of days from the first positive PCR test to the first day of two consecutive negative PCR tests. Each duration was significantly longer in the
critical group than in the non-critical group.

We described ROC curve of the age to set a cutoff value related to critical COVID-19 and detected that 43.5 years old was most distinguishable age (Fig. 2A). Finally, we put 45 years old as a cutoff value to divide the age group because it was the closest round number. Univariate analyses revealed 12 significant variables associated with the critical group: age, sex, smoking history, hypertension, DM, COPD, CVD, cancer, fever, dyspnea, olfactory disturbance, and taste disturbance. We included them into the multivariate logistic regression analysis. Multivariate analysis revealed that older age (≥ 45 years old), sex (male), hypertension, cancer, fever, and dyspnea were independent risk factors in the critical group (Table 3). Based on the estimated coefficients calculated by the logistic regression model, we counted each risk as one point (from 0 to 6 points). ROC curve of the total risk factors revealed that the AUC was 0.94 (0.9116–0.9683), and the most efficient cutoff point was 3.5 (Fig. 2B). We excluded four asymptomatic cases and classified the remaining patients into three groups based on the risk factors: high-risk (total risk factors ≥ 4), intermediate-risk (total risk factors = 3), and low-risk (total risk factors ≤ 2). Event-free survival between each group was calculated and revealed that the high-risk group was significantly associated with the occurrence of the critical event (the timing of diagnosing the critical COVID-19 including ARDS, sepsis, or septic shock), whereas the conditions of the low-risk group did not result in the critical event (Fig. 3).

Discussion

The results of our study showed that this simple risk prediction score was useful for identifying
high- and low-risk groups in patients with COVID-19.

One study in China proposed a simple risk prediction score, which reported that older age, male sex, and hypertension were related to a poor prognosis of patients with COVID-19 (15). Although the risk prediction score was simple and easy for primary care physicians, 8.3% of the patients without these risk factors developed a severe course of COVID-19 during hospitalization. Therefore, that risk prediction score was not enough to exclude the low-risk group. Another retrospective study in China reported that patients with COVID-19 along with ARDS had risk factors such as old age, higher temperature before admission, initial dyspnea, and a higher proportion of comorbidities (e.g., hypertension) when compared with patients without ARDS (16). The study previously reported was not specifically performed with the aim of developing a risk prediction score; however, our study found similar results to this study. Additionally, we found that cancer was independently associated with a critical course of COVID-19.

Patients with cancer were observed to have a higher risk of a critical event and might be the high-risk COVID-19 group (17). Other studies have revealed that age-adjusted CFRs of cancer patients with COVID-19 were significantly higher than those of non-cancer patients (18). Our study did not include any patients with human immunodeficiency virus infections or rheumatologic diseases. Although they might be potential risk factors for COVID-19, we could not assess these comorbidities. Therefore, we believe that clinicians should not underestimate these comorbidities.

Fever is a common clinical manifestation of COVID-19. In one study in China, almost all patients
presented with fever during hospitalization (5). In contrary, the percentage of patients with fever on admission was 42% in the study of the Diamond Princess cruise ship passengers (19). Another study in China showed that 43.8% of the patients had a fever on admission, and 88.7% developed a fever during hospitalization (6). Although fever is common as an initial symptom, in spontaneously cured cases, fever is reduced about one week after the initial symptoms (7, 20). Therefore, the cases in which a fever lasts for more than a week suggests an aggressive host immune response, such as severe cytokine release syndrome and relate to disease severity (21, 22).

Dyspnea is an indicative symptom highly associated with hypoxemia. Some retrospective studies to evaluate clinical characteristics and risk factors for outcome of COVID-19 have also revealed that dyspnea was related to the severity or death in patients with COVID-19 (5, 23–25). Clinicians should pay close attention to symptoms such as fever and dyspnea upon admission, because they may be warning signs for critical patients.

We excluded any method of treatment for patients with COVID-19 for the multivariate analysis. There are presently no definite treatment agents for patients with COVID-19, and we believe any treatment method does not affect the outcome. Recently, a large randomized study in the United Kingdom showed the effectiveness of dexamethasone for COVID-19 (25). Although we used systemic corticosteroids for patients in the critical group, a few patients in the non-critical group were also treated by systemic corticosteroids. Hence, we could not assess the efficacy of systemic corticosteroids, and further studies are necessary.

Six patients were transferred to other hospitals. Four patients of them developed ARDS during
hospitalization and were transferred to other hospitals which can provide higher intensive care. One patient was transferred because the patient developed type 2 atrioventricular block and another patient was transferred because of management of arterial thrombosis. These two patients had total three risk factors. After all, their outcomes did not affect the main result of our study.

This study has several limitations. First, this was a single-center study, and the population size was smaller than those in the cohort studies conducted in other countries. We could not perform a validation cohort study to confirm the effectiveness of the risk prediction score and there was a possibility of overfitting because of the small sample size. Second, most of the patients were Japanese, and external validation for other ethnicities was not evaluated. Lastly, we cannot rule out unmeasurable confounding factors. Larger cohort studies are needed to develop more definite risk prediction scores and to validate them.

In conclusion, older age (≥ 45 years), male sex, hypertension, and cancer were risk factors for the critical group of patients with COVID-19. Fever and dyspnea on admission were also warning signs indicating a critical group of patients with COVID-19. According to the risk prediction score, any clinician or health care provider can determine if a patient with COVID-19 is at a high or low risk, and they can easily select appropriate medical facilities to care for the patients using fundamental information in prehospital settings.
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Conflict of Interest:

All the authors have no conflict of interest to declare.
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Figure legends

**Figure 1.** Severity by age category.

A. The percentage of cases by severity classification.

B. The number of cases by severity classification.

**Figure 2.** Receiver operating characteristics curve.

A. Receiver operating characteristics curve of the age.

B. Receiver operating characteristics curve of the risk scores.

**Figure 3.** Event-free survival by the risk group.

Low-risk group = total risk factors ≤ 2

Intermediate-risk group = total risk factors = 3

High-risk group = total risk factors ≥ 4
### Table 1. Patient characteristics and symptoms

| Clinical characteristics                  | Overall (n=234) | Critical (n=41) | Non-Critical (n=193) | p-value |
|------------------------------------------|-----------------|----------------|----------------------|---------|
| Age (median [IQR])                       | 50.00 [34.00, 65.00] | 68.00 [55.00, 79.00] | 44.00 [30.00, 58.00] | <0.001  |
| Sex (male), n (%)                        | 154 (65.8)      | 37 (90.2)      | 117 (60.6)           | 0.001   |
| Nationality, n (%)                       |                 |                |                      | 0.316   |
| Japan                                    | 203 (86.8)      | 39 (95.1)      | 164 (85.0)           |         |
| Argentina                                | 1 (0.4)         | 0 (0.0)        | 1 (0.5)              |         |
| Australia                                | 4 (1.7)         | 0 (0.0)        | 4 (2.1)              |         |
| Bangladesh                               | 10 (4.3)        | 0 (0.0)        | 10 (5.2)             |         |
| China                                    | 2 (0.9)         | 0 (0.0)        | 2 (1.0)              |         |
| Finland                                  | 1 (0.4)         | 1 (2.4)        | 0 (0.0)              |         |
| Korea                                    | 1 (0.4)         | 0 (0.0)        | 1 (0.5)              |         |
| Nepal                                    | 5 (2.1)         | 1 (2.4)        | 4 (2.1)              |         |
| Philippines                              | 3 (1.3)         | 0 (0.0)        | 3 (1.6)              |         |
| USA                                      | 4 (1.7)         | 0 (0.0)        | 4 (2.1)              |         |
| Exposure, n (%)                          |                 |                |                      | 0.138   |
| Community-acquired                       | 105 (44.9)      | 19 (46.3)      | 86 (44.6)            |         |
| Nosocomial                               | 36 (15.4)       | 6 (14.6)       | 30 (15.5)            |         |
| Imported                                 | 16 (6.8)        | 0 (0.0)        | 16 (8.3)             |         |
| Others                                   | 16 (6.8)        | 1 (2.4)        | 15 (7.8)             |         |
| Unknown                                  | 61 (26.1)       | 15 (36.6)      | 46 (23.8)            |         |
| BMI (median [IQR])                       | 23.35 [20.62, 26.25] | 24.60 [22.00, 27.08] | 23.30 [20.48, 25.90] | 0.112   |
| Smoking history, n (%)                   |                 |                |                      | 0.001   |
| Current                                  | 58 (24.8)       | 13 (31.7)      | 45 (23.3)            |         |
| Past                                     | 31 (13.2)       | 12 (29.3)      | 19 (9.8)             |         |
| Never                                    | 126 (53.8)      | 12 (29.3)      | 114 (59.1)           |         |
| Condition                        | Group 1 | Group 2 | Group 3 |
|---------------------------------|---------|---------|---------|
| Hypertension, n (%)             | 53 (22.6) | 23 (56.1) | 30 (15.5) | <0.001 |
| Diabetes mellitus, n (%)        | 32 (13.7) | 13 (31.7) | 19 (9.8) | 0.001 |
| COPD n (%)                      | 8 (3.4)  | 5 (12.2) | 3 (1.6) | 0.005 |
| Asthma, n (%)                   | 20 (8.5) | 4 (9.8) | 16 (8.3) | 0.76 |
| Cancer, n (%)                   | 32 (13.7) | 14 (34.1) | 18 (9.3) | <0.001 |
| CVD, n (%)                      | 24 (10.3) | 11 (26.8) | 13 (6.7) | <0.001 |
| CKD, n (%)                      | 2 (0.9) | 1 (2.4) | 1 (0.5) | 0.320 |
| Initial severity, n (%)         |         |         | <0.001 |
| Asymptomatic                    | 4 (1.7) | 0 (0.0) | 4 (2.1) |         |
| Mild                            | 45 (19.2) | 0 (0.0) | 45 (23.3) |         |
| Moderate                        | 113 (48.3) | 6 (14.6) | 107 (55.4) |         |
| Severe                          | 66 (28.2) | 29 (70.7) | 37 (19.2) |         |
| Critical                        | 6 (2.6) | 6 (14.6) | 0 (0.0) |         |
| Days from onset to admission (median [IQR]) | 0.919 |         |         |
|                                 | 9.00 [7.00, 12.00] | 9.00 [7.00, 12.00] | 9.00 [7.00, 12.00] |
| Symptoms on admission, n (%)    |         |         |         |
| Fever (≥ 37.5 °C)               | 77 (32.9) | 30 (73.2) | 47 (24.4) | <0.001 |
| Cough                           | 134 (57.3) | 24 (58.5) | 110 (57.0) | 0.994 |
| Sputum                          | 33 (14.1) | 7 (17.1) | 26 (13.5) | 0.723 |
| Runny nose                      | 26 (11.1) | 2 (4.9) | 24 (12.4) | 0.271 |
| Sore throat                     | 54 (23.1) | 6 (14.6) | 48 (24.9) | 0.227 |
| Dyspnea                         | 72 (30.8) | 29 (70.7) | 43 (22.3) | <0.001 |
| Fatigue                         | 79 (33.8) | 13 (31.7) | 66 (34.2) | 0.901 |
| Nausea                          | 8 (3.4) | 1 (2.4) | 7 (3.6) | 1.000 |
| Diarrhea                        | 35 (15.0) | 6 (14.6) | 29 (15.0) | 1.000 |
| Headache                        | 42 (17.9) | 4 (9.8) | 38 (19.7) | 0.179 |
| Olfactory disorders             | 39 (16.7) | 1 (2.4) | 38 (19.7) | 0.005 |
| Condition                | IQR (Lower) | IQR (Upper) | Mean (Median) | p-value |
|--------------------------|-------------|-------------|---------------|---------|
| Taste disorders          | 48 (20.5)   | 3 (7.3)     | 45 (23.3)     | 0.019   |
| Anorexia                 | 5 (2.1)     | 0 (0.0)     | 5 (2.6)       | 0.590   |
| Muscle or joint pain     | 34 (14.5)   | 3 (7.3)     | 31 (16.1)     | 0.221   |

Abbreviations: IQR, interquartile range; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CVD, Coronary Vascular Disease; CKD, Chronic Kidney Disease
Table 2. Laboratory data on admission, treatment, and outcome

| Laboratory data, Median [IQR] | Overall (n=234) | Critical (n=41) | Non-Critical (n=193) | p-value |
|-------------------------------|----------------|----------------|---------------------|---------|
| WBC (/μL)                     | 5300 [4100, 6600] | 6000 [4500, 9500] | 5200 [4075, 6325] | 0.034   |
| Neutrophil (/μL)              | 3380 [2460, 4800] | 4960 [3130, 8180] | 3175 [2427, 4377] | <0.001  |
| Lymphocyte (/μL)              | 1180 [890, 1610]  | 780 [610, 1040]   | 1265 [980, 1715]   | <0.001  |
| Hb (g/dL)                     | 14.0 [13.0, 15.3]  | 13.4 [12.4, 14.6]  | 14.2 [13.2, 15.3]  | 0.015   |
| Plt (×10^4/μL)                | 20.30 [15.50, 24.80] | 16.90 [12.90, 21.00] | 20.65 [16.82, 25.45] | 0.004   |
| Albumin (mg/dL)               | 3.80 [3.30, 4.20]  | 3.10 [2.80, 3.30]   | 3.90 [3.50, 4.30]   | <0.001  |
| T-bil (mg/dL)                 | 0.50 [0.40, 0.70]  | 0.60 [0.40, 0.80]   | 0.50 [0.40, 0.62]   | 0.006   |
| AST (U/L)                     | 28.00 [21.00, 45.00] | 54.00 [35.00, 72.00] | 26.00 [20.00, 38.00] | <0.001  |
| ALT (U/L)                     | 28.00 [17.00, 47.00] | 38.00 [24.00, 52.00] | 27.00 [16.00, 43.25] | 0.004   |
| LDH (U/L)                     | 250.00 [191.00, 360.00] | 435.00 [381.00, 587.00] | 217.50 [185.00, 296.00] | <0.001  |
| CK (U/L)                      | 73.50 [50.75, 122.25] | 115.00 [69.00, 291.00] | 68.00 [49.00, 105.00] | 0.001   |
| Amylase (U/L)                 | 66.00 [51.50, 85.50] | 69.00 [48.50, 89.00] | 65.00 [52.00, 85.00] | 0.868   |
| BUN (mg/dL)                   | 13.00 [10.00, 17.00] | 20.00 [14.00, 25.00] | 12.00 [9.00, 15.00] | <0.001  |
| Cre (mg/dL)                   | 0.74 [0.62, 0.87]  | 0.93 [0.71, 1.13]   | 0.71 [0.61, 0.82]   | <0.001  |
| Glucose (mg/L)                | 105.00 [94.00, 123.50] | 122.00 [111.00, 156.25] | 101.00 [92.00, 118.00] | <0.001  |
| CRP (mg/dL)                   | 1.71 [0.22, 6.00]  | 11.23 [5.64, 17.54]  | 0.89 [0.15, 3.29]   | <0.001  |
| Ferritin (μg/L)               | 281.40 [128.77, 708.57] | 1094.00 [591.75, 1940.00] | 204.85 [95.02, 500.95] | <0.001  |
| KL-6 (U/mL)                   | 257.00 [202.00, 357.00] | 397.00 [341.00, 472.00] | 235.00 [197.75, 320.25] | <0.001  |
| PT-INR                        | 1.00 [0.95, 1.04]  | 1.04 [1.00, 1.08]   | 0.99 [0.95, 1.03]   | <0.001  |
| APTT (sec)                    | 31.40 [28.70, 34.50] | 33.80 [30.30, 36.70] | 30.80 [28.48, 33.42] | 0.001   |
| D-dimer (μg/mL)               | 0.80 [0.60, 1.30]  | 2.00 [0.98, 3.38]   | 0.70 [0.60, 1.00]   | <0.001  |
| Imaging findings, (%)                          |
|---------------------------------------------|
| Pneumonia                                   |
| 183 (78.2)                                  |
| 41 (100.0)                                  |
| 142 (73.6)                                  |
| <0.001                                      |

| Treatment, (%)                              |
|---------------------------------------------|
| Lopinavir/Ritonavir                         |
| 6 (2.6)                                     |
| 2 (4.9)                                     |
| 4 (2.1)                                     |
| 0.283                                       |
| Favipiravir                                 |
| 96 (41.0)                                   |
| 37 (90.2)                                   |
| 59 (30.6)                                   |
| <0.001                                      |
| Hydroxychloroquine                          |
| 18 (7.7)                                    |
| 6 (14.6)                                    |
| 12 (6.2)                                    |
| 0.130                                       |
| Ciclesonide                                 |
| 17 (7.3)                                    |
| 6 (14.6)                                    |
| 11 (5.7)                                    |
| 0.095                                       |
| Antibiotics                                 |
| 100 (42.7)                                  |
| 39 (95.1)                                   |
| 61 (31.6)                                   |
| <0.001                                      |
| Systemic corticosteroids                    |
| 34 (14.5)                                   |
| 30 (73.2)                                   |
| 4 (2.1)                                     |
| <0.001                                      |

| Oxygen supplementation therapy, (%)         |
|---------------------------------------------|
| Reserver Mask                               |
| 10 (4.3)                                    |
| 10 (24.4)                                   |
| 0 (0.0)                                     |
| HFNC                                        |
| 15 (6.4)                                    |
| 15 (36.6)                                   |
| 0 (0.0)                                     |
| NPPV                                        |
| 3 (1.3)                                     |
| 3 (7.3)                                     |
| 0 (0.0)                                     |
| MV                                          |
| 12 (5.1)                                    |
| 12 (29.3)                                   |
| 0 (0.0)                                     |

| Outcome                                     |
|---------------------------------------------|
| Days of hospital stay (median [IQR])        |
| 12.50 [8.00, 20.00]                         |
| 27.00 [10.00, 39.00]                        |
| 12.00 [8.00, 18.00]                         |
| <0.001                                      |
| Days from onset to first day of two consecutive negative tests (median [IQR]) |
| 20.00 [16.00, 27.00]                        |
| 39.00 [34.25, 42.75]                        |
| 19.00 [16.00, 25.00]                        |
| <0.001                                      |
| Days from first positive test to first day of two consecutive negative tests (median [IQR]) |
| 15.00 [10.75, 21.00]                        |
| 32.50 [29.25, 39.00]                        |
| 14.00 [10.00, 19.00]                        |
| <0.001                                      |
| Days from onset to critical event (median [IQR]) |
| 12.00 [10.00, 13.00]                        |
| Days from admission to critical event (median [IQR]) |
| 3.00 [1.00, 5.00]                           |
| In hospital Outcome (%)                     |
| <0.001                                      |
|        |        |        |        |
|--------|--------|--------|--------|
| Death  | 19 (8.1)| 19 (46.3)| 0 (0.0)|
| Discharge | 209 (89.3) | 18 (43.9) | 191 (99.0)|
| Transfer | 6 (2.6) | 4 (9.8) | 2 (1.0)|

Abbreviations; IQR, interquartile rang; WBC, White blood cell; Hb, Hemoglobin; Plt, Platelet; T-bil, Total bilirubin; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; LDH, Lactate dehydrogenase; CK, Creatine kinase; BUN, Blood urea nitrogen; Cre, Creatinine; CRP, C reactive protein; PT-INR, Prothrombin time internal normalized ratio; APTT, Activated partial thromboplastin time; HFNC, High Flow Nasal Canule; NPPV, Non-positive pressure ventilation; MV, Mechanical ventilation
Table 3. Multivariate analysis of the risk factors in the critical group.

| Risk Factor      | Estimate | SE  | aOR  | 95% CI          |
|------------------|----------|-----|------|-----------------|
| Age (≥ 45 years) | 2.74     | 1.10| 12.34| 2.98-67.67      |
| Sex (male)       | 2.51     | 0.79| 15.55| 2.64-300.15     |
| Hypertension     | 1.97     | 0.60| 7.15 | 2.34-25.55      |
| Cancer           | 1.91     | 0.66| 6.74 | 1.96-26.88      |
| Fever            | 1.90     | 0.54| 6.66 | 2.43-20.26      |
| Dyspnea          | 2.27     | 0.58| 9.70 | 3.31-33.32      |

Akaike information criterion (AIC): 115.2

Abbreviations: SE, Standard Error; aOR, Adjusted Odds Ratio; CI, Confidence Interval
