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Original article

Predictive model for the development of critical coronavirus disease 2019 and its risk factors among patients in Japan

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ABSTRACT

Background: This study aimed to examine risk factors associated with critical coronavirus disease 19 (COVID-19) and to establish a risk predictive model for Japanese patients.

Methods: We retrospectively assessed adult Japanese patients diagnosed with COVID-19 at the Japanese Red Cross Medical Center, Tokyo, Japan between February 1, 2020 and March 10, 2021. The patients were divided into critical and non-critical groups based on their condition during the clinical courses. Univariate and multivariate logistic regression analyses were performed to investigate the relationship between clinical characteristics and critical illness. Based on the results, we established a predictive model for the development of critical COVID-19.

Results: In total, 300 patients were enrolled in this study. Among them, 86 were included in the critical group. Analyses revealed that age ≥65 y, hemodialysis, need for O_2 supplementation upon diagnosis, and an initial serum C-reactive protein level of ≥6.5 mg/dL were independently associated with the development of critical COVID-19. Next, a predictive model for the development of critical COVID-19 was created, and this included the following variables: age ≥65 y, male sex, diabetes, hemodialysis, need for O_2 supplementation upon diagnosis, and an initial serum C-reactive protein level of ≥6.5 mg/dL. The area under the receiver operating characteristic curve of the model was 0.86 (95% confidence interval, 0.81–0.90). Using a cutoff score of 12, the positive and negative predictive values of 74.0% and 80.4% were obtained, respectively.

Conclusions: Upon diagnosis, the predictive model can be used to identify adult Japanese patients with COVID-19 who will require intensive treatment.

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1. Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is prevalent worldwide to date [1,2]. In Japan, by March 11, 2021, there were more than 430,000 confirmed cases and 8000 deaths [3]. Most patients present with mild symptoms. However, approximately 5% develop respiratory failure or even die [4]. Therefore, physicians should obtain a reasonable prognosis and manage patients appropriately. In addition, anticipating the need for intensive care management is essential because medical resources in each country are limited.

Observational studies that investigated risk factors for severe or critical COVID-19 were conducted in several countries. Some showed that male sex, old age, obesity, smoking history, need for O_2 supplementation upon diagnosis, and initial serum C-reactive protein (CRP) level are associated with disease severity and mortality [5–8]. Comorbidities, such as diabetes, hypertension, kidney and heart failure, cancer, chronic obstructive pulmonary disease (COPD), and interstitial lung disease (ILD) have been associated with COVID-19 severity [5–7,9,10].

Some studies conducted in other countries established risk scoring models for predicting patients who will develop severe or critical COVID-19 [11–13]. However, only a few studies to date examined the risk factors for critical COVID-19 in the Japanese population [14,15]. The potential risks of developing critical COVID-19 can vary according to ethnicity [16]. To ensure that Japanese patients with COVID-19 will receive appropriate treatment, predictive indicators that can provide insights as to whether a patient will develop the critical illness are important.

Thus, we conducted a retrospective observational study to investigate risk factors associated with critical COVID-19 among patients in Japan. Moreover, a risk predictive model was established.

2. Patients and methods

2.1. Eligibility criteria

This retrospective observational study enrolled all consecutive patients diagnosed with COVID-19 at the Japanese Red Cross Medical Center, Tokyo, Japan between February 1, 2020 and March 10, 2021. The diagnosis of COVID-19 was confirmed based on positivity to SARS-CoV-2 as assessed via polymerase chain reaction (PCR) using sputum or nasopharyngeal swab samples. SARS-CoV-2 RNA was detected using the TaqMan One-Step RT-PCR Kit (QIAGEN Co., Ltd., Hilden, Germany). We excluded non-Japanese patients and those aged <18 y.

2.2. Clinical analysis

Data on demographic and clinical characteristics, laboratory examination results, and outcomes were obtained from the electronic medical records of patients. Moreover, information regarding age, sex, body mass index (BMI), smoking history, comorbidities (including diabetes, hypertension, chronic heart disease, hemodialysis, cancer, COPD, and ILD), need for O_2 supplementation upon diagnosis, initial serum CRP level, and outcomes was collected. Chronic heart disease was defined as a condition requiring percutaneous cardiovascular intervention, bypass surgery for previous angina pectoris or myocardial infarction, and/or a need for pacemaker implantation for arrhythmia. Critical illness and severe illness were defined using the National Institutes of Health classification criteria: critical illness, for individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction, and severe illness, for individuals who have oxygen saturation <94% in room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen <300 mmHg, respiratory frequency >30 breaths/min, and/or lung infiltrates >50%. Clinical outcomes were monitored up to March 20, 2021.

2.3. Statistical analysis

Categorical variables were presented as number with proportion and continuous variables as median with interquartile ranges. Patients who presented with critical illness during the clinical course at our center were assigned to the critical group and the others, to the non-critical group. We transformed several continuous variables into categorical ones. The cutoff values for age, Brinkman index, BMI, and initial serum CRP level were 65 y, 600, 25 mg/m^2, and 6.5 mg/dL, respectively, according to previous studies [17–20]. Between-group comparisons were performed using the Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables. To select the variables for the predictive model, a univariate logistic regression analysis was conducted. Variables with a p-value of <0.05 in the univariate analysis were included in the multivariate analysis. The variables were narrowed down to eight using the backward conditional method. Variables with p-values <0.20 in multivariate analysis were included in the predictive model. Points, which are proportional to the β regression coefficient values (rounded to the nearest integer), were assigned to each variable. The performance of this model was assessed using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. Sensitivity, specificity, and positive and negative predictive values were calculated for each cutoff point. The optimal cutoff value was determined on the basis of the positive predictive value. Moreover, a graph for the predicted probability of developing critical illness in each group was evaluated. To perform a validation study, more Japanese adult patients with COVID-19 at the Japanese Red Cross Medical Center, Tokyo, Japan between March 10, 2021 and April 25, 2021 were enrolled in this study. The model performance was evaluated based on the AUC. All of the statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). A two-tailed p-value of <0.05 was considered statistically significant.

2.4. Ethics statement

Since this was a retrospective analysis, the need for informed consent was waived. This research was approved by the Ethical Committee for Clinical Studies of the Japanese Red Cross Medical Center (no. 1112; April 15, 2020).

3. Results

3.1. Characteristics of patients

A total of 333 patients diagnosed with COVID-19 visited our hospital from February 1, 2020 to March 11, 2021. Among them, 17 patients aged <18 y and 16 non-Japanese patients were excluded. Finally, 300 patients were included in this study (Fig. 1). In total, 86 and 214 patients were included in the critical and non-critical groups, respectively. Table 1 depicts the clinical characteristics of the derivation population. The median age of the patients was 60 y, and 187 (62.3%) patients were male. The median time from symptom onset to visiting our center was 6 d. The median number of comorbidities was 1 (0–2). In total, 48 (16.0%) patients required O_2 supplementation upon diagnosis, whereas none of the patients used home oxygen therapy before developing COVID-19. The median initial serum CRP level was 3.60 mg/dL. A total of 28 (83%) patients consequently died during the follow-up period.

3.2. Univariate logistic regression analysis

The univariate logistic regression analysis of the clinical and laboratory variables was performed (Table 2). The critical and non-critical groups significantly differed in terms of age (≥65 y; $p < 0.001$), male sex ($p = 0.014$), and Brinkman index (≥600; $p = 0.042$). In terms of comorbidities and clinical findings, hypertension ($p < 0.001$), diabetes ($p < 0.001$), hemodialysis ($p < 0.001$), need for O_2 supplementation upon diagnosis ($p < 0.001$), and an initial serum CRP level of ≥6.5 mg/dL ($p < 0.001$) were significantly associated with critical COVID-19.

3.3. Multivariate logistic regression analysis and risk predictive model for the development of critical illness

Using the backward method, age ≥65 y, male sex, current smoker status, cancer, diabetes, hemodialysis, need for O_2 supplementation upon diagnosis, and initial serum CRP level of ≥6.5 mg/dL were included in the final multivariate logistic regression analysis. The analysis revealed that age ≥65 y, hemodialysis, need for O_2 supplementation upon diagnosis, and an initial serum CRP level of ≥6.5 mg/dL were independent risk factors for the development of critical illness (Table 3). To establish a predictive model for critical illness among patients with COVID-19, variables having p-values <0.20 in the multivariate analysis were included in the predictive model. We finally included age ≥65 y, male sex, diabetes, hemodialysis, need for O_2 supplementation upon diagnosis, and an initial serum CRP level of ≥6.5 mg/dL in the predictive model. Based on the β regression coefficient values, each variable was assigned with 3, 2, 2, 6, 7, and 3 points, respectively (Table 4). The score had an AUC of 0.86 (95% confidence interval, 0.81–0.90) for predicting the development of critical COVID-19 (Fig. 2). The optimal cutoff score of 12 showed the highest positive predictive value. The sensitivity and specificity were 43.0% and 93.9%, respectively. The positive predictive value was 74.0%, and the negative predictive value was 80.4%. The probabilities of developing critical illness were 7%, 32%, 76%, 63%, and 89% in patients with scores of 0–4, 5–8, 9–12, 13–16, and 17–23, respectively (Fig. 3).

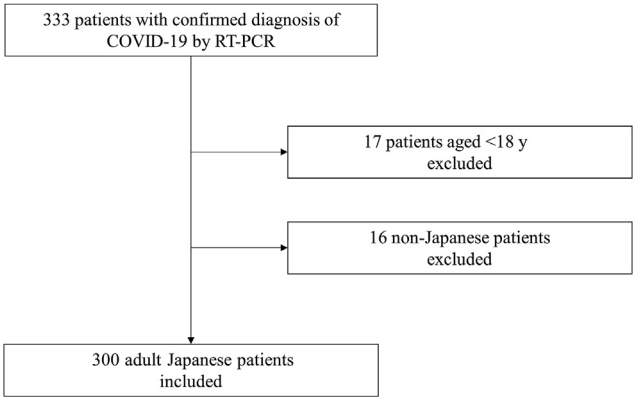

Fig. 1 – Flowchart of patient recruitment. COVID-19: coronavirus disease 2019, RT-PCR: real-time polymerase chain reaction.

3.4. Validation study

To assess the validation cohort, an additional 27 adult Japanese patients with COVID-19 were enrolled in this study. Table S1 shows the clinical characteristics of the validation population. In total, 5 and 22 patients were included in the critical and non-critical groups, respectively. The ROC curve showed an AUC of 0.83 (95% confidence interval, 0.58–1.0) for predicting the development of critical COVID-19. With the cutoff point of 12, the sensitivity and specificity were 40.0%

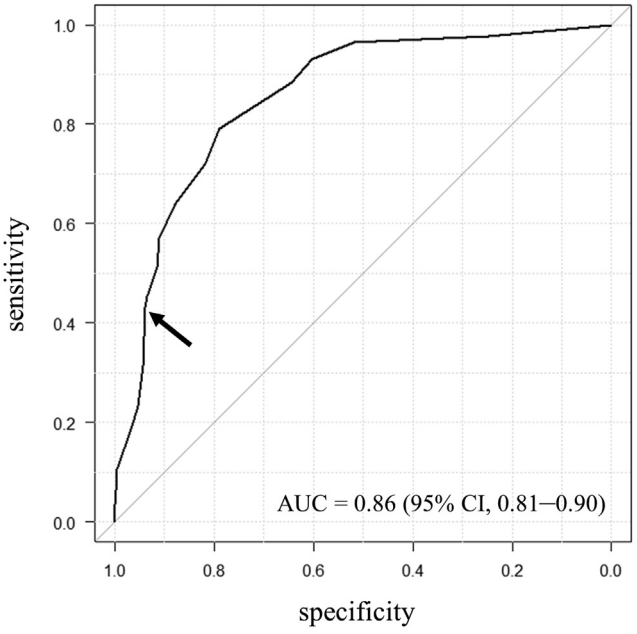

Fig. 2 – Receiver operating characteristic curve analyses to predict critical COVID-19. The arrow indicates the optimal cutoff point (12 points). With the cutoff, the sensitivity and specificity of the model were 43.0% and 93.9%, respectively. The positive predictive value was 74.0%, and the negative predictive value was 80.4%. COVID-19: coronavirus disease 2019, AUC: area under the curve, CI: confidence interval.

Table 1 – Characteristics of patients with COVID-19 and comparisons between the critical and non-critical groups.

Characteristics	Total number of patients (n = 300)	Critical group (n = 86)	Non-critical group (n = 214)	p-value[a]
Age, y	60 (41–74)	69 (60–78)	51 (35–67)	<0.001
Age ≥65 y, n (%)	118 (39.3)	53 (61.6)	65 (30.4)	<0.001
Male sex, n (%)	187 (62.3)	63 (73.3)	124 (57.9)	0.017
Body mass index, kg/m^2	22.9 (20.3–26.4)	23.1 (20.9–27.1)	23.0 (20.3–26.0)	0.20
Body mass index of ≥25 kg/m^2, n (%)	106 (35.3)	35 (40.7)	71 (33.2)	0.23
Time from onset to visiting our center, d	6 (4–9)	8 (5–11)	6 (3–9)	0.004
Never smoked, n (%)	176 (58.7)	46 (53.5)	130 (60.7)	0.30
Former smoker, n (%)	94 (31.3)	33 (38.4)	61 (28.5)	0.10
Current smoker, n (%)	30 (10.0)	7 (8.1)	23 (10.7)	0.67
Brinkman index of ≥600, n (%)	52 (17.3)	21 (24.4)	31 (14.5)	0.044
Comorbidities, n	1 (0–2)	1 (0–2)	0 (0–1)	<0.001
Hypertension, n (%)	95 (31.7)	41 (47.7)	54 (25.2)	<0.001
Diabetes, n (%)	76 (25.3)	37 (43.0)	39 (18.2)	<0.001
Cancer[b], n (%)	29 (9.7)	8 (9.3)	21 (9.8)	1.0
Hemodialysis, n (%)	21 (7.0)	14 (16.3)	7 (3.3)	<0.001
Chronic heart diseases, n (%)	36 (12.0)	15 (17.4)	21 (9.8)	0.078
COPD, n (%)	7 (2.3)	3 (3.5)	4 (1.9)	0.41
ILD, n (%)	5 (1.7)	2 (2.3)	3 (1.4)	0.63
Clinical findings				
Need for O_2 supplementation upon diagnosis, n (%)	48 (16.0)	36 (41.9)	12 (5.6)	<0.001
CRP level, mg/dL	3.60 (0.72–8.63)	8.33 (5.18–14.9)	1.86 (0.36–5.90)	<0.001
CRP level of ≥6.5 mg/dL, n (%)	101 (33.7)	53 (61.6)	48 (22.4)	<0.001
Outcome				
Death, n (%)	25 (8.3)	25 (29.1)	0 (0.0)	<0.001

Data were presented as number of patients (%) or median (interquartile ranges).
COVID-19: coronavirus disease 2019, COPD: chronic obstructive pulmonary disease, ILD: interstitial lung disease, CRP: C-reactive protein.
[a] Fisher's exact test was used to assess categorical variables and the Mann-Whitney *U* test, to compare continuous variables between the critical and non-critical groups.
[b] Cancer types included genitourinary (11 cases), gastrointestinal (7 cases), breast (7 cases), lung (4 cases), gynecologic (2 cases), and head and neck (2 cases) cancers. Four patients had histories of two cancers.

and 100%, respectively. The positive predictive value was 100%, and the negative predictive value was 88.0%. The probabilities of developing critical illness were 8%, 10%, 50%, 100%, and 100% in patients with scores of 0–4, 5–8, 9–12, 13–16, and 17–23, respectively (Fig. S1).

4. Discussion

We examined risk factors associated with critical illness in 300 Japanese patients with COVID-19. A predictive model was then established. Age ≥65 y, hemodialysis, need for O_2 supplementation upon diagnosis, and initial serum CRP level were considered as independent risk factors for developing critical illness. Using six simple categories, a prediction score with high positive and negative predictive values for the development of critical illness in the Japanese population was created.

In a previous study of patients with COVID-19 (n = 44,671) in China, 5% had critical illness, and the mortality rate was 2.3% [4]. In our study, 86 (28.7%) patients were assigned to the critical group, and the mortality rate was 8.3%. The proportion of critically ill patients and mortality rate in our study were higher than in the aforementioned Chinese study [4]. This might be attributed to the fact that our hospital was an accredited facility for critically ill patients. The relationship between old age and critical illness was consistent with that in previous studies conducted in other countries [5–7]. In terms of comorbidities, hemodialysis was associated with critical illness [21,22]. The reason why patients receiving hemodialysis are more likely to present with critical COVID-19 remains unclear. However, immune-senescence and malnourishment might play a role [23]. We focused on elevated initial serum CRP levels as a laboratory factor for predicting severe disease. CRP is a non-specific albeit useful marker and indicator of inflammation [24]. Based on a previous retrospective study in China, patients with an initial serum CRP level of >6.479 mg/dL should be closely monitored for disease progression [20]. This result was consistent with that of our study. Variables such as male sex, current smoker status, Brinkman index of ≥600, hypertension, and diabetes were associated with COVID-19 severity in some previous studies [5,6,18,25–27]. In contrast, there was no significant association between these factors and the development of critical illness in the multivariate analysis in our study, even though a univariate analysis showed their significant associations. Therefore, further studies are needed to examine whether these problems are unique among Japanese patients.

We established a predictive model for the development of critical COVID-19 using factors including age ≥65 y, male sex, diabetes, hemodialysis, need for O_2 supplementation upon diagnosis, and an initial serum CRP level of ≥6.5 mg/dL. Several studies conducted in other countries also created predictive models for the risk of severe or critical COVID-19. In China, the use of a predictive model for the risk of progression, referred to

Table 2 – Univariate logistic regression analysis of risk factors for critical COVID-19.

Variables	OR (95% CI)	*p*-value[a]
Age ≥65 y	3.68 (2.18–6.21)	<0.001
Male sex	1.99 (1.15–3.44)	0.014
Body mass index of ≥25 kg/m^2	1.38 (0.83–2.32)	0.22
Current smoker	0.74 (0.30–1.78)	0.50
Brinkman index of ≥600	1.91 (1.02–3.55)	0.042
Hypertension	2.70 (1.60–4.56)	<0.001
Diabetes	3.39 (1.95–5.87)	<0.001
Cancer[b]	0.94 (0.40–2.22)	0.89
Chronic heart diseases	1.94 (0.95–3.97)	0.069
Hemodialysis	5.75 (2.23–14.8)	<0.001
COPD	1.90 (0.42–8.66)	0.41
ILD	1.67 (0.28–10.2)	0.58
Need for O_2 supplementation upon diagnosis	12.1 (5.88–25.0)	<0.001
CRP level of ≥6.5 mg/dL	5.55 (3.24–9.54)	<0.001

COVID-19: coronavirus disease 2019, OR: odds ratio, CI: confidence interval, COPD: chronic obstructive pulmonary disease, ILD: interstitial lung disease, CRP: C-reactive protein.

[a] Univariate logistic regression analysis was used to compare the variables between the critical and non-critical groups.

[b] Cancer types included genitourinary (11 cases), gastrointestinal (7 cases), breast (7 cases), lung (4 cases), gynecologic (2 cases), and head and neck (2 cases) cancers. Four patients had histories of two cancers.

as the CALL score, was proposed. This model uses variables such as comorbidities, age, and lymphocyte and lactate dehydrogenase (LDH) levels [11]. Moreover, the application of a predictive model for intensive care unit admission among patients with COVID-19 in the U.S. was recommended. This model uses variables such as smoking history, oxygen saturation, lymphocyte and LDH levels, and use of procalcitonin [12]. A clinical risk score for identifying patients with COVID-19 who are at high risk of critical care admission or mortality was proposed in the U.K. This model uses variables including laboratory data and radiological findings [13]. These predictive

Table 3 – Multivariate logistic regression analysis of risk factors for critical COVID-19.

Variables	OR (95% CI)	*p*-value[a]
Age ≥65 y	2.81 (1.43–5.56)	0.003
Male sex	1.65 (0.81–3.40)	0.17
Current smoker	1.63 (0.56–4.72)	0.37
Cancer[b]	0.54 (0.19–1.54)	0.25
Diabetes	1.87 (0.93–3.73)	0.078
Hemodialysis	6.21 (2.07–18.7)	0.001
Need for O_2 supplementation upon diagnosis	6.89 (3.05–15.6)	<0.001
CRP level of ≥6.5 mg/dL	3.12 (1.63–6.00)	<0.001

COVID-19: coronavirus disease 2019, OR: odds ratio, CI: confidence interval, CRP: C-reactive protein.

[a] Multivariate logistic regression analysis was used for comparing the variables between the critical and non-critical groups.

[b] Cancer types included genitourinary (11 cases), gastrointestinal (7 cases), breast (7 cases), lung (4 cases), gynecologic (2 cases), and head and neck (2 cases) cancers. Four patients had histories of two cancers.

Table 4 – Predictive score for critical COVID-19.

Components	Points
Age ≥65 y	3
Male sex	2
Diabetes	2
Hemodialysis	6
Need for O_2 supplementation upon diagnosis	7
CRP level of ≥6.5 mg/dL	3

COVID-19: coronavirus disease 2019, CRP: C-reactive protein.

models are useful. However, they are not always suitable to the ethnical and social background characteristics of Japanese patients because COVID-19-associated mortality varies according to race or ethnicity [16,28]. A previous report showed that Asian patients with COVID-19 might have a lower disease severity than do European and Middle Eastern patients because Asians have a higher frequency of the angiotensin-converting enzyme 1 II genotype [29]. The predictive model of our study had several strengths. It can be used in Japanese populations, and the variables comprised background characteristics, vital signs, and routine laboratory data, which are available in medical clinics or home care facilities. Our model had high positive and negative predictive values (74.0% and 80.4%, respectively). The validation study also confirmed that the model had high positive and negative predictive values (100% and 88.0%, respectively). Therefore, the predictive score can be useful in evaluating patients with COVID-19 who should be referred to an intensive care medical facility upon diagnosis.

The current study also had several limitations. First, the sample size was small, and selection bias might have existed because this was a single-center retrospective observational study. Second, the treatment administered to each patient varied depending on when the patient was infected with SARS-CoV-2, as treatments for COVID-19 have advanced day by day. In Japan, remdesivir was approved in May 2020 and dexamethasone, in July 2020. These drugs could have affected the outcome of critical COVID-19. Finally, in this study, the genotype of the SARS-CoV-2 virus was not investigated. Thus,

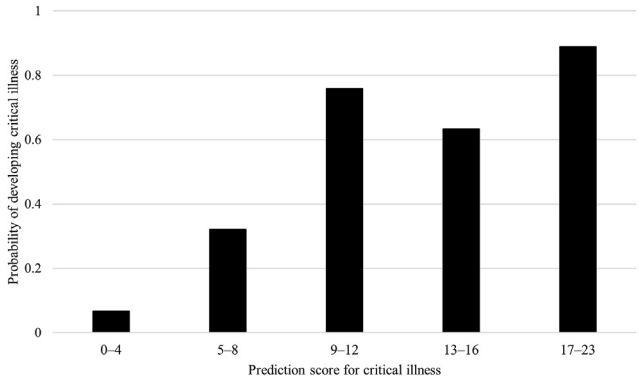

Fig. 3 – Relationship between the predictive score and the probability of developing critical COVID-19 in the derivation cohort. The probabilities of developing the condition were 7%, 32%, 76%, 63%, and 89% in patients with scores of 0–4, 5–8, 9–12, 13–16, and 17–23, respectively, based on the model. COVID-19: coronavirus disease 2019.

whether viral mutations affected patient outcomes was not confirmed.

5. Conclusions

The risk factors for critical COVID-19 among Japanese patients were investigated, and a predictive model was created. Upon diagnosis, this model can be used to identify adult Japanese patients who will require intensive treatment.

Conflict of Interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resinv.2021.08.001.

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