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Original Article

Clinical characteristics of Japanese patients with moderate to severe COVID-19



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ABSTRACT

Introduction: Although several reports on the risk factors for severe disease of COVID-19 already exist, reports on effective early indicators are still limited, especially from Japan. This study was conducted to clarify the patient's characteristics whose disease progressed to severe status.

Methods: The medical records of all consecutive 300 Japanese patients hospitalized at our institution between February and November 2020 were retrospectively reviewed. The clinical characteristics were evaluated to compare between mild (no oxygen needed), moderate (oxygen needs of 1–4 L/min), and severe diseases (oxygen needs of 5 L/min or more).

Results: The median age was 68 years old, with 123 (41.0%) males and 177 (59.0%) females. Of these, 199 patients (66.3%), 55 patients (18.3%), 46 patients (15.3%) patients were in the mild disease, moderate disease, severe disease groups, respectively. Patients with severe disease were more likely to be older, have more comorbidities, and tended to have higher body mass index. In laboratory data, lymphocyte count, levels of C-reactive protein (CRP), LDH, and AST on admission were significantly associated with the severity. In multivariate analysis, age and CRP were the independent risk factors for severe disease (OR = 1.050, 1.130, respectively). The optimal cut-off value for age was 74 years old and that for CRP was 3.15 mg/dL.

Conclusions: Age and CRP were independently associated with disease severity of COVID-19 in multivariate analysis. Additionally, the numbers of underlying disease, lymphocyte count, and inflammatory markers such as LDH and D-dimer may also be related to disease severity.

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Introduction

Approximately 5%–20% of patients with coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome

Abbreviations: list: AST, aspartate aminotransferase; AUC, area under curve; BMI, body mass index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; FiO₂, fraction of inspired oxygen; LDH, Lactate dehydrogenase; PaO₂, pressure of oxygen; ROC, receiver operating characteristic; SARS-CoV-2, severe acute respiratory syndrome coronavirus2; SpO₂, saturation of percutaneous oxygen.

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coronavirus 2 (SARS-CoV-2) develop severe pneumonia, and some of them progress to life-threatening respiratory failure, acute respiratory distress syndrome, and multiple organ failure [1–5]. One of the main challenges for clinicians is how to identify COVID-19 patients early at high risk for severe disease. Previous studies on COVID-19 have reported that age, gender, underlying diseases such as coronary artery disease and diabetes mellitus, and inflammatory markers including C-reactive protein (CRP), lactate dehydrogenase (LDH), and D-dimer are risk factors for poor prognosis [6–8]. However, reports on early indicators of risk factors for severe disease of COVID-19 are still limited, especially among Japanese patients.

Our hospital is one of the priority hospitals for COVID-19 patients in Kanagawa Prefecture in Japan, mainly treating COVID-19

Table 1
Baseline Characteristics of COVID-19 patients between the three groups.

	Mild (n = 199)	Moderate (n = 55)	Severe (n = 46)	P-value
Age	61.1 (18.1)	67.9 (14.2)	72.2 (10.3)	<0.001
Sex				
Male	85 (42.7%)	24 (43.6%)	14 (30.4%)	0.283
Female	114 (57.3%)	31 (56.4%)	32 (69.6%)	
Smoking history				
Current-smoker	27 (13.6%)	4 (7.3%)	0 (0%)	0.007
Ex-smoker	72 (36.2%)	24 (43.6%)	28 (60.9%)	
Never-smoker	100 (50.3%)	27 (49.1%)	18 (39.1%)	
Days from onset to hospitalization	5.2 (3.9)	6.1 (3.5)	5.5 (3.3)	0.235
Days from onset to severe disease	–	–	9.7 (3.7)	–
Underlying diseases				
Hypertension	68 (34.2%)	28 (50.9%)	25 (54.3%)	0.009
Diabetes	35 (17.6%)	15 (27.3%)	18 (39.1%)	0.006
Cardiovascular disease	28 (14.1%)	10 (18.2%)	10 (21.7%)	0.376
Cerebrovascular disease	12 (6.0%)	4 (7.3%)	7 (15.2%)	0.127
Chronic kidney disease	9 (4.5%)	2 (3.6%)	3 (6.5%)	0.779
COPD	29 (14.6%)	6 (10.9%)	10 (21.7%)	0.306
Interstitial Pneumonia	7 (3.5%)	2 (3.6%)	5 (10.9%)	0.128
Malignant disease	3 (1.5%)	2 (3.6%)	1 (2.2%)	0.476
Symptoms at admission				
Fever	153 (76.9%)	51 (92.7%)	41 (89.1%)	0.008
Cough	100 (50.3%)	34 (61.8%)	32 (69.6%)	0.034
Disorder of taste or smell	42 (21.1%)	8 (14.5%)	7 (15.2%)	0.483
Dyspnea	35 (17.6%)	21 (38.2%)	18 (49.1%)	<0.001
Diarrhea	23 (11.6%)	6 (10.9%)	6 (13.0%)	0.929
Laboratory data				
WBC (/μL)	5137.2 (1805.4)	6045.5 (2947.0)	5843.3 (2564.6)	0.009
Lymphocyte (/μL)	1201.1 (465.2)	1048.8 (409.9)	1004.6 (454.2)	0.002
LDH (U/L)	219.9 (62.6)	286.6 (99.0)	303.1 (123.5)	<0.001
AST (U/L)	33.3 (27.8)	41.4 (18.6)	51.9 (37.6)	<0.001
CRP (mg/dL)	3.02 (4.07)	5.98 (4.32)	8.44 (6.79)	<0.001
D-dimer (μg/ml)	1.21 (1.70)	1.54 (1.66)	1.84 (2.14)	0.080
Treatment regimen				
Ciclesonide	82 (41.2%)	26 (47.3%)	20 (43.5%)	0.708
Favipiravir	106 (53.3%)	32 (58.2%)	32 (71.7%)	0.073
Remdesivir	11 (5.5%)	24 (43.6%)	30 (65.2%)	<0.001
Corticosteroids	74 (37.2%)	49 (89.1%)	44 (95.7%)	<0.001
Tocilizumab	1 (0.5%)	5 (9.1%)	21 (45.7%)	<0.001
Immunoglobulin	1 (0.5%)	6 (10.9%)	11 (23.9%)	<0.001
Clinical course				
NIPPV or HFNC	0 (0%)	0 (0%)	11 (24.4%)	–
Mechanical ventilation	0 (0%)	0 (0%)	17 (37.8%)	–
ECMO	0 (0%)	0 (0%)	1 (2.2%)	–
Death	0 (0%)	0 (0%)	6 (13.0%)	–

Abbreviations: AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; LDH, Lactate dehydrogenase; NIPPV, noninvasive positive pressure ventilation; WBC, white blood cell.

Categorical data are presented as numbers (percentages) and were analyzed using Fisher's exact test. Continuous data are presented as mean (standard deviation) and were analyzed using an analysis of variance. A p value of <0.05 was considered statistically significant.

patients with moderate disease, defined by Japanese Ministry of Health, Labour and Welfare criteria as saturation of percutaneous oxygen (SpO₂) less than 96%, respiratory symptoms such as dyspnea, or pneumonia on imaging and those at high risk of severe illness. We have experienced that some patients became severe and were transferred to advanced medical institutions. Thus, our focus is on preventing the deterioration from moderate to severe disease to require a ventilator or extracorporeal membrane oxygenation (ECMO).

In this study, we retrospectively reviewed all the records of COVID-19 patients admitted at our hospital, a major Japanese COVID-19 hospital, to clarify the background and clinical characteristics of the patients and to identify risk factors for disease progression.

Material and methods

Study design and participants

This is a single-center, retrospective study performed at Kanagawa Cardiovascular and Respiratory Center in Yokohama, Japan.

All consecutive Japanese patients who were admitted to the hospital with the diagnosis of COVID-19 between February 1, 2020, and November 30, 2020, were retrospectively assessed. The diagnosis of COVID-19 was confirmed using polymerase chain reaction test or antigen testing for SARS-CoV-2 from sputum or nasopharyngeal swabs. The end of follow-up was the day when patients recovered and were discharged from the hospital, were transferred to the advanced medical institution for critically ill patients, or have died. The Ethics Committee of the Kanagawa Cardiovascular and Respiratory Center approved the study protocol (approved number, KCRC-20-0042), and the requirement of obtaining patient consent was waived because this was a retrospective study and high anonymity was ensured.

Clinical analysis

The following information was collected from the patient's medical records: age, sex, height, weight, body mass index (BMI), smoking history, comorbidities, days from onset to hospitalization, symptoms at initial visit, respiratory status, laboratory data, therapeutic medications, use of noninvasive positive pressure

ventilation, high-flow nasal cannula, mechanical ventilation and ECMO, and outcome. Comorbidities included cardiovascular disease, cerebrovascular disease, hypertension, diabetes mellitus, chronic kidney disease, interstitial pneumonia, chronic obstructive pulmonary disease, and active malignant disease. The Charlson Comorbidity Index was also evaluated on the basis of previous report [9]. Laboratory data included white blood cell count, lymphocyte count, CRP, LDH, aspartate aminotransferase (AST), and D-dimer at diagnosis.

Because pressure of oxygen (PaO₂) was not available in many cases, the ratio of SpO₂ to fraction of inspired oxygen (FiO₂) (SpO₂/FiO₂) was used to assess the respiratory state, referring to a previous report [8].

Definition of disease status

We classified COVID-19 patients into three categories according to their worst respiratory status during the course of the disease: 1) mild disease group, patients who did not require oxygen administration during their course; 2) moderate disease group, patients who required oxygen administration but whose maximum oxygen dose was less than or equal to 4 L/min; and 3) severe disease group, patients who required more than 5 L/min of oxygen administration.

Severe illness was defined as “worsening of respiratory status requiring oxygen administration of 5 L/min or more” because of the small number of events including mechanical intubation and death.

Naturally, patients who could not maintain their respiratory status with oxygen alone and required mechanical ventilation or ECMO were classified into the severe disease group.

Statistical analysis

Categorical data are presented as numbers (percentages) and are compared using Fisher’s exact test. Continuous data are presented as mean (standard deviation) and are compared using an analysis of variance. Risk factors for severe disease were also examined using a logistic regression model. Additionally, receiver

operating characteristic (ROC) curve analysis was used to obtain the optimal cutoff values for the risk factors obtained in the multivariate analysis.

A P-value of < 0.05 was considered to be statistically significant.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [10], which is a graphical user interface for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical characteristics on admission

A total of 300 Japanese COVID-19 patients were enrolled in the study. The median age of all patients was 68 years old (range: 21–96 years old), with 123 (41.0%) males and 177 (59.0%) females. Of these, 199 patients (66.3%) were in the mild disease group requiring no oxygen administration, 55 patients (18.3%) in the moderate disease group that required less than 5 L/min of oxygen, and 46 patients (15.3%) in the severe disease group that required more than 5 L/min of oxygen.

The patient characteristics of the three groups are shown in Table 1. The mean age was significantly older in the severe disease group. The mean time from onset to hospitalization was 5–6 days, with no significant difference. In the severe disease group, the mean time from onset to severe disease was 9.7 days.

Patients in the severe disease group were significantly more likely to have hypertension and diabetes. More patients in the moderate and severe disease groups had fever, cough, and dyspnea at the time of hospitalization than those in the mild disease groups.

The BMI average and the number of comorbidities indicated as the Charlson Comorbidity Index between the three groups are shown in Fig. 1. Although no statistically significant difference was found, the BMI average tended to increase with disease severity. The number of comorbidities tended to increase as the disease became more severe.

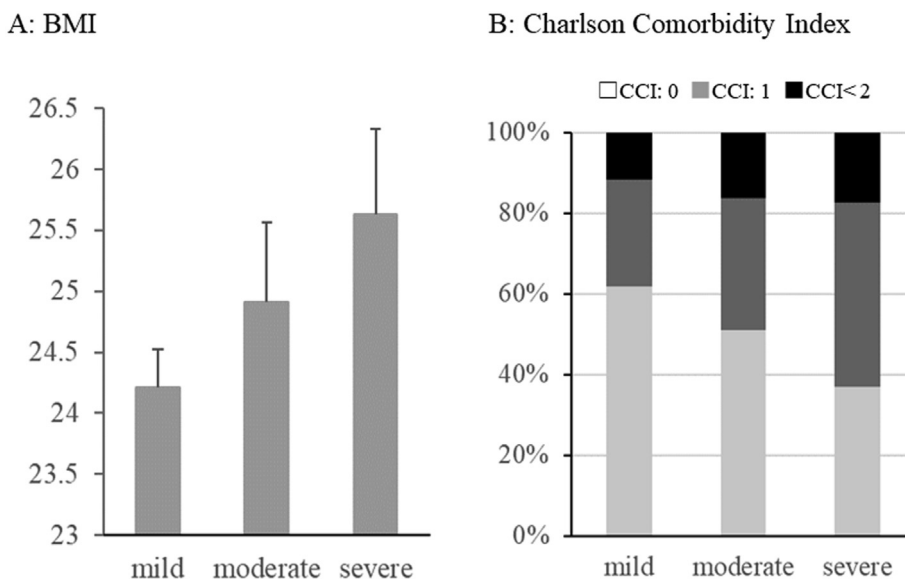


Fig. 1. The average of BMI, and distribution of Charlson comorbidity index score between the three groups. (A) The averages of BMI and standard errors were shown in the bar graph. The BMI average tended to increase with severity of disease. (B) The percentage of the number of Charlson Comorbidity Index between the three groups was shown in the bar graph. A higher proportion of patients in the mild disease group had a Charlson comorbidity index of 0, and the proportion of patients with a Charlson comorbidity index of 2 or more increased as the disease became more severe.

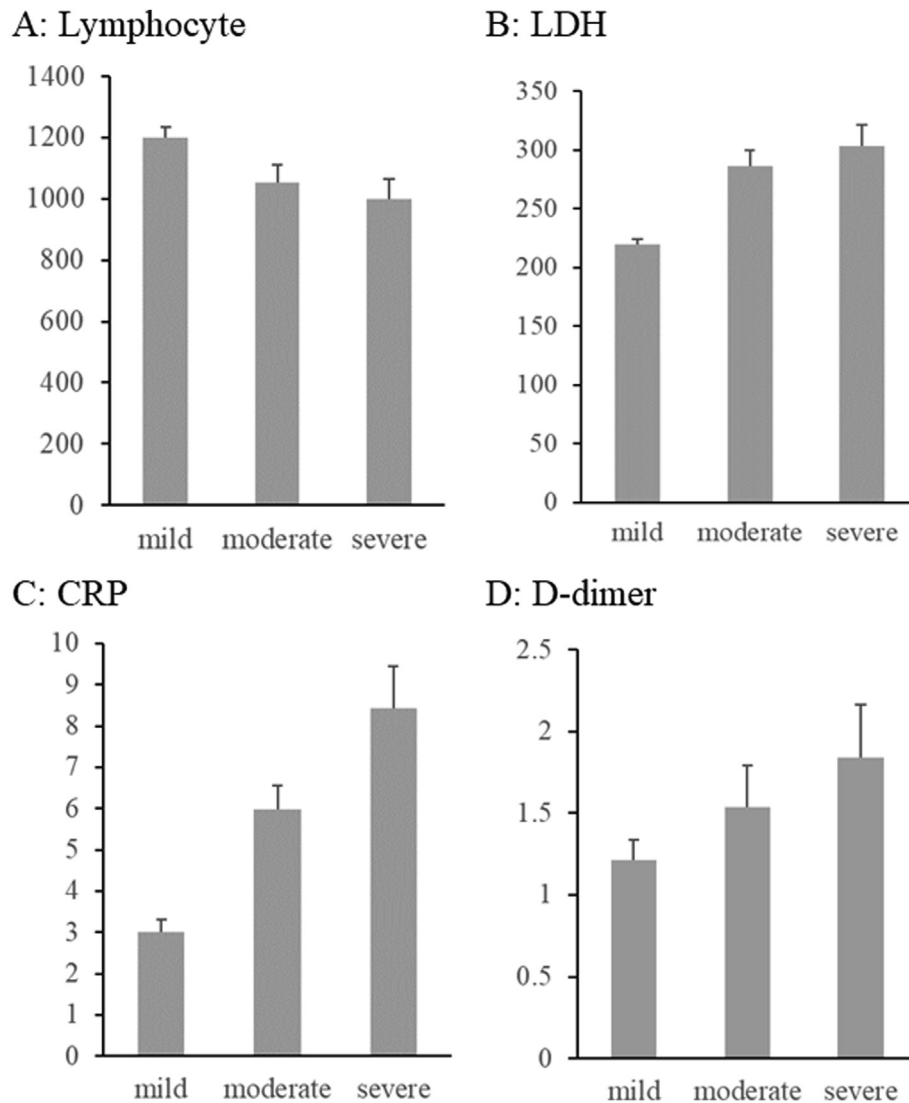


Fig. 2. The average of laboratory data between the three groups. The averages of laboratory data and standard errors were shown in the bar graph. The patients in more severe disease group were more likely to have lower lymphocyte count (A) and higher levels of LDH (B), CRP (C), and D-dimer (D).

Laboratory data and treatment status

The laboratory data on admission of the three groups are shown in Table 1, with the mean and standard deviation. Laboratory data showed that patients with more severe disease were more likely to have lower lymphocyte count and higher levels of LDH, CRP, AST, and D-dimer.

The averages of these variables between the three groups are shown in Fig. 2. The patients in more severe disease group were more likely to have lower lymphocyte count, and higher levels of LDH, CRP, and D-dimer.

The treatment regimen and outcomes are described in Table 1. Many drugs including remdesivir, corticosteroid, tocilizumab, and immunoglobulin were used more frequently in more severe disease group. However, despite these treatments, of the 46 patients in the severe disease group, 17 (37.8%) and one (2.2%) required mechanical ventilation and ECMO, respectively, and six (13.0%) died.

Correlation of respiratory status and laboratory findings

The correlations between patients' worst respiratory status (SpO₂/FiO₂) during hospitalization and the aforementioned continuous variables are shown in Fig. 3.

High CRP and LDH levels in the initial blood tests were strongly correlated with worsening of respiratory status. Moreover, older age and low lymphocyte count were also weakly associated with worsening of respiratory status.

Risk factors for the severity of COVID-19

Results of univariate and multivariate analyses of risk factors for severe disease are shown in Table 2. In univariate analysis, age, hypertension, diabetes, lymphocyte count, LDH, and CRP were significantly associated with severity of COVID-19. In multivariate

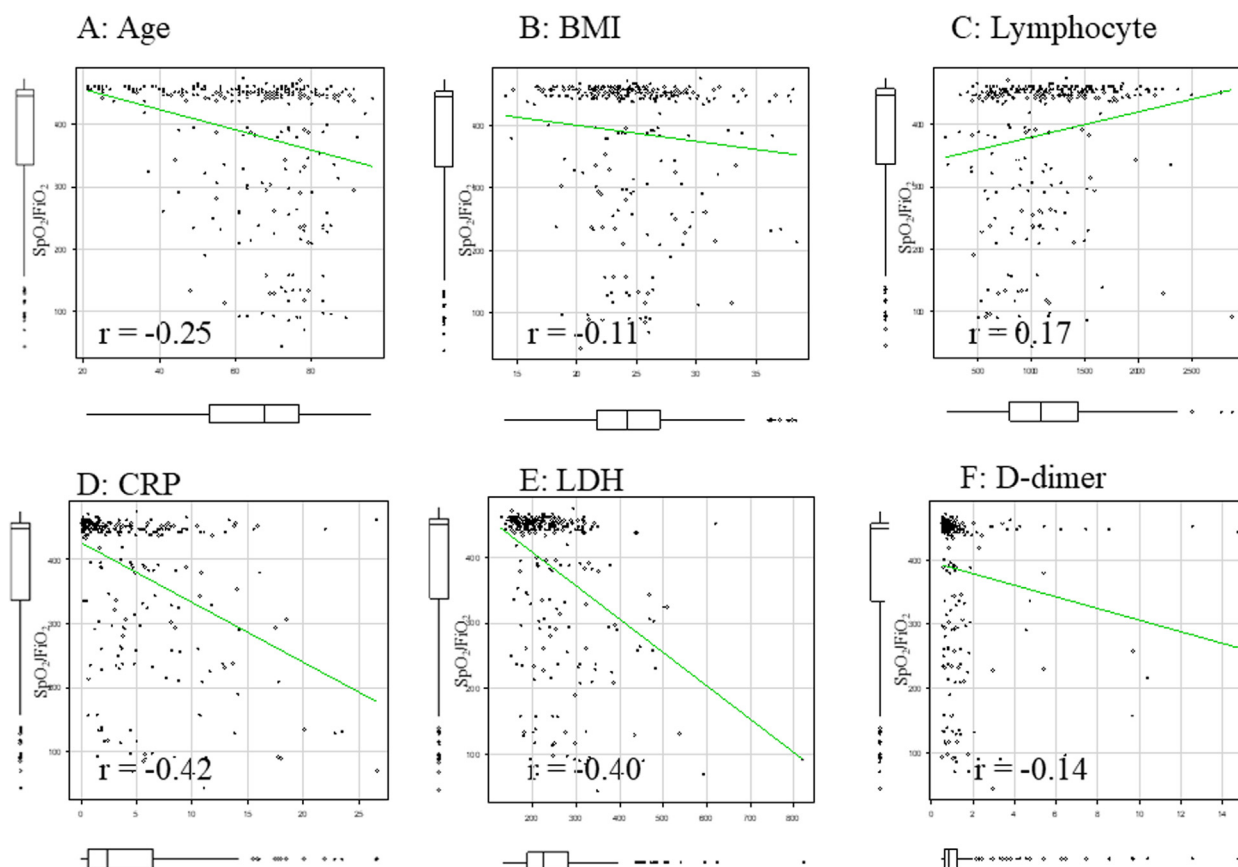


Fig. 3. The correlation between patients' worst respiratory status (SpO_2/FiO_2) and patient's characteristics.

The worst respiratory status (SpO_2/FiO_2) is shown on the vertical axis and each parameter is shown on the horizontal axis, and correlations were examined. High CRP and LDH levels in the initial blood tests were strongly correlated with worsening of respiratory status (D, E). Older age and low lymphocyte count were also weakly associated with worsening of respiratory status (A, C).

Table 2
Univariate and multivariate analyses of risk factors for severe disease.

Variable	Univariate model			Multivariate model		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Age	1.040	1.02–1.07	<0.001	1.050	1.02–1.08	0.003
Sex	1.720	0.87–3.38	0.116	–	–	–
Hypertension	1.960	1.04–3.69	0.037	–	–	–
Diabetes	2.620	1.34–5.12	0.005	2.160	0.98–4.76	0.057
Lymphocyte	0.999	0.998–1.00	0.043	–	–	–
LDH	1.010	1.00–1.01	<0.001	–	–	–
CRP	1.160	1.10–1.23	<0.001	1.130	1.04–1.22	0.003
D-dimer	1.150	0.99–1.32	0.065	–	–	–

Abbreviations: CI, confidence interval; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Risk Factors associated with severity of disease were analyzed by logistic regression model. A p value of <0.05 was considered statistically significant.

analysis, age and CRP were independently associated with the severity of the disease.

The ROC curves are shown in Fig. 4 to evaluate the cutoff values for age and CRP. The optimal cutoff value for age was 74 years old (sensitivity 58.5% and specificity 70.9%) and that for CRP was 3.15 mg/dL (sensitivity 76.1% and specificity 59.8%). Additionally, the area under curves (AUC) for age and CRP alone were not very high (0.67 and 0.75, respectively), but they increased to 0.81 when combined.

Discussion

In this study, we investigated the patient background and clinical characteristics of Japanese patients with COVID-19, and identified the risk factors for severe disease. Some studies on the risk factors for mortality or the need for mechanical ventilation of COVID-19 patients have been reported worldwide, especially in China. However, reports from Japan are limited, and our study focusing on Japanese patients is thought to be important. The

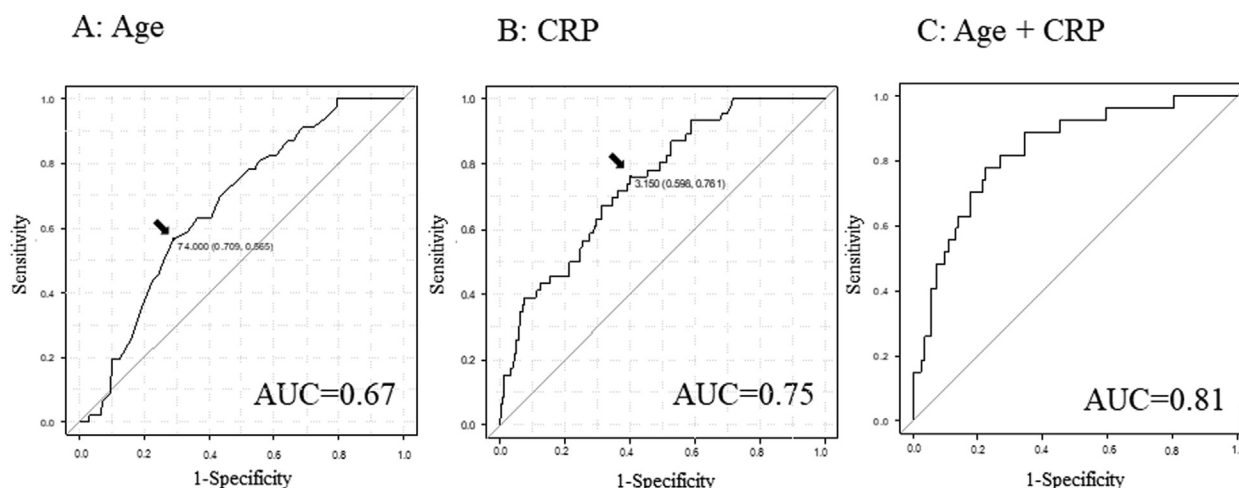


Fig. 4. Receiver operating characteristic curve analyses of age and CRP.

Receiver operating characteristic curve analyses of age (A) and CRP (B) at diagnosis. The arrows indicate the cut-off values.

mortality rate and the percentage of patients requiring a ventilator are low in Japan, and unlike in other countries, these events may not be suitable for accurate evaluation of the Japanese clinical practice. Therefore, this study took the present method of defining severe disease as requiring more than 5L/min of oxygen administration.

In this study, low lymphocyte count and elevated inflammatory markers such as CRP and LDH were significantly higher in patients with severe disease. The association between these parameters and prognosis has been reported in many previous reports. A previous cohort study on COVID-19 reported that the most influential marker of risk was lymphopenia, and patients with severely low lymphocyte count ($<0.5 \times 10^9/L$) had a higher mortality rate [11]. In our study, lymphocyte count in the severe disease group was lower than that in the mild and the moderate disease groups. Similarly, other reports that severe COVID-19 patients tended to have higher levels of inflammatory markers such as CRP and LDH support our findings [7,12,13]. Among these laboratory findings, it may be necessary to pay particular attention to CRP and LDH, which were more strongly correlated with respiratory status in the present study. Although the difference was not statistically significant, the BMI tended to be higher as the disease became more severe. The association between obesity and the severity of COVID-19 has been reported in several studies. However, it is important to demonstrate that the association was also observed in Japanese patients who are generally less obese than patients in Europe and the United States [14,15]. As regards underlying diseases, previous reports showed that comorbidities such as hypertension, diabetes mellitus, and cardiovascular disease correlate with COVID-19 mortality. In this study, hypertension and diabetes were more common in patients with severe disease [16–18]. Additionally, the Charlson Comorbidity Index, which scores these preexisting conditions, has a high percentage of patients with severe disease, which suggests that multiple comorbidities, not just a single comorbidity, may be a risk for severe disease [9]. Although these variables were not significantly correlated with severity of illness on multivariate analysis due to the small number of cases or events in the present study, the possibility of severe disease in patients with these backgrounds should always be kept in mind.

More importantly, in multivariate analysis of this study, age and CRP were the independent risk factors for the severe disease. Age has been reported as a risk factor for poor outcomes in previous reports, especially in patients over 65 years old, with a higher

mortality rate than in patients under 65 years old [19,20]. Moreover, other study also demonstrated that for each one-year increase in age, the odds of death increased by 5%, and this result is consistent with our results [21]. On the other hand, several reports on the correlation between CRP and the severity exit, and they reported that non-survivors have higher levels of CRP than survivors at the first visit [7,14,22,23]. However, reports of CRP as a risk factor for severe disease in multivariate analysis are limited, indicating that our results from the multivariate analysis are of great significance. As shown in the ROC curves, the AUC for age and CRP alone was small, but it increased to high accuracy level when combined. It is important to evaluate these risk factors in a comprehensive manner.

We have been mainly treating COVID-19 patients with moderate disease. In Kanagawa Prefecture, the policy is that patients who need more than 5L/min of oxygen should be transferred to advanced medical institutions where advanced medical care such as mechanical ventilator and ECMO can be performed. Thus, our focus is on preventing the deterioration from moderate to severe disease. Several reports on how to classify the severity of COVID-19 are present [24,25]. In this study, we defined severe illness as worsening of respiratory status requiring oxygen administration of 5 L/min or more to meet the clinical practice, mainly because the rate of mortality or the need for mechanical ventilation was too low to evaluate in Japan. We previously reported a case report of COVID-19 patient with interstitial pneumonia that improved with steroid treatment [26] and case series of 11 patients treated with Favipiravir in combination with steroids for COVID-19 [27]. Of course, effective treatment for COVID-19, including steroids, has not yet been fully established. However, on the basis of these experiences, we believe that aggressive treatment of patients with these risk factors with antiviral and anti-inflammatory drugs, even in cases that did not require oxygenation, would have prevented the deterioration. The accumulation of cases will lead to the establishment of risk factors and treatment methods.

This study had several limitations. First, it was a single-center retrospective study with a small number of patients. Therefore, a larger scale study is needed to establish our results. Second, various therapeutic agents were used, some of which were used at significantly different frequencies in the severe and non-severe disease groups, and these drugs may have influenced the progression of the disease. In particular, corticosteroids were administered to about 40% of patients in the mild disease group and to about 90% of

patients in the moderate and severe disease groups. It is reasonable to assume that steroid use may have affected the severity of the disease. However, because of the limitation of the retrospective study, it was difficult to determine its influence on the outcome. Furthermore, the natural course of the disease itself may have influenced our results. However, most of the previous reports on COVID-19 were also retrospective studies, and we do not believe that they had a significant impact on the analysis of risk factors for severe disease in our study. Third, the definition of severe illness of respiratory status requiring oxygen administration of 5 L/min or more may have influenced our results. Most of the previous studies have defined tracheal intubation and death as the severe illness, and in this respect, the results possibly differed from previous reports. However, as mentioned above, we believe that our definition of severity well fit the clinical setting in Japan.

Conclusions

This study demonstrated that age and CRP were independently associated with severity in multivariate analysis in Japanese patients with COVID-19. Additionally, underlying disease, BMI, lymphocyte count and, inflammatory markers such as LDH and D-dimer may also be related to the severity of the disease. Further investigation is required to establish the results of this study.

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Authorship statement

ROtoshi and EH were involved in study conception and design; ROToshi, EH, TK, TY, KH, KM, YS, ET, RS, HO, SI, TN, AN, TOda, ROKuda, AS, HK, TB, and SK were involved in data acquisition. All authors read and approved the final manuscript.

All authors meet the ICMJE authorship criteria.

Declaration of competing interest

All of the authors report they have no conflict of interest to disclose.

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References

- [1] Lu Hongzhou, Stratton Charles W, Tang Yi-Wei. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. *J Med Virol* 2020 Apr;92(4):401–2.
- [2] Wang Chen, Horby Peter W, Hayden Frederick G, Gao George F. A novel coronavirus outbreak of global health concern. *Lancet* 2020 Feb 15;395:470–3. 10223.
- [3] Wu Zunyou, Jennifer M McGoogan. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *J Am Med Assoc* 2020 Apr 7;323(13):1239–42.
- [4] Huang Chaolin, Wang Yeming, Li Xingwang, Ren Lili, Zhao Jianping, Hu Yi, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020 Feb 15;395:497–506. 10223.
- [5] Yoshimura Yukihiro, Sasaki Hiroaki, Horiuchi Hiroshi, Miyata Nobuyuki, Tachikawa Natsuo. Clinical characteristics of the coronavirus disease 2019 (COVID-19) outbreak on a cruise ship. *J Infect Chemother* 2020 Nov;26(11):1177–80.
- [6] Yang Xiaobo, Yuan Yu, Xu Jiqian, Shu Huaqing, Xia Jia'an, Liu Hong, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020 May;8(5):475–81.
- [7] Du Rong-Hui, Liang Li-Rong, Yang Cheng-Qing, Wang Wen, Cao Tan-Ze, Li Ming, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J* 2020 May 7;55(5):2000524. <https://doi.org/10.1183/13993003.00524-2020>.
- [8] Guisado-Vasco Pablo, Valderas-Ortega Sofia, Carralón-González Maria Maravillas, Roda-Santacruz Ana, González-Cortijo Lucia, Sotres-Fernández Gabriel, et al. Clinical characteristics and outcomes among hospitalized adults with severe COVID-19 admitted to a tertiary medical center and receiving antiviral, antimalarials, glucocorticoids, or immunomodulation with tocilizumab or cyclosporine: a retrospective observational study (COQUIMA cohort). *Eclin Med* 2020 Oct 15:100591. <https://doi.org/10.1016/j.eclinm.2020.100591>.
- [9] De Giorgi A, Fabbian F, S Greco E Di Simone, De Giorgio R, Passaro A, et al. Prediction of in-hospital mortality of patients with SARS-CoV-2 infection by comorbidity indexes: an Italian internal medicine single center study. *Eur Rev Med Pharmacol Sci* 2020 Oct;24(19):10258–66.
- [10] Kanda Y. Investigation of the freely available easy-to-use software "EZ" for medical statistics. *Bone Marrow Transplant* 2013;48:452–8.
- [11] Wang Kun, Zuo Peiyuan, Liu Yuwei, Zhang Meng, Zhao Xiaofang, Xie Songpu, et al. Clinical and laboratory predictors of in-hospital mortality in patients with COVID-19: a cohort study in Wuhan, China. *Clin Infect Dis* 2020 May 3. ciaa538, <https://doi.org/10.1093/cid/ciaa538>.
- [12] Terpos Evangelos, Ntanasis-Stathopoulos Ioannis, Elalamy Ismail, Kastritis Efstathios, Sergentanis Theodoros N, Politou Marianna, et al. Hematological findings and complications of COVID-19. *Am J Hematol* 2020;95:834–47.
- [13] Liu Wei, Tao Zhao-Wu, Wang Lei, Yuan Ming-Li, Liu Kui, Zhou Ling, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chin Med J (Engl)*. 2020 May 5;133(9):1032–8.
- [14] Rao Xinrui, Wu Chuangyan, Wang Sihua, Tong Song, Wang Geng, Wu Gang, et al. The importance of overweight in COVID-19: a retrospective analysis in a single center of Wuhan, China. *Medicine (Baltim)* 2020 Oct 23;99(43):e22766. <https://doi.org/10.1097/MD.00000000000022766>.
- [15] Al-Sabah Salman, Al-Haddad Mohannad, Al-Youha Sarah, Jamal Mohammad, Almazeedi Sulaiman. COVID-19: impact of obesity and diabetes on disease severity. *Clin Obes* 2020 Oct 20:e12414. <https://doi.org/10.1111/cob.12414>.
- [16] Guan Wei-jie, Ni Zheng-yi, Hu Yu, Liang Wen-hua, Ou Chun-quan, He Jian-xing, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020 Apr 30;382(18):1708–20.
- [17] Lippi G, Wong J, Henry BM. Hypertension in patients with coronavirus disease 2019 (COVID-19): a pooled analysis. *Pol Arch Intern Med* 2020 Apr 30;130(4):304–9.
- [18] Huang Ian, Lim Michael Anthonius, Raymond Pranata. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - a systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr Jul-Aug* 2020;14(4):395–403.
- [19] Mehra Mandeep R, Desai Sapan S, Kuy SreyRam, Henry Timothy D, Patel Amit N, et al. Cardiovascular disease, drug therapy, and mortality in covid-19. *N Engl J Med* 2020 Jun 18;382(25):e102. <https://doi.org/10.1056/NEJMoa2007621>.
- [20] Hu Ling, Chen Shaoqiu, Fu Yuanquan, Gao Zitong, Long Hui, Wang Jian-Ming, et al. Risk factors associated with clinical outcomes in 323 COVID-19 hospitalized patients in wuhan, China. *Clin Infect Dis* 2020 May 3. ciaa539, <https://doi.org/10.1093/cid/ciaa539>.
- [21] Nikpouraghdam Mohamad, Farahani Alireza Jalali, Alishiri GholamHossein, Heydari Soleyman, Ebrahimnia Mehdi, Samadinia Hossein, et al. Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in Iran: a single center study. *J Clin Virol* 2020 Jun;127:104378. <https://doi.org/10.1016/j.jcv.2020.104378>.
- [22] Wang Zhongliang, Yang Bohan, Li Qianwen, Lu Wen, Zhang Ruiguang. Clinical features of 69 cases with coronavirus disease 2019 in wuhan, China. *Clin Infect Dis* 2020 Jul 28;71(15):769–77.
- [23] Ishii Makoto, Terai Hideki, Kabata Hiroki, Masaki Katsunori, Chubachi Shotaro, Tateno Hiroki, et al. Clinical characteristics of 345 patients with coronavirus disease 2019 in Japan: a multicenter retrospective study. *J Infect* 2020 Nov;81(5):e3–5. <https://doi.org/10.1016/j.jinf.2020.08.052>.
- [24] National Institutes of Health. Management of persons with COVID-19. 2020. <https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/>. [Accessed 21 July 2020].
- [25] World Health Organization. Clinical management of severe acute respiratory infection when COVID-19 is suspected: interim guidance. 2020. [https://www.who.int/publicationsdetail/clinical-management-of-severe-acute-respiratoryinfection-when-novel-coronavirus-\(ncov\)-infection-issuspected](https://www.who.int/publicationsdetail/clinical-management-of-severe-acute-respiratoryinfection-when-novel-coronavirus-(ncov)-infection-issuspected). [Accessed 15 May 2020].
- [26] Kitayama Takaaki, Kitamura Hideya, Hagiwara Eri, Higa Katsuyuki, Okabayashi Hiroko, Oda Tsuneyuki, et al. COVID-19 pneumonia resembling an acute exacerbation of interstitial pneumonia. *Intern Med* 2020 Oct 21. <https://doi.org/10.2169/internalmedicine.5630-20>.
- [27] Murohashi K, Hagiwara E, Kitayama T, Yamaya T, Higa K, Sato Y, et al. Outcome of early-stage combination treatment with favipiravir and methylprednisolone for severe COVID-19 pneumonia: a report of 11 cases. *Respir Invest* 2020 Aug 28;58(6):430–4.